Stereochemical Control in Metal-Catalyzed [3 + 2] Cycloadditions of Methylenecyclopropanes

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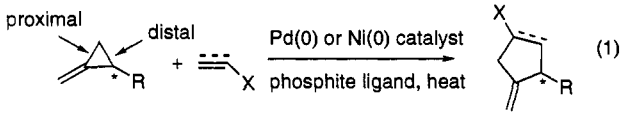
Received June 13, 1994

There is significant interest in the synthesis of five-membered rings via cycloaddition reactions. Of the strategies explored to date, the nickel- or palladium-catalyzed reaction between methylenecyclopropane and an alkene or alkyne and the trimethylenemethane (TMM)–Pd reaction have received considerable attention.[2-4] Intramolecular methylenecyclopropane reactions have also recently been reported.[5] However, the stereochemical integrity at C* in these cycloadditions has not yet been investigated, eq 1.[6] Our recent success in achieving regio- and diastereoselective cyclopropanation of α-allenic alcohols provided the first opportunity to address this important issue.[7]



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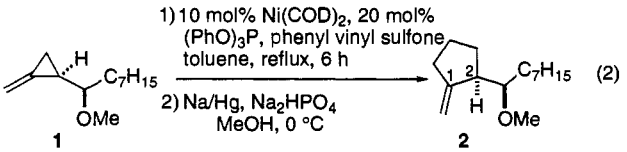
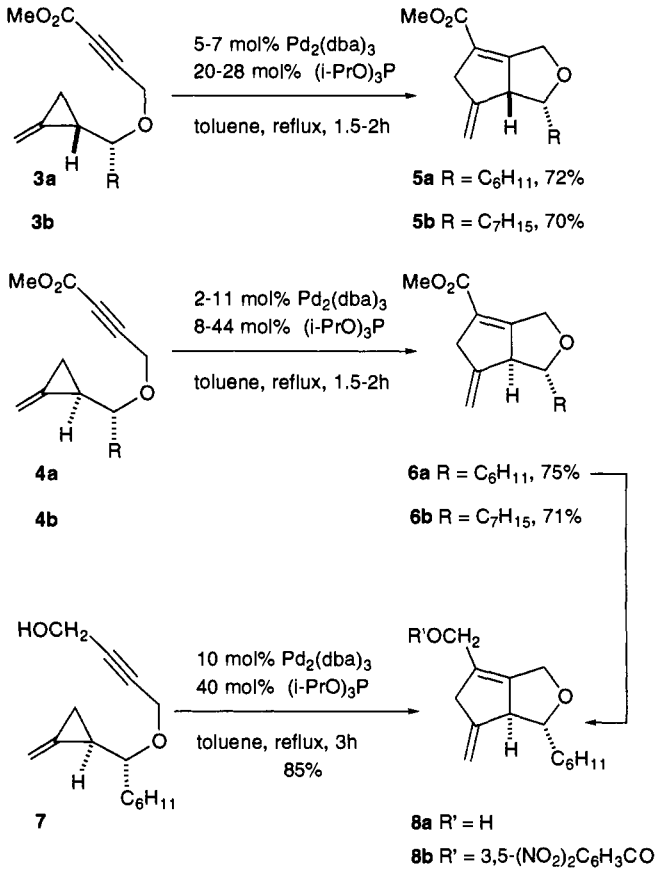
Our studies began with an investigation of the nickel-catalyzed cycloaddition between **1** and phenyl vinyl sulfone, eq 2. A mixture



(2)

of adducts was formed, which were desulfonylated to give **2** in 49% overall yield. Comparison with authentic samples revealed that a 10:1 mixture of diastereomers at C-2 was produced, with the major product arising from overall retention of stereochemistry at the cyclopropyl carbon.[8] This result is surprising because reactions catalyzed by nickel usually take place at the proximal C—C bond which should not lead to any epimerization. Loss of stereochemical integrity at C-2 can only occur via reaction at the distal bond.

Scheme 1



In contrast to cycloadditions using nickel, palladium catalysts react exclusively at the distal bond in methylenecyclopropanes, and it was of interest to learn if epimerization would also occur. Intermolecular cycloaddition failed between **1** and phenyl vinyl sulfone or dimethyl acetylenedicarboxylate in the presence of $Pd_2(dba)_3$ and $(i\text{-}PrO)_3P$. However, when **3a** was reacted with 5 mol % of $Pd_2(dba)_3$ and $(i\text{-}PrO)_3P$, intramolecular cycloaddition took place in 72% yield and gave **5a** as a single diastereomer, Scheme 1. The diastereomeric starting material **4a** afforded **6a** in 75% yield using 2 mol % of $Pd_2(dba)_3$ and $(i\text{-}PrO)_3P$. The ^1H NMR spectra (400 MHz) of the crude reaction mixtures established that both cycloadditions were stereospecific (>100:1). The reactions of **3b** and **4b** proceeded in an identical fashion and were equally stereospecific. Cycloaddition of the alcohol **7** gave **8a** in 85% yield, which illustrates that the substituent on the acetylene did not influence the stereospecificity. However, the substituent did affect the reactivity. For example, when the CH_2OH group was replaced by a TBDMS moiety, cycloaddition failed to occur.

NMR techniques (NOE, 2D NMR) failed to provide conclusive information on the relative stereochemistry of the cycloadducts from the Pd-catalyzed cycloadditions. Instead, we obtained unequivocal proof by an X-ray structure. Reduction of **6a** with DIBAL-H (–78 °C, THF) gave alcohol **8a**, which was esterified (3,5-dinitrobenzoic acid, DCC, DMAP) to provide a crystalline

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(2) For reviews, see: (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (b) Ohta, T.; Takaya, H. In: *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 1185. (c) Dzhemilev, U. M.; Khusnutdinov, R. I.; Tolstikov, G. A. *J. Organomet. Chem.* **1991**, *409*, 15.

(3) For the early reports using nickel and palladium, see: (a) Noyori, R.; Odagi, T.; Takaya, H. *J. Am. Chem. Soc.* **1970**, *92*, 5780. (b) Binger, P.; Schuchardt, U. *Angew. Chem. Int. Ed. Engl.* **1977**, *16*, 249. (c) Binger, P.; Schuchardt, U. *Chem. Ber.* **1980**, *113*, 3334.

(4) For a review, see: (a) Trost, B. M. *Angew. Chem., Int. Ed. Engl.* **1986**, *25*, 1. For a full account of the intramolecular cycloadditions, see: (b) Trost, B. M.; Grese, T. A.; Chan, D. M. T. *J. Am. Chem. Soc.* **1991**, *113*, 7350.

(5) (a) Lewis, R. T.; Motherwell, W. B.; Shipman, M. *J. Chem. Soc., Chem. Commun.* **1988**, 948. (b) Yamago, S.; Nakamura, E. *J. Chem. Soc., Chem. Commun.* **1988**, 1112. (c) Bapuji, S. A.; Motherwell, W. B.; Shipman, M. *Tetrahedron Lett.* **1989**, *30*, 7107. (d) Motherwell, W. B.; Shipman, M. *Tetrahedron Lett.* **1991**, *32*, 1103. The Motherwell group did show that a 1:1 mixture of diastereomers gave a 1:1 mixture of cycloadducts, but they were unable to determine if the reaction occurred with retention or inversion at the cyclopropane carbon.

(6) Control of the relative and absolute stereochemistry in the cycloaddition has been achieved using chiral auxiliaries for 2,2-dimethylmethylenecyclopropane and the parent compound. See: (a) Binger, P.; Brinkmann, A.; Richter, W. J. *Tetrahedron Lett.* **1983**, *24*, 3599. (b) Binger, P.; Schafer, B. *Tetrahedron Lett.* **1988**, *29*, 529. (c) Binger, P.; Brinkmann, A.; Roefke, P.; Schafer, B. *Liebigs Ann. Chem.* **1989**, 739.

(7) (a) Lautens, M.; Delanghe, P. H. M. *J. Org. Chem.* **1993**, *58*, 5037. For the development of the Sm cyclopropanation, see: (b) Molander, G. A.; Etter, J. B. *J. Org. Chem.* **1987**, *52*, 3942. (c) Molander, G. A.; Harring, L. S. *J. Org. Chem.* **1989**, *54*, 3525.

(8) See: (a) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *Tetrahedron Lett.* **1982**, *23*, 2387. (b) Sakurai, H.; Sasaki, K.; Hosomi, A. *Bull. Chem. Soc. Jpn.* **1983**, *56*, 3195. (c) Habaue, S.; Yasue, K.; Yanagisawa, A.; Yamamoto, H. *Synlett* **1993**, 788. The major products from the cycloaddition are epimeric at the carbon bearing the sulfone. D-labeling studies reveal that insertion in the proximal bond is the predominant product. However, epimerization leading to the 10:1 mixture in **2** must arise from insertion into the distal bond.

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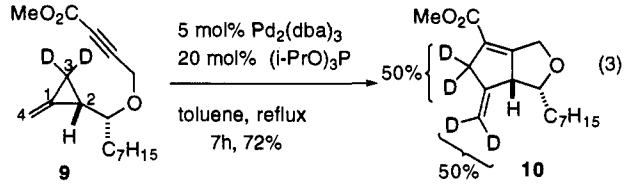
product, **8b**.[9] The relative stereochemistry between the cyclohexyl ring and the hydrogen at the bridge indicated that the cycloaddition not only was stereospecific but also occurred with overall *retention of stereochemistry*.

In order to gain more information on the reaction pathway, we prepared the deuterated methylenecyclopropane **9**.[10] Reaction of **9** with Pd(0) gave **10** with complete scrambling at the vinylic and allylic positions as determined by ^1H and ^2H NMR, eq 3. When the reaction was run to 18% conversion, the recovered starting material showed no scrambling of the label between C-3 and C-4! This is in contrast to studies by Noyori using nickel catalysts where significant isomerization in the recovered methylenecyclopropane was observed.[11]

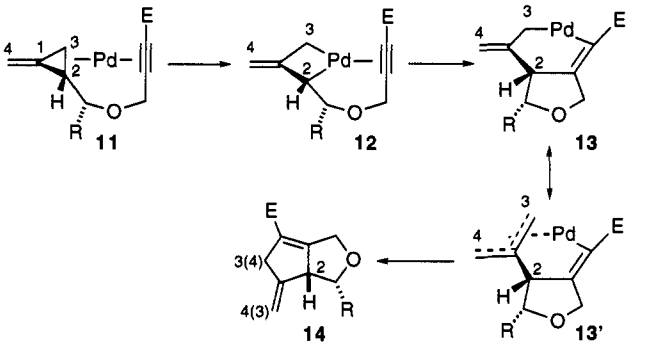


(3)

From these results, information on the relative rates of the various reaction processes in palladium-catalyzed cycloadditions can be obtained. Coordination of the alkyne to the palladium appears to be necessary to trigger the subsequent steps since increasing steric bulk, which inhibits complexation, had a marked effect on the efficiency of the cycloaddition. Following complexation in an edge-on orientation, insertion into the distal cyclopropane bond would generate metallacycle **12**. Since no scrambling is observed in the recovered starting material, the insertion step must be rate determining because we do see scrambling in the final product. A σ-allyl interconversion, which exchanges C-3 and C-4, occurs in either **12** or **13** (which can also be represented as the π-allyl species **13'**) prior to reductive elimination to **14** (Scheme 2).

Since the stereochemistry at C-2 is retained in the pathway leading to the cycloadduct, a retention or double inversion pathway must be considered. Insertion by low oxidation state metals in cyclopropanes typically occurs with retention of configuration.[12] This implies that the carbometalation step (i.e., **12** to **13**) also takes place with retention.

Scheme 2



In conclusion, we have shown that cycloaddition with $Ni(COD)_2$ gives synthetically useful levels of regio- and stereospecificity. Palladium-catalyzed intramolecular cycloaddition of diastereomerically pure methylenecyclopropanes is stereospecific and occurs with retention. We have also investigated the first deuterium-labeling studies with palladium catalysts and methylenecyclopropanes and shown that the insertion is irreversible. Importantly, application of these observations in synthetic endeavors can now be undertaken. The ease of preparing enantiomerically enriched starting materials is also noteworthy.[7a]

Acknowledgment. The A. P. Sloan Foundation, the Natural Science and Engineering Research Council (NSERC) of Canada, the Merck Frosst Centre for Therapeutic Research, Bio-Mega/Boehringer Ingelheim Inc., and Eli Lilly (U.S.A.) are thanked for financial support. We thank Dr. Alan Lough from our department for the X-ray structure.

Supplementary Material Available: General experimental procedures, specific details for representative reactions, and isolation and spectroscopic information for the compounds prepared (13 pages). This material is contained in many libraries on microfiche, immediately follows this article in the microfilm version of the journal, and can be ordered from the ACS; see any current masthead page for ordering information.

(9) The X-ray structure was solved by Dr. Alan Lough, University of Toronto. Full data have been submitted for publication in *Acta Crystallographica*.

(10) Replacement of CH_2I_2 by CD_2I_2 in the Sm-catalyzed cyclopropanation provided the deuterated starting materials. For the preparation of dideuteriodiiodomethane, see: Winstein, S.; Friedrich, E. C.; Baker, R.; Lin, Y. *Tetrahedron, Suppl.* **1966**, No. 8, 621.

(11) Noyori, R.; Yamakawa, M.; Takaya, H. *Tetrahedron Lett.* **1978**, 4823. Trost has reported that complete scrambling occurs in the cycloadducts of the TMM type, see ref 4a.

(12) See, for example: (a) Blomberg, M. R. A.; Siegbahn, P. E. M.; Backvall, J.-E. *J. Am. Chem. Soc.* **1987**, *109*, 4450 and references therein. (b) Attig, T. G. *Inorg. Chem.* **1978**, *17*, 3097. (c) Green, M.; Hughes, R. P. *J. Chem. Soc., Dalton Trans.* **1976**, 1880.