Hydroamination Hot Paper

How to cite: *Angew. Chem. Int. Ed.* **2022,** *61,* e202202160
International Edition: doi.org/10.1002/anie.202202160
German Edition: doi.org/10.1002/ange.202202160

Enantio- and Regioselective Construction of 1,4-Diamines via Cascade Hydroamination of Methylene Cyclopropanes

Jian Zhou, Qingjing Yang, Chi Sing Lee, and Jun (Joelle) Wang**

Abstract: Despite the widespread existence of chiral 1,4-diamines in bioactive molecules and their applications in asymmetric catalysis, the catalytic and asymmetric synthesis of such structures from readily accessible substrates remains a long-standing challenge. Here, we report a Cu-catalyzed asymmetric cascade hydroamination protocol to construct a wide range of chiral 1,4-diamine derivatives in high yields with excellent enatioselectivities (up to 95 % yield and up to >99 % ee). The use of two hydroxylamine esters containing different functionalized amino groups allowed us to increase the complexity of the final 1,4-diamine structures. The desired products could be easily transformed into chiral 1,4-diamines and chiral NH_2-Terfenadine. Mechanistic study demonstrates that this reaction proceeds through hydroamination ring-opening and cascade hydroamination sequence.

Chiral 1,4-diamines are an important structural scaffold widespread in bioactive compounds, natural products and pharmaceuticals (Figure 1).[1] For example, Lopinavir have received significant attention recently as recommended treatment for COVID-19.[1a] DuPont Merck molecule DMP 323 is deemed as peptidomimetic HIV protease inhibitors.[1b] Sinefungin is recognized to act as an efficient competitive inhibitor of multiple SAM-dependent methyltransferases.[1c] Also, they are served as a type of vital organic feedstock and chiral auxiliaries with transition metals in the field of asymmetric synthesis.[2] Yet, compared with related class of 1,2-diamines[3] and 1,3-diamines,[4] the construction of chiral 1,4-diamines is still underdeveloped. To date, there are very limited methodologies accessing optically active 1,4-diamines. In 2015, Hull and co-workers reported the Rh-catalyzed anti-Markovnikov hydroamination of terminal alkenes and synthesized various achiral 1,4-diamines derivatives with 1.4/1–>20/1 ratio of anti-Markovnikov to Markovnikov addition manners (Scheme 1a).[6] Subsequently, Zhu developed Cu-catalyzed three-component reaction of alkenes with acetonitrile and sodium azide giving a series of γ-azido alkyl nitriles, which could be hydrogenated and deliver achiral 1,4-diamine (Scheme 1a).[7] In 2014, Buchwald disclosed asymmetric hydroamination of well-designed N-containing vinylsilane and produced a chiral 1,4-diamine (Scheme 1b).[8] Nevertheless, the concise, direct, efficient and highly stereoselective approach of chiral 1,4-diamines still remains a great challenge.

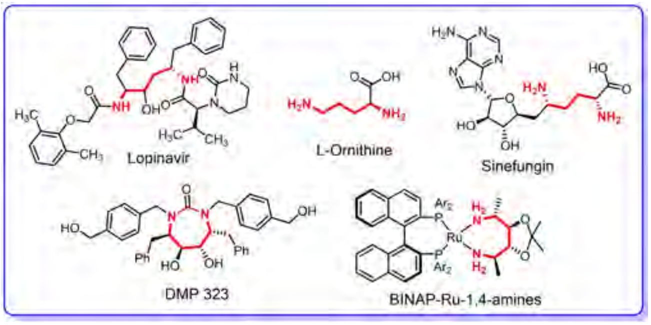
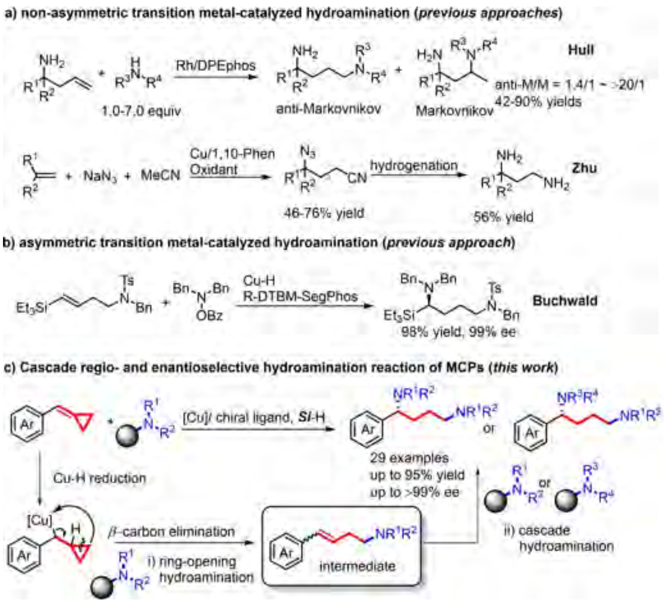


Figure 1. Representative examples of 1,4-diamines containing pharmaceuticals, natural products and ligands.



Scheme 1. Transition-metal catalyzed hydroamination for accessing 1,4-diamines.

---

[*] J. Zhou, Prof. C. S. Lee, Prof. J. Wang
Department of Chemistry, Hong Kong Baptist University
Kowloon, Hong Kong (China)
E-mail: cslee-chem@hkbu.edu.hk
junwang@hkbu.edu.hk

J. Zhou, Dr. Q. Yang
Department of Chemistry,
Southern University of Science and Technology
Shenzhen, Guangdong, 518055 (China)

GDCh Research Articles Angewandte Chemie International Edition www.angewandte.org

How to cite: *Angew. Chem. Int. Ed.* **2023,** *62,* e202303727
doi.org/10.1002/anie.202303727

Homogeneous Catalysis

Palladium-Catalyzed Enantio- and Regioselective Ring-Opening Hydrophosphinylation of Methylenecyclopropanes

*Jian Zhou⁺, Ling Meng⁺, Shujuan Lin, Baohua Cai, and Jun (Joelle) Wang**

Dedicated to Professor Weisheng Tian on the occasion of his 70th birthday

Abstract: Transition metal-catalyzed hydrofunctionalization of methylenecyclopropanes (MCPs) has presented a considerable challenge due to the difficult manipulation of regioselectivity and complicated reaction patterns. Herein, we report a straightforward Pd-catalyzed ring-opening hydrophosphinylation reaction of MCPs via highly selective C–C bond cleavage. This method allows for rapid and efficient access to a wide range of chiral allylic phosphine oxides in good yields and high enantioselectivities. Additionally, density functional theory (DFT) calculations were performed to elucidate the reaction mechanism and the origin of enantioselectivity.

Introduction

The rapid increase in the number of applications of chiral organophosphorus compounds in the synthesis of pharmaceuticals[1] and functionalized materials,[2] as well as their use as asymmetric ligands[3] have motivated chemists to develop new and efficient synthetic methodologies, particularly for asymmetric synthesis.[4] Transition metal-catalyzed enantioselective addition of phosphorus nucleophiles (such as phosphines and phosphine oxides) across unsaturated chemical bonds constitutes a highly efficient and atom-economic strategy for the construction of chiral P-containing molecules. Recently, several elegant examples of asymmetric hydrophosphination and hydrophosphinylation of alkenes were disclosed using Pd,[5] Cu,[6] Ni,[7] Mn,[8] and Co.[9] Dong and Yin reported the enantioselective hydrophosphinylation of dienes.[10] Furthermore, the asymmetric addition across diverse alkynes with phosphine and phosphine oxide was shown to be viable with Pd or Ni catalysts.[11] Recently, our group extended Pd-catalyzed hydrophosphinylation to allenes.[12] Notable complementary examples of asymmetric hydrophosphinylation and hydrophosphination of alkenes and alkynes were also realized by organocatalysis.[13] Despite this progress, the development of efficient and modular hydrophosphinylation methods for delivering new structural motifs is still highly desirable.

Carbon–carbon σ-bond cleavage facilitated by a transition metal catalyst towards the reconstruction of new chemical bonds still remains a formidable challenge in organic synthesis.[14] Methylenecyclopropanes (MCPs), a family of strained small carbocycles, are generally deemed to be a versatile and readily accessible synthon in organic synthesis.[15] The inherent high ring strain (40 kcal mol^{-1}) offers possibilities for MCPs to proceed in diverse addition reactions and ring-opening/expansion reactions triggered by transition metals, Lewis acids, Brønsted acids and radical species.[16] Among them, transition metals exhibit high catalytic efficiency and realize switchable reaction patterns of MCPs (Scheme 1a). For instance, a transition metal can insert into the proximal C2–C3 single bond or distal C3–C4 single bond to generate versatile metallacyclobutane species, which may undergo a variety of subsequent synthetic transformations.[17] When addition to the *exo* carbon–carbon double bond occurs, it is followed by a redox-neutral β-C elimination and provides the corresponding ring-opening products with concomitant formation of a π-bond.[18] Alternatively, the adducts could be potentially trapped by other reagents as well, delivering cyclopropane-containing molecules.[19]

There have been a number of examples reported showing the potential value of this methodology. However, only limited pronucleophiles (such as –N, –O, –B and –C) were found to be applicable and most functionalized products were generated in racemic form.[17d,20] Indeed, only a few examples of the asymmetric hydrofunctionalization of MCPs have been reported (Scheme 1b). Fang realized asymmetric hydrocyanation of MCPs for generating various chiral allylic nitriles.[17k] The Rh-catalyzed asymmetric hydroformylation of the double bond of MCPs was described by Zhang, delivering primarily chiral cyclopropyl aldehydes associated with a minimal amount of ring-opening products.[19c] Recently, we developed the Cu-catalyzed cascade hydroamination of MCPs to furnish chiral 1,4-

---

[*] J. Zhou,⁺ Dr. L. Meng,⁺ Prof. J. J. Wang
Department of Chemistry, Hong Kong Baptist University
Kowloon, Hong Kong (China)
E-mail: junwang@hkbu.edu.hk

J. Zhou,⁺ B. Cai
Department of Chemistry
Southern University of Science and Technology
Shenzhen, Guangdong, 518055 (China)

Dr. S. Lin
State Key Laboratory of Structural Chemistry, Fujian Institute of Research on the Structure of Matter, Chinese Academy of Sciences
Fuzhou, Fujian 350002 (China)

[+] These authors contributed equally to this work.

Enantio- and Regioselective Cascade Hydroboration of Methylenecyclopropanes for Facile Access to Chiral 1,3- and 1,4-Bis(boronates)

*Jian Zhou, Ling Meng, Ziyi Yang, and Jun (Joelle) Wang**

Chiral 1, n-bis(boronate) plays a crucial role in organic synthesis and medicinal chemistry. However, their catalytic and asymmetric synthesis has long posed a challenge in terms of operability and accessibility from readily available substrates. The recent discovery of the C═C bond formation through β-C elimination of methylenecyclopropanes (MCP) has provided an exciting opportunity to enhance molecular complexity. In this study, the catalyzed asymmetric cascade hydroboration of MCP is developed. By employing different ligands, various homoallylic boronate intermediate are obtained through the hydroboration ring opening process. Subsequently, the cascade hydroboration with HBpin or B_2pin_2 resulted in the synthesis of enantioenriched chiral 1,3- and 1,4-bis(boronates) in high yields, accompanied by excellent chemo- and enantioselectivities. The selective transformation of these two distinct C—B bonds also demonstrated their application potential in organic synthesis.

1. Introduction

Chiral 1,n- bis(boronate) compounds, known for their potential in the asymmetric construction of complex structures through selective and multiple conversions of two C-B bonds,[1] are recognized as highly versatile and valuable synthetic modules in chemical biology, material science and organic synthesis.[2] To date, transition metal-catalyzed hydroboration, diboration, hydrogenation and cross-coupling reactions have been developed for the synthesis of chiral geminal[3] and vicinal diboronates.[4] However, the efficient and straightforward approaches for preparation of chiral 1,3- and 1,4-bis(boronate) compounds are very limited, and only a few advancements have been made (**Scheme** 1A). Based on lithiation-borylation methodology,[5] Aggarwal and co-workers realized sparteine-ligated lithiated carbamate-promoted asymmetric homologation of optically pure 1,2-bis(boronic esters) and double homologation of diborylmethane to generate chiral 1,3-bis(boronic esters).[6] Besides, dienes were applied into the synthesis of such structures.[7] Morken and co-workers developed an enantioconvergent 1,4-diboration of diene catalyzed by Pt/TADDOL or OxaPhos.[7a-c] Other alternative methods include asymmetric hydroboration/boration of designed unsaturated substrates that require prior attachment of borane groups.[8] Indeed, there is still a strong desire for the development of a practical method that is capable of constructing 1,3- or 1,4-diboronates from readily accessible starting materials, providing a more efficient and accessible route to these valuable chiral compounds in an enantio- and regioselective manner.

Methylenecyclopropanes (MCPs), a type of highly versatile reagent commonly used in organic synthesis, can undergo various switchable reaction patterns through C—C bond cleavage facilitated by transition metals (Scheme 1B).[9] For example, the insertion of transition metals into proximal C2—C3 single bond or the distal C3—C4 single bond results in the formation of characteristic metallacyclobutane species.[10] While the addition of transition metal complexes to the exo C═C bond happened, the redox-neutral β-C elimination occurs, leading to the generation of various ring-opening structures and the formation of new C═C bond.[11] The newly formed double bond in MCPs has the potential for further transformation, especially in asymmetric version. Nevertheless, the merger of ring-opening process and the cascade enantioselective hydrofunctionalization of MCPs, which could lead to the synthesis of complex chiral molecules with high enantioselectivity is very rare. Recently, we reported the Cu/DTBM-SegPhos-catalyzed cascade hydroamination reaction of MCPs and chiral 1,4-diamines were obtained with high efficiency.[12]

On the other hand, copper-catalyzed asymmetric hydroboration of unsaturated bonds has emerged as a powerful tool for the construction of chiral organoborons, due to the mild reaction conditions, high efficiency, and the advantage of using low-cost of Cu catalysts.[13] In 2019, Engle and co-workers reported a copper-catalyzed hydroboration of benzylidenecyclopropanes with B_2pin_2, affording access to cyclopropylboronic

---

J. Zhou, L. Meng, Z. Yang, J. (Joelle) Wang
Department of Chemistry
Hong Kong Baptist University
Kowloon, Hong Kong, China
E-mail: junwang@hkbu.edu.hk

The ORCID identification number(s) for the author(s) of this article can be found under https://doi.org/10.1002/advs.202400096

DOI: 10.1002/advs.202400096

How to cite: *Angew. Chem. Int. Ed.* **2023**, *62*, e202215820
International Edition: doi.org/10.1002/anie.202215820
German Edition: doi.org/10.1002/ange.202215820

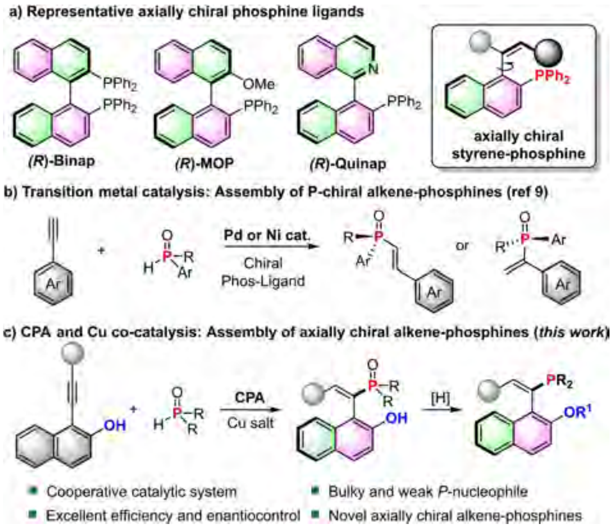
Asymmetric Catalysis *Hot Paper*

Asymmetric Hydrophosphinylation of Alkynes: Facile Access to Axially Chiral Styrene-Phosphines

Baohua Cai[+], Yuan Cui[+], Jian Zhou, Yong-Bin Wang, Limin Yang, Bin Tan,* and Jun (Joelle) Wang**

Dedicated to Professor Rick W. K. Wong on the occasion of his 70th birthday

Abstract: A Cu/CPA co-catalytic system has been developed for achieving the direct hydrophosphinylation of alkynes with phosphine oxides in delivering novel axially chiral phosphorus-containing alkenes in high yields and excellent enantioselectivities (up to 99 % yield and 99 % ee). DFT calculations were performed to elucidate the reaction pathway and the origin of enantiocontrol. This streamlined and modular methodology establishes a new platform for the design and application of new axially chiral styrene-phosphine ligands.



Scheme 1. Axially chiral phosphine ligands and hydrophosphinylation of alkynes.

Introduction

P-Containing chiral compounds have numerous applications in material, agricultural and medicinal chemistry,[1] especially in transition metal-catalyzed and organocatalytic transformations for their special electronic structure and molecular geometries.[2] Among the tremendous chiral phosphine ligands developed in the past, the axially chiral phosphine ligands still occupy a distinguished position in asymmetric catalysis as one of the most powerful and frequently employed ligand class, including (*R*)- BINAP,[3] (*R*)-MOP[4] and (*R*)-QUINAP[5] (Scheme 1a). Aside from allowing predictable spatial orientation of functionalities, the rigid chiral backbone of axially chiral compounds could enhance stereochemical differentiation in regio-controlling.

To cover the constant demand, more efficient methods to obtain these phosphine compounds in optically pure form and parallel development of new ligand frameworks become imperative. Intrigued by the recent emergence of axially chiral alkenes for which the chiral axis is defined across the alkene-arene bond,[6] we are interested to design novel axially chiral styrene-phosphine frameworks.

In contemplating a suitable synthetic scheme for this class of new compound, the synthesis of axially chiral biaryl phosphine compounds proved particularly instructive.[7] Specifically, concurrent installation of phosphorus functionality and revelation of axial chirality was deemed the most straightforward. In this respect, the addition of phosphines or phosphine oxides to alkynes to forge alkenyl phosphine compounds constitutes a most atom-efficient option. Recently, a series of elegant examples for construction of chiral phosphorus compounds emerged via asymmetric catalytic addition of phosphorus nucleophiles to unsaturated carbon bonds, including alkene,[8] alkyne,[9] diene[10] and allene.[11] Yet, existing hydrophosphinylation procedures involving Pd or Ni catalysis yielded only *P*-stereogenicity (Scheme 1b).[9] To implement a distinct reactivity mode in constructing vinyl phosphines adorned with a different chirality element, we considered translating this reaction to the organocatalytic

---

[*] B. Cai,[+] Y. Cui,[+] Dr. Y.-B. Wang, Prof. Dr. B. Tan, Prof. Dr. J. Wang
Shenzhen Grubbs Institute, Department of Chemistry and Guangdong Provincial Key Laboratory of Catalysis, Southern University of Science and Technology
Shenzhen 518055 (China)
E-mail: tanb@sustech.edu.cn
junwang@hkbu.edu.hk

J. Zhou, Prof. Dr. J. Wang
Department of Chemistry, Hong Kong Baptist University
Hong Kong (China)

Prof. Dr. L. Yang
College of Materials, Chemistry and Chemical Engineering, Hangzhou Normal University
Hangzhou 311121 (China)
E-mail: myang@hznu.edu.cn

[+] These authors contributed equally to this work.

Chemical Science

EDGE ARTICLE

View Article Online
View Journal | View Issue

Check for updates

Cite this: *Chem. Sci.*, 2023, **14**, 4413

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

Received 19th December 2022
Accepted 20th March 2023

DOI: 10.1039/d2sc06950d

rsc.li/chemical-science

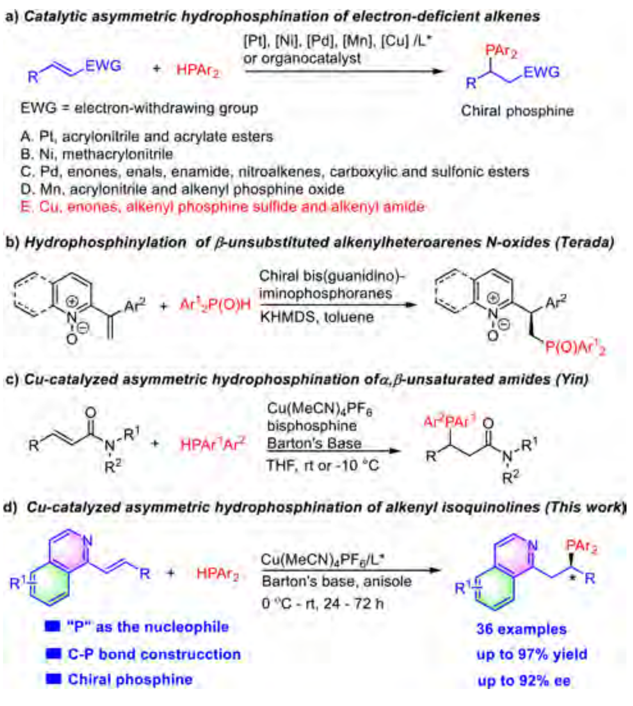
Enantioselective copper-catalyzed hydrophosphination of alkenyl isoquinolines†‡

Qingjing Yang,[a] Jian Zhou[ab] and Jun (Joelle) Wang *[b]

An enantioselective hydrophosphination of alkenyl isoquinolines is developed by using a copper-chiral diphosphine ligand catalyst. It provides a direct and atom-efficient approach to prepare a variety of chiral phosphines with an isoquinoline unit in good yields and high enantioselectivities. In addition, these chiral phosphine products are useful bidentate P,N-ligands which showed potential application in asymmetric catalysis.

Chiral organophosphorus compounds play a significant role in bioactive molecules, agrochemistry, and functional materials.[1] In addition, they are also broadly applied in transition metal catalysis and organocatalysis as chiral ligands and chiral catalysts.[2] Compared with conventional methods using a stoichiometric amount of chiral starting materials or chiral reagents,[3] asymmetric catalytic approaches have attracted increasing attention in the construction of chiral phosphines. Among them, catalytic asymmetric hydrophosphination is one of the most direct and atom-economical ways for preparation of optically active phosphines.

Pd-Catalyzed asymmetric hydrophosphination of α,β-unsaturated compounds (including α,β-unsaturated aldehydes, ketones, esters, pyrrole amides, sulfonic esters, and sulfonamides) with secondary phosphines has emerged as a versatile method for the construction of chiral phosphine compounds (Scheme 1a).[4] Other transition metal complexes such as chiral Ni,[5] Pt,[6] Cu[7] and Mn[8] catalysts and organocatalysts[9] were also applied in the asymmetric hydrophosphination of electron-deficient alkenes, recently. However, examples where heteroarenes were employed in alkene activation have not appeared due to the relatively poor reactivity of alkenylheteroarenes. In 2021, Terada reported hydrophosphinylation of β-unsubstituted alkenylheteroarene *N*-oxides with SPO (secondary phosphine oxide) catalyzed by their chiral bis(guanidino)iminophosphorane organosuperbase (Scheme 1b).[10] The subsequent reduction of the phosphine oxide product could give quinoline phosphine. Inspired by Yin's recent elegant work on the Cu/TANIAPhos-catalyzed enantioselective hydrophosphination of α,β-unsaturated amides in which the olefin moiety is sluggishly activated by the adjacent carboxamide group (Scheme 1c),[7a] we envisioned that the long-time unsolved asymmetric hydrophosphination of intrinsic low electrophilic alkenyl-heteroarenes might be realized with a suitable Cu/chiral phosphine catalyst because of its relative stability in the presence of excess $HPPh_2$. Furthermore, the chiral tertiary phosphine products bearing a N-heteroaromatic ring themselves are potentially useful chiral bidentate P,N-ligands in asymmetric catalysis.



Scheme 1 Examples of asymmetric hydrophosphination of electron-deficient alkenes and asymmetric hydrophosphination to alkenyl azaarenes.

---

[a] Department of Chemistry, Southern University of Science and Technology (SUSTech), Shenzhen, 518055, China

[b] Department of Chemistry, Hong Kong Baptist University, Kowloon, Hong Kong, China. E-mail: junwang@hkbu.edu.hk

† Dedicated to Professor Guo-Qiang Lin on the occasion of his 80th birthday.

‡ Electronic supplementary information (ESI) available. CCDC 2201645. For ESI and crystallographic data in CIF or other electronic format see DOI: https://doi.org/10.1039/d2sc06950d