JOC Note

pubs.acs.org/joc

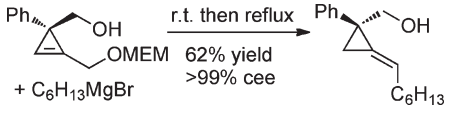
# Stereospecific Synthesis of Alkylidenecyclopropanes via Sequential Cyclopropene Carbomagnesation/1,3-Carbon Shift

Xiaocong Xie, Zhe Yang, and Joseph M. Fox*

*Brown Laboratories, Department of Chemistry and Biochemistry, University of Delaware, Newark 19716*

**jmfox@udel.edu*

*Received February 20, 2010*




Alkylidenecyclopropanes can be synthesized from enantiomerically enriched cyclopropene derivatives with >99% stereotransfer and good to excellent yield. The protocol comprises the stereoselective reaction of Grignard reagents with 1-alkoxymethyl-3-hydroxymethylcyclopropenes and a stereospecific [1,3] carbon shift reaction.

Alkylidenecyclopropanes have been the subject of considerable investigation because of their high strain energy and unique reactivity.[1] The utility of chiral alkylidenecyclopropanes is exemplified by stereospecific transformations that rapidly build stereochemical complexity through ring expansion,[2] cycloadditions,[3] or ring-opening reactions.[4] While a number of methods for generating alkylidenecyclopropanes[5] have been reported, access to enantiomerically enriched alkylidenecyclopropanes has been limited.[6]

An early approach to nonracemic alkylidenecyclopropanes utilized the stereospecific, formal [1,3] carbon shift of Fiest's ester, a methylenecyclopropane which is readily available in enantiomerically pure form.[7] However, the preparative utility of such rearrangements of methylenecyclopropanes to alkylidenecyclopropanes is typically limited by the need for pyrolytic conditions.[8] Studies by Gardner,[9] Creary,[10] and Nakamura[11] have shown that aryl-[10] or alkoxy-substituted[9,11] methylenecyclopropanes rearrange to alkylidenecyclopropanes under mild conditions. However, the stereospecificity of the rearrangements of methylenecyclopropanes with stabilizing substitutents had not been tested. Moreover, there was no method to access enantiomerically enriched methylenecyclopropanes with substituents that facilitate the [1,3]-carbon shift reaction.

Our group had previously demonstrated that enantiomerically enriched methylenecyclopropanes (e.g., **2**) can be obtained by addition of Grignard reagents to chiral cyclopropenes (e.g., **1**) with allylic ether leaving groups (Scheme 1).[12] Contemporaneously, Marek reported Grignard reagent addition to resolved cyclopropenylcarbinols to form chiral alkylidenecyclopropanes.[6c−f] We anticipated that the aromatic substituents of methylenecyclopropenes **2** would facilitate the rearrangement

(1) (a) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213. (c) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111.

(2) (a) Fürstner, A.; Aïssa, C. *J. Am. Chem. Soc.* **2006**, *128*, 6306. (b) Chowdhury, M. A.; Senboku, H.; Tokuda, M. *Tetrahedron Lett.* **2003**, *44*, 3329. (c) Liang, Y.; Jiao, L.; Wang, Y.; Chen, Y.; Ma, L.; Xu, J.; Zhang, S.; Yu, Z.-X. *Org. Lett.* **2006**, *8*, 5877. (d) Taillier, C.; Lautens, M. *Org. Lett.* **2007**, *9*, 591. (e) Scott, M. E.; Lautens, M. *Org. Lett.* **2005**, *7*, 3045. (f) Nair, V.; Suja, T. D.; Mohanan, K. *Synthesis* **2006**, 2531.

(3) (a) Siriwardana, A. I.; Nakamura, I.; Yamamoto, Y. *J. Org. Chem.* **2004**, *69*, 3202. (b) Durán, J.; Gulías, M.; Castedo, L.; Mascareñas, J. L. *Org. Lett.* **2005**, *7*, 5693. (c) Lautens, M.; Ren, Y.; Delanghe, P. *J. Am. Chem. Soc.* **1994**, *116*, 8821. (d) Lautens, M.; Ren, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9597. (e) Kamikawa, K.; Shimizu, Y.; Takemoto, S.; Matsuzaka, H. *Org. Lett.* **2006**, *8*, 4011. (f) de Meijere, A.; Kurahashi, T. *Angew. Chem., Int. Ed.* **2005**, *44*, 7881. (g) de Meijere, A.; Becker, H.; Stolle, A.; Kozhushkov, S. I.; Bes, M. T.; Salaün, J.; Noltemeyer, M. *Chem.—Eur. J.* **2005**, *11*, 2471. (h) Molchanov, A. P.; Diev, V. V.; Magull, J.; Vidović, D.; Kozhushkov, S. I.; de Meijere, A.; Kostikov, R. R. *Eur. J. Org. Chem.* **2005**, 593. (i) Hu, B.; Zhu, J.; Xing, S.; Fang, J.; Du, D.; Wang, Z. *Chem.—Eur. J.* **2009**, *15*, 324.

(4) (a) Zhou, H.; Huang, X.; Chen, W. *Synlett.* **2003**, *13*, 2080. (b) Shi, M.; Shao, L.-X. *Synlett.* **2004**, *5*, 807. (c) Zhu, Z.-b.; Liu, L.-p.; Shao, L.-x.; Shi, M. *Synlett.* **2007**, 115. (d) Shi, M.; Jiang, M.; Liu, L.-p. *Org. Biomol. Chem.* **2007**, *5*, 438. (e) Shi, M.; Liu, L.-p.; Tang, J. *Org. Lett.* **2006**, *8*, 4043. (f) Chen, W.-l.; Su, C.-l.; Huang, X. *Synlett* **2006**, *9*, 1446. (g) Huang, X.; Fu, W.-J. *Synthesis* **2006**, *6*, 1016. (h) Huang, X.; Yang, Y. *Org. Lett.* **2007**, *9*, 1667. (i) Yang, Y.; Huang, X. *J. Org. Chem.* **2008**, *73*, 4702. (j) Taniguchi, H.; Ohmura, T.; Suginome, M. *J. Am. Chem. Soc.* **2009**, *131*, 11298. (k) Ohmura, T.; Taniguchi, H.; Kondo, Y.; Suginome, M. *J. Am. Chem. Soc.* **2007**, *129*, 3518. (l) Hayashi, N.; Hirokawa, Y.; Shibata, I.; Yasuda, M.; Baba, A. *J. Am. Chem. Soc.* **2008**, *130*, 2912.

(5) (a) Rahman, W.; Kuivila, H. G. *J. Org. Chem.* **1966**, *31*, 772. (b) Satoh, T.; Saito, S. *Tetrahedron Lett.* **2004**, *45*, 347. (c) Ma, S.; Lu, L.; Zhang, J. *J. Am. Chem. Soc.* **2004**, *126*, 9645. (d) Meijs, G. F.; Eichinger, P. C. H. *Tetrahedron Lett.* **1987**, *28*, 5559. (e) Stafford, J. A.; McMurry, J. E. *Tetrahedron Lett.* **1988**, *29*, 2531. (f) Danheiser, R. L.; Lee, T. W.; Menichincheri, M.; Brunelli, S.; Nishiuchi, M. *Synlett* **1997**, 469. (g) Bernard, A. M.; Frongia, A.; Piras, P. P.; Secci, F. *Synlett* **2004**, 1064. (h) Bigeault, J.; Giordano, L.; de Riggi, I.; Gimbert, Y.; Buono, G. *Org. Lett.* **2007**, *9*, 3567. (i) Shono, T.; Nagasawa, T.; Tsubouchi, A.; Takeda, T. *Tetrahedron Lett.* **2007**, *48*, 3521. (j) Thomas, E.; Kasatkin, A. N.; Whitby, R. J. *Tetrahedron Lett.* **2006**, *47*, 9181.

(6) (a) Weatherhead-Kloster, R.; Corey, E. J. *Org. Lett.* **2006**, *8*, 171. (b) Rubina, M.; Woodward, E. W.; Rubin, M. *Org. Lett.* **2007**, *9*, 5501. (c) Masarwa, A.; Stanger, A.; Marek, I. *Angew. Chem., Int. Ed.* **2007**, *46*, 8039. (d) Simaan, S.; Masarwa, A.; Bertus, P.; Marek, I. *Angew. Chem., Int. Ed.* **2006**, *45*, 3963. (e) Simaan, S.; Marek, I. *Org. Lett.* **2007**, *9*, 2569. (f) Simaan, S.; Marek, I. *Chem. Commun.* **2009**, 292.

(7) (a) Feist, F. *Liebigs Ann.* **1924**, *436*, 125. (b) Goss, F. R.; Ingold, C. K.; Thrope, J. F. *J. Chem. Soc., Trans.* **1925**, *127*, 460.

(8) (a) Kon, G. A. R.; Nanji, H. R. *J. Chem. Soc.* **1932**, 2557. (b) Ettlinger, M. G. *J. Am. Chem. Soc.* **1952**, *74*, 5805. (c) Gajewski, J. J. *J. Am. Chem. Soc.* **1968**, *90*, 7178. (d) Ullman, E. F.; Fanshawe, W. J. *J. Am. Chem. Soc.* **1961**, *83*, 2379. (e) Sanjiki, T.; Kato, H.; Ohta, M. *Chem. Commun.* **1968**, 496. (f) Crandall, J. K.; Paulson, D. R. *J. Am. Chem. Soc.* **1966**, *88*, 4302. (g) Dolbier, W. R.; Lomas, J. D.; Tarrant, P. *J. Am. Chem. Soc.* **1968**, *90*, 3594.

(9) Shields, T. C.; Shoulders, B. A.; Krause, J. F.; Osborn, L. C.; Gardner, P. D. *J. Am. Chem. Soc.* **1965**, *87*, 3026.

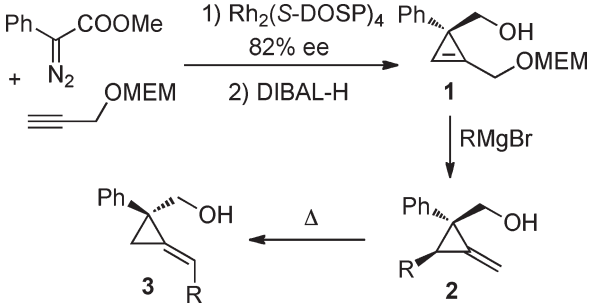
(10) (a) Creary, X. *J. Org. Chem.* **1978**, *43*, 1777. (b) Creary, X. *J. Org. Chem.* **1980**, *45*, 280. (c) Creary, X.; Losch, A.; Sullivan, W. *J. Org. Chem.* **2007**, *72*, 7930. (d) Creary, X.; Mehrsheikh-Mohammadia, M. E. *J. Org. Chem.* **1986**, *51*, 2664.

(11) Nakamura, E.; Yamago, S.; Ejiri, S.; Dorigo, A. E.; Morokuma, K. *J. Am. Chem. Soc.* **1991**, *113*, 3183.

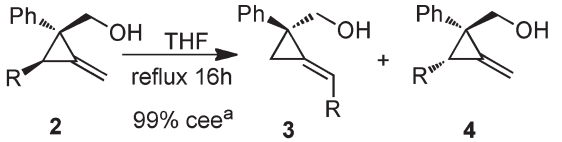
(12) (a) Yang, Z.; Xie, X.; Fox, J. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 3960. For related work on diastereoselective carbomagnesiation: (b) Liao, L.; Fox, J. M. *J. Am. Chem. Soc.* **2002**, *124*, 14322. (c) Liu, X.; Fox, J. M. *J. Am. Chem. Soc.* **2006**, *128*, 5600. (d) Yan, N.; Liu, X.; Fox, J. M. *J. Org. Chem.* **2008**, *73*, 563.

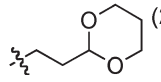
DOI: 10.1021/jo1002938 Published on Web 05/12/2010

**SCHEME 1. Stereospecific Synthesis of Chiral Alkylidenecyclopropanes (2) from Cyclopropenes with Allylic Leaving Groups**




**SCHEME 2. Synthesis of Alkylidenecyclopropanes from Methylenecyclopropanes**




| R | yield | ratio (3:4) |
|---|---|---|
| Me (**2a**) | 71% (**3a**) | 10:1 |
| Et (**2b**) | 85% (**3b**) | 14:1 |
| Hex (**2c**) | 70% (**3c**) | 23:1 |
| Cy (**2d**) | 72% (**3d**) | 18:1 |
| Bn (**2e**) | 84% (**3e**) | 13:1 |
| Allyl (**2f**) | 81% (**3f**) | 16:1 |
|  (**2g**) | 86% (**3g**) | 11:1 |

[a]cee = (product ee/starting material ee) × 100%. **2a**−**g** and **3a**−**g** were all measured to be 82% ee (±1% ee).

to alkylidenecyclopropenes **3** under mild conditions. Cyclopropenylcarbinols with aromatic substituents (e.g., **1**) are readily available with good levels of enantiomeric excess via $Rh_2$(*S*-DOSP)$_4$-catalyzed cyclopropenation.[13] Accordingly, we envisioned a general methodology that would produce alkylidenecyclopropanes (**3**) upon sequential treatment of **1** with Grignard reagents and heat (Scheme 1).

The rearrangements of methylenecyclopropanes **1** proceed in THF at reflux temperature (Scheme 2). For all of the reactions in Scheme 2, small amounts of starting material were recovered (5−10%). Prolonged heating did not result in higher conversion. Also, minor amounts of isomeric methylenecyclopropanes (**4a**−**g**) were observed. Compounds **4a**−**g** resulted from epimerization of **2a**−**g**.[14] It was possible to separate **3g** and **4g** via preparative HPLC. When purified, **3g** was heated to reflux in THF for 16 h, and compound **4g** (3%) and trace **2g** (∼1%) were observed along with recovered **3g** (96%). This result demonstrated that the reaction to form **3g** is reversible.

As anticipated,[10] the aryl substituent on the methylenecyclopropane was necessary for reactions to take place under mild conditions. Thus, compounds **5**−**7** did not produce the alkylidenecyclopropanes after refluxing in THF for 16 h;

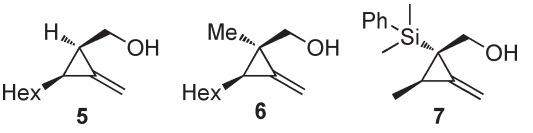
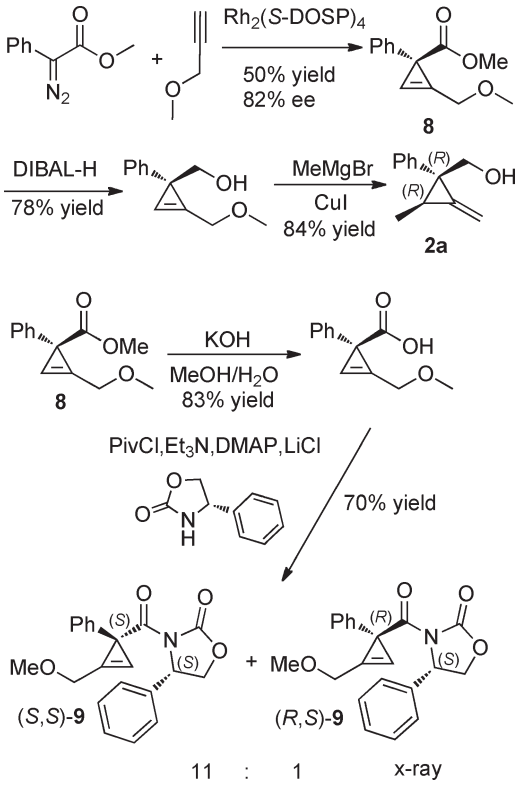



**FIGURE 1.** Methylenecyclopropanes that do not rearrange efficiently to alkylidenecyclopropanes.

**SCHEME 3. Assignment of Absolute Stereochemistry for 2a**

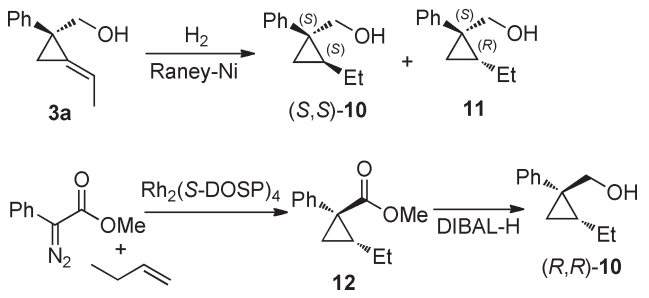



only starting material was recovered (Figure 1). The formal [1,3] shifts of **5**−**7** did take place at higher temperature (toluene, reflux for 10 h). However, significant decomposition took place, and only low yields of the alkylidenecyclopropanes (< 10% yield) were detected by $^1$H NMR.

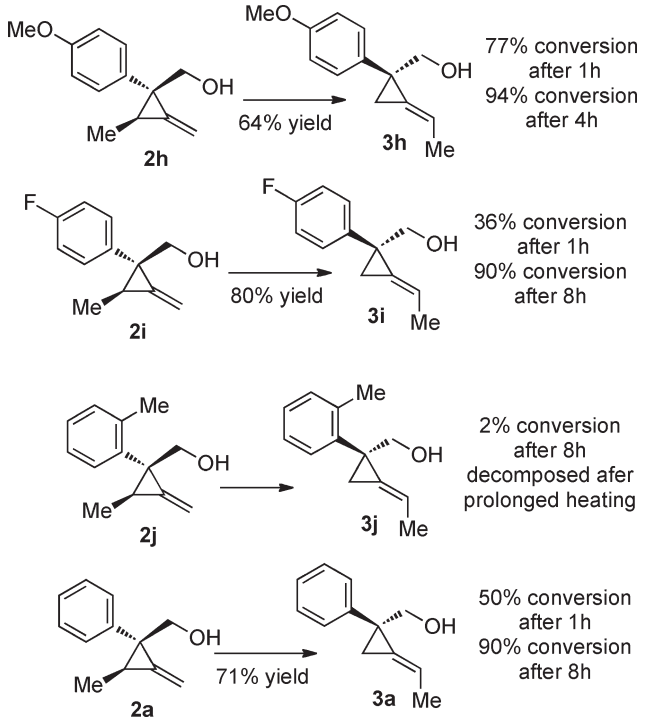
To verify that the methylenecyclopropane to alkylidenecyclopropane rearrangement took place with net inversion of stereochemistry, the absolute configuration of methylenecyclopropane **2a** and alkylidenecyclopropane **3a** were assigned. Thus, enantiomerically enriched methylenecyclopropane **2a** was prepared in 82% ee by the $Rh_2$(*S*-DOSP)$_4$-catalyzed reaction of methyl α-diazo-α-phenylacetate with methyl propargyl ether, followed by DIBAL reduction and reaction with MeMgBr (Scheme 3). The absolute configuration of intermediate **8** was assigned by conversion into (4*S*)-3-[(1*S*)-phenyl-2-(methoxymethyl)cycloprop-2-en-1-oyl]-4-phenyloxazolidinone [(*S*,*S*)-**9**]. The diastereomer (*R*,*S*)-**9** had been prepared previously,[15] and its absolute configuration has been established through X-ray crystallography (see the Supporting Information). Thus, $Rh_2$-(*S*-DOSP)$_4$ gives cyclopropane **8** with the (*S*)-configuration and ultimately provided (*R*,*R*)-**2a**.

(13) Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 1233.
(14) Gajewski, J. J. *J. Am. Chem. Soc.* **1971**, *93*, 4450.
(15) Liao, L.-A.; Zhang, F.; Olga, D.; Bach, R. D.; Fox, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 4490.

**SCHEME 4. Assignment of Absolute Configuration for 2a**




**SCHEME 5. Substituent Effects on Methylenecyclopropane to Alkylidenecyclopropane Rearrangement[a]**




[a]All reactions were carried out in THF at reflux temperature

The absolute configuration of **3a** was assigned by Raney Ni reduction, which gave separable diastereomers (*S*,*S*)-**10** and **11**. (Scheme 4). The opposite enantiomer of (*S*,*S*)-**10** was produced upon reduction of the known compound **12**, which was prepared as described by Davies. Davies had shown that **12** prepared from $Rh_2$(*S*-DOSP)$_4$ has the (1*R*,2*R*)-configuration.[16] Thus, (1*R*,2*R*)-**2a** rearranges to give (*S*)-**3a** and a net inversion of stereochemistry at the pivot carbon is observed.[17]

The effect of varying the aromatic ring of the methylenecyclopropane was also studied. An electronically releasing *p*-methoxyphenyl group accelerated the rearrangement, whereas an electron-withdrawing *p*-fluorophenyl substituent decreased the reaction rate. Thus, the rearrangement of **2h** to **3h** (Ar = *p*-methoxyphenyl) reached 77% conversion after reflux for 1 h (94% conversion after 4 h). By contrast, only 50% of **2a** to **3a** (Ar = Ph) had converted after 1 h (90% conversion after 8 h). The rearrangement of **2i** (Ar = *p*-fluorophenyl) reached only 36% conversion after 1 h (90% conversion after 8 h). The *o*-tolyl-substituted methylenecyclopropane **2j** (Ar = *o*-tolyl) led only to traces (2% yield) of **3j** upon prolonged heating in THF. At higher temperature (toluene, reflux 5 h) a 12% yield of **3j** was observed (Scheme 5).

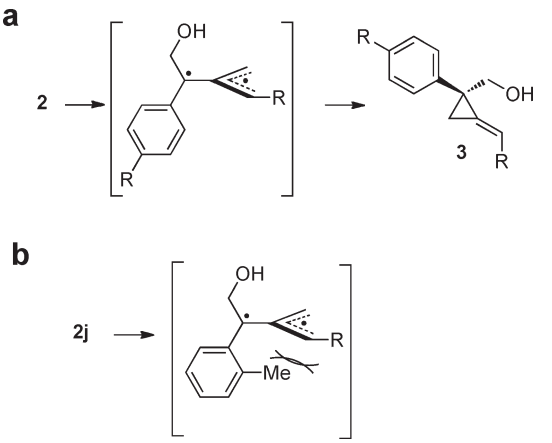



**FIGURE 2.** (a) Diradical mechanism for the methylenecyclopropane to alkylidenecyclopropane rearrangements. (b) For the rearrangement of **2j**, it is proposed that the *o*-methyl substituent hampers aromatic stabilization in a transition state with diradical character.

Excellent levels of chirality transfer [>99% conservation of enantiomeric excess (cee)] were observed for the transformations in Scheme 2. In prior studies on rearrangements of nonracemic methylenecyclopropanes, lower levels of chirality transfer were observed. Feist's ester was shown to rearrange to a mixture of (*E*)- and (*Z*)-methylcarboxycyclopropylideneacetic acid[18a,19] with 93% cee and 47% cee, respectively.[19] In studies on (*S*,*S*)-2,3-dimethylmethylenecyclopropane, high levels of chirality transfer were observed at low conversion (80% cee ± 20%), but less efficient chirality transfer and partial racemization of starting material was observed at higher conversion.[8c]

These observations are consistent with the accepted diradical mechanism for the methylenecyclopropane to alkylidenecyclopropane rearrangements.[10,18−20] Aromatic substituents have a dramatic stabilizing influence.[10] A *p*-methoxy substituent accelerates the rate of the reaction, and a *p*-fluoro substituent decreases the rate of the reaction, but the effect is only minor. However, the rate of rearrangement for **2j** is severly reduced by the *o*-methyl substituent, which hampers coplanarity in a transition state with diradical character and axial chirality (Figure 2). The observation of isomeric products **4** (Scheme 2) is also in line with a diradical mechanism, in accord with earlier observations by Gajewski.[8c]

(16) Davies, H. M. L.; Bruzinski, P. R.; Fall, M. J. *Tetrahedron Lett.* **1996**, *37*, 4133.

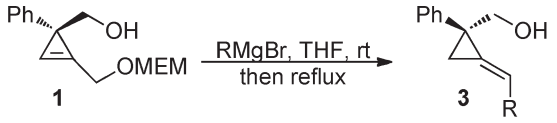
(17) Ullman, E. F. *J. Am. Chem. Soc.* **1960**, *82*, 505.

(18) Diradical intermediate mechanistic proposals for the methylenecyclopropane rearrangement: (a) Doering, W.; von, E.; Roth, H. D. *Tetrahedron* **1970**, *26*, 2825. (b) Doering, W.; von, E.; Birladeanu, L. *Tetrahedron* **1973**, *29*, 499.

(19) Diradical transition state mechanistic proposal for the methylenecyclopropane rearrangement: Buchwalter, S. L. *Tetrahedron* **1984**, *40*, 5097.

(20) Concerted mechanistic proposals for the methylenecyclopropane rearangement: (a) Zimmerman, H. E. *Acc. Chem. Res.* **1971**, *4*, 272. (b) Dewar, M. J. S. *Angew. Chem., Int. Ed.* **1971**, *10*, 761. (c) Woodward, R. B.; Hoffmann, R. *Angew. Chem., Int. Ed.* **1969**, *8*, 781. (d) Heilbronner, E. *Tetrahedron Lett.* **1964**, *5*, 1923. (e) Berson, J. A.; Nelson, G. L. *J. Am. Chem. Soc.* **1967**, *89*, 5503. (f) Berson, J. A.; Salem, L. *J. Am. Chem. Soc.* **1972**, *94*, 8917.

**SCHEME 6. One-Pot Reaction to Form Alkylidenecyclopropanes**




1 3

| R | yield |
|---|---|
| Me | **3a**, 43% |
| Et | **3b**, 62% |
| Hex | **3c**, 62% |
| Cy | **3d**, 46% |

Most conveniently, the rearrangement of methylenecyclopropanes to alkylidenecyclopropanes can be carried out in one pot from the cyclopropene precursor **1** (Scheme 6). The overall yields are comparable with the combined yields of separate Grignard addition and rearrangement reactions.

In conclusion, a stereospecific method for preparing alkylidenecyclopropanes from enantiomerically enriched methylenecyclopropanes has been described. The reaction takes place under mild conditions and takes place with excellent transfer of stereochemistry. This reaction can also be carried out in one pot from enantiomerically enriched cyclopropene precursors.

## Experimental Section

**Representative Procedure for the [1,3] Carbon Shift Reaction: (*S*,*E*)-2-Hydroxymethyl-2-phenylethylidenecyclopropane (3a).** To a 100 mL round bottomed flask was added a solution of **2a** (52 mg, 0.30 mmol) in THF (15 mL). The reaction mixture was heated to reflux temperature for 16 h. Subsequently, the mixture was allowed to cool and concentrated under reduced pressure. Purification by silica gel chromatography (10% ethyl acetate in hexane) gave 37 mg (0.21 mmol, 71% yield) of **3a** as a pale yellow oil. A similar experiment that began with 46 mg of **2a** gave **3a** in 70% yield. Small peaks attributable to **4a** (7%) were detected in the $^1$H NMR spectrum at 5.74, 5.57, 4.00, 3.58, 1.77, and 0.84 ppm and in the $^{13}$C NMR at 129.9, 126.9 ppm. HPLC analysis showed the material to be of 82% ee (using a Chiral OD column, flow rate of 1 mL/min, 1% IPA in hexanes): $[\alpha]^{20}_D$ −76 (*c* 0.28, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.37−7.40 (m, 2H), 7.28−7.34 (m, 2H), 7.20−7.25 (m, 1H), 6.09−6.15 (m, 1H), 3.87 (dd, $J$ = 11.3, 6.1 Hz, 1H), 3.72 (dd, $J$ = 11.2, 6.6 Hz, 1H), 1.86 (dt, $J$ = 6.5, 1.7 Hz, 3H), 1.51−1.55 (m, 1H), 1.41−1.45 (m, 1H), 1.37−1.40 (m, 1H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 141.4 (C), 128.4 (CH), 128.2 (C), 128.0 (CH), 126.7 (CH), 114.7 (CH), 68.8 ($CH_2$), 31.0 (C), 16.9 ($CH_3$), 15.6 ($CH_3$); IR (neat, cm$^{-1}$) 3351, 3083, 3059, 3028, 2957, 2924, 2855, 1602, 1495, 1464, 1416, 1378, 1303, 1222, 1176, 1029, 905, 760, 732, 699, 562, 542; HRMS-CI (M + $NH_4$) $m/z$ calcd for $C_{12}H_{18}NO$ 192.1388, found 192.1380.

**Representative Procedure for the One-Pot Grignard Addition/Rearrangement to Alkylidenecclopropanes: (*S*,*E*)-2-Hydroxymethyl-2-phenylheptylidenecyclopropane (3c).** To a 50 mL round bottomed flask was added a solution of 3-hydroxymethyl-1-methoxyethoxymethoxymethyl-3-phenylcyclopropene (63 mg, 0.24 mmol) in THF (5 mL). The mixture was stirred with a magnetic stir bar, and hexylmagnesium bromide (2.4 mmol, 1.2 mL of a 2.0 M solution in diethyl ether) was slowly added via syringe. The resulting mixture was allowed to stir at rt for 12 h and then heated to reflux for 5 h. The reaction was quenched with saturated $NH_4Cl$. The aqueous layer was extracted with ethyl acetate (5 mL) three times, and the combined organic layers were washed with brine and dried over anhydrous $MgSO_4$. The solvent was removed, and the crude product was purified by silica gel chromatography (10% ethyl acetate in hexanes) to give 37 mg (0.15 mmol, 64% yield) of **3c** as a pale yellow oil. A similar experiment that began with 55 mg of **1** gave **3c** in 59% yield. Small peaks attributable to **4c** (3%) were detected in the $^1$H NMR spectrum at 5.73, 5.57, 4.03, and 3.58 ppm. HPLC analysis showed the material to be of 82% ee (using a chiral OD column, flow rate of 1 mL/min, 1% IPA in hexanes: $[\alpha]^{20}_D$ −47 (*c* 0.34, $CHCl_3$); $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.35−7.40 (m, 2H), 7.28−7.33 (m, 2H), 7.20−7.24 (m, 1H), 6.07−6.12 (m, 1H), 3.88 (dd, $J$ = 11.3, 6.1 Hz, 1H), 3.72 (dd, $J$ = 11.3, 6.8 Hz, 1H), 2.19−2.25 (m, 2H), 1.24−1.56 (m, 11H), 0.88 (t, $J$ = 7.0 Hz, 3H); $^{13}$C NMR (100 MHz, $CDCl_3$) $\delta$ 141.5 (C), 128.4 (CH), 127.9 (CH), 127.3 (C), 126.6 (CH), 120.2 (CH), 68.8 ($CH_2$), 31.7 ($CH_2$), 31.6 ($CH_2$), 30.4 (C), 29.1 ($CH_2$), 29.0 ($CH_2$), 22.7 ($CH_2$), 16.1 ($CH_2$), 14.1 ($CH_3$); IR (neat, cm$^{-1}$) 2924, 2854, 2360, 2341, 1494, 1024, 764, 697, 502; HRMS-CI (M + $NH_4$) $m/z$ calcd for $C_{17}H_{28}NO$ 262.2171, found 262.2175.

**Acknowledgment.** For financial support we thank NIGMS (NIH R01 GM068650). We thank Dr. Lian-an Liao for growing a crystal of (*R*,*S*)-**9** and Glenn Yap for determining the X-ray structure.

**Supporting Information Available:** Full experimental and characterization details, $^1$H and $^{13}$C NMR spectra, and X-ray data for compound (*R*,*S*)-**9**. This material is available free of charge via the Internet at http://pubs.acs.org.