

Copper-catalyzed enantioselective 1, 4-reduction of α , β -unsaturated ketones using some air and moisture stable Cu (II) pre-catalysts

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Abstract: Some air and moisture stable Cu (II) salts were successfully used as catalyst precursors in asymmetric conjugate reduction of α , β -unsaturated ketones. There into, highly effective copper precatalysts were CuF_2 , $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$, $\text{Cu}(\text{acac}) \cdot 1/2\text{H}_2\text{O}$, $\text{Cu}(\text{CF}_3\text{COO})_2 \cdot \text{H}_2\text{O}$ and some other copper carboxylates. Compared with previous catalyst precursor ($\text{CuCl}/\text{NaOt-Bu}$), these catalyst precursors are not only easier to handle but also capable of avoiding the use of NaOt-Bu . In addition, it was founded that the addition of H_2O could inhibit 1, 2-reduction and enhance the selectivity of 1, 4- reduction. An alcohol acceleration effect was also observed in the asymmetric conjugate reduction of α , β -unsaturated ketones.

Keywords: *Enantioselective 1, 4-reduction; Chiral catalyst; Copper salt; α , β -Unsaturated ketone*

1. Introduction

Recently, chiral CuH complexes were discovered to be highly effective catalysts in asymmetric hydrosilylation reactions, such as asymmetric hydrosilylation of aromatic ketones, asymmetric conjugate reduction of α , β -unsaturated esters and ketones. In previous investigation of asymmetric hydrosilylation of aromatic ketones, chiral CuH catalysts were mainly generated in situ from $\text{CuCl}/\text{NaOt-Bu}$ and some chiral diphosphine ligands [1-3]. Instead of $\text{CuCl}/\text{NaOt-Bu}$, air and moisture CuF_2 [4] and $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ [5] were also effective. In

asymmetric conjugate reduction of α , β -unsaturated esters, $\text{CuCl}/\text{NaOt-Bu}$ and $\text{CuCl}_2 \cdot \text{H}_2\text{O}/\text{NaOt-Bu}$ were investigated as catalyst precursors [6-8].

Compared with the above reactions, copper-catalyzed asymmetric conjugate reduction of α , β -unsaturated ketones have received scantly attention [9-12]. Moreover, sometimes, conjugate reduction of α , β -unsaturated ketones would suffer from some drawbacks [9, 13, 14], such as competing 1, 2-reduction and competing over reduction (Fig. 1). To our knowledge, in this field, only $\text{CuCl}/\text{NaOt-Bu}$ and $(\text{Ph}_3\text{P})\text{CuH}$ were

investigated as catalyst precursors. Although excellent enantioselectivities have been obtained, the use of CuCl/NaOt-Bu and (Ph₃P) CuH may be a drawback to the broad application of these processes, because they are

sensitive to air. Thus, we became interested in searching catalysts, which are not only easy to handle but also capable of avoiding 1, 2-reduction and over reduction in asymmetric conjugate reduction of α , β -unsaturated ketones.

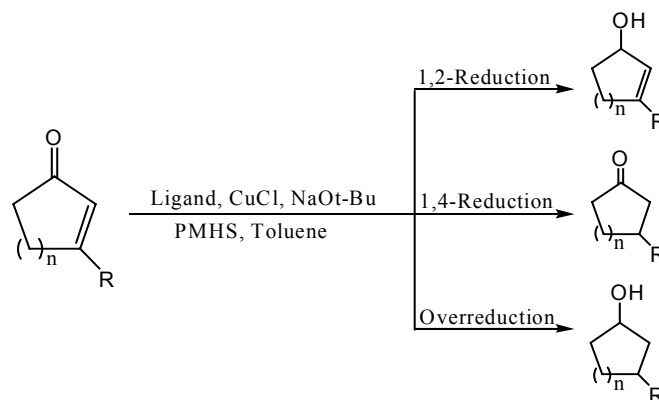


Fig. 1. Reduction of α , β -unsaturated ketones.

In this paper, Various Cu (I) and Cu (II) salts were screened to search for optimal catalysts in asymmetric conjugate reduction of α , β -unsaturated ketones. Moreover, it was attempted that appropriate equivalents of H₂O were added to inhibit 1, 2-reduction and some simple alcohols were added to accelerate the reaction rate. In these investigations, 3-ethyl-2-cyclopenten-1-one was chosen as the model substrate, and (S)-*p*-tol-BINAP was chosen as the chiral ligand.

2. Experimental

2.1. Materials and instruments

Toluene was freshly distilled from sodium benzophenone ketyl under argon before use. *i*-PrOH, *t*-BuOH and *t*-AmOH (*tert*-amyl alcohol) were freshly distilled from CaH₂ under argon before use. Ethanol was freshly distilled from MgSO₄ under argon before use. CuCl was prepared from CuCl₂ following a literature procedure

[15]. Other Cu (I) and Cu (II) salts were purchased from Chinese Tianjin Chemical Reagent Co. and used as received. NaOt-Bu and PMHS (polymethylhydrosiloxane) were purchased from Aldrich and used as received. (S)-*p*-tol-BINAP was purchased from Alfa Aesar and used as received.

¹H-NMR, ¹³C-NMR and ³¹P-NMR spectra were recorded on Bruker 300 or 400 MHz spectrometer in CDCl₃ and TMS as internal standard. GC analysis was performed using a Supelco β -Dex 120 chiral capillary column.

2.2. Preparation of diphosphine DDPPI

DDPPI was prepared by standard procedure described in literature from D-mannitol [16].

³¹P-NMR (400 MHz, CDCl₃): δ = -14.5 (s). ¹H-NMR (300 MHz, CDCl₃): δ = 7.26-7.56 (m, 20H, Ph), 4.54 (d, J =

8.1 Hz, 2H, $\underline{\text{CHO}}$), 4.10-4.20 (m, 2H, $\underline{\text{CHH}}$), 3.67-3.76 (m, 2H, $\underline{\text{CHH}}$), 3.18 (s, 2H, $\underline{\text{CHP}}$). $^{13}\text{C-NMR}$ (300 MHz, CDCl_3): δ = 128.5-136.5 (m), 87.45 (d, $J = 96.0$ Hz), 71.12 (d, $J = 87.0$ Hz), 44.35 (d, $J = 45.6$ Hz).

2.3. Procedure for Asymmetric Reduction of α,β -unsaturated ketone.

Copper salt (0.10 mmol) and (S)-*p*-tol-BINAP (0.10 mmol) were added into a flame-dried 10 ml round-bottomed flask (RBF). Then, the mixture was stirred in toluene (2 ml) at room temperature for 30 min to give a colorless solution. A flame-dried 5 ml pear bottomed flask (PBF) was cooled under argon and charged with toluene (2 ml), and then 3-ethyl-2-cyclopenten-1-one (2.03 mmol) was added at room temperature. The RBF was then charged with polymethylhydrosiloxane (PMHS) (0.2 ml, 3.23 mmol) at room temperature to give a colorless solution, which was then cooled to 0 °C. The contents of the PBF were then added to the RBF via cannula. Upon completion, the reaction was quenched with 2.5 M aqueous NaOH (15 ml) and THF (15 ml) and stirred for 3 h. The biphasic mixture was extracted with ether (5×20 ml), and the organic layer was concentrated to an oil before being redissolved in ether (25 ml) and dried over anhydrous Na_2SO_4 . Filtration followed by purification by column chromatography provided the desired product. The product and enantioselectivities were determined by $^1\text{H-NMR}$ spectra and GC analysis with a chiral capillary column.

3. Results and discussion

A series of Cu (I) and Cu (II) salts

were screened to search for optimal catalyst in asymmetric conjugate reduction of 3-ethyl-2-cyclopenten-1-one. We first tested the effectiveness of previous catalyst generated in situ from CuCl , NaOt-Bu and (S)-*p*-tol-BINAP in this reaction. The desired product was obtained in 82% yield with 90% ee. Minor amounts of over reduced product were also observed. In addition, 1, 2-reduction of the substrate was isolated (9% of 3-ethyl-2-cyclopenten-1-ol was isolated). Instead of CuCl , $\text{CuCl}_2 \cdot 2\text{H}_2\text{O}$ was also effective as catalyst precursor in the reaction (Table 1, entry 2). Undesired product of 1, 2-reduction (5%) was also isolated; but the over reduced product was not observed. The use of the above copper sources resulted in some questions. Firstly, it is troublesome that moisture sensitive NaOt-Bu was added to activate catalysts. Secondly, it is unsatisfactory that the observed yields were moderate (Table 1, entries 1, 2) after 24 h. The moderate yields possibly resulted from the concomitant production (NaCl), which would possibly inhibit the catalytic activity [17]. So we used isolated CuOt-Bu to enhance the reaction yield; and a yield of 97% was obtained after 10 h. But it is unfortunate that CuOt-Bu is an extremely air and moisture sensitive complex. These questions prompted us to search for other air stable copper sources to avoid the use of NaOt-Bu and the presence of NaCl .

Fortunately, some copper carboxylates and other copper salts could be activated without additive (NaOt-Bu) in the presence of PMHS (Table 1, entries 4-17). On the whole,

the use of different copper sources hardly affected the enantioselectivities of the reactions and the observed enantioselectivities ranged from 85 to 93%. For example, with Cu(OAc)₂ system, the product was obtained in high yield and enantioselectivity (93% ee) after 20 h. Air and moisture stable Cu(OAc)₂·H₂O was also as effective as Cu(OAc)₂ in the reaction. Moreover, it

was found that the H₂O molecule in Cu(OAc)₂·H₂O resulted in a slight increase of the reaction rate (Cu(OAc)₂ gave 92% yield after 20 h, while Cu(OAc)₂·H₂O gave the similar yield after 10 h). This behavior is slightly consistent with the literature reports [5], where Cu(OAc)₂·H₂O and Cu(OAc)₂ were used as the copper sources in hydrosilylation of acetophenone.

Table 1. Asymmetric conjugate reduction of 3-ethyl-2-cyclopenten-1-one using various copper precursors^a

Entry	Cu precursor	Time (h)	Yield (%) ^b	ee (%)
1	CuCl/NaOt-Bu ^c	24	82	90
2	CuCl ₂ ·2H ₂ O/NaOt-Bu ^c	24	78	88
3	CuOt-Bu	10	97	89
4	CuOAc	20	94	92
5	Cu(OAc) ₂	10	68	90
6	Cu(OAc) ₂	20	92	93
7	Cu(OAc) ₂ ·H ₂ O	10	93	90
8	Cu(acac) ₂ ·1/2H ₂ O	20	76	93
9	Cu(CF ₃ COO) ₂ ·H ₂ O	10	82	88
10	Cu[CH ₃ (CH ₂) ₃ CH(C ₂ H ₅)CO ₂] ₂	10	97	91
11	Cu(CH ₃ CH ₂ COO) ₂ ·xH ₂ O	10	93	89
12	Cu[CH ₃ (CH ₂) ₂ COO] ₂ ·xH ₂ O	10	92	92
13	Cu[CF ₃ (CF ₂) ₆ COO] ₂ ·xH ₂ O	10	98	93
14	Cu(NO ₃) ₂ ·3H ₂ O	48	21	87
15	Cu(SO ₄) ₂ ·5H ₂ O	48	32	89
16	CuF ₂	10	93	85
17	CuF ₂ ^d	48	24	37

^a Reaction conditions and analytical procedures were shown in the experimental portion of this paper. ^b Minor amounts of 1,2-reduction product were sometimes contained ^c The Cu to NaOt-Bu ratio was 1:1.2. ^d Instead of (S)-*p*-tol-BINAP, DDPPI was used.

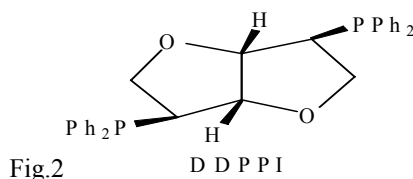
Among the screened catalyst precursors, CuF₂ and some copper carboxylates turned out to be highly effective in this reaction (Table 1). However, when Cu(NO₃)₂·3H₂O, Cu(SO₄)₂·5H₂O were used, low yields were obtained after 48 h (Table 1, entries 14, 15). As reported in previous literature [4], an oxygen acceleration

effect was observed in hydrosilylation of ketones catalyzed by air stable copper fluoride-phosphine complexes. This finding prompted us to examine exposing our system to oxygen (CuF₂ was used as copper source); however, it is unfortunate that the presence of oxygen led to significant inhibition of the conjugate reduction of unsaturated

ketones.

Instead of (S)-*p*-tol-BINAP, another diphosphine (Fig. 2) was also investigated as ligand in copper-catalyzed asymmetric conjugate reduction of

3-ethyl-2-cyclopenten -1-one using CuF_2 . A low yield with 37% ee was obtained after 48 h. By this token, the ligand plays an important role in copper-catalyzed asymmetric conjugate reduction.



Among the above results, the $\text{Cu}(\text{OAc})_2 \cdot \text{H}_2\text{O}$ system performed better than the $\text{Cu}(\text{OAc})_2$ system. It compelled us to purposefully examine the effect of H_2O on the reaction (Table 2, entries 1-5). Without additive, $\text{Cu}(\text{OAc})_2$ gave undesired 1, 2-reduction product of 7%. When some H_2O ($\text{H}_2\text{O}/\text{Cu}(\text{OAc})_2$ ratio of 5) was used, the undesired 1, 2-reduction was

completely suppressed and a slight increase of the reaction rate was observed (Table 1, entries 5, 6; Table 2, entries 2, 3), but the reaction yield was not beyond 89% after 48 h. When the $\text{H}_2\text{O}/\text{Cu}$ ratio was increased to 20, no 1, 2-reduction was observed, but the yields of 1, 4-reduction remarkably decreased.

Table 2. Reduction of 3, 5-dimethyl-2-cyclohexen-1-one in the presence of water or alcohol additives^{a, b}

Entry	Additive	Additive/Cu salt	Time (h)	Yield (%) ^c	ee (%)
1	H_2O	2	20	91	90
2	H_2O	5	8	88	89
3	H_2O	5	48	89	91
4	H_2O	7	20	73	88
5	H_2O	20	20	17	92
6	<i>t</i> -BuOH	40	4	94	87
7	<i>t</i> -AmOH	40	4	97	90
8	<i>i</i> -PrOH	40	1	85	89
9	<i>i</i> -PrOH	40	4	92	87
10	EtOH	40	1	66	91
11	EtOH	40	4	67	91

^a Reaction conditions and analytical procedures were shown in the experimental portion of this paper. ^b $\text{Cu}(\text{OAc})_2$ was used as copper source. ^c Minor amounts of 1,2-reduction product were sometimes contained.

Recently, it was observed by Buchwald that some alcohols could

result in rate-accelerating of conjugate reduction of unsaturated esters [7]. So,

we also added some alcohols to optimize our reaction system (Table 2, entries 6-11). When two equivalents of *t*-BuOH were added to the reaction mixture, a yield of 94% was obtained after 4 h. Other alcohols, such as EtOH,

t-AmOH and *i*-PrOH, also could enhance the reaction yield. However, with two equivalents of MeOH, rapid gas (H_2) evolution was observed, and no reduction reaction was observed in 10 h.

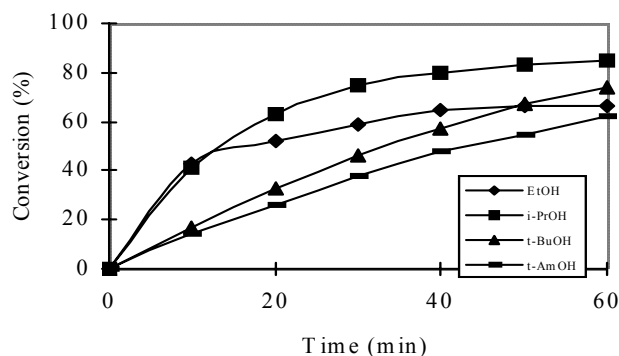


Fig. 3. Reduction of in the presence of various alcohol additives.

As shown in Fig.3 and Table 2, the rate of the reduction is dependent on the size of the alcohol additive. With EtOH, the reaction proceeded from 43% conversion (after 10 min) to 65% conversion (after 40 min), and then proceeded no further. Even if the reaction time was prolonged to 4 h, the reaction did not proceed beyond 67% conversion (Table 2, entry 11). The lower conversion may result from competitive silylation of EtOH with concomitant release of H_2 . *i*-PrOH and EtOH gave rise to similar reaction rates in the first 60 min (Fig. 3), but *i*-PrOH gave higher conversion (92%) after 4 h (Table 2, entry 9). The use of larger

alcohols resulted in slower reaction rates in the first 10 min (Fig. 3). However, when the reaction time was prolonged to 4 h, the reaction conversions were satisfying (Table 2, entries 6, 7). In conclusion, with smaller alcohol, the alcohol acceleration effect is more obvious. However, extremely small alcohol would result in a decrease of final conversion after longer reaction time. According to recent mechanism proposed by Buchwald [7], The rate-accelerating role of alcohol may well be due to more rapid quenching of a copper enolate by alcohol than by the silane (Fig. 4).

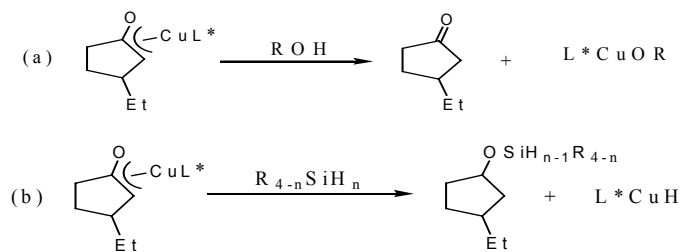


Fig. 4. Proposed mechanism for quenching of a copper enolate by alcohol and the silane.

Last, we attempted to investigate the unusual behaviors of H₂O. When the conjugate reduction was performed in benzene-D₆ and 0.2 equivalents of D₂O were used, the result is difficult to interpret. We suggest that H₂O possibly plays two roles in the reaction. On the one hand, H₂O would consume a portion of reducing reagent with concomitant release of H₂ and result in a decrease of the yield. On the other hand, H₂O would protonate the enolate and accelerate the reaction rate as the rate-accelerating role of alcohol (Fig. 4, (a)). So the addition of appropriate equivalents of H₂O is necessary to optimize the reaction. However, it is difficult to explain the phenomena that H₂O can inhibit 1, 2-reduction and enhance the selectivity of 1, 4-reduction.

In conclusion, some air and moisture stable Cu (II) salts were successfully used to catalyze the conjugate reduction of α , β -unsaturated ketones. There into, more effective copper precatalysts are CuF₂, Cu (OAc)₂·H₂O, Cu (acac)·1/2H₂O, Cu (CF₃COO)₂·H₂O and some other copper carboxylates. Compared with previous catalyst precursor (CuCl/NaOt-Bu), these catalyst precursors are not only easier to handle but also capable of avoiding the use of NaOt-Bu. In addition, it was founded that the addition of H₂O could enhance the selectivity of 1, 4-reduction. An alcohol acceleration effect was also observed in the asymmetric conjugate reduction of α , β -unsaturated ketones.

Acknowledgments:

We wish to thank Henan University of Science and Technology for financial support.

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