

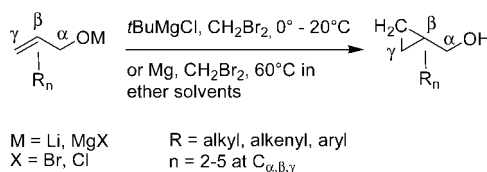
Tandem Cyclopropanation with Dibromomethane under Grignard Conditions

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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 CH₂Br₂ 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 substrates, which are in accord with a staggered Houk model. 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 carboxylates or vinyloxiranes. Using this methodology, numerous fragrance ingredients and their precursors were efficiently converted to the corresponding cyclopropyl carbinols.¹

Introduction

The Simmons–Smith cyclopropanation has evolved as a widely used tool for the conversion of alkenes, e.g. allylic alcohols, to the corresponding cyclopropanes, especially with carbenoids of the general structure MCH₂X (M = Zn, Al, Sm, and Cu).² However, for processes on a larger scale,³ one has to consider the use of stoichiometric amounts of environmentally problematic, expensive, and/or pyrophoric metal reagents. Stoichiometric quantities of iodinated carbenoid precursors such as CH₂I₂ or ClCH₂I are required to guarantee the necessary reactivity for carbenoid formation,⁴ which in turn generates large amounts of corrosive waste. CH₂Br₂ would be a much less expensive and more easily purified and storable reagent. An efficient cyclopropanation reaction with CH₂Br₂, however, has so far only been reported by Friedrich,⁵ who activates zinc and copper(I) chloride in the presence of CH₂Br₂ and the alkene substrate either by ultrasound^{5a} or by addition of acetyl halides^{5b}

to facilitate carbenoid formation. The latter method^{5b} has been adapted for the industrial preparation of cyclopropanated fragrance compounds,⁶ e.g. Javanol (**2a**). It is still desirable, however, to replace the large quantities of zinc and the even more eco-toxic copper of such processes by less harmful reagents.

Results

Cyclopropanation of Allyl Alcohol 1a under Grignard Conditions. An unusual cyclopropanation of allylic alcohols promoted by a Grignard reagent has been reported by Bolm and Pupowicz,⁷ who obtained moderate to good cyclopropanation yields from γ - and α,γ -substituted allylic alcohols in the presence of 4 equiv of *i*PrMgX (X = Cl, Br, I) and 3 equiv of CH₂I₂ in a mixture of CH₂Cl₂ and ether solvents after 2–3 days at –70 °C. After slight changes, we could apply this method to the cyclopropanation of one of our substrates (**1a**). To our surprise, the cyclopropanated product **2a** was readily obtained in ether solvents alone and at ambient temperature (Scheme 1, path A).

(1) Parts of this investigation were presented at the “Scale-Up of Chemical Processes” Scientific Update Conference, Boston, MA, August 29–31, 2007.

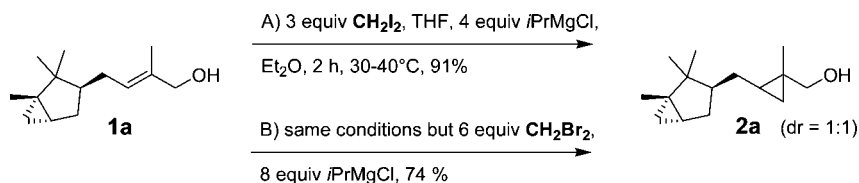
(2) Review: Charette, A. B.; Beauchemin, A. *Org. React.* **2001**, *58*, 1–415.

(3) DelMonte, A. J.; Dowdy, E. D.; Watson, D. J. *Top. Organomet. Chem.* **2004**, *6*, 97–122.

(4) The reactivity order of dihalomethanes is in accordance with that of the radical halogen abstraction from these compounds. See for example: (a) Menapace, L. H.; Kuivila, H. G. *J. Am. Chem. Soc.* **1964**, *86*, 3047–3051. (b) Kosower, E. M.; Schwager, I. *J. Am. Chem. Soc.* **1964**, *86*, 5528–5535.

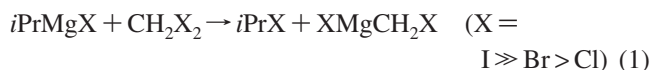
(5) (a) Friedrich, E. C.; Domek, J. M.; Pong, R. Y. *J. Org. Chem.* **1985**, *50*, 4640–4642. (b) Friedrich, E. C.; Lewis, E. J. *J. Org. Chem.* **1990**, *55*, 2491–2494. (c) Friedrich, E. C.; Niyati-Shirkhodae, F. *J. Org. Chem.* **1991**, *56*, 2202–2205.

(6) Bajgrowicz, J. A.; Frater, G.; EP 801049, priority 29.3.1997 to Givaudan-Roure (International) S.A. [*Chem. Abstr.* *127*, 358652].

SCHEME 1. Cyclopropanation of **1a**¹¹ with CH₂X₂ and *i*PrMgCl (X = Br, I) at Ambient Temperature^a^a Yields after distillation.

Interestingly, Bolm and Pupowicz reported also a partial (19%) cyclopropanation of cinnamyl alcohol (–70 °C, 60 h)⁷ using carbenoid precursor CH₂Br₂ instead of CH₂I₂. When we employed the less reactive CH₂Br₂ for the cyclopropanation of **1a** at ambient (!) temperature, a significantly improved yield of **2a** was again achieved (74%). However, 6 equiv of CH₂Br₂ and 8 equiv of *i*PrMgCl were necessary for an acceptable conversion (Scheme 1, path B).

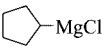
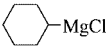
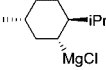
Villieras has reported that *i*PrMgCl and dihalomethanes undergo an exchange reaction at low temperatures, giving carbenoids XCH₂MgX (X = Br, I) which are unstable above –55 °C (eq 1).⁸ Pupowicz reported that the yields (0–47%) obtained from Grignard alkylation and tandem *i*PrMgCl/CH₂I₂ cyclopropanation of *E*-cinnamaldehyde (**5o**) roughly correlated to the order *t*Bu (47%) ≥ *i*Pr ≫ Et ≥ Me (R in RMgX).^{7b} Because it was unclear from her experiments if this effect was due to the different size of the R^α-substituents in the corresponding allyloxy magnesium intermediate or to the steric demands of R in RMgX, we investigated the influence of substituent R upon the cyclopropanation of allylic alcohol **1a**, keeping all other parameters constant (Table 1).



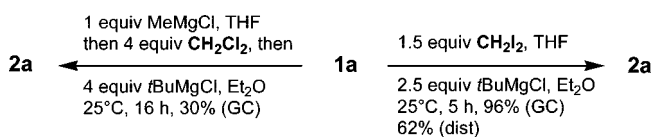
We were pleased to see that 3 equiv of tertiary magnesium chlorides completely converted allylic alcohol **1a** to cyclopropane **2a** after 6 h at 25 °C (Table 1), and that these were thus much better suited for this reaction than *i*PrMgCl. α-Unsubstituted alkyl magnesium chlorides (R = Me, Et, *n*Pr, or *i*Bu in RMgCl) did not effect cyclopropanation. Alkyl magnesium bromides RMgBr used in place of the corresponding chlorides were of no advantage. It is remarkable that even CH₂Cl₂ can effect a partial cyclopropanation under Grignard conditions (Scheme 2). The combination CH₂I₂/*t*BuMgCl reduced the load of dihalide and Grignard reagent necessary for complete conversion even further, although with slightly reduced isolated yield. We continued our experiments with the most efficient cyclopropanation system CH₂Br₂/*t*BuMgCl.

Allylic and Homoallylic Alcohols: Scope and Limits. Cyclopropanation of differently substituted allylic alcohols **1** with 3 equiv of CH₂Br₂ and 3 equiv of *t*BuMgCl gave the corresponding cyclopropanes **2** with good to very good yields and purities. Clean and extensive conversions under these conditions were obtained from substrates **1** that were at least α,γ or β,γ-substituted (Table 2). More substituents such as shown in **1d–h** and **1j** also gave good cyclopropanation rates.

TABLE 1. Influence of the Organic Substituent R in RMgCl upon the Cyclopropanation of **1a**¹¹ with Diastereomer Ratios ~1:1

Grignard reagent ^a	$\xrightarrow[\text{then 3 eq Grignard reagent}]{\text{MeMgCl in THF, 0}^\circ\text{C, then 3 eq CH}_2\text{Br}_2, 10 - 30^\circ\text{C, Et}_2\text{O}}$	
	Conversion after 1 h ^b	Conversion after 16 h
MeMgCl	none	none
EtMgCl	none	none
<i>n</i> PrMgCl	none	none
<i>i</i> BuMgCl	none	none
PhMgCl	none	4 %
 MgCl	40%	53%
 MgCl	58%	67%
<i>i</i> PrMgCl	62%	69% ^d
 MgCl ^e	n.d. ^g	60% ^d
<i>t</i> BuMgCl	76%	94% ^{d, f}
<i>t</i> PeMgCl ^e	56%	96% ^d

^a Cosolvent Et₂O. ^b Stirred after complete addition at 25 °C and followed by GC. ^c *tert*-Pentylmagnesium chloride = 1,1-dimethylpropylmagnesium chloride. ^d After 6 h. ^e Prepared from (1*R*)-(–)-menthyl chloride according to ref 9. ^f 89% of **2a** isolated after distillation. ^g Not determined.

SCHEME 2. Cyclopropanation of **1a**¹¹ with the Carbenoid Precursors CH₂Cl₂ and CH₂I₂^a^a GC conversions and yield after distillation.

These substitution patterns are abundant in various terpenic alcohols, which are important fragrance compounds, or their precursors such as *nor*-radjanol **1b**, α-santalol **1c**, artemol **1e**, methylgeraniol **1f**, Undecavertol **1g**, pulegol **1j**, and others (Table 2). Less substituted allylic alcohols, which gave only 30–60% conversions under these conditions,¹⁰ could be nevertheless completely cyclopropanated by using more CH₂Br₂ and *t*BuMgCl or by application of a further reaction cycle.

(7) (a) Bolm, C.; Pupowicz, D. *Tetrahedron Lett.* **1997**, 38, 7349–7352. (b) Pupowicz, D. Cyclopropanierungen mit Zink- und Magnesium-Carbenoiden, Dissertation, Philipps-Universität, Marburg, 1997.

(8) (a) Villieras, J. *Comptes Rendus* **1965**, 261, 4137–4138. (b) Villieras, J. *Bull. Chem. Soc. Fr.* **1967**, 5, 1520–1532.

(9) Prepared from (–)-methyl chloride: (a) Krause, H. W.; Kinting, A. J. *Prakt. Chem.* **1980**, 322, 485–486.

TABLE 2. $\text{CH}_2\text{Br}_2/t\text{BuMgCl}$ Promoted Cyclopropanation of Allylic Alcohols 1

R = H, alkyl or cyclopropyl
R' = Me, *t*Bu n = 2-4
for slightly different reaction
conditions see ^{e,g,i,k}

Substrate ^a	R	Product	Conversion ^b	Yield (dist) ^c	<i>syn</i> / <i>anti</i> (dr) ^d
1a	β, γ	2a	94%	89%	(1:1)
1b	β, γ	2b	91% ^{e,f}	87%	(1:1)
1c	β, γ	2c	quant.	68%	(1:1)
1d	β, γ	2d	73% ^g	66% ^h	
1e	α, β, γ	2e	94%	94%	97 : 3
1f	α, γ, γ	2f	quant.	95%	> 99 : 1
1g	α, β, γ	2g	91%	96%	> 99 : 1
1h	α, β, γ	2h	91%	96%	> 99 : 1
1i	α, γ	2i	87% ⁱ	80%	81 : 19
1j	$\alpha, \beta, \gamma, \gamma$	2j	quant. ^j	97%	> 99 : 1

^a Substrates **1** were prepared according to the literature,⁴⁰ except for **1d** (Scheme 7). ^b Determined by GC/MS of the crude product after workup. % = *syn* + *anti*. ^c Yields after distillation. ^d Diastereomer ratio relative to substrate stereocenter(s) in brackets. Configuration determined by GC/MS retention times (r_T), NMR, and/or X-ray analysis (see below). ^e 2.5 equiv of CH_2Br_2 and *t*BuMgCl after deprotonation ^f Contains 1–4% of remote cyclopropanation product **2a**. ^g 4 equiv of CH_2Br_2 and *t*BuMgCl and CH_2Br_2 after deprotonation. ^h Completely converted after a second reaction cycle. ⁱ Addition of 5 equiv of *t*BuMgCl to substrate in 5 equiv CH_2Br_2 . ^j Addition of 4 equiv of *t*BuMgCl to substrate in 4 equiv CH_2Br_2 .

The cyclopropanation of homoallylic alcohols **3** gave mainly either no conversion or only disappointing conversions. 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 3). For more details vide infra Figure 2 and the corresponding discussion of substrates and their substitution prerequisites.

Sequential Cyclopropanation: Conjugated Aldehydes. The direct conversion of conjugated aldehydes **5** to the corresponding cyclopropyl carbinols **2** demonstrates powerfully the advantages of a cyclopropanation under Grignard conditions. α, γ -, α, β, γ -,

(10) Allylic alcohols, which underwent incomplete conversions with 3 equiv of CH_2Br_2 and 4 equiv of *t*BuMgCl (GC-conversion to the corresponding cyclopropanes after 18 h in brackets): *E*-2-hexenol (35%), *Z*-2-hexenol (65%), nonadienol (50%), geraniol (50%), nerol (10%), oct-1-en-3-ol (50%), linalool (40%), nerolidol (50%).

TABLE 3. Sequential Grignard Addition and Cyclopropanation of Conjugated Aldehydes **5** via Intermediates **6**

$\text{R}-\text{CH}=\text{CH}-\text{CHO} \xrightarrow[\text{ether solvents}]{\text{R}^\alpha\text{MgX}} \left[\text{R}-\text{CH}=\text{CH}-\text{CH}(\text{R}')-\text{OMgX} \right] \xrightarrow[10-30^\circ\text{C, 3 equiv } t\text{BuMgCl, 20 h}]{3 \text{ equiv } \text{CH}_2\text{Br}_2} \text{H}_2\text{C}-\text{CH}(\text{R}')-\text{CH}(\text{R})-\text{OH}$							
Substrates 5 ^a	R ^α MgX	R in 6	Product ^e	Conversion ^b	Yield (dist) ^c	syn / anti (dr) ^d	R = H, alkyl, alkenyl or aryl R' = H or Me n = 0–1 R _n = alkyl X = Cl, Br for slightly different reaction conditions see ^e
5f	MeMgCl	α, γ, γ	2f	quant.	73%	> 99 : 1	
5g	<i>n</i> Heptyl-MgBr	α, β, γ	2g	93%	95%	> 99 : 1	
5k	MeMgCl	α, β, γ	2k	95% ^e	81%	> 99:1 (1:1)	
5l	<i>n</i> Heptyl-MgBr	α, γ	2l	91%	76%	> 99 : 1	
5m	EtMgBr	α, γ	2m	90%	36%	98 : 2	
5n	MeMgCl	α, γ	2n	84%	86%	79 : 21	
5o	MeMgCl	α, γ	2o	quant.	83%	82 : 18	
5p			2p				
5q	MeMgCl	α, γ	2q	97% ^e	77%	83 : 17	
5q	MeMgCl	α, γ	2q	93% ^e	77%	88 : 12	

^a *E*-Alkenes. Substrates **5** are commercial available, except **5k**, which was prepared according to the literature.¹³ ^b Determined by GC/MS of the crude product after workup. % = *syn* + *anti*. ^c Yields after distillation. ^d Diastereomer ratio relative to substrate stereocenter(s) in brackets. Configuration determined by GC/MS retention times (*r_T*), NMR, and/or X-ray analysis (see below). ^e 4 equiv of CH₂Br₂ and *t*BuMgCl after Grignard addition.

or α,γ,γ-substituted allylic alcoholates **6** are reactive intermediates, which are further cyclopropanated. Thus, *E*-citral **5f** or *E*-2-methylpent-2-enal **5g** (Table 3) gave, after pretreatment with appropriate Grignard reagents and subsequent cyclopropanation with excess *t*BuMgCl and CH₂Br₂, the corresponding cyclopropanes **2f** and **2g** in nearly the same yields and purities as obtained already from the allylic alcohols **1f** and **1g** (Table 2). Other conjugated aldehydes **5k–q** underwent this tandem alkylation/cyclopropanation with similar efficiency (Table 3).

By reverse addition of alkenyl magnesium halides to saturated aldehydes the same intermediates **6** are cyclopropanated. Thus, after pretreatment with *E,Z*-propenyl magnesiumbromide and subsequent cyclopropanation, octanal gave **2l** (as an *E/Z*-

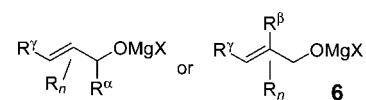


FIGURE 1. Substituents necessary for high conversions of magnesium alcoholates **6** to the corresponding cyclopropyl carbinols with 3–4 equiv of CH₂Br₂ and *t*BuMgCl. Higher substitution grades (*n* = 1–3) are possible.

mixture) with a comparable yield to the one obtained from croton aldehyde **5l** and *n*-heptyl magnesiumbromide (Scheme 4).

Conjugated Ketones and Esters. *tert*-Allylic alcoholates are unstable cyclopropanation substrates because of their sensitivity

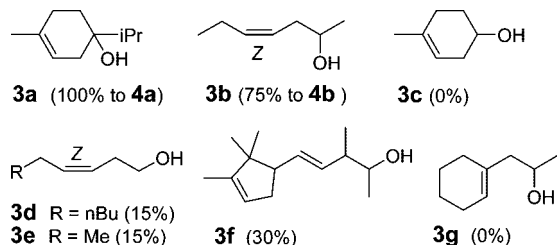
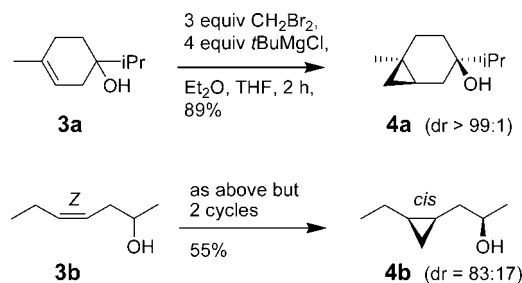


FIGURE 2. Cyclopropanation of homoallylic alcohols under Grignard conditions (as in Scheme 3). GC conversions in brackets. Substrates **3** are either commercially available (**3a,d,e**) or were prepared by known procedures (**3b**¹³ and **3c,f,g**³⁵).

SCHEME 3. Cyclopropanation of Homoallylic Alcohols 3a and 3b¹² under Grignard Conditions^a

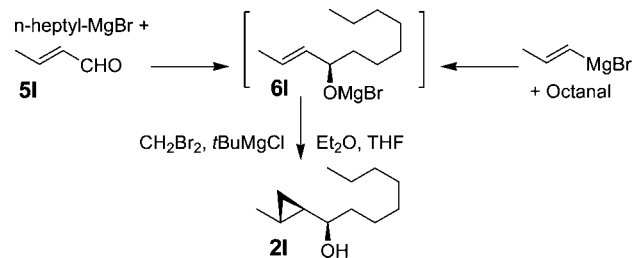


^a Yields after distillation.

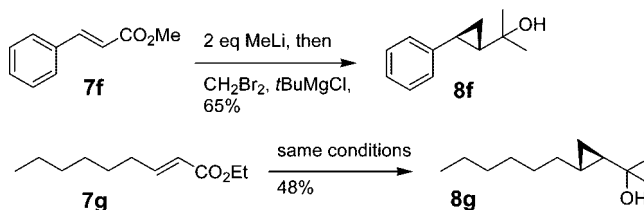
to elimination.^{14,15} Nevertheless, under Grignard conditions conjugated ketones **7** underwent a relatively smooth tandem 1,2-methylation/cyclopropanation (Table 4). MeLi addition/cyclopropanation gave yields and purities which were 15–30% better than the ones obtained from the corresponding MeMgCl addition/cyclopropanation sequence. *Trans*-isomers were generally not detected. Methylation/tandem cyclopropanation of **7c–e** proceed via an intermediate **6** with the highest substitution grade ($\alpha,\alpha,\beta,\gamma,\gamma$) possible. A tandem 1,2-MeLi addition/Simmons-Smith cyclopropanation of **7a** has been reported to give *cis*-Sabinene hydrate **8a** with 64% isolated yield.¹⁵ However, even with freshly prepared zinc–copper couple we had difficulties reproducing this reaction.¹⁶

tert-Allylic alcohols **6** are also accessible by exhaustive (≥ 2 equiv) MeLi addition to conjugated esters such as **7f** and

SCHEME 4. Addition of *n*-Heptyl Magnesium Bromide to Croton Aldehyde 5l and “Inverse Addition” of Prop-1-enyl Magnesium Bromide to Octanal, followed by Cyclopropanation of the Common Intermediate 6 under Grignard Conditions

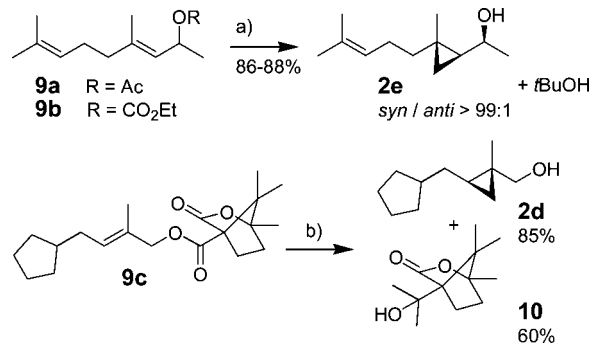


SCHEME 5. Tandem MeLi Alkylation/Cyclopropanation of Conjugated Esters^a



^a **7g** was prepared as described.¹⁹ Yields after distillation.

SCHEME 6. Sequential Ester Cleavage/Cyclopropanation of Allyl Esters and Carbonates^a



^a Preparation of **9c** from **1d** (Scheme 7): pyridine, cat. DMAP, (–)-camphanoyl chloride, 77% (FC). The preparation of **9a** and **9b** is described in the literature.^{20,21} Reagents and conditions: (a) 2–3 equiv of MeMgBr, THF, then 4 equiv of CH₂Br₂/4 equiv of *t*BuMgCl, Et₂O, 16 h. (b) 1.4 equiv of MeLi, Et₂O, then 3 × 1.5 equiv of CH₂Br₂/*t*BuMgCl, yields after flash chromatography.

7g. In situ cyclopropanation of the tertiary allylic alcoholate **6** gave the corresponding cyclopropyl carbinols **8f** and **8g** (Scheme 5).

Allylic Acetates and Carbonates. As the conversion of allylic acetate **9a**, allylic carbonate **9b**, and allylic camphanate **9c** to the cyclopropyl carbinols **2d** and **2e** is straightforward,

(11) Preparation of substrates **1** according to the literature: (**1a**) Schröder, F. WO 2006066436, priority 20.12.2005 to Givaudan S.A. Switz [Chem. Abstr. 145, 103855]. (**1b**) Bajgrowicz, J. A.; Frank, I.; Frater, G.; Hennig, M. *Helv. Chim. Acta* **1998**, *81*, 1349–1358. (**1c**) (a) Tamura, M.; Suzukamo, G. *Tetrahedron Lett.* **1981**, *22*, 577. (b) Tamura, M.; Suzukamo, G.; Hirose, K. EP 29603, Sumimoto Chemical Co., 1980 [Chem. Abstr. 95, 204220]. (**1e**) Levorse, A. T. US 5234902, priority 28.2.1992 to International Flavors and Fragrances Inc., USA [Chem. Abstr. 119, 210271]. (**1f**) Bajgrowicz, J. A.; Bringen, A.; Frater, G.; Mueller, U. EP 743297, priority 20.11.1996 to Givaudan-Roure, Switzerland [Chem. Abstr. 126, 103856]. (**1g**) Kaiser, R.; Lamparsky, D. EP 45453, Givaudan L. et Cie S.A., 1980 [Chem. Abstr. 96, 199080]. (**1h**) Berg-Schultz, K.; Bajgrowicz, J. A.; Baudin, J. WO 2005026092, priority to Givaudan S.A. Switz. 12.9.2003 [Chem. Abstr. 142, 336041]. (**1i**) Jacob, P.; Brown, H. C. *J. Org. Chem.* **1977**, *42*, 579–580. (**1j**) Martin, A. EP 770671, priority 30.10.1996 to Quest International B.V [Chem. Abstr. 126, 334220].

(12) Watson, S. C.; Malpass, D. B.; Yeargin, G. S. DE 2430287, Texas Alkyls Inc., USA, 1975 [Chem. Abstr. 83, 27544].

(13) Preparation of substrate **5k**: (a) Hall, J. B.; Wiegers, W. J. US 4010207, International Flavors & Fragrances Inc., 1977 [Chem. Abstr. 87, 5396].

(14) Fanta, W. I.; Erman, W. F. *J. Org. Chem.* **1968**, *33*, 1656–1658.

(15) Cheng, D.; Kreethadumrongdat, T.; Cohen, T. *Org. Lett.* **2001**, *3*, 2121–2123.

(16) Attempted reproduction on a 10 mmol scale and with freshly prepared zinc–copper couple under the conditions described in footnote 9 of ref 15 gave no conversion according to GC/MS.

(17) 2-Hexylcyclopent-2-enone = Isojasmane B 11. Commercially available from Oxford Chemicals.

(18) Preparation of substrates **7** according to the literature: (**7a**) Jurkauskas, V.; Sadighi, J. P.; Buchwald, S. L. *Org. Lett.* **2003**, *5*, 2417–2420. (**7c**) Berube, G.; Fallix, A. G. *Can. J. Chem.* **1991**, *69*, 77–78. (**7d**) Trost, B. M.; Keeley, D. E. *J. Am. Chem. Soc.* **1976**, *98*, 248–250. (**7e**) Berthelot, P.; Vaccher, C.; Devergnies, M.; Flouquet, N.; Debaert, M. *J. Heterocycl. Chem.* **1988**, *25*, 1525–1529.

(19) Rathke, M. W.; Nowak, M. *J. Org. Chem.* **1985**, *50*, 2624–2626.

(20) Agarwal, V. K.; Thappa, R. K.; Agarwal, S. G.; Mehra, M. S.; Dhar, K. L.; Atal, C. K. *Indian Perfumer* **1983**, *27*, 112–118.

TABLE 4. Sequential MeLi Addition/Cyclopropanation of Conjugated Ketones 7

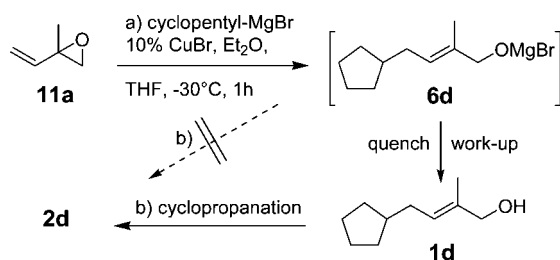
$\text{Substrate } 7 \xrightarrow[\text{-78}^\circ\text{C}]{\text{MeLi, THF}} \left[\text{Intermediate } 6 \right] \xrightarrow[\text{2.5-4 equiv } t\text{BuMgCl, Et}_2\text{O}]{\text{2.5-4 equiv } \text{CH}_2\text{Br}_2, 0^\circ\text{C}} \text{Product } 8$

$R = \text{H, alkyl}$
 $R' = \text{alkyl}$
 $n = 2-3$

Substrate 7 ^a	Substitution pattern in 6	equiv CH ₂ Br ₂ and tBuMgCl	Product	Conversion ^b	Yield (dist) ^c	cis/trans (dr)
	α,α,γ,γ	4 equiv		quant.	45%	> 99:1
	α,α,β,γ	4 equiv		93%	60%	94 : 6
	α,α,β,γ,γ	3 equiv		quant.	70%	> 99:1
	α,α,β,γ,γ	3 equiv		quant.	65%	> 99:1
	α,α,β,γ,γ	2.5 equiv		98%	53%	> 99:1

^a Substrates 7 are commercially available (7b)¹⁷ or were prepared by known procedures.¹⁸ ^b Determined by GC/MS of the crude product after workup. ^c Yields after flash chromatography or distillation.

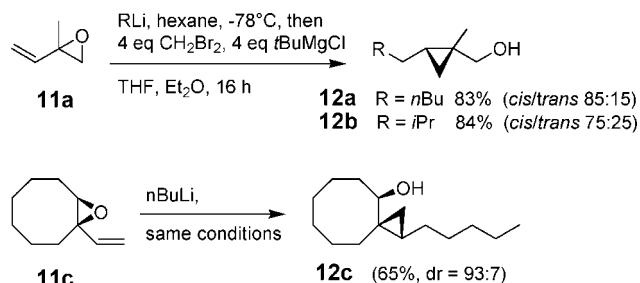
SCHEME 7. Preparation of 1d via 6d and Cyclopropanation under the Conditions of Table 2



we shall give only three examples of these relatively simple sequential transformations (Scheme 6).

Vinyl Oxiranes. An interesting extension of the tandem alkylation/cyclopropanation method is the S_N2' allylic substitution of vinyl oxiranes. We first turned our attention to the cyclopropanation of allyloxy magnesium halide 6d, prepared under CuBr-catalysis as described by Jung (Scheme 7).²² This intermediate, however, did not undergo cyclopropanation after addition of excess CH₂Br₂ and tBuMgCl, whereas 1d, once isolated, gave readily 2d (Table 2).

Consequently, alkyl lithium reagents were employed, which are known to open isoprene oxide 11a without additives by 1,3-

SCHEME 8. S_N2' Allylic Substitution of Vinyl Oxiranes 11a and 11c,²⁴ and Cyclopropanation of the Corresponding Z-Allyloxy Lithium Intermediates^a

^a Yields after distillation.

allylic substitution, giving mainly (Z)-configured 4-alkyl-2-methylbut-2-en-1-ols.²³ Indeed, the allyloxy lithium intermediates of this reaction were cleanly cyclopropanated under Grignard conditions giving the corresponding cyclopropyl carbinols 12 with the expected *cis*, *syn*-configuration (Scheme 8).

Discussion and Further Results

Mechanism. As described already by Villiéras, carbenoid XCH₂MgX should be formed from RMgX in the presence of excess CH₂X₂ (eq 1). So far it has not been explained why iPrMgCl is especially useful for this purpose,^{7,8} as we still cannot say why Grignard reagents with a higher degree of α-branching, such as tBuMgCl, give better cyclopropanation rates than their

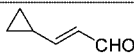
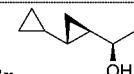
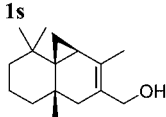
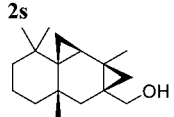
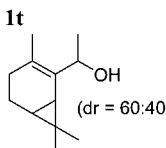
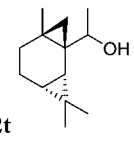
(21) Barras, J.-P.; Bourdin, B.; Schröder, F. *Chimia* **2006**, 60, 574–579.

(22) Jung, M. E.; D'Amico, D. C. *J. Am. Chem. Soc.* **1995**, 117, 7379–7388.

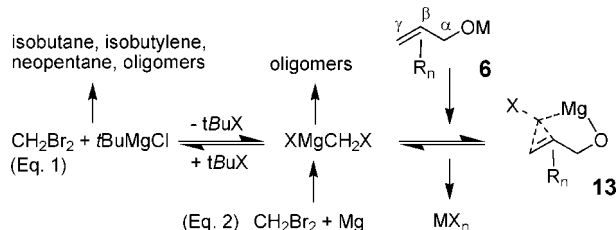
(23) (a) Tamura, M.; Suzukamo, G. *Tetrahedron Lett.* **1981**, 22, 577–580.

(b) Tamura, M.; Suzukamo, G.; Hirose, K. EP 0029603, Sumitomo Chemical Company Ltd., 1981 [*Chem. Abstr.* 95, 204220]. (c) Netland, P. *Org. Proc. Prep. Int.* **1980**, 12, 261–262, and references cited therein.

TABLE 5. Cyclopropanation of β - or γ -Cyclopropyl-Substituted Allylic Alcoholates 6

Substrate ^a	Substitution pattern in 6	Conditions and equiv Δ -reagents	Product	Conversion ^b	Yield ^c	syn / anti (dr)
1r 	α, γ - Δ	MeMgCl, then 5 x CH ₂ Br ₂ and <i>t</i> BuMgCl	2r 	80%	24% ^d	75 : 25
1s 	$\beta, \beta, \gamma, \gamma$ - Δ	5 x CH ₂ Br ₂ and <i>t</i> BuMgCl	2s 	92%	70%	(98 : 2)
1t  (dr = 60:40)	α, β, β - Δ , γ, γ	MeLi then 3 x CH ₂ Br ₂ and <i>t</i> BuMgCl	2t 	94%	57%	39 : 61

^a Substrates **1r–t** prepared by known procedures.³⁰ ^b Determined by GC/MS of the crude product after workup. ^c Yields after flash chromatography or distillation. ^d Yield (98%, crude, corrected by purity) not optimized.

SCHEME 9. Formation of Transition State **13**^a

^a M = Li, Na, MgX. X = Cl, Br. R_n = alkyl- or aryl-substituents at the α -, β -, and γ -positions of the allylic alcoholate with $n = 2$ –5. The most simple equations for the generation of **13** from CH₂Br and *t*BuMgCl are depicted; other exchange reactions and magnesium species (higher aggregates) are possible.²⁵

less branched analogues (Table 1). Hoffmann has considered the influence of the substituents R upon possible transition states and reaction profiles of the halogen/metal exchange reaction $R^1X + R^2M \leftrightarrow R^1M + R^2X$,²⁵ without correlation to reaction rates. The formation of higher aggregates and different possible carbenoids such as XMgCH₂X, XCH₂MgCH₂X, or *t*BuMgCH₂X make such a correlation in our case even more complex (Scheme 9).

Without substrate, *t*BuMgCl and CH₂Br₂ 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**. The formation of these byproducts shows that radical mechanisms are at least partially involved (Scheme 9).²⁶ Deprotonation of **1a** with 1 equiv of *t*BuMgCl produced the expected 1 equiv of isobutane, less than 1 equiv of isobutane was collected during addition of CH₂Br₂ and the next 3 equiv of *t*BuMgCl as well as after aqueous quench of the mixture. GC/MS of the distillation

prefractions shows that the missing isobutane is incorporated into oligomeric structures.²⁷

The final intramolecular cyclopropanation of carbenoid **13**, however, should be concerted.²⁸ Depending on the *E*- or *Z*-configuration of the substrate double bond, the corresponding *trans*- or *cis*-cyclopropanes are obtained stereospecifically. The observed *syn*-selectivity is further evidence. To check the nonradical nature of the intramolecular cyclopropanation more thoroughly, some β - or γ -cyclopropyl-substituted allylic alcoholates (from **1r–t**) were cyclopropanated under Grignard conditions. The expected biscyclopropyl carbinols **2r–t** (Table 5) were obtained readily, and no ring-opening of the cyclopropyl groups,²⁹ as a consequence of radical intermediates generated from the alkene to be cyclopropanated, was observed.

Ether **14** (Scheme 11), which cannot form transition state **13**, did not undergo cyclopropanation with CH₂Br₂ and *t*BuMgCl.

Cyclopropanation under Barbier Conditions. The mechanism in Scheme 9 posed the question as to what extent cyclopropanation occurs if carbenoid XMgCH₂X is not formed from *t*BuMgCl, but directly from Mg and CH₂Br₂ in the presence of the alkene substrate. For this purpose, **1b** was deprotonated with ≥ 1 equiv of BuLi or LiH prior to the addition of magnesium turnings.³¹ Subsequent dropwise addition of CH₂Br₂ at reflux (70 °C) kept the reaction controllable. After complete conversion and workup, this gave 65% of **2ab** (20:75). Other substrates were cyclopropanated with similar efficiency under these conditions (Table 6). It should be noticed that cyclopropanation occurs here at a temperature more than

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(25) (a) Müller, M.; Brönstrup, M.; Knopf, O.; Schulze, V.; Hoffmann, R. W. *Organometallics* **2003**, 22, 2931–2937. (b) Hoffmann, R. W.; Brönstrup, M.; Müller, M. *Org. Lett.* **2003**, 5, 313–316. (c) Hoffmann, R. W. *Chem. Soc. Rev.* **2003**, 32, 225–230.

(26) See also: (a) Ashby, E. C.; Deshpande, A. K.; Doctorovich, F. J. *Org. Chem.* **1994**, 59, 6223–6232. (b) Walton, J. C. In *Houben-Weyl, Methoden der Organischen Chemie*; de Meijere, A. Ed.; Georg Thieme Verlag: New York, 1997; Vol. E17c, pp 2438–2525.

(27) Among other byproducts identified by GC/MS: 2,2,4,4-tetramethylpentane (CAS 1070-87-7), 2,2,6,6-tetramethyl-4-methyleneheptane (CAS 141-70-8), 2-*tert*-butyltetrahydrofuran (CAS 38624-45-2), 2,2-dimethyldecane (CAS 17302-37-3), 2,2,8-trimethyldecane (CAS 62238-01-1), 2,2-dimethylundecane (CAS 17312-64-0), *tert*-butyl bromide (CAS 507-19-7), 1-bromo-2,2-dimethylpropane (CAS 630-17-1), 2-bromotetrahydrofuran (CAS 59253-21-3), 3-bromo-2,2,4,4-tetramethylpentane (CAS 107713-49-5).

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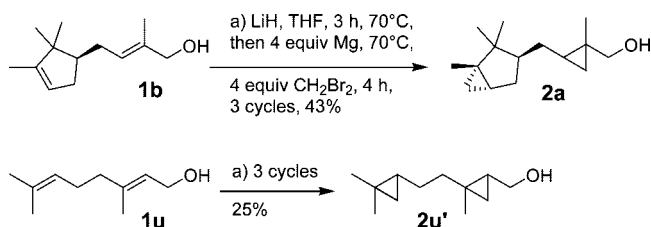
(29) Mariano, P. S.; Bay, E. J. *Org. Chem.* **1980**, 45, 1763–1769.

TABLE 6. Cyclopropanation under Barbier Conditions^a

Substrate ^b	Mg and CH ₂ Br ₂	Product ^c	Yield (dist) ^c	Purity ^d	syn / anti (mono / bis)
1b	3 equiv	2b/2a	65%	91% (3)	(75 : 20)
1g	6 equiv	2g	68%	84% (16)	97 : 3
1u	4 equiv	2u/2u'	66%	85% (5)	(71 : 24)
3b	6 equiv	4b	68%	93% (3)	73 : 27

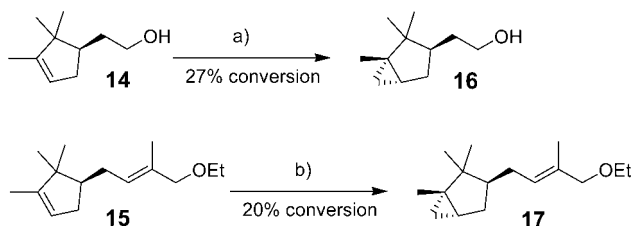
^a Deprotonation with BuLi (0 °C, 30 min) or LiH (THF, 70 °C, 3 h) followed by addition of Mg and CH₂Br₂ at 70 °C. Stirred at this temperature until no further conversion was detected by GC. ^b Substrates are either commercially available (**1u**) or were prepared by literature procedures (**1b**, **1g**¹¹ and **3b**¹²). ^c Yields after distillation corrected by purity. ^d Determined by GC/MS of the crude product after workup. % = syn + anti. Percentage of nonconverted substrate in brackets. ^e For the precise structures of **2a**, **2b**, **2u**, and **2u'** see Table 2, Table 7, and Scheme 10.

SCHEME 10. Remote Cyclopropanation of *nor*-Radjanol **1b**¹¹ and Geraniol **1u** under Barbier Conditions^a



^a Yields after distillation corrected by purity.

SCHEME 11. Partial Cyclopropanation of **14**¹¹ and **15**¹¹ under Barbier Condition Giving **16**¹¹ and **17**, respectively^a



^a Reference compound **17** was prepared from **1a**¹¹ by ethylation with NaH, EtI (see SI): (a) Conditions as in Scheme 10. (b) Same conditions but without prior deprotonation. GC-conversions.

100 °C above the decomposition temperature (−55 °C) of carbenoid BrCH₂MgBr reported by Villiéras.⁸

Cyclopropanation of substrate **1b** under Grignard conditions (Table 2) had not only given allylic cyclopropanation product **2b**, but also traces (1–4%) of the remote cyclopropanation product **2a**. Under Barbier conditions, a much higher content (20%) of remote cyclopropanation product **2a** was obtained. The **2ab** mixture could be completely converted to **2a** after application of another two reaction cycles (Scheme 11). The same bis-cyclopropanation strategy was applied to geraniol **1u**, which gave **2u'** via intermediate **2u** after three reaction cycles (Scheme 10).

Remote cyclopropanation seems to be effected directly by BrMgCH₂Br under Barbier conditions and not by a ROMgCH₂X type carbenoid such as **13** (Scheme 10) because the *trans*-configured cyclopentane **2a** was obtained,³² as well as the *trans*-configured products **16** and **17** from **14** and **15**, respectively (Scheme 11).

Not surprisingly the more sensitive tertiary allylic alcoholates **6** gave mainly decomposition (elimination) and only traces of cyclopropylcarbinols **8** under the relatively harsh Barbier conditions.³³

Substrates, Substitution Pattern, and Counterion. All substrates are either commercially available or can be prepared by known procedures (see the legends of schemes and tables). The substitution pattern has a profound effect upon the reaction rates, especially when magnesium alcoholates **6** (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 (Figure 1), are necessary to achieve high conversions through subsequent addition of 3–4 equiv of CH₂Br₂ and *t*BuMgCl.³⁴

Allyl alcoholates **6** lacking this substitution pattern gave only partial conversions under these conditions. These could be brought to completion by subjecting the crude substrate/product

(30) (**1r**) Ullrich, F. W.; Rotscheidt, K.; Breitmaier, E. *Chem. Ber* **1986**, *119*, 1737–1744. (**1s**) Traas, P. C.; Boelens, H. *Rec. Trav. Chim. Pays -Bas* **1973**, *92*, 985–995. (**1t**) Arbuzov, B. A.; Isaeva, Z. G.; Timoshina, T. N.; Efremov, Y. Y. *R. J. Org. Chem.* **1993**, *29*, 1647–1650.

(31) Alternative deprotonation reagents such as NaH or MeMgCl were less efficient. Alternative dihalides such as ClCH₂Br, ClCH₂I, and CH₂I converted **1b** similarly to **2b** but without remote cyclopropanation to **2a**. Evidence for exchange reactions between lithium alkoxides and Grignard reagents: Micha-Screttas, M.; Constantinou, G.; Steele, B. R.; Heropoulos, G. A. *Tetrahedron Lett.* **2002**, *43*, 4871–4873.

(32) The *trans*-configuration of the 5-ring carbacycles **2a** and **21** cannot arise from hypothetical 8- or 10-membered carbenoid transition states.

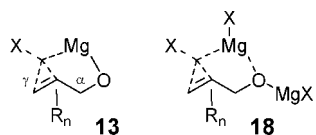
(33) MeLi addition to **7b** followed by addition of Mg and CH₂Br₂ at reflux gave only traces of **8b**.

(34) For the mention of similar effects see ref 7b. A probable correlation between substitution pattern, conformation, and reactivity of the (homo)allylic alcohols is presently under investigation and will be communicated in due course.

TABLE 7. Cyclopropanation of Lithium Allylic Alcoholates in Comparison to the Cyclopropanation of the Corresponding Magnesium–Ate Complexes

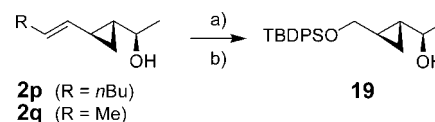
Substrate ^a	R	Product	A) Conversion after MeMgCl deprotonation ^b	B) Conversion after BuLi deprotonation ^b	Yield ^c from method B
1u 	γ,γ	2u 	60% (4 equiv)	93% (4 equiv)	73% (dist)
1v 	γ	2v 	29% (6 equiv)	93% (6 equiv)	94% (dist)
1w 	α	2w 	95% (5 equiv)	100% (6 equiv)	98% (dist)
1x 	γ	2x 	44% (5 equiv)	81% (4 equiv)	54% (dist)
1y 	α,α	2y 	47% (5 equiv)	100% (5 equiv)	80% (dist)
1z 	α,α	2z 	41% (5 equiv)	100% (5 equiv)	85% (dist)
3b 	homo-allylic	4b 	75% (6 equiv)	100% (5 equiv)	98% (dist)
3e 	homo-allylic	4e 	15% (4 equiv) ^e	91% (6 equiv) ^e	59% (dist)

^a Substrates **1** are commercially available, for the preparation of **3b** see ref 13. ^b Equivalents of CH₂Br₂ and *t*BuMgCl in brackets. ^c Yield after distillation. ^d Decomposition after addition of ≥ 5 equiv. ^e 50% conversion after addition of 4 equiv of CH₂Br₂ and *t*BuMgCl.

**FIGURE 3.** X = Cl, Br. R = alkyl, aryl, alkenyl. *n* = 1–5 at C_α, C_β, C_γ. Covalently bonded allyloxy magnesium carbenoid (transition state **13**) versus XMgCH₂X carbenoid coordinated to allyloxy-MgX (transition state **18**).

mixture (after workup) to another cyclopropanation cycle. More substituents such as those in tri- or tetrasubstituted alkenes were tolerated.

The cyclopropanation of homoallylic alcohols **3** was more sensitive to number and position of substituents (Figure 2). **3c** underwent no cyclopropanation, in strong contrast to the excellent conversion of **3a**. Whereas *Z*-hept-4-en-2-ol **3b** gave an acceptable conversion to **4b**, homoallylic alcohols **3d–f** were less reactive or unreactive.³⁴

SCHEME 12. Transformation of **2p** and **2q** to **19^a**

^a Reagents and conditions: (a) MeOH, CH₂Cl₂, −78 °C, O₃, then 2 equiv of NaBH₄. (b) NaH, THF, −20 °C, 1.5 h, then TBPSCl, −20 °C, 2.5 h.

Encouraged by the better performance of lithiated (**6**, M = Li) rather than magnesiated tertiary allylic alcoholates 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 alcohols³⁴ were deprotonated with 1.3 equiv of BuLi and cyclopropanated in situ with CH₂Br₂ and *t*BuMgCl (Table 7). Again, this gave much better and often complete conversions. A possible explanation for this rate enhancement is the more covalent character of the Mg–O bond of the MgX–

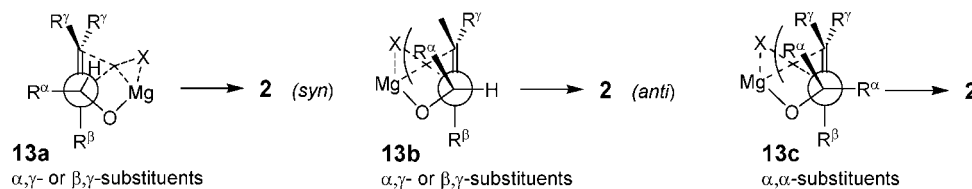
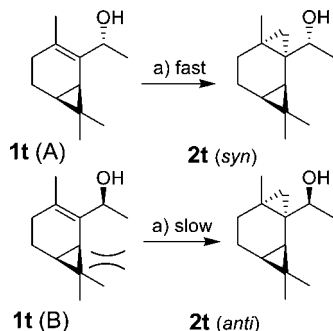


FIGURE 4. Staggered Houk models of **13**, according to refs 7b and 39. X = Cl, Br. Repulsive interaction by 1,2-allyl strain, 1,3-allyl strain, and between R^α and the carbenoid. R^γ = alkyl or H with at least one R^γ = alkyl. Higher substitution grades as well as higher magnesium aggregates are possible.

SCHEME 13. Formation of the *Syn/Anti* Mixture **2t** from **1t^a**



^a Reagents: (a) MeLi, then 3 $\times$ $\text{CH}_2\text{Br}_2/\text{tBuMgCl}$, 57%.

alcoholates (**6**, $M = \text{MgX}$, Scheme 9) versus the lithium alcoholate ion pair (**6**, $M = \text{Li}$, Scheme 9). The latter undergoes an exchange reaction of alcoholate **6** with carbenoid XMgCH_2X to allyloxy magnesium carbenoid **13** (Scheme 9) more readily.³⁶ Improved reaction rates have also been reported from the in situ cyclopropanation of lithiated tertiary allylic alcohols under Simmons–Smith conditions.¹⁵

Allylic ethers such as **15** and **17** (Scheme 11) cannot undergo cyclopropanation anymore, neither under Grignard nor under Barbier conditions, because carbenoid **13** cannot be formed. This is a significant difference compared to certain Simmons–Smith-like systems, which do cyclopropanate allylic ethers.³⁷ In this context we prefer transition state **13** (generated by a Li–Mg ate exchange reaction) over **18** (Figure 3) because if **18** would be effective, allylethers such as **15** and **17** also should be cyclopropanated to a certain extent, which is not the case.

Syn-Configuration of the Cyclopropylcarbinol Products. Cyclopropanation of α,γ -substituted allyl alcoholates **6** gave cyclopropyl carbinols, which were mainly (>80%) or exclusively (>99%) *syn* configured. 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

$r_T(\text{anti}) < r_T(\text{syn})$ on polar GC columns.³⁸ This analytical method has been used by others for the determination of the relative configuration of these compounds.³⁹ We routinely found the same elution order on a less polar GC column.⁴⁰ The relative configuration of all cyclopropyl carbinols was also routinely analyzed by NMR (NOESY, COSY, HMBC, and HMQC). This was especially necessary in the case of exocyclic *syn/anti* mixtures, e.g. **2e** and **12c**, which were inseparable by our GC method, and in the case of diastereopure cyclopropyl carbinols. If the NOESY experiment in water-free DMSO (to detect the OH-proton)⁴¹ gave ambiguous 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 analysis after crystallization (see SI). The *syn*-configuration of γ -alkenylcyclopropyl carbinols **2p** and **2q** (where all these methods failed) was determined after conversion to the known *syn*-TBDPS ether **19** (Scheme 12) and NMR comparison.⁴²

A staggered Houk model such as **13a** (Figure 4)⁴⁴ explains the formation of *syn*-isomers from cyclopropanation reactions with Mg-, Sm-, and Zn-allyloxy carbenoids.^{7b,28,39} In this model (**13a**) R^α occupies the most favorable position antiperiplanar to the incoming carbenoid to minimize steric interaction between R^α and R^γ . It was proposed that hyperconjugation between the $\sigma_{\text{C}(\alpha)-\text{C}(\text{R}^\alpha)}$ and the $\pi-\pi^*$ orbitals enhances the nucleophilicity of the olefin.²⁸

The cyclopropanation under relatively simple Grignard conditions gives higher *syn*-selectivities at ambient or higher temperatures than by other methods at lower ($-10\text{ }^\circ\text{C}$)^{38,39a} or much lower temperatures ($-78\text{ }^\circ\text{C}$).^{39b,c} *Anti*-byproducts (<20%) were detected in the case of the smallest substituent ($R^\alpha = \text{Me}$), where interaction between R^α and the incoming carbenoid is minimized, thus allowing transition state **13b**. Already with the first higher substituent $R^\alpha = \text{Et}$, this effect was negligible (see **2h**). Similarly, it can be explained why tertiary allyl alcohols are tricky cyclopropanation substrates. Here (**13c**), interaction between R^α and the carbenoid cannot be avoided,^{39b,c} and a shift to the less encumbered **13a** is structurally forbidden.

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(36) Excess $n\text{BuLi}$ cannot be responsible for the better conversion because the attempted cyclopropanation of the lithium alcoholates **6** with $\text{CH}_2\text{Br}_2/\text{BuLi}$ or $\text{CH}_2\text{Br}_2/\text{tBuLi}$ failed. Exchange reactions of lithium or magnesium alcoholates with Grignard reagents are well-known, see for example: Nützel, K. In *Houben-Weyl, Methoden der Organischen Chemie*; Müller, E. Ed.; Georg Thieme Verlag: Stuttgart, Germany, 1973; Vol. XIII/2a, pp 193–194.

(37) (a) Morikawa, T.; Sasaki, H.; Hanai, R.; Shibuya, A.; Taguchi, T. *J. Org. Chem.* **1994**, 59, 97–103. (b) Barret, A. G. M.; Kasdorf, K.; Williams, D. *J. Chem. Commun.* **1994**, 1781–1782. (c) Charette, A. B.; Lebel, H. *J. Org. Chem.* **1995**, 60, 2966–2967. (d) Charette, A. B.; Lacasse, M.-C. *Org. Lett.* **2002**, 4, 3351–3353.

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(39) (a) Ratier, M.; Castaing, M.; Godet, J.-Y.; Pereyre, M. *J. Chem. Res. (S)* **1978**, 179. (b) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, 52, 3942–3944. (c) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, 54, 3525–3532. (40) GC analysis on a 5% phenyl–95% dimethylpolysiloxane column.

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(42) Yamamoto, T.; Matsuda, A.; Shuto, S. *Tetrahedron* **2004**, 60, 6689–6703. Yamamoto, T.; Matsuda, A.; Shuto, S. *J. Org. Chem.* **2003**, 68, 3511–3521.

(43) Paddon-Row, M. N.; Rondan, N. G.; Houk, K. N. *J. Am. Chem. Soc.* **1982**, 104, 7162–7166.

(44) Commercial Citral was purified by distillation over a Sulzer column to afford a geranial/neral 88:12 mixture.

Whereas good to excellent *syn*-selectivities can be expected from this method, the cyclopropanation of **1t** (see also Table 5) represents an exception. Because the *syn/anti* diastereomers of **2t** are formed in nearly equal amounts from a 1:1 diastereomer mixture of **1t**, the *anti*-diastereomer of **2t** must be formed from diastereomer B of **1t** exclusively (Scheme 13). Repulsive interaction of the *gem*-dimethyl group with the incoming carbenoid hinders the cyclopropanation from the β -face and explains why the *syn*-diastereomer is formed much faster than the *anti*-diastereomer.

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 vinyl oxiranes, to give cyclopropyl carbinols with *syn*-stereochemistry and good yields. We are confident that this method will find its use in preparative organic chemistry.

Experimental Section

(1-Methyl-2-(((1*S*,3*R*,5*R*)-1,2,2-trimethylbicyclo[3.1.0]hexan-3-yl)methyl)-cyclopropyl)methanol (Javanol) (2a). Method A. *nor*-Radjanol **1b** (200 g, 1 mol)¹¹ and lithium hydride (10 g, 1.24 mol) [see Method A1 below] in tetrahydrofuran are heated under strong stirring and argon for 6 h at 65 °C until hydrogen evolution ceases. Magnesium turnings (100 g, 4.1 mol) and 1900 mL of tetrahydrofuran are added at 25 °C. After addition of dibromomethane (8.5 g, 50 mmol) the mixture is heated to 65 °C, and dibromomethane (280 mL, 4 mol) is added over 7 h. After another hour at 65 °C the suspension is quenched with 2 M HCl under cooling. *tert*-Butyl methyl ether extraction, washing of the organic phase with H₂O until pH 7, drying over MgSO₄, and concentration gives a crude (65% corr.) mono- and bicyclopropane mixture (**2a/2b** = 20:75) which, after two further reaction cycles, gives 95 g (43%) of pure Javanol **2a** after distillation (100 °C/0.05 Torr), whose analytical data (NMR, MS, IR, odor) are consistent with the ones described for this compound in the literature.⁶

Method A1. Alternative deprotonation with 1.6 M *n*-butyllithium in hexane (775 mL, 1.24 mol) followed by cyclopropanation under the conditions in method A gave similar yields.

Method B. Allyl alcohol **1a** (5 g, 24 mmol)¹¹ is added under cooling and stirring to 3 M methylmagnesium chloride in tetrahydrofuran (8 mL, 24 mmol) under nitrogen. This is followed by three additions of both dibromomethane (4.2 g) and *tert*-butylmagnesium chloride 2 M in diethyl ether (12 mL) in that order at 10–20 °C (making a total of 72 mmol each). Quenching with concentrated NH₄Cl, *tert*-butyl methyl ether extraction, washing of the organic phase with H₂O until pH 7, drying over MgSO₄, and concentration gives 16.6 g of an oily residue, which is bulb-to-bulb distilled at

120 °C/0.07 Torr giving 4.7 g (89%) of Javanol **2a** (dr = 1:1), whose analytical data are consistent with those described for this compound in the literature.⁶

(*syn,trans*)-1-((*E*)-2-Methyl-2-(4-methylpent-3-enyl)cyclopropyl)-ethanol (2f). Prepared from (a) **1f** (3.6 g, 24 mmol)¹¹ and 3 M methylmagnesium chloride in THF (8 mL, 24 mmol), or (b) (*E*)-Citral (4 g, 24 mmol)⁴⁴ and 3 M methylmagnesium chloride in THF (8 mL, 24 mmol), or (c) **9a** (5 g, 24 mmol)²⁰ and 3 M methylmagnesium chloride in THF (19 mL, 60 mmol), or (d) **9b** (6 g, 24 mmol)²¹ and 3 M methylmagnesium chloride in THF (25 mL, 60 mmol). Subsequent cyclopropanation of the alcoholate thus prepared (a–d) by portionwise addition of dibromomethane (3 × 4.2 g, 72 mmol) and 2 M *tert*-butylmagnesium chloride in diethyl ether (3 × 12 mL, 72 mmol) according to method B. Workup after 16 h at 25 °C and bulb-to-bulb distillation gives 3.7 g (86%) of product. Odour: citrus, weak. Analytical data are identical with those reported for this compound.^{39c} The *syn*-configuration was also confirmed by COSY, HSQC, and NOESY in CDCl₃.

(*syn*)-1-(2-Methylcyclopropyl)-octan-1-ol (2l). Heptyl magnesiumbromide was prepared from heptyl bromide (26 g, 0.14 mol) and magnesium (3.43 g, 0.14 mol) in tetrahydrofuran (68 mL) at 70 °C. This Grignard reagent was used in the preparation of **2l** from heptyl magnesiumbromide and *E*-crotonaldehyde (8.4 g, 0.12 mol) in tetrahydrofuran, dibromomethane (62.5 g, 0.36 mol), and 2 M *tert*-butylmagnesium chloride in diethyl ether (3 × 60 mL, 0.36 mol) at 10–20 °C according to method B. Workup and distillation at 60 °C/0.04 Torr gave 24.4 g (86%) of the *trans*-isomer as a colorless oil. Odour: green, earthy, substantive.

Alternatively, this compound was prepared by Grignard reaction of octanal (18 g, 0.14 mol) with *E/Z*-1-propenyl magnesiumbromide (prepared from magnesium (3.8 g, 0.14 mol), 1-bromopropene (17 g, 0.14 mol) in tetrahydrofuran (60 mL) at 60 °C), followed by tandem cyclopropanation and workup as described above giving 23.5 g (83%) of **2l** (*cis/trans* = 1:1).

¹H NMR (CDCl₃) (*trans*-isomer): δ 0.25 (m, 1 H), 0.4 (m, 1 H), 0.6 (m, 1 H), 0.9 (t, 3 H), 1.05 (d, 3 H), 1.2–1.45 (10 H), 1.5–1.55 (3 H), 2.88 (m, 1 H) ppm. ¹³C NMR (CDCl₃) (*trans*-isomer): δ 10.7 (t), 11.15 (d), 14.1 (q), 18.3 (q), 22.6 (t), 25.7 (t), 26.9 (d), 29.3 (t), 29.7 (t), 31.8 (t), 37.4 (t), 76.4 (d). The *syn*-configuration was confirmed by NMR analysis of the benzyl ether (see SI). MS (EI): *m/z* (%) 166 ([M – 18]⁺, 2), 85 (100), 67 (32), 57 (50), 55 (30), 43 (42), 41 (45). IR (film): 3355 (br), 2953 (m), 2924 (s), 2855 (m), 1455 (m), 1379 (w), 1269 (w), 1075 (w), 1046 (w), 1029 (m), 895 (w), 866 (w), 788 (w), 722 (w). Anal. Calcd for C₁₂H₂₄O: C, 78.20; H, 13.12. Found: C, 78.13; H, 13.02.

(*cis, syn*)-1-(2-Ethylcyclopropyl)propan-2-ol (4b). **4b** was prepared as described in method B but in two reaction cycles from (*Z*)-hept-4-en-2-ol (4 g, 35 mmol) and dibromomethane (2 × 18.2 g, 0.2 mol) in diethyl ether by dropwise addition of 2 M *tert*-butylmagnesium chloride in diethyl ether (2 × 52 mL, 0.2 mol) at 10–20 °C. After complete conversion the mixture is quenched with 2 M HCl and extracted with *tert*-butyl methyl ether. Washing with concentrated NaHCO₃ and concentrated NaCl, drying over MgSO₄, filtration, and evaporation of the solvent gives 5.7 g of a crude oil, which is distilled at 100 °C/10 mbar giving 2.5 g (55%) of a colorless oil (97% purity, *syn/anti* = 83:17).

Alternatively it can be prepared (method A1) from (*Z*)-hept-4-en-2-ol (3 g, 26 mmol),¹² *n*-butyllithium (16.5 mL, 26 mmol), magnesium powder (3.8 g, 0.16 mol), and dibromomethane (27 g, 0.16 mol). Workup and distillation as above gives 2.1 g (57% corr) of a colorless oil (*syn/anti* = 73:27).

It also can be prepared by dropwise addition of 1.6 M *n*-butyllithium in hexane (15.4 mL, 24 mmol) to (*Z*)-hept-4-en-2-ol (2 g, 18 mmol)¹² in 10 mL of tetrahydrofuran under cooling, followed by portionwise addition of dibromomethane (5 × 1.25 mL, 90 mmol) and 2 M *tert*-butylmagnesium chloride in diethyl ether (5 × 8.8 mL, 90 mmol) at 10–20 °C as described in method B. Workup and distillation as above gives 2.2 g (98%) of a colorless oil.

^1H NMR (CDCl_3): δ -0.2 (m, 1 H), 0.6 – 0.8 (2 m, 2 H), 1.0 (t, 3H), 1.2 (d, 3 H), 1.2–1.4 (3 H), 1.6 (1 H), 2.3 (br, OH), 3.9 (m, 1 H) ppm. ^{13}C NMR (*syn*-isomer): δ 10.5 (t), 12.4 (d), 14.2 (q), 16.6 (d), 22.0 (t), 23.0 (q), 37.8 (t), 68.8 (d). ^{13}C NMR (*anti*-isomer): δ 10.5 (t), 12.3 (d), 14.2 (q), 17.3 (d), 22.1 (t), 23.1 (q), 37.9 (t), 68.6 (d). The *syn*-configuration was confirmed by conversion to the camphanoyl ester and X-ray analysis (see SI). MS (EI): m/z (%) 110 ($[\text{M} - 18]^+$, 3), 95 (12), 84 (11), 81 (20), 68 (23), 55 (50), 45 (100). R_T = 5.82 (*syn*), 5.86 (*anti*) min. IR (film): 3340 (br), 2961 (s), 2929 (m), 2872 (m), 1456 (m), 1374 (m), 1308 (w), 1120 (m), 1084 (m), 1063 (m), 1022 (m), 994 (w), 940 (m), 927 (m), 855 (w), 815 (w), 739 (w). HRMS calcd for $\text{C}_7\text{H}_{13}\text{O}$ [$\text{M} - 15$] 113.09664, found 113.09541.

(*cis*)-5-Isopropyl-2-methylbicyclo[3.1.0]hexan-2-ol (8a). 8a was prepared from **7a**,¹⁸ and 1.6 M methylolithium in diethyl ether (2.8 mL, 4.5 mmol) at -78°C , followed by addition of dibromomethane (2.8 g, 16 mmol) and dropwise addition of 2 M *tert*-butylmagnesium chloride in diethyl ether (8 mL, 16 mmol) at 0 – 10°C . Inverse quench on concentrated NH_4Cl after 6 h, *tert*-butyl methyl ether extraction, and flash chromatography over silica gel (hexane/*tert*-butyl methyl ether 3:1) gave 0.23 g (45%) of a colorless oil. MS (EI): m/z (%) 196 (M^+ , 5), 139 ($[\text{M} - 15]^+$, 14), 136 ($[\text{M} - 18]^+$, 29), 121 (38), 107 (12), 93 (100), 71 (60), 55 (34), 43 (85). The other analytical data were identical with the ones reported for this compound.¹⁵

(1*SR*,3*RS*,4*RS*)-1-Pentylspiro[2.7]decan-4-ol (12c). **11c** (3 g, 18 mmol)²⁴ is added dropwise to 1.6 M *n*-butyllithium in hexane (11 mL, 18 mmol) in diethyl ether (20 mL) at -78°C . After 1 h at -78°C the solution is slowly warmed to room temperature. Dibromomethane (12.5 g, 72 mmol) is added followed by dropwise addition of *tert*-butylmagnesium chloride (36 mL, 72 mmol) at 10 – 20°C . After 24 h at 25°C the mixture is poured upon 2 M HCl. Extraction with *tert*-butyl methyl ether, washing of the organic phase with concentrated NaHCO_3 and concentrated NaCl, drying

over MgSO_4 , filtration, and evaporation of the solvents give a residue that is purified by bulb-to-bulb distillation at $98^\circ\text{C}/0.05$ mbar giving 2.6 g (65%) of a colorless oil (dr = 93:7). ^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 (22 H), 3.25 (1 H) ppm. ^{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). The Δ^3 -*cis*-configuration is assigned by COSY, HMBC, HSQC, and NOESY in $\text{DMSO}-d_6$. MS (EI): m/z (%) 224 (M^+ , 1), 206 ($[\text{M} - 18]^+$, 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). IR (film): 3362 (br, OH), 2919 (s), 2852 (m), 1456 (m), 1364 (w), 1106 (w), 1029 (m), 989 (m), 811 (w), 741 (w), 726 (w). HRMS calcd for $\text{C}_{15}\text{H}_{28}\text{O}$ 224.21402, found 224.21737. HRMS calcd for $\text{C}_{15}\text{H}_{26}$ 206.20345, found 206.20372.

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Supporting Information Available: Experimental procedures and analytical data for all new compounds. This material is available free of charge via the Internet at <http://pubs.acs.org>.

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