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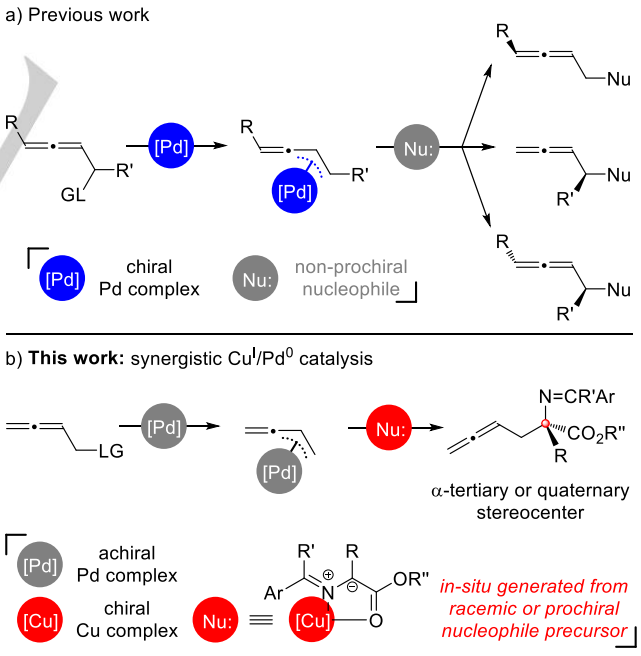
Synergistic Cu/Pd Catalyzed Asymmetric Allenylic Alkylation of Azomethine Ylides for the Construction of α-Allenylic Substituted Nonproteinogenic α-Amino Acids

Hua-Chao Liu,[a] Yuan-Zheng Hu,[a] Zuo-Fei Wang,[a] Hai-Yan Tao,[a] and Chun-Jiang Wang*[a,b]

Abstract: An unprecedented asymmetric allenylic alkylation of readily available imine esters enabled by a synergistic Cu/Pd catalysis has been developed. This dual catalytic system possesses good substrate compatibility, delivering a diverse array of nonproteinogenic α-allenylic α-mono- or α,α-disubstituted α-amino acids (α-AAs) with high yields and generally excellent enantioselectivities. Furthermore, the scalability and practicability of the current synthetic protocol were highlighted in the gram-scale reactions and the first catalytic asymmetric synthesis of naturally occurring (*S*)-γ-allenic α-amino acid, respectively.

Optically active nonproteinogenic α-monosubstituted or α,α-disubstituted α-amino acids (α-AAs) are privileged constituents of numerous biologically active natural compounds and pharmaceutical ingredients.[1] For example, these versatile structure motifs have been frequently found in unique enzyme inhibitors[2] and pharmacologically important non-natural peptides and proteins with enhanced functionalities.[3] On the other hand, allenic-containing compounds also attracted much attention due to their important chemical and biological properties in synthetic transformations[4] and drug molecules[5] as well as natural products.[4c,5a,6] In view of these unique features of both nonproteinogenic α-AAs and allene units, developing an efficient approach to access nonproteinogenic α-AAs bearing an allenic moiety in a highly enantioselective manner is of great significance and also very desirable.

With operationally simplicity and synthetically utility, the palladium-catalyzed enantioselective allenylic alkylation of racemic 2,3-allenol derivatives involving chiral vinyl-π-allylpalladium intermediate[7] has emerged as one of the commonly used tools to synthesize enantiomerically enriched allenes or allenylic substitution products. Among these elegant methodologies using chiral palladium η^3-butadienyl species as electrophiles, most of the reported examples focused on the construction of allenes with axial chirality,[8] and the established arts capable of acquiring allene derivatives containing central chirality[8g,9] are still rare to date (Scheme 1a). Furthermore, the enantiocontrol of nucleophiles has not been touched yet in all of these known cases, probably due to the synthetic challenge existed in palladium-catalyzed asymmetric allylation reaction, that is, the long distance between the catalytic site of chiral palladium complex and the reaction site in nucleophile reagents.[10] Recently, we and others have developed a new set of dual catalytic systems for the efficient asymmetric allylic alkylation reactions[10b,11,12] of readily-available imine esters, in which a combination of chiral Cu(I) complex and achiral Pd(0) complex[13] or chiral Pd(0) complex[14] has been successfully employed as the synergistic catalysts, leading to various α-quaternary nonproteinogenic α-AAs[15] with impressive results. Merging our previous work[13] and the proposed palladium-catalyzed allenylation mechanism,[7] we envisaged that a synergistic chiral Cu/achiral Pd complexes could be employed for the asymmetric α-allenylic functionalization of racemic or prochiral imine esters, providing a range of enantiomerically enriched α-allenylic α-AAs wherein the generated α-quaternary or α-tertiary stereogenic center was located in nucleophile moiety (Scheme 1b). In this catalytic manner, achiral palladium complex instead of chiral palladium complex commonly-used in conventional protocols produced the active vinyl-π-allyl-palladium intermediate as electrophile,[7] while chiral copper complex delivered metallated azomethine ylide as effective nucleophile under basic condition,[16] and the effective coupling of *in situ*-formed achiral electrophilic and chiral nucleophilic species provided an expedient access to optically active nonproteinogenic α-AAs featuring an allenic moiety and α-quaternary or tertiary stereogenic center.



Scheme 1. Catalytic asymmetric allenylic alkylation of *non*-prochiral nucleophiles with chiral Pd complex (Previous work) and prochiral or racemic nucleophiles with achiral Pd/chiral Cu dual catalysis (This work). LG = leaving group.

To probe this hypothesis, we first selected alanine-derived aldimine ester **2a** and buta-2,3-dien-1-yl diethyl phosphate **1a'** as the model substrates to identify the optimal reaction conditions. Based on our previous works,[14] the initial study was conducted with Cu(I)/**L1** complex and $Pd(PPh_3)_4$ as the

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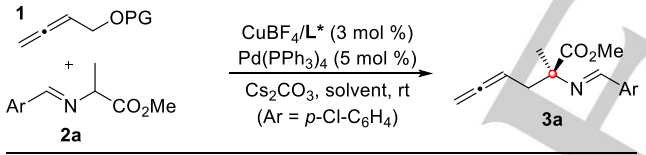
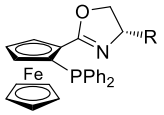
combined catalysts and Cs_2CO_3 as the base. To our delight, the reaction proceeded smoothly at room temperature, affording the desired α-allenylic product **3a** in 72% yield with good enantioselectivity and exclusive regioselectivity (no 1,3-dienes isomer was observed, Table 1, entry 1). Further evaluations of other chiral ligands (entries 2-5), protecting groups (entries 6-8), solvent (entries 9-11) revealed that the combination of Cu(I)/**L3** and $Pd(PPh_3)_4$ complexes as the catalyst, 2,3-allenol-derived allenylic carbonate **1a** as electrophile precursor and dichloromethane as solvent was the best of choice, affording enantiomerically enriched α-quaternary α-amino acid derivative **3a** with 85% yield and 97% ee (entry 7). However, when switching the nucleophile precursor to phenylalanine-derived aldimino ester **2i**, this allenylic alkylation process suffered from a sharp decrease of enantioselectivity (35% ee) (equation of Chart 1). To obtain a more satisfactory outcome, we further re-optimized reaction conditions through the screening of phosphine ligands with Pd_2dba_3 as a palladium source. Among a series of tested monophosphine and large-bite-angle bisphosphine ligands, ^{t}BuXPhos exhibited a dramatic improvement on stereocontrol, which was identified as the optimal reaction parameter to produce the product **3i** with still excellent yield and acceptable enantioselectivity. Additionally, the related control experiments proved that Cu(I)/**L3** complex was indispensable to the generation of active azomethine ylide (Table S1 in Supporting Information, entries 2-3). On the other hand, no reaction occurred when Pd(0)/^{t}BuXPhos complex was excluded, which implied that a directed S_N2 reaction did not existed in this allenylation process (Table S1, entry 4). It was notable that the reaction still worked without ^{t}BuXPhos ligand, affording the product **3a** with 99% ee but only 44% yield (Table S1, entry 5) and **3i** with 41% yield and 30% ee (Table S1, entry 7). Consequently, the combination of Cu(I)/**L3** complex and Pd(0)/^{t}BuXPhos complex as cocatalyst was essential for such asymmetric transformation.

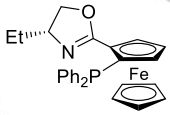
Table 1: Optimization of Reaction Conditions[a]





(*S*,*S*$_p$)-Phosferrox

L1: R = ^{i}Pr
L2: R = ^{t}Bu
L3: R = Ph
L4: R = Bn



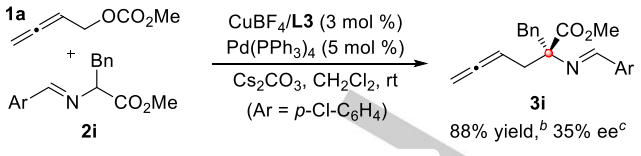
(*R*,*R*$_p$)-Et-Phosferrox (**L5**)

entry	L	PG	solvent	yield (%)[b]	ee (%)[c]
1	**L1**	P(O)(OEt)$_2$	CH_2Cl_2	72	88
2	**L2**	P(O)(OEt)$_2$	CH_2Cl_2	77	73
3	**L3**	P(O)(OEt)$_2$	CH_2Cl_2	84	95
4	**L4**	P(O)(OEt)$_2$	CH_2Cl_2	65	80
5	**L5**	P(O)(OEt)$_2$	CH_2Cl_2	82	-79
6	**L3**	Ac	CH_2Cl_2	56	91
7	**L3**	CO_2Me	CH_2Cl_2	85	97
8	**L3**	Boc	CH_2Cl_2	86	95
9	**L3**	CO_2Me	PhMe	41	60
10	**L3**	CO_2Me	THF	54	39
11	**L3**	CO_2Me	Et_2O	59	66

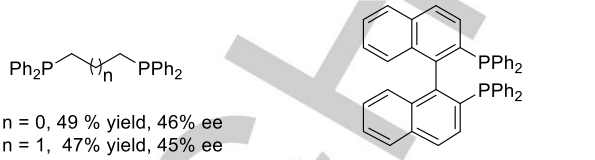
[a] All reactions were carried out with 0.20 mmol of aldimino ester **2a** and 0.24 mmol of terminal allenes **1** in 2 mL of solvent at rt for 12-16 h; $CuBF_4$ = $Cu(MeCN)_4BF_4$, PG = protecting group. [b] Isolated yield based on **2a**. [c] Ee was determined by HPLC analysis.

With the optimized reaction conditions established, we first explored the scope with respect to the nucleophile precursors and the related results were illustrated in Table 2. Various α-linear alkyl substituted aldimino esters **2a**-**2f** reacted well with terminal 2,3-alleneol derivative **1a**, leading to the corresponding

Chart 1: Re-optimization of Pd complexes[a]

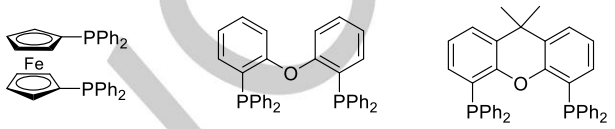


$Pd_2(dba)_3$ — *Bisphosphine ligands*



L6: n = 0, 49 % yield, 46% ee
L7: n = 1, 47% yield, 45% ee
L8: n = 2, 48 % yield, 43% ee
L9: n = 3, 56 % yield, 26% ee
L10: n = 4, 46 % yield, 11% ee

L11: (*R*)-BINAP, 91 % yield, 65% ee
L12: (*S*)-BINAP, 90 % yield, 52% ee
L13: (*rac*)-BINAP, 90 % yield, 61% ee

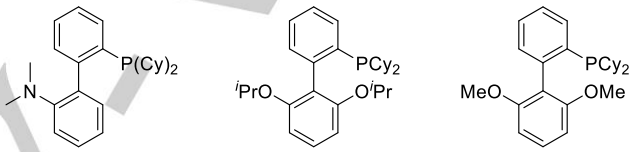


L14: DPPF
94 % yield, 46% ee

L15: DPEPhos
95 % yield, 57% ee

L16: XantPhos
trace

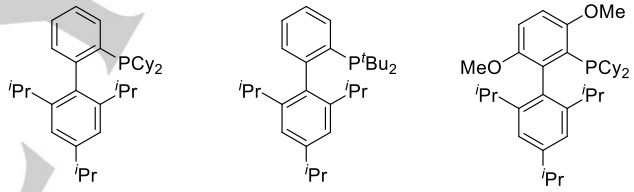
$Pd_2(dba)_3$ — *Monophosphine ligands*



L17: DavePhos
81 % yield, 30% ee

L18: RuPhos
93 % yield, 76% ee

L19: SPhos
90 % yield, 63% ee



L20: XPhos
91 % yield, 61% ee

L21: ^{t}BuXPhos
96 % yield, 80% ee

L22: BrettPhos
88 % yield, 31% ee

[a] All reactions were carried out with 0.20 mmol of aldimino ester **2i** and 0.24 mmol of terminal allene **1a** in 2 mL of CH_2Cl_2 at rt while 2.5 mol % Pd_2dba_3 and 5.0 mol % bisphosphine or monophosphine ligands **L6**-**L22** were used for further screening. [b] Isolated yield based on **2i**. [c] Ee was determined by HPLC analysis.

α-allenylic substitution products **3a**-**3f** exclusively in good yields (78-87%) and excellent enantioselectivities (96->99% ee) (Table 3, entries 1-6). Additionally, aldimino esters **2g** and **2h** bearing branched isobutyl and phenyl group could be also tolerated, resulting in high yield with relatively lower enantioselectivity (86% and 82% ee, respectively) presumably because of the steric repulsion (entries 7 and 8). Different from phenylalanine-derived imino esters **2i** (entry 9), homophenylalanine-derived **2j** did not suffered from a decrease of enantioselectivity (96% ee, entry 10). Then, when aldimine esters **2k** and **2l** decorated with allyl moiety at the α-position were used as the nucleophile precursors, the reactions also performed well to afford the corresponding products **3k** and **3l** with the satisfactory outcomes (93% and 95% ee, entries 11 and 12). Furthermore, high yield with excellent enantioselectivity were also obtained when aldimine esters **2m**-**2n** bearing heteroatom-containing α-functional groups underwent this process (entries 13 and 14). It was worth noting that lactonic imine derived from *rac*-homoserine was also a suitable reaction partner, furnishing the corresponding α-allenylic α-amino acid derivative **3o** in high yield and excellent enantioselectivity (87% yield and 98% ee, entry 15).

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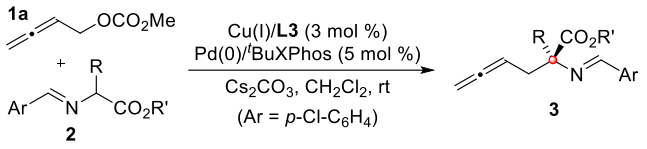
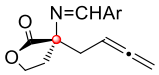
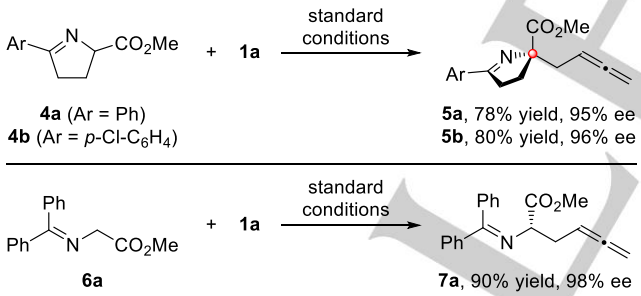
Table 2: Substrate Scope of Aldimino Esters[a]



entry	R	R'	3	yield (%)[b]	ee (%)[c]
1	Me	Me	**3a**	85	>99
2	Me	Et	**3b**	86	99
3	Me	*t*Bu	**3c**	78	>99
4	Et	Me	**3d**	86	>99
5	*n*Pr	Me	**3e**	87	96
6	*n*Bu	Me	**3f**	82	96
7	*i*Bu	Me	**3g**	88	86
8	Ph	Me	**3h**	93	82
9	$PhCH_2$	Me	**3i**	96	80
10	$PhCH_2CH_2$	Me	**3j**	76	96
11	Ally	Me	**3k**	81	93
12	Crotyl	Me	**3l**	84	95
13	$MeSCH_2CH_2$	Me	**3m**	78	90
14	$MeO_2CCH_2CH_2$	Me	**3n**	82	97
15			**3o**	87	87

[a] All reactions were carried out with 0.20 mmol of **2** and 0.24 mmol of **1a** in 2 mL of CH_2Cl_2. [b] Isolated yield based on **2**. [c] Ee was determined by HPLC analysis.

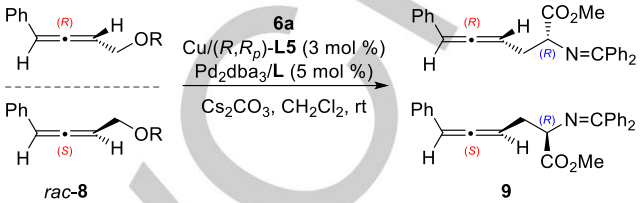
Next, we turned our attention to investigate a series of challenging ketimino esters with the relatively lower acidity of α-H atom.[17] As disclosed in Scheme 2, the processes employing cyclic ketimino esters **4a** and **4b** as nucleophilic precursors exhibited excellent asymmetric induction and the corresponding α-quaternary α-AAs **5a** and **5b** were isolated in high yield (78-80%) and excellent enantioselectivity (95-96% ee) (Scheme 2, upside). Meanwhile, the benzophenone-derived imine esters **6a** also performed well in such allenylation reaction giving a 90% yield of α-AAs **7a** bearing a α-tertiary stereogenic center with 98% ee (Scheme 2, bottom).



Scheme 2. Enantioselective Allenylic Alkylation of Cyclic and Acyclic Ketimino esters.

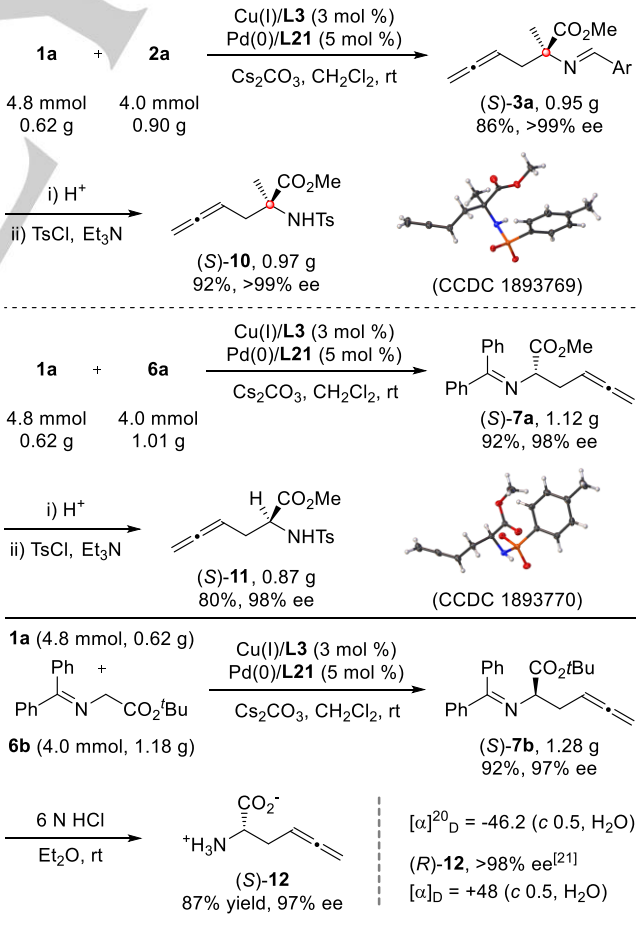
To further investigate the generality and limitation of this protocol, attempts with racemic internal allene **8** bearing a phenyl group were carried out and the preliminary dynamic kinetic resolution results were summarized in Table 3. First, the allenylation process utilizing the above optimized conditions proceeded smoothly, giving the α-allenylic product **9** with both axial chirality and central chirality in high yield albeit with low diastereoselectivity and moderate enantioselectivity (Table 1, entry 1). Subsequently, screening of a series of the ferrocene-based chiral P,N-ligand coordinated to copper salt (see the SI for more details) and chiral P-ligands coordinated to Pd_2dba_3 revealed that the combination of Cu(I)/(R,R_p)-**L5** and Pd(0)/(*S*)-BINAP complex was a feasible dual catalytic system to facilitate simultaneous control of central and axial chiralities, thus providing compound **9** in 80% yield, 97% ee with 9:1 dr (entry 3). Further evaluations of protecting groups, temperature and catalyst loading showed that the conditions in entry 7 were the best of choice leading to chiral allene **9** in 92% yield and 99% ee with 18:1 dr (See Table S2 in Supporting Information for details). Excellent enantioselectivity but poor diastereoselectivity could be observed in such challenging process when (*R*)-BINAP was coordinated with palladium precursor, which probably resulted from mismatching relationship between *in-situ* generated metallated azomethine ylide coordinated with Cu(I)/(R,R_p)-**L5** complex and vinyl-π-allylpalladium specie formed by Pd(0)/(*R*)-BINAP complex (entry 8).[18,19]

Table 3: Preliminary Results on Dynamic Kinetic Asymmetric Allenylation[a]



entry	L	R	dr	yield (%)[b]	ee (%)[c]
1	**L21**	CO_2Me	5:2	85	72
2	*rac*-**L13**	CO_2Me	2:1	86	78
3	(*S*)-**L12**	CO_2Me	9:1	78	97
4	(*S*)-**L12**	Ac	8:1	40	94
5	(*S*)-**L12**	Boc	9:1	81	98
6	(*S*)-**L12**	$P(O)(OEt)_2$	11:1	93	99
7[d][e]	(*S*)-**L12**	$P(O)(OEt)_2$	18:1	92	99
8[d][e]	(*R*)-**L11**	$P(O)(OEt)_2$	1:2	90	98

[a] All reactions were carried out with 0.20 mmol of **6a** and 0.24 mmol of *rac*-**8** in 2 mL of CH_2Cl_2 with Cs_2CO_3 as base. [b] Isolated yield. [c] Dr was determined by crude ^1H NMR, and ee was determined by HPLC analysis. [d] Carried out at 0 °C. [e] Run with 2 mol% Pd(0) complex catalyst.



Scheme 3. Gram-scale Reactions and the First Catalytic Asymmetric Synthesis of Naturally Occurring (*S*)-2-Aminohexa-4,5-dienoic acid **12**.

To demonstrate the scalability and utility of the current protocol, gram-scale synthesis of α-allenylic α-AAs **3a** and **7a** was performed, and comparable yields were obtained with maintained enantioselectivities. Subsequent acidic hydrolysis and tosylation furnished 92% yield of **10** with >99% ee and 80% yield of **11** with 98% ee, respectively (Scheme 3, upside). The absolute configuration of the **3a** and **7a** was identified as (*S*)-configuration by single-crystal X-ray diffraction analysis of Ts-protected **10** and **11**. Furthermore, with the developed protocol, catalytic asymmetric synthesis of naturally occurring (*S*)-2-aminohexa-4,5-dienoic acid **12** was successfully realized for the first time. With benzophenone-derived imine ester **6b** and allenylic carbonate **1a** as the starting materials, the coupling product **7b** was obtained in 92% yield with 97% ee with the current dual Cu/Pd catalytic system. Subsequent acidic hydrolysis of compound **7b** directly produced enantiomerically enriched natural product (*S*)-**12**[20,21] (Scheme 3, bottom).

In conclusion, we have successfully developed a highly efficient dual Cu/Pd catalytic system for asymmetric α-allenylation of readily-available aldimine, cyclic and acyclic ketimine esters. This protocol allows for the rapid construction of a range of synthetically important nonproteinogenic α-allenylic α-amino acids bearing α-quaternary or α-tertiary stereogenic center in a highly stereoselective fashion. This synergistic catalytic system also showcased the potential of simultaneous control of central and axial chirality with racemic internal allenylic diethyl phosphate. Furthermore, with the synergistic Cu/Pd catalytic system, naturally occurring (*S*)-γ-allenic α-amino acid was synthesized via a catalytic asymmetric manner for the first time. Further efforts on applications of this methodology are currently being conducted in our laboratory.

Acknowledgements

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Keywords: nonproteinogenic α-amino acids • allene • synergistic catalysis • asymmetric allenylic alkylation • asymmetric catalysis

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[19] The reaction with 3,4-allenol-derived secondary allenylic phosphate *rac*-**13** as the reaction partner was carried out in the presence of the combination of Cu(I)/(*S*,S_p)-**L3** and Pa(0)/(*S* or *R*)-BINAP as dual

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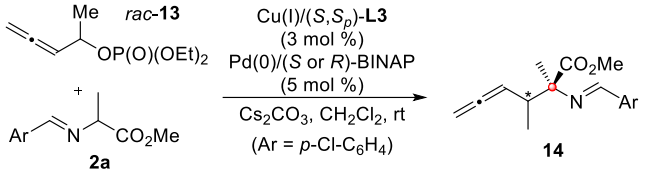
catalyst, providing α-allenylic product **14** with two contiguous stereogenic center with 4.6:1 and 4:1 dr, respectively (see supporting information for the detail). Unfortunately, the racemic **14** proved to be prohibitively challenging to separate into individual enantiomers by chiral-phase analytic HPLC.



[Cu/(S,S_p)-**L3** + Pd/(*S*)-BINAP]: 41% yield, 4.6:1 dr
[Cu/(S,S_p)-**L3** + Pd/(*R*)-BINAP]: 43% yield, 4.0:1 dr

[20] (*S*)-2-Aminohexa-4,5-dienoic acid is a naturally occurring α-amino acid of which several synthesis have been reported. Isolation: a) W. S. Chilton, G. Tsou, L. Kirk, R. G. Benedict, *Tetrahedron Lett.* **1968**, 6283. Racemic synthesis: b) D. K. Black, S. R. Landor, *J. Chem. Soc. (C)* **1968**, 281; c) D. K. Black, S. R. Landor, *J. Chem. Soc. (C)* **1968**, 283; d) B. Cazes, D. Djahanbini, J. Goré, J.-P. Genêt, J.-M. Gaudin, *Synthesis* **1988**, 983. (*S*)-Enantiomer synthesis: e) J. E. Baldwin, R. M. Adlington, A. Basak, *J. Chem. Soc., Chem Commun.* **1984**, 1284; f) M. J. Dunn, R. F. W. Jackson, J. Pietruszka, D. J. Turner, *J. Org. Chem.* **1995**, *60*, 2210.

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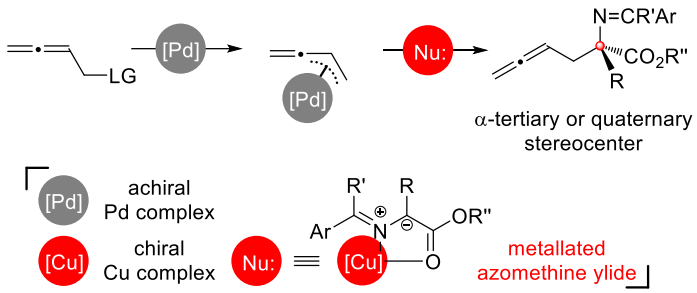

An unprecedented asymmetric allenylic alkylation of readily available imine esters enabled by a synergistic Cu/Pd catalysis has been developed. This dual catalytic system possesses good substrate compatibility, delivering a diverse array of nonproteinogenic α-allenylic α-mono- or α,α-disubstituted α-amino acids (α-AAs) with high yields and generally excellent enantioselectivities. Furthermore, the scalability and practicability of the current synthetic protocol were highlighted in the gram-scale reactions and the first catalytic asymmetric synthesis of naturally occurring (*S*)-γ-allenic α-amino acid, respectively.

Hua-Chao Liu, Yuan-Zheng Hu, Zuo-Fei Wang, Hai-Yan Tao, and Chun-Jiang Wang*

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Synergistic Cu/Pd Catalyzed Asymmetric Allenylic Alkylation of Azomethine Ylides for the Construction of α-Allenylic Nonproteinogenic Substituted α-Amino Acids