Asymmetric transfer hydrogenation of ketones promoted by manganese(I) pre-catalysts supported by bidentate aminophosphines

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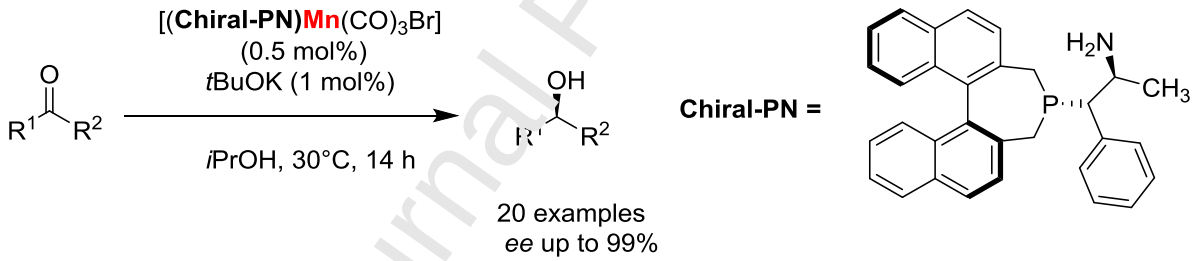
Graphical abstract



Abstract

A series of commercially available chiral amino-phosphines, in combination with $Mn(CO)_5Br$, has been evaluated for the asymmetric reduction of ketones, using isopropanol as hydrogen source. With the most selective ligand, the corresponding manganese complex was synthesized and fully characterized. A series of ketones (20 examples) was hydrogenated in the presence of 0.5 mol% of the manganese pre-catalyst at 30°C, affording the chiral alcohols in high yields with enantiomeric excesses up to 99%.

Highlights

- **Asymmetric reduction of ketones was achieved with enantioselectivity up to 99% under manganese catalysis**

- **Chiral bidendate amino-phosphine as promising ligand for asymmetric hydrogen transfer reaction promoted by manganese**
- **Well-defined manganese (I) complex based on aminophosphine ligand with binepine moieties as catalyst in reduction**

Keywords

Manganese, chiral aminophosphine ligands, transfer hydrogenation, reduction, ketones

1. Introduction

Chiral alcohols are highly valuable synthetic intermediates for the production of pharmaceutical, agrochemical and fine chemical products. As a result, intensive research work has been devoted to the development of chiral organometallic complexes and their implementation in asymmetric direct hydrogenation or transfer hydrogenation of prochiral ketones.[1]

Noble metal have proven to be particularly efficient for this class of transformation, and for this reason, are still widely used in this area.[2] Quite recently, this field of research has met a significant shift towards the use of earth-abundant, inexpensive and environmentally friendly first row transition metals such as Fe,[3-6] Co[7-9] and Mn.[3, 10-13] However, in this context, examples of Mn-based pre-catalysts are still quite scarce both in asymmetric transfer hydrogenation (ATH) and direct hydrogenation (ADH).

In 2017, Zirakzadeh and Kirchner[14] reported the first example of asymmetric transfer hydrogenation of aromatic ketones catalyzed by a manganese complex of a chiral ferrocenyl tridentate PNP ligand. Shortly after, Clarke[15] described a Mn-based catalytic system supported by a related PNN ligand for the asymmetric direct hydrogenation of ketones. In the same vein, Zhong and coworkers developed another class of ferrocenyl PNN tridentate ligands incorporating an imidazole moiety for the asymmetric direct hydrogenation of benzophenone derivatives with ee up to 99%.[16]

The pincer type complex incorporating a PNP tridentate ligand bearing chiral phospholane groups published by Beller[17, 18] proved to be a better catalyst for the reduction of prochiral aliphatic ketones (ee up to 99%) than for the aromatic ones. In contrast, Han and Ding reported very recently a manganese catalyst containing a NNP ligand that allowed the ADH of a large range of aromatic ketones with high activities (TON up to 9800) and enantioselectivities up to 98%. [19]

In the field of ATH, only a handful of examples, mainly based on tri- and tetradentate ligands, have been reported so far. Morris evidenced the ability of well-defined Mn complexes supported by tridentate PNN ligands to promote the transfer hydrogenation of ketones.[20] Recently, efficient catalytic systems based on tetradentate ligands were developed by Beller [21] and Mezzetti.[22, 23] While Beller showed that easily accessible and potentially tetradentate chiral oxamide ligands in combination with $Mn(CO)_5Br$ are highly effective in the ATH of aliphatic ketones with ee up to 93%, Mezzetti obtained excellent enantioselectivities (90 to 99%) for the asymmetric transfer hydrogenation of a large range of aryl/heteroaromatic alkyl ketones with Mn complexes supported by a tetradentate macrocyclic ligand.[22] In contrast, our group showed that simple chiral diamine mixed with $Mn(CO)_5Br$ are capable to hydrogenate enantioselectively acetophenone and related ketones.[24] Shortly after, this work was complemented by mechanistic studies performed by Pidko[25] on closely related catalytic systems involving well-defined manganese catalyst supported by a chiral diamine ligand.

In the continuation of our work on diamines and more generally on bidendate ligands in reduction reactions with Mn-catalysts,[26-30] we were interested in investigating the effect of the electronic and steric properties of commercially available chiral aminophosphines onto their activity and selectivity.

It should be noticed that in the course of this study, Pidko[25] and Lacy[31] independently reported the ability of aminophosphine ligands to promote the Mn-catalyzed transfer hydrogenation of ketones with good activities but the selectivities remained modest.

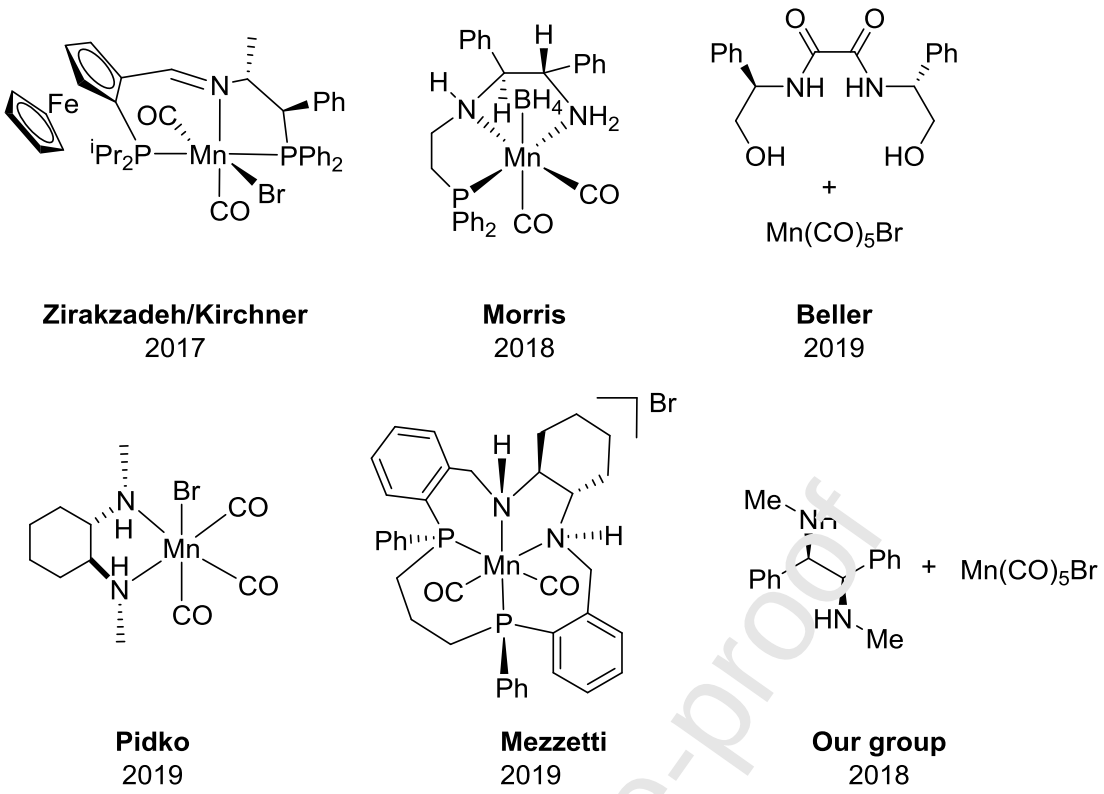


Chart 1: Manganese based catalysts for asymmetric transfer hydrogenation

2. Experimental

*2.1. Synthesis of complex **1***

In an argon-filled glovebox, a 100 mL Schlenk flask was charged with a solution of (1*S*,2*S*)-1-((4*R*,11*bS*)-3H-Dinaphtho[2,1-c:1′,2′-e]phosphepin-4(5H)-yl)-1-phenyl-2-propanamine **L8** (100 mg, 0.224 mmol) in degassed toluene (5 mL), and pentacarbonyl manganese bromide ($Mn(CO)_5Br$) (62 mg, 0.225 mmol) was added in one portion. The reaction mixture was then heated at 110°C for 4 h. Toluene was evaporated under reduced pressure and the yellow solid was washed three times with dry pentane. Complex [**L8**$Mn(CO)_3Br$] (**1**) was obtained as a yellow powder (131 mg, 87%). Single crystals suitable for X-ray diffraction analysis were grown by layering a solution of the complex in $CDCl_3$ with pentane at 5°C.

2.2 General procedure for hydrogen transfer reduction of acetophenone with the in situ generated catalytic system

To a solution of acetophenone (2 mmol, 232 µL) in 2-propanol (18 ml) were added a stock solution of manganese pentacarbonyl bromide in 2-propanol (0.5 mL, 0.02 $mol.L^{-1}$) and a

solution of ligand (0.01 mmol) in 2-propanol (1 mL) in this order. After 10 min of heating at 80°C, the solution was then cooled to 30°C and a stock solution of *t*BuOK in 2-propanol (0.5 mL, 0.04 mol.L^{-1}) was added. The mixture was stirred for 19 h in an oil bath at 30°C. The solution was then filtered through a small pad of silica (4 cm high in a column with a diameter of about 1cm). The silica was washed with ethyl acetate, volatiles were removed under reduced pressure and the conversion and enantiomeric excesses were determined by GC analyses performed on a Shimadzu GC-2010 apparatus equipped with a Supelco betaDEX 120 column (30 m x 0.25 mm) using Helium as the vector gas.

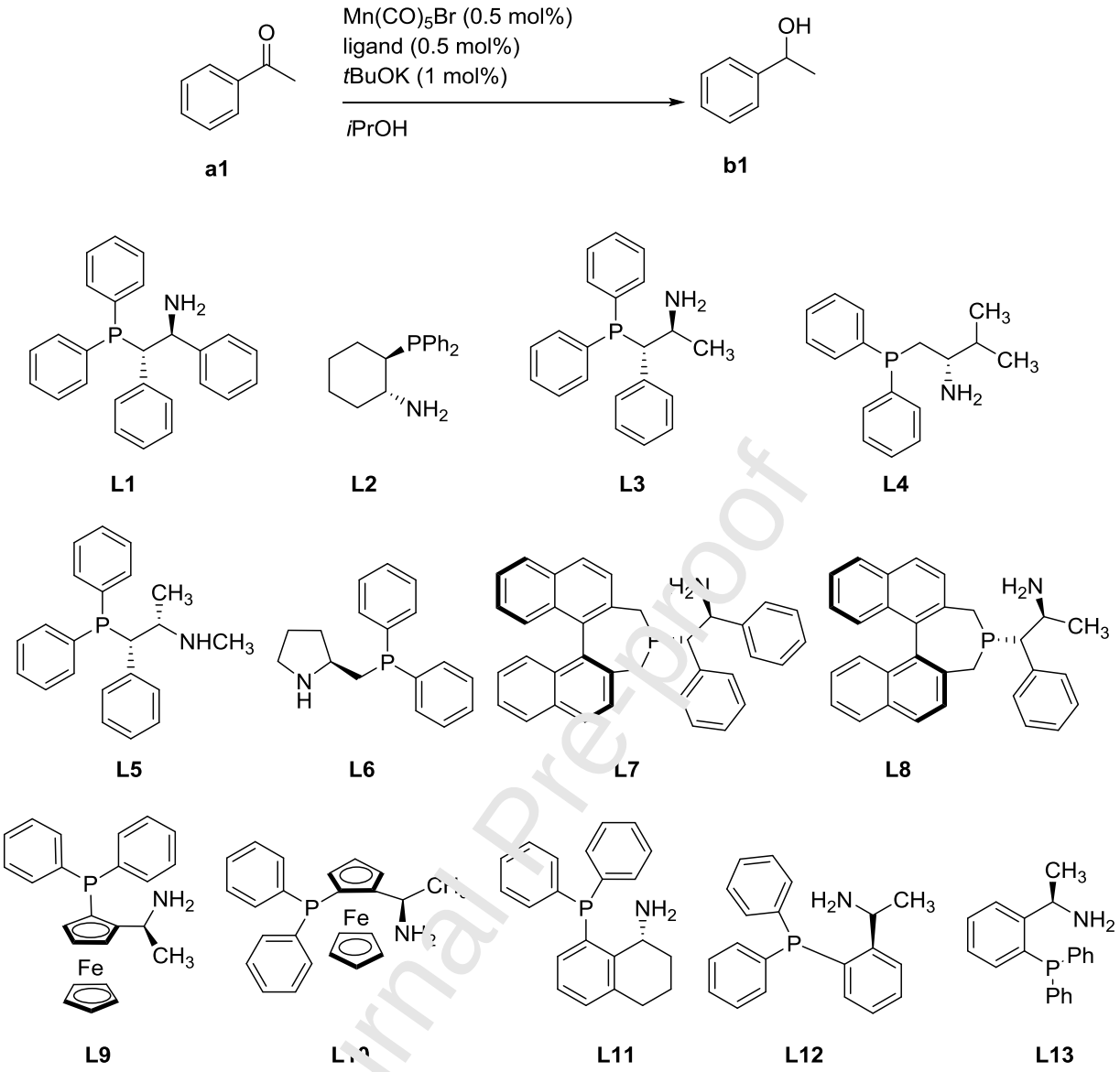
*2.3. General procedure for hydrogen transfer reduction of ketones with well-defined complex [**L8**Mn(CO)$_3$Br] **1***

To a solution of ketone (2 mmol) in 2-propanol (19 mL) were added in this order a stock solution of complex **1** in 2-propanol (0.5 mL, 0.02 mol.L^{-1}), and a stock solution of *t*BuOK in 2-propanol (0.5 mL, 0.04 mol.L^{-1}) at 30°C. The mixture was stirred for 14 h in an oil bath at 30°C. The solution was then filtered through a small pad of silica (4 cm high in a column with a diameter of about 1 cm). The silica was washed with ethyl acetate, volatiles were removed under reduced pressure and the conversion was determined by ^{1}H NMR. The crude reaction mixture was purified by column chromatography (SiO_2, a mixture of petroleum ether/ ethyl acetate as eluent) to afford the corresponding alcohol. This latter was analyzed by chiral GC. Enantiomeric excesses were determined by GC analyses performed on a Shimadzu GC-2010 apparatus equipped with a Supelco betaDEX 120 column (30 m x 0.25 mm) using Helium as the vector gas.

3. Results and discussion

We performed the initial catalytic reactions with ligand **L1** following the typical conditions of reaction optimized with diamine ligands[24] *ie* in the presence of Mn(CO)$_5$Br (0.5 mol%), ligands (0.5 mol%) and *t*BuOK as a base (1 mol%) at 80°C in isopropanol (c = 0.25 mol.L^{-1}). Although being highly active (80 % conversion after 15 min, Table 1, entry 1), ligand **L1** induced a very poor selectivity (3% ee) compared to its diamino counterpart, the (1*R*,2*R*)-(+)-1,2-diphenyl-1,2-ethanediamine (DPEN) ligand (36% ee)[24]. Operating in a more diluted medium (c = 0.1 mol.L^{-1}) and decreasing the reaction temperature to 30°C improved slightly the enantioselectivity to 12% ee after 19h (entry 2). Under these conditions, we tested the aminophosphine **L2** which can be considered as the analogue of the (1*R*,2*R*)-(−)-1,2-diaminocyclohexane ligand **L'2**. Despite its more rigid structure, 1-phenylethanol was

obtained in only 15% ee (*vs* 43% for **L'2**[24]) (entry 3). Decreasing the steric hindrance in alpha position to the amino function by replacing the phenyl group by a methyl (**L3)** significantly improved the enantioselectivity to 46% ee (entry 4) without any loss of activity whereas the introduction of an isopropyl (**L4**) resulted in a drop of the activity without any beneficial effect on the enantioselectivity (entry 5). We then investigated the use of the *N*-methylated ligand **L5** for the reduction of acetophenone which yielded the 1-phenylethanol with an encouraging 65% ee (entry 6), which is in line with what we observed with the diamine ligands. We were therefore interested in testing ligand **L6**, whose the 5-membered cyclic structure combined rigidity and alkylation of the nitrogen atom but the enantioselectivity disappointingly dropped to 5% (entry 7). We then envisaged the tuning of the phosphorus moiety. Introduction of a chiral bulky binepine moiety on the phosphorus atom led to an increase of the enantiomeric excess from 12% (**L1**, entry 2) to 57% (**L7**, entry 8). As ligand **L3** induced a better selectivity than ligand **L1**, we therefore conducted the reduction with ligand **L8** with a methyl in alpha position to the amino function, which further improved the enantioselectivity to 71 % ee (entry 10, *vs* 46 % ee, entry 4). As expected, due to the reversibility of the transfer hydrogenation reaction, a monitoring of the reaction evidenced a racemisation of the alcohol, the enantiomeric excess decreased from 77% ee after 14h (entry 9) to 71% after 19h (entry 10). Considering the coordination chemistry of the aminophosphines, it is noteworthy that aminophosphines **L1**-**L8** form 5-membered chelate rings upon coordination with manganese, we wondered to which extent the coordination mode of the ligand could affect the enantioselectivity. For this purpose, we submitted a range of aminophosphines able to afford 6-membered chelate rings on coordination to the metal center for the reduction of acetophenone. Since ferrocene-based ligands have proven their efficiency in asymmetric hydrogenation reaction,[14-16, 32] we tested ligands **L9** and **L10** displaying opposite planar chirality. Disappointingly, the enantiomeric excesses recorded did not exceed 20% (entries 11 and 12). Similarly, ligands **L11**-**L13** led to modest enantioselectivity not greater than 25% (entries 13-15). As ligand **L8** has proven to be the most selective one for the ATH of acetophenone, we performed the synthesis of complex [**L8**$Mn(CO)_3Br$] (**1**) by reacting the chiral amino phosphine ligand **L8** with the manganese precursor $Mn(CO)_5Br$ in toluene at 110°C for 4h. The NMR analyses revealed the formation of two diastereomers differing only in the configuration of the metal center,[33] one of which could be crystallized as monocrystals suitable for XRay analysis (Figure 1). The exact absolute configuration of each diastereomer was not assigned as the base is likely to cause epimerization at the metal by deprotonation of the amine function and elimination of KBr.[26]



Scheme 1. Chiral amino phosphine ligands screened in Mn-catalyzed asymmetric transfer hydrogenation of acetophenone.

Entry	Ligand	Temp.	V *i*PrOH (mL)	Time	Ee (%)[c]	Conv. (%)[d]
1	L1 L1	80[a] 80[a]	8 8	15 min. 45 min.	3 (*R*) 2 (*R*)	80 90
2	L1	80-30[b]	20	19h	12 (*R*)	90
3	L2	80-30 [b]	20	19h	15 (*S*)	97
4	L3	80-30[b]	20	19h	46 (*R*)	96
5	L4	80-30 [b]	20	19h	11 (*R*)	24
6	L5	80-30[b]	20	19h	65 (*R*)	90
7	L6	80-30[b]	20	19h	5 (*S*)	97
8	L7	80-30[b]	20	19h	57 (*R*)	96
9	L8	80-30[b]	20	14h	77 (*R*)	95
10	L8	80-30[b]	20	19h	71 (*R*)	95
11	L9	80-30 [b]	20	19h	20 (*S*)	8
12	L10	80-30 [b]	20	19h	18 (*R*)	10
13	L11	80-30[b]	20	19h	25 (*S*)	97
14	L12	80-30[b]	20	19h	1 (*R*)	97
15	L13	80-30[b]	20	19h	2 (*S*)	97

Table 1. Screening of chiral amino phosphine ligands in asymmetric transfer hydrogenation of acetophenone.

Reaction conditions: (a) pre-activation step was performed: acetophenone (2 mmol), chiral ligand (0.01 mmol) and $Mn(CO)_5Br$ (0.01 mmol) were stirred in *i*PrOH at 80°C for 10 min then *t*BuOK (0.02 mmol) was added. (b) pre-activation step was performed: acetophenone (2 mmol), chiral ligand (0.01 mmol) and $Mn(CO)_5Br$ (0.01 mmol) were stirred in *i*PrOH at 80°C for 10 min, then the reaction mixture was cooled down to 30°C before the addition of *t*BuOK (0.02 mmol) and stirred for 19 h at 30°C. (c) ee was measured by chiral GC. (d) Conversion was determined by ^{1}H NMR analysis of the crude reaction mixture.

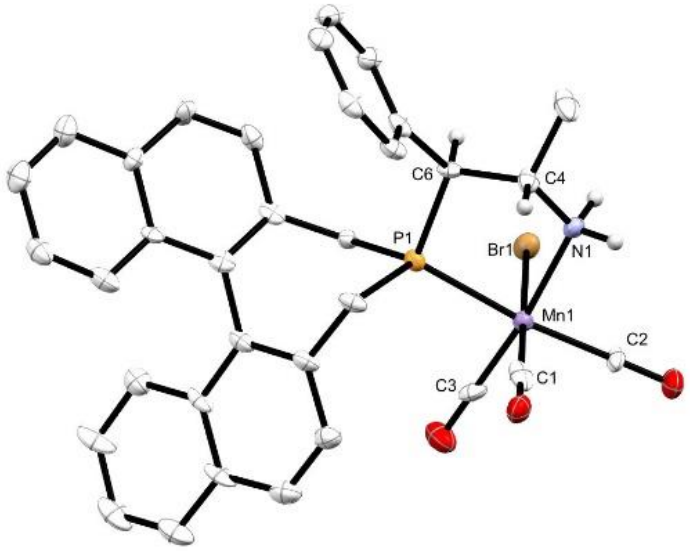
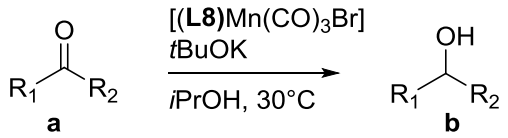
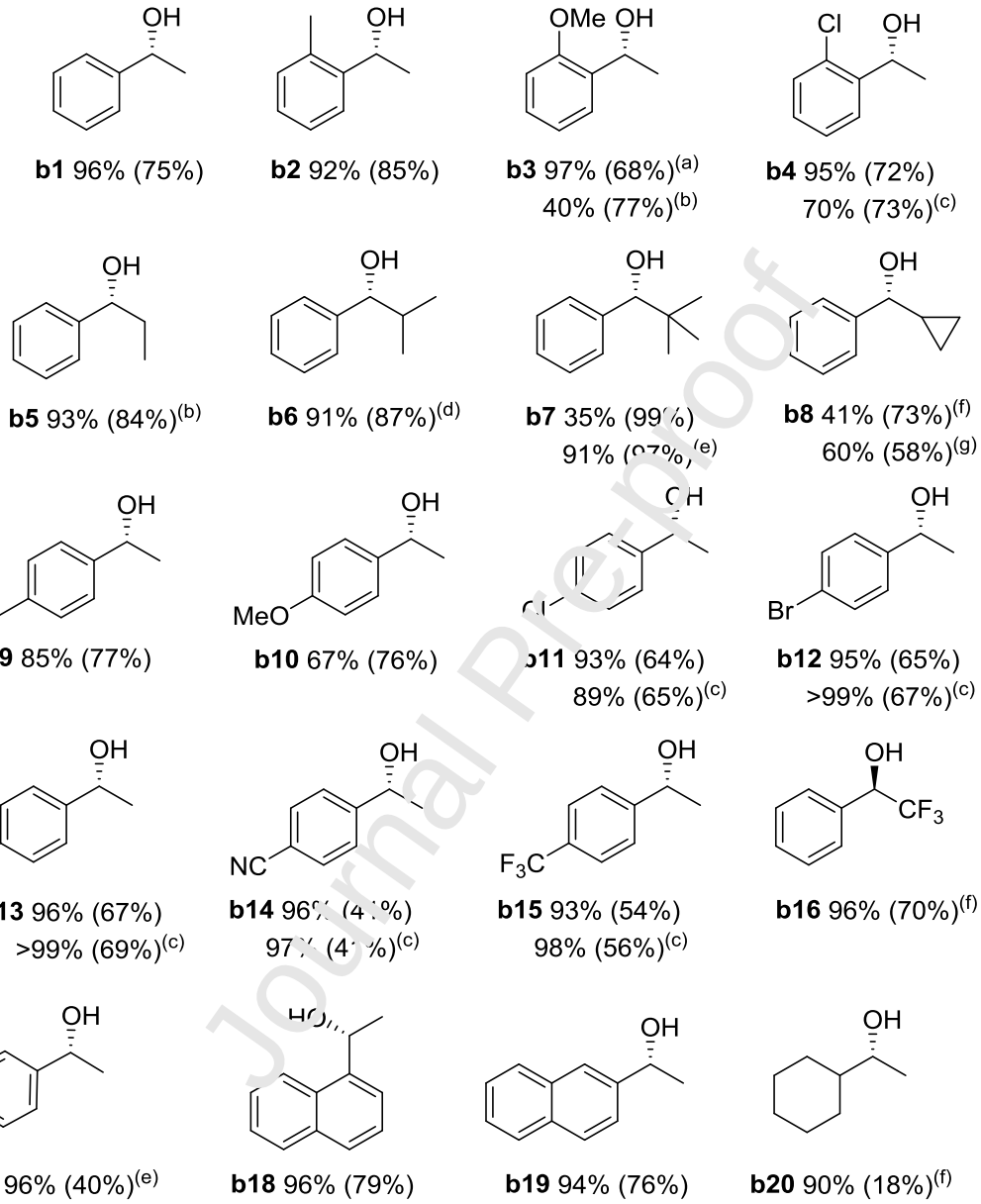


Figure 1. Molecular structure of complex **1** (ellipsoids drawn at the 50% probability level). H atoms have been omitted for clarity. Selected bond lengths (Å) and bond angles (deg): P1-Mn1 2.2977(17), N1-Mn1 2.094(5), Br1-Mn1 2.5385(10), C1-Mn1 1.841(8), C2-Mn1 1.843(5), C3-Mn1 1.800(6), P1-Mn1-N1 83.47(14), P1-Mn1-C3 92.02(19), C3-Mn1-C2 94.4(3), C2-Mn1-N1 90.0(2).

The mixture of the two diastereomers was tested in the asymmetric transfer hydrogenation of acetophenone. 1-phenylethanol **b1** was obtained with 75% ee and 96% isolated yield at 30°C for 14 hours (Scheme 2) which compares well with the result obtained with the in situ catalytic system after 14h (entry 9, Table 1). For ease of handling, we performed the scope of the asymmetric transfer hydrogenation of a range of ketones with the well-defined [**L8**Mn(CO)$_3$Br] pre-catalyst **1** (Scheme 2). Ortho substitution of acetophenone with electron donating (**a2-3**) or electron withdrawing groups (**a4**) had a beneficial effect on the selectivity affording the corresponding alcohols with enantiomeric excesses ranging from 72 to 85%. Substrates displaying bulky substituents at the alpha position to the ketone (**a5-8**) were hydrogenated with good to excellent enantioselectivities up to 99% ee. Although the steric hindrance renders these substrates more reluctant to reduction, increasing the reaction time to 24h for substrate **a5** or raising the temperature from 30°C to 80°C for substrates **a6-8** allowed the formation of the corresponding alcohols in moderate to good yields. In contrast to what was observed with diamine-based catalysts, para substitution of acetophenone with electron donating group did not alter the enantioselectivity, 1-(4-methylphenyl)ethanol **b9** and 1-(4-methoxyphenyl)ethanol **b10** were obtained in 77% ee and 76 % ee respectively compared to 72% ee for 1-phenylethanol **a1**. On the opposite, substrates bearing electron withdrawing

substituents at the para position led to higher activities (almost full conversions were observed at 30°C in 3h for substrates (**a11-15**)) but lower enantioselectivities were recorded ranging from 41% to 69 % ee. In the case of 2,2,2-trifluoroacetophenone **a16**, a reversed sense of asymmetric induction was observed suggesting that a different transition state is involved for this substrate compared to the other aryl/alkyl ketones, which has already been reported with Ru-based catalytic systems.[34, 35] The catalytic system is compatible with heteroaromatic ketones like 4′-acetylpyridine **a17** and polyaromatic ketones such as 1-acetonaphthone **a18** and 2-acetonaphthone **a19**. Regarding alkyl alkyl ketones, cyclohexyl methyl ketone **a20** was reduced to the corresponding alcohol in 90% yield, but with a low enantiomeric excess (18%).





Scheme 2. Scope of asymmetric transfer hydrogenation of carbonyl derivatives in the presence of catalyst **1**.

Typical conditions: In a Schlenk tube, ketone (2 mmol), *i*PrOH (19 mL), complex [**L8**$MnCO_3Br$] (0.5 mol%) and *t*BuOK (1 mol%) were added in this order. The solution was stirred at 30°C for 14h. Isolated yield, enantiomeric excess in parentheses.

(a) 80°C, 15 min; (b) 30°C, 24 h; (c) conversion after 3 h at 30 °C; (d) conversion after 30 min at 80°C; (e) 80 °C, 45 min; (f) 50°C, 14 h; (g) 80 °C, 7 h.

4. Conclusions

In conclusion, we have screened a range of commercially available chiral aminophosphines as ligands in the manganese catalyzed asymmetric transfer hydrogenation of acetophenone. The *in situ* generated catalytic system involving $Mn(CO)_5Br$ (0.5 mol%) as metal precursor and the aminophosphine **L8**, bearing a bulky binepine moiety on the phosphorus atom, afforded the best performances in terms of enantioselectivity. The well-defined manganese pre-catalyst **1** supported by this latter ligand was then synthesized, fully characterized and evaluated in the enantioselective reduction of carbonyl derivatives affording the corresponding alcohols in high yields and enantioselectivities with ee up to 99%.

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Declaration of interests

☒ The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

☐The authors declare the following financial interests/personal relationships which may be considered as potential competing interests:

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Highlights

- **Asymmetric reduction of ketones was achieved with enantioselectivity up to 99% under manganese catalysis**
- **Chiral bidendate amino-phosphine as promising ligand for asymmetric hydrogen transfer reaction promoted by manganese**
- **Well-defined manganese (I) complex based on aminophosphine ligand with binepine moieties as catalyst in reduction**