



Cite this: *Chem. Sci.*, 2025, 16, 7051

All publication charges for this article have been paid for by the Royal Society of Chemistry

Enantioselective Zn-catalyzed hydrophosphinylation of nitrones: an efficient approach for constructing chiral α -hydroxyamino-phosphine oxides†

Shihui Luo,^a Xinzhu Yuan,^a Jiangtao Cheng,^a Zhiping Yang,^a Zhongxing Huang^b and Jun (Joelle) Wang^{id}*^a

Although enantioselective hydrofunctionalizations of nitrones are established for the synthesis of various types of chiral hydroxylamines, the asymmetric catalytic hydrophosphinylation of nitrones remains highly challenging. Herein, an efficient asymmetric hydrophosphinylation of nitrones, catalyzed by the dinuclear zinc catalyst derived from ProPhenol, is presented, accommodating a variety of nitrones and phosphine oxides. This approach successfully addresses the long-standing challenge of catalytic hydrophosphinylation of the C=N bond, and offers an efficient and rapid access towards chiral α -hydroxyamino-phosphine oxides. Control experiments suggest that the oxide anion in the nitrone motif is crucial for the enantio-control.

Received 24th February 2025

Accepted 18th March 2025

DOI: 10.1039/d5sc01453k

rsc.li/chemical-science

Introduction

Chiral amino phosphorus compounds have garnered significant attention due to their crucial roles in medicinal chemistry and biochemistry,¹ as well as their applications as chiral P-N ligands or catalysts in organic synthesis.² For example, certain α - or β -amino-phosphorus compounds serve as antibacterial

agents, antibodies (Fig. 1a),² while other nitrogen-containing phosphorus compounds function as efficient chiral ligands or catalysts in asymmetric catalysis (Fig. 1c).³ Specifically, α -hydroxyaminophosphine oxides are valuable intermediates and building blocks in organic synthesis and drug discovery,³ with some exhibiting notable antitumor activities (Fig. 1d).^{3b} Despite their importance, the effective synthesis of chiral α -hydroxyaminophosphine oxides remains challenging, with no suitable catalytic systems reported to date. Therefore, a practical synthetic route towards enantioselective α -hydroxyaminophosphine oxides is highly desirable. Nitrones are ideal starting materials for constructing chiral α -hydroxyaminophosphine oxides due to their straightforward preparation through simple condensations and crystallizations.⁴ They are generally more stable and easier to handle than their corresponding imine motifs, and their configurational stability enhances the stereoselectivities in reactions.⁵

Asymmetric hydrofunctionalization is a powerful tool for introducing hydrogen and functional groups to C=C⁶ and C=N⁷ double bonds in an enantio- and regioselective manner. Elegant examples of asymmetric hydrofunctionalization of nitrones have been disclosed using carbon nucleophiles with organocatalysts, photocatalysts, Lewis acid catalysts, or transition-metal catalysts (Scheme 1a).⁸ In 2008, Scheidt's group developed a chiral NHC-catalyzed diastereo- and enantioselective hydrocarbonylation of nitrones with homoenolates.^{8a} In 2018, Huang and co-workers discovered an asymmetric hydrocarbonylation of nitrones with the combination of photocatalysts and chiral Lewis acids.^{8b} Very recently, Aponick's group reported a copper-catalyzed asymmetric hydrofunctionalization of nitrones with alkyne nucleophiles

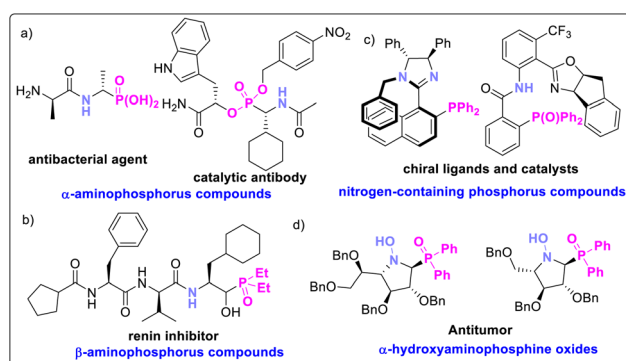


Fig. 1 Representative of chiral aminophosphorus compounds.

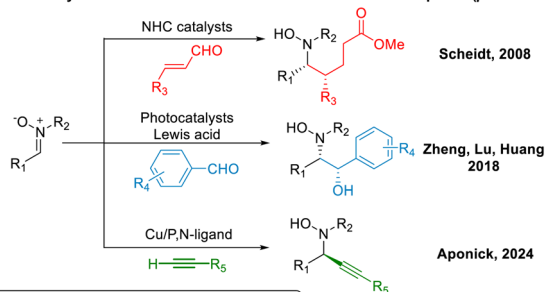
^aDepartment of Chemistry, Hong Kong Baptist University, Kowloon, Hong Kong, China. E-mail: junwang@hkbu.edu.hk

^bDepartment of Chemistry, The University of Hong Kong, Hong Kong, China

† Electronic supplementary information (ESI) available: The datasets supporting this article have been uploaded as part of the ESI. CCDC 2408217. For ESI and crystallographic data in CIF or other electronic format see DOI: <https://doi.org/10.1039/d5sc01453k>

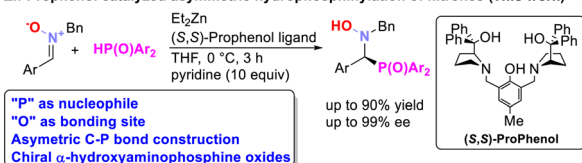


a) Asymmetric hydrofunctionalization of nitrones with carbon nucleophiles (previous work)



carbon nucleophiles: limited examples
heteroatoms as nucleophiles: underdeveloped

b) Zn-ProPhenol catalyzed asymmetric hydrophosphinylation of nitrones (This work)



"P" as nucleophile
"O" as bonding site
Asymmetric C-P bond construction
Chiral α -hydroxyaminophosphine oxides

Scheme 1 Overview of asymmetric hydrofunctionalization of nitrones.

using tunable axially chiral imidazole-based *P,N*-ligands.^{8c} Compared to the hydrofunctionalization of C=C bonds, reactions involving C=N bonds, particularly with heteroatoms nucleophiles, are less developed. While there are limited examples of catalytic enantioselective addition of imine/iminium with phosphonates⁹ and phosphine oxides¹⁰ using Lewis acid or transition-metal catalysts, catalytic hydrophosphinylation of nitrones is rare.

Therefore, developing an asymmetric hydrofunctionalization of nitrones with phosphorus nucleophiles addresses an unmet need. As part of our long-term interest in developing asymmetric hydrophosphination reactions,¹¹ we tackle the challenges of asymmetric hydrophosphinylation of nitrones with the dinuclear zinc catalyst derived from ProPhenol (Scheme 1b).

Results and discussion

The nitrogen atom in nitrone cannot directly interact with transition-metal catalysts due to the lack of the lone pair electrons,¹² which impairs the enantioselectivity of the reaction. Nevertheless, Lewis acid catalysts, such as the Zn-ProPhenol, may provide metal binding sites and create a chiral pocket to activate both the electrophile and the nucleophile.¹³ It is hypothesized that the Brønsted basic site binds to phosphine oxide, while the Lewis acidic site coordinates with the oxide anion of the nitrone, thereby promoting enantioselective C-P bond formation. Based on this hypothesis, we started our investigation using nitrone **1a** and diphenyl phosphine oxide **2a** as model substrates, with diethyl zinc and the (*S,S*)-ProPhenol ligand as the chiral catalytic system (Table 1). Without additives, the expected product **3aa** was obtained in racemic form along with byproduct **4aa** (Table 1, entry 1). Pyridine is well known to accelerate reaction rates and enhance enantioselectivities in Lewis acid-catalyzed asymmetric reactions.¹⁴ To our delight, the addition of pyridine did increase the ee value from 0% to 63% dramatically (Table 1, entry 2).

Table 1 Optimization of reaction conditions^a

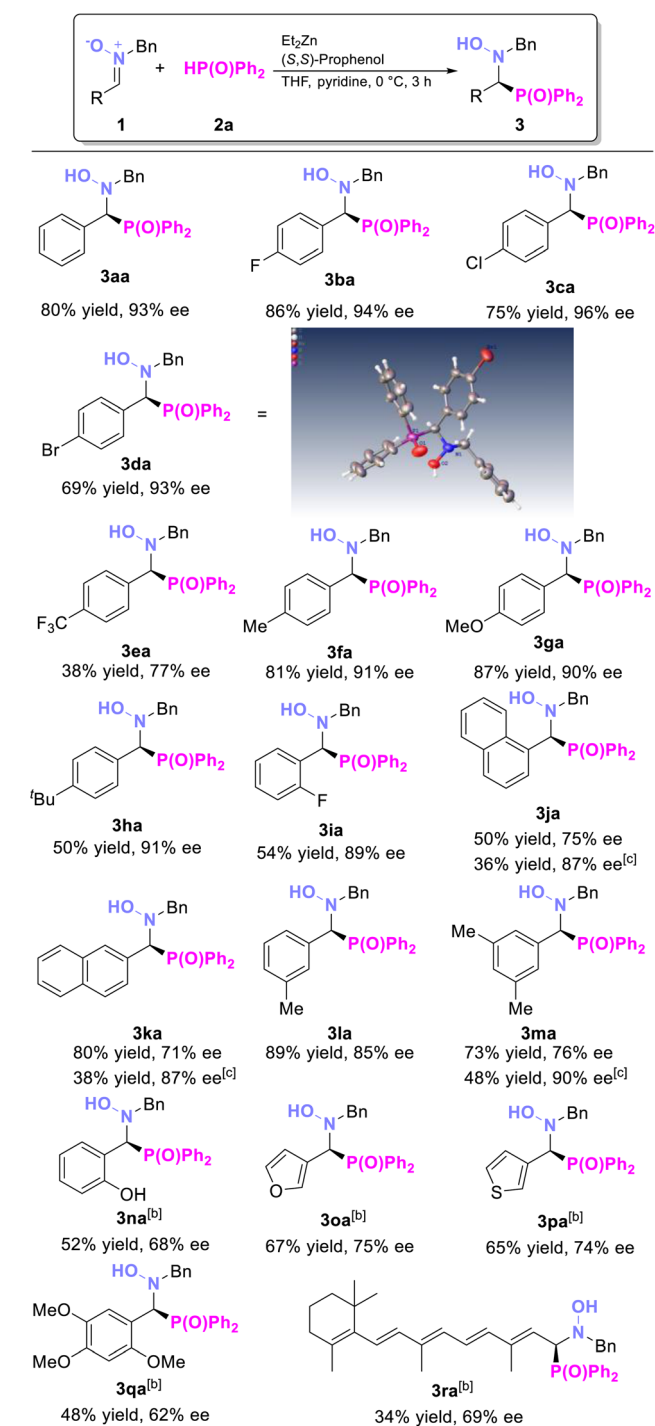
Entry	Solvent	<i>T</i> (°C)	Yield ^b (%)	3aa : 4aa ^c	ee of 3aa ^d (%)
1 ^e	Toluene	0	70	11 : 1	rac
2	Toluene	0	73	14 : 1	63
3	MeCN	0	68	8 : 1	91
4	1,4-Dioxane	0	98	14 : 1	86
5	Anisole	0	81	5 : 1	92
6	THF	0	87 (80) ^f	10 : 1	93
7 ^g	THF	0	90	11 : 1	80
8 ^h	THF	0	89	11 : 1	86
9	THF	rt	59	2 : 1	84

^a Reaction conditions: **1a** (0.1 mmol), **2a** (0.15 mmol), Et₂Zn (40 mol%), ligand (20 mol%), solvent (2 mL), under N₂, 3 h. ^b Yields are detected by ³¹P NMR using P(O)(OMe)₃ as the internal standard. ^c The ratios are detected by ¹H NMR. ^d Determined by HPLC analysis with a Chiralcel ID column (hexane/2-propanol 60 : 40, 1.0 mL min⁻¹, 210 nm). ^e No pyridine was added. ^f Isolated yield for **3aa**. ^g 5.0 equiv. of pyridine was added. ^h 8.0 equiv. of pyridine was added.

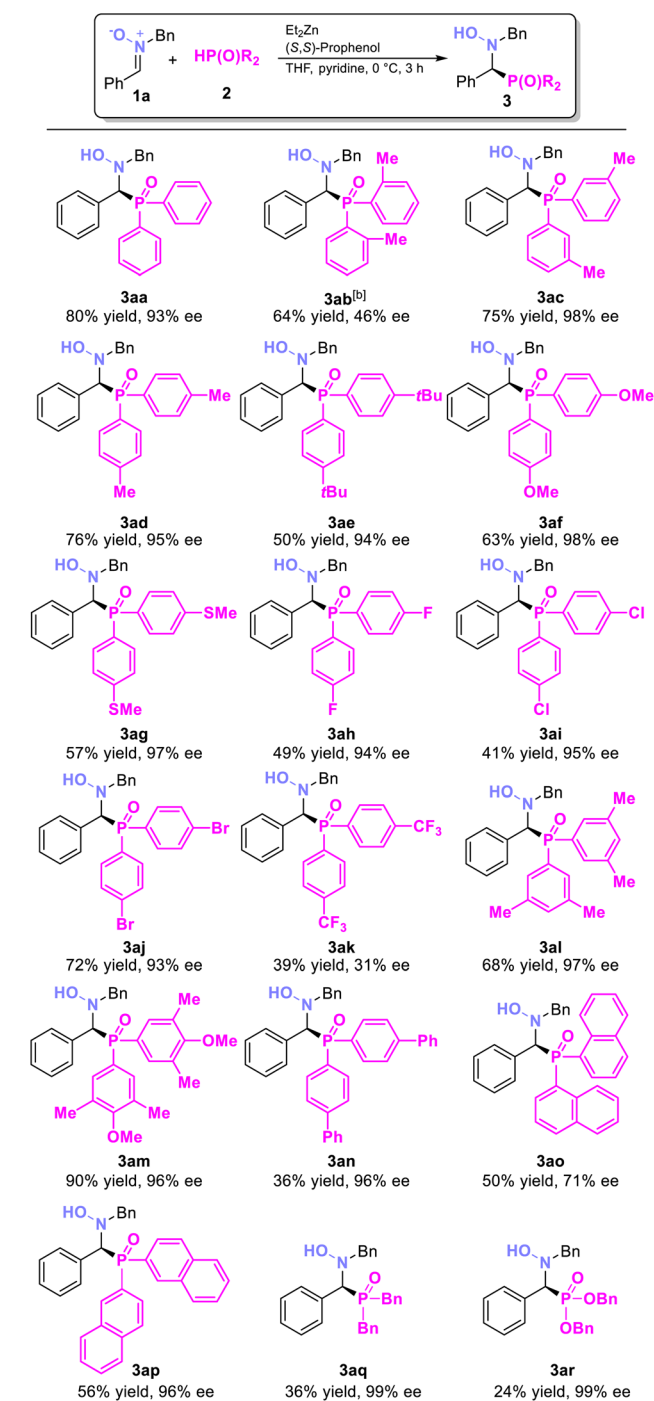
Further investigation of various solvents revealed that ether solvents consistently gave both good yields and high ee values (Table 1, entries 4–6). Reducing the amount of pyridine slightly decreased the ee values compared to the standard condition (Table 1, entries 6–8). The reaction temperature also played a crucial role in minimizing the side product **4aa**, with the ratio of product **3aa** to side product **4aa** increasing to 10 : 1 at 0 °C (Table 1, entry 9 vs. 6). Thus, the optimal conditions were determined to be 10.0 equiv. of pyridine in THF under 0 °C for 3 h (Table 1, entry 6, 80% yield, 93% ee).

With the optimized conditions in hand, we then investigated the substrate scope of nitrones (Table 2). Generally, nitrones with both electron-withdrawing and electron-donating groups at various positions on the phenyl ring were compatible, yielding the corresponding hydroxyamino phosphine oxides in good yields and high ee values. Nitrone with strong electron-withdrawing substituents (**3ea**, CF₃) on the aromatic ring was also compatible, although with lower conversion. The 1-naphthyl nitrone substrate, despite its steric hindrance, also yielded corresponding product in moderate yield and good ee (**3ja**, 50% yield and 75% ee). After that, we further explored the reaction's compatibility with more valuable and complex substrates (**3na–3ra**). For example, the substrate **3n**, derived from salicylaldehyde and featuring a free hydroxyl group, performed well, giving the expected product **3na** in 52% yield with 68% ee. Heteroaromatic compounds were also well tolerated, providing the desired products **3oa** and **3pa** with good yields and enantioselectivities. Additionally, the derivative of 2,4,5-TMBA, a known COX-2 inhibitor,¹⁵ was produced in 48% yield and 62% ee (**3qa**). The derivative of retinal, an essential chemical for visual phototransduction,¹⁶ gave the product in 34% yield, and



Table 2 Substrate scope of nitrones^a

^a Reaction conditions: **1a–1m** (0.1 mmol), **2a** (0.15 mmol), Et₂Zn (40 mol%), ligand (20 mol%), pyridine (10.0 equiv.), THF (2 mL), under N₂, 3 h. Yields are isolated yields. ee Values are determined by HPLC analysis. ^b Reacted for 24 h. ^c Reacted under –10 °C.

Table 3 Substrate scope of phosphine oxides^a

^a Reaction conditions: **1a** (0.1 mmol), **2a–2r** (0.15 mmol), Et₂Zn (40 mol%), ligand (20 mol%), pyridine (10.0 equiv.), THF (2 mL), under N₂, 3 h. Yields are isolated yields. ee Values are determined by HPLC analysis. ^b Reacted for 24 h.

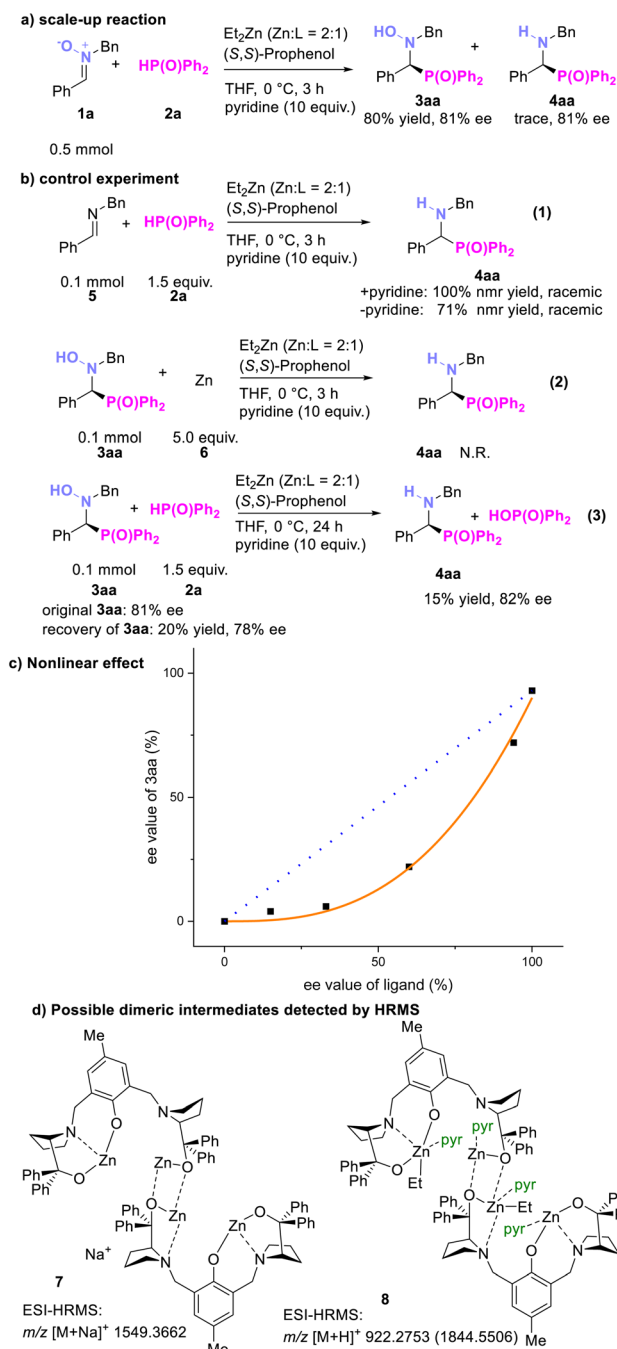
69% ee (**3ra**) under 0 °C for 24 hours, despite its structural complexity. The absolute configuration of **3da** was confirmed as (S) by X-ray crystallographic analysis.¹⁷

After exploring the nitron substrates, we turned our attention to various phosphine oxides (Table 3). Both di-*m*-tolylphosphine oxide and di-*p*-tolylphosphine oxide gave the desired products in good yield with excellent ee values (**3ac**, **3ad**). Di-*o*-

tolylphosphine oxide, despite its steric hindrance, also yielded the corresponding product in lower yield and ee (**3ab** 64% yield, 46% ee, 24 h). Phosphine oxides with electron-donating groups on the phenyl ring consistently delivered high yields and excellent ee values (**3ac–3ag**, **3al–3am**, 94–98% ee). In contrast, strong electron-withdrawing groups reduced the ee dramatically (**3ak**, 39% yield, 31% ee). 3,5-disubstituted and 3,4,5-trisubstituted phenyl phosphine oxides performed remarkably well (**3al** and **3am**, 68–90% yield, 96–97% ee). After that, we further investigated diaryl phosphine oxide with a π -extended conjugated system (**3an**, **3ao**, and **3ap**). The 1-naphthyl phosphine oxide substrate produces **3ao** in 50% yield and 71% ee due to the steric effect, while **3an** and **3ap** could be generated in very high ee values (96%, 96%). To our delight, dialkyl phosphine oxides and phosphonates also excelled under the standard reaction conditions, achieving extremely high ee values (**3aq**, 99% ee, **3ar**, 99% ee). While the reactivity of the substrates other than the diaryl phosphine oxide is low, this aligns with previous findings that the reactivity order toward electrophiles is $\text{Ar}_2\text{P}(\text{O})\text{H} > (\text{RO})_2\text{P}(\text{O})\text{H} > \text{R}_2\text{P}(\text{O})\text{H}$.^{14b,c}

A scale-up reaction using 0.5 mmol of nitron as the starting material under the standard conditions was performed. The isolated yield remained at 80%, but there was a decrease in enantioselectivity to 81% (Scheme 2a). Additionally, the by-product **4aa** was obtained in trace amount with 81% ee. To further elucidate the mechanism and the formation of the by-product **4aa**, we conducted several control experiments (Scheme 2b). Diphenylphosphinic acid was detected in the reaction system from HRMS (Fig. S1†) and ³¹P NMR spectra (Fig. S2†). We hypothesized that product **3aa** underwent reduction to form diphenylphosphinic acid and imine **5**, which subsequently transformed into **4aa**. Therefore, we conducted the reaction using **5** and **2a** as starting materials (Scheme 2b, eqn (1)). Surprisingly, the reaction yielded the product in its racemic form, even with or without the addition of pyridine. This suggests that the oxide anion in the nitron motif is crucial for forming a stronger bond with the zinc atom. Previous reports¹⁸ indicated that product **4aa** can be generated by the reduction of **3aa** via zinc metal present in the catalytic system. However, **3aa** did not react with zinc under the reaction conditions (Scheme 2b, eqn (2)). The significant loss of substrate **2a** in the reaction reminded us the possibility of **2a** as a reducing agent in the catalytic system. We then mixed **3aa** with **2a** under standard conditions (Scheme 2b, eqn (3)). To our delight, **4aa** was produced in 15% yield with 82% ee, with the recovery of **3aa** (20% yield, 78% ee). This suggests that the Zn-ProPhenol catalytic system can activate the product **3aa**, leading to a nucleophilic attack by diphenyl phosphine oxide, which results in N–O bond cleavage and the formation of **4aa** and diphenylphosphinic acid.

Furthermore, nonlinear effects of the catalyst were observed (Scheme 2c), suggesting the aggregation of the zinc complex.¹⁹ Notably, the dimeric assembly **7** was detected by HRMS during the reaction of **1a** and **2a** under standard conditions for 1 hour (Fig. S3,† the reaction solution was diluted in MeOH before HRMS analysis). Another dimeric assembly **8** was also detected by HRMS when diethylzinc, the (*S,S*)-ProPhenol ligand and



Scheme 2 Scale-up reaction and mechanistic study. ^aReaction conditions: unless indicated, **1a** (0.1 mmol), **2a** (0.15 mmol), Et₂Zn (40 mol%), ligand (20 mol%), pyridine (10.0 equiv.), THF (2 mL), under N₂, 3 h. Yields are isolated yields. ee Values are determined by HPLC analysis.

pyridine were mixed in THF (Fig. S4†). Additionally, a Job Plot with UV-vis spectra indicating the complexation²⁰ between zinc and pyridine is presented in Fig. S5.† While the presence of supramolecular species cannot be ruled out, we believed that a dimeric zinc complex **8** is possible to be the active catalyst based on the experimental results and previous reports on dinuclear zinc catalyzed reaction systems.^{14b,c,21}



Conclusions

In summary, we have developed an asymmetric pathway for accessing chiral α -hydroxyaminophosphine oxides using a Lewis acid catalytic system. A wide range of nitrones with various substitutions successfully underwent the reaction, giving the corresponding products in moderate to good yields, and good to excellent ee values. Also, yields of up to 90% and enantioselectivities of up to 99% ee were achieved when employing different types of diaryl phosphine oxides as nucleophiles. The catalytic system also demonstrated compatibility with structurally diverse and complex molecules. Furthermore, the plausible reaction mechanism and the formation of by-product are discussed to understand more about this novel reaction system. Many of the chiral α -hydroxyaminophosphine oxides delivered by this methodology are untouched scaffolds with potential bio-activities, and further studies on their properties are currently underway in our lab.

Data availability

The datasets supporting this article have been uploaded as part of the ESI.†

Author contributions

S. Luo performed the experiments and prepared the ESI.† X. Yuan and Dr Z. Yang repeated some experiments and collected some data. J. Cheng prepared some diaryl phosphine oxides. Prof. J. Wang and Prof. Z. Huang conceived and directed the project. S. Luo and Prof. J. Wang wrote the paper.

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

We gratefully thank the National Natural Science Foundation of China (NSFC 22271241), University Grants Committee (Hong Kong) (YCRF C7001-23Y), and HKBU KRPS grant and RC-SFCRG/23-24 for financial support.

Notes and references

- (a) J. G. Allen, F. R. Atherton, M. J. Hall, C. H. Hassall, S. W. Holmes, R. W. Lambert, L. J. Nisbet and P. S. Ringrose, *Nature*, 1978, **272**, 56; (b) P. Kafarski and B. Lejczak, *Phosphorus, Sulfur Silicon Relat. Elem.*, 1991, **63**, 193; (c) A. B. I. I. Smith, K. M. Yager and C. M. Taylor, *J. Am. Chem. Soc.*, 1995, **117**, 10879; (d) E. Alonso, E. Alonso, A. Solis and C. D. Pozo, *Synlett*, 2000, **5**, 698; (e) J. Grembecka, A. Mucha, T. Cierpicki and P. Kafarski, *J. Med. Chem.*, 2003, **46**, 2641; (f) K. Moonen, I. Laureyn and C. V. Stevens, *Chem. Rev.*, 2004, **104**, 6177; (g) S. J. Conway and G. J. Miller, *Nat. Prod. Rep.*, 2007, **24**, 687.
- (a) M. P. Carroll and P. J. Guiry, *Chem. Soc. Rev.*, 2014, **43**, 819; (b) P. H. S. Paioti, K. A. Abboud and A. Aponick, *ACS Catal.*, 2017, **7**, 2133; (c) S. Mishra, J. Liu and A. Aponick, *J. Am. Chem. Soc.*, 2017, **139**, 3352; (d) X.-Y. Dong, Y.-F. Zhang, C.-L. Ma, Q.-S. Gu, F.-L. Wang, Z.-L. Li, S.-P. Jiang and X.-Y. Liu, *Nat. Chem.*, 2019, **11**, 1158; (e) L. Liu, K.-X. Guo, Y. Tian, C.-J. Yang, Q.-S. Gu, Z.-L. Li, L. Ye and X.-Y. Liu, *Angew. Chem., Int. Ed.*, 2021, **60**, 26710.
- (a) C. De Risi, A. Dondoni, D. Perrone and G. P. Pollini, *Tetrahedron Lett.*, 2001, **42**, 3033; (b) P. Zhao, P. Li, J. Xiao and C. Liu, *Chem. Commun.*, 2023, **59**, 2624.
- S.-I. Murahashi and Y. Imada, *Chem. Rev.*, 2019, **119**, 4684.
- (a) S.-I. Murahashi, Y. Imada, T. Kawakami, K. Harada, Y. Yonemushi and N. Tomita, *J. Am. Chem. Soc.*, 2002, **124**, 2888; (b) V. G. Lisnyak, T. Lynch-Colameta and S. A. Snyder, *Angew. Chem., Int. Ed.*, 2018, **57**, 15162.
- (a) J. F. Hartwig, *Nature*, 2008, **455**, 314; (b) X. Zeng, *Chem. Rev.*, 2013, **113**, 6864; (c) L. Huang, M. Arndt, K. Gooßen, H. Heydt and L. J. Gooßen, *Chem. Rev.*, 2015, **115**, 2596; (d) N. J. Adamson and S. J. Malcolmson, *ACS Catal.*, 2020, **10**, 1060; (e) J. Zhou, Q. Yang, C. S. Lee and J. Wang, *Angew. Chem., Int. Ed.*, 2022, **61**, e20220216.
- (a) M. Shibasaki and M. Kanai, *Chem. Rev.*, 2008, **108**, 2853; (b) X. Fu, W.-T. Loh, Y. Zhang, T. Chen, T. Ma, H. Liu, J. Wang and C.-H. Tan, *Angew. Chem., Int. Ed.*, 2009, **48**, 7387; (c) S. Zhang, Z. Feng, C. Jiang, X. Yu, J. Pan, J. Du, Z. Jiang, Y. Chen and T. Wang, *Chem.-Eur. J.*, 2021, **27**, 11285.
- (a) E. M. Phillips, T. E. Reynolds and K. A. Scheidt, *J. Am. Chem. Soc.*, 2008, **130**, 2416; (b) C.-X. Ye, Y. Y. Melcamu, H.-H. Li, J.-T. Cheng, T.-T. Zhang, Y.-P. Ruan, X. Zheng, X. Lu and P.-Q. Huang, *Nat. Commun.*, 2018, **9**, 410; (c) S. Yin, K. N. Weeks and A. Aponick, *J. Am. Chem. Soc.*, 2024, **146**, 7185.
- (a) P. Merino, E. Marqués-López and R. P. Herrera, *Adv. Synth. Catal.*, 2008, **350**, 1195; (b) S. Nakamura, M. Hayashi, Y. Hiramatsu, N. Shibata, Y. Funahashi and T. Toru, *J. Am. Chem. Soc.*, 2009, **131**, 18240; (c) L. Yin, Y. Bao, N. Kumagai and M. Shibasaki, *J. Am. Chem. Soc.*, 2013, **135**, 10338; (d) K. Yamada, Y. Kondo, A. Kitamura, T. Kadota, H. Morimoto and T. Ohshima, *ACS Catal.*, 2023, **13**, 3158.
- (a) K. Yamakoshi, S. J. Harwood, M. Kanai and M. Shibasaki, *Tetrahedron Lett.*, 1999, **40**, 2565; (b) G. K. Ingle, Y. Liang, M. G. Mormino, G. Li, F. R. Fronczek and J. C. Antilla, *Org. Lett.*, 2011, **13**, 2054; (c) S. Duan, A. Pan, Y. Du, G. Zhu, X. Tian, H. Zhang, P. J. Walsh and X. Yang, *ACS Catal.*, 2023, **13**, 10887.
- (a) Z. Lu, H. Zhang, Z. Yang, N. Ding, L. Meng and J. Wang, *ACS Catal.*, 2019, **9**, 1457; (b) Z. Yang, X. Gu, L.-B. Han and J. Wang, *Chem. Sci.*, 2020, **11**, 7451; (c) Z. Yang and J. Wang, *Angew. Chem., Int. Ed.*, 2021, **60**, 27288; (d) Y. Zhang, Y. Jiang, M. Li, Z. Huang and J. Wang, *Chem Catal.*, 2022, **2**, 3163; (e) B. Cai, Y. Cui, J. Zhou, Y.-B. Wang, L. Yang, B. Tan and J. Wang, *Angew. Chem., Int. Ed.*, 2023, **135**, e202215820; (f) Q. Yang, J. Zhou and J. Wang, *Chem. Sci.*, 2023, **14**, 4413; (g) J. Zhou, L. Meng, S. Lin, B. Cai and J. Wang, *Angew. Chem., Int. Ed.*, 2023, **62**, e202303727; (h)



- X.-D. Gu, K. Y. Ngai, W. Wang, B. Li and J. Wang, *Chem Catal.*, 2024, **4**, 100903; (i) Y. Jiang, K. W. Cheng, Z. Yang and J. Wang, *Chin. Chem. Lett.*, 2024, 110231.
- 12 C. Zhao and D. Seidel, *J. Am. Chem. Soc.*, 2015, **137**, 4650.
- 13 (a) B. M. Trost and H. Ito, *J. Am. Chem. Soc.*, 2000, **122**, 12003; (b) B. M. Trost, H. Ito and E. R. Silcoff, *J. Am. Chem. Soc.*, 2001, **123**, 3367; (c) Y. Xiao, Z. Wang and K. Ding, *Chem.–Eur. J.*, 2005, **11**, 3668; (d) B. M. Trost and M. J. Bartlett, *Acc. Chem. Res.*, 2015, **48**, 688; (e) P. Xu and Z. Huang, *Nat. Chem.*, 2021, **13**, 634; (f) Y. Zheng, S. Zhang, K.-H. Low, W. Zi and Z. Huang, *J. Am. Chem. Soc.*, 2022, **144**, 1951.
- 14 (a) B. M. Trost, S. Malhotra and B. A. Fried, *J. Am. Chem. Soc.*, 2009, **131**, 1674; (b) D. Zhao, L. Mao, Y. Wang, D. Yang, Q. Zhang and R. Wang, *Org. Lett.*, 2010, **12**, 1880; (c) D. Zhao, L. Mao, D. Yang and R. Wang, *J. Org. Chem.*, 2010, **75**, 6756; (d) W. Chen, Y. Hui, X. Zhou, J. Jiang, Y. Cai, X. Liu, L. Lin and X. Feng, *Tetrahedron Lett.*, 2010, **51**, 4175; (e) B. M. Trost and A. Quintard, *Angew. Chem., Int. Ed.*, 2012, **51**, 6704; (f) B. M. Trost, S. Malhotra, P. Koschker and P. Ellerbrock, *J. Am. Chem. Soc.*, 2012, **134**, 2075; (g) B. M. Trost, S. Malhotra and P. Ellerbrock, *Org. Lett.*, 2013, **15**, 440.
- 15 (a) C.-C. Chen, C.-C. Chyau and T.-H. Hseu, *Lett. Appl. Microbiol.*, 2007, **44**, 387; (b) M.-R. Wu, M.-H. Hou, Y.-L. Lin and C.-F. Kuo, *J. Agric. Food Chem.*, 2012, **60**, 7262.
- 16 (a) G. Wald, *Nature*, 1934, **134**, 65; (b) G. Duester, *Cell*, 2008, **134**, 921; (c) A. Tsin, B. Betts-Obregon and J. Grigsby, *J. Biol. Chem.*, 2018, **293**, 13016.
- 17 CCDC 2408217 [for **3da**] contains the ESI crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via https://www.ccdc.cam.ac.uk/data_request/cif.
- 18 (a) P. Merino, A. Lanaspa, F. L. Merchan and T. Tejero, *Tetrahedron:Asymmetry*, 1997, **8**, 2381; (b) S. Pinet, S. U. Pandya, P. Y. Chavant, A. Ayling and Y. Vallee, *Org. Lett.*, 2002, **4**, 1463; (c) D. Dhavale and S. Jachak, *Molecules*, 2005, **10**, 893; (d) V. I. Supranovich, V. V. Levin, M. I. Struchkova and A. D. Dilman, *Org. Lett.*, 2018, **20**, 840.
- 19 P. J. Walsh, and M. C. Kozlowski in *Fundamentals of Asymmetric Catalysis*, University Science Books, Sausalito, 2009, pp. 330–374.
- 20 (a) C. Y. Huang, in *Determination of Binding Stoichiometry by the Continuous Variation Method: The Job Plot*, Methods in enzymology, 1982, pp. 509–525; (b) J. S. Renny, L. L. Tomasevich, E. H. Tallmadge and D. B. Collum, *Angew. Chem., Int. Ed.*, 2013, **52**, 11998.
- 21 N. Shao, Y.-Y. Luo, H.-J. Lu, Y.-Z. Hu and M.-C. Wang, *Tetrahedron*, 2018, **74**, 2130.

