Synthetic Methods

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An Efficient, Facile, and General Stereoselective Synthesis of Heterosubstituted Alkylidenecyclopropanes**

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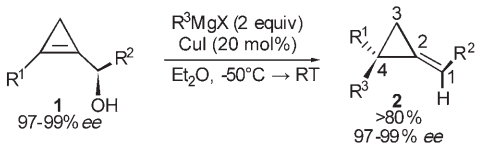
Dedicated to Professor Herbert Mayr on the occasion of his 60th birthday

Over the last few decades, the chemistry of racemic methylenecyclopropane and alkylidenecyclopropane derivatives[1] in the presence of transition-metal catalysts has been explored extensively.[2] The reactive nature of these compounds is commonly attributed to the strained double bond.[3] The mode of ring opening (at the distal C3–C4 bond or at the proximal C2–C3 bond) depends mainly on the choice of catalyst.[2c] The regioselectivity of the addition of an organometallic derivative RM across the exomethylene double bond C1–C2 depends on the nature of both the organometallic and the alkylidenecyclopropane derivative.[2] Furthermore, the presence of a carbon stereocenter on the cyclopropyl ring may lead to a transfer of chirality to the final product.[2] The presence of quaternary stereocenters in the alkylidenecyclopropane would be particularly interesting, as insertion into the distal bond may be inhibited completely. Unfortunately, as a result of inherent difficulties with their preparation, the availability of enantiomerically enriched methylenecyclopropanes and alkylidenecyclopropanes with quaternary stereocenters is rather limited.[4] In this context, we reported the copper-catalyzed addition of Grignard reagents to enantiomerically pure cyclopropenyl alcohols **1** to give alkylidenecyclopropane derivatives **2** with very high enantioselectivity [Eq. (1)].[5]



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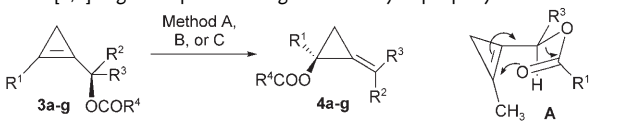
Alternatively, nonbonding interactions with substituents on the substrate may serve as the dominant stereochemical control element. In certain cases, reagents have been reported to preassociate with polar functional groups in the vicinity of the reactive center and to influence the stereochemical outcome of the process. Such interactions are frequently stronger than purely steric interactions and may lead to the opposite stereochemical outcome to that predicted on the basis of steric effects alone. Those cases in which such contrasteric selectivity has been observed have invariably involved substrates with polar functional groups and metal-based reagents.[6] In this context, a particularly interesting example would be the preparation of acetoxy-substituted alkylidenecyclopropane derivatives. Most of the methods known to date for the preparation of such compounds involve the reaction of an alkylidenecarbene with an enol ether,[7] the photolysis of a dithiolactone,[8] or the addition of *t*BuOH to 1,4-di-*tert*-butylmethylenecyclopropene.[9]

To further enrich the chemistry of alkylidenecyclopropanes in synthesis, in particular for the creation of quaternary stereocenters, we report herein the preparation of racemic and enantiomerically enriched alkylidene cyclopropane derivatives with polar functionalities through sigmatropic rearrangements.[10] Thus, racemic cyclopropenyl alcohols **1** were first transformed readily into cyclopropenyl acetate derivatives **3**, the rearrangement of which fulfilled our expectations (Table 1).

The [3,3] sigmatropic rearrangement of the tertiary allylic ester **3a** proceeded under very mild conditions upon simple filtration through a column of silica gel (method A; Table 1, entry 1), upon heating at reflux in CH_2Cl_2 (method B; Table 1, entry 2), or upon the addition of dry amberlyst-15, an acidic ion-exchange resin (method C; Table 1, entry 3).[11] In all cases, the desired rearrangement occurred to give the expected product 2-diphenylmethylene-1-methylcyclopropyl acetate (**4a**) in excellent yield. The relief of ring strain (an alkylidene cyclopropane is less strained than cyclopropene by 10.3 kcal mol^{-1})[12] is the driving force for rearrangement under such mild conditions.

It was found that the substituent R^1 on the double bond of the cyclopropenyl acetate can be either alkyl or aryl (Table 1, entries 1–4), whereas the substituents R^2 and R^3 can be alkyl, aryl, or hydrogen atoms. When secondary alcohols were used ($R^2 = H$, $R^3 = Ar$),[13] the issue of the configuration of the double bond was raised. In almost all experiments, only the *E* isomer of the product was detected (as determined by NOE experiments). The *E* isomer results from a chairlike conformation **A** in the transition state in which the R^3 substituent

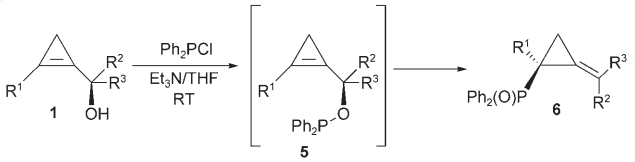
Table 1: [3,3] Sigmatropic rearrangement of cyclopropenyl acetates **3**.[a]



Entry	3	R^1	R^2	R^3	Method[b]	4	E/Z[c]	Yield [%][d]
1	**3a**	Me	Ph	Ph	A	**4a**	–	90
2	**3a**	Me	Ph	Ph	B	**4a**	–	92
3	**3a**	Me	Ph	Ph	C	**4a**	–	87
4	**3b**	Ph	Me	Me	A	**4b**	–	91
5	**3c**	Me	Ph	Me	A	**4c**	2:1[e]	83
6	**3d**	Me	H	*p*-BrC_6H_4-	C	**4d**	>99:1	75
7	**3e**	Me	H	Ph	C	**4e**	>99:1	76
8	**3fa**	Me	H	Ar[f]	C	**4fa**	>99:1	70
9	**3fb**	Me	H	Ar[f]	C	**4fb**	>99:1	60
10	**3g**	Bu	H	*p*-BrC_6H_4	C	**4g**	>99:1	77

[a] R^4 = Me with the exception of entry 9 where R^4 = Ph. [b] See the Experimental Section for details of methods A–C. [c] The E/Z ratio was determined by ^1H and ^{13}C NMR spectroscopy of the crude product. [d] The yield was determined after purification by chromatography on silica gel. [e] The configuration of the major isomer was determined by comparison with literature data (Ref. [7]). [f] Ar = 3,5-dibromophenyl.

Table 2: [2,3] Sigmatropic rearrangement of cyclopropenyldiphenylphosphinites **5**.



Entry	1	R^1	R^2	R^3	6	E/Z[a]	Yield [%][b]
1	**1g**	Bu	H	H	**6g**	–	94
2	**1b**	Ph	Me	Me	**6b**	–	87
3	**1h**	Bu	Me	Me	**6h**	–	93
4	**1e**	Me	H	Ph	**6e**	4:1[c]	90
5	**1i**	Bu	H	Ph	**6i**	4:1[c]	93
6	**1f**	Me	H	Ar[d]	**6f**	4:1[c]	90
7	**1j**	Me	H	CH_2CH_2Ph	**6j**	4:1[c]	85
8	**1k**	Bu	H	$CH(Ph)_2$	**6k**	4:1[c]	85

[a] The E/Z ratio was determined by ^1H and ^{31}P NMR spectroscopy of the crude product. [b] The yield was determined after purification by chromatography on silica gel. [c] The two geometrical isomers can be separated readily by column chromatography. [d] Ar = 3,5-dibromophenyl.

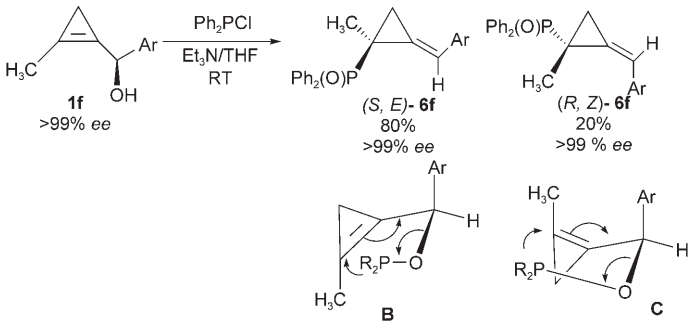
occupies a pseudoequatorial position (Table 1, entries 6–10). Only for **3c**, which was prepared from a nonsymmetrical ketone, were two geometrical isomers formed, in a 2:1 ratio (Table 1, entry 5). Because of the concerted, suprafacial nature of such rearrangements, 1,3-transfer of chirality can be expected. Indeed, when enantiomerically enriched cyclopropenyl acetates **3d**,**e** (>98% *ee*; readily obtained by kinetic resolution upon Sharpless epoxidation of the corresponding cyclopropenyl alcohols **1d,e**)[5] were treated with amberlyst-15 (Table 1, entries 6 and 7), the corresponding (*E*)-2-arylidene 1-methylcyclopropyl acetates (*S*)-**4d,e** were obtained with the same *ee* value (>98% *ee*; 100% chirality transfer).[14,15]

As the design and preparation of chiral phosphines for asymmetric catalysis is an active area of research,[16] we also investigated the [2,3] sigmatropic rearrangement[17] of allylic diphenylphosphinites of the general structure **5**. Although there have been a considerable number of reports on the rearrangement of propargylic phosphinites,[18] very few have addressed the stereochemical outcome of the rearrangement of an open-chain allylic system.[19] Herein, we describe the application of this sigmatropic rearrangement to the preparation of racemic and chiral diphenylphosphine oxides with a quaternary center (Table 2).

Such [2,3] sigmatropic rearrangements proceed extremely fast at room temperature and are complete within a few minutes for primary (Table 2, entry 1), secondary (Table 2, entries 4–8), and tertiary (Table 2, entries 2 and 3) cyclopropenyldiphenylphosphinite derivatives as a result of the release of strain. In all cases, the corresponding phosphine oxide of a methylenecyclopropane or alkylidenecyclopropane was obtained in excellent yield. When secondary phosphinites were used, two geometrical isomers of the corresponding phosphine oxide were obtained in an E/Z ratio of 4:1. The isomers were separated readily by column chromatography. The configuration of the double bond was confirmed by X-ray analysis of (*Z*)-**6f** and deduced by analogy for the other reaction products.

When enantiomerically pure cyclopropenyl alcohols **1i**,**f**,**j** (>99% *ee*; Table 2, entries 5—7; see Scheme 1 for a representative example) were treated with chlorodiphenylphosphane at room temperature, the expected *E* and *Z* alkylidenecyclopropane diphenylphosphine oxide derivatives **6i**,**f**,**j** were obtained in an 4:1 ratio with complete transfer of chirality (>99% *ee*; Scheme 1).[15] As opposed to the well-defined transition state **A** for cyclopropenyl acetates **3** (see Table 1), the transition state for phosphinite intermediates **5** involves a five-memebered ring, and the conformational issues with respect to such ring systems have to be addressed.[20] Thus, the major isomer forms via **B**, whereas the formation of the minor isomer is due to a rotation of the cyclopropenyl ring as shown in **C**.

Calculations were carried out to elucidate the absolute configurations of **4d**,**e** and **6i**,**f** (for both *E* and *Z* isomers).[5,21] The geometries of the different isomers and enantiomers were optimized at the B3LYP/6-311G(d) computational level,

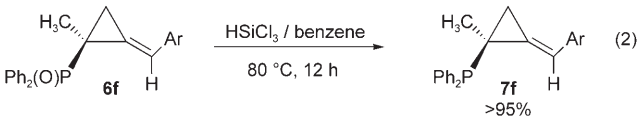


Scheme 1. [2,3] Sigmatropic rearrangement of the cyclopropenyldiphenylphosphinite derived from **1f** via the transition-state conformations **B** and **C**, which lead to the *E* and *Z* isomer of the product **6f**, respectively.

and analytical frequency calculations were carried out to ensure that real minima were found ($N_{img} = 0$). Only one stable conformer each was found for **4d** and **4e** and was used for the calculation of the spectra, whereas two rotamers were identified as minima for **6f**, one with the P=O bond *syn* and the other with the P=O bond *anti* with respect to the three-membered ring. For (*E*)-**6f** and (*Z*)-**6f**, the *anti* rotamers are more stable than the *syn* rotamers by 765 cal mol^{-1} and 2.95 kcal mol^{-1}, respectively. Thus, the *anti* rotamers have a population of 76.53 and 99.25%, respectively, at room temperature. As the CD spectra of the two rotamers of each isomer are rather different (see the Supporting Information), a weighted average of the two CD spectra was used for comparison with the experimental spectrum (see Figure 1).

To generate the electronic and CD spectra, TD-DFT calculations were carried out at the B3LYP/6-311++G(d) and B3LYP/aug-cc-pVDZ levels in dichloromethane (within PCM model)[22] for 20 singlet transitions. The comparison of these spectra with the experimentally measured electronic and CD spectra allowed straightforward determination of the absolute configurations. Figure 1 shows the correlation between the measured and computed CD spectra of (*Z*)- and (*E*)-**6f**, on the basis of which the configurations of the enantiomers prepared experimentally were determined.

Finally, phosphine oxide derivatives **6** can be converted readily into the corresponding phosphines **7** upon reduction with $HSiCl_3$ [see Eq. (2) for a representative example].[23]



(2)

The preparation of alkylidenecyclopropane diphenylphosphines as a new family of chiral ligands and their applications in asymmetric catalysis are currently under investigation.

Experimental Section

Method A: Rearrangement to give **4** occurred during the purification of **3** by column chromatography on silica gel (eluent: hexane/ethyl acetate 50:1).

Method B: A solution of **3** (1 mmol) in CH_2Cl_2 (3 mL) was heated at reflux overnight. The solvent was then removed under reduced pressure, and the crude product **4** was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 50:1).

Method C: A solution of **3** (1 mmol) in CH_2Cl_2 (5 mL) was treated with an excess of amberlyst-15 under argon, and the resulting mixture was stirred at room temperature overnight. The mixture was then filtered, and the solvent was removed under reduced pressure. The crude product **4** was purified by column chromatography on silica gel (eluent: hexane/ethyl acetate 50:1).

General procedure for the synthesis of **6**: A solution of chlorodiphenylphosphane (0.18 mL, 1 mmol) was added dropwise to a vigorously stirred mixture of **1** (1 mmol), 4-(*N*,*N*-dimethylamino)pyridine (12.4 mg, 0.1 mmol), and triethylamine (0.14 mL, 1 mmol) in THF (5 mL) at 0°C under argon in a 50-mL Schlenk flask. The ice bath was then removed, and the mixture was stirred for 1 h at room temperature. The precipitated salts were filtered off, the THF was removed under reduced pressure, and the crude product **6** was purified by column chromatography on silica gel (eluent: Et_2O). The *E* and *Z* isomers of **6** were separated by column chromatography (eluent: Et_2O) on silica gel.

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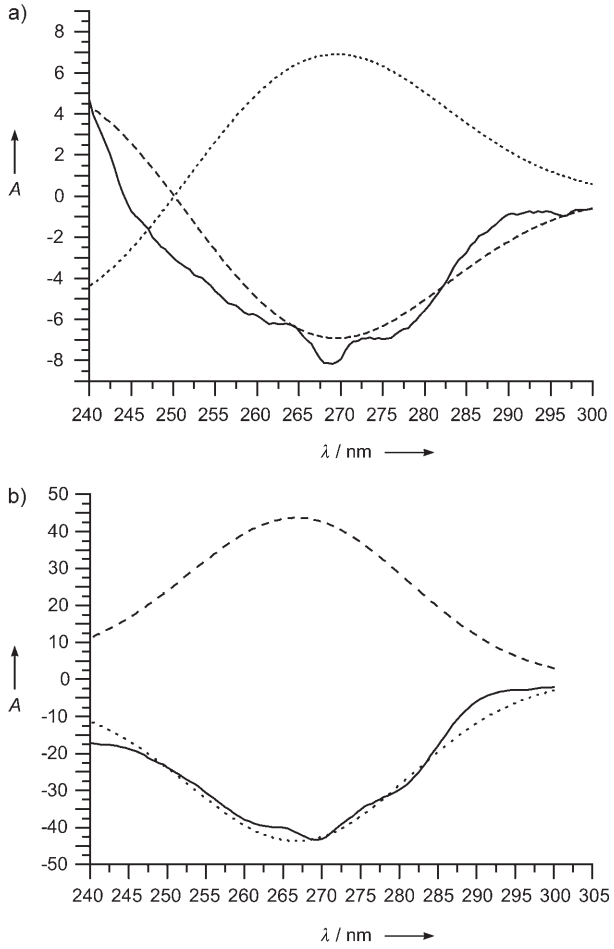

Figure 1. CD spectra of a) (*E*)-**6f** and b) (*Z*)-**6f**. Spectrum obtained experimentally: solid line; spectrum calculated for the *S* enantiomer: dotted line; spectrum calculated for the *R* enantiomer: dashed line.

[1] a) A. Brandi, A. Goti, *Chem. Rev.* **1998**, *98*, 589; b) A. Brandi, S. Cicchi, F. M. Cordero, A. Goti, *Chem. Rev.* **2003**, *103*, 1213.
[2] a) P. Binger, U. Schuchardt, *Chem. Ber.* **1981**, *114*, 3313; b) I. Nakamura, Y. Yamamoto, *Adv. Synth. Catal.* **2002**, 344; c) M. Lautens, W. Klute, W. Tam, *Chem. Rev.* **1996**, *96*, 49; d) A. de Meijere, S. I. Kozhushkov, A. F. Khlebikov, *Top. Curr. Chem.* **2000**, *207*, 89; e) A. de Meijere, S. I. Kozhushkov, *Eur. J. Org. Chem.* **2000**, 3809.
[3] R. D. Bach, O. Dmitrenko, *J. Am. Chem. Soc.* **2004**, *126*, 4444.
[4] a) For a recent review, see: I. Marek, S. Simaan, A. Masarwa, *Angew. Chem.* **2007**, *119*, 7508; *Angew. Chem. Int. Ed.*, **2007**, *46*,

7364; b) R. A. Weatherhead-Kloster, E. J. Corey, *Org. Lett.* **2006**, *8*, 171; c) Z. Yang, X. Xie, J. M. Fox, *Angew. Chem.* **2006**, *118*, 4064; *Angew. Chem. Int. Ed.* **2006**, *45*, 3960; d) E. Zohar, A. Stanger, I. Marek, *Synlett* **2005**, 2239.

[5] a) S. Simaan, A. Masarwa, P. Bertus, I. Marek, *Angew. Chem.* **2006**, *118*, 4067; *Angew. Chem. Int. Ed.* **2006**, *45*, 3963; b) S. Simaan, I. Marek, *Org. Lett.* **2007**, *9*, 2569.

[6] A. H. Hoveyda, D. A. Evans, G. C. Fu, *Chem. Rev.* **1993**, *93*, 1307.

[7] a) D. P. Fox, P. J. Stang, Y. Apeloig, M. Karni, *J. Am. Chem. Soc.* **1986**, *108*, 750; b) R. F. Cunico, Y.-K. Han, *J. Organomet. Chem.* **1978**, *162*, 1; c) P. J. Stang, M. G. Mangum, D. P. Fox, P. Haak, *J. Am. Chem. Soc.* **1974**, *96*, 4562; d) P. J. Stang, D. P. Fox, *J. Org. Chem.* **1977**, *42*, 1667; e) M. S. Newman, M. C. Van der Zwan, *J. Org. Chem.* **1974**, *39*, 1186.

[8] a) K. Muthuramu, V. Ramamurthy, *J. Chem. Soc. Chem. Commun.* **1980**, 243; b) K. Muthuramu, V. Ramamurthy, *J. Org. Chem.* **1980**, *45*, 4532.

[9] a) K. A. Lukin, A. Y. Masunova, B. I. Ugrak, N. S. Zefirov, *Tetrahedron* **1991**, *47*, 5769; b) W. E. Billups, L.-J. Lin, *Tetrahedron Lett.* **1983**, *24*, 1683.

[10] H. Frauenrath in *Stereoselective Synthesis*, *Houben-Weyl*, *Vol. 6* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1996**, p. 3301.

[11] L. E. Overman, *Angew. Chem.* **1984**, *96*, 565; *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 579.

[12] K. W. Wiberg, R. A. Fenoglio, *J. Am. Chem. Soc.* **1968**, *90*, 3395.

[13] When $R^2 = H$ and $R^3 =$ alkyl, the reaction does not proceed under such mild conditions.

[14] For the preparation of chiral 1-alkoxy 2-methylenecyclopropane by hydroboration of a racemic mixture, see: W. Kirmse, H.-R. Murawski, *J. Chem. Soc. Chem. Commun.* **1977**, 122.

[15] Enantiomeric ratios were determined by either GC or HPLC on a chiral phase; see experimental procedures in the Supporting Information.

[16] R. Noyori in *Asymmetric Catalysis in Organic Synthesis*, Wiley-Interscience, New York, **1994**.

[17] J. Kallmerten in *Stereoselective Synthesis*, *Houben-Weyl*, *Vol. 6* (Eds.: G. Helmchen, R. W. Hoffmann, J. Mulzer, E. Schaumann), Thieme, Stuttgart, **1996**, p. 3757.

[18] See, for example T. Pollok, H. Schmidbaur, *Tetrahedron Lett.* **1987**, *28*, 1085.

[19] a) S. Demay, K. Harms, P. Knochel, *Tetrahedron Lett.* **1999**, *40*, 4981; b) F. Liron, P. Knochel, *Chem. Commun.* **2004**, 304.

[20] K. Mikami, Y. Kimura, N. Kishi, T. Nakai, *J. Org. Chem.* **1983**, *48*, 279.

[21] Detailed procedures and optimized geometries can be found in the Supporting Information.

[22] TD-DTF: Time-dependent density functional theory, PCM: polarizable continuum method.

[23] S. Demay, F. Volant, P. Knochel, *Angew. Chem.* **2001**, *113*, 1272 – 1275; *Angew. Chem. Int. Ed.* **2001**, *40*, 1235.

