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Dianion Approach to Chiral Cyclopropene Carboxylic Acids

Lian-an Liao, Ni Yan, and Joseph M. Fox*

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

jmfox@udel.edu

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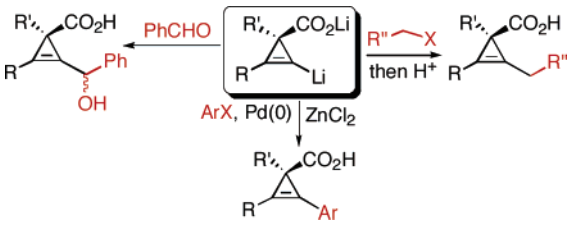
ABSTRACT



In this Letter, we describe a general method for preparing the dianions of cyclopropene carboxylic acids, and we show that their subsequent reactions with electrophiles provide a general means for selectively introducing diverse types of functional groups. This provides a general method for the synthesis of chiral 1,2-disubstituted cyclopropenes, and opens new avenues for the enantioselective preparation of cyclopropenes.

Cyclopropene carboxylic acids are easily prepared[1] materials with a diverse spectrum of applications in complex molecule synthesis.[2−4] Their usefulness has been increased significantly by recent developments that have made chiral cyclopropene carboxylic acids available in nonracemic form.[5] In their pioneering work, Doyle, Müller, and Shapiro first demonstrated that high enantioselectivities could be obtained through the catalytic cyclopropenation of alkynes with diazoacetates.[6] More recently, we[7] as well as Davies[8] addressed the problem of preparing enantiomerically pure or enriched derivatives of cyclopropene carboxylic acids in which C-3 is an all-carbon quaternary stereocenter. These include a method of resolution with broad scope,[7a] a parallel kinetic resolution strategy that is amenable to large scale,[7b] and a very efficient catalytic enantioselective method using $Rh_2(DOSP)_4$.[8] These methods are highly complementary, and

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although the field is still dynamic,[9] it can be said that there are good solutions to the problem of preparing "terminal"[10] cyclopropenes **1** in a single enantiomer form (Figure 1). In

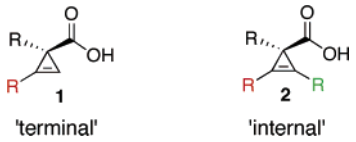
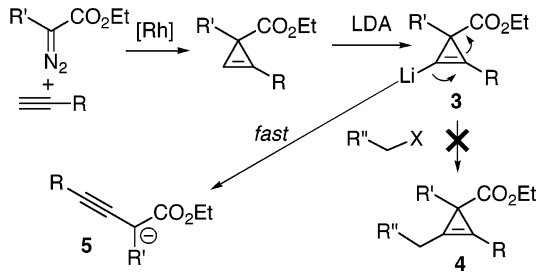


Figure 1. Classification of "terminal" and "internal" cyclopropenes.

contrast, there is no general method for preparing enantiomerically enriched "internal"[10] cyclopropenes **2**. Previous attempts to prepare internal cyclopropenes by enantioselective catalysis were either unsuccessful or proceeded with low enantiomeric excess.[6,8]

In the context of our program to develop synthetically useful reactions of strained molecules,[3f,7] we hoped to develop a seemingly straightforward solution to the problem of preparing chiral, internal cyclopropenes as shown in Scheme 1. The alkene hydrogens of cyclopropenes are more

Scheme 1. Ring-Opening Is Generally Too Fast for Reactions of Anions **3** to Provide a Useful Route to "Internal" Cyclopropenes **4**

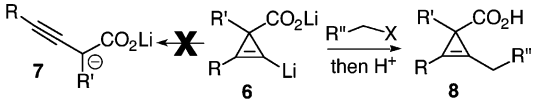


acidic than those of unstrained alkenes,[11] and it is well-known that deprotonation and subsequent reaction with electrophiles (e.g., alkyl halides, aldehydes, epoxides, silyl chlorides) are efficient for many types of cyclopropenes.[12] Furthermore, metalated cyclopropenes have been used as the nucleophiles in Pd(0)-catalyzed cross-coupling reactions.[13] Thus, it would seem that the deprotonation of an enantiomerically pure terminal cyclopropene **3** would provide simple access to chiral, internal cyclopropenes **4** in high yield after the addition of electrophiles (Scheme 1). It should also be possible to break the symmetry of a prochiral cyclopropene, ultimately in enantioselective fashion, and thereby provide a route to diverse types of chiral cyclopropenes through the reaction of electrophiles with a single, common precursor.

In practice, the transformations of anions **3** to internal cyclopropenes **4** are not straightforward. The deprotonations are followed by fragmentations to give ring-opened structures (via **5**) as shown in Scheme 1. To date, the only successful transformations of anions of structure **3** are those in which Me_3GeCl or Me_3SiCl is the electrophile,[14] procedures that are successful because of an inverse addition protocol that allows the electrophile to trap the 1-lithiocyclopropene as soon as it is formed. Our extensive efforts to broaden the reaction scope of **3** to other electrophiles have been largely unsuccessful.

Upon further consideration of the problem, we speculated that the dianion **6** might be more stable than monoanion **3**. We reasoned that the formation of **7** would be disfavored because of increased Coulombic repulsion upon ring opening (Scheme 2). We further speculated that the more reactive carbanion would react in preference to the carboxylate to selectively produce an internal cyclopropene of structure **8**.

Scheme 2. Dianion Strategy for Forming Internal Cyclopropenes



In this Letter, we describe a general method for preparing the dianions of cyclopropene carboxylic acids, and we show

(4) Reactions of cyclopropenone ketals: Nakamura, M.; Isobe, H.; Nakamura, E. *Chem. Rev.* **2003**, *103*, 1295.

(5) For a comprehensive bibliography of nonracemic cyclopropene synthesis, see ref 7a.

(6) (a) Doyle, M. P.; Protopopova, M.; Müller, P.; Ene, D.; Shapiro, E. A. *J. Am. Chem. Soc.* **1994**, *116*, 8492. (b) Müller, P.; Imogai, H. *Tetrahedron: Asymmetry* **1998**, *9*, 4419. (c) Doyle, M. P.; Ene, D. G.; Forbes, D. C.; Pillow, T. H. *Chem. Commun.* **1999**, 1691. (d) Timmons, D. J.; Doyle, M. P. *J. Organomet. Chem.* **2001**, *617*, 98. (e) Doyle, M. P.; Hu, W. *Tetrahedron Lett.* **2000**, *41*, 6265. (f) Doyle, M. P.; Hu, W. H. *Synlett* **2001**, 1364. (g) Imogai, H.; Bernardinelli, G.; Granicher, C.; Moran, M.; Rossier, J. C.; Muller, P. *Helv. Chim. Acta* **1998**, *81*, 1754.

(7) (a) Liao, L.-a.; Zhang, F.; Yan, N.; Golen, J. A.; Fox, J. M. *Tetradedron* **2004**, *60*, 1803. (b) Liao, L.-a.; Zhang, F.; Dmitrenko, O.; Bach, R. D.; Fox, J. M. *J. Am. Chem. Soc.* **2004**, *126*, 4490. (c) Fox, J. M.; Dmitrenko, O.; Liao, L.-a.; Bach, R. D. *J. Org. Chem.* **2004**, *69*, 7317.

(8) Davies, H. M. L.; Lee, G. H. *Org. Lett.* **2004**, *6*, 1233.

(9) For a recent modification of the Doyle, Müller, Shapiro cyclopropenation system, see: Luo, Y.; Horikawa, M.; Kloster, R. A.; Hawryluk, N. A.; Corey, E. J. *J. Am. Chem. Soc.* **2004**, *126*, 8916.

(10) In analogy to the common nomenclature of alkynes, we refer to cyclopropenes with a single alkene substituent as "terminal" cyclopropenes and to those with two alkene substitutents as "internal" cyclopropenes. To our knowledge, there are only two examples of resolutions for "internal" cyclopropenes. See ref 7a and Arrowood, T. L.; Kass, S. R. *J. Am. Chem. Soc.* **1999**, *121*, 7272.

(11) Fattahi, A.; McCarthy, R. E.; Ahmad, M. R.; Kass, S. R. *J. Am. Chem. Soc.* **2003**, *125*, 11746 and references therein.

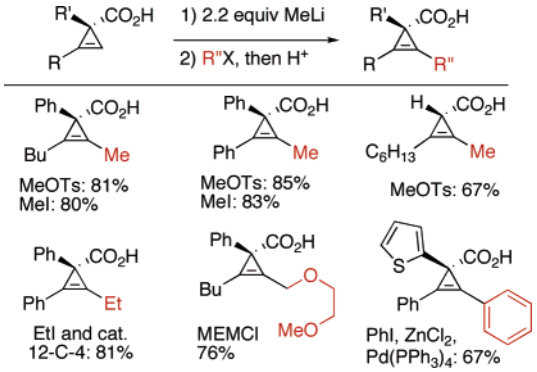
(12) Early examples of cyclopropene deprotonation/alkylation or deprotonation/silylation: see ref 4 and (a) Closs, G. L.; Closs, L. E. *J. Am. Chem. Soc.* **1963**, *85*, 99. (b) Avezov, I. B.; Bolesov, I. G.; Levina, R. Y. *J. Org. Chem. (USSR), Engl. Trans.* **1974**, *10*, 2129. (c) Isaka, M.; Matsuzawa, S.; Yamago, S.; Ejiri, S.; Miyachi, Y.; Nakamura, E. *J. Org. Chem.* **1989**, *54*, 4727. (d) Kirms, M. A.; Primke, H.; Stohlmeier, M.; de Meijere, A. *Recl. Trav. Chim. Pays-Bas.* **1986**, *105*, 462. (e) Schipperijn, A. J.; Smael, P. *Recl. Trav. Chim. Pays-Bas.* **1973**, *92*, 1159.

(13) Cyclopropene deprotonation/cross-coupling: see refs 4, 12c and (a) Grüger, G.; Szeimies, G. *Tetrahedron Lett.* **1986**, *27*, 1563. (b) Unteidt, S.; de Meijere, A. *Chem. Ber.* **1994**, *127*, 1511.

(14) (a) Zrinski, I.; Novak-Coumbassa, N.; Eckert-Maksic, M. *Organometallics* **2004**, *23*, 2806. (b) Zrinski, I.; Eckert-Maksic, M. *Synth. Commun.* **2003**, *33*, 4071. (c) Zrinski, I.; Gadanji, G.; Eckert-Maksic, M. *New J. Chem*, **2003**, *27*, 1270.

that their subsequent reactions with electrophiles provide a general means for selectively introducing diverse types of alkene functional groups. Scheme 3 shows the results

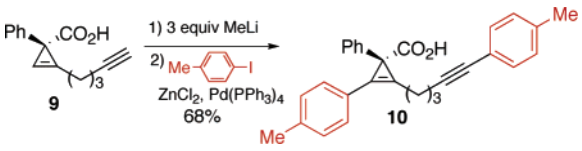
Scheme 3. Cyclopropene Dianion Alkylation and Arylation



obtained when a number of different terminal cyclopropene carboxylic acids were sequentially treated with 2.2 equiv of MeLi and an electrophile. Good yields were obtained for alkylations with MeI, MeOTs, or MEMCl. For reactions of EtI, the best yields were obtained when 12-C-4 was added. It was also shown that cyclopropene carboxylate dianions can serve as the nucleophile in Pd(0)-catalyzed cross-coupling chemistry:[13] transmetalation with $ZnCl_2$ followed by the addition of catalytic $Pd(PPh_3)_4$ leads to arene bond formation as shown in Scheme 3.

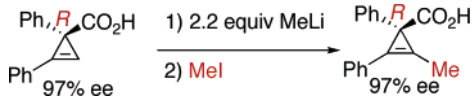
This tandem lithiation/transmetalation/cross-coupling cascade could also be applied to the simultaneous introduction of two aryl groups to alkyne-substitued cyclopropene **9**. Treatment of **9** with 3 equiv of MeLi forms a trilithiated species that produces **10** when sequentially treated with $ZnCl_2$, *p*-iodotoluene, and $Pd(PPh_3)_4$ (Scheme 4).

Scheme 4. Trianion Formation/Pd-Catalyzed Arylation



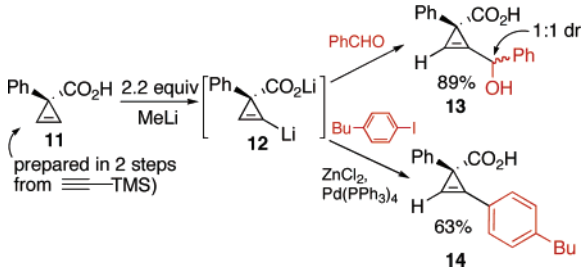
As shown in Scheme 5, the metalation/electrophilic capture sequence is stereospecific. This was demonstrated for the reaction of MeI with the dianion of (*R*)-1,3-diphenylcyclopropene carboxylic acid, a compound that could be obtained in highly enantiomerically enriched form using our previously described parallel kinetic resolution strategy.[7b] The enantiomeric excess did not diminish during course of deprotonation/alkylation.

Scheme 5. Dianion Formation/Alkylation Occurs without Loss of Stereochemical Integrity



We have also shown that it is possible to use to use dianion formation to break the symmetry of prochiral cyclopropenes such as **11**. As shown in Scheme 6, **13** and **14** were obtained by the treatment of dianion **12** with benzaldehyde and 4-*n*-butylphenyliodide/$ZnCl_2$/Pd(0), respectively.

Scheme 6. Desymmetrization of a Cyclopropene Carboxylic Acid



In summary, we have shown that the dianions of cyclopropene carboxylic acids are stable and do not rearrange in analogy to the corresponding monoanions of their esters. Subsequent capture by electrophiles provides a general synthesis of chiral "internal" cyclopropenes. The deprotonation/alkylation occurs with excellent transfer of absolute stereochemistry. It was also demonstrated that prochiral cyclopropenes could be desymmetrized via their dianions. The development of an asymmetric version of that reaction is underway.

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Supporting Information Available: Full experimental and characterization details and ^1H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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