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Cyclopropenylcarbinol Derivatives as New Versatile Intermediates in Organic Synthesis: Application to the Formation of Enantiomerically Pure Alkylidenecyclopropane Derivatives

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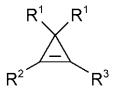
Dedicated to Professor Yitzhak Apeloig on the occasion of his 65th birthday

Abstract: The copper-catalyzed carbomagnesiation (or hydrometalation) reaction of chiral cyclopropenylcarbinol derivatives, obtained by means of a kinetic resolution of secondary allylic alcohols, leads to an easy and straightforward preparation of enantiomerically pure alkylidenecyclopropane derivatives. The reaction mechanism is composed of a *syn*-carbometalation followed by a *syn*-elimination reaction. To gain further insight into the reaction mechanism of the carbometalation, the diastereoselective formation of cyclopropylcarbinol was also achieved and was found to be very sensitive to the nature of the organometallic species used for the addition reaction. Cyclopropylcarbinol could also be prepared through a diastereoselective reduction of cyclopropenylcarbinol derivatives. Finally, functionalization of enantiomerically enriched cyclopropenylcarbinols into the corresponding acetate or phosphinite derivatives leads, under mild conditions, to various enantiomerically pure heterosubstituted alkylidenecyclopropanes.

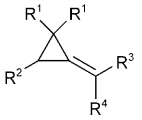
Keywords: alkylidenecyclopropanes · carbometalation · cyclopropenylcarbinols · sigmatropic rearrangement · strained molecules

Introduction

Cyclopropenes as well as alkylidenecyclopropanes are high-energy-possessing and, therefore, reactive molecules with a large spectrum of remarkable activities that extend far beyond simple reactions typical of olefins.[1] Their chemistries have been the subject of numerous reviews and most of their preparations in the racemic form were developed by the mid-1980s.[1]



Cyclopropenes



Alkylidenecyclopropanes

But in the last few years, strain[2] as a design principle for asymmetric reactions has led to a complete renaissance of the field.[1a] Indeed, upon breaking the π bond, the trigonally coordinated ring carbon atoms can pyramidalize, thus relieving the additional angle strain that results from the presence in the three-membered ring of carbon atoms that are nominally sp^2- rather than sp^3-hybridized. Initially, Wiberg suggested that the introduction of each trigonal carbon center into a three-membered ring introduces an additional 12–14 kcal mol^{-1}.[3] For instance, the strain energy of methylenecyclopropane ($R^3=R^4=H$) is estimated to be 41 kcal mol^{-1}, whereas the heat of formation of isomeric 1-methylcyclopropene is 10.2 kcal mol^{-1} higher.[4] The three-membered ring compounds represent the first case in which the exocyclic double bond is found to be more stable than the endocyclic

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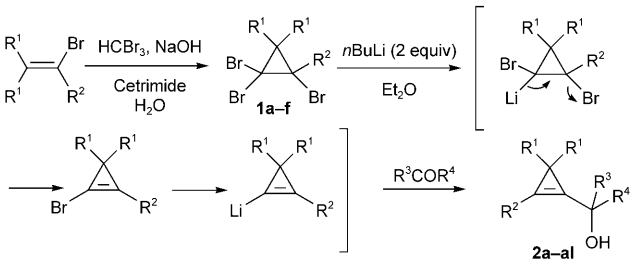
double bond. Johnson and Borden concurred with the explanation that increased angle strain does result from the presence of additional sp^2 centers.[5] Taking into account this strain release, if synthetic transformations could be performed on enantiomerically enriched cyclopropenes, synthetic interests would become clear as a new entry to functionalized enantiomerically enriched compounds. Due to this mounting interest, the synthesis of enantiomerically pure 1-substituted cyclopropene derivatives was reported either by means of the enantioselective metal-catalyzed addition of diazo species to monosubstituted alkynes,[6] or by means of optical resolution.[7] However, the preparation of 1,2-disubstituted (internal) cyclopropenes is still a challenging task and there is still no direct method for their preparation in an enantiomerically enriched form. Most of the methods known to date rely on an additional step to functionalize the remaining sp^2-carbon center.[6j,8] However, if chemistry on the C–H bond is desired, one of the key questions is the C–H bond energy and how it is affected by the strain of the system. A quantitative correlation between C–H bond-dissociation energy (BDE) and the hybridization of the carbon atom was recently described.[9] Cyclopropanes are of sp^n hybridization, where $n>3$. As a result, the two other hybridizations of the carbon atoms (at the C–H bonds but theoretically correct for all C–X bonds) are of sp^m hybridization, where $m<3$. It was shown that a specific C–H BDE can be easily estimated when the hybridization of the carbon at the C–H bonding lobe is known. In general, one could state that for cyclopropanes, the C–H bonds are stronger than the respective bonds in unstrained compounds.

Alkylidenecyclopropane derivatives have also proven their usefulness by their unique reactivity with transition-metal catalysts.[10] These catalyzed transformations, also based on the release of the high level of strain, can be performed either on the distal or proximal bonds of the three-membered ring or on the *exo*-alkylidene moiety.[11] However, the preparation of enantiomerically pure (or even enriched) alkylidenecyclopropane derivatives was also in its infancy. In this paper, we describe our approach to the preparation and reactivity of such challenging entities.

Results and Discussion

Preparation of cyclopropenylcarbinol derivatives: Cyclopropenylcarbinol derivatives **2a–al** are easily prepared in one-chemical step and in good to excellent chemical yields from 1,1,2-trihalogenocyclopropanes **1a–f** (themselves prepared by reaction of substituted vinyl halide derivatives with bromoform in the presence of phase-transfer catalysts such as Cetrimide),[12] by a successive 1,2-dehalogenation reaction followed by a halogen-lithium exchange and reaction with various carbonyl derivatives as described in Scheme 1 and Table 1.

The results summarized in Table 1 show that this approach leads to a large variety of diversely substituted cyclopropenylcarbinols. All of these cyclopropenylcarbinols are stable and can be stored under normal conditions with the exception of the aryl-substituted cyclopropene **2e** (Table 1, entry 5), which slowly decomposes in a day. Carbonyl compounds could be either aromatic or aliphatic ketones (Table 1, entries 1 and 2 and 3–5, respectively), formaldehyde (Table 1, entries 7 and 8), or various aliphatic and aromatic aldehydes (Table 1, entries 9–25 and 26–38). As far as aliphatic aldehydes are concerned, a broad nature of R^3



Scheme 1. Preparation of cyclopropenylcarbinol derivatives **2a–al**.

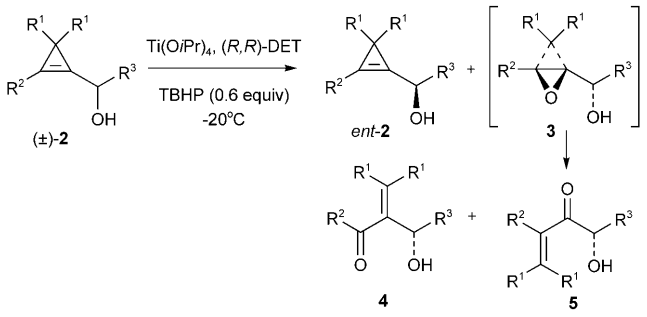
Table 1. Formation of cyclopropenylcarbinols **2a–al**.

Entry	R^1	R^2	R^3	R^4	Yield [%][a]
1 (**1a**)	H	CH_3	C_6H_5	C_6H_5	65 (**2a**)
2 (**1b**)	H	C_4H_9	C_6H_5	C_6H_5	82 (**2b**)
3 (**1a**)	H	CH_3	C_2H_5	C_2H_5	52 (**2c**)
4 (**1b**)	H	C_4H_9	CH_3	CH_3	81 (**2d**)
5 (**1f**)	H	C_6H_5	CH_3	CH_3	73 (**2e**)
6 (**1a**)	H	CH_3	CH_3	C_6H_5	75 (**2f**)
7 (**1b**)	H	C_4H_9	H	H	57 (**2g**)
8 (**1a**)	H	CH_3	H	H	46 (**2h**)
9 (**1a**)	H	CH_3	CH_2CH_2Ph	H	60 (**2i**)
10 (**1b**)	H	CH_2CH_2Ph	C_2H_5	H	56 (**2j**)
11 (**1c**)	CH_3	CH_3	CH_2CH_2Ph	H	65 (**2k**)
12 (**1b**)	H	C_4H_9	CH_3	H	76 (**2l**)
13 (**1a**)	H	CH_3	C_4H_9	H	61 (**2m**)
14 (**1c**)	CH_3	CH_3	CH_3	H	70 (**2n**)
15 (**1c**)	CH_3	CH_3	C_2H_5	H	88 (**2o**)
16 (**1d**)	CH_3	H	C_2H_5	H	85(**2p**)
17 (**1d**)	CH_3	H	CH_2CH_2Ph	H	79 (**2q**)
18 (**1a**)	H	CH_3	CH_2Ph	H	66 (**2r**)
19 (**1c**)	CH_3	CH_3	$CH_2CH{=}CHEt$	H	88 (**2s**)
20 (**1e**)	CH_3	Me_3Si	C_2H_5	H	55 (**2t**)
21 (**1a**)	H	CH_3	*i*Pr	H	55 (**2u**)
22 (**1b**)	H	C_4H_9	*i*Pr	H	35 (**2v**)
23 (**1a**)	H	CH_3	$CH(Ph)_2$	H	94 (**2w**)
24 (**1c**)	CH_3	H	*c*-C_6H_{11}	H	92 (**2x**)
25 (**1a**)	H	CH_3	*t*Bu	H	81 (**2y**)
26 (**1a**)	H	CH_3	C_6H_5	H	87 (**2z**)
27 (**1b**)	H	C_4H_9	C_6H_5	H	62 (**2aa**)
28 (**1c**)	CH_3	CH_3	C_6H_5	H	90 (**2ab**)
29 (**1c**)	CH_3	CH_3	*p*-$MeOC_6H_4$	H	90 (**2ac**)
30 (**1a**)	H	CH_3	*p*-MeC_6H_4	H	88 (**2ad**)
31 (**1d**)	CH_3	H	*p*-MeC_6H_4	H	64 (**2ae**)
32 (**1a**)	H	CH_3	*p*-BrC_6H_4	H	93 (**2af**)
33 (**1a**)	H	CH_3	*p*-$MeOC_6H_4$	H	78 (**2ag**)
34 (**1a**)	H	CH_3	*o*-$BnOC_6H_4$	H	76 (**2ah**)
35 (**1a**)	H	CH_3	3,4,5-$(MeO)_3C_6H_2$	H	77 (**2ai**)
36 (**1b**)	H	C_4H_9	*p*-BrC_6H_4	H	80 (**2aj**)
37 (**1a**)	H	CH_3	3,5-$(Br)_2C_6H_3$	H	85 (**2ak**)
38 (**1a**)	H	CH_3	2,3,5-$(Me)_3C_6H_2$	H	78 (**2al**)

[a] Yields determined after purification by column chromatography on silica gel.

groups can be used such as primary (Table 1, entries 9–20), secondary (Table 1, entries 21–24), and even tertiary alkyl groups (Table 1, entry 25). Aromatic aldehydes can also be sterically bulky without any negative effect on the chemical yields (Table 1, entry 38). Substituent R^2 could be an aryl group (Table 1, entry 5), hydrogen (Table 1, entries 17, 31), silyl groups (Table 1, entry 20), or various alkyl groups (Table 1). The only cyclopropenylcarbinol derivative that we could not isolate was the aryl substituted with $R^2=R^3=Ph$ (and $R^1=R^4=H$).

With an easy and straightforward method for the preparation of racemic cyclopropenylcarbinols, we then turned our attention to their asymmetric syntheses. Considering that these derivatives are a particular type of strained allylic alcohol, we envisaged their preparation in an enantiomerically enriched form through a Sharpless kinetic resolution.[13] When racemic allylic alcohols **2** were subjected to the epoxidation reaction conditions, using (*R*,*R*)-(+)-diethyl tartrate as a chiral ligand, we were pleased to observe, despite the reactive nature of the strained double bond, a very efficient kinetic resolution at −20 °C. Only one enantiomer was epoxidized to lead to the putative unstable chiral 2-oxabicyclo-[1.1.0]butane **3**. Although, Sharpless kinetic resolution implies that 50 % of the substrate undergoes an epoxidation reaction, we were never able to isolate nor to detect this 2-oxabicyclo[1.1.0]butane intermediate **3**. The only products formed were the two α,β-unsaturated ketols **4** and **5**, formed in almost equal amounts (each in 22–25 % isolated yields), as a result of the isomerization of the postulated intermediate **3** through a cleavage of the two peripheral σ bonds (Scheme 2).[14] Oxabicyclobutanes have been also postulated



Scheme 2. Kinetic resolution of cyclopropenylcarbinol derivatives **2** (DET = (+)-diethyl L-tartrate; TBHP = *tert*-butyl hydroperoxide).

several times as intermediates in various thermal and photochemical reactions,[15] but could also never be detected. However, recent high-level quantum chemical studies on the unimolecular (and acid-catalyzed) fragmentation of such intermediates suggested that this compound should be stable enough to be detected in chemical reactions. Since this is not the case, there must be another mechanism, which excludes the formation of oxabicyclobutane at the intermediate stage.[16] This very interesting discrepancy is currently under investigation in our research group and results will be reported in the near future.

Coming back to the kinetic resolution, the remaining non-oxidized products, namely, cyclopropenylcarbinols **2**, were obtained with very high enantiomeric excesses (*ee*) and yields (95–99 % *ee* and 40–47 % yield of isolated products) as described in Scheme 2.[17]

The scope of the kinetic resolution is broad since several different alkyl groups can be present either on the double bond of the cyclopropenyl unit ($R^2=CH_3$ and C_4H_9) or on the cyclopropene itself ($R^1=H$ or CH_3, Table 2).

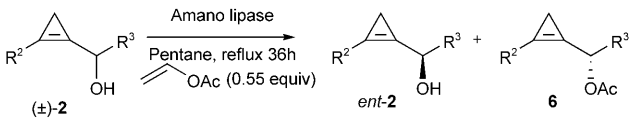
Table 2. Formation of enantiomerically enriched cyclopropenylcarbinols **2**.

Entry	R^1	R^2	R^3	*ee* [%][a]	Yield [%][b]
1	H	CH_3	C_6H_5	99	46 (**2z**)
2	H	CH_3	*p*-BrC_6H_4	99	44 (**2af**)
3	H	CH_3	CH_2CH_2Ph	96	42 (**2i**)
4	H	C_4H_9	C_6H_5	99	44 (**2aa**)
5	H	CH_3	3,5-$(Br)_2C_6H_4$	99	45 (**2ak**)
6	CH_3	CH_3	C_6H_5	99	47 (**2ab**)
7	CH_3	CH_3	CH_2CH_2Ph	95	40 (**2k**)

[a] Enantiomeric excess determined by chiral GC; see the Experimental Section. [b] Yields determined after purification by column chromatography on silica gel.

Aryl and alkyl groups can be arbitrarily used as secondary substituents at the allylic position, although the enantiomeric excess is slightly higher when R^3 is an aryl group (*ee* = 99 %; Table 2 entries 1, 2, and 4–6) instead of an alkyl group (*ee* = 95–96 %; Table 2, entries 3 and 7). Although the Sharpless kinetic resolution gave outstanding enantiomeric excesses and isolated chemical yields for the remaining cyclopropenylcarbinols **2**, half of our starting material was lost by the formation of the two enones **4** and **5** (Scheme 2).

Therefore, to have a better conversion, we were also interested in developing a biocatalytic resolution as depicted in Scheme 3. Indeed, the irreversible, enzyme-mediated acyla-



Scheme 3. Biocatalytic resolution of cyclopropenylcarbinol **2**.

tions in organic solvents mediated by the commercially available Pseudomonas AK (Amano K-10) is a powerful alternative to the Sharpless kinetic resolution.[18]

Generally, the most efficiently resolved alcohols have one small (R^3) and one relatively large group attached to the hydroxymethine functionality. In this context, the large group is the cyclopropenyl group and following this prediction, all the recovered alcohols have the same absolute configuration as the one obtained by means of the Sharpless kinetic resolution using (*R*,*R*)-(+)-diethyl tartrate (see Table 3).[19] The

Table 3. Biocatalytic resolution of cyclopropenylcarbinols **2**.

Entry	R^2	R^3	Yield of **6** [%][a]	*ee* of **6** [%]	Yield of **2** [%][a]	*ee* of **2** [%]
1[b]	C_4H_9	CH_3	42	ND[c]	39	>99[d]
2[e]	C_4H_9	CH_2CH_2Ph	39	>95	37	95[f]
3[g]	CH_3	CH_2CH_2Ph	48	>95	41	>99[e,f]
4[h]	CH_3	C_6H_5	45	ND[h]	40	20[f]
5	CH_3	*p*-BrC_6H_4	25	>99	24	99[f]

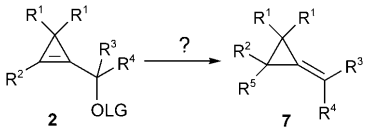
[a] Yields determined after purification by column chromatography on silica gel. [b] The reaction requires 17 h to complete. [c] ND = not determined because separations were difficult with chiral GC. [d] Enantiomeric excess determined by ^{1}H NMR spectroscopy by formation of Mosher ester; see the Experimental Section. [e] The reaction requires one week to complete. [f] Enantiomeric excess determined by chiral GC; see the Experimental Section. [g] The reaction requires 3 d to complete. [h] The reaction requires 24 h to complete.

enantiomeric excess was determined by either chiral GC or the transformation of **2** into its Mosher ester and further ^{1}H NMR spectroscopic analyses (see the Experimental Section). Both the cyclopropenylcarbinols **2** and esters **6** were found to be prepared with excellent enantiomeric excess.

This biocatalytic resolution proceeds smoothly when R^3 substituents are alkyl groups (Table 3, entries 1–3), but is either low yielding or non-enantioselective when this substituent is an aromatic group (Table 3, entries 4 and 5).

In most of the cases, the preparation of racemic and enantiomerically enriched cyclopropenylcarbinol derivatives could be easily achieved and the reaction of the strained double bond was then investigated.

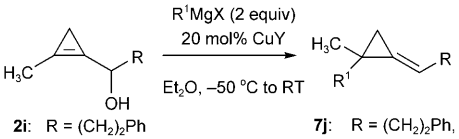
Reactivity of cyclopropenylcarbinol derivatives—New access to alkylidenecyclopropanes: We first focused our attention on the development of a general method for the formation of racemic alkylidenecyclopropanes **7** from cyclopropenylcarbinol derivatives **2** (Scheme 4).



Scheme 4. General preparation of alkylidenecyclopropane derivatives **7**.

Such transformations can be seen either as a metal-catalyzed (or promoted) allylic substitution (S_N2' reaction) or as a two-step mechanism through a carbometalation reaction of an organometallic species on the strained double bond followed by a β-elimination reaction. From the two possible mechanisms, the copper-promoted allylic substitution usually requires a good leaving group (OLG) such as esters, carbamates, sulfonates, phosphates, ethers, acetals, or halides.[20] Free alcohols are rarely used for such transformations. However, if one considers the two-steps mechanism, the reaction proceeds first through a carbometalation reaction, eventually controlled by the presence of the adjacent heteroatom[21] (here OLG), followed by a β elimination of the organometallic species with this OLG moiety. Among all the possible candidates for either a metal-catalyzed S_N2' process or a carbometalation reaction, we were interested in using organocopper species since they are known for their high stereo- and chemoselectivity, which enables them to participate in many synthetic transformations. Although the second mechanistic possibility (tandem carbometalation–elimination reactions) requires a perfect control of the stereochemical outcome for the carbometalation reaction as well as for the β elimination, we decided to consider first this sequence on a nonprotected alcohol moiety (LG = H). The stereochemistry of β-elimination reactions (*syn* versus *anti*) may be dependent on the nature of the halide X of the RMgX involved in the reaction (X = Cl, Br, I),[22] and we first checked, on a standard copper-catalyzed carbomagnesiation reaction, if the nature of the halide of the alkylmagnesium species as well as on the copper salt had an effect on the stereochemistry of the reaction. Representative examples of secondary aliphatic and aromatic alcohols were investigated (**2i** and **2z**, respectively) and the results are reported in Table 4. We can see from Table 4 that the nature of the halide of the

Table 4. Effect of the nature of the halide of RMgX on the stereochemistry of **7**.



2i: R = $(CH_2)_2Ph$
2z: R = Ph

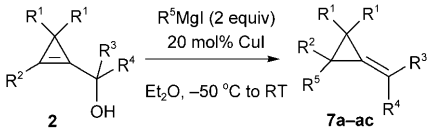
7j: R = $(CH_2)_2Ph$, R^1 = Et
7k: R = $(CH_2)_2Ph$, R^1 = Ph
7r: R = Ph, R^1 = Bu
7s: R = Ph, R^1 = Ph

Entry	R	R^1MgX[a]	CuY	*E*/*Z* ratio[b]
1 (**2i**)	CH_2CH_2Ph	EtMgBr	CuI	80:20
2 (**2i**)	CH_2CH_2Ph	EtMgI	CuI	100:0
3 (**2i**)	CH_2CH_2Ph	PhMgBr	CuI	86:14
4 (**2i**)	CH_2CH_2Ph	PhMgI	CuI	87:13
5 (**2z**)	Ph	BuMgCl	CuCl	80:20
6 (**2z**)	Ph	BuMgBr	CuBr	85:15
7 (**2z**)	Ph	BuMgBr	CuI	86:14
8 (**2z**)	Ph	BuMgBr	CuBr, $CuP(OEt)_3$	70:30
9 (**2z**)	Ph	BuMgI	CuI	97:3
10 (**2z**)	Ph	PhMgBr	CuI	87:13
11 (**2z**)	Ph	PhMgI	CuI	87:13

[a] All the Grignard reagents were prepared in Et_2O and titrated before use. [b] *E*/*Z* ratio determined from the NMR spectra of the crude reaction mixture; yields were always higher than 80%.

Grignard reagents has a very important effect on the *E*/*Z* ratio of the formed alkylidenecyclopropane derivatives: when secondary aliphatic alcohol **2i** was treated with EtMgI, a unique *E* isomer was obtained whereas the same starting material leads to two geometrical isomers in a 80:20 ratio when treated with EtMgBr (Table 4, entries 2 and 1, respectively).[23] However, the nature of the halide (X = Br versus I) for the copper-catalyzed addition of arylmagnesium halide derivatives has no effect on the stereochemistry of the formed double bond and both isomers were obtained.

Similarly, when secondary aromatic aldehyde **2z** was used, the same trend was observed (better *E*/*Z* ratio when X = Y = I) for the addition of aliphatic Grignard but has no effect again for the addition of aryl Grignard reagents (see the section "Mechanistic hypothesis" for a tentative rationalization). Without copper salt, no reaction was detected. Having established the best experimental conditions as described in Scheme 5, we then decided to generalize the formation of diversely substituted alkylidenecyclopropane derivatives **7** from cyclopropenylcarbinols **2**, and the results reported in Table 5 fulfilled our expectations.[17]



Scheme 5. Preparation of alkylidenecyclopropane derivatives **7a–ac**.

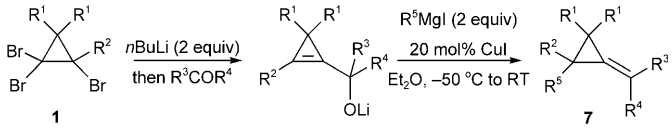
The reaction proceeded smoothly when tertiary alcohols were used (Table 5, entries 1–5) whatever the nature of the R^2 substituent on the cyclopropenyl units (alkyl or aryl) and the nature of the Grignard reagents (R^5 = alkyl or aryl). Similarly, the reaction led to methylenecyclopropanes when primary alcohols were utilized as starting materials (Table 5, entries 6 and 7). When secondary alcohols were used (R^3 = alkyl or aryl; R^4 = H), the fate of the stereochemistry of the resulting double bond in the alkylidenecyclopropane derivatives, raised in our previous study (Table 4), was also considered closely. When aliphatic Grignard reagents RMgI were added to secondary aliphatic cyclopropenylcarbinols **2** (R^3 = alkyl), only the *E* isomer of the alkylidenecyclopropanes **7** were formed (Table 5, entries 8, 10, and 12–15). Only when aromatic Grignard was added to **2m** and **2i** (Table 5, entries 9 and 11), was a mixture of two *E*/*Z* geometrical isomers obtained. Clearly, the added aryl Grignard behaves differently. When the substituent of the secondary allylic alcohol is aromatic, the *E* isomer is mainly obtained but some variations could be found depending on the nature of the aryl group (Table 5, entries 16–29; in entry 22, the configuration of the double bond was identical but the configuration of the product is now *Z* because of the interconversion of substituents R^1 and R^2). The stereochemistry of the double bond could be determined for **7ab** by means of NOE experiments (see the Experimental Section). Interestingly, **7** could also be prepared in a single-pot operation from **1** by the addition of Grignard reagent and copper catalyst to the intermediate lithium cyclopropenylcarbinol **2**·Li as described in Scheme 6. This one-pot strategy was performed for the preparation of **7d** (83%), **7g** (72%), **7h** (82%), **7j** (85%; *E*/*Z* = 90:10), **7q** (77%; *E*/*Z* = 90:10), **7r** (89%; *E*/*Z* = 88:12), and **7z** (90%; *E*/*Z* = 92:8).

Table 5. Preparation of alkylidenecyclopropane derivatives **7**.

Entry	R^1	R^2	R^3	R^4	R^5	*E*/*Z*[a]	Yield [%][b]
1 (**2c**)	H	CH_3	C_2H_5	C_2H_5	C_4H_9	–	76 (**7a**)
2 (**2c**)	H	CH_3	C_2H_5	C_2H_5	C_6H_5	–	81 (**7b**)
3 (**2e**)	H	C_6H_5	CH_3	CH_3	C_2H_5	–	85 (**7c**)
4 (**2a**)	H	CH_3	C_6H_5	C_6H_5	C_6H_5	–	61 (**7d**)
5 (**2b**)	H	C_4H_9	C_6H_5	C_6H_5	C_6H_5	–	62 (**7e**)
6 (**2h**)	H	CH_3	H	H	C_6H_5	–	72 (**7f**)
7 (**2g**)	H	C_4H_9	H	H	C_6H_{13}	–	82 (**7g**)
8 (**2m**)	H	CH_3	C_4H_9	H	CH_3	100:0	65 (**7h**)
9 (**2m**)	H	CH_3	C_4H_9	H	C_6H_5	83:17	72 (**7i**)
10 (**2i**)	H	CH_3	CH_2CH_2Ph	H	C_2H_5	99:1	85 (**7j**)
11 (**2i**)	H	CH_3	CH_2CH_2Ph	H	C_6H_5	87:13	77 (**7k**)
12 (**2u**)	H	CH_3	*i*Pr	H	C_4H_9	100:0	91 (**7l**)
13 (**2v**)	H	C_4H_9	*i*Pr	H	CH_3	100:0	80 (**7m**)
14 (**2w**)	H	CH_3	$CH(Ph)_2$	H	C_4H_9	100:0	75 (**7n**)
15 (**2w**)	H	CH_3	$CH(Ph)_2$	H	C_2H_5	100:0	84 (**7o**)
16 (**2z**)	H	CH_3	C_6H_5	H	CH_3	92:8	81 (**7p**)
17 (**2z**)	H	CH_3	C_6H_5	H	C_2H_5	96:4	72 (**7q**)
18 (**2z**)	H	CH_3	C_6H_5	H	C_4H_9	97:3	70 (**7r**)
19 (**2z**)	H	CH_3	C_6H_5	H	C_6H_5	87:13	66 (**7s**)
20 (**2ad**)	H	CH_3	*p*-MeC_6H_4	H	C_2H_5	95:5	88 (**7t**)
21 (**2ad**)	H	CH_3	*p*-MeC_6H_4	H	C_4H_9	88:12	89 (**7u**)
22 (**2ae**)	CH_3	H	*p*-MeC_6H_4	H	CH_3	12:88	91 (**7v**)
23 (**2ae**)	H	CH_3	*p*-MeC_6H_4	H	C_6H_5	88:12	85 (**7w**)
24 (**2ag**)	H	CH_3	*p*-$MeOC_6H_4$	H	C_2H_5	95:5	89 (**7x**)
25 (**2ah**)	H	CH_3	*o*-$BnOC_6H_4$	H	C_2H_5	60:40	91 (**7y**)
26 (**2ai**)	H	CH_3	3,4,5-$(MeO)_3C_6H_2$	H	C_6H_5	86:14	88 (**7z**)
27 (**2af**)	H	CH_3	*p*-BrC_6H_4	H	C_2H_5	95:5	88 (**7aa**)
28 (**2af**)	H	CH_3	*p*-$HOOCC_6H_4$	H	C_5H_{11}	92:8	89 (**7ab**)
29 (**2ak**)	H	CH_3	3,5-$Br_2C_6H_3$	H	C_2H_5	92:8	92 (**7ac**)

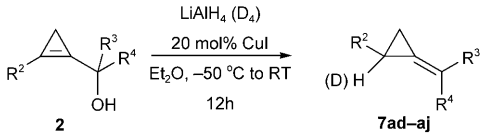
[a] Determined from the ^1H NMR spectra of the crude reaction mixture. [b] Determined after purification by column chromatography.

To extend this methodology, and particularly if aiming to prepare alkylidenecyclopropanes **7** possessing tertiary stereocenters ($R^1 = R^2 = H$), the more challenging tribromocyclopropane **1g** ($R^1 = R^2 = H$), resulting from the reaction of bromoform to gaseous bromoethene, had to be used to obtain **1g**. Despite many attempts, we constantly got the tribromocyclopropane **1g** in very low yield. Therefore, we thought to develop an alternative strategy to obtain **7** ($R^1 = R^2 = H$) using our easily prepared precursors **2** ($R^1 = H$, R^2 = alkyl). In such cases, the formal S_N2' addition of a hydride to the cyclopropenylcarbinols **2** should be the relevant strategy for the formation of the expected alkylidenecyclopropane derivatives **7**. The copper(I)-catalyzed hydride transfer is known to be a mild and often selective reducing agent, and among the most ex-



Scheme 6. Preparation of alkylidenecyclopropane derivatives **7** directly from **1**.

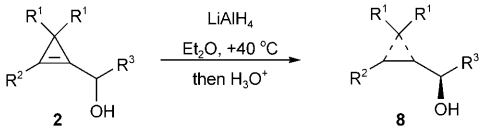
tensively studied and routinely used is the phosphine-stabilized hexameric complex $[\{CuH(PPh_3)\}_6]$, commonly referred to as Stryker's reagent.[24] It smoothly effects conjugate reductions of various α,β-unsaturated compounds.[25] More recently, alternatives such as stannanes,[26] boranes,[27] and in particular silanes[28] have been developed as hydrogen equivalents in CuH chemistry. Interestingly, since the initial report of Whitesides that reported the preparation of copper hydride by means of treatment of iBu$_2$AlH with CuBr,[29] the use of HCu generated from aluminum species has never been really developed. We were pleased to find that the addition of $LiAlH_4$ in Et_2O to a solution of 20 mol% of CuI and cyclopropenylcarbinol **2** at −50 °C slowly warmed to room temperature overnight gives the expected alkylidenecyclopropanes **7** in very good yield as described in Scheme 7.[30]



Scheme 7. Copper-catalyzed hydride transfer from $LiAlH_4$.

Tertiary and secondary alcohol derivatives (Table 6, entries 1–4 and 5–10, respectively) led similarly to alkylidenecyclopropane derivatives by means of a formal S_N2' reaction of HCu (the low yield observed for **7af** is most probably due to the volatile nature of the final product; Table 6, entry 4).

When commercially available $LiAlD_4$ was used as reducing agent, the alkylidenecyclopropane deuteriated in the allylic position was obtained in good yields with >95% deuterium incorporation (Table 6, entries 2 and 6). Substituents on the double bond of the cyclopropenyl ring (R^2) can be either methyl or butyl. Substituents R^3 and R^4 can be either alkyl or aryl groups, or hydrogen atoms. When secondary alcohols are used (R^3 = alkyl or aryl; R^4 = H; Table 6, entries 5 to 10), we always found that the major isomer was of *E* configuration. So, the copper-catalyzed hydride addition leads to the corresponding alkylidenecyclopropanes through a formal S_N2' process. What would be the chemical outcome of the addition of $LiAlH_4$ without copper salt? Reduction of cyclopropenes (non-copper catalyzed) is reported in the literature for simple substrates,[31] and since diastereoselection in the hydrometalation of acyclic compounds is controlled by allylic,[21b,32] homoallylic,[33] and even more remote stereogenic centers,[34] we thought that the diastereoselective reduction of cyclopropenylcarbinols **2** should be an interesting and powerful solution to the preparation of cyclopropylcarbinol derivatives **8** as described in Scheme 8.[35]



Scheme 8. Diastereoselective reduction of cyclopropenylcarbinol **2** into *trans*-cyclopropylcarbinol **8**.

We first reduced unsubstituted cyclopropenylcarbinols **2j** and **2c** (R^1 = H, R^2 = alkyl) with 1 equiv of $LiAlH_4$ in Et_2O at +40 °C. Under these conditions, we were pleased to obtain in good chemical yields the expected cyclopropylcarbinol products **8a**,**b** but with only a moderate *anti* selectivity (*anti*/*syn* 80:20)[36] as described in Table 7, entries 1 and 2.

On the other hand, when the three-membered ring of the cyclopropenylcarbinol has a geminal dialkyl group such as in Table 7 (R^1 = Me, entries 3–8), excellent diastereoselectivities are obtained. The reduction of the fully substituted cyclopropenylcarbinol **2o** occurs readily with 1 equiv of $LiAlH_4$ in Et_2O to give *anti*-cyclopropylcarbinol **8c** as a single diastereoisomer. If only 0.5 equiv of $LiAlH_4$ is used, reduced products are obtained but in lower yields. Similarly, if THF is used as solvent instead of Et_2O, the *anti*/*syn* ratio of the reaction drops to only 6:1 in low yield. It should be noted that the direct cyclopropanation of acyclic allylic alcohols with halomethylmetal reagents such as zinc, samarium, or aluminum carbenoids is a well-known process but generally leads to the *syn*-cyclopropylcarbinol derivatives.[37] The direct preparation of *anti*-cyclopropylcarbinol derivatives with good diastereoselection is a

Table 6. Copper-catalyzed formal S_N2' process.

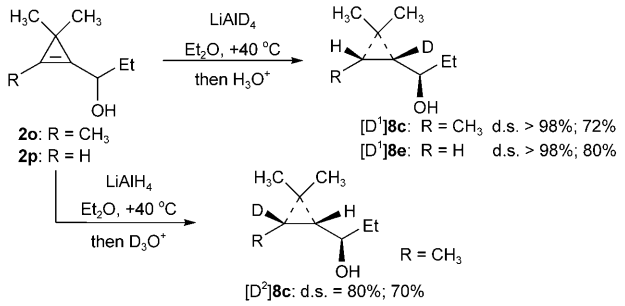
Entry	R^2	R^3	R^4	Hydride	*E*/*Z* ratio[a]	Yield [%][b]
1 (**2a**)	CH_3	C_6H_5	C_6H_5	H	–	87 (**7ad**)
2 (**2a**)	CH_3	C_6H_5	C_6H_5	D	–	85 ([D]**7ad**)
3 (**2b**)	C_4H_9	C_6H_5	C_6H_5	H	–	82 (**7ae**)
4 (**2c**)	CH_3	C_2H_5	C_2H_5	H	–	40 (**7af**)
5 (**2i**)	CH_3	CH_2CH_2Ph	H	H	85:15	68 (**7ag**)
6 (**2i**)	CH_3	CH_2CH_2Ph	H	D	85:15	70 ([D]**7ag**)
7 (**2r**)	CH_3	$CH_2C_6H_4$	H	H	93:7	76 (**7ah**)
8 (**2z**)	CH_3	C_6H_5	H	H	93:7	60 (**7ai**)
9 (**2aa**)	C_4H_9	C_6H_5	H	H	85:15	61 (**7aj**)
10 (**2af**)	CH_3	*p*-$HOOCC_6H_4$	H	H	90:10	83[c] (**7ak**)

[a] *E*/*Z* ratio determined from ^{1}H NMR spectra of the crude reaction mixture. [b] Yields determined after purification by column chromatography on silica gel. [c] Alkylidenecyclopropane (ACP) **7ak** was obtained directly through a bromine–lithium exchange and treatment with CO_2, see Experimental Section.

Table 7. Diastereoselective reduction of cyclopropenylcarbinols **2**.

Entry	R^1	R^2	R^3	*anti*/*syn* ratio[a]	Yield [%][b]
1 (**2j**)	H	CH_2CH_2Ph	C_2H_5	80:20	85 (**8a**)
2 (**2c**)	H	CH_3	C_2H_5	80:20	50 (**8b**)
3 (**2o**)	CH_3	CH_3	C_2H_5	>98:2	86 (**8c**)
4 (**2n**)	CH_3	CH_3	CH_3	>98:2	74 (**8d**)
5 (**2p**)	CH_3	H	C_2H_5	>98:2	80 (**8e**)
6 (**2x**)	CH_3	H	*c*-C_6H_{11}	>98:2	75 (**8f**)
7 (**2s**)	CH_3	CH_3	$CH_2CH{=}CHEt$	>98:2	80 (**8g**)
8 (**2t**)	CH_3	$Si(CH_3)_3$	C_2H_5	>98:2[c]	64 (**8h**)

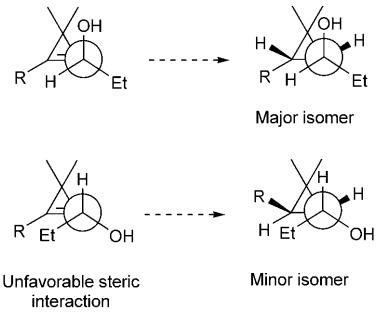
[a] Diastereomeric ratio was determined from ^{1}H NMR spectra of the crude reaction mixture. [b] Yields determined after purification by column chromatography on silica gel. [c] Diastereomeric ratio of the *trans*-cyclopropylcarbinol versus the secondary alcohol; ratio of the *cis*/*trans*-cyclopropane itself is 40:60.



Scheme 9. Deuterium-labeling experiments. The values represent the diastereoselectivity followed by the yield.

much more difficult task and some of these compounds are accessible by the reduction of the corresponding cyclopropyl ketone[38] or by a diastereoselective cyclopropanation of silyl-protected allylic alcohol[39] with use of the zinc carbenoid reported by Shi et al.[40] However, primary zinc carbenoid is mostly used and only a few examples are described for the cyclopropanation reaction with less stable secondary and tertiary carbenoids.[41] The presence of the free hydroxyl group is absolutely necessary for the reduction of cyclopropenylcarbinol derivatives **2**. When the alcohol is protected as its *tert*-butyldimethylsilyl ether, no reduced product was observed under our experimental conditions. Similarly, neither the Schwartz reagent [$ZrClCp_2(H)$] ($Cp = C_5H_5$) or diisobutylaluminum hydride (DIBAL-H) led to cyclopropylcarbinols **8**. The cyclopropenylcarbinol can also bear three alkyl substituents as in **2p** ($R^2 = H$, Table 7, entry 5) or be substituted by a secondary alkyl group (Table 7, entry 6) without altering the diastereoselectivity of the reduction. As the heat of hydrogenation for the conversion of cyclopropene to cyclopropane is approximately 54 kcal mol^{-1} and is considered larger than that for the conversion of ethylene to ethane,[42] the chemoselective reduction of cyclopropylcarbinol containing an *E* double bond such as in **2s** (Table 7, entry 7) has been investigated. The expected *anti*-cyclopropylcarbinol **8g** was obtained in good yield as a unique isomer without any further reduction of the external *E* double bond. The silyl cyclopropenylcarbinol **2t** (Table 7, entry 8), treated under our experimental conditions, leads to the expected product **8h** with an *anti* relationship between the cyclopropyl and the secondary alcohol moieties, but as a mixture of *trans* and *cis* isomers on the silylcyclopropane ring itself (*trans*/*cis* 60:40). The presence of these two isomers came from the remarkable facile configurational isomerization of 1-silyl-1-aluminocyclopropyl derivatives.[43] The regioselectivity of the hydroalumination reaction on the cyclopropenyl ring has been mapped out by deuterium-labeling experiments. When $LiAlD_4$ was used as the reducing agent followed by acidic hydrolysis, **2o** and **2p** led to the deuteriocyclopropanes [D^1]**8c** and [D^1]**8e**, respectively, as unique isomers in good chemical yields as shown in Scheme 9.

On the other hand, when **2o** was treated with $LiAlH_4$ followed by deuterio hydrolysis, [D^2]**8c** was obtained as the unique isomer (Scheme 9). Therefore, both deuteriocyclopropylcarbinol regioisomers can be selectively prepared. Considering that the deprotonation precedes the reduction and assuming that the reaction occurs intramolecularly, thus inducing the hydroalumination reaction on the same face as the oxygen atom, the *anti*-diastereofacial selectivity in the hydroalumination reaction of cyclopropenylcarbinol derivatives must involve a transition state with the smallest substituent at the preexisting stereogenic center (hydrogen) oriented "inside" over the face of the transition-state ring. Minimization of the allylic 1,3-strain (A-1,3-strain)[44] is therefore the main controlling element for the good diastereocontrol and then the oxygen atom is oriented slightly "outside" (Houk's transition-state model)[45] as described in Scheme 10. Moreover, the presence of the geminal dimethyl

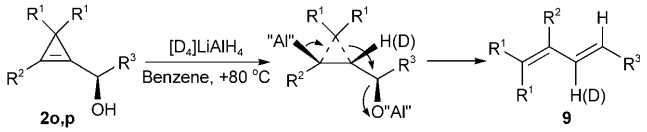


Scheme 10. Mechanistic rationalization for the diastereoselective reduction.

group on the upper carbon of the cyclopropenyl moiety also has an effect on the diastereoselectivity of the reduction (compare entries 2 and 3, Table 7). Due to the short bond lengths of the carbon–carbon bonds in the cyclopropene ring, *syn*-pentane interactions (between the R substituent at the preexisting center and the methyl group) have an important effect on the diastereoselectivity.

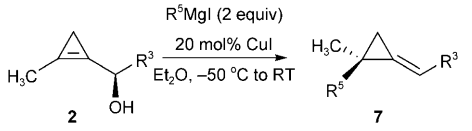
It should be noted that the regiochemistry of the hydroalumination reaction leads to the carbon–aluminum bond in a γ position (as determined by treatment with D_3O^+, see

Scheme 9), whereas the addition of a catalytic amount of copper(I) salt to $LiAlH_4$ reverses completely the chemical outcome of the reaction via a postulated copper hydride species. When R^3 is an aromatic group (Scheme 11), the reduction also occurs but the resulting vinyl aluminum species obtained before acidic hydrolysis undergoes a ring fragmentation into polysubstituted dienes **9**.[46] The same trend was observed when the intermediate cyclopropylaluminum species possessing alkyl groups R^3 was heated either at 80 °C in benzene (or stirred for a longer period of time in Et_2O at reflux).[46,47]



Scheme 11. Fragmentation of cyclopropylaluminum species into dienes.

Preparation of enantiomerically enriched alkylidenecyclopropane derivatives: By following the strategy that we described in Scheme 5 for the preparation of racemic alkylidenecyclopropanes from cyclopropenylcarbinols, enantiomerically pure alcohols **2** were treated with various Grignard reagents in the presence of 20 mol% of CuI as described in Scheme 12.



Scheme 12. Preparation of enantiomerically enriched alkylidenecyclopropanes.

The reaction proceeds with an excellent transfer of chirality from chiral cyclopropenylcarbinols to alkylidenecyclopropanes regardless of the nature of the secondary alcohols (Table 8; R^3 = alkyl (entry 1) or aryl (entries 2–6)) and of the alkyl magnesium iodides (Table 8; R^5 = aryl (entry 4) or alkyl (entries 1–3, 5, 6)) used in this transformation. The synthesis of alkylidenecyclopropane derivatives possessing enantiomerically pure quaternary stereocenters is therefore easily achieved.[48] The results are summarized in Table 8.

To establish the absolute configuration and therefore to have some insight into the reaction mechanism, we had to convert alkylidenecyclopropane **7aa** into a crystalline product as described in Scheme 13.

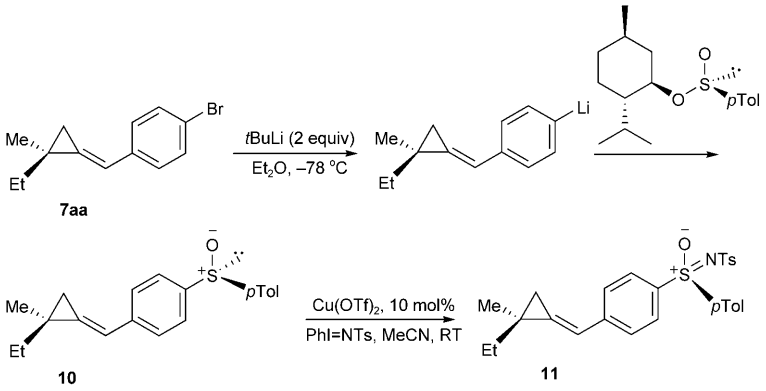
Table 8. Enantioselective preparation of alkylidenecyclopropanes.

Entry	*ee* of **2** [%]	R^3	R^5	*E*/*Z* ratio[a]	*ee* of **7** [%][b]	Yield [%][c]
1 (**2i**)	96	CH_2CH_2Ph	C_2H_5	>99:1	95	85 (**7j**)
2 (**2z**)	99	C_6H_5	C_2H_5	96:4	95	72 (**7q**)
3 (**2z**)	99	C_6H_5	C_4H_9	97:3	97	70 (**7r**)
4 (**2z**)	99	C_6H_5	C_6H_5	87:13	97	66 (**7s**)
5 (**2af**)	99	*p*-BrC_6H_4	C_2H_5	95:5	99	88 (**7aa**)
6 (**2ad**)	99	*p*-MeC_6H_4	C_2H_5	95:5	99	88 (**7t**)

[a] *E*/*Z* ratio determined from ^1H NMR spectra of the crude reaction mixture. [b] Enantiomeric excesses of the *E* isomers were determined by gas chromatography analyses on a chiral column (cyclodextrin B); see the Experimental Section. [c] Yields determined after purification by column chromatography on silica gel.

Treatment of **7aa** with *t*BuLi in Et_2O at low temperature leads to the corresponding aryl lithium species, which was reacted with enantiomerically pure (−)-menthyl-(*S*)-*p*-toluene sulfinate[49] to give the corresponding alkylidenecyclopropane **10** possessing an arylsulfoxide moiety. The reaction with sulfinate ester proceeds stereospecifically with inversion of configuration at the sulfur atom.[49] Then, the reaction of PhI=NTs (Ts = tosyl) with sulfoxide **10** in the presence of a catalytic amount of copper(II) salts afforded the corresponding *N*-tosylsulfoximines **11** in high yield. This method proceeds with complete retention of configuration at sulfur.[50] The absolute configuration of the stereogenic center on cyclopropane **11** was unambiguously determined by using X-ray analysis[51] (Figure 1) and the other reaction products described in Table 8 were assigned analogously. The *Z* isomer of alkylidenecyclopropanes has the opposite absolute configuration.

However, every synthetic organic chemist has at some time faced the problem of getting a single crystal of good quality for X-ray crystallography and this technique, although extremely powerful, may be time consuming. Therefore, we also developed an alternative approach in which experimental circular dichroism (CD) data of our alkylidene-



Scheme 13. Derivatization of **7aa** into crystalline product **11**.

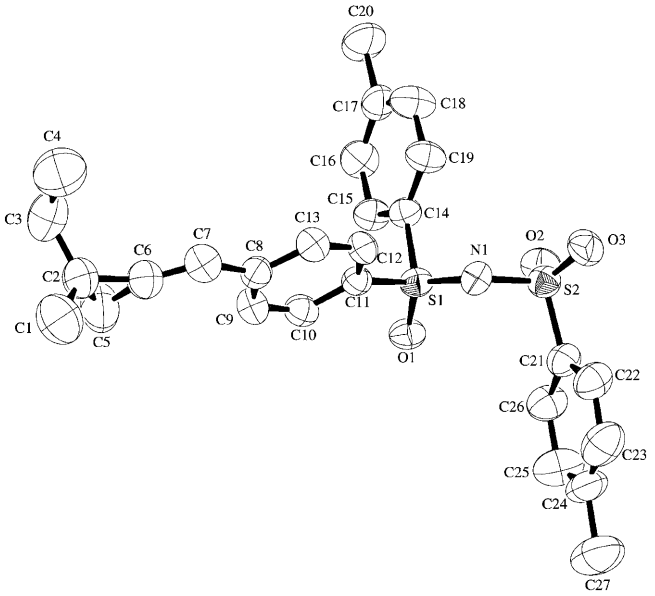


Figure 1. X-ray crystal structure determination of the absolute configuration of **11**.

cyclopropane derivatives were compared with calculated CD spectra of both enantiomers.

Time-dependent DFT (TD-DFT) calculations have proven to be very successful in predicting electronic spectra. In flexible compounds, the calculation of the electronic and CD spectra may become complicated since each of the conformers has different spectral characteristics and the observed spectra are a weighted average of the different conformers. However, in rigid molecules like the one discussed here, one or two (see below) conformations are enough to describe the molecules.

The geometries of the molecules were optimized at the B3LYP/6-311G(d) theoretical level, which is sufficient for an accurate description of the geometry. The spectral calculations should be carried out with a polarized and augmented basis set in the presence of solvent. In general, the TD-DFT simulations were carried out at the B3LYP/aug-cc-PVDZ level, using the polarizable continuum model (PCM) for the solvent description on B3LYP/6-311G(g) geometries. In some cases convergence problems appeared. It was found that TD-B3LYP/6-311+G(d) produced very similar spectra but generally shows no convergence problems. Thus, in some cases the latter computation level was used.

The number of transitions that were calculated was always twenty to be sure that tails of strong absorbencies that are outside of the measured region were included. Each absorbance maximum was placed in a center of a Gaussian with a line width of 20 nm, and the computed spectra are the sum of such twenty Gaussians. As a standard procedure the UV/Vis spectra were calculated and compared to the experimental spectra. This comparison allowed us to obtain the wavelength difference, typically between 5 and 17 nm, between the calculated and experimental spectra. This correction was applied to the correction of the wavelength of the computed CD spectra (see Figure 2).

On the top spectra, the simulated *R* enantiomer (gray line) does not fit with the experimental CD (black line). On the other hand, the spectra on the bottom (please note that the scales of the graphs are different) show the calculated CD (gray line) is similar to the experimental CD (black line). There is no complete superposition since the simulated CD was for the pure (*E*)-alkylidenecyclopropane **7aa**, whereas the experimental alkylidenecyclopropane is formed as an *E*/*Z* mixture of 95:5.

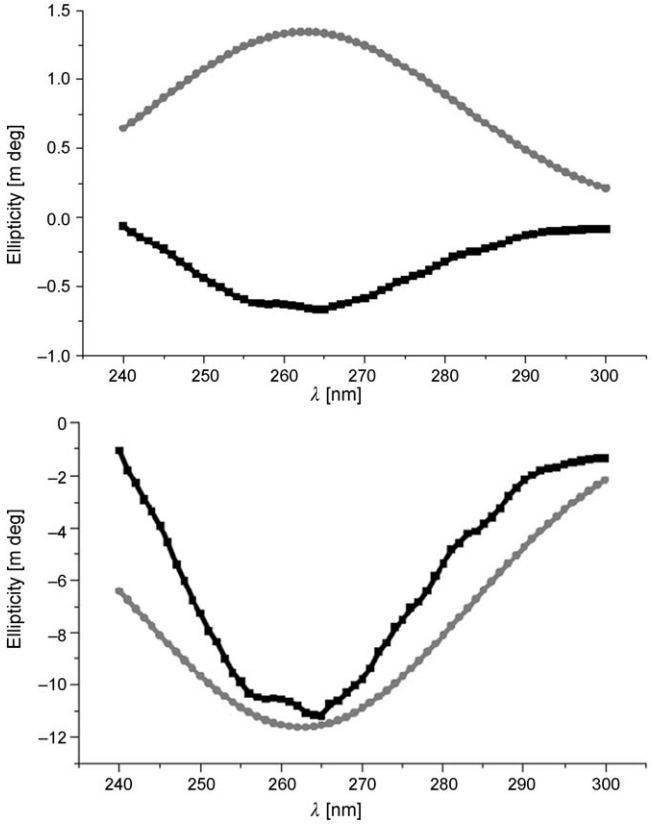
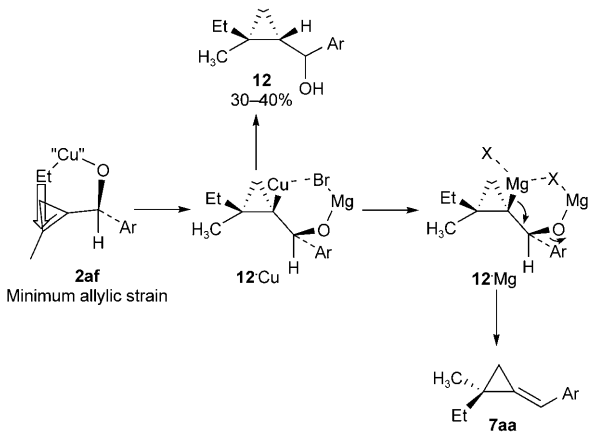


Figure 2. Simulated CD (gray circles) and experimentally measured (black circles) spectra of the *R* (top) and *S* (bottom) enantiomers of **7aa**.

Mechanistic hypothesis: The absolute configuration of the starting cyclopropenylcarbinol **2af** and the final alkylidenecyclopropane **7aa** implies an overall *syn* S_N2' displacement of the alcohol moiety. However, starting at −50 °C, when the stirred mixture was slowly warmed to room temperature and carefully monitored by analyses of hydrolyzed aliquots, we were able to isolate the addition product **12** in the range of 30 to 40 % and then this cyclopropylmetal (**12**·Cu or **12**·MgX) disappears in favor of the alkylidenecyclopropane **7aa**, which is obtained in good yields. Considering that the deprotonation of the alcohol precedes the addition, the most stable conformer of the cyclopropenylcarbinolate is given in Scheme 14 with the smallest substituent at the pre-



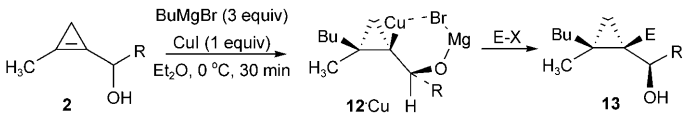
Scheme 14. Mechanistic hypothesis for the formation of alkylidenecyclopropane derivatives.

existing stereocenter (hydrogen) oriented "inside" and the aryl group "outside", away from the allylic methyl substituent (minimum A-1,3-strain). Thus, this catalytic reaction is composed of 1) a *syn* copper-catalyzed carbomagnesiation reaction leading to the corresponding cyclopropylcopper **12**·Cu, followed by 2) a transmetalation reaction into the corresponding cyclopropylmagnesium **12**·Mg, and then 3) a *syn*-elimination reaction (Scheme 14).

As the *E*/*Z* ratio is dependent on the nature of the halide used (see Table 4), the percentage of *syn* versus *anti* elimination may be indeed dependent of the size of halide X in the cyclic transition state of **12**·Mg (Scheme 14); if X = I, a cyclic transition state may be responsible for a *syn* elimination, whereas if X = Br or Cl, the size of the halide may not accommodate the cyclic transition state and a certain percentage of *anti* β elimination can result.

As quoted before, it was suggested that the elimination proceeds only when the contra-thermodynamic copper to magnesium transmetalation reaction occurs, as the intermediate **12** could be isolated in the range of 30–40% by hydrolysis of aliquots (with only 20 mol% copper salt from the beginning). Therefore, if such a transmetalation reaction could be avoided, then the carbometalated product **12**·Cu would be more stable towards β elimination (the carbon–copper bond is usually less prone to β elimination than the carbon–magnesium bond),[52] and should react with different electrophiles to give functionalized cyclopropylcarbinol derivatives **13**. To achieve this goal, the carbometalation reaction should therefore be performed with a stoichiometric amount of copper salt. Therefore, the same carbometalation reaction has been performed but using a full equivalent of copper salt. When cyclopropenylcarbinols **2** were treated with an excess of Grignard reagents (2 or 3 equiv) in the presence of 1 equiv of CuI in Et_2O at 0 °C, we were pleased to observe a fast carbometalation reaction that led to the corresponding *trans*-cyclopropylcarbinol **13** after hydrolysis (Scheme 15).[53]

Under such conditions, alkylidenecyclopropanes **7** were not observed, which indicates that cyclopropylcopper derivatives **12**·Cu are stable towards β-elimination reactions (Table 9). The formation of the *trans*-cyclopropylcarbinols can be rationalized by a *syn*-directed carbocupration reaction as indicated in Scheme 15. As summarized in Table 9,



Scheme 15. Carbometalation of cyclopropenylcarbinol species with $RCu{\cdot}MgBr_2$.

Table 9. Diastereoselective carbocupration of cyclopropenylcarbinols **2**.

Entry	R	E–X	E	*anti*/*syn* ratio[a]	Yield [%][b]
1 (**2i**)	CH_2CH_2Ph	H_3O^+	H	75:25	76 (**13a**)
2 (**2u**)	*i*Pr	H_3O^+	H	>95:5	82 (**13b**)
3 (**2w**)	$CH(Ph)_2$	H_3O^+	H	>95:5	73 (**13c**)
4 (**2y**)	*t*Bu	H_3O^+	H	>95:5	92 (**13d**)
5 (**2z**)	C_6H_5	H_3O^+	H	85:15	70 (**13e**)
6 (**2w**)	$CH(Ph)_2$	I_2	I	>95:5	84 (**13f**)
7 (**2w**)	$CH(Ph)_2$	allyl-Br	C_3H_5	>95:5	81 (**13g**)

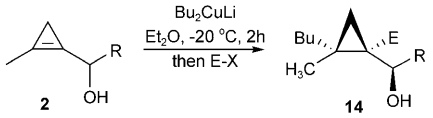
[a] Diastereomeric ratios were determined from the ^1H NMR spectra of the crude reaction mixture. [b] Yields determined after purification by column chromatography on silica gel.

the carbometalation reaction has been successfully extended to a large variety of substrates (R = primary, secondary, and tertiary alkyl groups; and aromatic groups; see entries 1 to 5, respectively, Table 9).

In general, these reactions exhibit excellent yields but the diastereomeric ratio is dependent on the steric hindrance of the R group at the carbinol center (compare Table 9, entries 1 and 5 with entries 2–4). The *anti*/*syn* ratio is higher than 95:5 with secondary and tertiary alkyl groups but only moderate with primary alkyl and aromatic groups. The reaction can also be performed with only two equivalents of RMgBr instead of three equivalents as quoted in Table 9 (1 equiv is necessary for the deprotonation reaction) with 1 equiv of CuI (i.e., **2i** leads to **13a** in identical diastereomeric ratio) but the reaction takes longer. The stereochemistry was deduced from comparison with authentic samples.[36] The presence of a discrete organometallic species was checked by iodinolysis or by reaction with allyl halide (Table 9, entries 6 and 7, respectively). Without copper salt, the reaction does not proceed. So, clearly, the carbometalation of $RCu{\cdot}MgX_2$ is stereochemically controlled by the substituent R, but more importantly, no β elimination was observed, which suggests that the formation of alkylidenecyclopropanes (see Scheme 14) resulted from the contra-thermodynamic transmetalation of cyclopropylcopper **12**·Cu into cyclopropylmagnesium halide **12**·Mg and the stereochemistry of the β elimination was dependent on the halide used (Grignard reagents with different halides lead to the same diastereoisomer for the conversion of **2i** into **13a**).

Surprisingly, when the same reaction was performed with an organocuprate coming from *n*BuLi (instead of

*n*BuMgBr) with the same copper salt, the observed diastereomeric ratio was 5:95 in favor of the *syn* isomer in good isolated yield (Scheme 16)! A complete reversal of stereoselectivity was therefore observed when dialkyl cuprate is used (compare Schemes 16 and 15).



Scheme 16. Carbometalation of cyclopropenylcarbinol species with R_2CuLi.

This discrepancy is only valid for the carbometalation of cyclopropenylcarbinol and cannot be extended to various different allylic alcohols.

Although we still do not have a rational explanation for this stereodivergent carbocupration reaction (we may assume that different aggregation states of the organocopper may lead to different stereoisomers), we have, however, concentrated our efforts to improve the scope of this reaction in favor of the *syn* isomer. The same *syn*/*anti* ratio can also be obtained when the carbocupration reaction is performed with only 1 equiv of lithium dialkyl cuprate on the pre-lithiated cyclopropenylcarbinol **2**. Whatever the stoichiometry used in the preparation of the organocopper derivatives from alkyllithium species and CuI (1–4 equiv of Bu_2CuLi, $Bu_2CuLi+n$BuLi, $Bu_2CuLi+2n$BuLi, $Bu_2CuLi+2$CuI, or $Bu_2CuCNLi_2$), the major isomer is always the *syn* isomer, although this ratio depends on the experimental conditions. Under our best conditions (see Table 10), the scope of the reaction is broad since it proceeds similarly on primary (Table 10, entry 1), secondary (Table 10, entries 2 and 3), tertiary (Table 10, entry 4), and even aromatic (Table 10, entries 5 and 6) cyclopropenylcarbinols. The presence of the organometallic species was checked by reaction with different electrophiles, such as iodine (Table 10, entry 7) and allylbromide (Table 10, entry 8) to lead to the preparation of functionalized cyclopropylcarbinols in good to excellent yields.[53]

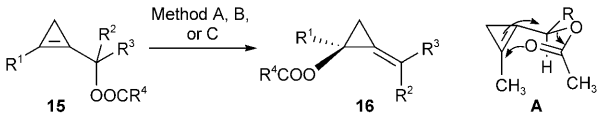
Table 10. Diastereoselective carbocupration of cyclopropenylcarbinols **2** with R_2CuLi.

Entry	R	E–X	E	*anti*/*syn* ratio[a]	Yield [%][b]
1 (**2i**)	CH_2CH_2Ph	H_3O^+	H	5:95	78 (**14a**)
2 (**2u**)	*i*Pr	H_3O^+	H	10:90	87 (**14b**)
3 (**2w**)	$CH(Ph)_2$	H_3O^+	H	6:94	81 (**14c**)
4 (**2y**)	*t*Bu	H_3O^+	H	5:95	83 (**14d**)
5 (**2z**)	C_6H_5	H_3O^+	H	10:90	75 (**14e**)
6 (**2al**)	mesityl	H_3O^+	H	1:99	75 (**14h**)
7 (**2w**)	$CH(Ph)_2$	I_2	I	6:94	86 (**14f**)
8 (**2w**)	$CH(Ph)_2$	allyl-Br	C_3H_5	6:94	77 (**14g**)

[a] Diastereomeric ratios were determined from ^{1}H NMR spectra of the crude reaction mixture. [b] Yields determined after purification by column chromatography on silica gel.

Here again, alkylidenecyclopropanes **7** were not observed, which suggests that the cyclopropylcopper derivatives formed after the carbocupration reactions are stable towards β-elimination reactions. The formation of each of the two possible diastereoisomers of polysubstituted cyclopropylcarbinols **13** and **14** from a unique cyclopropenylcarbinol derivative **2**, just by variation of the nature of the organometallic species is synthetically interesting but mechanistically puzzling. Efforts are still being directed towards elucidating the reaction mechanism. As nonracemic cyclopropenylcarbinols are now easily accessible by means of the kinetic resolution upon Sharpless epoxidation, this reaction represents a new and versatile preparation of cyclopropyl derivatives that possess two stereogenic quaternary stereocenters.

Formation of heterosubstituted alkylidenecyclopropane derivatives: To further enrich the chemistry of cyclopropenylcarbinol derivatives **2** in synthesis, we also thought to use the release of strain of the three-membered ring to promote easy sigmatropic rearrangements[54] as a new route to alkylidenecyclopropanes that possess polar functionalities, such as acetoxyalkylidenecyclopropane derivatives. Most of the methods known to date for their preparation concern either the reaction of alkylidene carbene with enol ether,[55] photolysis of dithiolactone,[56] or through the addition of *t*BuOH to 1,4-di-*tert*-butylmethylenecyclopropene.[57] Racemic cyclopropenylcarbinols **2** were first transformed easily into cyclopropenylacetate derivatives **15** through a classical esterification reaction and the sigmatropic rearrangement of tertiary cyclopropenylcarbinol was observed during the simple purification using column chromatography on silica gel to lead to acetoxyalkylidenecyclopropane derivatives (Scheme 17).



Scheme 17. [3,3] Sigmatropic rearrangement of cyclopropenylacetate **15**.

Therefore, the [3,3] sigmatropic rearrangement of tertiary allylic ester **15a** can be performed under very mild conditions either by simple filtration by column chromatography on silica gel (Method A; see Table 11, entry 1), by heating at reflux in CH_2Cl_2 (Method B; see Table 11, entry 2), or by addition of dry acidic ion-exchange resin Amberlyst-15 (Method C; see Table 11, entry 3).[58] In all cases, the rearrangement occurs to give the expected 2-(diphenylmethylene)-1-methylcyclopropyl acetate **16a** in quantitative yields. The relief of ring strain is again the driving force for such a mild rearrangement (See Table 11).

Substituents on the double bond of the cyclopropenylacetate (R^1) can be either alkyl or aryl (Table 11, entries 1–3 and 4), whereas substituents R^2 and R^3 are either alkyl, aryl,

Table 11. [3,3] Sigmatropic rearrangement of cyclopropenylacetate **15**.

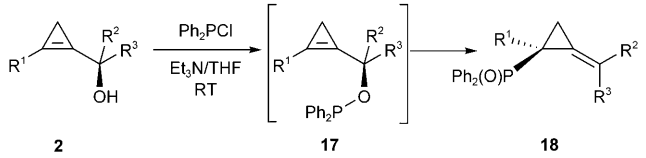
Entry	R^1	R^2	R^3	R^4	Method[a]	*E*/*Z* ratio[b]	Yield [%][c]
1 (**15a**)	CH_3	C_6H_5	C_6H_5	CH_3	A	–	90 (**16a**)
2 (**15a**)	CH_3	C_6H_5	C_6H_5	CH_3	B	–	92 (**16a**)
3 (**15a**)	CH_3	C_6H_5	C_6H_5	CH_3	C	–	87 (**16a**)
4 (**15b**)	C_6H_5	CH_3	CH_3	CH_3	A	–	91 (**16b**)
5 (**15c**)	CH_3	C_6H_5	CH_3	CH_3	A	2:1	83 (**16c**)
6 (**15d**)	CH_3	H	*p*-BrC_6H_4	CH_3	C	>99	75 (**16d**)
7 (**15e**)	CH_3	H	C_6H_5	CH_3	C	>99	76 (**16e**)
8 (**15f**)	CH_3	H	Ar[d]	CH_3	C	>99	70 (**16f**)
9 (**15g**)	CH_3	H	Ar[d]	C_6H_5	C	>99	60 (**16g**)
10 (**15h**)	C_4H_9	H	*p*-BrC_6H_4	CH_3	C	>99	77 (**16h**)

[a] Method A: the rearrangement is performed during the purification of cyclopropenylacetates **15** by column chromatography on silica gel; Method B: the rearrangement is performed at reflux in CH_2Cl_2; Method C: the rearrangement is performed at RT overnight in the presence of Amberlyst-15 in CH_2Cl_2. [b] Determined from the ^1H and ^{13}C NMR spectra of the crude reaction mixture. [c] Determined after purification by chromatography on silica gel. [d] Ar = 3,5-dibromophenyl.

Such [2,3] sigmatropic rearrangements proceed extremely fast at room temperature within a few minutes, due to the release of strain, for primary (Table 12, entry 1), secondary (Table 12, entries 4–8), and tertiary (Table 12, entries 2 and 3) cyclopropenyldiphenylphosphinite derivatives. In all cases, the corresponding phosphane oxide of methylene- and alkylidenecyclopropanes was obtained in excellent yields. When secondary phosphinites were used, two geometrical isomers of the corresponding phosphane oxides were obtained in a 80:20 *E*/*Z* ratio. Both isomers are readily separated by using column chromatography. The stereochemistry of the double bond was confirmed by X-ray analysis for (*Z*)-**18f** and deduced analogously for the other reaction products.

or hydrogen. When secondary aromatic alcohols were used (R^2 = H, R^3 = Ar), only the *E* isomer was found in all experiments (determined by NOE experiments) due to the chair-like conformation in the transition state in which the R^3 substituent occupies a pseudoequatorial position (Scheme 17 and Table 11, entries 6–10). When R^2 = H and R^3 = alkyl, the reaction does not proceed under such mild conditions. Only for **15c**, which is produced from a nonsymmetric ketone, were two geometrical isomers of **16c** formed in a 2:1 ratio (Table 11, entry 5). Due to the concerted, suprafacial nature of such a rearrangement, a 1,3-chirality-transfer process can be expected. Indeed, when enantiomerically enriched cyclopropenylacetates **15d**,**e** were treated with Amberlyst-15 (Table 11, entries 6 and 7), the corresponding (*S*,*E*)-2-arylidene-1-methylcyclopropyl acetates **16d**,**e** were obtained with the same enantioselectivity (>98% *ee*, 100% chirality transfer).[59]

As the design and the preparation of chiral phosphines for asymmetric catalysis is an active area of research,[60] the [2,3] sigmatropic rearrangement[61] of allylic diphenylphosphinites of general structure **17** was also investigated (Scheme 18). Although a considerable number of reports investigate the rearrangement of propargylic phosphinites,[62] very few have addressed the stereochemical outcome of an open-chain allylic system.[63] Herein, the application of this sigmatropic rearrangement for the preparation of racemic and chiral diphenylphosphane oxide bearing a quaternary center was developed.



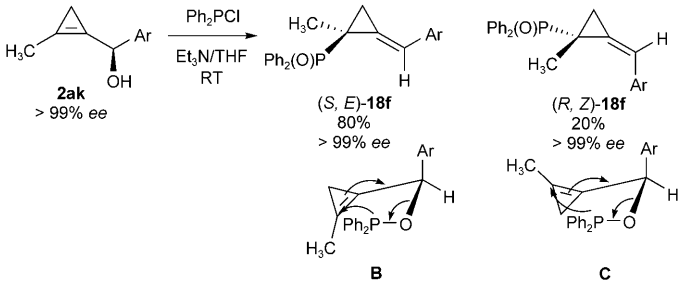
Scheme 18. [2,3] Sigmatropic rearrangement of cyclopropenyldiphenylphosphinites **17**.

Table 12. [2,3] Sigmatropic rearrangement of cyclopropenyldiphenylphosphinites **15**.

Entry	R^1	R^2	R^3	*E*/*Z* ratio[a]	Yield [%][b]
1 (**2g**)	C_4H_9	H	H	–	94 (**18a**)
2 (**2e**)	C_6H_5	CH_3	CH_3	–	87 (**18b**)
3 (**2d**)	C_4H_9	CH_3	CH_3	–	93 (**18c**)
4 (**2z**)	CH_3	C_6H_5	H	80:20	90 (**18d**)
5 (**2aa**)	C_4H_9	C_6H_5	H	80:20	93 (**18e**)
6 (**2ak**)	CH_3	Ar[c]	H	80:20	90 (**18f**)
7 (**2i**)	CH_3	CH_2CH_2Ph	H	80:20	85 (**18g**)
8 (**2w**)	C_4H_9	$CH(Ph)_2$	H	80:20	85 (**18h**)

[a] Determined from the ^1H and ^{31}P NMR spectra of the crude reaction mixture. [b] Determined after purification by chromatography on silica gel. [c] Ar = 3,5-dibromophenyl.

When enantiomerically pure cyclopropenylcarbinols such as **2aa**, **2ak**, and **2i** were treated with diphenylchlorophosphane at room temperature, the expected (*E*)- and (*Z*)-alkylidenecyclopropane diphenylphosphane oxide derivatives **18e**,**f**,**g** were obtained in a 80:20 ratio with a complete transfer of chirality (>99% *ee*, respectively, Scheme 19).[64] In



Scheme 19. Transfer of chirality in [2,3] sigmatropic rearrangement of cyclopropenyldiphenylphosphinites.

contrast to the well-defined transition state **A** for cyclopropenylacetates **15** (see Scheme 17), the transition state of phosphinite intermediates **17** requires that the conformational issues of five-membered ring systems be addressed.[65] The formation of the major isomer can be therefore rationalized by **B**, whereas the formation of the minor isomer is due to a rotation of the cyclopropenyl ring as shown in **C** (Scheme 19).

Theoretical calculations were employed for the elucidation of the absolute configurations of **16d**,**e** and **18e**,**f** (for both *E* and *Z* isomers). The different isomers and enantiomers were geometrically optimized at the B3LYP/6-311G(d) computational level and underwent analytical frequency calculations to ensure real minima ($N_{img}=0$). For **16d** and **16e**, only one stable conformer was found for each and used for the calculation of the spectra, whereas two rotamers were identified as minima for **18f**. One with the P=O bond *syn* and one *anti* with respect to the three-membered ring. For (*E*)-**18f** and (*Z*)-**18f**, the *anti* rotamers are more stable than the *syn* rotamers by 0.765 and 2.95 kcal mol^{-1}, respectively. Thus, the *anti* rotamers populate 76.53 and 99.25%, respectively, at room temperature. Since the CD spectra of each rotamer are rather different (see the Supporting Information), the CD spectrum that was used for comparison with the experimental spectra is the weighted average of the two for each isomer (see Figure 3).

TD-DFT calculations at the B3LYP/6-311++G(d) and B3LYP/aug-cc-pVDZ levels in dichloromethane (using the PCM model) for twenty singlet transitions were used for generating the electronic and CD spectra. These spectra were compared with the experimentally measured electronic and CD spectra, thus allowing straightforward determination of the absolute configurations. Figure 3 shows the correlation between the measured CD spectrum of (*Z*)- and (*E*)-**18f** and the computed ones, which allows the assignment of the experimentally prepared enantiomers.

Finally, phosphane oxide derivatives **18f** were readily converted into the corresponding phosphanes **19** after reduction with $HSiCl_3$ (Scheme 20).[66]

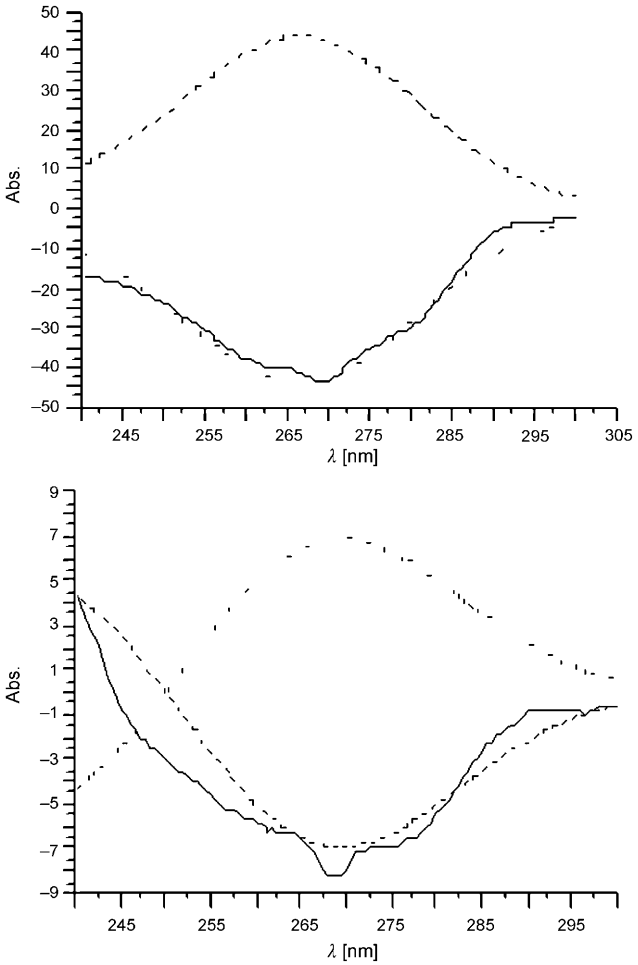
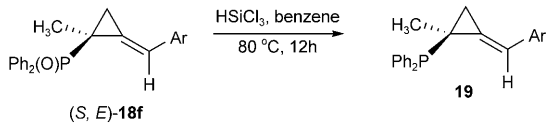


Figure 3. CD spectra of (*Z*)-**18f** (top), and (*E*)-**18f** (bottom): experimental (——); *S* enantiomer (•••••); *R* enantiomer (-----).



Scheme 20. Reduction of phosphane oxide **18** into phosphane **19**.

Conclusion

Cyclopropenylcarbinol **2**, an easily accessible starting material, is revealed to be an extremely versatile synthon in synthetic organic chemistry. A copper-catalyzed carbomagnesiation followed by a β elimination or a copper-catalyzed hydride addition leads to the preparation of alkylidenecyclopropane derivatives in good to excellent chemical yields. The reduction of **2** opens a new route to the diastereoselective preparation of *anti*-cyclopropylcarbinol, and the carbometalation reaction with either an organocopper from a Grignard reagent or from an alkyllithium species leads, at will, to the two opposite diastereoisomers. The strain resulting from this 3-membered ring can also be easily released through [3,3] and [2,3] sigmatropic rearrangements. As cyclopropenylcarbinol derivatives can be prepared enantiomerically pure, all of these transformations lead to enantiomerically enriched and pure functionalized substrates.

Experimental Section

General procedure for the preparation of cyclopropenylcarbinol derivatives 2a–al: *n*BuLi (20 mmol) was added at −70 °C to a solution of 1,1,2-tribromocyclopropane (10 mmol) dissolved in dry diethyl ether (70 mL). The temperature was allowed to reach −10 °C over 30 min, was then cooled to −20 °C, and an aldehyde or a ketone (12 mmol) was added. The mixture was allowed to reach room temperature and the evolution of the reaction was monitored by TLC.

After quenching with a saturated solution of ammonium chloride, the aqueous layer was extracted with diethyl ether (3×20 mL), and the or-

ganic phases were combined and washed with brine (1×20 mL), separated, dried, and evaporated. The crude product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 8:1 until the appearance of the product, then 5:1).

General procedure for the kinetic resolution of cyclopropenylcarbinol derivatives 2 by means of a Sharpless epoxidation: (+)-Diethyl L-tartrate (250 mg, 1.2 mmol) along with the corresponding cyclopropenylcarbinol (1 mmol) were added to a flame-dried three-necked flask containing 4 Å molecular sieves and dry CH_2Cl_2 (10 mL). The temperature was lowered to −20 °C and $Ti(OiPr)_4$ (1 mmol) was added. After this had been left stirring for 30 min, *t*BuOOH (0.65 mmol) was added and stirred at the same temperature for an additional 30 min. 30% NaOH (10 mL) was added to the reaction mixture and the mixture was stirred for 30 min. After extraction and phase separation, the organic phase was washed several times with water, then separated, dried, and evaporated. The pure product was separated by column chromatography on silica gel (eluent: hexane/ethyl acetate 8:1).

General procedure for the enzymatic resolution of cyclopropenylcarbinols 2: The racemic alcohol **2** (1 mmol) was dissolved in freshly distilled pentane (20 mL) containing activated 4 Å molecular sieves. Pseudomonas cepacia lipase (0.15 g, 0.5 mass equiv) was added to the solution along with distilled vinyl acetate (0.69 g). The solution was heated at reflux and the course of the reaction was followed by either ^{1}H NMR spectroscopy or GC analysis. The solution was filtered, and volatiles were removed by reduced pressure.

General procedure for the preparation of alkylidenecyclopropane derivatives 7a–ac: The cyclopropenylcarbinol (0.5 mmol) was dissolved in dry diethyl ether (10 mL) containing CuI (0.1 mmol). The temperature was lowered to −50 °C and the Grignard reagent (1.5 mmol) was added. The reaction mixture was warmed to 0 °C very slowly (over 6 h) then to room temperature over an additional 3 h. The reaction was hydrolyzed with a saturated solution of ammonium chloride and stirred until the aqueous phase became blue. The aqueous layer was extracted with diethyl ether (3×10 mL). The organic phases were combined and washed with brine (1×10 mL), separated, dried, and evaporated. The crude product was purified by column chromatography on silica gel (eluent: hexane).

General procedure for the preparation of alkylidenecyclopropane derivatives 7ad–ak: Cyclopropenylcarbinol **2** (1 mmol) was added to a dry three-necked flask containing CuI (0.2 mmol) in dry diethyl ether (20 mL). The temperature was lowered to −50 °C and a 1 M solution of $LiAlH_4$ in THF (1.0 mL) was added. The reaction mixture was heated slowly to room temperature overnight. After quenching with an aqueous saturated solution of ammonium chloride, the aqueous layer was extracted with diethyl ether (3×20 mL), the organic phases were combined and washed with brine (1×20 mL), separated, dried, and evaporated. The crude product was purified by column chromatography (eluent: hexane).

General procedure for the hydroalumination of cyclopropenylcarbinol derivatives: $LiAlH_4$ (1.4 mL, 1.0 M solution in Et_2O, 1.4 mmol) was added to a stirred solution of **2** (0.28 g, 1.386 mmol) in Et_2O (7 mL) at 0 °C. The reaction mixture was heated to +40 °C for 4.5 h and was then quenched with a 1 M aqueous solution of HCl (5 mL). The aqueous layer was extracted with Et_2O (3×10 mL) and the combined organic layers were dried over $MgSO_4$, filtered, and the solvent was removed under reduced pressure. Chromatography on silica gel (eluent: hexane/ethyl acetate 10:1) gave the cyclopropyl derivative.

Preparation of 4-(2-methyl-2-ethylcyclopropylidenemethyl)-*p*-tolylsulfoxide (10): Alkylidenecyclopropane (1 mmol) was dissolved in dry diethyl ether (50 mL). The temperature was lowered to −78 °C and *t*BuLi (2 mmol) was added. The mixture was stirred at −78 °C for 30 min then allowed to reach −50 °C and **40** was added. The solution was warmed to room temperature over 3 h, then hydrolyzed with a saturated aqueous solution of NH_4Cl. After extraction with diethyl ether (3×25 mL), the combined organic layers were washed with brine (2×25 mL), separated, dried, and evaporated. The crude product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 15:1). The product was isolated in 80% yield as a yellow solid.

Preparation of 4-(2-methyl-2-ethylcyclopropylidenemethyl)-*p*-tolylsulfoximine (11): 4-(2-Methyl-2-ethylcyclopropylidenemethyl)-*p*-tolylsulfoxide (0.5 mmol) was added to a solution of $Cu(OTf)_2$ (0.5 mmol; Tf = trifluoromethanesulfonate) in MeCN (3 mL) at RT. PhI = NTs (0.55 mmol) was then added in one batch. The reaction was monitored by the rapid disappearance of the yellowish powder from the reaction mixture, which turned homogeneous and green after two minutes. MeCN was removed in vacuo and the crude material was purified by flash chromatography on silica gel (10 g; hexane/AcOEt 7:3) to yield sulfoximine as a yellow solid (70%).

General procedure for the preparation of cyclopropylcarbinols 13a–g: A solution of *n*BuMgBr (1.1 M/Et_2O, 6 mmol, 5.5 mL) was added to a suspension of CuI (0.38 g, 2 mmol) in diethyl ether (35 mL) at 0 °C. The mixture was stirred for 15 min and a solution of cyclopropenylcarbinol **1a–e** (2 mmol) in diethyl ether (5 mL) was added very slowly so that the temperature did not rise above 0 °C. The reaction was followed by TLC analysis of hydrolyzed aliquots (eluent: ethyl acetate/hexane, 1:9) and was generally over after 30 min. After quenching with a saturated solution of ammonium chloride, the aqueous layer was extracted with diethyl ether (3×20 mL), and the organic phases were combined and washed with brine (1×20 mL), separated, dried, and evaporated. The crude product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 9:1).

General procedure for the preparation of cyclopropylcarbinols 14a–h: A solution of *n*BuLi (1.6 M/hexane, 8 mmol, 5.0 mL) was added to a suspension of CuI (4 mmol, 0.76 g) in diethyl ether (35 mL) at −50 °C. The mixture was stirred for 30 min while the temperature was raised slowly up to −20 °C and stirred at the same temperature for an additional 15 min. The mixture was cooled down to −50 °C and a solution of cyclopropenylcarbinol **1a–e** (2 mmol) in diethyl ether (5 mL) was added very slowly so that the temperature did not rise above −50 °C. TLC analysis of hydrolyzed aliquots (eluent: ethyl acetate/hexane, 1:9) showed that a reaction took place when the temperature reached −20 °C, and was over 2 h later at the same temperature. After quenching with a saturated solution of ammonium chloride, the aqueous layer was extracted with ether (3×20 mL), and the organic phases were combined and washed with brine (1×20 mL), separated, dried, and evaporated. The crude product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 9:1).

General procedure for the preparation of cyclopropenylacetate derivatives 15a–h: 4-*N*,*N*-Dimethylaminopyridine (DMAP; 13.6 mg, 1.1 mmol) was slowly added to a stirred solution of cyclopropenylcarbinol **2** (1 mmol) in CH_2Cl_2 (2 mL). Acetic anhydride (1.3 mL) in Et_2O (5 mL) was then added at 0 °C. The reaction mixture was warmed to 25 °C and stirred for an additional 30 min. The organic layer was washed with an aqueous 1 M HCl (3 mL) solution until neutral pH was reached, and was then washed with brine (5 mL) and the aqueous layer was extracted with Et_2O (3×5 mL). The combined organic layers were dried over $MgSO_4$ and the solvent was removed under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 15:1 until the appearance of the product, then 5:1).

General procedures for the preparation of acetoxyalkylidenecyclopropane derivatives 16a–h:

Method A: The rearrangement was performed during the purification of cyclopropenylacetate **15** by column chromatography on silica gel (eluent: hexane/ethyl acetate 50:1).

Method B: The rearrangement was performed when a solution of **15** (1 mmol) in CH_2Cl_2 (3 mL) was left at reflux overnight. The solvent was then removed from the solution in vacuo. The crude product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 50:1).

Method C: The rearrangement was performed when a solution of **15** (1 mmol) in CH_2Cl_2 (5 mL) was treated with an excess of Amberlyst-15 under an argon atmosphere. The solution was stirred at room temperature overnight. Then the solution was filtered and the solvent was removed from the solution under reduced pressure. The crude product was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 50:1).

General procedure for the preparation of alkylidenecyclopropanediphenylphosphane oxide derivatives 18: A 50 mL Schlenk flask was charged

with **2** (1 mmol), DMAP (12.4 mg, 0.1 mmol), and triethylamine (0.14 mL, 1 mmol) in THF (5 mL) under an argon atmosphere. The mixture was vigorously stirred at 0 °C and a solution of chlorodiphenylphosphine (0.18 mL, 1 mmol) was added dropwise to the solution. The ice bath was then removed and the mixture was stirred for an additional hour at room temperature. The precipitated salts were filtered off and the THF was removed from the solution under reduced pressure. The crude product was purified by column chromatography on silica gel (with Et_2O as eluent). The *E* and *Z* isomers of **18** can be easily separated by using column chromatography on silica gel.

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