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A Chiral Silyl Ether as Auxiliary for the Asymmetric Nucleophilic Addition to a- and b-Silyloxy Carbonyl Compounds

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Introduction

Silyl ethers are well established protective groups in organic synthesis [1]. They are easily prepared and cleaved, and their reactivity can readily be controlled by the appropriate choice of the groups attached to silicon. In the course of our ongoing investigation of the chiral (*tert*-butyl)(methyl)(benzyloxymethyl)silyl group (**I**) as an auxiliary to control stereoselective processes [2] we got interested in the combined use of **I** as a protective and stereochemically directing group.

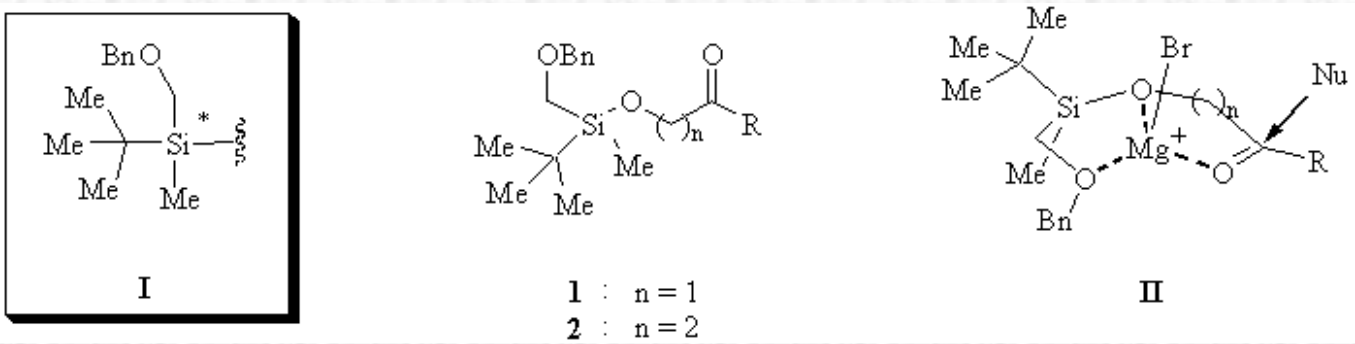
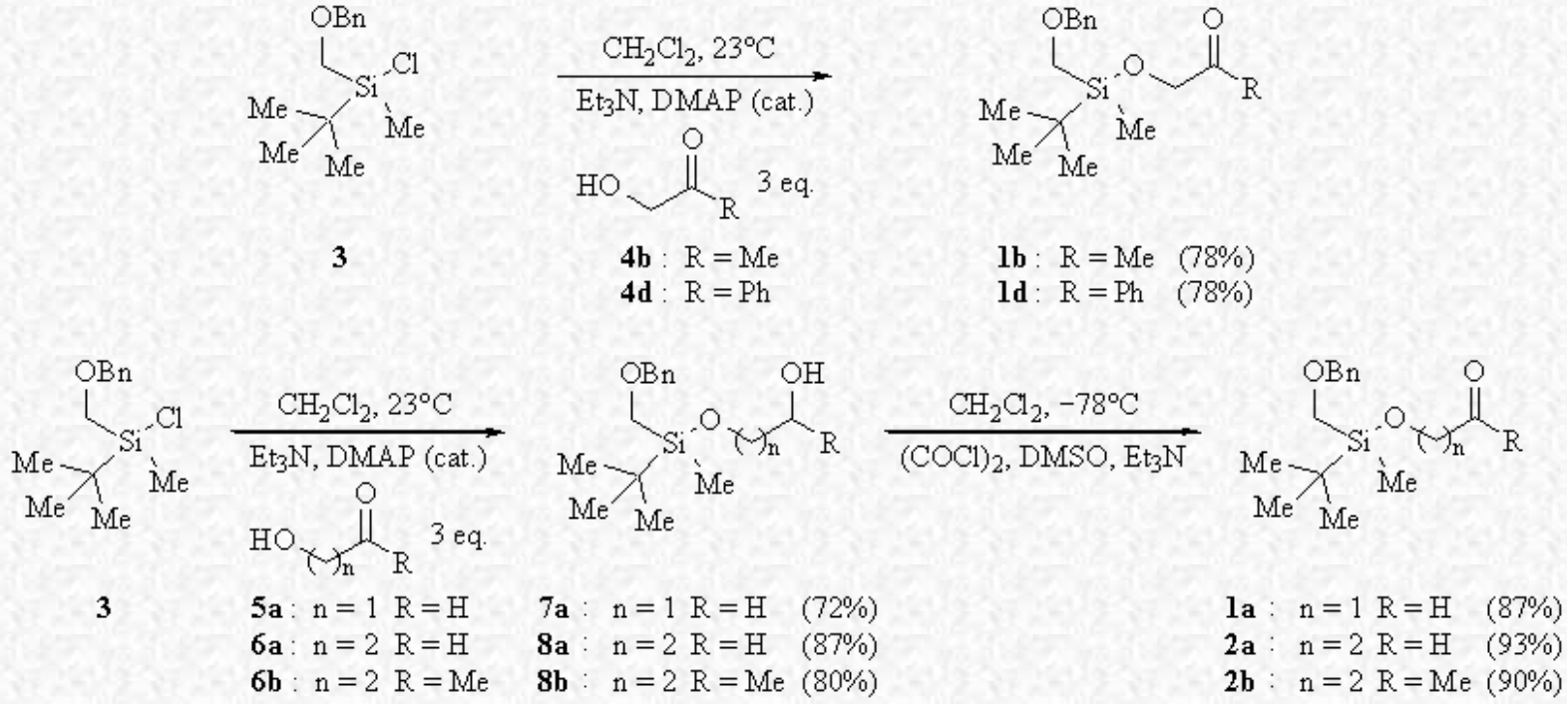


Figure 1

For an initial investigation, we envisioned racemic silyl ethers of a- and b-hydroxyketones (compounds of type **1** and **2**, *Figure 1*) as suitable substrates to study the stereodirecting effect of the ether-linked chiral silyl moiety on the $MgBr_2$-mediated nucleophilic addition of *Grignard* reagents to carbonyl groups. Tridentate chelate transition structures of type **II** were expected to effect efficient chirality transfer from the silicon center to the carbon framework.

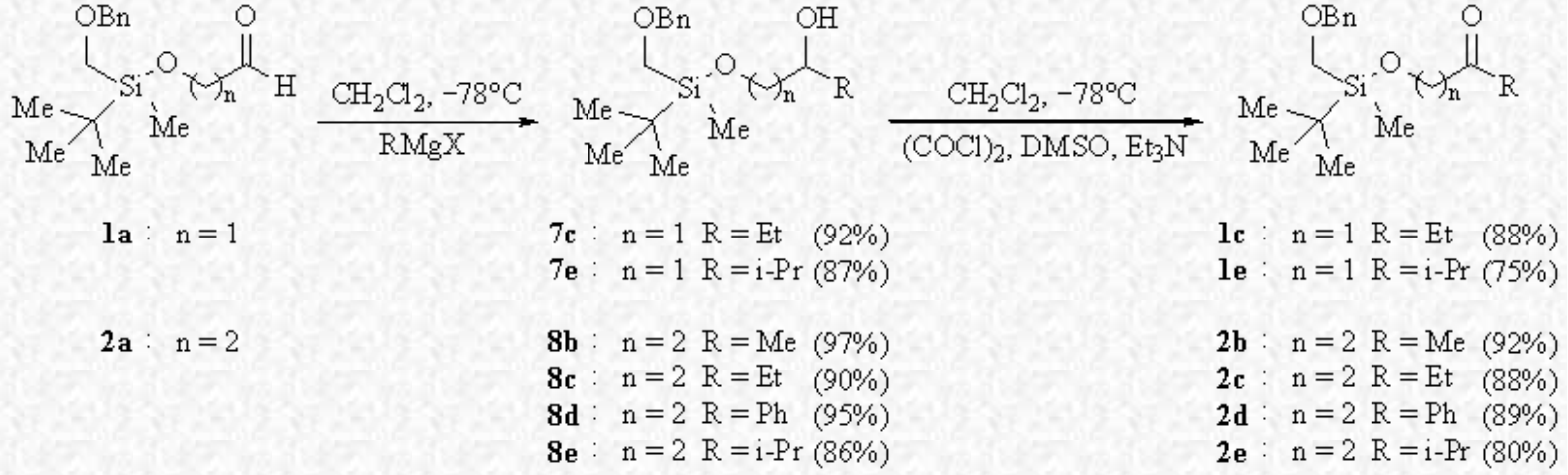
Results and Discussion

A series of silylated compounds of type **1** and **2**, the starting materials for our investigation, were prepared from readily available racemic chlorosilane **3** [3]. Direct silylation of commercial a-hydroxyketones **4b,d** afforded compounds **1b,d**. Silylation of 1,2-diol **5a** and 1,3-diols **6a,b** followed by oxidation gave rise to compounds **1a** and **2a,b**, respectively (*Scheme 1)*.



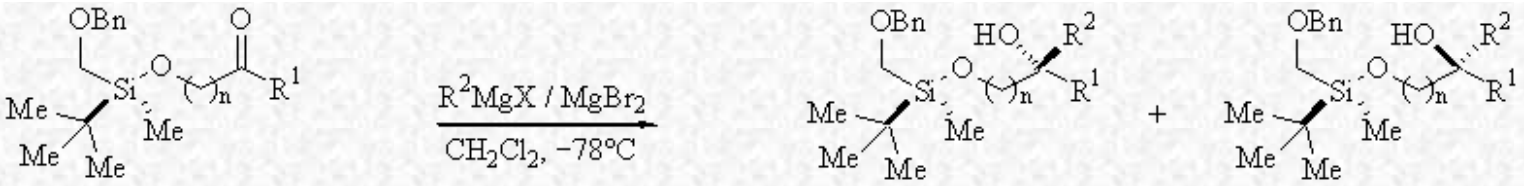
Scheme 1

Substrates **1c,e** and **2b–e** were obtained by the addition of the appropriate *Grignard* reagent to aldehyde **1a** resp. **2a** and subsequent oxidation (*Scheme 2*).



Scheme 2

The stereoselective addition reactions summarized in *Table 1* were performed as follows: silyl ethers **1a–e** or **2a–e** were precomplexed at –78°C in CH_2Cl_2 with 5 equivalents of $MgBr_2$ and 3 equivalents of the *Grignard* reagent were added. Reactions were quenched after approximately 2 h and worked up by extraction followed by chromatography. The yields of the addition products were generally high (80–95%), and the ratios of the diastereomeric products **9–31** and **9'–31'** were determined by ^{1}H-NMR spectroscopy on the crude mixtures (before chromatography).



1a-e
2a-e

9-31

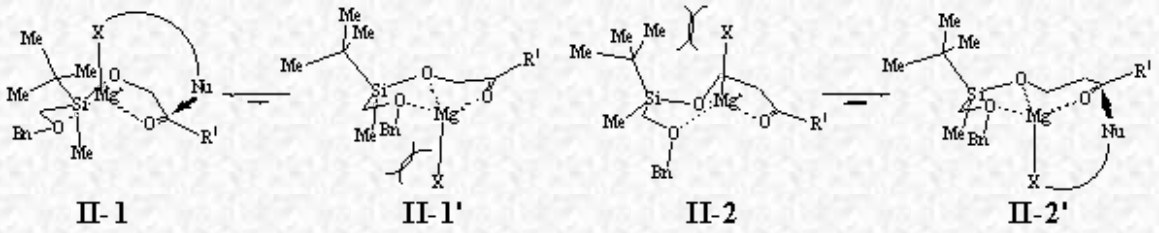
9'-31'

Table 1

Entry	n	Start. Material No.	R^1	R^2MgX	Produkt No.	dr
1	1	**1a**	H	MeMgBr	**9 / 9'**	66 : 34
2	1	**1a**	H	EtMgBr	**10 / 10'**	60 : 40
3	1	**1a**	H	PhMgBr	**11 / 11'**	59 : 41
4	1	**1a**	H	i-PrMgCl	**12 / 12'**	53 : 47
5	1	**1a**	H	t-BuMgCl	**13 / 13'**	50 : 50
6	1	**1b**	Me	PhMgBr	**14 / 14'**	76 : 24
7	1	**1c**	Et	PhMgBr	**15 / 15'**	72 : 28
8	1	**1e**	i-Pr	PhMgBr	**16 / 16'**	53 : 47
9	1	**1d**	Ph	MeMgBr	**17 / 17'**	71 :29
10	1	**1d**	Ph	EtMgBr	**18 / 18'**	66 : 34
11	1	**1d**	Ph	i-PrMgCl	**19 / 19'**	64 : 34
12	1	**1d**	Ph	t-BuMgCl	**20 / 20'**	52 : 48
13	2	**2a**	H	MeMgBr	**21 / 21'**	43 : 57
14	2	**2a**	H	EtMgBr	**22 / 22'**	37 : 63
15	2	**2a**	H	PhMgBr	**23 / 23'**	34 : 66
16	2	**2a**	H	i-PrMgCl	**24 / 24'**	36 : 64
17	2	**2b**	Me	PhMgBr	**25 / 25'**	13 : 87
18	2	**2c**	Et	PhMgBr	**26 / 26'**	16 : 84
19	2	**2e**	i-Pr	PhMgBr	**27 / 27'**	37 : 63
20	2	**2d**	Ph	MeMgBr	**28 / 28'**	25 : 75
21	2	**2d**	Ph	EtMgBr	**29 /29'**	18 : 82
22	2	**2d**	Ph	i-PrMgCl	**30 /30'**	20 : 80
23	2	**2d**	Ph	t-BuMgCl	**31 / 31'**	20 : 80

Several trends can be extracted from the results presented in *Table 1*. (1) It is obvious that p-facial selectivity under the influence of the group **I** is not very high and different for the two types of substrates: compounds of type **1** permit preferred *lk*- and substrates of type **2** *ul*-attacks of the nucleophiles. (2) Highest selectivities were obtained with

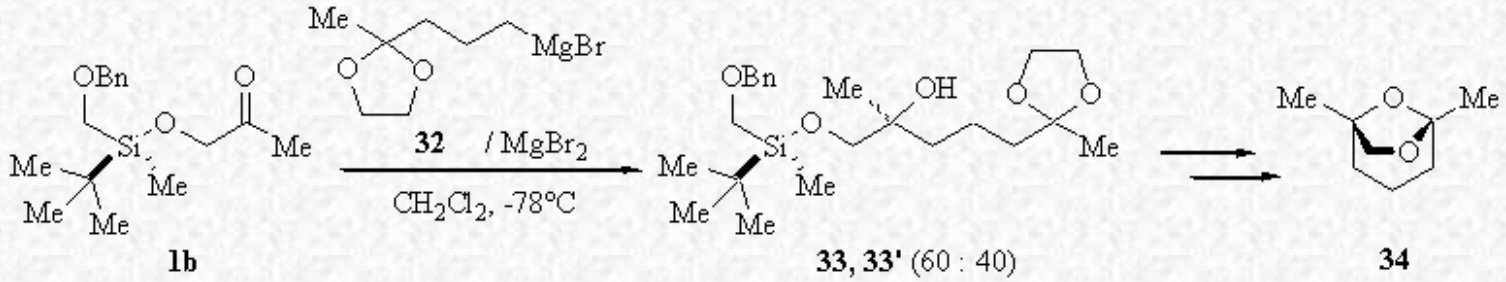
compounds of type **2**, compound of type **1** showing overall lower selectivities. (3) With the exception of the aldehydes **1a** and **2a**, increase of bulkiness of the R1 group for both types of substrates is accompanied by a decrease of diastereofacial preference of the attacks, and (4) increase of the size of the nucleophiles results in decreased selectivity for compounds **1** and increased selectivity for compounds **2**.



Scheme 3

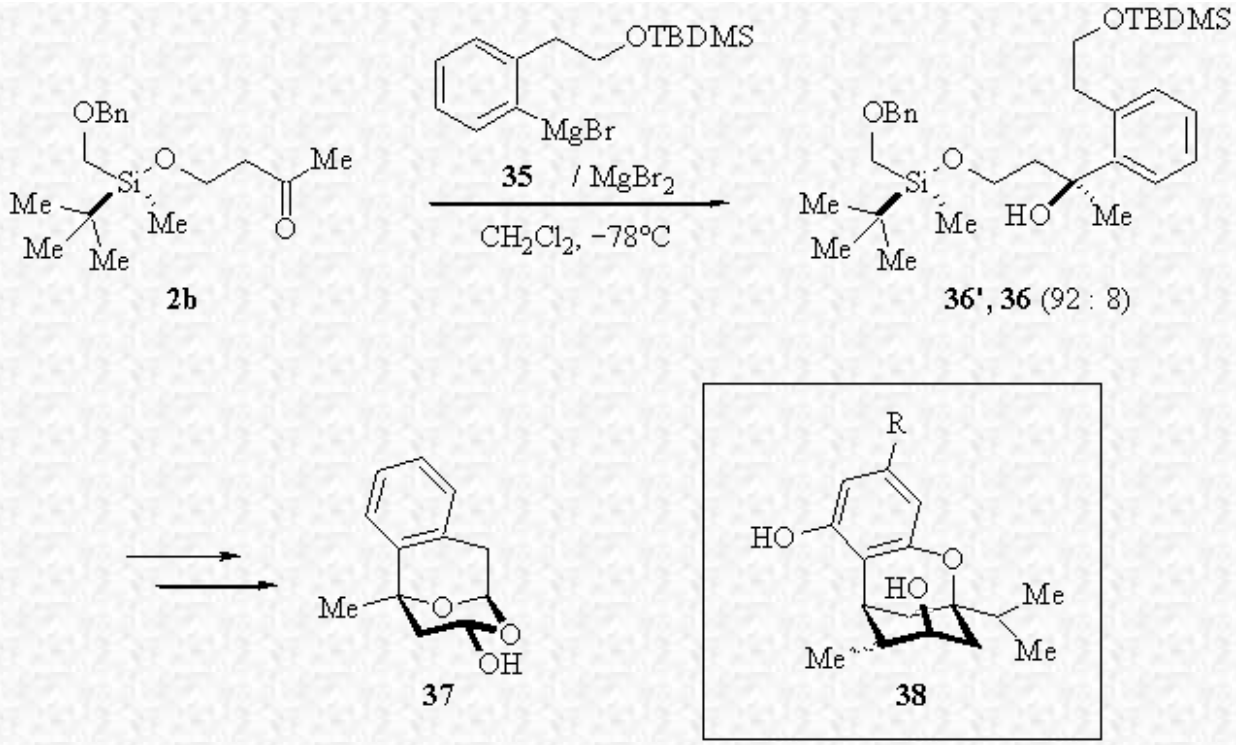
The results can be explained to a great extent by scrutinizing the proposed chelate structures **II-1**/**II-1'** and **II-2**/**II-2'** for the two types of substrates and sites of attack. Simple molecular models and semi-empirical calculations (PM3, *MacSpartan*) suppose **II-1** for compounds **1** and **II-2'** for compounds **2** to be the thermodynamically favored complexes, thus explaining the different p-facial selectivities for the two different substrates (*Scheme 3*). Both complexes **II-1** and **II-2'** are rather encumbered structures. Increase of steric strain by the incorporation of larger R1 groups is thus supposed to decrease the stability of both these complexes, favoring competitive ‚open-chain-controlled' processes, and accounting for the observed decrease of stereoselectivity (*Entries 6–8* and *17–19*). Increase of the size of R2 of the *Grignard* reagent, on the other hand, would affect the stability of related compexes of type **II-1** (*Entries 9–12*) more than those of complexes of type **II-2'** (*Entries 20–23*). As a consequence of the proximity of the residues at the Mg-atom to the *tert*-butyl group at the Si-atom in complexes of type **II-1**, their stability would be strongly decreased by the increase of the size of R2. This is expected to be lesser the case in complexes of type **II-2**, where the residues of the organometal is neighbored by the rather small methyl group only. Thus, the observed stereochemical effects accompanied by the increase of the size of R2 in the organometallic reagent can be explained by the increasing importance of ‚open-chain-controlled' processes in the case of compounds **1** and by enhanced steric discrimination in the case of compounds **2**.

With the above results at hand it is readily understood that the addition of *Grignard* reagent **32** to a-silyloxyketone **1b** leads with only low stereoselectivity to the alcohols **33**/**33'**, precursors of frontalin (**34**) the attracting pheromone of the pine beetle [4] (*Scheme 4*).



Scheme 4

It is not surprising, on the other hand, that the addition of the *Grignard* reagent **35** of a sterically demanding *ortho*-substituted benzene derivative to b-silyloxyketone **2b** led to the respective addition products **36**/**36'** with high stereoselectivity (dr 92:8). Compounds **36**/**36'** — hydrolyzed and subsequently oxidized at the primary alcohols, followed by acid catalyzed tandem-cyclization — afforded **37**, whose derivatives have shown interesting physiological properties due to their structural similarity to Isocannabinol **38**. (*Scheme 5*) [5].



Scheme 5

Conclusion

In conclusion it is shown with the above investigation that chiral silicon groups, attached to a prostereogenic functionality by means of an ether linkage, can act in principal — at least in specific cases — efficiently as stereochemical directors. The potential of this principle might be increased by the structural optimization of the auxiliary group, which has not been performed yet.

References

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