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Unprecedented Effects of Additives and Ligand-to-Metal Ratio on the Enantiofacial Selection of Copper-Catalyzed Alkynylation of α-Imino Ester with Arylacetylenes

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Abstract: The first catalytic asymmetric addition of arylacetylenes to α-imino esters was carried out using chiral copper(I) complexes as catalysts under mild reaction conditions, providing the corresponding alkynylation products in good yields with 67–74% *ee* values. Profound effects of the ligand-to-metal ratio and additives on the stereofacial selection were observed. Both enantiomers of a given product can be obtained with almost identical enantiomeric excess using the same chiral ligand by adjusting the ligand-to-metal ratio.

Keywords: asymmetric alkynylation; asymmetric catalysis; copper; enantioselectivity; α-imino ester; ligand-to-metal ratio

Optically active non-proteinogenic α-amino acids are important compounds in biological systems and chiral building blocks in drug syntheses.[1–6] A special class of these compounds are chiral β,γ-alkynyl-α-amino acid derivatives.[7] It is recognized that compounds containing carbon/carbon triple bonds serve to deactivate a variety of enzymes.[8] However, the synthesis of enantiomerically enriched β,γ-alkynyl-α-amino acid derivatives is a challenging undertaking.

Metal-catalyzed addition of terminal alkynes to imines represents one of the most convenient methods for the synthesis of propargylamines.[9] This reaction was extended to α-imino esters and an efficient synthesis of β,γ-alkynyl-α-amino acid derivatives was developed by the direct addition of phenylacetylene and alkylacetylenes to an α-imino ester in the presence of silver(I) salts.[10] Based on this method, we realized the first catalytic asymmetric synthesis of aliphatic alkynyl-α-amino acid derivatives by using copper(I) complexes with 48–91% enantiomeric excesses.[11] From a synthetic standpoint, an efficient and flexible approach to enantiomerically pure aromatic alkynyl-α-amino acid derivatives is highly desirable. In this paper, we report the first enantioselective addition of arylacetylenes to an α-imino ester, and reveal unprecedented effects of the ligand-to-metal ratio and additives on the enantiofacial selection of the Cu-catalyzed alkynylation of an α-imino ester with arylacetylenes.

The experiments were carried out under similar conditions to those used in our previous study of Cu-catalyzed addition of aliphatic alkynes to the α-imino ester.[11] The reaction of phenylacetylene **2a** and α-imino ester **1** was performed in dichloromethane (DCM) at −10 °C using 10 mol% CuOTf·0.5 C_6H_6 as a precatalyst, Pybox **10** (Figure 1) as a chiral ligand and 0.1 equivalent of PMP-NH_2 as additive. The desired product **3a** was obtained with moderate yield (51%) and low enantiomeric excess (41% *ee*) after 48 h. Although the cause of this phenomenon was not immediately clear, this result indicated the difference in reactivity between aliphatic and aromatic alkynes in the Cu-catalyzed akynylation of the α-imino ester, and that new reaction conditions must be established for arylacetylenes. To our delight, further experiments indicated that, in the absence of an additive, the yield and enantiomeric excess of the addition product **3a** increased significantly to 64% and 61%, respectively, at −10 °C after 48 h. After further optimization, we obtained the product **3a** in 75% yield and 60% *ee* at room temperature after 24 h.

These interesting results led us to examine the effect of a variety of chiral ligands (Figure 1) in the Cu-catalyzed asymmetric addition of phenylacetylene **2a** to the α-imino ester **1**. Similar to the previously reported results in the enantioselective addition of aliphatic alkynes to the α-imino ester,[11] BINAP was

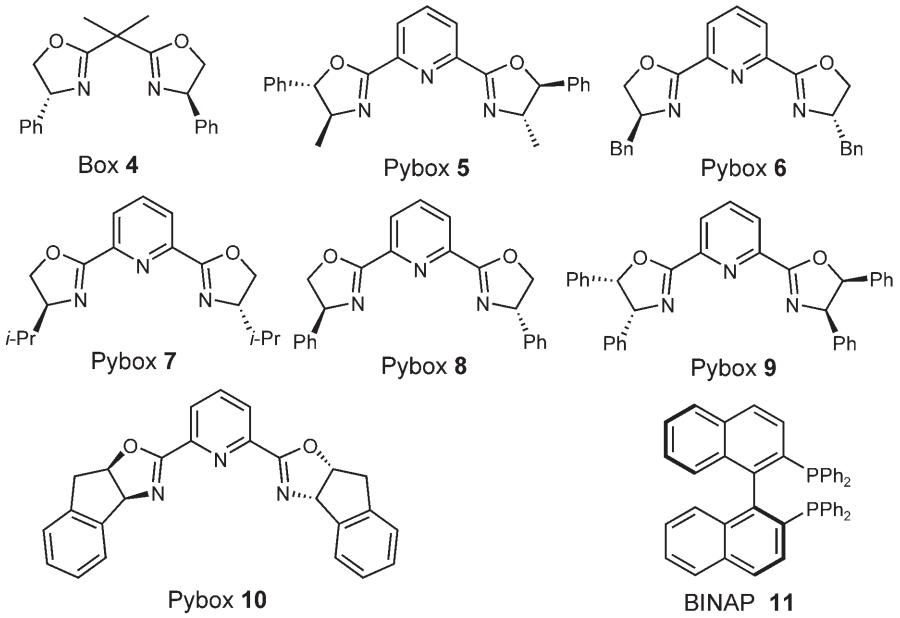


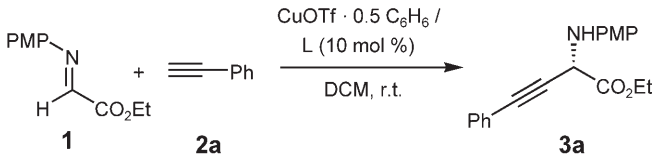
Figure 1. Chiral ligands tested in the addition of aromatic alkynes to an α-imino ester.

less effective in this reaction (Table 1, entry 8). Given that chiral copper-bis(oxazoline) (box) complexes have been successfully applied in numerous enantioselective addition reactions,[12–14] a variety of chiral bis(oxazolinyl) ligands were tested. Among the chiral ligands that we have investigated, the commercially available chiral ligand Pybox **8** furnished the target product **3a** with the best result (80% yield, 63% *ee*) (entry 5). Pybox **10**, which was the most effective ligand used in the enantioselective addition of aliphatic alkynes to the α-imino ester,[11] gave slightly lower yield (75% yield) and enantiomeric excess (60% *ee*) (entry 7).

Other Cu(I) pre-catalysts in combination with ligand **8** were also investigated in this reaction (Table 2). $CuPF_6$·4MeCN gave relatively lower yield (62% yield) and enantiomeric excess (54% *ee*) under the same conditions (entry 1), and CuBr and CuCl did not show any catalytic activity (entries 2 and 3).

We then studied the effect of ligand-to-metal ratio in this CuOTf·0.5C_6H_6-catalyzed reaction (Table 3).

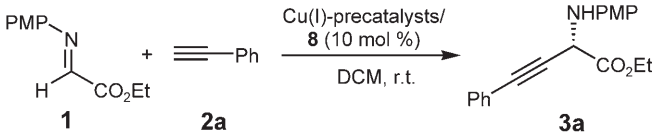
Table 1. Effects of different chiral ligands on reactivity and enantioselectivity.[a]



Entry	Ligand	Yield [%][b]	*ee* [%][c]
1	**4**	68	<5
2	**5**	65	<5
3	**6**	trace	not determined
4	**7**	66	49
5	**8**	80	63
6	**9**	65	61
7	**10**	75	60
8	**11**	54	<5

[a] All the reactions were carried out in a 0.25-mmol scale of **1** using 2 equivs. of phenylacetylene **2a** in 1.5 mL DCM with 10 mol% catalyst at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC using a Chiralpak AD-H column.

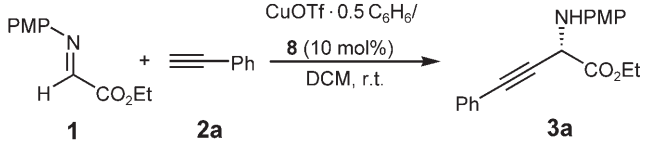
Table 2. Effects of different Cu(I) pre-catalysts on reactivity and enantioselectivity.[a]



Entry	Cu(I) pre-catalyst	Yield [%][b]	*ee* [%][c]
1	$CuPF_6$·4MeCN	62	54
2	CuBr	0	
3	CuCl	0	

[a] All the reactions were carried out in a 0.25-mmol scale of **1** using 2 equivs. of phenylacetylene **2a** in 1.5 mL DCM with 10 mol% catalyst at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC using a Chiralpak AD-H column.

Table 3. Effects of different ratio of CuOTf·0.5 C_6H_6 to chiral ligand **8** on reactivity and enantioselectivity.[a]



1 2a 3a

Entry	Ratio of **8** to CuOTf·0.5 C_6H_6	Yield [%][b]	*ee* [%][c]
1	1:1	80	63[d]
2	1.1:1	74	60[d]
3	1.2:1	64	23[e]
4	1.25:1	60	2[e]
5	1.3:1	57	−36[e]
6	1.5:1	54	−62[f]
7	2:1	34	−63[f]
8	1:1.2	70	50[d]
9	1:1	71	−23[g]
10	1.5:1	60	−70[h]

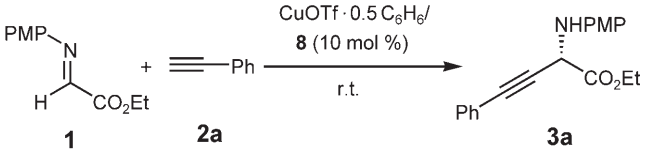
[a] All the reactions were carried out in a 0.25-mmol scale of **1** using 2 equivs. of phenylacetylene **2a** in 1.5 mL DCM with 10 mol% catalyst at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC using a Chiralpak AD-H column.
[d] 24 h.
[e] 36 h.
[f] 6 days.
[g] 24 h, 4 Å MS added.
[h] 6 days, 4 Å MS added.

When the ratio of Pybox **8** to CuOTf·0.5 C_6H_6 was changed from 1:1 to 1.1:1, a slightly lower *ee* was obtained (entry 2). The observation that a small excess of ligand is detrimental to enantioselectivity is in contrast to the usual observation in asymmetric catalysis that an excess of chiral ligand is beneficial to suppress the background reaction catalyzed by uncomplexed metal. When the ratio of Pybox **8** to CuOTf·0.5 C_6H_6 was changed from 1:1 to 1.25:1, the *ee* value dramatically decreased to almost 0% (entry 4). This observation indicated that the ligand-to-metal ratio might have a decisive influence on the enantioselectivity of the reaction. Further increase of the ratio of Pybox **8** to CuOTf·0.5 C_6H_6 to 1.5:1 dramatically switched the product enantioselectivity to the opposite sense. The product **3a** was obtained with almost identical *ee* (62% *ee*) but with opposite enantiofacial selection (entry 6). This is surprising yet most interesting since both enantiomers of a given product with almost the same enantiomeric excess can be prepared with the same chiral ligand by simply adjusting the ligand-to-metal ratio. Although usually both enantiomers of a chiral compound can be prepared by using the opposite enantiomers of a chiral ligand, sometimes one of the enantiomers of a chiral ligand may not be readily available. Our finding offers an interesting alternative to provide both enantiomers of a chiral compound.

Interestingly, the addition of 4 Å molecular sieve to the reaction system also resulted in the switch of the enantioselectivity of product **3a** (entry 9). When 4 Å MS was combined with CuOTf·0.5 C_6H_6/Pybox **8** (1:1.5), −70% *ee* was obtained (entry 10). The switch of the stereofacial selection might be due to a different mode of coordination. However, further studies certainly are needed to elucidate this interesting phenomenon.

A profound solvent effect on the yield and enantioselectivity of the reaction was also observed (Table 4). For example, when toluene was used as solvent, only 30% *ee* was obtained (entry 1). DCM was the best choice of solvent for reactivity and enantioselectivity (entry 5).

Table 4. Effects of the choice and concentration of solvent on the reactivity and enantioselectivity.[a]



1 2a 3a

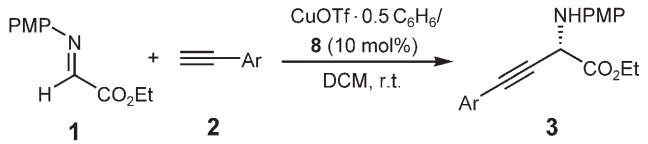
Entry	Solvent	Solvent volume [mL]	Yield [%][b]	*ee* [%][c]
1	toluene	1.5	81	30
2	THF	1.5	40	44
3	DCM	1.5	80	63
4	DCM	1.2	78	66
5	DCM	1.0	80	70
6	DCM	0.8	76	69
7	DCM	0.6	65	57

[a] All the reactions were carried out in a 0.25-mmol scale of **1** using 2 equivs. of phenylacetylene **2a** with 10 mol% catalyst at room temperature.
[b] Isolated yield.
[c] Determined by chiral HPLC using a Chiralpak AD-H column.

Under the optimized conditions, the scope of nucleophiles in the reaction system was examined, and the results are summarized in Table 5. The electronic property of the substituents on the aromatic ring did not show significant effects on the reactivity and stereoselectivity of Cu-catalyzed alkynylation of the α-imino ester. The arylacetylenes bearing either an electron-donating group or an electron-withdrawing group reacted smoothly with the α-imino ester, providing the corresponding alkynylation products with good yields and 67–74% *ee* values.

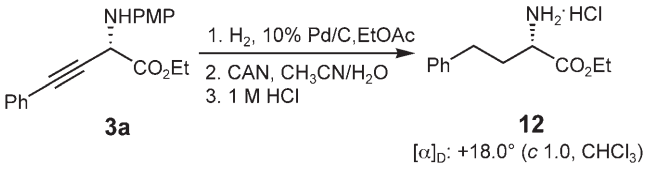
To determine the absolute configuration, product **3a** was converted to 2-amino-4-phenylbutyric ethyl ester hydrochloride **12** (Scheme 1). The (*S*) configura-

Table 5. Cu-catalyzed addition aromatic alkynes to α-imino ester **1**.[a]



Entry	**2** (Ar)	Yield [%][b]	*ee* [%][c]
1	Ph	80 (**3a**)	70
2	Ph	74 (**3a**)	73[d]
3	4-MeO-C_6H_4	65 (**3b**)	67
4	4-Me-C_6H_4	80 (**3c**)	74[e]
5	4-Br-C_6H_4	86 (**3d**)	69[f]

[a] All the reactions were carried out in a 0.25-mmol scale of **1** using 2 equivs. of aromatic alkynes **2** in 1.0 mL DCM with 10 mol % catalyst.
[b] Isolated yield.
[c] Determined by chiral HPLC using a Chiralpak AD-H column except entry 4.
[d] 0 °C, 48 h.
[e] Determined by chiral HPLC using a Chiralcel OD-H column.
[f] 0 °C, 24 h.



Scheme 1. Determination of the absolute configuration of **3a**.

tion was established by comparison of the optical rotation of **12** with the previously reported value of this compound.[15]

In conclusion, we have carried out the first catalytic asymmetric alkynylation of an α-imino ester with arylacetylenes using a commercially available chiral ligand **8**. There are several features to this enantioselective alkynylation: (1) the experimental procedure is convenient and simple, and the use of additives can be avoided; (2) two enantiomers of the desired product can be prepared in almost the same enantiomeric excess with the same chiral ligand simply by adjusting the ligand-to-metal ratio. The rich chemistry of the alkynyl functionality and the aromatic functionality makes the present method a powerful and versatile approach to a wide range of optically active α-amino acid derivatives. A study aiming at elucidating the reaction mechanism and improving the enantioselectivity is in progress.

Experimental Section

Typical Procedure for Catalytic Asymmetric Alkynylation of α-Imino Ester 1

Pybox **8** (9.2 mg, 0.025 mmol) and CuOTf·0.5 C_6H_6 (6.3 mg, 0.025 mmol) were added to a dried 5-mL reaction flask containing a magnetic stirring bar. CH_2Cl_2 (0.5 mL) was added, and the mixture was stirred at room temperature for 1 h. Then α-imino ester **1** (52 mg, 0.25 mmol) in CH_2Cl_2 (0.5 mL) and alkyne (0.5 mmol) were sequentially added under vigorous stirring. The resulting solution was stirred at room temperature until TLC monitored the completion of the reaction. The mixture was then passed through a short plug of silica gel that was subsequently washed with ether. The combined solution was concentrated under vacuum. The purification of the residue by flash silica gel column chromatography yielded the corresponding alkynylation product. The enantiomeric excess of the product was determined by chiral HPLC analysis.

Acknowledgements

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