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Communication

Manganese-Catalyzed Asymmetric Hydrogenation of Electron-Deficient Olefins

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Cite This: J. Am. Chem. Soc. 2026, 148, 10335−10343
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ABSTRACT: Earth-abundant manganese-catalyzed asymmetric hydrogenation has emerged as a sustainable alternative to noble metal systems, achieving remarkable success in the reduction of polar C═O, C═N, and heteroaromatic substrates. However, because the polar and nucleophilic Mn−H species are inherently mismatched with nonpolar C═C bonds, asymmetric hydrogenation of C═C bonds with manganese catalysts remains a challenging and unexplored area. Herein, we disclose the first manganese-catalyzed asymmetric hydrogenation of electron-deficient polarized olefins enabled by an efficient metal−ligand cooperation process utilizing 2-hydroxypyridine-oxazoline ligands. This strategy delivers a broad range of substrates with up to 99% yield with 98% enantiomeric excess. Moreover, this catalytic system enables the hydrogenation kinetic resolution of racemic 4-aryl-quinolin-2-ones, affording axial-chiral recovered substrates with selectivity factor up to 178. These results pave up a new platform for manganese-catalyzed asymmetric hydrogenation, expanding the scope of earth-abundant metal catalysis in enantioselective synthesis.

Asymmetric hydrogenation provides an efficient route to value-added chiral molecules,[1] yet conventional noble metal catalysts,[2] despite their high performance, are constrained by scarcity, cost, and environmental concerns. In recent years, earth-abundant metals have emerged as sustainable alternatives,[3] with manganese catalysis standing out as a particularly promising example.[4] Since the pioneering work of Beller, who demonstrated manganese-catalyzed hydrogenation of ketones,[5] this field has developed rapidly. Shortly thereafter, Clarke and co-workers reported the first example of manganese-catalyzed asymmetric hydrogenation of ketones,[6] thereby opening the door to the broader exploration of enantioselective manganese catalysis (Scheme 1a). Building upon these seminal studies, highly efficient catalytic systems for asymmetric hydrogenation of polar C═O, C═N, and heteroaromatic substrates have been established by Beller,[7] Zhong,[8] Zhang,[9] Ding,[10] Liu,[11] and others.[12] More recently, Liu and co-workers reported NNP ligands in which dual cooperative noncovalent attractive interactions operate within a confined and finely tuned catalytic pocket, thereby enabling the challenging asymmetric hydrogenation of minimally differentiated imines.[13] In parallel, manganese-catalyzed asymmetric transfer hydrogenation has also been successfully realized by Sun and co-workers recently, achieving the enantioselective reduction of ketones and heteroatom-containing imines and diarylimines.[14] Despite these impressive advances in polar C═X (X = O, NR) bonds, asymmetric hydrogenation of C═C bonds with chiral manganese catalysts remains unachieved, but great progress has been made with noble-metal systems and even some abundant metals in this regard.[15] To date, only a few examples of achiral manganese-catalyzed hydrogenation of C═C bonds have been developed,[16] leaving this basic transformation an important yet unexplored frontier.

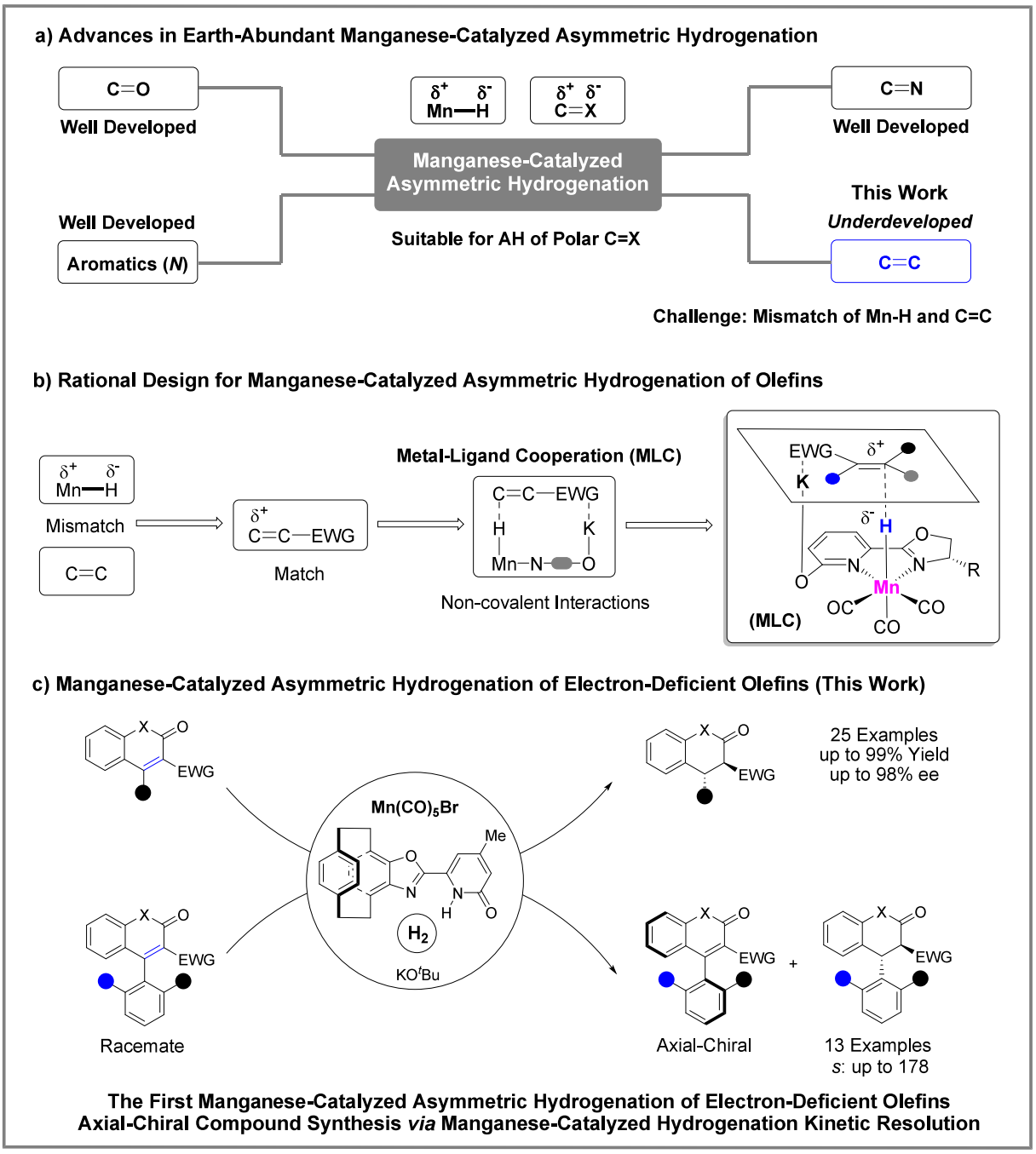
The realization of manganese-catalyzed asymmetric hydrogenation of C═C bonds has remained elusive primarily because the polarity and nucleophilicity of Mn−H species are inherently mismatched with nonpolar C═C bonds. To achieve this goal, we envisioned that the introduction of electron-withdrawing groups could activate unreactive olefins, thereby facilitating productive interactions with Mn−H. In addition, 2-hydroxypyridine-oxazoline (PYDOX) ligands, which have proven highly effective in asymmetric hydrogenation of heteroaromatic pyrazolo[1,5-*a*]pyrimidines and simple ketones,[17] were designed to generate an O−M motif under basic conditions, thereby promoting noncovalent interactions between manganese catalyst and substrates and enhancing the activation of C═C bonds (Scheme 1b). On this basis, we realized manganese-catalyzed asymmetric hydrogenation of tetrasubstituted electron-deficient olefins with excellent activity and enantioselectivity (Scheme 1c). Furthermore, this catalytic system could be applied in kinetic resolution of axial-chiral compounds through asymmetric hydrogenation with up to 178 of selectivity factor.

Asymmetric hydrogenation of quinolin-2-ones provides direct access to chiral 1,2-dihydroquinolin-2-ones, a privileged scaffold in numerous bioactive molecules.[18] Although several noble-metal catalytic systems have been reported,[19] the development of earth-abundant manganese-based catalysts remains highly desirable. In this context, quinolin-2-ones bearing electron-withdrawing groups were selected as representative substrates. The electron-deficient nature not only facilitates the activation of otherwise unreactive olefins but also promotes additional stabilization through noncovalent interactions with the tailored

Received: January 13, 2026
Revised: February 22, 2026
Accepted: February 26, 2026
Published: March 3, 2026

https://doi.org/10.1021/jacs.6c00643
J. Am. Chem. Soc. 2026, 148, 10335−10343

Scheme 1. Manganese-Catalyzed Asymmetric Hydrogenation: Status (a), Rational Design for Asymmetric Hydrogenation of Olefins (b), and This Work (c)



PYDOX ligands. Accordingly, 4-phenyl-3-ethoxy-carbonylquinolin-2-one (**1a**) was chosen as model substrate to explore the manganese-catalyzed asymmetric hydrogenation (Table 1).

The initial reaction, employing $Mn(CO)_5Br$ as a metal precursor, planar-chiral PYDOX **L1** as the chiral ligand, and potassium *t*-butoxide as the base, in THF at 80 °C under 50 bar of hydrogen gas afforded the desirable product **2a** in 30% yield with 69% ee (entry 1). Given the significant influence of the solvent, various solvents were screened (entries 1−5), and toluene provided the best results, delivering **2a** in 98% yield with 98% ee. Subsequently, several commercially available bases were evaluated (entries 6−11), among which potassium *t*-butoxide consistently provided the best activity and enantioselectivity. Furthermore, the ligand effect was then explored: electron-rich ligand **L2** (methoxy-substituted) performed similarly to **L1**, while electron-deficient ligand **L3** with trifluoromethyl slightly lowered reactivity but retained excellent enantioselectivity (entries 12−13). The unsubstituted **L4** also furnished **2a** with a high 96% yield and 95% ee (entry 14). By contrast, replacing the planar-chiral [2.2]paracyclophane skeleton with simple central-chiral backbones (**L5**-**L8**) led to erosion of enantioselectivity, though yields remained high (entries 15−18). The crucial role of the hydroxyl group in metal−ligand cooperation and olefin activation is underscored by ligands **L9** and **L10**, which lack this functionality and delivered significantly lower yields and enantioselectivities (entries 19−20). Finally, NNP-

https://doi.org/10.1021/jacs.6c00643
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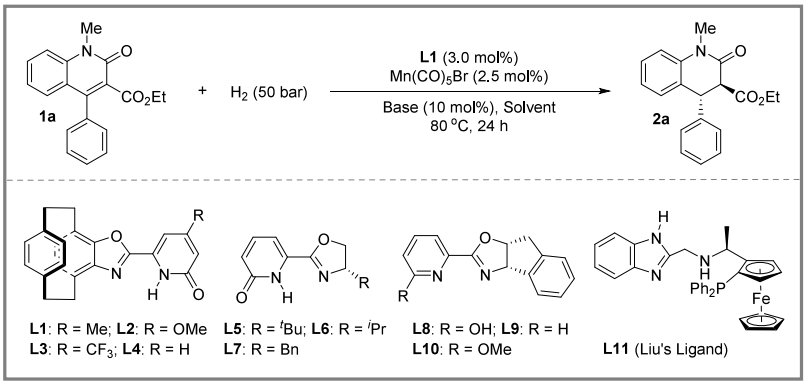
Table 1. Conditions Optimization[a]



entry	solvent	base	ligand	yield (%)[b]	e.e.[c]
1	THF	KO^{t}Bu	**L1**	30	69
2	DCE	KO^{t}Bu	**L1**	No Reaction	/
3	1,4-Dioxane	KO^{t}Bu	**L1**	29	96
4	Ethyl Acetate	KO^{t}Bu	**L1**	27	93
5	Toluene	KO^{t}Bu	**L1**	98	98
6	Toluene	NaO^{t}Bu	**L1**	28	85
7	Toluene	KO^{i}Pr	**L1**	98	97
8	Toluene	KTA	**L1**	98	98
9	Toluene	K_2CO_3	**L1**	72	99
10	Toluene	DBU	**L1**	No Reaction	/
11[d]	Toluene	KO^{t}Bu	**L1**	99	97
12	Toluene	KO^{t}Bu	**L2**	98	96
13	Toluene	KO^{t}Bu	**L3**	77	99
14	Toluene	KO^{t}Bu	**L4**	96	95
15	Toluene	KO^{t}Bu	**L5**	99	96
16	Toluene	KO^{t}Bu	**L6**	97	96
17	Toluene	KO^{t}Bu	**L7**	98	56
18	Toluene	KO^{t}Bu	**L8**	99	70
19	Toluene	KO^{t}Bu	**L9**	12	16
20	Toluene	KO^{t}Bu	**L10**	14	3
21	Toluene	KO^{t}Bu	**L11**	22	89
22[e]	**Toluene**	**KO^{t}Bu**	**L1**	**99**	**98**

[a]Reaction conditions: **1a** (61.4 mg, 0.20 mmol), $Mn(CO)_5Br$ (1.4 mg, 2.5 mol %), **L** (3.0 mol %), base (10.0 mol %), solvent (2.0 mL). [b]Determined by ^{1}H NMR spectra using 1,3,5-trimethoxybenzene as the internal standard. [c]Determined by the chiral HPLC. [d]Base (7.5 mol %). [e]H_2 (30 bar).

type ligand **L11**, which is known to be effective for the asymmetric hydrogenation of C═O, C═N, and heteroaromatic substrates, was tested but showed only poor performance in this olefin system (22% yield, 89% ee, entry 21). Finally, the effects of hydrogen pressure and temperature were optimized. The best results (99% yield, 98% ee) were obtained at 80 °C under 30 bar of hydrogen gas (entry 22).

With the optimized conditions established, the substrate scope was systematically investigated (Scheme 2). First, variations in the N-protecting groups were investigated. A series of alkyl-protected substrates (**1a**-**1e**) furnished the corresponding products with excellent yields (93−99%) and enantioselectivities (89−98% ee). Notably, the phenyl-protected substrate **1f** afforded the product **2f** in 95% yield and 94% ee. For unprotected substrate **1g**, the acidic N−H bond consumes the base, necessitating a higher base loading. Increasing the amount of potassium *tert*-butoxide from 7.5 mol % to 1.1 equiv afforded the desired product **2g** with 61% yield and 97% ee. The effects of C3 substituents were next examined. The substrates with 3-alkoxycarbonyl groups (CO_2Me **1h**; $CO_2{}^n$Pr **1i**) were also investigated, and both substrates were smoothly hydrogenated to afford the corresponding products with excellent yields (98% and 99%) and high enantioselectivities (96% and 98% ee). Substituents at the C4-aryl position exerted a minimal influence on the reaction. Whether bearing electron-donating (**1l**) or electron-withdrawing groups (**1m**), as well as halogens (**1n**-**1p**), substrates consistently afforded the hydrogenated products with 95−99% yields and 93−98% ees. Encouragingly, the heteroaromatic substrates (**1q**, **1r**) were also well-tolerated, giving the desired products in excellent yields and ees. For alkyl-substituted substrates **1s** and **1t**, high yields and ee values could be obtained, albeit with diminished diastereoselectivity, which might be ascribed to the absence of $\pi-\pi$ stacking between the substrate and chiral catalyst, complicating the stereocontrol. Finally, substrates bearing a methyl group at different positions on the quinolin-2-one core (**1u**-**1w**; C5, C6, and C7) were readily hydrogenated under the standard conditions, furnishing the desired products with 95−97% ee. In addition, these exciting results encouraged us to further explore asymmetric hydrogenation of chromen-2-ones. To our delight, the corresponding desired chiral dihydrocoumarins (**2x** and **2y**) were obtained with good yields and 64−83% of enantioselectivities. Notably, acyclic

https://doi.org/10.1021/jacs.6c00643
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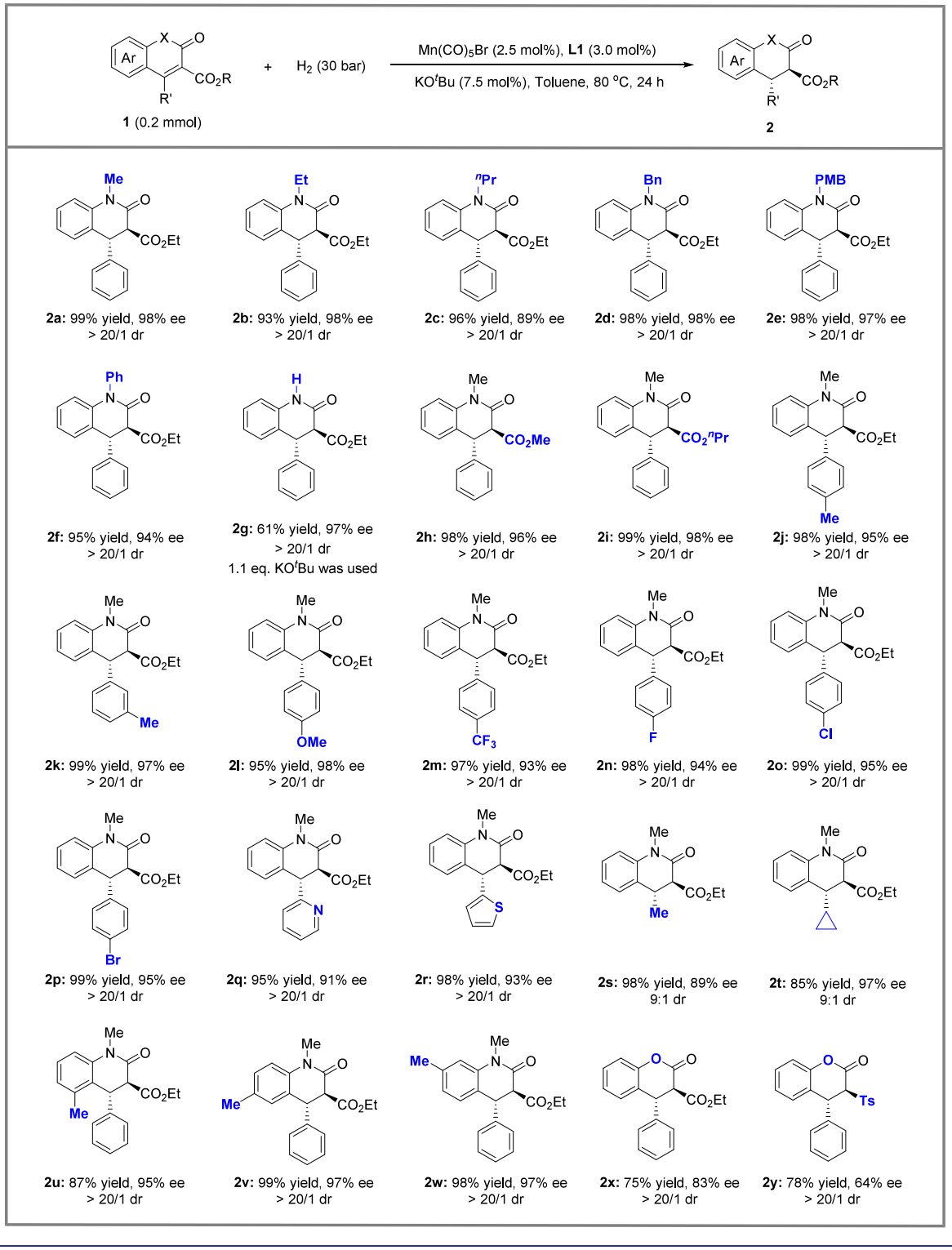
Scheme 2. Substrate Scope for 4-Substituted Quinolin-2-ones Scope

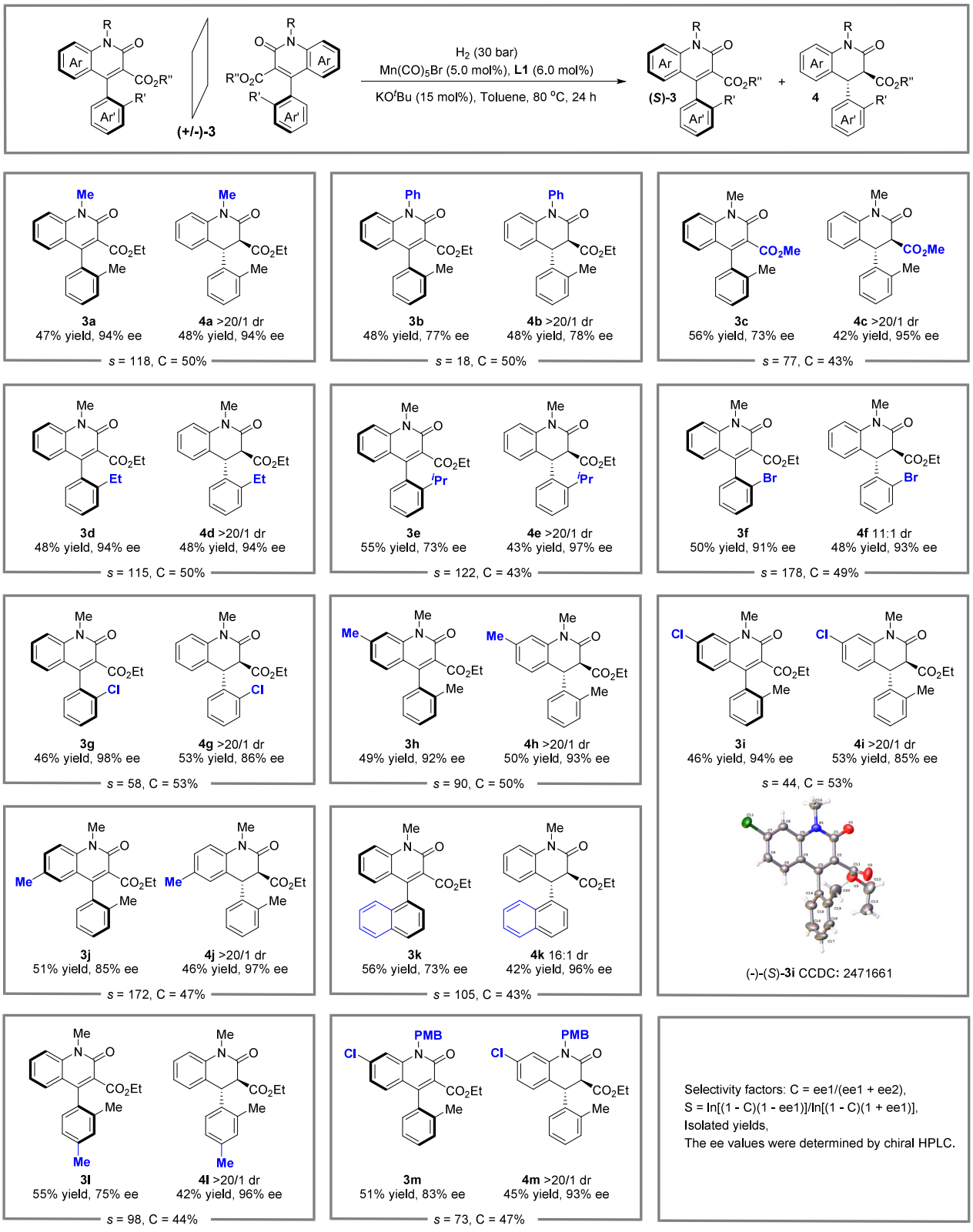


electron-deficient olefin proved to be a suitable substrate, consistently providing the desirable chiral product with excellent yield and moderate enantioselectivity (see the Supporting Information for details). Substrates lacking an exocyclic electron-withdrawing ester were unreactive under the standard conditions.

Given the potential biological relevance of axial-chiral quinolin-2-ones and chiral 1,2-dihydroquinolin-2-ones, we next applied our catalytic system to their kinetic resolution via asymmetric hydrogenation (Scheme 3). Racemate **3a** was selected as the model substrate for reaction condition optimization. Gratifyingly, doubling the catalyst loading afforded both the recovered axial-chiral substrate (−)-**3a** and the corresponding hydrogenation product **4a** with an impressive selectivity factor (s) of 118. The substrate scope was subsequently explored under the optimized conditions. Substitution of the N-protecting group with phenyl (*rac*-**3b**) resulted in a decreased level of s of 18. Modification of the C3

https://doi.org/10.1021/jacs.6c00643
J. Am. Chem. Soc. 2026, 148, 10335−10343

Scheme 3. Substrate Scope of 4-Aryl Substituted Quinolin-2-ones for Kinetic Resolution



position of CO_2Et with CO_2Me (*rac*-**3c**) resulted in slightly diminished reactivity (43% conversion) and a reduced selectivity factor (s = 77). Alteration of the 2-substituent on the 4-aryl ring significantly influenced selectivity: the ethyl (*rac*-**3d**) and isopropyl (*rac*-**3e**) analogues showed improved performance (s = 115 and 122, respectively). Remarkably, the 2-bromo-substituted substrate *rac*-**3f** provided the highest selectivity factor (s = 178), albeit with a lower diastereomeric ratio (dr = 11:1). The 2-chloro-substituted analogue *rac*-**3g** also gave good selectivity. Substitution at the C7-position of the quinoline-2-one ring with a methyl group (*rac*-**3h**) enhanced the selectivity factor to 90, while substitution with chlorine (*rac*-**3i**)

https://doi.org/10.1021/jacs.6c00643
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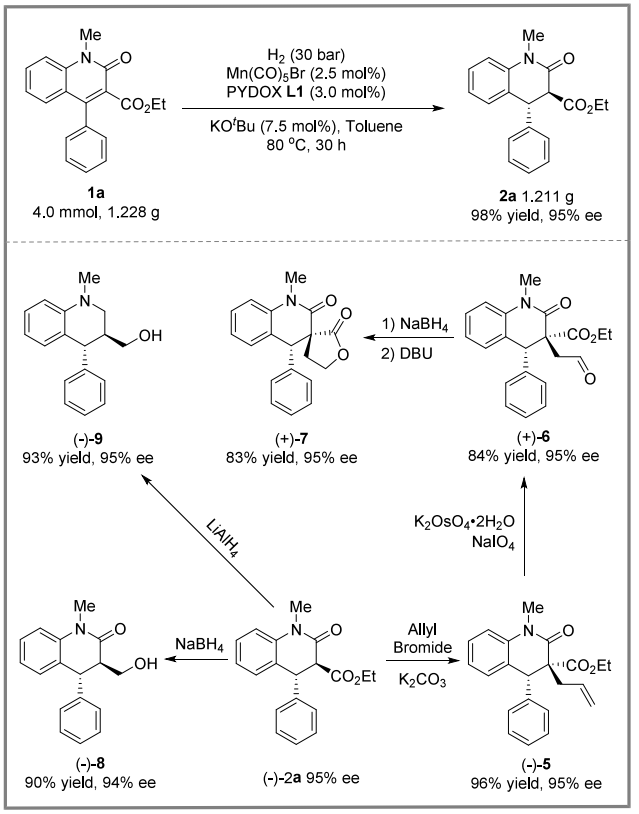
afforded moderate selectivity (s = 44). The absolute configuration of the recovered substrate (−)-**3i** was confirmed as *S* by X-ray diffraction.[20]

Encouragingly, C6-methyl substitution (*rac*-**3j**) delivered an excellent selectivity factor (s = 172). Moreover, both 1-naphthyl (*rac*-**3k**) and 4-aryl-disubstituted (*rac*-**3l**) substrates performed well with a high selectivity. This kinetic resolution protocol is also applicable to the chloro derivative *rac*-**3m**, further showcasing its versatility.

To demonstrate the practicability of the reaction, gram-scale experiment and product elaboration experiments were conducted (Scheme 4). When the hydrogenation of substrate **1a**

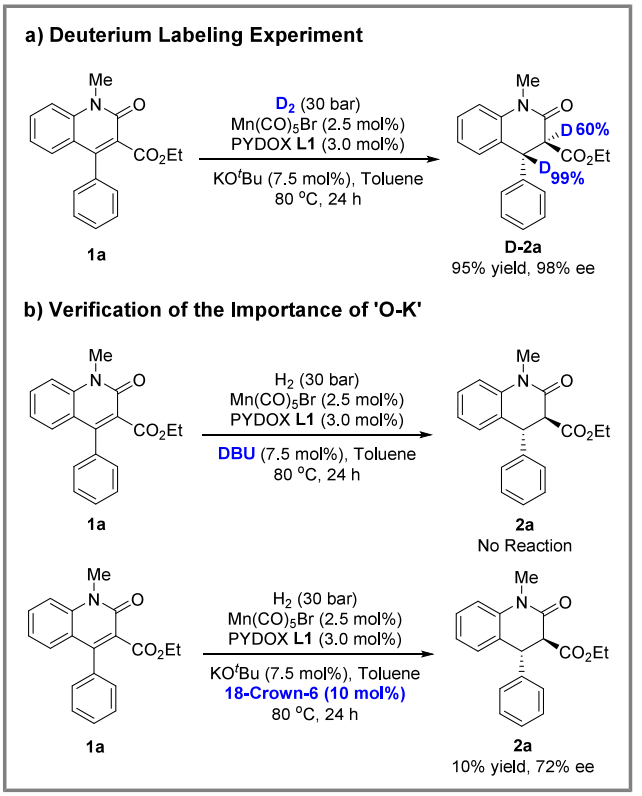
Scheme 4. Gram-Scale Experiment and Product Elaborations



was conducted at 4.0 mmol (1.228 g) and the reaction time was extended to 30 h, the product (−)-**2a** was isolated in 98% yield and 95% ee without loss in yield and enantioselectivity. Meanwhile, derivatizations of (−)-**2a** were conducted. The reaction of chiral compound (−)-**2a** with allyl bromide in the presence of potassium carbonate and tetrabutylammonium iodide (TBAI) afforded the alkylated product (−)-**5** with a high yield and diastereoselectivity. Subsequent osmium-catalyzed oxidation of (−)-**5** with sodium periodate furnished aldehyde (+)-**6** in 84% yield with 95% ee. Reduction of (+)-**6** with sodium borohydride provided the intermediate alcohol, followed by an intramolecular transesterification in the presence of base DBU to afford spirolactone (+)-**7** in 83% yield and 95% ee. Meanwhile, the direct reduction of (−)-**2a** with sodium borohydride in methanol gave the chiral alcohol (−)-**8** in 90% yield. In addition, reduction of (−)-**2a** with lithium aluminum hydride afforded aminoalcohol (−)-**9** with 93% yield and 95% ee. Notably, for all the above processes, no erosion of enantiomeric excess was observed.

To gain insight into the reaction mechanism, a deuterium-labeling experiment was conducted under D_2 atmosphere (Scheme 5a). The reaction proceeded smoothly to afford D-

Scheme 5. Deuterium-Labelling Experiments and O−K Proof of Importance



2a in 95% yield with 98% ee after 24 h. Deuterium incorporation at the C4 position was nearly complete (99%), whereas only 60% incorporation was observed at C3. The lower deuterium content at C3 is attributed to the acidity of the C3−H, which undergoes H−D exchange during workup and purification. These results are consistent with a mechanism in which the hydrogenation is initiated by hydride transfer from Mn−H to the C4 position of the activated olefin.

To verify the importance of the O−K unit, organic base DBU was used to replace potassium *t*-butoxide under the standard conditions, but no reaction occurred (Scheme 5b). In addition, adding 18-crown-6 to chelate K^+ under the same conditions significantly reduced the activity and enantioselectivity. These experimental results suggest that the O−K unit is essential for the manganese-catalyzed hydrogenation.

Based on the putative mechanism[17] on manganese-catalyzed hydrogenation and the above mechanistic study, a plausible hydrogenation mechanism was depicted (Scheme 6). The reaction begins with the coordination of $Mn(CO)_5Br$ with the chiral ligand PYDOX to form complex **Mn-1**. Subsequently, hydrogen bromide is eliminated to afford complex **Mn-2** in the presence of base potassium *tert*-butoxide. Activation of hydrogen gas in the presence of potassium *t*-butoxide generates the active species **I**, which then coordinates with substrate **1** and promotes a synergistic transfer of a hydride, yielding intermediate **II**. Intermediate **II** undergoes a rapid proton-transfer with *t*-butanol, forming enol intermediate **III** and

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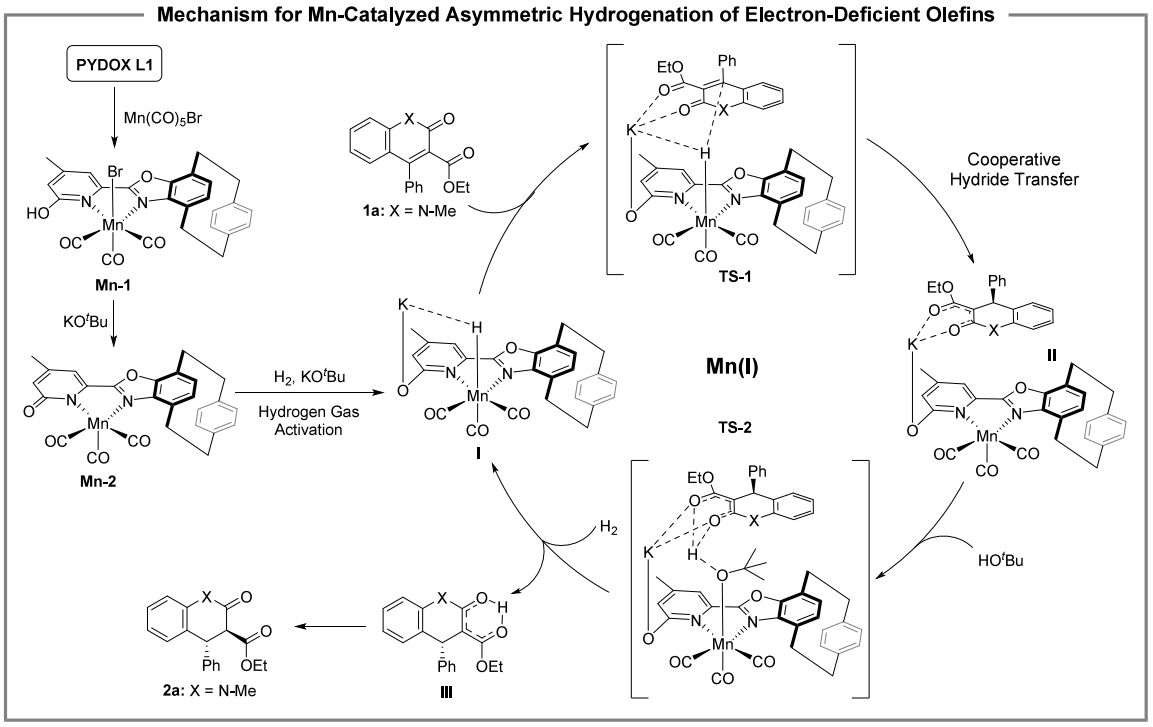
Scheme 6. Plausible Manganese-Catalyzed Hydrogenation Mechanism



generation of active species **I**. The enol intermediate **III** isomerizes to give the final chiral reductive products **2**.

In summary, we have developed the first earth-abundant manganese-catalyzed asymmetric hydrogenation of olefin 4-substituted quinolin-2-ones, enabled by a bifunctional chiral 2-hydroxypyridine-oxazoline (PYDOX) ligand framework. The ligand exerts two cooperative functions: (1) facilitating hydride transfer through a metal−ligand cooperative (MLC) process and (2) activating the electron-deficient olefin via the O−K unit. The synthetic potential of this system was further showcased by its application to hydrogenation kinetic resolution of racemic 4-aryl-substituted quinolin-2-ones. This protocol provided simultaneous access to axial-chiral quinolin-2-ones and central-chiral hydrogenative products with selectivity factor up to 178 and broad structural tolerance, including halogenated, heteroaryl, and disubstituted derivatives. Collectively, these findings establish manganese as a viable platform for asymmetric hydrogenation of olefins and offer a sustainable alternative to noble-metal-based systems, while opening a new avenue for the enantioselective synthesis of both central-chiral and axial-chiral heterocycles.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacs.6c00643.

Detailed experimental procedures, characterization of new compounds, spectra, and X-ray structure of (*S*)-3i (PDF)

Accession Codes

Deposition Number 2471661 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via the joint Cambridge Crystallographic Data Centre (CCDC) and Fachinformationszentrum Karlsruhe Access Structures service.

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Notes

The authors declare no competing financial interest.

https://doi.org/10.1021/jacs.6c00643
J. Am. Chem. Soc. 2026, 148, 10335−10343

■ ACKNOWLEDGMENTS

Financial support from the National Key Research and Development Program of China (2023YFA1507500), National Natural Science Foundation of China (22471264, 22371276), Dalian Institute of Chemical Physics (I202442, I202404), and United Foundation for DICP and Second Hospital of Dalian Medical University (UN202409) is acknowledged.

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(20) The CCDC 2471661 contains supplementary crystallographic data of compound (−)-**3i**.

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