

Reinvestigation of the chemoselective cyclopropanation of allylic alcohols, allylic ethers and alkenes: a comparison between various reagents and protocols

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Abstract

The relative reactivities of various Zn, Al and Sm carbenoids in the chemoselective Simmons–Smith cyclopropanation of geraniol and its benzyl ether derivative were studied. Directed cyclopropanation was obtained in all cases, even with a iodomethylaluminum reagent. By variation of the reaction protocols using aluminum carbenoids, cyclopropanation can favor the *proximal* or *distal* double bond. © 2001 Elsevier Science B.V. All rights reserved.

Keywords: Simmons–Smith; Aluminum; Samarium; Zinc; Carbenoids

1. Introduction

The occurrence of a combination of double bonds and cyclopropane rings in natural products stimulated interest in the chemoselective cyclopropanation of polyenes. The Simmons–Smith cyclopropanation [1], a well-established method for cyclopropane synthesis, will be investigated for its chemoselectivity. Even if the issue of chemoselectivity was addressed early on [1b,2], there are only a few reports on the chemoselective Simmons–Smith cyclopropanation of olefins. This is surprising since many new protocols and reagents have been developed for this transformation [3,4]. One improvement was reported by Yamamoto et al., who studied the chemoselective cyclopropanation of geraniol using an aluminum carbenoid [5]. They reported its use for the cyclopropanation of the *distal* double bond whereas a zinc carbenoid reacts at the *proximal* position. Samarium carbenoids are also known to direct the cyclopropanation to the *proximal* double bond (Table 1) as reported by Molander [6].

Surprisingly, there has been no reported explanation of the mechanism by which the aluminum carbenoid

reacts with the *distal* alkene. Additionally, a recent literature survey [7] indicated a lack of comparative studies between Zn, Al and Sm carbenoids, especially in substrate-directed reactions [8]. Herein, we wish to report our results in the chemoselective cyclopropanation of geraniol (**1a**) and its benzyl ether (**1b**) derivative.

2. Results and discussion

All directed Simmons–Smith protocols typically require a large excess of the methylene transfer units. We wanted to apply a recent Lewis acid-catalyzed protocol, developed in our laboratories, which typically proceeds with small reagent excesses [4e,9]. In the context of a chemoselective reaction this protocol could allow for an intramolecular Lewis acid catalyzed cyclopropanation (path a), compared to an intermolecular reaction with the zinc carbenoid (directed reaction, path b). To further investigate the scope of the intramolecular approach we also investigated aluminum carbenoids (path c) (Scheme 1).

2.1. Studies on geraniol and its benzyl ether derivative

Gratifyingly, when the mixed zinc carbenoid derived from geraniol was treated with 0.2 equivalents of

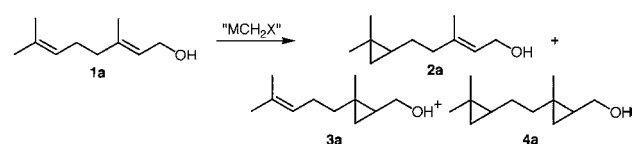
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Et_2AlCl at -40°C , the desired product was obtained in high yields [10]. The mixed carbenoid can be formed by deprotonation of geraniol by either EtZnCH_2I or $\text{Zn}(\text{CH}_2\text{I})_2$ (entries 1 and 2, Table 2). Both approaches are efficient, and the use of Furukawa's reagent (EtZnCH_2I) requires less CH_2I_2 for the reaction to proceed. The high conversions obtained suggest that the deprotonation step proceeds mainly via a regioselective reaction involving the ethyl substituent of the carbenoid.

In a similar fashion, we wanted to investigate an analogous reaction employing the aluminum carbenoid derived from $i\text{-Bu}_3\text{Al}$ and CH_2I_2 . Through addition of a small excess of geraniol to the preformed aluminum carbenoid ($i\text{-Bu}_2\text{AlCH}_2\text{I}$), the monocyclopropane at the *proximal* position was obtained in ca. 70% yield [11]. To the best of our knowledge, this is the first reported

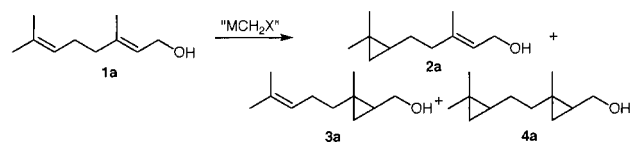
Table 1



'MCH ₂ X'	2a:3a:4a ^a
$i\text{-Bu}_3\text{Al}$ (2 equiv.), CH_2I_2 (1 equiv.), CH_2Cl_2 , r.t.	76:1:4
Et_2Zn (2 equiv.), CH_2I_2 (1 equiv.), Et_2O , r.t.	2:74:3
Sm/Hg, CH_2I_2 , THF, -78°C to r.t.	98:0:0

^a From Ref. [5c,6].

Table 2



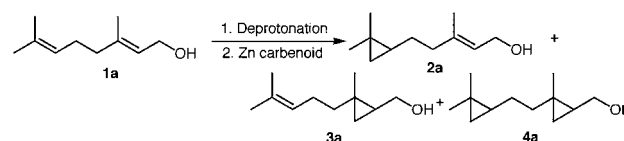
Entry	'MCH ₂ X'	2a:3a:4a ^a
1	EtZnCH_2I (1 equiv.); add 1a ; Et_2AlCl (0.2 equiv.), CH_2Cl_2 , -40°C	2:80:2
2	$\text{Zn}(\text{CH}_2\text{I})_2$ (1 equiv.); add 1a ; Et_2AlCl (0.2 equiv.), CH_2Cl_2 , -40°C	3:84:2
3	$i\text{-Bu}_2\text{AlCH}_2\text{I}$ (1 equiv.); add 1a , CH_2Cl_2 , -40°C to r.t.	1:67:0 ^b
4	$i\text{-Bu}_3\text{Al}$ (1.98 equiv.); add 1a ; CH_2I_2 (0.98 equiv.) CH_2Cl_2 , 0°C to r.t.	73:1:3
5	Sm/Hg, CH_2I_2 , THF, -78°C to r.t.	0:98:0 ^c

^a 10% excess **1** was added (except with Sm). Ratios were determined by GC analysis of TFA derivatives.

^b Some unreacted CH_2I_2 observed by crude $^1\text{H-NMR}$.

^c Result from Ref. [5].

Table 3



Entry	Deprotonation ^a	Zn carbenoid	2a:3a:4a ^b
1	Et_2Zn	EtZnCH_2I	2:80:8
2	Et_2Zn	$\text{Zn}(\text{CH}_2\text{I})_2$	2:88:6
3	Et_2Zn	$\text{Zn}(\text{CH}_2\text{I})_2\cdot\text{DME}$ ^c	2:70:1
4	Et_2Zn	$\text{IZnCH}_2\text{I}\cdot\text{Et}_2\text{O}$	2:91:3
5	Et_2Zn	$\text{CF}_3\text{CO}_2\text{ZnCH}_2\text{I}$ ^d	32:31:19
6	$\text{Et}_2\text{Zn}\cdot\text{Et}_2\text{O}$	EtZnCH_2I	2:89:4
7	$\text{EtZnI}\cdot\text{Et}_2\text{O}$	$\text{Zn}(\text{CH}_2\text{I})_2$ ^c	2:77:2
8	$\text{EtZnI}\cdot\text{Et}_2\text{O}$	$\text{IZnCH}_2\text{I}\cdot\text{Et}_2\text{O}$	2:83:2

^a Formation of 1.1 equivalents of the zinc alkoxide.

^b Ratios were determined by GC analysis of the TFA derivatives.

^c 0.5 equiv. of the carbenoid were used.

^d Protocol, see Ref. [4f].

example of a directed cyclopropanation of an allylic alcohol with an aluminum carbenoid. In contrast, under Yamamoto's conditions, the cyclopropanation occurs almost exclusively at the *distal* double bond [5c].

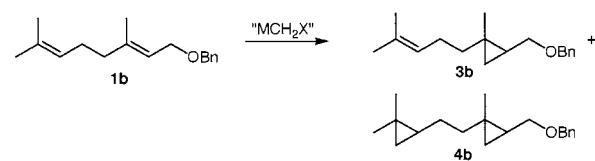
For comparison, we also investigated a variety of directed cyclopropanation protocols with zinc carbenoids (Table 3). All entries involved deprotonation of geraniol with Et_2Zn or with soluble $\text{EtZnI}\cdot\text{Et}_2\text{O}$. The zinc alkoxide was then added to the carbenoid in solution [12]. The two protocols involving iodomethylzinc iodide were slightly superior (entries 4 and 8). Interestingly, the reactive carbenoid developed by Shi [4f] led to a nearly statistical mixture of products (entry 5) [13].

Encouraged by our results in the chemoselective cyclopropanation of geraniol, we turned our attention to its benzyl ether derivative (Table 4). As expected, Zn, Sm and Al carbenoids exhibited high chemoselectivity for the *proximal* position. The cyclopropanation of the allylic ether with the samarium carbenoid formed using CH_2I_2 is an interesting example since previous reports suggest that isolated double bonds or homoallylic alcohols fail to react under the reaction conditions [6]. Alternatively, the use of CH_2I_2 under identical reaction conditions led to poor conversions. Therefore, the scope of the samarium carbenoid (prepared from Sm and CH_2I_2) in directed reactions is not limited to hydroxyl groups [14].

These results may provide some insight on the observed selectivity of the aluminum carbenoid. Currently, there is no satisfactory explanation for the selectivity of the aluminum carbenoid toward the *distal* double bond of the geraniol aluminum alkoxide

[ROAl(*i*-Bu₂)]. One could conclude that a covalent bond between Al and the oxygen atom is necessary, since cyclopropanation of the benzyl ether provides complete chemoselectivity at the *proximal* position. This results in a deactivation of the *proximal* double bond by inductive effect by the Lewis acidic Al center. Another reasonable alternative could be that under the reaction conditions (CH₂Cl₂), the aluminum alkoxides are forming higher aggregates [15] in which the *distal* double bond is more exposed than the *proximal* double bond.

Table 4



Entry	'MCH ₂ X'	3b:4b ^{a,b}
1	EtZnCH ₂ I, CH ₂ Cl ₂ , -40°C to r.t.	92:1
2	Zn(CH ₂ I) ₂ , CH ₂ Cl ₂ , -40°C to r.t.	97:1
3	IZnCH ₂ I-Et ₂ O, CH ₂ Cl ₂ , -40°C to r.t.	92:0
4	CF ₃ CO ₂ ZnCH ₂ I, CH ₂ Cl ₂ , -40°C to r.t.	91:6
5	<i>i</i> -Bu ₃ Al, CH ₂ I ₂ , CH ₂ Cl ₂ , -40°C to r.t. (ovn)	67:0
6	Sm/CH ₂ I ₂ , TMSCl ^c , THF ^{d,e} , -78°C to r.t.	75:0

^a 10% excess **1** was added (except with Sm). Ratios were determined by GC analysis of the crude reaction mixture.

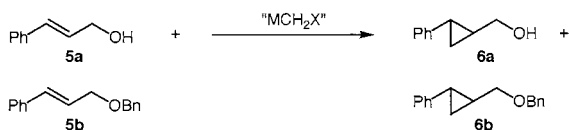
^b <1% monocyclopropane **2b** formed in all cases.

^c 0.5 equivalents of the carbenoid were used.

^d 10 equivalents of CH₂I₂ were used. The reaction with CH₂ICl gave poor conversions.

^e 0.2 equivalents TMSCl were used. HgCl₂ was an equally effective additive.

Table 5



Entry	'MCH ₂ X'	6a:6b ^a
1	EtZnCH ₂ I, Et ₂ AlCl, CH ₂ Cl ₂ , -40°C	0:0
2	Et ₂ Zn; IZnCH ₂ I-Et ₂ O, CH ₂ Cl ₂ , -78°C to r.t.	22:10
3	<i>i</i> -Bu ₂ AlCH ₂ I, CH ₂ Cl ₂ , -40°C to r.t.	68:0
4	<i>i</i> -Bu ₃ Al; <i>i</i> -Bu ₂ AlCH ₂ I, CH ₂ Cl ₂ , -40°C to r.t.	10:36
5	Sm/CH ₂ ICl, TMSCl, THF, -78°C to r.t.	84:0
6	Sm/CH ₂ I ₂ , TMSCl, THF, -78°C to r.t.	78:20

^a Reactions were performed using 0.5 mmol of carbenoid (except with Sm) and 0.5 mmol of each olefin. Ratios were determined by GC analysis (TFA derivatives) and quantitative ¹³C-NMR. The numbers represent the percentage of reacted starting material.

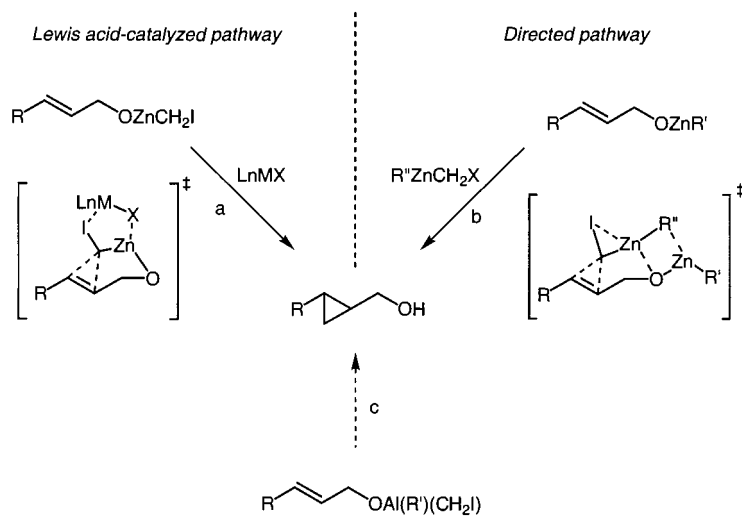
2.2. Competition studies on cinnamyl alcohol and its benzyl ether derivative

While high chemoselectivity can be achieved using specific protocols, information on the efficiency of these protocols in more complex systems would be valuable. In addition, there are only a few examples reported in which two basic groups compete to assist the delivery of the methylene unit. Therefore, we wanted to study the intermolecular competition of cinnamyl alcohol and its benzyl ether derivative toward Zn, Al and Sm carbenoids (Table 5).

Under the Lewis acid-catalyzed protocol previously employed for geraniol cyclopropanation, only complete recovery of the starting materials resulted. The presence of a basic benzyl ether functionality is believed to inhibit the reaction. Moreover, the procedure for directed cyclopropanation using zinc carbenoids led to a 32% yield based on carbenoid and a 2.2:1 ratio of **6a:6b** (entries 1 and 2). The cyclopropanation of the zinc alkoxide is slightly faster than the reaction with the benzyl ether. In contrast, the use of aluminum carbenoids proved superior for this system. The intramolecular approach led to an unoptimized yield of 68% for the cyclopropylmethanol-based carbenoid and no cyclopropanation was observed for the benzyl ether. Interestingly, Yamamoto's protocol favored reaction with the allylic benzyl ether (46% combined yield based on carbenoid, **6a:6b** = 1:3.6, entries 3 and 4). The samarium carbenoid derived from CH₂ICl proved to be highly chemoselective whereas the carbenoid employing CH₂I₂ reacted with the benzyl ether to some extent (entries 5 and 6). These results show that aluminium and samarium reagents are valuable alternatives in comparison to zinc carbenoids for polyfunctional substrates.

3. Conclusions

In summary, we investigated Zn, Al and Sm carbenoids in the chemoselective cyclopropanation of the geraniol, cinnamyl alcohol and their benzyl ether derivatives. These results show different reaction protocols can be used to selectively cyclopropanate the *proximal* or *distal* double bonds in geraniol. With iodomethylzinc and iodomethyl(alkyl)aluminum alkoxides as intermediates, the reaction is directed to the *proximal* position, while preformation of the dialkylaluminum alkoxides leads to reaction at the *distal* position. Selectivity for the *proximal* position was observed in all cases on the benzyl ether of geraniol. Furthermore, in competition experiments between an allylic alcohol and its benzyl ether, both aluminum and samarium carbenoids were shown to be highly chemoselective. Further studies for applications of aluminum and



Scheme 1.

samarium carbenoids in directed cyclopropanation reactions will be reported in due course.

4. Experimental

4.1. General procedures

All reactions were carried out under argon or nitrogen, using anhydrous, freshly distilled THF (dried over benzophenone/sodium), Et₂O (dried over benzophenone/sodium), 1,2-dimethoxyethane (DME, dried over benzophenone/sodium) or CH₂Cl₂ (dried over CaH₂). The diethylzinc (Akzo Nobel Inc.), triisobutylaluminum (Aldrich) and diethylaluminum chloride (Aldrich) were used neat and without further purification [16]. ¹H- and ¹³C-NMR spectroscopy was performed on a Bruker AMX-300 or Bruker ARX-400 spectrometer. Ratios of products were determined using GC and ¹H-NMR (geranyl scaffold) or GC and quantitative ¹³C-NMR (cinnamyl scaffold). GC analysis was performed on a HP 5890 Series II chromatograph, equipped with a DB-1701 column (J & W Scientific, length 30 m, I.D. 0.25 mm, 0.25 μm). Conditions A (geranyl template): 90–250°C, 5 min at 90°C then 10°C min⁻¹. TFA derivatives (**1a–4a**) were prepared from the crude oil. Carrier gas: helium. *t*_R (**1a**) 8.3 min, *t*_R (**2a**) 9.0 min, *t*_R (**3a**) 9.3 min, *t*_R (**4a**) 9.7 min (doublet). *t*_R (**1b**) 17.2 min, *t*_R (**2b**) 17.6 min, *t*_R (**3b**) 17.4 min, *t*_R (**4b**) 17.7 min. For comparison purposes, each product was independently prepared according to literature procedures. Conditions B (cinnamyl template): 120–160°C, 2°C min⁻¹. TFA derivatives were prepared from the crude oil. Carrier gas: hydrogen. *t*_R (**5a**) 2.34 min, *t*_R (**6a**) 2.76 min, *t*_R (**5b**) 21.2 min, *t*_R (**6b**) 22.4 min.

4.2. Cyclopropanation of geraniol using zinc carbenoids

4.2.1. Lewis acid-catalyzed protocol (Table 2, entry 1)

CH₂I₂ (1.0 mmol) was added dropwise to a solution of Et₂Zn (0.102 ml, 1.00 mmol) in CH₂Cl₂ (10 ml), at –40°C, under argon. A catalytic amount of oxygen was allowed in the reaction flask (to ensure carbenoid formation) by piercing of the septum with a needle for ca. 5 min. Geraniol (0.191 ml, 1.10 mmol) was added dropwise to the suspension, followed by Et₂AlCl (0.0251 ml, 0.20 mmol). After 4 h at –40°C, the reaction was quenched by adding Et₂O, followed by an equal volume of NH₄Cl. After extraction, the organic phase was then washed with NaHCO₃ and brine saturated solutions, dried on MgSO₄, filtered and concentrated under reduced pressure. TFA derivatives were analyzed by GC (**1a:2a:3a:4a** = 16:2:80:2). The colorless oil was then purified by flash chromatography to yield a mixture of cyclopropanes (70% yield).

4.2.2. Directed reaction protocol

4.2.2.1. Deprotonation with EtZnI (Table 3, entry 8). A previously dried round bottom flask, under Ar, was charged with iodine (0.254 g, 1.00 mmol) and Et₂O (0.207 ml, 2.00 mmol) in CH₂Cl₂ (5 ml). The flask was cooled at –10°C and diethylzinc (0.102 ml, 1.00 mmol) was added dropwise. After iodolysis was completed to afford a colorless solution, CH₂I₂ (0.0806 ml, 1.00 mmol) was added dropwise and a catalytic amount of oxygen was allowed in the reaction flask (to ensure carbenoid formation) by piercing of the septum with a needle for ca. 5 min. In a separate 10 ml round bottom flask, ethylzinc iodide (1.10 mmol; complexed to Et₂O) was formed as described above in CH₂Cl₂ (5 ml) at

–10°C. Geraniol (0.191 ml, 1.10 mmol) was then added dropwise and the resulting colorless solution was transferred via cannula on the carbenoid in solution. The flask was allowed to warm to room temperature (r.t.) overnight. The crude oil was isolated as described previously (Section 4.2.1). TFA derivatives were analyzed by GC (**1a:2a:3a:4a** = 13:2:83:2). The colorless oil was then purified by flash chromatography to yield a mixture of cyclopropanes (0.142 g, 77% yield).

4.2.2.2. Deprotonation with Et₂Zn (Table 3, entry 4). A previously dried round bottom flask, under Ar, was charged with iodine (0.254 g, 1.00 mmol) and Et₂O (0.207 ml, 2.00 mmol) in CH₂Cl₂ (5 ml). The flask was cooled at –10°C and diethylzinc (0.102 ml, 1.00 mmol) was added dropwise. After iodolysis was completed to afford a colorless solution, CH₂I₂ (0.0806 ml, 1.00 mmol) was added dropwise and a catalytic amount of oxygen was allowed in the reaction flask (to ensure carbenoid formation) by piercing of the septum with a needle for ca. 5 min. In a separate 10 ml round bottom flask, geraniol (0.191 ml, 1.10 mmol) was added dropwise to diethylzinc (0.113 ml, 1.10 mmol) in CH₂Cl₂ (3 ml) at –78°C. The resulting colorless solution was transferred via cannula on the carbenoid in solution. The flask was allowed to warm to r.t. and quenched after 6 h. The crude oil was isolated as described previously (Section 4.2.1). TFA derivatives were analyzed by GC (**1a:2a:3a:4a** = 5:2:91:3).

4.3. Cyclopropanation of geraniol using aluminum carbenoids

4.3.1. Reaction at the terminal double bond (Table 2, entry 4)

The reaction was performed under a modified Yamamoto's protocol [5c,d]. In a previously dried round bottom flask, the aluminum alkoxide was formed at 0°C by adding geraniol (0.174 ml, 1.00 mmol) to *i*-Bu₃Al (0.500 ml, 1.98 mmol) in CH₂Cl₂ (10 ml). CH₂I₂ (0.0789 ml, 0.98 mmol) was then added dropwise, and the flask was allowed to warm to r.t. and stirred for 5 h. The reaction was quenched by addition Et₂O, followed by an equal volume of Rochelle's salt (stirred overnight). After extraction, the organic phase was then washed with NaHCO₃ and brine saturated solutions, dried on MgSO₄, filtered and concentrated under reduced pressure. GC analysis of TFA derivatives showed **1a:2a:3a:4a** = 20:73:1:3 and a colorless oil (80% yield) was isolated after chromatography.

4.3.2. Directed cyclopropanation using an aluminum carbenoid (Table 2, entry 3)

In a previously dried round bottom flask, containing a solution of *i*-Bu₃Al (0.252 ml, 1.00 mmol) in CH₂Cl₂ (10 ml) under Ar at –40°C, CH₂I₂ (0.0806 ml, 1.00

mmol) was added dropwise. Typically, a catalytic amount of oxygen was allowed in the reaction flask (to ensure carbenoid formation [17]) by piercing of the septum with a needle for ca. 5 min. Then, geraniol (0.191 ml, 1.10 mmol) was added dropwise and the flask was allowed to warm to r.t. overnight. The crude oil was isolated as described previously (Section 4.3.1). The TFA derivatives were analyzed by GC (**1a:2a:3a:4a** = 23:2:72:0). The colorless oil was then purified by flash chromatography to yield a mixture of cyclopropanes (62% yield).

4.4. Cyclopropanation of the benzyl ether of geraniol

4.4.1. Reaction with zinc carbenoids (Table 4, entry 3)

A previously dried round bottom flask, under Ar, was charged with iodine (0.127 g, 0.50 mmol) and Et₂O (0.104 ml, 1.00 mmol) in CH₂Cl₂ (3 ml). The flask was cooled at –40°C and diethylzinc (0.0512 ml, 0.50 mmol) was added dropwise. After iodolysis was completed to afford a colorless solution, CH₂I₂ (0.0403 ml, 0.50 mmol) was added dropwise and a catalytic amount of oxygen was allowed in the reaction flask (to ensure carbenoid formation) by piercing of the septum with a needle for ca. 5 min. A pre-cooled solution of the benzyl ether of geraniol (0.134 g, 0.55 mmol) in CH₂Cl₂ (2 ml) was then transferred via cannula and the flask was allowed to warm to r.t. and stirred for 5 h. The reaction was diluted by adding Et₂O, and quenched using an equal volume of NH₄Cl. After extraction, the organic phase was then washed with NaHCO₃ and brine saturated solutions, dried on MgSO₄, filtered and then concentrated under reduced pressure. The crude oil was then analyzed by GC (**1b:2b:3b:4b** = 8:0:92:0).

4.4.2. Reaction with aluminum carbenoids (Table 4, entry 5)

To a solution of *i*-Bu₃Al (0.252 ml, 1.0 mmol) in CH₂Cl₂ (6 ml) under Ar at –40°C, CH₂I₂ (0.0806 ml, 1.0 mmol) was added dropwise. Typically, a catalytic amount of oxygen was allowed in the reaction flask (to ensure carbenoid formation) by piercing of the septum with a needle for ca. 5 min. The benzyl ether of geraniol (0.269 g, 1.10 mmol) in CH₂Cl₂ (4 ml) was then transferred via cannula and the flask was allowed to warm to r.t. overnight. The reaction was quenched by adding Et₂O, followed by an equal volume of Rochelle's salt (stirred overnight). After extraction, the organic phase was then washed with saturated NaHCO₃ and brine solutions, dried on MgSO₄, filtered and then concentrated under reduced pressure. The crude oil was diluted and analyzed by GC (**1b:2b:3b:4b** = 26:0:74:0). The colorless oil was then purified by flash chromatography to yield a mixture of cyclopropanes (0.166 g, 58% yield).

4.4.3. Reaction with samarium carbenoids (Table 4, entry 6)

In a previously dried round bottom flask was added samarium powder [18] (0.301 g, 2 mmol). The flask was flame-dried while being flushed with argon. After the flask was allowed to cool to r.t., THF (10 ml) was added, followed by TMSCl [19] (5 μ l, 0.04 mmol). The suspension was stirred for 30 min at r.t. The benzyl ether of geraniol (0.0489 g, 0.20 mmol) was then dissolved in THF (3 ml) and transferred via syringe to the flask. The suspension was stirred for 20 min at r.t. The flask was cooled to -78°C , and CH_2I_2 (0.163 ml, 2.02 mmol) was added dropwise. The flask was allowed to warm to r.t. overnight. The viscous dark blue reaction mixture was quenched with a saturated aqueous K_2CO_3 solution and extracted three times with Et_2O . The organic layers were collected, washed three times with brine, dried over anhydrous MgSO_4 , and filtered. After concentration, the crude oil was analyzed by GC (**1b:2b:3b:4b** = 25:0:75:0). The colorless oil was then purified by flash chromatography to yield a mixture of cyclopropanes (0.514 g, 99% yield).

4.5. Competition between cinnamyl alcohol and its benzyl ether

4.5.1. Reaction with zinc carbenoids

Lewis acid catalyzed approach (Table 5, entry 1). Following the protocol described in Section 4.2.1, a solution of cinnamyl alcohol (0.671 g, 0.50 mmol) and its benzyl ether (0.112 g, 0.50 mmol) in CH_2Cl_2 (2 ml + 1 ml rinse) was added to EtZnCH_2I (0.50 mmol) in CH_2Cl_2 (2 ml). Et_2AlCl (0.251 ml, 0.20 mmol) was then added and the solution was stirred at -40°C for 4 h. Both quantitative ^{13}C -NMR and GC analysis of the TFA derivatives showed **5a:5b:6a:6b** = 50:50:0:0.

Directed reaction protocol (Table 5, entry 2). Following the protocol described in Section 4.2.2, a solution of cinnamyl alcohol (0.671 g, 0.50 mmol) and its benzyl ether (0.112 g, 0.50 mmol) in CH_2Cl_2 (2 ml + 1 ml rinse) was treated with $i\text{-Bu}_3\text{Al}$ (0.126 ml, 0.50 mmol). The solution was added to $\text{IZnCH}_2\text{I}\cdot\text{Et}_2\text{O}$ (0.50 mmol) in CH_2Cl_2 (2 ml) and allowed to warm to r.t. overnight. Both quantitative ^{13}C -NMR and GC analysis of the TFA derivatives showed **5a:5b:6a:6b** = 39:45:11:5.

4.5.2. Reaction with aluminum carbenoids

4.5.2.1. Pseudo-intramolecular approach (Table 5, entry 3). Following the protocol described in Section 4.3.2, a solution of cinnamyl alcohol (0.671 g, 0.50 mmol) and its benzyl ether (0.112 g, 0.50 mmol) in CH_2Cl_2 (1 ml + 1 ml rinse) was treated with $i\text{-Bu}_3\text{Al}$ (0.126 ml, 0.50 mmol). The solution was added to $i\text{-Bu}_2\text{AlCH}_2\text{I}$ (0.50 mmol) in CH_2Cl_2 (3 ml). The solution was then allowed to warm to r.t. overnight. Both quantitative

^{13}C -NMR and GC analysis of the TFA derivatives showed **5a:5b:6a:6b** = 16:50:34:0.

4.5.2.2. Modified Yamamoto's protocol (Table 5, entry 4). Following the protocol described in Section 4.3.1, a solution of cinnamyl alcohol (0.671 g, 0.50 mmol) and its benzyl ether (0.112 g, 0.50 mmol) in CH_2Cl_2 (1 ml + 1 ml rinse) was added to $i\text{-Bu}_2\text{AlCH}_2\text{I}$ (0.50 mmol) in CH_2Cl_2 (3 ml) and allowed to warm to r.t. overnight. Both quantitative ^{13}C -NMR and GC analysis of the TFA derivatives showed **5a:5b:6a:6b** = 45:32:5:18.

4.5.3. Reaction with samarium carbenoids

4.5.3.1. Reaction with CH_2ICl (Table 5, entry 5). Following the protocol described in Section 4.4.3, a solution of cinnamyl alcohol (0.671 g, 0.50 mmol) and its benzyl ether (0.112 g, 0.50 mmol) in THF (8 ml) was added to the samarium powder [20] (5.00 mmol) in THF (50 ml). CH_2ICl (0.364 ml, 5.00 mmol) was added at -78°C and the flask was allowed to warm to r.t. overnight. Both quantitative ^{13}C -NMR and GC analysis of the TFA derivatives showed **5a:5b:6a:6b** = 8:50:42:0.

4.5.3.2. Reaction with CH_2I_2 (Table 5, entry 6). Following the protocol described in Section 4.4.3, a solution of cinnamyl alcohol (0.671 g, 0.50 mmol) and its benzyl ether (0.112 g, 0.50 mmol) in THF (8 ml) was added to the samarium powder [18] (5.00 mmol) in THF (50 ml). CH_2I_2 (0.403 ml, 5.00 mmol) was added at -78°C and the flask was allowed to warm to r.t. overnight. Both quantitative ^{13}C -NMR and GC analysis of the TFA derivatives showed **5a:5b:6a:6b** = 11:40:39:10.

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References

- [1] (a) H.E. Simmons, R.D. Smith, J. Am. Chem. Soc. 80 (1958) 5323. (b) H.E. Simmons, R.D. Smith, J. Am. Chem. Soc. 81 (1959) 4256.
- [2] (a) B. Rickborn, J.H.-H. Chan, J. Org. Chem. 32 (1967) 3576. (b) H.W. Whitlock, L.E. Overman, J. Org. Chem. 34 (1969) 1962. (c) E.J. Corey, H. Yamamoto, D.K. Herron, K. Achiwa, J. Am. Chem. Soc. 92 (1970) 6635.
- [3] (a) H.E. Simmons, T.L. Cairns, S.A. Vladuchick, C.M. Hoiness, Org. React. 20 (1973) 1. (b) A.B. Charette, J.-F. Marcoux, Synlett (1995) 1197.

- [4] (a) G. Wittig, K. Schwarzenbach, *Angew. Chem.* 71 (1959) 652. (b) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron Lett.* (1966) 3353. (c) J. Furukawa, N. Kawabata, J. Nishimura, *Tetrahedron* 24 (1968) 53. (d) S. Sawada, Y. Inouye, *Bull. Chem. Soc. Jpn.* 42 (1969) 2669. (e) S.E. Denmark, J.P. Edwards, *J. Org. Chem.* 56 (1991) 6974. (f) A.B. Charette, C. Brochu, *J. Am. Chem. Soc.* 117 (1995) 11367. (g) Z.Q. Yang, J.C. Lorenz, Y. Shi, *Tetrahedron Lett.* 39 (1998) 8621.
- [5] (a) H. Hoberg, *Just. Liebigs Ann. Chem.* 656 (1962) 1. (b) D.B. Miller, *Tetrahedron Lett.* (1964) 989. (c) K. Maruoka, Y. Fukutani, H. Yamamoto, *J. Org. Chem.* 50 (1985) 4412. (d) K. Maruoka, S. Sakane, H. Yamamoto, *Org. Synth.* 67 (1989) 176.
- [6] (a) G.A. Molander, J.B. Etter, *J. Org. Chem.* 52 (1987) 3942. (b) G.A. Molander, L.S. Harring, *J. Org. Chem.* 54 (1989) 3525.
- [7] A.B. Charette, A. Beauchemin, *Org. React.* 58 (2001) in press.
- [8] A.H. Hoveyda, D.A. Evans, G.C. Fu, *Chem. Rev.* 93 (1993) 1307.
- [9] For theoretical calculations: (a) E. Nakamura, A. Hirai, M. Nakamura, *J. Am. Chem. Soc.* 120 (1998) 5844. (b) A. Hirai, M. Nakamura, E. Nakamura, *Chem. Lett.* (1998) 927.
- [10] If Et_2AlCl is omitted, less than 1% of the cyclopropane is observed by GC.
- [11] Decomposition is observed when a Lewis acid (Et_2AlI , for example) is added to the mixed carbenoid.
- [12] For a study on the different iodomethylzinc species in solution, see: (a) S.E. Denmark, J.P. Edwards, S.R. Wilson, *J. Am. Chem. Soc.* 114 (1992) 2592. (b) A.B. Charette, J.-F. Marcoux, *J. Am. Chem. Soc.* 118 (1996) 4539.
- [13] Alternatively, reaction of geraniol with two equivalents of the carbenoid led to polymerization.
- [14] For directed reactions using Sm carbenoids, see: (a) M. Lautens, P.H.M. Delanghe, *J. Org. Chem.* 57 (1992) 798. (b) M. Lautens, P.H.M. Delanghe, *J. Org. Chem.* 58 (1993) 5037. (c) M. Lautens, P.H.M. Delanghe, *J. Am. Chem. Soc.* 116 (1994) 8526. (d) M. Lautens, P.H.M. Delanghe, *J. Org. Chem.* 60 (1995) 2474.
- [15] J.J. Eisch, in: E.W. Abel, F.G.A. Stone, G. Wilkinson (Eds.), *Comprehensive Organometallic Chemistry II*, vol. 1, Pergamon, Exeter, 1995 (Chapter 10).
- [16] Aldrich Technical Information Bulletin Number AL-134, Handling Air-Sensitive Reagents.
- [17] S. Miyano, H. Hashimoto, *Bull. Chem. Soc. Jpn.* 46 (1973) 892.
- [18] Samarium powder was used as received from Acros.
- [19] M. Lautens, Y. Ren, *J. Org. Chem.* 61 (1996) 2210. HgCl_2 proved an equally efficient activator.
- [20] Samarium powder was used as received from Strem Chemicals.