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# Organocatalytic Enantioselective Synthesis of Tetrasubstituted α-Amino Allenoates by Dearomative γ-Addition of β,γ-alkynyl-α-imino esters and 2,3-disubstituted indoles

Junxian Yang,[a] Zheng Wang,[b] Zeyuan He,[a] Guofeng Li,[c] Liang Hong,[c] Wangsheng Sun*[a] and Rui Wang*[a]

**Abstract:** The first asymmetric synthesis of tetrasubstituted α-amino allenoates by chiral phosphoric acid catalyzed dearomative γ-addition reaction of 2,3-disubstituted indoles to β,γ-alkynyl-α-imino esters is reported. This methodology allows access to a series of highly functionalized tetrasubstituted allenes featuring adjacent quaternary stereocenter in high yields, with excellent regio-, diastereo-, and enantioselectivities under mild conditions without generation of any waste. The representative large-scale reactions and diverse transformations of products to various scaffolds with potential biological activities render it more attractive. Moreover, the mechanism of the reaction was disclosed by control reaction and DFT calculations.

Axially chiral allenes and derivatives are ubiquitous not only in natural products, pharmaceutical compounds and functional materials, but also as key intermediates in organic synthesis (Figure 1).[1] Accordingly, the synthesis of enantioenriched allenic compounds has inspired ample interest,[2] thus resulting in a variety of strategies towards their construction, such as chirality transfer from enantioenriched propargylic derivatives,[3] resolution of racemic allenes,[4] asymmetric synthesis of chiral allenes based on metal catalysis[5] and organocatalysis.[6] Despite these graceful efforts, most of the cases enabled constructing the allenes with relatively limited types of substituents and atomic economy. Therefore, it is urgently needed to develop a novel and direct strategy to achieve asymmetric construction of multifunctional tetrasubstituted chiral allenes.

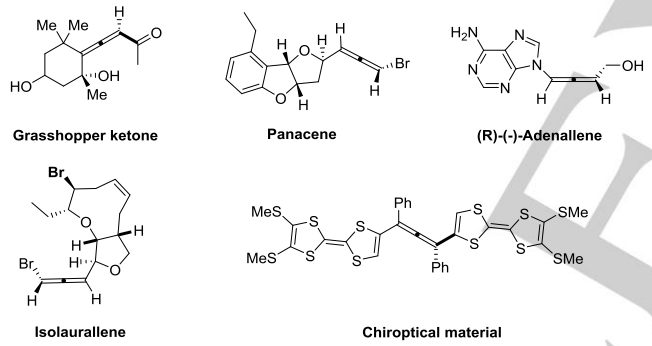
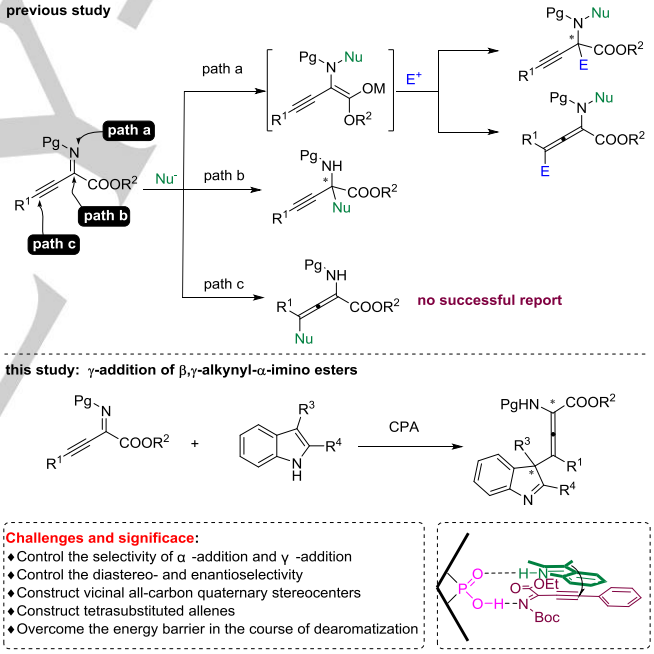



**Figure 1**. Biologically active compounds featuring allenic group.




**Scheme 1**. Reaction development of β ,γ-alkynyl-α-imino esters.

On the other hand, nonproteinogenic amino acids are vital synthetic building blocks of biologically active natural products and novel non-natural peptides with improved potency and increased the ability of resistance towards protease degradation under physiological conditions.[7] β,γ-Alkynyl-α-imino esters have been recognized as potential useful precursors for the synthesis alkynyl or alkenyl α-amino acids derivatives for more than a decade.[8] Surprisingly, however, very limited success has been achieved using this building block, probably due to its multiple reactive sites. For instance, Shimizu et al. reported an umpolung N-addition to β,γ-alkynyl α-imino esters followed by nucleophilic α- or γ-acylation for the synthesis of α-quatenary alkynyl amino

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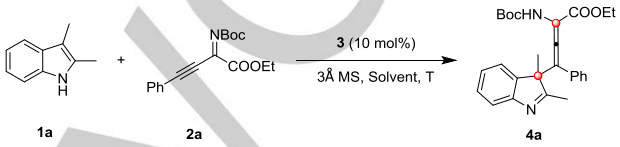
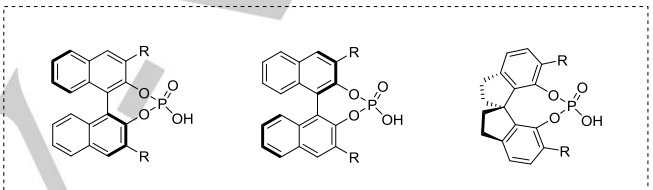
esters and allenoates (Scheme 1, path a).[8a] Meanwhile, Ishihara et al. developed a regio- and diastereoselective C-alkyl addition to chiral β,γ-alkynyl α-imino esters using a Grignard reagent (RMgX)-derived zinc(II)ate to construct optically active α-quaternary alkynyl amino acid derivatives (Scheme 1, path b).[8b] More recently, the same group has accomplished an enantioselective aza-Friedel-Crafts reaction of 2-methoxyfuran with β,γ-alkynyl-α-imino esters through the use of a chiral Brønsted acid catalyst, albeit with only one successful case.[8c] Nevertheless, a direct γ-addition of a nucleophile to β,γ-alkynyl-α-imino esters to form α-quatenary amino allenoates has never been disclosed (Scheme 1, path c).

In this context, as part of our recent interests in unnatural amino acid synthesis[9] and indole chemistry[10], we first chose indole as nucleophilic reagent to react with β,γ-alkynyl-α-imino ester. As a result, only the α-addition reaction occurs, which is consistent with the above precedents. Considering the steric hindrance may has an effect on the regioselectivity of the reaction, we replaced the nucleophilic reagent with 2,3-disubstituted indoles[11] in order to explore a new synthetic route to valuable tetrasubstituted α-amino allenoates. However, several challenges have to be considered: 1) the choice of an appropriate catalytic system to effective control of the regioselectivity, diastereoselectivity and enantioselectivity, 2) the formation of a vicinal all-carbon quaternary stereocenter, 3) the construction of a highly functionalized tetrasubstituted allene and 4) overcoming energy barriers caused by dearomatization. Considering the significant advantages of chiral phosphoric acid in the realm of asymmetric catalysis,[12,13,10a,10b] we hypothesized that a double-activation mode by hydrogen bonding could be applied to promote asymmetric γ-addition of 2,3-disubstituted indoles to β,γ-alkynyl-α-imino esters. If successful, this formidably challenging process would provide an attractive approach for efficient synthesis for fully substituted chiral α-amino allenoates.

We began our investigations by using the β,γ-alkynyl-α-imino esters **2a** in combination with 2,3-dimethylindole **1a** as a nucleophile in the presence of a catalyst **3** with 3 Å MS as an additive[14] (Table 1). As expected, the reaction proceeded smoothly at room temperature in the presence of catalyst **3a**, providing allene **4a** in satisfactory conversion within 6 h, albeit with poor selectivity (Table 1, entry 1). Some other catalysts with different scaffold were then evaluated. It was found that the chiral backbone and the steric environment of the catalysts have very strong influence on the diastereoselectivity and enantioselectivity (Table 1, entries 2−12). Pleasingly, we found that the use of **3l** resulted in quantitative conversion of **1a** and excellent diastereoselectivity, although the enantioselectivity of **4a** is not the highest (Table 1, entry 12). Notably, the **4a** with the opposite configuration could be synthesized in > 99% conversion with 96% ee and 15:1 dr when **3e** was used as a catalyst (Table 1, entry 5). Encouraged by these promising results, we then evaluated various solvents and a significant solvent effect was observed (Table 1, 12 - 16). The reaction has the worst outcome (7% ee, 2:1 dr) when THF was used as the solvent, while DCE was the most ideal for the reaction, affording **4a** in 88% yield , > 20:1 dr and 99% ee. The yield could be improved to 96% when the amount of substrate **1a** was increased to 1.2 equiv along with a slightly lower ee value. Further investigation revealed that lowering the reaction temperature was beneficial for improving the enantioselectivity (Table 1, entry 17-18). Ultimately, we recognized that the axially chiral α-amino allenoates **4a** could be obtained in 96% isolated yield with > 20:1 dr and 98% ee when the reaction was run at 0 °C with catalyst **3l** (10 mol%) and solvent DCE (0.05 M) (Table 1, entry 18). It was noteworthy that, in addition to replacing the catalyst with **3e**, the products with the opposite configuration could also be acquired with excellent efficiencies (92% yield, 18:1 dr, - 97% ee) under the optimum conditions.

**Table 1**. Optimization of the Reaction Conditions.[a]




**3a**: R=H
**3b**: R=3,5-$^{i}$PrC$_6$H$_3$
**3c**: R= 9-anthryl
**3d**: R= 2,4,6-$^{i}$Pr$_3$C$_6$H$_2$
**3e**: R= 2,3,4,5,6-Me$_5$C$_6$
**3f** : R= 3,5-Me$_2$C$_6$H$_3$

**3g**: R= Si$^{t}$BuPh$_2$
**3h**: R=3,5-$^{t}$BuC$_6$H$_3$
**3i**: R= 3,5-(CF$_3$)$_2$C$_6$H$_3$
**3j** : R= 1-pyrenyl

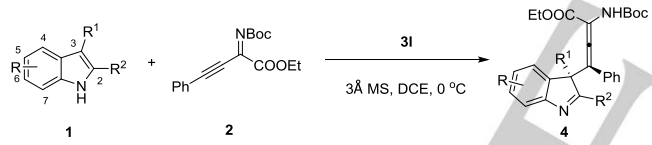
**3k**: R= 2,4,6-$^{i}$Pr$_3$C$_6$H$_2$
**3l** : R= 9-anthryl

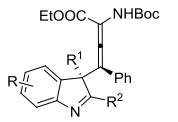
| Entry | Cat | Solvent | T(℃) | t(h) | Conv(%)[b] | dr[b] | ee(%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **3a** | DCM | r.t. | 6 | 90 | 1:1 | -43/44 |
| 2 | **3b** | DCM | r.t. | 6 | 90 | 6:1 | -93 |
| 3 | **3c** | DCM | r.t. | 6 | 95 | 6:1 | -97 |
| 4 | **3d** | DCM | r.t. | 6 | 85 | 10:1 | -82 |
| 5 | **3e** | DCM | r.t. | 6 | > 99 | 15:1 | -96 |
| 6 | **3f** | DCM | r.t. | 6 | 92 | 5:1 | -90 |
| 7 | **3g** | DCM | r.t. | 6 | 70 | 1:1 | -3/44 |
| 8 | **3h** | DCM | r.t. | 6 | 80 | 5:1 | 84 |
| 9 | **3i** | DCM | r.t. | 6 | 89 | 4:1 | -99 |
| 10 | **3j** | DCM | r.t. | 6 | > 99 | 2:1 | 92 |
| 11 | **3k** | DCM | r.t. | 6 | 70 | 3:2 | -17/3 |
| 12 | **3l** | DCM | r.t. | 6 | > 99 | > 20:1 | 95 |
| 13 | **3l** | $CHCl_3$ | r.t. | 6 | 97 | 20:1 | 84 |
| 14 | **3l** | Tol. | r.t. | 6 | 93 | 15:1 | 82 |
| 15 | **3l** | THF | r.t. | 6 | 80 | 2:1 | 77 |
| 16 | **3l** | DCE | r.t. | 6 | > 99(88)[d] | > 20:1 | 99 |

| | | | | | | | |
|---|---|---|---|---|---|---|---|
| 17[e] | **3l** | DCE | r.t. | 6 | > 99(96) [d] | > 20:1 | 96 |
| 18[e] | **3l** | DCE | 0 | 10 | > 99(96) [d] | > 20:1 | 98 |
| 19[e] | **3e** | DCE | 0 | 10 | > 99(92) [d] | 18:1 | -97 |

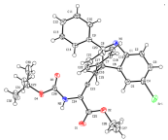
[a]Unless otherwise stated, the reaction was carried out with **1a** (0.07 mmol), **2a** (0.07 mmol), **3** (0.007 mmol) and 3 Å molecular sieves (70 mg) in 1.4 ml of the solvent. [b]Determined by $^1$H NMR analysis of the crude reaction mixture. [c]Ee of the major product was determined by HPLC using a chiralcel stationary phase. [d] Isolated yield of the major product was given in the parentheses. [e]The reaction was carried out with **1a** (0.084 mmol), **2a** (0.07 mmol).

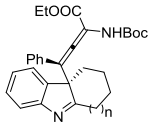
With the established optimal conditions, we next investigated the substrate scope of the dearomative γ-addition reaction of 2,3-disubstituted indoles with β,γ-alkynyl-α-imino esters. In general, the protocol was applicable to a wide range of 2,3-disubstituted indoles **1**, affording the desired products in moderate to excellent yields (69 − 99%), dr (9:1 - >20:1) and excellent ees (91 − 99%)(Scheme 2). Representative 2,3-dimethyl indoles with different electronic substituents at C5 position were all tolerated to give the corresponding products **4a** – **4f** in 96 - 98% yields, >20:1 dr with 99% ee. 2,3-Disubstituted indoles with various substitutions at C2 and C3 positions were also examined, and exhibited high efficiency in the reaction (**4g** – **4n**). Notably, the cyclic tetrahydrocarbazole and hexahydrocyclohepta[*b*]indole participated smoothly in the desired reaction, affording the polycyclic product **4m – 4n** with moderate to excellent yield, diastereoselectivity with excellent enantioselectivity. The absolute stereochemistry of the products **4** were assigned by analogy to **4i**, which was determined unambiguously by X-ray crystallographic analysis[15].




**4a**, R = H, $R^1$ = $R^2$ = Me, 96% yield, >20:1 dr, 98% ee
**4b**, R = 5-Me, $R^1$ = $R^2$ = Me, 98% yield, >20:1 dr, 99% ee
**4c**, R = 5-MeO, $R^1$ = $R^2$ = Me, 98% yield, >20:1 dr, 99% ee
**4d**, R = 5-F, $R^1$ = $R^2$ = Me, 96% yield, >20:1 dr, 99% ee
**4e**, R = 5-Cl, $R^1$ = $R^2$ = Me, 98% yield, >20:1 dr, 99% ee
**4f**, R = 5-Br, $R^1$ = $R^2$ = Me, 98% yield, >20:1 dr, 99% ee
**4g**, R = H, $R^1$ = Me, $R^2$ = Et, 92% yield, >20:1 dr, 96% ee
**4h**, R = 5-F, $R^1$ = Me, $R^2$ = Et, 90% yield, 19:1 dr, 99% ee
**4i**, R = 5-Br, $R^1$ = Me, $R^2$ = Ph, 99% yield, >20:1 dr, >99% ee[b]
**4j**, R = H, $R^1$ = Et, $R^2$ = Me, 95% yield, >20:1 dr, 98% ee
**4k**, R = H, $R^1$ = Bn, $R^2$ = Me, 98% yield, >20:1 dr, 95% ee
**4l**, R = H, $R^1$ = $^n$Pr, $R^2$ = Me, 95% yield, > 20:1 dr, 96% ee

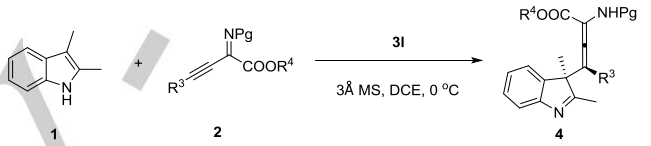

X-ray structure of **4i**

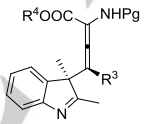



**4m**, n = 1, 97% yield, >20:1 dr, 98% ee
**4n**, n = 2, 69% yield, 9:1 dr, 91% ee[c]

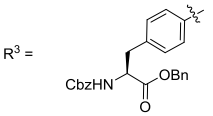
**Scheme 2**. Scope of the disubstituted indoles.[a] [a]Unless otherwise stated, the reaction was carried out with **1a** (0.084 mmol), **2a** (0.07 mmol), **3l** (0.007 mmol) and 3 Å molecular sieves (70 mg) in 1.4 ml of DCE for 10 h. The yield refers to the isolated yield of the major product. Dr was determined by $^1$H NMR analysis of the crude reaction mixture. Ee was determined by HPLC using a chiralcel stationary phase. [b]The reaction was carried out for 6 h. [c]The reaction was carried out for 14 h.

To further study the scope of this catalytic system, we then evaluated the reaction of 2,3-dimethylindole with various β,γ-alkynyl-α-imino esters (Scheme 3). The catalytic system proved to be suitable for the γ-addition of β,γ-alkynyl-α-imino esters with either electron-donating (**4o** - **4s**) or electron-withdrawing substituents (**4t** - **4v**) present in the phenyl ring at $R^3$ group, giving rise to the allenoates with ee values generally higher than 95%. Furthermore, not only bulky naphthyl groups (**4w**, **4x**) but also heterocycle (**4y**), alkenyl (**4z**, **4aa**), alkyl (**4ab**) could be incorporated into the reactions. It is particularly noteworthy that this protocol can also be applied to side chain modification of Cbz-Tyr-OBn to construct new diaminodiacid derivative with different types of protective groups (**4ac**, 91% yield, 16:1 dr, 95% ee). Similarly, late-stage installation to an estrone-derived complex molecule (**4ad**, 92% yield, 18:1 dr, 91% ee) could be achieved. By this means, we might introduce complex active molecules into amino acid molecules. In addition, the reactions were also applicable to β, γ-alkynyl-α-imino esters with N-Cbz, COOMe or COOBn substitution, producing the corresponding products **4ae** - **4ag** in outstanding results.

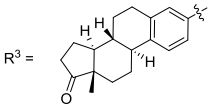


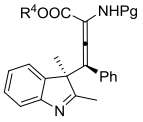

**4o**, $R^3$ = 2-Me$C_6H_4$, 99% yield, > 20:1 dr, 99% ee
**4p**, $R^3$ = 3-Me$C_6H_4$, 96% yield, > 20:1 dr, 99% ee
**4q**, $R^3$ = 4-Me$C_6H_4$, 98% yield, > 20:1 dr, 99% ee
**4r**, $R^3$ = 4-$^t$Bu$C_6H_4$, 95% yield, 18:1 dr, 96% ee
**4s**, $R^3$ = 4-OMe$C_6H_4$, 97% yield, > 20:1 dr, 95% ee
**4t**, $R^3$ = 4-F$C_6H_4$, 98% yield, > 20:1 dr, 96% ee
**4u**, $R^3$ = 4-Cl$C_6H_4$, 99% yield, > 20:1 dr, 95% ee
**4v**, $R^3$ = 4-Br$C_6H_4$, 97% yield, > 20:1 dr, 95% ee
**4w**, $R^3$ = 1-Naphthyl, 97% yield, > 20:1 dr, 97% ee
**4x**, $R^3$ = 2-Naphthyl, 98% yield, > 20:1 dr, 95% ee
**4y**, $R^3$ = 2-thienyl, 98% yield, > 20:1 dr, 95% ee
**4z**, $R^3$ = PhCH=CH, 99% yield, > 20:1 dr, 86% ee
**4aa**, $R^3$ = 1-Cyclohexenyl, 98% yield, > 20:1 dr, 96% ee[b]
**4ab**, $R^3$ = Cyclopropyl, 70% yield, 18:1 dr, 92% ee[c]




**4ac**, 91% yield, 16:1 dr, 95% ee




**4ad**, 92% yield, 18:1 dr, 91% ee




**4ae**, Pg=Cbz, $R^4$ = Et, 95% yield, > 20:1 dr, 98% ee
**4af**, Pg=Boc, $R^4$ = Me, 99% yield, > 20:1 dr, 99% ee
**4ag**, Pg=Boc, $R^4$ = Bn, 99% yield, > 20:1 dr, 99% ee

**Scheme 3**. Scope of β,γ-alkynyl-α-imino esters.[a] [a]Unless otherwise stated, the reaction was carried out with **1a** (0.084 mmol), **2a** (0.07 mmol), **3l** (0.007 mmol) and 3 Å molecular sieves (70 mg) in 1.4 ml of DCE for 10 h. The yield refers to the isolated yield of the major product. Dr was determined by $^1$H NMR analysis of the crude reaction mixture. Ee was determined by HPLC using a chiralcel stationary phase. [b]The reaction was carried out for 14 h. [c]The reaction was carried out for 6 h.

To demonstrate the potential scalability and utility of this protocol, we conducted a gram-scale reaction with **1a** and **2a** under the standard reaction conditions (Scheme 4a). Gratifyingly, the reaction proceeded smoothly and product **4a** was isolated

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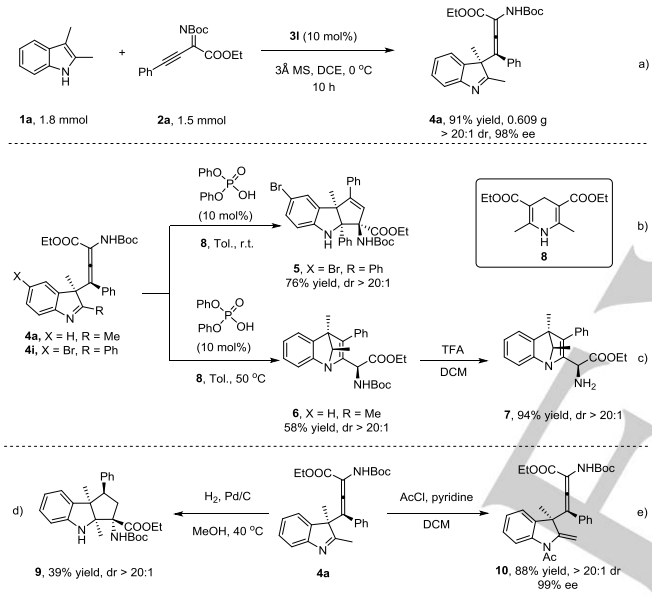
without significant erosion of yield, diastereoselectivity, and enantioselectivity. Furthermore, a series of representative transformations of the products **4a** and **4i** were also carried out. In the presence of catalyst diphenyl phosphates and Hantzsch esters **8**, **4i** and **4a** could be straightforward transformed into tetrahydrocyclopenta[*b*]indoline **5** and 4*H*-1,4-methanoquinoline **6** with perfect diastereoselectivities (d.r. > 20:1) and moderate yields (76% and 58%)(Scheme 4b and 4c). These two products might serve as candidates or building blocks of biologically active molecules.[16] Notably, the N-Boc protecting group in **6** could be removed to give product **7** bearing a free amino group in 94% yield (Scheme 4c). Furthermore, subjecting **4a** to a Pd/C catalyzed reduction reaction afforded hexahydrocyclopenta[*b*]indoline **9** in 39% yield and >20:1 dr under $H_2$ atm (Scheme 4d). In addition, **10** was formed by treating **4a** with AcCl in DCM without any loss of enantiopurity (Scheme 4e).




**Scheme 4**. Gram-scale Preparation of **4a** and Representative Transformations of Products **4**.

To get an insight of this reaction, control experiments were performed (Scheme 5). Under the above optimized reaction conditions, in contrast to the above high efficiency of the reaction, moderate yield and enantioselectivity of γ-addition product **12** was obtained when 3-methyl indole was used (Scheme 5a), while only α-addition product **14** was formed when 2-methyl indole was used (Scheme 5b). It indicated that the steric hindrance of the C3 substituents of indoles is vital for the selectivity of α or γ-addition to β, γ-alkynyl-α-imino esters **2a**, meanwhile, the C2 substituent of indoles is beneficial for its enantioselectivity. In addition, when an alkynyl trifluoromethyl ketimine was subjected to the reaction, only the α-addition product **16** was still prepared (Scheme 5c), thus implying that the COOR group of the β,γ-alkynyl-α-imino esters plays a crucial role in the reaction, possibly by generation of spatial steric hindrance.

In an effort to better understand the reaction profile, density functional theory (DFT) calculations at the the M06-2X/6-311+G(d,p)-PCM (dichloroethane)//B3LYP/6-31G(d)-PCM (dichloroethane) level of theory were carried out[17].It revealed that a kinetically favored transition state of $\mathbf{TS_{BC\text{-}R}}$ (Figure 2. For more details, see the SI) could be formed during the reaction. The phosphoric acid moiety of the catalyst plays a bifunctional role for activation of both partners via H-bond interaction and the steric chiral backbone of the catalyst controls the stereoselectivity via steric effect and π - π interaction.

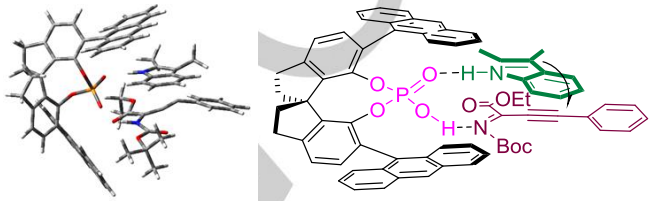
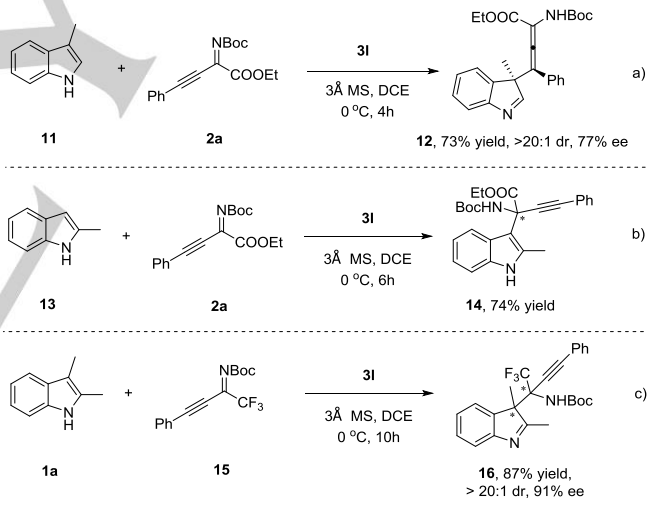


**Figure 2**. The geometrical structures of $\mathbf{TS_{BC\text{-}R}}$ (left) and proposed transition state (right).




**Scheme 5**. Control experiments.

In summary, we have developed a chiral phosphoric acid catalyzed asymmetric dearomative γ-addition reaction of 2,3-disubstituted indoles with β,γ-alkynyl-α-imino esters, which represented the first example of synthesis chiral tetrasubstituted α-amino allenoates featuring adjacent quaternary stereocenters with outstanding efficiencies, ample reaction scope and high atom economy. The resultant amino allenoates could be easily converted into other important building blocks as exemplified by the synthesis of the cyclopenta[*b*]indolines and 4*H*-1,4-methanoquinoline. Furthermore, the reaction mechanism was investigated by control reactions and DFT calculations.

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**Keywords:** allenes • α-amino acid • disubstituted indoles • γ-addition • organocatalysis

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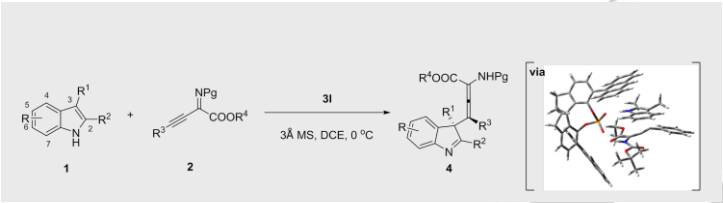


The first asymmetric synthesis of tetrasubstituted α-amino allenoates by chiral phosphoric acid catalyzed dearomative γ-addition reaction of 2,3-disubstituted indoles to β,γ-alkynyl-α-imino esters is reported. This methodology allows access to a series of highly functionalized tetrasubstituted allenes featuring adjacent quaternary stereocenter in high yields, with excellent regio-, diastereo-, and enantioselectivities.

*Junxian Yang, Zheng Wang, Zeyuan He, Guofeng Li, Liang Hong, Wangsheng Sun* and Rui Wang**

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**Organocatalytic Enantioselective Synthesis of Tetrasubstituted α-Amino Allenoates by Dearomative γ-Addition of β,γ-alkynyl-α-imino esters and 2,3-disubstituted indoles**