A Journal of the Gesellschaft Deutscher Chemiker

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To be cited as: *Angew. Chem. Int. Ed.* 10.1002/anie.201814751
Angew. Chem. 10.1002/ange.201814751

Link to VoR: http://dx.doi.org/10.1002/anie.201814751
http://dx.doi.org/10.1002/ange.201814751

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Lutidine-Based Chiral Pincer Manganese Catalysts for Enantioselective Hydrogenation of Ketones

Linli Zhang,[ab] Yitian Tang,[ca] Zhaobin Han,[a*] and Kuiling Ding[abcd*]

Dedication ((optional))

Abstract: A series of Mn(I) complexes containing lutidine-based chiral pincer ligands with modular and tunable structures has been developed. The complex features unprecedentedly high activity (up to 9800 TON), broad substrate scope (81 examples), good functional group tolerance, and excellent enantioselectivity (85~98% *ee*) in the hydrogenation of various ketones, which are rare in earth-abundant metal catalyzed hydrogenation. The utilities of the protocol have been demonstrated in the asymmetric synthesis of a variety of key intermediates of chiral drugs. Preliminary mechanistic investigation indicates that an outer-sphere mode of substrate-catalyst interaction probably dominates the catalysis.

Asymmetric hydrogenation of carbonyl compounds to produce optically active secondary alcohols generally involved the use of chiral catalysts based on precious metal(Ru, Rh, Ir etc).[1] In contrast, chiral catalysts made of earth-abundant metals,[2] e.g. copper,[3] nickel,[4] iron[5] or cobalt,[6] have only gained some recent popularity in this area. In this regard, chiral catalysts based on iron are particularly noteworthy.[7-9]However, the activity and/or enantioselelctivity of these base metal catalysts still remained a great challenge, which severely hamper their wide applications. On the other hand, the recent discovery of achiral manganese catalysts in carbonyl hydrogenation[10] stimulated several groups to explore their chiral counterparts for enantioselective ketone hydrogenation. In this context, Clarke et al. introduced the first chiral Mn catalyst **Mn-1** for the asymmetric hydrogenation of aryl alkyl ketones at 50 ℃ with *ee*'s up to 97%.[11] A bulky alkyl group (e.g. *t*Bu) on the ketone to be necessary for keeping the *ee* above 80%. Beller and co-workers demonstrated that **Mn-2** catalyzed the hydrogenation of some dialkyl ketones with up to 84% *ee*.[12] Several chiral Mn complexes for asymmetric transfer hydrogenation and hydroboration of ketones were also disclosed very recently.[13]

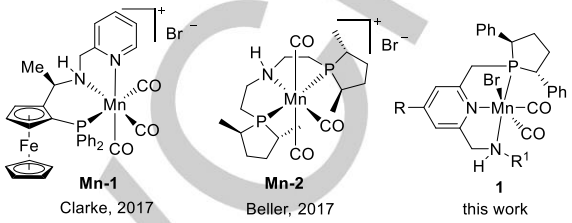

Figure 1. Selected chiral Mn catalysts for enantioselective hydrogenation of ketones

Despite these efforts, the state of the art with non-precious metal catalysts in ketone hydrogenation are still far from satisfactory in terms of activity, selectivity and substrate scope. We envisioned that this situation might be dramatically changed by judicious design of chiral earth-abundant metal catalysts containing modular chiral ligands by fine tuning the electronic property and steric hindrance of the ligand moieties. Herein, we reported the development of a new type of modular PNN ligands **2** and their Mn(I) complexes **1** for the catalysis of asymmetric hydrogenation of a broad spectrum of ketones with high activities (TON up to 9800) and good to excellent enantioselectivities (85~98% *ee*).

The lutidine based chiral PNN ligands (**2**) combined the features of Milstein's privileged achiral PNN-type motif[14] and Fiaud's chiral phospholane segment,[15] and were readily synthesized via the sequence shown in Scheme **1** stating from **3a-e**[16] in good overall yields... Treatment of ligands **2a-f** with $Mn(CO)_5Br$, respectively, furnished Mn complexes **1a-f** in good yields (Scheme 1). ^{31}P NMR spectra showed these complexes were composed of two isomers in a ratio ranging from 1:1 to 4:1, probably caused by the *syn* or *anti* orientation of the flexible N-H moiety relative to Mn-Br bond. The solid-state structures of (*R*, *R*)-**1d** and (*S*, *S*)-**1e** were established by X-ray crystallographic analysis.

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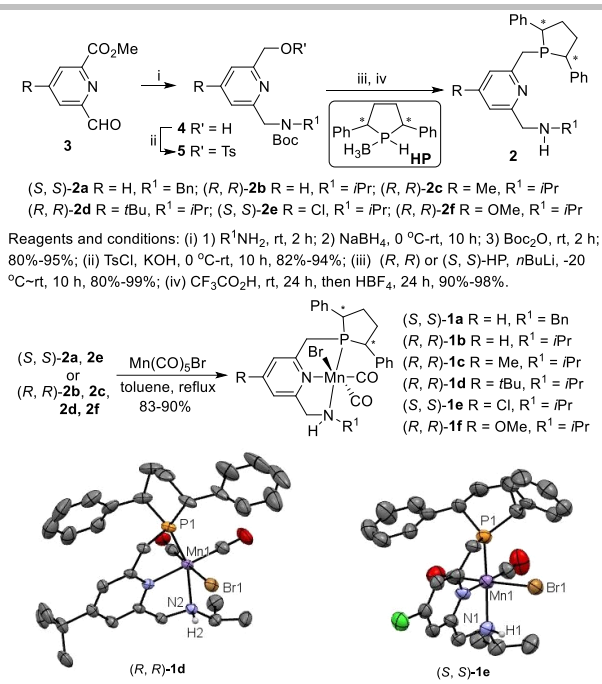
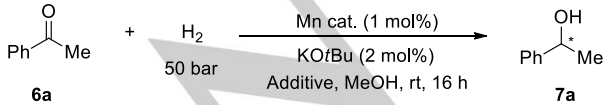
10.1002/anie.201814751



Scheme 1. Synthesis of chiral PNN ligands **2a-f** and Mn complexes **1a-f**.

Subsequently, these Mn complexes were tested as catalysts for the hydrogenation of acetophenone **6a** (Table 1). Under 1 mol% loading, complex (*S*, *S*)-**1a** catalyzed the hydrogenation smoothly at room temperature in methanol under 50 bar of H_2, affording (*S*)-**7a** with 67% *ee* in a full conversion of **6a** (entry1). Improved enantioselectivity (81% *ee*) was obtained with (*R*, *R*)-**1b** as the catalyst (entry 2). Interestingly, addition of alcohols such as *i*PrOH, CF_3CH_2OH (TFE) and $(CF_3)_2CHOH$ (HFIP) to the reaction affects the activity and selectivity of these Mn catalysts (entries 3-5).[17] Use of a substoichiometric amount of HFIP (10 mol%) as additive improved the enantioselectivity to 87%, albeit at a cost of incomplete conversion of **6a** (92%) (entry 5). Full conversion of substrate was realized by simply increasing substrate concentration to 0.5 M, affording (*R*)-**7a** with 86% *ee* (entry 6). Accordingly, complexes **1c-f** are evaluated in the presence of HFIP (entries 7-10). Complex (*R*, *R*)-**1d**, with a *t*Bu group on the 4- position of pyridine ring, turned out to be optimal, yielding (*R*)-**7a** with 90% *ee* (entry 8). Reducing the H_2 pressure to 30 bar had no effect on the outcome of the reaction (entry 11). Remarkably, (*R*, *R*)-**1d** shows an unprecedentedly high productivity in the hydrogenation of **6a** (entries 12-14). When the catalyst loading was diminished to 0.01 mol%, 98% conversion of **6a** was achieved and 86% *ee* was observed in (*R*)-**7a**, attaining to a TON of 9800 at elevated reaction temperature (60 ℃) in prolonged reaction time (48 h) (entry 14).

Table 1. Enantioselective hydrogenation of acetophenone **6a**[a]



Entry	Mn cat.	Additive	Conv.[%][b]	*Ee* [%][b]
1	(*S*, *S*)-**1a**	\	>99	67 (*S*)
2	(*R*, *R*)-**1b**	\	>99	81 (*R*)
3	(*R*, *R*)-**1b**	*i*PrOH (2 equiv)	>99	84 (*R*)
4	(*R*, *R*)-**1b**	TFE (0.1 equiv)	>99	84 (*R*)
5	(*R*, *R*)-**1b**	HFIP (0.1 equiv)	92	87 (*R*)
6	(*R*, *R*)-**1b**	HFIP (0.1 equiv)	>99	86 (*R*)
7	(*R*, *R*)-**1c**	HFIP (0.1 equiv)	99	86 (*R*)
8	(*R*, *R*)-**1d**	HFIP (0.1 equiv)	>99	90 (*R*)
9	(*S*, *S*)-**1e**	HFIP (0.1 equiv)	>99	80 (*S*)
10	(*R*, *R*)-**1f**	HFIP (0.1 equiv)	93	88 (*R*)
11[c]	(*R*, *R*)-**1d**	HFIP (0.1 equiv)	>99	90 (*R*)
12[d]	(*R*, *R*)-**1d**	HFIP (0.1 equiv)	99	88 (*R*)
13[e]	(*R*, *R*)-**1d**	HFIP (0.1 equiv)	98	85 (*R*)
14[f]	(*R*, *R*)-**1d**	HFIP (0.1 equiv)	98	86 (*R*)

[a] Conditions: **6a** (0.5 mmol), MeOH (5 mL for entries 1-5 and 1 mL for entries 6-12). [b] Conversions and *ee* were determined by GC analysis. [c] $p(H_2)$ = 30 bar. [d] 0.1 mol% **1d**, 2.0 mmol **6a**, 60 ºC, 24 h. [e] 0.02 mol% **1d**, 25 mmol **6a**, 60 ºC, 24 h. [f] 0.01 mol% **1d**, 50 mmol **6a**, 60 ºC, 48 h.

We subsequently explored the substrate scope of the reaction with (*R*, *R*)-**1d** as the catalyst (Table 2). A wide range of aryl alkyl ketones **6b-z** and heteroaromatic ketones **6aa-ad** were reduced to the corresponding chiral secondary alcohols **7b-z** and **7aa-ad** in 85~97% *ee*. Under identical conditions, aliphatic ketone **6ae** gives **7ae** in 80% yield, albeit with only modest enantioselectivity (31% *ee*). This catalytic system is highly chemoselective for ketone reduction, tolerating carbon-carbon double bond, ester or amide carbonyl groups very well, to give the corresponding alcohol products in excellent *ee* (**7af**, **7ag** and **7am**, 90~93%) or *dr* (**7al**, 12/1). Amino ketones **6ah-ak** are also amenable to the procedure, giving the corresponding amino alcohols **7ah-ak** with 87~95% *ee*. It is worth noting that chiral alcohols **7j**, **7t**, **7aj**, **7ak**, **7al** and **7am** are the key intermediates for the synthesis of chiral drugs rivastigmine,[18] phenylephrine,[19] duloxetine,[20] ezetimibe[21] and montelukast,[22] respectively.

Table 2. Enantioselective hydrogenation of aryl alkyl ketones [a]

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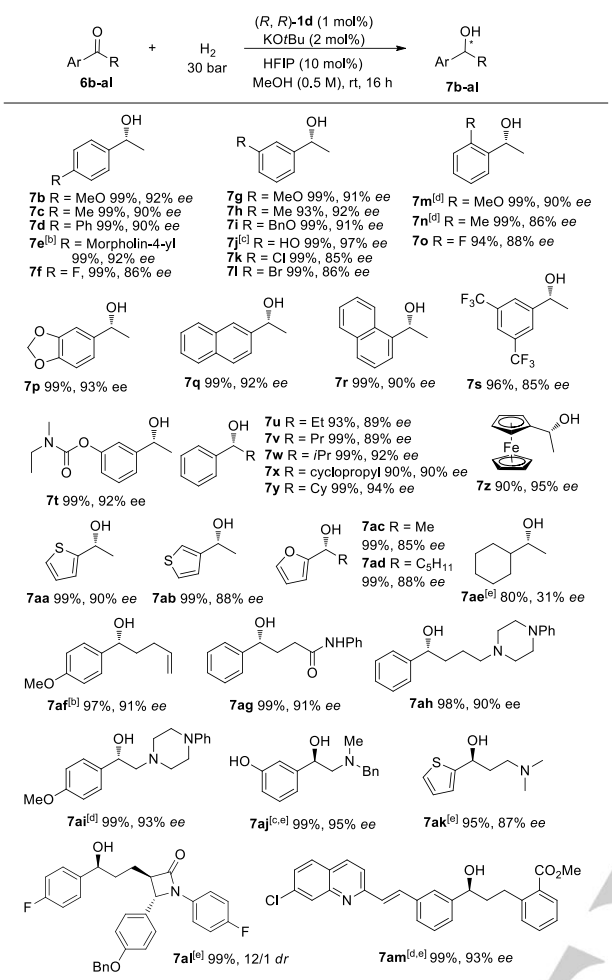
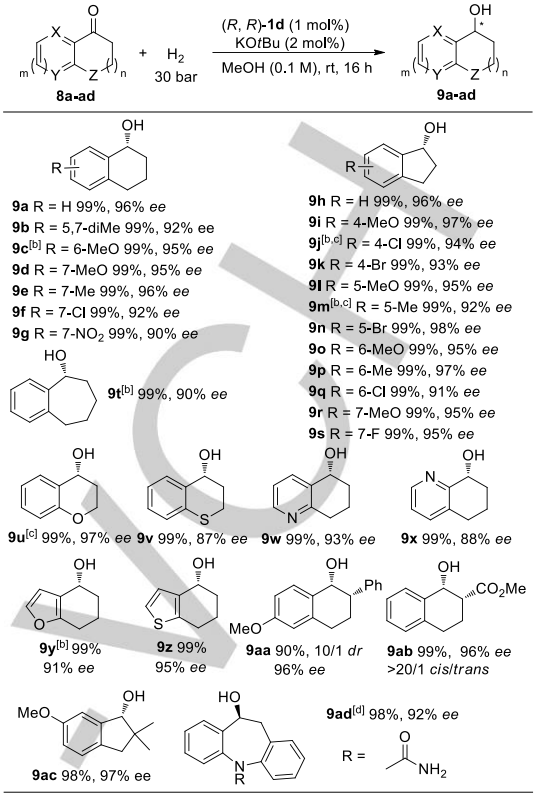


[a] For conditions see SI. The yields of isolated products. [b] $p(H_2)$ = 50 bar. [c] 1.02 equiv. KO*t*Bu was employed. [d] No HFIP was added and MeOH (5 mL) was used. [e] (*S*, *S*)-**1d** was employed.

Mn complex (*R*, *R*)-**1d** is also found highly selective in the hydrogenation of benzo-fused ketones **8a**-**z**, affording the corresponding chiral alcohols **9a**-**z** in nearly quantitative yields with excellent enantioselectivities (87~98% *ee*). (Table 3). Racemic α-substituted benzo-fused cyclic ketones **8aa** and **8ab** undergoes an efficient dynamic kinetic resolution, providing *cis* chiral alcohols **9aa** and **9ab** with 96% *ee* in 10/1 and >20/1 *dr*, respectively. The challenging steric hindered α, α-di-substituted ketone **8ac** can be reduced smoothly, affording the corresponding alcohol **9ac**, a key intermediate of Maruoka's chiral selenium catalyst,[23] with 97% *ee*. The hydrogenation of ketone **8ad** containing a urea moiety gives (*S*)-**9ad**, a key intermediate of eslicarbazepine acetate,[24] in 98% yield wih 92% *ee*.

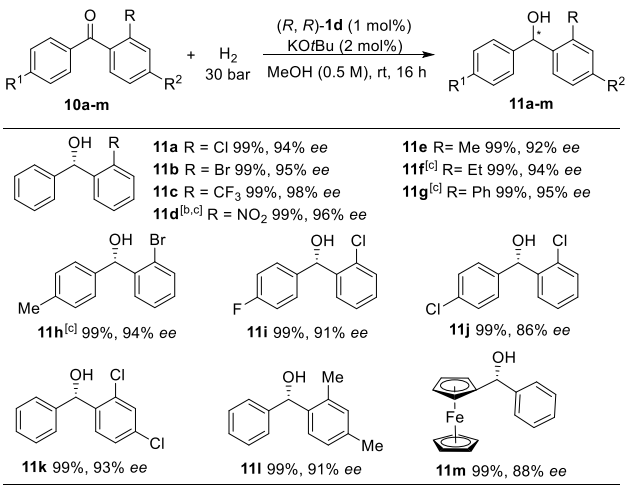
Table 3. Enantioselective hydrogenation of benzo-fused cyclic ketones[a]



[a] For conditions see SI. [b] $p(H_2)$ = 50 bar. [c] (*R*, *R*)-**1b** was employed. [d] (*S*, *S*)-**1d** was employed.

Catalytic asymmetric hydrogenation of diaryl ketones is challenging, due to the difficulty for catalysts to differentiate two structurally similar aryl groups in substrates. Mn catalyst (*R*, *R*)-**1d** turns out to be also highly selective in the hydrogenation of *ortho*-substituted benzophenones **10a**-**m** (Table 4). A range of unsymmetrical benzhydrols **11a**-**m** were synthesized in almost quantitative yields and good to excellent *ee* values (86~98%), including (*S*)-phenyl(*o*-tolyl)methanol **11e** and (*S*)-(2-bromophenyl)(*p*-tolyl)methanol **11h,** which are precursors for the synthesis of antihistaminic agents (*S*)-orphenadrine[25] and (*R*)-neobenodine,[25] respectively.

Table 4. Enantioselective hydrogenation of benzophenones[a]



[a] For conditions see SI. [b] 2 mol% (*R*, *R*)-**1d**, 50 °C. [c] $p(H_2)$ = 50 bar.

To further exemplify the utilities of the developed Mn catalyst system, hydrogenation of ketones **8a**, **6j**, **8ac** and **10h** with (*R*, *R*)-

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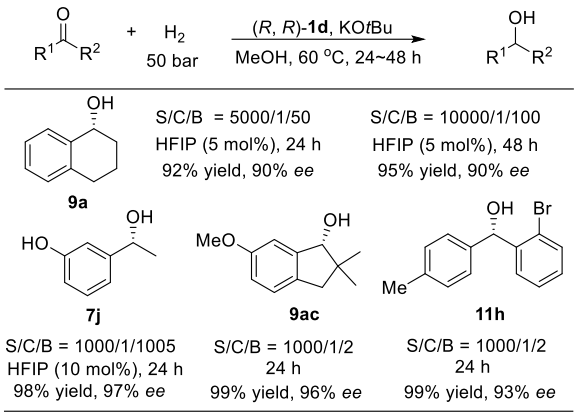
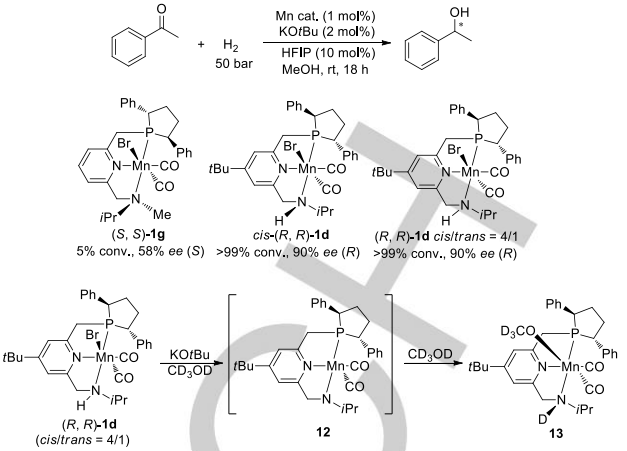
1d under reduced catalyst loading are carried out in gram scale (Table 5). The 50 mmol-scale asymmetric hydrogenation of 1-tetralone **8a** proceeds smoothly with a catalyst loading of 0.01 mol%, affording (*R*)-**9a** in 95% yield and 90% *ee*. In the presence of 0.1 mol% catalyst, pharmaceutically relevant ketones **6j**, **10h** and chiral ligand precursor **8ac** were hydrogenated to the corresponding alcohols **7j, 11h** and **9ac** in nearly quantitative yields with 97%, 93% and 96% *ee*, respectively.

Table 5. Enantioselective hydrogenation of **8a**, **6j**, **8ac** and **10h** under low catalyst loading



Mechanistically, the NH moiety in the ligands can play a critical role in transition metal catalyzed asymmetric hydrogenation.[26] To understand the role of the NH moiety in the present system, the Mn complex ((*S, S*)-**1g**) with *N*-methylated ligand of (*S, S*)-**2b** was prepared (see SI) and tested in the hydrogenation of **6a**. Under the otherwise identical conditions, the catalytic activity of (*S, S*)-**1g** declined dramatically (5% conv.), and the *ee* value of **7a** decreased sharply (Scheme 2). These results indicated that NH functionality in the ligands was crucial for achieving high reactivity and enantioselectivity, suggesting that the catalysis was likely dominated by an outer-sphere mechanism. Furthermore, when isolated pure *cis*-(*R, R*)-**1d** (obtained *via* crystallization) was employed in the catalysis, both the activity and enantioselectivity of the reaction were found to be essentially identical to those obtained using *cis*/*trans* (4:1) mixture of (*R, R*)-**1d** (Scheme 2). We speculate that both the *cis* and *trans*-(*R, R*)-**1d** might be transformed to a common active Mn species by deprotonation of the NH site with KO*t*Bu. Indeed, treatment of *cis*/*trans* (4:1) mixture of (*R, R*)-**1d** with 2 equiv. of KO*t*Bu in MeOH-d_4 led to observation of a new single signal in the ^{31}P NMR spectrum (see SI), indicating the catalyst precursor (*R, R*)-**1d** was probably transformed into **13**, a Mn-OCD_3 species on the basis of Milstein's observation in an analogous achiral Mn-PNN system.[27] The more detailed mechanistic investigation was currently underway.



Scheme 2. Examination of effect of NH moiety on the outcome of catalysis and the proposed active species in the reaction.

In summary, the modular feature of a class of chiral pincer-type PNN ligands has enabled their manganese complexes to catalyze the hydrogenation of a board spectrum of ketones with outstanding activity (up to 9800 TON) and excellent enantioselectivity (up to 98% *ee*). The utilities of the protocol have also been exemplified in asymmetric synthesis of a variety of key intermediates of chiral drugs. Preliminary mechanistic investigation indicates that an outer-sphere mode of substrate-catalyst interaction probably dominates the catalysis and the NH moiety in the ligand turns out to be critically important for activity and enantioselectivity in the hydrogenation.

Acknowledgements

We are grateful for financial support from Ministry of Science and Technology of China (2016YFA0202900), the National Natural Science Foundation of China (21472215, 21790333), CAS (XDB20000000), Youth Innovation promotion Association CAS (2015205), and the Science and Technology Commission of Shanghai Municipality.

Keywords: asymmetric catalysis • hydrogenation • manganese • PNN ligand • ketone

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[16] **3a**-**e** can be prepared in 2 steps from the corresponding dimethyl pyridine-2,6-dicarboxylate. For details, see supporting information.

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[28] CCDC numbers for the X-ray structures of (*R*,*R*)-**1d** (1879709), (*S*,*S*)-**1e** (1879715), (*S*,*S*)-**1g** (1879716) and (*R*)-**9k** (1897357) are available free of charge, on application to the CCDC, 12 Union Road, Cambridge CB2 1EZ, UK [fax: +44(1223)336033; e-mail: deposit@ccdc.cam.ac.uk].

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10.1002/anie.201814751

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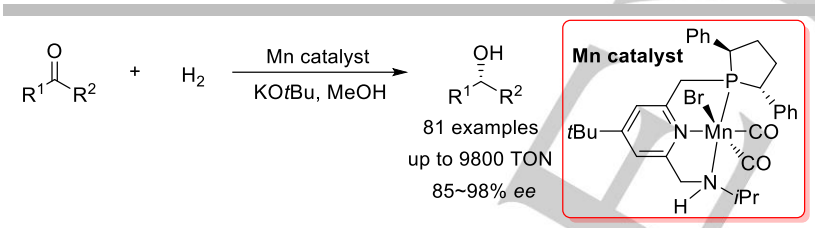

Chiral PNN-Mn catalysts for asymmetric hydrogenation of a board spectrum of ketones were developed (up to 9800 TON and 85~98% *ee*). The utilities of the protocol have also been demonstrated in the asymmetric synthesis of a variety of key intermediates of chiral drugs. Preliminary mechanistic investigation indicated that an outer-sphere manner of substrate-catalyst interaction probably dominates the catalysis.

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Lutidine-Based Chiral Pincer Manganese Catalysts for Enantioselective Hydrogenation of Ketones

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