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Efficient Enantioselective Hydrosilylation of Ketones Catalyzed by Air Stable Copper Fluoride–Phosphine Complexes

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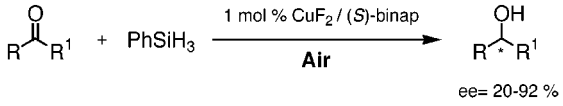
ABSTRACT



Copper(II) fluoride–chiral diphosphine systems catalyze the hydrosilylation of several ketones with moderate to excellent enantioselectivities. An oxygen acceleration effect was observed and led to a practical protocol with low catalyst loading.

The selective reduction of unsaturated double bonds (C═O, C═N, C═C) catalyzed by homogeneous transition metal complexes is of great interest in organic synthesis.[1] Hydrosilanes, which are by themselves inert toward nonactivated carbonyl compounds, become suitable reductive agents for the hydrosilylation of these compounds in the presence of catalytic amounts of rhodium or titanium complexes.[2] However, in most cases, the cost of the catalysts as well as the rigorously anaerobic conditions required in those reactions have limited their use in the laboratory. More recently, new methods for the asymmetric hydrosilylation of prochiral ketones using inexpensive hydride sources such as PMHS (polymethylhydrosiloxane) and easily accessible catalysts based on titanium,[3] zinc,[4] and tin[5] have opened a new pathway in this area in the view of practical applications.

The potential of copper for hydride delivery was recognized early, but it had mainly been used as a stoichiometric reducing agent. It was later shown that phosphine−copper(I) systems such as $[CuH(PPh_3)]_6$ or $CuCl/PPh_3/Bu_4NF$ act as a catalyst for the hydrogenation as well as the 1,4-reduction of enones or enals in combination with silanes.[6] Related work on copper(I)−phosphine systems has shown that highly enantioselective 1,4-reduction of α,β-unsaturated esters (80−92% enantiomeric excess (ee)) and cyclic enones (87−98% ee) can be achieved with a catalyst formed from CuCl/NaO*t*Bu/chiral diphosphine (binap or BIPHEMP) and PMHS.[7] Very recently, Lipshutz has also demonstrated the effectiveness of $[CuH(PPh_3)]_6$ for the hydrosilylation of aromatic and nonconjugated aldehydes and ketones.[8] This report prompted us to display our own results on the

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asymmetric hydrosilylation of prochiral ketones by easy-to-handle copper-based catalysts.

We report here the asymmetric reduction of ketones by a copper-catalyzed hydrosilylation reaction. On a preliminary screening, various copper salts and ligands were combined and tested in hydrosilylation of acetophenone when using phenylsilane as a stoichiometric reducing agent (Figure 1).

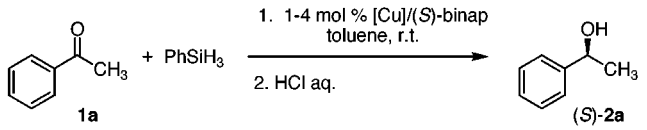

Figure 1. Asymmetric hydrosilylation of acetophenone catalyzed by modified copper fluoride catalysts.

A study on the reaction parameters led us to point out some special features (Table 1). First, it was shown that a fluoride ligand on the copper precursor was essential to generate an active catalyst. Thus, combinations of diphosphine ligands with either copper(II) or copper(I) fluoride precursors (CuF_2 or $[CuF(PPh_3)_3]$) gave short reaction times at low catalyst loadings. No reaction was observed when other copper halides were used. However, when copper(I) iodide was combined with binap and an anhydrous fluoride source (entry 8), some catalytic activity was restored. It was also noted that the use of a diphosphine ligand was crucial for the catalytic activity as monophosphine- and bidentate nitrogen-based ligands did not show any activity. Among the various diphosphines tested, the best results were obtained with dppb and binap. It should also be noted that the copper fluoride sources used are stable to the atmosphere and can be either bought (CuF_2) or easily prepared ($[CuF(PPh_3)_3]$).[9]

Table 1. Hydrosilylation of Acetophenone by Diphosphine-Modified Copper Fluoride Catalysts[a]

entry	precursor (mol %)	atm.	time (h)	conv. (%)[b]	ee (%)
1	CuF_2/dppb (2)	Ar	8	90	
2	CuF_2/dppb (2)	air	2	99	
3	CuF_2/(*S*)-binap (4)	Ar	16	>99	79
4	CuF_2/(*S*)-binap (1)	air	2	98	78
	CuF_2/(*S*)-binap (0.5)		6	94	78
5	$[CuF(PPh_3)_3$·MeOH]/dppb (4)	Ar	2	90	
6	$[CuF(PPh_3)_3$·MeOH]/(*S*)-binap (4)	Ar	40	91	71
7	$[CuF(PPh_3)_3$·MeOH]/(*S*)-binap (2)	air	1	100	74
8	$CuI/Ph_3SiF_2NBu_4$/(*S*)-binap (1)	Ar	24	40	76
9	$[PPh_3CuH]_6$/(*S*)-binap (2)	Ar	16	95	80
10	CuF_2/(*S*)-binap (4)[c]	air	54	93	74
11	CuF_2/(*S*)-binap (4)[d]	air	24	94	76
12	CuF_2/(*S*)-binap (4)[e]	Ar	24	100	72

[a] Reactions were conducted at room temperature with acetophenone (0.25 M), toluene, and $PhSiH_3$ (1.2−1.5 equiv) except when another silane is indicated. [b] Determined by GC. [c] PMHS (5 equiv) and acetophenone (1 M). [d] PMHS (5 equiv) and acetophenone (1M in THF). [e] $Me(EtO)_2SiH$ (1.5 equiv).

At this stage, the role of the fluoride is still unclear, but some control experiments allowed us to think that it acts essentially in the initiation step of the catalytic cycle by activating the Si−H bond to generate a copper(I) hydride species. This hypothesis was supported by the fact that the combination of a copper hydride complex $[CuH(PPh_3)]_6$ and binap showed a significant catalytic activity, while no conversion was obtained when $[CuH(PPh_3)]_6$ was used alone (entry 9). However, this should be supported by some spectroscopic evidence of the generation of a copper hydride complex.

The most important feature of the present CuF_2/diphosphine/hydrosilane system is that experiments are preferably run in air. Not only is the system air stable, at least for the reaction time, but also the reactivity is highly enhanced when the reaction is carried out under oxygen instead of an argon atmosphere (entries 1−4). While 16 h were needed to reach complete conversion of acetophenone with 4 mol % CuF_2 and (*S*)-binap under argon (entry 3), a reaction carried out in air was complete after 2 h with only 1 mol % catalyst and without loss of the enantioselectivity (entry 4). This acceleration effect was even more pronounced when $[CuF(PPh_3)_3$·MeOH] was used as a copper source (entries 6−7). This observed reactivity contrasts the reported sensitivity of copper hydride to oxygen.[7a,10] Although we are not able at the present time to explain this effect, it seems that oxygen plays a role in the formation of the precatalyst at the early stage of the catalytic cycle.[11]

Finally, we have tried various silanes with almost no effect on the enantioselectivity. While the trihydrophenylsilane $PhSiH_3$ is the most active reducing agent with our catalytic system, two cheaper and readily available siloxanes can be employed, i.e., PMHS (entries 10 and 11) and methyldiethoxysilane, $Me(OEt)_2SiH$ (entry 12), albeit with slower reaction rates.

After optimization, we were able to build up a practical and low-cost catalytic protocol for the asymmetric hydrosilylation of ketones. It should be noted that undried glassware and undistilled toluene can be used as the system is quite compatible with the presence of traces of water. Low catalyst loading (as low as 0.5 mol % CuF_2/binap) can be used in some cases (Table 1, entry 4). Several ketones could be converted in their corresponding secondary alcohols by using anhydrous CuF_2 and (*S*)-binap in toluene at room temperature, in the presence of phenylsilane (Figure 2, Table 2).[12]

(9) $[CuF(PPh_3)_3$/MeOH] is easily prepared from hydrated copper(II) fluoride: Gulliver, D. J.; Levason, W.; Webster, M. *Inorg. Chim. Acta* **1981**, *52*, 153−159. The use of unmodified $[CuF(PPh_3)_3$·2EtOH] for the reduction of ketones by hydrosilanes was first reported by Mori in stoichiometric conditions: (a) Mori, A.; Fujita, A.; Nishihara, Y.; Hiyama, T. *Chem. Commun.* **1997**, 2159−2160. (b) Mori, A.; Fujita, A.; Kajiro, H.; Nishihara, Y.; Hiyama, T. *Tetrahedron* **1999**, *55*, 4573−4582.

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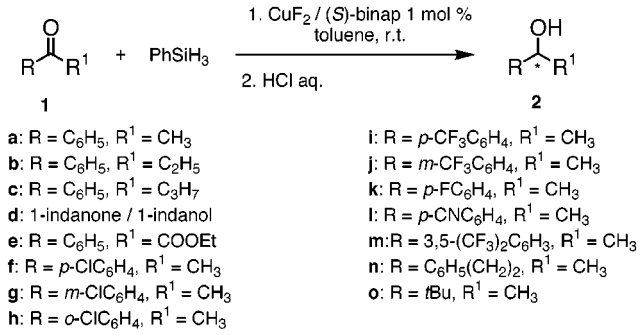

Figure 2. Asymmetric reduction of ketones.

Complete reduction of aromatic ketones proceeds in a few hours (2−14 h) with excellent enantioselectivities (ee up to 92%). In general, 1 mol % Cu was used for the complete reduction of the substrate. However, in some cases, complete conversion required an increase of the catalyst loading to 2 mol % (entry 4). Under the conditions used, several functional groups (e.g., ester, halides, cyanide, CF_3) remained unaffected. The reaction proceeds cleanly to give the corresponding aromatic alcohols after hydrolysis. Introduction of withdrawing para-substituents on acetophenone (**1f**, **1i**, **1k**, **1l**) produced a small amelioration of enantioselectivity (82−86% ee), while total conversion was reached in 3−8 h.

Different groups (Me, Et, Pr, COOEt, CF_3, cyclic chain) in an α-position to the carbonyl were also examined. The α-ketoester **1e** was selectively reduced to the corresponding α-hydroxyester **2e** with an excellent yield (100% in 3 h) but a very low ee (11%). Longer reaction times were required for bulkier alkyl groups (entries 2−3), while the enantioselectivity was slightly affected. It should also be noted that dialkyl ketones can be reduced under these conditions, albeit with reduced enantioselectivities (entries 14 and 15).

Table 2. Asymmetric Reduction of Ketones by $PhSiH_3$ Using CuF_2 and (*S*)-Binap, in Air[a]

entry	substrate	time (h)	conversion (%)[b]	yield of **2** (%)[c]	ee (%)[d]
1	**1a**	2	98	79	78 (*S*)
2	**1b**	9	97	82	84 (*S*)
3	**1c**	8	100	80	92 (*S*)
4	**1d**	14[e]	100	80	70 (*S*)
5	**1e**	3	100	99	11 (*R*)
6	**1f**	4	96	100 (7 h)	85 (*S*)
7	**1g**	8	63	97 (24 h)	75 (*S*)
8	**1h**	8	82	96 (20 h)	64 (*S*)
9	**1i**	3	100	89	86 (*S*)
10	**1j**	3	95	100 (6 h)	80 (*S*)
11	**1k**	4	100	100	82 (*S*)
12	**1l**	8	95	100 (16 h)	86 (−)
13	**1m**	3	100	88	85 (−)
14	**1n**	8	100	93	20 (*R*)
15	**1o**	29	75		20

[a] Reactions were conducted at room temperature with substrate (2 mmol, 0.25M), toluene (8 mL), CuF_2 (1%), (*S*)-binap (1%), and $PhSiH_3$ (1.2 equiv). [b] Substrate conversion determined by GC. [c] Isolated yield (time in parentheses for 100% conversion). [d] Determined by GC using a chirasil DEX CB column (25 cm × 0.25 mm × 0.25 μm). Absolute configurations were determined by comparison of optical rotations with literature values. [e] CuF_2 (2%) and (*S*)-binap (2%).

In conclusion, a practical and efficient method has been developed that allowed the asymmetric reduction of ketones in aerobic and mild conditions. The catalyst could be activated by the hydrosilylating agent itself. Moreover, the system displays a high level of functional group compatibility. Studies to clarify the reaction mechanism are underway in our laboratory.

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(12) General procedure for the hydrosilylation of ketones in air: a 25 mL round-bottomed flask was charged with copper fluoride (2 mg, 0.02 mmol, 1 mol %) and (*S*)-binap (13 mg, 0.02 mmol, 1 mol %), and a stirring bar was added in air. Toluene (8 mL) was added, and the mixture was stirred for 5−10 min. Phenylsilane (0.30 mL, 2.4 mmol, 1.2 equiv) and acetophenone (0.235 mL, 2 mmol) were sequentially added under vigorous stirring, and the flask was stoppered. Conversion and ee determination were followed by gas chromatography performed on aliquots. Hydrolysis of the silyl ether by 1 N HCl and workup gave the crude alcohol. Bulb-to-bulb distillation gave analytically pure product (194 mg, 79% yield). GC analysis on a chiral column gave a 78% ee.

New efficient Copper Fluoride-Based Catalyst for Enantioselective Hydrosilylation of Ketones in Aerobic Conditions

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Abstract. A new copper(II) fluoride–chiral diphosphines catalytic system was developed. This one is very efficient and selective for the hydrosilylation of several substituted or unsubstituted aromatic ketones in so far as moderate to excellent enantioselectivities were obtained. An oxygen acceleration effect was observed that led us to propose a practical protocol with a low amount of catalyst.

INTRODUCTION

The selective reduction of unsaturated double bonds (C=O, C=N, C=C) catalyzed by homogeneous transition metal complexes is of great interest in organic synthesis.[1] Hydrosilanes, which are by themselves inert towards nonactivated carbonyl compounds, became suitable reductive agents for the hydrosilylation of these compounds in the presence of catalytic amounts of rhodium or titanium complexes.[2]

Pioneer work in the field of asymmetric hydrosilylation was reported in the early 70s by the group of H.B. Kagan, who first described the hydrosilylation of prochiral ketones using Wilkinson's catalyst modified with DIOP.[3] For a long time the field was restricted to the use of rhodium and iridium complexes and chiral bidentate phosphine ligands. Recently, the asymmetric hydrosilylation of ketones has been studied extensively in relation to the rapid development of new chiral ligands.[4] Thus, enantiomeric excesses (ee) over 90% have been obtained for the reduction of aromatic ketones, between 60 to 90% for dialkyl ketones, and up to 97% for the 1,2-reduction of α,β-unsaturated ketones. The best processes rely mainly on three different systems: (i) chiral titanocene(IV) precursors activated to Ti(III) state, developed by Buchwald[5] and Harrod;[6] (ii) asymmetric zinc complexes, developed by Mimoun;[7] and (iii) Rh complexes bearing chiral nitrogen-based ligands, developed by Brunner, Nishiyama, and Itoh.[4b,8]

The hydrosilylation of aromatic ketones was performed with high ee (91–99%) by using rhodium catalysts containing chiral nitrogen-based polydentate ligands like pyridine-oxazolines, named Pymox[8a] and Pybox,[8b,c] but working at low temperatures, between 0 and –5 °C. Good enantioselectivities were also achieved with dimeric ferrocenyl-phosphines, named TRAP, at –30 to –40 °C, to reduce bulky dialkylketones (80–91% ee) and also enones to allylic alcohols (95% ee), ketoesters to alkoxyesters (69–93% ee), and diketones to (*2S*,*4S*)-diols (89–99% ee).[8d,e,f] Good ee from 60 to 89% were also obtained with dialkyl ketones at room temperature using Rh complexes of the chiral oxazolinylferrocene-phosphine ligand DIPOF.[9]

Remarkably high ee have been achieved in the hydrosilylation of aromatic ketones (up to 99%) and enones (84–97% ee) by PMHS (polymethylhydrosiloxane) using chiral titanocenes(IV) [(*R*,*R*,*R*-BTHIE)-TiX_2] (BTHIE = ethylenebis(tetrahydroindenyl)) first activated by *n*-BuLi[5a] (X_2 = binaphtholate) or by $PhSiH_3$

This paper is dedicated to Professor Henri B. Kagan in recognition of his pioneer work in asymmetric catalysis.

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and MeOH[5b] (X = F). However, these systems suffer from low to moderate enantioselectivities for the reduction of nonconjugated ketones (around 50% ee). It is interesting to notice that α,β-unsaturated ketones were reduced in a 1,2-fashion. In a broader study, ee up to 40–50% for certain dialkyl ketones were obtained with the opposite form of the catalyst prepared by alkylation of [(*S*,*S*,*S*-(BTHIE)Ti(binaphtholate)$_2$] with MeLi or *n*-BuLi.[6]

Several other chiral titanocene dichloride complexes have been employed as precatalysts in the hydrosilylation of aryl alkyl ketones by triethoxysilane with high yields but low ee (up to 40%). The precatalysts were reduced with 2 equiv of *n*-BuLi.[10]

Nakai also reported the asymmetric hydrosilylation of ketones with HSi(OEt)$_3$ using (*R*)-binol-Ti(O*i*-Pr)$_2$ as precatalyst. It offered the advantage of not requiring activation by alkyllithiums, but it was shown to proceed at a low rate and with moderate enantioselectivity.[11]

With some chiral ligands like bis-oxazoline, only moderate enantioselectivity in the reduction of aromatic ketones was obtained, either with a titanium fluoride precursor, TiF_4, in the presence of triethoxysilane (61–85% ee)[12] or with tin(II)triflate and PMHS in methanol (12–58% ee).[13] The product of this tin-based protocol is an alcohol and not a silyl ether as in titanium-, rhodium-, and zinc-catalyzed reactions, and a further advantage is that an activation step is not needed.

Finally, the last highly efficient system described for the asymmetric hydrosilylation of aromatic ketones with 64 to 88% ee is based on PMHS and zinc(II) species activated by chiral diamines.[7]

In most cases, it has been postulated that the involved active species is a metal hydride complex, although its exact nature was not determined.[2b,2e,5a,10–13] But free radical processes cannot be ruled out as being responsible for at least part of the products in these reactions.[5a]

A very interesting result is the recent discovery of the potential of copper for hydride delivery, mainly used as a stoichiometric reductant. A system consisting of copper(II) salts ($Cu(BF_4)_2$, $Cu(OTf)_2$, CuF_2, etc.) and hydrosilanes in a protic solvent (*i*-PrOH or MeOH) was used in substoichiometric conditions for the 1,2-reduction of acetylenic sulfones to *cis* vinylic sulfones.[14] However, this system was very inefficient for 1,4-reduction of enones.

The authors postulated that cationic copper(II) hydride species were generated in situ. Later, phosphine-copper(I) systems such as $[CuH(PPh_3)]_6$ or $CuCl/PPh_3/Bu_4NF$ were shown to act as catalyst for the preferential 1,4-reduction of enones or enals in combination with silanes.[15]

More recently, Lipshutz has also demonstrated the effectiveness of $[CuH(PPh_3)]_6$ on aromatic and non-conjugated aldehydes and ketones.[16] Related work on copper(I)-phosphine systems has shown that highly enantioselective 1,4-reduction of α,β-unsaturated esters (80–92% ee) and cyclic enones (87–98% ee) can be achieved with a catalyst formed from CuCl/NaO*t*-Bu/chiral diphosphines (BINAP or BIPHEMP) catalyst and PMHS.[17]

We recently reported a new, efficient copper fluoride-based catalyst for the enantioselective hydrosilylation of prochiral ketones, and we wish here to give a full account of the work performed on the optimization steps concerning this system.[18]

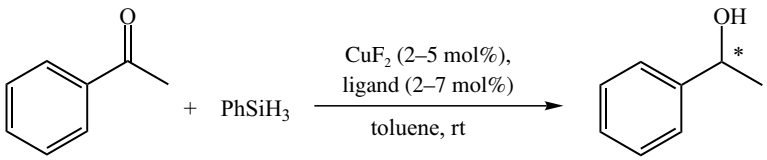
RESULTS AND DISCUSSION

Efficient Hydrosilylation in Achiral Conditions

Our first goal was to know if copper(II) fluoride (CuF_2) would be a good hydride source, the latter being generated in situ, in order to reduce a carbonyl double bond. Thus, in a preliminary study, the system CuF_2–$PhSiH_3$ was tested in association with various achiral ligands in the hydrosilylation of acetophenone (Scheme 1 and Table 1).

As stated, no reactivity was observed in the absence of a ligand (entry 1). Furthermore, monophosphines proved to be inefficient as well as various classes of bidentate nitrogen ligands (such as terpyridine, diimines, or bis-oxazolines).

Whereas monophosphines did not react (entries 2, 3), the use of diphosphines led to the shorter reaction time (3h), and the best reactivity was observed with diphenylphosphinobutane, dppb (entry 6). This ligand was retained for further optimization, and we noted a detrimental effect on the reactivity upon heating, which was attributed to fast decomposition of the catalyst (entry 10). At this stage of the optimization process, reproductibility of the catalytic process showed some disparities upon numerous assays. After careful screening



Scheme 1

Table 1. Hydrosilylation of acetophenone using CuF_2 and mono- or bidentate ligands in the presence of $PhSiH_3$[a]

entry	ligand	atm	time (h)	conv. (%)[b]
1	–	Ar	40	2
2	P(2-furyl)$_3$	Ar	40	4
3	P(*t*-Bu)$_3$	Ar	40	4
4	dppf	Ar	18	20
5	dppe[c]	Ar	8 (23)	75 (95)
6	dppb[d]	Ar	3	99
7	dppb[c]	Ar	8 (23)	90 (99)
8	dppb[e]	O_2	1.5	100
9	dppb[d]	air	1 (2)	84 (99)
10	dppb[f]	Ar	9	68

[a]Reactions were run using 1 mmol of acetophenone (0.23 M), $PhSiH_3$ (1.2–1.5 equiv), CuF_2 (5 mol%), ligand (7 mol%) in toluene at room temperature. [b]Conversion determined by GC. [c]CuF_2 (2 mol%), ligand (2 mol%). [d]CuF_2 (4 mol%), ligand (4 mol%). [e]CuF_2 (4 mol%), ligand (4 mol%) with a balloon of O_2. [f]reacted at 60 °C.

of the manipulation conditions, we found that the inadvertent introduction of air during the sampling of the reaction mixture led to an acceleration of the reaction. When the reaction was carried out in air or under pure oxygen (entries 8, 9), the effect was even more pronounced, and complete reduction occurred after 2 h using a 2 mol% catalyst. We can then conclude that the system is not only air stable, but it also shows strong acceleration when the reaction is carried out in aerobic conditions. At this stage, the role of oxygen is still unclear but it obviously plays a role in the formation of the active catalyst in the early stage of the reaction. NMR experiments showed that no complexation occurred when copper(II) fluoride and a diphosphine ligand are mixed together in toluene, as expected for a copper(II) salt. Upon addition of the silane under inert atmosphere, a black precipitate appears. This precipitate was assumed to be copper(I) hydride, which must be unreactive as a catalyst. When the reaction was carried out in air, no precipitate appeared and the reaction remained homogeneous throughout the reaction. We believe that the first effect of oxygen is to regulate the formation of the active catalytic species. These species are most likely formed by reduction of copper(II) to copper(I), followed by complexation by the diphosphine ligand. The exact structure of the catalyst still remains unclear and the exact role of oxygen in this unusual acceleration effect will require further mechanistic studies. It should be noted that a similar effect was recently observed by Magnus and Fielding,[19] who reported a strong acceleration effect by dioxygen on the Mn(III)-catalyzed hydrosilylation of ketones by phenylsilane.

These first results prompted us to test our copper fluoride system for the reduction of a range of aldehydes and ketones (Table 2). These experiments were carried out at the early stage of the optimization, and for a full comparison of the structural effects, all the reductions were performed under inert atmosphere.

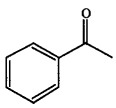
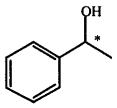
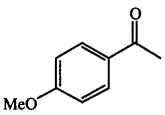
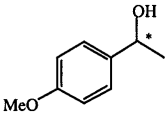
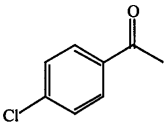
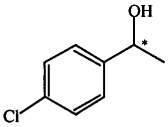
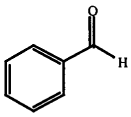
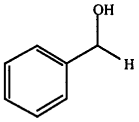
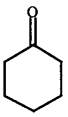
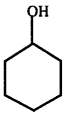
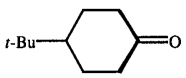
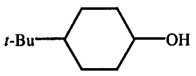
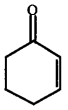
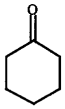
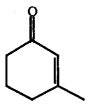
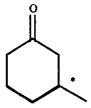
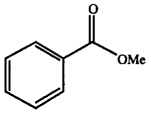
The method proved to be quite general for the reduction of aromatic or cyclic, substituted or not substituted, carbonyl compounds to the corresponding primary and secondary alcohols. Aromatic esters remained unchanged under these conditions (entry 9), and in the case of α,β-unsaturated cyclic ketones, selectivity of the reduction gave only the 1,4 addition product (entries 7, 8). In the case of aryl methyl ketones, introduction of an electron-withdrawing group at the *para* position did not affect the reactivity (entry 3), whereas a significant decrease in the reaction rate was observed when a *para* donating group was introduced (entry 2). However, this catalytic system proved to be quite efficient for the reduction of both aromatic and aliphatic ketones and thus, potentially interesting regarding developing a chiral version of our catalyst.

Efficient Hydrosilylation in Chiral Conditions

On a preliminary screening, various chiral bidentate ligands were tested in hydrosilylation of acetophenone using the previous conditions (Table 3).

Thus, retaining a 4 mol% amount of the copper(II) fluoride salt and a 1:1 copper/ligand ratio (unless otherwise stated), the reduction of acetophenone was carried out using a slight excess of phenylsilane under inert atmosphere. Most of the ligands used here are commercially available chiral diphosphines or were graciously provided from various sources (see Experimental Section). When comparing chiral diphosphines, best reactivities as well as enantioselectivities were reached with atropophosphines such as (*S*)-BINAP (entries 17–20), (*R*)-MeO-BIPHEP (entry 21) and (+)-tetraMe-BITIOP (entries 14, 15). The high reaction rates obtained with these ligands as well as the lack of reactivity displayed by other diphosphines with similar electronic properties such as (*R*)-PHANEPHOS (entries 6, 7) are a good indication that the byte angle of the diphosphine has a crucial influence on the reactivity of the catalytic species, presumably, a chelated copper(I) hydride.[20] Some assays were also run with chiral ligands where one of the phosphorus atoms was replaced by a nitrogen atom (entries 2, 5). In these cases, almost no reactivity was obtained with a phosphino-oxazoline backbone. As was already noted in the case of achiral ligands, oxygen has a strong influence on the reaction rate. This observation proved to be quite general for the diphosphines tested in this study. One interesting feature relies on the fact that

Table. 2. Reduction of various carbonyl compounds using CuF_2/dppb in the presence of $PhSiH_3$[a]

entry	substrate	product	time (h)	yield (%)[b]
1			3	98
2			22	82[c]
3			3	99
4			3	100
5			3	97
6			24	99 (cis/trans : 66/34)
7			3	100[c]
8			3	90[c]
9		-	24	1[c]

[a]Reactions were run using 3 mmol of substrate (0.23 M), CuF_2 (4 mol%), dppb (4 mol%), $PhSiH_3$ (1.2–1.5 equiv) in toluene at room temperature under argon atmosphere. [b]Yields given are isolated. [c]Converstion determined by GC.

in each case, if shorter reaction times were obtained to reach completion of the reaction, no difference was observed for the enantioselectivity whether the reaction was carried out in air or under inert atmosphere. At this point, we do not know if the oxygen acts as an oxidant in some complex redox step of the catalytic cycle or in the formation of a new reactive catalyst. Copper(I) complexes are known to be reactive toward dioxygen and this has been extensively studied in the case of copper enzyme models.[21] Running the reduction in air allowed us to reduce the catalyst amount to 0.5–1 mol% while retaining reasonable reaction time and the same enantioselectivity of the reduction product (entries 18, 19). When we attempted to further lower the catalyst-to-substrate ratio (i.e., to less than 0.5 mol%), the reaction usually stopped after reaching a certain conversion, due to a deactivation of the catalyst. We also checked the influence of water on the reaction, and it was found that the addition of water lowers the reaction rate, albeit without inhibiting the catalyst. Thus, the whole system is quite compatible with the presence of traces of water. All these observations are very important from a practical point of view, as the reduction can be carried out not only in air, but using glassware that is not dried and solvents that are not

Table 3. Asymmetric hydrosilylation using CuF_2 and chiral ligands in the presence of $PhSiH_3$ [a]

entry	ligand	atm	time (h)	conv (%)[b]	ee (%)[b]
1	–	Ar	40	2	–
2	(*R*,*S*)-QUIPHOS	Ar	24	0	–
3	(*R*,*R*)-Me-DUPHOS	Ar	40	20	2(*R*)
4	(*S*,*S*)-*S*UDPHOS	Ar	48	3	12(*R*)
5	A[c]	air	22	3	24(*R*)
6	(*R*)-PHANEPHOS	Ar	24	2	–
7	(*R*)-PHANEPHOS	O_2	24	7	69(*R*)
8	B[d]	Ar	40	92	22(*R*)
9	(*R*)-(*S*)-JOSIPHOS	Ar	24	97	19(*R*)
10	(*R*,*R*)-NORPHOS	Ar	70	13	10(*R*)
11	(*S*,*S*)-CHIRAPHOS	Ar	70	72	18(*S*)
12	(*S*,*S*)-DIOP	Ar	16	100	17(*S*)
13	(*S*,*S*)-DIOP[c]	air	3	92	15(*S*)
14	(+)-tetraMe-BITIOP	Ar	24	22	60(*S*)
15	(+)-tetraMe-BITIOP[c]	air	24	46	62(*S*)
16	(*S*)-*p*-Tol-BINAP[d]	Ar	24	96	81(*S*)
17	(*S*)-BINAP	Ar	16	99	79(*S*)
18	(*S*)-BINAP[e]	air	2	98	78(*S*)
19	(*S*)-BINAP[f]	air	6	94	78(*S*)
20	(+/-)-BINAP[g]	Ar	19	71	–
21	(*R*)-MeO-BIPHEP[c]	air	5	100	80(*R*)

[a] Reactions were run using 1 mmol of acetophenone (0.23 M), $PhSiH_3$ (1.2–1.5 equiv), CuF_2 (4 mol%), ligand (4 mol%) in toluene at room temperature. [b] Determined by GC. [c] CuF_2 (2 mol%), ligand (2 mol%). [d] Ligand (7 mol%), CuF_2 (5 mol%). [e] CuF_2 (1 mol%), ligand (1 mol%). [f] CuF_2 (0.5 mol%), ligand (0.5 mol%). [g] Realized in toluene and water (10 mmol) and (+/–)-BINAP.

distilled. It should be noted at this point that we obtained very reproducible results by using a simple experimental protocol with some chiral ligands such as BINAP. Although the best enantioselectivities reached for acetophenone were up to 81% (entry 16), it seems reasonable to think that structural variations on the BINAP structure as well as the use of related chiral atropophosphines[22] should lead to higher enantioselectivities.

Using the optimized CuF_2/(*S*)-BINAP system and phenylsilane as a reductant, other standard parameters such as solvent, temperature, and concentration were tested. While the use of chlorinated solvents inhibited the reaction, ethereal solvents such as THF gave results similar to toluene and could also be used. However, the use of protic solvents such as methanol gave a fast decomposition of the silane and had to be avoided. On the other hand, lowering the temperature to 0 °C strongly decreased the reaction rate, but without noticeable beneficial effect on the enantioselectivity. Also, the substrate concentration had very little effect on the course of the catalysis and no influence on the ee of the product.

In order to further understand the effective catalyst, several copper sources were tested using BINAP as ligand and phenylsilane as reductant. A study of some different precursors led us to point out some special features when the reaction was carried out under inert atmosphere (Table 4).

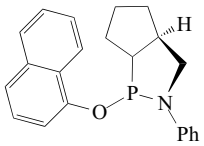
It was shown that the presence of fluoride on Cu(I) or Cu(II) precursor is necessary to obtain some activity (entries 1, 2) whereas with other copper halides, no reaction was observed (entries 3, 4). When a copper(I) or (II) salt was mixed with BINAP, followed by addition of an anhydrous fluoride source (entries 5, 6; one equiv fluoride per counteranion on copper), some catalytic activity was restored. The Strycker's reagent $[CuH(PPh_3)]_6$ (entries 7, 8) was also catalytically active when BINAP was used as additional ligand. This observation supports the hypothesis that the role of the fluoride relies essentially on the activation of the precatalyst to generate a copper(I) hydride catalyst.

In order to limit the cost of our catalytic system, we have tested some other silanes, especially PMHS, which is a safe and inexpensive reagent (Table 5). This silane has already proved to be highly efficient when used in the zinc-catalyzed hydrosilylation of ketones.[7] Thus, the replacement of phenylsilane by PMHS would potentially give an easy to handle and low cost procedure for the asymmetric reduction of prochiral ketones.

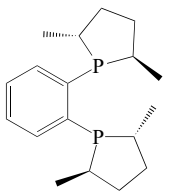
Table 4. Hydrosilylation of acetophenone with different precursors[a]

entry	precursor (mol%)	time (h)	conv (%)[b]	ee (%)[b]
1	CuF_2 / (+/-) BINAP (4)	16	99	79(S)
2	$CuF(PPh_3)_3$. MeOH /(S)-BINAP (5)	40	91	71(S)
3	$CuBr_2$ / (+/-)BINAP (4)	112	0	–
4	CuCl / (+/-)BINAP (4)	112	0	–
5	$Cu(OTf)_2$/ Ph_3SiF_2 Bu_4N (2eq.)/ (+/-)BINAP (4)	112	100	–
6	CuI / $Ph_3SiF_2Bu_4N$ (1 eq)/ (S)-BINAP (1)	24	40	76(S)
7	$[CuH(PPh_3)]_6$/ -	40	ε	–
8	$[CuH(PPh_3)]_6$ / (*S*)-BINAP (2)	16	95	80(S)

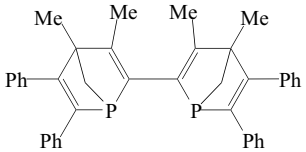
[a] Reactions were run using 1 mmol of acetophenone (0.23 M), $PhSiH_3$ (1.2–1.5 equiv) in toluene at room temperature under argon atmosphere. [b] Determined by GC.



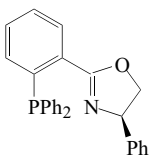
(*R*,*S*)-QUIPHOS



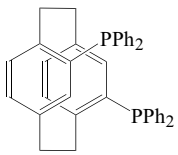
(*R*,*R*)-Me-DUPHOS



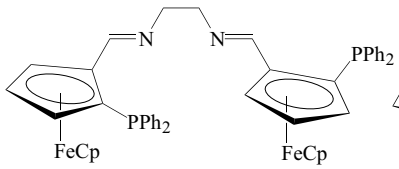
(*S*,*S*)-SUDPHOS



A



(*R*)-PHANEPHOS



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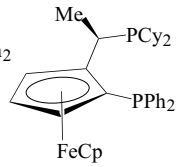
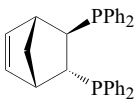
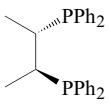


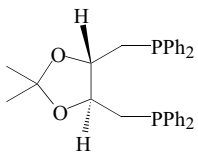
(*R*)-(*S*)-JOSIPHOS



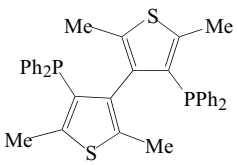
(*R*,*R*)-NORPHOS



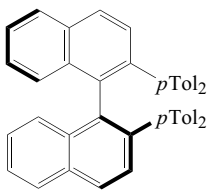
(*S*,*S*)-CHIRAPHOS



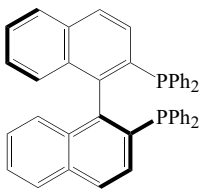
(*S*,*S*)-DIOP



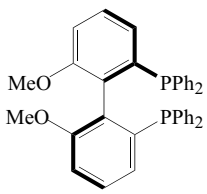
(+)-tetraMe-BITIOP



(*S*)-*p*-Tol-BINAP



(*S*)-BINAP



(*R*)-MeO-BIPHEP

Scheme 2. Different chiral ligands tested for the hydrosilylation.

Table 5. Hydrosilylation of acetophenone with different silanes [a]

entry	silane	atm (h)	time (%)[b]	yield (%)[b]	ee
1	$PhSiH_3$	Ar	16	100	80(*S*)
2	$PhSiH_3$	Air	2	98	78(*S*)
3	Ph_2SiH_2	Ar	24	83	76(*S*)
4	PMHS [c]	Ar	24	4	77(*S*)
5	PMHS [c]	Air	54	93	74(*S*)
6	PMHS [c,d]	Air	24	96	76(*S*)
7	$Me(OEt)_2SiH$	Ar	24	100	72(*S*)
8	$(OEt)_3SiH$	Ar	24	42	80(*S*)

[a] Reactions were run using 1 mmol of acetophenone (0.23 M), silane (1.5 equiv), CuF_2 (4 mol%), (S)-BINAP (4 mol%) in toluene at room temperature. [b] Determined by GC. [c] PMHS (5 equiv hydride per ketone), acetophenone (1M). [d] Reacted in THF.

Preliminary results showed that phenylsilane could be efficiently replaced by diphenylsilane (entry 3) and methyl diethoxysilane (entry 7). The standard procedure uses a slight excess of phenylsilane (1.2 equiv typically in the optimized procedure), for which three hydride units are potentially available. When the amount of phenylsilane was lowered to less than 1 equiv per substrate, the reaction time was strongly increased and deactivation of the catalysts occurred before completion of the reaction. The use of PMHS gave very poor reactivity when the reaction was carried out under inert atmosphere (entry 4). However, using a 4 mol% catalyst and 5 equiv PMHS (5 equiv hydride per ketone) in air in THF, the system was able to reach a full conversion in a reasonable time (entry 6).

In order to illustrate the versatility and the methodological value of our new asymmetric protocol for the hydrosilylation of ketones, we examined the reduction of various representative ketones using the CuF_2/(*S*)-BINAP/$PhSiH_3$ system in aerobic conditions (Scheme 3 and Table 6).

In general, 1 mol% of Cu was used for the complete reduction of the substrate. However, in some cases, complete conversion required an increase of the catalyst loading to 2 mol% (entry 15).

As shown in the table, the method is quite general for the asymmetric reduction of a wide range of ketones, and the secondary alcohols were isolated in good to excellent yield (79–100%) with high ee after purification.

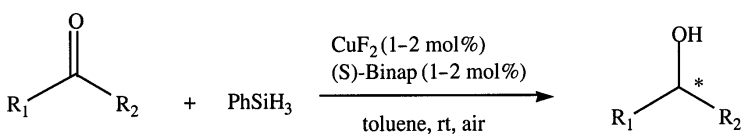
As the reduction of acetophenone is very efficient in 2 h with an ee of 78% (entry 1), the reactivity of some acetophenone derivatives with different alkyl groups (Et, *n*-Pr, *i*-Pr, COOEt) in α-position were examined. Thus, the reductions of 1-phenylpropanone **1b** and 1-phenylbutanone **1c** proceed to completion in 8–9 h with 84% and 92% (entries 2, 3), respectively, and an increase of the enantioselectivity was observed. However, when further increasing the bulkiness of the alkyl group, as with 2-methyl-1-phenylpropanone **1d**, reaction time is significantly longer to reach 78% conversion (entry 4) but with a good ee. However, a strong decrease in the enantioselectivity was obtained when an ester group was introduced next to the carbonyl but without modification of the reaction time (entry 5).

Introduction of withdrawing *para*-substituents on acetophenone (Cl, F, CF_3, CN) produced a small amelioration of the enantioselectivity (82–85%). With *p*-chloroacetophenone **1f**, *p*-fluoroacetophenone **1i**, *p*-trifluoroacetophenone **1j**, and *p*-cyanoacetophenone **1n** high conversion was reached in 3 to 8 h (entries 6, 9, 10, 14). The *meta*- or *ortho*-substituted acetophenones **1g**, **1h**, **1k**, and **1l,** were reduced with slower rates and a decrease of the enantioselectivities (entries 7, 8, 11, 12). Two hypotheses could be proposed to explain this observation; either the steric hindrance next to the C=O bond, or the position of the withdrawing substituent that could not really activate the C=O bond. So we can conclude that the enantioselectivity seems to decrease following the order *para* > *meta* > *ortho*. It should be noted that 1-(3′,5′-bis-trifluoromethyl-phenyl)ethanol **1m** bearing two withdrawing groups has rate (100% conversion in 3 h) and ee (85%) similar to *para*-substituted acetophenones (entry 13).

On the one hand, the results obtained with dialkyl ketones **1q**, **1r**, and **1s**, albeit with reduced enantioselectivities, are always comparable to those described in the literature with titanocene[5,9] and zinc[7] catalysts (entries 17, 18, 19). On the other hand, the cyclic ketones **1o** or **1p** were reduced with satisfactory ee (70–76%) (entries 15, 16). The reason for this increase could be that the ketone is very enhanced.

Finally, it must be noted that the reaction is very chemoselective in so far as several functional groups (e.g., ester, halides, cyanide, CF_3) remained unaffected.

In summary, we have developed a new, very efficient method that promotes the asymmetric reduction of



Scheme 3

Table 6. Asymmetric reduction of ketones using CuF_2/(*S*)-BINAP/$PhSiH_3$ in air [a]

entry	substrate R_1	substrate R_2		time (h)	conv (%) [b]	yield (%) [c]	ee (%) [b]
1	Ph	Me	**1a**	2	98	79	78(*S*)
2	Ph	Et	**1b**	9	97	82	84(*S*)
3	Ph	*n*-Pr	**1c**	8	100	80	92(*S*)
4	Ph	*i*-Pr	**1d**	18	78	–	81(*S*)
5	Ph	COOEt	**1e**	3	100	99	11(*R*)
6	*p*-ClC_6H_4	Me	**1f**	4	96	100	85(*S*)
7	*m*-ClC_6H_4	Me	**1g**	(8) 24	(63) 100	97	75(*S*)
8	*o*-ClC_6H_4	Me	**1h**	8	96	96	64(*S*)
9	*p*-FC_6H_4	Me	**1i**	4	100	100	82(*S*)
10	*p*-$CF_3C_6H_4$	Me	**1j**	3	100	82	86(*S*)
11	*m*-$CF_3C_6H_4$	Me	**1k**	(3) 6	(95) 100	100	80(*S*)
12	*o*-$CF_3C_6H_4$	Me	**1l**	6	50	–	39(*S*)
13	3′,5′-$(CF_3)_2C_6H_3$	Me	**1m**	3	100	88	85(–)
14	*p*-CNC_6H_4	Me	**1n**	8 (16)	95 (100)	100	86(–)
15	1-indanone [d]		**1o**	14	100	80	70(*S*)
16	1-tetralone		**1p**	24	74	–	76(*R*)
17	*t*-Bu	Me	**1q**	30	75	–	20(–)
18	*n*-Bu	Me	**1r**	24	93	–	7(–)
19	$C_6H_4(CH_2)_2$	Me	**1s**	8	100	93	20(*R*)

[a] Reactions were run using 2 mmol of substrate (0.23 M), $PhSiH_3$ (1.2 equiv), CuF_2 (1 mol%), (*S*)-BINAP (1 mol%) in toluene at room temperature in air. [b] Determined by GC. [c] Isolated yields. [d] CuF_2 (2 mol%), (*S*)-BINAP (2 mol%).

ketones in alcohols with a high level of compatibility with numerous groups. This system is used under aerobic and mild conditions. In order to clarify the reaction mechanism, some studies are now underway in our laboratory.

Note added in proof: After the submission of the article, the group of B.H. Lipshutz published a new efficient method for enantioselective hydrosylilation of ketones with copper(I)/sodium *tert*-butoxide/diphosphine catalysts and using PMHS as a reducing agent.[24] High ee were reached when a modified xylyl-BIPHEP was used as a chiral ligand, showing that the key paramaters in those reactions strongly depend on the choice of ligand.

EXPERIMENTAL SECTION

General Techniques

Toluene and THF were distilled under argon over sodium wire before use. Proton nuclear magnetic resonance spectra were recorded on a Varian GEMINI at 200 MHz, with TMS as internal standard and $CDCl_3$ as solvent. *J* values are given in Hz, δ are given in ppm.

Enantiomeric excesses were determined by GC analysis using a CHIRASIL cyclodextrine B column (25 m × 0.25). Optical rotations were recorded on a Perkin Elmer 241 MC polarimeter.

Ketones, silanes, ligands, and CuF_2 were purchased from Acros, Sigma-Aldrich and Strem. $CuF(PPh_3)_3$. MeOH was prepared.[23] The following ligands were generously provided by Chirotech Company (Phanephos), Rhodia Company (Sudphos), Prof. I.E. Marko (tetraMe-Bitiop), and Dr. J.M. Brunel (Quiphos).

General Procedure

Hydrosilylation of ketones under air atmosphere. A 25 mL round-bottomed flask, equipped with a magnetic stirrer, was charged with solid copper fluoride (2 mg, 0.02 mmol, 1 mol%), (*S*)-BINAP (13 mg, 0.02 mmol, 1 mol%). Toluene (8 mL) was added and the mixture was stirred for 30 min. The phenylsilane (0.30 mL, 2.4 mmol, 1.2 equiv) and then the substrate (2 mmol) were sequentially added under vigorous stirring, and the flask was stoppered. Conversion and ee were followed by gas chromatography on aliquot sample (hydrolyzed by 1 mL of aqueous HCl 1 M and filtered through a plug of silica). The reaction mixture was quenched and thus the silyl ether hydrolyzed by adding 5 mL of aqueous HCl 1 M. The product was then extracted with Et_2O. The combined organic layers were dried on $MgSO_4$ and the solvent was concentrated in vacuo. The crude product was purified by Kugelrohr distillation bulb-to-bulb or by column chromatography to give an analytically pure product characterized by ^1H NMR and optical rotation.

Hydrosilylation of ketones under argon atmosphere. CuF_2 and a ligand were placed in a Schlenck or a round-bottomed flask, previously dried in an oven at 150 °C overnight and purged under argon. The flask was replaced under argon atmosphere and toluene was added. The mixture was stirred for

30 min, then the silane and the substrate were sequentially added under vigorous stirring. Aliquots were taken under a flow of argon. The procedure described above was followed.

The absolute configurations of the chiral alcohols were determined by the sign of their optical rotation and comparison with published values.

*(*S*)-1-Phenylethanol (**2a**)*. 78% ee; 79% yield; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.50 (d, *J* = 6.5 Hz, 3 H); 1.80 (br s, 1 H); 4.91 (q, *J* = 6.2 Hz, 1 H) ; 7.25–7.38 (m, 5 H); GC conditions: T = 120 °C; t_r (min) = 9.66 (*R*), 10.18 (*S*).

*(*S*)-1-Phenylpropanol (**2b**)*. 84% ee; 82% yield; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.91 (t, *J* = 7.4 Hz, 3 H); 1.69–1.83 (m, 2 H) ; 2.09 (br s, 1 H) ; 4.58 (t, *J* = 6.8 Hz, 1 H); 7.25–7.35 (m, 5 H); $[\alpha]_D$ = –40.5° (c = 2.05, Hexane) (lit. $[\alpha]_D$ = –47.0° (c = 2.25, Hexane); GC conditions : T = 100 °C (5 min.); 2 °C/min.; 140 °C (10 min.); t_R (min) = 21.17 (*R*), 21.66 (*S*).

*(*S*)-1-Phenylbutanol (**2c**)*. 92% ee; 80% yield; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.93 (t, *J* = 7.2 Hz, 3 H) ; 1.32–1.47 (m, 2 H); 1.69–1.86 (m, 2 H); 1.81 (br s, 1 H) ; 4.68 (t, *J* = 5.9 Hz, 1 H); 7.28–7.37 (m, 5 H); $[\alpha]_D$ = –35.0° (c = 1, $CHCl_3$), (lit. $[\alpha]_D$ = –48.6° (c = 5, $CHCl_3$); GC conditions: T = 110 °C; t_R (min) = 38.52 (*S*), 39.90 (*R*).

(S)*-2-Methyl-1-phenylpropanol (**2d**)*. 81% ee; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 0.79 (d, *J* = 6.7 Hz, 3 H); 1.00 (d, *J* = 6.6 Hz, 3 H); 1.87–2.00 (m, 1 H); 2.01 (br s, 1 H); 4.34 (q, *J* = 6.9 Hz, 1 H); 7.27–7.98 (m, 5 H); GC conditions: T = 90 °C (5 min.); 1 °C/min; 120 °C (10 min); t_R (min) = 41.5 (*R*), 42.0 (*S*).

*(*R*)-Ethyl mandelate (**2e**)*. 11% ee; 99% yield; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.23 (t, *J* = 7.0 Hz, 3 H); 3.53 (br s, 1 H); 4.12–4.32 (m, 2 H); 5.16 (br s, 1 H); 7.31–7.46 (m, 5 H); $[\alpha]_D$ = –10.2° (c = 3.05, $CHCl_3$), (lit. $[\alpha]_D$ = –134° (c = 3, $CHCl_3$); GC conditions: T = 100 °C (10 min.); 1 °C/min.; 120 °C (10 min); t_R (min) = 44.3 (*R*), 45.6 (*S*).

*(*S*)-1-(4′-Chlorophenyl)ethanol (**2f**)*. 85% ee; 100% yield; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.48 (d, *J* = 6.5 Hz, 3 H); 1.80 (br s, 1 H); 4.89 (q, *J*=6.5 Hz, 1 H); 7.32 (s, 4 H); $[\alpha]_D$ = –0.438° (c = 1.1, Et_2O), (lit. $[\alpha]_D$ = –48.98° (c = 0.0613, Et_2O); GC conditions: T = 135 °C; t_R = 16.45 (*R*), 17.65 (*S*).

*(*S*)-1-(3′-Chlorophenyl)ethanol (**2g**)*. 75% ee; 97% yield; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.49 (d, *J* = 6.4 Hz, 3 H); 1.80 (br s, 1 H); 4.89 (q, *J* = 6.5 Hz, 1 H); 7.22–7.29 (m, 3 H); 7.39 (s, 1 H); GC conditions: T (°C) = 130; t_R = 13.52 (*R*), 14.47 (*S*).

*(*S*)-1-(2′-Chlorophenyl)ethanol (**2h**)*. 64% ee; 96% yield; ^{1}H NMR ($CDCl_3$, 200 MHz) : δ 1.50 (d, *J* = 6.4 Hz, 3 H); 1.93 (br s, 1 H); 5.30 (d, *J*= 6.3 Hz, 1 H); 7.19–7.36 (m, 3 H) ; 7.58–7.63 (d, *J*= 9.2 Hz, 1 H); GC conditions: T = 140 °C; t_R = 10.69 (*R*), 12.65 (*S*).

*(*S*)-1-(4′-Fluorophenyl)ethanol (**2i**)*. 82% ee; 100% yield; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.49 (d, *J* = 6.4 Hz, 3 H); 1.76 (br s, 1 H); 4.89 (q, *J* = 6.5 Hz, 1 H); 6.99–7.08 (m, 2 H); 7.27–7.39 (m, 2 H); $[\alpha]_D$ = –38.5° (c = 1.1, $CHCl_3$) (lit. $[\alpha]_D$ = –41.0° (c = 1.3, $CHCl_3$); GC conditions: T = 130 °C; t_R = 6.64 (*R*), 7.07 (*S*).

*(*S*)-1-[4′-(Trifluoromethyl)phenyl]ethanol (**2j**)*. 86% ee; 82% yield; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.50 (d, *J* = 6.6 Hz, 3 H); 1.84 (br s, 1 H); 4.98 (q, *J* = 6.5 Hz, 1 H); 7.56 (AB or dd, *J* = 8.4 Hz, Δν = 32.9 Hz, 4 H); $[\alpha]_D$ = –0.480° (c = 1.25, MeOH) (lit. $[\alpha]_D$ = –24.7° (c = 1.90, MeOH); GC conditons: T = 120 °C; t_R (min) = 12.29 (*R*), 13.88 (*S*).

*(S)-1-[3′-(Trifluoromethyl)phenyl]ethanol (**2k**)*. 82% ee; 100% yield; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.51 (d, *J* = 6.5 Hz, 3 H); 1.84 (br s, 1 H); 4.99 (q, *J* = 6.5 Hz, 1 H); 7.47–7.59 (m, 3 H); 7.66 (s, 1 H); GC conditions: T = 120 °C; t_R (min) = 9.88 (*R*), 10.77 (*S*).

*(S)-1-[2′-(Trifluoromethyl)phenyl]ethanol (**2l**)*. 64% ee; 96% yield; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.50 (d, *J* = 6.5Hz, 3 H); 1.93 (br s, 1 H); 5.30 (d, *J* = 6.4Hz, 1 H); 7.19–7.36 (m, 4 H); GC conditions: T (°C) = 120; t_R (min) = 9.05 (*R*); 9.52 (*S*).

*1-(3′,5′-bis-Trifluoromethyl-phenyl)ethanol (**2m**)*. 85% ee; 88% yield; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.55 (d, *J* = 6.5 Hz, 3 H); 2.13 (br d, 1 H); 4.99–5.09 (m, 1 H); 7.78–7.85 (m, 3 H).

*1-(4′-Cyanophenyl)ethanol (**2n**)*. 86% ee; 100% yield; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.50 (d, *J* = 6.5 Hz, 3 H); 1.89 (br s, 1 H); 4.97 (q, *J* = 6.5 Hz, 1 H); 7.57 (AB, *J* = 10 Hz, Δν = 40 Hz, 4 H); GC conditions: T = 170 °C ; t_R = 10.64 (*S*), 11.59 (*R*).

*(*S*)-1-Indanol (**2o**)*. 78% ee; 80% yield; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.76 (br s, 1 H); 1.88–2.02 (m, 1 H); 2.40–2.58 (m, 1 H); 2.76–2.88 (m, 1 H); 3.00–3.15 (m, 1 H); 5.25 (t, *J* = 6.1 Hz, 1 H); 7.22–7.44 (m, 4 H); GC conditions: T = 100 °C (5 min.); 1 °C/min; 150 °C (10 min); t_R = 20.85 (*S*), 21.43 (*R*).

*(*R*)-1-tetranol (**2p**)*. 76% ee.

*(*R*)-4-phenyl-2-butanol (**2s**)*. 20% ee; 93% yield; ^{1}H NMR ($CDCl_3$, 200 MHz): δ 1.20 (d, *J* = Hz, 3 H); 1.55 (br s, 1 H); 1.8 (m, 2 H) ; 2.75 (m, 2 H) ; 3.8 (m, 1 H) 7.15–7.36 (m, 5H) ; $[\alpha]_D$ = –0.032° (c = 1, $CDCl_3$) (lit. $[\alpha]_D$ = –2.1° (c = 0.0621, $CDCl_3$); GC conditions: T = 105 °C (5 min); 1°C/min; 170 °C (10 min); t_R = 21.87 (*S*); 22.45 (*R*).

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