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Synthesis of *N*-aryl β -amino acid derivatives via Cu(II)-catalyzed asymmetric 1,4-reduction in air†

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In the presence of the inexpensive and stable stoichiometric reductant polymethylhydrosiloxane (PMHS) as well as certain amounts of appropriate alcohol and base additives, the non-precious metal copper-catalyzed asymmetric 1,4-hydrosilylation of β -aryl or β -alkyl-substituted *N*-aryl β -enamino esters was well realized to afford a diverse range of *N*-aryl β -amino acid esters in high yields and excellent enantioselectivities (26 examples, 90–98% ee). This approach tolerated the handling of both catalyst and reactants in air without special precautions. The chiral products obtained have been successfully converted to the corresponding enantiomerically enriched β -lactam and unprotected β -amino acid ester, which highlighted the synthetic utility of the developed catalytic procedure.

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Introduction

Enantiomerically pure *N*-aryl β -amino acids and their derivatives are very attractive targets for asymmetric synthesis in view of their usefulness as key structural backbones of many drug intermediates and natural products.¹ For instance, they are important synthons in the synthesis of β -lactam, which have proven to be of interest as antibiotics,² human leucocyte elastase inhibitors or β -lactamase inhibitors.³ One of the most facile methods toward enantiomerically enriched *N*-aryl β -amino acids and their derivatives is the catalytic enantioselective reduction of *N*-aryl β -dehydroamino acid derivatives.⁴ Ru,^{4,5} Rh,^{4,6} and Ir^{4e,7}-catalyzed asymmetric hydrogenation of *N*-acyl protected β -dehydroamino acid esters have been intensively pursued and good to excellent enantioselectivities have been realized. With respect to the studies on the reduction of *N*-aryl β -dehydroamino acid derivatives, Zhang *et al.* presented the first Rh-catalyzed asymmetric hydrogenation of *N*-aryl β -enamino esters with good to high ee's in 2005.⁸ The enantioselective hydrogenation of exocyclic *N*-arylamines mediated by Ir catalyst system was described by Zhou and co-workers in 2009.⁹ In 2014, Zhou *et al.* reported the non-noble metal nickel-catalyzed asymmetric transfer hydrogenation for the preparation of β -amino acid derivatives in good to excellent enantioselectivities while only 30% ee and 10% yield were obtained for

the substrate ethyl β -phenyl β -(phenylamino)acrylate.¹⁰ In addition, organocatalytic asymmetric hydrosilylation of *N*-aryl β -enamino esters using HSiCl₃ as the reducing reagent has also emerged as an efficient alternative to transition metal-catalyzed hydrogenation for the synthesis of chiral β -amino acid derivatives.¹¹

Employing stoichiometric amounts of silane as reductant, copper hydride-catalyzed stereoselective conjugate reduction of β,β -disubstituted Michael acceptors represents a practical, efficient, and cost-effective method that generate enantio-enriched carbonyl compounds possessing a tertiary stereocenter at the β -position.¹² The first copper mediated asymmetric 1,4-hydrosilylation of various β -amino-substituted α,β -unsaturated esters to β -azaheterocyclic acid derivatives of excellent enantiopurities was disclosed by Buchwald *et al.* in 2004.¹³ Zheng and co-workers then successfully applied this catalyst system in the preparation of γ -amino butyric acid derivatives.¹⁴ By utilizing a Cu(II)/dipyridylphosphine (P-Phos)¹⁵/PMHS (polymethylhydrosiloxane) system, we described the highly enantioselective conjugate reduction of a variety of β -alkyl-substituted β -(acylamino)acrylates with up to 99% ee in 2011.¹⁶ Later on, we attempted to extend this catalyst system to the asymmetric 1,4-hydrosilylation of β -methyl β -(arylamino) acrylates, which rendered low-to-moderate yields and enantioselectivities (7 examples, 33–72% yield, 23–91% ee) in the presence of certain amounts of MeONa and *t*BuOH as additives.¹⁷ To the best of our knowledge, a highly stereoselective 1,4-reduction of β -substituted *N*-aryl β -enamino esters mediated by non-noble metal catalysts has not been realized at present. Herein, we report our systematical studies on the CuH-catalyzed asymmetric conjugate reduction in ambient atmosphere for constructing a broad assortment of chiral β -aryl or β -alkyl-substituted β -(arylamino) acid derivatives. Further, the

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synthetic utility of the methodology was demonstrated by efficient conversion of representative enantiomerically enriched *N*-aryl β -amino acid esters to the corresponding unprotected β -amino acid ester and β -lactam.

Results and discussion

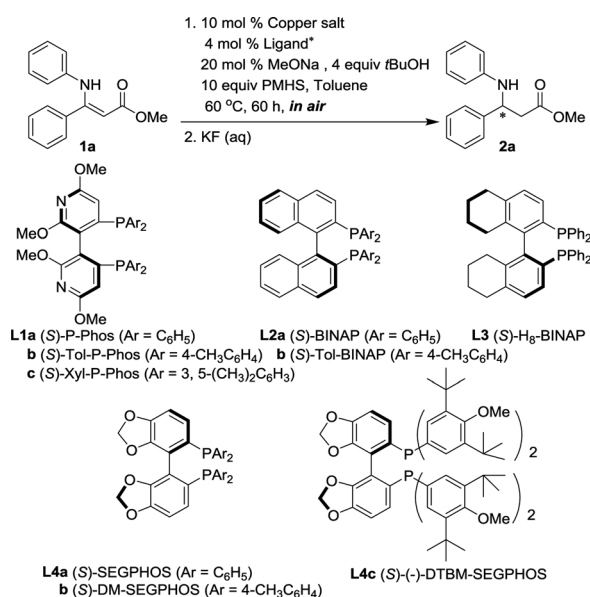
As almost no (*E*)-geometric isomers were obtained during the synthesis of substrates,^{18,19} we commenced our studies by examining the effects of various copper precursors on the conjugate reduction of the model substrate (*Z*)-methyl 3-phenyl-3-(phenylamino)acrylate **1a** (Table 1). PMHS, which is a by-product of the organosilicon industry and has been well-known for its low-cost, non-toxicity and air stability, was selected as the hydride donor. As shown in entry 1, when **1a** was

submitted to a given set of conditions [10 mol% of CuF₂, 4 mol% of **L1a** as the chiral ligand, 10 equiv. of PMHS as the reductant, 20 mol% of MeONa and 4 equiv. of *t*BuOH as the additives], the reaction proceeded in toluene at 60 °C under ambient atmosphere to 53% conversion after 60 h to furnish (–)-methyl 3-phenyl-3-(phenylamino)propionate (**2a**) in 91% ee. Similar to previous findings,²⁰ the extent of conversions varied considerably as function of the counterions of copper. Although promising enantioselectivities were achieved as well by applying Cu(OAc)₂·H₂O or Cu(OAc)₂, lower activities exhibited (entries 3 and 4 vs. entry 1). Almost no reaction was observed by using CuCl₂ or Cu(CH₃COCH₂COCF₃)₂ as the copper precursor (entries 2 and 6). With respect to CuTC, 45% conversion and 90% ee were reached (entry 5). In consideration of both activity and enantioselectivity, CuF₂ appeared to be the preponderant choice.

Subsequently, the abilities of chiral ligands were investigated for the hydrosilylation of **1a** (Table 1, entries 7–14). Among the chiral diphosphines screened, (*S*)-Tol-P-Phos (**L1b**) gave comparative ee with that of (*S*)-P-Phos under otherwise identical conditions (entry 7 vs. entry 1). Besides, a higher ee (95%) was achieved by employing (*S*)-SEGPHOS (**L4a**) as the chiral ligand while the reaction conversion was only 25% after 60 h (entry 12).

Further studies demonstrated that the reaction outcomes also largely relied on the selection of both base and alcohol additives (Table 2), which was consistent with previous findings.^{12c,13,16,21} When MeONa was replaced with more bulky EtONa or *t*BuONa, the enantioselectivity remained almost unchanged using (*S*)-P-Phos as the chiral ligand whilst a lower reaction activity was rendered (Table 2, entries 1 and 2 vs. Table 1, entry 1). To our delight, the replacement of *t*BuOH with less sterically encumbered alcoholic additive MeOH led to dramatic enhancements in reaction activity [53% conv. to 98% conv. for (*S*)-P-Phos **L1a**, 25% conv. to >99% conv. for (*S*)-SEGPHOS **L4a**,

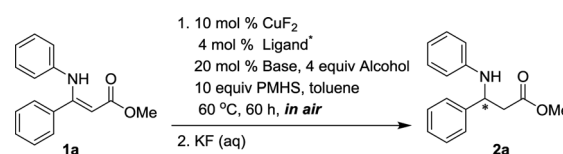
Table 1 Effects of copper salts and ligands on the asymmetric 1,4-reduction of (*Z*)-methyl 3-phenyl-3-(phenylamino)acrylate **1a**^a



Entry	Copper salt	Ligand	Conv. ^b (%)	ee ^c (%)
1	CuF ₂	L1a	53	91 (–)
2	CuCl ₂	L1a	<5	n.d. ^d
3	Cu(OAc) ₂	L1a	31	90 (–)
4	Cu(OAc) ₂ ·H ₂ O	L1a	10	90 (–)
5	CuTC	L1a	45	90 (–)
6	Cu(CH ₃ COCH ₂ COCF ₃) ₂	L1a	<5	n.d. ^d
7	CuF ₂	L1b	27	90 (–)
8	CuF ₂	L1c	<5	85 (–)
9	CuF ₂	L2a	<5	n.d. ^d
10	CuF ₂	L2b	16	84 (–)
11	CuF ₂	L3	<5	n.d. ^d
12	CuF ₂	L4a	25	95 (–)
13	CuF ₂	L4b	<5	84 (–)
14	CuF ₂	L4c	<5	n.d. ^d

^a Reaction conditions: 0.30 mmol substrate, substrate concentration = 0.30 M in toluene. ^b The conversions were determined by NMR and GC analysis. ^c The ee values were determined by chiral HPLC analysis (see the ESI). ^d n.d. = not determined.

Table 2 Effects of additives on the asymmetric 1,4-reduction of (*Z*)-methyl 3-phenyl-3-(phenylamino)acrylate **1a**^a



Entry	Ligand	Alcohol	Base	Conv. ^b (%)	ee ^c (%)
1	L1a	<i>t</i> BuOH	EtONa	44	90 (–)
2	L1a	<i>t</i> BuOH	<i>t</i> BuONa	44	90 (–)
3	L1a	MeOH	MeONa	98	89 (–)
4	L1a	MeOH	EtONa	98	90 (–)
5	L1a	MeOH	<i>t</i> BuONa	>99%	89 (–)
6	L4a	MeOH	MeONa	>99%	95 (–)
7	L4a	MeOH	<i>t</i> BuONa	>99% ^d	96 (–)

^a Reaction conditions: 0.30 mmol substrate, substrate concentration = 0.30 M in toluene. ^b The conversions were determined by NMR and GC analysis. ^c The ee values were determined by chiral HPLC analysis. ^d The isolated yield was 92%.



Table 2, entries 3 and 6 vs. Table 1, entries 1 and 12]. Moreover, utilizing (*S*)-SEGPHOS as the ligand, in the presence of MeOH and *t*BuONa as the additives, the desirable product **2a** was obtained quantitatively (>99% conversion, 92% isolated yield) with 96% ee (entry 7).

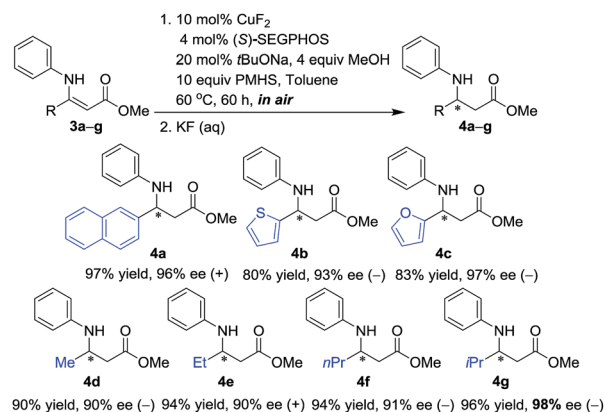
With the aforementioned preferred conditions in hand, we set out to establish the general utility of this copper-catalyzed protocol for the asymmetric conjugate reduction of a vast array of *N*-aryl β-aryl β-enamino esters **1b–s** in air. As the results summarized in Table 3 indicated, consistently high enantioselectivities were obtained in all cases (91–98% ee). Replacing the methyl ester of **1a** with ethyl ester (**1b**) slightly diminished the enantiopurity of the product (entry 1 vs. Table 2, entry 7). The introduction of a *para*-MeO substituent to the *N*-arene ring of **1a** resulted in distinct decreases in reaction activities (entries 4 and 6 vs. Table 2, entry 7). Similarly, the presence of an electron-donating group on the β-aryl group had a pronounced influence on the reactivities (entries 7, 8, 13 and 14 vs. Table 2, entry 7). For instance, when the *ortho*-position of β-phenyl on **1a** was substituted by a methoxy group (**1h**), the isolated yield of chiral product dropped from 92% (Table 2, entry 7) to 22% (entry 7). Nonetheless, the existence of an electron-withdrawing group on the β-aryl group favored the conjugate reductions in terms of both activities and enantioselectivities (entries 3, 9–12 and 15–18).

Table 3 Copper-catalyzed asymmetric hydrosilylation of various *N*-aryl β-aryl β-enamino esters^a



Entry	Substrate	R ¹	R ²	R ³	Yield ^b (%)	ee ^c (%)
1	1b	H	Et	H	90	93 (+)
2	1c	4-MeO	Et	H	65	92 (+)
3	1d	4-Br	Et	H	94	94 (+)
4	1e	H	Me	4-MeO	30	94 (+)
5	1f	4-Me	Me	4-MeO	90	93 (+)
6	1g	4-Cl	Me	4-MeO	30	95 (-)
7	1h	2-MeO	Me	H	22	92 (-)
8	1i	3-MeO	Me	H	62	95 (-)
9	1j	3-F	Me	H	95	94 (+)
10	1k	3-Cl	Me	H	94	94 (-)
11	1l	3-Br	Me	H	93	98 (+)
12	1m	3-CF ₃	Me	H	95	96 (+)
13	1n	4-Me	Me	H	88	91 (+)
14	1o	4-MeO	Me	H	65	94 (-)
15	1p	4-F	Me	H	96	94 (+)
16	1q	4-Cl	Me	H	95	94 (-)
17	1r	4-Br	Me	H	94	95 (-)
18	1s	4-CF ₃	Me	H	96	94 (+)

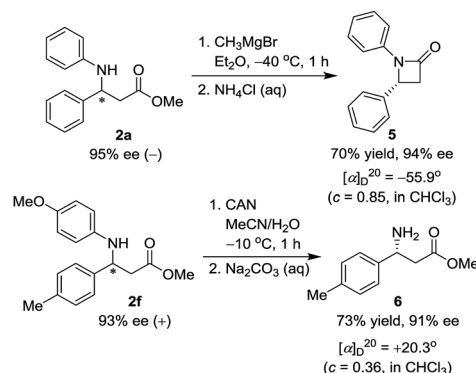
^a Reaction conditions: 0.30 mmol substrate, substrate concentration = 0.30 M in toluene. ^b Isolated yield. ^c The ee values were determined by chiral HPLC analysis.



Scheme 1 Copper-catalyzed asymmetric hydrosilylation of β-heteroaryl or β-alkyl-substituted *N*-phenyl β-enamino esters.

Encouraged by the successful 1,4-hydrosilylation of *N*-aryl β-aryl β-enamino esters, we then applied the present catalyst system in the enantioselective conjugate reduction of a wide scope of β-alkyl, β-naphthyl or β-heteroaryl substituted *N*-phenyl β-enamino esters (**3a–g**). Gratifyingly, as illustrated in Scheme 1, the present protocol worked effectively for the productive access to a variety of desirable products (**4a–g**) of excellent enantiopurities (90–98% ee) under a given set of conditions. The sterically hindered β-alkyl substituent on the substrates was conducive to higher ee values (**4g** vs. **4d–f**).

With the availability of an effective catalytic method for the asymmetric preparation of structurally diverse β-substituted β-(arylamino) acid esters, a range of other enantiomerically enriched molecules become accessible. For instance, as Scheme 2 outlined, treatment of (–)-methyl 3-phenyl-3-(phenylamino)propionate (**2a**, 95% ee) with methylmagnesium bromide in ether at –40 °C furnished chiral β-lactam (*R*)-1,4-diphenylazetidin-2-one (**5**) in 70% yield with 94% ee after 1 h.²² The β-lactam derivatives possess the basic skeleton of monobactam antibiotics,² β-lactamase inhibitors,³ and cholesterol absorption inhibitors.²³ Moreover, *N*-(*para*-methoxyphenyl) group of **2f** (93% ee) was readily deprotected by using ceric ammonium nitrate (CAN) at –10 °C for only 1 h to provide β-



Scheme 2 Conversion of *N*-aryl β-amino esters **2a** and **2f** to chiral β-lactam **5** and unprotected β-amino ester **6**.



amino ester (*R*)-methyl 3-amino-3-(*p*-tolyl)propanoate **6** in 73% yield and 91% ee,²⁴ which constitutes crucial structural elements of β -peptides and many other biologically active compounds.²⁵

Conclusions

In conclusion, in the presence of certain amounts of appropriate additives *t*BuONa and MeOH, the combination of catalytic amounts of CuF₂ and chiral ligand SEGPHOS as well as the stoichiometric hydride donor PMHS generated *in situ* an efficient catalyst system for the asymmetric conjugate reduction of a broad spectrum of β -aryl, β -heteroaryl, or β -alkyl-substituted *N*-aryl β -enamino esters with good activity and uniformly high ee values (26 examples, 90–98% ee). The present catalyst system features high air-stability, excellent stereocontrols, cost efficiency, and mild conditions and therefore offers a good opportunity for the practical preparation of *N*-aryl β -amino acid derivatives. The efficient transformation of enantiomerically enriched *N*-aryl β -amino esters to β -lactam and unprotected β -amino ester further evinced the good utility of this methodology.

Experimental

General procedure of asymmetric hydrosilylation in air [Table 2, entry 7, (*Z*)-methyl 3-phenyl-3-(phenylamino)acrylate, **1a**]

CuF₂ (3.0 mg, 3.0×10^{-2} mmol), (*S*)-SEGPHOS (**L4a**, 7.3 mg, 1.2×10^{-2} mmol) and sodium *tert*-butoxide (5.8 mg, 6.0×10^{-2} mmol) were weighed under air and placed in a 25 mL round-bottomed flask equipped with a magnetic stirring bar. Toluene (0.5 mL) was added and the mixture was stirred at room temperature for 30 min. Then PMHS (200 μ L, 3.0 mmol) was added, and the solution was allowed to stir for further 10 min. Finally, a solution of (*Z*)-methyl 3-phenyl-3-(phenylamino)acrylate **1a** (76 mg, 0.3 mmol) and MeOH (49 μ L, 1.2 mmol) in toluene (0.5 mL) was added under vigorous stirring and the flask was stoppered. The reaction was carried out at 60 °C and monitored by TLC. Upon completion, the reaction mixture was treated with saturated KF solution (2 mL) and 2.0 mL diethyl ether. The mixture was stirred vigorously for 1 h. The aqueous layer was extracted with diethyl ether (3 \times 3 mL). The combined organic layer was washed with water, dried over anhydrous Na₂SO₄, filtered through a plug of silica gel and concentrated *in vacuo* to provide the crude product. The conversion was determined by NMR and GC (column, HP-5; 25 m \times 0.25 mm, carrier gas, N₂). The enantiomeric excess of the product (–)-methyl 3-phenyl-3-(phenylamino)propanoate **2a** was determined by chiral HPLC (column, Daicel Chiralcel OD-H, 25 cm \times 4.6 mm) analysis. The pure product was isolated by column chromatography (ethyl acetate : petroleum ether = 1 : 10).

Procedure for the synthesis of β -lactam (*R*)-1,4-diphenylazetididin-2-one (**5**)²²

To a solution of compound (–)-**2a** (95% ee, 50 mg, 0.20 mmol) in anhydrous Et₂O (5 mL) was added dropwise a solution of 1 M

CH₃MgBr in Et₂O (0.4 mL, 0.40 mmol) at –40 °C under nitrogen atmosphere. After stirring at –40 °C for 1 h, the reaction was quenched by adding an excess amount of saturated aqueous NH₄Cl solution, followed by extracting with Et₂O (2 \times 10 mL). The organic phase was washed with brine and then dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (ethyl acetate : petroleum ether = 1 : 15) to afford the chiral β -lactam **5** (31 mg, 70% yield, 94% ee) as a white solid. The ee value was determined by chiral HPLC analysis with a 25 cm \times 4.6 mm Daicel Chiralcel OD-H column (eluent, 2-propanol/hexane 4 : 96; flow rate: 1.0 mL min^{–1}; detection: 254 nm light).

Procedure for the synthesis of (*R*)-methyl 3-amino-3-(*p*-tolyl)propanoate (**6**)^{24a}

A solution of ceric ammonium nitrate (280 mg, 0.51 mmol) in water (5 mL) was added dropwise to a solution of compound (+)-**2f** (93% ee, 50 mg, 0.17 mmol) in acetonitrile (5 mL) at –10 °C over 10 min. After the mixture was stirred for 1 h, water (5 mL) was added and MeCN was evaporated under vacuum. The residue was washed with Et₂O (2 \times 10 mL) and then added 10% aqueous Na₂CO₃ solution until pH = 6. The mixture was further washed with Et₂O (2 \times 10 mL). After the pH of the aqueous solution was tuned to be 8 by further adding 10% aqueous Na₂CO₃ solution, the mixture was extracted with EtOAc (3 \times 10 mL). The combined organic layers were dried over anhydrous Na₂SO₄, filtered, and concentrated under vacuum. The residue was purified by column chromatography on silica gel (ethyl acetate : petroleum ether = 1 : 1) to give **6** (24 mg, 73% yield, 91% ee) as a brown oil. The ee value was determined by chiral HPLC analysis with a 25 cm \times 4.6 mm Daicel Chiralcel OD-H column (eluent, 2-propanol/hexane 1 : 99; flow rate: 1.0 mL min^{–1}; detection: 215 nm light).

Conflicts of interest

There are no conflicts to declare.

Acknowledgements

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