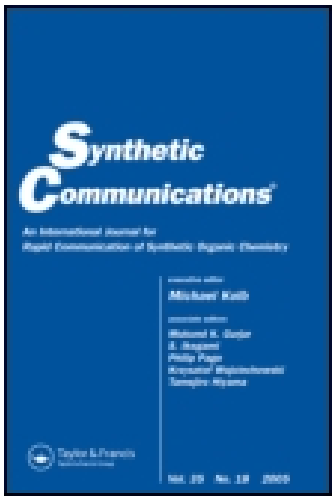

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A New Entry to Alkylidenecyclopropanes Through a Ramberg-Backlund Rearrangement of Cyclopropylsulfones

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A New Entry to Alkylidenecyclopropanes Through a Ramberg-Backlund Rearrangement of Cyclopropylsulfones

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ABSTRACT

The first use of the Ramberg-Backlund rearrangement of cyclopropylsulfones in the synthesis of alkylidenecyclopropanes is reported.

Key Words: Cyclopropanes; Alkylidenecyclopropanes; Ramberg-Backlund; Cyclopropylsulfones.

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INTRODUCTION

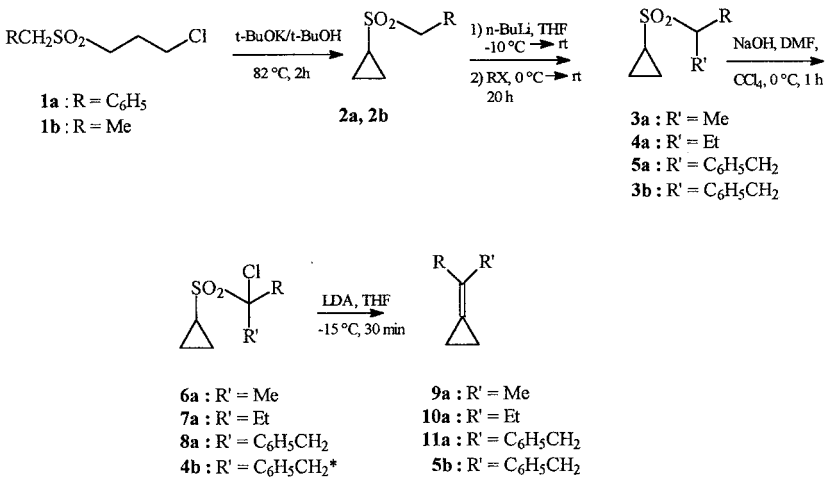
Highly strained molecules are generally not very stable and this fact limits their use in organic synthesis. Methylene and alkylidenecyclopropanes are particularly interesting molecules because, despite the high level of strain, they are very often stable and exhibit an otherwise unattainable chemical reactivity.[1] As a matter of fact their Ni(0)- or Pd(0)-catalyzed reaction with alkenes and alkynes constitutes an important route for the synthesis of five membered rings[1a,2–6]; they undergo ring opening with palladium chloride to give π-allyl palladium complexes,[7] 1,3-dipolar cycloaddition with nitrones[8] and are suitable precursors of cyclobutanones[9–12] and cyclobutanols.[13] On the other hand, an indication of their stability is given by the aminoacids hypoglycine[14,15] and methylenecyclopropyl glycine,[16] two natural products exhibiting relevant biological activity, one isolated from the unripe fruits of the ackee tree (*Blighia sapida*) and the other from the kernels of the litchi fruits.

The increasing interest in these molecules has stimulated a number of synthetic strategies that have been recently reviewed.[17] In spite of the several methods used for their synthesis,[18–34] only one unsuccessful attempt[35] has been published using the well known Ramberg-Backlund reaction for the synthesis of the bicyclopropylidene. The failure of this attempt was attributed by the authors to the established unreactivity of cyclopropyl halides and sulfonate esters toward displacement reactions due to the adverse hybridization characteristic of external bonds attached to three-membered rings (I strain). They pointed out that α-haloalkyl cyclopropylsulfones might be expected to afford the corresponding methylenecyclopropanes when treated with base since the I strain factor is not present in these cases.

RESULTS AND DISCUSSION

As a part of our continuing interest in alkylidenecyclopropanes chemistry,[13] we herein report our successful use of the Ramberg-Backlund reaction for their synthesis. Derivatives **6a–8a**, and **4b** prepared, as shown in Sch. 1, in 60–69% and 30% yield, were submitted to basic treatment to give the corresponding alkylidenecyclopropanes **9a–11a**, **5b** in yields ranging from 35% to 90%.

A preliminary study was carried out using derivative **6a**, to find the best base to be used (Table 1). The use of MeLi or *n*-BuLi gave the expected alkylidenecyclopropane **9a** accompanied by **3a** (70:30), probably coming from a lithium–halogen exchange.



1a : R = C_6H_5
1b : R = Me

2a, 2b

3a : R' = Me
4a : R' = Et
5a : R' = $C_6H_5CH_2$
3b : R' = $C_6H_5CH_2$

6a : R' = Me
7a : R' = Et
8a : R' = $C_6H_5CH_2$
4b : R' = $C_6H_5CH_2$*

9a : R' = Me
10a : R' = Et
11a : R' = $C_6H_5CH_2$
5b : R' = $C_6H_5CH_2$

*The chlorination was carried out by treating **3b** with *n*-BuLi and NCS. See experimental part.

Scheme 1.

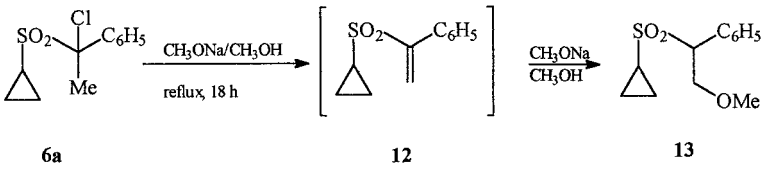
Table 1. Reaction of derivative **6a** with different bases.

Entry	Substrate	Base	React. cond.	Time	Products[a]	Yields[b] (%)
1	**6a**	*n*-BuLi	THF, −25°C → r.t.	10 h	**9a**, **3a** (70:30)	70
2	**6a**	MeLi	THF, −80°C → r.t.	10 h	**9a**, **3a** (68:32)	72
3	**6a**	MeONa	MeOH, 65°C	18 h	**13**[c]	73
4	**6a**	LDA	THF, −15°C	30 min	**9a**	90

[a]In parentheses the ratios evaluated by ^{1}H NMR (Entries 1, 2).
[b]Isolated products.
[c][1-(Cyclopropylsulfonyl)-2-methoxyethyl]benzene was the only isolated product.

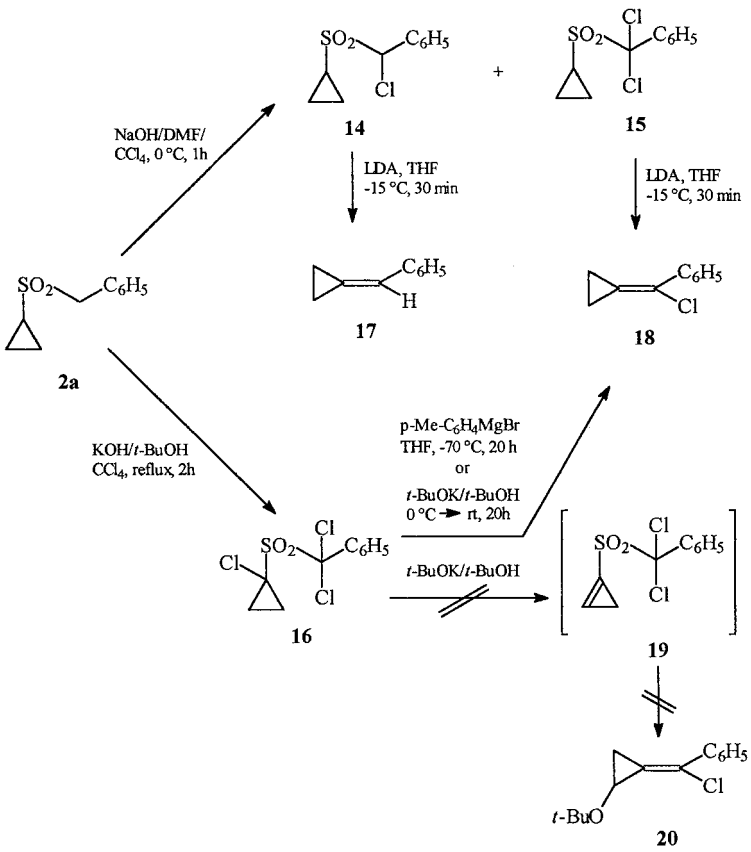
On the other hand, despite the reported[35] deprotonation of a cyclopropyl proton adjacent to a phenylsulfone group in a cyclopropylsulfone by MeONa, the use of this base led to the formation of the [1-(cyclopropylsulfonyl)-2-methoxyethyl]benzene **13** in 73% yield, probably through an elimination–addition reaction involving the vinyl sulfone **12** as an intermediate (Sch. 2). The best results were obtained using LDA at −15°C as reported in the Table 1.

Direct chlorination of **2a** using CCl_4/NaOH in DMF,[36] led to a mixture of mono- and dichloro derivatives **14** and **15** easily separated by column chromatography. When we forced the conditions during the



6a **12** **13**

Scheme 2.



Scheme 3.

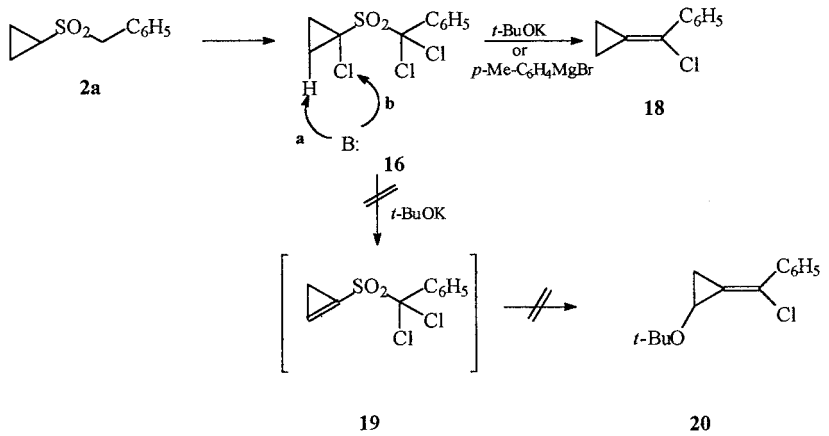
chlorination of **2a** the trichloro sulphone **16** was obtained in 65% yield (Sch. 3). Reaction of **14** and **15** with LDA gave the alkylidenecyclopropane **17** and **18** in low yield (25% and 32%), probably as a consequence of a very acidic proton in **14** that competes with the cyclopropylic proton

triggering other reaction paths. In the case of **15**, the low yields of **18** are, probably due to different reaction paths on which, at the moment, we cannot make any hypothesis.

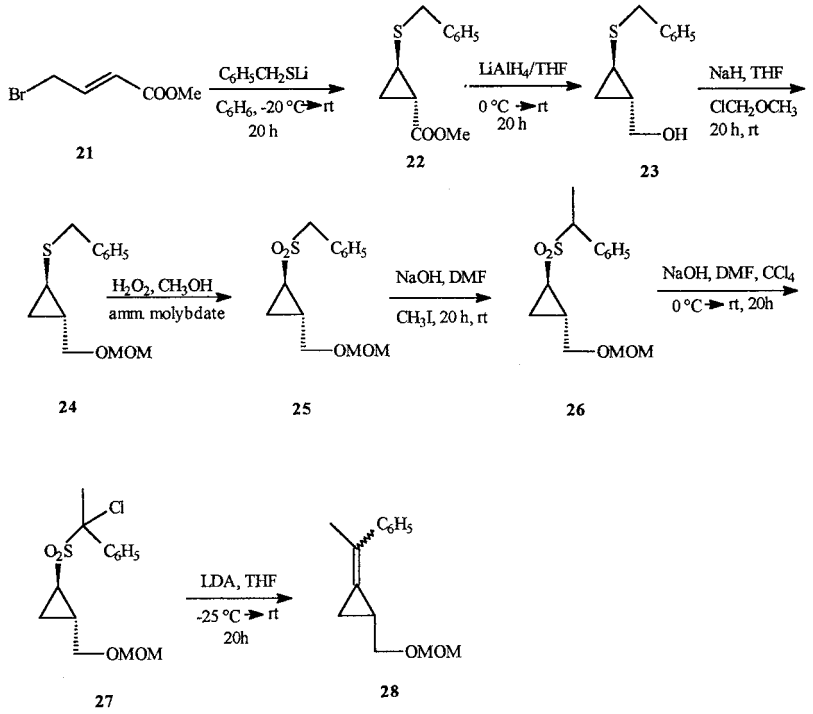
The trichloro derivative **16** seemed to be the ideal candidate to carry out the transformation into the alkylidenecyclopropane **20** through an elimination addition sequence implying the intermediacy of the cyclopropenylsulfone **19**. As a matter of fact a similar elimination–addition sequence has previously been reported by Paquette.[35] Reaction of **16** either with *t*-BuOK or *p*-Me–C_6H_4MgBr always led to the alkylidenecyclopropane **18** in 27% and 50% yields allowing, in this way, to overcome the difficulties previously found by starting from the dichlorosulphone **15**.

This reaction path can be justified on the basis of the high positive character of an halogen atom in α- position to a sulphone group. In fact (Sch. 4) the base could attack the chlorine (path b) causing the formation of a carbanion that could trigger the Ramberg-Backlund process, instead of attacking the cyclopropyl proton (path a) to give the intermediate cyclopropene **19**.

Our method for the synthesis of alkylidenecyclopropanes is complementary to the already published ones and can exploit the great facility of preparing cyclopropanes carrying sulfide, sulfoxide, or a sulfone group for example through a Michael addition to a suitably substituted alkene. As an example we have prepared the MOM protected alkylidenecyclopropanemethanol **28**, that is to be considered a key intermediate for the synthesis of a hypoglycine[14,15] carrying substituents on the double bond. The sequence, shown in Sch. 5, involves several steps with yields ranging



Scheme 4.



Scheme 5.

from 70% to 94%, except for the last step that occurs with poor yields (30%).

The synthesis has been achieved through the preliminary synthesis of the *E*-cyclopropyl ester **22** by a Michael addition in benzene of the lithium salt of benzylmercaptane on the commercially available methyl 4-bromo crotonate **21**. The structure of **22** has been unambiguously assigned from NOESY and differential NOE experiments and it is in accordance with analogous products previously reported.[36,37] Reduction with $LiAlH_4$ and protection of the alcohol with chloromethyl methyl ether led to the compound **24** that has been first oxidized to the corresponding sulfone **25** and then alkylated with methyl iodide to give **26**. The chlorination of **26** in the previously reported conditions[38] gave **27** that by treatment with LDA at $-15^{\circ}C$ in THF afforded **28** in 30% yields as a *Z*/*E* mixture (60:40) of the two geometric isomers. The stereochemistry of 28 has been tentatively assigned on the basis of the different chemical shift of the methyl group in the geometric isomers. The signal at 2.23 ppm has been

attributed to the isomer with the *Z* configuration where the deshielding effect of the ether group could be exerted, and consequently the other at 2.34 ppm to the *E* isomer.

CONCLUSIONS

A new access to alkylidenecyclopropanes through a Ramberg-Backlund rearrangement of cyclopropylsulphones is reported. The reaction is quite versatile due to the facility of synthesis of cyclopropylsulphones and several new applications can be envisaged. Further studies are in progress especially for what concerns the optimization of the conditions of α-halogenation of the sulphone group and the results will be published in due course.

EXPERIMENTAL

Reagent-grade commercially available reagents and solvents were used. Analytical TLC plates and silica gel were purchased from Merck. IR spectra were recorded on a Perkin-Elmer 1310 grating spectrophotometer using NaCl plates. ^{1}H and ^{13}C NMR spectra were recorded on a Varian VXR-300 spectrometer with tetramethylsilane as internal reference; δ values are given in ppm and J values in Hz. Mass spectra were obtained at 70 eV with a Hewlett-Packard 5989A mass spectrometer. Microanalyses were carried out on a Carlo-Erba 1106 Elemental Analyzer. The methyl-4-bromo crotonate **21** was commercially available. Products **1a**,[39] **2a**,[39,40] **14** and **15**,[40] **1b**,[41] **9a** and **17**,[19] have been previously reported.

Cyclopropyl Ethyl Sulfone (2b)

t-BuOK (8.1 g, 72 mmol) was added to a solution of **1b** (6.2 g, 36 mmol) in *t*-BuOH (50 mL). After refluxing for 2 h the solution was poured onto brine and extracted with diethyl ether. Evaporation of the solvent and column chromatography (silica gel) with ethyl acetate–light petroleum 4:3 gave pure **2b** as a yellow oil. Yield: 75%. IR (neat, cm^{-1}): 1130, 1303. ^{1}H NMR ($CDCl_3$) δ: 1.03–1.23 (m, 4H), 1.43 (t, 3H, $J = 7.5$ Hz), 2.37–2.44 (m, 1H), 3.07 (q, 2H, $J = 7.5$ Hz). ^{13}C NMR ($CDCl_3$) δ: 4.41, 6.93, 28.34, 48.19. Anal. calcd. for $C_5H_{10}O_2S$: C, 44.75; H, 7.51; S, 23.89. Found: C, 44.90; H, 7.50; S, 23.96.

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General Method for the Synthesis of Cyclopropylsulfones 3a, 4a, 5a, 3b

To a stirred solution of cyclopropanes **2a** or **2b** (5.1 mmol) in THF (10 mL) at −10°C, a 2.08 M solution of *n*-butyllithium in hexane (2.45 mL, 5.1 mmol) was added. The mixture was stirred for 1 h while it reached room temperature, cooled to 0°C, and then the alkyl halide (5.1 mmol) was added. After 20 h at room temperature the solution was poured onto water and ice and extracted repeatedly with diethyl ether. The ethereal solution was dried (Na_2SO_4) and evaporated under vacuum. The remaining oil was chromatographed on a silica gel column (light petroleum/diethyl ether 1:3).

[1-(Cyclopropylsulfonyl)ethyl]benzene (3a): Pale yellow oil. Yield: 80%. IR (neat, cm^{-1}): 1136, 1317. ^1H NMR ($CDCl_3$) δ: 0.82–1.28 (m, 4H), 1.80 (d, 3H, $J = 7$ Hz), 2.12 (m, 1H), 4.22 (q, 1H, $J = 7$ Hz), 7.41 (s, 5H). ^{13}C NMR ($CDCl_3$) δ: 4.60, 13.64, 27.06, 63.74, 128.61, 128.78, 129.17, 136.38. Anal. calcd. for $C_{11}H_{14}O_2S$: C, 62.83; H, 6.71; S, 15.25. Found: C, 62.70; H, 6.58; S, 15.06.

[1-(Cyclopropylsulfonyl)propyl]benzene (4a): Yellow oil. Yield: 60%. IR (neat, cm^{-1}): 1126, 1310. ^1H NMR ($CDCl_3$) δ: 0.78–0.88 (m, 2H), 0.90 (t, 3H, $J = 7.5$ Hz), 1.02–1.08 (m, 2H), 1.86–2.02 (m, 1H), 2.10–2.22 (m, 1H), 2.38–2.54 (m, 1H), 3.94 (dd , 1H, $J = 4.2$ Hz, $J = 11.2$ Hz), 7.37–7.46 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 4.56, 4.62, 11.29, 20.65, 27.66, 70.82, 128.73, 128.81, 129.68, 132.80. Anal. calcd. for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19; S, 14.29. Found: C, 64.40; H, 7.28; S, 14.45.

[1-(Cyclopropylsulfonyl)-2-phenylethyl]benzene (5a): White solid, m.p. 105°C. Yield: 70%. IR (film, cm^{-1}): 1125, 1310. ^1H NMR ($CDCl_3$) δ: 0.71–0.82 (m, 2H), 1.08–1.09 (m, 2H), 1.92–2.01 (m, 1H), 3.35 (dd, 1H, $J = 11.4$ Hz, $J = 13.6$ Hz), 3.76 (dd, 1H, $J = 13.6$ Hz, $J = 3.6$ Hz), 4.28 (dd, 1H, $J = 11.4$ Hz, $J = 3.6$ Hz), 6.98–7.41 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 4.76, 27.91, 33.62, 70.60, 126.59, 128.33, 128.62, 128.83, 128.99, 129.88, 132.47, 136.79. Anal. calcd. for $C_{17}H_{18}O_2S$: C, 71.30; H, 6.34; S, 11.19. Found: C, 71.22; H, 6.28; S, 11.30.

2-(Cyclopropylsulfonyl)propyl benzene (3b): Yellow oil. Yield: 71%. IR (neat, cm^{-1}): 1132, 1310. ^1H NMR ($CDCl_3$) δ: 1.02–1.07 (m, 2H), 1.23–1.33 (m, 2H), 1.32 (d, 3H, $J = 5.1$ Hz), 2.31–2.37 (m, 1H), 2.69 (dd, 1H, $J = 10.2$ Hz, $J = 8.1$ Hz), 3.21–3.26 (m, 1H), 3.50 (dd, 1H, $J = 10.2$ Hz, $J = 2.7$ Hz), 7.19–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 4.05, 4.21, 12.23, 26.54, 34.81, 59.58, 126.48, 128.29, 128.746, 136.65. Anal. calcd. for $C_{12}H_{16}O_2S$: C, 64.25; H, 7.19; S, 14.29. Found: C, 64.38; H, 7.02; S, 14.45.

General Method for the Synthesis of the Chloro Cyclopropylsulfones 6a, 7a, 8a

To a vigorously stirred solution of powdered NaOH (88 mg, 2.3 mmol) in DMF (10 mL) at 0°C, CCl_4 (215 mg, 1.4 mmol), and the cyclopropylsulfones (1.1 mmol) **3a** or **4a**, **5a** were added in one portion. After stirring for 1 h at this temperature, the solution was poured onto brine and ice and repeatedly extracted with diethyl ether. The organic layer was washed with saturated NaCl, dried (Na_2SO_4), and evaporated under vacuum. The residual oil was chromatographed on a silica gel column (light petroleum/diethyl ether 1:3).

[1-Chloro-1-(cyclopropylsulfonyl)ethyl]benzene (6a): Yield: 66%. White solid m.p. 42°C. ^{1}H NMR ($CDCl_3$) δ: 0.81–1.22 (m, 4H), 1.82 (m, 1H), 2.34 (s, 3H), 7.41 (s, 5H). ^{13}C NMR ($CDCl_3$) δ: 5.46, 24.40, 25.59, 85.74, 128.13, 128.63, 129.67, 134.78. Anal. calcd. for $C_{11}H_{13}ClO_2S$: C, 53.99; H, 5.35; S, 13.10. Found: C, 54.30; H, 5.61; S, 12.96.

[1-Chloro-1-(cyclopropylsulfonyl)propyl]benzene (7a): Yield: 69%. White solid m.p. 38°C. ^{1}H NMR ($CDCl_3$) δ: 0.62–1.26 (m, 4H), 0.98 (t, 3H, $J = 7.2$ Hz), 2.34–2.44 (m, 1H), 2.53–2.64 (m, 1H), 2.84–2.93 (m, 1H), 7.40–7.77 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 5.14, 5.23, 7.72, 24.64, 28.42, 92.14, 128.16, 129.12, 129.44, 132.28. Anal. calcd. for $C_{12}H_{15}ClO_2S$: C, 55.70; H, 5.84; S, 12.39. Found: C, 55.38; H, 5.61; S, 12.76.

[1-Chloro-1-(cyclopropylsulfonyl)-2-phenylethyl]benzene (8a): Yield: 60%. Pale yellow oil. ^{1}H NMR ($CDCl_3$) δ: 0.58–0.70 (m, 2H), 0.94–1.04 (m, 1H), 1.21–1.32 (m, 1H), 2.31–2.41 (m, 1H), 3.80, 4.16 (AB q, 2H, $J = 14.2$ Hz), 6.96–7.87 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 5.19, 5.35, 25.12, 40.66, 91.26, 127.30, 127.82, 128.13, 129.39, 129.61, 131.11, 132.55, 132.88. Anal. calcd. for $C_{17}H_{17}ClO_2S$: C, 63.64; H, 5.34; S, 9.99. Found: C, 63.43; H, 5.61; S, 10.22.

[2-Chloro-2-(cyclopropylsulfonyl)propyl]benzene (4b): To a stirred solution of **3b** (250 mg, 1.1 mmol) in THF (8 mL) at −25°C, a 2.2 M solution of BuLi (0.5 mL, 1.1 mmol) was added. After stirring for 30 min at 0°C, *N*-chlorosuccinimide (146 mg, 1.1 mmol) was added and the reaction mixture was left at room temperature for 20 h before pouring it into brine. Extraction with diethyl ether, drying with Na_2SO_4 and evaporation of the solvent gave a pale yellow oil that was chromatographed on a silica gel column using diethyl ether–light petroleum 5:1 as eluant. Yield: 30%. ^{1}H NMR ($CDCl_3$) δ: 1.13–1.39 (m, 4H), 1.76 (s, 3H), 2.74–2.80 (m, 1H), 3.42, 3.51 (AB q, 2H, $J = 13.8$ Hz), 7.30 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 5.29, 5.78, 23.23, 24.48, 41.77, 85.32, 127.73, 128.26, 131.34, 132.90. Anal. calcd. for $C_{12}H_{15}ClO_2S$: C, 55.70; H, 5.84; S, 12.39. Found: C, 55.49; H, 5.70; S, 12.22.

General Procedure for the Synthesis of the Alkylidene Cyclopropanes 9a,[19] 10a, 11a, 5b

To a solution of lithium diisopropylamide (LDA) (2.4 mmol) in THF (2.5 mL) at −15°C, 2 mmol of α-chloro cyclopropylsulfones **6a–8a**, **4b** in THF (2.5 mL) were added. After stirring for 30 min at room temperature the reaction mixture was diluted with water and ice, and extracted with diethyl ether. The ethereal solution was washed with 10% HCl, dried (Na_2SO_4), and the solvent removed in vacuo. The residual oil was chromatographed on a silica gel column with diethyl ether/light petroleum 1:1.

(3-Cyclopropylidene-3-propyl)benzene (10a): Yield: 66%. Yellow oil. ^{1}H NMR ($CDCl_3$) δ: 0.88–1.35 (m, 4H), 1.52 (t, 3H, $J = 7.5$ Hz), 2.66 (q, 2H, $J = 7.5$ Hz), 7.21–7.57 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 1.07, 4.25, 13.29, 26.99, 119.70, 125.86, 126.33, 128.12, 128.56, 140.14. Anal. calcd. for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 91.10; H, 8.88. MS m/z (relative intensity): 158 (M^+ (4)), 143 (9), 129 (100), 115 (16), 91 (7).

(2-Cyclopropylidene-2-phenylethyl)benzene (11a): Yield: 35%. Yellow oil. ^{1}H NMR ($CDCl_3$) δ: 0.82–1.58 (m, 4H), 4.03 (s, 2H), 7.12–7.57 (m, 10H). ^{13}C NMR ($CDCl_3$) δ: 1.24, 5.50, 40.01, 123.47, 125.79, 126.06, 126.49, 128.09, 128.22, 128.40, 131.57, 139.67, 140.48. Anal. calcd. for $C_{17}H_{16}$: C, 92.68; H, 7.32. Found: C, 92.50, 7.15. MS m/z (relative intensity): 220 (M^+ (7)), 205 (25), 129 (100), 91 (53).

(2-Cyclopropylidenepropyl)benzene (5b): Yield: 45%. Yellow oil. ^{1}H NMR ($CDCl_3$) δ: 0.84–1.27 (m, 4H), 1.75 (s, 3H), 3.46 (s, 2H), 7.14–7.26 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 2.29, 2.86, 20.14, 43.31, 117.42, 123.54, 125.79, 128.14, 128.84, 140.60. Anal. calcd. for $C_{12}H_{14}$: C, 91.08; H, 8.92. Found: C, 90.95; H, 8.87. MS m/z (relative intensity): 158 (M^+ (10)), 143 (100), 129 (70), 115 (35), 104 (30), 91 (49), 77 (15).

[1-(Cyclopropylsulfonyl)-2-methoxyethyl]benzene (13): A solution of **6a** (700 mg, 2.8 mmol) and sodium methoxide (16.8 mmol) in 10 mL of CH_3OH was heated at reflux for 18 h, cooled and then quenched with water (5 mL). The aqueous layer was extracted with CH_2Cl_2. The organic layer washed with 10% HCl and saturated NaCl, dried (Na_2SO_4), evaporated to give an oil which was chromatographed on a silica gel column (ethyl acetate–light petroleum 4:1). Yield: 73%. ^{1}H NMR ($CDCl_3$) δ: 0.85–1.10 (m, 4H), 2.24–2.36 (m, 1H), 3.38 (s, 3H), 4.02 (dd, 1H, $J = 6.6$ Hz, $J = 10.2$ Hz), 4.25, 4.37 (AB q, 1H, $J = 6.3$ Hz), 4.28, 4.35 (AB q, 1H, $J = 6.3$ Hz), 7.36–7.48 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 4.64, 4.70, 29.26, 58.91, 68.48, 70.34, 128.65, 128.91, 129.61, 131.29. Anal. calcd. for $C_{12}H_{16}O_3S$: C, 59.98; H, 6.71; S, 13.34. Found: C, 59.73; H, 6.65; S, 13.12.

Chlorination of Benzyl Cyclopropyl Sulfone (2a)

To a vigorously solution of powdered NaOH (1.12 g, 28 mmol) in DMF (30 mL), at 0°C the cyclopropylsulfone **2a** (5 g, 25 mmol) and CCl_4 (4.9 mL, 50 mmol) were added. After stirring for 1 h at the same temperature, the reaction mixture was poured onto water and ice, extracted with diethyl ether, dried (Na_2SO_4), and evaporated under vacuum. The residue was chromatographed on a silica gel column with a diethyl ether–light petroleum 3:1 to give 1.5 g of the chloro-(phenyl)methyl cyclopropyl sulfone **14** as a yellow liquid and 3.1 g of the cyclopropyl dichloro(phenyl)methyl sulfone **15** as white crystals, m.p. 78°C.

14: ^{1}H NMR ($CDCl_3$) δ: 0.92–1.35 (m, 4H), 2.26–2.74 (m, 1H); 5.70 (s, 1H), 7.30–7.72 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 5.25, 5.57, 26.63, 74.01, 128.57, 129.50, 130.35, 130.44. Anal. calcd. for $C_{10}H_{11}ClO_2S$: C, 52.05; H, 4.80; S, 13.88. Found: C, 52.20; H, 4.70; S, 13.97.

15: ^{1}H NMR ($CDCl_3$) δ: 0.90–1.20 (m, 4H), 2.40–2.82 (m, 1H); 7.22–7.88 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 6.45, 24.56, 99.23, 128.10, 129.53, 131.07, 132.82. Anal. calcd. for $C_{10}H_{10}Cl_2O_2S$: C, 45.29; H, 3.80; S, 12.07. Found: C, 45.40; H, 3.65; S, 11.97.

Dichloro[(1-chlorocyclopropyl)sulfonyl]-methyl Benzene (16)

To a vigorously stirred solution of powdered KOH (5 g, 89 mmol) in *t*-butanol (30 mL), the cyclopropylsulfone **2a** (0.5g , 2.5 mmol) and CCl_4 (7.5 mL) were added. After stirring 2 h at reflux, the reaction mixture was poured onto water, extracted with dichloromethane, dried (Na_2SO_4), and evaporated under vacuum.

The residue was chromatographed on a silica gel column with a diethyl ether–light petroleum 3:1 to give 0.48 g of white crystals, m.p. 74°C. Yield: 65%. ^{1}H NMR ($CDCl_3$) δ: 1.34 (m, 2H), 1.69 (m, 2H); 7.45–8.01 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 18.84, 50.18, 125.21, 128.28, 128.64, 131.46, 133.57. Anal. calcd. for $C_{10}H_9Cl_3O_2S$: C, 40.08; H, 3.02; S, 10.68. Found: C, 40.20; H, 3.14; S, 10.87.

Following the method used for the synthesis of **9a** the compounds **17**[19] and **18** have been prepared in low yields (25% and 32%) starting from **14**[38]and **15**.[38] On the other hand, **18** was also prepared from **16** by treatment with *p*-tolyl-magnesium bromide (Method a) or *t*-butoxide in *t*-butanol (Method b).

[Chloro(Cyclopropylidene)methyl]benzene (18)

Method a: To a solution of **16** (0.3 g, 1 mmol) in THF (10 mL), at −70°C was added 2 mL (2 mmol) of *p*-tolyl-magnesium bromide (1.0 M solution in diethyl ether). After stirring 20 h at room temperature, the mixture was treated with brine and extracted with diethyl ether. The organic solution was dried and evaporated to give, after chromatography (silica gel, diethyl ether–light petroleum 3:1) a yellow oil. Yield: 50%. ^{1}H NMR ($CDCl_3$) δ: 0.82–1.78 (m, 4H), 7.25–7.83 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 4.28, 9.68, 121.21, 126.19, 128.13, 129.36, 132.37, 136.80. Anal. calcd. for $C_{10}H_9Cl$: C, 72.96; H, 5.51. Found: C, 72.81; H, 5.42. MS m/z (relative intensity): 166 ($M^+ + 2$ (5)), 164 (M^+ (15)), 129 (100).

Method b: To a solution of **16** (0.5 g, 1.7 mmol) in THF (20 mL) at 0°C, *t*-BuOK (0.57 g, 5.1 mmol) was added in small portions. After stirring 20 h at room temperature the mixture was treated with brine and extracted with diethyl ether. The organic solution was dried and evaporated to give, after chromatography (silica gel, diethyl ether–light petroleum 3:1) **18** as a yellow oil. Yield: 27%.

(*E*)-Methyl [2-(benzylsulfanyl)cyclopropyl]carboxylate (22)

To a solution of benzylmercaptane (10 g, 81 mmol) in benzene (50 mL), 1.4 M solution of BuLi in hexane (57.5 mL, 81 mmol) was added dropwise at −20°C under an argon atmosphere. After 20 min the solution of the so formed lithium thiolate was added dropwise at 0°C to a solution of methyl 4-bromo crotonate **21** (14.5 g, 81 mmol) in benzene (70 mL). The reaction mixture was kept for 20 h at room temperature under stirring and then diluted with diethyl ether, washed first with 10% NaOH and then with brine. After drying and evaporation of the solvent, the oil obtained (18 g) was chromatographed on a silica gel column with (light petroleum–diethyl ether) (10:1). Eleven point five grams of **22** as a pale yellow oil were obtained (yield: 70%) together with 5 g of methyl 3-(benzylsulfanyl)-2-propenoate coming from direct substitution of the bromine of the methyl 4-bromo crotonate. ^{1}H NMR ($CDCl_3$) δ: 1.06 (ddd, 1H, $J = 4.8$ Hz, $J = 5.7$ Hz, $J = 8.7$ Hz), 1.41 (ddd, 1H, $J = 4.8$ Hz, $J = 5.2$ Hz, $J = 8.4$ Hz), 1.66 (ddd, 1H, $J = 3.6$ Hz, $J = 5.2$ Hz, $J = 8.7$ Hz), 2.28 (ddd, 1H, $J = 3.6$ Hz, $J = 5.7$ Hz, $J = 8.4$ Hz), 3.63 (s, 3H), 3.76 (s, 2H), 7.27 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 16.78, 22.54, 23.59, 37.71, 51.64, 126.89, 128.33, 128.65, 172.69. IR (neat, cm^{-1}): 1731. Anal. calcd. for $C_{12}H_{14}O_2S$: C, 64.84; H, 6.35; S, 14.42. Found: C, 64.68; H, 6.16; S, 14.22.

[2-(Benzylsulfanyl)cyclopropyl]methanol (23)

A solution of 1 M $LiAlH_4$ (20 mL, 20 mmol) was added at 0°C to a solution in THF (60 mL) of **22** (4 g, 18 mmol) under an argon atmosphere. After 20 h at room temperature, the reaction mixture was treated with wet Na_2SO_4, filtered on a buchner, and the salt washed with diethyl ether. The organic layer, after drying and evaporation of the solvent gave a pale yellow oil that was chromatographed (ethyl acetate–light petroleum 4:3) on a silica gel column to give 2.7 g of pure **23**. Yield: 77%. ^{1}H NMR ($CDCl_3$) δ: 0.68–0.73 (m, 2H), 1.15–1.21 (m, 1H), 1.59–1.65 (m, 1H), 2.87 (br s, 1H), 3.24–3.39 (AB q, 1H, $J = 11.4$ Hz), 3.26–3.37 (AB q, 1H, $J = 11.4$ Hz), 3.71 (s, 3H), 7.12–7.32 (m, 4H). ^{13}C NMR ($CDCl_3$) δ: 12.62, 17.24, 24.32, 37.66, 64.53, 126.52, 128.08, 128.52, 138.4. IR (neat, cm^{-1}): 3347. Anal. calcd. for $C_{11}H_{14}OS$: C, 68.00; H, 7.26; S, 16.50. Found: C, 68.24; H, 7.06; S, 16.22.

[({2-[(Methoxymethoxy)methyl]cyclopropyl}sulfanyl)-methyl]benzene (24)

A solution of **23** (1.8 g, 9.3 mmol) in THF (30 mL) was treated with NaH (0.22 g, 18.6 mmol) previously washed with light petroleum. After 5 min chloromethyl methylether (1.4 mL, 18.6 mmol) was slowly added and the reaction mixture was stirred for 20 h at room temperature. Methanol was slowly added before treatment with brine and extraction with diethyl ether. Drying (Na_2SO_4) and evaporation of the solvent gave an oil that, after chromatography with ethyl acetate–light petroleum (4:3), left 2 g of pure **24** as a yellow oil. Yield: 93%. ^{1}H NMR ($CDCl_3$) δ: 0.69–0.78 (m, 2H), 1.20–1.26 (m, 1H), 1.64–1.68 (m, 1H), 3.25–3.40 (m, 2H), 3.30 (s, 3H), 3.73 (s, 2H), 4.56 (s, 2H), 7.19–7.33 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 12.99, 17.74, 22.12, 37.89, 54.99, 69.86, 95.93, 126.65, 128.24, 128.73, 138.73. Anal. calcd. for $C_{13}H_{18}O_2S$: C, 65.51; H, 7.61; S, 13.45. Found: C, 65.49; H, 7.70; S, 13.22.

[({2-[(Methoxymethoxy)methyl]cyclopropyl}sulfonyl)methyl]-benzene (25)

To a solution of **24** (1.7 g, 7.1 mmol) in MeOH (32 mL), in the presence of a catalytic amount of ammonium molybdate, 35% hydrogen

peroxide (1.2 g, 34.7 mmol) was added dropwise. After refluxing for 24 h, the reaction mixture was poured onto water and extracted with dichloromethane. Drying and evaporation of the solvent led to an oil that after chromatography (ethyl acetate–light petroleum 4:3) gave 1.8 g of pure **25** as an yellow oil. Yield: 94%. ^{1}H NMR ($CDCl_3$) δ: 0.91–1.01 (m, 1H), 1.17–1.30 (m, 1H), 1.70–1.76 (m, 1H), 2.15–2.19 (m, 1H), 3.26 (s, 3H), 3.29–3.48 (m, 2H), 7.36–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 8.80, 18.36, 32.39, 55.27, 60.17, 66.56, 96.17, 128.78, 128.83, 130.75, 134.80. IR (neat, cm^{-1}): 1120, 1310. Anal. calcd. for $C_{13}H_{18}O_4S$: C, 57.76; H, 6.71; S, 11.86. Found: C, 57.49; H, 6.70; S, 12.02.

[1-({2-[(Methoxymethoxy)methyl]-cyclopropyl}sulfonyl)ethyl]benzene (26)

To a stirred mixture of finely grounded NaOH (0.13 g, 3.3 mmol) with DMF (20 mL), the cyclopropane **25** (0.9 g, 3.3 mmol) was added under stirring at room temperature. Methyl iodide (0.22 mL, 3.4 mmol) was then added in one portion and the reaction mixture was left at room temperature for 20 h. The solution was poured onto water and extracted with diethyl ether. The organic phase, dried and then evaporated under vacuum, left an oil that was chromatographed with ethyl acetate–light petroleum (4:3) to give 0.8 g of pure **26** as a yellow oil. Yield: 85%. ^{1}H NMR ($CDCl_3$) δ: 0.86–0.97 (m, 1H), 1.20–1.32 (m, 1H), 1.62–1.86 (m, 1H), 1.77 (d, 3H, $J = 6.9$ Hz), 1.79 (d, 3H, $J = 6.9$ Hz), 2.01–2.11 (m, 1H), 3.27 (s, 3H), 3.29 (s, 3H), 3.35 (dd, 1H, $J = 10.9$ Hz, $J = 6$ Hz), 3.48 (dd, 1H, $J = 5.1$ Hz, $J = 10.9$ Hz), 4.19–4.26 (m, 1H), 4.49 (s, 2H), 4.55 (s, 2H), 7.31–7.40 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 8.46, 8.60, 13.66, 13.76, 18.04, 18.51, 31.07, 31.41, 55.11, 55.17, 60.05, 63.74, 63.91, 66.28, 66.63, 96.00, 96.06, 128.52, 128.61, 128.67, 128.72, 129.12, 129.22, 130.66, 134.28. Anal. calcd. for $C_{14}H_{20}O_4S$: C, 59.13; H, 7.09; S, 11.27. Found: C, 59.33; H, 7.20; S, 11.42.

[1-Chloro({2-[(methoxymethoxy)methyl]-cyclopropyl}sulfonyl)ethyl]benzene (27)

In a two necked flask finely grounded NaOH (0.084 g, 2.1 mmol) and DMF (15 mL) were mixed under magnetic stirring keeping the temperature at 0°C. CCl_4 (0.23 g, 1.5 mmol) and the cyclopropylsulfone **26** (0.4 g,

1.4 mmol) were then added in sequence. The reaction was left at room temperature for 20 h and then poured into brine and extracted several times with diethyl ether. Drying and evaporation of the solvent gave 0.43 g of almost pure **27** as a yellow oil that was chromatographed on a silica gel column using light petroleum–ethyl acetate (1:2). Yield: 90%. ^{1}H NMR ($CDCl_3$) δ: 0.92–1.56 (m, 2H), 1.78–1.89 (m, 1H), 2.38 (s, 3H), 2.39 (s, 3H), 2.40–2.47 (m, 1H), 3.31 (s, 3H), 3.33 (s, 3H), 3.34–3.40 (m, 1H), 3.47–3.58 (m, 1H), 4.52 (s, 2H), 4.58 (s, 2H), 7.41–7.82 (m, 5H). ^{13}C NMR ($CDCl_3$) δ: 9.26, 9.36, 19.03, 25.53, 25.80, 28.41, 28.52, 55.24, 55.27, 65.74, 65.09, 85.75, 96.09, 96.11, 128.11, 128.16, 128.70, 128.74, 129.67, 134.64, 134.73. Anal. calcd. for $C_{14}H_{19}ClO_4S$: C, 52.74; H, 6.01; S, 10.06. Found: C, 52.49; H, 5.90; S, 10.22.

(1*E*- and 1*Z*-)-1-{2-[((Methoxymethoxy)methyl]-cyclopropylidene}ethyl)benzene (28)

To a magnetically stirred solution of **27** (0.2 g, 0.63 mmol) in THF (15 mL), LDA (0.8 mmol), prepared in a separate flask from 0.6 mL of a 1.2 M solution of *n*-BuLi (0.8 mmol) and 0.1 mL of diisopropylamine (0.8 mmol), was added very slowly at -25°C under an argon atmosphere. The reaction mixture was kept at room temperature for 20 h and then poured onto ice-water. After acidification with diluted HCl the mixture was extracted several times with diethyl ether. The organic solvent was dried and then evaporated to give an oil that, after chromatography on a silica gel column using light petroleum–ethyl acetate (1:2), gave a 60: 40 *Z*/*E* mixture of unseparated **28**. Yield: 30%. ^{1}H NMR of the *Z*/*E* mixture ($CDCl_3$) δ: 1.02–1.40 (m, 3H), 2.23 (s, 3H), 2.34 (s, 3H), 3.20–3.35 (m, 2H), 3.33 (s, 3H), 3.36–3.42 (m, 2H), 3.39 (s,3H), 4.63 (s, 2H), 4.69 (s, 2H), 7.22–7.81 (m, 10H). MS *m*/*z* (major isomer): 203 ($M^+ - 15$ (8)), 173 (21), 156 (62), 143 (100), 129 (83); MS *m*/*z* (minor isomer): 203 ($M^+ - 15$ (4)), 173 (30), 156 (56), 143 (100), 129 (79).

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REFERENCES

1. For reviews on this topic see: (a) Binger, P.; Buch, H.M. Top. Curr. Chem. **1987**, *135*, 77; (b) Goti, A.; Cordero, F.M.; Brandi, A. Top. Curr. Chem. **1996**, *178*, 2.
2. Noyori, R.; Odagi, T.; Takaya, H. J. Am. Chem. Soc. **1970**, *92*, 5780.
3. Ohta, T.; Takaya, H. *Comprehensive Organic Synthesis*; Trost, B.M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p. 1185.
4. Hsiao, C.N.; Hannick, S.M. Tetrahedron Lett. **1990**, *31*, 6609.
5. Motherwell, W.B.; Shipman, M. Tetrahedron Lett. **1991**, *32*, 1103 and references therein.
6. Trost, B.M. Angew. Chem. Int. Ed. Engl. **1986**, *25*, 1.
7. Donaldson, W.A.; Wang, J.; Cepa, V.G.; Suson, J.D. J. Org. Chem. **1989**, *54*, 6056.
8. Pisaneschi, F.; Cordero, F.M.; Goti, A.; Paugam, R.; Ollivier, J.; Brandi, A.; Salaun, J. Tetrahedron: Asymmetry **2000**, *11*, 897.
9. Salaun, J. Rearrangements involving the cyclopropyl group. In *The Chemistry of the Cyclopropyl Group*; Rappoport, Z., Ed.; Wiley: New York, 1987; 809 pp.
10. Salaun, J.; Conia, J.M. J. Chem. Soc. Chem. Commun. **1971**, 1579.
11. Salaun, J.; Champion, J.; Conia, J.M. Org. Synth. **1977**, *57*, 36.
12. Salaun, J. Top. Curr. Chem. **1988**, *144*, 1.
13. Bernard, A.M.; Floris, C.; Frongia, A.; Piras, P.P. Tetrahedron **2000**, *56*, 4555.
14. Hassall, C.H.; Reyle, K. Biochem. J. **1955**, *60*, 334.
15. Fowden, L.; Pratt, H.M. Phytochemistry **1973**, *12*, 1677.
16. Grey, D.O.; Fowden, L. Biochem. J. **1962**, *82*, 385.
17. Brandi, A.; Goti, A. Chem. Rev. **1998**, *98*, 589.
18. Sisido, K.; Utimoto, K. Tetrahedron Lett. **1966**, 3267.
19. Utimoto, K.; Tamura, M.; Sisido, K. Tetrahedron **1973**, *29*, 1169.
20. Salaun, J.; Bennani, F.; Compain, J.C.; Fadel, A. J. Org. Chem. **1980**, *45*, 4129.
21. Koster, R.; Arora, S.; Binger, P. Angew. Chem. Int. Ed. Engl. **1969**, *8*, 205.
22. Arora, S.; Binger, P.; Koster, R. Synthesis **1973**, 146.
23. Piers, E.; Gavai, A.V. J. Org. Chem. **1990**, *55*, 2380.
24. Satoh, T.; Kawase, Y.; Yamakawa, K. Bull. Chem. Soc. Jpn. **1991**, *64*, 1129.
25. Halazy, S.; Dumont, W.; Krief, A. Tetrahedron Lett. **1981**, *22*, 4737.
26. Hiyama, T.; Kanakura, A.; Morizawa, Y.; Nozaki, H. Tetrahedron Lett. **1982**, *23*, 1279.

27. Hassig, R.; Siegel, H.; Seebach, D. Chem. Ber. **1982**, *115*, 1990.
28. Cohen, T.; Sherbine, J.P.; Matz, J.R.; Hutchins, R.R.; McHenry, B.M.; Willey, P.R. J. Am. Chem. Soc. **1984**, *106*, 3245.
29. Prieto, J.A.; Pallares, M.T.; Larson, G.L. Synlett **1993**, 199.
30. Ollivier, J.; Piras, P.P.; Stolle, A.; Aufranc, P.; de Meijere, A.; Salaun, J. Tetrahedron Lett. **1992**, *33*, 3307.
31. Stolle, A.; Ollivier, J.; Piras, P.P.; Salaun, J.; de Meijere, A. J. Am. Chem. Soc. **1992**, *114*, 4051.
32. Bertrand, M.; Maurin, R. Bull. Soc. Chim. Fr. **1967**, 2779.
33. Creary, X. J. Org. Chem. **1978**, *43*, 1777.
34. Lautens, M.; Delanghe, P.H.M. J. Am. Chem. Soc. **1994**, *116*, 8526.
35. Galardon, E.; Le Maux, P.; Simonneaux, G. Tetrahedron **2000**, *56*, 615.
36. Amputch, M.A.; Matamoros, R.; Little, R.D. Tetrahedron **1994**, *50*, 5591.
37. Paquette, L.A.; Houser, R.W. J. Org. Chem. **1971**, *36*, 1015.
38. Regis, R.R.; Doweyko, A.M. Tetrahedron Lett. **1982**, *23*, 2539.
39. Truce, E.W.; Lindy, L.B. J. Org. Chem. **1961**, *26*, 1463.
40. Bordwell, F.G.; Wolfinger, M.D.; Dwyer, J.B. J. Org. Chem. **1974**, *39*, 2516.
41. Anklam, E. Synthetic Commun. **1989**, *19*, 1583.

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