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Stereodivergent Synthesis of α,α-Disubstituted α-Amino Acids *via* Synergistic Cu/Ir Catalysis

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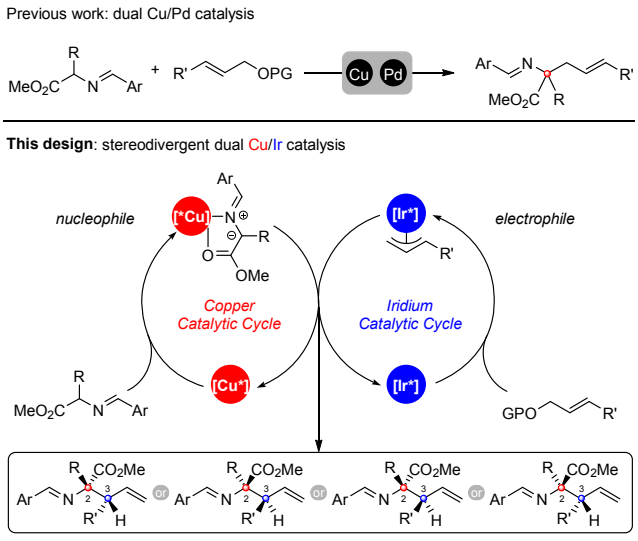
ABSTRACT: A Cu/Ir dual catalysis has been developed for the stereodivergent α-allylation of aldimine esters. The method enables the preparation of a series of nonproteinogenic α-AAs bearing two contiguous stereogenic centers in high yield with excellent stereoselectivity. All of the four product stereoisomers could be obtained from the same set of starting materials *via* pairwise combination of two chiral catalysts. Notably, one-pot protocol could be successfully applied for the preparation of the bimetallic Cu/Ir complexes to simplify the manipulation of Cu/Ir dual catalysis. This method could be further utilized for the construction of the key intermediate of a bioactive pyrrolidine derivative and the concise synthesis of a plant growth regulator (2*S*,3*S*)-2-amino-3-cyclopropylbutanoic acid.

INTRODUCTION

Stereochemically rigid α,α-disubstituted α-amino acids (α-AAs) have been widely used in the design of novel non-natural peptides and proteins with enhanced biological properties[1] due to its stability towards racemization and restricted conformational flexibility.[2] Furthermore, α,α-disubstituted α-AAs are also found in a series of natural product antibiotics such as altemicidin.[3] Accordingly, development of efficient methods for the construction of α,α-disubstituted α-AAs, especially in a catalytic asymmetric way, has become of great importance.[4] With great efforts have been paid, chemists now are able to synthesize different types of enantioenriched α,α-disubstituted α-AAs, for example through catalytic asymmetric Strecker reaction, Mannich-type reaction and alkylation of amino acids derived nucleophiles.[5] In those methodologies, both enantiomers of the α-AAs can be obtained by switching a pair of enantiomeric catalysts. In contrast, construction of α-AAs bearing multiple stereocenters with full control of the absolute and relative configuration is still an elusive goal.[6] In consideration of the stereoscopic configurations of α-AAs are often crucial for the design of peptides,[7] chiral ligands/catalysts,[8] and the expression of biological activities,[9] developing an efficient method for the stereodivergent synthesis of α-AAs is of great significance.

Synergistic catalysis has emerged as a powerful synthetic strategy to enantioselective bond forming process.[10] Recently, Carreira and coworkers further advanced this concept to the use of two distinct chiral catalyst and each is capable of exercising full control over the configuration of its corresponding stereogenic center independently.[11a] Inspired by the elegant work on stereodivergent dual catalysis[11] and our continuous interest in the construction of unnatural α-amino acids with metallated azomethine ylides,[12,13] we envisioned a synergistic Cu/Ir catalyzed asymmetric allylic alkylation[14] of aldimine esters would furnish the branched α,α-disubstituted α-AAs bearing two adjacent stereogenic centers, in which full complement of stereoisomers could be readily prepared by using four available catalyst permutations. Herein, we report our investigation on the stereodivergent allylic alkylation of aldimine esters with synergistic Cu/Ir catalysis. The synthetic utility of this method is exemplified by the synthesis of a bioactive pyrrolidine derivative and the natural product (2*S*,3*S*)-2-amino-3-cyclopropylbutanoic acid. Notably, one-pot protocol could be successfully applied for the preparation of the bimetallic catalysts to simplify the manipulation process.

Scheme 1. Synergistic Catalysis for Stereoselective Construction of Nonproteinogenic α-Amino Acids (α-AAs)

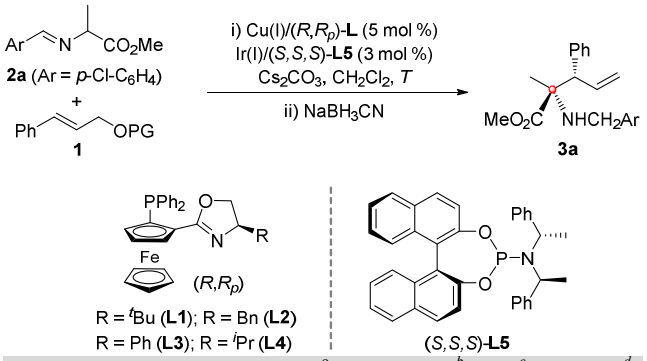


RESULTS AND DISCUSSION

Initial trials were carried out using cinnamyl methyl carbonate **1a** and alanine derived aldimine ester **2a** as model substrates, Cs_2CO_3 as the base and Ir(I)/(*S*,*S*,*S*)-**L5** complex[15,16] as the allylation catalyst at room temperature. To our delight,

when Cu(I)/(R,R_p)-Phosferrox(**L1**)[17] complex was employed to activate aldimine ester, the desired product **3a** was isolated in 67% yield with exclusively branched selectivity, high diastereoselectivity and 97% ee *via* an allylation/reduction process (Table 1, entry 1). After examination of different Phosferrox ligands, we found that Cu(I)/**L1-L4** all show high catalytic activity with excellent asymmetric introduction, and the combination of [Cu(I)/(R,R_p)-**L4** + Ir/(S,S,S)-**L5**] were the superior synergistic catalysts, affording **3a** in 82% yield with 15:1 dr and 97% ee (entries 2-4). With optimized catalysts in hand, we then evaluated the leaving groups of the π-allyl precursors. The yield was slightly decreased when *tert*-butyl carbonate **1b** was used, and acyl protected cinnamyl alcohol **1c** gave no better results than **1a** either (entries 5 and 6). Reducing the reaction temperature to 15 °C with increasing the concentration of **1a** to 0.2 M further improved the stereoselectivity with maintained yield (entries 7 and 8). The control experiments suggested that both copper and iridium catalysts were indispensable for this transformation (entries 9 and 10). Additionally, the combined copper and iridium complexes with the identical chiral ligand **L4** or **L5** cannot promoted this allylic alkylation reaction either (entries 11 and 12).

Table 1. Optimization of Reaction Conditions[a]



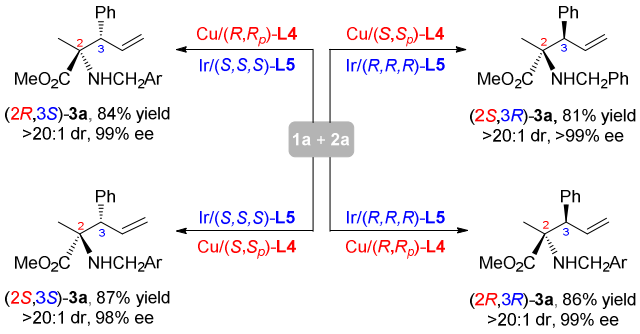
entry	L for Cu	PG	T (°C)	yield (%)[b]	dr[c]	ee (%)[d]
1	**L1**	CO_2Me	25	67	15:1	97
2	**L2**	CO_2Me	25	78	14:1	91
3	**L3**	CO_2Me	25	75	15:1	95
4	**L4**	CO_2Me	25	82	15:1	97
5	**L4**	Boc	25	58	16:1	97
6	**L4**	Ac	25	71	12:1	91
7	**L4**	CO_2Me	15	65	>20:1	99
8[e]	**L4**	CO_2Me	15	84	>20:1	99
9[f]	-	CO_2Me	25	trace	n.d.	n.d.
10[g]	**L4**	CO_2Me	25	0	-	-
11[h]	**L4**	CO_2Me	25	0	-	-
12	**L5**	CO_2Me	25	trace	n.d.	n.d.

[a] All reactions were carried out with 0.20 mmol of **1** and 0.30 mmol of **2a** in 2 mL of CH_2Cl_2 for 12 h. Cu(I) = $Cu(MeCN)_4BF_4$. [b] Isolated yield. [c] Dr was determined by the crude ^1H NMR. [d] Ee was determined by HPLC analysis. [e] 1 mL of DCM was used. [f] Without Cu(I)/(R,R_p)-**L4**. [g] Without Ir(I)/(S,S,S)-**L5**. [h] With Ir(I)/(R,R_p)-**L4**.

With optimized reaction conditions in hand, we then set out to test whether all four stereoisomers could be prepared with the current dual Cu/Ir catalysis. By simply selecting from the complete set of catalyst permutations Cu(I)/(R,R_p)-**L4** or Cu(I)/(S,S_p)-**L4** along with Ir(I)/(R,R,R)-**L5** or Ir(I)/(S,S,S)-**L5**, full array of stereoisomers of α,α-disubstituted α-AAs **3a** were produced in good yield (81-87%) with excellent enantioselectivity (98->99% ee) and exclusive diastereoselectivity (>20:1 dr) from the same set of starting materials (Scheme 2).

The results suggested that the two distinct metal catalysts exerts almost absolute control over the corresponding stereogenic centers, respectively.

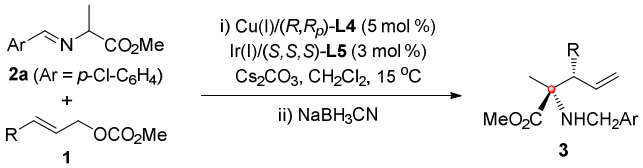
Scheme 2. Synthesis of All Stereoisomers of 3a[a]



[a] Conditions see Table 1, entry 8.

The scope of the α-allylation with regard to π-allyl precursors was then explored (Table 2). First, we assessed cinnamyl methyl carbonate with different functional groups. The current method shows good tolerance towards both electronic properties (electron- deficient, -neutral or -rich) and substitution positions (*ortho*-, *meta*- or *para*-), and the corresponding products **3a-3g**, **3i** and **3j** were achieved in good yield with excellent enantioselectivity and exclusive diastereoselectivity (Table 2, entries 1-7, 9 and 10). A slightly lower diastereoselectivity (14:1 dr) was observed when *meta*-chloro substituted cinnamyl methyl carbonate **1h** was employed as π-allyl precursor (entry 8). Fused aryl- and various heteroaryl-substituted **1k-1m** and **1o-1q** were then subjected to α-allylation leading to the desired products in 62-96% yield with excellent diastereoselectivity and >99% ee (entries 11-13 and 15-17). For 2-thiazolyl-substituted allylic ester **1n**, the corresponding product could be achieved in good yield with 98% ee and 7:1 dr (entry 14). Furthermore, styrenyl- and methyl-substituted allylic esters **1r** and **1s** also reacted smoothly with **2a** affording the desired products **3r** and **3s** with satisfied results (entries 18 and 19). The absolute configuration of compound **3o** was determined as (2R,3S) by the X-ray analysis (CCDC 1578014) (Figure 1).

Table 2. Substrate Scope of Allyl Carbonates[a]



entry	R	3	yield (%)[b]	dr[c]	ee (%)[d]
1	Ph	**3a**	84	>20:1	99
2	*p*-Me-C_6H_4	**3b**	95	>20:1	>99
3	*m*-Me-C_6H_4	**3c**	73	>20:1	>99
4	*o*-Me-C_6H_4	**3d**	71	>20:1	98
5	*p*-MeO-C_6H_4	**3e**	67	>20:1	>99
6	*p*-F-C_6H_4	**3f**	69	>20:1	98
7	*p*-Cl-C_6H_4	**3g**	81	>20:1	>99
8	*m*-Cl-C_6H_4	**3h**	79	14:1	98
9[e]	3,4-Cl_2-C_6H_3	**3i**	89	>20:1	99
10	*p*-Br-C_6H_4	**3j**	78	>20:1	>99
11	2-naphthyl	**3k**	79	>20:1	>99
12	2-furyl	**3l**	71	>20:1	>99

13	2-thienyl	**3m**	62	>20:1	>99
14[f,g]	2-thiazolyl	**3n'**	86	7:1	98
15	3-pyridinyl	**3o**	73	>20:1	>99
16	4-MeO-3-pyridinyl	**3p**	90	>20:1	>99
17[f]	6-quinolinyl	**3q'**	96	>20:1	>99
18	styrenyl	**3r**	71	>20:1	99
19	CH_3	**3s**	69	>20:1	99

[a] Conditions see Table 1, entry 8. [b] Isolated yield. [c] Dr was determined by the crude ^{1}H NMR. [d] Ee was determined by HPLC analysis. [e] Catalysts combination: [Cu(I)/(*S*,*S*$_p$)-**L4** + Ir(I)/(*R*,*R*,*R*)-**L5**], work up with citric acid. [f] Without reduction. [g] Yield of the mixture of two diastereoisomers, and ee referred to that of the major isomer.

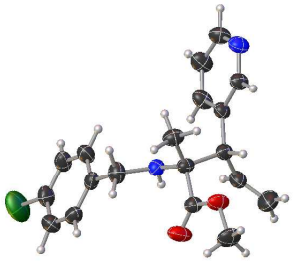
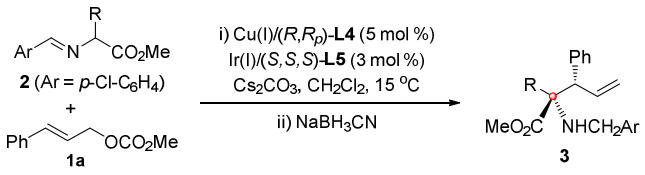
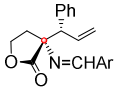


Figure 1. X-Ray structure of (2*R*,3*S*)-**3o**.

Subsequently, the scope with respect to the α-substituted aldimine esters was also evaluated. As shown in Table 3, we were pleased to find that both natural and non-natural α-AAs derived aldimine esters are suitable azomethine ylide precursors for the current asymmetric allylic alkylation. Diverse substituents including alkyl (**2b-d**), (substituted)benzyl (**2e-g**), (substituted)allyl (**2h-j**), thioether (**2k**) and ester (**2l**) were all well-tolerated giving α,α-disubstituted α-AAs derivatives in high yield with excellent stereoselectivity (Table 3, entries 1-11). In addition, aldimine esters **2m** derived from 2-amino-γ-butyrolactone also worked well in this protocol and **3ae'** was isolated in 89% yield with 98% ee and 8:1 dr (entry 12).

Table 3. Substrate Scope of Aldimine Esters[a]

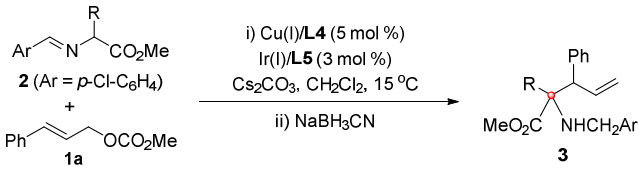


entry	R	3	yield (%)[b]	dr[c]	ee (%)[d]
1	Et	**3t**	85	>20:1	>99
2	*n*-Pr	**3u**	84	>20:1	>99
3	*n*-Bu	**3v**	75	>20:1	>99
4	$PhCH_2$	**3w**	72	>20:1	99
5	*p*-$MeC_6H_4CH_2$	**3x**	62	>20:1	97
6	*p*-$BrC_6H_4CH_2$	**3y**	60	>20:1	>99
7	allyl	**3z**	71	>20:1	98
8	crotyl	**3aa**	89	>20:1	94
9	cinnamyl	**3ab**	88	>20:1	>99
10	$MeSCH_2CH_2$	**3ac**	88	>20:1	98
11	$MeO_2CCH_2CH_2$	**3ad**	78	>20:1	>99
12[e,f]		**3ae'**	89	8:1	98

[a] Conditions see Table 1, entry 8. [b] Isolated yield. [c] Dr was determined by the crude ^{1}H NMR. [d] Ee was determined by HPLC analysis. [e] Without further reduction. [f] Yield of the mixture of two diastereoisomers, and ee referred to that of the major isomer.

After examining the substrate scope of both electrophile and nucleophile precursors, we further explored the stereodivergence of the current method with cinnamyl methyl carbonate **1a** under the standard reaction conditions. Aldimine esters **2e**, **2j** and **2k** were selected as the representative substrates. As shown in Table 4, in each case, with the pairwise combination of Cu/Ir catalysts, all of the four stereoisomeric products were readily-obtained in good yields with 91->99% ee and >20:1 dr.

Table 4. Representative Examples of Stereodivergence[a]

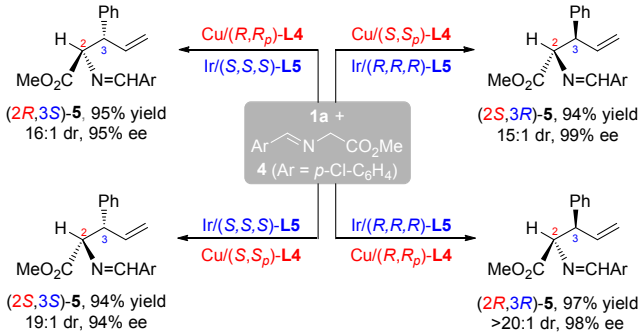


entry	Cu/Ir dual catalyst	R: $PhCH_2$-	R: PhCH=CH-	R: $MeSCH_2CH_2$-
1	Cu/(*R*,*R*$_p$)-**L4** Ir/(*S*,*S*,*S*)-**L5**	(2*R*,3*S*)-**3w** 72% yield >20:1 dr 99% ee	(2*R*,3*S*)-**3ab** 88% yield >20:1 dr >99% ee	(2*R*,3*S*)-**3ac** 88% yield >20:1 dr 98% ee
2	Cu/(*R*,*R*$_p$)-**L4** Ir/(*R*,*R*,*R*)-**L5**	(2*R*,3*R*)-**3w** 71% yield >20:1 dr >99% ee	(2*R*,3*R*)-**3ab** 88% yield >20:1 dr 99% ee	(2*R*,3*R*)-**3ac** 90% yield >20:1 dr >99% ee
3	Cu/(*S*,*S*$_p$)-**L4** Ir/(*R*,*R*,*R*)-**L5**	(2*S*,3*R*)-**3w** 81% yield >20:1 dr 98% ee	(2*S*,3*R*)-**3ab** 84% yield >20:1 dr 99% ee	(2*S*,3*R*)-**3ac** 82% yield >20:1 dr 91% ee
4	Cu/(*S*,*S*$_p$)-**L4** Ir/(*S*,*S*,*S*)-**L5**	(2*S*,3*R*)-**3w** 77% yield >20:1 dr 99% ee	(2*S*,3*R*)-**3ab** 89% yield >20:1 dr >99% ee	(2*S*,3*R*)-**3ac** 86% yield >20:1 dr >99% ee

[a] Conditions see Table 1, entry 8.

With a variety of α,α-disubstituted α-AAs have been obtained from α-substituted aldimine ester, we determined to investigate the compatibility of glycine derived aldimine ester in this α-allylation protocol to synthesize α-monosubstituted α-AAs bearing two contiguous tertiary/tertiary stereogenic centers. A notable challenge associated with this process is that the products contain a racemizable proton at the α-position of carbonyl group, rendering them prone to epimerization which was further enhanced by the coordination of the carbonyl and imine moieties to copper center under basic condition. Indeed, preliminary experiment indicated that desired product with 1:1 dr was isolated under the standard reaction condition. Fortunately, after switching the inorganic base Cs_2CO_3 to a weaker organic base Et_3N under otherwise similar reaction conditions, we successfully realized the stereodivergent α-allylation of glycinate derived aldimine ester **4**. All four stereoisomers of α-AAs **5** bearing vicinal tertiary/tertiary stereogenic centers were readily constructed in high yield with 94-99% ee and 15:1->20:1 dr (Scheme 3).

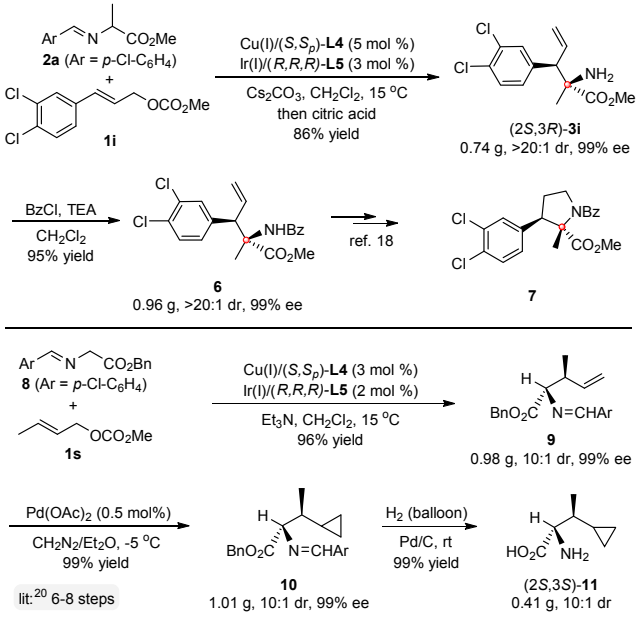
Scheme 3. Synthesis of All Stereoisomers of 5 Containing Contiguous Tertiary/Tertiary Stereogenic Centers[a,b]



[a] Conditions see Table 1, entry 8 except with Et_3N as the base. [b] Without further reduction.

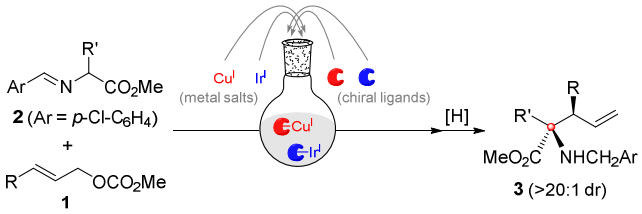
To showcase the utility of this methodology, further transformation were conducted as shown in Scheme 4. (2*S*,3*R*)-**3i** was obtained through allylation/hydrolysis in 3 mmol scale catalyzed by [Cu(I)/(S,S_p)-**L4** + Ir(I)/(*R*,*R*,*R*)-**L5**)] without loss of stereoselectivity. By a simple benzoylation **3i** was then transformed to compound **6**, which was the key intermediate for the synthesis of pyrrolidine **7** possessing monoamine-reuptake-blocking activity.[18] Furthermore, starting from glycine derived aldimine ester **8** and crotyl carbonate **1s**, an efficient asymmetric total synthesis of natural product (2*S*,3*S*)-2-amino-3-cyclopropylbutanoic acid[19] was carried out. Under the standard reaction conditions with Cu(I)/(S,S_p)-**L4** and Ir(I)/(*R*,*R*,*R*)-**L5** as the catalysts combination, compound **9** was isolated in 96% yield with 10:1 dr and 99% ee (without further optimization). Pd(II)-Catalyzed cyclopropanation of compound **9** with diazomethane provided compound **10** in quantitative yield and with maintained stereoselectivity. Hydrogenation/debenzoylation of compound **10** under mild condition delivered the target compound (2*S*,3*S*)-**11** in 99% yield. It is noteworthy that both compound **10** and **11** were separated without column chromatography, and filtering the catalysts followed by removing the solvents afforded the corresponding products in high purity. Compared with previous 6-8 steps synthetic protocols from the optically active starting materials,[20] the current method shows its convenience and high efficiency.

Scheme 4. Formal Synthesis of Bioactive Pyrrolidine 7 and Total Synthesis of Plant Growth Regulator 11 in 3 Steps



When testing the substrate scope, we realized one drawback of the bimetallic dual catalysis is the complicated operation. Unlike Carreria's amine/Ir dual catalysis,[11a-c] the two distinct metal/ligand complexes were usually prepared in separated tubes to avoid the potential ligand scrambling and then merged together, which obviously enlarged the manipulation complexity compared with traditional mono-transition-metal catalysis. The mechanistic studies on the Feringa-type ligand **L5** conducted by Hartwig[15] revealed that the active catalytic species of the chiral iridium complex was formed via an insertion of the Ir center into the C(sp^3)-H bond in the methyl group of the ligand with the aid of base. The preferential formation of the cyclometalated iridium complex reminds us that the two desired Cu(I) and Ir(I) complexes could be readily-formed through directly mixing two metal sources and two chiral ligands in one pot. It is believed that the dynamic equilibrium of coordination and dissociation of the mixtures of metal/ligand complexes was broken by the event of C(sp^3)-H insertion under basic condition between iridium and phosphoramidite ligand. With Ir/**L5** complex formed completely, the coordination of the remaining Cu(I) cation and chiral P,N-ligand would lead to the desired copper complex.

Table 5. Stereodivergent Synthesis of α,α-Disubstituted α-AAs with Bimetallic Cu/Ir Catalysts Prepared in One-Pot Protocol[a]



entry	R	R'	3	yield (%)[c]	ee (%)[c]
1	Ph	Me	(2*S*,3*R*)-**3a**	75	99
2	*p*-MeC_6H_4	Me	(2*S*,3*R*)-**3b**	88	>99
3	2-furyl	Me	(2*S*,3*S*)-**3l**	72	99
4	2-thienyl	Me	(2*S*,3*S*)-**3m**	65	99
5	Ph	*n*-Pr	(2*S*,3*R*)-**3u**	78	>99
6	Ph	cinnamyl	(2*S*,3*R*)-**3ab**	75	98

[a] Conditions see Table 1, entry 8 except with catalyst combination [Cu(I)/(*S*,S_p)-**L4** + Ir(I)/(*R*,*R*,*R*)-**L5**].

To verify this hypothesis, the bimetallic catalysts were prepared from a mixture of $Cu(MeCN)_4BF_4$, $[Ir(cod)Cl]_2$, (*S*,S_p)-**L4** and (*R*,*R*,*R*)-**L5** in one pot protocol (see Supporting Information for details) and then applied to the α-allylation of aldimine esters to examine the catalytic efficiency. All the tested substrates reacted smoothly, giving a set of (2*S*,3*R*)- or (2*S*,3*S*)-configured α,α-disubstituted α-AAs with comparable levels of yield and stereoselectivity (Table 5, entries 1-6). The one-pot protocol for the preparation of the bimetallic catalysts clearly demonstrated that the practicability of the current dual catalysis process. The ^{31}P NMR and control experiments further confirmed that the ligand scrambling was negligible in the catalytic system (See Supporting Information for details).

CONCLUSIONS

In summary, we have developed a stereodivergent synergistic Cu/Ir catalyzed α-allylation of aldimine esters. The method enables the preparation of a series of nonproteinogenic α-AAs bearing vicinal quaternary/tertiary or tertiary/tertiary stereogenic centers with high yield and excellent stereoselectivity. The pairwise combination of two chiral catalyst provide access to all possible stereoisomers under identical conditions from the same set of starting materials. Furthermore, the utility of the method was proven in the construction of the key intermediate of a bioactive pyrrolidine derivative and the concise asymmetric synthesis of a natural product (2*S*,3*S*)-2-amino-3-cyclopropylbutanoic acid.

ASSOCIATED CONTENT

Supporting Information

Experimental procedures and characterization data for all reactions and products, including ^1H and ^{13}C NMR spectra, HPLC spectra, crystal data (**3o**). The Supporting Information is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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