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Letter

Copper(I)-Catalyzed Asymmetric α-Selenenylation of 2-Acylimidazoles

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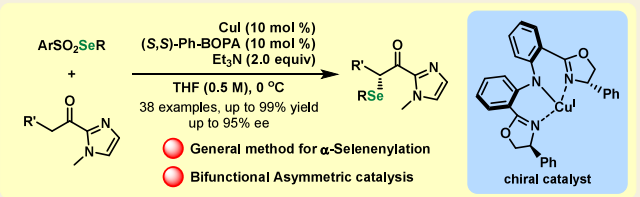
ABSTRACT: A general method for the catalytic asymmetric α-selenenylation of simple carbonyl compounds is lacking. Herein, a copper(I)-catalyzed enantioselective α-selenenylation of 2-acylimidazoles with electrophilic selenosulfonates is uncovered. The reaction enjoys the advantages of mild conditions, easy reaction protocol, and broad substrate scopes on both 2-acylimidazoles and selenosulfonates. Mechanistic studies reveal a pincer Cu(I)-(*S*,*S*)-Ph-BOPA complex as the active catalyst. Some traditional electrophilic selenenylation reagents, such as PhSeCl, PhSeSePh, and 2-(phenylselanyl)isoindoline-1,3-dione lead to inferior results in terms of both yield and enantioselectivity, highlighting the superiority of selenosulfonates. Finally, several transformations based on both the 2-acylimidazole group and the selenoether group are successfully carried out, demonstrating the synthetic utilities of the present methodology.



KEYWORDS: *copper(I) catalysis, asymmetric catalysis, selenenylation, 2-acylimidazoles, selenosulfonates*

Chiral organoselenium compounds, especially α-seleno carbonyl compounds, serve as versatile intermediates in organic synthesis.[1] Furthermore, some chiral seleno-bearing organic molecules have been found as powerful organocatalysts[2−7] and bioactive molecules[8] (Scheme 1(a). Classically, chiral organoselenium compounds were built heavily on "chiral−pool" strategy,[9] which suffered from some drawbacks, such as poor both chirality economy and step economy. With the flourishing of asymmetric catalysis, catalytic asymmetric synthesis of these compounds serves as an alternative, powerful strategy. However, such methodologies remain limited. Evidently, limited synthetic methods led to limited seleno-compounds, resulting in limited application in various fields, such as asymmetric catalysis and medicinal chemistry. Therefore, it is highly demanding to develop efficient synthetic methods.[10]

Available methods based on asymmetric catalysis could be divided into two types, including asymmetric transformations with seleno-containing building blocks[9,10] and asymmetric introduction of seleno-segments to starting molecules through C−Se bond formation.[11−18] In the latter case, common methods include bifunctionalization of olefins,[11] monofunctionalization of olefins,[12] nucleophilic selenenylation,[13] and electrophilic selenenylation.[14−17] The representative method for nucleophilic selenenylation is the asymmetric addition of selenols to α,β-unsaturated compounds. In 2022, Huang and co-workers reported a highly enantioselective Michael addition of selenols to α,β-unsaturated ketones under organocatalysis.[13e] Later, our group disclosed a copper(I)-catalyzed asymmetric addition of selenols to α,β-unsaturated thioamides with high to excellent enantioselectivity.[13f] The most

Scheme 1. Introduction and Our Working Hypothesis

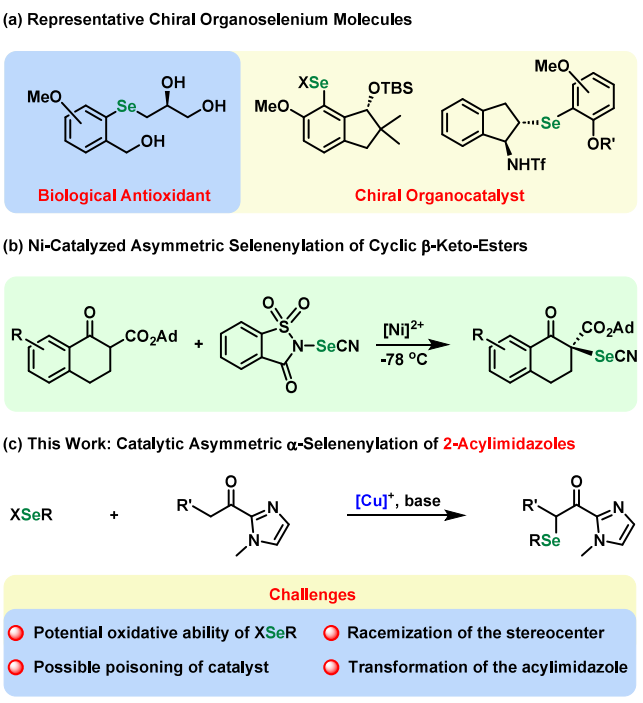


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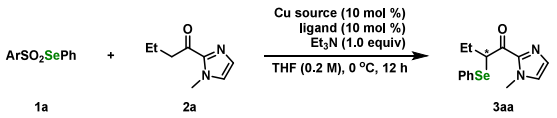
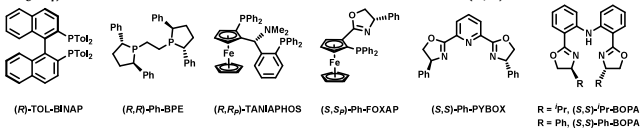
Table 1. Optimization of the Reaction Conditions[a]



entry	$ArSO_2SePh$	Copper source	ligand	yield/%[b]	ee/%[c]
1	**1a-1** (Ar = C_6H_5)	CuI	(*R*)-TOL-BINAP	18	1
2	**1a-1** (Ar = C_6H_5)	CuI	(*R*,*R*)-Ph-BPE	50	−1
3	**1a-1** (Ar = C_6H_5)	CuI	(R,R_P)-TANIAPHOS	14	1
4	**1a-1** (Ar = C_6H_5)	CuI	(*S*,*S*)-Ph-FOXAP	12	1
5	**1a-1** (Ar = C_6H_5)	CuI	(*S*,*S*)-Ph-PYBOX	52	51
6	**1a-1** (Ar = C_6H_5)	CuI	(*S*,*S*)-^{i}Pr-BOPA	24	67
7	**1a-1** (Ar = C_6H_5)	CuI	(*S*,*S*)-Ph-BOPA	42	90
8	**1a-1** (Ar = C_6H_5)	$Cu(CH_3CN)_4PF_6$	(*S*,*S*)-Ph-BOPA	52	89
9[d]	**1a-1** (Ar = C_6H_5)	CuI	(*S*,*S*)-Ph-BOPA	86	90
10[d]	**1a-2** (Ar = 4−F-C_6H_4)	CuI	(*S*,*S*)-Ph-BOPA	78	91
11[d]	**1a-3** (Ar = 4−Cl-C_6H_4)	CuI	(*S*,*S*)-Ph-BOPA	66	93
12[d]	**1a-4** (Ar = 4−Br-C_6H_4)	CuI	(*S*,*S*)-Ph-BOPA	74	92
13[d]	**1a-5** (Ar = 4-Me-C_6H_4)	CuI	(*S*,*S*)-Ph-BOPA	80	87
14[d,e]	**1a-3** (Ar = 4−Cl-C_6H_4)	CuI	(*S*,*S*)-Ph-BOPA	89	92



[a] **1a**: 0.10 mmol, **2a**: 0.10 mmol. [b] Determined by ^{1}H NMR analysis of reaction crude mixture using CH_2Br_2 as an internal standard. [c] Determined by chiral-stationary-phase HPLC analysis. [d] **1a**: 0.10 mmol, **2a**: 0.20 mmol, Et_3N: 0.20 mmol, THF (0.5 M). [e] 24 h.

straightforward method for electrophilic selenenylation is the catalytic asymmetric α-selenenylation of carbonyl compounds with certain electrophilic seleno-reagent. However, most of such reported reactions were enabled by organocatalysis with aldehydes, ketones, and cyclic carbonyl compounds as pronucleophiles.[14−16] Obviously, the produced chiral α-seleno aldehydes or ketones are labile to racemization, as the reduction of the carbonyl group was usually required for easy manipulation. In 2020, Chen and co-workers disclosed a Ni-catalyzed asymmetric selenocyanation of β-ketoesters with *N*-selenocyanatosaccharin in good to high enantioselectivity (Scheme 1b), which served as the leading example under transition metal catalysis.[17] Evidently, a general method for the catalytic asymmetric α-selenenylation of simple carboxylic acid derivatives (not cyclic ones) is still lacking.

2-Acylimidazoles are a type of synthetic equivalent of esters and broadly employed in asymmetric catalysis.[19] Obviously, stabilized copper(I) enolates would be generated in the presence of 2-acylimidazoles, a chiral copper(I) complex, and a mild base. If there was a suitable seleno-bearing electrophile (XSeR), nucleophilic attack of the stabilized chiral copper(I) enolates on it would furnish chiral α-seleno 2-acylimidazoles (Scheme 1c). However, challenges exist, such as suspicious oxidative ability of XSeR, doubtful racemization of the α-stereogenic carbon centers, potential poisoning of the copper(I) catalyst by the products, and difficulty in subsequent acylimidazole transformations in the presence of a seleno-ether moiety.

The α-selenenylation of *N*-Me-2-butyrylimidazole (**2a**) with selenosulfonate **1a-1**, which was identified as an excellent electrophilic seleno-reagent,[20] was initially investigated as a model reaction for the optimization of reaction conditions at 0 °C (Table 1). In the presence of 10 mol % CuI, 10 mol % (*R*)-TOL-BINAP, and 1.0 equiv of Et_3N, **3aa** was generated in 18% yield with 1% ee in 12 h (entry 1). Switching the ligand to some other commercially available chiral phosphines did not lead to improved enantioselectivity (12%−50%, −1%−1% ee, entries 2−4). Fortunately, the selenenylation with (*S*,*S*)-Ph-PYBOX afforded **3aa** in 52% yield with 51% ee (entry 5). By using (*S*,*S*)-^{i}Pr-BOPA, another typical chiral tridentate nitrogen ligand, **3aa** was generated in 24% yield with 67% ee (entry 6). Increasing the steric hindrance of the ligand resulted in enhanced both yield and enantioselectivity (42%, 90% ee, entry 7). The commonly used copper(I) salt $Cu(CH_3CN)_4PF_6$ did not lead to superior results (52%, 89% ee, entry 8). $Cu(OAc)_2$ was also tested as the copper source. However, inferior enantioselectivity was obtained (54%, 79% ee). By increasing the amounts of both **1a** and Et_3N to 2.0 equiv and the concentration of **2a** from 0.2 to 0.5 M, **3aa** was delivered in 86% yield with 90% ee (entry 9). Then four selenosulfonates with different electronic effects (**1a-2**-**1a-5**) were prepared and thus screened (entries 10−13). Reagent **1a-3** outperformed as **3aa** was generated in the highest enantioselectivity (66%, 93% ee, entry 11). By extending the reaction time from 12 to 24 h, **3aa** was produced in elevated yield and maintained enantioselectivity (89%, 92% ee, entry 14). It was noted that the variation of *N*-CH_3 to *N*-Ph did not help to improve the enantioselectivity further.

Under the optimized reaction conditions, the substrate scope of selenosulfonates (**1**) was first studied with **2a** as a model pronucleophile (Table 2). As for the selenosulfonates of aryl selenols, both the yields and the enantioselectivity were not significantly impacted by the electronic nature of the aryl groups (**3ba**-**3ia**, 80%−99%, 82%−92% ee). Furthermore, the substitution patterns, including *ortho*-, *meta*-, and *para*-substitutions, did not disturb the reaction results. Both 1-naphthyl and 2-naphthyl were well accepted at the R position (**3ja**-**3ka**, 81%−82%, 93%−94% ee). 2-Thienyl was also well

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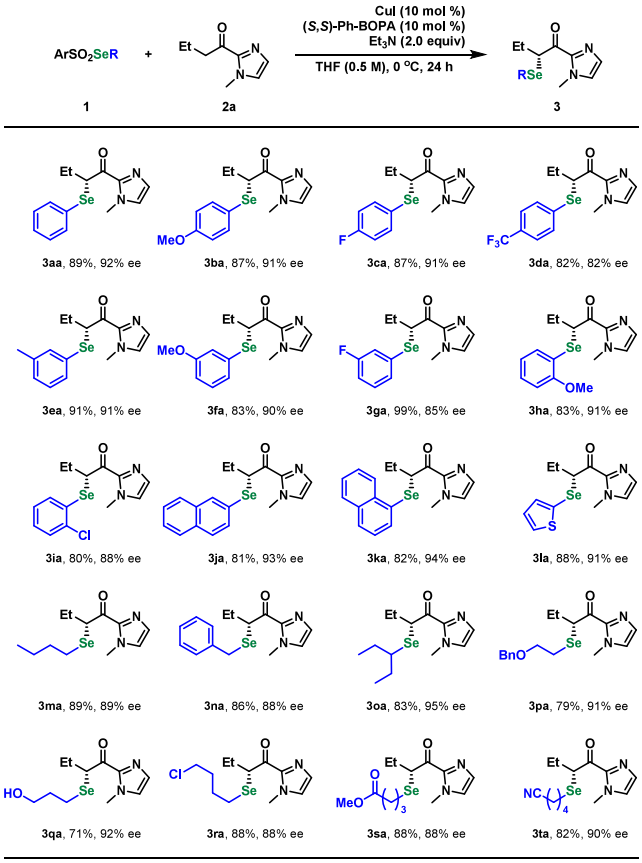
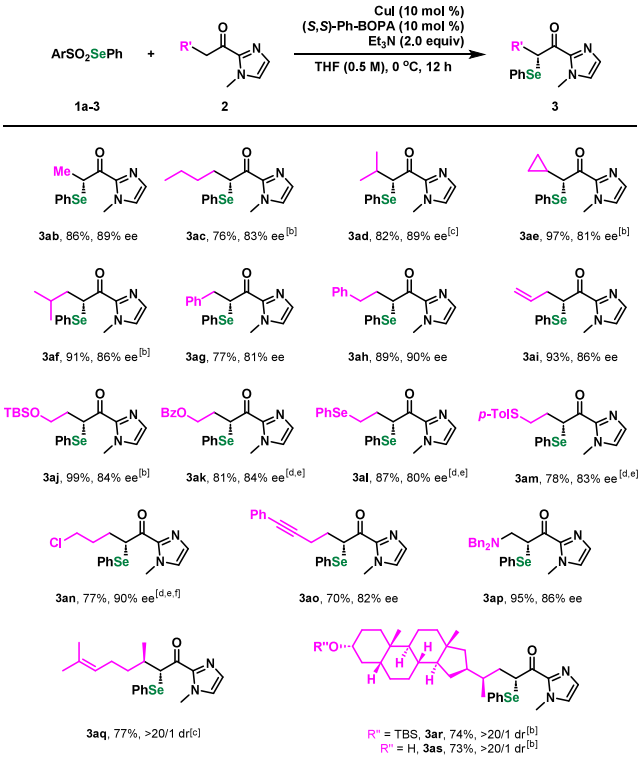
Table 2. Substrate Scope of Selenosulfonates (1)[a]



[a]**1**−**3**: 0.20 mmol, **2a**: 0.40 mmol. Isolated yield. The enantioselectivity was determined by chiral-stationary phase HPLC analysis.

Table 3. Substrate Scope of 2-Acylimidazoles (2)[a]



[a]**1a-3**: 0.20 mmol, **2**: 0.40 mmol. Isolated yield. The enantioselectivity was determined by chiral-stationary-phase HPLC analysis [b]24 h. [c]96 h. [d]36 h. [e]−20 °C. [f]20 mol % copper catalyst.

tolerated, and the corresponding product was isolated with satisfactory results (**3la**, 88%, 91% ee). As for the selenosulfonates of aliphatic selenols, simple alkyls as well as functionalized alkyls served as wonderful R substituents (**3ma**-**3ta**, 71%−89%, 88%−95% ee). The presence of some functional groups, such as ether, free alcohol, alkyl chloride, ester, and cyanide did not interrupt the reaction process. Thio(4-chlorobenzene)sulfonates were also studied as the electrophile instead of **1a**-**3**. The corresponding product was furnished in 66% yield with 63% ee, indicating the similarity of thiosulfonates to selenosulfonates.

Then the substrate scope of 2-acylimidazoles (**2**) was investigated with **1a-3** as a model electrophile (Table 3). Simple alkyls, including methyl, ^{n}butyl, ^{i}propyl, cyclopropyl, 2-methyl-propyl, benzyl, phenylethyl, and allyl worked as suitable R′ substituents as the corresponding products were isolated in satisfying results (**3ab**-**3ai**, 76%−97%, 81%−90% ee). Alkyls bearing a functional group, such as silylether, ester, selenoether, thioether, alkyl chloride, internal alkyne, and amine, were found to be appropriate R′ substituents too (**3aj**-**3ap**, 70%−99%, 80%−90% ee). It should be noted that several reactions (**3ak**, **3al**, **3am**, and **3an**) were performed at −20 °C for higher enantioselectivity and 20 mol % copper catalyst loading was required for good yield in the case of **3an**. Finally, the present catalytic system was successfully applied to chiral 2-acylimidazoles. Three chiral seleno-ethers (**3aq**, **3ar** and **3as**) were prepared in synthetically useful yields with excellent dr (73%−77%, > 20/1 dr), indicating that the asymmetric induction was mainly controlled by the chiral copper catalyst. 2-Phenylacetylimidazole was also tested, which provided the corresponding product in 90% yield with 5% ee. The very low ee might be caused by the racemization under the basic reaction conditions. It was noted that the reaction of α-methyl-α-phenyl-2-acetylimidazole did not occur at all.

Subsequently, some control experiments were carried out. As shown in Figure 1a, the presence of TEMPO, BHT, or 1,1-diphenylethylene did not prohibit the reaction, indicating that the α-selenenylation might not proceed in a radical process. The *N*-H moiety in (*S*,*S*)-Ph-BOPA was found to be indispensable as the reaction with (*S*,*S*)-*N*-Me-Ph-BOPA occurred in low yield and **3aa** was generated in nearly racemic form (Scheme 2b). The reaction with mesitylcopper(I) as the copper source afforded **3aa** in nearly the same results as the one with CuI and Et_3N, indicating that the copper(I) enolate would be the real nucleophile (Scheme 2c). Finally, the reactions with other electrophilic seleno-reagents were examined. As shown in Scheme 2d, the α-selenenylation with PhSeCl afforded **3aa** in moderate yield with moderate enantioselectivity (64%, 61% ee). The reaction with PhSeSePh was even worse as **3aa** was generated in 18% yield with 60% ee. 2-(Phenylselanyl)isoindoline-1,3-dione was also not a suitable electrophile as **3aa** was produced in 44% yield with 68% ee. These experimental facts demonstrated that selenosulfonates were a type of efficient electrophilic seleno-reagents.

Next, some experiments were performed to grow single crystals of the active copper catalyst. After extensive trials, some crystals were obtained from the THF solution of the complex formed by MesCu and (*S*,*S*)-Ph-BOPA in open air (Figure 1a). However, the X-ray analysis indicated a structure

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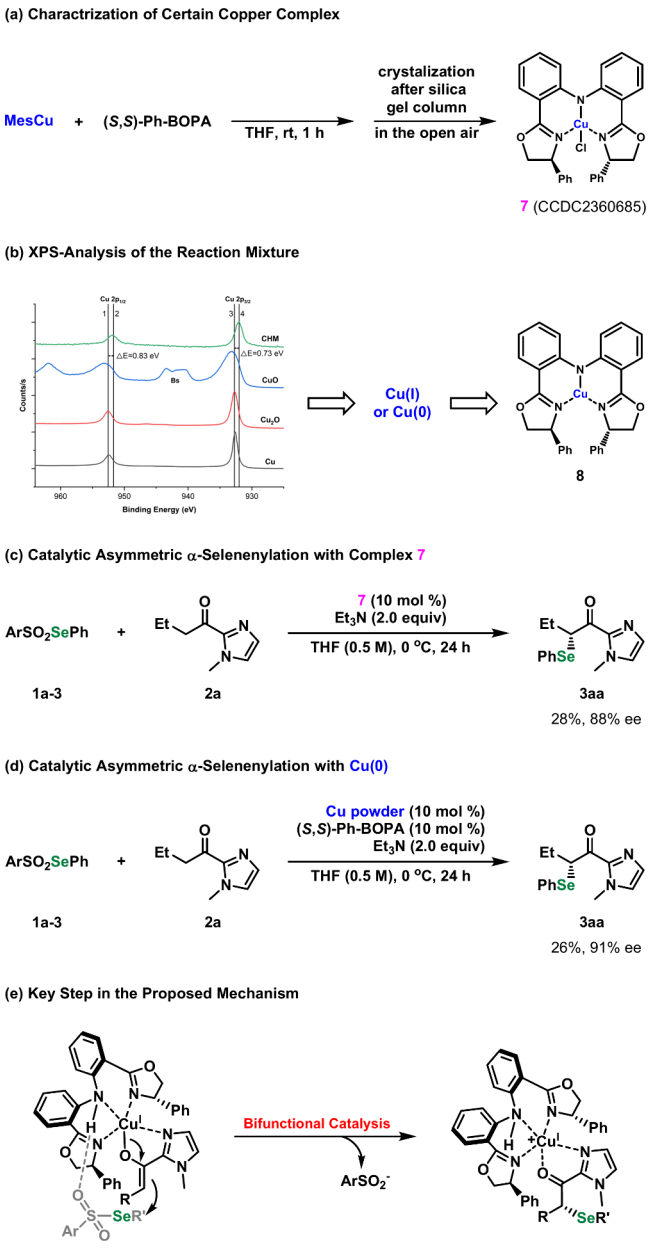
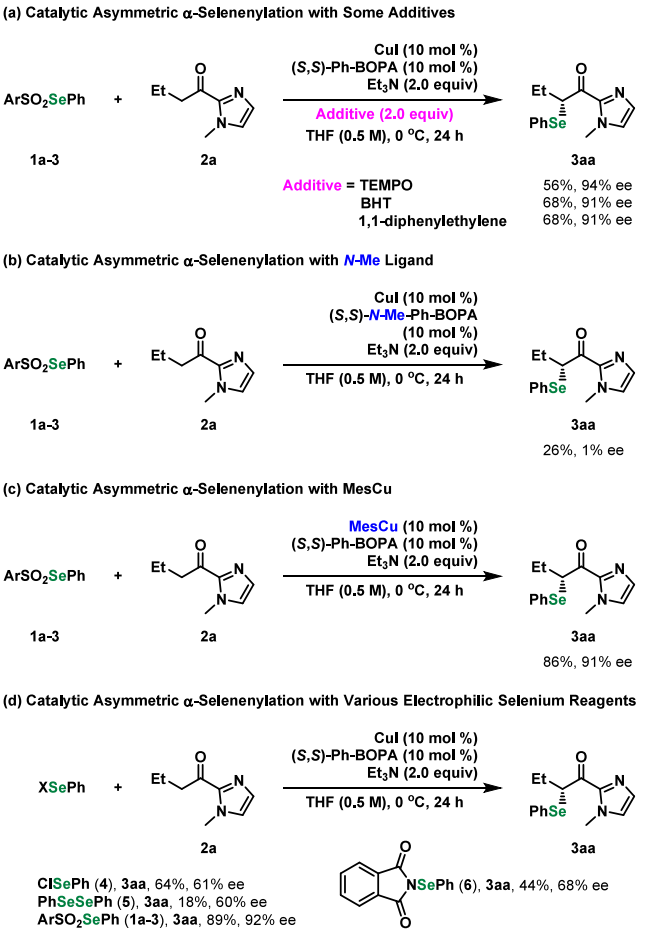


Figure 1. Investigation of some copper complexes.

of copper(II) complex 7.[21] At this moment, it was believed that copper(II) complex 7 was generated through the oxidation of the corresponding labile Cu(I) complex by air. In order to further get information on the active catalyst, XPS analysis of the reaction mixture was performed. By comparing the sample spectrum with known spectra of Cu(0), Cu_2O and CuO (Figure 1b), it was concluded that the active catalyst would not be the Cu(II) species. Furthermore, the α-selenenylation of **2a** catalyzed by 7 afforded **3aa** in very low yield, suggesting that 7 was not the active catalyst (Figure 1c). Surprisingly, the reaction with copper powder as a copper source proceeded, providing **3aa** in 26% yield with 91% ee (Figure 1d). Certain copper(I) species would be generated from copper powder in the presence of **1a-3** as **1a-3** was reported as a potential oxidant in the literature.[20] Actually, it was difficult to generate copper enolate from copper power and **2a** directly. Based on all of the above experimental facts, it was believed at this stage that complex **8** was the real active chiral

Scheme 2. Control Experiments



catalyst. Furthermore, a mechanism based on copper(I)/hydrogen-bonding cooperative bifunctional catalysis was proposed based on the important role of the *N*-H moiety in (*S*,*S*)-Ph-BOPA,[22] which was indispensable for the success of the reaction (Figure 1e).

Finally, several transformations of **3aa** were employed to demonstrate the synthetic utilities of the method as given in Scheme 3. The removal of the imidazole group was proved easy as carboxylic acid **9** was prepared from **3aa** in 86% yield with 90% ee for two steps. Acid **9** successfully coupled with L-alanine methyl ester to give peptide **10** in 74% yield with >20/1 dr. The exact stereochemistry of **10** was established by X-ray crystallographic analysis of its single crystals.[23] The absolute configurations of **3aa** and other products (**3**) in the α-selenenylation were assigned analogically. The reduction of acid **9** with $BH_3{\cdot}SMe_2$ worked very well, furnishing alcohol **11** in 96% yield with 91% ee. The transformation of **3aa** to ketone was successfully carried out with **12** generated in 70% yield with 91% ee. Ester **13** was synthesized in 83% yield with 85% ee from **3aa** under methanolysis condition. The slight decrease of ee was caused by the strong basic conditions. The transformation of the seleno-ether moiety was exerted successfully by following a literature report on the transformation of the thioether group,[24] affording chiral α-Cl-2-acylimidazole **14** in 88% yield with 90% ee.

In summary, a general method for the asymmetric α-selenenylation of simple carbonyl compounds was developed under copper catalysis. Both electrophilic selenosulfonates and

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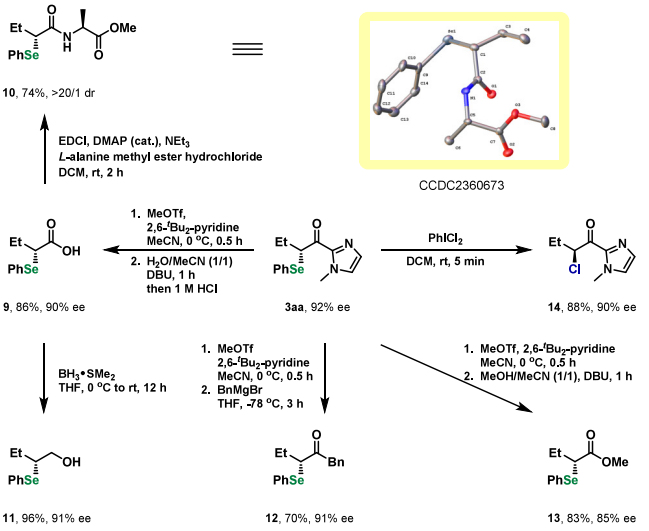
Scheme 3. Transformations of Product 3aa



2-acylimidazoles enjoyed broad substrate scopes. In the characterization of the active copper catalyst, the pincer Cu(II)Cl-(*S*,*S*)-Ph-BOPA complex formed in the open air was obtained instead of the pincer Cu(I)-(*S*,*S*)-Ph-BOPA complex. In light of the XPS analysis, it was concluded that the pincer Cu(I)-(*S*,*S*)-Ph-BOPA complex was the active chiral catalyst. The free *N*-H moiety in (*S*,*S*)-Ph-BOPA was found to be pivotal for both a high yield and high enantioselectivity, leading to the proposed copper(I)/hydrogen-bonding cooperative catalysis. Studies on the electrophilic seleno-reagents revealed that selenosulfonate was superior to PhSeCl, PhSeSePh, and 2-(phenylselanyl)isoindoline-1,3-dione. Finally, diversified transformations of **3aa** demonstrated the synthetic utilities of the present method. Further combined applications of selenosulfonates and copper catalysis are currently on going in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge at https://pubs.acs.org/doi/10.1021/jacsau.4c01182.

Experimental procedures, characterizations and analytical data of new compounds, and spectra of NMR and HPLC for new compounds (PDF)

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Notes

The authors declare no competing financial interest.

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(22) At this stage, we can not rule out the possibity that the selenenylation proceeded via a simple copper(I) catalysis rather than the proposed bifunctional catalysis.

(23) Deposition number CCDC2360673 (for **10**) contains the supplementary crystallographic data for this paper. The data are

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