Plans exist to extend this methodology to develop a competitive binding assay.

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[12] Mass spectra were recorded on a Micromass Quattro II mass spectrometer (Micromass, Manchester, UK) fitted with a Z-Spray electrospray source. NH_4OAc (2.5 mM, pH 7.0 unless otherwise stated) was used as a spraying buffer at a flow rate of 5 μL min^{-1}. The BmPBP solution (5 mg mL^{-1}, 2 μL, in 2.5 mM NH_4OAc, pH 7.0) was introduced into the flow using an injection valve. The cone voltage was 20 V and the drying gas temperature was 30 °C, unless otherwise stated. Recombinant BmPBP was produced and purified as previously described, except the hydroxylapatite column step was replaced by dialysis against 10 mM tris(hydroxymethyl)aminomethane (Tris) buffer (pH 8.0) with a Slide-A-lyzer cassette (Pierce, Rockford, IL, USA).[5, 13] BmPBP was concentrated and transferred into NH_4OAc buffer (see above) with a Vivaspin concentrator (molecular weight cut-off 5000 Da; Vivascience, Lincoln, UK). Data was analyzed with MassLynx 3.1 (Micromass) software which had MaxEnt (maximum entropy based) software embedded.

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[14] The BmPBP solution[12] was incubated with a 50-fold molar excess of each ligand overnight at 4 °C. Alcohols were added to buffered BmPBP as 0.6 M ethanolic solutions. The control was BmPBP without added ligand. The nonzero values for the control result from baseline noise.

Chemo-, Regio-, and Stereoselective Cyclization of 1,3-Bis(trimethylsilyloxy)-1,3-butadienes with Functionalized Epoxides**

Peter Langer* and Tobias Eckardt

Domino reactions are of interest in organic chemistry since they enable the rapid assembly of complex products in a one-pot process.[1] Despite the simplicity of the idea, only few reactions of 1,3-dianions and 1,3-dianion equivalents with 1,2-dielectrophiles have been reported so far.[2] Several drawbacks hinder these reactions: on the one hand, dianions are highly reactive compounds that can react both as a nucleophile and a base; on the other hand, 1,2-dielectrophiles often represent rather labile compounds, which can undergo a series of side reactions (formation of open-chain 2:1 products, single-electron transfer (SET) reactions, elimination, polymerization, decomposition, fragmentation). In the course of work on the development of domino reactions of dianions and dianion equivalents,[3] we recently developed the first cyclization reaction of dilithiated 1,3-dicarbonyl compounds with oxalic acid dielectrophiles.[4] These reactions provide an efficient, regio- and stereoselective route to the pharmacologically important class of γ-alkylidenebutenolides.

Herein, we report, to our knowledge, the first Lewis acid mediated cyclizations of 1,3-bis(trimethylsilyloxy)-1,3-butadienes, electroneutral equivalents of 1,3-dicarbonyl dianions,[5] with epoxides. These reactions allow, for the first time, a highly efficient and chemoselective synthesis of 2-alkylidenetetrahydrofurans with a great variety of substitution patterns and functional groups.[6, 7] The cyclizations not only proceed with very good chemo-, but also with very good regio- and stereoselectivities. The products are useful precursors for the synthesis of pharmacologically relevant tetrahydrofuran derivatives and natural products.[8] The preparative usefulness of the new cyclization reaction was demonstrated by the synthesis of methyl nonactate, a known precursor to the natural product nonactin.

Our first attempts to induce a cyclization reaction of propenoxide **2a** with 1,3-bis(trimethylsilyloxy)-1,3-butadiene **1a**, which was prepared in two steps from ethyl acetoacetate,[5c] were unsuccessful (Scheme 1, Table 1). The use of $BF_3 \cdot OEt_2$ as the Lewis acid resulted in formation of a complex reaction mixture. Only starting materials were isolated when trimethylsilyl trifluoromethanesulfonate (Me_3SiOTf) was employed. Equally disappointing results were obtained when the reaction was carried out at 20 °C in the presence of $ZnCl_2$. A complex mixture was obtained when the reaction was carried out at 0 → 20 °C using $TiCl_4$ as the Lewis acid (Table 1, entry 4).

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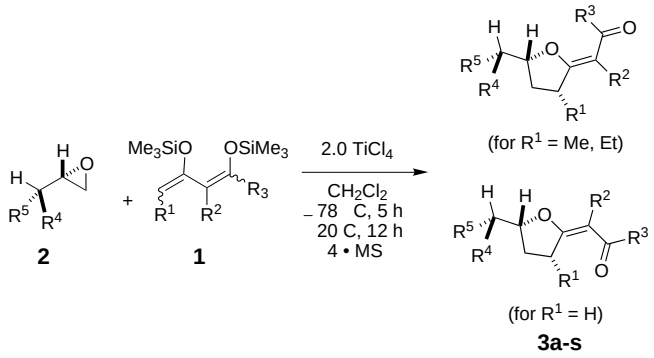

Scheme 1. Cyclization of epoxides **2** with 1,3-bis(trimethylsilyloxy)-1,3-dienes **1**.

Table 1. Optimization of the reaction of epoxide **2a** with diene **1a**.

Entry	Lewis acid (equiv)	**2a** [equiv]	*t* [h] [a]	Yield [%] [b]
1	$BF_3 \cdot Et_2O$ (2.0)	1	5 + 12	0
2	Me_3SiOTf (2.0)	1	5 + 12	0
3	$ZnCl_2$ (2.0)	1	0 + 12	0
4	$TiCl_4$ (2.0)	1	0 + 12 [c]	0
5	$TiCl_4$ (2.0)	1	5 + 0	12
6	$TiCl_4$ (2.0)	1	5 + 5	57
7	$TiCl_4$ (2.0)	1	5 + 12	70
8	$TiCl_4$ (2.0)	1.5	5 + 12	62
9	$TiCl_4$ (1.0)	1.0	5 + 12	24

[a] Reaction time at $-78 \rightarrow 20\,^{\circ}C$ + reaction time at 20 °C. [b] Yield of isolated product. [c] The reaction was started at 0 °C.

The reaction of diene **1a** with epoxide **2a** at $-78 \rightarrow 20\,^{\circ}C$ (5 h) gave 2-alkylidenetetrahydrofuran **3a** in low yield (Table 1, entry 5). After much experimentation (Table 1), optimal yields (up to 70 %) were obtained when the reaction was stirred at $-78 \rightarrow 20\,^{\circ}C$ for 5 h and subsequently at 20 °C for 12 h and when 1.0 equivalent of the epoxide and 2.0 equivalents of $TiCl_4$ were used (Table 1, entry 8). The reaction proceeded by attack of the terminal carbon atom of the diene on the sterically less hindered carbon atom of the epoxide and subsequent regioselective cyclization at the oxygen atom (vide infra). Interestingly, excellent selectivity was observed in favor of the product containing an *E*-configured exocyclic double bond.

The preparative scope of the new cyclization reaction was investigated by systematically varying the substituents of the 1,3-bis(trimethylsilyloxy)-1,3-diene and the epoxide (Scheme 1, Table 2). Reaction of diene **1a** with 1,2-butenoxide (**2b**) and 1-benzyloxy-2,3-propenoxide (**2c**) afforded the *E*-configured 2-alkylidenetetrahydrofurans **3b** and **3c**, respectively, in good yields and with very good stereoselectivities. Reaction of **1a** with 1-chloro- and 1-bromo-2,3-propenoxide (**2d** and **2e**) afforded the *E*-configured 2-alkylidenetetrahydrofurans **3d** and **3e**, respectively, in good yields and with very good chemo-, regio-, and *E*-selectivities. Reaction of diene **1a** with *threo*-3-bromo-1,2-butenoxide **2f** afforded the diastereomerically pure 2-alkylidenetetrahydrofuran **3f** in good yield and with very good *E*-selectivity. No epimerization could be detected in the side chain attached to carbon C5. Reaction of diene **1a** with ethyl 3,4-epoxy-3-butenoate (**2g**) and ethyl 4,5-epoxy-4-pentenoate (**2h**) afforded the 2-alkylidenetetrahydrofurans **3g** and **3h** containing ester groups in the side chain. It is noteworthy that reaction of the dianion of ethyl acetoacetate with epoxides **2d**–**f** resulted in attack of the dianion on the carbon attached to the halogen atom rather than at the epoxide.[9] Reaction of the dianion with the ester-substituted epoxides **2g** and **2h** gave complex mixtures only. Reaction of 1-chloro-2,3-propenoxide with 1,3-bis(trimethylsilyloxy)-1,3-diene **1b**, containing a methyl group at the central carbon atom, afforded the 2-alkylidenetetrahydrofuran **3i** with very good chemo-, regio-, and *E*-selectivity. Reaction of dienes **1b** and **1c** with 1-bromo-2,3-propenoxide (**2e**) and ethyl 3,4-epoxy-3-butenoate (**2g**), both containing base-labile functional groups, afforded the bromo- and ester-substituted 2-alkylidenetetrahydrofurans **3j** and **3k**, respectively, in good yields and with very good regio- and *E*-selectivities.

Table 2. Synthesis of 2-alkylidenetetrahydrofurans **3a**–**s**.

1	**2**	**3**	R^1	R^2	R^3	R^4	R^5	Yield [%] [a,b]	*E*:*Z*
a	**a**	**a**	H	H	OEt	H	H	70	> 98:2
a	**b**	**b**	H	H	OEt	Me	H	62	> 98:2
a	**c**	**c**	H	H	OEt	OBn	H	58	> 98:2
a	**d**	**d**	H	H	OEt	Cl	H	52	> 98:2
a	**e**	**e**	H	H	OEt	Br	H	48	> 98:2
a	**f**	**f**	H	H	OEt	Br	Me	41	> 98:2
a	**g**	**g**	H	H	OEt	CO_2Et	H	50	> 98:2
a	**h**	**h**	H	H	OEt	CH_2CO_2Et	H	51	> 98:2
b	**b**	**i**	H	Me	OEt	Cl	H	45	> 98:2
c	**e**	**j**	H	Et	OEt	Br	H	50	> 98:2
b	**g**	**k**	H	Me	OEt	CO_2Et	H	54	> 98:2
d	**b**	**l**	Me	H	OMe	Me	H	46	> 98:2
e	**b**	**m**	Et	H	OMe	Me	H	50	> 98:2
f	**b**	**n**	H	H	Ph	Me	H	62	> 98:2
f	**d**	**o**	H	H	Ph	Cl	H	51	> 98:2
f	**e**	**p**	H	H	Ph	Br	H	44	> 98:2
f	**f**	**q**	H	H	Ph	CO_2Et	H	41	> 98:2
g	**g**	**r**	H	H	CH_2OMe	Me	H	51	> 98:2
g	**d**	**s**	H	H	CH_2OMe	Cl	H	45	> 98:2

[a] Yield of isolated product. [b] The diastereoselectivity observed for **3f** was > 98:2 in favor of the isomer drawn in Scheme 1. The diastereoselectivity observed for **3l** and **3m** was 4:1.

The reaction of butenoxide **2b** with the dienes **1d** and **1e**, containing a methyl and an ethyl group at the terminal carbon atom, respectively, afforded the *Z*-configured 2-alkylidenetetrahydrofurans **3l** and **3m**, respectively, in good yields and with good 1,3-diastereoselectivities. The change of the geometry of the exocyclic double bonds from *E*- to *Z*-configuration can be explained by the steric influence of the substituents R^1. Reaction of the benzoylacetone derived diene **1f** with 1,2-butenoxide (**2b**) afforded the 2-alkylidenetetrahydrofuran **3n** in good yield and with very good chemo-, regio-, and *E*-selectivity. Reaction of diene **1f** with epoxides **2d**–**e** and **2g** afforded the chloro-, bromo-, and ester-substituted 2-alkylidenetetrahydrofurans **3o**–**q** in good yields and with very good regio- and *E*-selectivities. Reaction of 1,2-butenoxide and 1-chloro-2,3-propenoxide with 1,3-bis(trimethylsilyloxy)-1,3-diene **1g**, derived from 5-methoxy-2,4-pentanedione, afforded the 2-alkylidenetetrahydrofurans **3r** and **3s**, respectively, with very good chemo-, regio-, and *E*-selectivity.

To obtain some insight into the mechanism of the reaction, the reactions of 1,3-bis(trimethylsilyloxy)-1,3-diene **1a** with

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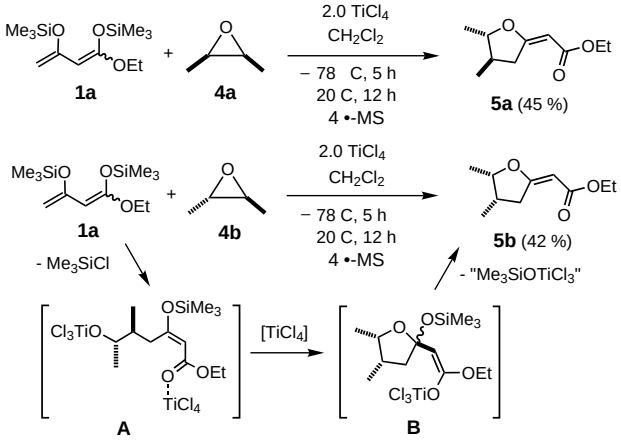
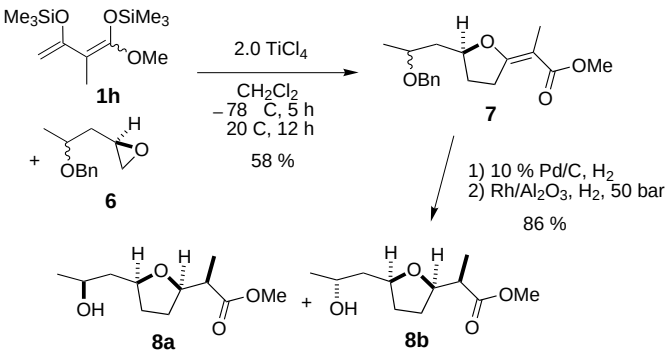
the 1,2-disubstituted epoxides **4a** and **4b** were studied (Scheme 2): reaction of **1a** with *cis*-2,3-butenoxide **4a** afforded the *E*-configured 2-alkylidenetetrahydrofuran **5a** containing two *trans*-configured methyl groups in good yield. In contrast, reaction of **1a** with *trans*-2,3-butenoxide **4b** gave the 2-alkylidenetetrahydrofuran **5b** containing two *cis*-configured methyl groups. The observed stereoselectivity suggests that formation of 2-alkylidenetetrahydrofurans **3a–s** and **5a**, **b** can be explained by the following working hypothesis:



Scheme 2. Cyclization of epoxides **4a**, **b** with 1,3-bis(trimethylsilyloxy)-1,3-diene **1a**.

regioselective attack of the terminal carbon atom of the diene on the epoxide affords intermediate **A** with inversion of the configuration. The retention of the configuration of the carbon atom attached to the oxygen atom suggests that the cyclization proceeds by $TiCl_4$-mediated attack of the epoxide-derived hydroxy group on the α,β-unsaturated ester to give intermediate **B**.[10] In contrast, attack of the silyl enol ether derived oxygen atom of intermediate **A** on the hydroxy group would have resulted in inversion of the configuration. Elimination of silanolate subsequently leads to the final product. The presence of the Lewis acid seems to be important for both the initial condensation step and the subsequent cyclization. The stereoselectivity in favor of the products containing *E*-configured exocyclic double bonds can be explained by the W-shaped configuration of intermediate **A** which allows a minimization of the dipole–dipole repulsion of the oxygen atoms.[11]

To demonstrate the preparative usefulness of our new cyclization we have studied its application to the synthesis of methyl nonactate, a precursor to the natural product nonactin.[7, 8a, 12] This compound belongs to the class of macrotetrolide antibiotics (nactins) isolated from a variety of *Streptomyces* cultures.[13] Reaction of the 1,3-bis(trimethysilyloxy)-1,3-butadiene **1h** with epoxide **6** (1:1 diastereomeric mixture) afforded the 2-alkylidenetetrahydrofuran **7** in 58% yield (Scheme 3). Deprotection and subsequent stereoselective hydrogenation[12c] afforded, following a known protocol,[7c] methyl nonactate **8a** and methyl 8-*epi*-nonactate **8b** as a diastereomeric mixture (1:1) in 86% yield.



Scheme 3. Synthesis of methyl nonactate and methyl 8-*epi*-nonactate.

The first cyclization reactions of 1,3-bis(trimethysilyloxy)-1,3-butadienes—electroneutral equivalents of 1,3-dicarbonyl dianions—with epoxides reported herein provide an efficient, chemo-, regio-, and *E*-selective synthesis of a variety of functionalized 2-alkylidenetetrahydrofurans that are useful precursors for the synthesis of pharmacologically relevant tetrahydrofuran derivatives and natural products.

Experimental Section

3f: $TiCl_4$ (2 mmol, 0.38 g) in CH_2Cl_2 (5 mL) was added at $-78\,^{\circ}C$ to a solution of *threo*-3-bromo-1,2-epoxybutane (1.5 mmol, 0.23 g), 1,3-bis(trimethylsilyloxy)-1,3-diene **1a** (1.5 mmol, 0.40 g), and molecular sieves (4 Å) in CH_2Cl_2 (30 mL). The temperature of the reaction mixture was allowed to rise to 20 °C over 5 h. After the mixture had been stirred for 12 h at 20 °C, a saturated solution of NaCl was added, the organic layer was separated, and the aqueous layer was repeatedly extracted with diethyl ether. The combined organic extracts were dried ($MgSO_4$), filtered, and the solvent of the filtrate was removed in vacuo. The residue was purified by column chromatography (silica gel, diethyl ether/petroleum ether 1/10 → 1/3) to give **3f** as a colorless oil. ^1H NMR ($CDCl_3$, 200 MHz): $\delta = 1.18$ (t, 3H, $J =$ 7 Hz; CH_2CH_3), 1.70 (d, 3H, $J = 8$ Hz; $CHCH_3$), 1.97, 2.30 (2 × m, 2 × 1H; CH_2), 2.98, 3.30 (2 × m, 2 × 1H; CH_2), 4.05 (q, 2H, $J = 7$ Hz; OCH_2), 4.35, 4.58 (2 × m, 2 × 1H; 2 × CH), 5.21 (t, 1H, $J = 1$ Hz; =CH); ^{13}C NMR ($CDCl_3$, 50 MHz): $\delta_c = 13.94$, 21.42, 26.80, 30.29, 51.06, 58.58, 86.43, 89.04, 167.44, 176.18; MS (70 eV): m/z: 262 (100, $[M^+]$); elemental analysis (%): calcd for $C_{10}H_{15}O_3Br$: C 45.65, H 5.75; found: C 45.46, H 5.87. The geometry of the exocyclic double bond of all products and the relative configuration of **5a**, **b** were determined by NOE measurements and based on analogy of chemical shifts and coupling constants to compounds with known configuration.[14] The relative configuration of the *Z*-configured products **3l**, **m** could not be unambigiously determined. All compounds were characterized by spectroscopic methods and gave correct elemental analyses and/or high-resolution mass spectra.

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Eight-Membered Carbocycles from a Dötz-Like Reaction**

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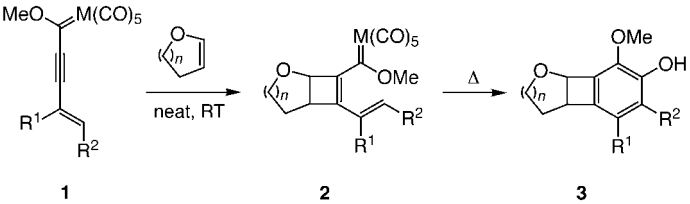
The reaction of Fischer carbene complexes with alkynes can lead, under appropriate conditions, to a diverse array of structures.[1] The most important and widely used among these reactions is the well-known Dötz benzannulation,[2] which affords *p*-alkoxyphenol derivatives by successive insertion of one molecule of alkyne and one CO ligand in an α,β-unsaturated carbene, and subsequent electrocyclic ring closure.[1] Although reaction of chromium arylcarbene complexes with alkynes can produce more than fifteen different types of organic compounds as side products,[1a,c] alkenylcarbenes yield benzannulated products with greater fidelity.[3] The formation of cyclopentadiene derivatives from the coupling of acetylenes and vinylcarbenes has been observed in a few cases.[4] On the other hand, compounds such as cyclopentenones,[5] heterocycles,[6] or spirocycles,[7] have been achieved when (2-amino-1-vinyl)carbenes were used.[8] The presence of additional unsaturation, either in the starting carbene or in the alkyne, allows entry to new types of structures, usually polycycles.[9] However, as far as we know, the reaction of dienyl carbenes and alkynes has never been reported.[10]

One of the current interests in our research group focuses on the preparation and synthetic applications of 1-metalla-1,3,5-hexatrienes. In this context, we have recently described the synthesis of stable dienyl complexes **2** by [2+2] cycloaddition of alkynyl carbenes **1** and enol ethers (Scheme 1).[11] The complexes **2** were unreactive at room temperature, but



1 **2** **3**

Scheme 1. M = Cr, W; $n = 1, 2$.

gave benzannulation products when heated. Cyclopentadiene derivatives, which usually result from 1-metalla-1,3,5-hexatrienes, were not observed, not even as side products. We assumed that this different behavior was due to the presence of the cyclobutene ring. In order to ascertain whether the unusual reactivity of **2** could be extended to other processes,

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