Chemoselective Activation of Trimethylsilyl Enol Ether Functionalities in the Presence of Silyl-Protected Alcohols by Trimethylsilyl–Nonaflyl Exchange

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This article is dedicated to the memory of our colleague and friend Dr. Ilya Lyapkalo who passed away September 10, 2010

Abstract: Trimethylsilyl enol ethers bearing trialkylsilyl-protected hydroxy groups were converted into synthetically valuable bifunctional alkenyl nonaflates under the action of nonafluorobutane-1-sulfonyl fluoride combined with potassium fluoride in the presence of catalytic amounts of dibenzo-18-crown-6. The methodology has been demonstrated for structurally diverse substrates possessing various trialkylsilyl-protected hydroxy groups which remained intact during the reaction course.

Key words: biphasic catalysis, crown ether, sulfonylating reagent, trialkylsilyl ethers, alkenyl nonaflates

Sulfonic acid enol esters (alkenyl sulfonates) constitute a synthetically important link that enables the extension of transition-metal-catalyzed cross-coupling methodology to enolizable carbonyl compounds, one of the most abundant and ubiquitous classes of organic substrates. The applications of alkenyl triflates in palladium(0)-catalyzed cross-coupling reactions have been systematically studied and reviewed.[2] Alkenyl nonaflates (nonafluorobutanesulfonates) represent a useful alternative[3–10] to the triflates, not least owing to the advantageous properties of nonafluorobutane-1-sulfonyl fluoride[11,12] (hereinafter referred to as NfF), a mild and easy-to-handle sulfonylating reagent routinely used for the preparation of nonaflates from carbonyl compounds.

Most generally, alkenyl nonaflates are accessed either by direct O-sulfonylation of aldehydes or cyclic ketones with NfF combined with phosphazene bases,[7c,13] or by fluoride-catalyzed $SiMe_3$ for $SO_2(CF_2)_3CF_3$ group exchange in trimethylsilyl enol ethers.[3a,c,11d] While the former procedure is more straightforward, the latter is milder and exhibits greater scope as it allows alkenyl nonaflates[14] to be derived from acyclic ketones, which are unstable in the presence of phosphazene bases.[7c,13] Tetrabutylammonium fluoride (TBAF) is routinely employed as a soluble source of catalytic fluoride for such exchanges, which can be problematic in the case of polyfunctional substrates bearing silyl-protected alcohol groups as TBAF is known to be one of the most general and efficient deprotecting reagents for silyl ethers (protected alcohol groups) ranging widely in steric and electronic demands.[15]

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The major challenge consists of the extension of the trimethylsilyl–nonaflyl-exchange methodology to the synthesis of complex products. This requires studying the chemo- and regioselectivity of the reaction. It is therefore especially important to develop a soluble anhydrous fluoride catalyst able to efficiently activate trimethylsilyl enol ether functionalities,[11d] while not affecting alkylsilyl ether groups, with a high degree of chemo- and regiocontrol. The activator must be robust and not too basic[16] to avoid E2 elimination of NfOH from acyclic alkenyl nonaflates. Ideally, it should be easy to generate in an anhydrous form, preferably shortly prior to the reaction, to ensure reproducibility of results.

In a previous study by Reissig, Lyapkalo and co-workers,[3e] a single example of a selective activation of a trimethylsilyl enol ether functionality in the presence of silyl-protected hydroxy using potassium fluoride with a catalytic amount of dibenzo-18-crown-6 was shown. The study, however, was not devoted to this transformation; therefore, neither scope and limitations nor the possibility to perform such reactions using other catalytic systems was explored. The aim of the present work was to study the scope of this transformation as well as to gain mechanistic insight. As far as we can ascertain, there is no focused study prior to this work.[17,18]

In this paper, we present a selective method for the exchange of easy-to-generate silyl enol ether functionalities to versatile alkenyl nonaflates in the presence of silyl-protected alcohol groups. This method opens the way to synthetically valuable polyfunctional building blocks bearing nonaflyl enol ether groups along with silyl-protected hydroxy units which can be subsequently used in metal-catalyzed cross-coupling reactions.[3–10]

A first attempt to prepare alkenyl nonaflate **2a** from the model compound (*R*)-2-methyl-3-(trimethylsilyloxy)-5-[2-(trimethylsilyloxy)propan-2-yl]cyclohexa-1,3-diene (**1a**)[3e] using TBAF[11d] resulted in a mixture containing only a minor quantity of desired **2a**, along with enone **3a**, parent hydroxy enone **4** and several unidentified products[19] (Table 1, entry 1).

Gratifyingly, a combination of thoroughly ground and dried potassium fluoride with a catalytic amount of dibenzo-18-crown-6 (db-18-c-6) turned out to be a much more selective catalyst (Table 1, entry 2). Although the rate of conversion of the starting bis-trimethylsilyl ether **1a**

slowed down considerably, the reaction proceeded much more cleanly; the formation of the protiodesilylated product **3a** was insignificant, while the tertiary trimethylsilyl ether function was not affected. Switching from THF to the dipolar aprotic solvent DMF resulted in an appreciable acceleration of the reaction rate, although the selectivity was slightly lower (Table 1, entry 3). Finally, the biphasic solvent mixture DMSO–hexane (1:1.5) gave the optimal result in terms of selectivity and reaction rate, furnishing the desired alkenyl nonaflate **2a** in 84% isolated yield (Table 1, entry 4). Dibenzo-18-crown-6 was found to be vital for the reaction to occur. In its absence, the nonaflation did not proceed at all (Table 1, entry 5).

Encouraged by this finding, the generality of this optimal protocol was tested using a number of bis-trialkylsilyl substrates **1b–j** (Tables 2 and 3). The secondary trimethylsilyl ether moiety in compound **1b** was not affected under the reaction conditions and the desired product **2b** was obtained in high yield (Table 2, entry 1). However, there remained a legitimate suspicion that erosion of selectivity may occur due to silyl scrambling by means of a putative intramolecular *O*,*O*-silyl migration,[13] especially via the entropically favorable five- or six-membered (n = 0 or 1, respectively) cyclic pentacoordinated silicate intermediate **A** (see Scheme 1, path I).

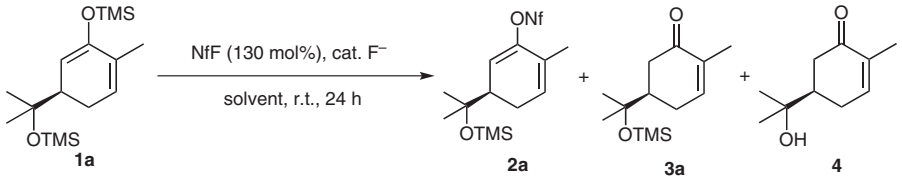
To address this, a range of bis-silyl derivatives **1c**,**i** (n = 1) and **1d–h**,**j** (n = 0) was tested under the optimized nonaflation conditions (Table 2). The reactions proceeded cleanly in the biphasic DMSO–hexane medium, furnishing the anticipated silylated alkenyl nonaflates **2** in good to high yields for all substrates examined (Table 2, entries 2–8), except **1i** and **1j**. The reaction outcome achieved in the case of substrate **1i** in DMSO–hexane (Table 2, entry 9) was significantly improved by switching to THF (Table 2, entry 10) as the reaction medium. Although it took much longer for the reaction to complete (120 h in THF vs 18 h in DMSO–hexane), pure product **2i** was isolated in 76% yield compared to 42% yield in DMSO–hexane.

Experiments using substrates **1b** and **1e** were run in duplicate, and the results demonstrated that the methodology is fully reproducible. On the other hand, a 10-fold increase of the substrate concentration in the case of substrate **1d** (Table 2, entry 4) led to a very similar result (72% vs 69% yield).

The reactivity of **1j** exemplifies a limitation of the protocol for substrates possessing a trimethylsilyl ether derived from a secondary alcohol (Table 3). No alkenyl nonaflate **2j** was formed in the biphasic DMSO–hexane system (according to the ^{1}H NMR data of the crude reaction mixture, conversion of starting **1j** was 96% and only protiodesilylated product **3j** was formed) (Table 3, entry 1), while the reaction was sluggish in THF at room temperature (<20% conversion of **1j** after 20 h, according to the ^{1}H NMR data of the crude reaction mixture) (Table 3, entry 2). Thus, heating had to be applied to achieve reasonable conversion (94% after 24 h at 50 °C, according to the ^{1}H NMR data of the crude reaction mixture) (Table 3, entry 3). The desired alkenyl nonaflate **2j** was nonetheless isolated in only 39% yield and ca. 80% purity. The use of THF mixtures with polar NMP or DMF as reaction medium at room temperature (Table 3, entries 4 and 5, respectively) improved the reaction rate and selectivity compared to those observed in the DMSO–hexane mixture and pure THF. Unfortunately, it proved impossible to isolate the desired product **2j** from the reaction mixtures due to decomposition during the unavoidable aqueous workup. In contrast, the transformation of the TBS-protected analogue (**1g** → **2g**) in DMSO–hexane proceeded smoothly with good yield and selectivity (Table 2, entry 7).

To investigate a possible pathway of the trimethylsilyl–nonaflyl exchange, aliquots (30–40 μL) were collected from the hexane phase or the THF solution and diluted with the deuterated solvent. The reaction progress could

Table 1 Model Reaction for Optimization of the Fluoride Source



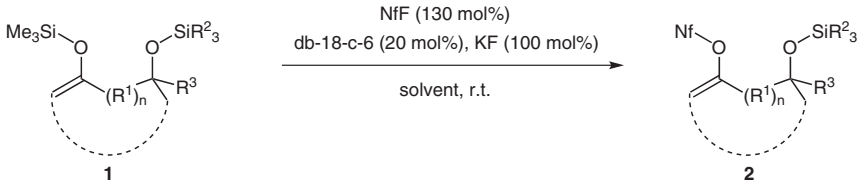
Entry	Fluoride catalyst	Solvent	Conv. of **1a**[a] (%)	Ratio **2a/3a/4**[a]
1	TBAF (10 mol%), KF (100 mol%)	THF	~85	1:1.7[b]
2	db-18-c-6 (15 mol%), KF (100 mol%)	THF	25	12:1:0
3	db-18-c-6 (15 mol%), KF (100 mol%)	DMF	95	9:1:0
4	**db-18-c-6 (15 mol%), KF (100 mol%)**	**DMSO–hexane**	**>99[c]**	**10:1:0**
5	KF (100 mol%)	DMSO–hexane	0 (no change)	–

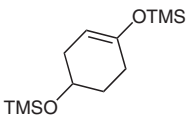
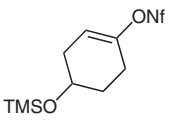
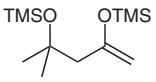
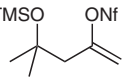
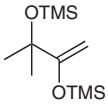
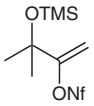
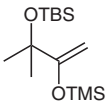
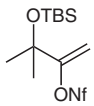
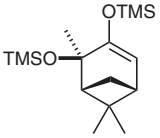
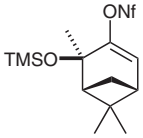
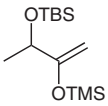
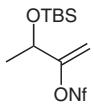
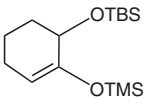
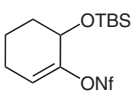
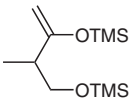
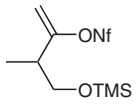
[a] Estimated based on the ^{1}H NMR data of the crude reaction mixtures.
[b] Combined amount of **3a** and **4**.
[c] Isolated yield 84%.

be easily monitored by the appearance and steady increase of the Me_3SiF signal in the ^1H NMR spectrum (d, $\delta = 0.235$ ppm, $^3J_{1H,19F} = 7.4$ Hz in $CDCl_3$ or $\delta = 0.022$ ppm, $^3J_{1H,19F} = 7.3$ Hz in C_6D_6).

Besides the fact that the fluoride source had to be soluble (cf. Table 1), control experiments showed that prolonged exposure (20–24 h) of **1a** or **1b** to 15–20 mol% of [(db-18-c-6)·K]$^+$F$^-$ in the absence of NfF did not produce any detectable amount of Me_3SiF. This excludes **A** or a free enolate **C** (Scheme 1) as intermediates within the detection limits of the NMR method. However, shortly after the addition of NfF, the signal of Me_3SiF became visible. Mechanistically, these observations can be rationalized as depicted in path II of Scheme 1. Soluble fluoride in the form [(db-18-c-6)·K]$^+$F$^-$ adds reversibly to the silicon center of the silyl enol ether group to produce pentacoordinated anionic silicate intermediate **B**. The formation of **B** is apparently preferred over that of the alternative silyl ether derived silicate. The silicate enolate unit should additionally be a better nucleophile compared to a simple alcoholate-derived silicate. The exact further pathway to products **2** cannot be derived with certainty from the experimental data. The attack of NfF may proceed subsequently by direct O-sulfonylation of **B**. The very low

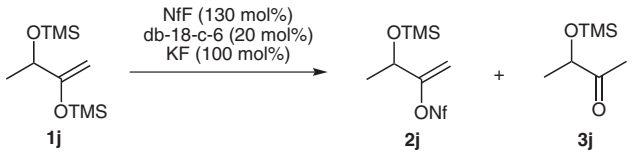
Table 2 Selective Conversion of TMS Enol Ethers Possessing Trialkylsilyl-Protected Hydroxy Groups into the Corresponding Alkenyl Nonaflates



Entry	Substrate		Solvent	Time (h)	Product		Yield[a] (%)
1[b]	**1b**		DMSO–hexane	22	**2b**		83
2[c]	**1c**		DMSO–hexane	19	**2c**		90
3	**1d**		DMSO–hexane	48	**2d**		69
4[d]			DMSO–hexane	48			72
5[b]	**1e**		DMSO–hexane	23	**2e**		72
6	**1f**		DMSO–hexane	48	**2f**		74[e]
7	**1g**		DMSO–hexane	36	**2g**		73
8	**1h**		DMSO–hexane	24	**2h**		51
9[c,f]	**1i**		DMSO–hexane	18	**2i**		42
10[c,f]			THF	120			76

[a] Isolated yield.
[b] Duplicate experiments for substrates **1b**,**e** were carried out. The yields of products **2b**,**e** were identical in each pair of experiments.
[c] Reaction was carried out with 15 mol% db-18-c-6.
[d] Repetitive experiment using a 10-fold increase of the starting **1d** amount and conditions similar to entry 3.
[e] Purity of the isolated product was 88% based on the ^1H NMR data.
[f] Room temperature was 28 °C.

Table 3 Optimization of the Reaction Conditions for **1j**



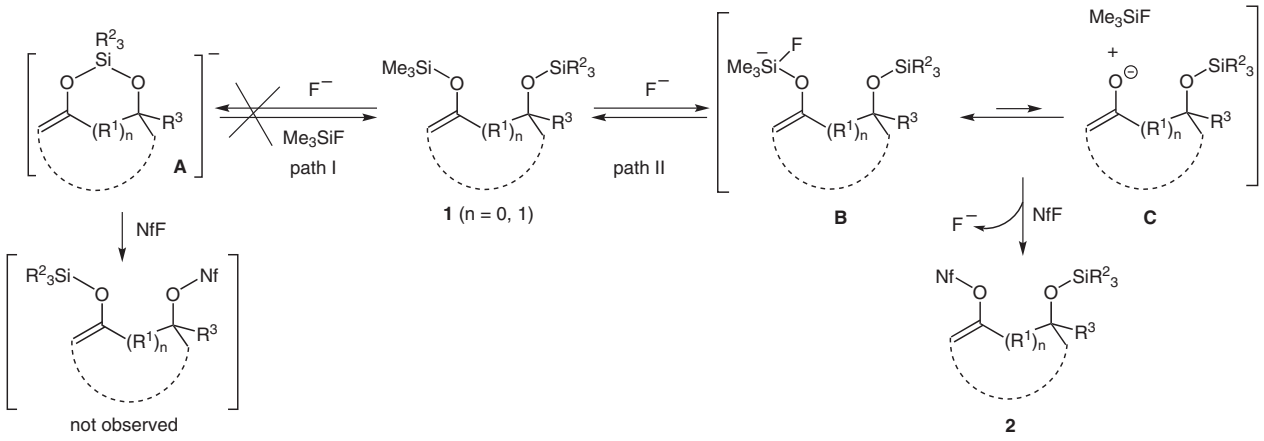
Entry	Conditions	Ratio **1j/2j/3j**[a]
1	DMSO–hexane, r.t., 20 h	1:0:18
2	THF, r.t., 20 h	9:1:1
3[b]	**THF, 50 °C, 24 h**	**0.2:2.1:1**
4	THF–NMP (2:1), r.t., 20 h	0:1.9:1
5	THF–DMF (2:1), r.t., 20 h	0:2.3:1

[a] Estimated based on the ^{1}H NMR data of the crude reaction mixtures.
[b] Isolated yield 39%, purity ca. 80% based on the ^{1}H NMR data.

inclination for the aforementioned migration (Scheme 1, path I) points to a very transient, if at all, existence of a free enolate intermediate **C**; however, although the equilibrium between **B** and **C** is shifted to the left to such an extent that the concentration of free Me_3SiF remains beyond the detection limit of the NMR method in the absence of the electrophile, the nonaflation reaction might be then driven by reaction of transient **C** with the large excess of NfF compared to it. Alternatively, the reaction with NfF can also proceed via a contact ion pair laying in between the two limiting equilibrium structures **B** and **C** + Me_3SiF, accounting for the preparative and mechanistic results (Scheme 1, path II).

In summary, we have developed a general, efficient and highly selective protocol for the anhydrous fluoride-catalyzed conversion of trimethylsilyl enol ethers into the corresponding nonaflates. Catalytic dibenzo-18-crown-6 combined with potassium fluoride offers a remarkable selectivity as it activates trimethylsilyl enol ether functions readily while not affecting trialkylsilyl alcohol protection regardless of its nature (primary to tertiary), bulkiness (TMS or TBS) or position in the molecule. Even fragile TMS protection of primary hydroxy groups largely remains intact during the reaction. Both components of the fluoride catalytic system can be conveniently dried by heating under high vacuum, thus ensuring the reproducibility of the results. The highest reaction rate was observed in a DMSO–hexane biphasic system, from which the nonaflate products **2** can be conveniently isolated by nonaqueous extraction with hexane. The reaction rate in THF medium was lower; however, the selectivity was higher, thus THF should be the solvent of choice for those substrates which give unsatisfactory results in DMSO–hexane.

All reactions were carried out in oven-dried glassware (140 °C) equipped with PTFE-coated magnetic stirrer bars in anhydrous solvents under an atmosphere of dry argon. Air- and moisture-sensitive reagents were transferred using a syringe. ^{1}H NMR spectra of the reaction mixtures were routinely recorded to ensure complete conversion of the starting materials. Solvents were dried by standard procedures: THF was distilled over Na/K alloy with addition of benzophenone; MeCN was distilled over CaH_2 and stored over 4 Å molecular sieves; hexane and CH_2Cl_2 were distilled over P_2O_5. Anhyd DMSO was prepared as described previously.[20] Commercially available, dry KF (ca. 20 g) (Fluka) was placed in a mortar and maintained in an oven at 200 °C for 12 h. Then, whilst still hot, it was thoroughly ground to a fine powder using a hot pestle. This predried KF was dried further under vacuum (0.01 mbar) using a heat gun (heating program 350 °C) before each reaction. Commercially available NaI (Penta) was dried under vacuum (10^{-2} mbar) at 120 °C (oil bath) for 2 h before each reaction. 2.4 M *n*-BuLi solution in hexanes was purchased from Aldrich. Unless otherwise stated, materials obtained from commercial suppliers were used without further purification. Recondensation was carried out as bulb-to-bulb distillation at r.t. under high vacuum with the trapping bulb cooled by a liquid N_2–EtOH bath (for picture, see Supporting Information). All the products obtained were of >95% purity according to the ^{1}H NMR data, unless otherwise noted. NMR spectra were recorded in C_6D_6 or $CDCl_3$ on a Bruker Avance I 400 (400 MHz for ^{1}H, 100 MHz for ^{13}C) or WH 270 (270 MHz for ^{1}H, 67.5 MHz for ^{13}C) spectrometer (Bruker BioSpin GmbH). Chemical shifts are reported as the δ scale in ppm relative to TMS (δ = 0) as an internal standard for ^{1}H NMR and to $CDCl_3$ (δ = 77.16) or C_6D_6 (δ = 128.06) for ^{13}C NMR. The ^{13}C NMR signals of the $(CF_2)_3CF_3$ fragment of the nonaflates are not given, as no unambiguous assignments were possible due to strong coupling with the ^{19}F nuclei. High-resolution mass spectra were measured on an LTQ Orbitrap XL spectrometer



Scheme 1 Proposed mechanism of the [(db-18-c-6)·K]$^+$F$^-$ induced transformation of TMS enol ethers to alkenyl nonaflates

(Thermo Fisher Scientific) using APCI and ESI methods with MeOH or MeCN, or on a GTC Premier spectrometer (Waters) using EI. IR spectra were recorded as films or in $CDCl_3$ on a Bruker Equinox 55 IR spectrometer (Bruker BioSpin GmbH). Preparative separations were performed using silica gel gravity column chromatography (silica gel 60, Fluka, 12479). Column chromatography was monitored by TLC (silica gel 60, glass plates, Merck, 105631) and visualized using 5% phosphomolybdic acid solution in EtOH. Elemental analysis was performed using a PE 2400 Series II CHN analyzer.

tert-Butyldimethylsilyloxy Ketones (Starting Materials for 1g and 1h); General Procedure 1 (GP1)

The corresponding starting hydroxy ketone (1 equiv) was dissolved in anhyd CH_2Cl_2 (15–20 mL per 1.00 mmol of substrate), and the obtained solution was cooled to 0 °C whereupon imidazole (1.3 equiv) and TBSCl (1.1 equiv) were added. The reaction mixture was allowed to warm to r.t. and stirred overnight. The resulting inhomogeneous mixture was filtered through a pad of silica gel (CH_2Cl_2, 65–130 mL per 1.00 mmol of substrate) and concentrated. The obtained *tert*-butyldimethylsilyloxy ketones were of >95% purity according to the ^{1}H NMR data and were used without further purification.

3-(*tert*-Butyldimethylsilyloxy)butan-2-one (Starting Material for 1g)

This compound was obtained according to GP1 using 2.00 g (22.7 mmol) of 3-hydroxybutan-2-one; yield: 4.50 g (quantitative); colorless oil. The spectroscopic data were in accordance with the literature values.[21]

2-(*tert*-Butyldimethylsilyloxy)cyclohexanone (Starting Material for 1h)

This compound was obtained according to GP1 using 0.50 g (2.2 mmol) of 2-hydroxycyclohexanone dimer; yield: 0.97 g (97%); colorless oil. The spectroscopic data were in accordance with the literature values.[22]

Bis(trialkylsilyloxy) Derivatives 1b,c,e,g,i,j; General Procedure 2 (GP2)

Predried NaI (2.3 equiv) [or 1.15 equiv] was suspended in anhyd MeCN (3–10 mL per 1.00 mmol of substrate) under argon. The corresponding starting hydroxy ketone (1 equiv) or *tert*-butyldimethylsilyloxy ketone [1 equiv] and Et_3N (2.7 equiv) [or 1.35 equiv] were added and the obtained suspension was cooled to –30 °C. TMSCl (2.5 equiv) [or 1.25 equiv] was added dropwise and the reaction mixture was allowed to warm to r.t. After being stirred overnight, the reaction mixture was quenched with an ice–hexane mixture. The layers were separated and the aqueous phase was extracted with hexane (2 ×). The combined extracts were washed with H_2O and brine, dried over Na_2SO_4 and concentrated. Products **1b**,**c**,**e**,**g**,**i**,**j** were isolated by recondensation or distillation under reduced pressure.

1,4-Bis(trimethylsilyloxy)cyclohex-1-ene (1b)

Starting 4-hydroxycyclohexanone was prepared according to a literature procedure from cyclohexane-1,4-diol,[23] and its spectroscopic data were in accordance with the literature values. Product **1b** was prepared according to GP2 using 0.50 g (4.37 mmol) of 4-hydroxycyclohexanone and purified by recondensation at 0.01 mbar; yield: 1.04 g (92%); colorless oil. The spectroscopic data were in accordance with the literature values.[24]

4-Methyl-2,4-bis(trimethylsilyloxy)pent-1-ene (1c)

Product **1c** was prepared according to GP2 using 2.33 g (20.04 mmol) of 4-hydroxy-4-methylpentan-2-one and purified by distillation; yield: 4.28 g (82%); colorless liquid; bp 79–80 °C/2 mbar. The spectroscopic data were in accordance with the literature values.[25]

3-(*tert*-Butyldimethylsilyloxy)-3-methyl-2-(trimethylsilyloxy)but-1-ene (1e)

Starting 3-(*tert*-butyldimethylsilyloxy)-3-methylbutan-2-one was obtained according to a literature procedure,[26] and its spectroscopic data were in accordance with the literature values. Product **1e** was prepared according to GP2 using 0.70 g (3.20 mmol) of 3-(*tert*-butyldimethylsilyloxy)-3-methylbutan-2-one and purified by distillation.

Yield: 0.849 g (91%); colorless liquid; bp 92–94 °C/3 mbar.

IR ($CDCl_3$): 3010–2880, 1623, 1453, 1253 cm^{-1}.

^{1}H NMR (400 MHz, C_6D_6): δ = 0.17 (s, 6 H, 2 Me-TBS), 0.17 (s, 9 H, TMS), 1.04 (s, 9 H, *t*-Bu-TBS), 1.41 (s, 6 H, CMe_2), 4.12 (d, *J* = 1.0 Hz, 1 H, H-1), 4.72 (d, *J* = 1.0 Hz, 1 H, H-1).

^{13}C NMR (100 MHz, C_6D_6): δ = –1.94, 0.13, 18.54, 26.24, 29.10, 75.23, 86.68, 164.62.

HRMS (EI$^+$): *m*/*z* [M]$^+$ calcd for $C_{14}H_{32}O_2Si_2$: 288.1941; found: 288.1938.

3-(*tert*-Butyldimethylsilyloxy)-2-(trimethylsilyloxy)but-1-ene (1g)

Product **1g** was prepared according to GP2 using 4.50 g (22.23 mmol) of 3-(*tert*-butyldimethylsilyloxy)butan-2-one and purified by distillation; yield: 5.83 g (96%); colorless liquid; bp 110 °C/3.5 mbar (Lit.[27] 140 °C/18 mbar). The spectroscopic data were in accordance with the literature values.

3-Methyl-2,4-bis(trimethylsilyloxy)but-1-ene (1i)

Product **1i** was prepared according to GP2 using 2.04 g (19.97 mmol) of 4-hydroxy-3-methylbutan-2-one and purified by distillation; yield: 3.84 g (78%); colorless liquid; bp 71.5–72.5 °C/2 mbar. The spectroscopic data were in accordance with the literature values.[25]

2,3-Bis(trimethylsilyloxy)but-1-ene (1j)

Product **1j** was prepared according to GP2 using 2.00 g (22.70 mmol) of 3-hydroxybutan-2-one and purified by distillation; yield: 3.06 g (58%); pale yellow oil; bp 52 °C/6 mbar. The analytical data were in accordance with the literature values.[28]

(*R*)-2-Methyl-3-(trimethylsilyloxy)-5-[2-(trimethylsilyloxy)propan-2-yl]cyclohexa-1,3-diene (1a)

Compound **1a** was obtained as described previously.[3e] The spectroscopic data were in accordance with the literature values.

3-Methyl-2,3-bis(trimethylsilyloxy)but-1-ene (1d)

Compound **1d** was obtained according to a literature procedure.[29] The spectroscopic data were in accordance with the literature values.

(1*R*,4*R*,5*R*)-4,6,6-Trimethyl-3,4-bis(trimethylsilyloxy)bicyclo[3.1.1]hept-2-ene (1f)

(1*R*,2*R*,5*R*)-2-Hydroxy-2,6,6-trimethylbicyclo[3.1.1]heptan-3-one (1.00 g, 5.94 mmol) dissolved in anhyd THF (5 mL) was added to LDA soln [prepared from BuLi (8.60 mL, 21.40 mmol) and *i*-Pr_2NH (2.17 g, 21.40 mmol) in anhyd THF (20 mL)] at –15 °C and the reaction mixture was allowed to warm to r.t. After 2 h at r.t., TMSCl (2.91 g, 26.70 mmol) was added and the reaction mixture was stirred for 1 h. It was then poured into an ice–sat. $NaHCO_3$–hexane mixture (100 mL, 20:20:60). The organic layer was separated; the aqueous layer was extracted with hexane (3 × 20 mL). The combined organic layers were washed with H_2O (25 mL) and brine (25

mL), dried over Na_2SO_4 and concentrated. Product **1f** was purified by distillation.

Yield: 1.633 g (88%); colorless oil; bp 104–105 °C/0.4 mbar.

IR (neat): 2953, 1635, 1420, 1247 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 0.23 (s, 9 H, TMS), 0.28 (s, 9 H, TMS), 0.98 (s, 3 H), 1.25 (s, 3 H), 1.45 (s, 3 H), 1.96–2.01 (m, 2 H, H-1 and H-5), 2.12–2.15 (m, 1 H, H-7), 2.31–2.36 (m, 1 H, H-7), 5.20 (d, *J* = 6.9 Hz, 1 H, H-2).

^{13}C NMR (100 MHz, C_6D_6): δ = 0.45, 2.80, 24.23, 24.91, 27.75, 33.96, 41.03, 46.70, 55.39, 79.03, 110.84, 151.70.

HRMS (EI^+): *m*/*z* $[M]^+$ calcd for $C_{16}H_{32}O_2Si_2$: 312.1941; found: 312.1935.

6-(*tert*-Butyldimethylsilyloxy)-1-(trimethylsilyloxy)cyclohex-1-ene (1h)

LDA [prepared from BuLi (2.03 mL, 5.07 mmol) and *i*-Pr_2NH (0.56 g, 5.49 mmol) in anhyd THF (5 mL)] was added dropwise to a soln of 2-(*tert*-butyldimethylsilyloxy)cyclohexanone (0.965 g, 4.22 mmol) in anhyd THF (20 mL) at –100 °C and the reaction mixture was stirred at this temperature for 40 min. Then, the temperature was allowed to reach –78 °C and, after 30 min with stirring at this temperature, TMSCl (0.688 g, 6.33 mmol) was added dropwise. The reaction mixture was allowed to warm to r.t., stirred for 30 min and quenched with an ice–hexane mixture (50 mL, 1:1). The organic layer was separated; the aqueous was extracted with hexane (3 × 20 mL). The combined organic extracts were washed with H_2O (20 mL) and brine (20 mL), dried over Na_2SO_4 and concentrated. Product **1h** was purified by flash chromatography on silica gel (hexane).

Yield (purity 87% by NMR): 1.00 g (71%); colorless oil.

IR (neat): 2933–2857, 1662, 1467, 1251 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 0.24 (s, 3 H, Me-TBS), 0.31 (s, 3 H, Me-TBS), 0.32 (s, 9 H, TMS), 1.14 (s, 9 H, *t*-Bu-TBS), 1.45–1.50 (m, 1 H), 1.60–1.70 (m, 1 H), 1.82–1.93 (m, 2 H), 1.94–2.01 (m, 1 H), 2.02–2.09 (m, 1 H), 4.13 (t, *J* = 3.93 Hz, 1 H, H-6), 4.96 (dd, *J* = 3.0, 4.9 Hz, 1 H, H-2).

^{13}C NMR (100 MHz, C_6D_6): δ = –4.62, –3.98, 0.51, 18.10, 18.50, 24.55, 26.21, 33.46, 68.54, 104.81, 151.94.

HRMS (ESI): *m*/*z* $[M + H]^+$ calcd for $C_{15}H_{33}O_2Si_2$: 301.2014; found: 301.2011.

Alkenyl Nonaflates 2; General Procedure 3 (GP3)

Exact quantities of the reaction components and solvents are specified in the individual entries. Finely ground, predried KF (0.058 g, 1.00 mmol) was placed in a reaction flask equipped with a three-way tap and heated with a heat gun (heating program 350 °C) under vacuum for 5 min, then cooled under a stream of argon. Dibenzo-18-crown-6 (0.072 g, 0.20 mmol) was added and the contents were heated with a heat gun (heating program 150–160 °C) for 2–3 min and then cooled to r.t. An appropriate reaction medium [DMSO–hexane (1:1.5) or THF], the corresponding starting bis-silyl ether **1** (1 mmol) and NfF (0.393 g, 1.30 mmol) were successively added, and the reaction mixture was vigorously stirred under the conditions (time and temperature) given in Table 2. The reaction progress was monitored by ^1H NMR spectroscopy. Unless described otherwise, upon completion of the reaction, the mixture was diluted with hexane and cooled with a dry ice–MeOH bath. The hexane layer was decanted; the DMSO layer was allowed to warm to r.t. and the procedure was repeated four times. The combined hexane extracts were concentrated and the products were isolated by column chromatography on silica gel (hexane or hexane–EtOAc), distillation or recondensation under reduced pressure.

(*R*)-6-Methyl-3-[2-(trimethylsilyloxy)propan-2-yl]cyclohexa-1,5-dien-1-yl Nonaflate (2a; Table 1, Entry 4)

Compound **2a** was prepared according to GP3 from **1a** (0.625 g, 2.00 mmol) and NfF (0.785 g, 2.60 mmol), employing KF (0.116 g, 2.00 mmol) and dibenzo-18-crown-6 (0.108 g, 0.30 mmol) in DMSO–hexane (2 mL:3 mL). Product **2a** was isolated by column chromatography on silica gel (hexane).

Yield: 0.874 g (84%); pale yellow oil; R_f = 0.62 (hexane–EtOAc, 10:1).

IR (neat): 2989–2893, 1637, 1421, 1239, 1147 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 0.11 (s, 9 H, TMS), 1.18 and 1.22 (both s, 3 H, CMe_2), 1.81 (m, 3 H, Me-6), 2.11–2.30 (m, 2 H, H-4), 2.53–2.64 (m, 1 H, H-3), 5.67 (m, 1 H, H-5), 5.80 (d, *J* = 3.4 Hz, 1 H, H-2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = 2.33, 16.64, 24.08, 26.80, 27.58, 46.83, 75.60, 117.41, 126.26, 127.20, 148.13.

HRMS (ESI): *m*/*z* $[M - CH_3]^+$ calcd for $C_{16}H_{20}F_9O_4SSi$: 507.0702; found: 507.0703.

Anal. Calcd for $C_{17}H_{23}F_9O_4SSi$: C, 39.08; H, 4.44. Found: C, 38.91; H, 4.32.

4-(Trimethylsilyloxy)cyclohex-1-en-1-yl Nonaflate (2b; Table 2, Entry 1)

Compound **2b** was prepared according to GP3 from **1b** (0.258 g, 1.00 mmol) and NfF (0.393 g, 1.30 mmol), employing KF (0.058 g, 1.00 mmol) and dibenzo-18-crown-6 (0.072 g, 0.20 mmol) in DMSO–hexane (1 mL:1.5 mL). Product **2b** was purified by recondensation at 0.01 mbar.

Yield: 0.386 g (83%); colorless liquid.

IR ($CDCl_3$): 3000–2900, 1623, 1418, 1239, 1144 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 0.01 (s, 9 H, TMS), 1.33–1.45 (m, 2 H), 1.78–1.84 (m, 2 H), 1.94–2.02 (m, 1 H), 2.12–2.19 (m, 1 H), 3.49–3.55 (m, 1 H, H-4), 5.24–5.26 (m, 1 H, H-2).

^{13}C NMR (100 MHz, C_6D_6): δ = 0.10, 25.36, 31.10, 33.22, 65.13, 115.98, 148.60.

HRMS ($APCI^-$): *m*/*z* $[M - H]^-$ calcd for $C_{13}H_{16}F_9O_4SSi$: 467.0400; found: 467.0397.

4-Methyl-4-(trimethylsilyloxy)pent-1-en-2-yl Nonaflate (2c; Table 2, Entry 2)

Compound **2c** was prepared according to GP3 from **1c** (0.521 g, 2.00 mmol) and NfF (0.785 g, 2.6 mmol), employing KF (0.116 g, 2.00 mmol) and dibenzo-18-crown-6 (0.108 g, 0.30 mmol) in DMSO–hexane (2 mL:3 mL). Product **2c** was isolated by column chromatography on silica gel (hexane).

Yield: 0.845 g (90%); colorless oil; R_f = 0.58 (hexane).

IR (neat): 2965–2930, 1665, 1420, 1237, 1145 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 0.12 (s, 9 H, TMS), 1.32 (s, 6 H, CMe_2), 2.46 (s, 2 H, CH_2), 5.03 (d, *J* = 3.2 Hz, 1 H, H-1), 5.21 (d, *J* = 3.2 Hz, 1 H, H-1).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 2.30, 29.61, 49.00, 72.82, 107.56, 154.34.

HRMS (ESI): *m*/*z* $[M]^+$ calcd for $C_{13}H_{19}F_9O_4SSi$: 470.0624; found: 470.0625.

3-Methyl-3-(trimethylsilyloxy)but-1-en-2-yl Nonaflate (2d) Table 2, Entry 3

Compound **2d** was prepared according to GP3 from **1d** (0.493 g, 2.00 mmol) and NfF (0.785 g, 2.60 mmol), employing KF (0.116 g, 2.00 mmol) and dibenzo-18-crown-6 (0.144 g, 0.40 mmol) in

DMSO–hexane (2 mL:3 mL). Product **2d** was purified by distillation.

Yield: 0.630 g (69%); pale yellow liquid; bp 85–86 °C/0.5 mbar.

IR (neat): 2962–2890, 1663, 1420, 1235, 1142 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 0.12 (s, 9 H, TMS), 1.19 (s, 6 H, CMe_2), 4.74 (d, *J* = 3.9 Hz, 1 H, H-1), 4.89 (d, *J* = 3.9 Hz, 1 H, H-1).

^{13}C NMR (100 MHz, C_6D_6): δ = 2.16, 28.12, 73.63, 101.24, 161.26.

HRMS (APCI$^-$): *m*/*z* [M – H]$^-$ calcd for $C_{12}H_{16}F_9O_4SSi$: 455.0400; found: 455.0388.

Table 2, Entry 4

Compound **2d** was prepared according to GP3 from **1d** (4.920 g, 20.00 mmol) and NfF (7.854 g, 26.00 mmol), employing KF (1.16 g, 20.00 mmol) and dibenzo-18-crown-6 (1.44 g, 4.00 mmol) in DMSO–hexane (20 mL:30 mL). Product **2d** was purified as in entry 3; yield: 6.57 g (72%).

3-(*tert*-Butyldimethylsilyloxy)-3-methylbut-1-en-2-yl Nonaflate (2e; Table 2, Entry 5)

Compound **2e** was prepared according to GP3 from **1e** (0.240 g, 0.83 mmol) and NfF (0.326 g, 1.08 mmol), employing KF (0.048 g, 0.83 mmol) and dibenzo-18-crown-6 (0.060 g, 0.166 mmol) in DMSO–hexane (1 mL:1.5 mL). Product **2e** was purified by column chromatography on silica gel (hexane–EtOAc, 40:1).

Yield: 0.298 g (72%); colorless liquid; R_f = 0.51 (hexane–EtOAc, 20:1).

IR ($CDCl_3$): 2933–2859, 1664, 1467, 1238, 1144 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 0.02 (s, 6 H, 2 Me-TBS), 0.93 (s, 9 H, *t*-Bu-TBS), 1.18 (s, 6 H, CMe_2), 4.91 (d, *J* = 4.0 Hz, 1 H, H-1), 4.96 (d, *J* = 4.0 Hz, 1 H, H-1).

^{13}C NMR (100 MHz, C_6D_6): δ = –2.26, 18.28, 25.91, 28.08, 73.83, 100.88, 161.15.

HRMS (APCI$^-$): *m*/*z* [M – H]$^-$ calcd for $C_{15}H_{22}F_9O_4SSi$: 497.0870; found: 497.0866.

(1*R*,4*R*,5*R*)-4,6,6-Trimethyl-4-(trimethylsilyloxy)bicyclo[3.1.1]hept-2-en-3-yl Nonaflate (2f; Table 2, Entry 6)

Compound **2f** was prepared according to GP3 from **1f** (0.313 g, 1.00 mmol) and NfF (0.393 g, 1.30 mmol), employing KF (0.058 g, 1 mmol) and dibenzo-18-crown-6 (0.072 g, 0.20 mmol) in DMSO–hexane (1 mL:1.5 mL).

Yield (purity 88% by NMR): 0.409 g (74%); pale yellow oil.

IR (neat): 2956, 1655, 1419, 1225, 1126 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 0.17 (s, 9 H, TMS), 0.80 (s, 3 H, Me), 1.04 (s, 3 H, Me), 1.37 (s, 3 H, Me), 1.74–1.79 (m, 1 H, H-1), 1.85 (d, *J* = 9.4 Hz, 1 H, H-5), 1.95–1.99 (m, 1 H, H-7), 2.06–2.14 (m, 1 H, H-7), 5.96 (d, *J* = 7.3 Hz, 1 H, H-2).

^{13}C NMR (100 MHz, C_6D_6): δ = 2.41, 23.66, 23.95, 27.32, 32.96, 41.24, 47.17, 55.37, 77.81, 126.72, 149.96.

HRMS (APCI$^-$): *m*/*z* [M – H]$^-$ calcd for $C_{17}H_{22}F_9O_4SSi$: 521.0870; found: 521.0870.

3-(*tert*-Butyldimethylsilyloxy)but-1-en-2-yl Nonaflate (2g; Table 2, Entry 7)

Compound **2g** was prepared according to GP3 from **1g** (1.000 g, 3.64 mmol) and NfF (1.429 g, 4.73 mmol), employing KF (0.211 g, 3.64 mmol) and dibenzo-18-crown-6 (0.262 g, 0.728 mmol) in DMSO–hexane (3 mL:4.5 mL). Product **2g** was purified by column chromatography on silica gel (hexane–EtOAc, 30:1 to 10:1).

Yield: 1.28 g (73%); pale yellow liquid; R_f = 0.26 (hexane–EtOAc, 10:1).

IR (neat): 2933–2860, 1668, 1420, 1238, 1143 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.09 (s, 3 H, Me-TBS), 0.10 (s, 3 H, Me-TBS), 0.91 (s, 9 H, *t*-Bu-TBS), 1.34 (d, *J* = 6.4 Hz, 3 H, Me-3), 4.33 (q, *J* = 6.4 Hz, 1 H, H-3), 5.17 (d, *J* = 3.42 Hz, 1 H, H-1), 5.26 (dd, *J* = 3.42, 0.93 Hz, 1 H, H-1).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –5.02, –4.96, 18.23, 22.13, 25.80, 67.99, 102.72, 158.93.

HRMS (APCI$^-$): *m*/*z* [M – H]$^-$ calcd for $C_{14}H_{20}F_9O_4SSi$: 483.0713; found: 483.0705.

6-(*tert*-Butyldimethylsilyloxy)cyclohex-1-en-1-yl Nonaflate (2h; Table 2, Entry 8)

Compound **2h** was prepared according to GP3 from **1h** (0.270 g, 0.90 mmol) and NfF (0.353 g, 1.17 mmol), employing KF (0.052 g, 0.90 mmol) and dibenzo-18-crown-6 (0.065 g, 0.18 mmol) in DMSO–hexane (1 mL:1.5 mL). Product **2h** was purified by column chromatography on silica gel (hexane–EtOAc, 40:1 to 30:1).

Yield: 0.231 g (51%); colorless liquid; R_f = 0.49 (hexane–EtOAc, 20:1).

IR (neat): 2954–2860, 1637, 1419, 1236, 1142 cm^{-1}.

^1H NMR (400 MHz, $CDCl_3$): δ = 0.10 (s, 3 H, Me-TBS), 0.12 (s, 3 H, Me-TBS), 0.90 (s, 9 H, *t*-Bu-TBS), 1.56–1.63 (m, 1 H), 1.71–1.87 (m, 3 H), 2.09–2.18 (m, 1 H), 2.22–2.30 (m, 1 H), 4.29–4.31 (m, 1 H, H-6), 5.86 (dd, *J* = 3.6, 4.6 Hz, 1 H, H-2).

^{13}C NMR (100 MHz, $CDCl_3$): δ = –4.76, –4.57, 16.98, 18.13, 24.58, 25.86, 33.10, 66.54, 121.03, 150.41.

HRMS (APCI$^-$): *m*/*z* [M – H]$^-$ calcd for $C_{16}H_{22}F_9O_4SSi$: 509.0870; found: 509.0869.

3-Methyl-4-(trimethylsilyloxy)but-1-en-2-yl Nonaflate (2i) Table 2, Entry 9

Compound **2i** was prepared according to GP3 from **1i** (0.247 g, 1.00 mmol) and NfF (0.393 g, 1.30 mmol), employing KF (0.058 g, 1.00 mmol) and dibenzo-18-crown-6 (0.054 g, 0.15 mmol) in DMSO–hexane (1 mL:1.5 mL). Typical workup followed by purification using Kugelrohr distillation at 90–95 °C/0.5 mbar afforded product **2i** as a colorless liquid.

Yield: 0.191 g (42%).

IR (neat): 2997–2903, 1659, 1423, 1241, 1145 cm^{-1}.

^1H NMR (270 MHz, $CDCl_3$): δ = 0.10 (s, 9 H, TMS), 1.15 (d, *J* = 6.9 Hz, 3 H, Me-3), 2.54–2.62 (m, 1 H, H-3), 3.54 (dd, *J* = 10.1, 5.8 Hz, 1 H, H-4), 3.65 (dd, *J* = 10.1, 5.8 Hz, 1 H, H-4), 4.99 (dd, *J* = 3.9, 0.7 Hz, 1 H, H-1), 5.17 (d, *J* = 3.9 Hz, 1 H, H-1).

^{13}C NMR (67.5 MHz, $CDCl_3$): δ = 2.44, 29.79, 49.19, 72.93, 107.71, 154.49.

HRMS (ESI): *m*/*z* [M]$^+$ calcd for $C_{12}H_{17}F_9O_4SSi$: 456.0468; found: 456.0468.

Table 2, Entry 10

Compound **2i** was prepared according to GP3 from **1i** (0.247 g, 1.00 mmol) and NfF (0.393 g, 1.30 mmol), employing KF (0.058 g, 1.00 mmol) and dibenzo-18-crown-6 (0.054 g, 0.15 mmol) in anhyd THF (2 mL). Aqueous workup with ice water–hexane (30 mL, 1:1), quick extraction with hexane (2 × 15 mL) while the aqueous phase still contained some ice, and drying of the combined hexane layers over Na_2SO_4 followed by Kugelrohr distillation at 90–95 °C/0.5 mbar afforded product **2i**; yield: 0.346 g (76%); colorless liquid.

3-(Trimethylsilyloxy)but-1-en-2-yl Nonaflate (2j; Table 3, Entry 3)

Compound **2j** was prepared according to GP3 from **1j** (0.968 g, 4.16 mmol) and NfF (1.634 g, 5.41 mmol), employing KF (0.241 g, 4.16

mmol) and dibenzo-18-crown-6 (0.300 g, 0.83 mmol) in THF (8 mL). Aqueous workup with ice water–hexane (30 mL, 1:1), quick extraction with hexane (2 × 15 mL) while the aqueous phase contained still some ice, and drying of the combined hexane layers over Na_2SO_4 followed by distillation afforded product **2j**.

Yield (purity 80% by NMR): 0.720 g (39%); colorless liquid; bp 73–77 °C/0.5 mbar.

IR ($CDCl_3$): 2960–2924, 1658, 1453, 1234, 1142 cm^{-1}.

^1H NMR (400 MHz, C_6D_6): δ = 0.04 (s, 9 H, TMS), 1.11 (d, *J* = 6.4 Hz, 3 H, Me-3), 4.11 (q, *J* = 6.4 Hz, 1 H, H-3), 4.79 (dd, *J* = 3.6, 0.9 Hz, 1 H, H-1), 4.87 (d, *J* = 3.6 Hz, 1 H, H-1).

^{13}C NMR (100 MHz, C_6D_6): δ = 0.29, 21.88, 67.73, 102.96, 158.90.

HRMS (APCI$^-$): *m/z* $[M - H]^-$ calcd for $C_{11}H_{14}F_9O_4SSi$: 441.0238; found: 441.0234.

Supporting Information for this article is available online at http://www.thieme-connect.com/ejournals/toc/synthesis. ^1H and ^{13}C NMR spectra for all new compounds are included.

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