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Synthesis of Enantioenriched Allenes from 1,1-Cyclopropanediesters

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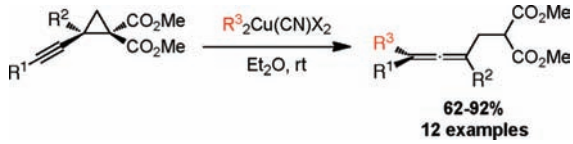
ABSTRACT



Highly substituted allenes were obtained by the S_N2' addition of organocuprate reagents on 2-propargyl-1,1-cyclopropanediesters. This new methodology permits the synthesis of highly enantioenriched allenes as the reaction proceeds with retention of the enantiomeric purity of the starting cyclopropane. The use of higher order cuprates was instrumental in obtaining the reported results.

Electrophilic cyclopropane derivatives possessing two geminal electron-withdrawing groups[1] have attracted considerable interest as versatile 1,3-zwitterionic or electrophilic synthons.[2] These valuable intermediates have been applied toward the enantioselective synthesis of complex molecules, as they are readily reactive in cycloaddition reactions[3] and nucleophilic additions,[4] retaining the stereogenic information of the starting cyclopropane. Generally, 1,5-addition is observed in these processes, except in the particular case of the addition of organocuprates on a vinylcyclopropane, where only the 1,7-addition product was obtained.[2a,5] From this observation, we envisioned that the synthesis of enantioenriched allenes might be achieved by the addition of organocuprates to optically active propargylcyclopropanes.[6,7]

(1) For recent examples on the synthesis of electrophilic cyclopropanes, see: (a) Moreau, B.; Charette, A. B. *J. Am. Chem. Soc.* **2005**, *127*, 18014–18015. (b) González-Bobes, F.; Fenster, M. D. B.; Kiau, S.; Kolla, L.; Kolotuchin, S.; Soumeillant, M. *Adv. Synth. Catal.* **2008**, *350*, 813–816. (c) Marcoux, D.; Charette, A. B. *Angew. Chem., Int. Ed.* **2008**, *47*, 10155–10158. (d) Zhu, S.; Perman, J. A.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2008**, *47*, 8460–8463. (e) Goudreau, S. R.; Marcoux, D.; Charette, A. B. *J. Org. Chem.* **2009**, *74*, 470–473. (f) Marcoux, D.; Azzi, S.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 6970–6972. (g) Lindsay, V. N. G.; Lin, W.; Charette, A. B. *J. Am. Chem. Soc.* **2009**, *131*, 16383–16385. (h) Marcoux, D.; Goudreau, S. R.; Charette, A. B. *J. Org. Chem.* **2009**, *74*, 8939–8955.

(2) For reviews, see: (a) Danishefsky, S. *Acc. Chem. Res.* **1979**, *12*, 66–72. (b) Wong, H. N. C.; Hon, M. Y.; Tse, C. W.; Yip, Y. C.; Tanko, J.; Hudlicky, T. *Chem. Rev.* **1989**, *89*, 165–198. (c) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151–1196. (d) Yu, M.; Pagenkopf, B. L. *Tetrahedron* **2005**, *61*, 321–347. (e) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179.

(3) For recent examples, see: (a) Young, I. S.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2003**, *42*, 3023–3026. (b) Pohlhaus, P. D.; Johnson, J. S. *J. Am. Chem. Soc.* **2005**, *127*, 16014–16015. (c) Young, I. S.; Kerr, M. A. *J. Am. Chem. Soc.* **2007**, *129*, 1465–1469. (d) Jackson, S. K.; Karadeolian, A.; Driega, A. B.; Kerr, M. A. *J. Am. Chem. Soc.* **2008**, *130*, 4196–4201. (e) Leduc, A. B.; Kerr, M. A. *Angew. Chem., Int. Ed.* **2008**, *47*, 7945–7948. (f) Pohlhaus, P. D.; Sanders, S. D.; Parsons, A. T.; Li, W.; Johnson, J. S. *J. Am. Chem. Soc.* **2008**, *130*, 8642–8650. (g) Perreault, C.; Goudreau, S. R.; Zimmer, L. E.; Charette, A. B. *Org. Lett.* **2008**, *10*, 689–692. (h) Carson, C. A.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 777–779. (i) Dias, D. A.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 3694–3697. (j) Parsons, A. T.; Johnson, J. S. *J. Am. Chem. Soc.* **2009**, *131*, 3122–3123. (k) Sapeta, K.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 2081–2084. (l) Lebold, T. P.; Kerr, M. A. *Org. Lett.* **2009**, *11*, 4354–4357.

(4) For examples, see: (a) Zefirov, N. S.; Kozhushkov, S. I.; Kuznetsova, T. S.; Ershov, B. A.; Selivanov, S. I. *Tetrahedron* **1986**, *42*, 709–713. (b) Seebach, D.; Häner, R.; Vettiger, T. *Helv. Chim. Acta* **1987**, *70*, 1507–1515. (c) Bambal, R.; Kemmitt, R. D. W. *J. Chem. Soc., Chem. Commun.* **1988**, 734–735. (d) O'Bannon, P. E.; Dailey, W. P. *Tetrahedron* **1990**, *46*, 7341–7358. (e) Vettiger, T.; Seebach, D. *Liebigs Ann. Chem.* **1990**, *1990*, 195–201. (f) Corey, E. J.; Gant, T. G. *Tetrahedron Lett.* **1994**, *35*, 5373–5376. (g) Trost, B. M.; Tanimori, S.; Dunn, P. T. *J. Am. Chem. Soc.* **1997**, *119*, 2735–2736. (h) Burgess, K. *J. Org. Chem.* **1987**, *52*, 2046–2051. (i) England, D. B.; Woo, T. K.; Kerr, M. A. *Can. J. Chem.* **2002**, *80*, 992–998. (j) Wurz, R. P.; Charette, A. B. *Org. Lett.* **2005**, *7*, 2313–2316. (k) Budynina, E. M.; Ivanova, O. A.; Averina, E. B.; Kuznetsova, T. S.; Zefirov, N. S. *Tetrahedron Lett.* **2006**, *47*, 647–649. (l) Sebelius, S.; Olsson, V. J.; Wallner, O. A.; Szabó, K. J. *J. Am. Chem. Soc.* **2006**, *128*, 8150–8151. (m) Yang, Y.-H.; Shi, M. *Org. Lett.* **2006**, *8*, 1709–1712. (n) Shi, M.; Tang, X.-Y.; Yang, Y.-H. *Org. Lett.* **2007**, *9*, 4017–4020. (o) Lifchits, O.; Charette, A. B. *Org. Lett.* **2008**, *10*, 2809–2812. (p) Lifchits, O.; Alberico, D.; Zakharian, I.; Charette, A. B. *J. Org. Chem.* **2008**, *73*, 6838–6840.

(5) (a) Daviaud, G.; Miginiac, P. *Tetrahedron Lett.* **1972**, *13*, 997–1000. (b) Grieco, P. A.; Finkelhor, R. *J. Org. Chem.* **1973**, *38*, 2100–2101.

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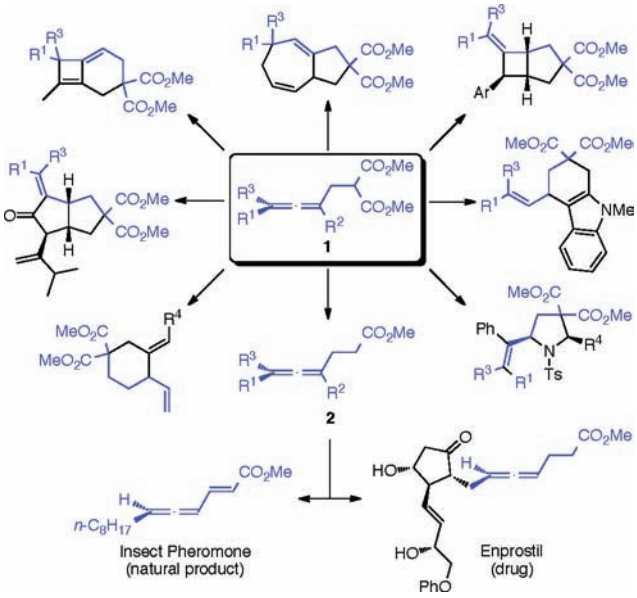
Continuous efforts have been invested in the synthesis of allenes, and its unique chiral structure was accessed by multiple strategies.[8,9] Although few catalytic enantioselective methods have been reported to date,[10] expedient syntheses of enantioenriched allenes remains a challenge. Allenes may be synthesized by formal S_N2' displacement of propargylic alcohols, although many other leaving groups have been used, such as carbonates, sulfonates, ethers, β-lactones, halides, epoxides, and aziridines.[8] Allenes are present in many biologically active compounds, and they have proven to be highly valuable substrates in the synthesis of complex molecules (Scheme 1).[8,11,12]

Scheme 1. Synthetic Utilities of the Allene Scaffold **1**

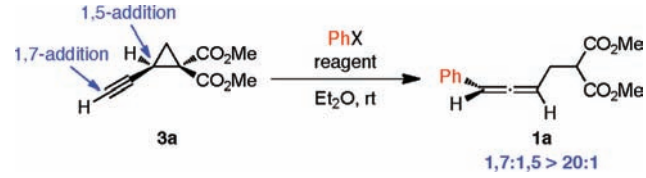


Herein, we describe a new methodology to synthesize allenes from propargylcyclopropanes by the S_N2' addition of organocuprates. The retention of the enantiomeric purity during the process allows the synthesis of highly enantioenriched allenes.

We began our study by the addition of different nucleophilic phenyl reagents on the propargylcyclopropane **3a**. This cyclopropane was easily accessible by a method previously developed in our group.[1e,h] Since previously reported cycloaddition reactions using the cyclopropane **3a** as a substrate led to poor results,[6] we were concerned by the compatibility of the substrate under nucleophilic addition conditions and the lack of selectivity for 1,5- vs 1,7-additions.

Inspired by reported works on the addition of organometallic reagents on 2-vinyl-1,1-cyclopropanediesters,[5] we started to look at higher order cuprates as source of soft nucleophiles.[13] Interestingly, forming the reagent from 2.2 equiv of PhMgBr and 1.1 equiv of CuBr·DMS led to very promising results: 52% yield of the allene **1a** was obtained as the only product (Table 1, entry 1). Other copper sources were examined, and the best result was achieved with CuCN with 92% yield without any 1,5-addition

Table 1. Optimization



entry	PhX	reagent	yield[a] (%)
1	PhMgBr (2.2 equiv)	CuBr·DMS (1.1 equiv)	52
2	PhMgBr (2.2 equiv)	CuI (1.1 equiv)	76
3	**PhMgBr (2.2 equiv)**	**CuCN (1.1 equiv)**	**92**
4	PhMgBr (1.1 equiv)	CuCN (1.1 equiv)	59
5	PhMgBr (1.1 equiv)	(2-Th)Cu(CN)Li (1.1 equiv)	46
6	PhMgBr (2.2 equiv)		0
7	**PhLi (2.2 equiv)**	**CuCN (1.1 equiv)**	**89**
8	PhLi (2.2 equiv)		0
9	PhMgBr (1.1 equiv)	Ph_2Zn (1.1 equiv)	49
10	Ph_2Zn (1.1 equiv)		0
11	Ph_2Zn (1.1 equiv)	CuCN (5 mol %)	51
12	Ph_2Zn (1.1 equiv)	CuOTf (5 mol %)	49

[a] Isolated yields.

(6) For examples of cycloaddition reactions involving 2-propargyl-1,1-cyclopropanediesters protected as cobalt complexes, see: (a) Christie, S. D. R.; Davoile, R. J.; Elsegood, M. R. J.; Fryatt, R.; Jones, R. C. F.; Pritchard, G. J. *Chem. Commun.* **2004**, 2474–2475. (b) Christie, S. D. R.; Davoile, R. J.; Jones, R. C. F. *Org. Biomol. Chem.* **2006**, *4*, 2683–2684. (c) Christie, S. D. R.; Davoile, R. J.; Elsegood, M. R. J.; Fryatt, R.; Jones, R. C. F.; Pritchard, G. J. *Chem. Commun.* **2004**, 2474–2475.

(7) During the preparation of this manuscript, Fürstner published the addition of *i*-PrMgCl on propargylcyclopropane **3a** catalyzed by $Fe(acac)_3$ to form the allene **1f**. However, only one example was reported, and the retention of the stereochemistry was not demonstrated: Sherry, B. D.; Fürstner, A. *Chem. Commun.* **2009**, 7116–7118.

(8) For reviews, see: (a) Sydnes, L. K. *Chem. Rev.* **2003**, *103*, 1133–1150. (b) *Modern Allene Chemistry*; Krause, N., Hashmi, A. S. K., Eds.; Wiley-VCH: Weinheim, 2004. (c) Hoffmann-Röder, A.; Krause, N. *Angew. Chem., Int. Ed.* **2004**, *43*, 1196–1216. (d) Krause, N.; Hoffmann-Röder, A. *Tetrahedron* **2004**, *60*, 11671–11694. (e) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, 795–818. (f) Ogasawara, M. *Tetrahedron: Asymmetry* **2009**, *20*, 259–271.

(9) Selected examples: (a) Myers, A. G.; Zheng, B. *J. Am. Chem. Soc.* **1996**, *118*, 4492–4493. (b) Wan, Z.; Nelson, S. G. *J. Am. Chem. Soc.* **2000**, *122*, 10470–10471. (c) Fürstner, A.; Méndez, M. *Angew. Chem., Int. Ed.* **2003**, *42*, 5355–5357. (d) Pu, X.; Ready, J. M. *J. Am. Chem. Soc.* **2008**, *130*, 10874–10875. (e) Kolakowski, R. V.; Manpadi, M.; Zhang, Y.; Emge, T. J.; Williams, L. J. *J. Am. Chem. Soc.* **2009**, *131*, 12910–12911.

(10) (a) Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915–12916, and references cited therein. (b) Han, J. W.; Tokunaga, N.; Hayashi, T. *J. Am. Chem. Soc.* **2001**, *123*, 12915–12916. (c) Ogasawara, M.; Ueyama, K.; Nagano, T.; Mizuhata, Y.; Hayashi, T. *Org. Lett.* **2003**, *5*, 217–219. (d) Trost, B. M.; Fandrick, D. R.; Dinh, D. C. *J. Am. Chem. Soc.* **2005**, *127*, 14186–14187. (e) Li, C.-Y.; Wang, X.-B.; Sun, X.-L.; Tang, Y.; Zheng, J.-C.; Xu, Z.-H.; Zhou, Y.-G.; Dai, L.-X. *J. Am. Chem. Soc.* **2007**, *129*, 1494–1495. (f) Liu, H.; Leow, D.; Huang, K.-W.; Tan, C.-H. *J. Am. Chem. Soc.* **2009**, *131*, 7212–7213.

(11) Ma, S. *Chem. Rev.* **2005**, *105*, 2829–2872.

(12) For examples of reactions using the allene scaffold **1**, see: (a) Wender, P. A.; Glorius, F.; Husfeld, C. O.; Langkopf, E.; Love, J. A. *J. Am. Chem. Soc.* **1999**, *121*, 5348–5349. (b) Brummond, K. M.; Chen, H.; Sill, P.; You, L. *J. Am. Chem. Soc.* **2002**, *124*, 15186–15187. (c) Ma, S.; Jiao, N. *Angew. Chem., Int. Ed.* **2002**, *41*, 4737–4740. (d) Zhu, G.; Zhang, Z. *Org. Lett.* **2004**, *6*, 4041–4044. (e) Wender, P. A.; Croatt, M. P.; Deschamps, N. M. *Angew. Chem., Int. Ed.* **2006**, *45*, 2459–2462. (f) Zhang, Z.; Liu, C.; Kinder, R. E.; Han, X.; Qian, H.; Widenhoefer, R. A. *J. Am. Chem. Soc.* **2006**, *128*, 9066–9073. (g) Luzung, M. R.; Mauleón, P.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 12402–12403. (h) Trillo, B.; López, F.; Gulías, M.; Castedo, L.; Mascareñas, J. L. *Angew. Chem., Int. Ed.* **2008**, *47*, 951–954. (i) Saito, N.; Tanaka, Y.; Sato, Y. *Org. Lett.* **2009**, *11*, 4124–4126.

product observed (entry 3). Modifying the nature of the reagent by using 1.1 equiv of PhMgBr with 1.1 equiv of CuCN was detrimental to the reaction, affording only 59% yield. Lithiated species can be employed instead of Grignard reagents without significantly altering the yield (89%, entry 7). As expected, control experiments using PhMgBr or PhLi without any source of copper led to a mixture of 1,2-addition products, and no allenic compound was observed (entries 6 and 8).[5a] Interestingly, phenyl zincate also produced a 1,7-addition on the activated cyclopropane **3a** to generate the allene **1a**, albeit in moderate yield (49%, entry 9). Diphenylzinc did not produce the allene in these conditions, but using CuCN or CuOTf as the catalyst afforded the desired product in 51% and 49% yields, respectively (entries 11 and 12). Overall, after extensive optimization of the temperature, solvents, and amounts of reagents, we found that the best reaction conditions were to use 2.2 equiv of Grignard or organolithium reagents with 1.1 equiv of CuCN in Et_2O at rt.

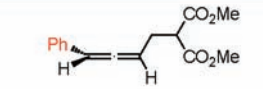
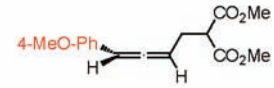
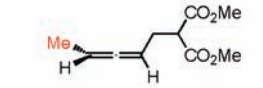
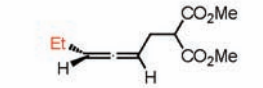
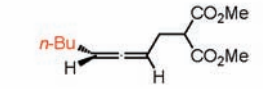
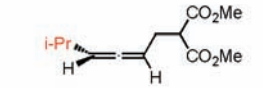
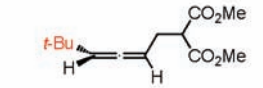
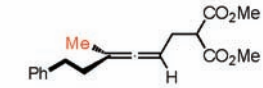
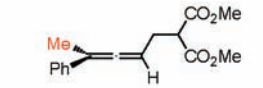
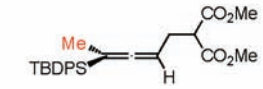
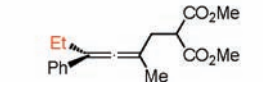
Having these optimal conditions in hand, we studied the scope of the reaction. Different aryl or alkyl cuprates successfully underwent 1,7-addition (Table 2, entries 1−7). Primary, secondary, and even tertiary alkyl cuprates were well tolerated, providing yields of the corresponding allenes ranging from 78% to 89% (entries 3−7). Substituted alkynes were also investigated by the addition of methyl cuprate: 84% and 73% yields were obtained, respectively, with an alkyl- and an aryl-substituted alkyne (entries 8 and 9). In the latter case, a 1,7:1,5 ratio of 5:1 was obtained; however, using MeCu(CN)MgBr with *n*-Bu_3P increased this ratio to 10:1.[14] Interestingly, a bulky silyl group afforded the allene in good yields without any 1,5-addition (entry 10). Tetrasubstituted allenes were also accessible by this method, as 77% yield was obtained in the addition of ethyl cuprate to the corresponding cyclopropane (R^1 = Ph, R^2 = Me, entry 11).

Considering the high importance of enantioenriched allenes, we wondered if these conditions proceed with retention of the enantiomeric purity of the starting cyclopropanes. Although it is known that S_N2' additions on propargylic leaving groups preserve the stereogenic information,[8,9a] there are no such examples with propargylcyclopropanes, and the retention of the stereogenic information has not been reported in the case of 1,7-addition on vinylcyclopropanes. To our delight, starting from the cyclopropane *ent*-**3a** in 96% ee afforded the allene *ent*-**1a** in 96% ee (Table 1, entry 1), demonstrating the high potential of this method in enantioselective synthesis. Indeed, we synthesized allene **1l**, an intermediate in the reported synthesis of methyl (*R*,*E*)-(−)-tetradeca-2,4,5-trienoate (Pheromone of *Acanthoscelides obtectus*),[15] in 86% yield and retention of the enantiomeric purity (Scheme 2). This formal enantioselective synthesis also confirmed the absolute stereochemistry of the allene and thereby the *anti* selectivity of the addition.

The proposed mechanism for this transformation begins with the complexation of the copper reagent to the triple

Table 2. Scope Study

3a-e 1a-k

entry	product		X	yield (%)[a]	1,7:1,5[b]
1		**1a**	MgBr	**92 (96% ee)**[c]	>20:1
2		**1b**	Li	**79**	>20:1
3		**1c**	MgBr	**86**	>20:1
4		**1d**	MgBr	**78**	>20:1
5		**1e**	Li	**79**	>20:1
6		**1f**	MgBr	**82**	>20:1
7		**1g**	Li	**89**	>20:1
8		**1h**	MgBr	**84**	>20:1
9		**1i**	MgBr	**73**	5:1[d]
10		**1j**	MgBr	**62**	>20:1
11		**1k**	MgBr	**77**	18:1

[a] Isolated yield. [b] Ratio between 1,7- and 1,5-addition products determined by ^{1}H NMR on the crude reaction mixture. [c] *ent*-**1a** was obtained in 96% ee starting from cyclopropane *ent*-**3a** in 96% ee. [d] A 1,7:1,5 ratio of 10:1 was obtained when MeCu(CN)MgBr (1.1 equiv) and *n*Bu_3P (2.2 equiv) were used.

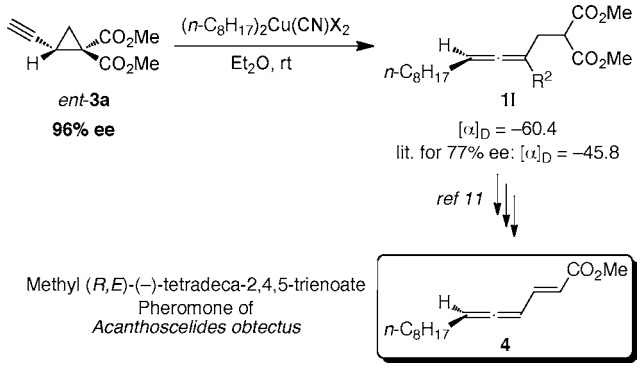
(13) For reviews, see: (a) Lipshutz, B. H.; Wilhelm, R. S.; Kozlowski, J. A. *Tetrahedron* **1984**, *40*, 5005–5038. (b) Lipshutz, B. H. *Synthesis* **1987**, *1987*, 325–341. (c) Lipshutz, B. H. *Synlett* **1990**, *1990*, 119–128. (d) Lipshutz, B. H.; Sengupta, S. *Org. React.* **1992**, *41*, 135–589. (e) Krause, N.; Gerold, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 186–204.

(14) Krause, N.; Hoffmann-Röder, A.; Canisius, J. *Synthesis* **2002**, 1759–1774.

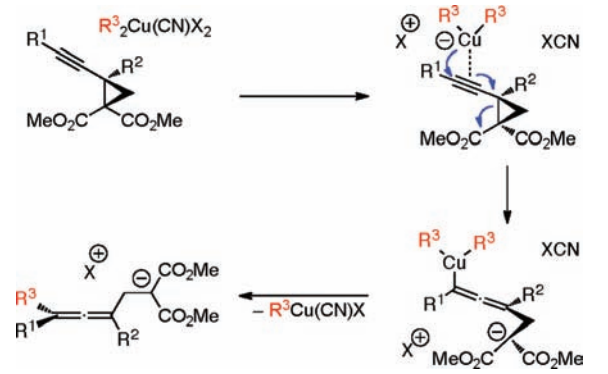
(15) Ogasawara, M.; Nagano, T.; Hayashi, T. *J. Org. Chem.* **2005**, *70*, 5764–5767.

(16) Elsevier, C. J.; Vermeer, P. *J. Org. Chem.* **1989**, *54*, 3726–3730.

Scheme 2. Formal Synthesis of the Natural Allene **4**



Scheme 3. Proposed Mechanism



bond (Scheme 3). Then follows an antiperiplanar opening of the cyclopropane forming the allenyl copper enolate that undergoes reductive elimination to generate the substituted allene. This mechanism previously proposed for S_N2' additions of cuprates on propargylic derivatives[8c,16] is in accordance with the retention of the enantiomeric purity of the starting material and the absolute stereochemistry observed.

In summary, we described the synthesis of allenes by the S_N2' addition of organocuprates to propargylcyclopropanes. This new methodology allows the synthesis of enantioenriched tetrasubstituted allenes. We believe that this reaction will find applications in asymmetric synthesis, as it was demonstrated in the formal synthesis of methyl (*R*,*E*)-(−)-tetradeca-2,4,5-trienoate. Further applications of electrophilic cyclopropanes will be published in due course.

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Supporting Information Available: Experimental procedure for the preparation of compounds and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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