Available online at www.sciencedirect.com
ScienceDirect
Tetrahedron
Tetrahedron 63 (2007) 8485–8491

# Mild and efficient Sonogashira couplings of 8-oxa- and 8-thiabicyclo[3.2.1]octanone derived alkenyl nonaflates

Jens Högermeier[†] and Hans-Ulrich Reissig[*]

*Freie Universität Berlin, Institut für Chemie und Biochemie, Takustrasse 3, 14195 Berlin, Germany*

Received 27 March 2007; revised 15 May 2007; accepted 17 May 2007
Available online 24 May 2007

Dedicated to Professor Hisashi Yamamoto

**Abstract**—We demonstrate in this report that bicyclic alkenyl nonaflates (nonafluorobutanesulfonates) generated from 8-heterobicyclo[3.2.1]octan-3-one derivatives are excellent substrates for Sonogashira couplings with alkynes. Employing CuI, $Pd(OAc)_2$, $PPh_3$ in DMF/*i*-$Pr_2NH$ as standard reagents structurally diverse bicyclic nonaflates were coupled with phenyl acetylene in generally high yields. Particularly efficient are transformations of precursors **16**, **18**, and **20** bearing methyl groups at the bridgehead carbons, which furnished the expected enynes **17**, **19**, and **21** in approximately 90% yield. With respect to the alkyne component the scope of this palladium-catalyzed reaction seems also to be fairly broad. Thus, trimethylsilyl acetylene and propargyl alcohol could also be used, affording coupling products **22**, **23**, and **25** with high efficacy. The protocol of Grieco was applied to induce a domino coupling of tricyclic alkenyl nonaflate **14** with trimethylsilyl acetylene affording product **26** in moderate yield and as 1:1 mixture of the expected two diastereomers.


## 1. Introduction

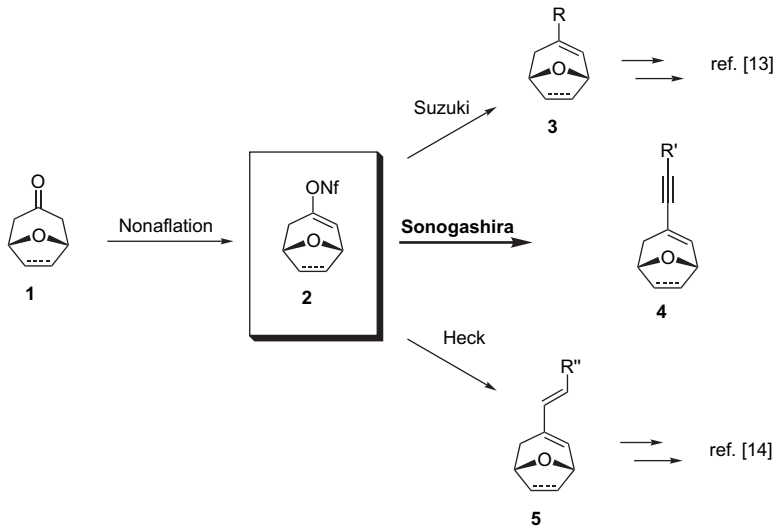
Among the many palladium-catalyzed coupling reactions the Sonogashira reaction has emerged as the primary reaction to introduce C, C triple bonds.[1] A lot of different protocols are available for this kind of reaction using aryl and alkenyl halides or triflates.[2] However, only few examples of nonafluorobutanesulfonates (nonaflates) as coupling partners in Sonogashira reactions have been published so far.[3] Maleczka demonstrated that CsF in the presence of PMHS (polymethylhydrosiloxane) facilitates the Sonogashira reaction of several alkynes with aryl nonaflates[4] and Swager used aryl nonaflates for the synthesis of new poly(phenylene ethynylene) derivatives (PPEs).[5] Examples of alkenyl nonaflates in Sonogashira reactions have also been disclosed by Wada who used Stille and Sonogashira reactions to synthesize $^{13}C$-labeled retinal.[6] Other examples of alkenyl nonaflates in Sonogashira reactions were published by Brückner[7] and Minami.[8] Very recently Lyapkalo and Vogel reported an efficient and elegant one-pot procedure for forming the required alkyne component in situ by elimination from an alkenyl nonaflates, which was subsequently coupled with a second alkenyl nonaflate.[9]

Over the last years our research group has systematically investigated the synthesis and application of alkenyl nonaflates from ketones or silyl enol ethers[10] and their use in palladium-catalyzed coupling reactions.[11] These studies (and the above mentioned literature reports) clearly revealed that alkenyl nonaflates are as easy accessible as the corresponding triflates, that they are considerably more stable, but at least as reactive as the alkenyl triflates; furthermore, the generally employed sulfonylating reagent (nonafluorobutanesulfonyl fluoride) is considerably less expensive than the commonly used triflating reagents. Therefore, after these first studies our interest turned toward the use of 8-heterobicyclo[3.2.1]octanones and their derivatives. These densely functionalized bicyclic ketones are very valuable building blocks and have been used in numerous asymmetric total syntheses.[12]

Bicyclic nonaflates **2** are easily accessible by deprotonation of the corresponding ketones **1** with LDA (Scheme 1) and reaction with nonafluorobutanesulfonyl fluoride. We successfully employed intermediates **2** in Suzuki couplings[13] with different boron compounds to give substituted bicyclic compounds **3** and in Heck couplings[14] yielding dienes **5**. Products **3** and **5** were further transformed and molecular frameworks with high diversity were obtained. Furthermore we applied azabicyclic nonaflates in the synthesis of new tropinone derivatives.[15] During these investigations we also included an example of a Sonogashira reaction of a bicyclic alkenyl nonaflate. Encouraged by this first successful application we decided to broaden the scope of (bicyclic)

*Keywords*: Alkenyl nonaflates; Alkynes; Palladium catalysis; Enynes; Thioether; Bicyclo[3.2.1]octane derivatives.
* Corresponding author. E-mail: hans.reissig@chemie.fu-berlin.de
† Present address: Australian National University, Research School of Chemistry, Canberra, ACT, Australia.

0040–4020/$ - see front matter © 2007 Elsevier Ltd. All rights reserved.
doi:10.1016/j.tet.2007.05.072

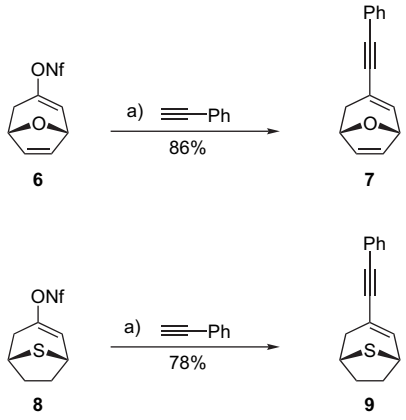



**Scheme 1**. Oxabicyclo[3.2.1]octanone derived nonaflates **2** as crucial intermediates for palladium-catalyzed coupling reactions.

alkenyl nonaflates to the coupling reactions with alkynes since the expected products incorporate enyne moieties being of interest as versatile intermediates for subsequent transformations. We also wanted to demonstrate that alkenyl nonaflates are generally good precursors for Sonogashira reactions and hence we undertook a brief investigation of coupling several oxa- and thiabicyclic alkenyl nonaflates with different alkynes.

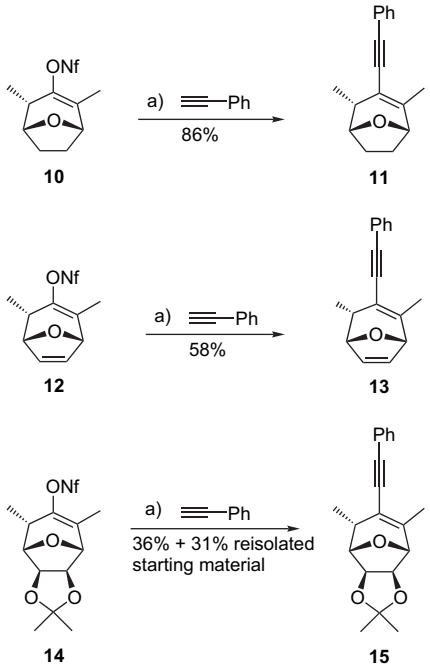
## 2. Results and discussion

The synthesis of all bicyclic alkenyl nonaflates employed in this study from the corresponding ketones has previously been reported.[13,14] We started our study with oxabicyclic nonaflate **6** and phenyl acetylene employing a mixture of DMF/*i*-$Pr_2NH$ as solvent and base together with the catalyst system CuI (10%), $Pd(OAc)_2$ (5%), and $PPh_3$ at room temperature (Scheme 2). This protocol was successful in the case of azabicyclic nonaflate[15] and it converted **6** into the desired coupling product **7** in 86% yield. Encouraged by this result we turned our interest on the influence of sulfur as the bridging atom of the alkenyl nonaflate component. Sulfur might potentially poison the palladium catalyst. Fortunately we were able to couple nonaflate **8** under the conditions used before providing the thiabicyclic enyne **9** in 78% yield. This nicely demonstrates that thioether moieties are tolerated in the Sonogashira reaction and do not poison the catalyst.




**Scheme 2**. Reagents and conditions: (a) 5% $Pd(OAc)_2$, $PPh_3$, 10% CuI, $(i\text{-Pr})_2NH$, DMF, rt, 17 h (All chiral compounds in this report are racemic mixtures, arbitrarily only one enantiomer is depicted in Schemes 2–6).

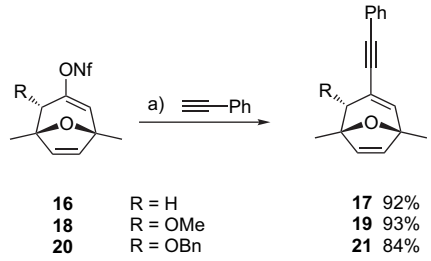
For further investigations the screening of sterically more demanding nonaflates was undertaken employing bicyclic nonaflates **10**, **12**, and **14** with two methyl groups in α-position as precursors. Starting with **10** under the conditions described above, this nonaflate was smoothly converted into alkyne derivative **11** in 86% yield (Scheme 3). However, alkenyl nonaflate **12** bearing a double bond in the C6–C7 position furnished product **13** only in 58% yield. This relatively low yield may be due to fragmentation of **12**. We had observed and investigated fragmentations of this type of




**Scheme 3**. Reagents and conditions: 5% $Pd(OAc)_2$, $PPh_3$, 10% CuI, $(i\text{-Pr})_2NH$, DMF, rt, 17 h.

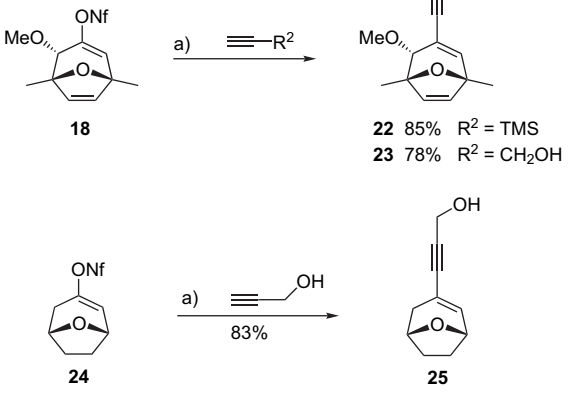
alkenyl nonaflates in the case of Heck reactions where furan[14] and pyrrole[15] derivates were obtained instead of the desired products. We therefore studied a compound without the double bond and employed nonaflate **14** bearing a protected 1,2-diol moiety. However, under the conditions applied we could obtain no better yield than 36% of the desired product **15**; 31% of starting material **14** was recovered. We believe that besides the sterical effect, the protected 1,2-diol moiety reduces the reactivity of the alkenyl nonaflate in the coupling reaction. This may lead to an increased homocoupling of phenyl acetylene to furnish 1,4-diphenylbutadiyne, which was detected by TLC analysis.

We also studied bicyclic nonaflates bearing methyl substituents at the bridgehead carbons, which—according to our suggested mechanism[14,15]—cannot undergo the fragmentation reaction and therefore are ideal substrates for further investigations of the Sonogashira coupling. Nonaflate **16** was converted to enyne **17** in 92% yield (Scheme 4). In this experiment control of the reaction progress by TLC analysis showed that complete conversion was already achieved after 30 min instead of the previously used 17 h. All subsequent coupling reactions were therefore performed in much shorter times. The influence of α-oxygenated bicyclic nonaflates was also investigated: α-methoxy-substituted nonaflate **18** was converted into **19** in excellent 93% yield, whereas α-benzyloxy nonaflate **20** gave **21** in 84% yield, respectively.



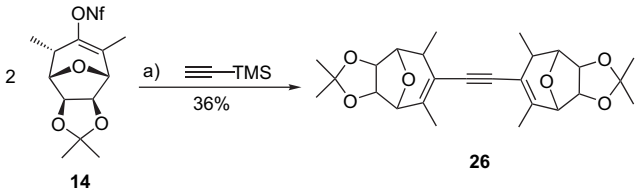

**Scheme 4**. Reagents and conditions: (a) 5% $Pd(OAc)_2$, $PPh_3$, 10% CuI, $(i\text{-}Pr)_2NH$, DMF, rt, 30 min.

With a fast and mild protocol for the coupling in hand further investigations with different alkynes were conducted (Scheme 5). For these experiments α-methoxy-substituted nonaflate **18** was chosen because of its easy availability and its good results in the first couplings. Under the conditions as used before trimethylsilyl acetylene was easily coupled with nonaflate **18** to furnish **22** in 85% yield (Scheme 5). It was important that this reaction was quenched after 30 min, otherwise decomposition of the product and formation of a strongly UV-active starting line spot were observed on TLC. In an analogous fashion couplings were conducted using propargyl alcohol transforming nonaflate **18** into **23** in 78% yield and compound **24** into product **25** in 83% yield. All these examples demonstrate that bicyclic alkenyl nonaflates are excellent coupling partners in Sonogashira reactions and can be coupled under fairly mild conditions providing synthetically useful enynes in good yields.




**Scheme 5**. Reagents and conditions: (a) 5% $Pd(OAc)_2$, $PPh_3$, 10% CuI, $(i\text{-}Pr)_2NH$, DMF, rt, 30 min.

Recently Grieco and co-workers have disclosed an efficient one-pot procedure for a twofold Sonogashira reaction of aryl halides and triflates, which involves an initial coupling with trimethylsilyl acetylene, a subsequent desilylation of the intermediate alkyne and a second coupling reaction to provide a symmetrical and unsymmetrical bisarylalkyne derivative.[16] We applied these conditions to one of our bicyclic alkenyl nonaflates as the Grieco group did not include nonaflates in their studies. The reaction was carried out as outlined in the literature using a $DBU/H_2O$ mixture as base and deprotection agent (Scheme 6). In case of nonaflate **14** the coupling with trimethylsilyl acetylene furnished the expected disubstituted alkyne **26** as a 1:1 mixture of diastereomers in a low yield of 36%. The relative configuration within each tricyclic moiety is still retained, however, due to the fact that **14** was used as racemic mixture alkyne **26** was obtained as the expected mixture of two diastereomers (D/L and meso). This domino transformation[17] of nonaflate **14**, a compound which was also not particularly efficient in simple couplings with phenyl acetylene (see Scheme 3), may be improved by further optimization. Nevertheless, it clearly demonstrates that fairly complex structures such as **26** are simply available from alkenyl nonaflates.




**Scheme 6**. Reagents and conditions: (a) 6% $Pd(PPh_3)_2Cl_2$, 10% CuI, DBU, $H_2O$, benzene, rt, 18 h (1:1 mixture of two diastereomers **26**, relative configuration within one tricyclic moiety of **26** as depicted for **14**).

## 3. Conclusion

We have demonstrated in this study that bicyclic alkenyl nonaflates can successfully be employed as coupling partners in Sonogashira reactions. First experiments were carried out using phenyl acetylene, and in most cases the coupling products were smoothly obtained in good to excellent yields. Several other synthetically useful alkynes were coupled in good yields to furnish new bicyclic enynes. The extension of Grieco's protocol to generate a symmetrically disubstituted alkyne was only moderately successful with our bicyclic alkenyl nonaflate as precursor. Overall, our brief study reveals that bicyclic alkenyl nonaflates are not only

excellent precursors for Heck or Suzuki couplings, but also for Sonogashira reactions which provided a series of new enynes with good to excellent efficacy. These enynes incorporated into oxa- or thiabicyclo[3.2.1]octane skeletons are promising starting materials for the synthesis of a variety of compounds with interesting structural features.

## 4. Experimental part

### 4.1. General information

NMR spectra were recorded on Bruker AC 500 and Joel Eclipse 500 (500 MHz) instruments. $^1$H and $^{13}$C chemical shifts are expressed as parts per million down field from tetramethylsilane ($\delta$=0) or $CDCl_3$ ($\delta$=7.26 and 77.0 in $^{13}$C NMR) used as an internal standard. Mass spectra were registered with Varian MAT 711 spectrometer. IR spectra were measured with a spectrometer 5 SXC Nicolet. TLC analysis was performed using Merck silica gel 60 $F_{254}$ plates. Column chromatography was conducted on silica gel 60 (40–63 μm, Fluka). All reactions were carried out under an atmosphere of argon in heat-gun dried reaction flasks by adding the components via syringes. Solvents for reactions were dried by standard procedures. Starting materials: the nonaflates were prepared according to our previously published procedure.[13b,14] DMF was purchased from Acros Organics (99.8%, extra dry, <50 ppm water), *i*-$Pr_2NH$ was distilled prior to use from KOH and stored over KOH under an argon atmosphere. CuI was purchased from Aldrich (99.999%) and $Pd(OAc)_2$ from Acros Organics (47.5% Pd).

### 4.2. General procedure (GP)

The alkenyl nonaflate was dissolved in a DMF/*i*-$Pr_2NH$ mixture in a heat-gun dried and argon flushed round-bottomed flask. The alkyne (1.2 equiv), $PPh_3$ (0.2 equiv), CuI (0.1 equiv), and $Pd(OAc)_2$ (0.05 equiv) were added. The mixture was stirred at room temperature for the time given in the individual experiment. The resulting reaction mixture was then taken up with EtOAc. The organic layer was washed twice with water and once with brine and then dried with $MgSO_4$, and the solvent was removed in vacuo. The crude product was purified on silica gel using flash column chromatography.

**4.2.1. 3-(Phenylethynyl)-8-oxabicyclo[3.2.1]octa-2,6-diene (7).** According to the general procedure, nonaflate **6** (300 mg, 0.74 mmol) was dissolved in DMF (2 mL) and *i*-$Pr_2NH$ (1 mL). Phenyl acetylene (91 mg, 0.89 mmol), $PPh_3$ (19 mg, 0.08 mmol), CuI (14 mg, 0.08 mmol), and $Pd(OAc)_2$ (8 mg, 0.04 mmol) were added and the mixture was stirred for 17 h. Purification of the product (Hex/EtOAc 90:10) afforded **7** (205 mg, 86%) as a yellow solid. Mp: 116–118 °C; IR (KBr): 3080–3020 (=C–H), 2970–2850 (–C–H), 2000 (C≡C), 1610 (C=C), 1590, 1570 cm$^{-1}$ (Ph); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 7.31–7.27, 7.42–7.38 (2m, 3H, 2H, Ph), 6.52–6.48 (m, 2H, 2-H, 7-H), 6.02 (dd, *J*=5.9, 1.8 Hz, 1H, 6-H), 4.96 (dd, *J*=6.0, 1.8 Hz, 1H, 5-H), 4.79 ($m_c$, 1H, 1-H), 2.80 (dddd, *J*=17.8, 6.0, 2.0, 1.3 Hz, 1H, 4-$H_{ax}$), 1.88 (dd, *J*=17.8, 1.6 Hz, 1H, 4-$H_{eq}$); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$/ppm: 136.9 (d, C-2), 136.7 (d, C-7), 131.5, 128.2, 128.1 (3d, Ph), 127.6 (d, C-6), 123.0 (s, Ph), 116.9 (s, C-3), 89.4, 87.5 (2s, C≡C), 77.1 (d, C-5), 75.5 (d, C-1), 30.7 (t, C-4); MS (EI, 80 eV) *m*/*z* (%) 208 ($M^+$, 8), 179 (100), 77 ($C_6H_5^+$, 4); HRMS calcd for $C_{15}H_{12}O$: 208.08882, found: 208.08665.

**4.2.2. 3-(Phenylethynyl)-8-thiabicyclo[3.2.1]oct-2-ene (9).** According to the general procedure, nonaflate **8** (423 mg, 1.00 mmol) was dissolved in DMF (2 mL) and *i*-$Pr_2NH$ (1 mL). Phenyl acetylene (143 mg, 1.40 mmol), $PPh_3$ (26 mg, 0.10 mmol), CuI (19 mg, 0.10 mmol), and $Pd(OAc)_2$ (11 mg, 0.05 mmol) were added and the mixture was stirred for 17 h. Purification of the product (Hex/EtOAc 95:5) afforded **9** (176 mg, 78%) as a light yellow solid. Mp: 95–97 °C; IR (KBr): 3080–3070 (=C–H), 2990–2810 (C–H), 2210 (C≡C), 1620, 1590 cm$^{-1}$ (C=C); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 7.30–7.26, 7.42–7.38 (2m, 3H, 2H, Ph), 6.62 (dt, *J*=7.3, 1.9 Hz, 1H, 2-H), 3.88 (br t, *J*=3.4 Hz, 1H, 5-H), 3.71 ($m_c$, 1H, 1-H), 2.83 (dt, *J*=17.9, 2.0 Hz, 1H, 4-$H_{ax}$), 2.43–2.37 (m, 1H, 7-H), 2.29 (dt, *J*=17.9, 2.0 Hz, 1H, 4-$H_{eq}$), 2.30–2.23 (m, 1H, 6-H), 2.10 ($m_c$, 1H, 7-H), 2.02–1.95 (m, 1H, 6-H); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$/ppm: 139.9 (s, C-2), 131.4, 128.2, 128.0 (3d, Ph), 123.3 (s, Ph), 119.1 (s, C-3), 89.9, 88.1 (2s, C≡C), 45.5 (d, C-5), 43.8 (d, C-1), 42.2 (t, C-4), 40.3 (t, C-7), 34.6 (t, C-6); MS (EI, 80 eV) *m*/*z* (%) 226 ($M^+$, 100), 202 ($M^+-C\equiv C$, 36), 197 ($M^+-29$, 57), 184 ($M^+-C_2H_2O^+$, 18), 178 (17), 165 (19), 115 (18); Anal. calcd for $C_{15}H_{14}S$ (226.1): C, 79.60; H, 6.23. Found: C, 80.10; H, 6.20%.

**4.2.3. 2,4-Dimethyl-3-(phenylethynyl)-8-oxabicyclo[3.2.1]oct-2-ene (11).** According to the general procedure, nonaflate **10** (436 mg, 1.00 mmol) was dissolved in DMF (2 mL) and *i*-$Pr_2NH$ (1 mL). Phenyl acetylene (143 mg, 1.40 mmol), $PPh_3$ (26 mg, 0.10 mmol), CuI (19 mg, 0.10 mmol), and $Pd(OAc)_2$ (11 mg, 0.05 mmol) were added and the mixture was stirred for 17 h. Purification of the product (Hex/EtOAc 90:10) afforded **11** (205 mg, 86%) as a colorless. Mp: 57–59 °C; IR (KBr): 3050–3030 (=C–H), 2950–2870 (C–H), 2200 (C≡C), 1590 cm$^{-1}$ (C=C); $^1$H NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 7.45–7.38, 7.32–7.24 (2m, 3H, 2H, Ph), 4.38 (t, *J*=5.5 Hz, 1H, 5-H), 4.32 (d, *J*=4.9 Hz, 1H, 1-H), 2.93 ($m_c$, 1H, 4-H), 2.05–1.75 (m, 4H, 6-H, 7-H), 1.19 (d, *J*=2.3 Hz, 3H, 2-Me), 1.09 (d, *J*=7.4 Hz, 3H, 4-Me); $^{13}$C NMR (126 MHz, $CDCl_3$) $\delta$/ppm: 144.5 (s, C-3), 131.3, 128.2, 127.9 (3d, Ph), 123.8 (s, Ph), 125.8 (s, C-2), 93.7, 86.9 (2s, C≡C), 78.4 (d, C-5), 77.2 (d, C-1), 37.3 (d, C-4), 32.8 (t, C-7), 22.9 (t, C-6), 18.1 (q, 2-Me), 14.1 (q, 4-Me); MS (EI, 80 eV) *m*/*z* (%) 238 ($M^+$, 100), 223 ($M^+-12$, 30), 209 ($M^+-CHO$, 40), 195 ($223-C_2H_4^+$, 26), 181 (14), 179 (11), 165 (19), 115 (18), 105 (25), 91 (17), 77 ($Ph^+$, 13), 69 (11); HRMS calcd for $C_{17}H_{18}O$: 283.13577, found: 238.13732.

**4.2.4. 2,4-Dimethyl-3-(phenylethynyl)-8-oxabicyclo-[3.2.1]octa-2,6-diene (13).** According to the general procedure, nonaflate **12** (434 mg, 1.00 mmol) was dissolved in DMF (2 mL) and *i*-$Pr_2NH$ (1 mL). Phenyl acetylene (143 mg, 1.40 mmol), $PPh_3$ (26 mg, 0.10 mmol), CuI (19 mg, 0.10 mmol), and $Pd(OAc)_2$ (11 mg, 0.05 mmol) were added and the mixture was stirred for 17 h. Purification of the product (Hex/EtOAc 90:10) afforded **13** (138 mg, 58%) as a light brown solid. Mp: 61–63 °C; IR (KBr):

3080–3060 (=C–H), 2955–2870 (C–H), 2200 (C≡C), 1720, 1590–1490 $cm^{-1}$ (C=C); $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 7.43–7.41, 7.41–7.39 (2m, 3H, 2H, Ph), 6.65 (dd, $J$=5.9, 1.4 Hz, 1H, 7-H), 6.02 (dd, $J$=5.9, 1.4 Hz, 1H, 6-H), 4.93 (dd, $J$=5.6, 1.4 Hz, 1H, 5-H), 4.56 (br s, 1H, 1-H), 2.77 ($m_c$, 1H, 4-H), 1.98 (d, $J$=2.0 Hz, 3H, 2-Me), 1.03 (d, $J$=7.3 Hz, 3H, 4-Me); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$/ppm: 145.6 (s, C-3), 138.4 (d, C-7), 131.3, 128.2, 127.9 (3d, Ph), 127.8 (d, C-6), 123.7 (s, Ph), 115.7 (s, C-2), 92.2, 87.6 (2s, C≡C), 82.3 (d, C-5), 80.2 (d, C-1), 33.3 (d, C-4), 18.3 (q, 2-Me), 12.3 (q, 4-Me); MS (EI, 80 eV) $m/z$ (%) 236 ($M^+$, 28), 222 ($M^+-CH_3$, 18), 208 ($M^+-CO$, 24), 207 ($M^+-CHO$, 100), 192 ($207-CH_3$, 36), 191 (18), 178 (15), 165 (12), 129 (29), 128 (12), 115 (39), 105 (30), 96 (18), 95 (45), 91 (19), 77 ($C_6H_5^+$, 16), 69 (10), 43 (24); HRMS calcd for $C_{17}H_{16}O$: 236.12012, found: 236.12332.

**4.2.5. 2,2,5,7-Tetramethyl-6-(phenylethynyl)-4,5,8,8a-tetrahydro-3a*H*-4,8-epoxycyclohepta-[*d*][1,3]dioxole (15).** According to the general procedure, nonaflate **14** (200 mg, 0.394 mmol) was dissolved in DMF (2 mL) and *i*-$Pr_2NH$ (1 mL). Phenyl acetylene (60 mg, 0.591 mmol), $PPh_3$ (21 mg, 0.079 mmol), CuI (8 mg, 0.04 mmol), and $Pd(OAc)_2$ (4 mg, 0.02 mmol) were added and the mixture was stirred for 17 h. Purification of the product (Hex/EtOAc 98:2) afforded 129 mg of a mixture of starting material and the product which was further purified by HPLC (Nucleosil 50-5, 2 mL/min, 5% EtOAc/Hex). This afforded starting material **14** (61 mg, 31%) and product **15** (43 mg, 36%) as a colorless solid. Mp: 132–134 °C; IR (KBr): 2990–2950 (C–H), 1700 (C=C), 1420 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 7.43–7.40, 7.32–7.28 (2m, 3H, 2H, Ph), 4.78, 4.56 (2d, $J$=5.7 Hz, 1H each, 6-H, 7-H), 4.29 (s, 1H, 1-H), 4.27 (d, $J$=5.4 Hz, 1H, 5-H), 2.83 ($m_c$, 1H, 4-H), 1.95 (d, $J$=2.3 Hz, 3H, 2-$CH_3$), 1.51, 1.32 [2s, 3H each, $C(CH_3)_2$], 1.18 (d, $J$=7.6 Hz, 3H, 4-$CH_3$); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$/ppm: 140.2 (s, C-3), 131.4, 128.3, 128.1 (3d, Ph), 123.3, 118.4 (2s, Ph, C-2), 112.3 [s, $C(CH_3)_2$], 94.3, 85.8 (2s, C≡C), 84.2 (d, C-5), 81.2 (d, C-1), 84.4, 80.3 (2d, C-6, C-7), 34.3 (d, C-4), 26.2, 24.9 [2q, $C(CH_3)_2$], 18.3, 13.9 (2q, 2-$CH_3$, 4-$CH_3$); MS (EI, 80 eV) $m/z$ (%) 310 ($M^+$, 23), 236 (12), 234 (13), 223 (79), 209 (23), 195 (66), 180 (37), 165 (67), 152 (23), 141 (22), 139 (19), 128 (15), 115 (51), 105 (19), 77 (15), 69 (11), 55 (27), 43 ($CH_3CO^+$, 100); HRMS calcd for $C_{20}H_{22}O_3$: 310.15689, found: 310.15722.

**4.2.6. 1,5-Dimethyl-3-(phenylethynyl)-8-oxabicyclo-[3.2.1]octa-2,6-diene (17).** According to the general procedure, nonaflate **16** (200 mg, 0.462 mmol) was dissolved in DMF (2 mL) and *i*-$Pr_2NH$ (1 mL). Phenyl acetylene (57 mg, 0.554 mmol), $PPh_3$ (18 mg, 0.069 mmol), CuI (44 mg, 0.023 mmol), and $Pd(OAc)_2$ (5 mg, 0.023 mmol) were added and the mixture was stirred for 30 min. Purification of the product (Hex/EtOAc 97:3) afforded **17** (100 mg, 92%) as a light yellow solid. Mp: 70 °C; IR (film): 3060–3040 (=C–H), 2980–2870 (C–H), 2200 (C≡C), 1600 (C=C), 1490, 1450 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 7.42–7.38, 7.30–7.27 (2m, 3H, 2H, Ph), 6.43 (t, $J$=1.9 Hz, 1H, 2-H), 6.19, 5.72 (2d, $J$=5.6 Hz, 1H each, 6-H, 7-H), 2.49 (dd, $J$=17.9, 1.9 Hz, 1H, 4-H), 1.96 (dd, $J$=17.9, 1.9 Hz, 1H, 4-H), 1.66, 1.47 (2s, 3H each, 1-$CH_3$, 5-$CH_3$); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$/ppm: 140.7 (d, C-2), 139.8, 131.6 (2d, C-6, C-7), 131.5, 128.2, 128.1 (3d, Ph), 123.2, 118.6 (2s, Ph, C-3), 89.3, 87.8 (2s, C≡C), 83.1, 82.3 (2s, C-1, C-5), 37.1 (t, C-4), 24.4, 21.4 (2q, 1-$CH_3$, 5-$CH_3$); MS (EI, 80 eV) $m/z$ (%) 236 ($M^+$, 7), 221 ($M^+-CH_3$, 8), 193 ($M^+-CH_3CO$, 96), 189 (14), 178 (90), 165 (26), 152 (18), 115 (100), 109 (16), 91 (31), 77 (12), 65 (10), 43 ($CH_3CO^+$, 64); HRMS calcd for $C_{17}H_{16}O$: 236.12077, found: 236.12012.

**4.2.7. 4-Methoxy-1,5-dimethyl-3-(phenylethynyl)-8-oxabicyclo[3.2.1]octa-2,6-diene (19).** According to the general procedure, nonaflate **18** (200 mg, 0.431 mmol) was dissolved in DMF (2 mL) and *i*-$Pr_2NH$ (1 mL). Phenyl acetylene (53 mg, 0.517 mmol), $PPh_3$ (23 mg, 0.086 mmol), CuI (8 mg, 0.043 mmol), and $Pd(OAc)_2$ (5 mg, 0.023 mmol) were added and the mixture was stirred for 30 min. Purification of the product (Hex/EtOAc 95:5) afforded **19** (107 mg, 93%) as a yellow oil. IR (film): 3080–3060 (=C–H), 2980–2930, 2870–2830 (C–H), 2200 (C≡C), 1730, 1680 (C=C), 1620, 1490, 1440 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 7.42–7.39, 7.31–7.27 (2m, 3H, 2H, Ph), 6.53 (d, $J$=1.2 Hz, 1H, 2-H), 6.38, 5.83 (2d, $J$=5.7 Hz, 1H each, 6-H, 7-H), 3.73 (d, $J$=1.2 Hz, 1H, 4-H), 3.70 (s, 3H, $OCH_3$), 1.60, 1.40 (2s, 3H each, 1-$CH_3$, 5-$CH_3$); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$/ppm: 143.5 (d, C-2), 142.5, 132.7 (2d, C-6, C-7), 131.4, 128.3, 128.1 (3d, Ph), 123.2, 121.3 (2s, Ph, C-3), 89.2, 87.9 (2s, C≡C), 86.5, 83.1 (2s, C-1, C-5), 80.3 (d, C-4), 61.3 (q, $OCH_3$), 22.5, 21.2 (2q, 1-$CH_3$, 5-$CH_3$); MS (EI, 80 eV) $m/z$ (%) 266 ($M^+$, 6), 265 ($M^+-H$, 10), 251 ($M^+-CH_3$, 36), 234 (10), 223 (16), 208 (17), 192 (23), 186 (20), 165 (15), 115 (23), 109 (22), 96 (24), 91 (14), 77 ($Ph^+$, 11), 69 (11), 60 (12), 57 (20), 55 (17), 43 ($CH_3CO^+$, 100); HRMS calcd for $C_{18}H_{18}O_2$ [$M^+-CH_3$]: 251.10655, found: 251.10721.

**4.2.8. 4-Benzyloxy-1,5-dimethyl-3-(phenylethynyl)-8-oxabicyclo[3.2.1]octa-2,6-diene (21).** According to the general procedure, nonaflate **20** (200 mg, 0.370 mmol) was dissolved in DMF (2 mL) and *i*-$Pr_2NH$ (1 mL). Phenyl acetylene (45 mg, 0.444 mmol), $PPh_3$ (19 mg, 0.074 mmol), CuI (7 mg, 0.037 mmol), and $Pd(OAc)_2$ (4 mg, 0.02 mmol) were added and the mixture was stirred for 30 min. Purification of the product (Hex/EtOAc 95:5) afforded **21** (107 mg, 84%) as a yellow oil. IR (film): 3060–3020 (=C–H), 2970–2870 (C–H), 2200 (C≡C), 1720–1700, 1600–1590, 1490, 1440 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 7.34–7.29, 7.26–7.20 (2m, 3H, 7H, Ph), 6.57 (d, $J$=1.1 Hz, 1H, 2-H), 6.38, 5.85 (2d, $J$=5.8 Hz, 1H each, 6-H, 7-H), 5.07, 4.76 (2d, $J$=11.1 Hz, 1H each, $OCH_2$), 4.02 (d, $J$=1.1 Hz, 1H, 4-H), 1.49, 1.40 (2s, 3H each, 1-$CH_3$, 5-$CH_3$); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$/ppm: 143.8 (d, C-2), 138.1 (s, Bn), 142.4, 132.9 (2d, C-6, C-7), 131.4, 128.3, 128.2*, 127.8 (4d, Ar), 123.2, 121.4 (2s, Ph, C-3), 89.5, 88.2 (2s, C≡C), 86.6, 83.2 (2s, C-1, C-5), 78.1 (d, C-4), 75.1 (t, $OCH_2$), 22.5, 21.3 (2q, 1-$CH_3$, 5-$CH_3$), * signal shows threefold intensity; MS (EI, 80 eV) $m/z$ (%) 342 ($M^+$, 1), 299, ($M^+-CH_3CO$, 3), 251 ($M^+-Bn$, 40), 209 (23), 109 (18), 105 (71), 91 ($Bn^+$, 100), 79 (13), 77 ($Ph^+$, 33), 51 (12), 43 ($CH_3CO^+$, 91); HRMS calcd for $C_{24}H_{22}O_2$: 342.16199, found: 342.16211.

**4.2.9. [(4-Methoxy-1,5-dimethyl-8-oxabicyclo[3.2.1]octa-2,6-dien-3-yl)ethynyl](trimethyl)silane (22).** According to

the general procedure, nonaflate **18** (400 mg, 0.862 mmol) was dissolved in DMF (2 mL) and *i*-$Pr_2NH$ (1 mL). Trimethylsilyl acetylene (102 mg, 1.03 mmol), $PPh_3$ (45 mg, 0.172 mmol), CuI (16 mg, 0.086 mmol), and $Pd(OAc)_2$ (10 mg, 0.043 mmol) were added and the mixture was stirred for 30 min. Purification of the product (Hex/EtOAc 98:2) afforded **22** (192 mg, 85%) as a colorless solid. Mp: 46–48 °C; IR (KBr): 3040 (=C–H), 2980–2820 (C–H), 2140 (C≡C), 1600 (C=C), 1450 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 6.47 (d, $J$=1.2 Hz, 1H, 2-H), 6.33, 5.78 (2d, $J$=5.6 Hz, 1H each, 6-H, 7-H), 3.63 (d, $J$=1.2 Hz, 1H, 4-H), 3.62 (s, 3H, $OCH_3$), 1.55, 1.35 (2s, 3H each, 1-$CH_3$, 5-$CH_3$), 0.16 [s, 9H, $Si(CH_3)_3$]; $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$/ppm: 144.3 (d, C-2) 142.3, 132.8 (2d, C-6, C-7), 121.3 (s, C-3), 103.7 (s, Si–C), 94.5 (s, C≡C), 86.5, 83.0 (2s, C-1, C-5), 80.2 (d, C-4), 61.3 (q, $OCH_3$), 22.4, 21.2 (2q, 1-$CH_3$, 5-$CH_3$), −0.22 [q, $Si(CH_3)_3$]; Anal. Calcd for $C_{15}H_{22}O_2Si$ (262.4): C, 68.65; H, 8.45. Found: C, 68.68; H, 8.47%.

**4.2.10. 3-(4-Methoxy-1,5-dimethyl-8-oxabicyclo[3.2.1]-octa-2,6-dien-3-yl)prop-2-yn-1-ol (23).** According to the general procedure, nonaflate **18** (440 mg, 0.948 mmol) was dissolved in DMF (2 mL) and *i*-$Pr_2NH$ (1 mL). Propargyl alcohol (64 mg, 1.14 mmol), $PPh_3$ (50 mg, 0.190 mmol), CuI (18 mg, 0.095 mmol), and $Pd(OAc)_2$ (11 mg, 0.047 mmol) were added and the mixture was stirred for 30 min. Purification of the product (Hex/EtOAc 80:20 then 70:30) afforded **23** (163 mg, 78%) as a yellow oil. IR (film): 3440 (OH), 3080–3030 (=C–H), 2980–2830 (C–H), 2220, 2180 (C≡C), 1640 (C=C), 1450 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 6.46 (s, 1H, 2-H), 6.36, 5.80 (2d, $J$=5.7 Hz, 1H each, 6-H, 7-H), 4.36 (s, 2H, $OCH_2$), 3.65 (d, $J$=1.1 Hz, 1H, 4-H), 3.62 (s, 3H, $OCH_3$), 2.18 (br s, 1H, OH), 1.58, 1.37 (2s, 3H each, 1-$CH_3$, 5-$CH_3$); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$/ppm: 144.1 (d, C-2), 142.4, 132.5 (2d, C-6, C-7), 120.6 (s, C-3), 87.5, 84.0 (2s, C≡C), 86.6, 83.1 (2s, C-1, C-5), 80.1 (d, C-4), 61.3 (q, $OCH_3$), 51.3 (t, $OCH_2$), 22.4, 21.1 (2q, 1-$CH_3$, 5-$CH_3$); MS (EI, 80 eV) $m/z$ (%) 220 ($M^+$, 3), 205 ($M^+-CH_3$, 14), 189 ($M^+-CH_3O$, 15), 177 ($M^+-CH_3CO$, 18), 160 (22), 159 (35), 145 (61), 131 (58), 129 (24), 117 (59), 115 (46), 109 (47), 15 (21), 91 (59), 77 (35), 65 (21), 63 (11), 55 (28), 53 (27), 51 (16), 45 (11), 43 ($CH_3CO^+$, 100), 41 (31), 39 (32), 29 (21); HRMS calcd for $C_{13}H_{16}O_3$: 220.10994, found: 220.10955.

**4.2.11. 3-(8-Oxabicyclo[3.2.1]oct-2-en-3-yl)prop-2-yn-1-ol (25).** According to the general procedure, nonaflate **24** (150 mg, 0.37 mmol) was dissolved in DMF (2 mL) and *i*-$Pr_2NH$ (1 mL). Propargyl alcohol (25 mg, 0.44 mmol), $PPh_3$ (19 mg, 0.07 mmol), CuI (7 mg, 0.04 mmol), and $Pd(OAc)_2$ (4 mg, 0.02 mmol) were added and the mixture was stirred for 30 min. Purification of the product (Hex/EtOAc 70:30) afforded **25** (50 mg, 83%) as a yellow oil. IR (film): 3400 (OH), 3040 (=C–H), 2970–2830 (C–H), 2220 (C≡C), 1620 (C=C), 1430 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 6.26 (dt, $J$=4.7, 1.9 Hz, 1H, 2-H), 4.56–4.50 (m, 1H, 5-H), 4.49 ($m_c$, 1H, 1-H), 4.36 (s, 2H, $CH_2O$), 2.76 (dd, $J$=17.1, 4.4 Hz, 1H, 4-H), 2.17–2.09, 2.04–1.90 (2m, 2H, 2H, 6-H, 7-H, OH), 1.82 (d, $J$=17.1 Hz, 1H, 4-H), 1.76–1.68 (m, 1H, 6/7-H); $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$/ppm: 138.2 (d, C-2), 116.3 (s, C-3), 86.7, 85.2 (2s, C≡C), 72.9, 72.5 (2d, C-1, C-5), 51.4 (t, $CH_2O$), 38.1 (t, C-4), 34.9, 29.5 (2t, C-6, C-7); MS (EI, 80 eV) $m/z$ (%) 164 ($M^+$, 8), 135 (13), 121 ($M^+-CH_3CO$, 8), 117 (51), 116 (23), 107 (49), 105 (26), 103 (22), 93 (12), 92 (16), 91 (88), 79 (100), 77 (81), 67 (19), 66 (15), 65 (41), 63 (19), 55 (38), 53 (46), 51 (38), 43 ($CH_3CO^+$, 24), 39 (69), 29 (53); HRMS calcd for $C_{10}H_{12}O_2$: 164.08372, found: 164.08422.

**4.2.12. Bis[(2,2,5,7-tetramethyl-4,5,8,8a-tetrahydro-3a*H*-4,8-epoxycyclohepta[*d*][1,3]dioxol)-3-yl]ethyne (26).** Nonaflate **12** (600 mg, 1.18 mmol), $PdCl_2(PPh_3)_2$ (50 mg, 0.07 mmol), and CuI (22 mg, 0.12 mmol) were dissolved in dry benzene (5 mL) in a heat-gun dried and argon flushed round-bottomed flask. Then DBU (1.08 g, 7.08 mmol), trimethylsilyl acetylene (58 mg, 0.59 mmol), and finally water (9 µl, 0.47 mmol) were added. The flask was covered with aluminum foil and the mixture was stirred for 18 h. The reaction mixture was taken up with $Et_2O$, washed with water, HCl (10%), and brine, and the organic layer was separated and dried ($MgSO_4$). The solvent was removed in vacuo and the crude product was purified by column chromatography on silica gel (Hex/EtOAc 95:5 then 90:10) to afford **26** (93 mg, 36%) as a pale yellow solid. Mp: 177–179 °C; IR (KBr): 3050 (=C–H), 2970–2870 (C–H), 2180 (C≡C), 1460, 1440 $cm^{-1}$; $^1H$ NMR (500 MHz, $CDCl_3$) $\delta$/ppm: 4.74, 4.72 (2d, $J$=5.8, $J$=5.6 Hz, 1H each, 6/7-H), 4.52, 4.49 (2d, $J$=5.6, $J$=5.8 Hz, 1H each, 6/7-H), 4.26 (s, 2H, 1-H), 4.23 (t, $J$=4.8 Hz, 2H, 5-H), 2.75 ($m_c$, 2H, 4-H), 1.91, 1.87 (2d, $J$=2.3 Hz, 3H each, 2-$CH_3$), 1.49, 1.30 [2s, 6H each, $C(CH_3)_2$], 1.12 (d, $J$=7.6 Hz, 6H, 4-$CH_3$); almost all $^{13}C$ NMR signals appear doubled due to diastereomers. The diastereomers are marked with C–X and C–X′: $^{13}C$ NMR (126 MHz, $CDCl_3$) $\delta$/ppm: 144.58, 144.57 (2s, C-2, C-2′), 139.9 (s, C-3, C-3′), 112.4, 112.3 [2s, $C(CH_3)_2$], 84.3, 84.2 (2d, C-6/7, C-6′/7′), 84.1, 84.0 (2d, C-5, C-5′), 81.24, 81.22 (2d, C-1, C-1′), 80.2, 80.1 (2d, C-6/7, C-6′/7′), 78.7, 78.1 (2s, C≡C), 34.3, 34.0 (2d, C-4, C-4′), 26.18, 26.16, 26.14, 24.9 [4q, $C(CH_3)_2$], 18.52, 18.51, 18.29, 18.27 (4q, 2-$CH_3$, 2′-$CH_3$), 14.0, 13.7 (2q, 4-$CH_3$, 4′-$CH_3$); MS (EI, 80 eV) $m/z$ (%) 442 ($M^+$, 50), 355 (21), 109 (12), 105 (10), 91 (11), 85 (16), 69 (13), 60 (11), 57 (17), 55 (27), 43 ($CH_3CO^+$, 100), 41 (19), 39 (13), 29 (29), 28 (38), 27 (17); Anal. Calcd for $C_{26}H_{34}O_6$ (442.5): C, 70.56; H, 7.74. Found: C, 70.41; H, 7.39%.

## Acknowledgements

Support of this work by the Fonds der Chemischen Industrie and the Schering AG, Berlin, is most gratefully acknowledged. We also thank the Bayer AG, Leverkusen, for continuous support with NfF. We thank Ms. Franziska Gottschalk for experimental assistance and Dr. Reinhold Zimmer for help during preparation of this manuscript.

## References and notes

1. Sonogashira, K.; Tohda, Y.; Hagihara, N. *Tetrahedron Lett.* **1975**, 4467–4470.

2. Selected reviews: Sonogashira, K. *Handbook of Organopalladium Chemistry for Organic Synthesis*; Negishi, E.-I., de Meijere, A., Eds.; Wiley: New York, NY, 2002; pp 493–529; Sonogashira, K. *J. Organomet. Chem.* **2002**, *653*, 46–49; Marsden, J. A.; Haley, M. M. *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds.; Wiley-VCH: Weinheim, 2004; pp 317–394.
3. In preliminary experiments we found that cycloheptenyl nonaflate and phenyl acetylene provide the expected coupling product in moderate yield: Webel, M. Dissertation, Technische Universität Dresden, 2000.
4. (a) Gallagher, W. P.; Maleczka, R. E., Jr. *Synlett* **2003**, 537–541; (b) Gallagher, W. P.; Maleczka, R. E., Jr. *J. Org. Chem.* **2003**, *68*, 6775–6779.
5. Zhu, Z.; Swager, T. M. *Org. Lett.* **2001**, *3*, 3471–3474.
6. (a) Wada, A.; Ieki, Y.; Ito, M. *Synlett* **2002**, 1061–1064; (b) Wada, A.; Ieki, Y.; Nakamura, S.; Ito, M. *Synthesis* **2005**, 1581–1588.
7. Suffert, J.; Eggers, A.; Scheuplein, S. W.; Brückner, R. *Tetrahedron Lett.* **1993**, *34*, 4177–4180.
8. Okauchi, T.; Yano, T.; Fukamachi, T.; Ichikawa, J.; Minami, T. *Tetrahedron Lett.* **1999**, *40*, 5337–5340.
9. Lyapkalo, I. M.; Vogel, M. A. K. *Angew. Chem.* **2006**, *118*, 4124–4127; *Angew. Chem., Int. Ed.* **2006**, *45*, 4019–4023.
10. Hirsch, E.; Hünig, S.; Reissig, H.-U. *Chem. Ber.* **1982**, *115*, 3687–3696.
11. (a) Webel, M.; Reissig, H.-U. *Synlett* **1997**, 1141–1142; (b) Lyapkalo, I. M.; Webel, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2001**, 4189–4194; (c) Lyapkalo, I. M.; Webel, M.; Reissig, H.-U. *Synlett* **2001**, 1293–1295; (d) Lyapkalo, I. M.; Webel, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2002**, 1015–1025; (e) Lyapkalo, I. M.; Webel, M.; Reissig, H.-U. *Eur. J. Org. Chem.* **2002**, 3646–3658.
12. For an excellent review, see: (a) Hoffmann, H. M. R.; Hartung, I. V. *Angew. Chem.* **2004**, *116*, 1968–1984; *Angew. Chem., Int. Ed.* **2004**, *43*, 1934–1949; Further reviews on the synthesis of 8-oxabicyclo[3.2.1]octenones by [4+3] cycloaddition: (b) Lautens, M. *Synlett* **1993**, 177–185; (c) Rigby, J. H.; Pigge, C. F. *Org. React.* **1997**, *51*, 351–478.
13. (a) Högermeier, J.; Reissig, H.-U. *Synlett* **2006**, 2759–2762; (b) Högermeier, J.; Reissig, H.-U. *Chem.—Eur. J.* **2007**, *13*, 2410–2420.
14. Högermeier, J.; Reissig, H.-U.; Brüdgam, I.; Hartl, H. *Adv. Synth. Catal.* **2004**, *346*, 1868–1879.
15. Lyapkalo, I. M.; Högermeier, J.; Reissig, H.-U. *Tetrahedron* **2004**, *60*, 7721–7729.
16. Mio, M. J.; Kopel, L. C.; Braun, J. B.; Gadzikwa, T. L.; Hull, K. L.; Brisbois, R. G.; Markworth, C. J.; Grieco, P. A. *Org. Lett.* **2002**, *4*, 3199–3202.
17. Tietze, L. F.; Brasche, G.; Gericke, K. M. *Domino Reactions in Organic Synthesis*; Wiley-VCH: Weinheim, 2006.