An Efficient Copper−Aluminum Hydrotalcite Catalyst for Asymmetric Hydrosilylation of Ketones at Room Temperature

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ABSTRACT

Ar = aromatic ring
R = Me, Et, -(CH₂)₃-
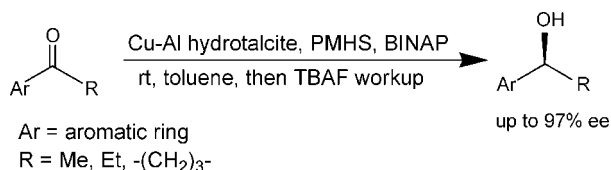
A catalyst system consisting of a copper−aluminum hydrotalcite−chiral diphosphine ligand effects asymmetric hydrosilylation of several ketones, using polymethylhydrosiloxane (PMHS) as the stoichiometric reducing agent at room temperature, with moderate-to-excellent enantioselectivities. The catalyst is recovered by simple centrifugation, and the efficiency of the catalyst remains almost unaltered even after several cycles.

The development of asymmetric catalytic systems is a major challenge because of its importance in synthetic organic chemistry and fine chemicals manufacturing.[1] Enantiomerically pure chiral alcohols have numerous applications in the field of pharmaceuticals,[2] agrochemicals,[3] flavors, and fragrances,[4] and they can be obtained by asymmetric hydrogenation[5] or transfer hydrogenation of carbonyl compounds.[6] However, due to exceedingly mild reaction conditions and technical simplicity, much effort has been placed upon the asymmetric hydrosilylation of a wide range of substrates, normally using Rh- or Ti-based catalysts.[7]

Recently the use of copper, a less expensive base metal, and polymethylhydrosiloxane (PMHS), an inexpensive,

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nontoxic polymer coproduct of the silicone industry as the stoichiometric reducing agent, has opened up a new perspective to asymmetric hydrosilylation.

Buchwald described a highly enantioselective 1,4-reduction of α,β-unsaturated esters and β-substituted enones, using an active catalyst generated in situ from the CuCl/NaO-t-Bu/chiral diphosphine ligand and PMHS.[8] The effectiveness of copper for hydrosilylation of carbonyl compounds was reported by Lipshutz and his group.[9] Their subsequent studies led to the development of highly enantioselective hydrosilylation of ketones based on CuCl/NaO-t-Bu and chiral diphosphine ligands.[10] Besides copper alkoxides, copper fluoride and copper(II) acetate also catalyze the asymmetric hydrosilylation of ketones in the presence of a BINAP ligand under homogeneous conditions.[11]

Industry favors the catalytic process induced by a heterogeneous catalyst over the homogeneous one in view of its ease of handling, simple workup, and regenerability. Recently, Lipshutz reported copper-in-charcoal, and we reported nanocrystalline copper(II) oxide for asymmetric hydrosilylation reactions.[12] Layered double hydroxides or hydrotalcite-like compounds (HTs) have received much attention in view of their potential applications as adsorbents, anion exchangers, and most importantly, as catalysts.[13] As part of our ongoing research aimed at the development of solid catalysts for asymmetric synthesis,[14] we herein present the results on the use of Cu−Al hydrotalcite catalyst for the asymmetric hydrosilylation of ketones to chiral secondary alcohols in good yields with excellent enantiomeric excess (ee) at room temperature using BINAP as a chiral auxiliary and PMHS as the stoichiometric reducing agent (Scheme 1).

Scheme 1

Ar = aromatic ring
R = Me, Et, -(CH₂)₃-
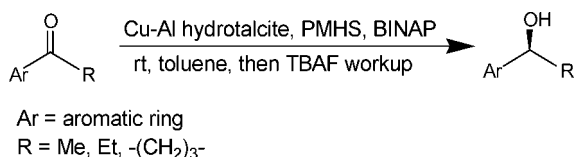
To identify and develop the best copper catalyst for the asymmetric hydrosilylation of ketones, a series of hydrotalcites

containing different ratios of Cu:Al, such as 2:1, 2.5:1, and 3:1, were prepared according to the literature procedure[15] (see Supporting Information) and screened in the presence of PMHS using 4-methylacetophenone as a model substrate. Catalyst A (Cu:Al = 3:1) was found to be more active than catalyst B (Cu:Al = 2.5:1) and catalyst C (Cu:Al = 2:1). The effect of organic solvents and chiral ligands on the asymmetric hydrosilylation of 4-methylacetophenone was also examined (see Table 1). A significant decrease in the rate of reaction and a small

Table 1. Screening of Reaction Parameters for the Asymmetric Hydrosilylation of 4-Methylacetophenone at Room Temperature[a]

entry	catalyst	ligand	time (h)	yield (%)[b]	ee (%)
1	Cat A	BINAP	9	91	83
2	Cat A	BINAP	24[c], 5[d]	21[c], 87[d]	83[c], 75[d]
3	Cat B	BINAP	12	56	80
4	Cat C	BINAP	12	72	80
5	Cat A	BIPHEP	12	44	81
6	Cat A	BINAM	24	14	78
7	Cat A	bisoxazoline	24	trace	-
8	Cat A	BINOL	24	-	-
9	Cat A	BINAP	24	10	75[e]
10	Cat A	BINAP	24	15	68[f]
11	Cat A	BINAP	12	52	78[g]
12	Cat A	BINAP	2	87	80[h]

[a] Reaction conditions: 4-methylacetophenone (1 mmol), PMHS (4 mmol), Cu−Al hydrotalcite (10 mg), solvent (3 mL), chiral ligand (7 mg). [b] Isolated yields, [c] Reaction at − 40 °C. [d] Reaction at 60 °C. [e] THF was used. [f] CH₂Cl₂ was used. [g] Ether was used. [h] 2 equiv of PhSiH₃ was used. Copper content (wt %): Cat A = 34.11; Cat B = 47.15; Cat C = 46.07.

amount of reduced product were obtained using polar solvents such as THF. Nonpolar solvents such as toluene produced S-1-(4-methylphenyl)ethanol in excellent yields and enantiomeric excess (ee) at room temperature. Among the different chiral ligands screened (Figure 1), commercially available BINAP
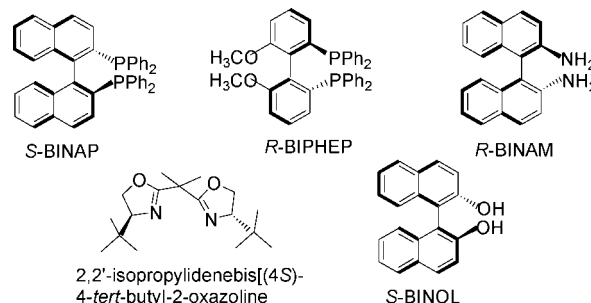

Figure 1. Different chiral ligands used.

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gave excellent yields and ee's greater than R-(+)-2,2′-bis(diphenylphosphino)-6,6′-dimethoxy-1,1′-biphenyl (BIPHEP). The use

of bidentate nitrogen-based ligands gave poor yields, and the ee's decreased significantly (Table 1, entries 5 and 6). Although phenylsilane is an active reductant, the inexpensive and nontoxic polymer siloxane PMHS has been used in this work. Eventually, the catalytic system consisting of catalyst A, BINAP as the chiral auxiliary, and PMHS as the stoichiometric reducing agent in the presence of toluene was chosen for the asymmetric hydrosilylation of an array of aryl alkyl ketones at room temperature. The results are listed in Table 2. Acetophenone is hydrosilylated cleanly with good ee

Table 2. Asymmetric Hydrosilylation of Prochiral Ketones Catalyzed by Cu−Al Hydrotalcite and BINAP at Room Temperature

entry	substrate	time (h)	yield (%)[b]	ee (%)[c]
	R_1—⬡—C(=O)R_2			
1	R_1 = H, R_2 = Me	5	87	82
2	R_1 = 4-Br, R_2 = Me	4	86	97
3	R_1 = 3-Br, R_2 = Me	24	30	82
4	R_1 = 2-Br, R_2 = Me	5	81	52
5	R_1 = 4-Cl, R_2 = Me	5	78	94
6	R_1 = 3-Cl, R_2 = Me	24	70	77
7	R_1 = 2-Cl, R_2 = Me	5	92	59
8	R_1 = 4-F, R_2 = Me	5	75	86
9	R_1 = 4-CN, R_2 = Me	7	81	73
10	R_1 = 4-NO_2, R_2 = Me	10	30	85
11	R_1 = 4-CF_3, R_2 = Me	9	68	97
12	R_1 = 3-CF_3, R_2 = Me	24	36	84
13	R_1 = 4-Me, R_2 = Me	9	91	83
14	R_1 = 3-Me, R_2 = Me	24	62	76
15	R_1 = 2-Me, R_2 = Me	7	86	62
16	R_1 = 2-OMe, R_2 = Me	18	51	73
17	R_1 = H, R_2 = Et	24	88	84
18	R_1 = 4-Cl, R_2 = Et	16	65	94
19	(tetralone structure)	28	58	87
20	(2-acetonaphthone structure)	11	69	79
21	(1-acetonaphthone structure)	11	62	62

[a] Reaction conditions: substrate (1 mmol), PMHS (4 mmol), Cu−Al hydrotalcite (10 mg), toluene (3 mL), BINAP (7 mg). [b] Isolated yields. [c] Absolute configurations were determined to be S.

(Table 2, entry 1). Introduction of an electron-withdrawing group at the para-position produced an increase in ee, and a shorter reaction time was required for completion of the reaction (Table 2, entries 2, 5, 8, 9, 11, and 18).

Conversely, the presence of an electron-donating group at the para-position (Table 2, entry 13) has little effect on enantioselectivity but requires longer reaction time for full conversion. Another important observation is the dependence of enantiomeric excess on the position of the substituent group (irrespective of electron-withdrawing or electron-donating) of the acetophenone. The ee value was highest when the substituent group was present at the para-position of the acetophenone rather than at the meta-position, which in turn was higher than at the ortho-position (Table 2, entries 2−7). This demonstrates the ability of steric hindrance of meta- and ortho-substituents to modify the enantiomeric excess of the reaction, which is in contrast to the recently reported asymmetric hydrogenation of aryl ketones catalyzed by copper catalyst reported by Shimizu et al., where the obtained ee was highest in the case of ortho-substituted substrates.[5f] Sterically demanding 2-acetonaphthone and 1-acetonaphthone (Table 2, entries 20 and 21) also afforded good yields with excellent enantioselectivity. When the methyl group of the aryl alkyl ketone is substituted with an ethyl group, the asymmetric hydrosilylation reaction still gave excellent enantioselectivity, albeit with moderate yields (Table 2, entries 17 and 18). It is significant to note that different substituents like fluoro, bromo, chloro, and nitro (Table 2, entries 2−8 and 10) were not affected during the hydrosilylation reaction.

Catalyst-recycling experiments were also carried out, using 4-methylacetophenone as a model substrate. As can be seen in Table 3, the catalyst A was used for three cycles without

Table 3. Method for Recycling Catalyst **A**[a]

run	time (h)	yield (%)[b]	ee (%)[c]
1	9	91	83
2	9	85	80
3	9	83	81

[a] Reaction conditions: 4-methylacetophenone (1 mmol), PMHS (4 mmol), Cu−Al hydrotalcite (10 mg), toluene (3 mL), BINAP (7 mg). [b] Isolated yields. [c] Absolute configurations were determined to be (S).

loss of activity and selectivity. No reaction occurred when the reaction was conducted with the filtrate obtained after removal of the solid catalyst. This indicates that the active catalyst species was not leached out of the solid catalyst.

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Atomic absorption spectroscopy (AAS) was employed to determine the copper content of the catalyst A, and it was found to be 34.11 wt %. The leaching of the metal after the first cycle was determined by AAS and was found to be negligible (0.0149%).

The plausible mechanism of hydrosilylation may be through the formation of copper hydride species from the reduction of ligated Cu−Al hydrotalcite by PMHS. At this stage, we are not sure whether the active catalytic species is copper(I) or copper(II) hydride.[11b] X-ray photoelectron spectroscopic (XPS) investigations of fresh Cu−HT and Cu−Al hydrotalcite treated with the BINAP ligand at the Cu 2p level shows $2p_{3/2}$ lines at 934.3 and 934.4 eV, respectively. This corresponds to a +2 oxidation state (Figure 2).[16]
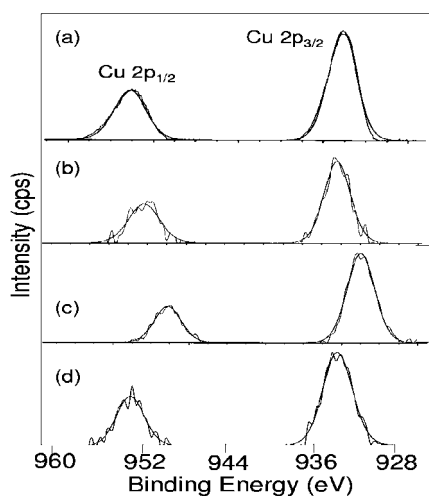
Figure 2. XPS high-resolution narrow scans of Cu $2p_{3/2}$ for (a) fresh Cu−HT, (b) Cu−HT treated with BINAP, (c) recovered catalyst under inert conditions, and (d) recovered catalyst at normal conditions.

However, XPS spectra of the recovered catalyst after the reaction under inert conditions show Cu $2p_{3/2}$ peaks at 933.1 eV, which correspond to Cu in the +1 oxidation state. The copper hydride species reacts with the ketone, resulting in the formation of copper alkoxide, and subsequently under-goes σ-bond metathesis with the organosilane to afford the silyl ether (Scheme 2).[8a,11b] The XPS spectra of the recovered catalyst at normal conditions show the $2p_{3/2}$ peak at 934.3 eV, which corresponds to Cu in the +2 oxidation state only. This is probably due to the reoxidation of Cu(I) to Cu(II) under normal conditions.[17]

The present protocol has several advantages. A heterogeneous and recyclable catalyst, namely, copper− aluminum

Scheme 2. Possible Mechanism of Asymmetric Hydrosilylation Catalyzed by Cu−HT
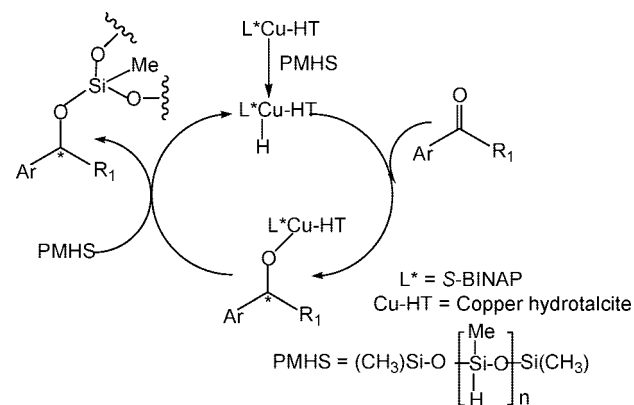
hydrotalcite, is used for the asymmetric hydrosilylation of ketones. A high level of ee can be obtained by using an inexpensive and nontoxic reducing agent such as PMHS at room temperature using commercialy available BINAP as the chiral auxiliary. The catalyst can be activated by the hydrosilylating reagent itself and thus obviates the need to use alkoxide bases.

In conclusion, enantioselective hydrosilylation of ketones to afford chiral secondary alcohols with good yields and excellent enantioselectivities using Cu−Al hydrotalcite and BINAP in the presence of PMHS as the stoichiometric reducing agent is reported.[18] No inorganic base was required for the activation of the catalyst.

Supporting Information Available: General experimental procedures and characterization data of products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(18) **Representative Procedure for the Asymmetric Hydrosilylation of Ketones by Cu−Al hydrotalcite:** Cu−Al hydrotalcite (0.010 g) and (*S*)-BINAP (0.01 mmol, 0.007 g) were placed in a dried Schlenk tube containing dry toluene (3 mL) at room temperature and stirred for 1 h under a nitrogen atmosphere. PMHS (4 mmol, 0.24 mL) was then added dropwise and allowed to stir for 30 min. To the reaction mixture, ketone (1 mmol) was added, and stirring was continued. After completion of the reaction (monitored by TLC), the reaction mixture was centrifuged to separate the catalyst and washed several times with ether. The catalyst was reused for another cycle after vacuum drying. The reaction mixture was quenched with water and transferred to a round-bottom flask with the aid of Et$_2$O (10 mL), and then tetrabutylammonium fluoride (TBAF) (1.0 M in THF, 1.2 mL) was added. The reaction mixture was stirred vigorously for 0.5 h. The layers were separated, and the aqueous layer was extracted with ether. The combined organic layers were dried over MgSO$_4$, and the solvent was removed under reduced pressure. The residue was purified by silica gel flash column chromatography (eluent: hexane/ethyl acetate) to afford the desired product.