More than a Protective Group: Synthesis and Applications of a New Chiral Silane

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Maurizio Campagna, Michael Trzoss, and Stefan Bienz*

Institute of Organic Chemistry, University of Zurich, Winterthurerstrasse 190, 8057 Zurich, Switzerland

sbienz@oci.uzh.ch

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ABSTRACT



Enantiomerically pure (-)-(R)- and (+)-(S)-(1-methoxy-2,2,2-triphenylethyl)dimethylsilanes (MOTES-H) were synthesized from triphenylacetaldehyde in five synthetic steps and with 60% overall yield. MOTES-protected α - and β -hydroxycarbonyl compounds were used in Grignard and Diels– Alder reactions in the presence of MgBr₂ to afford addition products with 87–98% yield and selectivities of up to >120:1 dr. With this method, the pine beetle pheromone (-)-frontalin (67%, 98.5% ee) and naturally occurring (-)-(R)-octane-1,3-diol (90%, >99% ee) were synthesized.

Silyl groups have been extensively used in organic chemistry mainly as protecting or activating moieties¹ but also as auxiliaries for stereoselective synthesis.² We have introduced a number of chiral silicon groups that were applied in diastereoselective transformations.^{3,4} Here we present a new

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silicon group that is more readily synthesized, not prone to racemization, and that can be used as a protective group, highly efficient chiral auxiliary, and chiral derivatizing agent.

Enantiomerically pure silanes (-)-(R)-**3** and (+)-(S)-**3** ((1methoxy-2,2,2-triphenylethyl)dimethylsilane, MOTES-H) were synthesized from triphenylacetaldehyde⁵ (**1**) (Scheme 1). Reaction with Me₂PhSiLi⁶ and Me₂SO₄ formed phenylsilane (±)-**2**, and treatment with Br₂/Fe followed by reduction with LAH afforded racemic product (±)-**3** (overall 82%). Resolution of the enantiomers was effected by chromatographic separation of the silyl ethers obtained with (S)-1,1,2triphenylethane-1,2-diol, followed by reduction with LAH, and the absolute configuration of the enantiomers was determined by X-ray analysis of a crystalline derivative. The

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hydrosilanes MOTES-H are stable compounds that can be stored at 23 $^{\circ}$ C for several months without decomposition.



^{*a*} Only major isomers shown. ^{*b*} To a solution of **4** or **5** (1.0 mmol) in CH₂Cl₂ (10.0 mL) was added subsequently a solution of MgBr₂ (4.0 mL, 1.0 M in Et₂O) and dropwise, at -78 °C, a solution of the Grignard reagent (3.0 mL, 1.0 M in Et₂O). After 20 min, the reaction was quenched with saturated aqueous NH₄Cl solution. ^{*c*} To a solution of **6** or **7** (0.46 mmol) in CH₂Cl₂ (7.0 mL) was added a solution of Mg(OTf)₂ (1.4 mL, 1.0 M in Et₂O), followed by cyclopentadiene (0.57 mL, 7.0 mmol) at -78 °C. After 20 min, the reaction was quenched with H₂O. ^{*d*} Combined yields of the two isomers in %.

The versatility of the MOTES group is demonstrated with the highly stereoselective chelate-controlled 1,2-addition of organometallics to the α - and β -silyloxycarbonyl compounds 4 and 5⁷ and the Lewis-acid-mediated Diels–Alder addition of cyclopentadiene to the enones 6 and 7^8 (Table 1).⁹ In the reactions of the Grignard reagents we focused our attention on the 1,2-additions to α - and β -silyloxyaldehydes since they have been reported to show lower selectivities in these types of reactions as compared to their corresponding ketones.^{4,10} Diastereometic ratios (dr) of up to >120:1 were observed in the transformations; the dr values of up to 16:1 for the reactions with 5 are among the best found for chiral 1,6inductions so far.¹¹ Selectivities were determined by ¹H NMR, and the absolute configurations were deduced by chemical correlation. The enantiomerically pure auxiliary can be recovered almost quantitatively as (R)- or (S)-MOTES-H ((-)-(R)- or (+)-(S)-3) through reductive deprotection of the addition products.

The stereochemical outcome of the reactions is consistent with the formation of intermediary tridentate chelate complexes, where the π -facial attack is sterically controlled (Figure 1). It was experienced that the Lewis acid plays a



Figure 1. Proposed transition structures for the MOTES-directed stereoselective reactions.

pivotal role with regard to the extent of the selectivities without pre-complexation of the substrates, distinctively lower selectivities were observed for all transformations.

MgBr₂ was used as the Lewis acid since this additive proved advantageous over other metal salts in previous related investigations.^{3,4} The scope of possible alternative Lewis acids and other additives, however, has not been fully explored yet and could give rise to interesting effects.¹²

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Applications of the MOTES group are shown with the enantioselective syntheses of naturally occurring (-)-fron $talin^{13}$ and (-)-(R)-octane-1,3-diol (26)¹⁴ (Scheme 2).

Table 2. MOTES as a Chiral Derivatizing Group

Due to its rather simple structure and its bioactivity, frontalin has attracted the interest of the chemical community, which has led to more than 40 syntheses of the natural product so far.¹⁵ Our enantioselective preparation of (-)frontalin is rather simple: silulation of α -hydroxyacetone with (R)-MOTES-Br afforded α -silvloxyketone (R)-22, which was treated with MgBr₂ and Grignard reagent 23^{16} to deliver directly the natural product in 67% overall yield and 98.5% ee after acidic workup (Scheme 2). When the addition product 24 was isolated first (96%) and subsequently reduced with LAH, diol 25 was formed in 95% yield together with the auxiliary, recovered as (R)-MOTES-H in almost quantitative yield. Treatment of 24 with TBAF in THF resulted in cleavage of the silvl ether under mild conditions and delivered diol 25 in 96% yield. Transacetalization of 25 to (-)-frontalin was effected in 98% yield by treatment with a catalytic amount of p-TsOH.

(-)-(R)-Octane-1,3-diol ((R)-27) was prepared by addition of pentylmagnesium bromide to aldehyde (R)-5, followed by reductive cleavage of silvl ether 26. The addition product 26 arose with a dr of 16:1 and was further enriched by chromatography to a dr of >99:1. Thus, the final 1,3-diol (R)-27 was obtained in essentially enantiomerically pure form.

As described above, the diastereomeric ratios observed in our transformations were easily determined by ¹H NMR. Even though different chemical shifts for diastereomeric compounds are common, the MOTES group shows distinct and in most cases baseline resolved signals (singlets at ca. 5, ca. 3.5, ca. 0.3, and ca. -0.1 ppm) in different areas of the spectra. This observation along with the ease of the formation of MOTES ethers prompted us to investigate the application of the MOTES group as a silicon-based chiral derivatizing agent (CDA).^{17,18} Thus, a number of diastereo-

	нс	$ \begin{array}{c} \mathcal{O}_{\mathcal{O}}(S) \\ \mathcal{O}_{\mathcal{O}}(R) \\ \mathcal{R}^{2} \end{array} \xrightarrow{(S)-3/(R)-3} $		DMe , O,(^{S)} R ¹ , Si / + MeMe R ²	$\begin{array}{c} \text{OMe} \\ \vdots \\ \text{Ph} \\ (R) \begin{array}{c} \text{Si} \\ (R) \begin{array}{c} \text{Si} \\ (R) \end{array} \end{array} \\ \text{Ph} \begin{array}{c} \text{Output} \\ (R) \end{array} \\ \text{Ph} \begin{array}{c} \text{MeMe} \\ \text{R}^2 \end{array} \end{array}$		
	28–33 H ₂ N,(S) Ph (S)-3/(R)-3 3:1 Me 34		35	5a–40a	35b-40b Ph (R) Si N_{J} (S) Ph Ph MeMe Me		
			$ \begin{array}{c} 3:1 \\ \hline \end{array} \begin{array}{c} Ph \\ Ph \end{array} $	DMe H N (S) Ph S) Si + MeMe Me			
				41a	41b		
entry	educt	\mathbb{R}^1	\mathbb{R}^2	products	yield ^{a}	$\Delta {\delta_{\mathrm{a}}}^b$	$\Delta \delta_{ m b}{}^b$
1	28	Et	Me	35a/35b	95	0.312	0.324
2	29	i-Pr	${ m Me}$	36a/36b	93	0.339	0.332
3	30	Ph	${ m Me}$	37a/37b	96	0.132	0.527
4	31	Ph	\mathbf{Et}	38a/38b	97	0.144	0.531
5	32	Nph	${ m Me}$	39a/39b	97	0.208	0.541
6	33	$\dot{\rm CO}_2 { m Me}$	${ m Me}$	40a/40b	93	0.121	0.372
7	34			41a/41b	82	0.084	0.258

^a Combined yields in % of the two isomers. ^b $\Delta \delta_{a}$ and $\Delta \delta_{b}$: chemical shift differences in ppm of the signals of the diastereotopic Me₂Si of **35a**-**41a** and 35b-41b, respectively.



meric pairs of silylated ethers and an amine were prepared and studied by ¹H NMR. The derivatives of the α -aryl/alkyland alkoxycarbonyl/alkyl-substituted alcohols/amines, compounds **37a**-**41a**/**37b**-**41b**, in particular showed highly distinctive spectra, which allows for unambiguous identification and quantification of the compounds (Table 2).

As an example, a typical ¹H NMR spectrum of a mixture of (S,S)- and (R,S)-**39** (ratio 2.8:1) is shown in Figure 2. Interestingly, the effect of the CDA on the NMR is particularly pronounced at the signals of Si-bound groups rather than those of the original chiral alcohols. Above all, the signals of the two pairs of diastereotopic MeSi groups are typically well separated (see Table 2), which is beneficial since they are registered in an otherwise signal-free region of the spectrum.

The NMR results also suggest a potential application of the MOTES group as a CDA for the direct determination of absolute configurations. Except for the derivatives of the alkyl/alkyl-substituted alcohols, where the diastereomeric silyl ethers are not sufficiently differentiated (entries 1 and 2, Table 2), the relative shifting of the several signals due to the CDA is consistently related to the relative configurations of the two chiral moieties contained in the molecules: the chemical shift differences of the two MeSi signals of the silylated (R^*,R^*)-derivatives ($\Delta \delta_a$) are always smaller than those of the two MeSi signals of the (R^*,S^*)-derivatives ($\Delta \delta_b$), and in all cases the MeSi signals of the (R^*,R^*)derivatives are enframed by those of the (R^*,S^*)-counterparts. Whether this pattern proves reliable over a larger range of compounds is presently under investigation.

In conclusion, the MOTES group was shown to act efficiently as a protective and stereodirecting group as well as a potential CDA to differentiate enantiomeric alcohols and to determine their absolute configurations. Diastereo-selectivities of up to 98.8% and 94.2% respectivel, were obtained by 1,5- and 1,6-chiral inductions with MOTES-derivatized hydroxyaldehydes, -ketones, and -enones, and a synthetic application of the group was shown with the enantiospecific two-step preparation of (–)-frontalin. We believe that the MOTES group can be multifunctionally applied to any substrate that is able to chelate in derivatized form, and thus it can be used as a universal tool in enantioselective synthesis.

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Supporting Information Available: All experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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