Chemo and enantioselective addition of grignard reagents to ketones and enolizable ketimines
Ortiz, Pablo

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Chapter 4:
Stereospecific Brook Rearrangement of Tertiary Benzylic α-Hydroxysilanes

4.1. Introduction
Contrary to the substrates discussed in the previous chapter, i.e. allylic hydroxysilanes, benzylic hydroxysilanes have been less explored in the [1,2] Brook rearrangement. Short after the discovery of the Brook rearrangement both Brook and coworkers\[1a\] and Mosher and coworkers\[1b\] reported examples of the rearrangement of secondary benzylic α-hydroxysilanes with the aim of determining the stereochemistry of the process. For the same purpose Brook et al. used a chiral silicon whereas Mosher et al. used chiral deuterated hydroxysilanes and reported that they underwent the rearrangement with inversion of configuration at the carbon center (Scheme 1, a).\[1b\] Shortly after, West et al. showed that the inverse rearrangement, the migration of silicon from oxygen to carbon, is also stereospecific and proceeds with inversion of configuration.\[2\] Interestingly, they noted that in the presence of MeI the carbanion racemised and the product of the Brook rearrangement and subsequent trapping were obtained racemic.

Scheme 1. a) Mosher and coworkers’ stereosepecific Brook rearrangement of deuterated, secondary benzylic hydroxysilanes.\[1b\] b) Johnson and coworkers’ enantioselective cyanation/Brook rearrangement/C-acylation of acylsilanes.\[3\]
The topic was left abandoned for decades, till Johnson et al. reported the enantioselective cyanation/Brook rearrangement/C-acylation of acylsilanes in 2004 (Scheme 1, b).[3] This is the only example in the literature of the stereospecific trapping of electrophiles other than proton or deuterium (attached to the oxygen) in a benzylic system. However, the reasons for the chirality transfer are not clear and the authors proposed two possible scenarios. In the first, the enantioselective cyanation could be catalyzed by the chiral salen ligand, followed by stereospecific Brook rearrangement and subsequent stereospecific acylation with cyanoformate (Scheme 1b, top). Alternatively, induction of chirality could take place after the Brook rearrangement, either by dynamic kinetic resolution or by enantioselective acylation of the azaallene (Scheme 1b, bottom). In any case, the Brook rearrangement/stereospecific trapping of simple, benzylic, chiral tertiary α-hydroxysilanes remains underexplored and having access to them prompted us to undertake their study.

4.2 Results and discussion

We reasoned that the alkoxide formed upon the asymmetric addition of iBuMgBr could undergo Brook rearrangement and thus, our first approach was a one-pot asymmetric addition/Brook rearrangement/trapping sequence. We performed the asymmetric addition following the standard conditions (Scheme 2) but it was quenched with BzCl before warming up to room temperature.

Unfortunately, only the \( O \)-benzoylated addition product was recovered and no traces of any Brook rearrangement product were detected by NMR analysis (scheme 2). Consequently, we decided to investigate the reaction of isolated benzyl α-hydroxysilane 2a with a variety of metal bases that could trigger the Brook rearrangement (Table 1). A brief screening was carried out for the model reaction of 2a with 1 equivalent of base and 10 equivalents of methyl iodide as the electrophile.
in THF. The deprotonation with MeMgBr did not lead to Brook rearrangement and the same result was observed using Et$_2$Zn as base (Table 1, entries 1 and 2). When the reaction conditions were forced by a light warm up only decomposition products were observed in both cases. In contrast, in the presence of a lithium base (LiOtBu) Brook rearrangement and trapping of the electrophile was observed at room temperature and the corresponding product 3a was cleanly obtained after desilylation with TBAF. Several electrophiles were evaluated, namely AcCl, BnCl, Ac$_2$O, PhCHO, MeI and allyl bromide. Only the last two led to the trapping products 3a (trapping of Me) and 3b (trapping of allyl) (Table 1, entries 3 and 4). In both cases, together with the trapping product variable amounts of protonated product 4a is observed (Table 1, entries 3 and 4). This is derived from the trapping of the proton from tBuOH, the conjugate acid of LiOtBu.

Table 1. Attempts for stereoselective trapping of electrophiles.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal Base</th>
<th>Electrophile (equiv.)</th>
<th>Solvent</th>
<th>Additive (2 equiv.)</th>
<th>Conv. (%)$^a$</th>
<th>ee (%)$^b$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>MeMgBr</td>
<td>Mel (10)</td>
<td>THF</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>2</td>
<td>Et$_2$Zn</td>
<td>Mel (10)</td>
<td>THF</td>
<td>-</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>3</td>
<td>LiOtBu</td>
<td>Mel (10)</td>
<td>THF</td>
<td>-</td>
<td>3a 88 : 12</td>
<td>Rac : n.d.</td>
</tr>
<tr>
<td>4</td>
<td>LiOtBu</td>
<td>allylBr (5)</td>
<td>THF</td>
<td>-</td>
<td>3b 83 : 17</td>
<td>Rac : 56</td>
</tr>
<tr>
<td>5</td>
<td>LiOtBu</td>
<td>tBuOH (1)</td>
<td>THF</td>
<td>-</td>
<td>0 : 100</td>
<td>- : 60</td>
</tr>
<tr>
<td>6</td>
<td>$n$BuLi</td>
<td>Mel (10)</td>
<td>Et$_2$O</td>
<td>DMF</td>
<td>3a 100 : 0</td>
<td>8</td>
</tr>
<tr>
<td>7</td>
<td>$n$BuLi</td>
<td>MeSO$_4$(2)</td>
<td>Et$_2$O</td>
<td>DMF</td>
<td>3a 100 : 0</td>
<td>5</td>
</tr>
<tr>
<td>8</td>
<td>$n$BuLi</td>
<td>Mel (10)</td>
<td>Et$_2$O</td>
<td>HMPA</td>
<td>3a 100 : 0</td>
<td>5</td>
</tr>
<tr>
<td>9</td>
<td>$n$BuLi</td>
<td>Mel (10)</td>
<td>Et$_2$O</td>
<td>TMEDA</td>
<td>3a 100 : 0</td>
<td>5</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.1 mmol of 2a, 1 mL of solvent, electrophile and base (1 equiv.) -78 °C, 2 hours, then to r.t. overnight. Deprotected using TBAF (tetrabutyl ammonium fluoride). $^a$ Determined by $^1$H NMR spectroscopy. $^b$ Enantiomeric excess was determined by chiral HPLC.
On the contrary, with AcCl and Ac₂O starting material was recovered. Using BnCl as electrophile led to the protonation product and the reaction with benzaldehyde produced a complex reaction crude. Interestingly, although the methylated product 3a and allylated product 3b were racemic, protonation product 4a partially retained the chirality (56% ee, entry 4). Performing the reaction in the presence of tBuOH and no other electrophile, the protonation product was obtained with a slightly better enantioselectivity (60% ee, entry 5).

The fact that no other electrophile but the proton could be trapped with some retention of chirality can be rationalized on the basis that such a non-stabilized carbanion (without any stabilizing substituent) will racemize very fast. As mentioned in the previous chapter, to overcome this problem systems are designed to either lead to configurationally stable allenyl species or to configurationally stabilize the carbanion by a coordinating group such as carbamoyl (See chapter 3). Using these strategies Takeda et al. could achieve the stereoselective protonation of alkynyl[14a] and allyl hydroxysilanes.[4b]

In our case, we envision a coordination of both silicon and lithium atoms using an external Lewis base (DMF, HMPA and TMEDA) in order to configurationally stabilize the carbanion (Figure 1).

![Figure 1. Envisioned coordination of external Lewis bases to stabilize carbanion.](image)

In order to avoid protonation and thus to secure the trapping of electrophiles other than proton, nBuLi was used as base. Full conversion to the trapped product was observed but the ee did not surpass the 8% (Table 1, entries 6-9). Consequently, we decided to focus on studying the retention of chirality upon the protonation process.

It is known that even catalytic amounts of base can trigger the Brook rearrangement.[8] Interestingly, we found that when we added a catalytic amount of LiOtBu we not only obtained full conversion to the rearranged product, but also nearly full transfer of chirality (Table 2, entry 1). We also realized that there was no
need to mix the reagents at low temperature and allow a slow warm up: analogous results were obtained when carrying out the reaction at room temperature or at 0 °C (Table 2, entries 3-4). Only a slight decrease in ee was observed at -50 °C. Although the ee value was not very sensitive to the temperature, we observed a dependence on the rate of the reaction. Longer reaction time was required in order to reach full conversion (3h at r.t. vs overnight at -50 °C). In view of these results subsequent experiments were carried out at room temperature.

Table 2. Stereospecific Brook rearrangement

<table>
<thead>
<tr>
<th>Entry</th>
<th>Metal base (equiv.)</th>
<th>Temperature (°C)</th>
<th>Conversion (%)</th>
<th>ee (%)</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>LiO\textsubscript{t}Bu (5%)</td>
<td>-78 to r.t.</td>
<td>100</td>
<td>88</td>
</tr>
<tr>
<td>2</td>
<td>LiO\textsubscript{t}Bu (5%)</td>
<td>-50</td>
<td>100</td>
<td>73</td>
</tr>
<tr>
<td>3</td>
<td>LiO\textsubscript{t}Bu (5%)</td>
<td>0</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>4</td>
<td>LiO\textsubscript{t}Bu (5%)</td>
<td>r.t.</td>
<td>100</td>
<td>80-88\textsuperscript{[c]}</td>
</tr>
<tr>
<td>5</td>
<td>LiO\textsubscript{t}Bu (20%)</td>
<td>r.t.</td>
<td>100</td>
<td>75</td>
</tr>
<tr>
<td>6</td>
<td>LiO\textsubscript{t}Bu (50%)</td>
<td>r.t.</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>7</td>
<td>LiO\textsubscript{t}Bu (100%)</td>
<td>r.t.</td>
<td>100</td>
<td>40</td>
</tr>
<tr>
<td>8</td>
<td>LiO\textsubscript{t}Bu (1%)</td>
<td>r.t.</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>9</td>
<td>MeMgBr (5%)</td>
<td>r.t.</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>10</td>
<td>Et\textsubscript{z}Zn (5%)</td>
<td>r.t.</td>
<td>0</td>
<td>-</td>
</tr>
<tr>
<td>11</td>
<td>KO\textsubscript{t}Bu (5%)</td>
<td>r.t.</td>
<td>100</td>
<td>80</td>
</tr>
<tr>
<td>12</td>
<td>Li Naphthoxide (5%)</td>
<td>r.t.</td>
<td>80</td>
<td>84</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.1 mmol of \textit{2a}, 1 mL of THF and base. Stirred for 3-24 h. Deprotected using TBAF (tetrabutyl ammonium fluoride). [a] Determined by \textsuperscript{1}H NMR spectroscopy. [b] Enantiomeric excess was determined by chiral HPLC. [c] Range due to variability in the experiments.

We noticed that \textit{ee} of the product would vary from experiment to experiment (Table 2, entry 4), and we thought that it might be due to small variabilities in the amount of base added (2,5 \textmu L of LiO\textsubscript{t}Bu). Therefore we decided to have a closer look at the
effect of the amount of base on the outcome of the reaction and a clear trend was observed. With 5% of LiOtBu the product 4a showed 80% ee. With 20% of base the enantioselectivity decreased to 75% and with more than 50% of LiOtBu the ee plunged to 40% (Table 2, entries 5-7). Achieving full transfer of chirality by lowering the amount of base was unsuccessful, as with 1% of LiOtBu no Brook rearrangement took place (Table 2, entry 8).

The stoichiometry of the base has crucial effect on the position of the equilibrium. With catalytic amounts the equilibrium depends on the relative stabilities of the neutral hydroxysilane and silyl ether, while with excess base the equilibrium is determined by the relative stabilities of the charged species, namely the alkoxide and the carbanion\textsuperscript{[5]} (Scheme 3). Consequently, it could be hypothesized that an excess amount of base generates the lithium carbanion, which, being non-stabilized, leads to racemization and this is reflected afterwards in the capture of the proton. On the other hand, following this reasoning, a catalytic amount of base would favor the neutral species, namely the pentacordinated species, which would retain the configuration (Scheme 3).

\[
\text{Scheme 3. Equilibria between the different species in the [1,2] Brook rearrangement.}
\]

Then we examined again the role of the metal base (Table 2, entries 9-12). As expected from the previous results, no Brook rearrangement took place if MeMgBr or EtZn were used. Interestingly, with KOtBu full conversion was observed and lithium naphthoxide triggered the Brook rearrangement too. From these results it can be concluded that alkali metals trigger the Brook rearrangement. This is further supported by the observation that NaH can start the process too (not shown in the table). The alkoxides formed from alkali metals can be expected to be less stable than the ones derived from Mg or Zn and that could be the reason for the rearrangement taking place.

To get a better understanding of the mechanism we conducted further experiments. First we synthesized several analogues of the standard hydroxysilane 2a and subjected them to the Brook rearrangement (Table 3). In all the cases full conversion
was obtained but the ee’s of the products were lower than with the standard reaction. This might be again due to the lack of accuracy of adding 2.5 μL LiO\textsubscript{t}Bu. In any case, the results were insightful. Both substrates 2b and 2c, with electron withdrawing and donating groups respectively, had the same loss of ee (18 percentage points). This indicates that electronics play a minimal role in the transfer of chirality during the rearrangement step (Table 3, entries 2-3). Similarly, the substitution at the silicon atom seems not to affect the stereochemical outcome of the Brook rearrangement, as the loss of chirality with compound 2d was 14 percentage points on the ee, comparable to the other results (Table 3, entry 4).

Table 3. Influence of the substituent in the reaction.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Substrate, ee (%)</th>
<th>R</th>
<th>Si moiety</th>
<th>ee (%)\textsuperscript{[a]}</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>2a, 88</td>
<td>H</td>
<td>SiPh\textsubscript{2}Me</td>
<td>80-88</td>
</tr>
<tr>
<td>2</td>
<td>2b, 85</td>
<td>F</td>
<td>SiPh\textsubscript{2}Me</td>
<td>67</td>
</tr>
<tr>
<td>3</td>
<td>2c, 92</td>
<td>tBu</td>
<td>SiPh\textsubscript{2}Me</td>
<td>74</td>
</tr>
<tr>
<td>4</td>
<td>2d, 74</td>
<td>H</td>
<td>SiPhMe\textsubscript{2}</td>
<td>60</td>
</tr>
</tbody>
</table>

Reaction conditions: 0.1 mmol of 2, 1 mL of THF, 5 mol % of LiO\textsubscript{t}Bu. Stirred for 3h, deprotected using TBAF (tetrabutyl ammonium fluoride). [a] Enantiomeric excess was determined by chiral HPLC.

As mentioned in the introduction the [1,2] Brook rearrangement of α-silyl secondary benzyl alcohols has been reported to proceed with inversion of configuration\textsuperscript{[1]} in order to see if this held true for the tertiary counterparts we needed to know the absolute configuration of both the starting material and the product. The later could be obtained by comparison with the reported data for the desililated product 4a, and was determined to be S (See Experimental section). Determination of the stereochemistry of the hydroxysilane 2a was more difficult. Being an oil, it happened to be impossible to grow crystals from it, so we thought of having an acid group in the molecule to increase the chances of crystallization. To that end molecule 5 was prepared, with the idea of performing the asymmetric addition to it followed by hydrolysis of the ester (Scheme 4). However, in the test experiment
carried out to study the feasibility of hydrolysis we saw that basic conditions (NaOH in MeOH/THF/H₂O) led to decomposition of compound 5. Acidic conditions (HCl in THF) left the ester untouched at r.t. and decomposed it upon heating. We then thought of performing the addition directly to acylsilane 6 having the free acid. Attempts to synthesize compound 6 with the usual silylation procedure using the diacyl chloride 7 led to a complex crude and the desired product could not be obtained after column chromatography (Scheme 4).

**Scheme 4.** Attempts to obtain the acid-containing acylsilane 6.

For a similar type of oily molecules, α-hydroxysilanes 8, (see Chapter 3) Marek et al.[6] determined the absolute configuration from X-ray structure of selenium oxide 9 (Scheme 5, a). We thought of applying a similar strategy of derivatization to product 10. However it could not be prepared, as the silyl lithium reagent containing the vinyl group polymerized (Scheme 5, c).

a) Derivatization of α-hydroxysilane 8 by Marek et al.[6]

b) Target molecule

c) Attempt of synthesis of vinyl containing silyl lithium reagent

**Scheme 5.** Attempts to form product 10 with the aim to derivatize it to a cyclic selenium oxide.
The lack of success with the modification of the acylsilane, together with the difficulties in its derivatization imposed by the fragile nature of silicon group, led us to consider using VCD spectroscopy to determine its absolute configuration. We measured the experimental VCD of both hydroxysilane 2a and ent-2a (Figure 1) and we saw that the first fitted well with the calculated spectra for the S enantiomer (Figure 2).

**Figure 1.** Measured VCD spectra for 2a (S enantiomer) and ent-2a (R enantiomer).

**Figure 2.** Experimental and calculated IR and VCD for compound 2a.
As we knew that the product 4a was S (See Experimental section) we can assert that the Brook rearrangement of tertiary benzylic α-hydroxysilanes proceeds with inversion of configuration (Scheme 6).

With the obtained results we propose a tentative mechanism in which LiOttBu deprotonates the hydroxysilane 2a, followed by the attack of oxygen to the silicon and formation of the pentacoordinate intermediate. At this stage we believe that the trapping of the proton takes places directly from the pentacoordinate silicon intermediate, being the proton in the proximity thanks to the coordination of the tBuOH to the lithium. When the deprotonation/Brook rearrangement was carried out with nBuLi and the reaction was warmed up before adding the proton source, the corresponding protonated product was formed, but completely racemic. The concerted mechanism would explain the stereospecificity of the reaction in the case of trapping of protons and the loss of it for external electrophiles. In the latter case the pentacoordinate silicon intermediate would evolve to the chiral carbanion which would quickly racemize and thus the product of the trapping would loose the enantioenrichment (Scheme 6).[2b]

Scheme 6. Proposed mechanism for the stereospecific protonation of benzyl α-hydroxysilane 2a.

With the aim of ruling out the possibility of intermolecular trapping of proton (from another α-hydroxysilane) we planned two sets of deuteration experiments: One starting with the deuterated hydroxysilane 2a and having tBuOH in the medium, while in the other the deuterium source would come from tBuOD. The aim was to
see the degree of deuteration of the final product. Unfortunately, in both cases H/D exchange took place at room temperature and at -50 °C, in a similar time-range of the Brook rearrangement. Consequently, no conclusion could be made from these experiments, as the extent of the exchange before the rearrangement is not known. Nevertheless, the fact that after deprotonation with nBuLi and subsequent quenching with an external proton source the protonated product was racemic suggests that, most likely, the mechanism is concerted.

4.3. Conclusions
In summary, in this chapter we have explored the Brook rearrangement of simple, chiral tertiary benzylic α-hydroxysilanes. Brook rearrangement can be followed by trapping of methyl or allyl, but in all cases with minimal retention of chirality. This is not surprising, since the carbanion formed is not stabilized. The fact that the trapping of proton proceeds with transfer of chirality can be attributed to a concerted mechanism in which the trapping of the proton takes place from the pentacoordinate intermediate before the formation of the carbanion. We have also seen that a catalytic amount of base is not only sufficient, but beneficial for the enantiospecificity of the process. Finally, we have proved that the rearrangement of chiral tertiary benzylic α-hydroxysilanes, analogously to their secondary counterparts, proceeds with inversion of configuration at the carbon. Due to the difficulty of knowing the fine details of the retention of chirality in the key step of proton transfer there is not an established proposal for the mechanism. For the secondary benzylic α-hydroxysilanes, there are different possible scenarios:[1b] 1) fast protonation of the carbanion before flipping takes place; 2) transfer of the proton from the solvated base to the carbon in the pentacoordinated intermediate; 3) transfer of the proton from the base coordinated to the oxygen to the carbon in the pentacoordinated intermediate. In our case, although none can be completely discarded, the results point to the third scenario.
4.4 Experimental section

4.4.1. General information

All reactions using oxygen- and/or moisture-sensitive materials were carried out with anhydrous solvents (vide infra) under a nitrogen atmosphere using oven dried glassware and standard Schlenk techniques. Analytical thin-layer chromatography was performed on precoated aluminium-backed plates (Silica Gel 60 F254; Merck), and visualized using UV light (254 nm). Flash column chromatography was carried out using Merck silica gel 60, 230-400 mesh. Cooling of reaction mixtures to -78/-50 °C was achieved using a Julabo FT902 immersion cooler. ¹H-, ¹³C- and ¹⁹F- NMR spectra were recorded on a Varian AMX400 (400, 100 and 376 MHz respectively) using CDCl₃ as solvent at room temperature. Chemical shift values are reported in ppm with the solvent resonance as the internal standard (CDCl₃: δ 7.26 for ¹H, δ 77.16 for ¹³C). Data are reported as follows: chemical shifts, multiplicity (s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (Hz), and integration. Exact mass spectra were recorded on a LTQ Orbitrap XL apparatus with ESI. Enantiomeric excesses were determined by HPLC analysis using a Shimadzu LC-10ADVP HPLC equipped with a Shimadzu SPD-M10AVP diode array detector. Dry THF and Et₂O were collected fresh from solvent purification system. Commercially available reagents were purchased from Sigma-Aldrich, Acros or ABCR. Acyl silanes 1a-c as well as α-hydroxysilanes 2a-c were synthesized according to the literature procedure,[8] and the analytical data were found to be in accordance with those reported.[8,9] Acylsilane 5 and α-hydroxysilane 2d have not been previously reported.

**methyl 3-((methyldiphenylsilyl)carbonyl)benzoate (5)**

First Ph₂MeSiLi was prepared by adding 5 mmol (1 equiv.) of Ph₂MeSiCl to 20 mmol (4 equiv.) of lithium (granular) in 12.5 mL of dry THF, in a dry Schlenk flask under N₂ atmosphere. We observed that higher conversions to the lithiated products were obtained if catalytic amount of naphthalene (5 mol%) were added to the solution. The reaction was stirred overnight and next morning the conversion checked by ¹H NMR, upon which the solution was transferred to a dry Schlenk flask, cooled down to -78 °C and ZnCl₂ (1 equiv.) was added slowly. The solution turned yellow and then it as allowe to warm up to 0 °C for one hour. The now brown solution was cooled down again to -78 °C and CuCN (0.5 equiv.) was added.
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together with 8 mL of dry THF. Then it was allowed to warm up again to 0 °C, upon which it turned purple. It was stirred at this temperature for 30 minutes and afterwards it was cooled down to -20 °C and the acyl chloride (0.5 equiv.) added dissolved in THF (4 mL). The acyl chloride, methyl 3-(chlorocarbonyl)benzoate, was prepared from the acid by refluxing the acid two hours with 2.4 equiv. of SOCl₂ and used directly without purification. It was stirred at this temperature for 3 hours and at room temperature overnight. Next morning it was quenched with NH₄Cl, extracted with Et₂O (3 x 10 mL) and combined organic phases were dried with MgSO₄ and the solvent was evaporated under reduced pressure. Purification was performed by flash chromatography on silica gel (Pentane:Et₂O 10:1) and the product was obtained in 27% yield.

\(^{1}\)H NMR (CDCl₃, 400 MHz): δ 8.42 (s, 1H), 8.13 (d, J = 7.7 Hz, 1H), 7.92 (d, J = 7.8 Hz, 1H), 7.63 – 7.59 (m, 4H), 7.47 – 7.37 (m, 7H), 3.85 (s, 3H), 0.89 (s, 3H). \(^{13}\)C NMR (CDCl₃, 101 MHz): δ 231.4, 166.1, 141.7, 135.1, 133.9, 133.6, 133.2, 131.8, 130.6, 130.2, 129.7, 128.8, 128.3, 127.8, 52.2, -3.5. HRMS (ESI+, m/z) calc. for 383.10739 [M+Na], found 383.10712.

(S)-1-(dimethyl(phenyl)silyl)-3-methyl-1-phenylbutan-1-ol (2d)

Following the reported procedure,[8] in a flame-dried Schlenk flask, CuBr-SMe₂ 5.13 mg, 0.025 mmol) and ligand L1 (18 mg, 0.030 mmol) were dissolved in dry iBuOMe (2 mL) under nitrogen atmosphere and the solution was stirred at room temperature for 10 min. Then acylsilane 1d (120.2 gm, 0.5 mmol) in 2 mL of iBuOMe and CeCl₃ (123 mg, 0.5 mmol) were added and the mixture was stirred for another 30 min before being cooled to -78 °C. BF₃·OEt₂ (0.062 mL, 0.5 mmol) was added to the cooled mixture and the mixture was stirred for another 30 min, followed by slow addition (over 2 h by syringe pump) of iBuMgBr (0.55 mL, 1 mmol). After 1 h of additional stirring, the reaction was quenched with saturated aqueous NH₄Cl solution (4 mL) and warmed up to room temperature. The reaction mixture was extracted with Et₂O (3 x 10 mL). The combined organic layers were dried with anhydrous MgSO₄, filtered and the solvent was evaporated. The crude product was purified by flash chromatography on silica gel (Pentane:Et₂O 40:1) and the product was obtained in 58% yield.

\(^{1}\)H NMR (CDCl₃, 400 MHz): δ 7.44 – 7.40 (m, 3H), 7.38 – 7.34 (m, 2H), 7.31 – 7.27 (m, 2H), 7.18 – 7.14 (m, 3H), 2.14 (dd, J = 14.6, 4.9 Hz, 1H), 1.79 (dd, J = 14.6, 7.3 Hz, 1H), 1.75 – 1.66 (m, 1H), 1.50 (s, 1H), 0.90 (d,
1H), 7.63 – 7.59 (m, 4H), 7.47 – 7.37 (m, 7H), 3.85 (s, 3H), 0.89 (s, 3H). 13C NMR performed by flash chromatography on silica gel (Pentane:Et$_2$O 10:1) and the acylsilane atmosphere and the solution was stirred at room temperature for 10 min. Then up to room temperature. The reaction mixture was extracted with Et$_2$O (3 x 10 ml) and combined organic phases were dried with anhydrous MgSO$_4$, filtered and the solvent was evaporated. The next morning it was quenched with NH$_4$Cl, used directly without purification. It was stirred at this temperature for 3 hours and cooled to -78 °C. BF$_3$·OEt$_2$ (0.062 mL, 0.5 mmol) was added to the cooled mixture and the mixture was stirred for another 30 min before being warmed to room temperature. The reaction was quenched with saturated aqueous NH$_4$Cl solution (4 mL) and warmed to room temperature. The reaction mixture was filtered through a plug of silica, the solvent evaporated and concentrated under vacuum. If full conversion was not complete it was purified by flash chromatography on silica gel using different mixtures pentane:Et$_2$O as the eluent. But under optimized conditions full conversion was obtained in all the cases. Then, the product was dissolved in THF (0.1 M) and transferred to a flame-dried Schlenk to which a solution of TBAF in THF was added (5 equiv.) and the mixture was stirred for an additional 5 hours. Then it was quenched with saturated NH$_4$Cl (2 mL) and the organic phase extracted with Et$_2$O (3x4 mL). The combined organic phases were dried with MgSO$_4$ and solvent was evaporated under reduced pressure. The product could not be separated from the fluorosilane by column chromatography neither by PLC, and thus the crude was used to determine the enantiomeric excess was determined by chiral HPLC analysis. Racemic compounds were prepared by addition of iBuLi to the corresponding ketone.

### 4.4.2. General procedure for the Brook rearrangement/trapping of benzylic α-hydroxysilanes

In a flame-dried Schlenk flask 0.1 mmol (1 equiv.) of hydroxysilane 2 was dissolved in 1 mL of Et$_2$O, under N$_2$ atmosphere. For the trapping attempts the electrophile was added to the medium and cooled down to -78 °C, after which nBuli (1 equiv.) was added. It was allowed to stir at that temperature for two hours and then gradually warm up to room temperature overnight. For the experiments without external electrophiles (proton trapping) to hydroxysilane 2 in THF, LiO$^-$Bu (0.05 equiv.) was added and stirred at room temperature for 3 h. In both cases, after the indicated time, the reaction mixture was filtered through a plug of silica, the solvent evaporated and concentrated under vacuum. If full conversion was not complete it was purified by flash chromatography on silica gel using different mixtures pentane:Et$_2$O as the eluent. But under optimized conditions full conversion was obtained in all the cases. Then, the product was dissolved in THF (0.1 M) and transferred to a flame-dried Schlenk to which a solution of TBAF in THF was added (5 equiv.) and the mixture was stirred for an additional 5 hours. Then it was quenched with saturated NH$_4$Cl (2 mL) and the organic phase extracted with Et$_2$O (3x4 mL). The combined organic phases were dried with MgSO$_4$ and solvent was evaporated under reduced pressure. The product could not be separated from the fluorosilane by column chromatography neither by PLC, and thus the crude was used to determine the enantiomeric excess was determined by chiral HPLC analysis. Racemic compounds were prepared by addition of iBuLi to the corresponding ketone.
4-methyl-2-phenylpentan-2-ol (3a)

The analytical data were found to be in accordance with those reported in the literature.[10]

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.44 (d, $J$ = 8.0 Hz, 2H), 7.34 (t, $J$ = 7.7 Hz, 2H), 7.23 (t, $J$ = 7.3 Hz, 1H), 1.80 (dd, $J$ = 14.3, 5.7 Hz, 1H), 1.71 (dd, $J$ = 14.3, 6.2 Hz, 1H), 1.66 – 1.57 (m, 1H), 1.56 (s, 3H), 0.88 (d, $J$ = 6.6 Hz, 3H), 0.76 (d, $J$ = 6.6 Hz, 3H).

$^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 148.4, 128.2, 126.5, 124.9, 75.4, 52.9, 31.5, 24.6, 24.5.

6-methyl-4-phenylhept-1-en-4-ol (3b)

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.40 – 7.38 (m, 2H), 7.33 (t, $J$ = 7.7 Hz, 2H), 7.24 – 7.20 (m, 1H), 5.51 (dddd, $J$ = 17.1, 10.1, 8.9, 5.9 Hz, 1H), 5.16 – 5.09 (m, 2H), 2.70 (ddt, $J$ = 13.7, 5.8, 1.2 Hz, 1H), 2.47 (dd, $J$ = 13.6, 8.8 Hz, 1H), 1.82 (dd, $J$ = 14.2, 5.2 Hz, 1H), 1.68 (dd, $J$ = 14.2, 6.8 Hz, 1H), 1.61 – 1.53 (m, 1H), 0.90 (d, $J$ = 6.6 Hz, 3H), 0.68 (d, $J$ = 6.7 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 146.3, 133.6, 128.2, 126.4, 125.4, 120.0, 77.3, 76.3, 51.4, 48.8, 24.7, 24.3, 24.3.

(S)-3-methyl-1-phenylbutan-1-ol (4a)

The analytical data were found to be in accordance with those reported in the literature.[11]

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.36-7.32 (m, 4H), 7.30 – 7.27 (m, 1H), 4.75 (dd, $J$ = 8.2, 5.3 Hz, 1H), 1.78-1.66 (m, 2H), 1.59 (s, 1H), 1.54-1.47 (m, 1H), 0.96 (d, $J$ = 6.5 Hz, 3H), 0.95 (d, $J$ = 6.5 Hz, 3H). $^{13}$C NMR (CDCl$_3$, 101 MHz): $\delta$ 145.3, 128.6, 127.6, 126.0, 72.9, 48.5, 24.9, 23.3, 22.4. The $[\alpha]$$_D^{20}$ was measured to be -36.0 (c 0.7, CHCl$_3$) and the absolute configuration of the alcohol was determined to be S by comparison of the sign of the reported optical rotation.[11] The enantiomeric excess was dependent on the reaction (30-88 %), determined by chiral HPLC analysis, Chiralcel ODH column, n-heptane/iPrOH 99:1, 0.5 mL/min, detection at 190 nm. Retention times 36.0 min (major) and 42.7 min (minor).

(S)-1-(4-fluorophenyl)-3-methylbutan-1-ol (4b)

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.31 (dd, $J$ = 8.5, 5.6 Hz, 2H), 7.02 (t, $J$ = 8.7 Hz, 2H), 4.73 (dd, $J$ = 7.9, 5.6 Hz, 1H), 1.82 (s, 1H), 1.75 – 1.63 (m, 2H), 1.51 – 1.43 (m, 1H), 0.95 (d, $J$ = 6.4 Hz, 3H), 0.94 (d, $J$ = 6.4 Hz, 3H). 13C NMR (CDCl$_3$, 101 MHz): $\delta$ 162.3 (d, $J$ = 245.3 Hz), 141.1 (d, $J$ = 3.1 Hz), 127.6 (d, $J$ = 8.0 Hz), 115.4 (d, $J$ = 21.3 Hz), 72.3, 48.6, 24.9, 23.2, 22.4. 19F NMR (CDCl$_3$, 376 MHz): $\delta$ -115.3 (tt, $J$ = 8.8, 5.5 Hz). HRMS (ESI-, m/z) calc. for 181.10232 [M-H] $^-$, found 181.10324. The enantiomeric excess was 67 %, determined by chiral HPLC analysis, Chiralcel ODH column, n-heptane/iPrOH 99:1, 0.5 mL/min, detection at 190 nm. Retention times 29.4 min (major) and 30.7 min (minor).

(S)-1-(4-(tert-butyl)phenyl)-3-methylbutan-1-ol (4c)

$^1$H NMR (CDCl$_3$, 400 MHz): $\delta$ 7.38 (d, $J$ = 8.4 Hz, 2H), 7.29 (d, $J$ = 8.3 Hz, 2H), 4.72 (dd, $J$ = 8.1, 5.3 Hz, 1H), 1.86 (s, 1H), 1.79 – 1.68 (m, 2H), 1.56 – 1.48 (m, 1H), 1.34 (s, 9H), 0.969 (d, $J$ = 6.4 Hz, 3H), 0.965 (d, $J$ = 6.4 Hz, 3H). 13C NMR (CDCl$_3$, 101 MHz): $\delta$ 150.5, 142.4, 125.7, 125.5, 72.6, 48.3, 34.6, 31.5, 24.9, 23.3, 22.4. HRMS (ESI-, m/z) calc. for 219.17434 [M-H] $^-$, found 219.17512. The enantiomeric excess was 74 %, determined by chiral HPLC analysis, Chiralcel ODH column, n-heptane/iPrOH 99:1, 0.5 mL/min, detection at 190 nm. Retention times 24.0 min (minor) and 25.1 min (major).
The analytical data were found to be in accordance with those reported in the literature.\[10\]

\[\text{1H NMR (CDCl}_3, 400 MHz): \delta\] 7.31 (dd, J = 8.5, 5.6 Hz, 2H), 7.02 (t, J = 8.7 Hz, 2H), 4.73 (dd, J = 7.9, 5.6 Hz, 1H), 1.82 (s, 1H), 1.75 – 1.63 (m, 2H), 1.51 – 1.43 (m, 1H), 0.95 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H).

\[\text{13C NMR (CDCl}_3, 101 MHz): \delta\] 148.4, 128.2, 126.5, 124.9, 75.4, 52.9, 31.5, 24.6, 24.5.

\[\text{6-methyl-4-phenylhept-1-en-4-ol (3b)}\]

\[\text{1H NMR (CDCl}_3, 400 MHz): \delta\] 7.40 – 7.38 (m, 2H), 7.33 (t, J = 7.7 Hz, 2H), 7.24 – 7.20 (m, 1H), 5.51 (dddd, J = 17.1, 10. 1, 8.9, 5.9 Hz, 1H), 5.16 – 5.09 (m, 2H), 2.70 (ddt, J = 13.7, 5.8, 1.2 Hz, 1H), 2.47 (dd, J = 13.6, 8.8 Hz, 1H), 1.82 (dd, J = 14.2, 5.2 Hz, 1H), 1.68 (dd, J = 14.2, 6.8 Hz, 1H), 1.61 – 1.53 (m, 1H), 0.90 (d, J = 6.6 Hz, 3H), 0.68 (d, J = 6.7 Hz, 3H).

\[\text{13C NMR (CDCl}_3, 101 MHz): \delta\] 146.3, 133.6, 128.2, 126.4, 125.4, 120.0, 77.3, 76.3, 51.4, 48.8, 24.7, 24.3, 24.3.

\[\text{(S)-3-methyl-1-phenylbutan-1-ol (4a)}\]

The analytical data were found to be in accordance with those reported in the literature.\[11\]

\[\text{1H NMR (CDCl}_3, 400 MHz): \delta\] 7.36-7.32 (m, 4H), 7.30 – 7.27 (m, 1H), 4.75 (dd, J = 8.2, 5.3 Hz, 1H), 1.78-1.66 (m, 2H), 1.59 (s, 1H), 1.54- 1.47 (m, 1H), 0.96 (d, J = 6.5 Hz, 3H), 0.95 (d, J = 6.5 Hz, 3H).

\[\text{13C NMR (CDCl}_3, 101 MHz): \delta\] 145.3, 128.6, 127.6, 126.0, 72.9, 48.5, 24.9, 23.3, 22.4. The [α] D20 was measured to be -36.0 (c 0.7, CHCl3) and the absolute configuration of the alcohol was determined to be S by comparison of the sign of the reported optical rotation.\[11\] The enantiomeric excess was dependent on the reaction (30-88 %), determined by chiral HPLC analysis, Chiralcel ODH column, n-heptane/iPrOH 99:1, 0.5 mL/min, detection at 190 nm. Retention times 36.0 min (major) and 42.7 min (minor).

\[\text{(S)-1-(4-fluorophenyl)-3-methylbutan-1-ol (4b)}\]

\[\text{1H NMR (CDCl}_3, 400 MHz): \delta\] 7.31 (dd, J = 8.5, 5.6 Hz, 2H), 7.02 (t, J = 8.7 Hz, 2H), 4.73 (dd, J = 7.9, 5.6 Hz, 1H), 1.82 (s, 1H), 1.75 – 1.63 (m, 2H), 1.51 – 1.43 (m, 1H), 0.95 (d, J = 6.4 Hz, 3H), 0.94 (d, J = 6.4 Hz, 3H).

\[\text{13C NMR (CDCl}_3, 101 MHz): \delta\] 162.3 (d, J = 245.3 Hz), 141.1 (d, J = 3.1 Hz), 127.6 (d, J = 8.0 Hz), 115.4 (d, J = 21.3 Hz), 72.3, 48.6, 24.9, 23.2, 22.4. \[\text{19F NMR (CDCl}_3, 376 MHz): \delta\] -115.3 (tt, J = 8.8, 5.5 Hz). HRMS (ESI-, m/z) calc. for 181.10232 [M-H] -, found 181.10324. The enantiomeric excess was 67 %, determined by chiral HPLC analysis, Chiralcel ODH column, n-heptane/iPrOH 99:1, 0.5 mL/min, detection at 190 nm. Retention times 29.4 min (major) and 30.7 min (minor).

\[\text{(S)-1-(4-(tert-butyl)phenyl)-3-methylbutan-1-ol (4c)}\]

\[\text{1H NMR (CDCl}_3, 400 MHz): \delta\] 7.38 (d, J = 8.4 Hz, 2H), 7.29 (d, J = 8.3 Hz, 2H), 4.72 (dd, J = 8.1, 5.3 Hz, 1H), 1.86 (s, 1H), 1.79 – 1.68 (m, 2H), 1.56 – 1.48 (m, 1H), 1.34 (s, 9H), 0.969 (d, J = 6.4 Hz, 3H), 0.965 (d, J = 6.4 Hz, 3H).

\[\text{13C NMR (CDCl}_3, 101 MHz): \delta\] 150.5, 142.4, 125.7, 125.5, 72.6, 48.3, 34.6, 31.5, 24.9, 23.3, 22.4. HRMS (ESI-, m/z) calc. for 219.17434 [M-H] -, found 219.17512. The enantiomeric excess was 74 %, determined by chiral HPLC analysis, Chiralcel ODH column, n-heptane/iPrOH 99:1, 0.5 mL/min, detection at 190 nm. Retention times 24.0 min (minor) and 25.1 min (major).

\[\text{4.4.3. Vibrational Circular Dichroism (VCD) studies}\]

Experimental InfraRed (IR) and Vibrational Circular Dichroism (VCD) spectra were measured on a Bruker Vertex 70 Fourier Transform IR spectrometer interfaced with a PMA 50 module. The PEM center frequency was set to 1400 cm\(^{-1}\). Both enantiomers of hydroxysilane (2a and ent-2a) were measured in deuterated chloroform using a CaF transmission cell with a path length of 50 µm. To have appropriate IR absorptions for the VCD measurements, concentrations of 1.0 and 1.9 molar were used for the frequency intervals 1000 - 1140 cm\(^{-1}\) and 1140 - 1650 cm\(^{-1}\), respectively. Baseline correction was performed using the spectrum of the solvent.

Conformational searches were performed with the MacroModel module of Schrödinger software package\[^{[12]}\] using the Merck Molecular Force Field\[^{[13]}\] and an
energy cutoff of 10 kcal/mol. The resulting conformers were further optimized with Density Functional Theory at the BP86/TZP\cite{14} level of theory using the QUILD\cite{15} optimization routines from the ADF 2016 software suite.\cite{16,17} IR and VCD calculations\cite{18} were performed for all low-energy conformers within an energetic window of 2 kcal/mol (i.e., 20 conformers). The resulting dipole and rotational strengths were broadened with a Lorentzian function using a half-width of 8 cm\(^{-1}\). The computed frequencies were uniformly scaled with a factor of 1.009.

In Fig. S1 the VCD spectrum simulated for compound 2a is shown on top of the experimental VCD spectrum. An excellent agreement was found in the spectral regions between 1000 - 1200 cm\(^{-1}\) and 1350 - 1650 cm\(^{-1}\). This suggests that the absolute configuration (AC) of the experimental sample is \(S\). In the frequency interval between 1200 - 1350 cm\(^{-1}\), however, the simulated spectrum exhibits intense bands that are absent in the experimental spectrum. To assess whether this discrepancy can affect the assignment of the AC, the structures and spectra of the individual conformers have been carefully analyzed. The analysis of the structures has revealed that the low-energy conformers can be grouped into families consisting of conformers that differ only in the orientation of the hydroxyl bond, while the analysis of the spectra has shown that the conformers in a given family have VCD spectra that differ mostly in the problematic region. As an example, the spectra and structures of the conformers in such a family are compared in Fig. S1.

As can be seen, the VCD spectra of the three conformers are similar outside the 1200 - 1350 cm\(^{-1}\) frequency interval and very different inside this interval. Further, a general coupled oscillator (GCO) VCD analysis\cite{19} of the bands in the problematic region has shown that the intense VCD signals originate from the coupling between the hydroxyl group and the rest of the molecule. This clarifies the origin of the discrepancies highlighted in Fig. S1 and assures that they are of no concern for the AC assignment. As shown\cite{19,20} previously, the magnitude (and sign) of such GCO VCD bands depends sensitively on the relative orientation of the coupling fragments. Changes of a few degrees in the orientation of the OH bond (which will not affect much the energies of the conformers), will induce large magnitude changes in the VCD intensity of these bands. Since this perturbation affects only this particular region of the spectrum, and since outside this region the agreement between theory and experiment is excellent, it is clear that the assignment of the AC of the experimental sample as \(S\) is conclusive.
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Energy cutoff of 10 kcal/mol. The resulting conformers were further optimized with Density Functional Theory at the BP86/TZP [14] level of theory using the QUIL [15] optimization routines from the ADF 2016 software suite. IR and VCD calculations [18] were performed for all low-energy conformers within an energetic window of 2 kcal/mol (i.e., 20 conformers). The resulting dipole and rotational strengths were broadened with a Lorentzian function using a half-width of 8 cm⁻¹. The computed frequencies were uniformly scaled with a factor of 1.009.

In Fig. S1 the VCD spectrum simulated for compound 2a is shown on top of the experimental VCD spectrum. An excellent agreement was found in the spectral regions between 1000 - 1200 cm⁻¹ and 1350 - 1650 cm⁻¹. This suggests that the absolute configuration (AC) of the experimental sample is S. In the frequency interval between 1200 - 1350 cm⁻¹, however, the simulated spectrum exhibits intense bands that are absent in the experimental spectrum. To assess whether this discrepancy can affect the assignment of the AC, the structures and spectra of the individual conformers have been carefully analyzed. The analysis of the structures has revealed that the low-energy conformers can be grouped into families consisting of conformers that differ only in the orientation of the hydroxyl bond, while the analysis of the spectra has shown that the conformers in a given family have VCD spectra that differ mostly in the problematic region. As an example, the spectra and structures of the conformers in such a family are compared in Fig. S1. As can be seen, the VCD spectra of the three conformers are similar outside the 1200 - 1350 cm⁻¹ frequency interval and very different inside this interval. Further, a general coupled oscillator (GCO) VCD analysis [19] of the bands in the problematic region has shown that the intense VCD signals originate from the coupling between the hydroxyl group and the rest of the molecule. This clarifies the origin of the discrepancies highlighted in Fig. S1 and assures that they are of no concern for the AC assignment. As shown [19, 20] previously, the magnitude (and sign) of such GCO VCD bands depends sensitively on the relative orientation of the coupling fragments. Changes of a few degrees in the orientation of the OH bond (which will not affect much the energies of the conformers), will induce large magnitude changes in the VCD intensity of these bands. Since this perturbation affects only this particular region of the spectrum, and since outside this region the agreement between theory and experiment is excellent, it is clear that the assignment of the AC of the experimental sample as S is conclusive.

Figure S1. Comparison of the experimental (black) and simulated (red) VCD spectra of 2a. The simulated spectrum was obtained by averaging the VCD spectra computed for the low-energy conformers within an energetic window of 2 kcal/mol. To illustrate the effects induced in the VCD spectra by the general coupled oscillator (GCO) VCD mechanism, the spectra and structure of conformers 2, 8 and 17 are also compared. As highlighted, the sign and magnitude of the intense GCO VCD bands in the frequency interval between 1250 and 1370 cm⁻¹ depend sensitively on the orientation of the hydroxyl bonds in the three conformers (indicated by the blue arrows).
4.5 References


4.5 References


If you have built castles in the air, your work need not be lost; that is where they should be. Now put the foundations under them.

Henry David Thoreau, *Walden*

In this chapter the use of organomagnesium reagents for a swift and a versatile derivatisation of diarylimines to the corresponding α-substituted diarylmethylamines is described, leading to α-tertiary amines in excellent yields, through fast and clean reactions. Where it occurs, 1,2-reduction can be circumvented using readily accessible dialkylmagnesium reagents.