Cyclopropanation with Dibromomethane under Grignard and Barbier Conditions

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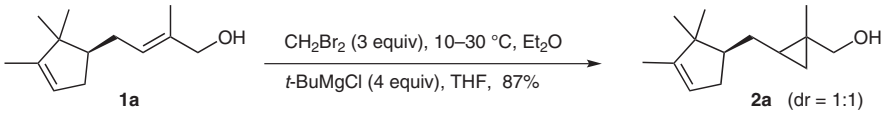
Abstract: Tertiary Grignard reagents and dibromomethane efficiently cyclopropanate allylic (and certain homoallylic) magnesium and lithium alcoholates at ambient temperature in ether solvents. Lithium (homo)allyl alcoholates are directly cyclopropanated with magnesium and dibromomethane under Barbier conditions at higher temperatures. The reaction rates depend on the substitution pattern of the (homo)allylic alcoholates and on the counterion with lithium giving best results. Good to excellent *syn*-selectivities are obtained from α-substituted (homo)allyl alcohols. In tandem reactions, cyclopropyl carbinols are obtained from allyloxylithium or -magnesium intermediates, generated in situ by alkylation of conjugated aldehydes, ketones, and esters as well as from allyl esters and carbonates or vinyloxiranes.[1]

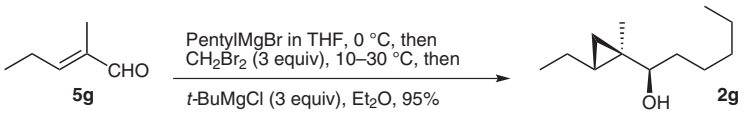
Key words: cyclopropanation, Barbier conditions, Grignard addition, alkyllithium addition, dibromomethane

Procedure 1: Deprotonation with *t*-BuMgCl and cyclopropanation with CH_2Br_2



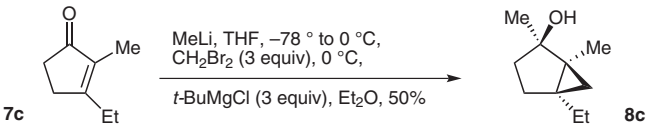
1a **2a** (dr = 1:1)

Procedure 2: Sequential Grignard addition / cyclopropanation of conjugated aldehydes



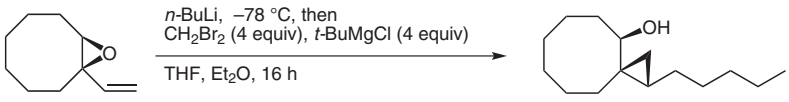
5g **2g**

Procedure 3: Sequential alkyl lithium addition / cyclopropanation of conjugated ketones



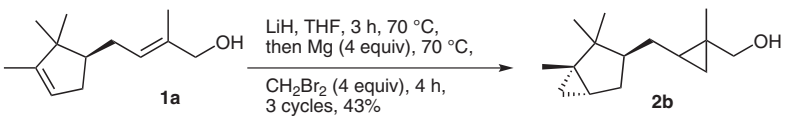
7c **8c**

Procedure 4: Sequential alkyl lithium addition / cyclopropanation of vinyloxiranes



10c **11c** (65%, dr = 93:7)

Procedure 5: Barbier mode



1a **2b**

Scheme 1

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Introduction

The Simmons–Smith cyclopropanation has evolved as a widely used tool for the conversion of alkenes, e.g. allylic alcohols, into the corresponding cyclopropanes, especially with carbenoids of the general structure MCH_2X (M = Zn, Al, Sm, Cu).[2] However, stoichiometric amounts of expensive and/or pyrophoric metal reagents as well as iodinated carbenoid precursors such as diiodomethane or chloroiodomethane are required to guarantee the necessary reactivity for carbenoid formation,[3] which in turn generates large amounts of waste. Dibromomethane is a much less expensive and more easily purified and storable reagent. An efficient cyclopropanation reaction with dibromomethane, however, has so far only been reported by Friedrich,[4] who activated zinc and copper(I) chloride in the presence of dibromomethane and the alkene substrate either by ultrasound[4a] or by addition of acetyl halides[4b] to facilitate carbenoid formation. An unusual cyclopropanation of allylic alcohols promoted by a Grignard reagent has been reported by Bolm and Pupowicz,[5] who obtained moderate to good cyclopropanation yields from γ- and α,γ-substituted allylic alcohols in the presence of isopropylmagnesium halides (4 equiv)/diiodomethane (3 equiv) in a mixture of dichloromethane and ether solvents after 2–3 days at –70 °C. Although these conditions can be realized with normal laboratory equipment (cryostat), a more practical procedure was desired.

This article focuses on experimental procedures and the results of a (tandem) cyclopropanation with dibromomethane under Grignard and Barbier conditions developed in our laboratories, to provide a basis for the rapid reproduction of this reaction on our, and related, substrates (Scheme 1). A more detailed discussion, the theoretical background, and analytical data of all compounds produced already by this method is available.[1]

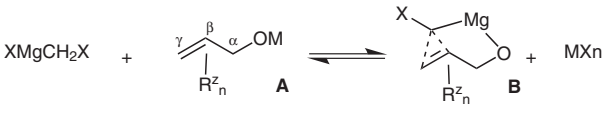
Scope and Limitations

After an investigation of the influence of substituent R in RMgX upon the cyclopropanation of allylic alcohol **1a**, we found that yield and reaction rate correlate with the order R = *tert*-alkyl > *sec*-alkyl >> *n*-alkyl. To avoid decomposition, carbenoid $XMgCH_2X$ has to be generated in the presence of the allylic alcohol to be cyclopropanated (Equation 1).[5,6]

$$RMgX + CH_2X_2 \rightarrow RX + XMgCH_2X \quad \text{(with X = I >> Br > Cl)}$$

Equation 1

Dibromomethane was found to be the ideal carbenoid precursor, which at 25 °C and in combination with three equivalents of a tertiary magnesium chloride such as *tert*-butylmagnesium chloride completely converted allylic alcohol **1a** into cyclopropane carbinol **2a** within a few hours (Scheme 1, Procedure 1). The selectivity for the proximal (allylic) double bond of **1a** follows from intramolecular



Equation 2

cyclopropanation transition state **B**, formed from allylic alcoholate **A** in the presence of XCH_2MgX (Equation 2).[7]

Without substrate, *tert*-butylmagnesium chloride and dibromomethane react exothermically and vigorously with each other and a gaseous isobutane/isobutylene/neopentane (4:3:1) mixture is collected from this test reaction (as well as in the presence of **1a**).[8] Deprotonation of **1a** with one equivalent of *tert*-butylmagnesium chloride produces the expected one equivalent of isobutane, less than one equivalent of isobutane is collected during the addition of dibromomethane and the next three equivalents of *tert*-butylmagnesium chloride, as well as after aqueous quench of the mixture. GC/MS of the distillation pre-fractions shows that the missing isobutane is incorporated into oligomeric structures.[9]

The substitution pattern has a profound effect upon the reaction rates, especially when magnesium alcoholates **A** (M = MgX) are cyclopropanated in situ. At least two substituents, one in the γ- (*E* or *Z*) and another one in the α- or β-position **I** and **II** (Figure 1), are necessary to achieve high conversions through subsequent addition of 3–4 equivalents of CH_2Br_2/*t*-BuMgCl. Additional substituents R^z have no detrimental effect.

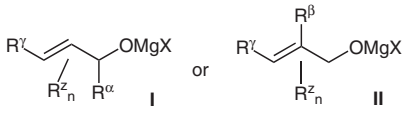


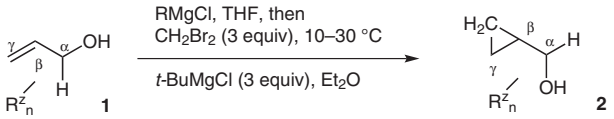
Figure 1 Substituents necessary for high conversions of magnesium alcoholates **A** to the corresponding cyclopropyl carbinols with 3–4 equiv CH_2Br_2/*t*-BuMgCl; higher substitution grades (n = 1–3) are possible.

Allyl alcoholates **A** lacking this substitution pattern give only partial conversions under these conditions. These can be brought to completion by subjecting the crude substrate/product mixture (after workup) to another cyclopropanation cycle. More substituents such as those in tri- or tetrasubstituted alkenes are tolerated. In case of less reactive or sensitive substrates the generation of allyloxylithiums prior to cyclopropanation is generally recommended (vide infra).

The cyclopropanation under Grignard conditions gives (in case of substrates with substituents in the α-position) higher *syn*-selectivities at ambient or higher temperatures than by other methods which are run at lower (–10 °C) or much lower temperatures (–78 °C).[10] *anti*-Byproducts (<20%) were detected in the case of the smallest substituent (R^α = Me). Already with the first higher substituent R^α = Et, this effect was negligible.

Cyclopropanation of differently substituted allylic alcohols **1** with CH_2Br_2 (3 equiv)/*t*-BuMgCl (3 equiv) gave after deprotonation with *t*-BuMgX or MeMgX the corresponding cyclopropanes **2** with good to very good yields and purities (Procedure 1). Clean and extensive conversions under these conditions were obtained from substrates **1** that were at least α,γ- or β,γ-substituted (Table 1, entries 1–4). More substituents such as in **1e–l** gave also good cyclopropanation rates (entries 5–12). These substitution patterns are abundant in various terpenic alcohols. Less-substituted allylic alcohols, which gave only 30–60% conversions under these conditions,[11] could be nevertheless completely cyclopropanated using more CH_2Br_2/*t*-BuMgCl or by application of a further reaction cycle.

Table 1 Procedure 1: CH_2Br_2/*t*-BuMgCl-Promoted Cyclopropanation of Allylic Alcohols **1**[a]



1 **2**

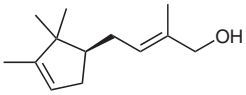
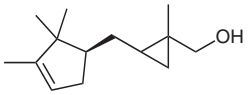
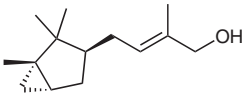
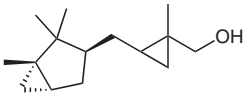
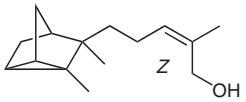
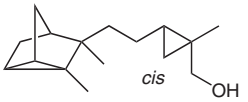
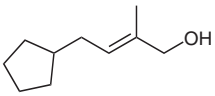
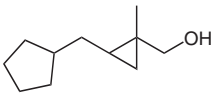
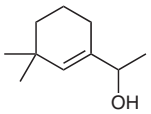
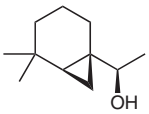
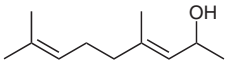
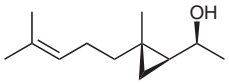
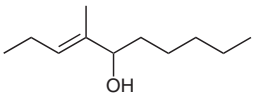
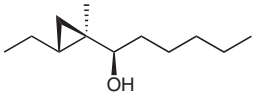
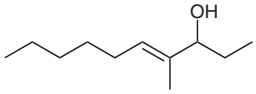
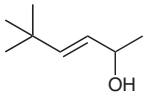
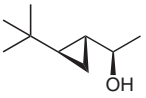
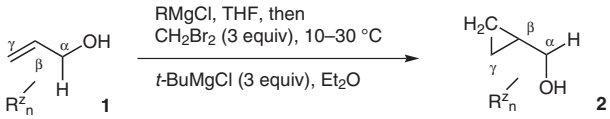
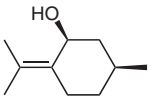
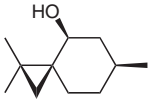
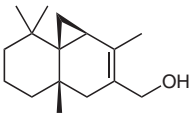
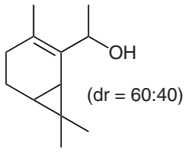
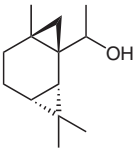
Entry	Substrate[b]	Subst. pattern	Product	Conv.[c] (%)	Yield[d] (%)	Ratio[e] *syn*/*anti* (dr)
1	 **1a**	β,γ	 **2a**	91[f,g]	87	(1:1)
2	 **1b**	β,γ	 **2b**	94	89	(1:1)
3	 **1c**	β,γ	 **2c**	quant.	68	(1:1)
4	 **1d**	β,γ	 **2d**	73[h]	66[i]	
5	 **1e**	α,β,γ	 **2e**	94	94	97:3
6	 **1f**	α,γ,γ	 **2f**	quant.	95	>99:1
7	 **1g**	α,β,γ	 **2g**	91	96	>99:1
8	 **1h**	α,β,γ	 **2h**	91	96	>99:1
9	 **1i**	α,γ	 **2i**	87[j]	80	81:19

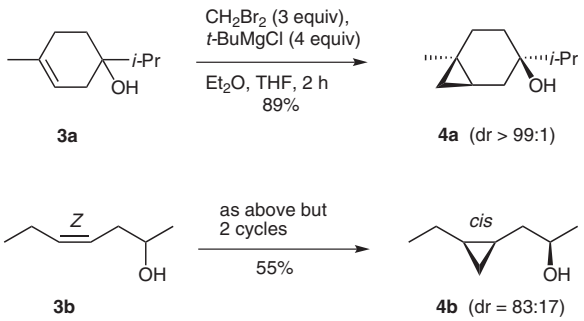
Table 1 Procedure 1: CH_2Br_2/*t*-BuMgCl-Promoted Cyclopropanation of Allylic Alcohols **1**[a] (continued)



Entry	Substrate[b]	Subst. pattern	Product	Conv.[c] (%)	Yield[d] (%)	Ratio[e] *syn*/*anti* (dr)
10	 **1j**	α,β,γ,γ	 **2j**	quant.[k]	97	>99:1
11	 **1k**	β,γ,γ-Δ	 **2k**	92[k]	70	(98:2)
12	 (dr = 60:40) **1l**	α,β-Δ,γ,γ	 **2l**	94[l]	57	39:61[m]

[a] R^z_n = H, alkyl, cyclopropyl, n = 2–4. R = *t*-Bu, Me. Conditions as given unless otherwise stated.
[b] Substrates **1** were prepared according to the literature.[12]
[c] Total conversion *syn* + *anti*, determined by GC/MS of the crude product after workup.
[d] Yields after distillation.
[e] Diastereomeric ratio, relative to substrate stereocenter(s), in brackets. Configuration determined by GC/MS retention times (t_R), NMR, and/or X-ray crystal structure analysis (see below).
[f] CH_2Br_2 (2.5 equiv) and *t*-BuMgCl (2.5 equiv) after deprotonation.
[g] Contains 1–4% of remote cyclopropanation product **2b**.
[h] CH_2Br_2 (4 equiv) and *t*-BuMgCl (4 equiv) after deprotonation.
[i] Completely converted after a second reaction cycle.
[j] Addition of *t*-BuMgCl (5 equiv) to substrate in CH_2Br_2 (5 equiv).
[k] Addition of *t*-BuMgCl (4–5 equiv) to substrate in CH_2Br_2 (4 equiv).
[l] MeLi deprotonation.
[m] For a discussion of the unusual *anti*-selectivity see ref.1

The cyclopropanation of homoallylic alcohols gave either no or only disappointing conversions under these conditions. Nevertheless, some of these substrates, such as terpinen-4-ol (**3a**) and to a certain extent also (*Z*)-hept-4-en-2-ol (**3b**), underwent cyclopropanation surprisingly well (Scheme 2).

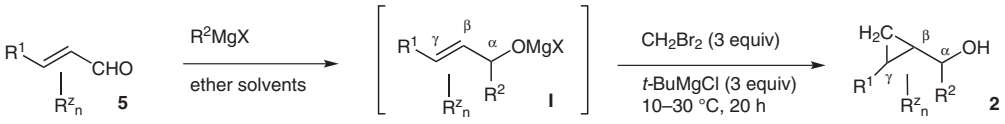


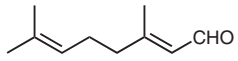
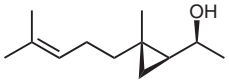
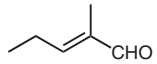
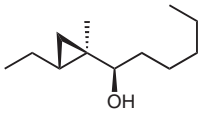
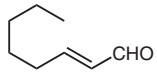
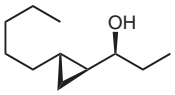
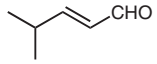
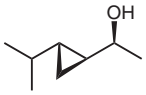
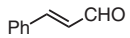
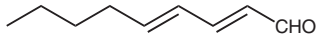
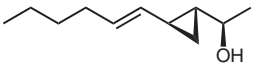
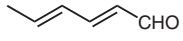
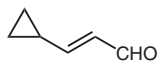
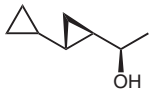
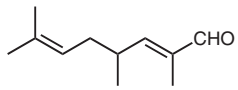
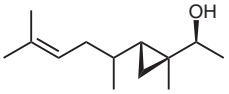
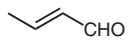
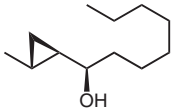
Scheme 2 Cyclopropanation of homoallylic alcohols **3a** and **3b**[13] under Grignard conditions (yields after distillation)

The direct conversion of conjugated aldehydes **5** into the corresponding cyclopropyl carbinols **2** demonstrates powerfully the advantages of cyclopropanation under Grignard conditions (Procedure 2). α,γ-, α,β,γ- or α,γ,γ-Substituted allylic alcoholates **I** are the reactive intermediates, which are further cyclopropanated. Thus, (*E*)-citral (**5f**) or (*E*)-2-methylpent-2-enal (**5g**) (Table 2, entries 1 and 2) gave, after pretreatment with appropriate Grignard reagents und subsequent cyclopropanation with excess *t*-BuMgCl/CH_2Br_2, the corresponding cyclopropanes **2f** and **2g** in nearly the same yields and purities as obtained already from the allylic alcohols **1f** and **1g** (Table 1). Other conjugated aldehydes **5m–t** underwent this tandem alkylation/cyclopropanation with similar efficiency (Table 2).

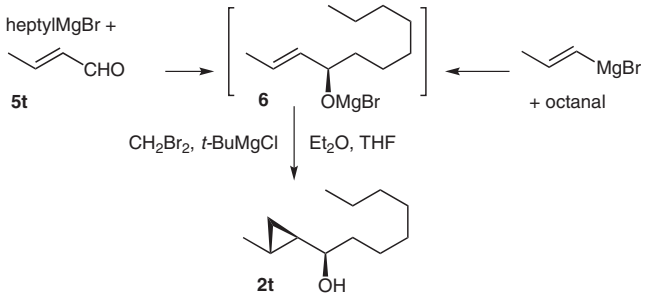
By reverse addition of alkenylmagnesium halides to saturated aldehydes the same intermediate **6** is cyclopropanated. Thus, after pretreatment with (*E*,*Z*)-propenylmagnesium bromide and subsequent cyclopropanation, octanal gave **2t** (as *E*/*Z*-mixture) with a comparable yield to that obtained from crotonaldehyde (**5t**) and heptylmagnesium bromide (Scheme 3).

Table 2 Procedure 2: CH_2Br_2/*t*-BuMgCl-Promoted Cyclopropanation of Conjugated Aldehydes **5** via Intermediate **I**[a]

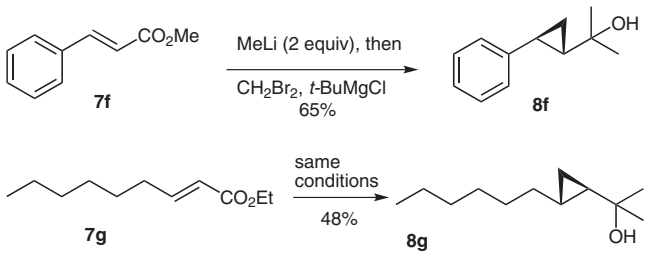


Entry	Substrates[b]	R^2MgX	Subst. pattern **I**	Product	Conv.[c] (%)	Yield[d] (%)	Ratio[e] *syn*/*anti* (dr)
1	 **5f**	MeMgCl	α,γ,γ	 **2f**	quant.	73	>99:1
2	 **5g**	pentylMgBr	α,β,γ	 **2g**	93	95	>99:1
3	 **5m**	EtMgBr	α,γ	 **2m**	90	36	98:2
4	 **5n**	MeMgCl	α,γ	 **2n**	84	86	79:21
5	 **5o**	MeMgCl	α,γ	 **2o**	quant.	83	82:18
6	 **5p**	MeMgCl	α,γ	 **2p**	97[f]	77	83:17
7	 **5q**	MeMgCl	α,γ	 **2q**	93[f]	77	88:12
8	 **5r**	MeMgCl	α,γ-Δ	 **2r**	80[f]	98[g]	75:25
9	 **5s**	MeMgCl	α,β,γ	 **2s**	95[f]	81	>99:1 (1:1)
10	 **5t**	heptylMgBr	α,γ	 **2t**	91	76	> 99:1

[a] R^1 = H, alkyl, alkenyl, aryl; R^2 = alkyl; X = Cl, Br; R^z_n = H, Me
[b] *E*-Alkenes. Substrates **5** are commercial available, except **5r** and **5s** which were prepared according to the literature.[14]
[c] Total conversion *syn* + *anti*, determined by GC/MS of the crude product after workup.
[d] Yields after distillation.
[e] Diastereomeric ratio, relative to substrate stereocenter(s), in brackets. Configuration determined by GC/MS retention times (t_R), NMR, and/or X-ray crystal structure analysis.[1]
[f] CH_2Br_2 (4–5 equiv) and *t*-BuMgCl (4–5 equiv) after Grignard addition.
[g] Crude yield, 24% after distillation, not optimized.



Scheme 3 Addition of heptylmagnesium bromide to crotonaldehyde (**5t**) and inverse addition of prop-1-enylmagnesium bromide to octanal, followed by cyclopropanation of the common intermediate **6** under Grignard conditions



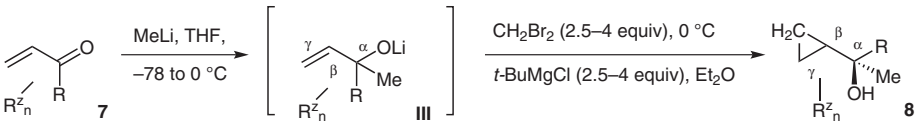
Scheme 4 Tandem methyllithium alkylation/cyclopropanation of conjugated esters; **7g** was prepared as described[19] (yields after distillation).

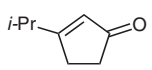
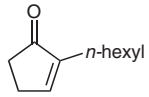
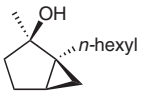
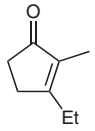
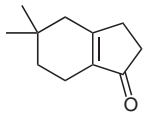
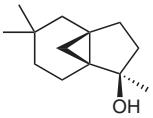
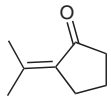
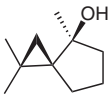
tert-Allylic alcoholates are unstable cyclopropanation substrates because of their sensitivity to elimination.[15,16] Nevertheless, under Grignard conditions conjugated ketones **7** underwent a relatively smooth tandem 1,2-methylation/cyclopropanation (Procedure 3). Methyllithium addition/cyclopropanation gave yields and purities, which were 15–30% better than those obtained from the corresponding methylmagnesium chloride addition/cyclopropanation sequence. *trans*-Isomers were generally not detected. Methylation/tandem cyclopropanation of **7c–e** proceed via an intermediate **III** with the highest substitution grade (α,α,β,γ,γ) possible (Table 3, entries 3–5).

tert-Allylic alcoholates **III** are also accessible by exhaustive (2 equiv) methyllithium addition to conjugated esters such as **7f** and **7g**. In situ cyclopropanation of the tertiary allylic alcoholate **III** gave the corresponding cyclopropyl carbinols **8f** and **8g** (Scheme 4).

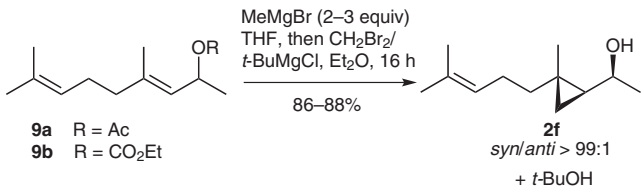
Similarly allylic acetate **9a**, and allylic carbonate **9b** were converted into the cyclopropyl carbinol **2f** (Scheme 5).

Table 3 Procedure 3: Sequential Methyllithium Addition/Cyclopropanation of Conjugated Ketones **7**[a]

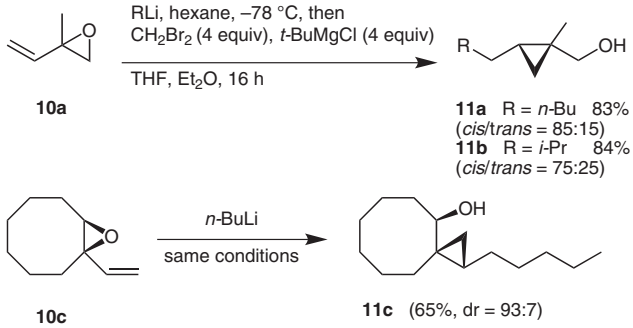


Entry	Substrate **7**[b]	Subst. pattern **III**	CH_2Br_2 and *t*-BuMgCl	Product	Conv.[c] (%)	Yield[d] (%)	Ratio *cis*/*trans* (dr)
1	 **7a**	α,α,γ,γ	4 equiv	 **8a**	quant.	45	>99:1
2	 **7b**	α,α,β,γ	4 equiv	 **8b**	93	60	94:6
3	 **7c**	α,α,β,γ,γ	3 equiv	 **8c**	quant.	70	>99:1
4	 **7d**	α,α,β,γ,γ	3 equiv	 **8d**	quant.	65	>99:1
5	 **7e**	α,α,β,γ,γ	2.5 equiv	 **8e**	98	53	>99:1

[a] R = alkyl; R^z_n = H, alkyl; n = 2–3.
[b] Substrates **7** are commercial available (**7b**)[17] or were prepared by known procedures.[18]
[c] Determined by GC/MS of the crude product after work-up.
[d] Yields after flash chromatography or distillation.



Scheme 5 Sequential ester cleavage/cyclopropanation of allyl esters and carbonates **9a**,**b**[20,21]



Scheme 6 Procedure 4: S_N2' allylic substitution of vinyloxiranes **10a** and **10c**,[23] and cyclopropanation of the corresponding (*Z*)-allyloxylithium intermediates (yields after distillation)

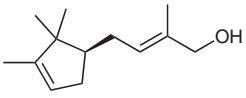
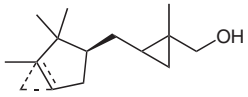
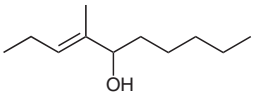
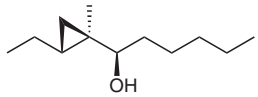
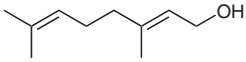
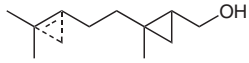
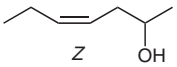
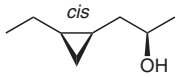
An interesting extension of the tandem alkylation/cyclopropanation method is the S_N2' allylic substitution and cyclopropanation of vinyloxiranes (Procedure 4). Alkyllithium reagents are known to open isoprene oxide **11a** without additives by 1,3-allylic substitution, giving mainly *Z*-configurated 4-alkyl-2-methylbut-2-en-1-ols.[12d,22] The allyloxylithium intermediates of this reaction were cleanly cyclopropanated under Grignard conditions giving the corresponding cyclopropyl carbinols **12** with the expected *cis*,*syn*-configuration (Scheme 6).

Cyclopropanation with bromomethylmagnesium bromide, directly formed from magnesium and dibromomethane (Barbier conditions), in the presence of the alkene substrate, is also possible (Procedure 5). For this purpose, **1b** was deprotonated with 1 equivalent of butyllithium or lithium hydride prior to the addition of magnesium turnings.[24] Subsequent dropwise addition of dibromomethane at reflux (70 °C) kept the reaction controllable. After complete conversion and workup, this gave **2a/2b** (75:20) in 65% yield (Table 4, entry 1). Other substrates were cyclopropanated with similar efficiency under these conditions (Table 4). It should be noticed that cyclopropanation occurs here at a temperature (70 °C) more than 100 °C above the reported decomposition temperature (–55 °C) of carbenoid bromomethylmagnesium bromide.[6]

Cyclopropanation of substrate **1a** under Grignard conditions (CH_2Br_2/*t*-BuMgCl, Table 2) had not only given allylic cyclopropanation product **2a**, but also traces (1–4%) of the remote cyclopropanation product **2b**. Under Barbier conditions, a much higher content (20%) of remote cyclopropanation product **2b** was obtained. The **2a**/**2b** mixture could be completely converted into **2b** through another two reaction cycles (Procedure 5). The same bis-cyclopropanation strategy was applied to geraniol (**1u**), which gave biscyclopropanation product **2u′** via cyclopropyl carbinol **2u** after three reaction cycles.

Encouraged by the better performance of lithiated rather than magnesiated tertiary allylic alcoholates **III** (Table 3)

Table 4 Procedure 5: Cyclopropanation under Barbier Conditions[a,b]

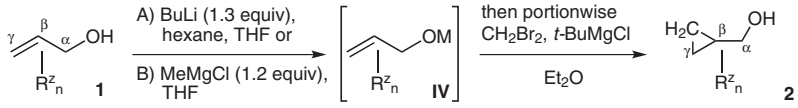
Entry	Substrate[c]	Mg and CH_2Br_2	Product	Yield[d] (%)	Purity[e] (%)	Ratio *syn*/*anti* (*mono*/*bis*)
1	 **1a**	3 equiv	 **2a/2b**	65	91 (3)	(75:20)
2	 **1g**	6 equiv	 **2g**	68	84 (16)	97:3
3	 **1u**	4 equiv	 **2u/2u′**	66	85 (5)	(71:24)
4	 **3b**	6 equiv	 **4b**	68	93 (3)	73:27

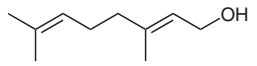
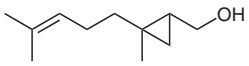
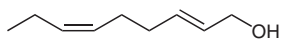
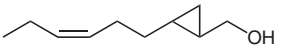
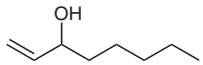
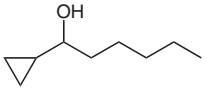
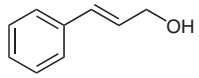
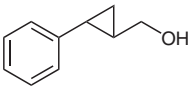
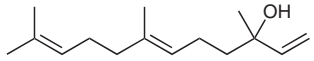
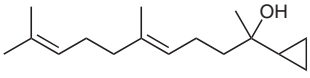
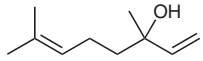
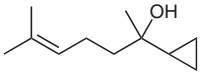
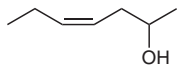
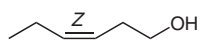
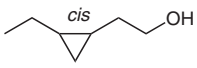
[a] For the precise structures of **2a**, **2b**, and **2u** see Tables 1 and 5. **2u′** indicates the bis-cyclopropanation product.
[b] Deprotonation with BuLi (0 °C, 30 min) or LiH (THF, 70 °C, 3 h) followed by addition of Mg and CH_2Br_2 at 70 °C. Stirred at this temperature until no further conversion detected by GC.
[c] Substrates are either commercially available (**1u**) or were prepared by literature procedures (**1a**, **1g**[11] and **3b**[12]).
[d] Yields after distillation corrected by purity.
[e] Determined by GC/MS of the crude product after workup for *syn* + *anti*. Percentage of unconverted substrate in brackets.

as well as by the much better conversions obtained from lithiated (homo)allylic alcoholates under Barbier conditions (compared to the corresponding magnesiated ones), some less reactive (homo)allylic alcohols were deprotonated with butyllithium (1.3 equiv) and cyclopropanated in situ with the CH_2Br_2/*t*-BuMgCl system (Table 5). Again, this gave much better and often complete conversions.[25]

Cyclopropanation of α,γ-substituted allyl alcoholates **I** gave cyclopropyl carbinols, which were mainly (>80%) or exclusively (>99%) *syn*-configurated.[26] The (nearly) identical mass spectra of the *syn*- and *anti*-diastereomers allow the detection of the minor isomer (*anti*) by GC/MS. Because of the higher sterical congestion of the *anti*-diastereomers, mixtures of *syn*- and *anti*-cyclopropyl carbinols show the typical elution order t_R (*anti*) < t_R (*syn*) on polar GC columns.[27] This analytical method has been used by others for the determination of the relative configuration of these compounds.[10] We routinely found the same elution order on a less polar GC column.[28] The relative configuration of all cyclopropyl carbinols was also routinely analyzed by NOESY (together with COSY, HMBC, HMQC). This was necessary in case of exocyclic *syn*/*anti* mixtures, e.g., **2e** and **11c**, which were inseparable by our GC method, and in case of diastereopure cyclopropyl carbinols. If the NOESY experiment in water-free dimethyl sulfoxide (to detect the OH proton)[29] gave am-

Table 5 Cyclopropanation of Lithium Allylic Alcoholates in Comparison to the Cyclopropanation of the Corresponding Magnesium 'Ate' Complexes[a]



Entry	Substrate[b]	Subst. pattern **IV**	Product	Conversion (%) after deprotonation A: with MeMgCl[c]	B: with BuLi[c]	Yield[d] (%) Method B
1	 **1u**	γ,γ	 **2u**	60 (4 equiv)	93 (4 equiv)	73
2	 **1v**	γ	 **2v**	29 (6 equiv)	93 (6 equiv)	94
3	 **1w**	α	 **2w**	95 (5 equiv)	100 (6 equiv)	98
4	 **1x**	γ	 **2x**	44 (5 equiv)	81 (4 equiv)	54
5	 **1y**	α,α	 **2y**	47 (5 equiv)	100 (5 equiv)	80
6	 **1z**	α,α	 **2z**	41 (5 equiv)	100 (5 equiv)	85
7	 **3b**	homoallylic	 **4b**	75 (6 equiv)	100 (5 equiv)	98
8	 **3c**	homoallylic	 **4c**	15 (4 equiv)	91 (6 equiv)[e]	59

[a] M = MgCl or Li. R^z_n = H, alkyl, aryl, n = 1, 2.
[b] Substrates **1** are commercially available, for the preparation of **3b** see ref.[13]
[c] Equiv CH_2Br_2 and *t*-BuMgCl in brackets.
[d] Yield after distillation.
[e] 50% conversion after addition of 4 equiv CH_2Br_2/*t*-BuMgCl.

biguous results, ethylation or benzylation of the hydroxy function furnished more encumbered derivatives, whose relative configuration was tentatively assigned by this method. If that was not possible (e.g., on **2e** or **4b**), the corresponding camphanates were analyzed by X-ray crystal structure analysis after crystallization.[1] The *syn*-configuration of γ-alkenylcyclopropyl carbinols **2p** and **2q** (where all these methods failed) was determined after conversion to known derivatives.[1]

Conclusion

Tertiary Grignard reagents such as *tert*-butylmagnesium chloride and dibromomethane efficiently cyclopropanate allylic (and certain homoallylic) magnesium and lithium alcoholates at ambient temperature in ether solvents. The reaction rates depend on the substitution pattern of the (homo)allyl alcoholates and on the counterion. Lithium allyl alcoholates gave best cyclopropanation rates, e.g. under Barbier conditions or in the cyclopropanation of relatively unsubstituted allyl or sensitive α-tertiary allyl alcoholates, which are less reactive. Under these relatively simple conditions good to excellent *syn*-selectivities are obtained, which are higher than the ones obtained from other cyclopropanation methods, which are carried out at lower temperatures. In conclusion we provide a new cyclopropanation method, which proceeds simply and rapidly with relatively inexpensive reagents, and which has relatively positive environmental and safety aspects. This method can be integrated into the sequential conversion of conjugated aldehydes and ketones, allylic acetates, and carbonates, as well as vinyloxiranes. We are confident that this methodology will find use in preparative organic chemistry.

Reagents and solvents were purchased from commercial suppliers and used without further purification. Solvents for moisture-sensitive reactions contained < 0.1% H_2O. Moisture-sensitive reactions were conducted under argon and in oven-dried (130 °C) glassware. The given temperatures refer to reaction thermometers. All reactions were carried out under stirring. The silica gel used for flash chromatography was Sorbsil, 0.04–0.063 mm. ^{1}H and ^{13}C NMR: all spectra were recorded at 400 MHz and in $CDCl_3$ or C_6D_6 relative to TMS. ^{13}C NMR peaks were assigned with q (CH_3), t (CH_2), d (CH) and s (C). GC/MS: nonpolar column: 5% diphenyl/95% Dimethylpolysiloxan 30 × 250 × 0.2. Program: 50 °C/3 min, 10 °C/min to 60 °C, 6 °C/min to 240 °C, 30 °C/min to 270 °C. Conditions: injector: 240 °C; split 1:50; flow: 1.0 mL/min; transferline: 250 °C. MS Quadrupole: 106 °C; source: 230 °C; carrier gas: He. IR: samples were measured neat in ATR modus. For preparative procedures and analytical data of all compounds see ref.[1]

Procedure 1: Deprotonation with *t*-BuMgCl and Cyclopropanation with CH_2Br_2; Typical Procedure for 2a

nor-Radjanol (**1a**, 12.6 g, 65 mmol)[12] was added with cooling and stirring to 2 M *t*-BuMgCl in Et_2O (33 mL, 66 mol) under N_2. This was followed by 3 additions of both CH_2Br_2 (3 × 10 g, 0.17 mol) and 2 M *t*-BuMgCl in Et_2O (3 × 28 mL, 0.17 mol) each time in that order at 10–20 °C. The mixture was quenched with concd NH_4Cl, extracted with *t*-BuOMe, and the combined extracts were washed with H_2O until pH 7. The soln was dried ($MgSO_4$) and concentrated to give an oily residue that was bulb-to-bulb-distilled (110 °C/0.133 mbar) to give **2a** (12.5g, 87% after purification) as a colorless oil; dr 1:1. The analytical data (NMR, MS, IR, odor) for **2a** were consistent with those in the literature.[12]

Procedure 2: Sequential Grignard Addition/Cyclopropanation of Conjugated Aldehydes; Typical Procedure for 2g

A 2 M soln of pentylmagnesium bromide in Et_2O (75 mL, 0.15 mol) was added dropwise to (*E*)-2-methylpent-2-enal (12.6 g, 0.15 mol) in THF under N_2 with cooling and stirring. CH_2Br_2 (77 g, 0.44 mol) was added to the Grignard product followed by dropwise addition of 2 M *t*-BuMgCl in Et_2O (220 mL, 0.44 mol) at 10–20 °C; the mixture was stirred at 25 °C for 16 h. Then 2 M HCl was added and the mixture was extracted with *t*-BuOMe, and the combined extracts were washed with concd $NaHCO_3$, H_2O, and concd NaCl. The soln was dried ($MgSO_4$), filtrated, and concentrated to give an oily residue (30.3 g), which was distilled (45 °C/0.04 mbar) to give **2g** (24.4 g, 90%) as colorless oil. The ^{1}H NMR data were (within limits) identical to those described in ref.[30] Odor: green, fresh, spicy, chocolate. The *syn*-configuration confirmed by NMR analysis of the corresponding benzyl ether.[1]

IR (film): 3373 (br, OH), 2957 (s), 2930 (s), 2859 (m), 1456 (m), 1377 (w), 1310 (w), 1120 (w), 1060 (w), 1023 cm^{-1} (s).

^{1}H NMR ($CDCl_3$): δ = –0.05 (m, 1 H), 0.5 (2 H), 0.9 (t, 3 H), 0.99 (t, 3 H), 1.01 (s, 3 H), 1.25–1.35 and 1.35–1.6 (11 H), 2.7 (dd, 1 H).

^{13}C NMR ($CDCl_3$): δ = 11.6 (q), 14.0 (q), 14.3 (q), 17.8 (t), 22.0 (t), 22.6 (t), 24.0 (d), 24.9 (s), 26.0 (t), 32.0 (t), 33.9 (t), 80.9 (d).

MS (EI): *m*/*z* (%) = 166 ([M – 18]$^+$, 3), 141 (5), 128 (15), 113 (10), 99 (32), 84 (35), 72 (85), 71 (100), 69 (60), 55 (70), 43 (75).

Anal. Calcd for $C_{12}H_{24}O$: C, 78.20; H, 13.12. Found: C, 78.05; H, 13.04.

Procedure 3: Sequential Alkyllithium Addition/Cyclopropanation of Conjugated Ketones; Typical Procedure for 8c

Prepared from **7c** (4 g, 32 mmol)[18] using 1.6 M MeLi in Et_2O (28 mL, 45 mmol) at –20 °C, followed by dropwise addition of CH_2Br_2 (2 × 8.4 g, 97 mmol) and 2 M *t*-BuMgCl in Et_2O (2 × 24.3 mL, 97 mmol) at 0–10 °C. After 18 h at 25 °C the mixture was inversely quenched with concd NH_4Cl. Extraction with *t*-BuOMe and bulb-to-bulb distillation gave **8c** (0.23 g, 45%) as a colorless oil. *cis*-configuration assigned by COSY, HMBC, HSQC, NOESY in DMSO-d_6.

IR (film): 3297 (br, OH), 2959 (s), 2933 (m), 2859 (m), 1453 (s), 1365 (s), 1300 (w), 1200 (m), 1115 (s), 993 (s), 938 (s), 926 cm^{-1} (s).

^{1}H NMR ($CDCl_3$): δ = –0.1 (d, 1 H), 0.75 (d, 1 H), 0.95 (t, 3 H), 1.1 (s, 3 H), 1.25 (s, 3 H), 1.3 (1 H), 1.4 (2 H), 1.55 (2 H), 1.8 (1 H).

^{13}C NMR ($CDCl_3$): δ = 11.4 (q), 12.7 (q), 18.4 (t), 24.9 (q), 25.8 (t), 28.5 (t), 32.35 (s), 34.6 (s), 36.5 (t), 81.3 (s).

MS (EI): *m*/*z* (%) = 154 (M$^+$, 1), 139 ([M – 15]$^+$, 36), 136 (55), 125 (34), 121 (27), 107 (85), 96 (58), 81 (100), 67 (30), 57 (42), 55 (36), 43 (84).

HRMS: *m*/*z* [M – CH_3] calcd for $C_9H_{15}O$: 139.11229; found: 139.11031.

Procedure 4: Sequential Alkyllithium Addition/Cyclopropanation of Vinyloxiranes; Typical Procedure for 11c

Oxirane **10c** (3 g, 18 mmol)[23] was added dropwise to 1.6 M BuLi in hexane (11 mL, 18 mmol) in Et_2O (20 mL) at –78 °C, after 1 h at this temperature it was slowly warmed up to r.t. CH_2Br_2 (12.5 g, 72 mmol) was added followed by dropwise addition of *t*-BuMgCl (36 mL, 72 mmol) at 10–20 °C. After 24 h at 25 °C, it was poured into 2 M HCl. The mixture was extracted with *t*-BuOMe and the com-

bined extracts were washed with concd $NaHCO_3$ and concd NaCl, dried ($MgSO_4$), filtered, and the solvent evaporated to give a residue that was purified by bulb-to-bulb distillation (98 °C/0.05 mbar) to give **11c** (2.6 g, 65%) as a colorless oil; dr 93:7. Δ^3-*cis*-configuration assigned by COSY, HMBC, HSQC, NOESY in DMSO-d_6.

IR (film): 3362 (br, OH), 2919 (s), 2852 (m), 1456 (m), 1364 (w), 1106 (w), 1029 (m), 989 (m), 811 (w), 741 (w), 726 cm^{-1} (w).

^1H NMR ($CDCl_3$): δ = 0.3 (m, 1 H), 0.5 (m, 1 H), 0.8 (m, 1 H), 0.8–1.1 and 1.2–2.4 (24 H), 3.25 (1 H).

^{13}C NMR ($CDCl_3$): δ = 14.1 (q), 20.7 (t), 22.7 (t), 23.3 (t), 23.5 (t), 24.3 (d), 26.5 (t), 26.8 (t), 28.9 (t), 29.4 (s), 29.7 (t), 30.4 (t), 31.2 (t), 31.7 (t), 73.7 (d).

MS (EI): *m*/*z* (%) = 224 (M^+, 1), 206 ([M – 18]$^+$, 10), 178 (4), 163 (5), 149 (12), 135 (22), 126 (24), 109 (22), 107 (24), 98 (58), 97 (33), 96 (80), 95 (46), 93 (54), 69 (41), 68 (42), 67 (84), 55 (100), 41 (80).

HRMS: *m*/*z* calcd for $C_{15}H_{28}O$: 224.21402; found: 224.21737; calcd for $C_{15}H_{26}$: 206.20345; found: 206.20372.

Procedure 5: Barbier Mode; Typical Procedure for 2b

nor-Radjanol (**1a**, 200 g, 1 mol)[12] and LiH (10 g, 1.24 mol) in THF (400 mL) were heated with strong stirring and under argon at 65 °C for 6 h until H_2 evolution ceased. Mg turnings (100 g, 4.1 mol) and THF (500 mL) were added at 25 °C. After addition of CH_2Br_2 (8.5 g, 50 mmol) the mixture was heated to 65 °C, and CH_2Br_2 (280 mL, 4 mol) was added over 7 h. After a further 1 h at 65 °C the suspension was quenched with 2 M HCl with cooling. The mixture was extracted with *t*-BuOMe, the combined extracts were washed with H_2O until pH 7, dried ($MgSO_4$), and concentrated to give a crude mixture of mono- and biscyclopropanes (65% corr., **2a/2b** 75:20) which, after two further reaction cycles and distillation (100 °C/0.07 mbar) gave pure javanol (**2b**) (95 g, 43%). The analytical data (NMR, MS, IR, odor) for **2b** were consistent with the literature.[31]

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