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Copper-catalyzed enantioselective conjugate reduction of α,β-unsaturated esters with chiral phenol–carbene ligands

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Full Research Paper

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Abstract

A chiral phenol–NHC ligand enabled the copper-catalyzed enantioselective conjugate reduction of α,β-unsaturated esters. The phenol moiety of the chiral NHC ligand played a critical role in producing the enantiomerically enriched products. The catalyst worked well for various (*Z*)-isomer substrates. Opposite enantiomers were obtained from (*Z*)- and (*E*)-isomers, with a higher enantiomeric excess from the (*Z*)-isomer.

Introduction

Since the leading work of Stryker and co-workers on triphenylphosphine-stabilized copper hydride complexes [1,2], copper hydrides have been widely used for conjugate reductions of α,β-unsaturated carbonyl compounds [3]. Especially a chiral copper catalyst combined with a stoichiometric amount of a silane reagent, which generated copper hydride in situ, has successfully been utilized for enantioselective reactions with β,β-disubstituted α,β-unsaturated carbonyl compounds [4-11]. The pioneering work of Buchwald and co-workers on the enantioselective conjugate reduction of α,β-unsaturated esters using a chiral *p*-tol-BINAP/copper catalyst established the excellent utility of chiral bisphosphine ligands for this type of reaction [4]. Surprisingly, however, chiral ligands based on *N*-heterocyclic carbenes (NHCs) [12] have not been applied to the conjugate reduction of α,β-unsaturated carbonyl compounds, while an achiral NHC/copper catalyst has successfully been utilized in this reaction [13].

Meanwhile, we devoted our effort to develop novel enantioselective C–C bond formation reactions utilizing chiral phenol–NHC/copper catalyst systems [14-18], in which the phenol group of the NHC ligand plays crucial roles in both the catalytic activity and stereoselectivity [19-21]. Notably, these catalyst systems were also applicable for three-component

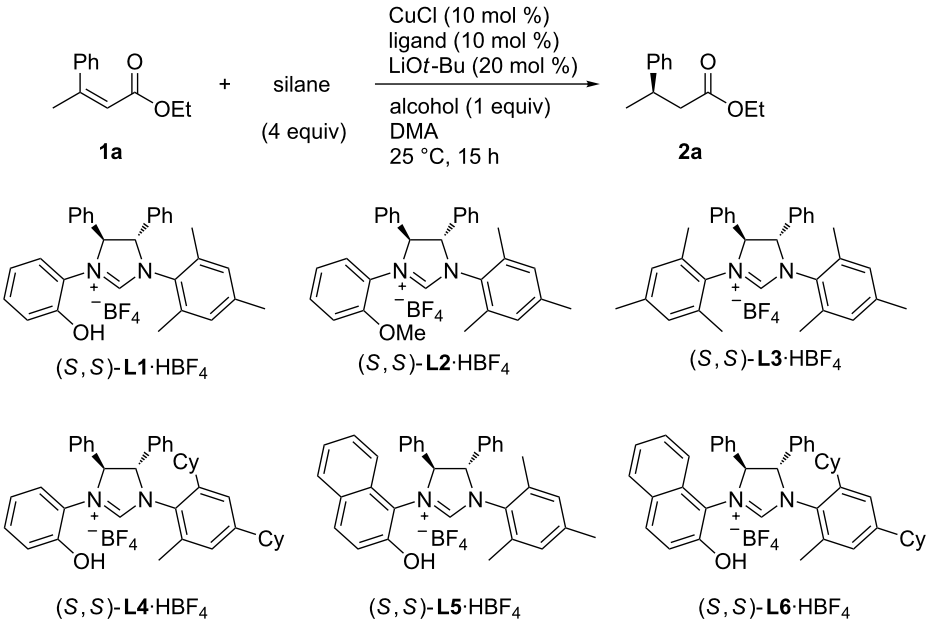
coupling reactions using hydrosilanes as hydride reagents [17]. Based on this knowledge, we decided to investigate the effects of the phenol–NHC ligand on the copper-catalyzed enantioselective conjugate reduction of α,β-unsaturated esters with hydrosilanes, placing a focus on (*Z*)-isomer substrates, which generally gave slightly lower enantiomeric excess with the chiral bisphosphines compared to the (*E*)-isomer substrates.

Results and Discussion

Optimization

The initial investigation of the reaction conditions was carried out with ethyl (*Z*)-3-phenylbut-2-enoate (**1a**) as a substrate (Table 1). When chiral NHC precursor **L1**·HBF_4 (10 mol %) was used in combination with CuCl (10 mol %) and Li*O*t-Bu (20 mol %) for the conjugate reduction of **1a** with diethoxymethylsilane (4 equiv) as a reductant and *t*-AmOH (1 equiv) as a protonation reagent in DMA as the solvent at 25 °C for 15 h, the product **2a** was produced in 98% yield (^{1}H NMR analysis) with a promising enantioselectivity of 69% ee (Table 1, entry 1). When the phenolic hydroxy group of **L1** was changed to a methoxy group (in **L2**), the enantioselectivity drastically dropped to −10% ee, while the yield remained 99% (Table 1, entry 2). Similarly, *N*,*N*′-dimesityl-NHC **L3**, which lacked an oxygen functionality in the *N*-aryl group, showed poor enantioselectivity (9% ee) with high yield (99%

Table 1: Optimization of the copper-catalyzed enantioselective conjugate reduction of **1a**.[a]



entry	ligand	silane	alcohol	yield (%)	ee (%)
1	(*S*,*S*)-**L1**·HBF_4	$(EtO)_2MeSiH$	*t*-AmOH	98	69
2	(*S*,*S*)-**L2**·HBF_4	$(EtO)_2MeSiH$	*t*-AmOH	99	−10
3	(*S*,*S*)-**L3**·HBF_4	$(EtO)_2MeSiH$	*t*-AmOH	99	9
4	(*S*,*S*)-**L4**·HBF_4	$(EtO)_2MeSiH$	*t*-AmOH	97	90
5	(*S*,*S*)-**L5**·HBF_4	$(EtO)_2MeSiH$	*t*-AmOH	99	26
6	(*S*,*S*)-**L6**·HBF_4	$(EtO)_2MeSiH$	*t*-AmOH	97	58
7	(*S*,*S*)-**L4**·HBF_4	$(MeO)_2MeSiH$	*t*-AmOH	98	84
8	(*S*,*S*)-**L4**·HBF_4	$(TMSO)_2MeSiH$	*t*-AmOH	94	71
9	(*S*,*S*)-**L4**·HBF_4	$(EtO)_3SiH$	*t*-AmOH	0	–
10	(*S*,*S*)-**L4**·HBF_4	PMHS	*t*-AmOH	5	–
11	(*S*,*S*)-**L4**·HBF_4	$(EtO)_2MeSiH$	*t*-BuOH	99	82
12	(*S*,*S*)-**L4**·HBF_4	$(EtO)_2MeSiH$	iPrOH	7	–
13	(*S*,*S*)-**L4**·HBF_4	$(EtO)_2MeSiH$	MeOH	4	–

[a]The yield was determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. The enantiomeric excess (ee) was determined by HPLC analysis with a chiral stationary phase column CHIRALCEL® OD-H.

yield, Table 1, entry 3). Thus, the hydroxy group of **L1** was essential for the enantioselectivity by the catalyst. When the mesityl group of **L1** was changed to a bulkier 2-Me-4,6-Cy_2-C_6H_2 group in **L4**, the enantioselectivity was markedly improved to 90% ee, with a high yield (97%, Table 1, entry 4). A naphthol substituent on the nitrogen atom of the NHC (in **L5** and **L6**) instead of the phenol substituent was not suitable, giving significantly lower enantioselectivities (Table 1, entry 5, 99% yield, 26% ee; entry 6, 97% yield, 58% ee).

Further optimization of the conditions was conducted with **L4**. Changing the silane group affected both the reactivity and selectivity (Table 1, entries 7–10), while the replacement of the ethoxy groups of $(EtO)_2MeSiH$ with methoxy or trimethylsilyloxy groups resulted in only moderate reductions in the enantioselectivity and high yields. At the same time, trialkoxysilane $(EtO)_3SiH$ and polymeric silane PMHS gave only trace amounts of the product.

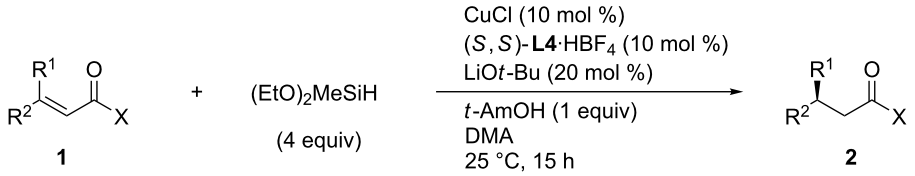
The nature of the alcoholic protonation reagent also had a strong impact. The presence of a tertiary alcohol, *t*-AmOH or *t*-BuOH, was essential for the reaction to occur with a reasonable yield, while iPrOH and MeOH markedly suppressed the reaction (Table 1, entries 12 and 13). However, the bulkier *t*-AmOH was superior to *t*-BuOH in terms of enantioselectivity (Table 1, entries 4 and 11).

Substrate scope

Having established optimized conditions for the reaction of **1a** (**2a**, 97% yield, 90% ee (*R*), Table 2, entry 1), the scope of α,β-unsaturated carbonyl compounds was examined. Because the separation of the product from silicon-based byproducts was troublesome, the isolated yields were lower than the yields determined by NMR spectroscopy (**2a**, 52%, Table 2, entry 1).

When (*E*)-**1a** was used as the substrate, the opposite enantiomer (*S*)-**2a** was obtained in >99% yield, with slightly lower en-

Table 2: Substrate scope of the copper-catalyzed enantioselective conjugate reduction.[a]



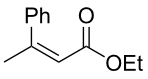
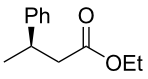
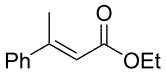
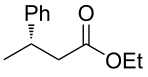
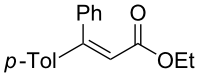
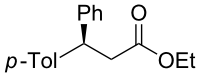
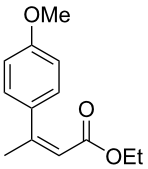
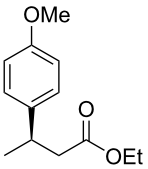
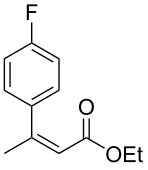
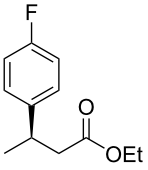
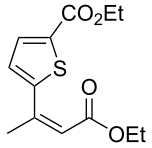
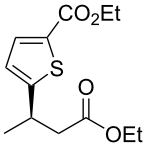
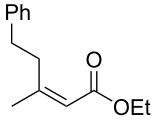
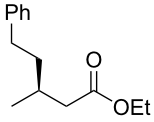
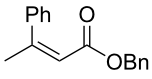
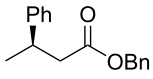
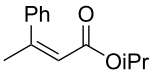
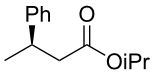
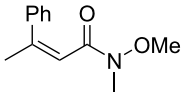
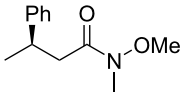
entry	substrate	product	yield (%)	ee (%)
1	 **1a**	 **2a**	97 (52)	90
2	 (*E*)-**1a**	 (*S*)-**2a**	>99 (75)	82
3[b]	 **1b**	 **2b**	>99 (60)	75
4	 **1c**	 **2c**	>99 (44)	84
5	 **1d**	 **2d**	96 (74)	76

Table 2: Substrate scope of the copper-catalyzed enantioselective conjugate reduction.[a] (continued)

6[b,c]	 **1e**	 **2e**	>99 (75)	84
7	 **1f**	 **2f**	>99 (45)	85
8[b,c]	 **1g**	 **2g**	>99 (55)	70
9	 **1h**	 **2h**	>99 (79)	83
10	 **1i**	 **2i**	81 (59)	79

[a]The yields were determined by ^{1}H NMR analysis using 1,1,2,2-tetrachloroethane as an internal standard. Isolated yields are shown in parentheses. [b]*t*-BuOH was used instead of *t*-AmOH. [c]$(EtO)_2MeSiH$ (1 equiv) was used.

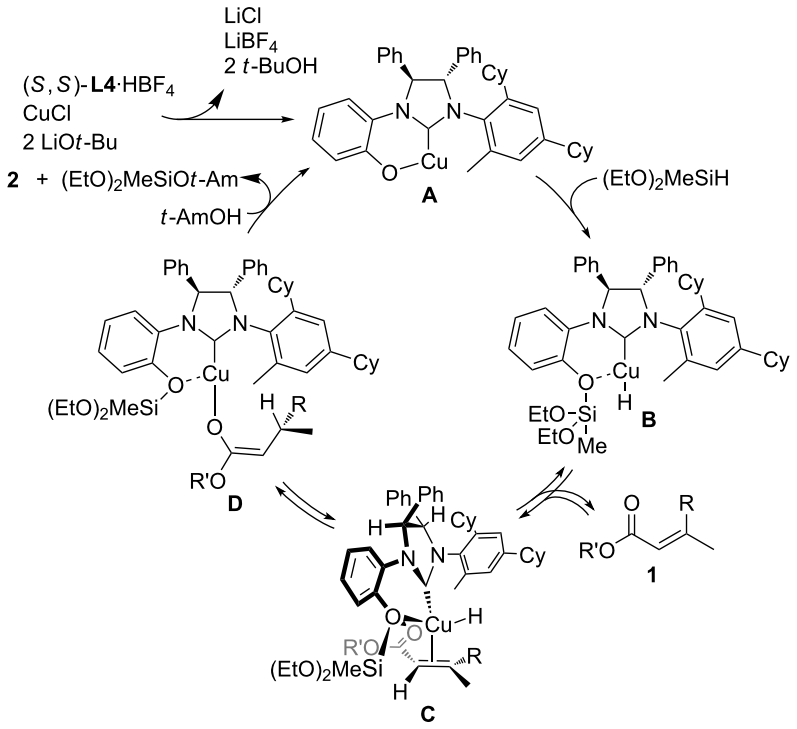
antioselectivity (Table 2, entry 2, 82% ee (*S*) vs 90% ee (*R*) in entry 1). The inversion of the absolute configuration of the product depended on the *E*/*Z* geometry of the substrates, and this was analogous to the reported results obtained with the chiral bisphosphine ligand systems, while the observation of a higher enantioselectivity for the (*Z*)-isomer substrate **1a** was characteristic for the phenol–NHC chiral ligand [4,6,8]. The result suggested that the chiral catalyst may mainly discriminate the hydrogen atom and the ethoxycarbonyl group at the α-position rather than the two substituents at the β-position. In good agreement with this assumption is the reaction of substrate **1b**, carrying a phenyl group and a *p*-tolyl group as β-substituents, which seemed to be difficult for the catalyst to differentiate, both sterically and electronically, affording the product **2b** in good enantioselectivity (Table 2, entry 3, >99% yield, 75% ee).

Next, the effects of the β-substituent (R^1) were examined. Both electron-donating and -withdrawing substituents on the *para*-position of the β-aryl substituent gave excellent reactivities and good enantioselectivities (Table 2, entry 4, **2c**: >99% yield, 84% ee; entry 5, **2d**: 96% yield, 76% ee). Further, a heteroaryl substituent, 2-ethoxycarbonylthiophene, was tolerated (Table 2, entry 6, **2e**: >99% yield, 84% ee), and a β-alkyl-substituted substrate **1f** was also competent (entry 7, **2f**: >99% yield, 85% ee).

The structure of the ester moiety affected the stereoselectivities: Lower enantioselectivities were observed with benzyl ester **2g** (Table 2, entry 8, >99% yield, 70% ee) and isopropyl ester **2h** (Table 2, entry 9, >99% yield, 83% ee). In addition to the α,β-unsaturated esters, an α,β-unsaturated Weinreb amide **1i** afforded the corresponding product **2i** with comparable results (Table 2, entry 10, 81% yield, 79% ee).

Proposed catalytic cycle

Based on the experimental observations and previous knowledge of the catalysis of phenol–NHC chiral ligands [14-18], we propose a catalytic cycle as shown in Scheme 1. LiO*t*-Bu abstracts the two protons of the acidic imidazolium C–H and phenol O–H groups of the **L4**·HBF_4 adduct in the presence of CuCl to generate a phenoxy copper(I) species **A**. As a result, all LiO*t*-Bu (20 mol %) is consumed in this step. Thus, the system is neutral. Transmetalation between **A** and $(EtO)_2MeSiH$ produces the copper hydride species **B**. This transmetalation adds the silyl group to the phenoxy oxygen atom of the NHC ligand. The coordination of an α,β-unsaturated carbonyl compound **1** to the copper atom occurs in such a way that the bulky *O*-silyl group of the copper catalyst can avoid steric repulsions with the alkoxycarbonyl group of the substrate **1**, forming π-complex **C**, and thus explaining the marked influence of the hydrosilane structure on the enantioselectivity. During this stereodetermining step, coordination of the phenoxy oxygen



Scheme 1: Proposed catalytic cycle.

atom to the copper atom may render the chiral environment better defined. Then, the π-complex **C** undergoes 1,4-hydrocupration to afford copper enolate **D**. During our initial investigations, we observed configurational isomerization from **1a** to (*E*)-**1a** when the reaction was conducted in the absence of alcoholic protonation reagents. This observation implied that the 1,4-hydrocupration step (**C** to **D**) is reversible. Finally, protonation of **D** by *t*-AmOH gives the product **2** and silyl ether $(EtO)_2MeSiOt$-Am, regenerating the phenoxy copper(I) complex **A**. Due to the reversibility of the 1,4-hydrocupration, the choice of the alcoholic protonation reagent affects both the reactivity and enantioselectivity.

Conclusion

A chiral phenol–NHC ligand efficiently promoted the enantioselective conjugate reduction of α,β-unsaturated esters with a hydrosilane. To the best of our knowledge, this is the first demonstration of the applicability of chiral NHC ligands in Cu-catalyzed enantioselective conjugate reductions. The phenolic *N*-substituent of the chiral NHC ligand was essential for the high enantioselectivity. Good enantioselectivities were observed for the various (*Z*)-configured substrates with different β-substituents. Further investigations on the catalyst development based on this knowledge are ongoing in our laboratory.

Experimental

A typical procedure for the copper-catalyzed enantioselective conjugate reduction (Table 1, entry 4; Table 2, entry 1): In a glove box, CuCl (1.5 mg, 0.015 mmol), **L4**·HBF_4 (9.8 mg, 0.015 mmol), and Li*Ot*-Bu (2.4 mg, 0.03 mmol) were placed in a vial containing a magnetic stirring bar. The vial was sealed with a teflon-coated silicon rubber septum. *N*,*N*-Dimethylacetamide (0.90 mL) was added to the vial, and then the mixture was stirred at room temperature for 5 min. Next, *t*-AmOH (16.3 μL, 0.15 mmol) was added, and the vial was taken out of the glove box. To the reaction mixture was added **1a** (28.5 mg, 0.15 mmol). After stirring for 5 min at room temperature, diethoxymethylsilane (101 μL, 0.60 mmol) was added to the mixture. After stirring for 15 h at 25 °C, the reaction mixture was diluted with diethyl ether (1.0 mL) and quenched with H_2O (0.6 mL). The organic layer was separated, and the aqueous layer was extracted three times with diethyl ether. The combined organic layer was filtered through a short plug of silica gel by using diethyl ether as an eluent. After the solvent was removed under reduced pressure, the yield of the product was determined to be 97% by ^1H NMR analysis with 1,1,2,2-tetrachloroethane as an internal standard. After a rough purification of the crude product by silica gel chromatography (eluent: 0 to 1% EtOAc/hexane), the collected residue was further purified by GPC (eluent: $CHCl_3$) to afford the pure product **2a** as color-

less oil (15.1 mg, 52% yield, 90% ee). ^{1}H NMR (400 MHz, $CDCl_3$) δ 1.17 (t, J = 7.2 Hz, 3H), 1.29 (d, J = 7.2 Hz, 3H), 2.50–2.63 (m, 2H), 3.27 (sext, J = 7.2 Hz, 1H), 4.06 (q, J = 7.2 Hz, 2H), 7.16–7.22 (m, 3H), 7.28 (t, J = 7.2 Hz, 2H); ^{13}C NMR (100.5 Hz, $CDCl_3$) δ 14.1, 21.7, 36.4, 42.9, 60.2, 126.3, 126.7, 128.4, 145.6, 172.3; $[\alpha]_D^{27.3}$ −23.2 (*c* 1.25, $CHCl_3$). The spectral data matched those reported in the literature [22].

The ee value was determined by HPLC analysis with a chiral stationary column CHIRALCEL® OD-H (Daicel Chemical Industries, 4.6 mm, 250 mm, hexane/2-propanol, 98:2, v/v, 0.5 mL/min, 40 °C, 220 nm UV detector, retention time = 9.1 min for the (*R*)-isomer and 13.3 min for the (*S*)-isomer). The absolute configuration of **2a** was assigned by the comparison of the optical rotation with the same compound prepared by a reported method [4].

Supporting Information

Supporting Information File 1

Experimental procedures, characterization data, HPLC charts, and NMR spectra (^{1}H, ^{13}C) for the new compounds.
[https://www.beilstein-journals.org/bjoc/content/supplementary/1860-5397-16-50-S1.pdf]

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