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COMMUNICATION

Manganese-Catalyzed Asymmetric Hydrogenation of Quinolines Enabled by π–π Interaction

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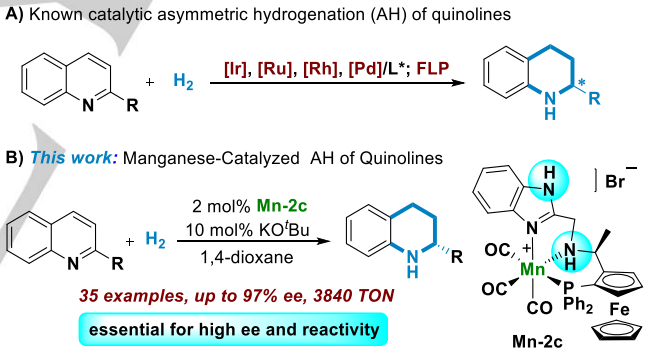
Abstract: The first example of non-noble metal-catalyzed asymmetric hydrogenation of *N*-heteroaromatics is reported. A new chiral pincer manganese catalyst showed outstanding catalytic activity in the asymmetric hydrogenation of quinolines, affording high yields and enantioselectivities (up to 97% *ee*). A turnover number of 3840 was reached at a low catalyst loading (S/C=4000), which was competitive with the activity of most effective noble metal catalysts for this reaction. The precise regulation of the enantioselectivity were ensured by a π–π interaction.

Optically active 1,2,3,4-tetrahydroquinolines (THQs), as an important structural motif, widely found in bioactive molecules and natural products.[1] Numerous methods for constructing these chiral skeletons have been explored.[2] Significantly, the direct asymmetric hydrogenation (AH) of quinolines remains one of the most efficient approaches to producing these compounds.[3] With the development of catalytic systems based on precious metals, including Ir[4], Ru[5], Rh[6], and Pd[7], both the efficiency and substrate scope of the AH of quinolines have been greatly improved (Scheme 1A). Specifically, iridium catalysts containing chiral bisphosphine ligands have proven to be effective for AH of quinolines activated by iodine since the pioneering work of Zhou in 2003.[4a] Furthermore, Fan, Chan, and coworkers have shown cationic complex Ru(OTf)(TsDPEN)-(η^6-cymene) to be a state-of-the-art catalyst for this transformation, affording outstanding enantioselectivity and a broad substrate scope.[5a, 5c] In addition to transition metal catalysts, frustrated Lewis pairs (FLPs) are also powerful catalysts for the AH of quinolines.[8] Although the above catalytic systems remain unsurpassed at present, they still have some shortcomings. For precious metal catalysts, issues of high cost, uncertain supply, and toxicity concerns remain unsolved. Meanwhile for FLP catalysis, preparation of chiral bisborane catalysts are usually complicated and a higher catalyst loading is required compared with transition metal catalysis. Such limitations may restrict their wide applications on a large scale. Therefore, the development of more sustainable and practical catalysts for the AH of quinolines remains a highly desirable, but challenging task.

To achieve such a goal, the application of non-noble metals, such as iron[9], cobalt[9d, 9f, 10] and nickel[11], to the development of new AH catalysts is a feasible strategy[12]. Accordingly, manganese, which is the third most abundant transition metal on earth and exhibits low toxicity, is another ideal choice.[13] Mn-catalyzed hydrogenation reactions have seen significant progress[14] since the seminal work of Beller's group in 2016.[15] In particular, Mn-catalyzed AH of ketone has also been reported[16], among which Ding, Han and co-workers developed a highly efficient chiral manganese catalyst.[16c, 16d] This demonstrates the great potential of Mn-based catalysts in AH. However, no example of Mn-catalyzed AH of unsaturated compounds other than ketones has been reported to date.



Scheme 1. AH of 2-substituted quinolines.

Following our continued pursuit of Mn-catalyzed (de)hydrogenation reactions[17], herein we disclosed an Mn-catalyzed AH of quinolines with up to 97% *ee* and a maximum turnover number (TON) of 3840. The high reactivity and effective enantioselectivity control of this chiral catalyst are enabled by a newly designed chiral NNP tridentate ligand (Scheme 1B). To our knowledge, this is the first example of AH of *N*-heteroaromatics catalyzed by a first-row earth-abundant transition metal.

In a recent study, we found that an imidazole based NNP-Mn pincer catalyst performed with high efficiency in the hydrogenation of *N*-heteroaromatics owing to the enhanced electron-donating ability and low steric hindrance of the imidazole group.[17c, 18] Inspired by this ligand effect, we aimed to design an imidazole-based chiral NNP-tridentate ligand for the Mn-catalyzed AH of quinolines. Coincidentally, Zhong and co-workers recently developed *in-situ* formed Mn(I) catalysts containing imidazole-based chiral NNP tridentate ligands, which enabled the

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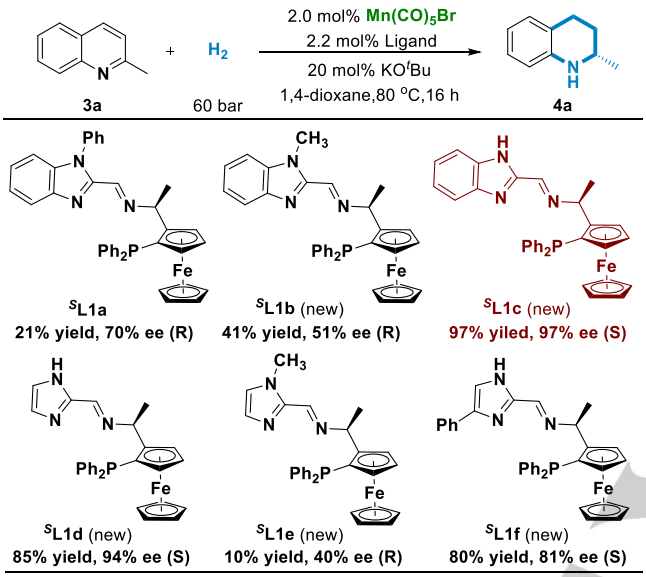
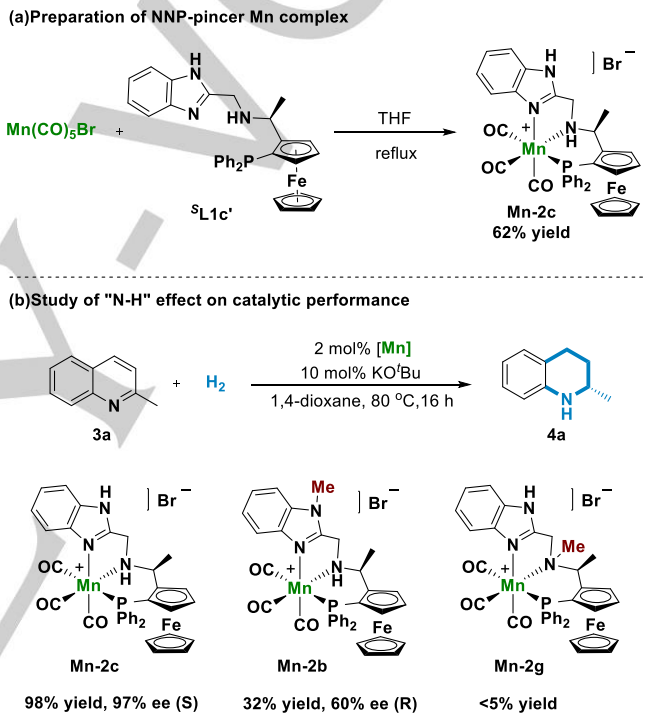
enantioselective hydrogenation of unsymmetrical benzophenones.[19] In this case, the use of ligand **^{S}L1a** with a bulky substituent on the *N*-atom of the benzo[d]imidazole segment was essential for achieving a high enantioselectivity. Initially, we attempted to use **^{S}L1a** for the hydrogenation of 2-methylquinoline **3a** in the presence of $Mn(CO)_5Br$ as the catalyst precursor (Scheme 2). However, low conversion and moderate enantioselectivity were observed. We hypothesized that this sterically hindered ligand prevented the coordination of bulky substrates to the metal center and reduced the reactivity of the Mn-H species.



Scheme 2. Ligand Screening. Reaction conditions: **3a** (0.25 mmol), $Mn(CO)_5Br$ (2.0 mol%), **^{S}L1** (2.2 mol%), and KO^{t}Bu (20 mol%) in 1,4-dioxane (0.5 mL) at 80 °C for 16 h. Yields (%) and enantioselectivities (%ee) were determined by GC and chiral-phase HPLC.

This unsatisfactory result reminded us of our previous work, in which mechanistic studies showed that both the steric and electronic effects of the heterocyclic segment in the ligand are crucial for the reactivity.[17c] Accordingly, we envisaged controlling the reactivity and enantioselectivity by regulating the structures of heterocycle motifs in the ligands. Improved yield and reduced enantioselectivity (45% conv, 51% ee) were obtained by changing the substituent on N-atom from a phenyl to methyl group (**^{S}L1b**). Notably, **3a** was almost quantitatively converted into product **4a** with excellent reversed enantioselectivity (97% ee) by further changing the methyl group to an H-atom (**^{S}L1c**). These results showed that reduced steric hindrance on the N-atom of the benzo[d]imidazol group was highly important for increasing both reactivity and enantioselectivity. Furthermore, imidazole-based NNP tridentate ligands were synthesized to confirm this conjecture. Compared with the methyl-substituted ligand (**^{S}L1e**), the NH-imidazole-based ligand (**^{S}L1d**) also furnished **4a** with a substantially increased yield and fully reversed configuration (88% conv, 94% ee). This comparison again highlights the essential effect of the less hindered NH unit. Monoaryl substituted imidazole (mixture of 4/5-tautomers[20]) ligand **^{S}L1f** was also synthesized to further investigate the substituent effect on the imidazole ring, while a decreased enantioselectivity was observed. Other reaction parameters were also optimized to improve the reaction efficiency (see Supporting Information for details). The best result was achieved using $Mn(CO)_5Br$ (2.0 mol%), **^{S}L1c** (2.2 mol%), KO^{t}Bu (10 mol%), and 1,4-dioxane as solvent at 80 °C.

To elucidate the structure of *in-situ* formed active catalyst, we synthesized the NNP-pincer manganese complex by reacting $Mn(CO)_5Br$ with saturated pincer ligand **^{S}L1c'** (Scheme 3a). The catalytic activity of **Mn-2c** was further evaluated for comparison with the performance of *in-situ* formed catalytic systems. A similar yield and enantioselectivity were obtained using well-defined catalyst **Mn-2c** and the catalytic system formed *in-situ* from $Mn(CO)_5Br$ and **^{S}L1c'** (or **^{S}L1c**). In addition, it was demonstrated that a mixture of imine ligand **^{S}L1c** and $Mn(CO)_5Br$ could be converted to the saturated complex **Mn-2c** under hydrogen pressure, which was an active catalyst precursor (see Schemes S1 and S2 for details).



Scheme 3. Synthesis and reactivity of pincer complexes **Mn-2**.

The NH moiety on pincer ligands can greatly impact the reactivity in catalytic hydrogenation *via* metal–ligand cooperation.[21] To investigate the effect of two NH moieties on optimal catalyst **Mn-2c**, two *N*-methylated complexes, **Mn-2b** and **Mn-2g**, were prepared and their catalytic activities were evaluated (Scheme 3b). A much lower yield and *ee* value were observed for the AH of **3a** using **Mn-2b** as catalyst compared with the result using **Mn-2c**. However, almost no conversion was observed when using complex **Mn-2g** as catalyst. These results indicated the strong beneficial influence of cooperative N–H functionality on this transformation. Specifically, the central NH group was crucial for reactivity via metal–ligand cooperation. Although the imidazole-NH motif also influenced the reactivity, it was more important for achieving high enantioselectivity owing to its very low steric hindrance. Density functional theory (DFT) calculations were conducted to understand origin of chirality in the AH of **3a**. Analysis of the noncovalent interactions (NCI) showed that **12-ts** was calculated to be more stable than **15-ts** by a free energy of

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2.0 kcal/mol, owing to the π–π nonbonding interaction between the imidazole ring and C=N double bond in **12-ts** (Figure 1). This was in agreement with the experimental results. Therefore, the *S*-configured product was preferentially formed with excellent enantioselectivity. The NH unit of the imidazole motif in the ligand ensured an effective π–π interaction owing to its small volume, playing a key role in enantio-induction.

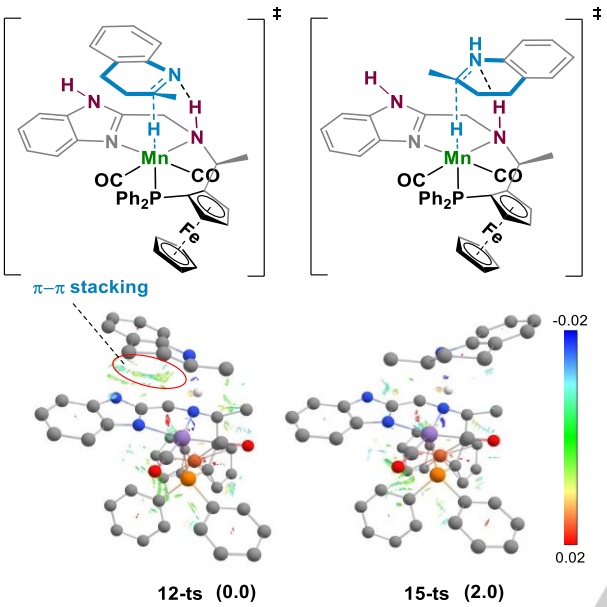
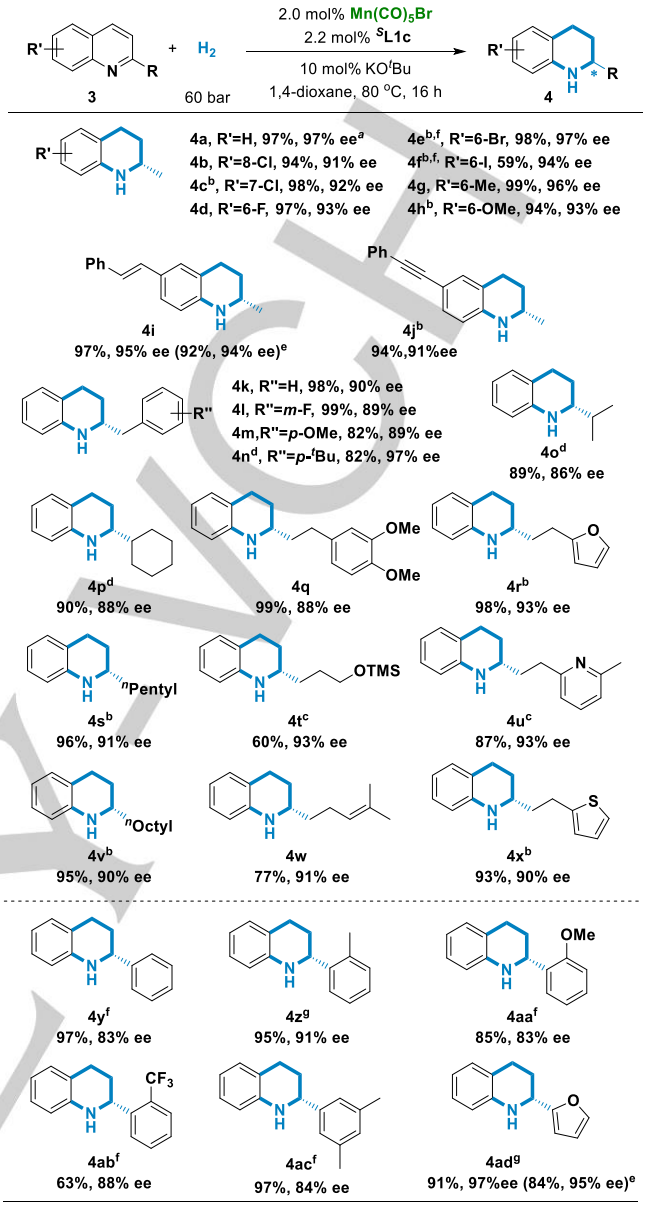


Figure 1. NCI analysis of **12-ts** and **15-ts** (blue: attraction; green: weak interaction; red: repulsion). Relative Gibbs free energies (in kcal/mol) are reported in parentheses.

With optimized reaction conditions in hand, the scope of 2-substituted quinoline substrates was studied (Scheme 4). A wide range of substrate(**3b-3j**) with substituents on benzene ring were hydrogenated to the corresponding chiral 1,2,3,4-THQs (**4b-4j**) with *ee* values ranging from 91% to 97%. Notably, other reducible functional groups, such as halogens (**4b-4f**), and carbon–carbon double(**4i**) and triple(**4j**) bonds, were all well tolerated (See Table S3 for a test of tolerance for additional functional groups.). Various 2-benzyl substituted quinolines, bearing substituents with different electronic properties, were converted to the corresponding products (**4k-4n**) effectively in 82%–99% yields with 89%–97% ee values. This method was also proved to be applicable to the AH of other 2-substituted (*n*-pentyl, *n*-octyl, isopropyl, cyclohexyl, phenemyl and distal olefins) substrates (**3o-3q**, **3s-3t**, **3v-3w**), with excellent yields and *ee* values (86-93%). Furthermore, substrates bearing other heteroaromatics (furan (**3r**), pyridine (**3u**), and thiophene (**3x**)) were also efficiently hydrogenated, affording 90%–93% *ee* values with the additional heterocycles untouched. Notably, chiral THQs **4d**, **4s** and **4q** were key intermediates for the synthesis of natural products (S)-flumequine[22], (+)-angustrureine[23] and (-)-cuspareine[23], respectively.

Various 2-aryl substituted quinolines were subsequently subjected to Mn-catalyzed AH. A further ligand screening showed that ligand **^{S}L1f** gave the best results for these substrates (Scheme S3), with 63%-97% yields and 83%-97% *ee* values. Various substituents on the phenyl ring were well tolerated (**4z-4ac**). Notably, a furan-substituted quinoline was also a suitable substrate for this transformation (**4ad**).



Scheme 4. AH of 2-substituted quinoline. Reaction conditions: **3** (0.25 mmol), $Mn(CO)_5Br$ (2.0 mol%), **^{S}L1c** (2.2 mol%), and KO^{t}Bu (10 mol%) in 1,4-dioxane (0.5 mL) at 80 °C for 16 h. [a] The percentages shown are yields of isolated products and *ee* values in that order. [b] 20 mol% KO^{t}Bu was used. [c] 20 mol% KO^{t}Bu was used at 110 °C. [d] **^{S}L1d** (2.2 mol%) and 20 mol% KO^{t}Bu were used at 110 °C. [e] Saturated ligands **^{S}L1c'** or **^{S}L1d'** (2.2 mol%) was used. [f] **^{S}L1f** was used. [g] **^{S}L1d** was used.

The hydrogenation products of bis(quinoline-2-yl)-methanes are synthetic precursors for chiral *N*-heterocyclic carbene (NHC) ligands[24]. This new catalytic system was applied to constructing such compounds containing two chiral centers (Scheme 5). The AH of various bis(quinoline-2-yl)-methanes bearing methyl, isopropyl and phenyl groups gave the desired products (**6a–6d**) with excellent stereoselectivities. Subsequent treatment of **(*R*, *R*)-6c** with triethyl orthoformate and NH_4BF_4 afforded six-membered rigid chiral NHC ligand precursor **7c** in 97% yield.

To further evaluate the efficiency of this catalytic system, a gram-scale reaction was performed with a catalyst loading of 0.025 mol% (Scheme 6a). Excellent enantioselectivity was maintained with a TON of 3840 achieved. The synthetic utility of

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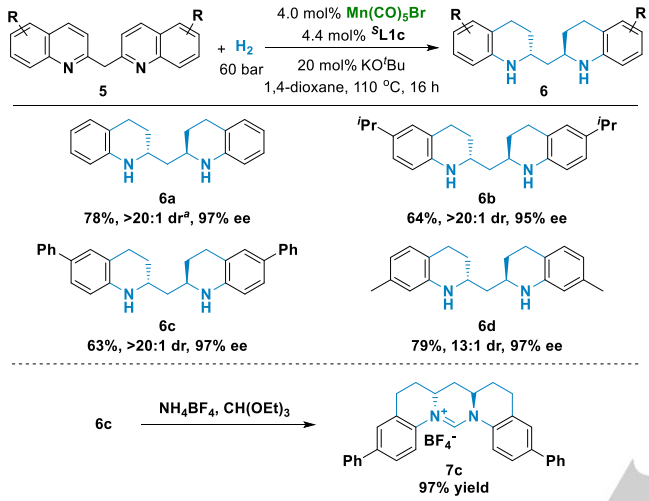
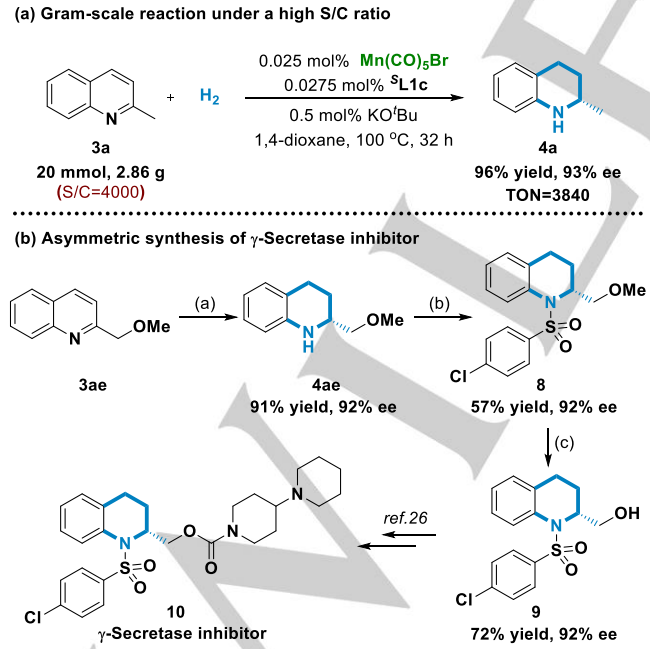
this Mn-catalyzed AH was demonstrated by the synthesis of a drug lead compound (Scheme 6b). The enantiomer of compound **10** has been reported as an effective γ-secretase inhibitor for the treatment of Alzheimer's disease.[25] Synthesis of this molecule started with the AH of commercially available substrate **3ae**, followed by sulfonylation to give sulfonamide **8**. Deprotection of methyl group provided chiral alcohol **9**, which could be converted to final product **10** with retention of the enantioselectivity.[26] This is the first example of the enantioselective synthesis of **10** via asymmetric catalysis, which is a more sustainable process compared with the reported chiral resolution protocol.[26]



Scheme 5. AH of bis(quinolin-2-yl)methanes. Reaction conditions: **5** (0.25 mmol), $Mn(CO)_5Br$ (4.0 mol%), **^{S}L1c** (4.4 mol%), and KO^{t}Bu (20 mol%) in 1,4-dioxane (0.5 mL) at 110 °C for 16 h. [a] Diastereoselectivities were determined by ^{1}H NMR analysis of crude products and chiral-phase HPLC.



Scheme 6. Catalytic efficiency and synthetic application. Reaction conditions: (a) **3ae** (8.8 mmol), $Mn(CO)_5Br$ (0.11 mol %), **^{S}L1c** (0.12 mol %) KO^{t}Bu (2.2 mol %), 1,4-dioxane (1 mL), 80 °C, H_2 (60 bar) for 16h. (b) $ArSO_2Cl$, Et_3N, THF, reflux. (c) BBr_3, 15-crown-5, NaI, DCM, -30 °C.

In summary, we have developed the first non-noble metal-catalyzed asymmetric hydrogenation of *N*-heteroaromatics, using a newly designed chiral manganese catalyst. This catalytic system was applicable to the asymmetric hydrogenation of 2-substituted quinolines and bis(quinoline-2-yl)-methanes with excellent diastereoselectivities and enantioselectivities. Furthermore, a TON of 3840 was achieved, along with excellent yields and enantioselectivities, demonstrating the high efficiency of this newly designed chiral manganese catalyst.

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Keywords: Manganese • Asymmetric hydrogenation • Chiral ligand • *N*-Heteroaromatics • Metal–ligand cooperation

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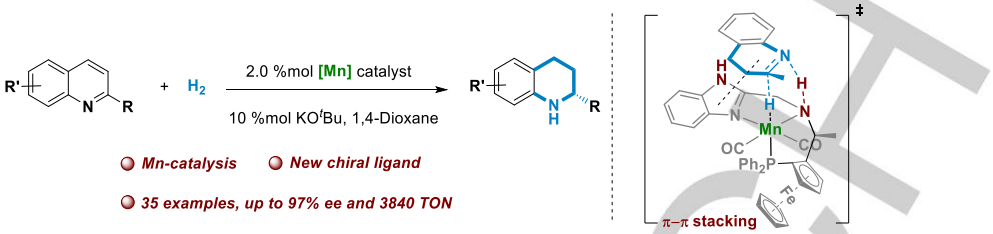

First example of non-noble metal-catalyzed asymmetric hydrogenation of *N*-heteroaromatics has been realized by using a well-defined chiral pincer manganese catalyst, with up to 97% ee and 3840 TON.

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