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Palladium-Catalyzed Intramolecular [3 + 2] Cycloadditions of Methylenecyclopropanes With Alkenes: Diastereomeric Methylenecyclopropanes Exhibit Complementary Facial Selectivity

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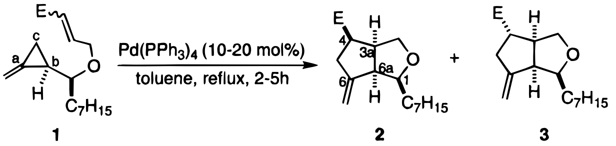
The synthesis of five-membered carbocycles *via* metal-catalyzed [3 + 2] cycloaddition reactions with methylenecyclopropane (MCP) has remained a subject of study for more than 25 years.[1] Intramolecular methylenecyclopropane cycloadditions were first reported in 1988, and interest in this process also continues to grow.[2] We recently reported the Pd^0-catalyzed intramolecular [3 + 2] cycloaddition reaction using diastereomerically pure MCPs with alkynes and revealed for the first time that this reaction is stereospecific and occurs with overall retention of configuration at the cyclopropane carbon involved in the reaction.[3]

The corresponding reaction with an alkene would generate a saturated bicyclo[3.3.0] system with the potential to create two new stereogenic centers in addition to the pre-existing stereocenter in the cyclopropane. We now report that the cycloaddition with alkenes is stereospecific (with respect to the pre-existing stereocenter) but that the two diastereomeric starting materials react on opposite faces of the electron-deficient olefin and lead to either *cis* or *trans* bicyclo[3.3.0] ring systems.

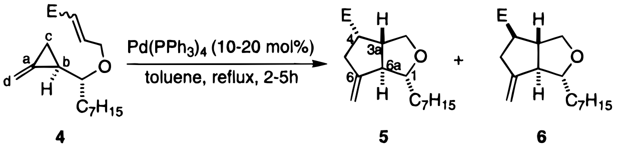
Our initial studies were carried out with **1a** which was treated with 18 mol % of $Pd(PPh_3)_4$ in refluxing toluene for 2 h to provide **2a** as a single diastereomer in 78% yield (Table 1). NOE experiments indicated that the stereochemistry of the ring junction was *cis* (*vide infra*). Changing the substituent on the alkene did not affect the stereochemistry of the stereogenic center which originates in the cyclopropyl ring or significantly influence the reactivity of the substrate (Table 1). Alkenes **1a**−**d** reacted in a highly stereoselective manner and were unaffected by the initial olefin stereochemistry (entry 1 *vs* 2 and entry 5). However, the major diastereomer formed was related to the nature of the electron-withdrawing group with an ester and ketone favoring formation of **2**, whereas a sulfone yielded **3**. Reaction of the substrate with a nitrile was nonselective at C_4 (entry 5).

Table 1



Entry	Substrate	E	Alkene	Product	Yield (%)
1	**1a**	COOEt	*E*	**2a**	78
2	**1b**	COOEt	*Z*	**2a**	75
3	**1c**	COMe	*E*	**2c**	81
4	**1d**	SO_2Ph	*E*	**3d**	60
5	**1e**	CN	*Z*:*E* = 1:2	**2e**:**3e** = 1:1	92

Table 2



Enrty	Substrate	E	Alkene	Product	Yield (%)
1	**4a**	COOEt	*E*	**5a**:**6a** = 1:1	87
2	**4b**	COOEt	*Z*	**5a**:**6a** = 1:1	83
3	**4d**	SO_2Ph	*E*	**5d**:**6d** = 4:1	86
4	**4e**	CN	*Z*:*E* = 1:4	**5e**:**6e** = 1:1.5	91

The most interesting observation was that the diastereomeric MCP (*i.e.*, **4a**) yielded *only trans*-fused bicyclic products (**5a** and **6a**) when treated under similar conditions (13 mol % of $Pd(PPh_3)_4$, Table 2). Complete selectivity was observed at the ring juncture (C_{3a}) but the carbon bearing the electron-withdrawing group at C_4 was always a mixture of epimers for a variety of substituents.

The ^1H NMR spectrum of **2a** is very different from that of **5a** and **6a**, and these differences were typical for all the *cis* and *trans* cycloadducts prepared.[4] NOEs were used to assign the stereochemistry of **5a**, and the alcohol **2b** prepared by reduction of **2a** with DIBAL-H((*i*-Bu)$_2$AlH) and further support for the stereochemical assignments was provided by a series of chemical transformations.[5]

Firm evidence in support of the formation of *trans* ring adducts was obtained with the adduct bearing a sulfone substituent (Scheme 1). Cycloadducts **5d** and **6d** were desulfonylated to give a single product which was ozonolyzed to provide cyclopentanone **7**. When **7** was treated with K_2CO_3 in methanol, rapid epimerization occurred to form the corresponding *cis*-cyclopentanone **8**, whose stereochemistry was further confirmed by NOE experiments. Methylenation of **8** yielded **9** which was identical to the product isolated from the desulfonylation of **3d**.

We demonstrated that the mixture of isomers formed during the cycloadditions (Table 1, entry 5 and Table 2) were epimeric at C_4 rather than at the ring junction. For instance, pure **3e** was treated with *t*-BuOK in *t*-BuOH at room temperature (rt) to give a 1:1 mixture of **2e** and **3e**, whereas **6e** gave a mixture of **5e** and **6e**. Quantitative deprotonation of a 5.4:1 mixture **5a** and **6a** with LDA at −78 °C and quenching with HOAc at −78 °C led to a 1:4.3 mixture of **5a** and **6a**.

The integrity of the alkene geometry is not preserved during the cycloaddition in either diastereomeric series, suggesting that an equilibrium must have been established in which epimerization of the carbon bearing the electron-withdrawing substituent occurred. However, even when a single product is formed, it is not always the thermodynamically most stable one. For

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[1] For a review of transition metal mediated cycloadditions, see: (a) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. For a review of [3 + 2] cycloadditions, see: (b) Chan, D. M. T. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 271. For reviews of [3 + 2] cycloaddition involving methylenecyclopropane, see: (c) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77. (d) Ohta, T.; Takaya, H. In *Comprehensive Organic Synthesis*; Trost, B. M., Ed.; Pergamon Press: Oxford, 1991; Vol. 5, p 1185. (e) Dzhemilev, U. M.; Khusnutdinov, R. I.; Tolstikov, G. A. *J. Organomet. Chem.* **1991**, *409*, 15. (f) Binger, P.; Fox, D. In *Methods of Organic Chemistry* (Houben Weyl); Georg Thieme Verlag: Stuttgart, 1995; Vol. E 21C, Part D, 1.6.1.2.3, p 2997.

[2] (a) Lewis, R. T.; Motherwell, W. B.; Shipman, M. *J. Chem. Soc., Chem. Commun.* **1988**, 948. (b) Bapuji, S. A.; Motherwell, W. B.; Shipman, M. *Tetrahedron Lett.* **1989**, *30*, 7107. (c) Motherwell, W. B.; Shipman, M. *Tetrahedron Lett.* **1991**, *32*, 1103. (d) Lewis, R. T.; Motherwell, W. B.; Shipman, M.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1995**, *51*, 3289. (e) Corlay, H.; Lewis, R. T.; Motherwell, W. B.; Shipman, M. *Tetrahedron* **1995**, *51*, 3303. (f) Yamago, S.; Nakamura, E. *J. Chem. Soc., Chem. Commun.* **1988**, 1112. (g) Yamago, S.; Nakamura, E. *Tetrahedron* **1989**, *45*, 3081. (h) Corlay, H.; Motherwell, W. B.; Pennell, A. M. K.; Shipman, M.; Slawin, A. M. Z.; Williams, D. J. *Tetrahedron* **1996**, *52*, 4883.

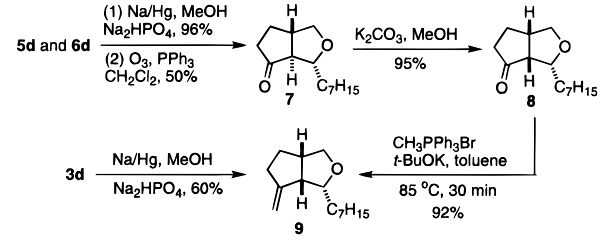
[3] (a) Lautens, M.; Ren, Y.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8821. (b) Lautens, M.; Ren, Y. *J. Am. Chem. Soc.* **1996**, *118*, 0000.

[4] For example, in **2a** the vinylic protons appear at 5.00 and 4.78 ppm, whereas in **5a** they appear at 4.77 and 4.69 ppm and in **6a** at 4.77 and 4.71 ppm. See Supporting Information for further details.

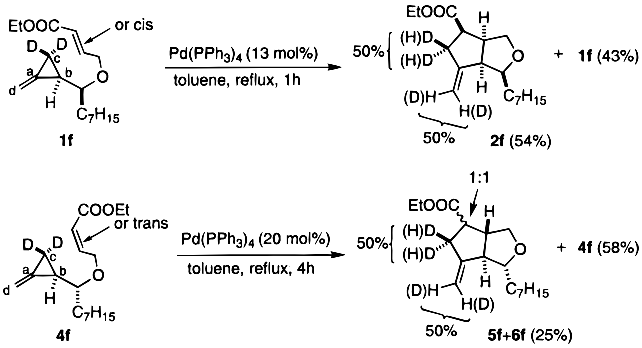
[5] See Supporting Information.

S0002-7863(96)02148-8 CCC: $12.00

Scheme 1



Scheme 2

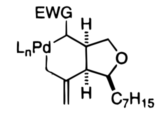


example, the ester and ketone substituents are produced exclusively on the concave face in adducts **2a** and **2c**. When **2c** was treated with *t*-BuOK in *t*-BuOH at rt, quantitative epimerization occurred to give **3c**. No epimerization occurred when **3d** was subjected to the same conditions.

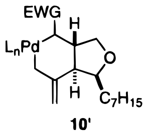
A brief comment concerning the choice of catalyst is warranted. Unlike the cycloadditions of MCPs bearing an alkyne group in the tether, $Pd_2(dba)_3/P(OiPr)_3$ led to complex mixtures when used with **1a** or **1b**. Adding 7−10 equiv of 4 Å molecular sieves to the reaction mixture (by weight *vs* $Pd_2(dba)_3$) improved the yield, although 30 mol % of the catalyst was needed for complete consumption of the starting material.[6] For example, **1a** or **1b** gave **2a** in 53% yield, whereas **4a** or **4b** produced a 1.9:1 mixture of **5a** and **6a** in 95% yield. In general, we found that $Pd(PPh_3)_4$, which has not been widely used in MCP cycloadditions, was by far the best catalyst for intramolecular MCP−alkene cycloadditions.

Selectively deuterated MCPs **1f** and **4f** (both *cis* and *trans* alkenes) were prepared to determine the rate of the scrambling of C_c and C_d.[7] Reaction with $Pd(PPh_3)_4$ gave cycloadduct **2f** and a mixture of **5f** and **6f** with complete scrambling at the vinylic and allylic positions, as shown by ^1H and ^2H NMR. The recovered starting material showed no scrambling of the label between C_c and C_d, nor had isomerization of the double bound occurred for either the *cis* or *trans* alkene in either diastereomer (Scheme 2). These results support the idea that the insertion of Pd^0 into the distal bond of the MCP is irreversible, as is the carbopalladation of the olefin.

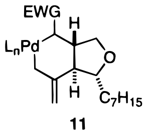
Further experiments are required to determine the factors which control the facial selectivity in the two diastereomers. If a palladacycle is an intermediate *en route* to the product, then **10** and **11** must be generated from **1** and **4**, respectively. However, it is not obvious why the related intermediates **10′** and **11′** are of sufficiently higher energy that cycloadducts from these species are not observed.



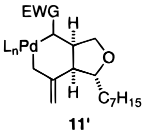
10



10'

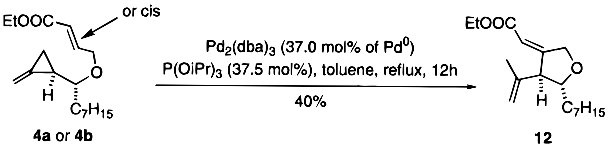


11



11'

The formation of *trans*-fused adducts from **11** is particularly intriguing.[8] While the *trans*-palladabicyclo[4.3.0] intermediate may not be highly strained, the transition state leading to *trans*-bicyclo[3.3.0] products should be of higher energy and *β*-elimination might be expected to compete with reductive elimination.[9,10] In fact, when **4a** or **4b** was reacted in the presence of $Pd_2(dba)_3/P(OiPr)_3$, the major product was diene **12** (eq 1).



(1)

In conclusion, we have investigated Pd^0-catalyzed intramolecular cycloadditions of diastereomerically pure methylenecyclopropanes bearing tethers with electron-deficient alkenes. The reaction was found to be stereospecific with regard to the stereochemistry at the ring junction, and cycloaddition occurs with retention of configuration at the cyclopropane carbon C_b. *trans*-Bicyclo[3.3.0] compounds were formed from only one of the diastereomeric methylenecyclopropanes. $Pd(PPh_3)_4$ was found to be the best catalyst for this reaction. Deuterium labeling studies support the formation of a *π*-allyl intermediate and the irreversibility of the insertion and carbopalladation steps.

Acknowledgment. The E. W. R Steacie Fund administered by the Natural Science and Engineering Research Council (NSERC) of Canada, the Merck Frost Center for Therapeutic Research, Upjohn/Pharmacia (USA), and Eli Lilly (USA) are thanked for financial support. Y.R. thanks the University of Toronto for a graduate scholarship.

Supporting Information Available: NOE measurements of compounds **2b** and **5a**, detailed information supporting the stereochemical assignments of the cycloadducts including chemical transformations, text describing the details of experimental procedures, and compound characterization data (28 pages). See any current masthead page for ordering and Internet access instructions.

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(6) Molecular sieves have been shown to improve some metal-catalyzed reactions. For examples, see: (a) Sharpless, K. B.; Michaelson, R. C. *J. Am. Chem. Soc.* **1973**, *95*, 6136. (b) Mihelich, E. D. *Tetrahedron Lett.* **1979**, *20*, 4729. (c) Rossiter, B. E.; Verhoeven, T. R.; Sharpless, K. B. *Tetrahedron Lett.* **1979**, *20*, 4733.

(7) Reaction with CD_2I_2 in the Sm-catalyzed cyclopropanation provided the deuterated starting materials, see: ref 3. (a) Lautens, M.; Delanghe, P. H. M. *J. Am. Chem. Soc.* **1994**, *116*, 8526. (b) Lautens, M.; Ren, Y. *J. Org. Chem.* **1996**, *61*, 2210. For the preparation of dideuteriodiiodomethane, see: (c) Winstein, S.; Friedrich, E. C.; Baker, R.; Lin, Y. *Tetrahedron Suppl.* **1966**, *8*, 621.

(8) For the stereochemical course of Pd^0 insertion into MCP, see: (a) Blomberg, M. R. A.; Siegbahn, P. E. M.; Bäckvall, J.-E. *J. Am. Chem. Soc.* **1987**, *109*, 4450 and references therein. The fate of the stereogenic carbon atom in a carbon−palladium complex upon reaction with an alkyne has been studied by Pfeffer. See: (b) Spencer J.; Pfeffer, M. *Tetrahedron: Asymmetry* **1995**, *6*, 419.

(9) *trans*-Bicyclo[3.3.0]octane is reported to be 6.1−6.4 kcal/mol less stable than its *cis* isomer. With the C−O bond length shorter than a C−C bond and the bond energy higher, the strain energy for the *trans*-fused cycloadduct can be very high. For examples of *trans*-bicyclo[3.3.0]octane, see: (a) Chang, S.; McNally, D.; Shary-Tehrany, S.; Hickey, M. J.; Boyd, R. H. *J. Am. Chem. Soc.* **1970**, *92*, 3109. (b) Allinger, N. L.; Tribble, M. T.; Miller, M. A.; Wertz, D. H. *J. Am. Chem. Soc.* **1971**, *93*, 1637. (c) Li, J.-H.; Allinger, N. L. *J. Am. Chem. Soc.* **1989**, *111*, 8566. (d) Linstead, R. P.; Meade, E. M. *J. Chem. Soc.* **1934**, 935. (e) Funk, R. L.; Bolton, G. L.; Daggett, J. U.; Hansen, M. M. M.; Horcher, L. H. M. *Tetrahedron* **1985**, *41*, 3479. (f) Shibasaki, M. M. T.; Ikegami, S. *J. Am. Chem. Soc.* **1986**, *108*, 2090. (g) Rousset, C. J.; Swanson, D. R.; Lamaty, F.; Negishi, E. *Tetrahedron Lett.* **1989**, *30*, 5101. (h) Bailey, W. F.; Khanolkar, A. D. *Tetrahedron Lett.* **1990**, *31*, 5993. (i) Keese, R. *Angew. Chem., Int. Ed. Engl.* **1992**, *31*, 344. (j) Hirschi, D.; Luef, W.; Gerber, P.; Keese, R. *Helv. Chim. Acta* **1992**, *75*, 1897. (k) Bourgin, D.; Buchel, R.; Gerber, P.; Keese, R. *Tetrahedron Lett.* **1994**, *35*, 3267. (l) Probert, G. D.; Whitby, R. J. *Tetrahedron Lett.* **1995**, *36*, 4113.

(10) Motherwell also reported the formation of a *trans*-bicyclo[3.3.0]-octane cycloadduct when a mixture of diastereomeric MCPs was reacted with $Pd_2(dba)_3/P(OiPr)_3$ and proposed that a benzyloxy substituent exogenous to the tether was chelated to the Pd in a TMM (trimethylenemethane) complex which led selectively to a *trans*-fused product.[2c,e,h] The oxygen is part of the tether for each of the diastereomers we studied and cannot be solely responsible for the stereochemical outcome in the cycloaddition. Further studies will be reported in our full account of this work.