DOI: 10.1002/ejoc.201100528

Transition-Metal-Catalyzed Cyclopropanation of Nonactivated Alkenes in Dibromomethane with Triisobutylaluminum

Gerhard Brunner,[a] Susanne Elmer,[a][‡] and Fridtjof Schröder*[a]

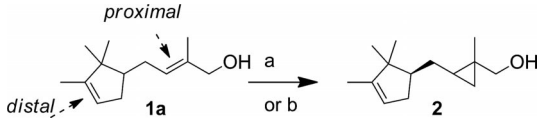
Keywords: Alkenes / Aluminum / Carbenoids / Fragrances / Regioselectivity / Solvent effects / Synthetic methods / Terpenoids

The cyclopropanation of nonactivated alkenes with inexpensive triisobutylaluminum (TIBA), in dibromomethane as solvent and reagent, is efficiently catalyzed by $FeCl_3$ at ambient temperature. Catalytic amounts of Cu^I salts, $CpTiCl_3$, and $[CpFe(CO)_2]_2$ are similarly effective. 2-Methylpropane, generated after quench of excess TIBA can be trapped, and excess dibromomethane can be recycled, which makes the method industrially applicable. Solvent-free DIBAH or TIBA reduction of unsaturated carbonyl compounds, followed by in situ TIBA cyclopropanation of the unsaturated aluminum alcoholates in dibromomethane give cyclopropyl alkanols. Dienols such as geraniol, linalool or *nor*-radjanol are selectively cyclopropanated in their distal position, which allows the synthesis of flavor and fragrance compounds such as Δ-citral, *cis*-javanol, and 7-methyl-georgywood. Uncontrollable exothermic events are avoided due to relatively low reaction temperatures made possible by the catalysts and by the addition mode of the reagents.[1]

Introduction

The Simmons–Smith cyclopropanation and its variations are widely used for the conversion of alkenes to cyclopropanes, especially with carbenoids of the general structure MCH_2X (M = Zn, Al, Sm, and Cu).[2] For processes on a larger scale, however, the requirement for stoichiometric amounts of environmentally problematic, expensive, and/or pyrophoric metal reagents is a disadvantage.[3] Therefore, we turned our attention to dibromomethane, a much less expensive and more easily purified and stored reagent. Efficient cyclopropanation reactions with CH_2Br_2, however, are scarce due to its low reactivity in these reactions.[4] Nevertheless, CH_2Br_2 was successfully employed by Friedrich,[5] who activated zinc and copper(I) chloride in the presence of CH_2Br_2 and the alkene substrate, either by ultrasound[5a] or by addition of acetyl halides[5b] to facilitate carbenoid formation, and various alkenes have been cyclopropanated under these conditions.[5,6] The large amounts of zinc and especially the ecotoxic copper wastes produced by this method, however, prompted us to look for alternative methods. In this context we have recently developed a cyclopropanation under Grignard conditions that uses dibromomethane as carbenoid precursor (Scheme 1).[7]

This method selectively cyclopropanates allylic alcoholates, such as the proximal[8] double bond of **1a**, simply and rapidly with inexpensive reagents, and has positive environmental aspects. The cyclopropanation of nonactivated alkenes, such as the distal[8] double bond of *nor*-radjanol (**1a**), however, was less efficient under both the Grignard (≤ 2% conversion) and the more drastic Barbier variation of this method (≤ 20% conversion). We were therefore interested in a similarly robust method to cyclopropanate nonactivated (distal) alkenes under copper-, zinc- and iodine-free conditions, using inexpensive solvents and (organo)metallic reagents that can be handled and discarded without excessive precautions.



Scheme 1. Proximal cyclopropanation of *nor*-radjanol (**1a**): (a) *t*BuMgCl, CH_2Br_2, Et_2O, THF, 10–20 °C; (b) Mg, CH_2Br_2, THF, 60 °C.

Results

Cyclopropanation with TIBA in Dibromomethane

Nonactivated alkenes have been efficiently cyclopropanated with $Zn/Cu/CH_2I_2$ (Simmons–Smith), $ZnEt_2/CH_2I_2$ (Furakawa), $Zn/CuBr/CH_2Br_2$ (Friedrich) or AlR_3/CH_2I_2 (Yamamoto) systems.[2] The attractive[9] combination AlR_3/CH_2Br_2 was unknown at the beginning of our studies and commented as "with diethylzinc and triethylaluminum, dibromomethane has not been reported to react".[5c] Indeed,

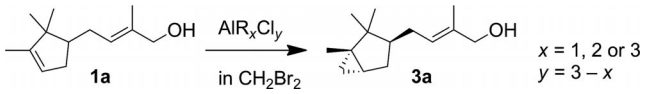
[a] Research Chemistry Department, Givaudan Schweiz AG, 8600 Dübendorf, Switzerland
E-mail: fridtjof.schroeder@givaudan.com
[‡] New address: Novartis Pharma AG, Klybeckstrasse 141, 4057 Basel, Switzerland

Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/ejoc.201100528.

we observed by ^1H NMR spectroscopy that CH_2Br_2 and $AlEt_3$ are inert in [D_{12}]cyclohexane up to 70 °C, whereas $AlEt_3$ and CH_2I_2 rapidly react/decompose already at 25 °C. Accordingly, *nor*-radjanol (**1a**) underwent no conversion with excess $AlEt_3$ and CH_2Br_2 in hexane at 75 °C. Nevertheless, with neat $AlEt_3$ (Table 1, Runs 5 and 6) in CH_2Br_2 a 30% distal monocyclopropanation to **3a** was observed. The more Lewis acidic $AlMe_3$, Et_2AlCl, and $EtAlCl_2$ gave decomposition (Runs 1–3), other Lewis acids such as $(i\text{Bu})_2$AlF or DIBAH were not reactive enough (Run 4). Higher trialkylaluminum compounds such as Al(nPr)$_3$ (Run 8) and Al(iBu)$_3$ (Run 9) gave by far the best conversions to **3a**, Al(nOct)$_3$ (Run 7) was slightly less reactive than $AlEt_3$ [Equation (1)].

$$Al(i\text{Bu})_3 \approx Al(n\text{Pr})_3 >> AlEt_3 > Al(n\text{Oct})_3 \quad (1)$$

Table 1. Cyclopropanation of **1a** with organoaluminum compounds in CH_2Br_2 as solvent.[a]



Run	Organoaluminum reagent	T	t	GC conversion[b]
1	$AlMe_3$	70 °C	1 h	decomposition
2	$EtAlCl_2$	25 °C	1 h	decomposition
3	Et_2AlCl	50 °C	2 h	decomposition
4	DIBAH or $(i\text{Bu})_2$AlF	70–85 °C	1–6 h	no conversion
5	$AlEt_3$	95 °C	2 h	36%[c]
6	$AlEt_3$	70 °C	22 h	57%[c]
7	Al(n-octyl)$_3$	70 °C	3 h	30%[c]
8	Al(nPr)$_3$[d]	70 °C	6 h	91%
9	Al(iBu)$_3$	70 °C	4 h	96%

[a] *nor*-Radjanol (**1a**)[6] and 4 equiv. organoaluminum reagent dissolved in 30 equiv. of CH_2Br_2 and heated to reaction temperature. [b] Relative peak area: product/(substrate + product) × 100. [c] Accompanied by decomposition. [d] 2.5 equiv. of Al(nPr)$_3$.

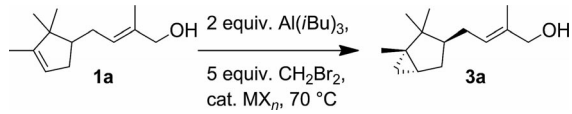
The trialkylaluminum reagents had to be added neat, cosolvents such as dichloromethane and hexane slowed the reaction, whereas Lewis bases such as THF or NEt_3 suppressed the reaction completely. We continued our studies with the readily available and inexpensive Al(iBu)$_3$, which can be handled neat by obeying the usual precautions.[10] The temperature, however, had to be carefully monitored during the cyclopropanation reaction, especially at the stage of nearly complete conversion to **3a**, where at ≥ 80 °C critical runaway situations[11] were encountered (vide infra the mechanistic discussion for details).

Table 2 shows that good yields and purities of **3a** were obtained by running the cyclopropanation with smaller amounts (2.5 equiv.) of Al(iBu)$_3$ in an excess (85 equiv.) of CH_2Br_2 (Run 1) or with larger amounts (3–4 equiv.) of Al(iBu)$_3$ in less CH_2Br_2 (20 equiv.) and quench of the latter system at nearly completed conversion to **3a** before decomposition sets in (Run 3).

Cyclopropanation with TIBA in Dibromomethane Catalyzed by Transition-Metal Complexes

Zinc- or Et_2Zn-promoted cyclopropanation reactions have been accelerated by the addition of Brønsted[12] or Lewis acids.[5,13] Through screening of different additives with the TIBA/CH_2Br_2 system for the cyclopropanation of *nor*-radjanol (**1a**) at 70 °C we found that metal halides such as $CuBr_2$, CuCl, CuBr, and $FeCl_3$ significantly accelerated the reaction (Table 3) in relatively low amounts of dibromomethane (5 equiv. instead of 30 equiv.) compared to a control reaction in the absence of these catalysts (Run 1). However, sudden and exothermic decomposition of the reaction mass at the end of the cyclopropanation reaction was still a problem, as was incomplete conversion of substrate **1a**.

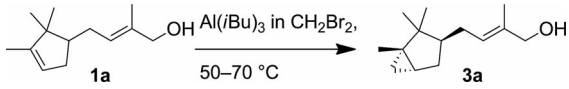
Table 3. Cyclopropanation of **1a**[a] with 2 equiv. of Al(iBu)$_3$ in 5 equiv. of CH_2Br_2 and with catalytic amounts of metal halides MX_n.



Run	MX_n	Catalyst amount	t	GC conversion[b]
1	none	none	3.5 h	7%
2	$CuBr_2$	15 mol-%	2 h	89%
2	CuBr	5 mol-%	4 h	91%
3	CuCl	10 mol-%	2 h	90%
4	$FeCl_3$	5 mol-%	1 h	92%

[a] Preparation of **1a**: ref.[6] Dibromomethane used as solvent (and reagent). [b] Internal standard dodecane, relative peak area.

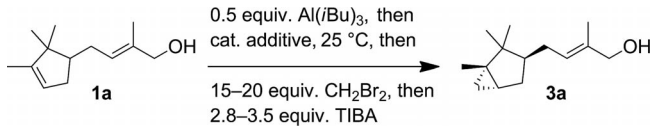
Table 2. Cyclopropanation of **1a** with Al(iBu)$_3$ in CH_2Br_2.[a]



Run	T	t	CH_2Br_2	Al(iBu)$_3$	Unconverted substrate **1a**	Yield of **3a** (dist., corr.)[b]	Purity (GC)	Volume yield[c]
1	50 °C	3.5 h	85 mol-equiv.	2.5 mol-equiv.	2%	86%	88%	2%
2	65 °C	3.5 h	30 mol-equiv.	3.2 mol-equiv.	3%	80%	84%	5%
3	70 °C	4.0 h	20 mol-equiv.	3.6 mol-equiv.	7%	76%	78%	6%

[a] *nor*-Radjanol (**1a**)[6] (10 g) and Al(iBu)$_3$ dissolved in CH_2Br_2 and heated to reaction temperature, which was maintained by slight external cooling. Inverse quench onto 30% NaOH at –20 °C, when no further conversion was detected by GC. [b] Yield after distillation, corrected by purity of substrate and product. [c] % product (in g) from maximal reaction volume (in mL, before quench).

Table 4. Cyclopropanation of **1a** with cat. additives, 2.8–3.5 equiv. of Al(*i*Bu)$_3$ in 15–20 equiv. of CH_2Br_2 at 25 °C.

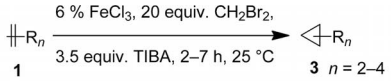


1a **3a**

Run	Al(*i*Bu)$_3$[a]	CH_2Br_2	Catalyst amount	*t*	*nor*-Radjanol (**1a**)[b]	Yield of **3a**[c]
1	3.2 equiv.	15 equiv.	6 mol-% $FeCl_3$	22 h	5%	86%
2	2.8 equiv.	20 equiv.	2 mol-% $FeCl_3$	6 h	3%	93%
3	3.5 equiv.	20 equiv.	6 mol-% $CpTiCl_3$	3 h	n.d.	85%
4	3.5 equiv.	20 equiv.	6 mol-% $FeCl_2$	4 h	1%	99%
5	3.5 equiv.	20 equiv.	6 mol-% $[CpFe(CO)_2]_2$	3 h	3%	93%

[a] GC of the crude product before distillation. [b] Preparation of **1a**: ref.[6] [c] Distilled and corrected by purity.

Table 5. $FeCl_3$-catalyzed cyclopropanation of alkenes **1** with Al(*i*Bu)$_3$ in dibromomethane.[a]



1 **3** *n* = 2–4

Substrate[a]	*t*	Product	Substrate **1**	Yield (dist.)[b]	GC purity[c]
1a	4 h	**3a**	9%	81%	93%
1b	3 h	**3b**	2%	85%	90%
1c	5 h	**3c**	9%	85%	91%
1d	6 h	**3d**	9%	81%	85%
1e	4 h	**3e**	3%	62%[d]	88%
1f	3 h	**3f**	1%	98%	98%
1g	4 h	**3g**	11%	86%	89%
1h	2 h	**3h**	none	59%	85%
1i	7 h	**3i**	46%	41%	93%
1j	20 h	**3j**	57%	51%	90%
1k	6 h	**3k**	5%	52%	84%
1l	6 h	**3l**	1%	30% (2 cycles)	97%
1m	5 h	**3m**	2%	38%[e]	97%
1n	18 h	**3n**	none	59% (2 cycles)	71%
1o	2 h	**3o**	none	83%	96%

[a] The substrates are either commercially available (**1d**–**f**,**h**–**l**,**n**,**o**) or were prepared according to the literature (**1a**,**b**,**g**,**m**).[20] For the cyclopropanation of additional substrates, see ref.[1a] [b] Corrected by purity. [c] After workup and distillation. Relative peak area. [d] Partially unstable to distillation. [e] 40 equiv. of CH_2Br_2.

We chose the environmentally most friendly $FeCl_3$ for further optimization, and found that 2% of $FeCl_3$ efficiently catalyzes the cyclopropanation of **1a** with 2.8–3.2 equiv. of Al(*i*Bu)$_3$ in 15–20 equiv. of dibromomethane at *ambient temperature* (Table 4, Runs 1 and 2). At this temperature, the reaction with smaller amounts of reagents (catalyst and 2 equiv. of TIBA in 5 equiv. of CH_2Br_2 as in Table 3) had been rather incomplete. $FeCl_2$, $CpTiCl_3$ and $[CpFe(CO)_2]_2$ were similarly efficient (Runs 3–5). In contrast to the non-catalyzed version (Table 1, Run 11) and due to the lower reaction temperature, the mixture is stable at the end of the conversion and can be kept for a few days as such.[14]

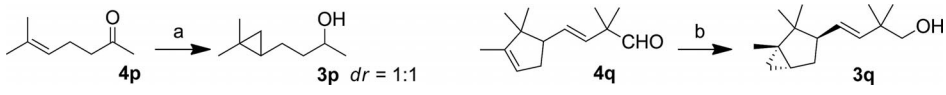
The addition mode is important to run the reaction safely: addition of cat. $FeCl_3$ to substrate **1a** dissolved in the full amount of Al(*i*Bu)$_3$ and CH_2Br_2 can cause uncontrollable exotherms,[15] whereas slow addition of Al(*i*Bu)$_3$ to the aluminum alcoholate of the substrate (e.g. of **1a**) *and* cat. $FeCl_3$ in dibromomethane is the method of choice.[16]

In summary we found with $CuBr_2$, CuBr, CuCl, $FeCl_3$, $FeCl_2$, $[CpFe(CO)_2]_2$, and $CpTiCl_3$ a series of catalysts that allows a safe and reproducible TIBA cyclopropanation of substrate **1a** in CH_2Br_2 at ambient temperature (Tables 3 and 4). Similar results were also obtained without catalyst, when using Al(*i*Bu)$_3$ from certain providers, but reproducibility was problematic. This may be due to metallic impurities in some samples that catalyze the reaction. The exact reason for the catalytic activity remains unclear, as closely related complexes could not be used for this purpose.[17]

Scope of the Reaction

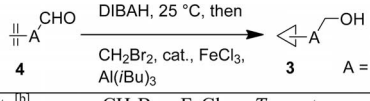
Alkenols **1a**–**h** (Table 5) underwent readily the $FeCl_3$-catalyzed TIBA cyclopropanation in CH_2Br_2 to give the corresponding cyclopropanols with good to excellent yields and purities. Tri- (**1a**,**b**,**f**,**g**) and tetra-substituted (**1c**) electron-rich alkenes are easily cyclopropanated, steric hindrance (as in **1a**–**c**) is not impairing. The cyclopropanation is distal-selective (as in **1a**, **1d** and **1e**) with allylic (proximal) cyclopropanation observed to a minor extent (≤ 3%). In case of terminal alkene **1h** concomitant reduction occurred[18] and produced some 2,6-dimethyloctan-2-ol (ca. 15%) as by-product. Isoeugenol (**1i**) and eugenol (**1j**) are less reactive substrates,[19] and gave only 50% conversions to the corresponding cyclopropanes **3i** and **3j**. Esters and lactones (**1k**–**m**) undergo side-reactions, such as ester reduction and the corresponding lactone cleavage, giving **3k**–**m** in only moderate yields (30–50%). Nitrile **1n** was another poorly reactive substrate, requiring two additional cycles for complete conversion to cyclopropane **3n**, and giving byproducts citral (**4e**) (8%) and alcohol **3e** (11%). Cyclododecene (**1o**), a substrate without a polar functional group, was smoothly converted to cyclopropane **3o**.

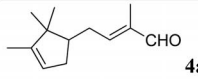
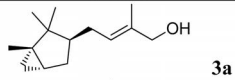
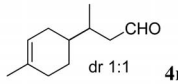
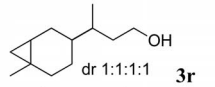
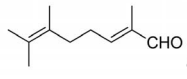
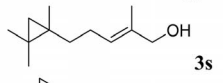
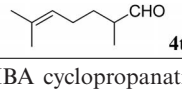
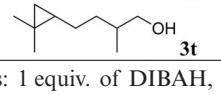
Unsaturated aldehydes or ketones **4** undergo under these conditions TIBA reduction,[21,22] and in situ cyclopropanation of the corresponding aluminum alcoholates. This obviates the need for an independent reduction step, which is often used to prepare the unsaturated alcohol substrates of



Scheme 2. Solvent-free TIBA reduction/cyclopropanation of unsaturated aldehydes and ketones. For the synthesis for aldehyde **4q**, see ref.[23] (a) 20 equiv. of CH_2Br_2, cat. $FeCl_3$, 3.5 equiv. of TIBA, 25 °C, 76% (dist.); (b) same conditions, 74% (crude).

Table 6. $FeCl_3$-catalyzed cyclopropanation of unsaturated aldehydes **4** with Al(*i*Bu)$_3$ in dibromomethane.[a]



Substrate[b]	CH_2Br_2	$FeCl_3$	T	t	Product	Yield[c]	GC purity[d]
 **4a**	30 equiv.	none	70 °C	6 h	 **3a**	86%	90%
 dr 1:1 **4r**	20 equiv.	6%	0 °C	2 h	 dr 1:1:1:1 **3r**	78 %	98%
 **4s**	20 equiv.	6%	20 °C	18 h	 **3s**	93%	80%
 **4t**	20 equiv.	6%	20 °C	5 h	 **3t**	98%	98%

[a] DIBAH reduction/TIBA cyclopropanation of unsaturated aldehydes: 1 equiv. of DIBAH, room temp., 2 h, then CH_2Br_2, then cat. $FeCl_3$, then 3–3.5 equiv. of TIBA. [b] Substrates: limonene aldehyde (**4r**) and melonal (**4t**) are commercial available, *nor*-radjaldehyde (**4a**) was prepared as described,[25] for **4s**, see ref.[26] [c] Corrected yield after distillation. [d] Relative peak area.

Table 5, e.g. **1a**,**b**,**e**,**f**, from α,β-unsaturated aldehyde precursors. Thus, TIBA reduction/cyclopropanation of unsaturated ketone **4p** gave readily cyclopropane alcohol **3p** (Scheme 2).

Whereas product **3q** was also obtained with relatively good purity by this method, sterically less shielded unsaturated aldehydes, such as **4a** suffered from partial isobutyl addition to the formyl group.[24] Solvent-free reduction with 1 equiv. of DIBAH at 0–25 °C, prior to the addition of excess CH_2Br_2, the catalyst, and TIBA was then the method of choice to give **3a** with good yield and purity (Table 6). Other unsaturated aldehydes (**4r**–**t**) were converted into the corresponding cyclopropane alcohols (**3r**–**t**) with similar efficiencies.

Discussion

Thermal Stability of the Reaction Mass

In analogy to the formation of Et_2AlCH_2I from CH_2I_2 and $AlEt_3$, as proposed by Yamamoto,[27] $(i\text{Bu})_2AlCH_2Br$ should be formed according to Equation (2).[28] Accordingly, NMR investigation of the reaction of CH_2Br_2 and $Al(i\text{Bu})_3$ in [D_{12}]cyclohexane showed conversion of CH_2Br_2 to *i*BuBr, with sudden decomposition of the components after 50% conversion.

$$CH_2Br_2 + Al(i\text{Bu})_3 \rightarrow i\text{BuBr} + (i\text{Bu})_2AlCH_2Br \quad (2)$$

Exothermic decomposition at the end of the cyclopropanation of **1a** with $Al(i\text{Bu})_3$ in CH_2Br_2 at 70 °C can be explained by the generation of the stronger Lewis acid ($i\text{Bu}_2AlBr$) during the course of the cyclopropanation reaction [Equation (3)], which decomposes $i\text{Bu}_2AlCH_2Br$ or CH_2Br_2.[29]

$$i\text{Bu}_2AlCH_2Br + \text{Alkene} \rightarrow \text{Cyclopropane} + i\text{Bu}_2AlBr \quad (3)$$

Critical runaway situations above 80 °C were nevertheless avoided by running the reaction either in 30 equiv. of CH_2Br_2 at ≤ 70 °C (Table 2, Run 2), in an even higher (85 equiv.) excess of CH_2Br_2 at 50 °C (Table 2, Run 1), or in the presence of catalyst at 0–25 °C. See the Supporting Information for details.

Role of the Catalysts

Apart from the use of Lewis acids,[5,13] other methods for the acceleration of cyclopropanation reactions have been reported, such as ultrasound[5a] or the presence od radical initiators such as oxygen, e.g. in the formation of the $EtZnCH_2I$ carbenoid from CH_2I_2 and Et_2Zn.[30] Similarly, formation of $(i\text{Bu})_2AlCH_2I$ from CH_2I_2 and $Al(i\text{Bu})_3$ has been facilitated by bubbling oxygen through the reaction mass.[31] This effect was much less pronounced when oxygen was bubbled through a reaction mixture consisting of TIBA, CH_2Br_2 and substrate **1a** (under conditions as in Table 1, Run 9 for example), consistent with the lower reactivity of CH_2Br_2 to radical halogen abstraction.[4]

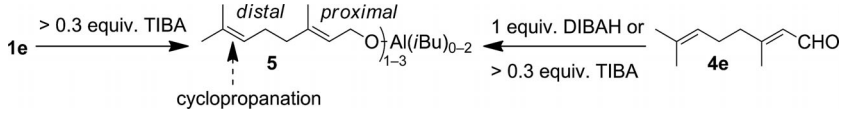
To address the role of the catalysts $CuBr_2$, CuBr, CuCl, $FeCl_3$, $FeCl_2$, $[CpFe(CO)_2]_2$, and $CpTiCl_3$ (Table 4), ESI/MS analysis was considered;[32] however, only $[CpFe(CO)_2]_2$ was completely soluble in CH_2Br_2. Nevertheless, $[CpFe(CO)_2]_2Br^+$ with m/z = 434 [M^+] was detected in the corresponding ESI mass spectrum,[33] either without or in the presence of **1a** (injection of a sample during reaction). This hints at an X-philic reaction mechanism,[34] with Lewis acid coordination to the leaving group to assist the cleavage of the C–X bond, but transmetallation to copper, iron or titanium carbenoids cannot be excluded.

Selective Cyclopropanation of the Distal Double Bond

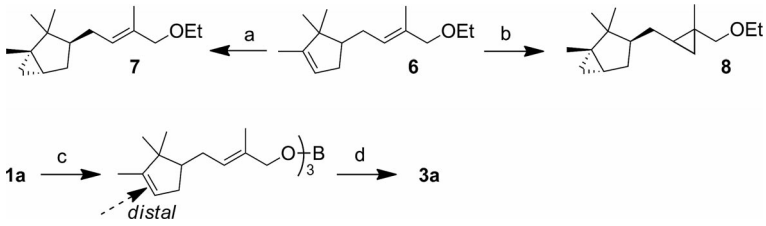
Simmons–Smith systems preferentially cyclopropanate the proximal double bond of dienols, via Mg, Zn or Sm carbenoids covalently linked to the oxygen function, which transfer their methylene group intramolecularly onto the allylic double bond.[7a,35] The distal cyclopropanation of dienols such as **1a**, **1d** or **1e** (Table 5) with TIBA in dibromomethane has its analogy in Yamamoto's distal cyclopropanation of geraniol **1e** with $Al(i\text{Bu})_3$ and CH_2I_2.[27,31] According to Yamamoto's addition mode, aluminum dienolate **5** is first formed, with the proximal double bond being less nucleophilic and sterically blocked against cyclopropanation. After addition of CH_2X_2 (X = Br, I), the carbenoid attacks the sterically less hindered distal double bond. DIBAH or TIBA reduction of dienals such as citral (**4e**) gives the same aluminum dienolate (**5**) with the same reactivity towards subsequent cyclopropanation (Scheme 3).

The sterically less hindered proximal double bond of ether **6** is therefore less inert to cyclopropanation compared to the one of dienolate **5** (Scheme 3).[36] An equimolar mixture of cyclopropane **7**[7a] and **8** was rapidly formed under standard conditions [Scheme 4, conditions (a)], and complete double cyclopropanation to **8** was achieved by using a higher excess of cyclopropanation reagents [conditions (b)]. Like the aluminum dienolate **5**, the covalently complexed borate of **1a** was cyclopropanated at its distal position.

These results indicate that the oxygen lone pairs of complexes such as **5**, which are less available for reagent pre-

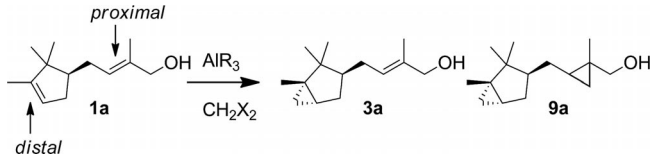


Scheme 3. Distal cyclopropanation of aluminum dienolate **5**, generated from geraniol (**1e**) or citral (**4e**). The exact ligation of aluminum dienolate **5** depends on the addition mode and the number of equivalents of TIBA employed.



Scheme 4. Al(*i*Bu)$_3$/CH_2Br_2 cyclopropanation of ether **6**: (a) 30 equiv. of CH_2Br_2, 3.2 equiv. of Al(*i*Bu)$_3$, 60 °C, 6 h (GC); for analytical data of compound **7**, see ref.[7b]; (b) 55 equiv. of CH_2Br_2, 8.5 equiv. of Al(*i*Bu)$_3$, 15% $FeCl_3$, 1.5 h, 25 °C, 52% (dist.); (c) 0.2 equiv. of B_2O_3 80 °C, removal of water in vacuo, quant.;[37] (d) 20 equiv. of CH_2Br_2, 3.2 equiv. of Al(*i*Bu)$_3$, 6% $FeCl_3$, 50% (dist.).

Table 7. Distal/proximal cyclopropanation of **1a** with different AlR_3/CH_2X_2 systems (X = Br, I).



Run	AlR_3	Amount	Co-solvent	CH_2X_2	Amount	*T*	*t*	**3a**[a] (distal)	Javanol (**9a**)[a]	Yield[b] of **3a** + **9a**
1	Al(*i*Bu)$_3$	3.5 equiv.	none	CH_2Br_2	30 equiv.	60 °C	3 h	90%	5%	78%
2	Al(*i*Bu)$_3$	2.0 equiv.	none	CH_2I_2	105 equiv.	60 °C	6 h	81%	5%	62%
3	Al(*i*Bu)$_3$	4.0 equiv.	hexane[c]	CH_2I_2	4.0 equiv.	25 °C	20 h	23%	54%	n.d.
4	$AlEt_3$	3.5 equiv.	hexane	CH_2I_2	4.0 equiv.	25 °C	20 h	15%	80%	76%

[a] According to GC. [b] Corrected by purity after distillation. [c] Decomposition without hexane.

complexation due to backbonding, are not the primary reason for the distal-selective cyclopropanation of dienols such as **1a**, **1d** or **1e**. Another indication for the predominance of steric factors is the selective cyclopropanation of dienol **18** to give **20** (vide infra). Accordingly, the relatively unreactive carbenoid precursor CH_2Br_2 cyclopropanates dienols such as **1a** with higher selectivity than CH_2I_2 (Table 7).

No cyclopropanation occurred with trialkylaluminum reagents in CH_2Cl_2, in the absence or presence of catalysts such as $FeCl_3$.[38]

Environmental and Safety Aspects

Transition-metal-catalyzed TIBA cyclopropanations are run safely under two provisions:
(a) The slight exotherm has to be monitored and kept at ≤ 40 °C during the reaction in order to avoid runaway situations that are imminent at ≥ 80 °C. The exotherm is easily controlled by slight external cooling.
(b) The addition order is important, with TIBA to be added to the substrate and transition-metal catalyst in dibromomethane. In case of proton-active functional groups such as OH in **1a**, these are first quenched with 0.35 equiv. TIBA, then the catalyst is added, then excess TIBA.

The quench of the reaction mixture, which is slowly pumped on cooled aqueous NaOH on a larger scale, is highly exothermic. Alternatively, alcoholysis of the remaining TIBA after complete conversion, with ≥ 3 equiv. (based on TIBA) of, for example, 2-propanol is less exothermic, as well as the final HCl treatment (2 M) of the thus generated Al(O*i*Pr)$_3$. Another option is air-quenching[39] of the TIBA-containing product mixture. In this case the exotherm is easily controlled by the flow rate, and the quench is terminated when the exotherm ceases. This gives smoothly first Al(O*i*Bu)$_3$ and, after addition of 2 M HCl, isobutyl alcohol instead of gaseous 2-methylpropane.

Both alternative quenching procedures are applicable on a smaller scale. On a > 100 g scale, however, the quantities of the alcohols ROH added or generated [from Al(OR)$_3$] and the excess of solvent needed for extraction is problematic. In these cases the following workup procedure was found to be more appropriate: After complete cyclopropanation, the reaction mixture was inversely quenched by passing it through a cannula onto 25% aqueous NaOH, stirring strongly and cooling to –15 °C.[40] The strong exotherm was controlled by the flow rate and the released 2-methylpropane (b.p. –12 °C) kept as liquid in the quenching vessel, which – upon slow warming to 40 °C – released gaseous 2-methylpropane, which was condensed in a cooling trap at –78 °C; 85% of the theoretical amount of 2-methylpropane based on employed TIBA was trapped (to avoid emission into the atmosphere).[41]

Recovery and recycling of the solvent/reactant dibromomethane after phase separation was addressed by addition of some 2-propanol and distillation of the azeotropes,[42] giving first the azeotrope water/2-propanol, then the azeotrope CH_2Br_2/2-propanol, then a mixture of CH_2Br_2/isobutyl bromide, which was separated by a second distillation step to finally yield 85% of dry, acid- and *i*BuBr-free dibromomethane (99.7% purity according to an accurate NMR integration),[43] which was successfully recycled as solvent/reactant.

Synthesis of Selected Flavor & Fragrance Compounds

The cyclopropanation of alkenes is of importance in fragrance chemistry. This transformation does not change the conformation of the unsaturated functionalized terpenes too much if it is carried out under the stereospecific Simmons–Smith conditions. Due to the slightly enhanced molecular weight, products with slightly increased vapor pressure and substantivity can be obtained without a major impact on the odor character. The new fragrance compounds of Scheme 2 and Tables 5 and 6 have therefore interesting odor profiles (see Supporting Information). In another aspect the distal-selective TIBA cyclopropanation of dienols or dienals provides, after further derivatization, access to fragrance compounds that are otherwise difficult to synthesize, as shown by the following synthetic sequences.

Δ-Citral

This compound (**10**)[44] has been recently claimed for flavor applications, due to its improved stability compared to citral (**4e**).[45] Direct cyclopropanation of **4e** with CH_2N_2/ZnI_2 or $ZnEt_2$/CH_2I_2, as described in the literature,[44,45] is problematic due to the excess of harmful reagents and concomitant side-reactions that occur on the unprotected aldehyde group, giving **10** with unsatisfactory yields and purities.[45] The distal-selective TIBA cyclopropanation of **1d** and **1e** (Table 1) gave products **3d** and **3e**, which furnished, after Saucy–Lindlar- (step b)[46] and Cu^I-catalyzed TEMPO oxidation (step d),[47] Δ-citral (**10**) on a multigram scale (Scheme 5) and with sufficient chemical purity to be submitted to sensory testing and to be used as substrate for further derivatization (Scheme 6).

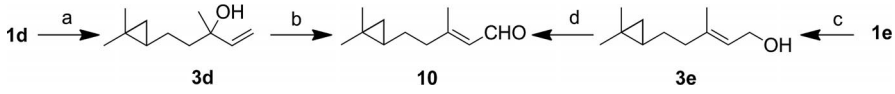
7-Methyl-Georgywood

Georgywood™[48] analogues, modified at their western cyclohexene ring, are of olfactory interest and have been synthesized by E. J. Corey[49] and at Givaudan.[50] Analogues such as **15a**, methylated at C-7 of Georgywood™, were expected to be obtained from **14** (Scheme 6) by Frater's acid-promoted (alk-3-en-1-yl)cyclopropane cyclization.[51] Thus, **13** was prepared through a sequence similar to the one described for *pseudo*-Georgywood from citral:[52] Pd-catalyzed 1,4-elimination of **12**, prepared in 2 steps from Δ-citral (**10**), gave the diene isomer mixture **13** with preference of the *exo* isomer **13a**, which selectively underwent the Diels–Alder reaction with methyl isopropenyl ketone (MIPK). Cyclization of **14** with H_3PO_4 in toluene gave regioisomer mixture **15**.

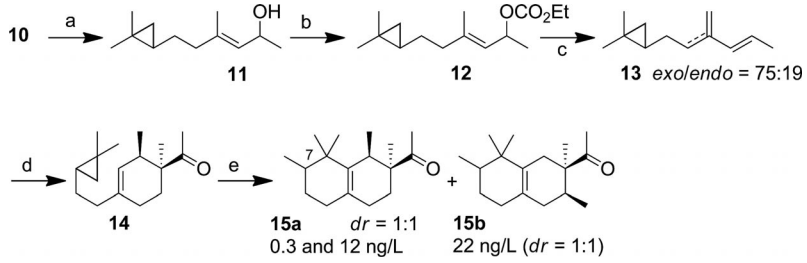
Sniff-GC revealed that the olfactory vector of the woody-ambery, warm, powdery and powerful smelling mixture **15** is one of the 2 diastereomers of **15a**, which was separated from **15b** by semi-preparative HPLC.

cis-Javanol (9b)

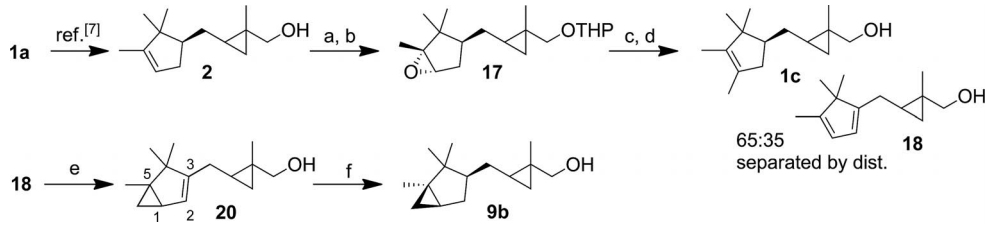
Javanol® (**9a**)[53] is formed by cyclopropanation of *nor*-radjanol (**1a**), which occurs with high selectivity at the less hindered face of the cyclopentene double bond opposite to the butenol side chain.[54] The corresponding *cis* isomer **9b** had so far not been detected among the mostly unidentified, but olfactorily interesting trace impurities of *trans* isomer **9a**.[55] We were curious about the odor profile and threshold of **9b** as well as the exact *cis*/*trans* ratio of the cyclopropanation of the cyclopentene unit of **1a**. The synthetic challenge was another incentive, because some alternative approaches towards **9b** had failed, especially when the crucial construction of the *cis*-3-alkyl-1-methylbicyclo[3.1.0]hexane unit was addressed.



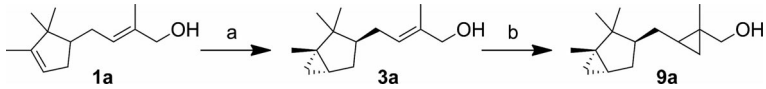
Scheme 5. Synthesis of Δ-citral (**10**) from linalool (**1d**) and geraniol (**1e**) by distal cyclopropanation and oxidation. (a) 3.5 equiv. of TIBA, 20 equiv. of CH_2Br_2, 6% $FeCl_3$, 5 h, 20 °C, 81% (dist.); (b) 0.5 equiv. of PBr_3, –5 °C, 1 h, quant. (crude); then 2-nitropropane, 35% KOH, *i*PrOH, 53% (dist.); (c) 3.5 equiv. of TIBA, 20 equiv. of CH_2Br_2, 6% $FeCl_3$, 5 h, 20 °C, quant. (crude); (d) 10% TEMPO, 10% CuCl, DMF, O_2, 1 h, 25 °C, 54% (flash chromatography, dist.).



Scheme 6. Synthesis of 7-methyl-georgywood (**15a**) from Δ-citral (**10**). (a) MeMgCl, 86% (dist.); (b) $ClCO_2Et$, toluene, pyridine, 90% (dist.); (c) 0.2% $Pd(OAc)_2$, 0.5% dpppe, 80 °C, 90% (dist.); (d) cat. $BF_3{\cdot}OEt_2$, toluene, methyl isopropenyl ketone (MIPK), –5 °C, 82% (dist.); (e) 85% H_3PO_4, toluene, 100 °C, 3 h, quant. (dist.).



Scheme 7. Synthesis of *cis*-javanol (**9b**) from *nor*-radjanol (**1a**). (a) DHP, H^+, 74% (FC); (b) Na_2CO_3, CH_2Cl_2, AcO_2H, 45 °C, 4 h, 72% (crude); (c) 3 equiv. of MeLi in diethoxymethane (DEM), 30 h, 80 °C; (d) 2% *p*TSA, MeOH, 25 h, 25 °C, 48% (FC); for a more selective synthesis of **1c** see the Supporting Information; (e) 5 equiv. of TIBA, 20 equiv. of CH_2Br_2, cat. $FeCl_3$, 30 h, 87% (dist.); (f) Pt/C, ethanol, H-cube, 3 bar, quant. (crude), HPLC purification.



Scheme 8. Transformation of **1a** via **3a** to javanol (**9a**) by two cyclopropanation steps in dibromomethane. (a) 3.5 equiv. of Al(*i*Bu)$_3$, 20 equiv. of CH_2Br_2, 6% $FeCl_3$, 25 °C; (b) 3 equiv. of *t*BuMgCl, *tert*-butyl methyl ether, tetrahydrofuran, 25 °C, 3 h, 82% (dist., over all steps).

Due to the distal-selective TIBA cyclopropanation of **18**, *cis* isomer **9b** was finally prepared in seven steps from *nor*-radjanol (**1a**) involving Grignard methylation and double elimination of epoxide **17** followed by conversion of the diene **18** through a diastereo- and regioselective cyclopropanation/hydrogenation sequence (Scheme 7).

During the synthesis of compound **1c**,[1b] diene **18** is formed as byproduct from epoxide **17** by elimination and a second 1,4-elimination under strongly basic conditions. This compound could be partially enriched by distillation of the **1c**/**18** mixture. This gave gram quantities of **18** with 63% purity. The loss of stereochemical information [(1*R*) stereocenter of **2**] is an advantage here, because this enhances the diversity of the olfactory evaluation of the final *cis*-javanol (**9b**) (4 isomers). Regarding the regioselective TIBA/CH_2Br_2 cyclopropanation of diene **18** we expected a higher steric hindrance by the butanol side chain, which would allow the regioselective cyclopropanation of **18** to **20**. This turned out to be true, and a 45:18:10 mixture of **20**/**21**/**18** was obtained, from which tricyclopropane **21** was separated, with 90% purity after distillation and preparative GC. Regarding the face selectivity of the hydrogenation of **20**, a PM3 calculation with Oasis showed that hydrogenation would give the desired *cis*-cyclopentane isomer **9b**,[56] because the quasi-axial cyclopropane methylene group shields this face of the cyclopentene double bond to a higher extent (Figure 1): **9b** was purified from byproducts, formed during the synthetic sequence, such as tricyclopropane **21** as well as hydrogenation products **22**[57] and **23** were separated by semi-preparative HPLC from **9b**, to allow the determination of its configuration by NMR spectroscopy and its olfactory threshold by sniff-GC analysis (Figure 2).

After screening different catalyst cartridges through the H-cube,[58] hydrogenation of **20** with excess Pt/C gave the desired *cis*-javanol (**9b**) with sufficient purity for olfactory evaluation. Comparison of its GC/MS data and co-injection showed, that javanol (**9a**) contains 1% of the *cis* isomer **9b**. Thus, Simmons–Smith cyclopropanation of *nor*-radjanol (**1a**) according to ref.[54] occurs with a face selectivity of 99:1 at the cyclopentene ring of **1a**.

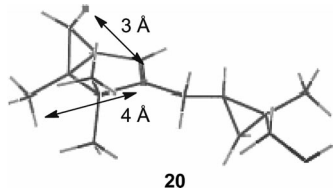


Figure 1. Minimum-energy conformation of **20**.[56] Distance between the *cisoid* proton of the cyclopropyl CH_2 group and the sp^2 carbon atom C-3: ca. 3 Å. Distance between the closest proton of the CH_3 group at C-5 and the sp^2 carbon atom C-3: ca. 4 Å.

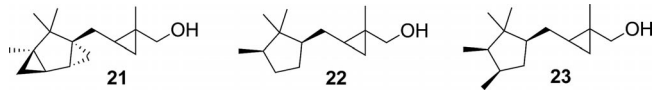


Figure 2. Byproducts **21**, **22**,[57] and **23** formed by cyclopropanation of **18** and hydrogenation of **18** and **1c**, respectively (Scheme 7). Compound **21** was separated by preparative GC from the late distillation fractions of **20**.

Javanol®

The TIBA/CH_2Br_2 and our recently published Grignard cyclopropanation method,[7] the first one distal- and the second one proximal-selective, can be efficiently combined due to the common solvent/reactant dibromomethane. Thus, crude intermediate **3a**, obtained by $FeCl_3$-catalyzed TIBA cyclopropanation of *nor*-radjanol (**1a**) in dry CH_2Br_2 (after removal of the azeotropes), was, without further purification, treated with *t*BuMgCl in ether solvents to give **9a** (Scheme 8).

Conclusion

A transition-metal-catalyzed cyclopropanation method was developed that cyclopropanates nonactivated alkenes with high regioselectivity at ambient temperature by using inexpensive TIBA and transition-metal catalysts in dibromomethane. Solvent-free DIBAH or TIBA 1,2-reduction of unsaturated carbonyl compounds, followed by in situ TIBA cyclopropanation of the unsaturated aluminum alcoholates in dibromomethane give cyclopropane alkanols in a consecutive process. Dienols such as geraniol, linalool or *nor*-radjanol are selectively cyclopropanated in the distal position. This makes flavor and fragrance compounds accessible that are otherwise difficult to synthesize. Convenient conditions, workup, and recycling of the solvent compare well with other known cyclopropanation methods.

Experimental Section

Method A. Typical Procedure for the TIBA Cyclopropanation of Unsaturated Alcohols and Phenols

(2*E*)-2-Methyl-4-[(1*S*,3*S*,5*R*)-1,2,2-trimethylbicyclo[3.1.0]hex-3-yl]-but-2-en-1-ol (3a): To (*R*)-*nor*-radjanol (**1a**) (194 g, 1 mol)[54] in dibromomethane (1.4 L, 20 mol) was added neat TIBA (100 g, 0.5 mol) under cooling (10–20 °C) through a cannula. After 15 min, anhydrous $FeCl_3$ (22 mg, 0.13 mmol) was added in one portion followed by neat TIBA (620 g, 3.1 mol) through the cannula. The mixture was stirred at 25 °C for 4.5 h, then cooled to –10 °C and pumped through a cannula onto cooled (–10 to 0 °C) 25% NaOH. Under stirring the biphasic mixture was slowly warmed to room temperature. The evolving 2-methylpropane was collected in a cooling trap at –78 °C. The phases were separated. The organic phase was washed with 4% oxalic acid, then with satd. $NaHCO_3$ until pH ≈ 8, dried with $MgSO_4$, filtered, and the dibromomethane was stripped off under reduced vacuum. The residue was distilled (b.p. 160 °C/0.1 Torr) to give 190 g (93%) of **3a** as a colorless oil [86% GC purity, 2% *nor*-radjanol (**1a**), 7% javanol (**9a**)], whose analytical data are consistent with the ones described for **3a** in the literature.[54]

Method B. Typical Procedure for the TIBA Cyclopropanation of Unsaturated Esters, Ethers, Lactones, Nitriles and Unfunctionalized Alkenes

Ethyl (2*E*)-5-(2,2-Dimethylcyclopropyl)-3-methylpent-2-enoate (3k): Anhydrous $FeCl_3$ (0.1 g, 0.7 mmol) was added whilst stirring to geranic acid ethyl ester (**1k**) (2.2 g, 11 mmol) in dibromomethane (31 mL, 0.44 mol) at 10–20 °C, followed by dropwise addition of neat TIBA (17 mL, 66 mmol) at this temperature. The mixture is stirred at 25 °C for 6 h, then poured carefully onto 25% NaOH at –10 to 0 °C. Workup as described in Method A and bulb-to-bulb distillation (b.p. 92 °C/0.2 Torr) gave 1.2 g (52%) of **3k** as colorless oil. Odor: fruity, pear. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 5.7 (s, 1 H), 4.15 (q, 2 H), 2.2 (t, 1 H), 2.18 (s, 3 H), 1.5 (1 H), 1.3 (t, 3 H), 1.1 (s, 3 H), 1.0 (s, 3 H), 0.9 (2 H), 0.45 (1 H), 0.4 (1 H), –0.1 (1 H) ppm. ^{13}C NMR ($CDCl_3$, 400 MHz): δ = 166.7 (s), 160.1 (s), 115.4 (d), 59.2 (t), 41.4 (t), 28.0 (t), 27.4 (q), 24.1 (d), 19.8 (q), 19.6 (t), 18.7 (q), 15.4 (s), 14.2 (q) ppm. GC/MS: *m*/*z* (%) = 210 (0.1) [M^+], 195 (4) [M – 15]$^+$, 153 (10), 136 (35), 82 (45), 55 (100). IR (film): $\tilde{\nu}$ = 2925 (m), 2869 (m), 1719 (s), 1648 (m), 1453 (m), 1366 (m), 1219 (m), 1147 (s), 1042 (m), 970 (w), 859 (w) cm^{-1}. HRMS: calcd. for $C_{13}H_{22}O_2$ 210.1619; found 210.1673. HRMS: calcd. for $C_{12}H_{19}O_2$ 195.1385; found 195.1390.

Method C. Typical Procedure for the DIBAH Reduction/in situ TIBA Cyclopropanation of Unsaturated Aldehydes

3-(6-Methylbicyclo[4.1.0]hept-3-yl)butan-1-ol (3r): To (+)-limonene aldehyde (**4r**) (*dr* = 1:1, 50 g, 0.3 mol) was added at 0–35 °C and stirring neat DIBAH (43 g, 0.3 mol) through a cannula within 2 h. The viscous mixture was stirred at 25 °C for another 2 h. Anhydrous $FeCl_3$ (3 g, 18 mmol) and dibromomethane (430 mL, 6 mol) were added, followed by neat TIBA (215 g, 1.1 mol) through the cannula over 1.5 h. After another 2 h at 0 °C, the solution was transferred through a cannula onto ice-cooled NaOH and stirred at 25 °C for 1 h until gas evolution ceases. Extraction with *tert*-butyl methyl ether, washing of the combined organic phases with 2 M HCl, satd. $NaHCO_3$ and satd. NaCl, drying with $MgSO_4$, filtration and concentration under reduced pressure gave 54 g of crude product; 11 g of this were purified by bulb-to-bulb distillation at 160 °C/0.05–0.1 mbar to give 9 g (82%) of **3r** as a colorless oil; diastereomer ratio 1:1:1:1. ^{1}H NMR ($CDCl_3$, 400 MHz): δ = 0.1 (1 H), 0.3 (1 H), 0.6–0.8 (1 H), 0.8 (4 d, 3 H), 0.8–1.0 (1 H), 1.0 (4 s, 3 H), 1.0–1.2 (1 H), 1.2–2.0 (8 H), 3.55–3.75 (2 H) ppm. ^{13}CNMR ($CDCl_3$, 400 MHz): δ = 14.7 (s), 15.8 (q), 16.03 (q), 16.04 (q), 16.07 (q), 17.83 (2 t), 17.9 (t), 18.2 (d), 18.3 (d), 20.3 (2 d), 23.2 (t), 24.8 (t), 25.5 (t), 26.0 (t), 26.7 (t), 27.0 (t), 27.3 (q), 27.7 (t), 27.8 (q), 28.7 (t), 31.51 (t), 31.54 (t), 33.7 (d), 33.8 (d), 34.0 (d), 35.7 (d), 36.0 (d), 36.9 (t), 37.0 (t), 39.5 (d), 39.7 (d), 61.53 (t), 61.55 (t), 61.57 (t) ppm. GC/MS: *m*/*z* (%) = 182 (0.2) [M^+], 167 (0.4) [M – 15]$^+$, 149 (4) [M – H_2O – 15]$^+$, 138 (20), 109 (100) [M – 73]$^+$, 95 (24), 93 (27), 81 (38), 79 (24), 67 (78), 55 (50), 41 (40). IR (film): $\tilde{\nu}$ = 3327 (br.), 3055 (w), 2920 (m), 2860 (m), 1446 (m), 1378 (m), 1192 (m), 1052 (m), 1008 (m), 885 (w), 639 (s) cm^{-1}. $C_{12}H_{22}O$ (182.30): calcd. C 79.06, H 12.16; found C 79.30, H 12.11. Odor profile: floral, mayol.

Supporting Information (see footnote on the first page of this article): Experimental procedures, characterization data, and copies of the ^{1}H and ^{13}C NMR spectra for all new compounds.

Acknowledgments

For valuable discussions we thank Prof. Sir Jack Baldwin (University of Oxford), Dr. J. Bajgrowicz, Prof. P. Chen (ETH Zürich), Prof. G. Frater, Dr. A. Gabbai, Dr. J. Membrez, and Prof. A. Vasella (ETH Zürich). For skilful experiments we thank P. Aebersold, L. Eberhard, J. Oetiker and T. Reinmann. For GC/MS and HRMS measurements we thank Dr. J. Schmid, H. Gfeller, and M. Bornand (ETH Zürich). We thank Dr. A. Borosy for molecular modelling studies, K. Grman for GC threshold measurements, B. Cranen for sensorical testing, and J.-J. Rouge for olfactory evaluation. For proof reading we thank Dr. S. Ellwood and Dr. M. Gautschi (Givaudan if not otherwise indicated).

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[16] Similar exothermic effects linked to the addition mode are known from other acid-catalyzed reactions, e.g. the acetalization of alcohols with enolates.
[17] Most other metallocenes were inactive: $CpFe(CO)_2Br$, Cp_2ZrCl_2, Cp_2Ni, Cp_2Fe (no effect), Cp_2Ru (slow decomposition). Carbonylmetal compounds such as $Fe(CO)_5$ and $Mo(CO)_6$ catalyzed the cyclopropanation at 25 °C, but with sudden exothermic peaks; $Fe_2(CO)_9$, Fe powder, or $Fe(acac)_3$ were inactive.
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Received: April 15, 2011
Published Online: June 28, 2011

