OL Organic Letters

pubs.acs.org/OrgLett

Letter

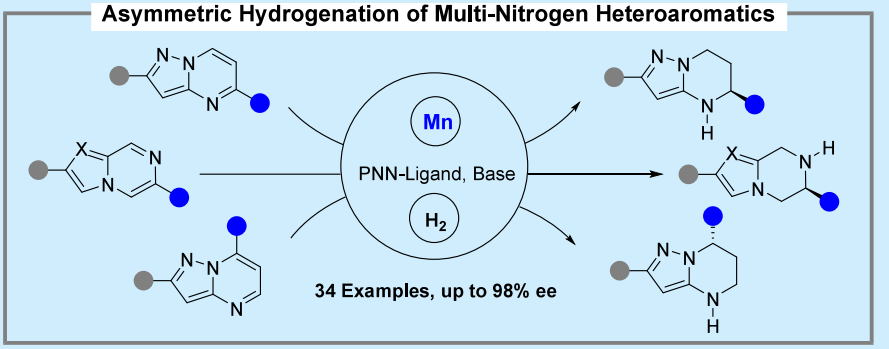
Manganese-Catalyzed Asymmetric Hydrogenation of Multi-Nitrogen Heteroaromatic Compounds

Zheng Liu, Yan-Jiang Yu, Gao-Wei Wang, Sheng-Mei Lu, Yong-Gui Zhou, and Mu-Wang Chen*

Cite This: *Org. Lett.* 2025, 27, 9890−9895

Read Online

ACCESS | Metrics & More | Article Recommendations | Supporting Information



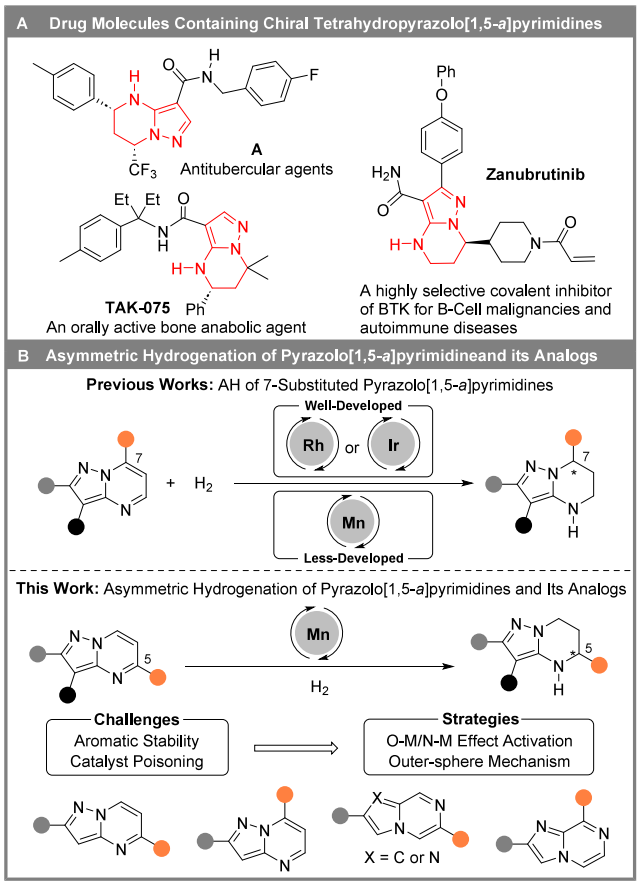
ABSTRACT: Using the chiral *NNP*-manganese complex as catalyst, asymmetric hydrogenation of multi-nitrogen aromatic heterocycles including 5- or 7-substituted pyrazolo[1,5-*a*]pyrimidines, pyrrolo[1,2-*a*]pyrazines, and imidazo[1,2-*a*]pyrazines has been successfully developed, providing the corresponding reductive products with high enantioselectivity, reactivity, and wide substrate scope.

As a fundamental structural element within functional molecules, chiral multi-nitrogen-containing heterocycle skeletons are prevalent across various fields including pharmaceuticals, pesticides, and material sciences.[1] There was particular emphasis on the prevalent and ubiquitous structure found in biologically active compounds known as the 4,5,6,7-tetrahy-dropyrazolo[1,5-*a*]pyrimidine scaffold, which has gained increasing recognition among pharmacologists and chemists. For instance, Zanubrutinib for the treatment of mantle cell lymphoma[2] and TAK-075, an oral active bone synthesis metabolic agent for the treatment of osteoporosis[3] as well as a potential drug for the treatment of drug-resistant tuberculosis,[4] both contain a chiral 4,5,6,7-tetrahydropyrazolo-[1,5-*a*]pyrimi-dine core skeleton in their molecular structures (Scheme 1A). Therefore, some methods for the synthesis of chiral 4,5,6,7-tetra-hydropyrazolo[1,5-*a*]pyrimidines have been developed. One of the most efficient approaches to accessing chiral 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines is direct asymmetric reduction of the corresponding pyrazolo[1,5-*a*]pyrimidines. However, the direct asymmetric hydrogenation of pyrazolo [1,5-*a*]pyrimidines is a challenge, owing to its aromatic stability, which results in lower reactivity. In addition, the substrate contains multiple nitrogen atoms that may coordinate with the catalyst, potentially inhibiting its activity. Nevertheless, it was not until 2023 that the successful development of Rh-catalyzed asymmetric hydrogenation of pyrazolo[1,5-*a*] pyrimidines was achieved by Hou and co-workers (Scheme 1B).[5] Subsequently, the chiral iridium systems were independently employed for hydrogenation of pyrazolo[1,5-*a*] pyrimidines by the Zhou and Nie groups in 2024.[6,7] Very recently, Zhou, Chen and co-workers successfully achieved enzyme-inspired biomimetic asymmetric hydrogenation of the pyrazolo[1,5-*a*]pyrimidines.[8] Although great advances have been made in the asymmetric hydrogenation of pyrazolo[1,5-*a*]pyrimidines, its substrate scope is limited to 7-substituted pyrazolo[1,5-*a*]pyrimidines. Moreover, the catalysts for this type of hydrogenation are mainly limited to precious metals and the reaction conditions are often relatively strict. Therefore, developing a facile and efficient methodology for synthesis of 4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidines and its analogs with high enantioselectivity is still desirable in organic synthesis and drug research. Within the past few decades, significant progress has been made in asymmetric hydrogenation of aromatics catalyzed by chiral rhodium and iridium complexes. To further expand the scope for asymmetric hydrogenation of multi-nitrogen aromatic heterocycles, 5-phenylpyrazolo[1,5-*a*]pyrimidine **1a** was chosen as a model substrate, and utilizing a well-established chiral Rh and

Received: July 4, 2025
Revised: August 26, 2025
Accepted: September 1, 2025
Published: September 3, 2025

https://doi.org/10.1021/acs.orglett.5c02777
Org. Lett. 2025, 27, 9890−9895

Scheme 1. Mn-Catalyzed Asymmetric Hydrogenation of Heteroaromatics

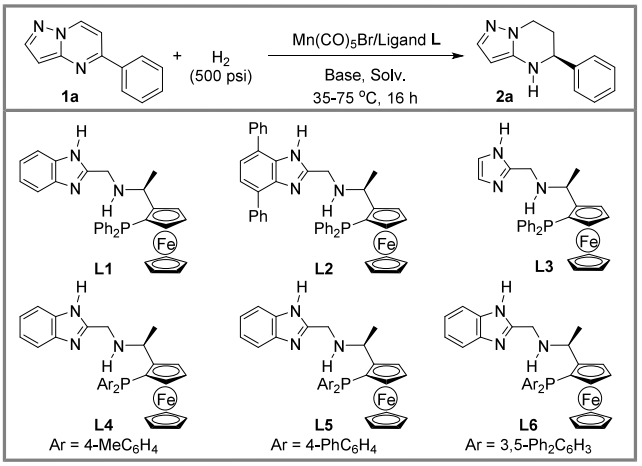


Ir catalytic system, this approach did not afford the desired outcome (See Supporting Information).[5−7] Recently, manganese has gained attention in catalytic hydrogenation for its low cost and lower toxicity compared to noble metals such as rhodium, iridium, and palladium.[9] Since Beller[10] and Clarke[11] pioneered the Mn-catalyzed asymmetric hydrogenation of C═O bonds in 2017, significant progress has been made in Mn-catalyzed asymmetric hydrogenation of both C═N and C═O bonds.[9i,k] However, the Mn-catalyzed asymmetric hydrogenation of nitrogen-containing heteroaromatic compounds is still in its infancy.

In 2021, the first Mn-catalyzed asymmetric hydrogenation of quinolines with high ee values and yields was accomplished in the presence of an *NNP*-Mn pincer catalyst with the N−M effect in the catalytic process to promote the hydrogenation, as reported by Liu and co-workers.[12] Then, this catalytic system was utilized by Liu's group to achieve stereodivergent asymmetric hydrogenation of 2,3-disubstituted quinoxalines.[13] Zhou's group developed a biomimetic chiral Mn/hydroxy-pyridine-oxazoline system that was applied to asymmetric hydrogenation of 7-substituted pyrazolo[1,5-*a*]pyrimidines.[8] Mechanistic studies showed that the O−M effect significantly enhanced the hydrogenation reactivity. In addition, asymmetric transfer hydrogenation of quinolines using a Mn/*NNP* system has also been successively reported by Zhong's group, which further enriches the application in the field of manganese-catalyzed asymmetric hydrogenation of nitrogen-containing heteroaromatic substrates.[14]

Inspired by previous works, chiral manganese catalysts were tested in the asymmetric hydrogenation of 5-phenylpyrazolo[1,5-*a*]pyrimidines **1a**. The manganese-based catalytic systems offer several features and advantages: (1) the manganese-based system operates via an outer-sphere mechanism, which avoids direct coordination between the substrate and catalyst, thereby preventing its poisoning and inactivation; (2) under alkaline conditions, ligands containing N−H/O−H can form N−M/O−M interactions with substrates and enhance their reactivity. This concept led to a preliminary investigation using the manganese-catalytic system with the *NN*-Ligand (chiral 2-hydroxy-pyridine-oxazoline ligand, PYDOX)[8] or *NNP*-Ligand (**L1**). Notably, the promising outcomes were exclusively observed with the ligand **L1** (Table 1, entry 1), whereas the

Table 1. Condition Optimization of Asymmetric Hydrogenation of 5-Substituted Pyrazolo[1,5-*a*]pyrimidines[a]



Entry	Solvent	Base	L	Conversion[b]	ee[c]
1	^{i}PrOH	^{i}PrOK	**L1**	>95	29
2	THF	^{i}PrOK	**L1**	>95	80
3	1,4-Dioxane	^{i}PrOK	**L1**	>95	89
4	DCE	^{i}PrOK	**L1**	<5	55
5	Toluene	^{i}PrOK	**L1**	>95	79
6	1,4-Dioxane	^{i}PrONa	**L1**	>95	95
7	1,4-Dioxane	^{i}PrOLi	**L1**	10	58
8	1,4-Dioxane	^{t}BuONa	**L1**	>95	95
9	1,4-Dioxane	Cs_2CO_3	**L1**	No Reaction	
10	1,4-Dioxane	DABCO	**L1**	No Reaction	
11	1,4-Dioxane	^{t}BuONa	**L2**	<5	81
12	1,4-Dioxane	^{t}BuONa	**L3**	48	86
13	1,4-Dioxane	^{t}BuONa	**L4**	76	92
14	1,4-Dioxane	^{t}BuONa	**L5**	>95	94
15	1,4-Dioxane	^{t}BuONa	**L6**	82	92
16[d]	1,4-Dioxane	^{t}BuONa	**L1**	No Reaction	
17[e]	1,4-Dioxane	^{t}BuONa	**L1**	70	94
18[f]	1,4-Dioxane	^{t}BuONa	**L1**	>95	97
19[g]	1,4-Dioxane	^{t}BuONa	**L1**	>95	97
20[h]	1,4-Dioxane	^{t}BuONa	**L1**	99	96

[a]Reaction conditions: **1a** (0.20 mmol), $Mn(CO)_5Br$ (2.0 mol %), ligand (2.2 mol %), base (7.5 mol %), H_2 (500 psi), solvent (3.0 mL), 75 °C, 16 h. [b]Determined by ^{1}H NMR. [c]Determined by HPLC [d]Base (3.5 mol %). [e]Base (15 mol %). [f]35 °C. [g]25 °C. [h]**1a** (0.30 mmol), isolated yield.

https://doi.org/10.1021/acs.orglett.5c02777
Org. Lett. 2025, 27, 9890−9895

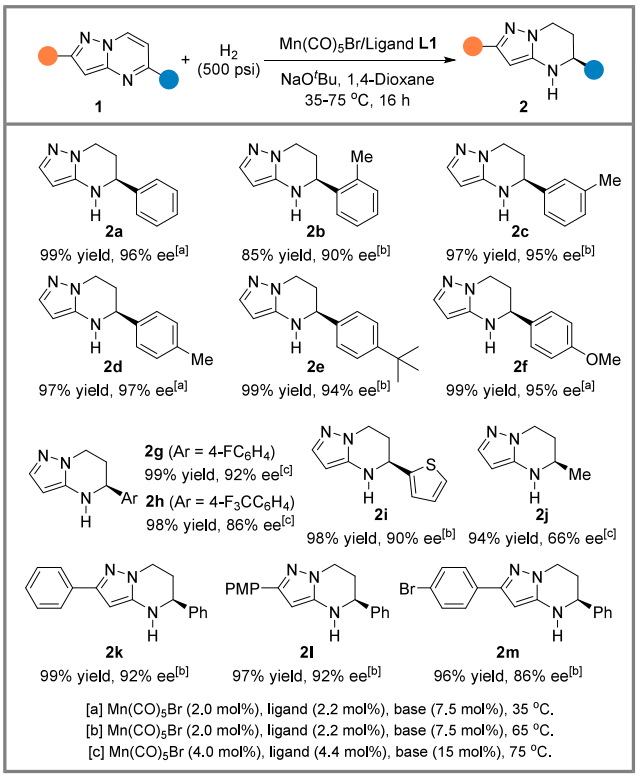
use of PYDOX resulted in a yield of less than 5% (See Supporting Information). Herein, we report asymmetric hydrogenation of multi-nitrogen heteroaromatics using N−H containing chiral *NNP*-manganese complex as catalyst. This methodology exhibits high yields, enantioselectivities, and wide substrate scope including 5- or 7-substituted pyrazolo[1,5-*a*]pyrimi-dines, pyrrolo[1,2-*a*]pyrazines, and imidazo[1,2-*a*]-pyrazines. In addition, a series of mechanistic studies were conducted, revealing the existence of an unusual parallel metal−ligand cooperation protonolysis process in manganese-catalyzed hydrogenation.

After acquiring the preliminary results, subsequent condition optimization was performed to enhance the outcomes (Table 1). It was discovered that the solvent played a crucial role (entries 1−5) and 1,4-dioxane was superior to others, affording the product with full conversion and 89% ee (entry 3). To further improve enantioselectivity, the types of bases were investigated (entries 6−10). It was found that similar enantioselectivities and reactivities could be achieved using sodium isopropoxide (entry 6, >95% conversion, 95% ee) and sodium *tert*-butoxide (entry 8, >95% conversion, 95% ee). However, a narrower margin was observed in the conversion of the reaction with sodium isopropoxide and sodium *tert*-butoxide, as indicated by a comparison of results from thin-layer chromatography. The further evaluation of the chiral *NNP* ligands (entries 11−15) showed that ligand **L1**, containing diphenylphosphanyl and 1*H*-benzo[*d*]imidazol-2-yl, was the best in terms of conversion and enantioselectivity (entry 8). The optimal concentration of *tert*-butoxide was determined to be 3.75 mol %; 95% conversion and 95% ee could be achieved in manganese-catalyzed hydrogenation for 5-phenyl pyrazolo[1,5-*a*]pyrimidine (entries 8, 16, and 17). To our delight, over 95% conversion and 97% ee were obtained within the temperature range of 25 to 35 °C (entries 18 and 19). To ensure the stability and reproducibility of the reaction conditions, a temperature of 35 °C was chosen for the substrate scope investigation.

After determining optimal conditions of Mn-catalyzed asymmetric hydrogenation of multi-nitrogen-containing heterocycles, the substrate scope was investigated and summarized in Scheme 2. First, we evaluated the position of substituents on the phenyl ring of C5 and found that the reactivity increased steadily with the methyl group on ortho, meta, and para positions of the phenyl ring (**2b−2d**). Then, we evaluated the substituents on the para position phenyl ring of C5 (**2d−2h**). The electronic properties and steric effects of the substituents had a minor effect on the yield (85−95%) and resulted in good to excellent enantioselectivities (86−97% ee). When the phenyl group at C5 was replaced with 2-thiophenyl, it proceeded with excellent results (98% yield, 90% ee), which may be ascribed to the outer-sphere mechanism of asymmetric hydrogenation (**2i**). Additionally, moderate enantioselectivity and an excellent yield could be achieved when methyl was placed at C5 (**2j**). Moreover, substrates **2k−2m** with aryl substituents on the C2-position also performed well, providing the desired products with excellent yields and ee values.

To further expand the application possibilities of manganese-catalyzed asymmetric hydrogenation, we applied this attractive protocol to the asymmetric hydrogenation of 7-substituted pyrazolo[1,5-*a*]pyrimidines (Scheme 3), pyrrolo[1,2-*a*]pyrazines, and imidazo[1,2-*a*]pyrazines (Scheme 4). Following reoptimization of the reaction conditions, sodium *iso*-propoxide was identified as an optimized base for

Scheme 2. Substrate Scope: 5-Substituted Pyrazolo[1,5-*a*]pyrimidines



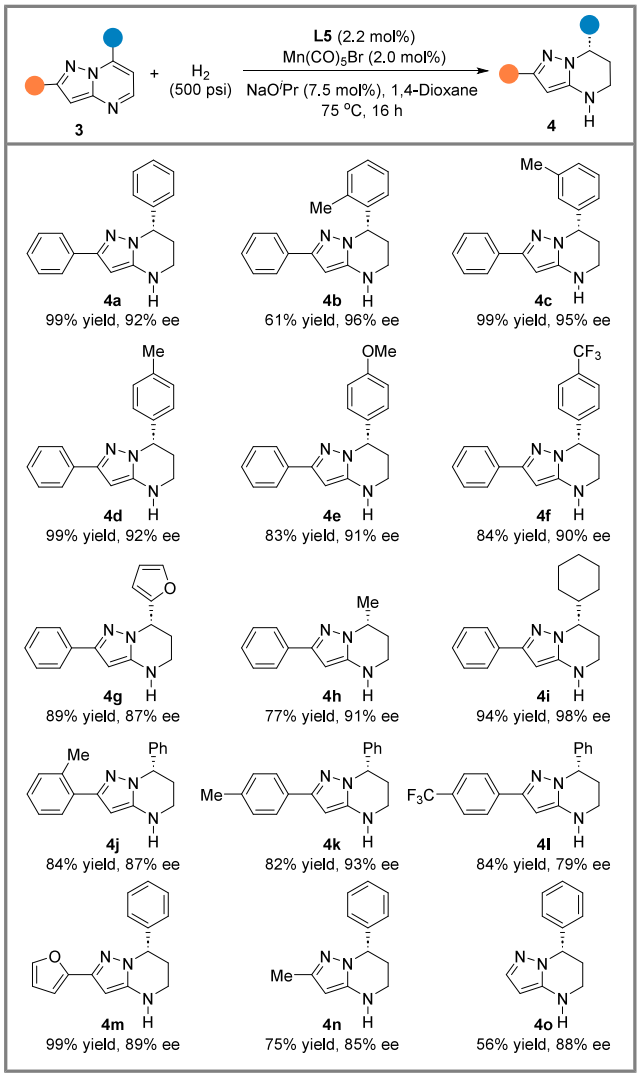
manganese catalyzed asymmetric hydrogenation of 7-substituted pyrazolo [1,5-*a*]pyrimidines (for a detailed optimization, see Supporting Information). First, the substituents on the phenyl of C7 have been evaluated, and moderate to excellent activities (61−99%) and excellent ee values (90−96%) have been observed (**4a−4f**). When the phenyl of C7 was replaced with 2-furanyl, the reaction gave a good yield (89%) and enantioselectivity (87%) (**4g**). Interestingly, the 7-alkyl pyrazolo[1,5-*a*]pyrimidines exhibit good to excellent reactivities (61−94%), while preserving commendable enantioselectivity (91%) (**4h** and **4i**). In addition, the substituents on the phenyl group of C2 have been evaluated, showing moderate to good reactivity and enantiomeric selectivity (**4j−4o**). Moreover, the pyrrolo[1,2-*a*]pyrazines and imidazo[1,2-*a*]pyrazines also performed well, demonstrating good tolerance toward the heterocyclic framework (Scheme 4). Compound **6e** and compound **8** exhibited only moderate enantioselectivity, which may be attributed to the presence of an additional nitrogen atom that induces supplementary hydrogen bonding interactions, the positional effects of substituents.

In addition, to demonstrate synthetic efficacy of this methodology, a manganese-catalyzed asymmetric hydrogenation of multi-nitrogen-containing aromatic heterocycles at the gram scale was conducted (Scheme 5). To our delight, the desired chiral product **2a** was obtained in 96% yield and 96% ee without loss of activity or enantioselectivity.

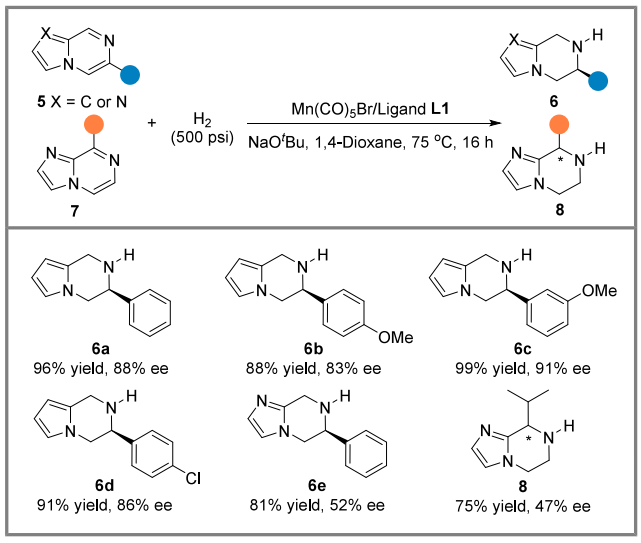
In recent years, the concept of metal−ligand cooperation (MLC) has achieved remarkable development.[15] Inspired by elegant research on MLC reactivity by Liu's group,[16] we conjecture that, during the reaction process, in addition to the predominant classical direct hydrogenation pathway, a parallel MLC-protonolysis pathway exists. The protonolysis of the resulting manganese(I) complex will yield target product **2k**.

https://doi.org/10.1021/acs.orglett.5c02777
Org. Lett. 2025, 27, 9890−9895

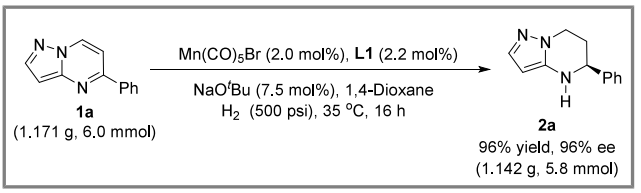
Scheme 3. Substrate Scope: 7-Substituted Pyrazolo[1,5-*a*]pyrimidines



Scheme 4. Substrate Scope: Pyrrolo[1,2-*a*]pyrazines and Imidazo[1,2-*a*]pyrazines



Scheme 5. Gram Scale of Manganese-Catalyzed Asymmetric Hydrogenation of Pyrazolo[1,5-*a*]pyrimidines



(For detailed mechanistic experiments and proposed catalytic cycles, see Supporting Information.)

In conclusion, we have developed asymmetric hydrogenation of multi-nitrogen aromatic heterocycles using the chiral *NNP*-manganese complexes as catalysts. This methodology exhibits high enantioselectivity, reactivity, and substrate scope including 5- or 7-substituted pyrazolo[1,5-*a*]pyrimidines, pyrrolo[1,2-*a*]pyrazines, and imidazo[1,2-*a*]pyrazines. This work not only expands the application scope of earth-abundant manganese-catalyzed asymmetric hydrogenation of multi-nitrogen heteroaromatics but also offers novel hints for rationale design of new chiral manganese catalytic systems. Further development of asymmetric hydrogenation of the multi-nitrogen aromatic heterocycles using earth-abundant transition metals is currently ongoing in our laboratory and will be reported in due course.

■ ASSOCIATED CONTENT

Data Availability Statement

The data underlying this study are available in the published article and its Supporting Information.

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/acs.orglett.5c02777.

Experimental procedures, characterization data, crystal data, and NMR spectra (PDF)

Accession Codes

Deposition Number 2340788 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.

■ AUTHOR INFORMATION

Corresponding Author

Mu-Wang Chen − *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China;* orcid.org/0000-0001-6493-1363; Email: chemmuwang@dicp.ac.cn

Authors

Zheng Liu − *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China; University of Chinese Academy of Sciences, Beijing 100049, P. R. China*

Yan-Jiang Yu − *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China*

Gao-Wei Wang − *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China*

https://doi.org/10.1021/acs.orglett.5c02777
Org. Lett. 2025, 27, 9890−9895

Sheng-Mei Lu − *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China;* orcid.org/0009-0001-8858-0841

Yong-Gui Zhou − *State Key Laboratory of Catalysis, Dalian Institute of Chemical Physics, Chinese Academy of Sciences, Dalian 116023, P. R. China;* orcid.org/0000-0002-3321-5521

Complete contact information is available at: https://pubs.acs.org/10.1021/acs.orglett.5c02777

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

Financial support from National Natural Science Foundation of China (22371276), Dalian Institute of Chemical Physics (DICP I202404, I202202), United Foundation for DICP and the Second Hospital of Dalian Medical University (DMU-2&DICP UN202409), and Energy Revolution S&T Program of Yulin Innovation Institute of Clean Energy (E412020705) is acknowledged.

■ REFERENCES

(1) (a) Yakaiah, T.; Kurumurthy, C.; Lingaiah, B. P. V.; Narsaiah, B.; Pamanji, R.; Velatooru, L. R.; Venkateswara Rao, J.; Gururaj, S.; Parthasarathy, T.; Sridhar, B. $GdCl_3$ Promoted Synthesis of Novel Pyrimidine Fused Indazole Derivatives and Their Anticancer Activity. *Med. Chem. Res.* **2012**, *21*, 4261−4273. (b) Asano, T.; Yamazaki, H.; Kasahara, C.; Kubota, H.; Kontani, T.; Harayama, Y.; Ohno, K.; Mizuhara, H.; Yokomoto, M.; Misumi, K.; Kinoshita, T.; Ohta, M.; Takeuchi, M. Identification, Synthesis, and Biological Evaluation of 6-[(6*R*)-2-(4-Fluorophenyl)-6-(hydroxymethyl)-4,5,6,7-tetrahydropyrazolo[1,5-*a*]pyrimidin-3-yl]-2-(2-methylphenyl)pyridazin-3(2*H*)-one (AS1940477), a Potent p38 MAP Kinase Inhibitor. *J. Med. Chem.* **2012**, *55*, 7772−7785.

(2) (a) Li, G.; Liu, X.; Chen, X. Simultaneous Development of Zanubrutinib in the USA and China. *Nat. Rev. Clin. Oncol.* **2020**, *17*, 589−590. (b) Guo, Y.; Liu, Y.; Hu, N.; Yu, D.; Zhou, C.; Shi, G.; Zhang, B.; Wei, M.; Liu, J.; Luo, L.; Tang, Z.; Song, H.; Guo, Y.; Liu, X.; Su, D.; Zhang, S.; Song, X.; Zhou, X.; Hong, Y.; Chen, S.; Cheng, Z.; Young, S.; Wei, Q.; Wang, H.; Wang, Q.; Lv, L.; Wang, F.; Xu, H.; Sun, H.; Xing, H.; Li, N.; Zhang, W.; Wang, Z.; Liu, G.; Sun, Z.; Zhou, D.; Li, W.; Liu, L.; Wang, L.; Wang, Z. Discovery of Zanubrutinib (BGB-3111), a Novel, Potent, and Selective Covalent Inhibitor of Bruton's Tyrosine Kinase. *J. Med. Chem.* **2019**, *62*, 7923−7940. (c) Guo, Y.; Hu, N.; Liu, Y.; Zhang, W.; Yu, D.; Shi, G.; Zhang, B.; Yin, L.; Wei, M.; Yuan, X.; Luo, L.; Wang, F.; Song, X.; Xin, L.; Wei, Q.; Li, Y.; Guo, Y.; Chen, S.; Zhang, T.; Zhang, S.; Zhou, X.; Zhang, C.; Su, D.; Liu, J.; Cheng, Z.; Zhang, J.; Xing, H.; Sun, H.; Li, X.; Zhao, Y.; He, M.; Wu, Y.; Guo, Y.; Sun, X.; Tian, A.; Zhou, C.; Young, S.; Liu, X.; Wang, L.; Wang, Z. Discovery of BGB-8035, a Highly Selective Covalent Inhibitor of Bruton's Tyrosine Kinase for B-Cell Malignancies and Autoimmune Diseases. *J. Med. Chem.* **2023**, *66*, 4025−4044.

(3) Yoshida, M.; Mori, A.; Morimoto, S.; Kotani, E.; Oka, M.; Notoya, K.; Makino, H.; Ono, M.; Shirasaki, M.; Tada, N.; Fujita, H.; Ban, J.; Ikeda, Y.; Kawamoto, T.; Goto, M.; Kimura, H.; Baba, A.; Yasuma, T. Novel and Potent Calcium-Sensing Receptor Antagonists: Discovery of (5*R*)-*N*-[1-Ethyl-1-(4-ethylphenyl)propyl]-2,7,7-trimethyl-5-phenyl −4,5,6,7-tetrahydr-opyrazolo[1,5-*a*]pyrimidine-3-carboxamide Mono-tosylate (TA K-075) as an Orally Active Bone Anabolic Agent. *Bioorg. Med. Chem.* **2011**, *19*, 1881−1894.

(4) Yokokawa, F.; Wang, G.; Chan, W. L.; Ang, S. H.; Wong, J.; Ma, I.; Rao, S. P. S.; Manjunatha, U.; Lakshminarayana, S. B.; Herve, M.; Kounde, C.; Tan, B. H.; Thayalan, P.; Ng, S. H.; Nanjundappa, M.; Ravindran, S.; Gee, P.; Tan, M.; Wei, L.; Goh, A.; Chen, P.-Y.; Lee, K. S.; Zhong, C.; Wagner, T.; Dix, I.; Chatterjee, A. K.; Pethe, K.; Kuhen, K.; Glynne, R.; Smith, P.; Bifani, P.; Jiricek, J. Discovery of Tetrahydropyrazolopyr-imidine Carboxamide Derivatives as Potent and Orally Active Antitubercular Agents. *ACS Med. Chem. Lett.* **2013**, *4*, 451−455.

(5) Xie, C.; Xiao, G.; Guo, Q.; Wu, X.; Zi, G.; Ding, W.; Hou, G. Highly Enantioselective Rh-catalyzed Asymmetric Reductive Dearomatization of Multi-nitrogen Polycyclic Pyrazolo[1,5-*a*]pyri-midines. *Chem. Sci.* **2023**, *14*, 9048−9054.

(6) Chen, M.-W.; Li, H.-W.; Wang, Y.-Q.; Wu, B.; Liu, Z.; Lai, X.; Deerberg, J.; Zhou, Y.-G. Iridium-Catalyzed Asymmetric Hydrogenation of Heteroaromatics with Multiple N Atoms via Substrate Activation: An Entry to 4,5,6,7-Tetrahydropyr-azolo[1,5-*a*]-pyrimidine-3-carbonitrile Core of a Potent BTK Inhibitor. *J. Org. Chem.* **2024**, *89*, 4336−4348.

(7) Yuan, H.; Yao, W.; Zhang, X.; Wei, Z.; Xi, J.; Hao, Y.; Liu, X.; Jiang, R.; Nie, H. Highly Enantioselective Ir-Catalyzed Hydrogenation of Pyrazolo[1,5-*a*]pyrimidine for the Synthesis of Zanubrutinib. *J. Org. Chem.* **2024**, *89*, 1748−1752.

(8) Wang, G.-W.; Chen, M.-W.; Wu, Y.-Q.; Xie, Q.-X.; Liu, Z.; Liao, R.-Z.; Zhou, Y.-G. Design and Synthesis of Chiral Bidentate Phosphine-Free 2-Hydroxypyridine-Oxazoline Ligands for Manganese-Catalyzed Hydrogenation. *ACS Catal.* **2025**, *15*, 3418−3427.

(9) (a) Garbe, M.; Junge, K.; Beller, M. Homogeneous Catalysis by Manganese-Based Pincer Complexes. *Eur. J. Org. Chem.* **2017**, *2017*, 4344−4362. (b) Maji, B.; Barman, M. Recent Developments of Manganese Complexes for Catalytic Hydrogenation and Dehydrogenation Reactions. *Synthesis* **2017**, *49*, 3377−3393. (c) Kallmeier, F.; Kempe, R. Manganese Complexes for (De)Hydrogenation Catalysis: A Comparison to Cobalt and Iron Catalysts. *Angew. Chem., Int. Ed.* **2018**, *57*, 46−60. (d) Filonenko, G. A.; van Putten, R.; Hensen, E. J. M.; Pidko, E. A. Catalytic (De)Hydrogenation Promoted by Non-Precious Metals-Co, Fe and Mn: Recent Advances in an Emerging Field. *Chem. Soc. Rev.* **2018**, *47*, 1459−1483. (e) Alig, L.; Fritz, M.; Schneider, S. First-Row Transition Metal (De)Hydrogenation Catalysis Based On Functional Pincer Ligands. *Chem. Rev.* **2019**, *119*, 2681−2751. (f) Wang, Y.; Wang, M.; Li, Y.; Liu, Q. Homogeneous Manganese-catalyzed Hydrogenation and Dehydrogenation Reactions. *Chem.* **2021**, *7*, 1180−1223. (g) Wen, J.; Wang, F.; Zhang, X. Asymmetric Hydrogenation Catalyzed by First-Row Transition Metal Complexes. *Chem. Soc. Rev.* **2021**, *50*, 3211−3237. (h) Das, K.; Waiba, S.; Jana, A.; Maji, B. Manganese-Catalyzed Hydrogenation, Dehydro-genation, and Hydroelementation Reactions. *Chem. Soc. Rev.* **2022**, *51*, 4386−4464. (i) Liu, C.; Liu, Q. Earth-Abundant Metal-Catalyzed Asymmetric Hydrogenation of Carbon-Nitrogen Unsaturated Bonds. *Chin. J. Org. Chem.* **2022**, *42*, 3213−3220. (j) Liu, C. Progress in Asymmetric Hydrogenation of Aromatic *N*-Heterocyclic Compounds. *Chin. J. Org. Chem.* **2024**, *44*, 1403−1422. (k) Fu, D.; Wang, Z.; Liu, Q.; Prettyman, S. J.; Solan, G. A.; Sun, W.-H. Organometallic Mn(I) Complexes in Asymmetric Catalytic (Transfer) Hydro-genation and Related Transformations. *ChemCatChem.* **2024**, *16*, No. e202301567.

(10) Garbe, M.; Junge, K.; Walker, S.; Wei, Z.; Jiao, H.; Spannenberg, A.; Bachmann, S.; Scalone, M.; Beller, M. Manganese-(I)-Catalyzed Enantioselective Hydrogenation of Ketones Using a Defined Chiral *PNP* Pincer Ligand. *Angew. Chem., Int. Ed.* **2017**, *56*, 11237−11241.

(11) Widegren, M. B.; Harkness, G. J.; Slawin, A. M. Z.; Cordes, D. B.; Clarke, M. L. A Highly Active Manganese Catalyst for Enantioselective Ketone and Ester Hydrogenation. *Angew. Chem., Int. Ed.* **2017**, *56*, 5825−5828.

(12) Liu, C.; Wang, M.; Liu, S.; Wang, Y.; Peng, Y.; Lan, Y.; Liu, Q. Manganese-Catalyzed Asymmetric Hydrogenation of Quinolines Enabled by $\pi-\pi$ Interaction. *Angew. Chem., Int. Ed.* **2021**, *60*, 5108−5113.

(13) Liu, C.; Liu, X.; Liu, Q. *Stereodivergent Asymmetric Hydrogenation of Quinoxalines. Chem.* **2023**, *9*, 2585−2600.

(14) Mao, W.; Song, D.; Guo, J.; Zhang, K.; Zheng, C.; Lin, J.; Huang, L.; Zheng, L.; Zhong, W.; Ling, F. Manganese-Catalyzed Asymmetric Transfer Hydrogenation of Quinolines in Water Using Ammonia Borane as a Hydrogen Source. *Green Chem.* **2024**, *26*, 5933−5939.

(15) (a) Ben-Ari, E.; Leitus, G.; Shimon, L. J. W.; Milstein, D. Metal-Ligand Cooperation in C-H and H_2 Activation by an Electron-Rich *PNP* Ir(I) System: Facile Ligand Dearomatization-Aromatization as Key Steps. *J. Am. Chem. Soc.* **2006**, *128*, 15390−15391. (b) Gunanathan, C.; Ben-David, Y.; Milstein, D. Direct Synthesis of Amides from Alcohols and Amines with Liberation of H_2. *Science* **2007**, *317*, 790−792. (c) van der Vlugt, J. I.; Pidko, E. A.; Vogt, D.; Lutz, M.; Spek, A. L. Cu^I Complexes with a Noninnocent *PNP* Ligand: Selective Dearomatization and Electrophilic Addition Reactivity. *Inorg. Chem.* **2009**, *48*, 7513−7515. (d) Huff, C. A.; Kampf, J. W.; Sanford, M. S. Role of a Noninnocent Pincer Ligand in the Activation of CO_2 at (PNN)Ru(H)(CO). *Organometallics* **2012**, *31*, 4643−4645. (e) Balaraman, E.; Khaskin, E.; Leitus, G.; Milstein, D. Catalytic Transformation of Alcohols to Carboxylic Acid Salts and H_2 Using Water as the Oxygen Atom Source. *Nat. Chem.* **2013**, *5*, 122−125. (f) Vogt, M.; Nerush, A.; Diskin-Posner, Y.; Ben-David, Y.; Milstein, D. Reversible CO_2 Binding Triggered by Metal-Ligand Cooperation in a Rhenium(I) *PNP* Pincer-Type Complex and the Reaction with Dihydrogen. *Chem. Sci.* **2014**, *5*, 2043−2051. (g) Khusnutdinova, J. R.; Milstein, D. Metal-Ligand Cooperation. *Angew. Chem., Int. Ed. Engl.* **2015**, *54*, 12236−12273. (h) Milstein, D. Metal-Ligand Cooperation by Aromatization-Dearomatization as a Tool in Single Bond Activation. *Philos. Trans. A Math. Phys. Eng. Sci.* **2015**, *373*, 20140189. (i) Morris, R. H. Exploiting Metal-Ligand Bifunctional Reactions in the Design of Iron Asymmetric Hydrogenation Catalysts. *Acc. Chem. Res.* **2015**, *48*, 1494−1502. (j) Chirik, P. J. Iron- and Cobalt-Catalyzed Alkene Hydrogenation: Catalysis with Both Redox-Active and Strong Field Ligands. *Acc. Chem. Res.* **2015**, *48*, 1687−1695. (k) Omann, L.; Königs, C. D. F.; Klare, H. F. T.; Oestreich, M. Cooperative Catalysis at Metal-Sulfur Bonds. *Acc. Chem. Res.* **2017**, *50*, 1258−1269. (l) Higashi, T.; Kusumoto, S.; Nozaki, K. Cleavage of Si-H, B-H, and C-H Bonds by Metal-Ligand Cooperation. *Chem. Rev.* **2019**, *119*, 10393−10402. (m) Li, H.; Gonçalves, T. P.; Lupp, D.; Huang, K.-W. $PN^3(P)$-Pincer Complexes: Cooperative Catalysis and Beyond. *ACS Catal.* **2019**, *9*, 1619−1629. (n) Irrgang, T.; Kempe, R. 3d-Metal Catalyzed *N*- and *C*-Alkylation Reactions via Borrowing Hydrogen or Hydrogen Autotransfer. *Chem. Rev.* **2019**, *119*, 2524−2549. (o) Elsby, M. R.; Baker, R. T. Strategies and Mechanisms of Metal-Ligand Cooperativity in First-Row Transition Metal Complex Catalysts. *Chem. Soc. Rev.* **2020**, *49*, 8933−8987. (p) Luo, J.; Montag, M.; Milstein, D. Metal-Ligand Cooperation with Thiols as Transient Cooperative Ligands: Acceleration and Inhibition Effects in (De) Hydrogenation Reactions. *Acc. Chem. Res.* **2024**, *57*, 1709−1721.

(16) (a) Li, H.; Fan, M.; Liu, Q. Unveiling the Unique Reactivity of Anionic Mn(I) Complexes via Metal-Ligand Cooperation: Nucleophilic Attack on $C(sp^3)$-X Bonds. *J. Am. Chem. Soc.* **2024**, *146*, 26649−26656. (b) Yang, H.; Liu, S.; Dong, H.; Huang, H.; Wang, Y.; Hao, W.; Lan, Y.; Liu, Q. Amplifying the Reactivity of Anionic Mn(I)-H Catalysts via the Cation Effect: Mechanistic Investigation and Application to the Hydrogenation of α-Trisubstituted Carboxylic Esters. *J. Am. Chem. Soc.* **2025**, *147*, 13491−13501.

https://doi.org/10.1021/acs.orglett.5c02777
Org. Lett. 2025, 27, 9890−9895