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Efficient Enantioselective Hydrosilylation of Aryl Ketones Catalyzed by a Chiral BINAP-Copper(I) Catalyst-Phenyl-(methyl)silane System

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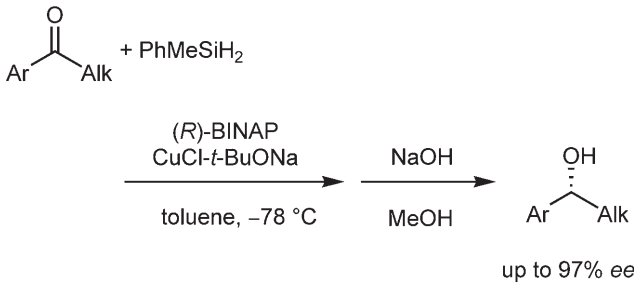
Abstract: The Cu(I)-chiral diphosphine (BINAP) system was found to efficiently catalyze the hydrosilylation of aryl alkyl ketones with excellent enantioselectivities by using phenyl(methyl)silane as stoichiometric hydride source.

Keywords: asymmetric catalysis; copper; hydride; hydrosilylation

Chiral secondary alcohols are important intermediates in organic synthesis whether for the development of biologically active molecules or in the fields of agrochemicals, fragrance and flavour. Catalytic asymmetric reduction of prochiral ketones using transition metal complexes (i.e., hydrogenation, hydrogen transfer or hydrosilylation) appears to be the most attractive way for the production of such chiral non-racemic molecules.[1]

Early works on hydrosilylation reactions involving rhodium-phosphine systems[2] have led to the development of several efficient systems that achieve high levels of enantiomeric excess (above 90%).[3,4] Systems involving ruthenium complexes may also afford good enantioselectivity.[5] More recently, efficient asymmetric hydrosilylation reactions using cheaper and less toxic metals such as zinc,[6] titanium[7] and copper[8] have been reported. Brunner and Miehling first introduced the use of copper hydride along with a chiral phosphine for asymmetric hydrosilylations.[9] Since then, an important breakthrough was accomplished by Lipshutz and co-workers.[8,10] Thus, when coordinated by a highly sterically demanding BIPHEP- or SEGPHOS-type ligand, CuH appears to be an efficient catalyst for the hydrosilylation of ketones with a high level of enantioselectivity. Moreover, inexpensive silanes such as PMHS can be used. Among the ligands tested, readily available and cheap BINAP was found to give a lower level of enantioselectivity (e.g., 75% *ee* with acetophenone).[11]

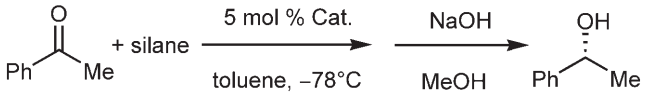
We here report the asymmetric reduction of various aryl alkyl ketones catalyzed by a BINAP-Cu(I)-silane system with a high level of enantioselectivity (Scheme 1). The choice of the silane substrate appears to be crucial and enantiomeric excesses up to 97% are observed when commercially available $PhMeSiH_2$ is used as a stoichiometric reducing agent.



Scheme 1. Asymmetric reduction of ketone.

We used the hydrosilylation of acetophenone as a reference reaction to test the potential of the (*R*)-BINAP/CuCl/*t*-BuONa system (generated *in situ*).[12] As an initial study, we noticed that the level of enantioselectivity is highly dependent on the nature of the silane (Table 1). A similar *ee* to that reported in previous results is observed for diphenylsilane (Entry 1).[8,11] In general, a significant increase of the steric bulk of the aromatic group provokes a decrease of the enantiomeric excess (Entries 2–4) while the use of aryl(alkyl)silanes improves it (Entries 5 and 6). In particular, we found that the hydrosilylation of acetophenone is highly enantioselective in the presence of $PhMeSiH_2$ or $Ph(t\text{-Bu})SiH_2$. The commercial availability of phenyl(methyl)silane prompted us to use this silane for further studies. A study of reaction parameters for these reactions showed that toluene as a sol-

Table 1. Asymmetric hydrosilylation of acetophenone with the (*R*)-BINAP/CuCl/*t*-BuONa system by various silanes.



Entry	Silane	*ee* [%] at room temperature	−78 °C
1	Ph_2SiH_2	76	80
2	$(Mes)_2SiH_2$	78	79
3	(1-naphth)$PhSiH_2$	0	3
4	(*o*-tol)$PhSiH_2$	79	91
5	$PhMeSiH_2$	81	93
6	Ph(*t*-Bu)SiH_2	79	93

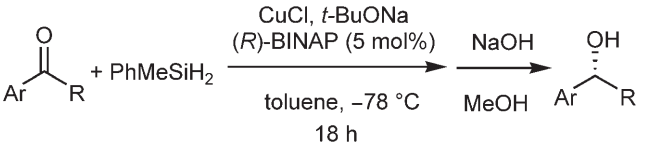
Cat.: CuCl, *t*-BuONa, (*R*)-BINAP; reaction time: 18 h; *ee* values were determined by chiral GC analysis.

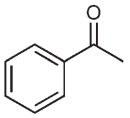
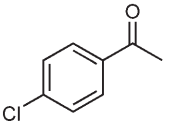
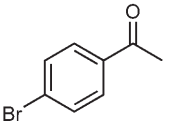
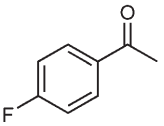
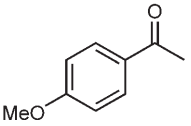
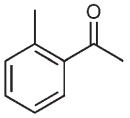
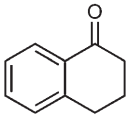
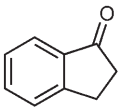
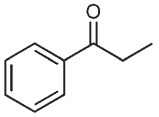
vent and a −78 °C reaction temperature are the optimal conditions for enantioselectivity.

Similarly, high enantioselectivities were obtained in the reduction of a variety of aryl alkyl ketones under these optimized reaction conditions (Table 2). For all substrates, the reductions were completed within 18 h using 5 mol % catalyst and 2 equivalents of silane. Ketone derivatives (Entries 2–5) exhibiting different steric or/and electronic properties are reduced with exceptional *ee* and yields. Propiophenone is also reduced with good enantioselectivity and yield (entry 9). As anticipated, this system seems to be limited to aryl alkyl ketones. For example, the reduction of phenyl-3-butanone proceeds with a good yield (92 %) but a low enantioselectivity (5 % *ee*).

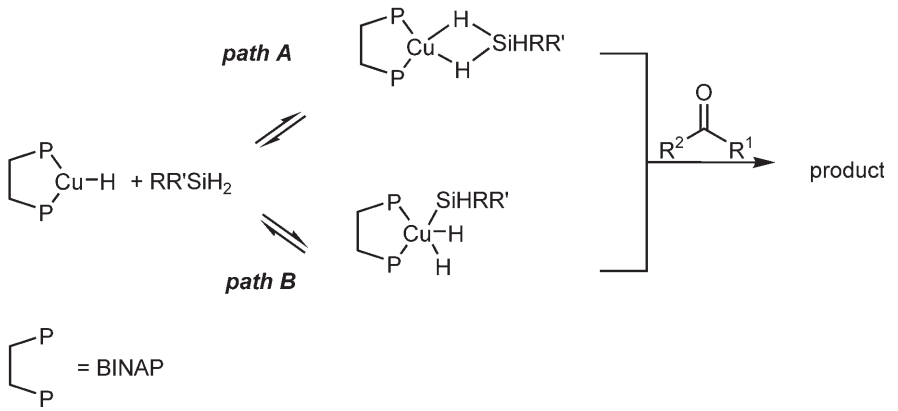
The strong dependence of the enantioselectivity on the nature of the silane is of great importance with regards to the mechanism of the Cu(I)-catalyzed hydrosilylation reaction. The classically proposed mechanism involves the insertion of the ketone into the Cu–H bond, followed by a metathesis process between the copper alkoxide and the silane to yield the corresponding silyl ether with concomitant regeneration of the Cu–H catalyst. From the results reported here, it becomes clear that this mechanism is not sufficient to account for the silane effect. Moreover, the reduction of ketone does not take place in the presence of a stoichiometric amount of (BINAP)CuH. This result is in accordance with Lipshutz's observations: thus, no reaction occurs when propiophenone was reacted with a stoichiometric amount of $(Ph_3P)CuH$.[8] On this basis, the authors concluded that the silane should be an integral part of the catalyst and postulated that a silyl-hydrido-cuprate salt species may act as the active catalyst. To gain further insight on the mechanism of this hydrosilylation reaction, kinetic studies using acetophenone as a substrate were carried out. Thus, the kinetic dependence measured at 298 K in toluene was found to obey the following rate equation: $v_i = k[cat.][silane][ketone]$.[13]

Table 2. Asymmetric hydrosilylation of aryl alkyl ketones by $PhMeSiH_2$ with the (*R*)-BINAP/CuCl/*t*-BuONa system (5 mol %).



Entry	Ketone	*ee* [%]	Yield [%]
1		93	99
2		96	99
3		97	90
4		96	99
5		92	75
6		87	92
7		65	75
8		94	80
9		97	91

Based on the observed results, two plausible mechanisms can be proposed (Scheme 2): (i) an oxidative addition of the silane to the copper(I) hydride complex in order to generate a copper(III) intermediate (path A)[14] or (ii) (BINAP)CuH may interact with one equivalent of silane to form a pentacoordinate silicon[15] intermediate species (BINAP)CuH_2Si-



Scheme 2. Possible mechanism that accounts for the silane effect.

(HMePh), which would then be able to react with the ketone (path B). Further studies are required to fully understand the mechanistic pathway.

In summary, we have shown that the enantioselectivity of hydrosilylation reactions mediated by Cu(I) systems is strongly dependent upon the nature of the silane. Among the tested silane substrates, phenyl(methyl)silane appears to be the most promising candidate. Thus, the combination of this silane with a catalytic amount of Cu(I)/BINAP catalyst is a remarkably efficient system for the highly enantioselective hydrosilylation of aryl alkyl ketones. Two likely mechanisms for this reaction may be proposed on the basis of kinetic studies; however, further studies are needed and will be the focus of our work in this area.

Experimental Section

General Procedure for the Hydrosilylation Reaction (Table 2, entry 1).

A Schlenk tube was charged with CuCl (0.025 mmol), NaO-*t*-Bu (0.025 mmol) and (*R*)-BINAP (0.025 mmmol). Dry toluene was added under argon (5.0 mL) and the solution was stirred for 20 min at room temperature. After cooling to −78 °C, the silane ($PhMeSiH_2$, 1.0 mmol) was added dropwise followed by the acetophenone (0.5 mmol). The yellow solution was stirred at −78 °C for 16 h. Upon completion, a solution of NaOH in methanol was added (2 mL, 1.0 M) and the resulting mixture was stirred for 1 h at room temperature. Column chromatography provided the desired alcohol; yield: 60.4 mg (99 %). GC analysis on a chiral column gave a 93 % *ee* (*R*). The absolute configuration was determined by comparison of the optical rotation with literature values.

Acknowledgements

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[12] Two equivalents of silane were used in order to increase the reaction rate. In principle, both hydrides of $PhMeSiH_2$ can be used for the reduction. However, when only 0.5 equivalent of silane was used, 50% of alcohol was isolated indicating that only one H is reactive toward reduction.

[13] Note: the temperature dependence of the *ee* values was found to be linear from −78 °C to room temperature. This indicates that the rate-determining step remains the same over this range of temperature.

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