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# Enantiomerically Pure Cyclohexenones by Fe-Mediated Carbonylation of Alkenyl Cyclopropanes

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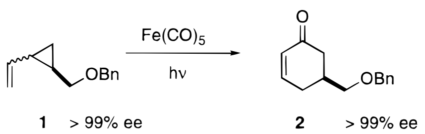
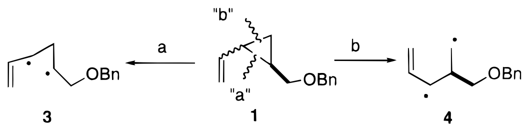
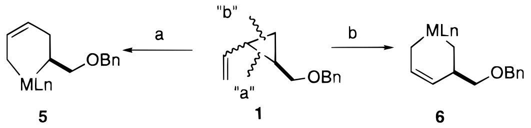
We report a general method for the construction of 5-alkyl cyclohexenones (e.g., **2**) of high enantiomeric purity, by ultraviolet irradiation of enantiomerically pure alkenyl cyclopropanes such as **1** in the presence of $Fe(CO)_5$.[2] Given the many strategies for the preparation of enantiomerically pure alkenyl cyclopropanes that are available,[3] this promises to be a versatile method for the construction of cyclohexane derivatives.



Most ring-expanding reactions of vinyl cyclopropanes, as exemplified by the thermal vinyl cyclopropane rearrangement,[4] proceed with preferential cleavage of bond “a”, to give the more stable diradical **3**. Unfortunately, cleavage at “a” destroys the stereogenic centers of the cyclopropane. If preferential cleavage of bond “b” could be achieved, to give **4**, one of the ring stereogenic centers could be a spectator, and the enantiomeric purity of the product could be maintained.

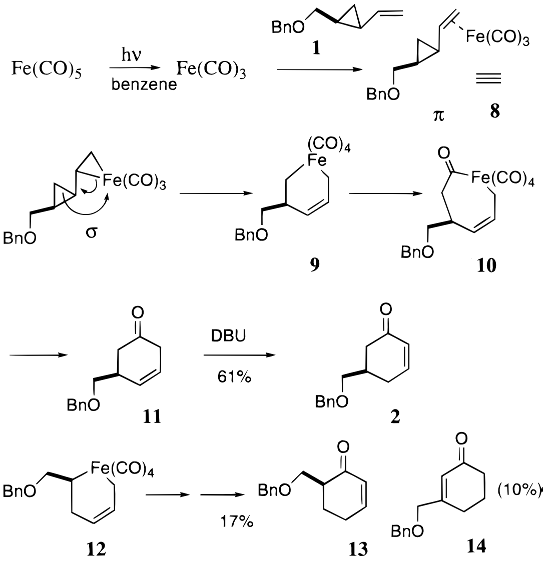


We envisioned that an organometallic cleavage, perhaps by way of initial complexation with the alkene, could lead to either metallacycle **5**, by cleavage of bond “a”, or to metallacycle **6**, by cleavage of bond “b”. We thought that with such an organometallic cleavage the desired product **6** could be preferred, since **6** would have a primary carbon-metal bond, rather than the less-stable secondary carbon-metal bond of **5**.



Photochemically initated $Fe(CO)_5$ carbonylation of alkenyl cyclopropanes had been reported,[2] but the regioselectivity of the process had not been explored. The accepted mechanism (Scheme 1),[2d] however, presented exactly the choice we wanted to set up, that is, between metallacycle **9** and metallacycle **12**. In fact, UV irradiation with $Fe(CO)_5$ in benzene converted the cyclopropane **1** predominantly to the desired 5-alkyl cyclohexenone **2**, the product from bond “b” cleavage.[5,6] In practice, we have found it convenient to add DBU after the irradiation, to convert the intermediate products to their more stable conjugated isomers.

**Scheme 1**



While the enone **14** was a minor product from the Fe-mediated carbonylation of **1**, the corresponding enone was the dominant product from the Fe-mediated carbonylation of **18** (Table 1). We concluded that **14** was formed by “Fe-H” isomerization of **2**, and thus we tried several different additives to suppress this unwanted alkene migration. We eventually found that we could minimize the formation of the isomerized byproduct by running the reaction in 2-propanol.

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[1] Undergradutate research participant.

[2] (a) The photochemical $Fe(CO)_5$-mediated carbonylation of vinyl cyclopropanes was first reported in 1970: Sarel, S. *Acc. Chem. Res.* **1978**, *11*, 204. For more recent references, see: (b) Khusnutdinov, R. I.; Dzhemilev, U. M. *J. Organomet. Chem.* **1994**, *471*, 1. (c) Schulze, M. M.; Gockel, U. *Tetrahedron Lett.* **1996**, *37*, 357. (d) Schulze, M. M.; Gockel, U. *J. Organomet. Chem.* **1996**, *525*, 155.

[3] For an overview of strategies that could be used for the construction of alkenyl cyclopropanes of high enantiomeric purity, see: (a) Davies, H. M. L.; Bruzinski, P. R.; Lake, D. H.; Kong, N.; Fall, M. J. *J. Am. Chem. Soc.* **1996**, *118*, 6897. For more recent examples, see: (b) Zhou, S.-M.; Deng, M.-Z.; Xia, L.-J. *Angew. Chem., Int. Ed.* **1998**, *37*, 2845. (c) Lo, M. M.-C.; Fu, G. C. *J. Am. Chem. Soc.* **1998**, *120*, 10270. (d) Charette, A. B.; Juteau, H.; Lebel, H.; Molinaro, C. *J. Am. Chem. Soc.* **1998**, *120*, 11943. (e) Schwarz, J. B.; Meyers, A. I. *J. Org. Chem.* **1998**, *63*, 1619. (f) Temme, O.; Taj, S.-A.; Andersson, P. G. *J. Org. Chem.* **1998**, *63*, 6007. (g) Sakaguchi, K.; Mano, H.; Ohfune, Y. *Tetrahedron Lett.* **1998**, *39*, 4311. (h) Yang, Z.; Lorenz, J. C.; Shi, Y. *Tetrahedron Lett.* **1998**, *39*, 8621. (i) Fox, M. E.; Li, C.; Marino, J. P., Jr.; Overman, L. E. *J. Am. Chem. Soc.* **1999**, *121*, 5467. (j) Dorizon, P.; Su, G.; Ludvig, G.; Nikitina, L.; Paugam, R.; Ollivier, J.; Salaun, J. *J. Org. Chem.* **1999**, *64*, 4712. (k) Davies, H. M. L.; Panaro, S. A. *Tetrahedron Lett.* **1999**, *40*, 5287. (l) Cai, L.; Mahmoud, H.; Han, Y. *Tetrahedron: Asymmetry* **1999**, *10*, 411.

[4] For preferential bond “a” opening of alkenyl cyclopropanes, see: (a) Feldman, K. S.; Romanelli, A. L.; Ruckle, R. E., Jr.; Miller, R. F. *J. Am. Chem. Soc.* **1988**, *110*, 3300. (b) Feldman, K. S.; Bervan, H. M.; Romanelli, A. L.; Parvez, M. *J. Org. Chem.* **1993**, *58*, 6851. (c) Feldman, K. S.; Bervan, H. M.; Weinreb, P. H. *J. Am. Chem. Soc.* **1993**, *115*, 11364. (d) Takeda, K.; Sakurama, K.; Yoshii, E. *Tetrahedron Lett.* **1997**, *38*, 3257. (e) Pattenden, G.; Wiedenau, P. *Tetrahedron Lett.* **1997**, *38*, 3647 and references therein.

[5] (a) For an overview of carbonylative diene and enyne cyclometalation, see: Hegedus, L. S. *Transition Metals in the Synthesis of Complex Organic Molecules*, 2nd ed.; University Science Books: Sausalito, 1999. For other recent references to carbonylative cyclometalation, see: (b) Taber, D. F.; Wang, Y. *J. Am. Chem. Soc.* **1997**, *119*, 22. (c) Zhao, Z.; Ding, Y.; Zhao, G. *J. Org. Chem.* **1998**, *63*, 9285. (d) Negishi, E.-I.; Montchamp, J.-L.; Anastasia, L.; Elizarov, A.; Choueiry, D. *Tetrahedron Lett.* **1998**, *39*, 2503. (e) Shiu, Y.-T.; Madhushaw, R. J.; Li, W.-T.; Lin, Y.-C.; Lee, G.-H.; Peng, S.-M.; Liao, F.-L.; Wang, S.-L.; Liu, R.-S. *J. Am. Chem. Soc.* **1999**, *121*, 4066.

[6] Concurrently with our work, three other groups reported preferential metal-mediated bond “b” opening of alkenyl cyclopropanes: (a) Murakami, M.; Itami, K.; Ubukata, M.; Tsuji, I.; Ito, Y. *J. Org. Chem.* **1998**, *63*, 4. (b) Wender, P. A.; Dyckman, A. J.; Husfield, C. O.; Kadereit, D.; Love, J. A.; Rieck, H. *J. Am. Chem. Soc.* **1999**, *121*, 10442. (c) Trost, B. M.; Toste, F. D.; Shen, H. *J. Am. Chem. Soc.* **2000**, *122*, 2379.

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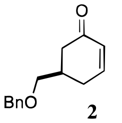
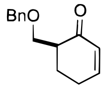
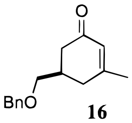
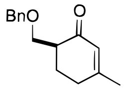
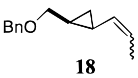
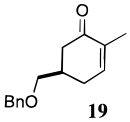
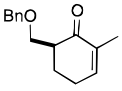
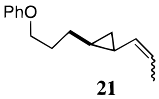
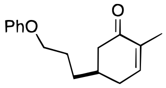
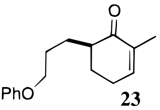
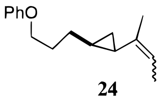
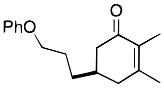
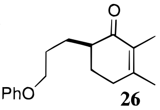
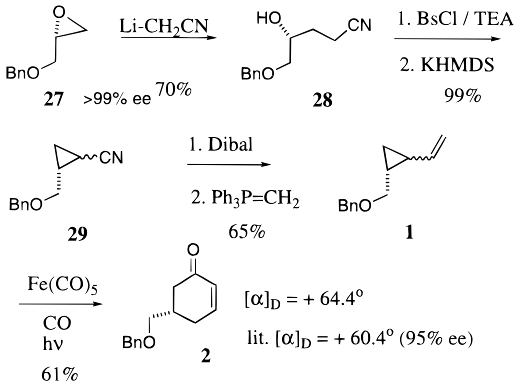
**Table 1.** Carbonylation of Alkenyl Cyclopropanes

| | | | | | |
|---|---|---|---|---|---|
| 1 | <br>**1** | <br>**2** | 59% | <br>**13** | 15% |
| 2 | <br>**15** | <br>**16** | 67% | <br>**17** | 11% |
| 3 | <br>**18** | <br>**19** | 83% | <br>**20** | 5% |
| 4 | <br>**21** | <br>**22** | 83% | <br>**23** | 5% |
| 5 | <br>**24** | <br>**25** | 56% | <br>**26** | 10% |

We have made a preliminary exploration of the scope of this cyclocarbonylation (Table 1). It was apparent that disubstituted alkenes participated efficiently. The yield with a trisubstituted alkene was a little lower.[7] The examples in Table 1 were carried out in 2-propanol (0.05 M), using 2 mol equiv of the inexpensive $Fe(CO)_5$, under one atmosphere of CO pressure, irradiated in Pyrex tubes in a Rayonet apparatus. With 10 mol % of $Fe(CO)_5$ (CO atmosphere) the yield of **22** was 77%, and with 5 mol % of $Fe(CO)_5$ the yield of **22** was 73%. With 2 mol equiv of $Fe(CO)_5$ and an $N_2$ atmosphere the yield of **22** was 57%.

**Scheme 2**



The appearance of the alkene-migrated product **14** suggested that **2** might have undergone racemization under the reaction conditions. To explore this, we prepared **1** (Scheme 2) from the epoxide **27**, which is commercially available in high enantiomeric purity. We were pleased to observe that the product **2** had maintained[8] its enantiomeric purity. Cyclopropane **15** was also prepared from epoxide **27**. The product enone **16** was shown to be >99% ee by chiral HPLC.[9]

The $Fe(CO)_5$-mediated cyclocarbonylation of alkenyl cyclopropanes described here should be a general method for the preparation of enantiomerically pure 5-alkylcyclohexenones, which are key building blocks for natural product synthesis.[10] We are also exploring the application of this method to polycyclic ring construction.

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**Supporting Information Available:** Spectroscopic data for all new compounds (PDF). This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The starting cyclopropanes were mixtures of stereoisomers. Each of the stereoisomers appeared to participate efficiently in the carbonylation reaction.

(8) Carda, M.; Van der Eycken, J.; Vandewalle, M. *Tetrahedron: Asymmetry* **1990**, *1*, 17.

(9) To make this determination, *ent*-**16** was prepared from enantiomerically pure **2** by addition of $CH_3MgBr$ followed by PCC oxidation. On an analytical Chiralcel OD column, eluting with 95:5 hexanes/2-propanol at 1.0 mL/min, **16** (13.5 min) and *ent*-**16** (12.3 min) showed baseline resolution.

(10) For leading references to alternative methods for the preparation of 5-alkylcyclohexenones of high enantiomeric purity, see: (a) Asaoka, M.; Shima, K.; Takei, H. *Tetrahedron Lett.* **1987**, *28*, 5669. (b) Schwarz, J. B.; Devine, P. N.; Meyers, A. I. *Tetrahedron* **1997**, *53*, 8795. (c) Hareau, G. P.-J.; Koiwa, M.; Hikichi, S.; Sato, F. *J. Am. Chem. Soc.* **1999**, *121*, 3640. (d) Sarakinos, G.; Corey, E. J. *Org. Lett.* **1999**, *1*, 811.