COMMUNICATION

Enantio-, regio- and chemoselective copper-catalysed 1,2-hydroborylation of acylsilanes

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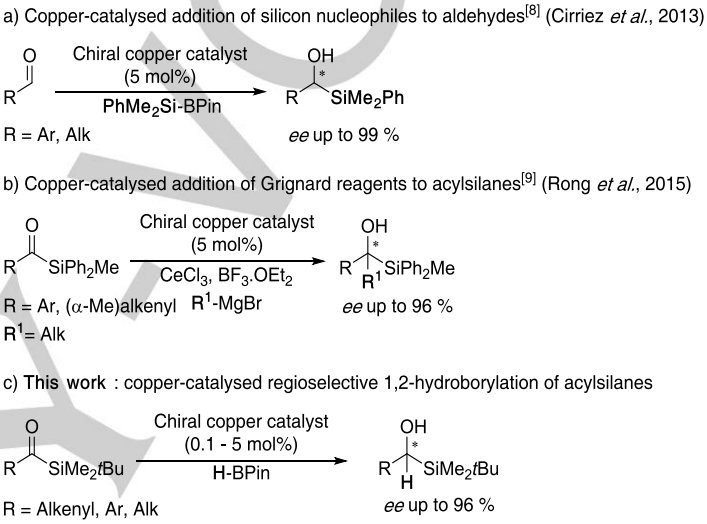
Dedication ((optional))

Abstract: *The enantioselective synthesis of synthetically significant (α-hydroxyallyl)silanes, (α-hydroxyaryl)silanes and (α-hydroxyalkyl)silanes is reported. The present copper-catalysed 1,2-hydroborylation of acylsilanes affords the aforementioned products in high yields and high enantiomeric excesses. This robust and scalable additive-free catalytic system relies on the use of low copper(II) acetate and diphosphine ligand loadings at room temperature in the presence of a commercially available and bench stable hydride source.*

The importance of α-chiral organosilanes in organic chemistry arises from the post-functionalisation opportunities offered by silicon chemistry[1] and from the growing interest in silicon atoms as non-toxic and metabolically stable bioisosters in pharmaceutically important compounds.[2] Optically active (α-hydroxyallyl)silanes,[3] (α-hydroxyaryl)silanes[4] and their derivatives have particular synthetic relevance in stereospecific C-C bond forming reactions and rearrangements leading to a variety of chiral organic molecules. The discovery of new enantioselective synthetic methods leading to those silicon containing molecules are therefore crucial.

The most direct entry to enantioenriched secondary α–hydroxysilanes is the enantioselective reduction of prochiral acylsilanes. However most reports of such chiral reduction reactions depend on the use of stoechiometric amounts of chiral reducing agents[5] or transition metal[6] and thus suffer from poor atom economy and important costs. Recently, catalytic methods to achieve this transformation were reported.[7] For instance Arai *et al.* reported an extremely efficient ruthenium-catalysed hydrogenation reaction of acylsilanes but high hydrogen gas pressure is required as well as the expensive noble metal complex and degassing of the reaction media.[7b] Besides reduction reactions, α-hydroxysilanes are accessible with high enantiomeric excesses through copper-catalysis by addition of silyl nucleophiles to aldehydes[8] (Scheme 1a) and addition of Grignard reagents to acylsilanes[9] (Scheme 1b). Nevertheless those approaches suffer from severe limitations. While the former requires the use of a preformed diphosphine copper(I) bifluoride complex at low temperatures, the latter requires stoechiometric amounts of lewis acids, moisture sensitive nucleophiles and gives rise to a competing non enantioselective Meerwein-Ponndorf-Verley (MPV)-type reduction.

Even though the above-mentioned reactions give access to α-hydroxysilanes, they mainly focus on aromatic substituted α-hydroxysilanes, highlighting the need for new catalytic methodologies towards optically active (α-hydroxyallyl)silanes.



Scheme 1. Copper-catalysed syntheses of α-hydroxysilanes..

Herein we report an enantioselective copper-catalysed 1,2-selective hydroborylation reaction of acylsilanes with emphasis on αβ-unsaturated acylsilanes. The resulting α-hydroxysilanes are obtained after short reaction time at room temperature in the presence of as low as 0.1 mol% catalyst with yields up to 98 % and enantiomeric excesses up to 96 % (Scheme 1c).

We started our investigation by seeking the best chiral ligand to affect the reduction of αβ-unsaturated acylsilane **1a** (Table 1). The initial experiments were carried out in toluene at room temperature in the presence of 5 mol% of $(PPh_3)_3CuF.2MeOH$ (**3**)[10] and five equivalents of (diethoxy)methylsilane as the hydride source. Several families of chiral diphosphine ligands were tested and the best ligand of each family is presented in Table 1. Among the BINAP family **L1** gave (α-hydroxyallyl)silane **2a** with 46 % enantiomeric excess (Entry 1). Segphos **L2** increased the enantioselectivity to 65 % (Entry 2). DTBM-Segphos **L3** which gave the best results in a previous study on α-hydroxysilanes[8] disappointingly yielded **2a** in 39 % *ee* only (Entry 3). The Josiphos family was ineffective in promoting the copper-catalysed hydride transfer in an asymmetric manner (Entry 4). Finally the MeO-biphep **L5** exhibited similar enantioinduction as **L2** with the added benefit of reaching complete conversion within a few seconds (Entry 5).

Having established chiral MeO-biphep **L5** as the best ligand, other reaction parameters were next studied (Table 2). Replacing

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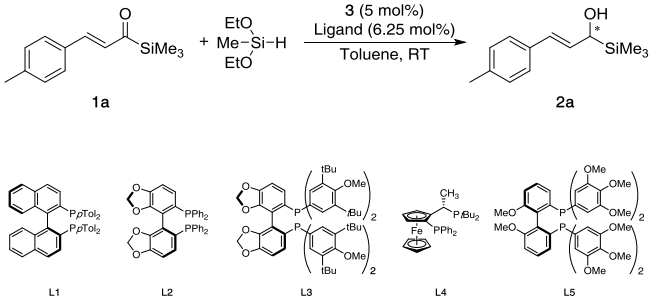
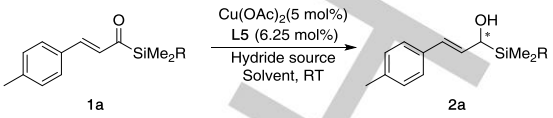
Table 1. Chiral ligands screening.



Entry	Ligand	Time (minutes)	*ee* [%][a]
1	**L1**	30	46
2	**L2**	30	65
3	**L3**	30	39
4	**L4**	30	10
5	**L5**	< 1	65

[a] Enantiomeric excesses were determined by chiral HPLC analysis on crude samples after hydrolysis of the (α-siloxyallyl)silanes.

Table 2. Reaction parameters screening.



Entry	Hydride source[a]	R	Solvent	Yield [%][b]	*ee* [%][c]
1	$(EtO)_2MeSi$-H (5)	Me	toluene	n.d.	72
2	$(EtO)_2MeSi$-H (5)	*t*Bu	toluene	n.d.	84
3	$(EtO)_2MeSi$-H (5)	*t*Bu	MeCN	25	94
4	PinB-H (5)	*t*Bu	MeCN	92	92
5[d]	PinB-H (1.5)	*t*Bu	MeCN	92	92
6[e]	PinB-H (1.5)	*t*Bu	MeCN	32	16
7[f]	PinB-H (1.5)	*t*Bu	MeCN	63	90

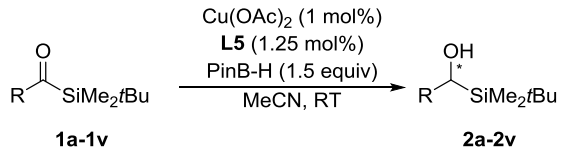
[a] Number of equivalents used are given in brackets. [b] Isolated yields after hydrolysis and flash column chromatography over SiO_2 gel. [c] Determined by chiral HPLC analysis. [d] The reaction was run with 0.1 mol% copper salt and 0.125 mol% **L5.** [e] The reaction was run with 0.01 mol% copper salt and 0.0125 mol% **L5.** [f] The reaction was run at – 20 °C.

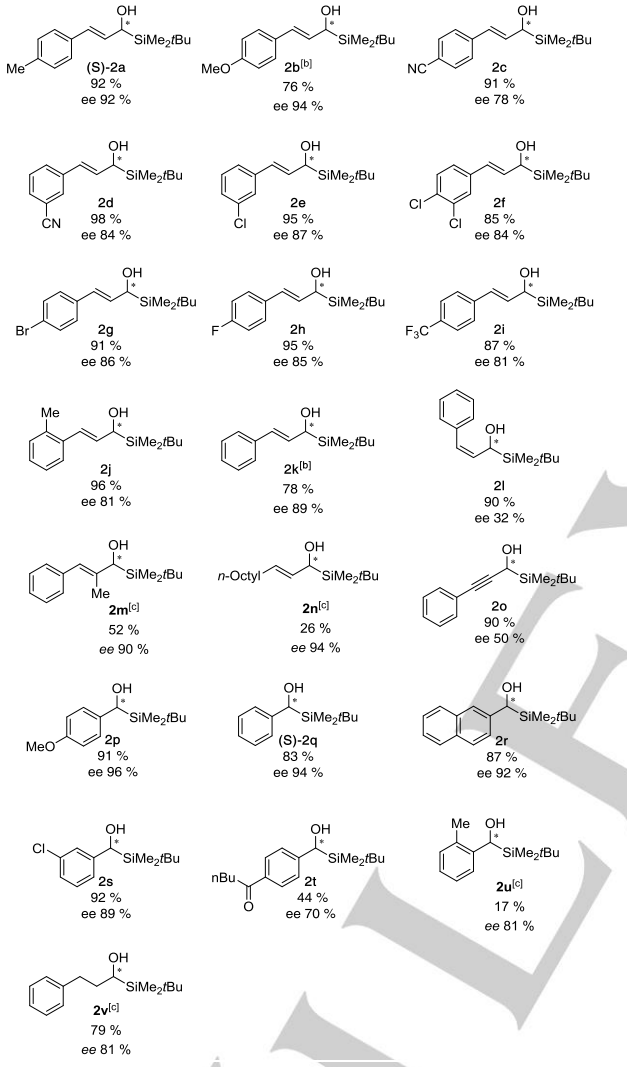
copper source **3** by copper(II) acetate increased the enantioselectivity to 72 %. This improvement is attributed to suppression of the competing racemic hydride transfer by **3** (Entry 1). The effect of the silyl group size on the outcome of the reaction was then investigated. Replacing the trimethylsilyl group by the bulkier *tert*-butyldimethylsilyl group caused a rise of the enantiomeric excess (Entry 2). Among several solvents acetonitrile was finally found to be optimal regarding the enantioselectivity of the reaction as 94 % *ee* was observed. Despite high enantioselectivity only 25 % of pure (α-hydroxyallyl)silane **2a** could be isolated (Entry 3). This low yield is due to the relative instability of the product under the hydrolysis conditions for long periods. This issue was tackled by using pinacolborane instead of (diethoxy)methylsilane as hydride donor. The resulting (α-boryloxyallyl)silane showed better hydrolysis behaviour thereby shortening the time needed to reach full hydrolysis. As a result **2a** was isolated with 92 % yield and 92 % *ee* (Entry 4). Satisfyingly, the amount of pinacolborane could be reduced to 1.5 equivalents while the loading of copper salt and ligand were lowered to 0.1 mol% and 0.125 mol% respectively without loss of yield nor enantiomeric excess (Entry 5). Further diminishing the catalytic loading resulted in a dramatic drop of both yield and *ee* (Entry 6). Running the reaction at lower temperatures afforded **2a** with moderate yield and similar *ee* (Entry 7).

In order to demonstrate the method's applicability a range of αβ-unsaturated acylsilanes **1a**-**1o** and aromatic acylsilanes **1p-1u** were submitted to the optimal conditions though 1 mol% catalyst was used for practical reasons[11] (Table 3). All αβ-unsaturated substrates reacted well affording very high yields regardless the substitution pattern of their aromatic ring. The electronic properties of the substituents however seem to affect the enantioselectivity. Electron rich acylsilanes **1a** and **1b** gave the corresponding (α-hydroxyallyl)silanes **2a** and **2b** with high *ee*'s, while a slight drop in enantioselectivity was observed for electron poor acylsilanes **1c** and **1d**. Various halogenated acylsilanes **1e**-**1h** as well as trifluoromethylated **1i** were well tolerated under the reported conditions yielding the corresponding α-hydroxysilanes with very good *ee*'s. *Ortho*-substituted acylsilane **1j** suffered from slightly lower enantioselectivity compared to its *para*-substituted analog **1a**. Then the substitution pattern of the double bond was studied. While the (*E*) isomer **1k** gave **2k** with good *ee*, the corresponding (*Z*) isomer **1l** underwent a dramatic drop in *ee* during the reduction. Due to the steric strain of its α-substituent, **2m** was obtained with moderate yield while β-alkylated **1n** disappointingly gave poor yield upon reduction. However **2m** and **2n** were both obtained with very high *ee*'s. Interestingly despite moderate *ee* alkynyl acylsilane **1o** was efficiently transformed to the corresponding propargylic α-hydroxysilane **2o** without any competing β-addition to the triple bond.

The reaction conditions were then successfully applied to aromatic acylsilanes **1p**-**1u**. The same reactivity pattern as for αβ-unsaturated acylsilanes was observed. Acylsilanes **1p-1s** reacted well independently on the electronic properties of their substituents. A trend in terms of enantioselectivity could again be observed as electron rich acylsilane **1p** gave higher *ee* upon

Table 3. Scope of the Cu-catalysed hydroborylation of acylsilanes.[a]





[a] 0.2 mmol scale. Yields and *ee*'s are determined after hydrolysis of the (α-boryloxy)silanes and purification over SiO_2 gel chromatography. [b] $PhSiH_3$ was used as hydride donor. [c] Modified reaction conditions: 5 mol% $Cu(OAc)_2$, 6.25 mol% **L5**, 40 °C, 16h.

reduction than the electron poor **1s** and **1t**. Selective hydroborylation of the challenging ketone-bearing **1t** highlighted the extremely desirable chemoselectivity of the catalytic system for acylsilanes as no ketone reduction was observed. Moderate yield was however obtained due to spontaneous Brook rearrangement of the electron poor **2t** under the reaction conditions. In opposition to αβ-unsaturated substrates, *ortho* substitution of arylacylsilanes resulted in a dramatic drop in yield as **2u** was obtained in only 17 % yield with most of **1u** recovered. Satisfyingly, aliphatic acylsilane **1v** gave very good yield and *ee* after hydroborylation.

Finally the method was scaled up to demonstrate its robustness and potential applicability to industrial processes. αβ-unsaturated acylsilane **1a** was successfully hydroborylated within 90 minutes in the presence of 0.1 mol% catalyst on a 5 mmol scale affording 1.2 grams of **2a** in 91 % enantiomeric excess. **1p** was also efficiently transformed on a 5 mmol scale with excellent 97 % isolated yield and 95 % *ee* although 1 mol% catalyst was necessary to reach complete conversion.

In conclusion we reported an enantio-, regio- and chemoselective copper-catalysed hydroborylation reaction of acylsilanes. In the presence of as low as 0.1 mol% catalyst our conditions give rapid and easy access to a wide range of otherwise difficult to prepare optically active secondary (α-hydroxyallyl)silanes, (α-hydroxyaryl)silanes and (α-hydroxyalkyl)silanes with high yields and enantiomeric excesses. The hydroborylation operates on the gram scale without significant loss of yield nor *ee*. The method relies on the use of commercially available and bench stable copper source, ligand and hydride donor without the need for any additive making it a highly user-friendly process.

Experimental Section

A flame-dried Schlenk tube was charged with **L5** (1.25 mol%) under argon. A solution of copper(II) acetate in freshly distilled acetonitrile (4 mM, 1 mol%) was added followed by pinacolborane (0.3 mmol). When the reaction mixture had turned pale yellow, a saturated solution of acylsilane **1a** (0.2 mmol) in freshly distilled acetonitrile was added. The reaction mixture was stirred at room temperature until complete consumption of **1a** as monitored by TLC. The reaction mixture was transferred to a separation funnel, diluted with Et_2O (15 mL) and submitted to hydrolysis by vigorous shaking in the presence of diluted aqueous K_2CO_3 (0.5 M, 15 mL). The organic phase was separated and the volatiles were removed under reduced pressure. The residue was purified by flash column chromatography on SiO_2 gel (PE/EtOAc, 90:10) yielding pure (α-hydroxyallyl)silane **2a** in 92% yield and 92% *ee*.

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Keywords: Copper • Acylsilane • α-hydroxysilane • Hydroborylation • Asymmetric

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[11] 1 mol% catalyst was used in order to ensure accurate weighing of the ligand.