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Copper(I)-catalyzed enantioselective alkynylation of α-imino esters: ligand-to-metal ratio effects and mechanistic studies

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ABSTRACT

An unprecedented effect of the ligand-to-metal ratio on the stereofacial selection in the copper-catalyzed enantioselective addition of terminal alkynes to *N*-PMP-α-imino esters was observed. An excess of ligand was found not to be beneficial, on the contrary, an excess of copper was found to be beneficial. Moreover, both enantiomers of the alkynylation product were obtained with almost the same enantiomeric excess with the same chiral ligand by simply adjusting the ligand-to-metal ratio. The investigation of the mechanism demonstrated the presence of a positive nonlinear effect [(+)-NLE].

1. Introduction

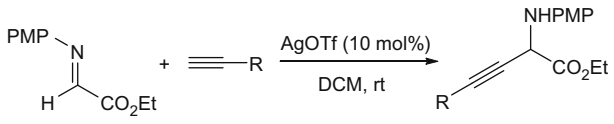
Asymmetric transition-metal catalysis, in which chiral transition-metal complexes act as catalytically active species, is one of the most efficient and powerful approaches for the preparation of enantiopure compounds.[1] In this context, the discovery of efficient chiral transition-metal complexes is of importance. To achieve the optimum enantioselectivity in a given reaction, a slight excess of chiral ligand is generally utilized to suppress the background reaction catalyzed by uncomplexed metal.

However, we recently observed a profound effect of the ligand-to-metal ratio on the stereofacial selection in the copper-catalyzed asymmetric addition of phenylacetylene to an *N*-PMP-α-imino ester.[2] An excess of chiral ligand was found not to be beneficial. Moreover, both enantiomers of the alkynylation product with almost the same enantiomeric excess were obtained with the same chiral ligand simply by adjusting the ligand-to-metal ratio.[2] Triggered by this interesting observation of the effect of ligand-to-metal ratio,[2,3] the effect of ligand-to-metal ratio on the copper-catalyzed alkynylation of an *N*-PMP-α-imino ester was investigated further. An excess of chiral ligand was found to be detrimental, on the contrary, an excess of copper was found to be beneficial. We herein report these experimental results in detail and also a primary investigation of the mechanism.

Since Kagan reported for the first time the nonlinear effect of the enantioselectivity of the auxiliary or ligand on the product ee in 1986,[4] numerous examples of positive or negative nonlinear effects have been reported, and the study of relationship between the ee value of the auxiliary or ligand and the ee value of the product has become a simple but useful tool to investigate the mechanism of the reaction.[5] Therefore, we are interested in investigating the relationship between the enantiopurity of the ligand and the product ee to obtain some helpful information about the reaction.

2. Results and discussion

Recently, we developed an efficient synthesis of β,γ-alkynyl α-amino acid derivatives by the direct addition of the terminal alkynes to an *N*-PMP-α-imino ester in the presence of silver(I) salts (Scheme 1).[6a,7] Based on this method, we realized the first catalytic asymmetric addition of aliphatic alkynes to an *N*-PMP-α-imino ester by using chiral copper(I) complexes with 48–91% enantiomeric excess.[6b] To extend the scope of substrates, we initiated a study toward developing a procedure for the catalytic enantioselective addition of arylacetylenes to an *N*-PMP-α-imino ester.[2]



Scheme 1. Silver(I)-catalyzed alkynylation of an α-imino ester.

The reaction of α-imino ester **1** and phenylacetylene **2** was performed in DCM at room temperature using CuOTf·0.5C_6H_6 (10 mol %) as a precatalyst and pybox **3a** (10 mol %) as a chiral ligand. The desired product **4** was obtained with 80% yield and 63% ee (Table 1, entry 1). Based on the usual observation in asymmetric catalysis that an excess of chiral ligand is beneficial to suppress the background reaction catalyzed by uncomplexed metal, we changed the ratio of pybox **3a** to CuOTf·0.5C_6H_6 from 1:1 to 1.1:1, and hoped

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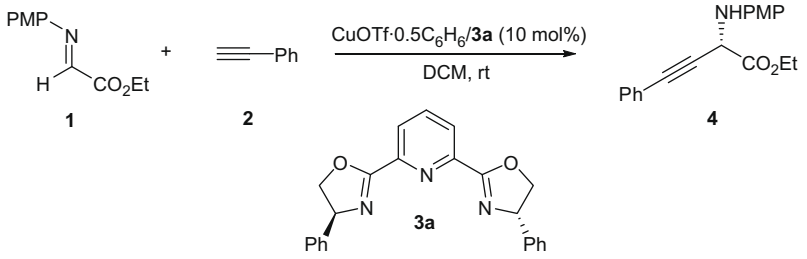
Table 1
Effects of different ratio of chiral ligand (pybox **3a**) to copper salt (CuOTf·0.5C_6H_6) on reactivity and enantioselectivity of the title reaction



Entry[a]	Ratio of pybox **3a** to CuOTf·0.5C_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	1:1.1	75	71[d]
9	1:1.2	73	69[d]
10	1:1.3	74	66[d]
11	1:1.5	71	62[d]
12	1:2	70	50[d]

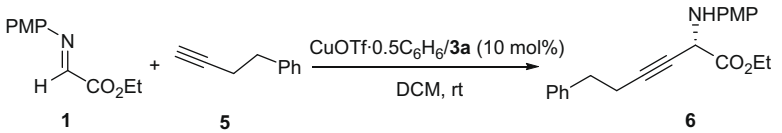
[a] All the reactions were carried out in a 0.25 mmol scale of **1** using 2 equiv of phenylacetylene **2** in 1.5 mL DCM with 10 mol % catalyst at rt.
[b] Isolated yield.
[c] Determined by chiral HPLC using a Chiralpak AD-H column.
[d] 24 h.
[e] 36 h.
[f] 6 days.

that this might improve the enantioselectivity of the title reaction. Nevertheless, a slightly lower ee (60%) was obtained when the ratio of pybox **3a** to CuOTf·0.5C_6H_6 was 1.1:1 (entry 2). The observation that a small excess of ligand was detrimental to the 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 **3a** to CuOTf·0.5C_6H_6 was changed from 1:1 to 1.25:1, the ee value decreased dramatically 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. Surprisingly, a further increase in the ratio of pybox **3a** to CuOTf·0.5C_6H_6 to 1.5: 1 dramatically switched the product chirality to the opposite sense. The product **4** was obtained with almost identical ee (62% ee) but with opposite enantiofacial selection (entry 6).

More interestingly, when the ratio of pybox **3a** to CuOTf·0.5C_6H_6 was 1:1.1, the enantioselectivity of the title reaction did not decrease but increased (71% ee, entry 8). This observation indicated that an excess of metal was beneficial to the enantioselectivity. To the best of our knowledge, the whole phenomena are unprecedented in a given transition-metal-catalyzed asymmetric reaction. Further change in the ratio of pybox **3a** to CuOTf·0.5C_6H_6 to 1:1.2 had less effect on the enantioselectivity (69% ee, entry 9). Moreover, when the ratio of pybox **3a** to CuOTf·0.5C_6H_6 was 1:1.3, the product **4** was obtained in 66% ee (entry 10), which was still higher than the ee (63% ee, entry 1) achieved at 1:1 ratio of pybox **3a** to CuOTf·0.5C_6H_6. Even when pybox **3a** to CuOTf·0.5C_6H_6 ratio was 1:1.5, comparable enantioselectivity (62% ee, entry 11) was still obtained. Finally, when the pybox **3a** to CuOTf·0.5C_6H_6 ratio was changed to 1:2, lower enantioselectivity (50% ee) was achieved (entry 12).

Development of a novel approach for the asymmetric synthesis of both enantiomers is highly useful in organic synthesis and in the pharmaceutical industry.[8] This interesting finding might provide a novel approach to obtain both enantiomers of a chiral compound. To investigate whether this effect of ligand-to-metal ratio is suitable for aliphatic terminal alkynes, the direct addition of aliphatic terminal alkynes such as 4-phenyl-1-butyne to an α-imino ester was examined. To our delight, the desired product *ent*-**6** was obtained with 64% ee when the ratio of pybox **3a** to CuOTf·0.5C_6H_6 was changed from 1:1 to 1.5:1 (Eq. 1).



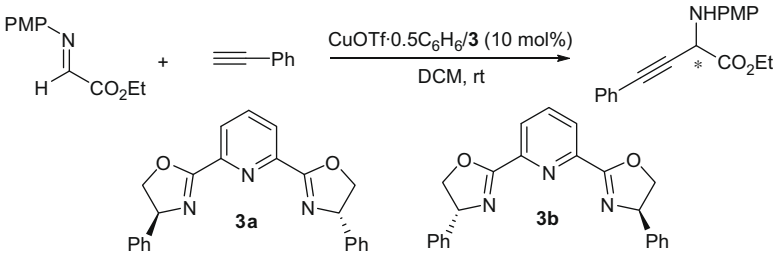
(1)

3a:CuOTf·0.5C_6H_6 = 1:1, 74%, 61% ee
3a: CuOTf·0.5C_6H_6 = 1.5:1, 47%, -64% ee

The use of other α-imino esters such as *N*-Ts-α-imino ester has also been investigated for the copper(I)-catalyzed alkynylation reactions. Surprisingly, although an *N*-Ts-α-imino ester is more electrophilic than an *N*-PMP-α-imino ester, the desired reactions did not occur regardless of the ligand-to-metal ratio.

In order to gain some insights into how the ligand-to-metal ratio affected the enantioselectivity of copper(I)-catalyzed alkynylation of α-imino esters, the experiments were performed to determine if NLEs were operative in the copper(I)–pybox-catalyzed asymmetric addition of terminal alkynes to an *N*-PMP-α-imino ester.[9]

The reaction of α-imino ester **1** and phenylacetylene **2** was carried out in DCM at room temperature using 10 mol % of $CuOTf{\cdot}0.5C_6H_6$ and 10 mol % of scalemic pybox **3** with different ees that were prepared via mixing (*S*)-pybox **3a** with its enantiomer (*R*)-pybox **3b** (Eq. 2). The results are summarized in Figure 1, when the ee of the product was plotted against the ee of the ligand **3**. Indeed, a moderate (+)-NLE was observed.



(2)

The positive nonlinear effect suggested the presence and importance of heterochiral bis-(or higher) coordinated complexes in the present catalytic asymmetric alkynylation of α-imino esters. It was postulated that different enantioselectivities obtained with different ligand-to-metal stoichiometries might result from the change in the coordination geometry of the copper center, leading to the formation of different transition states.

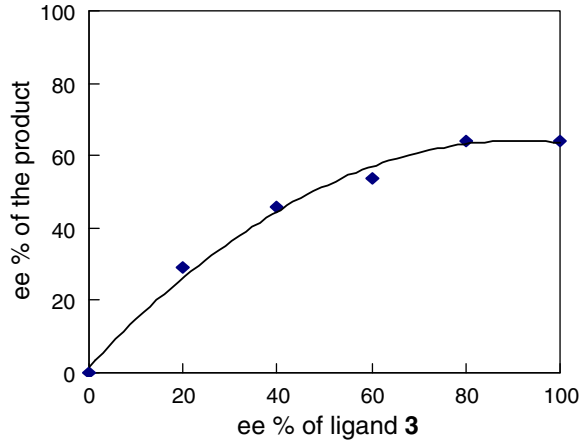


Figure 1. NLE in the addition of phenylacetylene **2** to α-imino ester **1**.

While we cannot delineate definitely the mode of coordination at different ligand-to-metal ratio at this stage, on the basis of the coordination chemistry of pybox ligands,[10] a tentative explanation was made to help facilitate an understanding of some experimental results (Fig. 2). It is generally considered that the complex of type **A** can form when pybox **3a** is coordinated to copper. As the excess ligand used provided a third oxazoline moiety for coordination with copper, one of the nitrogens of pybox **3** might dissociate. Thus, the pybox–copper complex **B** might form. The resulting species **B** becomes steric bulky and less active due to the coordination of excess pybox ligand. When the ratio of pybox **3a** to copper increased to1.5:1 or 2:1, a less active complex such as **C1** or **C2** with different coordination mode might form, leading to a reversal in the enantioselectivity. However, further studies are certainly needed to elucidate the specific reason for the switch of the stereofacial selection.

3. Conclusion

In conclusion, we found an effect of ligand-to-metal ratio on the stereofacial selection in the copper-catalyzed asymmetric addition of terminal alkynes to an α-imino ester. An excess of ligand was found not to be beneficial, on the contrary, an excess of copper was found to be beneficial. Moreover, both enantiomers of a given product with almost the same enantiomeric excess were obtained with the same chiral ligand simply by adjusting the ligand-to-metal ratio. The primary investigation of the mechanism indicated the presence of a moderate (+)-NLE. The present study hints that ligand-to-metal ratio should be assessed carefully in transition-metal-catalyzed asymmetric transformations.

4. Experimental

4.1. General methods

^{1}H NMR and ^{13}C NMR spectra were recorded in $CDCl_3$ on a Bruker Avance DPX 400 (400 and 100 MHz, respectively) NMR spectrometer at room temperature. Chemical shifts (δ) are expressed in ppm, and *J* values are given in hertz. High-resolution mass spectrometry (HRMS) was carried out by using the electrospray ionization (ESI) method on a Fisons VG platform (Finnigan-MAT, San Jose, CA). HPLC analyses were performed by using a Waters 600 analytical liquid chromatography system with a Waters 486 UV detector. Optical rotations were measured on a Perkin–Elmer 341 polarimeter in a 10-cm cell. All the reactions were conducted under a nitrogen atmosphere. The enantiomeric excess was determined by Chiralpak AD-H using *n*-hexane and iso-propanol as eluents at 25 °C. CH_2Cl_2 was distilled from CaH_2. Flash column chromatography was performed on silica gel (230–400 mesh).

4.2. Typical procedure for nonlinear Cu(I)-catalyzed asymmetric addition of phenyl acetylene to an α-imino ester

Ph-pybox **3** with different ee (9.2 mg, 0.025 mmol) and $CuOTf{\cdot}0.5C_6H_6$ (6.3 mg, 0.025 mmol) was added to a dried 5-mL reaction flask containing a magnetic stirring bar. CH_2Cl_2 (0.5 mL)

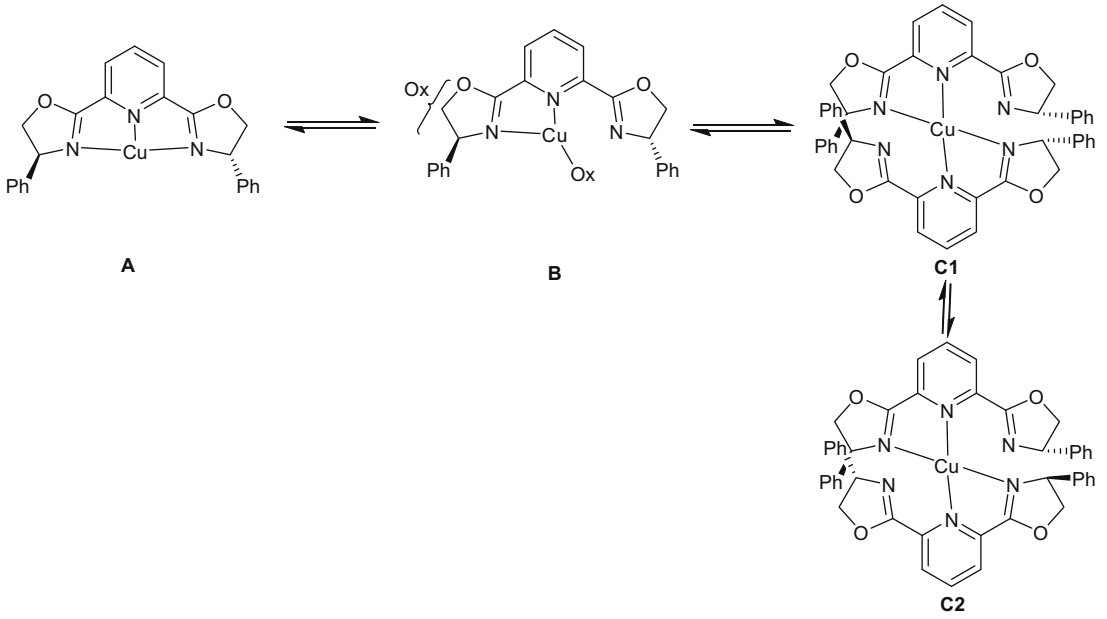


Figure 2. Proposed coordination model for the copper-catalyzed alkynylation of an α-imino ester.

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 phenylacetylene (0.5 mmol) were added sequentially 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 in vacuo. The purification of the residue by flash silica gel column chromatography yielded the desired alkynylation product. The enantiomeric excess of the product was determined by chiral HPLC analysis as described in the literature.[2]

Acknowledgments

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