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Radical-Mediated 5-*Exo*-*Trig* Cyclizations of 3-Silylhepta-1,6-dienes

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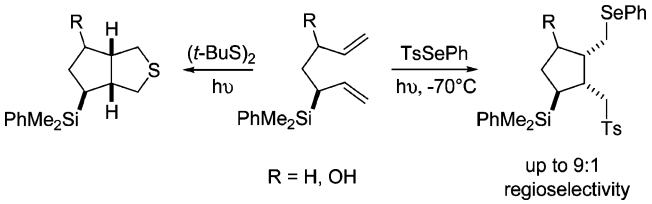
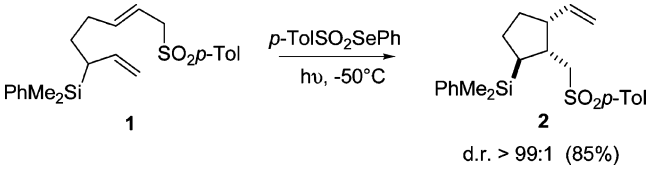


Regioselectivity of the sulfonyl radical mediated 5-*exo*-*trig* cyclization of 3-silylheptadienyl systems **3a**−**d** has been studied. At low temperature, the reaction of the sulfonyl radical occurs regioselectively at the allylsilane terminus, while a reversal of regioselectivity is observed at 80 °C. This general trend has been rationalized on the basis of polar effects and radical stabilization. Thiyl-mediated radical cyclization of dienes **3a**, **3c**−**d**, **7** with subsequent sulfur atom transfer was also studied, providing thiabicyclo[3.3.0] skeleton in one step with excellent stereocontrol.

Radical-mediated 5-*exo*-*trig* cyclizations of dienyl systems have enjoyed much success in the synthesis of five-membered ring carbocycles and heterocycles.[1] Continuing interest in such processes has prompted a number of research groups to study the kinetics and the stereochemistry of these reactions. In this context, we recently initiated a study on the sulfonyl-radical mediated cyclizations of chiral 3-silylhepta-1,6-dienes such as **1** (Scheme 1), with the aim of investigating the effect of an allylic silicon group on the stereoselectivity of this process.[2] We found that cyclization of 3-silylhepta-1,6-diene **1**, led to the expected cyclopentane **2** with high levels of diastereocontrol at low temperature, demonstrating the unique role of the silicon group in this context.[2] Interestingly, changing the silicon substituent with alkyl or alkoxy substituents led to no or a reversal of stereochemistry, respectively. In this study, regioselectivity during attack of the sulfonyl group on the diene system

SCHEME 1. 5-*Exo*-*Trig* Cyclization of 3-Silylhepta-1,6-dienyl Systems



of **1** was not a matter of concern as only the allylsilane terminus could react. We thus envisaged investigating the regiocontrol which could arise from addition of *p*-TolSO$_2$SePh onto dienes **3a**−**d** containing an allylsilane moiety at one end and a monosubstituted olefin or an allylic alcohol moiety at the other terminus. Selenosulfonylation of dienes is indeed an attractive method to construct five-membered ring systems, as a new C−C bond is formed while two functionalities and two new stereogenic centers are introduced in a single step.[3] We report here our investigations on the radical mediated addition/cyclization of sulfur reagents onto dienes of type **3** to give five-membered-ring systems **4** and **5** and provide a tentative rationalization of our results.

Preliminary studies were conducted with the simple model **3a**[4] possessing a single stereogenic center. The results summarized in Table 1 show that under thermal conditions (6 h at 80 °C) a 38/62 mixture of the two regioisomers **4a**−**5a** was obtained in 53% yield (Table 1, entry 1). Interestingly, when the reaction was carried out at −70 °C under photochemical conditions, the ratio was reversed with regioisomer **4a** now largely predominant (entry 3). At room temperature, a nearly equimolar amount of both regioisomers was obtained, pointing out again the temperature dependence of the regioselectivity of this radical process. Compounds **4a** and **5a** were readily separated and their structure unambiguously assigned using extensive NMR studies (1D, 2D, COSY, HSQC, and 2D ^{1}H−^{77}Se correlations). Compounds **4a** and **5a** were found to be diastereomerically pure, possessing the *trans*-*cis* relative configuration, in line with our previous reports.[2] It is important to notice that as yields are moderate, one cannot completely rule out the formation of other stereoisomers of **4a**−**5a** in the reaction mixture, although ^{1}H NMR of the crude reaction mixture indicates that if these are formed they are in trace amount. Better yields and similar regioselectivities were observed with model **3b** (entries 4−7), although the ratio **4b**/**5b** at −70 °C was not as pronounced as with **3a**. The structure and the relative configuration of major **4b** were secured through an X-ray structure determination, supporting the above assignment for **4a**. Changing the solvent from benzene to CH_2Cl_2 (entries 5 and 6) led to a similar ratio indicating that the solvent had little influence on the regiocontrol outcome. High isolated yield during selenosulfonylation of **3b** (entry 7) is of interest as it shows that at low temperature the reaction is both regioselective

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(1) (a) Beckwith, A. L. J. *Tetrahedron* **1981**, *37*, 3073−3100. (b) Majumdar, K. C.; Mukhopadhyay, P. P.; Basu, P. K. *Heterocycles* **2004**, *63*, 1903−1958 and references therein.
(2) (a) James, P.; Landais, Y. *Org. Lett.* **2004**, *6*, 325−328. (b) James, P.; Felpin, F.-X.; Landais, Y.; Schenk, K. *J. Org. Chem.* **2005**, *70*, 7985−7995.
(3) (a) Wang, C.; Russell, G. A. *J. Org. Chem.* **1999**, *64*, 2346−2352. (b) Harvey, I. W.; Philips, E. D.; Whitham, G. H. *Tetrahedron* **1997**, *53*, 6493−6508. (c) De Riggi, I.; Surzur, J.-M.; Bertrand, M.-P.; Archavlis, A.; Faure, R. *Tetrahedron* **1990**, *46*, 5285−5294. (d) Brumwell, J. E.; Simpkins, N. S. *Tetrahedron Lett.* **1993**, *34*, 1219−1222. (e) De Riggi, I.; Gastaldi, S.; Surzur, J.-M.; Bertrand, M.-P.; Virgili, A. *J. Org. Chem.* **1992**, *57*, 6118−6125.
(4) For the synthesis of precursors **3a**−**d**, see the Supporting Information.

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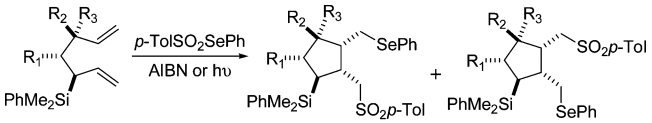
TABLE 1. Regioselectivity of the Selenosulfonylation of Dienes 3a−d

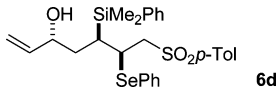


3a, $R_1=R_2=R_3=H$
3b, $R_1=CO_2Me$; $R_2=R_3=H$
3c, $R_1=R_2=H$; $R_3=OH$
3d, $R_1=R_3=H$; $R_2=OH$

entry	diene **3**	solvent	*T* (°C)	**4**/**5**[c]	yield[d] (%)
1	**3a**	C_6H_6	80[a]	38:62	53
2	**3a**	C_6H_6	24[b]	45:55	63
3	**3a**	CH_2Cl_2	−70[b]	90:10	58
4	**3b**	C_6H_6	80[a]	38:62	92
5	**3b**	C_6H_6	24[b]	56:44	86
6	**3b**	CH_2Cl_2	24[b]	53:47	85
7	**3b**	CH_2Cl_2	−70[b]	77:23	80
8	**3c**	C_6H_6	80[a]	25:75	49
9	**3c**	CH_2Cl_2	24[b]	55:45	70
10	**3c**	CH_2Cl_2	−70[b]	85:15	87
11	**3d**	C_6H_6	80[a]	11:89	50
12	**3d**	CH_2Cl_2	−70[b]	90:10	61

[a] AIBN. [b] *hν* (sunlamp). [c] Estimated ratio through ^{1}H NMR of the crude reaction mixture. [d] Isolated yield of both isomers.

SCHEME 2. Selenium Group Transfer during Selenosulfonyation of 3d



6d

and highly stereoselective. The study was then extended to precursors **3c**,**d** possessing an allylic alcohol function (entries 8−12). As before, good regiocontrol and better yields were observed at low temperature, with cyclopentanes **4c**,**d** obtained as major isomers in each case (entries 10 and 12). At 80 °C, a reversal of regiocontrol was again observed with regioisomers **5c**,**d** formed predominantly. Cyclization of **3d** also led at −70 °C to addition product **6d** with the stereochemistry as shown (Scheme 2).[5] Although the formation of **6d** was poorly reproducible, this indicates that at low temperature the cyclization is slow, with the selenium group transfer becoming a competitive process.

A general trend thus emerges from these results. At low temperature, the sulfonyl radical species prefers to react at the allylsilane terminus while at higher temperature the reaction occurs on the less sterically demanding olefin. Two different pathways may thus be drawn, as summarized in Figure 1. At low temperature, the addition of the electrophilic sulfonyl radical would occur preferentially on the more electron-rich allylsilane olefin ($k_1 > k'_1$, polar effect),[6,7] leading to a radical β to silicon (i.e., **A**). Such a polar effect has been well studied by Gozdz and Maslak,[6c] who established that a methylsulfonyl radical reacts with allyltrimethylsilane 2.5 times faster than with hex-1-ene at 0 °C. Although this polar effect may reflect in part the regioisomer ratio, other factors may be operative. Attack of a sulfonyl radical on the allylsilane moiety generates a radical β to silicon (C2) which is known to be stabilized by 2−3 kcal/mol.[8] Such a weak stabilization may, however, be sufficient to slow the β-fragmentation process, so that concentration of intermediate **A** is more important than that of **A′**. Rate constants for β-fragmentation of *p*-tosyl radical have been estimated in the range 10^3-10^6 s^{-1},[7a] the lower rate being observed with compounds possessing a substituent able to stabilize the radical intermediate. Although a β-silyl group does not exert such a strong β-stabilization, this and the polar effect discussed above may be sufficient to control the regioselectivity. Then, assuming than **A** and **A′** cyclize at a similar rate ($k_c \approx k'_c$), accumulation of the former would ensure the formation of larger amount of **4a−d** in the mixture of products. The possibility that **B** and **B′** might interconvert through an intramolecular tosyl group transfer has also been ruled out based on the results of kinetic studies on related processes.[3a] Chairlike conformations such as **A** and **A′** having the bulky silicon group in pseudoequatorial position explain the high level of stereocontrol observed and the relative configuration observed for regioisomers **4a−d** and **5a−d**.[2] In contrast, the nature of the effects controlling the regioselectivity of the process at higher temperature (between rt and 80 °C) appears more difficult to rationalize. Although the allylsilane olefin is sterically more demanding, this factor is probably not predominant as the reaction occurs on a site (C1) remote from the bulky silicon group. An alternative explanation may be provided, based on a kinetic versus thermodynamic control. At higher temperature, fragmentation would be faster[9] and **A** and **A′** would thus reach the equilibrium. The regioisomer ratio would then only rely on the relative energies of cyclization transition states (Curtin−Hammett regime). When **A** and **A′** are structurally similar (as is the case with **3a**,**b** having no substituent at C5), such transition-state energies should be very close,[10] leading to low regiocontrol as is observed experimentally (Entries 1, 2, and 4−6). Finally, under such conditions a better regiocontrol in the favor of cyclopentanes **5** (entries 8 and 11) is only observed when an OH group is present at C5. The exact nature of the effect of this OH group remains speculative at this stage, but its presence modifies the reactivity of the β-radical center, leading to a stabilization of the transition state of cyclization **A′** → **B′**.[2b,8e]

This work thus demonstrates that sulfonyl radical addition to 1,6-dienes possessing olefins of similar reactivities proceeds yet regioselectively in the first step and is followed by a stereocontrolled cyclization in the second step to provide useful polysubstituted cyclopentanes.

The selenosulfonylation was then extended to diene **7** having two differently substituted olefins.[11] Surprisingly, when submit-

(5) The *syn* relative configuration between $SiMe_2Ph$ and SePh was assigned on the basis of related studies; see: (a) Chabaud, L.; Landais, Y. *Tetrahedron Lett.* **2003**, *44*, 6995−6998. (b) Masterson, D. S.; Porter, N. D. *Org. Lett.* **2002**, *4*, 4253−4256. (c) Chabaud, L.; Landais, Y.; Renaud, P. *Org. Lett.* **2002**, *4*, 4257−4260.

(6) (a) Sakurai, H.; Hosomi, A.; Kumada, M. *J. Org. Chem.* **1969**, *34*, 1764−1768. (b) Jarvie, A. W. P.; Rowley, R. J. *J. Chem. Soc. B* **1971**, 2439−2442. (c) Gozdz, A. S.; Maslak, P. *J. Org. Chem.* **1991**, *56*, 2179−2189.

(7) (a) Timokhin, V. I.; Gastaldi, S.; Bertrand, M.-P.; Chatgilialoglu, C. *J. Org. Chem.* **2003**, *68*, 3532−3537. (b) Wagner, P. J.; Sedon, J. H.; Lindstrom, M. J. *J. Am. Chem. Soc.* **1978**, *100*, 2579−2580.

(8) (a) Kawamura, T.; Kochi, J. K. *J. Am. Chem. Soc.* **1972**, *94*, 648−650. (b) Griller, D.; Ingold, K. U. *J. Am. Chem. Soc.* **1974**, *96*, 6715−6720. (c) Jackson, R. A.; Ingold, K. U.; Griller, D.; Nazran, A. S. *J. Am. Chem. Soc.* **1985**, *107*, 208−211. (d) Auner, N.; Walsh, R.; Westrup, J. *J. Chem. Soc., Chem. Commun.* **1986**, 207−207. (e) d'Antuono, P.; Fritsch, A.; Ducasse, L.; Castet, F.; James, P.; Landais, Y. *J. Phys. Chem. A* **2006**, *110*, 3714−3722.

(9) As mentioned by one referee, fragmentation of the tosyl group is probably more affected than the 5-*exo*-*trig* cyclization by lowering the temperature due to entropy effects.

(10) Lusztyk, J.; Maillard, B.; Deycard, S.; Lindsay, D. A.; Ingold, K. U. *J. Org. Chem.* **1987**, *52*, 3509−3514.

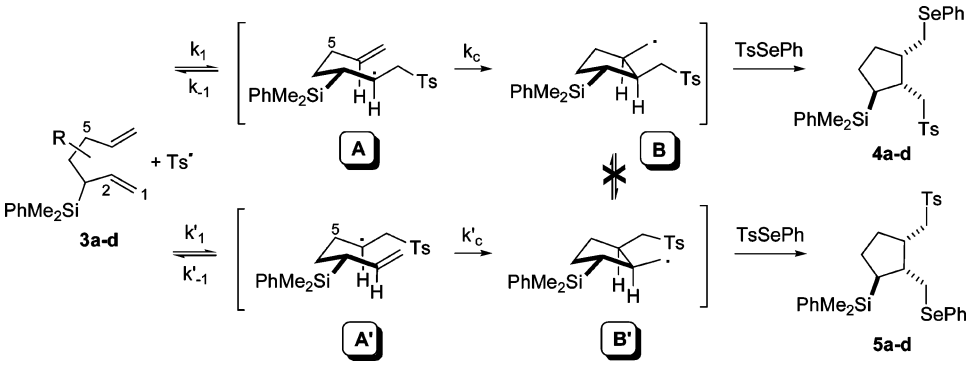
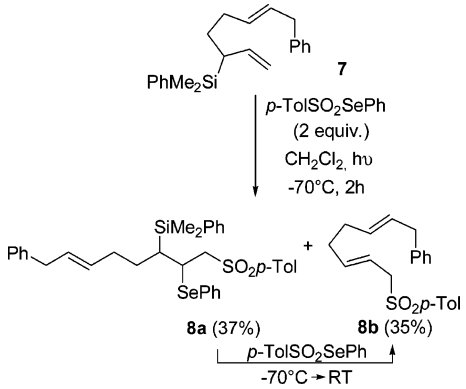


FIGURE 1. Regioselectivity of the selenosulfonylation of dienes **3a**−**d**.

SCHEME 3. Attempt of Cyclization of Diene 7



ted to the above conditions at −70 °C, **7** led to a mixture of inseparable products in which the desired cyclopentane was present in low amount (<30%) (removal of the PhSe group using Bu_3SnH or H_2O_2 led to the desired cyclopentanes confirming the structure of the cyclized product) (Scheme 3) (Supporting Information). Interestingly, when the reaction was carried out in a more concentrated medium, using 2 equiv of *p*-$TolSO_2SePh$, the addition product **8a** (as a 9:1 mixture of *syn*/*anti* stereoisomers) and the desilylated diene **8b** were isolated. This and the formation of addition product **6d** (Scheme 2) further indicate that the 5-*exo-trig* cyclization is rather slow at −70 °C. After purification, **8a** was treated with 1 equiv of *p*-$TolSO_2SePh$ at −70 °C. While no reaction occurred at this temperature, **8a** was converted into **8b** upon warming to room temperature,[12] indicating that **8b** is probably formed through β-elimination[5,13] of the β-selenosilane moiety under the reaction conditions.[14,15]

Finally, we studied the thiyl-mediated radical cyclization of our diene with sulfur atom transfer.[16] This cascade process is particularly useful to functionalize dienyl systems with the formation of thiabicyclo[3.3.0] skeleton in one step in moderate to good yields but with generally low stereocontrol.[16b−e] Having demonstrated that high level of 1,2- and 1,5-stereocontrol could be reached during 5-*exo-trig* cyclization of our systems,[2] we investigated the thiyl-mediated cascade with the 3-silahepta-1,6-dienes **3a**,**c**,**d** and **7**. This would generate the required cyclopentane skeleton without the regiochemical issue described above. Precursors **3a**,**c**,**d** were thus treated with (*t*-BuS)$_2$ under irradiation and led to the expected bicyclic systems **10a**−**c** in reasonable yields and interestingly as single isomers having the *trans-cis* relative configuration (Table 2, entries 1−3). Compound **7** led to **10d** as a mixture of two stereoisomers in a 2:1 ratio (entry 4). It is noteworthy that **10d** is prepared in 41% overall yield starting form butadiene and $PhMe_2SiCl$.[11] Attempted 6-*exo-trig* cyclization using precursor **11**[11] led to a complex mixture of products (entry 5). Reactions were usually complete in less than 3 h and thus appear to be much faster and stereoselective than those described in the literature on related systems lacking the allylic silicon group.[16b−d] This may reflect again the matched polarity between the electrophilic thiyl radical and the allylsilane olefin. The reaction is thought to proceed though the addition of a thiyl radical to one of the olefin (likely at the allylsilane terminus, vide supra), followed by the cyclization through a chairlike transition state such as **A** or **A′** (Figure 1) and termination by homolytic substitution at sulfur.[16a] Only the *cis* ring junction is obtained as the *trans* isomer (probably formed in very low amount) and cannot react with the sulfur center in the termination step to form the heterocycle.

In summary, we have reported above a rapid method to access 3-thiabicyclo[3.3.0]octane systems in a regio- and stereoselective manner. Our studies also shed light on the regiocontrol arising

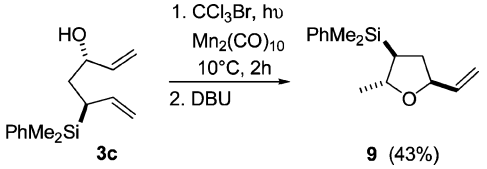
(11) Terao, J.; Oda, A.; Ikumi, A.; Nakamura, A.; Kuniyasu, H.; Kambe, N. *Angew. Chem., Int. Ed.* **2003**, *42*, 3412−3414.

(12) Treatment of **8a** under irradiation (sunlamp) without *p*-$TolSO_2SePh$, at temperatures ranging from −70 °C to rt, led to no reaction.

(13) Guindon, Y.; Guérin, B.; Chabot, C. C.; Ogilvie, W. W. *J. Am. Chem. Soc.* **1996**, *118*, 12528−12535.

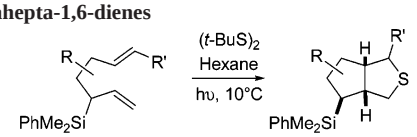
(14) The exact mechanism of the elimination process **8a** → **8b**, under such conditions, is unknown, and one cannot exclude the β-elimination of the silicon group through an ionic pathway.

(15) An ionic process and the formation of a β-silyl carbocation intermediate may be invoked for the $Mn_2(CO)_{10}$-mediated radical functionalization of diene **3c**, which unexpectedly provided tetrahydrofuran **9** as a unique diastereomer, without a trace of the product resulting from addition of the CCl_3 group. This probably results from a protonation of the allylsilane moiety under the reaction conditions, followed by a rapid electrophilic 5-*exo* cycloetherification. For a similar process, see: Akiyama, T.; Ishida, Y. *Synlett* **1998**, 1150−1152.

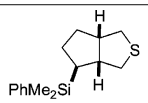
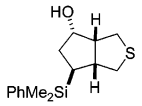
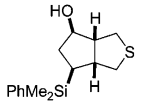
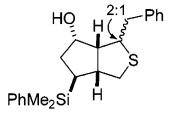
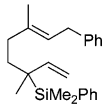


(16) (a) Schiesser, C. H.; Wild, L. M. *Tetrahedron* **1996**, *52*, 13265−13314. (b) Harrowven, D. C.; Hannam, J. C.; Lucas, M. C.; Newman, N. A.; Howes, P. D. *Tetrahedron Lett.* **2000**, *41*, 9345−9349. (c) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron Lett.* **1999**, *40*, 4443−4444. (d) Harrowven, D. C.; Hannam, J. C. *Tetrahedron* **1999**, *55*, 9341−9346. (e) Harrowven, D. C.; Lucas, M. C.; Howes, P. D. *Tetrahedron* **2001**, *57*, 791−804.

TABLE 2. Thiyl Radical Mediated Cyclization of 3-Silahepta-1,6-dienes



3a, c-d, 7 → 10a-d

Entry	Diene	Time (h)	Product	Yield (%)[a]
1	**3a**	3	 **10a**	54
2	**3c**	3	 **10b**	67
3	**3d**	3	 **10c**	57
4	**7**	8	 **10d**	58
5	 **11**	5	-	-

[a] Isolated yield.

from radical addition of sulfonyl radicals onto dienes possessing an allylsilane moiety. At low temperature, excellent regiocontrol in the favor of the attack at the allylsilane moiety is observed. Polar effects and stabilization of the β-silyl radical may be at the origin of the control of the regioselectivity. Such cyclopentanes bearing several stereochemically defined contiguous stereogenic centers should be valuable intermediates in the synthesis of recently discovered isoprostanoids[17] and more generally of ubiquitous cyclopentane-containing natural products.[2b,18]

Experimental Section

Typical Experimental Procedure for the Selenosulfonylation of 3-Silylhepta-1,6-dienes 3a−d under Irradiation. A mixture containing diene **3a−d** (1 equiv) and *p*-TolSO_2SePh (1 equiv) in degassed CH_2Cl_2 (0.013 M) under a nitrogen atmosphere was irradiated at − 70 °C with a sunlamp (placed at 10−15 cm of the flask) until complete consumption of starting material as shown by TLC. The solvent was then evaporated and the residue purified by chromatography (petroleum ether or petroleum ether/ethyl acetate) to afford **4a−d/5a−d**.

Typical Experimental Procedure for the Selenosulfonylation of 3-Silylhepta-1,6-dienes 3a−d under Thermal Conditions. In a flask equipped with a condenser were dissolved diene **3a−d** (1 equiv) and *p*-TolSO_2SePh (1 equiv) in degassed benzene (0.013 M) under a nitrogen atmosphere. AIBN was added (0.1 equiv by portions every 1−1.5 h), and the mixture was heated under reflux until complete consumption of starting material as shown by TLC. The solvent was then evaporated and the residue purified by chromatography (petroleum ether or petroleum ether/ethyl acetate) to afford **4a−d/5a−d**.

Typical Experimental Procedure for the Preparation of Fused Thiabicyclo[3.3.0]octanes 10a−d. A degassed solution of diene **3a**,**c**,**d** or **7** (1 equiv) and di-*tert*-butyl disulfide (5 equiv) in hexane (0.05 M) under a nitrogen atmosphere was irradiated using a high-pressure mercury lamp in a quartz cell at +10 °C until complete consumption of starting material as shown by TLC. The brown solution was then concentrated under vacuum and the product purified by chromatography (petroleum ether or petroleum ether/ethyl acetate) to give **10a−d**.

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Supporting Information Available: Experimental procedures and copies of ^{1}H and ^{13}C NMR spectra for all products **3−10**. X-ray crystallographic data for compound **4b** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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