有机化学 DOI: 10.6023/cjoc202201033 研究专题
Chinese Journal of Organic Chemistry ACCOUNT

铜催化的直接型插烯反应研究进展

李 晖*,[a] 殷 亮*,[b]
([a]运城学院应用化学系 山西运城 044000)
([b]中国科学院上海有机化学研究所 中国科学院天然产物有机合成化学重点实验室 上海 200032)

摘要 插烯反应可以在母体官能团的 γ-位(或更远的位置)引入一个新的官能团, 所生成的含有多个官能团的结构单元(尤其是手性结构单元)广泛存在于天然产物、生物活性分子和药物分子中, 并且可用作有机合成的中间体. 因而, 插烯反应(尤其是不对称插烯反应)近年来引起了化学家的广泛关注. 铜作为一种廉价过渡金属, 被广泛用作多种反应的金属催化剂(包括插烯反应). 我们对自己课题组在铜催化的直接型插烯反应领域的研究工作进行了总结. 根据亲电试剂的不同, 将研究分为三部分内容: 不对称插烯羟醛缩合反应、不对称插烯曼尼希反应和插烯氧化羟基化反应. 线性的 α,β-或 β,γ-不饱和化合物(包括酯、醛酮、酰胺、磷酸酯、砜和腈等)被用作插烯反应中亲核试剂的前体. 通过选用不同的铜催化剂, 反应过程中的区域选择性、非对映选择性和对映选择性得到了较好的控制.
关键词 插烯反应; 铜催化; 不对称催化; aldol 反应; Mannich 反应; 氧化羟基化

Research Progress of Copper-Catalyzed Direct Vinylogous Reactions

Li, Hui*,[a] Yin, Liang*,[b]
([a] *Department of Applied Chemistry, Yuncheng University, Yuncheng, Shanxi 044000*)
([b] *CAS Key Laboratory of Synthetic Chemistry of Natural Substances, Shanghai Institute of Organic Chemistry, Chinese Academy of Sciences, Shanghai 200032*)

Abstract Vinylogous reaction serves as an efficient tool to introduce a new functional group at the γ-position (or even more remote position) of the parent functional group. The produced highly functionalized structure motifs (especially chiral ones) are ubiquitous in natural products, biologically active compounds and pharmaceuticals. Moreover, they work as important synthetic intermediates in organic syntheses. Therefore, asymmetric vinylogous reaction has gained extensive attention in recent years. Our group is interested in the development of efficient direct vinylogous reactions by using copper catalysts with a focus on the catalytic asymmetric variants. Herein, the advances in our group in this field are reviewed. Both α,β-unsaturated and β,γ-unsaturated compounds (including esters, aldehydes, ketones, phosphonates, sulfones, and nitriles) are used as the vinylogous pronucleophiles. Aldehydes, ketones, imines, and molecular oxygen are employed as the electrophiles. This account is divided into three sections based on the varied electrophiles: asymmetric vinylogous aldol reaction, asymmetric vinylogous Mannich reaction and vinylogous aerobic oxidative hydroxylation. By using suitable copper catalysts, these reactions generally afforded the vinylogous products in good to excellent yields with good to excellent control of regio-, diastereo-, and enantioselectivities.
Keywords vinylogous reaction; copper catalysis; asymmetric catalysis; aldol reaction; Mannich reaction; oxidative hydroxylation

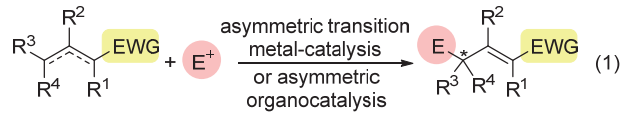
The principle of vinylogy, which has been formulated for nearly a century,[1] explains how the electronic effect of a functional group can be transmitted to a distal position in a molecule when these two points are linked to each other by a conjugated unsaturated bond system. This principle has been leveraged to functionalize the γ- or/and even more remote position(s) of the parent functional group. The resulting highly functionalized structural motifs, especially

* Corresponding authors. E-mail: lihuiwf@ycu.edu.cn; liangyin@sioc.ac.cn
Received January 20, 2022; revised February 25, 2022; published online March 8, 2022.
Project supported by the Grants from the Shanxi Scholarship Council of China (No. 2020-141), the Key R & D Program of Shanxi Province (No. 201903D121105), the National Natural Science Foundation of China (Nos. 21871287, 21922114) and the Science and Technology Commission of Shanghai Municipality (Nos. 20JC1417100, 21XD1424800).
山西省回国留学人员科研基金(No. 2020-141)、山西省重点研发计划(No. 201903D121105)、国家自然科学基金(Nos. 21871287, 21922114)及上海市科委基金(Nos. 20JC1417100, 21XD1424800)资助项目.

the chiral ones, are frequently encountered in naturally occurring compounds and man-made biologically active products. Furthermore, the vinylogous products serve as extremely valuable building blocks in the total synthesis of complex natural products. As a result, straightforward preparative methods to these useful compounds through vinylogous reactions, especially the asymmetric ones, have been a topic of intense research since last century.

The past decades have witnessed the fast evolution of vinylogous reaction, from non-enantioselective processes to enantioselective processes, from non-catalytic version to catalytic version, and from indirect types to direct types.[2] In the indirect methodologies, namely the typical Mukaiyama-type reactions, dienolsilanes, which are usually unstable, are firstly prepared at a separate step. In contrast, the vinylogous nucleophilic species are generated through deprotonation *in situ* in the direct reactions. Obviously, the direct protocols, which skip the tedious preparation of highly active vinylogous nucleophiles, possess higher efficiency and higher atom economy. Therefore, significant research efforts have been put in the field of direct catalytic asymmetric vinylogous reactions.

Strategies based on both transition-metal-catalysis[3] and organocatalysis[4] have been reported for the direct asymmetric vinylogous reaction (Eq. 1). Compared with organocatalysis, transition-metal-catalysis is more versatile and efficient. Among the numerous transition metal catalysts, copper has the advantages of earth abundance, low cost and high sustainability. Therefore, copper complexes are widely considered to be ideal catalysts. Furthermore, copper salts could serve as a Lewis acid to coordinate with numerous functional groups via σ or π coordination. What's more, various bidentate ligands, including the powerful bisphosphine ligands, are available for Cu salts, which enable chiral copper complexes as arsenal weapons in asymmetric catalysis.



Herein, the recent advances of our group in the field of copper-catalyzed vinylogous reaction are summarized. Both *α*,*β*-unsaturated and *β*,*γ*-unsaturated carbonyl compounds (or the phosphonate and sulfone counterparts) are employed as vinylogous pronucleophiles. The electrophiles include aldehydes, ketones, imines, and oxygen. Thus, this account is divided into three sections: direct asymmetric vinylogous aldol reaction (AVAR), direct asymmetric vinylogous Mannich reaction (AVMR) and vinylogous aerobic oxidation, based on the nature of electrophiles.

1 Direct asymmetric vinylogous aldol reaction

The competent catalytic system for direct AVAR and AVMR mentioned below consists of a chiral soft Lewis acid and a Brønsted base. A copper(I)/chiral bisphosphine complex is recognized as an ideal soft Lewis acid. Firstly, there are numerous commercially available chiral bisphosphines which can coordinate with copper(I) salts. Secondly, copper(I) cation is four-coordinated. Thus, it is easily coordinatively saturated in the catalytic system, which enhances the asymmetric induction. Thirdly, the electron-donating effect of the bisphosphine ligands will increase the nucleophilicity of the nucleophiles generated *in situ*. Some of the most widely used and commercially available chiral bisphosphines are listed in Figure 1. The typical catalytic system could be categorized into two variants in light of the varied Brønsted base: (1) $[Cu(CH_3CN)_4]PF_6$/chiral bisphosphine/common organic base and (2) mesitylcopper/chiral bisphosphine. In the former variant, the reaction is initiated by the deprotonation with the organic base (external base). While in the latter variant, oligomeric mesitylcopper serves as a Brønsted base (internal base) to firstly enable the deprotonation.

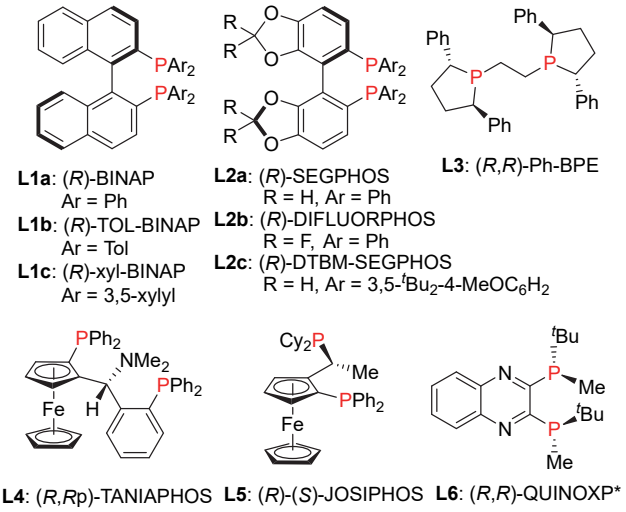


Figure 1 Typical commercially available chiral bisphosphine ligands

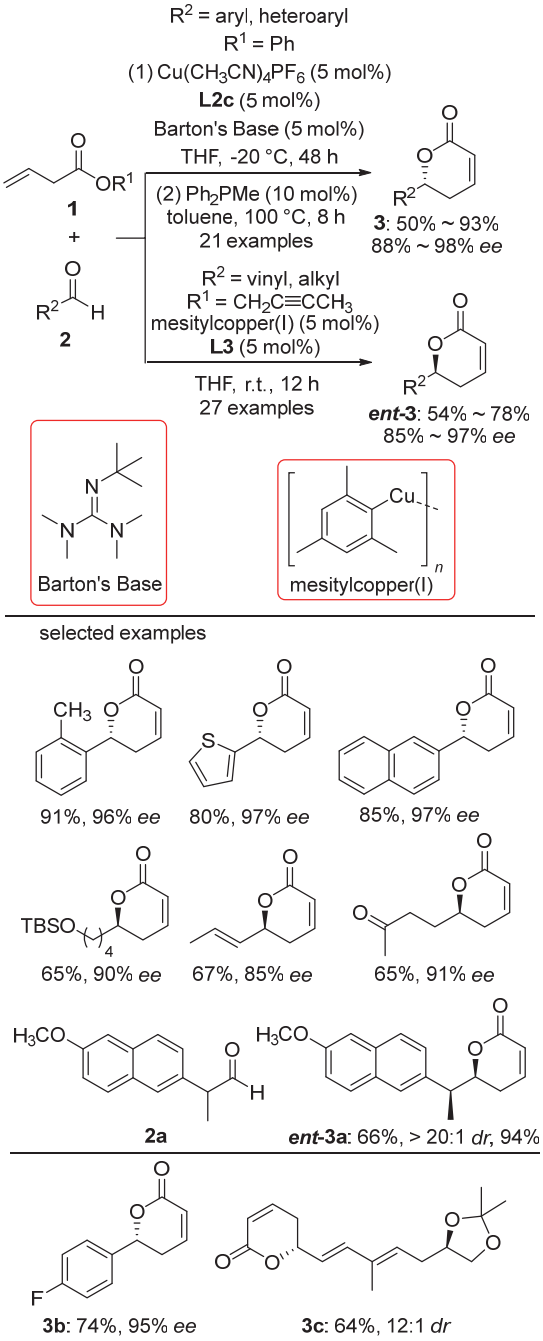
In Mukaiyama-type AVAR, both cyclic[5] and linear dienolsilanes[6] are excellent substrates, which furnish the desired vinylogous products in excellent regioselectivity. However, in the direct vinylogous reaction, only cyclic pronucleophiles are wonderful substrates to give the *γ*-adducts.[3a] The most important obstacle in the reaction of linear pronucleophiles originates from their inherent tendency to favor *α*-addition.[7] Thus, how to achieve both high regio- and high stereoselectivities in such vinylogous reactions is a challenging issue. It is also noted that, as for the electrophiles in the direct AVAR, most of reports focus on the activated ketones (such as *α*-ketoesters) rather than common aldehydes.[8] Taken together, general and powerful methods for the direct catalytic AVAR with linear vinylogous pronucleophiles and various aldehydes (aliphatic aldehydes, especially) are still urgently needed.

2.1 Direct asymmetric vinylogous aldol reaction of β,γ-unsaturated esters

Chiral δ-hydroxylated α,β-unsaturated carbonyl compounds function as precursors for the synthesis of optically active α,β-unsaturated δ-lactones, which are ubiquitous subunits in natural products and bioactive compounds.[9] The vinylogous version of asymmetric aldol reaction, namely AVAR, offers a simple, yet powerful strategy for the facile synthesis of chiral δ-hydroxylated α,β-unsaturated carbonyl compounds. However, challenges are present because of the difficult control of the regioselectivity and stereoselectivity.

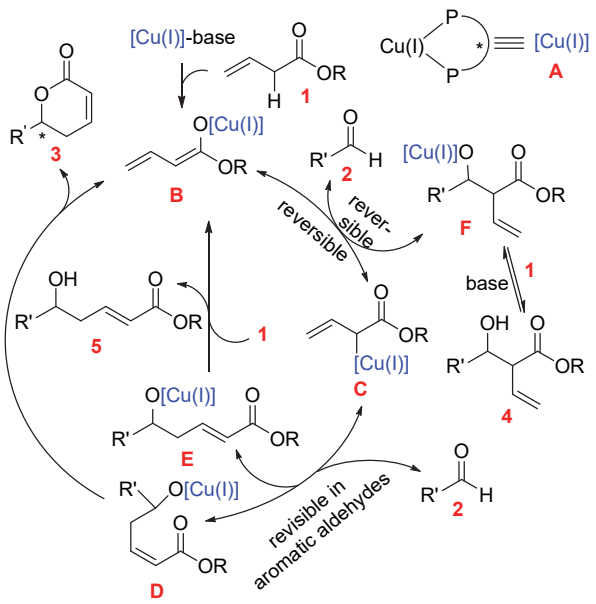
In 2018, our group[10] disclosed the first direct catalytic AVAR of linear β,γ-unsaturated esters **1** and various aldehydes **2**, including (hetero)aromatic aldehydes, aliphatic aldehydes and conjugated α,β-unsaturated aldehydes (Scheme 1). It is noteworthy that α,β-unsaturated esters, which usually serve as versatile synthetic intermediates in organic chemistry and are more commonly available, are ineffective substrates. It is probably owing to the fact that the pK_a value of their γ-protons is relatively higher than the pK_a value of the α-protons in β,γ-unsaturated esters **1**.

When aromatic and heteroaromatic aldehydes were used, phenyl but-3-enoates **1** (R^1=Ph) were found as the most suitable vinylogous pronucleophiles. The catalytic AVAR/isomerization of (*E*)-form product to (*Z*)-form product/intramolecular transesterification sequence was successfully incorporated into a one-pot reaction, which afforded an array of synthetically useful chiral α,β-unsaturated δ-lactones **3** in moderate to high yields with high enantioselectivity. In the catalytic AVAR, the combination of [Cu(CH_3CN)$_4$]PF_6/(*R*)-DTBM-SEGPHOS **L2c**/Barton's base was identified as the best choice. When aliphatic and α,β-unsaturated aldehydes were used by replacing R^1 in substrates **1** with 2-butyn-1-yl and replacing the catalytic system with mesitylcopper(I)/(*R*,*R*)-Ph-BPE **L3**, the desired chiral lactones ***ent*-3** were furnished directly through the AVAR in high enantioselectivity, albeit with moderate yields in most cases. This protocol enjoyed a broad substrate scope of aldehydes with various functional groups well tolerated, such as methoxyl, TBS-ether, sulfone, acetal, terminal olefin and internal alkyne. Even the methyl ketone moiety, which was suspicious to undergo a side aldol reaction with the aldehyde, was well applicable under this reaction condition. What's interesting is that, when racemic aldehyde **2a** was employed as the electrophile, ***ent*-3a** was obtained through a dynamic kinetic transformation. Remarkably, natural products and their derivatives, as well as derivatives of drugs, featuring an aldehyde functional group were also feasible substrates. The potential application of this methodology was exemplified by the preparation of lactones **3b** and **3c**, which served as key intermediates in the formal syntheses of ezetimibe (drug molecule) and fostriecin (*anti*-cancer natural product), respectively.



Scheme 1 Direct catalytic AVAR of linear β,γ-unsaturated esters

After an in-depth experimental study, a tentative mechanism was outlined in Scheme 2. The reaction began with the formation of copper(I) complex **A**, followed by the deprotonation of **1** under basic conditions to afford copper(I)-dienolate **B**, which had an equilibrium with allylcopper(I) species **C**. Then **B** and **C** reacted with aldehydes **2** competitively via six-member ring transition states to generate the corresponding copper(I)-alkoxides **F** (α-addition), **D** and **E** (both are from γ-addition). Upon protonation, α-adduct **4**, γ-adducts **5** and **3** were obtained respectively. γ-Addition was thermodynamically favored

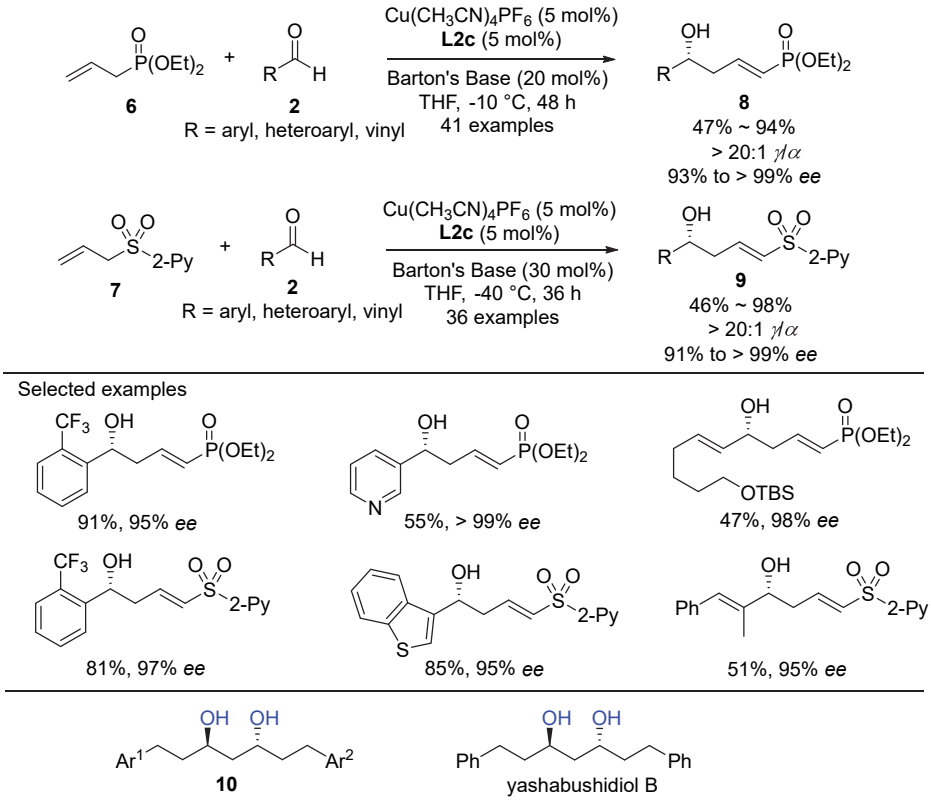


Scheme 2 Proposed mechanism for the catalytic AVAR of linear *β*,*γ*-unsaturated esters

while *α*-addition was kinetically favored. Thus under the present basic catalytic system, *α*-adduct **4** was transformed to *γ*-adducts **5** and **3** by retro-aldol reaction and subsequent catalytic asymmetric vinylogous aldol reaction, which was supposed to be the key to achieving the satisfactory regioselectivity. It was difficult to control the geometry of the conjugated carbon-carbon double bond in the vinylogous products under present catalytic system, thus a mixture of **5** (*E*-form) and **3** (*Z*-form) was obtained. Fortunately, the following one-pot isomerization and intramolecular transesterification promoted by Ph_2PMe worked efficiently to transform **5** to **3** and **3** was finally obtained as the only vinylogous product.

2.2 Direct asymmetric vinylogous aldol-type reaction of allyl phosphonate or allyl sulfone

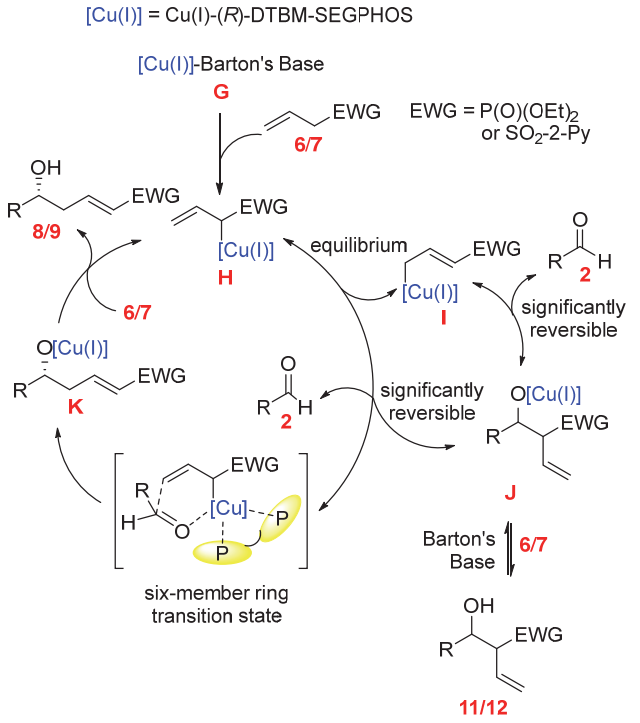
Allyl phosphonate **6** and allyl sulfone **7** were other types of potential linear vinylogous pronucleophiles that were hardly used in AVAR also due to their natural tendency for *α*-addition rather than *γ*-addition.[11] This problem was nicely addressed by utilizing of the bulky ligand (*R*)-DTBM-SEGPHOS **L2c** (Scheme 3) in copper(I) catalysis.[12] Under the optimized conditions, aromatic aldehydes bearing diverse electronic and steric demands on the aromatic ring, heteroaromatic aldehydes, as well as *α*,*β*-unsaturated aldehydes with various functional groups at the *β*-position, were identified as satisfying substrates. The corresponding chiral vinylogous adducts **8** and **9** were furnished in good to high yields with excellent regio- and enantioselectivities. Of particular note, the reaction conditions were thoroughly not applicable to aliphatic aldehyde **2** with *α*-adducts obtained in low yields. Fortunately, the *γ*-adducts of aliphatic aldehydes could be accessed by the conversion of the *γ*-adducts of *α*,*β*-unsaturated aldehydes through the versatile transformation of carbon-carbon double bond.



Scheme 3 Direct catalytic AVAR of allyl phosphonate and sulfone

The obtained vinylogous aldol products **8** and **9** proved to be versatile synthetic building blocks, which were utilized in various transformations, including Horner-Wadsworth-Emmons and Julia olefinations. Furthermore, the adducts **8** and **9** were structurally elaborated into some natural (such as yashabushidiol B) and man-made chiral diols **19**, some of which were reported to exhibit significant cytotoxic activity on human cancer cell lines.[13]

Upon the deprotonation of **6** and **7** by Barton's Base in the presence of a copper(I) catalyst, allylcopper(I) species **H** was generated. Its α-addition to aldehyde **2** afforded copper(I) alkoxide complex **J**, which would result in α-adduct **11** or **12** after protonation. The γ-addition of **H** to aldehyde **2** underwent a six-member ring transition state to afford copper(I) alkoxide complex **K** with excellent control of enantioselectivity, which would lead to chiral γ-adduct **8** or **9**. The perfect control of regioselectivity benefited from the experimental fact that the α-addition was significantly reversible while the γ-addition was slightly reversible. It was concluded that the α-adduct was kinetically favored while the γ-adduct was thermodynamically favored.



Scheme 4 Proposed mechanism for the direct catalytic AVAR of allyl phosphonate and sulfone

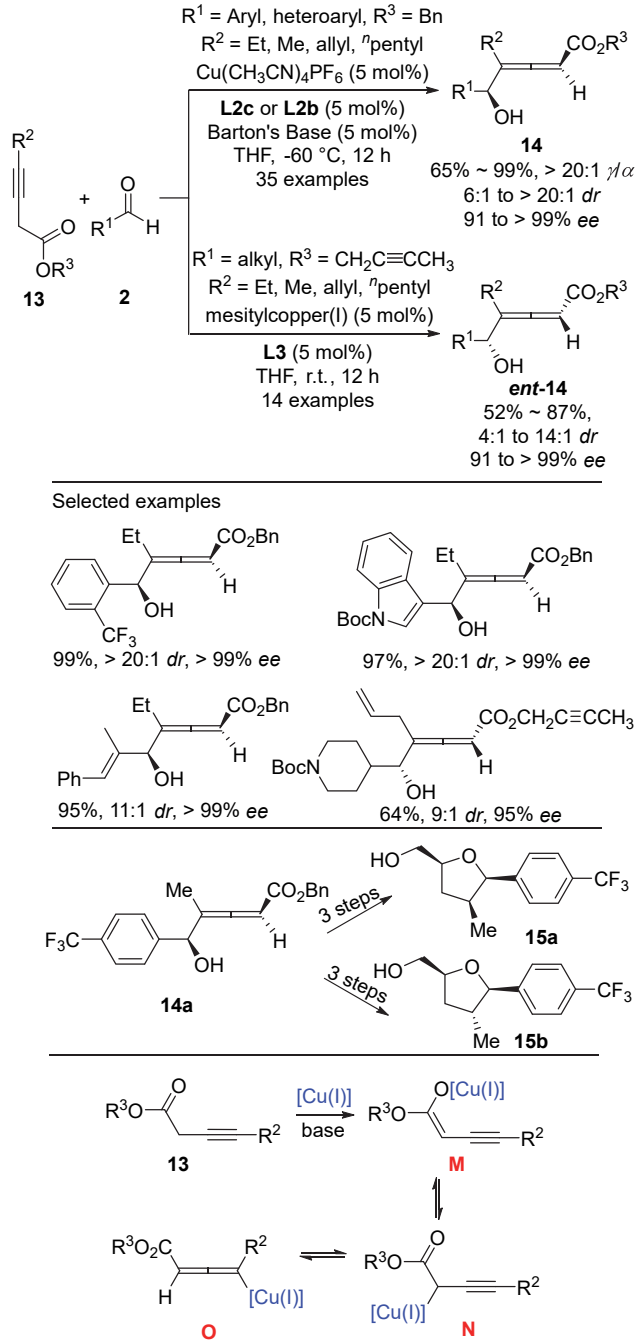
2.3 Direct asymmetric alkynylogous aldol reaction of propargyl esters

Allenes, a class of compounds containing two cumulated carbon-carbon double bonds, display a particular axial chirality deriving from their elongated tetrahedral geometry. Chiral allenes are valuable structural motifs in many naturally occurring products and man-made pharmaceuticals.[14] Furthermore, they are employed as crucial synthetic intermediates in various chemical manipulations in organic synthesis.[15] They also work as chiral ligand skeletons for the construction of chiral organocatalysts and chiral bisphosphine ligands in asymmetric catalysis.[16] Therefore, the facile synthesis of chiral allenes has gained significant attention from synthetic chemists.

The catalytic asymmetric alkynylogous aldol reaction, which is the variant of AVAR, serves as a powerful tool for the building of chiral allenes. However, there is a lack of general methodologies for the direct catalytic asymmetric alkynylogous aldol reaction of aldehydes, especially aliphatic aldehydes. The copper(I)-chiral bisphosphine catalysts succeeded in tackling this problem (Scheme 5).[17] Benzyl hex-3-ynoate **13** (R^2=ethyl) was incorporated as a wonderful alkynylogous pronucleophile to react with a broad array of (hetero)aromatic aldehydes **2**, affording the chiral adducts **14** in moderate to excellent yields with excellent regio-, good to high diastereo- and excellent enantioselectivities. (*R*)-DTBM-SEGPHOS **L2c** and (*R*)-DIFLUORPHOS **L2b** served as complementary ligands as the former delivered higher both yields and enantioselectivity while the latter gave superior diastereoselectivity. It should be mentioned that the desired aldol adducts **14** were also obtained with satisfying results when α,β- unsaturated aldehydes were subjected to the standard reaction conditions.

When electrophiles **2** were switched to aliphatic aldehydes by using but-2-yn-1-yl hex-3-ynoate **13** as the pronucleophile and using the copper(I)-(*R*,*R*)-Ph-BPE **L3** complex as the chiral catalyst, the catalytic asymmetric alkynylogous aldol reaction proceeded smoothly to provide the chiral allenes ***ent*-14**. Experimental study indicated that esters of but-2-yn-1-ol played a pivotal role in achieving good yields and good regio-, diastereo-, and enantioselectivities. This reaction enjoyed a broad substrate scope on electrophiles with a good functional group (such as phenyl, TBS-ether and *N*-Boc) tolerance. The R^2 group in **13** was successfully extended from ethyl to allyl, methyl, and *n*-pentyl. Remarkably, the alkynylogous products could be easily transformed to chiral 2-furanones without erosion of diastereoselectivity. The diastereoisomers **15a** and **15b**, both of which were important synthetic intermediates for the fast synthesis of pharmaceutically active compounds, could be obtained after a three-step synthetic sequence starting from the same allene **14a**, showcasing the synthetic utility of this methodology.

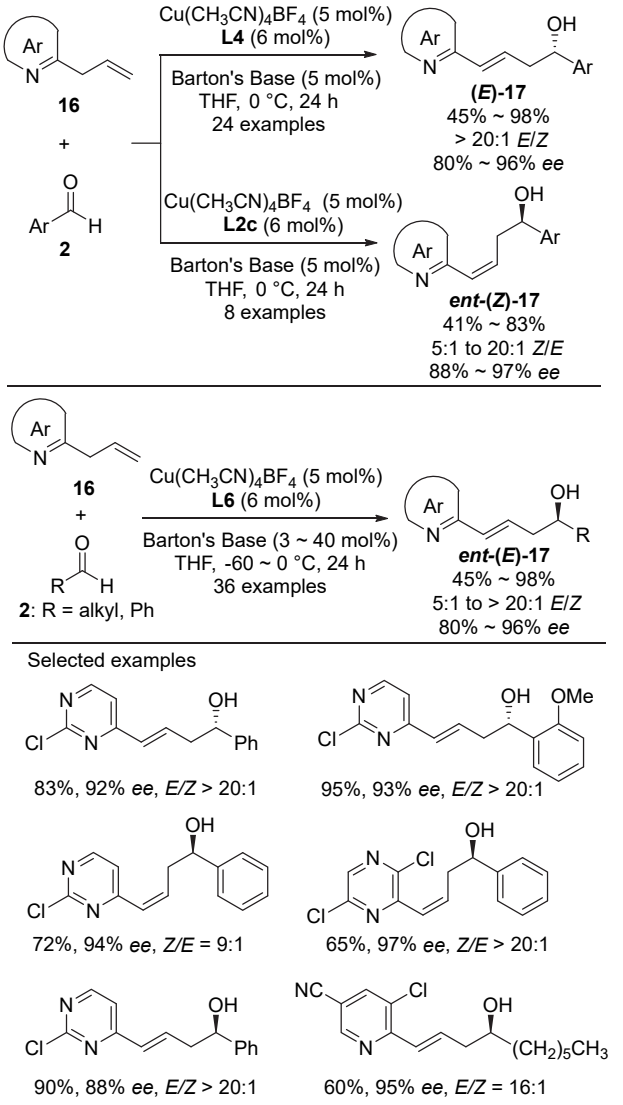
The proposed mechanism showed that the propargyl ester **13** would generate the corresponding copper(I)-akynylenolate intermediate **M** in the presence of a mild base, which isomerized to propargyl copper(I) species **N** and allenyl copper(I) species **O**. The working nucleophile in the alkynylogous aldol reaction was proposed as **N**. In 2020, Chen group[18] uncovered an interesting example of enantioselective α-allenylation reaction of activated ketimines by using benzyl 3-butynoate **13** (R^2=H) as the pronucleophile and copper(I)-(*R*)-DTBM-SEGPHOS (**L2c**) complex as the catalyst. In this Mannich reaction, **O** was supposed to be the reactive nucleophile.



Scheme 5 Catalytic asymmetric alkynylogous aldol reaction

2.4 Direct asymmetric vinylogous aldol type reaction of allylazaarenes

As analogues of α-vinyl carbonyl compounds, allylazaarenes were scarcely employed as vinylogous pronucleophiles in direct AVAR because of their poor reactivity.[19] Furthermore, other worrying issues emerged, including the regioselectivity (α-addition or γ-addition) and the geometry of carbon-carbon double bond in the vinylogous products (*Z*-form or *E*-form). Based on Jiang group's[19] excellent work on the organocatalytic asymmetric addition of allylazaarenes to activated ketones, our group[20] established a catalytic asymmetric γ-selective aldol-type reaction between allylazaarenes **16** and aldehydes **2** in 2021 (Scheme 6). In most cases, the regioselectivity was high to excellent. $Cu(CH_3CN)_4BF_4$ was chosen as the optimum copper(I) source in terms of yield and enantioselectivity. The geometry of the carbon-carbon double bond in γ-adducts **17** was thoroughly controlled by bisphosphine ligands. With (R,R_p)-TANIAPHOS **L4** as the ligand, the vinylogous reaction of aromatic aldehydes **2** occurred smoothly to furnish (*E*)-form adducts. Switching the ligand to (*R*)-DTBM-SEGPHOS **L2c** resulted in (*Z*)-selective vinylogous aldol-type reaction. (*R*,*R*)-QUINOXP* **L6** was found as the best ligand for aliphatic aldehydes **2** to afford (*E*)-products. As a matter of fact, aliphatic aldehydes were challenging electrophiles because the α-deprotonation of aliphatic aldehydes under basic conditions would lead to some side reactions (such as self-aldol reaction). Under the optimized reaction conditions, a variety of aliphatic aldehydes **2** underwent vinylogous aldol-type reaction smoothly to deliver the products in satisfactory results.



Scheme 6 Catalytic asymmetric vinylogous aldol-type reaction of allylazaarenes

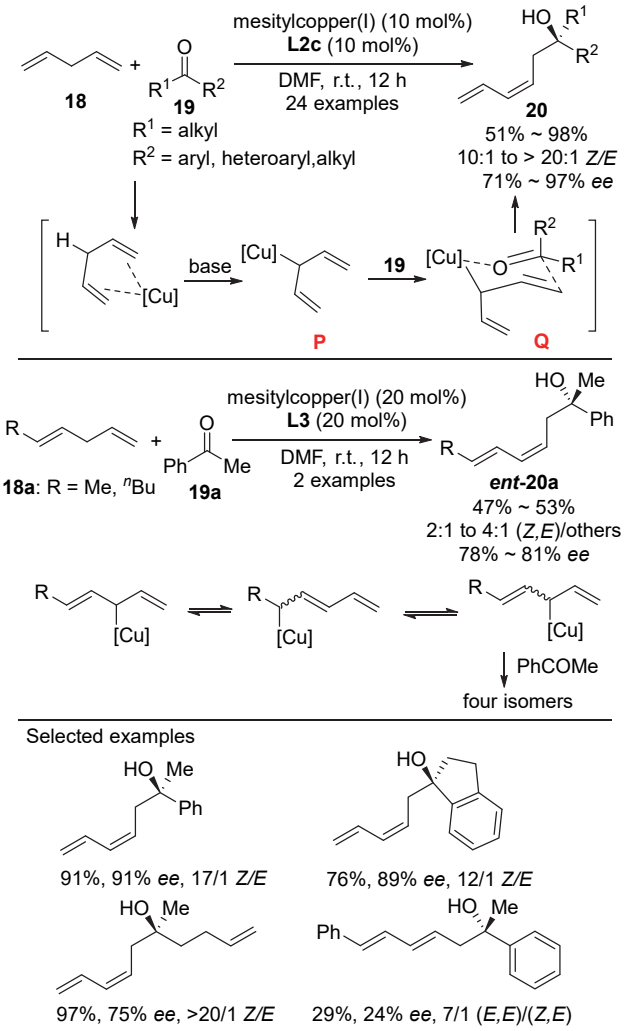
With respect to the vinylogous pronucleophiles **16**, various nitrogen-containing heterocycles, such as pyridine, pyrimidine, pyrazine, quinoline, quinazoline, quinoxaline and benzo[d]imidazole were all satisfactorily applicable. However, varied amounts of the base and different reaction temperatures were needed to obtain both good yields and good stereoselectivity for different allylazaarenes, which contain the α-protons of different pK_a values. It is interesting to note that only 2-allylazaarenes were feasible pronucleophiles under the present reaction conditions. The reaction of 4-allylazaarenes suffered from significantly attenuated enantioselectivity and 3-allylazaarenes were thoroughly inert. The vinylogous adducts **17** were implemented as valid Michael acceptors towards CuI-catalyzed 1,4-addition with organomagnesium reagents. Although moderate diastereoselectivity was obtained in the conjugate addition, a simple separation with silica gel column chromatography led to diastereoenriched products.

2.5 Regioselective asymmetric addition of 1,4-pentadiene to ketones

Hydrocarbons (except for terminal alkynes) are rarely used as pronucleophiles in catalytic asymmetric addition reactions.[21] It is usually difficult to deprotonate the hydrocarbons to form the corresponding reactive organometallic reagents because of the high pK_a values. Considering that the allylic methylene was more acidic than the normal methylene, 1,4-pentadiene **18** was selected as a potential candidate of competent pronucleophiles. In 2021, we disclosed a novel copper(I)-catalyzed asymmetric allylation of ketones **19** and 1,4-pentadiene **18**. (*R*)-DTBM-SEGPHOS **L2c** was identified as the best ligand (Scheme 7).[22] It was envisioned that two carbon-carbon double bonds in **18** could coordinate with the copper(I) catalyst, which would acidify the adjacent methylene. Upon deprotonation, an α-vinyl allylcopper(I) species **P** was generated. Then, **P** attacked ketones **19** via a six-member ring transition state to afford chiral tertiary alcohols **20**, which featured a terminal (*Z*)-1,3-diene motif. Unfortunately, the proposed chelation between 1,4-pentadiene **18** and the copper(I) catalyst was not observed through both ^{1}H NMR and ^{31}P NMR spectroscopic experiments.

The use of high polar *N*,*N*-dimethylformamide (DMF) as the solvent was the key to achieving high yields. The evaluation of the scope of ketones revealed a broad collection of various linear (hetero)aromatic ketones, cyclic aromatic ketones and linear aliphatic ketones. The regioselectivity was excellent with linear ketones and was moderate with cyclic ketones. Both the (*Z*)/(*E*) ratio and the enantioselectivity were high in most cases. However, the reaction with acetophenones **19** carrying a strong electron-withdrawing substituent suffered from an obvious drop in yield. It was because that the relatively acidic α-protons would quench the highly basic mesitylcopper(I) complex.

By switching the ligand to (*R*,*R*)-Ph-BPE **L3**, the addition of (*E*)-1-alkyl-1,4-pentadiene **18a** to acetophenone **19a** was achieved with partial success. There were four



Scheme 7 Catalytic regioselective asymmetric addition of 1,4-pentadiene to ketones

isomers in the products ***ent*-20a** with (*Z*,*E*)-form as the major one. The appearance of (*Z*,*Z*)-form and (*E*,*Z*)-form isomers was attributed to the partial isomerization of (*E*)-allylcopper(I) species to (Z)-allylcopper(I) species through facile 1,3-migration. (*E*)-1-Ph-1,4-pentadiene was much less efficient pronucleophile indicated by both very low yield and extremely poor enantioselectivity in the reaction with acetophenone. It is surprising that (*E*,*E*)-product is the major product. However, there is no rationale for the unusual (*E*)-selectivity at this stage. The 1,3-diene moiety in **20** could be efficiently functionalized through Heck reaction, olefin metathesis, and borylation, which demonstrated the potential utilities of the product in organic synthesis. It should be pointed out that this reaction was a very nice extension of the copper(I)-catalyzed vinylogous addition in terms of the similar nucleophilic allylcopper(I) species.

3 Direct asymmetric vinylogous Mannich reaction

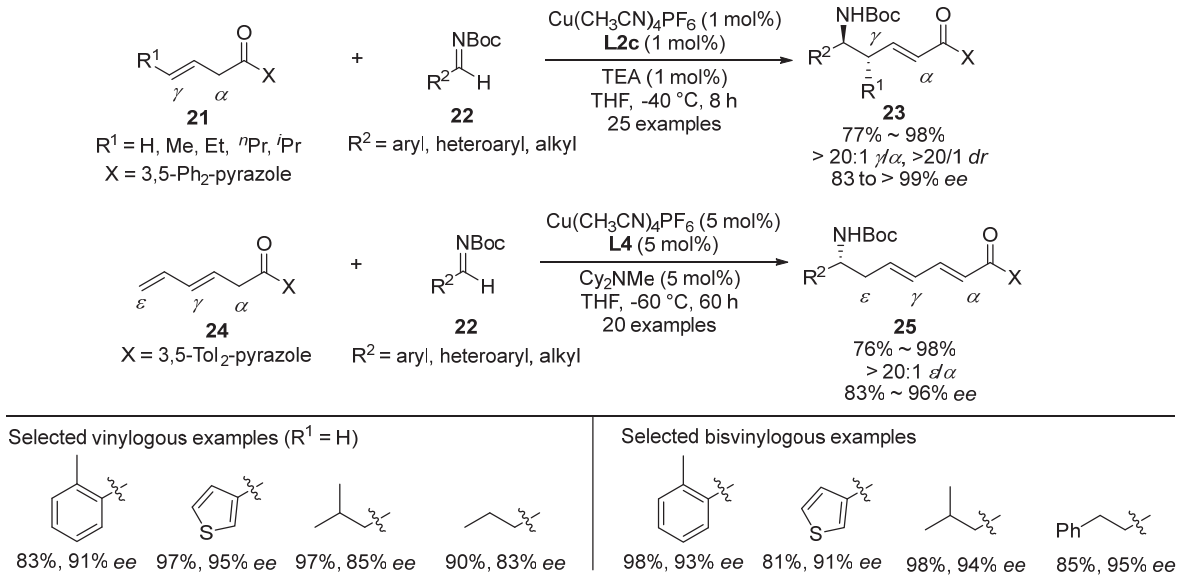
The conjugated version of direct catalytic asymmetric Mannich reaction, namely direct catalytic AVMR, has

been viewed as one of the most efficient strategies for the rapid synthesis of chiral *δ*-amino-*α*,*β*-unsaturated carbonyl compounds. Given that chiral *δ*-amino-*α*,*β*-unsaturated carbonyl structure is widely found in a variety of bioactive natural compounds and pharmaceuticals, and appreciated as a privileged synthon for the construction of nitrogen-containing natural compounds,[23] extensive attentions have been paid to the catalytic AVMR. Pioneering works in this subfield mostly focus on the cyclic vinylogous pronucleophiles possibly due to their natural tendency of *γ*-addition. However, examples on AVMR of linear vinylogous pronucleophiles are limited largely due to their natural tendency to favor *α*-addition.[24]

A mild copper(I)-catalyzed direct AVMR between linear *β*,*γ*-unsaturated *N*-acylpyrazoles **21** and *N*-Boc-aldimines **22** was achieved by using a bulky ligand (*R*)-DTBM-SEGPHOS **L2c** and a weak organic base triethylamine (Scheme 8).[25] Highly regio-, diastereo- and enantioselectivity were observed in this reaction. Various aromatic aldimines featuring either electron-donating groups or electron-withdrawing groups at *ortho*, *meta* or *para* position on the aromatic substituent, heteroaromatic aldimines, and even aliphatic aldimines, which were sensitive to basic reaction conditions, were all competent electrophiles under the optimized reaction conditions. The copper(I) catalyst was employed as little as 1 mol%, and a gram-scale reaction was successfully performed with maintained both yield and enantioselectivity, highlighting the robustness of this reaction protocol. Even for *β*-methyl pronucleophile **21**, the corresponding product was furnished in excellent regio- and moderate enantioselectivity, although higher catalyst loading, higher reaction temperature and longer reaction time were essential. As an ester equivalent, the *N*-acylpyrazole moiety in the vinylogous Mannich-type products **23** was easily transformed to various functional groups, such as common amide, ester and acid. After the transformation of the conjugated *α*,*β*-unsaturated double bond by Sharpless asymmetric dihydroxylation, an optically active molecular framework bearing two adjacent stereocenters at the *α*- and *β*-positions and one remote stereocenter at the *δ*-position was assembled in good yield with moderate diastereoselectivity. Interestingly, a "match and mismatch" phenomenon was observed in these two diastereoselective oxidation reactions.

In comparison with catalytic asymmetric vinylogous reaction, the catalytic asymmetric bisvinylogous version is evidently more challenging. Due to the competitive *α*-addition and *γ*-addition, the control of *ε*-regioselectivity is exceptionally difficult. Moreover, the nucleophilic site (*ε*-site) is far away from the coordinating carbonyl group, which may lead to difficult control of the enantioselectivity. Therefore, examples on the catalytic asymmetric bisvinylogous Mannich-type reaction are very few, all of which are indirect reactions.[26] By extending the pronucleophiles to *β*,*γ*,*δ*,*ε*-unsaturated *N*-acylpyrazoles **24** and switching the chiral ligand to (*R*,*Rp*)-TANIAPHOS **L4**, the first example of direct catalytic asymmetric bisvinylogous Mannich reaction was accomplished. Both the catalyst loading and the base loading were increased to 5 mol% to ensure satisfactory results at −60 ℃. The bisvinylogous reaction also had a broad substrate scope with both (hetero)aromatic aldimines and aliphatic aldimines well applied. In most cases, the corresponding bisvinylogous adducts **25** were obtained in excellent yields with excellent regio- and enantioselectivities.

Compared to *β*,*γ*-unsatruated *N*-acylpyrazoles, *α*,*β*-unsaturated *N*-acylpyrazoles were supposed to be less efficient vinylogous pronucleophiles in catalytic AVMR. By the introduction of a weakly electron-withdrawing halogen atom (F, Cl or Br) at the *γ*-position of *α*,*β*-unsaturated *N*-acylpyrazoles, it was deduced that the *γ*-protons would be slightly acidified and the nucleophilicity of the *γ*-carbon would not be significantly reduced. Thus, *γ*-halo-*α*,*β*-unsaturated *N*-acylpyrazoles **26** could be employed as proper



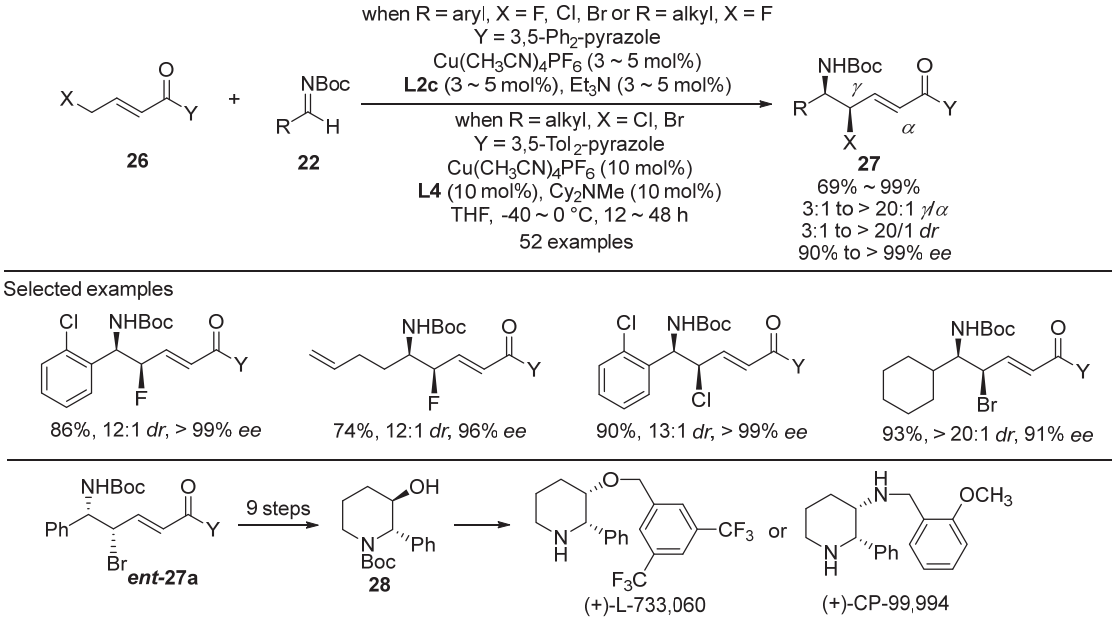
Scheme 8 Catalytic vinylogous and bisvinylogous Mannich reactions of *β*,*γ*-unsaturated *N*-acylpyrazoles

pronucleophiles to enable a smooth vinylogous Mannich reaction (Scheme 9).[27] As for (hetero)aromatic aldimines **22**, the best catalytic system was comprised of 3～5 mol% $Cu(CH_3CN)_4PF_6$, 3～5 mol% (*R*)-DTBM- SEGPHOS **L2c** and 3～5 mol% triethylamine. When the halogen in **26** was fluorine, aliphatic aldimines **22** were also viable electrophiles. However, *α*-adducts were inevitably generated as side products. Interestingly, when the halogen of **26** was chlorine or bromine, the reactions of aliphatic aldimines **22** exhibited lower reactivity and 10 mol% Cu(I)-(R,R_p)-TANIAPHOS **L4** complex and 10 mol% *N*,*N*-dicyclohexylmethylamine (Cy_2NMe) were required. A variety of chiral products **27** featuring a halogenated chiral allylic carbon center was prepared in high yields with good to excellent regio-, diastereo-, and enantioselectivities.

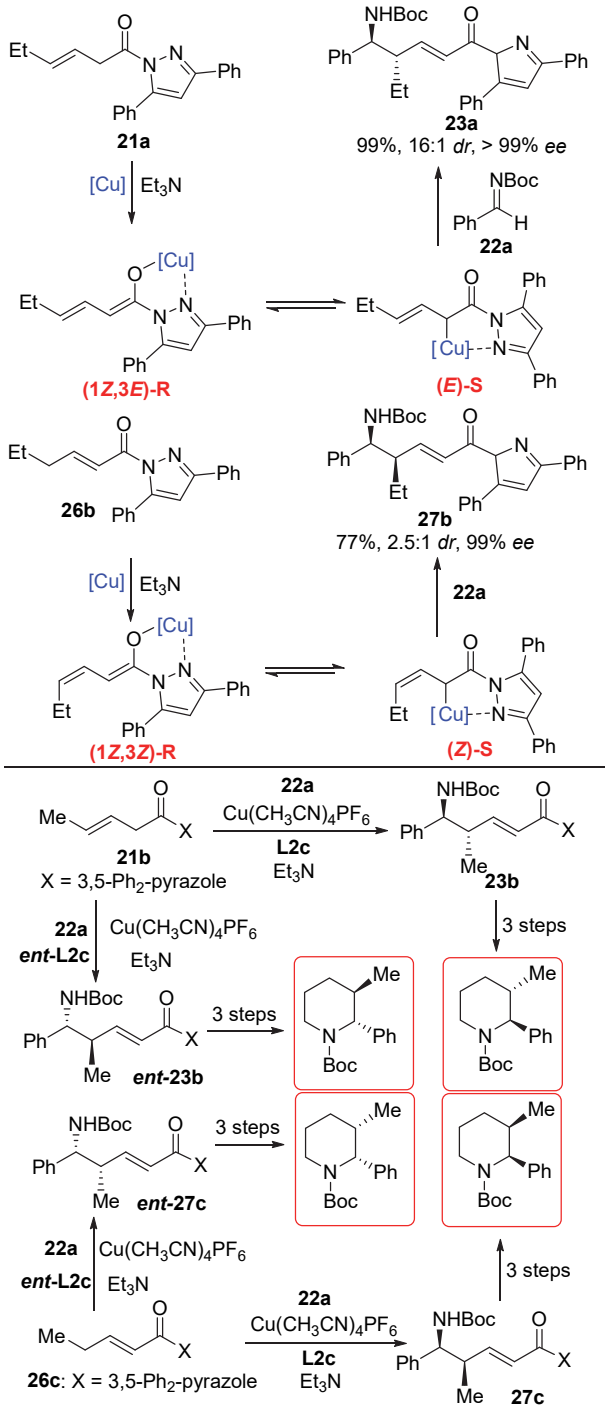
This reaction was an atom-economic pathway for the construction of halogenated stereogenic carbon centers, which was ubiquitous in bioactive natural compounds.[28] Moreover, these chiral halogenated compounds served as wonderful substrates for further structure elaboration through a diastereoselective reaction. Chiral allyl bromide (**27**) produced by this methodology exhibited high reactivity in common S_N2 reaction with NaN_3 and PhSH as the pronucleophiles. Moreover, both chiral allyl bromide and chiral allyl chloride (**27**) worked as wonderful substrates in the copper-catalyzed S_N2' reaction, providing enantioenriched compounds in good to high yields with high to excellent diastereoselectivity. The utility of this protocol was showcased by the transformation of ***ent*-27a** to chiral piperidine **28**, which served as a useful intermediate for the syntheses of two chiral pharmaceuticals, (+)-L-733,060 and (+)-CP-99,994.

It should be noted that although *β*,*γ*-unsaturated *N*-acylpyrazoles **21** were excellent pronucleophiles in the catalytic AVMR (Scheme 8), they were thoroughly incompetent pronucleophiles in the catalytic AVAR to react with aldehydes (Scheme 1). Meanwhile, in Scheme 8, replacing *β*,*γ*-unsaturated *N*-acylpyrazoles **21** with *β*,*γ*-unsaturated esters **1** led to no conversion, either. Previously, *α*,*β*-unsaturated esters were found to be unsuitable pronucleophiles in the catalytic AVAR while *β*,*γ*-unsaturated esters worked efficiently. It was because the *γ*-protons in *α*,*β*-unsaturated esters were much more less acidic than the *α*-protons in *α*,*β*-unsaturated esters. Interestingly, it was found that *α*,*β*-unsaturated *N*-acylpyrazoles were appropriate substrates in the catalytic AVMR,[29] probably due to the electron-deficient nature and the twisted structure of the pyrazoleamide moiety. Of course, *α*,*β*-unsaturated *N*-acylpyrazoles exhibited less reactivity than *β*,*γ*-unsaturated *N*-acylpyrazoles under the copper(I) catalysis. Remarkably, it was found that the reaction of *α*,*β*-unsaturated *N*-acylpyrazoles afforded *syn*-selective vinylogous products (Scheme 9) while the reaction of *β*,*γ*-unsaturated ones furnished *anti*-selective vinylogous products (Scheme 8), which was a very interesting event.

Based on control experiments (Scheme 10), it was verified that allylcopper(I) species were the reactive nucleophiles rather than the copper(I)-dienolates. Under the optimum reaction conditions, *β*,*γ*-unsaturated *N*-acylpyrazole **21a** was transformed to copper(I)-(1*Z*,3*E*)-dienolate **R** through deprotonation, which had an equilibrium with (*E*)-allylcopper(I) species **S**. On the other hand, upon the deprotonation of *α*,*β*-unsaturated *N*-acylpyrazole **26b**, copper(I)-(1*Z*,3*Z*)-dienolate **R** was obtained as the major intermediate, which formed an equilibrium with (*Z*)-allylcopper(I) species **S**. (*E*)-**S** and (*Z*)-**S** then reacted with aldimine **22a** via six-member ring transition states to afford *anti*-adduct **23a** and *syn*-adduct **27b**, respectively. As a



Scheme 9 Catalytic AVMR of *γ*-halo-*α*,*β*-unsaturated *N*-acylpyrazoles



Scheme 10 Catalytic diastereoselective AVMR with *β*,*γ*-unsaturated and *α*,*β*-unsaturated *N*-acylpyrazoles

result, the stereodivergent synthesis of all four stereoisomers of **23** was accomplished by using *α*,*β*-unsaturated *N*-acylpyrazoles, *β*,*γ*-unsaturated *N*-acylpyrazoles, (*R*)-DTBM-SEGPHOS **L2c**, and (*S*)-DTBM-SEGPHOS ***ent*-L2c**. After a three-step synthetic sequence starting from the vinylogous products **23b**, ***ent*-23b**, **27c**, and ***ent*-27c**, all four stereoisomers of *N*-Boc-2-Ph-3-Me-piperidine were obtained in high yields, which were potentially useful structure motifs in pharmaceutically active compounds.

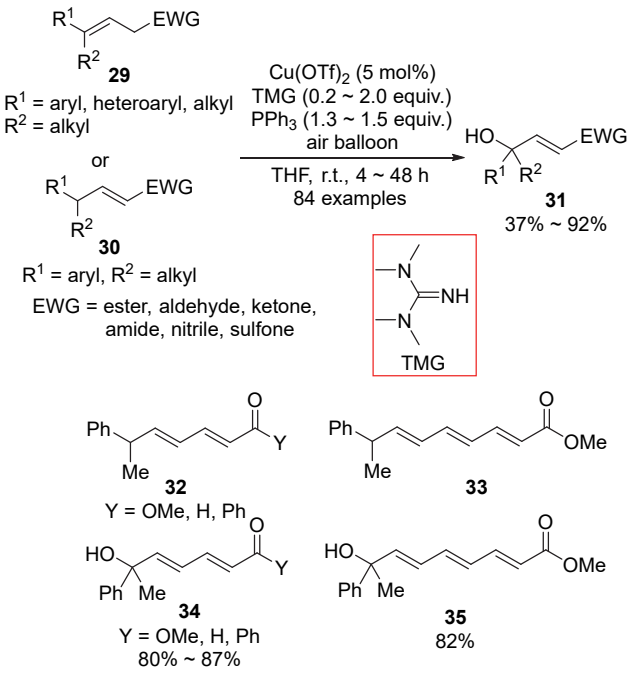
4 Aerobic vinylogous oxidative hydroxylation reaction

Functional group-rich *γ*-hydroxy-*α*,*β*-(*E*)-alkenoic esters are key structure elements existing in a broad range of natural products and biologically active compounds,[30] and serve as versatile intermediates in organic synthesis.[31] Transition-metal-catalyzed vinylogous oxidation of dienolates generated from the deprotonation of *α*,*β*-unsaturated or *β*,*γ*-unsaturated esters is an ideal strategy for the construction of *γ*-hydroxy-*α*,*β*-(*E*)-alkenoic ester motifs. Such a reaction is very challenging. Firstly, it is challenging to control the regioselectivity (*α*-hydroxylation versus *γ*-hydroxylation). Secondly, it is difficult to control the chemoselectivity, which is caused by the presence of the carbon-carbon double bond in both the starting materials and the products, as well as other presenting functional groups. Thirdly, the over oxidation is generally a worrying issue, which usually leads to low yield. As a result, there is no example on efficient transition-metal catalyzed vinylogous oxidation.

Inspired by the success of chiral copper(I) complex catalyzed asymmetric vinylogous reaction and aerobic oxidation of enolates via copper catalysis,[32] our group[33] accomplished an efficient copper-catalyzed vinylogous aerobic oxidation of *β*,*γ*-unsaturated or *α*,*β*-unsaturated compounds **29** and **30** with air as the oxidant (Scheme 11). The reaction was performed at room temperature in tetrahydrofuran (THF) in the presence of $Cu(OTf)_2$, tetramethylguanidine (TMG), and triphenylphosphine. A variety of *α*,*β*-unsaturated and *β*,*γ*-unsaturated esters successfully engaged in this methodology, which produced an array of *γ*-hydroxy-*α*,*β*-(*E*)-alkenoic esters **31** in good yields with good chemo- and regioselectivities.

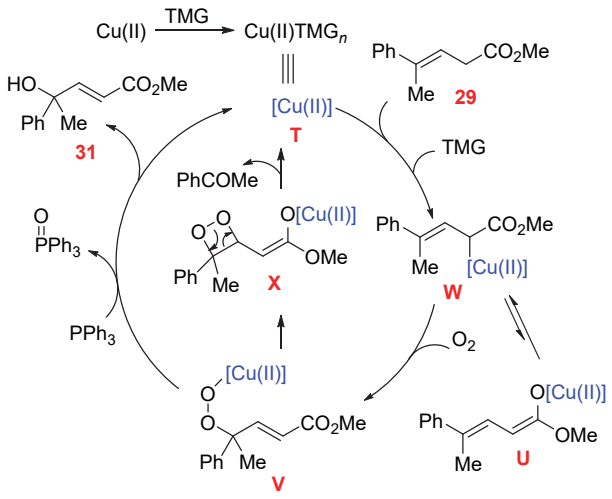
As for *β*,*γ*-unsaturated esters **29** and *α*,*β*-unsaturated esters **30**, the substituent R^2 could be various alkyls. The substituent R^1 in **29** could be either (hetero)aryls containing various electron-donating or electron-withdrawing group or alkyls. It should be noted that although the substrates were more inert in the latter cases and thus harsh reaction conditions (pure oxygen balloon instead of air balloon and refluxing) and increased amount of TMG were necessary. In contrast to **29**, the pK_a value of the *γ*-protons in **30** was much higher. Consequently, the amount of TMG was increased to enable the reaction of **30**. The substituent R^1 must be aryl because *γ*,*γ*-dialkyl-substituted *α*,*β*-unsaturated esters was completely inert even under the optimized reaction conditions. It is worth noting that both R^1 and R^2 in **29** and **30** could not be hydrogen as side products were obtained mainly. The substrate scope was successfully extended from unsaturated esters to other *α*,*β*-unsaturated or *β*,*γ*-unsaturated compounds, such as aldehydes, ketones, amides, sulfones and nitriles. It is worthy to note that this methodology enjoyed a wonderful functional group tolerance. Tertiary amine, primary and secondary alcohol, and olefin, which were suspicious to oxidative conditions, were well tolerated. Interestingly, both the bis-

vinylogous oxidation of substrates **32** and trivinylogous oxidation of substrate **33** proceeded very well, which afforded the corresponding products **34** and **35** in high yields. The robustness of this reaction was demonstrated by a 10 gram-scale oxidation with almost the same efficiency. The application of this protocol in organic synthesis was showcased by the modification of several complex steroid compounds and in the total synthesis (±)-andirolide N.



Scheme 11 Catalytic vinylogous aerobic oxidative hydroxylation

Based on some experimental observations and previous reports, a possible reaction mechanism was proposed (Scheme 12). TMG acted as a base to deprotonate the substrate **29** and a ligand to coordinate with copper(II), simultaneously. The *in situ* generated copper(II) dienolate **U** formed an equilibrium with allylcopper(II) species **W**. The aerobic oxidation of **U** and **W** via six-membered transition states resulted in *α*-oxidation and *γ*-oxidation, respectively. The copper(II) peroxide complex **V** produced in *γ*-oxidation was then reduced by triphenylphosphine to afford the corresponding copper(II) alkoxide complex, the protonation of which would deliver the desired product **31**. The complex **V** would undergo an intramolecular oxa-Michael addition to give four-membered endoperoxide **X**, the cleavage of which resulted in acetophenone as the major side product. Interestingly, the reaction rate was seriously affected by the alkene geometry of the substrate as indicated by the reaction time and yield. Essentially, the alkene geometry of the substrate determined the geometry of the allylcopper(II) **W**. The (*E*)-form allylcopper(II) species and (*Z*)-form allylcopper(II) species had different reaction rates with molecular oxygen.



Scheme 12 Proposed mechanism for the catalytic vinylogous aerobic oxidation

5 Summary and outlook

Copper-bisphosphine complexes have been appreciated as versatile and powerful catalysts, which enabled several catalytic AVARs and AVMRs in both milligram-scale and gram-scale. In the presence of these chiral copper catalysts, linear *α*,*β*-unsaturated compounds, which easily underwent *α*-functionalization, served as competent substrates to generate vinylogous products in excellent regioselectivity together with good to excellent diastereo-, and enantioselectivities. Furthermore, these vinylogous reactions often enjoyed broad substrate scope and good functional group tolerance. Remarkably, some methodologies have been utilized in synthesis of pharmaceutical molecules or bioactive compounds.

Although achievements in vinylogous reaction have been made as shown above and in literature, some challenging issues still exist, which require to be addressed in future. First, the electrophiles are mainly limited to aldehydes, ketones, and imines. Diversified reaction types, such as vinylogous alkylation, allylation, and arylation are highly demanded. The future research would be focused on the identification of more suitable electrophiles, such as alkyl halides, allyl carbonates, and aryl halides, which may require new catalytic systems. Secondly, it is difficult to trigger a vinylogous reaction at more remote positions (such as *ε*-site), especially in a catalytic asymmetric pathway. Although the catalytic asymmetric bisvinylogous Mannich reaction was achieved with satisfying regio-, diastereo- and enantioselectivities, other types of bisvinylogous (or even poly-vinylogous) reaction remain very rare and significant efforts are highly demanding in this particularly challenging subfield. Thirdly, given that the vinylogous products are highly functionalized, significant efforts would be devoted to the application of these vinylogous reactions in the efficient syntheses of complex naturally occurring products and related bioactive molecules.

Fourthly, the catalytic system could be expanded from the single chiral copper(I)-catalysts to the combination with other transition metal catalysts or organocatalyst, which would unlock new catalytic modes and thus enable new vinylogous reactions.

Moreover, allylcopper(I) species are identified as the working nucleophiles rather than the corresponding copper(I) dienolates in these reactions. Therefore, to some extent, these vinylogous reactions are viewed as copper(I)-catalyzed allylation. In this sense, the pronucleophiles could be further expanded from unsaturated carbonyl and related compounds to other compounds containing an allyl group. The addition of 1,4-pentadiene to ketones is a nice extension of the vinylogous reaction to allylation reaction. Thus research efforts could be put on the design and identification of suitable alkenes, which bear an acidic allylic hydrogen. With these compounds in hand, the target catalytic asymmetric allylation through deprotonation would be an excellent complement to the classical allylation starting from allylsilane or allyl borates. At last, the vinylogous reaction with a radical intermediate would be a fascinating subfield. The distinct characters of the radical would lead to new selectivities and new reaction patterns. Therefore, research efforts in this subfield are highly expected.

References

[1] Fuson, R. C. *Chem. Rev*. **1935**, *16*, 1.

[2] For selective reviews, see: (a) Denmark, S. E.; Heemstra, J. R.; Beutner, G. L. *Angew. Chem.*, *Int. Ed*. **2005**, *44*, 4682.
(b) Casiraghi, G.; Battistini, L.; Curti, C.; Rassu, G.; Zanardi, F. *Chem. Rev.* **2011**, *111*, 3076.
(c) Pansare, S.V.; Paul, E. K. *Chem.-Eur. J*. **2011**, *17*, 8770.
(d) Bisai, V. *Synthesis* **2012**, *44*, 1453.
(e) Schneider, C.; Abels, F. *Org. Biomol. Chem*. **2014**, *12*, 3531.
(f) Jusseau, X.; Chabaud, L.; Guillou, C. *Tetrahedron* **2014**, *70*, 2595.
(g) Roselló, M. S.; Pozo, C. D.; Fustero, S. *Synthesis* **2016**, *48*, 2553.
(h) Yin, Y.; Jiang, Z. *ChemCatChem* **2017**, *9*, 4306.
(i) Li, H.; Yin, L. *Tetrahedron Lett.* **2018**, *59*, 4121.
(j) Li, Z.; Noda, H.; Kumagai, N.; Shibasaki, M. *Tetrahedron* **2018**, *74*, 3301.

[3] For some recent examples for transition-metal-catalyzed asymmetric vinylogous reaction, see: (a) Tang, Q.; Lin, L.; Ji, J.; Hu, H.; Liu, X.; Feng, X. *Chem.-Eur. J.* **2017**, *23*, 16447.
(b) Trost, B. M.; Gnanamani, E.; Tracy, J. S.; Kalnmals, C. A. *J. Am. Chem. Soc.* **2017**, *139*, 18198.
(c) Ji, J.; Lin, L.; Tang, Q.; Kang, T.; Liu, X.; Feng, X. *ACS Catal.* **2017**, *7*, 3763.
(d) Mei, H.; Lin, L.; Wang, L.; Dai, L.; Liu, X.; Feng, X. *Chem. Commun.* **2017**, *53*, 8763.
(e) Sarkar, R.; Mitra, S.; Mukherjee, S. *Chem. Sci*. **2018**, *9*, 5767.
(f) Shi, C.-Y.; Xiao, J.-L.; Yin, L. *Chem. Commun.* **2018**, *54*, 11957.
(g) Xu, H.; Laraia, L.; Schneider, L.; Louven, K.; Strohmann, C.; Antonchick, A. P.; Waldmann, H. *Angew. Chem.*, *Int. Ed.* **2017**, *56*, 11232.

[4] For some recent examples for organocatalyzed asymmetric vinylogous reaction, see: (a) Han, J.-L.; Tsai, Y.-D.; Chang, C.-H. *Adv. Synth. Catal.* **2017**, *359*, 4043.
(b) Sakai, T.; Hirashima, S.; Yamashita, Y.; Arai, R.; Nakashima, K.; Yoshida, A.; Koseki, Y.; Miura, T. *J. Org. Chem.* **2017**, *82*, 4661.
(c) Kumar, K.; Jaiswal, M. K.; Singh, R. P. *Adv. Synth. Catal.* **2017**, *359*, 4136.
(d) Han, M.-Y.; Luan, W.-Y.; Mai, P.-L.; Li, P.; Wang, L. *J. Org. Chem.* **2018**, *83*, 1518.
(e) Bai, X.; Zeng, G.; Shao, T.; Jiang, Z. *Angew. Chem.*, *Int. Ed.* **2017**, *56*, 3684.
(f) Rout, S.; Joshi, H.; Singh, V. K. *Org. Lett.* **2018**, *20*, 2199.
(g) Arlt, A.; Toyama, H.; Takada, K.; Hashimoto, T.; Maruoka, K. *Chem. Commun.* **2017**, *53*, 4779.
(h) Silva, S.; Matsuo, B. T.; da Silva, R. C.; Pozzi, L. V.; Correa, A. G.; Rollin, P.; Zukerman-Schpector, J.; Ferreira, M. A. B.; Paixão, M. W. *J. Org. Chem.* **2018**, *83*, 1701.

[5] Curti, C.; Brindani, N.; Battistini, L.; Sartori, A.; Pelosi, G.; Mena, P.; Brighenti, F.; Zanardi, F.; Del Rio, D. *Adv. Synth. Catal.* **2015**, *357*, 4082.

[6] Denmark, S. E.; Heemstra, J. R., Jr.; Beutner, G. L. *Angew. Chem.*, *Int. Ed.* **2005**, *44*, 4682.

[7] (a) Cui, J.; Ohtsuki, A.; Watanabe, T.; Kumagai, N.; Shibasaki, M. *Chem.-Eur. J*. **2018**, *24*, 2598.
(b) Takeuchi, T.; Kumagai, N.; Shibasaki, M. *J. Org. Chem.* **2018**, *83*, 5851.

[8] Jing, Z.; Bai, X.; Chen, W.; Zhang, G.; Zhu, B.; Jiang, Z. *Org. Lett*. **2016**, *18*, 260.

[9] Boucard, V.; Broustal, G.; Campagne, J. M. *Eur. J. Org. Chem*. **2007**, *2007*, 225.

[10] Zhang, H.-J.; Yin, L. *J. Am. Chem. Soc.* **2018**, *140*, 12270.

[11] (a) Yuan, C.; Yao, J.; Li, S. *Phosphorus Sulfur Silicon Relat. Elem*. **1990**, *53*, 21.
(b) Yuan, C.; Yao, J.; Li, S. *Phosphorus Sulfur Silicon Relat. Elem*. **1991**, *55*, 125.
(c) Kisanga, K.; Verkade, J. G. *J. Org. Chem*. **2002**, *67*, 426.
(d) Chinkov, N.; Majumdar, S.; Marek, I. *J. Am. Chem. Soc.* **2003**, *125*, 13258.

[12] Yue, W.-J.; Zhang, C.-Y.; Yin, L. *iScience* **2019**, *14*, 88.

[13] Narasimhulu, M.; Reddy, T. S.; Mahesh, K. C.; Krishna, A. S.; Rao, J. V.; Venkateswarlu, Y. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 3125.

[14] Rivera-Fuentes, P.; Diederich, F. *Angew. Chem.*, *Int. Ed.* **2012**, *51*, 2818.

[15] (a) Zimmer, R.; Reissig, H.-U. *Chem. Soc. Rev.* **2014**, *43*, 2888.
(b) Wang, Z.; Xu, X.; Kwon, O. *Chem. Soc. Rev.* **2014**, *43*, 2927.

[16] (a) Pu, X.; Qi, X.; Ready, J. M. *J. Am. Chem. Soc.* **2009**, *131*, 10364.
(b) Cai, F.; Pu, X.; Qi, X.; Lynch, V.; Radha, A.; Ready, J. M. *J. Am. Chem. Soc.* **2011**, *133*, 18066.

[17] (a) Zhong, F.; Xue, Q.-Y.; Yin, L. *Angew. Chem.*, *Int. Ed.* **2020**, *59*, 1562.
(b) Ran, G.; Chen, Y. *Chin. J. Org. Chem.* **2020**, *40*, 814 (in Chinese).
(冉光尧, 陈应春, 有机化学, **2020**, *40*, 814.)

[18] Ran, G.-Y.; Chen, C.; Yang, X.-X.; Zhao, Z.; Du, W.; Chen, Y.-C. *Org. Lett.* **2020**, *22*, 4732.

[19] Bai, X.; Zeng, G.; Shao, T.; Jiang, Z. *Angew. Chem.*, *Int. Ed.* **2017**, *56*, 3684.

[20] Wang, S.-Q.; Liu, Z.-C.; Yue, W.-J.; Yin, L. *Angew. Chem.*, *Int. Ed.* **2021**, *60*, 4604.

[21] Wei, X.-F.; Xie, X.-W.; Shimizu, Y.; Kanai, M. *J. Am. Chem. Soc.* **2017**, *139*, 4647.

[22] (a) Zhong, F.; Pan, Z.-Z.; Zhou, S.-W.; Zhang, H.-J.; Yin, L. *J. Am. Chem. Soc.* **2021**, *143*, 4556.
(b) Gu, X.; Xu, L. *Chin. J. Org. Chem.* **2021**, *41*, 2528 (in Chinese).
(顾幸威, 徐利文, 有机化学, **2021**, *41*, 2528.)

[23] Ruan, S.-T.; Luo, J.-M.; Du, Y.; Huang, P.-Q. *Org. Lett*. **2011**, *13*, 4938.

[24] Trost, B. M.; Gnanamani, E.; Tracy, J. S.; Kalnmals, C. A. *J. Am. Chem. Soc.* **2017**, *139*, 18198.

[25] Zhang, H.-J.; Shi, C.-Y.; Zhong, F.; Yin, L. *J. Am. Chem. Soc.* **2017**, *139*, 2196.

[26] (a) Zhou, Z.; Feng, X.; Yin, X.; Chen, Y.-C. *Org. Lett.* **2014**, *16*, 2370.
(b) Dell'Amico, L.; Rassu, G.; Zambrano, V.; Sartori, A.; Curti, C.; Battistini, L.; Pelosi, G.; Casiraghi, G.; Zanardi, F. *J. Am. Chem. Soc*. **2014**, *136*, 11107.
(c) Ratjen, L.; García-García, P.; Lay, F.; Beck, M. E.; List, B. *Angew. Chem., Int. Ed.* **2011**, *50*, 754.
[27] 琵籣ong, F.; Yue, W.-J.; Zhang, H.-J.; Zhang, C.-Y.; Yin, L. *J. Am. Chem. Soc.* **2018**, *140*, 15170.
[28] Gribble, G. W. *Environ. Chem.* **2015**, *12*, 396.
[29] Zhang, H.-J.; Zhong, F.; Xie, Y.-C.; Yin, L. *Chin. J. Chem*. **2021**, *39*, 55.
[30] (a) Shiina, I.; Takasuna, Y.; Suzuki, R.; Oshiumi, H.; Komiyama, Y.; Hitomi, S.; Fukui, H. *Org. Lett.* **2006**, *8*, 5279.
(b) Fukui, H.; Shiina, I. *Org. Lett.* **2008**, *10*, 3153.
[31] Keeri, A. R.; Gualandi, A.; Mazzanti, A.; Lewinski, J.; Cozzi, P. G. *Chem.-Eur. J.* **2015**, *21*, 18949.
[32] (a) Arai, T.; Sato, T.; Noguchi, H.; Kanoh, H.; Kaneko, K.; Yanagisawa, A. *Chem. Lett.* **2006**, *35*, 1094.
(b) Tsang, A. S.-K.; Kapat, A.; Schoenebeck, F. *J. Am. Chem. Soc.* **2016**, *138*, 518.
[33] Zhang, H.-J.; Schuppe, A. W.; Pan, S.-T.; Chen, J.-X.; Wang, B.-R.; Newhouse, T. R.; Yin, L. *J. Am. Chem. Soc.* **2018**, *140*, 5300.

(Cheng, F.)

