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**Authors:** Chun-Jiang Wang, Liang Wei, Shi-Ming Xu, Qiao Zhu, and Chao Che



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# A Cu/Pd Synergistic Dual Catalysis for Enantioselective Allylic Alkylation of Aldimine Esters: A Facile Access to α,α-Disubstituted α-Amino Acids

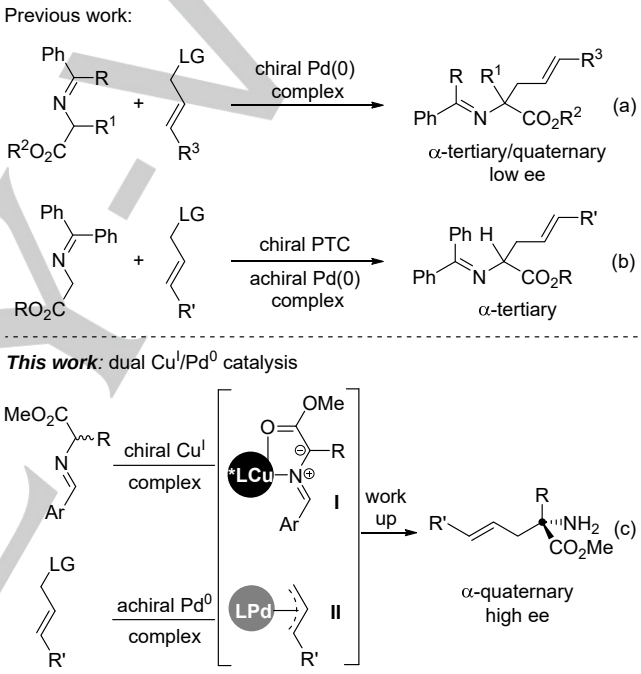
Liang Wei,[a] Shi-Ming Xu,[a] Qiao Zhu,[a] Chao Che,[a] and Chun-Jiang Wang*[a,b]

Dedicated to Professor Qi-Lin Zhou on the occasion of his 60th Birthday

**Abstract:** An unprecedented enantioselective allylic alkylation of readily-available aldimine esters has been developed, which was efficiently catalyzed by a Cu/Pd synergistic dual catalyst. This strategy provides a facile access to nonproteinogenic α,α-disubstituted α-amino acids (α-AAs) in high yield with excellent enantioselectivity. The more challenging double allylic allylation of glycinate derived imine esters could also be realized. Furthermore, this methodology was applied for the construction of the key intermediate of PLG peptidomimetics.

Nonproteinogenic α,α-disubstituted α-amino acids (α-AAs) are not only capable of behaving as enzyme inhibitors themselves[1] but also constituents of biologically active natural products.[2] Furthermore, α,α-disubstituted α-amino acids have played a crucial role in the design of novel non-nature peptides and proteins with enhanced properties such as the ability of resistance against chemical/enzymatic degradation.[3] The importance of nonproteinogenic α,α-disubstituted α-amino acids stimulates the development of efficient synthetic methods, however, only few examples have been reported in a highly enantioselective manner to date.[4] Undoubtedly, developing new approaches in acquiring chiral α-quaternary amino acids is of great significance.

The α-functionalization of benzophenone Schiff base is one of the commonly-used strategies to synthesize enantioenriched nonproteinogenic α-amino acids.[5,6] Among the most promising are asymmetric allylic alkylation (AAA)[7] since it is easy operating and the corresponding products have kinds of potential applications. However, previous work using $Pd^0$ and chiral ligand as the catalyst produced the α-amino acids with only low enantioselectivity in most cases[8] which might cause by the long-distance between the stereogenic center and catalytic center[9] (scheme 1a). In transition-metal-catalyzed AAA[9b,10] reaction, the prochiral or racemic nucleophile generally attacked π-allyl complex from the opposite side of the chiral catalyst, which made the stereocontrol of nucleophile difficult.[9] A significant improvement of the enantioselectivity was achieved when a chiral phase-transfer-catalyst (PTC) and an achiral $Pd^0$ complex were employed as the co-catalyst,[11] but only α-monosubstituted α-amino acids could be effectively constructed (scheme 1-b). Despite considerable progress have been made, the construction of α,α-disubstituted α-AAs though AAA reaction with high enantioselectivity is still underdeveloped. Inspired by metallated azomethine ylides were not only the dipoles in cycloaddition[12] but also the viable nucleophiles in Michael addition[6d,13] from this research group, we envisioned that the synergistic dual Cu/Pd catalyst system[14-16] would be an ideal solution to overcome these problems. As shown in Scheme 1c, we reasoned that intercepting a reactive achiral allylpalladium intermediate **II** with in situ-formed α-substituted metallated azomethine ylides **I** activated by a chiral copper(I) complex could result in a linearly selective allylic alkylation process that permits control of the configuration of the generated α-quaternary stereogenic center.




***Scheme 1.*** Catalytic asymmetric allylic alkylation of imine esters for the construction of nonproteinogenic α-amino acids (α-AAs).

To probe our hypothesis, aldimine ester **2a** derived from *p*-chlorobenzaldehyde and *t*-butyl cinnamic carbonate **1a** were selected as the model substrates, $Pd(PPh_3)_4$ as the allylation catalyst and $Cs_2CO_3$ as the base. Based on our previous work, the $Cu(MeCN)_4BF_4$/(*S*)-TF-BiphamPhos complex were firstly selected as catalyst to generate the metallated azomethine ylide (Table 1, entries 1-2), however, no reaction occurred between **1a** and **2a**. Then, we turn our attention to $Cu^I$/Phosferrox complex, which have shown the ability to activate imine ester with excellent asymmetric induction.[6e,12b] To our delighted, when ($S,S_p$)-*t*Bu-Phosferrox **L3** was chosen as the chiral ligand, the adduct **3a** was obtained in 79% yield and 42% ee via the designed allylic alkylation followed by reduction (entry 3). Encouraging by this result, we tested a series of Phosferrox ligand **L4-L7**, and ($S,S_p$)-**L6** gives the superior results, producing **3a** in 89% yield with 91% ee, thus $Cu^I$/**L6** complex was identified as the optimal $Cu^I$-catalyst (entries 4-7). The effect of the leaving group in **1** was then evaluated (entries 8-10). Acyl, benzoyl and $CO_2Me$ protected

[a] L. Wei, S.-M Xu, Q. Zhu, C. Che Prof. Dr. C.-J. Wang
College of Chemistry and Molecular Sciences
Wuhan University
Wuhan, 430072, China
E-mail: cjwang@whu.edu.cn
[b] Prof. Dr. C.-J. Wang
State Key Laboratory of Elemento-organic Chemistry
Nankai University
Tianjin, 300071, China

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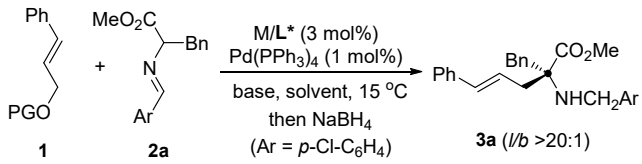
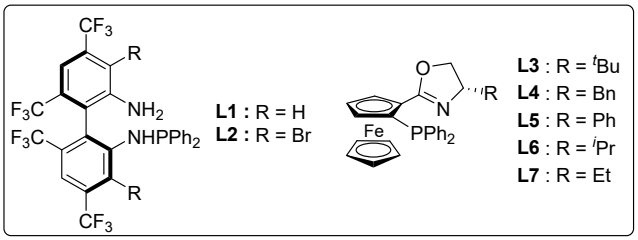
***Table 1:*** Optimization of reaction conditions.[a]




**1** **2a** **3a** (*l*/*b* >20:1)




| Entry | M/**L** | PG | Base | solvent | Yield[b] (%) | ee[c] (%) |
|---|---|---|---|---|---|---|
| 1 | $CuBF_4$/**L1** | Boc | $Cs_2CO_3$ | DCM | 0 | - |
| 2 | $CuBF_4$/**L2** | Boc | $Cs_2CO_3$ | DCM | 0 | - |
| 3 | $CuBF_4$/**L3** | Boc | $Cs_2CO_3$ | DCM | 79 | 42 |
| 4 | $CuBF_4$/**L4** | Boc | $Cs_2CO_3$ | DCM | 84 | 83 |
| 5 | $CuBF_4$/**L5** | Boc | $Cs_2CO_3$ | DCM | 81 | 5 |
| 6 | $CuBF_4$/**L6** | Boc | $Cs_2CO_3$ | DCM | 89 | 91 |
| 7 | $CuBF_4$/**L7** | Boc | $Cs_2CO_3$ | DCM | 88 | 89 |
| 8 | $CuBF_4$/**L6** | Ac | $Cs_2CO_3$ | DCM | 77 | 82 |
| 9 | $CuBF_4$/**L6** | Bz | $Cs_2CO_3$ | DCM | 71 | 85 |
| 10 | $CuBF_4$/**L6** | $CO_2Me$ | $Cs_2CO_3$ | DCM | 81 | 86 |
| 11 | $CuBF_4$/**L6** | Boc | $K_2CO_3$ | DCM | 79 | 82 |
| 12 | $CuBF_4$/**L6** | Boc | $Et_3N$ | DCM | 62 | 80 |
| 13 | $CuBF_4$/**L6** | Boc | $Cs_2CO_3$ | THF | 56 | 81 |
| 14 | $CuBF_4$/**L6** | Boc | $Cs_2CO_3$ | PhMe | 61 | 77 |
| 15[d] | $CuBF_4$/**L6** | Boc | $Cs_2CO_3$ | DCM | 91 | 95 |
| 16 | - | Boc | $Cs_2CO_3$ | DCM | 5 | - |
| 17 | **L6** | Boc | $Cs_2CO_3$ | DCM | 6 | 0 |
| 18[e] | $CuBF_4$/**L6** | Boc | $Cs_2CO_3$ | DCM | trace | - |

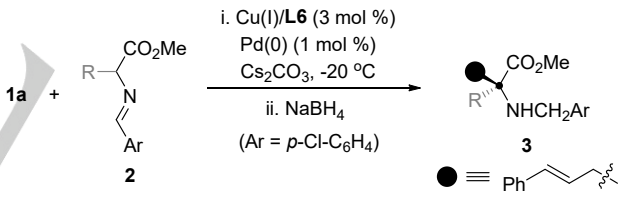
[a] All reactions were carried out with 0.24 mmol of **1** and 0.20 mmol of **2a** in 2 mL of solvent. $CuBF_4$ = $Cu(MeCN)_4BF_4$. [b] Isolated yield. [c] Determined by HPLC analysis. [d] Run at -20 °C [e] Without $Pd(PPh_3)_4$.

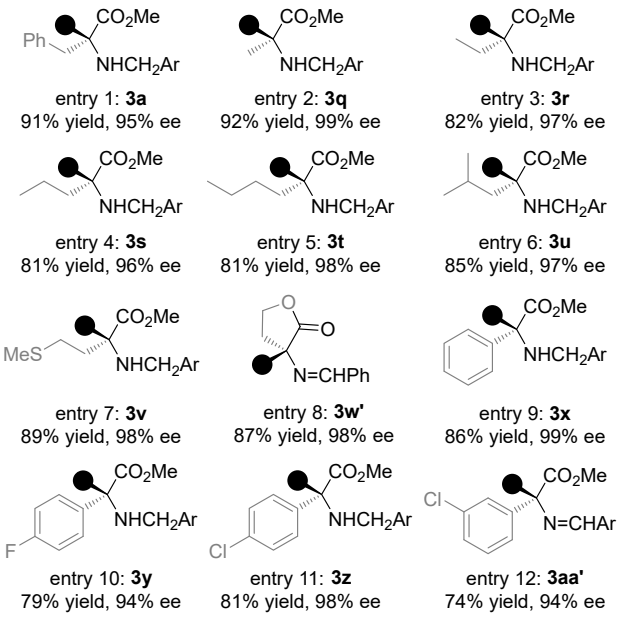
cinnamic alcohol were all proven to be efficient electrophile precursors under the standard condition, albeit with slightly lower yield and enantioselectivity. To further examine the impact of other condition parameters, we then screened various bases and solvents. The results indicated that changing the $Cs_2CO_3$ either to a weaker inorganic base or an organic base would reduce both the reactivity and enantioselectivity (entries 11-12). Dichloromethane was the best reaction solvent compare to all other tested (entries 13-14). After reducing the reaction temperature to -20 °C, we were pleased to find that the product could be isolated in 91% yield with 95% ee (entry 15). To gain insight into the mechanism aspects of this dual catalysis, we conducted the paralleled control experiments. Only a trace amount of product was obtained in the absence of $Cu^I$/**L6**, suggested that $Pd(PPh_3)_4$ is incapable of promoting the formation of azomethine ylide as nucleophile (entry 16). Similar result was observed when only $Cu(MeCN)_4BF_4$ was excluded, the racemic product clearly ruled out the possibility that the enantioselectivity of this reaction was controlled by Pd/**L6** complex. No product obtained in the absence of $Pd(PPh_3)_4$ demonstrated that the product was not formed *via* a directed $S_N2$ pathway between **1a** and **2a,** and the palladium catalyst was indispensable to this transformation. The $^{31}P$ NMR analyses further confirmed that ligand scrambling was negligible or absent in the dual catalytic system (See SI for the details).

The scope of electrophile precursors in the α-allylation was investigated under the optimal condition. To avoid the partial hydrolysis of the imine moiety in **3'** during separation, all the allylation products were further reduced by $NaBH_4$. As shown in Table 2 (See next page), an array of substituted cinnamic carbonates bearing electron-withdrawing and electron-donating groups at *para*-, *meta*-, and *ortho*-position of the phenyl ring reacted smoothly with aldimine ester **2a**, giving the corresponding α,α-disubstituted α-amino acid derivatives **3a-3j** in good yield with excellent enantioselectivity (up to 98% ee) (Table 2, entries 1-10). In addition, heteroaryl 2-thienyl, 3-(*N*-tosyl)-indolyl substituted allylic carbonate **3k** and **3l** were suitable substrates for this transformation (entries 11 and 12). Styrenyl substituted allylic carbonate **3m** also worked well in this dual catalytic system (entry 13). Notably, besides the aromatic allylic carbonates, crotyl, allyl and 2-methyl-allyl carbonate also proven to be compatible in this reaction, furnishing products **3n-3p** in 72-92% yield with 88-90% ee (entries 14-16). It is noteworthy that the challenging styrenyl and crotyl carbonates give the corresponding products with exclusive regioselectivity,[17] indicating that the current catalytic system have excellent linear selectivity.

Having established the scope of π-allyl precursors, we then set out to examine a series of aldimine esters with different α-substituent group. The results were summarized in Table 3. α-

***Table 3:*** Substrate scope of imine esters.[a]




[a] All reactions were carried out with 0.24 mmol of **1a** and 0.20 mmol of **2** in 2 mL of DCM. All yields refer to isolated yields following silica gel chromatography. Ee values were determined by HPLC analysis.

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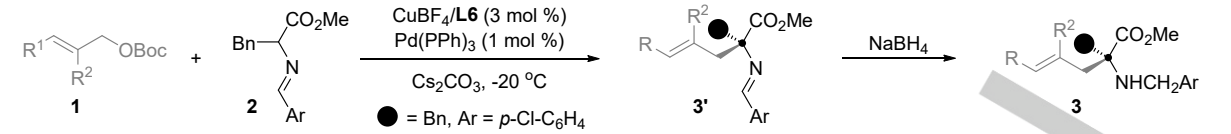
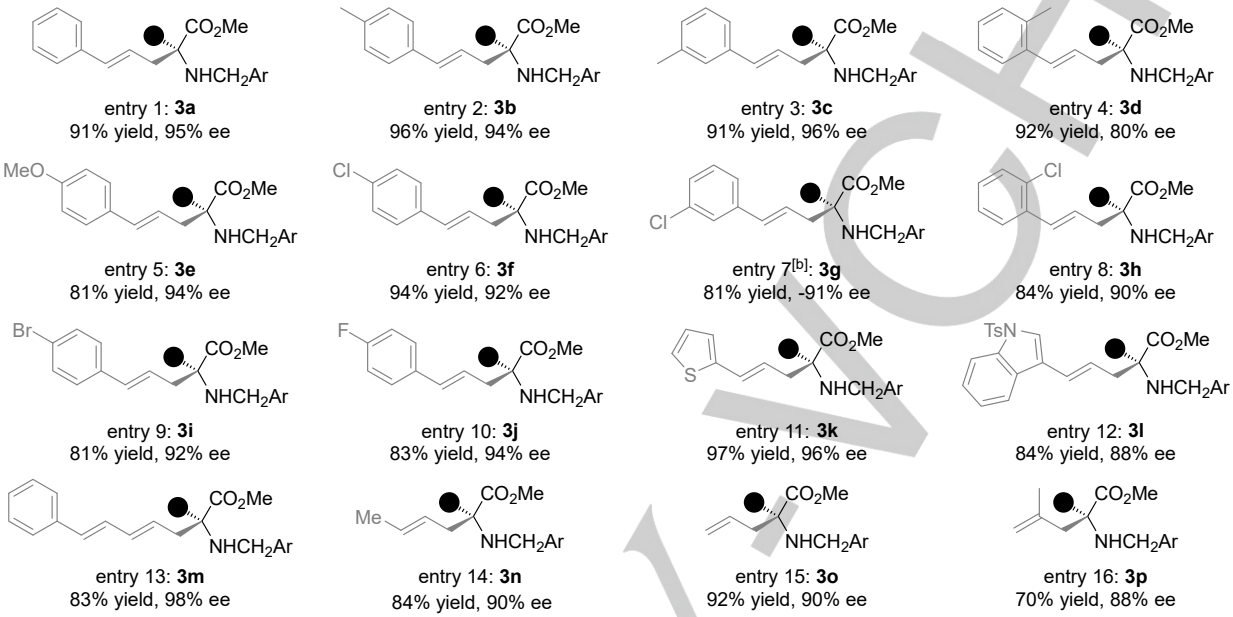
***Table 2:*** Substrate scope of *t*-butyl allyl carbonates.[a]

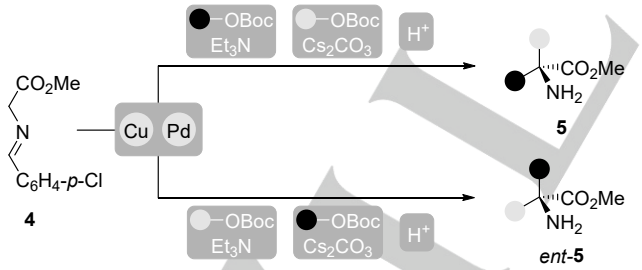


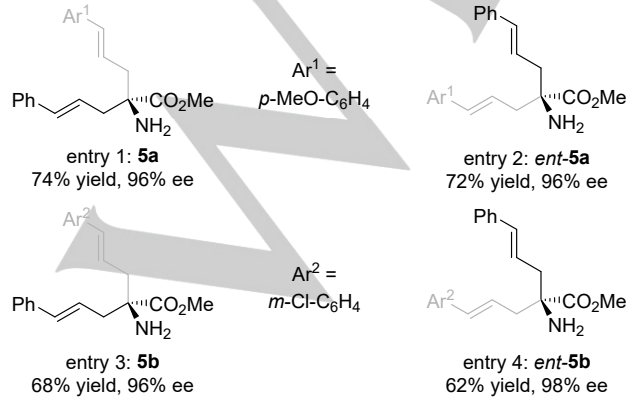




[a] All reactions were carried out with 0.24 mmol of **1a** and 0.20 mmol of **2** in 2 mL DCM. All yields refer to the isolated yields following silica gel chromatography. Ee values were determined by HPLC analysis. [b] Catalyzed by Cu(I)/($R$,$R_p$)-**L6**.

Alkyl substituted aldimine esters derived from alanine, 2-aminobutyric acid, norvaline, norleucine and leucine gave the desired nonproteinogenic α-quaternary amino acids **3q-3u** in 81-92% yield and 96-99% ee (Table 3, entries 2-6). Methionine derived aldimine esters **2v** bearing thioether group was also tolerated under the current dual catalyst system, affording **3v** in 89% yield with 98% ee (entry 7). Reaction between 2-amino-γ-butyrolactone derived imine ester **2h** and **1a** finished in 12 h

***Chart 1.*** Catalytic asymmetric double allylic alkylation.




producing the desired product with good result (entry 8). Finally, α-Aryl substituted aldimine esters incorporating arenes with different substituents were further tested in this reaction, providing the desired products **3x-3aa'** in good yield with excellent ee (entries 9-12).

The successful of mono-allylation of α-substituted aldimine ester encouraged us to further investigate the practicality of the dual $Cu^I/Pd^0$ catalysis. We determined to realize the double-allylic alkylation of glycine derived aldimine ester, which is obviously more challenging than mono-allylation process. Several tough issues should be considered: 1) whether the catalytic efficiency is sufficient for the double-AAA process; 2) how to avoid the formation the undesired gem-allylation products; 3) whether the chiral $Cu^I$ catalyst is able to distinguish the smaller steric differentiation between two allylic substituents After carefully optimized the reaction parameters (see SI for the details), we successfully disclosed the one-pot, sequential double-allylic alkylation reaction with satisfied results (Chart 1). By switching the adding sequence of π-allyl precursors, both enantiomers of the double-allylated products can easily obtained in acceptable yields and excellent enantioselectivity.

To probe the scalability and utility of the present method, we first conducted a gram-scale synthesis of **3'** with comparable yield, which could be further transformed to the free amino acid **6** under acidic condition in 95% yield and 95% ee (Scheme 2). Subsequently, using $Cu^I$/*ent*-**L6** as the catalyst, α-quaternary amino acids **7a-c** bearing different substituents were obtained in good yields with excellent enantioselectivities, which are the key building blocks for the synthesis of a series of PLG peptidomimetics with enhanced ability to modulate $D_2$ dopamine receptors within the CNS.[18] The absolute

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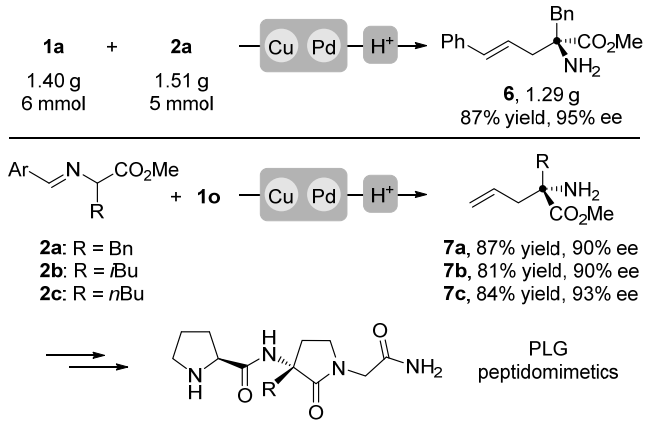
configuration of the allylation products was determined by comparison the optical rotation of **7** with the literature values.




***Scheme 2.*** Gram-scale reaction and synthetic transformation.

In summary, we have developed a highly efficient dual $Cu^{I}/Pd^{0}$ catalysis for the α-allylic alkylation of readily-available aldimine esters, which provide a directed and facile access to a range of nonproteinogenic α,α-disubstituted α-amino acids in high yield with excellent enantioselectivity. The current catalytic system was further demonstrated to be able to realize the more challenging double allylic alkylation of glycine derived imine ester. Moreover, this methodology can be utilized for the asymmetric formal synthesis of PLG peptidomimetics.

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**Keywords:** α-quaternary amino acids • dual catalysis • asymmetric allylic alkylation • azomethine ylides

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[19] During the preparation of this manuscript, Zhang and co-workers reported a similar α-allylic alkylation of aldimine esters with two chiral metal complex, See: X. Huo, R. He, J. Fu, J. Zhang, G. Yang, and W. Zhang, *J. Am. Chem. Soc.* 2017, DOI: 10.1021/jacs.7b05460. In our case, the α-allylic alkylation reaction was realized with the combined chiral $Cu^{I}$ complex and achiral $Pd^{0}$ complex.

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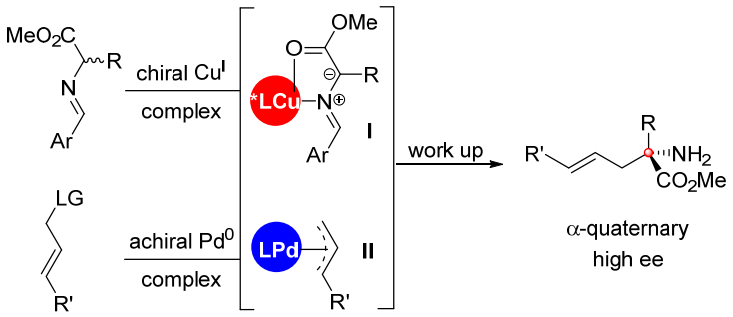


*Liang Wei, Shi-Ming Xu, Qiao Zhu, Chao Che, and Chun-Jiang Wang**

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**A Cu/Pd Synergistic Dual Catalysis for Enantioselective Allylic Alkylation of Aldimine Esters: A Facile Access to α,α-Disubstituted α-Amino Acids**

An unprecedented enantioselective allylic alkylation of readily-available aldimine esters has been developed, which was efficiently catalyzed by a Cu/Pd synergistic dual catalyst. This strategy provides a facile access to nonproteinogenic α,α-disubstituted α-amino acids (α-AAs) in high yield with excellent enantioselectivity. The more challenging double allylic allylation of glycinate derived imine esters could also be realized. Furthermore, this methodology was applied for the construction of the key intermediate of PLG peptidomimetics.