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S$_N$2 Reactions at Tertiary Carbon Centers in Epoxides

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Abstract: We describe a novel concept for S$_N$2 reactions at tertiary carbon centers in epoxides without activation of the leaving group. Quantum chemical calculations show why S$_N$2 reactions at tertiary carbon centers are proceeding in these systems. Our reaction allows a flexible synthesis of 1,3-diol building blocks for natural product synthesis with excellent control of relative and absolute configuration.

Designing novel reactions based on mechanisms that are commonly considered as unfavorable is a challenging approach to research in chemistry. It allows the overcoming of limitations in our mechanistic understanding and lays the basis for the discovery of novel synthetic strategies.

S$_N$2 reactions at tertiary carbon atoms provide an attractive starting point for such a strategy. As yet, S$_N$2 reactions at tertiary carbon centers require either destabilization of the cation to be formed for the competing S$_N$1 reaction[1,2] or substrates with very good leaving groups.[3,4] A recent excellent example is the synthesis of isonitriles from tertiary trifluoroacetates and Me$_3$SiCN catalyzed by Sc(OTf)$_3$[5] that proceeds via stereoselective trapping of the contact ion-pair. A slight erosion of the exclusive inversion of configuration was observed, however. The reaction of epoxides with BF$_3$ and NaBH$_3$CN is conceptually similar.[6] It results in a ring-opening with hydride as nucleophile at the higher substituted carbon atom with inversion of configuration. The strong Lewis acid BF$_3$ may lead to rearrangements of the epoxide.

Here we report S$_N$2 reactions at tertiary carbon centers of epoxides relying on enforcing a favorable 'backside attack' of the nucleophile rather than on activating the leaving group. With unsymmetrically substituted epoxides typical S$_N$2 reactions occur at the less substituted carbon center and not at the more substituted carbon center. With our system, this selectivity is overcome by binding a pronucleophile to the substrate with subsequent activation of the intermediate formed by a catalyst. In this manner, the key-feature of S$_N$2 reactions, the complete inversion of configuration, is preserved, while side-reactions with activated leaving groups, such as skeletal rearrangements or erosion of stereochemical integrity via cation formation are avoided.

The reductive opening of Sharpless epoxides[7] affords an efficient approach to the synthetically important 1,3-diol unit. The regioselective opening at tertiary centers remains unresolved. Here, we chose PhSiH$_3$ with catalytic amounts of

tetrabutylammonium fluoride (TBAF)[8] to realize this goal via an epoxide hydrosilylation.[9] This reagent combination does not open simple trisubstituted epoxides. In 1,2-disubstituted epoxides hydroxy substitution is mandatory as demonstrated in a synthesis of 1,4-diols via S$_N$2 at secondary carbon centers that occurs via formation of a silyl ether and activation of the silyl ether by fluoride.
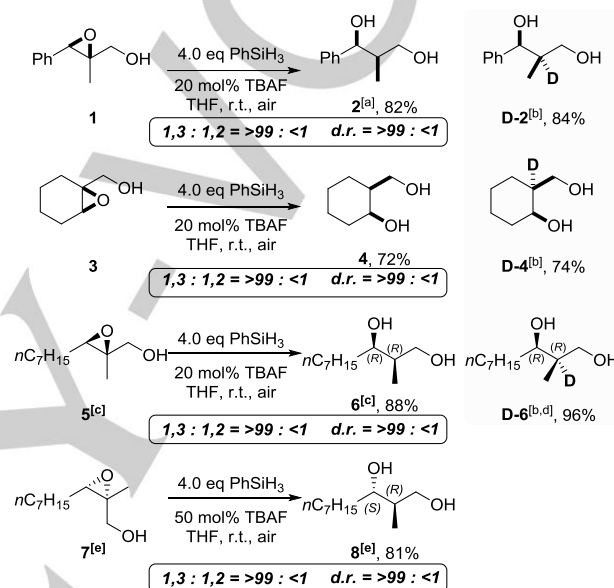
Scheme 1. Reductive opening of Sharpless epoxides containing tertiary carbon centers with PhSiH$_3$/cat. TBAF. [a] 80% yield obtained in 10 mmol scale of substrate with 1.5 eq PhSiH$_3$. [b] PhSiD$_3$ used instead of PhSiH$_3$. [c] e.r. = 94:6. [d] e.r. = 95:5. [e] e.r. = 81:19.

	reductant	1,3-diol [%]	1,2-diol [%]	ratio [1,3:1,2]
(1)	Red-Al	16	28	36:64
	BF$_3$/NaBH$_3$CN	—[a]	—[a]	—
(3)	Red-Al	—[a]	72	<1 : >99
	BF$_3$/NaBH$_3$CN	—[a]	63	<1 : >99
(5)	Red-Al	—[a]	70	<1 : >99
	BF$_3$/NaBH$_3$CN	—[a]	12	<1 : >99

Scheme 2. Comparison of the products distribution in the opening of **1**, **3**, and **5** with other systems (For conditions see SI). [a] The indicated product was not detected.

Opening of **1**, **3**, **5** with PhSiH$_3$/cat. TBAF results in exclusive formation of 1,3-diols with complete inversion of configuration (Scheme 1; see SI for structural assignments). No diastereomers or regioisomers of the desired products are detected or isolated from the reactions. With PhSiD$_3$/20 mol% TBAF D-**2**, D-**4**, and D-**6** were obtained regiospecifically ruling

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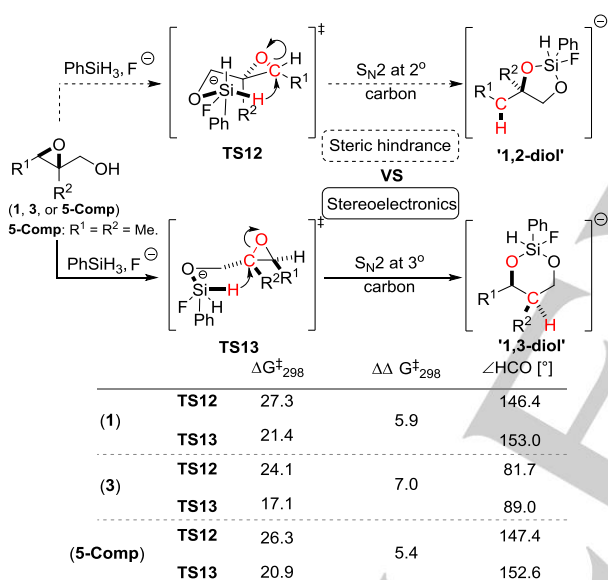   Gerhard Domagk Strasse 1, 53121 Bonn, Germany
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     Supporting information (SI) is given via a link at the end of the document.

out Meinwald or the concerted Semi-Pinacol rearrangements.[10,11] The observation that **8** and not **6** is obtained from **7** lends further support to the S_N2-mechanism. With **1**, **3**, and **5** (Scheme 2), well-established systems for epoxide opening either fail to yield the desired 1,3-diols (BF$_3$/NaBH$_3$CN)[6] or fail to provide them efficiently (Red-Al, [NaAlH$_2$(OCH$_2$CH$_2$OCH$_3$)$_2$]).[7]

This raises the question why PhSiH$_3$/cat. TBAF is efficient for S_N2 reactions at tertiary carbon atoms. We analyzed the transition states of the epoxide opening using a well-established quantum chemical calculation protocol.[12] Geometries were optimized with the global hybrid density functional PBEh-3c.[13] Thermostatistical contributions (ΔG_{RRHO}) were evaluated at the same level of theory. Highly accurate single point energy calculations (ΔE) have been carried out with the hybrid functional PW6B95-D3[14,15] in a large basis set (def2-QZVP). Solvation free energy contributions ($\Delta \delta$ Gsolv) were computed by COSMO-RS.[16] Free energies (ΔG) were obtained as sum of electronic energy (ΔE), thermostatistical (ΔG_{RRHO}) and solvation free energy ($\Delta \delta$ Gsolv) contributions.

center is substantially larger than that at the secondary carbon center (Figure 1). This results in an increased orbital overlap for the transition state of attack at the tertiary carbon atom. (Wiberg bond order for the developing H-C bond [**TS1 (1,3)**: 0.292 vs. **TS1 (1,2)**: 0.270; **TS5-Comp (1,3)**: 0.288 vs. **TS5-Comp (1,2)**: 0.242]).[17]

Scheme 4. Computed activation free energies for the ring-opening of **9** and **10** (in kcal mol^{-1}).

		$\Delta G^{\ddagger}_{298}$	$\Delta\Delta G^{\ddagger}_{298}$	$\angle$HCO [°]
(9)	**TS12**	25.7		147.3
	TS13	18.3	7.4	157.1
(10)	**TS12**	25.1		146.6
	TS13	18.8	6.3	157.2

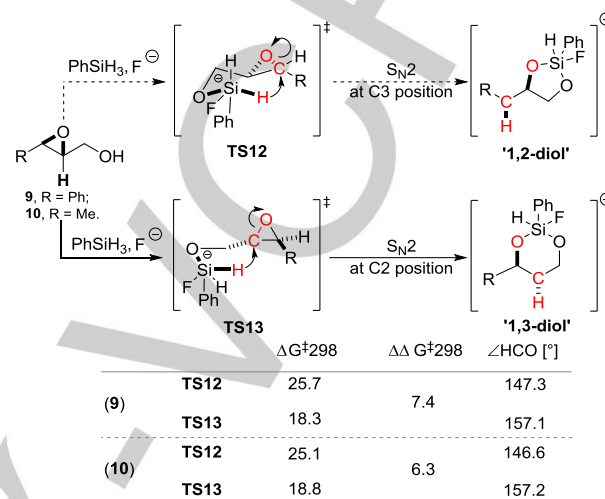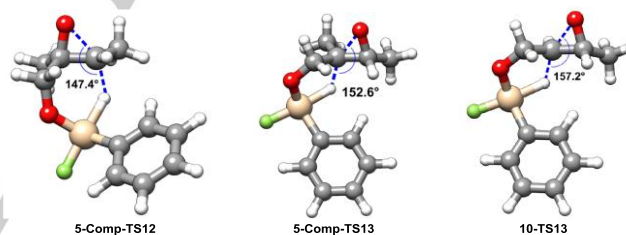**Figure 1.** Selected DFT-transition state structures (TS), see SI for details.

Scheme 3. Computed activation free energies (in kcal mol^{-1}) for the ring opening of **1**, **3**, and **5-Comp** at tertiary and secondary carbon atoms and H-C-O angle of 'backside' approach of the nucleophile.

		$\Delta G^{\ddagger}_{298}$	$\Delta\Delta G^{\ddagger}_{298}$	$\angle$HCO [°]
(1)	**TS12**	27.3		146.4
	TS13	21.4	5.9	153.0
(3)	**TS12**	24.1		81.7
	TS13	17.1	7.0	89.0
(5-Comp)	**TS12**	26.3		147.4
	TS13	20.9	5.4	152.6

The computed differential activation free energies [values for $\Delta G^{\ddagger}$ and $\Delta\Delta G^{\ddagger}$] of the ring-opening steps of **1**, **3**, and **5-Comp** – a simplified model for **5** – are summarized in Scheme 3. In all cases, the barriers for ring-opening at the tertiary carbon center are markedly lower than for opening at the secondary carbon center. Absolute free energy barriers are between 17.1 and 21.4 kcal mol^{-1}. The complete calculated mechanism is provided in the SI (Figure **S3**).

To identify the reason for the difference in $\Delta G^{\ddagger}$, we compared the H-C-O angles (H: H transferred from Si, C epoxide C approached by H, O: epoxide O) in the transition states of ring-opening. All angles obtained are smaller than the ideal 180°. In every case the angle for the opening at the tertiary carbon

We analyzed the opening step of **9** and **10** (Scheme 4), where a secondary carbon replaces the tertiary carbon in **1** and **5-Comp**. Opening to the 1,3-diol is even more favorable for **9** and **10** than for **1** and **5-Comp**. For 1,2-diol generation the H-C-O angle does not change significantly. In 1,3-diol generation, the H-C-O angle is substantially larger for **9** and **10** than for **1** and **5-Comp**. Replacing methyl substitution by hydrogen substitution (**1** and **5-Comp** vs. **9** and **10**) results in an increase of orbital overlap in the transition state leading to the 1,3-diol [**TS1 (1,3)**: 0.292 vs. **TS9 (1,3)**: 0.304; **TS5-Comp (1,3)**: 0.288 vs. **TS10 (1,3)**: 0.304]. The same trends were observed for the natural bond orders (NBOs, see SI for details).[18]

The preference of the S_N2 at the tertiary carbon center is thus due to a better orbital overlap in the transition state. These quantitative data are of relevance for the conceptually related cyclization reactions of mono-substituted epoxides discussed in the context of Baldwin's rules.[19]

The opening of **13** and **15** demonstrates the usefulness of our method in the preparation of diols with stereotriads (**14** and **16**) (Table 1). Such building blocks are pertinent to the synthesis of natural products with polyol units. Our reaction also provides excellent results for epoxides with secondary carbon centers. With Red-Al, we observed mixtures of 1,3- and 1,2-diols with **17** and **19** (83:17 for **18** and 22:78 for **20**)[7d].

Table 1. Examples for 1,3-diols via S$_N$2 reaction with Sharpless epoxides.[a]

Sharpless epoxide	1,3-diol	Yield (%)[b]
11	**12**	83
13	**14**	72
15	**16**	70
17	**18**	92
19	**20**	64

[a] 1.0 eq epoxide, 4.0 eq PhSiH$_3$, 20 mol% TBAF in THF at r.t. under air, work-up with NaOH solution. [b] No diastereomers and regioisomers were detected or isolated.
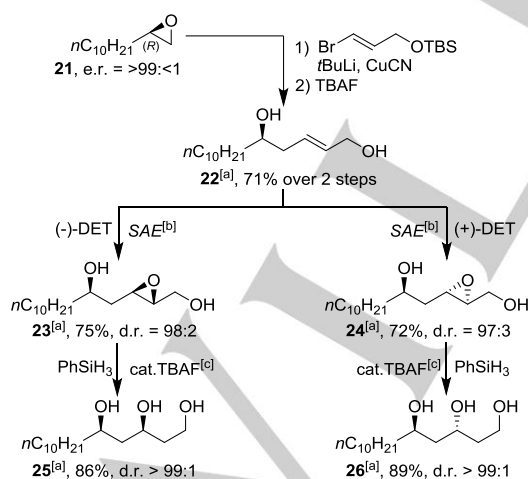
Scheme 5. Stereodivergent synthesis of acetate derived 1,3,5-triols **25** and **26** from **21**. [a] e.r. = >99:<1. [b] Sharpless epoxidation (SAE): 1.0 eq allylic alcohol, 5 mol% Ti(OiPr)$_4$, 6 mol% (+)-DET (diethyl tartrate) or (-)-DET, 2.0 eq tert-butylhydroperoxide in CH$_2$Cl$_2$. [c] 4.0 eq PhSiH$_3$, 20 mol% TBAF in THF at r.t. under air.
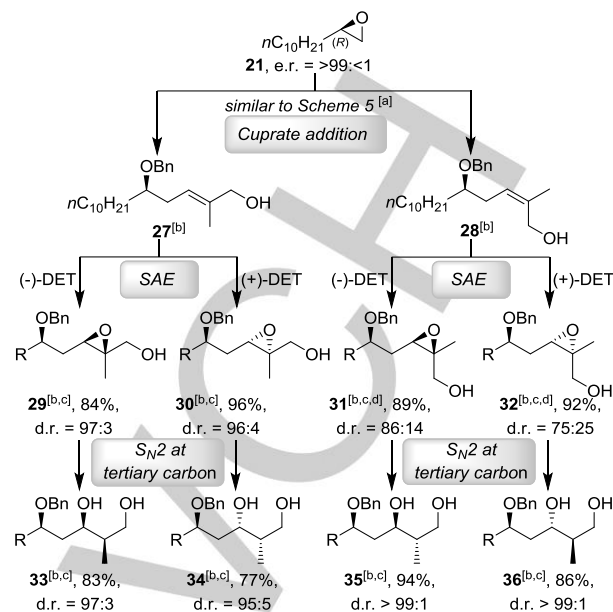
Scheme 6. Stereodivergent synthesis of all stereoisomers of acetate- and propionate derived trios via cuprate addition, SAE, and epoxide hydrosilylation [a] For details, see SI. [b] e.r. = >99:<1. [c] R = nC$_{10}$H$_{21}$. [d] Minor isomers were removed by chromatography.

Our system is attractive as key reaction for the development of a flexible and modular approach to the stereodivergent synthesis of acetate and propionate derived 1,3,5-triol units (Schemes 5 and 6). The syntheses of the acetate derived 1,3,5-triols start from **22** that can be obtained from enantiopure **21**[20] via a cuprate addition and deprotection. The Sharpless epoxidation (SAE)[21] provides **23** and **24** with excellent reagent control and **25** and **26** are obtained as single stereoisomers. Their enantiomers can be prepared from *ent*-**21** (Scheme 5).

The flexibility of our approach to 1,3,5-triols (Scheme 6) becomes evident in the synthesis of all stereoisomers of a 1,3,5-triol. The sequence features cuprate addition and SAE to provide trisubstituted allylic alcohols **27** and **28**, and the epoxides **29**, **30**, **31**, and **32**. Benzyl protection was employed to show that a differentiation of the hydroxy groups is possible. The triols were obtained with complete inversion of configuration.

We have developed a hydrosilylation of epoxides that allows S$_N$2 reactions at tertiary carbon centers through control of the angle of 'backside attack' of the H-nucleophile. Our method provides a flexible approach to molecules with 1,3-diol building blocks.

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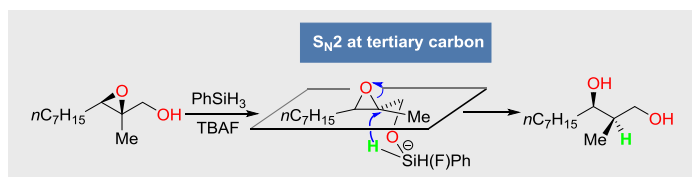
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S$_N$2 reactions at tertiary carbon centers in epoxides are possible when the angle of 'backside attack' is controlled! This is achieved by binding of the reagent and its activation to hydride transfer by fluoride. The reaction proceeds with excellent regioselectivity and allows the synthesis of many acetate and propionate derived 1,3-diol units pertinent to natural product synthesis.