Communication

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Stereoselective and Site-specific Allylic Alkylation of Amino Acids and Small Peptides via a Pd/Cu Dual Catalysis

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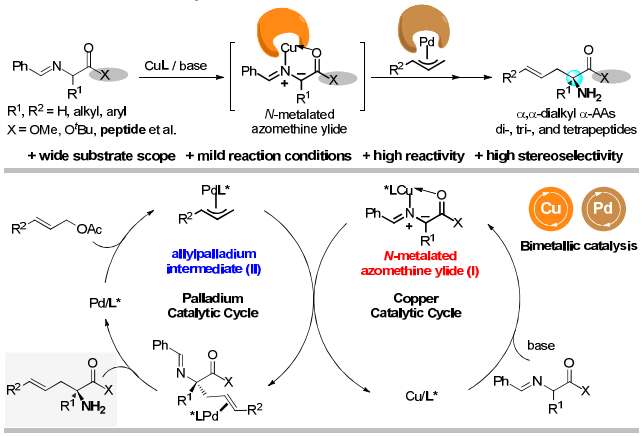
Supporting Information Placeholder

ABSTRACT: We report a stereoselective and site-specific allylic alkylation of Schiff base activated amino acids and small peptides via a Pd/Cu dual catalysis. A range of noncoded α,α-dialkyl α-amino acids were easily synthesized in high yields and with excellent enantioselectivities (up to >99% ee). Furthermore, a direct and highly stereoselective synthesis of small peptides with enantiopure α-alkyl or α,α-dialkyl α-amino acids residues incorporated at specific sites was accomplished using this dual catalyst system.

The transition-metal-catalyzed asymmetric allylic alkylation reaction serves as a versatile and powerful tool for enantioselective C-C bond formation and is widely employed in the synthesis of biologically important molecules.[1] The development of increasingly elaborate nucleophiles to facilitate this process is a major research area. The introduction of a second catalyst to this process, which is responsible for generating active nucleophiles in a catalytic manner, would provide an effective and reliable strategy for promoting this reaction.[2] Despite achieving remarkable progress in this area using a combination of transition-metals and organocatalysts,[3-6] cooperative bimetallic catalyst systems consisting of two distinct chiral metal complexes have not been widely reported, an attribute that is expected to provide a series of unprecedented asymmetric transformations.[7]

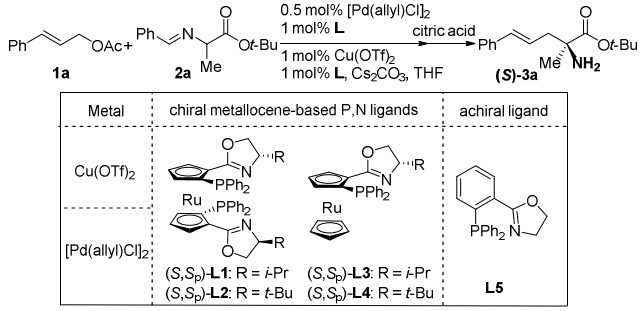
Non-proteinogenic, optically active α,α-disubstituted α-amino acids (α-AAs) are present in numerous biologically active compounds and are frequently utilized as building blocks in organic synthesis and new drug discovery.[8] The development of efficient methods for the rapid generation of enantiopure α,α-dialkyl α-AAs has thus attracted a great deal of attention.[9] Among various methodologies, the Pd-catalyzed asymmetric allylic alkylation of aldimine Schiff bases derived from the corresponding α-AAs represents an attractive and powerful catalytic process in terms of starting material availability, operational simplicity and derivation convenience. However, this transformation suffered from low reactivity and enantioselectivity,[10] mainly because of the congested three-dimensional configuration[11] and challenging stereocontrol of prochiral nucleophiles.[1] On the other hand, the postsynthetic modification of peptides represents an essential and flexible synthetic concept for the conformational control and design of peptidomimetics for biomedical applications.[12] In particular, the appropriate incorporation of noncoded α-AAs into peptides has proven to induce significant conformational constraints and has allowed for the preparation of peptides with new functionalities for use in pharmaceutics.[8] However, the regio- and stereoselective modification of a given peptide is far from trivial, mainly due to (1) the demand for harsh reaction conditions; (2) the steric effect of peptides on the reactivity and stereoselectivity; (3) the presence of multiple reactive functional groups in various peptides. Despite great advances in metal-catalyzed asymmetric reactions, the stereoselective and site-specific modification of peptides using transition-metal-based reactions has not been reported yet.[13]

Scheme 1. Bimetallic Catalysis for Stereoselective Modification of Amino Acids and Peptides



Herein, we report a Pd/Cu dual catalyst system, which was applied not only to the asymmetric synthesis of non-natural α,α-dialkyl α-AAs but also to the highly stereoselective N-terminal α-allylation of small peptides (Scheme 1). Under the assistance of a copper complex and a weak base, an aldimine Schiff base could be easily converted to nucleophiles possessing greater stability (*N*-metalated azomethine ylides **I**).[14] The rigid structure of the five membered N,O-bidentate metalated azomethine ylide **I** facilitates the asymmetric induction from the chiral ligand. Furthermore, the ylide **I** generated in situ and in catalytic amounts may also have a positive influence on the enantio-determining step.[15] Additionally, the cooperative use of two chiral reactive species, **I** and π-allypalladium **II**, may allow for the ready control of the stereocenter. We envisioned that the proposed stereoselective and site-specific α-allylation of amino acids and small peptides via this bimetallic catalysis strategy would take advantage of preexisting structures and provide a convienent method to rapidly generate large arrays of amino acids and peptides for biological studies.

Table 1. Optimization of Reaction Conditions[a]



entry	**L** for Pd	**L** for Cu	t (h)	yield (%)[b]	ee (%)[b]
1[c]	**L1**	**L1**	12	91	76 (*S*)
2[c]	**L2**	**L2**	12	88	98 (*S*)
3	**L3**	**L3**	12	89	75 (*S*)
4	**L4**	**L4**	12	86	97 (*S*)
5	**L2**	--	24	<10	26 (*S*)
6	--	**L2**	24	0	--
7	**L2**	**L5**	12	92	40 (*S*)
8	**L5**	**L2**	12	91	52 (*S*)

[a]Conditions: **2a** (0.25 mmol), **1a** (1.2 equiv), Cu/**L** (1 mol%), Pd/**L** (1 mol%), Cs_2CO_3 (1.0 equiv), THF (2 mL), rt. [b]The isolated yields and *ee* values of the desired products were measured following hydrolysis to the unprotected α-AAs. The absolute configurations of **3a** were determined to be *S* by comparison of its optical rotation with the literature value.[16] [c]0.5 mol% **L** for 0.5 mol% [Pd(allyl)Cl]$_2$ and 1.0 mol% Cu(OTf)$_2$.

Initially, cinnamyl acetate **1a** was selected as an electrophilic precursor for the asymmetric allylation of the aldimine Schiff base **2a** (Table 1). A bimetallic catalysts library was created via random combination of any two of the Pd/**Lm**[17] and Cu/**Ln**[14] complexes using the phosphino-oxazoline (PHOX) ligands (**L1**-**L4**).[18,19] After primary screening, the [Pd/**L2**+Cu/**L2**] catalyst was found to be outstanding, affording the desired product in 88% yield and with 98% ee (entries 1-4). The use of identical ligands in the optimal combinations avoids the troublesome problem of ligand exchange. In order to gain insight into the nature of the cooperative effect, control experiments were conducted. The reaction proceeded with substantially lower reactivity and enantioselectivity (<10% yield, 26% ee) when only the Pd/**L2** catalyst was used (entry 5). No reaction occurred using only the Cu/**L2** catalyst (entry 6). The Cu and Pd complex activated the reaction in a synergistic manner. To further probe the relative role of the chiral environments, bimetallic catalyst systems consisting of a chiral metal complex and an achiral metal complex were created to give products with much lower enantioselectivities (entries 7 and 8). Although the underlying mechanism requires further clarification, the combined use of two chiral metal complexes seems to be important for the reactivity and stereocontrol of the reaction.

The allylic electrophile scope was explored using the aldimine Schiff base **2a** as a representive substrate (Table 2). A range of allylic acetates substituted with arenes bearing electron-donating and electron-withdrawing substituents all furnished the corresponding products with high reactivities and excellent selectivities (entries 1-17). Reactions involving naphthyl- and furyl-substituted allyl acetates also proceeded well to deliver their desired products in good to high yields and with excellent enantioselectivities (entries 18-20). Furthermore, 1,3-diphenyl-substituted substrate **1u** proved to be compatible with the reaction conditions, providing the product **3u** in 88% yield, 6:1 dr, and 95% ee (entry 21).

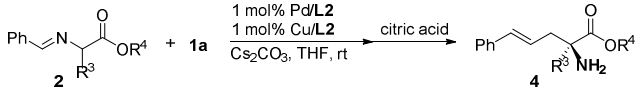
Table 2. The Substrate Scope of Allylic Acetates[a]

entry	**1**	R^1	R^2	yield (%)[b]	ee (%)[b]
1	**1a**	C_6H_5	H	88	98 (*S*)
2	**1b**	(*Z*)-C_6H_5	H	82	98 (*S*)
3	**1c**	2-MeC_6H_4	H	85	88 (*S*)
4	**1d**	2-FC_6H_4	H	85	97 (*S*)
5	**1e**	3-MeC_6H_4	H	92	98 (*S*)
6	**1f**	3-FC_6H_4	H	93	98 (*S*)
7	**1g**	3-ClC_6H_4	H	90	>99 (*S*)
8	**1h**	4-MeC_6H_4	H	91	97 (*S*)
9	**1i**	4-OMeC_6H_4	H	85	>99 (*S*)
10	**1j**	4-FC_6H_4	H	89	99 (*S*)
11	**1k**	4-ClC_6H_4	H	86	99 (*S*)
12	**1l**	4-$CF_3C_6H_4$	H	92	99 (*S*)
13	**1m**	4-$NO_2C_6H_4$	H	74	>99 (*S*)
14	**1n**	2,4-$Me_2C_6H_3$	H	82	99 (*S*)
15	**1o**	3,4-$Me_2C_6H_3$	H	85	95 (*S*)
16	**1p**	3,5-$Cl_2C_6H_3$	H	84	>99 (*S*)
17	**1q**	3,4-(methylenedioxy)	H	86	98 (*S*)
18	**1r**	1-naphthyl	H	67	>99 (*S*)
19	**1s**	2-naphthyl	H	84	>99 (*S*)
20	**1t**	2-furyl	H	65	95 (*S*)
21[c]	**1u**	C_6H_5	C_6H_5	88	95 (*S,R*)

[a,b]Conditions: see Table 1, entry 2. [c]6:1 dr.

Next, an array of aldimine Schiff bases derived from α-substituted α-AAs were treated with **1a** under the optimized conditions (Table 3). To our delight, the aldimine Schiff bases derived from both natural and non-natural α-AAs gave the corresponding α,α-dialkyl α-AAs in good to high yields and with excellent enantioselectivities (up to >99% ee).

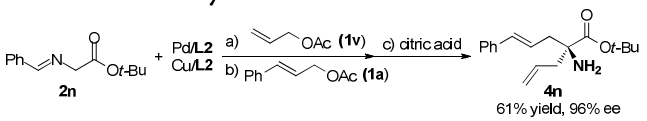
Table 3. The Substrate Scope of Aldimine Schiff Bases[a]



entry	**2**	R^3	R^4	yield (%)[b]	ee (%)[b]
1	**2a**	Me	*t*-Bu	88	98 (*S*)
2	**2b**	Me	Me	87	94 (*S*)
3	**2c**	Me	*i*-Pr	88	96 (*S*)
4	**2d**	Et	*t*-Bu	86	98 (*S*)
5	**2e**	*i*-Bu	*t*-Bu	84	94 (*S*)
6	**2f**	Bn	*t*-Bu	69	84 (*R*)
7	**2g**	CH_2CH_2Ph	Et	85	93 (*S*)
8	**2h**	allyl	*t*-Bu	85	96 (*S*)
9	**2i**	CH_2O*t*-Bu	*t*-Bu	89	98 (*R*)
10	**2j**	CH_2CO_2*t*-Bu	*t*-Bu	86	97 (*R*)
11	**2k**	$CH_2CH_2CO_2$*t*-Bu	*t*-Bu	82	98 (*S*)
12	**2l**	CH_2CH_2SMe	*t*-Bu	89	94 (*S*)
13	**2m**	$(CH_2)_4NHCbz$	*t*-Bu	78	>99 (*S*)

[a,b]Conditions: see Table 1, entry 2.

Scheme 2. Stereoselective Double Alkylations of Aldimine Schiff Base Derived from Glycine[a]

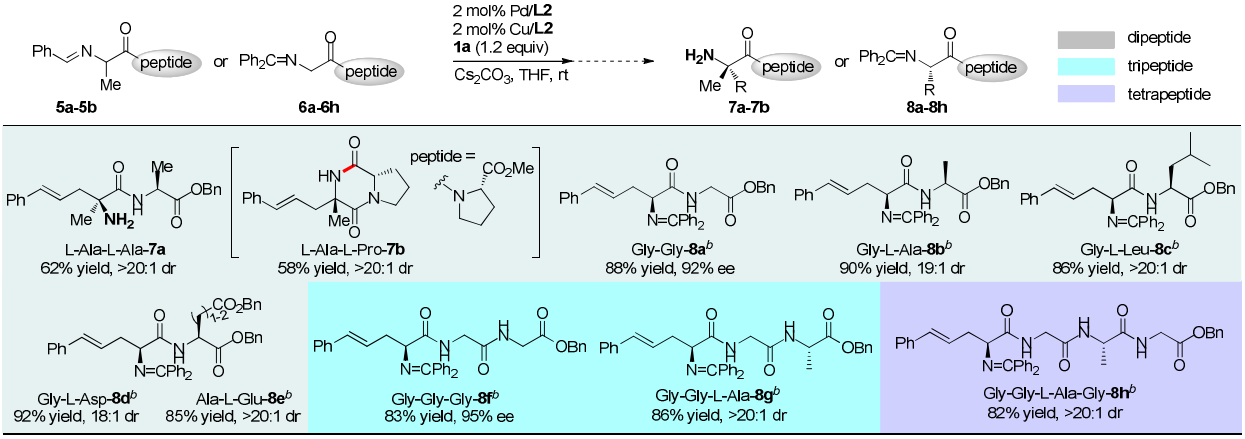


[a]The reaction was performed by the sequential treatment of aldimine Schiff base **2n** (0.25 mmol) with **1v** (1 equiv) and **1a** (1.2 equiv) in the presence of Cu/**L2** (2 mol%), Pd/**L2** (2 mol%), Cs_2CO_3 (2.0 equiv), THF (2 mL), rt, 18 h.

With the feasibility of this stereoselective quaternization method established, a one-pot asymmetric double alkylation of **2n** derived from the simple amino acid, glycine, was conducted under the optimized reaction conditions (Scheme 2). The desired product **4n** was obtained in 61% yield and 96% ee.

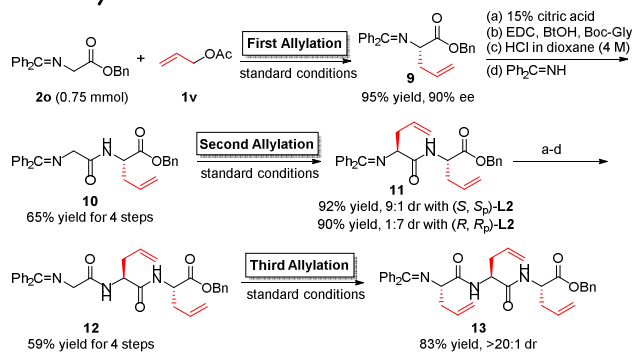
The successful development of a stereoselective process for the α-allylation of aldimine Schiff bases prompted us to question whether α-AAs embedded in long peptide chains could be modified using our catalyst system (Table 4). To verify this transformation, a dipeptide L-Ala-L-Ala derivative **5a** was first subjected to our bimetallic catalyst system to furnish the desired product **7a** in 62% yield and >20:1 dr. The reaction of dipeptide L-Ala-L-Pro derivative **5b** also proceeded smoothly, providing the cyclization product in 58% yield and >20:1 dr. In a similar manner, a variety of dipeptide derivatives **6a-6e** could also be employed in this alkylation, where excellent stereoselectivities were uniformly observed. These results clearly demonstrate that the efficiency of the transmission of stereochemical information is not affected by the side-chain structure of the preexisting amino acid residues. Encouraged by these results, we extended the bimetallic catalyst system to the stereoselective *N*-terminal alkylation of the tripeptides Gly-Gly-Gly derivative **6f**, Gly-Gly-L-Ala derivative **6g**, and even tetrapeptide Gly-Gly-L-Ala-Gly derivative **6h**. To our delight, the desired peptides were all obtained in good yields and with high stereoselectivities, thus verifying the feasibility of this bimetallic catalysis for the stereoselective and site-specific incorporation of non-natural α-AAs residues in long peptides.

Table 4. The Substrate Scope of Small Peptides[a]



[a]Conditions: see Table 1, entry 2; ratio of dr was determined by ^{1}H NMR integration. [b]K_2CO_3 (1.0 equiv).

Scheme 3. Synthesis of a Novel Tripeptide via Sequential Asymmetric Allylations



Based on the results above, we envisioned that sequential C-functionalizations of peptides of different lengths may provide multiple structural modifications of peptides at other sites. Indeed, the tripeptide **13** was readily prepared from simple glycine by employing three asymmetric allylations and by introducing two new glycine subunit using the well-established methods (Scheme 3). The tripeptide **13** can be potentially incorporated into longer peptide sequences using the steps described above.

In summary, we have developed a Pd/Cu dual catalyst system for the asymmetric α-allylation of Schiff base activated amino acids and small peptides. A range of noncoded α,α-dialkyl α-amino acids were easily synthesized in high yields and with excellent enantioselectivities under mild conditions. Furthermore, a highly stereoselective and site-specific construction of enantiopure α-AAs embedded small peptides was realized using this dual catalyst system. We believe that this bimetallic catalysis strategy will provide new opportunities for other challenging asymmetric reactions.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all reactions and products, including ^{1}H and ^{13}C NMR spectra, HPLC spectra, crystal data, and crystallographic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interests.

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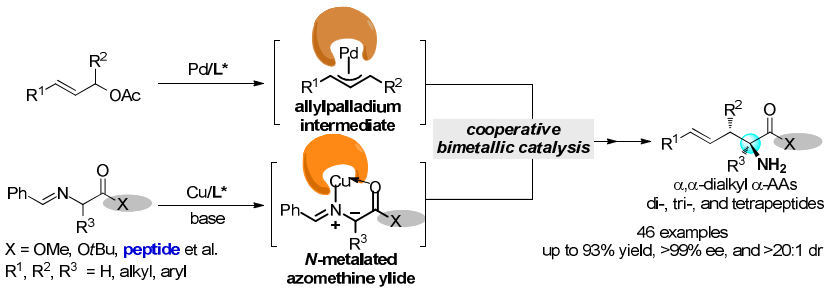
(19) See SI for the whole data of screening of bimetallic catalysts library.


Pd/L*
allylpalladium intermediate
Cu/L*
base
X = OMe, OtBu, peptide et al.
R1, R2, R3 = H, alkyl, aryl
N-metalated azomethine ylide
cooperative bimetallic catalysis
α,α-dialkyl α-AAs
di-, tri-, and tetrapeptides
46 examples
up to 93% yield, >99% ee, and >20:1 dr