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Review

Stereoselective Synthesis of Axially Chiral Allenes and Styrenes via Chiral Phosphoric Acid Catalysis: An Overview

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Cite This: *ACS Omega* 2024, 9, 33351−33364

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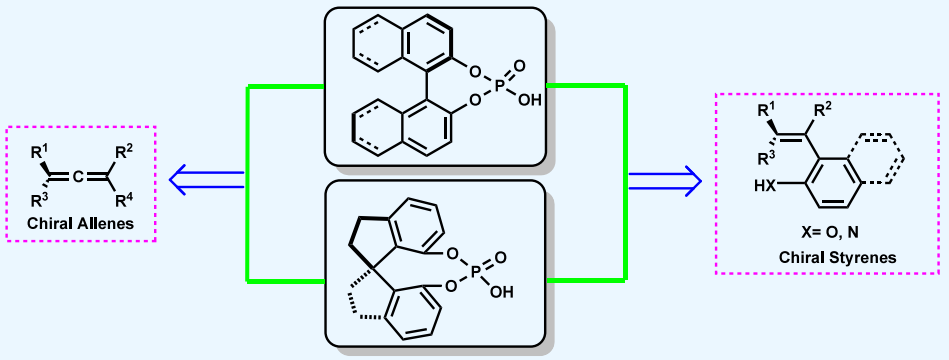


ABSTRACT: Chiral allenes and styrenes are essential components in fields like medicinal chemistry, materials science, and organic synthesis. They serve a crucial role as chiral ligands and catalysts in asymmetric synthesis. Over the past decade, there has been a significant advancement in the development of practical methods utilizing organocatalytic strategies for the synthesis of chiral allenes and styrenes. It is noteworthy that despite extensive studies on the formation of allenes and styrenes, existing reviews on their construction confined to a specific organocatalysis, called chiral phosphoric acid catalysis, are less documented. This review aims to explore different conceptual approaches based on the electrophilic species involved in the reaction to produce stereoselective chiral allenes and styrenes, providing insights into recent advancements in the field. Emphasis is placed on works published since 2017, with detailed discussions on reaction mechanisms and examples from recent literature.

1. INTRODUCTION

Biomolecules that exhibit chirality in their natural state are enantiomerically enriched, and different enantiomers have different biological functions. Therefore, there is still a great interest in the development of new enantioselective methods for chiral compounds. Allenes (1,2-propadiene derivatives) are an important class of compounds and have gained increasing attention as interesting building blocks in synthetic organic chemistry. They have two cumulative carbon−carbon double bonds, and their characteristic reactivity and unique steric properties originate from propadienyl structures.[1−3] They first appeared in the chemical literature over 140 years ago when van't Hoff predicted their existence in a now historic publication in 1875.[4,5]

Allenes are a special group of chemicals that can display axial chirality. They have been studied for their biological effects for more than 40 years and are present in more than 2,900 natural metabolites and synthetic molecules.[6,7] The incorporation of allenes to steroid, prostaglandin, carbacyclin, artificial amino acid, and nucleoside compounds has been shown to increase their metabolic stability, bioavailability, and efficacy.[8,9] Due to the unique structural properties and versatile reactivity of allenes, they have found significant applications not only in medicinal chemistry and materials science but also as important intermediates in synthetic transformations and as backbones of chiral ligands in asymmetric catalysis.[10−12] Allenes with axial chirality are present in many natural products with biological activity, such as neoxanthin, grasshopper ketone, allenic carbacyclin, okamurallene, the fungal metabolite A82775C and others. In addition, the chiral allene structural motifs are also found in catalysts, ligands and chiroptical materials (Figure 1).[13−15]

In the past three decades, a variety of sophisticated asymmetric catalytic strategies have been developed for chiral

Received: May 2, 2024
Revised: July 2, 2024
Accepted: July 15, 2024
Published: July 26, 2024

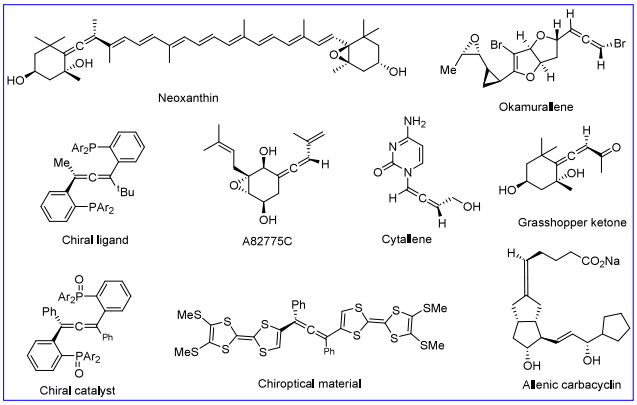


Figure 1. Representative examples of useful chiral allenes with different functions.

allene synthesis due to their wide range of applications. These strategies include nucleophilic additions of 1,3-enynes,[16−19] dynamic kinetic asymmetric transformations (DyKAT) of racemic allenes,[20,21] rearrangement of alkynes,[22] coupling of alkynes with diazo compounds,[23] Pd-catalyzed asymmetric β-hydride elimination from enol triflates,[24] asymmetric amination and imidation of 2,3-allenylphosphates with nitrogen nucleophiles,[25] addition of allenic esters to N-acylimines,[26] coupling reactions between propargylic phosphates and aryl- or alkenylboronates,[27] among others.[21,23,28−37] Significant progress has also been made in the organocatalytic asymmetric synthesis of allenes, although this remains a challenging task. Despite the demand for chiral allenes, there are few enantioselective methods for their synthesis.[24] Recently, however, some work has been published on organocatalysis, and in particular chiral phosphoric acid-catalyzed, asymmetric synthesis of chiral allenes.

Compounds with axial chirality, characterized by fascinating atropisomerism, have been crucial in the process of asymmetric synthesis. The confined rotation of single bond due to ring strain, steric hindrance of associated groups or other structural considerations are the primary cause of atropisomerism. It is a significant strategy by which chiral compounds lacking stereogenic centers can exhibit their three-dimensional nature. Biaryls are frequently encountered in bioactive compounds, medications, and materials research as representative atropisomers.[38−40] An influential scaffold that has been extensively researched is atropisomeric biaryls, that have multiple uses in asymmetric synthesis and rigid chiral axis. On the contrary, there has been very little research on the asymmetric production and uses of axially chiral styrenes, which have a chiral axis between the aromatic ring and ordinary alkene.[41,42] Despite the fact that Kawabata et al.[43] initially proposed this kind of atropisomer in 1991 to illustrate an innovative idea of the retention of chirality, further studies on the formation or use of axially chiral styrenes have not received significant attention.[44−46] It is significantly more difficult for styrene derivatives to prohibit the unrestricted rotation along the axis joining the vinyl and aryl groups, and additional sterically impeded substituents are required. It is evident that the low stiffness of the axis would result in low rotation barrier in styrenes as compared to biaryls.[47−49]

Motivated by elegant findings regarding the construction of axially chiral derivatives of styrene, Gu et al.,[50−52] Xu et al.[53] and Shi et al.[54,55] reported palladium catalyzed enantioselective synthesis of axially chiral styrene derivatives. This advancement serves as a model for the atroposelective catalytic synthesis of derivatives of the axially chiral styrene. As one of the most prevalent and important feedstocks, simple styrenes are well-known to make great potential constituents for chemical synthesis. Only a limited number of reports have been published regarding the organocatalytic asymmetric synthesis of styrenes.[56−59]

It is noteworthy that the chiral phosphoric acid catalysis approach, a relatively new subfield for catalytic asymmetric organic synthesis, has also contributed greatly to this area of research since the pioneering studies of the groups of Akiyama and Terada in 2004.[60,61] CPAs, bifunctional Brønsted acid/base catalysts derived from BINOL, H8-BINOL and 1,1′-spirobiindane-7,7′-diol (SPINOL) backbones[62,63] are the most commonly used catalysts that can achieve perfect asymmetric induction by transferring the chiral information from the catalyst to the products either via double hydrogen bonds or synergetic hydrogen bonds (the P═O bond is considered the basic moiety, and the P−OH hydrogen is considered the acidic moiety) and ion-pair interactions.[64] Therefore, some of the recent important developments in chiral phosphoric acid-catalyzed asymmetric synthesis of chiral allenes and styrenes are highlighted in this review. The asymmetric catalysis achieved is categorized according to the types of electrophiles involved in the reactions.

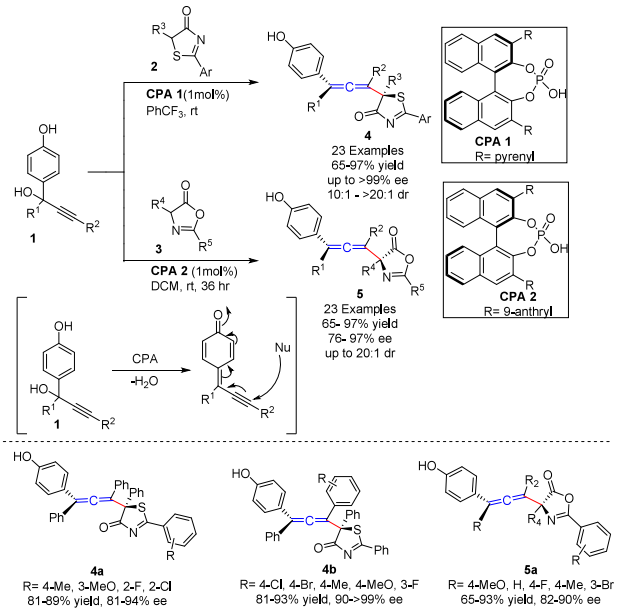
2. CPA CATALYZED SYNTHESIS OF CHIRAL ALLENES

2.1. Propargylic *p*-Quinone Methides as Electrophiles. In 2019, Li and co-workers published a study on the use of chiral phosphoric acid for facilitating direct diastereo- and enantioselective 1,8-conjugate additions of thiazolones **2** and azlactones **3** to para-quinone methides formed in situ from propargylic alcohols (**1**).[65] With the presence of CPA, they were able to successfully create vicinal axially chiral tetrasubstituted allenes and heteroatom-functionalized quaternary carbon stereocenters with high efficiency (up to 94% yield) and excellent stereoselectivity (up to >99% ee, > 20:1 dr) as depicted in Scheme 1. Various propargylic alcohols containing electronically diverse substituents at different positions on the aromatic ring were found to be compatible with this asymmetric 1,8-conjugate addition process. In terms of mechanism, under the influence of chiral phosphoric acid, the propargylic alcohol **1** underwent a conversion process to form para-quinone methide (*p*-QM) through the elimination of water. Subsequently, nucleophiles like thiazolones and azlactones engaged in a 1,8-conjugate addition reaction with the para-quinone methide, leading to the formation of the corresponding products.

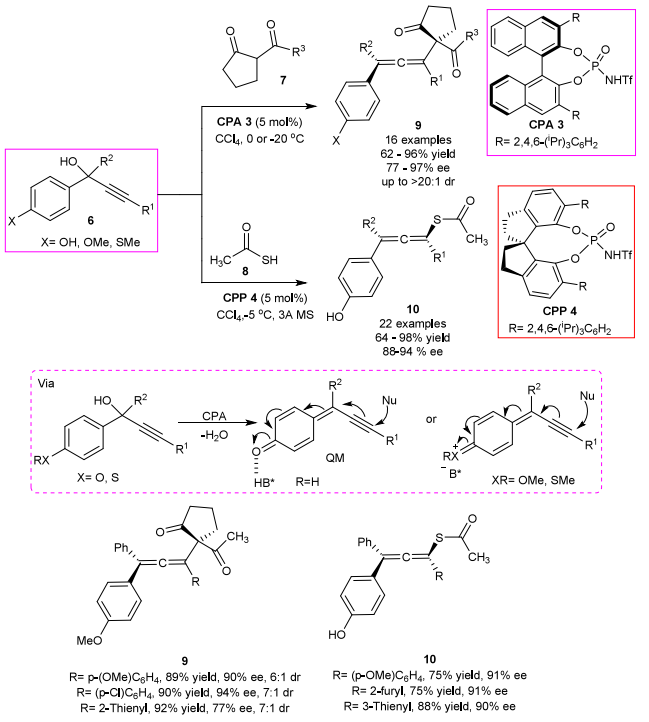
In addition, Sun and co-workers reported in 2017 the asymmetric synthesis of chiral tetrasubstituted allenes from the para-quinone methide intermediate (QM) prepared *in situ* from racemic propargyl alcohols **6** with cyclic and acyclic 1,3-diketones **7** and thioacetic acid derivatives **8** using chiral phosphoric acid.[66] High yields (62−98%) and enantioselectivity (77−97% ee) were observed for a series of tetrasubstituted allenes with intermolecular C−C **9** and C−S bond formation **10** (Scheme 2). In addition to axial chirality, the authors demonstrated an adjacent quaternary stereocenter. A wide range of racemic propargyl alcohols with electron-rich, electron-neutral, and electron-poor aryl substituents were well tolerated. The presence or absence of a free hydroxy group influences the formation of key intermediates, with a cation

https://doi.org/10.1021/acsomega.4c04206
ACS Omega 2024, 9, 33351−33364

Scheme 1. Enantioselective Remote 1,8-Conjugate Additions of Thiazolones and Azlactones to Propargyl Alcohols



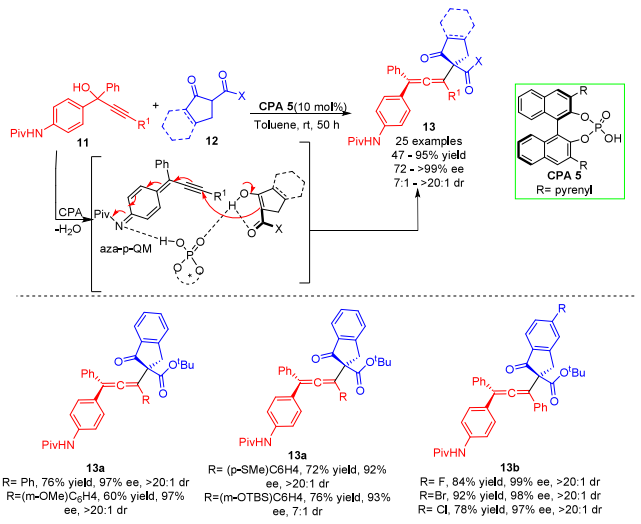
Scheme 2. Synthesis of Chiral Tetrasubstituted Allenes from the Para-Quinone Methide Intermediate



bearing a chiral counteranion being crucial in the absence of a free hydroxy group. In the presence of a free hydroxy group, the initially formed cation could lead to proton loss, forming a neutral para-quinone methide intermediate (QM). This information highlights the importance of understanding the role of different functional groups and counterions in directing the reaction pathway. Based on initial DFT calculations, control experiments, and kinetic studies, it has been determined that the chiral catalyst serves a dual function in activating both reactants and enabling remote stereocontrol in the reaction.

2.2. Propargylic Aza-*p*-quinone Methides as Electrophiles. Unlike well-studied unique electrophiles such as quinone methides (QMs) and aza-ortho QMs, aza-para QMs have received less attention when it comes to asymmetric transformations. In this regard, in 2019, Sun and his team published a study detailing the successful chiral phosphoric acid-catalyzed enantioconvergent asymmetric 1,8-addition of aza-para-quinone methides (**11**) with 1,3-dicarbonyl nucleophiles (**12**).[67] This process proved to be highly efficient. By utilizing the **CPA 5** catalyst, a variety of racemic aniline-containing propargylic tertiary alcohols underwent reactions to form the aza-para-quinone methide intermediate *in situ*. Subsequently, these intermediates underwent 1,8-addition with different 1,3-dicarbonyl nucleophiles, resulting in the formation of a range of chiral tetrasubstituted allenes (**13**) with an adjacent quaternary stereocenter. The overall process demonstrated good to excellent efficiency, with yields reaching up to 95%, and high stereoselectivity, achieving over 99% enantiomeric excess and greater than 20:1 diastereomeric ratio. This showcased significant remote stereocontrol, as illustrated in Scheme 3. Other nucleophilic species such as *β*-ketoamide,

Scheme 3. Enantioselective Synthesis of Allenes from Aza-Para-QMs and 1,3-Dicarbonyl Nucleophiles



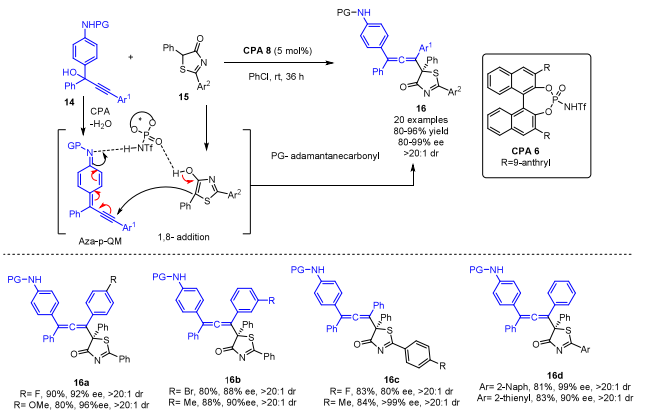
1,3-diketones, and acetylacetones could be used as excellent nucleophiles. Racemic propargyl alcohols with various functional groups such as ether, thioether, nitrile, aldehyde, and TBS -protected alcohol were well tolerated. The chiral phosphoric acid acts as a bifunctional catalyst in the activation of both reactants. The authors have also shown that the aza-para-QM can react through the "*E*" isomer to produce a favored transition state by allowing hydrogen bonding with nitrogen on the same side of the triple bond, thus reducing the distance between the reactive nucleophilic and electrophilic sites.

Pengfei Li, Wenjun Li and co-workers developed a remote stereocontrolled 1,8-conjugate addition of thiazolones (**15**) to propargylic aza-*p*-quinone methides formed from propargylic alcohols (**14**) in the presence of chiral phosphoramide catalyst.[68] Using **CPA 6** as an optimal catalyst, a wide range of thiazolones and propargylic alcohols were involved in this

https://doi.org/10.1021/acsomega.4c04206
ACS Omega 2024, 9, 33351−33364

1,8-conjugate addition to afford vicinal axially chiral tetrasubstituted allenes and sulfur-containing quaternary carbon stereocenters (**16**) in high yield and stereoselectivity (Scheme 4). The authors evaluated different protecting groups on

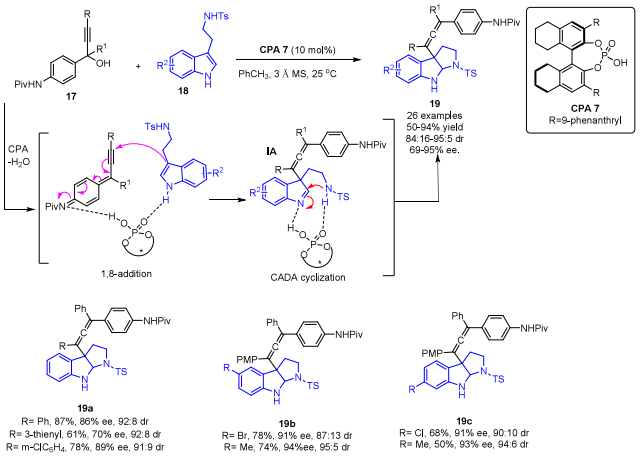
Scheme 4. CPA Catalyzed Remote Stereocontrolled 1,8-Conjugate Addition of Thiazolones to Propargylic Aza-*p*-Quinone Methides



nitrogen of propargylic alcohol substrates and found that the bulky adamantanecarbonyl group proved to be superior for furnishing the 1,8-adduct as compared to *N*-[4-(1-hydroxy-1,3-diphenylprop-2-ynyl)phenyl]-pivalamide and Ts-protected propargylic alcohol. Generally, propargylic alcohols and thiazolones with different aromatics bearing various electron-withdrawing (F, Cl, and Br) and electron-donating (Me and MeO) were well tolerated. It should be noted that both the electronic nature and the position of the substituents on the aromatic ring of propargylic alcohols affected the yield and asymmetric induction slightly. Mechanistically, mediated by chiral phosphoramide catalyst, aza-*p*-QM intermediate was generated from propargylic alcohol **14** and 2,5- diphenylthiazol-4(5*H*)-one **15** was isomerized to 2,5-diphenylthiazol-4-ol. Both aza-*p*-QM intermediate and 2,5- diphenylthiazol-4-ol were synergistically activated by **CPA- 6** via a bifunctional activation mode. Then, intramolecular conjugate addition generated 1,8-adduct **16**.

In 2022, Zhang, Tan, Shi, and their co-workers presented a method for the enantio- and diastereoselective synthesis of hexahydropyrrolo[2,3-*b*]indole-containing tetrasubstituted allenes (**19**) with axial and central chirality. This was achieved through a cascade 1,8-addition/dearomatization-cyclization reaction.[68] By utilizing chiral phosphoric acid as a catalyst, para-aminophenyl propargylic alcohols (**17**) underwent dehydration to form alkynyl (aza)-*p*-QMs intermediates. Tryptamines (**18**) then acted as nucleophiles, attacking the alkynyl (aza)-p-QMs to produce tetrasubstituted allenes with multiple chiral elements (**19**) in good yields (50−94%) and high diastereo- and enantioselectivities (84:16−95:5 dr, 69−95% ee) as depicted in Scheme 5. The researchers explored various N-protective groups (PG) for propargyl alcohols, including pivaloyl, *t*-butoxycarbonyl, iso-butyryl, N-tosyl groups, and the bulky adamantanecarbonyl group, ultimately determining the pivaloyl group as the optimal choice under the specified reaction conditions. Control experiments revealed that, the NH of tryptamines is very important for the success of the reaction. In addition, the cytotoxicity test of some of these compounds was evaluated and chiral tetrasubstituted allenes

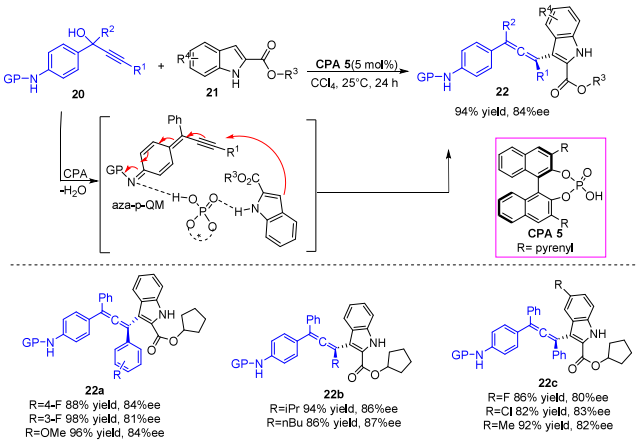
Scheme 5. CPA Catalyzed Asymmetric Synthesis Hexahydropyrrolo[2,3-*b*]indole



could inhibit the growth of pancreatic cancer cells to some extent, which might find their potential applications in medicinal chemistry.

In order to enhance the chemistry of axially chiral tetrasubstituted allenes and indoles, Li's group in 2023 proposed **CPA 5** catalyzed asymmetric 1,8-conjugate incorporation of *in situ* generated propargylic aza-*p*-QMs from propargylic alcohol **20** with indole-2-carboxylates **21** (as shown in Scheme 6). This work proposed an alternative

Scheme 6. Stereocontrolled Synthesis of Tetrasubstituted Allenes via Asymmetric 1,8-Addition



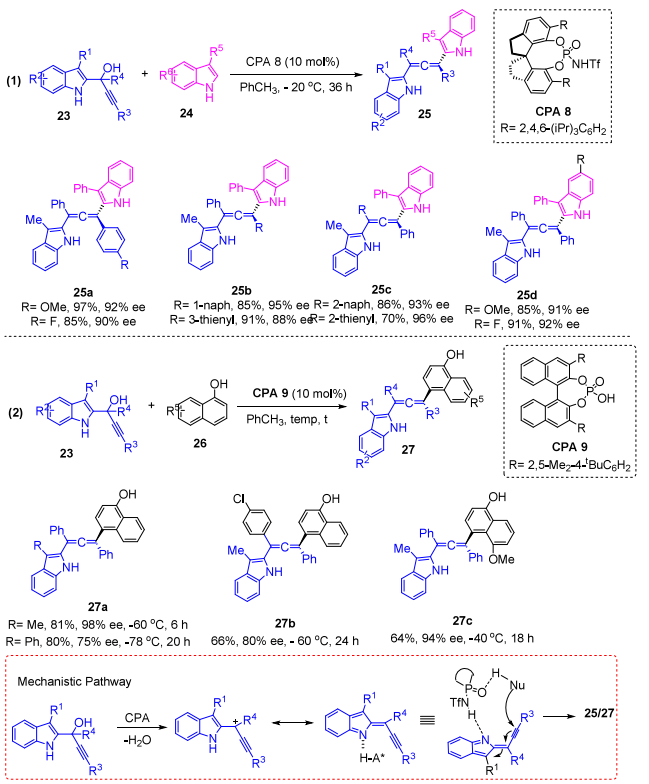
route to produce axially chiral tetrasubstituted allenes **22** with 95% yield and 86% ee. A series of alkyl-substituted, aromatic residues and protecting group bearing propargylic alcohols **20** afford the corresponding 1,8-adducts in 88−99% yields with 80−87% ee. Similarly, a variety of indole-2-carboxylates **21** bearing electron-donating and -withdrawing groups reacted with **20** to furnish the corresponding products with excellent yields and enantioselectivities. Further transformation of tetrasubstituted allene **22** into alcohol having 92% yield with 80% ee was also successfully carried out.[69]

2.3. α-(Indolyl) Propargylic Alcohols as Electrophiles. Sun and Li reported the chiral phosphoric acid catalyzed enantioconvergent synthesis of chiral tetrasubstituted allenes.[70] Using **CPA 8** as an optimal catalyst, an array of indole imine methides generated *in situ* from racemic indole-substituted

https://doi.org/10.1021/acsomega.4c04206
ACS Omega 2024, 9, 33351−33364

propargylic alcohols (**23**) reacted with nucleophiles such as 3-substituted indoles (**24**) and 1-napthols (**26**) to provide efficient access to a series of enantioenriched allenes **25** and **27** with high yield and enantioselectivities (Scheme 7). A diverse

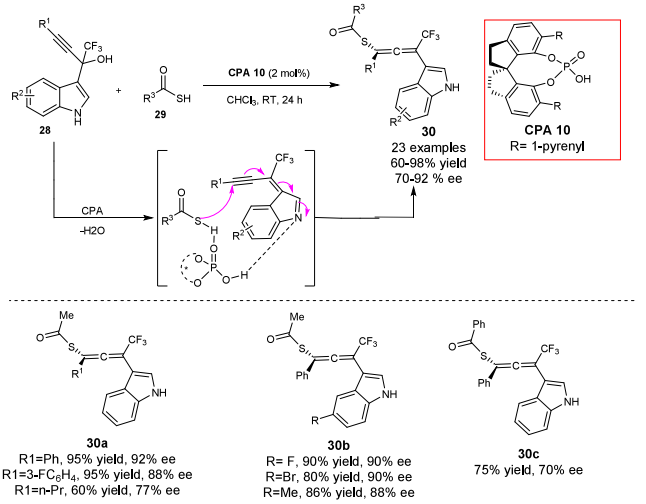
Scheme 7. Chiral Phosphoric Acid Catalyzed Enantioconvergent Synthesis of Chiral Tetrasubstituted Allenes



range of electrophilic racemic propargylic alcohols bearing various functional groups with different electronic properties and substitution patterns on the aryl moieties and nucleophilic species with different substitution patterns were worked well in this asymmetric reaction. However, the location of the substituent on the indole motif has strong influence on enantioselectivity, presumably because of an increased steric effect in close proximity to the NH unit, which likely interferes with the hydrogen-bonding network. The authors revealed that the mechanism involving irreversible formation of the imine methide intermediate followed by fast nucleophilic attack via remotely asymmetric 1,8-addition is occurred. Notably, the nucleophilic attack predominantly occurs through the more structured *Z* isomer, facilitated by the reversible equilibrium between the *Z* and *E* isomers as shown in Scheme 7. Additional validation was obtained through further kinetic investigations and the observation of nonlinear effects.

In 2021, Li and co-workers presented a study showcasing the chiral phosphoric acid-catalyzed enantioselective 1,6-conjugate addition of thiolacetic acid (**29**) to an alkynylindole imine methide formed in situ from α-(3-indolyl)-propargyl alcohol (**28**).[71] Utilizing **CPA 10**, a variety of α-(3-indolyl)-propargyl alcohols **28** with different substituents such as electron-withdrawing (F, Cl, and Br), electron-donating (Me and MeO), 3-thienyl, and aliphatic groups on R1, along with thiobenzoic and thioacetic acids **29**, were successfully accommodated to yield axially chiral sulfur-containing tetrasubstituted allenes **30** in high yields (60−98%) and with high enantioselectivity (77−92% ee) (Scheme 8). Control

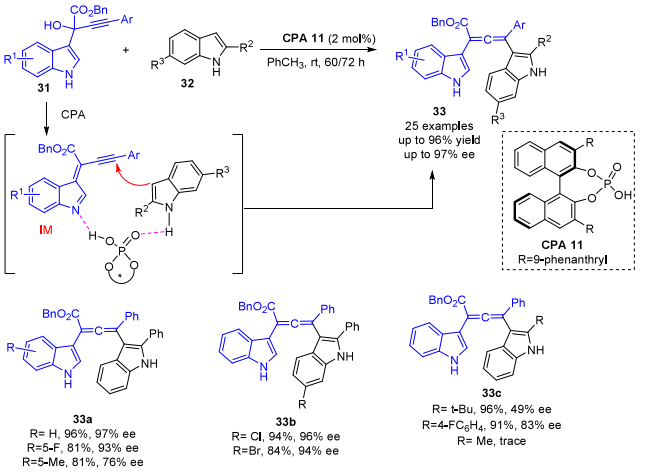
Scheme 8. Enantioselective Construction of Axially Chiral Sulphur-Containing Allenes



experiments indicated the significance of the hydrogen atom on the nitrogen atom of the indole moiety for reactivity and enantiocontrol, forming a hydrogen bond with CPA. Furthermore, the presence of a CF3 group on the indole substrate was found to be crucial for reactivity under the specified reaction conditions, suggesting that the reaction is governed by the nature of the substrate.

In 2022, Li and co-workers developed a method for synthesizing axially chiral indole-containing tetrasubstituted allenes using chiral phosphoric acid (CPA) as a catalyst.[72] This method involved the asymmetric 1,6-conjugate addition of 2-substituted indoles to alkynyl indole imine methides generated *in situ* from α-(3-indolyl)propargylic alcohols. The reaction was successful with a wide range of α-(3-indolyl)propargylic alcohols and indoles containing various electron-withdrawing and electron-donating groups, resulting in high yields and enantioselectivity (Scheme 9). However, 2-substituted indoles with aliphatic groups like methyl and *tert*-butyl were not

Scheme 9. Asymmetric Synthesis of Axially Chiral Indole-Containing Tetrasubstituted Allenes



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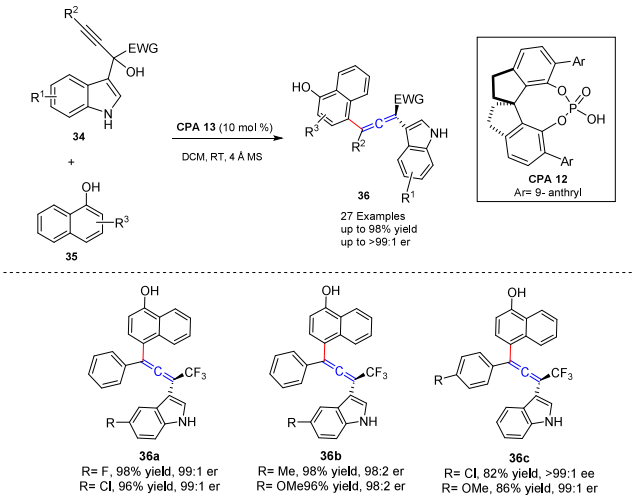
ACS Omega 2024, 9, 33351−33364

compatible under the standard reaction conditions. The mechanism involved the generation of alkynyl indole imine methide intermediate **IM** from α-(3-indolyl)propargylic alcohol in the presence of CPA, followed by the activation of both **IM** and 2-substituted indole through dual hydrogen bonding. This led to intramolecular conjugate addition and the formation of the 1,6-adduct **33**.

Because of the importance of chiral tetrasubstituted allenes with aryl substituents, the asymmetric synthesis of these scaffolds has received much attention. In 2020, Lu and co-workers carried out the enantioselective dehydrative γ-arylation of α-indolyl-α-trifluoromethyl propargyl alcohol **34** and 1-naphthol **35** catalyzed by chiral phosphoric acids (**CPA 12**), to produce a wide range of chiral tetrasubstituted allenes (**36**) in high yield (up to 98% yield) with excellent regio- and enantioselectivities (>99:1 er) (Scheme 10).[73] However, when

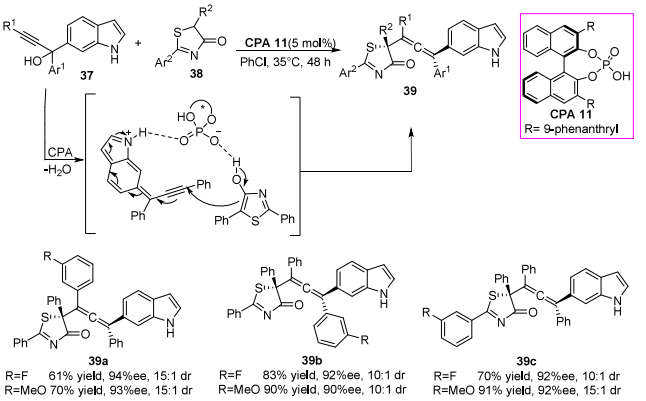
Scheme 10. Synthesis of Naphthol Based Chiral Tetrasubstituted Allenes



substituents are present at the C-4 or C-7 position of the indole ring of the propargyl alcohol, the yield decreases, which could be due to steric effects. Since the chiral phosphoric acid catalysts can interact with these groups via double hydrogen bonds, control studies have shown that the free OH on naphthol/phenol and the NH groups on α-indolyl-α-trifluoromethyl propargyl alcohol are very important for the reaction.

Li and co-workers disclosed an asymmetric 1,10-conjugate incorporation of alkynyl indole imine methides which are generated in situ from α-(6-indolyl)propargylic alcohols **37** with thiazolones **38** catalyzed by **CPA 11** in 2022 (Scheme 11). This process resulted in 60−91% yields of axially chiral tetrasubstituted allenes **39** with sulfur-containing quaternary carbon stereocenters along with 86−95% ee, and 6:1−15:1 dr. This method produced the requisite 1,10-adducts for a wide range of α-(6-indolyl) propargylic alcohols **37** and thiazol-4(5*H*)-ones **38** with various aromatic substituents. Significantly, the efficiency and selectivity were marginally impacted by the location effect as well as the electrical nature. DFT calculations and control measures helped to clarify the reaction process. The complexation of **CPA 11** with **37** via hydrogen bonding, followed by dehydration generates iminium phosphate intermediate which interact with the enol form of **38**. Due to the geometric constraints, the nucleophilic addition of

Scheme 11. Synthesis of Tetrasubstituted Allenes via CPA Catalyzed 1,10-Addition of Alkynyl Indole Imine Methides with Thiazolones



38 is more facile through *E* isomer. Notably, axially chiral tetrasubstituted allenes **39** were constructed from 1,10-addition for the first time, in addition to organocatalytic enantioselective 1,10-conjugate additions.[74]

In 2023, Li and co-workers reported the construction of indole and hexahydropyrrolo[2,3-*b*]indole bearing axially chiral tetrasubstituted allene **42** by 1,6 addition of tryptamines **41** with alkynyl 7-methylene-7*H*-indoles obtained in situ from α-(7-indolyl)propargylic alcohols **40** in the presence of **CPA 13** as catalyst. The reaction of **41** with alkynyl 7-methylene-7*H*-indoles in room temperature for 24 h produce tetrasubstituted allenes **42** 88% yield with 86% ee and 7:1 dr. The formation of the hydrogen bond between **CPA 13** and **41** followed by dehydration lead to the formation of alkynyl 7-methylene-7*H*-indoles (**Int 1**). Subsequently, the **Int 1** interacts with substrate **41** to give the active intermediate II (**Int 2**). 1,6-Nucleophilic addition of **Int 2** via bifunctional activation by the catalyst followed by intramolecular conjugate addition−annulation and intramolecular proton transfer from the NHTs group generates the final product and regenerate **CPA 13** (Scheme 12).[75]

In 2022, Terada and co-workers have demonstrated **CPA 8** catalyzed enantioconvergent substitution reaction between racemic indolylmethanol bearing tetrahydrocarbazole (THC) **43** and *N*-methylpyrrole **44** which produces the corresponding chiral THC bearing allene moiety **45** exhibiting 80% yield and 95% ee via a 1,8-addition. The introduction of bulky TMS group on alkynyl terminal of the substrate also generated the desired product with good yield and enantioselectivity. The substituents (Me, MeO, Br and Ph) at the C4, C5 and C6 position of the indole ring furnish high enantioselective 1,8-adducts in fair to good yields. Chiral THC **45** was further tested for the synthesis of a spiro compound. Cyclization of **45** with *N*-iodosuccinimide (NIS) at the C3 position of pyrrole moiety produce spiro compound **46** in 72% yield with no discernible loss of enantiopurity (94% ee). The integration of **CPA 8** into a bond recombination process that involves interaction between electrophile and nucleophile, served as the foundation for the extrapolation of this concept. The triple bond is orientated on a similar direction as the hydrogen bond that forms between the imine methide unit and the acid catalyst (Scheme 13).[76]

2.4. β,γ-Alkynyl-α-Imino Esters as Elecrophiles. In 2019, a novel method for synthesizing tetrasubstituted α-amino allenoates (**52**) using chiral phosphoric acid as a catalyst

https://doi.org/10.1021/acsomega.4c04206
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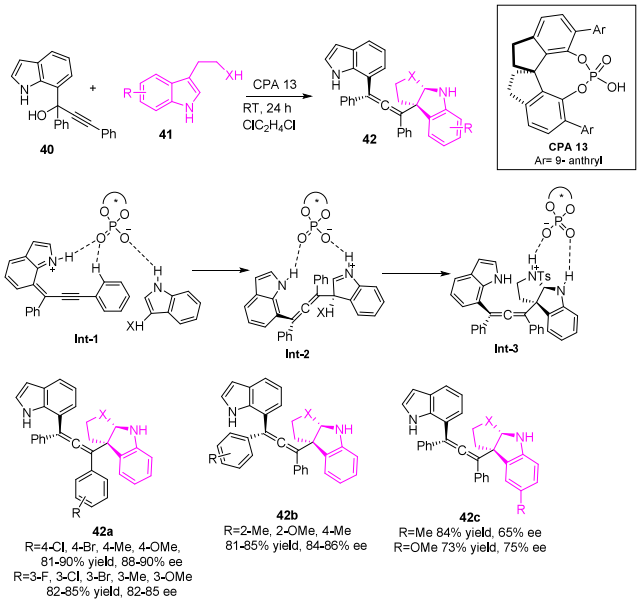
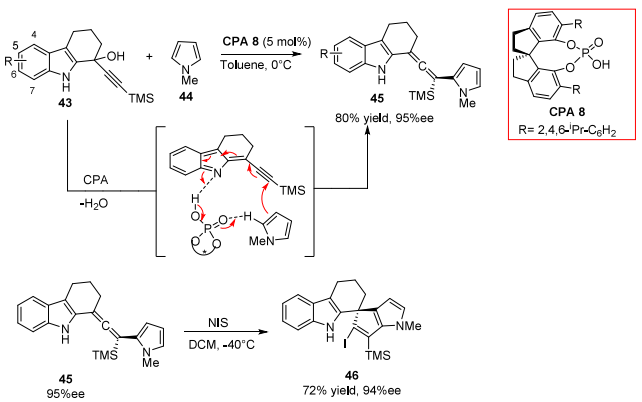
Scheme 12. Asymmetric Synthesis of Indole and Hexahydropyrrolo[2,3-*b*]indole Bearing Axially Chiral Tetrasubstituted Allene

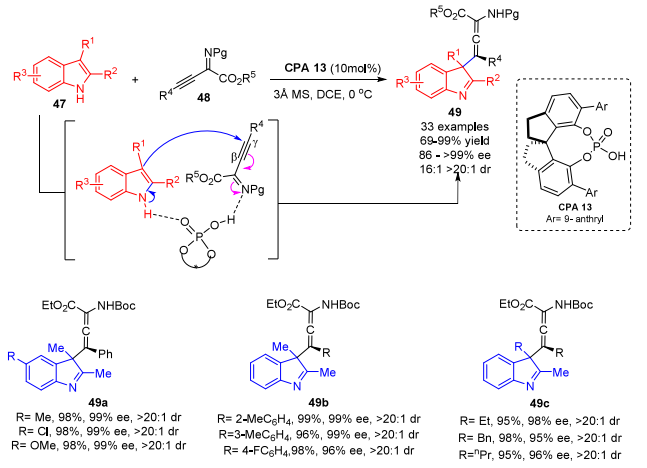


Scheme 13. CPA Catalyzed Enantioconvergent Synthesis of Chiral Tetrahydrocarbazoles with Allenylsilanes



was introduced by Wang, Sun, and their co-workers. This involved a dearomative γ-addition reaction of 2,3-disubstituted indoles **47** to β,γ-alkynyl-α-imino esters **48**.[77] The specific substituents on the second and third positions of the indole molecule played a crucial role in creating chiral allenes. By utilizing **CPA 13**, a broad range of 2,3-dimethylindoles and β,γ-alkynyl-α-imino esters were successfully employed to produce enantioenriched tetrasubstituted α-amino allenoates with quaternary stereocenters. This process delivered high product yields (69−99%) and excellent stereoselectivity (86 - > 99% ee, 16:1 > 20:1 dr) as shown in Scheme 14. Based on control experiments, the authors reported that when an alkynyl trifluoromethyl ketimine was used as an electrophile, the desired products were not obtained; rather, addition on the α-position occurs. Therefore, the COOR group of the β,γ-alkynyl-α-imino esters plays a vital role in the reaction, possibly by generation of spatial steric hindrance. DFT calculations have shown that the chiral phosphoric acid group of the catalyst serves a dual function by activating both partners through hydrogen-bonding interactions. Additionally, the

Scheme 14. CPA Catalyzed Asymmetric Synthesis of Tetrasubstituted α-Amino Allenoates

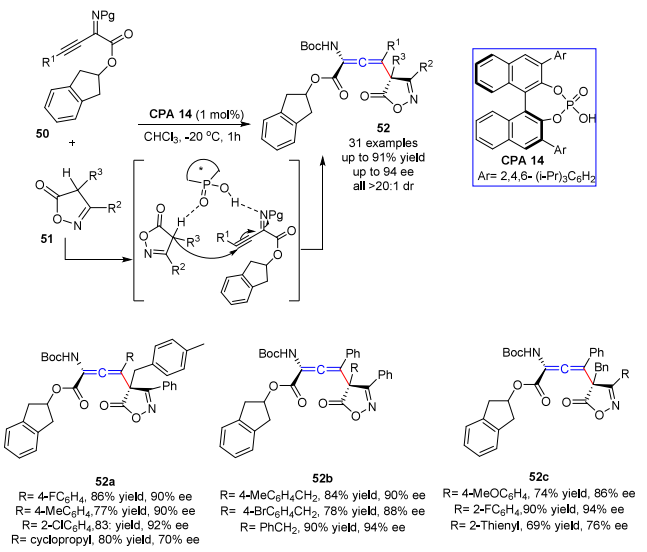


chiral backbone of the catalyst governs the stereoselectivity by influencing steric effects and $\pi-\pi$ interactions.

Isoxazol-5(4*H*)-ones, which have an imine-like C═N bond, a weak N−O bond, a doubly activated C−H bond, and a lactone-type moiety, have presented an array of applications in the fields of synthetic chemistry and medicinal chemistry. Herein, in 2021, Li and co-workers developed the chiral phosphoric acid catalyzed regio-, diastereo- and enantioselective reaction of isoxazol-5(4*H*)-ones **51** with β,γ-alkynyl-α-imino esters **50** for the synthesis of axially chiral tetrasubstituted α-amino allenoates **52** containing an adjacent quaternary carbon stereocenter.[78] Although isoxazol-5(4*H*)-ones have different nucleophilic sites, these authors succeeded in the C-allenylation of isoxazol-5(4*H*)-ones with high efficiency (up to 91% yields) and high regioselectivities and stereoselectivities (up to 94% ee and >20:1 dr) (Scheme 15).

In 2021, Lin and co-workers established a chiral phosphoric acid catalyzed a highly regio-, diastereo-, and enantioselective dearomatization reaction of 1-substituted 2-naphthols (**53**) and β,γ-alkynyl-α-imino esters (**48**). The highly functionalized

Scheme 15. Regio- and Stereoselective γ-Additions of Isoxazol-5(4*H*)-ones to β,γ-Alkynyl-α-imino Esters



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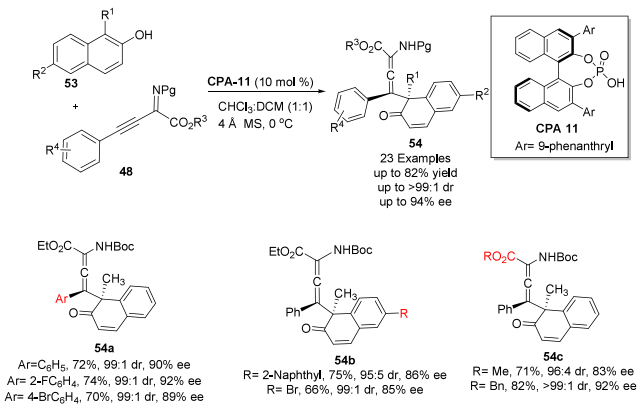
naphthalenone derivatives (**54**) with allene moiety, exhibiting both a quaternary stereocenter and axial chirality, were obtained in good yields (up to 82%) with high diastereoselectivities (up to >99:1 dr) and enantioselectivities (up to 96% ee) (Scheme 16). Control experiments showed that high to

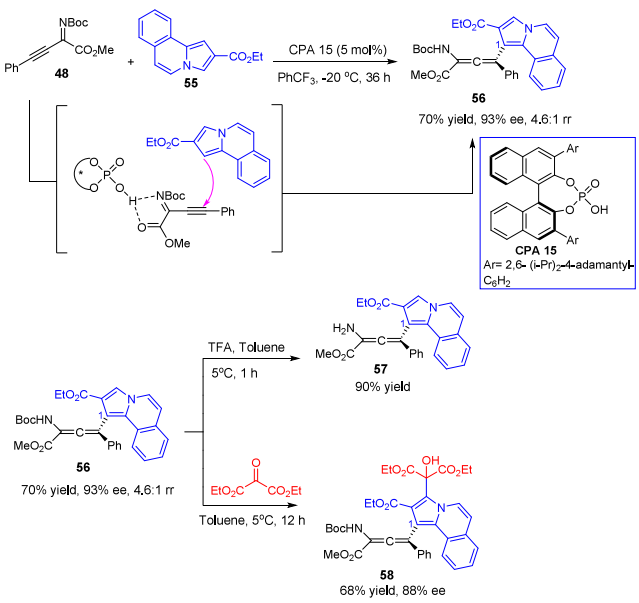
Scheme 16. Asymmetric Synthesis of Chiral Allenes from 1-Substituted 2-naphthols



excellent stereoselectivity is the result of a dual hydrogen bonding interaction between substrates and chiral phosphoric acid, with the substituent at the 1-position of 2-naphthol playing a key role in controlling regioselectivity.[79]

In 2023, Ni Q. et al. have efficiently devised asymmetric γ-arylation of β,γ-alkynyl-α-imino esters **48** with pyrrolo[2,1-α]isoquinolines **55** promoted by **CPA 15** for the regio and enantioselective formulation of tetrasubstituted α -amino allenoates **56** (Scheme 17). Under moderate conditions, exceptionally high site- and stereoselectivity were demonstrated by this approach concordant with an extensive variety of substrate. This transformations involves the C1-regioselective and enantioselective activation of pyrrolo[2,1- α]-isoquinolines. The hydrogen bonding interaction of **CPA 15** activates the alkynyl ketimine **48** and facilitates the γ-addition

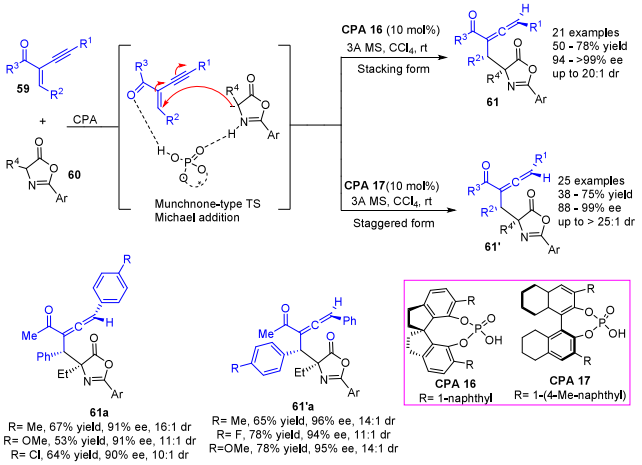
Scheme 17. Regio- and Enantioselective C1-Arylation of β,γ-alkynyl-α-imino Esters with Pyrrolo[2,1-α]isoquinolines



of pyrroloisoquinoline **55** from its *Re*-face that controlled the enantioselectivity of product. Under the optimal reaction conditions, the required product **56** was extracted in adequate yield of 70%, along with the 93% ee and 4.6:1 rr ratio. The N-Boc deprotection of **56** with trifluoroacetic acid (TFA) afforded 90% yield of α-amino allenoate **57**. Further functionalization of pyrroloisoquinoline **56** at C3 position utilizing ketomalonate generated derivative **58** with a minor loss of ee.[80]

2.5. Prochiral 1,3-Enynes as Electrophiles. Given the widespread availability of prochiral 1,3-enynes, the direct addition of these compounds in an asymmetric manner has emerged as an attractive approach for synthesizing compounds with multiple chiral centers. In a study conducted by Yang, Peng, and their team in 2019, an enantioselective and diastereodivergent synthesis of trisubstituted allenes was established through the asymmetric conjugate Michael additions of oxazolones **60** to activated 1,3-enynes **59** under the catalysis of chiral phosphoric acid.[81] This reaction is characterized by its broad substrate scope and mild reaction conditions, allowing for structural variations at different positions of the substrates. By utilizing **CPA 16** and **CPA 17**, the asymmetric additions of various oxazolones to activated 1,3-enynes proceeded smoothly, resulting in the formation of trisubstituted allenes with two adjacent chiral centers in good yield (up to 78%) with high enantioselectivity (up to >99% ee) and diastereoselectivity (up to >25:1 dr), as shown in Scheme 18. Through density functional theory (DFT) calculations

Scheme 18. CPA Catalyzed Stereoselective Synthesis of Trisubstituted Allenes



under CPA catalysis, the authors investigated the origin of diastereodivergence in the transition state of the allene formation step, highlighting a munchnone-type activation mode of oxazolones. With **CPA 16**, the products exhibited a stacking form, while **CPA 17** predominantly yielded the staggered form of the products, allowing for effective modulation of the axial stereogenicity of the chiral allene products through modifications of the CPA catalysts.

2.6. Proton or Deuterium as Electrophile. In 2023, Jiang and co-workers developed **CPA 18** catalyzed kinetic resolution of azaarylethynyl tertiary alcohols **65** via phosphine mediated sequential deoxygenation and protonation. In the presence of **CPA 18**, two enantiomers of a variety of tertiary alcohols demonstrate significantly contrasting aptitude toward

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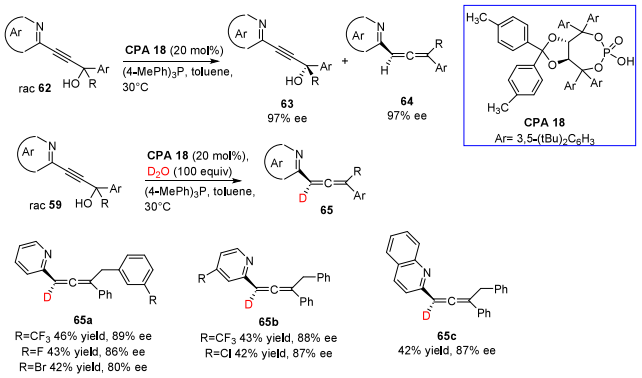
ACS Omega 2024, 9, 33351−33364

the incorporation of phosphines to the alkyne group. This approach offers preliminary access to highly enantioselective azaarylethynyl tertiary alcohols **63** that are essential for both synthetic and biological applications. Moreover, azaaryl-functionalized allenes **64** are produced by deoxygenation of oxaphosphetanes and the subsequent removal of phosphine oxides. Extensive modification of azaaryl groups demonstrated the flexibility and viability of the reported procedure. Furthermore, using deuterium (D) as the electrophile rather than a proton enables the production of first enantioselective deuterated azaarylfunctionalized allenes **65**, by using economical D_2O as the deuterium source (Scheme 19).[82]

Scheme 19. CPA Catalyzed Kinetic Resolution of Azaarylethynyl Tertiary Alcohols



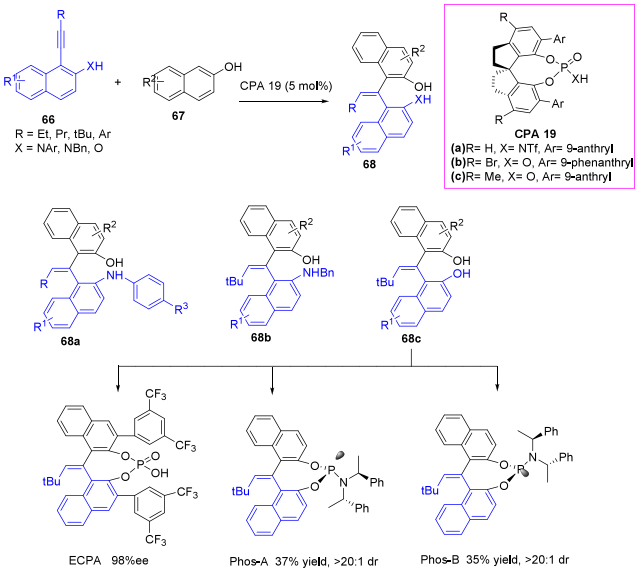
3. CPA CATALYZED ENANTIOSELECTIVE SYNTHESIS OF CHIRAL STYRENES

In this review, an in-depth analysis of diverse electrophilic substrates including vinylidene quinone methide, (3-Alkynyl-2-indolyl) methanols, and isatins utilized for the synthesis of chiral styrenes is presented.

3.1. Vinylidene Quinone Methide (VQM) as Electrophile. In 2019, Tan and co-workers[83] successfully synthesized a range of disubstituted derivatives of atropisomeric 1,1′-(ethene-1,1-diyl)binaphthol (EBINOL) in high yield. This was achieved by reacting 2-naphthol **67** with different alkynes **66** in the presence of **CPA 19** as a catalyst (Scheme 20). Under mild reaction conditions, the alkynes **69** containing different activated groups (N-aryl amino arylethynylene, N-benzyl amino arylethynylene and hydroxynaphthylalkyne) interacted with **CPA 19** via hydrogen bond to form VQM followed by the addition of **70** resulted in the production of atropisomeric styrenes (EBINOL) **68** exhibited high enantioselectivity, and complete E/Z selectivity. The formation of atropisomeric EBINOL-based chiral phosphonic acid (ECPA) and phosphoramidites (obtained as a pair of diastereomers EBINOL-Phos-A and EBINOL-Phos-B) illustrated the importance of this transformation. The utilization of ECPA as catalysis in the alkylation of indole via N-(1-phenylvinyl)acetamide generated moderately enantioselective tertiary amine with ease. In contrast to ECPA, BINOL-CPA provided lower stereoselectivity and SPINOL-CPA did not induce enantioselectivity. Moreover, EBINOL-Phos-A prompted the effective asymmetric hydrogenation of enamides with the yield of 97% and ee of 90%, while EBINOL-Phos-B afforded low yield of product.

In 2022, Lv and co-workers developed the intermolecular C2 and C3 Friedel−Crafts alkylation of ortho-alkynylnaphthols

Scheme 20. CPA Catalyzed Synthesized of Disubstituted Atropisomeric 1,1′-(Ethene-1,1-diyl)binaphthol (EBINOL) Derivatives



72 and substituted indoles (**70** and **71**) catalyzed by **CPA 13**[84]. Axially chiral alkenes or styrenes, **72** and **73** having the yield of 93%, ee up to 98% and E/Z > 20:1 were obtained under mild conditions by using different 2-substituted indoles **70**, 3-substituted indoles, and *N*-methylindoles **71**. The authors provide a mechanistic explanation for the formation of a chiral complex of (a*S*)-vinylidenequinone methides (VQM) with phosphoric acid, whereby indole insertion is facilitated by **CPA 13** first activating alkyne **72** by means of hydrogen bonds. A **CPA 13** then uses a two-hydrogen bond interaction to activate the indole, which allows it to target the reactive VQM and afford the desired end product (Scheme 21). Additionally, the authors explored the thermal durability of the resultant compounds in dichloromethane and discovered that the rotational barriers of 2-substituted indole-fused styrenes are significantly higher than those of 3-substituted styrenes.

In 2023, Lin and co-workers[85] reported the first asymmetric reactions between C2-unsubstituted racemic naphthylindoles **74** and orthoalkynyl naphthols **69** catalyzed by SPINOL-CPA (**CPA 20**). This novel strategy enabled the atroposelective synthesis of a complex organic framework via dynamic kinetic resolution that linked axially chiral styrenes with axially chiral naphthyl-indoles **78** (Scheme 22). Excellent yield (up to 96%) and outstanding stereoselectivity (up to >99.9% ee, > 99:1 E/Z and >20:1 dr) were achieved from this technique under mild circumstances. Two axial chiralities were demonstrated by the synthesized moieties **75**: axial chiral styrene and axial chiral biaryl. It is anticipated that this groundbreaking effort will pave the way for the creation of innovative chiral substances with a wide range of uses in multiple industries.

Zhou and co-workers achieved the pioneering enantioselective cycloaddition of alkynyl naphthols **72** with o-quinone methides **76** and imines **77** (Scheme 23).[86] An entirely novel series of naphthyl-2H-chromenes **78** and **79** carrying axial and central chirality and axially chiral quinone-naphthols were synthesized successfully exhibiting good to exceptional yield, diastereoselectivity, and enantioselectivity. The resultant products can be further processed to yield useful phosphine

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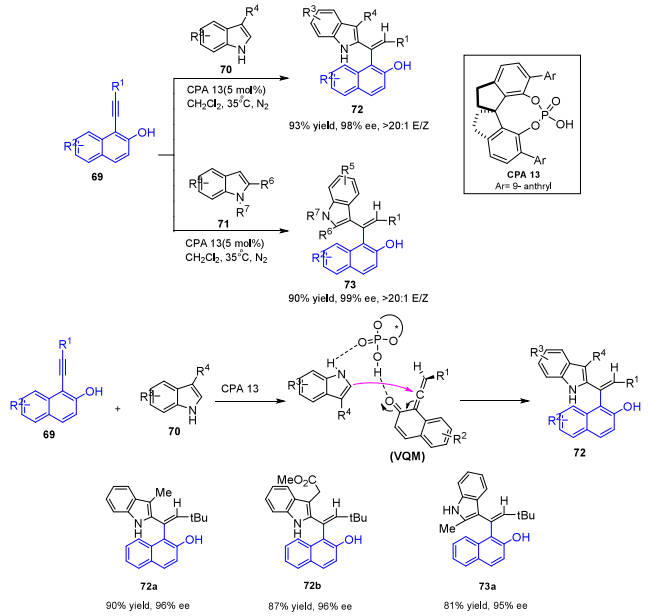
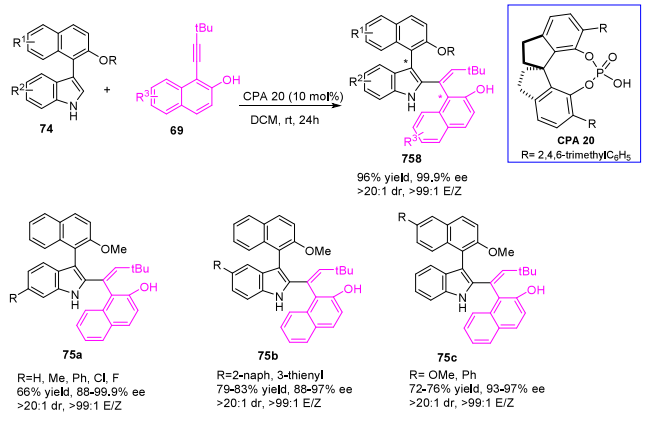
Scheme 21. Construction of Axially Chiral Styrene via Intermolecular Friedel–Crafts Alkylation of Ortho-Alkynylnaphthols and Substituted Indoles



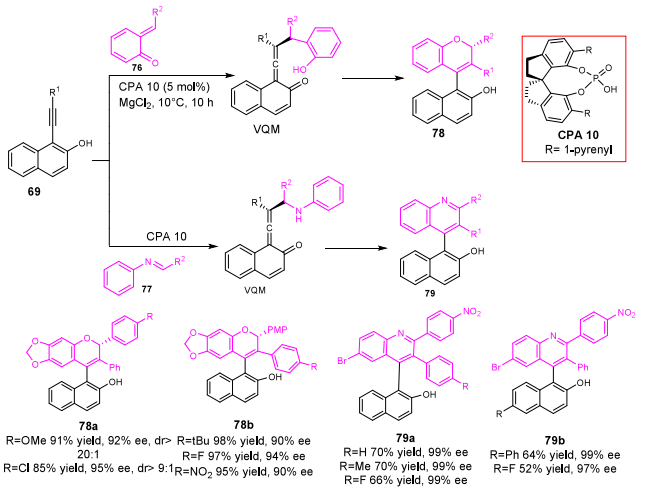
Scheme 22. Atroposelective Synthesis of Axially Chiral Styrenes Linked with Axially Chiral Naphthyl Indoles



ligands and various other useful compounds. Based on experimental studies and DFT calculations, the reaction between alkynyl naphthols **69** and o-quinone methides **76** undergoes a [2 + 2] cycloaddition, 4π-electrocyclic ring opening, and 6π-electrocyclization. Conversely, the cycloaddition of alkynyl naphthols **69** with imines **77** involves an auto-oxidation process followed by a [2 + 4] cycloaddition.

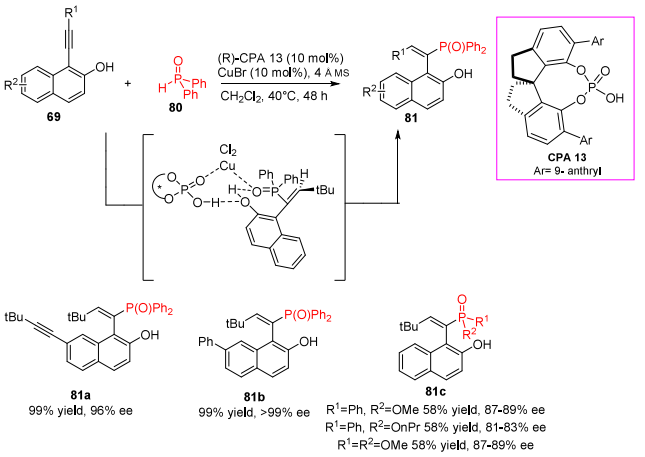
Inspired by the numerous applications of phosphorus-containing chiral compounds in the field of material, agricultural and medicinal chemistry, especially in transition metal-catalyzed and organocatalytic transformations, Wang et al. reported **Cu/CPA 13** catalyzed hydrophosphinylation of hydroxynaphthylalkynes. The treatment of 1-(3,3-dimethylbut-1-yn-1-yl)naphthalen-2-ol **72** with diphenylphosphine oxide **80** produce axially chiral phosphorus containing alkenes (styrene) **81** having yields up to 99% and enantioselectivities up to 99%.[87] DFT calculations were performed to elucidate the reaction pathway and the origin of enantiocontrol. The reaction involves **CPA 13** mediated transformation of alkyne

Scheme 23. Synthesis of Heterobiaryl Atropisomers and Axially Chiral Styrenes



69 into axially chiral allene (VQM). The tautomerization of diphenylphosphine oxide **80** generated hydroxydiphenylphosphane bearing a nucleophilic phosphorus which attack onto (*S*)-VQM from the side contrary to bulky *tert*-butyl group of the allene (*E*-face). It results in the formation of C–P bond and simultaneous transfer of axial chirality of allene into alkene-aryl bond. During the formation of C–P linkage, four coordination positions of Cu are inhabited by two chlorine atoms and two oxygen atoms from CPA and hydroxydiphenylphosphane. Concurrently, the Cu–O coordination encourages the creation of a new hydrogen bond between the oxygen of VQM and hydroxyl H atom of hydroxydiphenylphosphane (Scheme 24).

Scheme 24. Synthesis of Axially Chiral Styrene-Phosphines via Asymmetric Hydrophosphinylation of Alkynes



3.2. AzaVinylidene Quinone Methide (azaVQM) as Electrophile. In 2020, Zhang et al.[88] reported the synthesis of atropisomeric styrenes in excellent yield and enantioselectivity by asymmetric nucleophilic addition of 1-(ethynyl)naphthalen-2-amines **82** into indoles **83** or 4-hydroxycoumarins **84** (Scheme 25). The π–π interaction and hydrogen bonding of **CPA 14** with **82** would generate azaVQM. The nucleophilic attack of indole **83** or 4-hydroxycoumarins **84** onto aza-VQM would result in the preparation of enantioenriched products **85**

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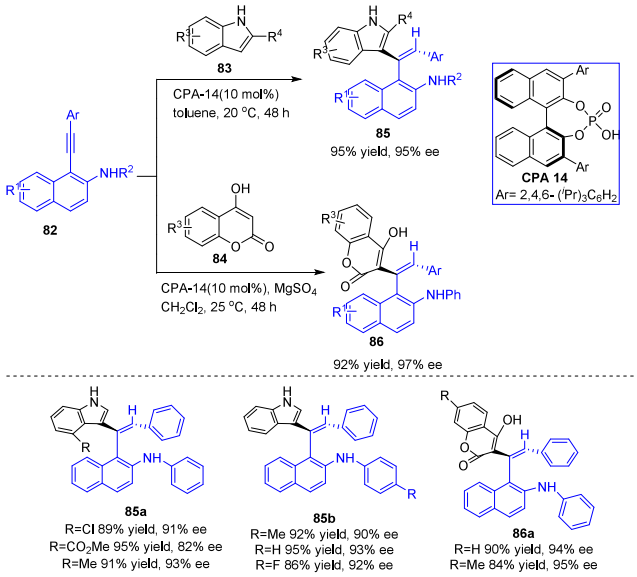
Scheme 25. CPA Catalyzed Enantioselective Construction of Heterocycle-Substituted Styrenes

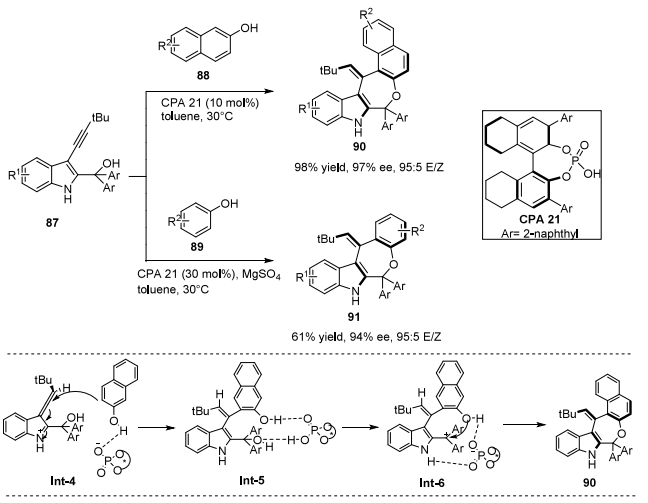


and **86** with 95% yield and 95% ee along with the regeneration of **CPA 14**. The reactivity and enantiocontrol in the product were brought about by hydrogen bond. *N*-methylindole, on the other hand, showed no selectivity under same reaction conditions. Following chemical changes, product **85** produced chiral squaramide, which allowed for more diversification through amination. Alkyl, ester, and halogens substituted indoles **83** under the standard conditions generated desired enantioselective axially chiral products in good to excellent yields. Additionally, 1-alkyne-2-naphthylamines **82** featuring aryl groups with diverse electron-donating and electron-withdrawing functionalities at the para-positions yielded axially chiral products with 60−90% yield and 90−95% ee. However, the presence of steric hindrance from ortho- and meta-substituents on the aryl group led to a reduction in reaction yield.

3.3. (3-Alkynyl-2-indolyl)methanols as Electrophiles. In 2020, Shi and co-workers used the approach of organo-catalytic E/Z selective enantioselective (4 + 3) cyclization of (3-Alkynyl-2-indolyl)methanols **87** with phenols **89** or 2-naphthols **88** to synthesized a new seven-membered bridging ring axially chiral styrene scaffolds (**90** and **91**).[89] With the introduction of **CPA 21**, (3-Alkynyl-2-indolyl)methanols **87** smoothly yield optically active allenes (**Int 4**). 2-Naphthol attacked optically active allenes selectively to produce acyclic chiral styrenes (**Int 5**) which undergoes intramolecular dehydration (**Int 6**) to synthesize a novel fused atropisomeric styrene **90** showing 97% ee, > 95:5 E/Z and 98% yield (Scheme 26). This method has addressed the significant difficulties associated with creating axially chiral alkene-heteroaryl scaffolds and offered a potent technique for the enantioselective synthesis of axially chiral aryl-alkene-indole scaffolds.

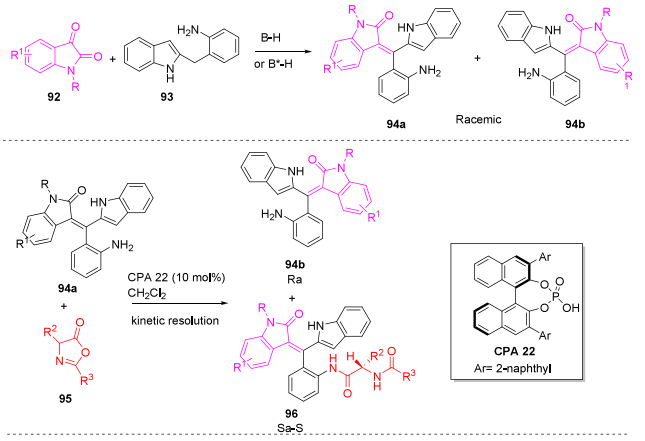
3.4. Isatins as Electrophiles. Liang J. et al. reported the synthesis of axially chiral oxindole based styrene derivatives by the condensation reaction between isatin **92** and (*o*-amino-benzyl) indole **93** using Bronsted acid as a catalyst. Unfortunately, the racemic mixture of oxindole based styrene derivatives **94a** and **94b** was obtained because Bronsted acid catalyzed condensation reaction did not offer enantiocontrol.[90]

Scheme 26. Enantioselective Synthesis of Seven-Membered Bridging Ring Axially Chiral Styrene Using CPA as Catalyst



In 2020, to overcome the problem of racemization, Shi and co-workers used the strategy of catalytic kinetic resolution of racemic mixture of oxindole based styrenes (Scheme 27). They

Scheme 27. CPA Catalyzed Synthesis of Axially Chiral Oxindole Based Styrene



used azlactones **92** for kinetic resolution which undergoes ring opening by the attack of amino group of oxindole based styrenes. The **CPA 22** was used as a catalyst in this reaction which formed hydrogen bonding with both reacting species which enhances the reaction rate of one atropisomer **94a** with azlactone **95**, thus producing enantiomerically pure product **96** as well as accumulate enantiomerically pure substrate **94b**. Two types of oxindole-based axially chiral styrene compounds with high selectivity factors and good diastereoselectivities (up to 94:6 dr) and great enantioselectivities (up to 98% ee) were provided by this technique. Along with the synthesis of axially chiral oxindole based styrene, this reaction also provides a reliable technique to prepare bisamide derivatives displaying axial and central chirality.[91]

CONCLUSIONS AND OUTLOOK

Axial chiral allenes, characterized by a chiral axis along the allenic bond, and axial chiral styrenes, featuring a chiral axis along the olefinic bond, have emerged as versatile building

https://doi.org/10.1021/acsomega.4c04206
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blocks with intriguing stereochemical properties. These compounds have found widespread applications in agrochemicals, pharmaceuticals, and molecular materials, showcasing remarkable achievements in the past decade. Additionally, their unique stereochemical properties make them valuable tools for the construction of chiral ligands, catalysts, and functional materials with tailored properties. Recent advancements in asymmetric organocatalysis have significantly contributed to the catalytic asymmetric synthesis of chiral allenes and styrenes.

This review highlights key developments in utilizing chiral phosphoric acid and its derivatives for the synthesis of chiral allene and styrene units. Notably, chiral phosphoric acids derived from BINOL, H8-BINOL, TADDOL, and SPINOL have been effectively employed in the asymmetric construction of these compounds. While substantial progress has been made in this area, challenges persist with current methods. The review delves into recent advancements in highly enantio- and diastereoselective synthesis of these valuable compounds.

Through in-depth exploration of the reactivity and synthetic capabilities of axial chiral allenes and styrenes, researchers have the potential to open up novel pathways for the advancement of innovative synthetic approaches and the identification of new chemical reactions. This exploration is anticipated to enable the creation of organic molecules featuring multiple axial chiral centers and diverse axial chiralities. The advancement of efficient synthetic protocols and the design of chiral organocatalyst systems are poised to expand the utility of these compounds in the synthesis of natural products, pharmaceuticals, materials, and various organic substances, offering significant benefits to both academic research and industrial applications.

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The manuscript was a collaborative effort among all authors, with Author 1 and 2 responsible for writing the initial draft.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

This work was supported by Bule Hora University and Adama Science and Technology University.

ABBREVIATIONS

CPA Chiral Phosphoric Acids
VQM vinylidine quinone methides
TMS Trimethyl silane

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https://doi.org/10.1021/acsomega.4c04206
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