Asymmetric Hydrogenation of α,β-unsaturated ester with Copper Catalyst

Miao RUI, Changjin ZHU*
Department of Applied Chemistry, Beijing Institute of Technology, No. 5, Zhongguancun South Street, Beijing 100081, China

ABSTRACT: A copper catalyst system for the asymmetric hydrogenation of the α,β-unsaturated esters class was developed by which synthesis of enantiomer of 1,2-benzothiazine-1,1-dioxide acetates has been achieved with a good yield and an excellent level of enantioselectivity (up to 94% ee).
KEYWORD: Asymmetric hydrogenation; α,β-Unsaturated ester

1 INTRODUCTION

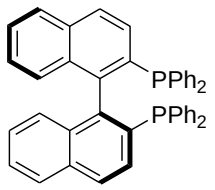
Since chirality has emerged as an important issue in many industrial production, especially in the areas connected to life sciences such as agrochemical, pharmaceutical, and fragrance industries, extensive efforts have been made to obtain the pure enantiomers.[1] It has become increasingly clear that enantiomerically pure drugs have many advantages over racemic drug mixtures because of fewer side effects and greater potency in many cases.[2] Asymmetric catalytic reactions have been recognized as one of the most useful tools for preparing a wide range of enantiomerically pure compounds.[3]

The catalytic asymmetric reduction of α,β-unsaturated carbonyl compounds offers a convenient and efficient method for preparing the optically active compounds bearing a stereogenic center at the β-position. In the past few decades, many catalysts derived from various transition metals have been successfully developed to achieving this transformation.[4] Copper hydride complexe with chiral ligands has emerged as a powerful reagent[5,6] for effecting asymmetric reductions of various α,β-unsaturated compounds. For example, 2-alkenylheteroarenes,[7-11] α,β-unsaturated nitriles,[12-13] α,β-unsaturated sulfones,[14] nitroalkenes[15-16] and enones.[17] The present study focuses on the catalytic asymmetric 1,4-hydrosilylation of benzothiazine-1,1-dioxide acid methyl ester, which is a potential inhibitor of aldose reductase involved in the formation of diabetic complications.

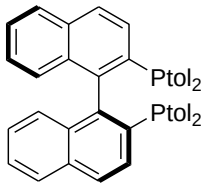
2 RESULTS AND DISCUSSION

The catalytic reduction of 1,2-benzothiazine-1,1-dioxide-4-acid methyl ester was started by screening of a number of copper salts, diphosphine ligands, silanes, hydrogen sources, and solvents in order to identify a suitable catalyst system.

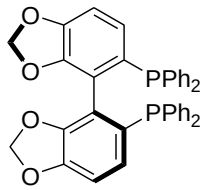
Initially, we screened several chiral diphosphine ligands (Figure 1). The results are summarized in Table 1. Firstly, We employed the procedure[18] for the reaction including the catalyst complex of S-BINAP (L1) and the hydrogen source of PMHS (polymethylhydrosiloxane), $Cu(OAc)_2 \cdot H_2O$ and t-BuOH in toluene (Entry 1, Table 1), but there was no reaction after 24 h at the room temperature.



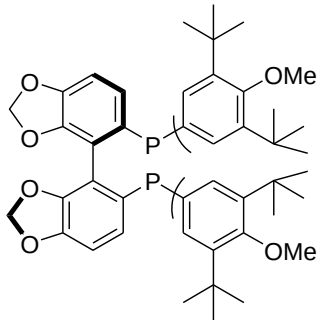
L1 (S)-BINAP



L2 (S)-p-tol-BINAP



L3 (R)-SEGPHOS



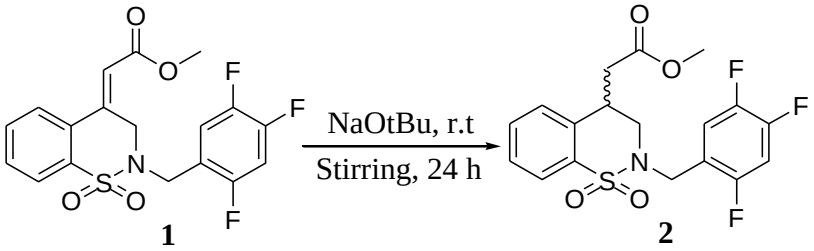
L4 (R)-DTBM-SEGPHOS

Figure 1. Chiral diphosphine ligands evaluated in the asymmetric 1,4-reduction.

However, the reaction proceeded in 24 h by using NaOtBu as the additive instead of t-BuOH, and this

additive promoted the reaction in 10% yield and 36% ee (Entry 2, Table 1). Based on this result, we conducted a systematic exploration of different reaction conditions to optimize the enantiomeric excess of the reaction. We made a brief survey of the efficiency of ligands for this process and found that (S)-p-tol-BINAP (L2) displayed an excellent performance in the asymmetric conjugate reduction of α,β-unsaturated esters. However, this reaction gave low yields, while the reaction using (R)-SEGPHOS (L3) and (R)-DTBM-SEGPHOS (L4) failed to reduce the substrate (Entries 4 and 5). Then we investigated some different copper salts (Entries 6-9). The results suggest that anhydrous $Cu(OAc)_2$ was the best catalyst precursor in terms of yield and enantiomeric excess, providing the reduction product in 43% yield and 91% ee (Entry 7). Silane reagents (Entries 7 and 10−12) were then screened and revealed that PMHS, $PhSiH_3$, Ph_2SiH_2 and TMDS (1,1,3,3-tetramethyldisiloxane) gave the similar yield. Although $PhSiH_3$ was slightly superior with respect to yield (Entry 11), it gave an obviously lower enantiomeric excess in comparison with those of other silane reagents. So Ph_2SiH_2 was chose as the hydrogen source with a high enantiomeric excess. Solvent effects were also tested (Entries 12–17) and tetrahydrofuran was proved to be the best solvent. When tetrahydrofuran was utilized as the solvent, the reaction proceeded at a higher yield and enantiomeric excess than other solvents, and the reaction conversion could be completed even at lower temperatures (0−20 °C) and in a shorter time (18 h). This outcome is presumably due to the good solubility of the copper catalyst. In the end, tetrahydrofuran was found to be the most suitable solvent at 20 ℃, leading to a high yield and the highest enantiomeric excess of 94% (Entry 13). These efforts eventually resulted in the establishment of the catalyst system and reaction conditions for 1,4-hydrosilylation of compound 1.

Table 1. Asymmetric 1,4-Reduction of **1**[a]



1 **2**

Entry	Ligand	Copper Salt	Hydrogen source	Solvent	Yield(%)[b]	ee(%)[c]
1	L1	$Cu(OAc)_2{\cdot}H_2O$ /t-BuOH	PMHS	toluene	-	-
2	L1	$Cu(OAc)_2{\cdot}H_2O$	PMHS	toluene	10	36
3	L2	$Cu(OAc)_2{\cdot}H_2O$	PMHS	toluene	28	86
4	L3	$Cu(OAc)_2{\cdot}H_2O$	PMHS	toluene	-	-
5	L4	$Cu(OAc)_2{\cdot}H_2O$	PMHS	toluene	-	-
6	L2	CuCl	PMHS	toluene	25	80
7	L2	$Cu(OAc)_2$	PMHS	toluene	43	91
8	L2	$[(Ph_3P)CuH]_6$	PMHS	toluene	29	85
9	L2	$Cu(Otf)_2$	PMHS	toluene	39	89
10	L2	$Cu(OAc)_2$	TMDS	toluene	42	91
11	L2	$Cu(OAc)_2$	$PhSiH_3$	toluene	45	92
12	L2	$Cu(OAc)_2$	Ph_2SiH_2	toluene	51	77
13	L2	$Cu(OAc)_2$	Ph_2SiH_2	THF	57	94
14	L2	$Cu(OAc)_2$	Ph_2SiH_2	DMF	-	-
15	L2	$Cu(OAc)_2$	Ph_2SiH_2	CH_2Cl_2	30	86
16	L2	$Cu(OAc)_2$	Ph_2SiH_2	1,4-dioxane	21	91
17	L2	$Cu(OAc)_2$	Ph_2SiH_2	$(C_2H_5)_2O$	15	73

[a]Substrate 1 (0.5 mmol), 0.1 equiv of chiral phosphine ligand (L), 0.05 equiv of Cu precursor, 0.1 equiv of NaOtBu, and 4 equiv of silane at room temperature in 6 mL of solvent for 24 h. [b]Isolated yields. [c]Enantiomeric excesses were determined by chiral HPLC.

3 CONCLUSION

We have developed an efficient protocol for the copper-catalyzed asymmetric hydrogenation of the α,β-unsaturated benzothiazine ester. Key factors in the success of this reaction are the presence of p-tol-BINAP as the ligand, $Cu(OAc)_2$ as the catalyst precursor, Ph_2SiH_2 as the silane reagent, and tetrahydrofuran as the solvent.

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