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# Pd/Cu Dual Catalysis: Highly Enantioselective Access to α-Substituted α-Amino Acids and α-Amino Amides

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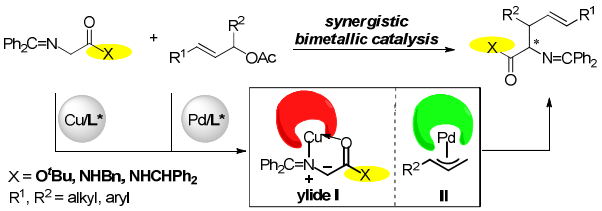
Xiaohong Huo,[a,†] Jingke Fu,[a,†] Xiaobo He,[a] Jianzhong Chen,[a] Fang Xie,[a] and Wanbin Zhang*[ab]

**The asymmetric allylation of glycine iminoesters has been accomplished through a synergistic Pd/Cu catalyst system, affording a range of α-substituted α-amino acids in high yields and with excellent enantioselectivities (94->99% ee). The introduction of a Cu-*P,N*-metallocenyl complex-activated glycine iminoester to the chiral palladium-catalyzed allylic allylation process is crucial for its high reactivity and excellent enantioselectivities. Importantly, this Pd/Cu dual catalysis strategy can be used for the asymmetric allylic alkylation of prochiral glycine amide derivatives, which could be further utilized to synthesize biologically important vicinal diamines.**

Non-proteinogenic, optically active α-substituted α-amino acids (α-AAs) are valuable structural motifs in biological and pharmacological compounds.[1] Accordingly, the enantioselective construction of α-substituted α-AAs is of great importance and has sparked considerable synthetic interest.[2] Among various methodologies, the asymmetric allylic alkylation (AAA) of readily available glycine iminoesters is one of the most straightforward methods for the synthesis of enantioenriched α-substituted α-AAs.[3] Unfortunately, the stereocontrol of prochiral glycine iminoesters represents a great challenge owing to the long distance between the nucleophile and the chiral environment of the ligand.[3] Consequently, novel catalysts or catalytic strategies for the asymmetric allylation of prochiral glycine iminoesters in a highly enantioselective manner are greatly required.

Synergistic catalysis is gaining increasing attention due to its advantages, such as improved catalytic activity, wide substrate scope, increased selectivity, and cost efficiency.[4] Indeed, through the combination of a chiral-phase transfer catalyst (PTC) and an achiral palladium(0) complex developed by the research groups of Gong and Takemoto, the enantioselectivity of the allylic alkylation of glycine iminoesters was greatly improved.[5] Compared with synergistic transition-metal and organocatalyst strategy,[5-8] cooperative bimetallic catalysis consisting of two distinct metal complexes possesses distinct advantages: (a) an amount of available chiral ligands and metal catalysts could be employed;[9] (b) a variety of metal-catalyzed asymmetric reactions exist;[10] and (c) a versatile bimetallic catalyst library could be generated *via* combinatorial chemistry, which thus has accommodated a broad range of challenging asymmetric transformations.[11] Very recently, we reported a Pd/Cu bimetallic catalyst system for the highly AAA of aldimine esters.[11h] However, glycine-based aldimine esters always give biallylated products. In order to obtain the highly enantiopure α-substituted α-AAs, several problems must be overcome: (a) the internal contradictions of keeping the high reactivity of the bimetallic catalysis and lowering the reactivity of glycine-based aldimine esters to avoid the biallylated products, must be addressed; (b) the stereocontrol of the prochiral nucleophile; and (c) the potential enolization of α-substituted α-AAs in the presence of a Lewis acid or under basic conditions. Herein, we describe a new development in cooperative bimetallic catalysis: a chiral Cu-*P*,*N*-metallocenyl complex was introduced to the chiral Pd complex-catalyzed allylic alkylation process, which leads to the construction of α-substituted α-AAs with high reactivity and excellent enantioselectivity (Scheme 1). It was anticipated that the two chiral metal complexes could work in tandem to activate the allyl and glycine susbtrates and contribute to the reaction




**Scheme 1** Bimetallic catalysis for the asymmetric allylation of glycine iminoesters/amides to get access to α-substituted α-amino acids/amides.

[a] Shanghai Key Laborotary for Molecular Engineering of Chiral Drugs, School of Chemistry and Chemical Engineering, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, China. Email: wanbin@sjtu.edu.cn
[b] School of Pharmacy, Shanghai Jiao Tong University, 800 Dongchuan Road, Shanghai 200240, P. R. China.
† X. Huo and J. Fu contributed equally
† Electronic Supplementary Information (ESI) available. See DOI: 10.1039/x0xx00000x

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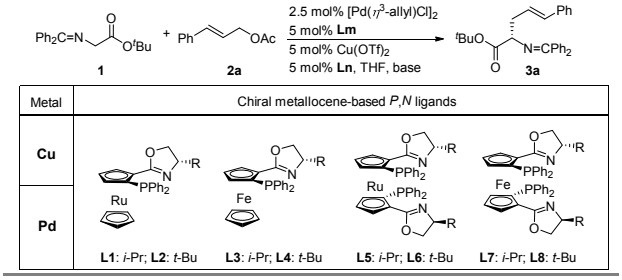
efficiency and the enantioselectivity of the prochiral nucleophile. Compared with the PTC-mediated allylic alkylation of glycine iminoesters, this homogeneous Pd/Cu co-catalyzed AAA reaction proceeded under mild conditions and thus provided much better substrate compatibility.

On the other hand, despite the significant progress in expanding the scope of applicable carbon nucleophiles in AAA reactions, α-amino amide deriatives are still difficult to enolize and thus have not been used as nucleophiles in catalytic allylation reactions. Based on the potential advantages of the bimetallic catalysis strategy, this Pd/Cu catalytic system was used for the AAA of prochiral glycine amide deriatives.[12] A range of α-substituted α-amino amides could be smoothly obtained in high yields and with excellent enantioselectivity, which could be utilized to further synthesize biologically important vicinal diamines by simple transformation.[13]

The investigation was initiated by the asymmetric allylation of the diphenylimino glycinate **1** with the cinnamyl acetate **2a** in the presence of a weak base ($K_2CO_3$) using Pd/Cu bimetallic catalysis (Table 1). In order to evaluate the effect of the bimetallic catalyst system, a bimetallic catalyst library was created by the combination of metal precursors {[Pd($\eta^3$-allyl)Cl]$_2$ and Cu(OTf)$_2$} and chiral *P,N*-metallocenyl ligands (**L1**-**L8**). To our delight, almost quantitative yields and good to high

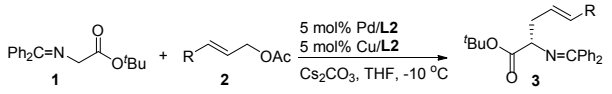
**Table 1** Optimization of the reaction conditions[a]




| Entry | Pd /**Lm** | Cu /**Ln** | Base | T (°C) | t (h) | Yield (%)[b] | ee (%)[c] |
|---|---|---|---|---|---|---|---|
| 1 | **L1** | **L1** | $K_2CO_3$ | rt | 4 | 94 | 76 |
| 2 | **L2** | **L2** | $K_2CO_3$ | rt | 4 | 93 | 94 |
| 3 | **L3** | **L3** | $K_2CO_3$ | rt | 4 | 94 | 88 |
| 4 | **L4** | **L4** | $K_2CO_3$ | rt | 4 | 93 | 94 |
| 5 | **L5** | **L5** | $K_2CO_3$ | rt | 4 | 95 | 75 |
| 6 | **L6** | **L6** | $K_2CO_3$ | rt | 4 | 94 | 92 |
| 7 | **L7** | **L7** | $K_2CO_3$ | rt | 4 | 93 | 80 |
| 8 | **L8** | **L8** | $K_2CO_3$ | rt | 4 | 92 | 84 |
| 9 | **L2** | **L2** | $K_2CO_3$ | -10 | 12 | NR | ND |
| 10 | **L4** | **L4** | $K_2CO_3$ | -10 | 12 | NR | ND |
| 11 | **L2** | **L2** | $Cs_2CO_3$ | -10 | 12 | 96 | 97 |
| 12 | **L4** | **L4** | $Cs_2CO_3$ | -10 | 12 | 25 | ND |
| 13 | **L2** | - | $Cs_2CO_3$ | -10 | 12 | 18 | ND |
| 14 | - | **L2** | $Cs_2CO_3$ | -10 | 12 | NR | NR |

[a]Reaction conditions: **1** (0.25 mmol), **2a** (1.2 equiv), Pd/**Lm*** (5 mol%), Cu/**Ln*** (5 mol%), base (1.0 equiv), THF (2 mL); [b]Isolated yield; [c]The ee values were determined by HPLC using chiral columns. NR = not reaction, ND = not determined.

**Table 2** Allylic substrates scope of alkylation of glycine iminoesters[a]




| Entry | 2 | Yield [%][b] ee [%][c] |
|---|---|---|
| 1<br>2<br>3<br>4 | **2a** (R = H)<br>**2b** (R = Me)<br>**2c** (R = F)<br>**2d** (R = Cl) | 96% yield, 97% ee<br>96% yield, 99% ee<br>97% yield, 99% ee<br>98% yield, 99% ee |
| 5<br>6<br>7 | **2e** (R = Me)<br>**2f** (R = F)<br>**2g** (R = Cl) | 95% yield, 97% ee<br>94% yield, 96% ee<br>97% yield, 97% ee |
| 8<br>9<br>10<br>11<br>12 | **2h** (R = Me)<br>**2i** (R = OMe)<br>**2j** (R = F)<br>**2k** (R = Cl)<br>**2l** (R = $CF_3$) | 96% yield, 94% ee<br>97% yield, 98% ee<br>96% yield, 97% ee<br>97% yield, 98% ee<br>96% yield, 98% ee |
| 13 | **2m** | 95% yield, 96% ee |
| 14 | **2n** | 98% yield, 99% ee |
| 15[d] | **2o** | 96% yield, 94% ee |
| 16 | **2p** | 97% yield, 98% ee |
| 17 | **2q** | 92% yield, 95% ee |
| 18 | **2r** | 90% yield, 97% ee |
| 19 | **2s** | 98% yield, 98% ee |
| 20[d] | **2t** | 65% yield, 88% ee |
| 21[e] | **2u** | 95% yield, 96% ee |

[a]Reaction conditions: see Table 1, entry 11. [b]Isolated yields. [c]Determined by HPLC using chiral columns. [d]At room temperature. [e]18 h.

enantioselectivities were uniformly obtained under all the [Pd/**Lm**+Cu/**Ln**] catalyst combinations. In particular, the [Pd/**L2**+Cu/**L2**] and the [Pd/**L4**+Cu/**L4**] catalysts were the best, affording the desired product **3a** in 93% yield and with 94% ee (Table 1, entries 1-8). It was found that the substituent R on the oxazolinyl ring had much effect on the enantioselectivity and a bulkier group gave a better ee value. We assumed that the enantioselectivity may be further improved by reducing the reaction temperature. However, the catalytic reaction did not proceed at -10 $^0$C, even with a prolonged reaction time (entries 9 and 10). Interestingly, this situation could be reversed by using $Cs_2CO_3$ as the base, delivering the desired product **3a** in 96% yield and with 97% ee under the [Pd/**L2**+Cu/**L2**] catalyst combination (entry 11). It was reasoned that the better solubility and stronger basicity of the $Cs_2CO_3$ may help to promote the reactivity and the enantioselectivity of the reaction. In an effort to probe the cooperative interplay of the bimetallic catalyst system, control experiments were conducted. It turned out that the Pd-

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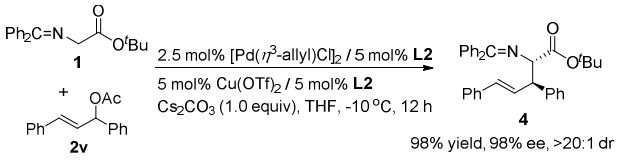
catalyzed allylic substitution reaction furnished only a trace amount of products (18% yield) without the participation of the Cu catalyst (entry 13). Additionally, no products were obtained using only the Cu catalyst (entry 14). These results suggested the synergistic role of the bimetallic catalysts in improving both the reactivity and enantioselectivity of the reaction.

With the optimized reaction conditions in hand, we then explored the substrate scope of the allylic electrophiles (Table 2). Allylic acetates substituted with arenes bearing alkyl, halogen, electron-donating and electron-withdrawing substituents at different positions were all tolerated in this transformation, affording their respective products in high yields and with high enantioselectivities (Table 2, entries 1-14). Notably, allylic acetates containing naphthalene, furan and thiophene substituents, were also compatible with this reaction (entries 15-18). To our delight, simple allyl acetate, prenylacetate, and branched 1-phenyl-2-propenyl acetate also proved to be good substrates, affording the desired α-AAs in high yields and enantioselectivities (entries 19-21).

Additionally, the allylic allylation of **1** with the symmetrical 1,3-disubstitued allyl acetate **2v** was examined under the optimized conditions (Scheme 2). The desired product with two contiguous stereocenters was successfully obtained in 98% yield, 98% ee, and >20:1 dr.

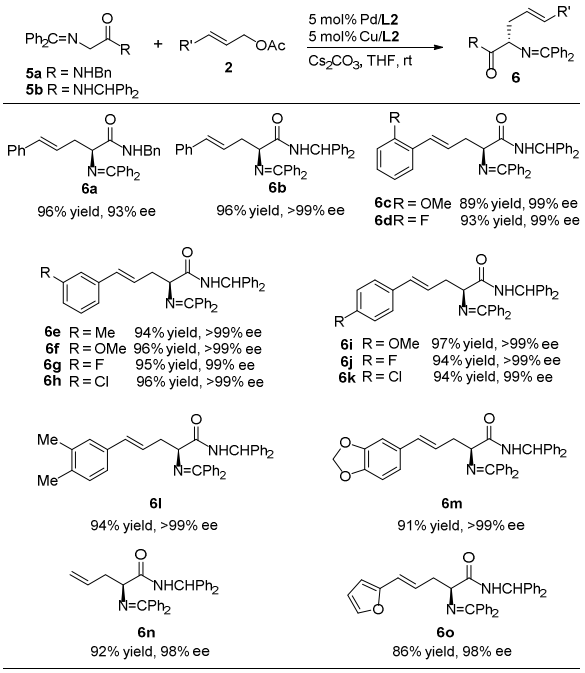



**Scheme 2** Allylic alkylation of the diphenylimino glycinate with 1,3-disubstitued allyl acetate **2v**.

Having established the feasibility of enantioselective construction of α-substituted α-AAs with high reactivity, we then set out to verify the high catalytic efficiency of the bimetallic catalyst system by applying this methodology to the asymmetric allylation of prochiral glycine amide derivatives (Table 3). The allylation reactions of *N*-benzylglycinamide **5a** and diphenylmethyl derivative **5b** with the cinnamyl acetate **2a** proceeded smoothly, furnishing the corresponding alkylation products **6a** and **6b** in high yields and with 93%->99% ee. The generality of allylic substrates was then investigated using **5b** as the representative prochiral nucleophile. A range of allylic acetates with substituents at the *ortho*-, *meta*-, or *para*-position of the phenyl ring were all well employed in this transformation, affording their desired products (**6c**-**6m**) in high yields and enantioselectivities (99->99% ee). Importantly, simple allyl acetate and allylic acetates bearing furan substituent were also good substrates, affording the desired products (**6n** and **6o**) in high yields with 98% ee.

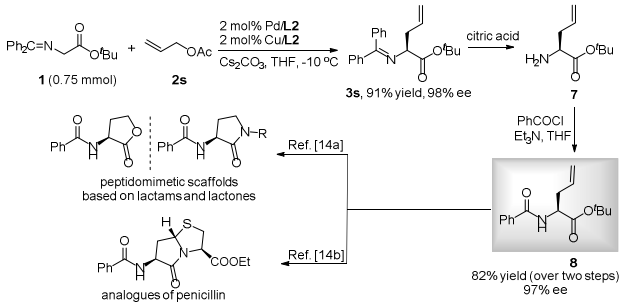
Finally, in order to demonstrate the synthetic utility of this bimetallic catalytic process, we endeavored to apply the allylation product **3s** to the synthesis of a stable intermediate **8**, which is a versatile intermediate used for the construction of penicillin. The Pd/Cu catalyzed allylation of **2s** with

**Table 3** Allylic substrates scope of alkylation of glycine amide s[a]




[a]Reaction conditions: see Table 1, entry 12.

diphenylimino glycinate **1** delivered **3s** in 91% yield with 98% ee (Scheme 3). Then the key intermediate **8** was obtained after hydrolysis and benzoylation of **3s**. We anticipate that the enantioselective construction of α-substituted α-AAs is attractive for their use in medicinal chemistry.




**Scheme 3** Synthetic utility of methodology.

In summary, we have developed a synergistic Pd/Cu catalyst system for the asymmetric allylation of glycine iminoesters. A range of noncoded α-substituted α-amino acids were efficiently synthesized in high yields and with excellent enantioselectivities under mild conditions (94->99% ee). Additionally, a highly enantioselective construction of enantiopure α-substituted α-amino amides was achieved using this Pd/Cu dual catalyst system, which were expected to further synthesize biologically important vicinal diamines. We envision that this bimetallic catalysis strategy will allow access to more difficult asymmentric transformations.

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## Conflicts of interest

There are no conflicts to declare.

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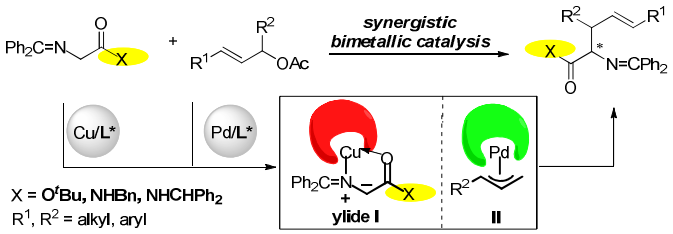
# Pd/Cu Dual Catalysis: Highly Enantioselective Access to α-Substituted α-Amino Acids and α-Amino Amides

Xiaohong Huo,[a,†] Jingke Fu,[a,†] Xiaobo He,[a] Jianzhong Chen,[a] Fang Xie,[a] and Wanbin Zhang*[ab]




In this paper, we have developed a synergistic Pd/Cu catalyst system for the asymmetric allylation of glycine iminoesters/amides, affording a range of α-substituted α-amino acids/amides in high yields and with excellent enantioselectivities (94->99% ee).