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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.

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*-arylenamines 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 $HSiCl_3$ as the reducing reagent has also emerged as an efficient alternative to transition metal-catalyzed hydrogenation for the synthesis of chiral β-amino acids 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 enantioenriched 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. Furtherly, the

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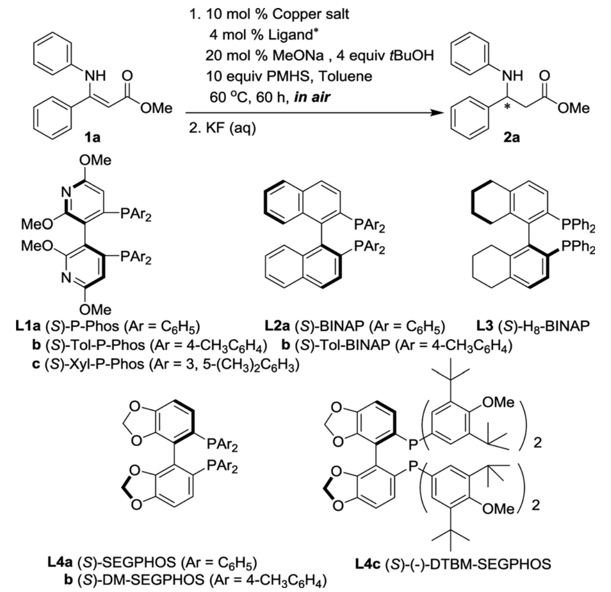
synthetic utility of the methodology was demonstrated by efficient conversion of representative enantiomerically enriched *N*-aryl β-amino acid esters to the corresponding unprotected β-amino acid ester and β-lactam.

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 CuF_2, 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 $Cu(OAc)_2 \cdot H_2O$ or $Cu(OAc)_2$, lower activities exhibited (entries 3 and 4 *vs.* entry 1). Almost no reaction was observed by using $CuCl_2$ or $Cu(CH_3COCH_2COCF_3)_2$ 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, CuF_2 appeared to be the preponderant choice.

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



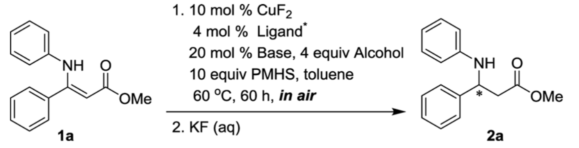
Entry	Copper salt	Ligand	Conv.[b] (%)	ee[c] (%)
1	CuF_2	**L1a**	53	91 (−)
2	$CuCl_2$	**L1a**	<5	n.d.[d]
3	$Cu(OAc)_2$	**L1a**	31	90 (−)
4	$Cu(OAc)_2 \cdot H_2O$	**L1a**	10	90 (−)
5	CuTC	**L1a**	45	90 (−)
6	$Cu(CH_3COCH_2COCF_3)_2$	**L1a**	<5	n.d.[d]
7	CuF_2	**L1b**	27	90 (−)
8	CuF_2	**L1c**	<5	85 (−)
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.

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



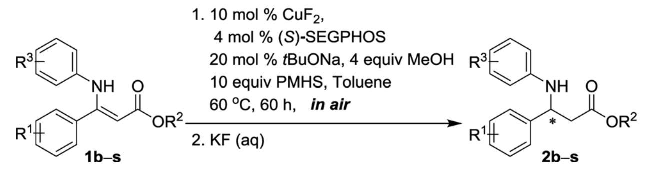
Entry	Ligand	Alcohol	Base	Conv.[b] (%)	ee[c] (%)
1	**L1a**	*t*BuOH	EtONa	44	90 (−)
2	**L1a**	*t*BuOH	*t*BuONa	44	90 (−)
3	**L1a**	MeOH	MeONa	98	89 (−)
4	**L1a**	MeOH	EtONa	98	90 (−)
5	**L1a**	MeOH	*t*BuONa	>99%	89 (−)
6	**L4a**	MeOH	MeONa	>99%	95 (−)
7	**L4a**	MeOH	*t*BuONa	**>99%**[d]	**96** (−)

[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).

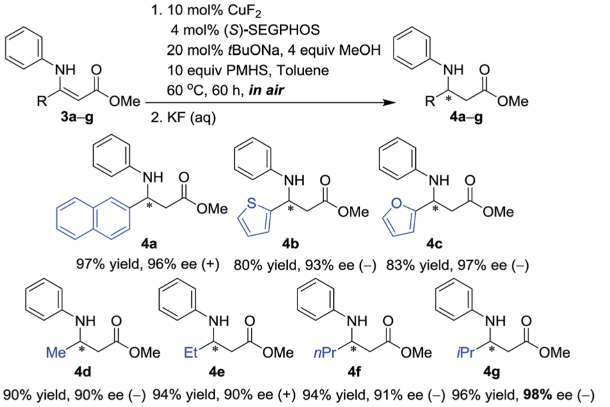
With the aforementioned preferred conditions in hand, we set out to establish the general utility of this copper-catalyzed protocol for the asymmetric conjugate reduction of a vast array of *N*-aryl β-aryl β-enamino esters **1b–s** in air. As the results summarized in Table 3 indicated, consistently 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 (+)

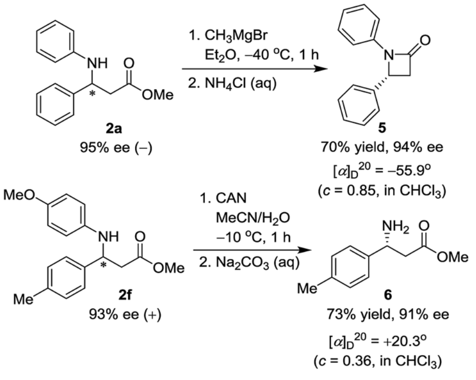
[a] Reaction conditions: 0.30 mmol substrate, substrate concentration = 0.30 M in toluene. [b] Isolated yield. [c] The ee values were determined by chiral HPLC analysis.



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 conductive 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 CuF_2 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]

CuF_2 (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 μL, 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 μL, 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 × 3 mL). The combined organic layer was washed with water, dried over anhydrous Na_2SO_4, 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 × 0.25 mm, carrier gas, N_2). 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 × 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-diphenylazetidin-2-one (5)[22]

To a solution of compound (−)-**2a** (95% ee, 50 mg, 0.20 mmol) in anhydrous Et_2O (5 mL) was added dropwise a solution of 1 M CH_3MgBr in Et_2O (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 NH_4Cl solution, followed by extracting with Et_2O (2 × 10 mL). The organic phase was washed with brine and then dried over anhydrous Na_2SO_4, 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 × 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 Et_2O (2 × 10 mL) and then added 10% aqueous Na_2CO_3 solution until pH = 6. The mixture was further washed with Et_2O (2 × 10 mL). After the pH of the aqueous solution was tuned to be 8 by further adding 10% aqueous Na_2CO_3 solution, the mixture was extracted with EtOAc (3 × 10 mL). The combined organic layers were dried over anhydrous Na_2SO_4, 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 × 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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