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Combining Chiral Aldehyde Catalysis and Transition-Metal Catalysis for Enantioselective α-Allylic Alkylation of Amino Acid Esters

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Supporting Information

ABSTRACT: A chiral aldehyde is rationally combined with a Lewis acid and a transition metal for the first time to form a triple catalytic system. This cocatalytic system exhibits good catalytic activation and stereoselective-control abilities in the asymmetric α-allylation reaction of *N*-unprotected amino acid esters and allyl acetates. Optically active α,α-disubstituted α-amino acids (α-AAs) are generated in good yields (up to 87%) and enantioselectivities (up to 96% ee). Preliminary mechanism investigation indicates that the chiral aldehyde **3f** acts both as an organocatalyst to activate the amino acid ester via the formation of a Schiff base, and as a ligand to facilitate the nucleophilic attack process by coordinating with π-allyl Pd(II) species.

Chiral aldehyde catalysis has gradually become a powerful asymmetric synthesis strategy in amine chemistry.[1] Using this approach, various asymmetric organic reactions including transamination,[2] hydroamination[3] and the α-functionalization of amino acids[4−7] can be realized. Among these, the direct catalytic asymmetric α-functionalization of amino acids is undoubtedly the most important, because of the exceptional importance of amino acids in biological processes. To date, four types of transformations have been successful disclosed in this field. The earliest report concerned the aldol-based addition of amino acids to aldehydes by employing chiral pyridoxal-based enzymatic catalysis.[4] More recently, our group first reported a chiral aldehyde catalytic strategy involving the reversible formation of an imine in asymmetric alkylation of 2-aminomalonate.[5] Subsequently, the catalytic asymmetric activations of glycine derivatives by aldehydes were disclosed by Zhao and Yuan[6] and our group[7] independently. These works suggest that chiral aldehyde catalysis could be a powerful means to achieve the asymmetric transformations of amino acids and even amines, because the catalytically generated nucleophilic carbanion in such syntheses can be trapped by a variety of electrophiles. However, in its present form, chiral aldehyde catalysis will only proceed in the presence of highly active electrophiles, and thus the potential range of applications is very limited.

Combinations of organic and transition metal catalysts have been shown to provide a level of reactivity not achievable with a single catalyst,[8] and transition metals combined with chiral organic catalysts such as quaternary ammonium salts,[9] amines[10] and acids[11] have already become important chiral catalytic systems. Thus, we envisioned that the combination of a transition metal catalyst with a chiral aldehyde could overcome the limitations currently associated with chiral aldehyde catalysis. As exemplified in Figure 1, with a primary amine substrate, the chiral aldehyde can generate a nucleophilic α-imine carbanion intermediate (**II**), while the transition metal can promote the formation of an active electrophilic species ($\mathbf{E}^+$) simultaneously. The subsequent asymmetric nucleophilic reaction between **II** and $\mathbf{E}^+$ affords a chiral imine (**III**), whereupon, either by hydrolysis or amine exchange, the chiral amine product (**P***) is released and the catalyst or imine **I** is regenerated. However, although this concept provides a good blueprint for chiral aldehyde catalysis, the combination of chiral aldehyde catalysts with transition metals has not been explored.

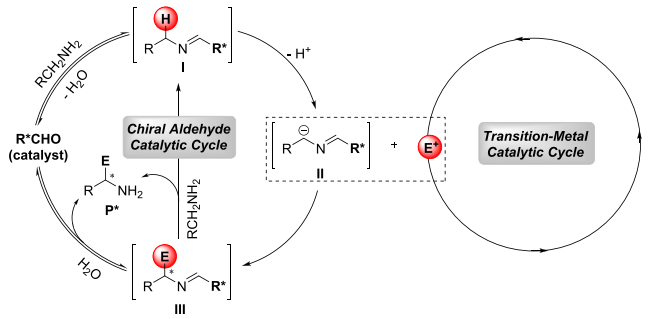

Figure 1. New catalytic strategy based on combining a chiral aldehyde and a transition metal.

Because of its exceptional ability to activate inert chemical bonds and its suitable level of compatibility with other catalysts, palladium has become an important transition metal for use with various organic catalysts to realize challenging organic transformations.[12] Among these achievements, the well-established π-allyl Pd(II) complexes[13] inspired us to evaluate our above proposal by combing chiral aldehyde and palladium in direct α-allylation reaction of *N*-unprotected amino acid esters and allyl acetates, which could provide one of the most straightforward methods for the preparation of optically active nonproteinogenic α,α-disubstituted α-amino acids (α-AAs) containing chiral quaternary carbon centers.

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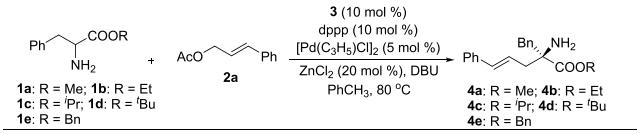
However, it is a very challenging work because the undesired *N*-allylation always exists in reaction. In fact, all of the reported examples except one utilized *N*-protected amino acid esters as reactants to avoid this side reaction.[14,15]

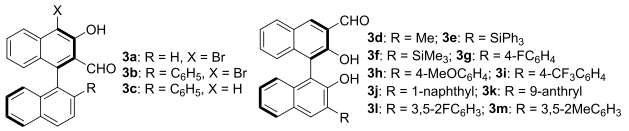
Initially, the direct α-allylation of methyl phenylalaninate (**1a**) with cinnamyl acetate (**2a**) was assessed in the promotion of a chiral aldehyde (**3a**) and palladium. Besides, the Lewis acid $ZnCl_2$ was added to stabilize the Schiff base and improve the α-carbon acidity of amino ester via the formation of a Zn-Schiff base complex.[16] The base, 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), was added to accelerate the deprotonation process. As expected, the desired product **4a** could be obtained in 13% yield and 58% enantioselective excess (ee) (Table 1, entry 1), while the *N*-allylation product became the major. The results obtained using other chiral aldehydes (**3b**, **3c**) indicated that this type of catalyst was not a suitable promoter for this transformation. Employing **3d**, a chiral BINOL-analogue bearing two hydroxyl groups, increased both the yield and enantioselectivity of **4a**, to 30% and 73% ee, respectively (Table 1, entry 4). Based on this outcome, the catalysts **3e**–**3m** were also screened, and the results demonstrated that **3f** gave the best enantioselectivity (Table 1, entry 6) while **3i** produced the highest yield (Table 1, entry 9). Using **3f** as the catalyst, other reaction conditions were also optimized. For example, the alkoxy screening showed that ethyl phenylalaninate (**1b**) gave better yield and enantioselectivity (Table 1, entry 14); while lowering the reaction temperature could inhibit the *N*-allylation side reaction and improve the yield as well as enantioselectivity of **4a** greatly (Table 1, entry 18 and 19). Bases, Lewis acids and phosphine ligands were then screened, but no better results were obtained (see Supporting Information). The chiral aldehyde **3i**, which gave the best yield, was then used to promote this reaction under the above optimized reaction conditions, giving product **4a** in 85% yield and 87% ee (Table 1, entry 20). In terms of the enantioselectivities, the reaction conditions depicted in entry 19 was utilized in the following substrate scope investigation.

Various substituted allyl acetates were subsequently used as acceptors. The allyl acetates bearing substituted phenyls gave the corresponding products **4f**–**4l** in good yields and excellent enantioselectivities, and the electronic properties and position of substituents on the phenyl rings were found not to significantly affect the experimental outcomes. Nonphenyl aryls, including naphthyl, furyl, thienyl and indolyl-substituted allyl acetates, also produced products **4m**–**4p** in good yields and enantioselectivities. Alkyl, alkenyl and alkynyl-substituted allyl acetates were then examined. The yield was found to decrease when phenyl acetenyl-substituted allyl acetate was used as the acceptor (Table 2, **4t**), while all the other allyl acetates gave the corresponding products **4q**–**4s** in good yields and excellent enantioselectivities. The allyl-substituted chiral amino acid ester **4q** represents one of the most useful building blocks for the preparation of PLG peptidomimetics.[14c]

The amino acid substrate scope was then investigated (Table 3). Phenylglycines were found to be good substrates in this reaction, while steric effects were determined to modify

Table 1. Reaction Condition Optimization[a]

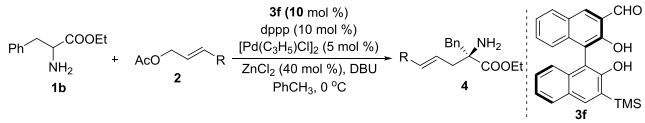


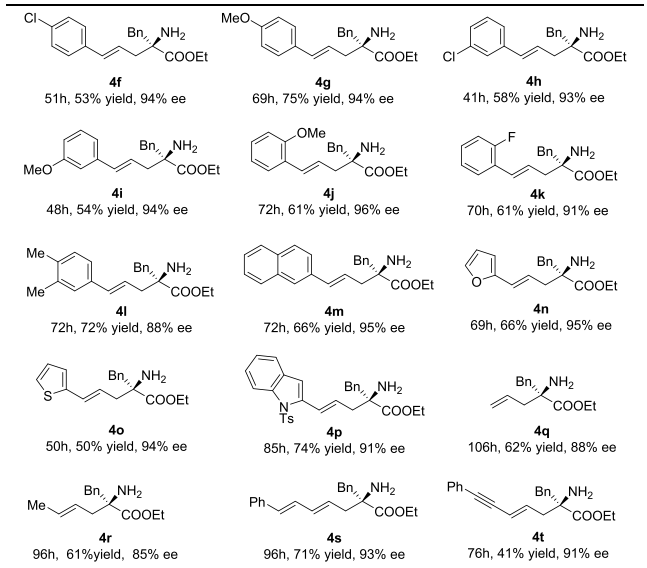


entry	3	4	time (h)	yield (%)[b]	ee (%)[c]
1	**3a**	**4a**	3.5	13	58
2	**3b**	**4a**	18	trace	ND[d]
3	**3c**	**4a**	18	trace	ND[d]
4	**3d**	**4a**	18	30	73
5	**3e**	**4a**	2	44	50
6	**3f**	**4a**	1.5	35	75
7	**3g**	**4a**	1.0	55	59
8	**3h**	**4a**	4	30	60
9	**3i**	**4a**	1.5	74	62
10	**3j**	**4a**	4	41	44
11	**3k**	**4a**	3.5	40	25
12	**3l**	**4a**	0.5	60	64
13	**3m**	**4a**	5	29	59
14	**3f**	**4b**	2	40	82
15	**3f**	**4c**	1	35	80
16	**3f**	**4d**	3.5	37	79
17	**3f**	**4e**	1	38	77
18	**3f**	**4b**	4	60	89[e]
19	**3f**	**4b**	48	74	94[f,g]
20	**3i**	**4b**	48	85	87[f,g]

[a]Reaction conditions: D,L-**1** (0.3 mmol), **2a** (0.2 mmol), **3** (0.02 mmol), dppp (0.02 mmol), $[Pd(C_3H_5)Cl]_2$ (0.01 mmol), $ZnCl_2$ (0.04 mmol), DBU (0.2 mmol), in $PhCH_3$ (1.5 mL) at 80 °C. [b]Isolated yield. [c]Determined by chiral HPLC. [d]ND = not determined. [e]At 50 °C. [f]At 0 °C. [g]40 mol % $ZnCl_2$.

Table 2. Scope of Allyl Acetates[a]





[a]Reaction conditions: D,L-**1b** (0.3 mmol), **2** (0.2 mmol), **3f** (0.02 mmol), dppp (0.02 mmol), $[Pd(C_3H_5)Cl]_2$ (0.01 mmol), $ZnCl_2$ (0.08 mmol), DBU (0.2 mmol), in $PhCH_3$ (1.5 mL), at 0 °C.

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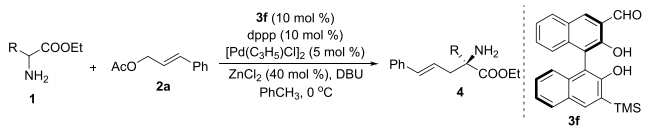
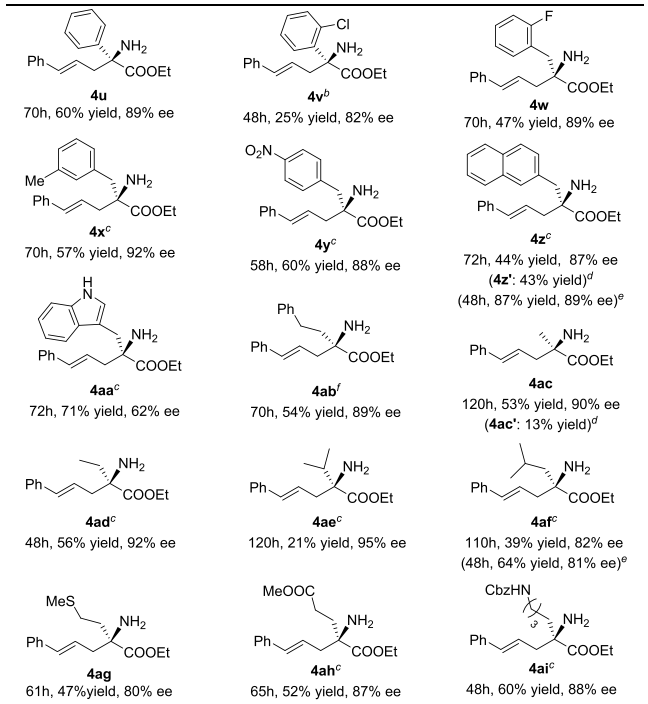
Table 3. Scope of Amino Acid Esters[a]



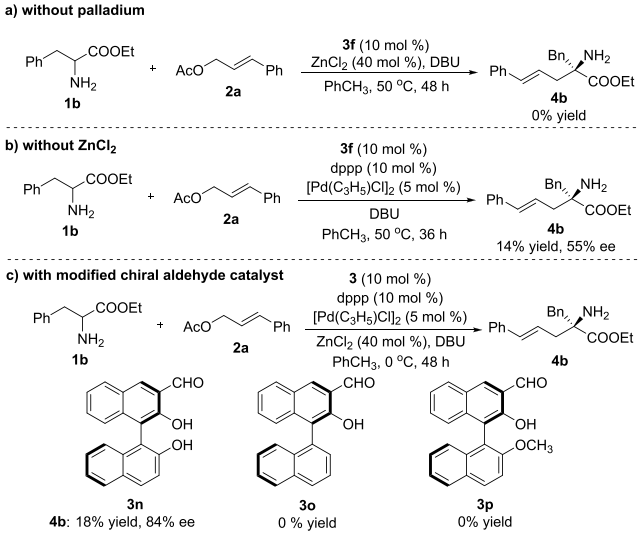


[a]Reaction conditions: D,L-**1** (0.2 mmol), **2a** (0.2 mmol), **3f** (0.02 mmol), dppp (0.02 mmol), $[Pd(C_3H_5)Cl]_2$ (0.01 mmol), $ZnCl_2$ (0.08 mmol), DBU (0.2 mmol), in $PhCH_3$ (1.5 mL), at 0 °C. [b]At 30 °C. [c]Using L-amino ester **1** as reactant. [d]Yield of the *N*-allylation byproduct. [e]Using **3i** as catalyst. [f]Using D-amino ester **1** as reactant.

the yields. As an example, product **4u** was generated in good yield, but **4v** was only obtained in a 25% yield, although both were generated in high enantioselectivities. Ethyl phenylalaninates bearing *otho-*, *meta-* or *para*-substituted phenyls gave excellent enantioselectivities. A moderate yield was obtained with ethyl 2-F phenylalaninate (Table 3, **4w**) and the yields increased when the substituent was moved to the *meta-* or *para*-position of the phenyl ring (Table 3, **4x** and **4y**). Other aryl-substituted amino acid derivatives, including ethyl 2-naphthylalaninate, tryptophanate and homophenylalaninate, were also introduced as donors, and the corresponding products **4z**–**4ab** were obtained in 44%–71% yields and with 62%–89% ees. Alkyl-substituted amino acids were also observed to react with phenyl allyl acetate (**2a**) smoothly, giving products **4ac**–**4af** in moderate yields and high-to-excellent enantioselectivities. However, only a 21% yield resulted from the reaction of ethyl valinate and **2a** (Table 3, **4ae**), possibly due to the steric effect of the isopropyl group. Amino acids containing thioether, ester and amino groups were also applicable to this reaction, giving products **4ag**–**4ai** in moderate yields and high enantioselectivities. Two amino acid substrates that did not give satisfactory yields in association with **3f** were re-examined using the chiral aldehyde **3i** as the catalyst. The yield of **4z** was increased from 44% to 87%, while that of **4af** was increased from 39% to 64%, and the enantioselectivities of these two products were maintained at a high level. Generally, the *N*-allylation side reaction is one of the main factors affecting the yields of products **4**. For example, the *N*-allylation byproducts **4z′** and **4ac′** were isolated in 43% and 13% yields, respectively. The absolute configuration of products **4ab** was established on the basis of the comparison of the literature data with the experimental values (see Supporting Information). The stereochemistries of compounds **4** were assigned by analogy with that of **4ab**.

To the best of our knowledge, the triple catalytic system consisting of a chiral aldehyde, a Lewis acid and a transition metal has not been explored previously. To gain insight into this multicooperative catalytic process, control experiments were carried out. As shown in Scheme 1, the model reaction

Scheme 1. Control Experiments



does not work without palladium catalyst (Scheme 1a), so, a classic Tsuji–Trost allylation mechanism is possible.[12,13] Besides, in the absence of $ZnCl_2$, this reaction can proceed successfully, but much lower yield and enantioselectivity was obtained (Scheme 1b vs Table 1, entry 18). This result indicates that it is possible to form a zinc-Schiff base complex (**I**) in this reaction, because the formation of this complex can stabilize the Schiff base and further improve the α-carbon acidity of the amino acid ester.[16] Thus, facilitate the Schiff base formation and subsequent deprotonation processes. With these information in hand, a possible reaction mechanism is summarized in Figure 2. First, a Schiff base is generated from chiral aldehyde **3f** and amino acid ester **2b**, and then combines with $ZnCl_2$ to form the Zn-Schiff base complex (**I**). This Zn-Schiff base intermediate is deprotonated by DBU and transformed into the active enolate intermediate (**II**). At the same time, an electrophilic π-allyl Pd(II) complexes (**E**) is generated from allyl acetate and palladium by oxidative addition. Subsequently, the enolate intermediate **II** attacks the π-allyl Pd(II) complex **E** via an inter- or intramolecular manner. As results, the Zn-Schiff base complex (**III**) is produced and the active palladium catalyst is regenerated. Finally, the product **4b** is released from Zn-Schiff base (**III**) by amine exchange or hydrolysis. In order to clarify what manner is favored in the nucleophilic attack step, three modified chiral aldehydes were used as catalysts in the model reaction (Scheme 1c). We found compound **4b** was obtained in 18% yield and 84% ee when using chiral aldehyde **3n**, but none of

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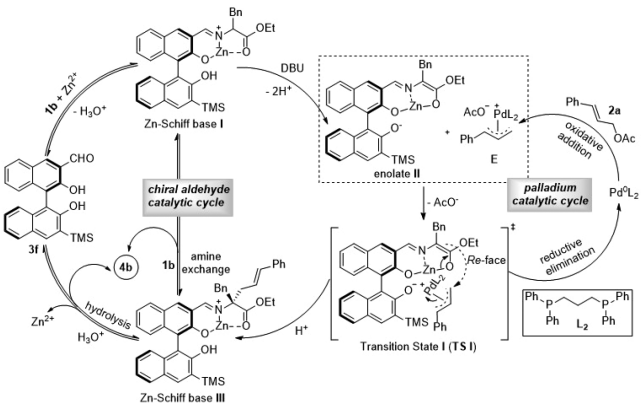

Figure 2. Proposed catalytic cycles.

the desired product was generated with chiral aldehydes **3o** and **3p**. These results indicate that the presence of a hydroxyl group at the 2′ position of the BINOL aldehyde (**3**) is crucial to this reaction. One of the most reasonable interpretations is that a temporary intramolecular transition state **I** (Figure 2, TS **I**) can be formed from the enolate intermediate (**II**) and the π-allyl Pd(II) species **E** via an anion exchange between 2′ hydroxyl and acetate anion. Thus, the intramolecular nucleophilic attack becomes a dominant pathway.

In conclusion, this work demonstrated the first catalytic strategy based on a combination of a chiral aldehyde, a Lewis acid and a transition metal. Using this triple catalytic system, the α-allylation reactions of *N*-unprotected amino esters and allyl acetates proceeded smoothly, giving chiral nonproteinogenic α,α-disubstituted α-amino acids (α-AAs) in good yields and excellent enantioselectivities. The proposed mechanism demonstrates that the presence of a 2′ hydroxyl group is vital to the success of this reaction, possibly because this hydroxyl group coordinates with the π-allyl Pd(II) species, thus facilitating the reaction process.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.9b01910.

Copies of ^{1}H, ^{13}C NMR and HPLC spectra; representative experimental procedures and analytical data for all new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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