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Palladium-Mediated Ring Opening of Hydroxycyclopropanes

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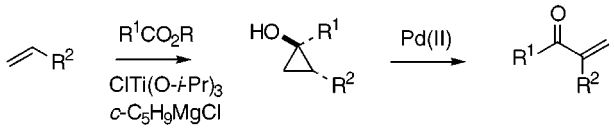
ABSTRACT



The palladium-mediated ring opening of substituted cyclopropanols has been found to take place predominantly at the less substituted C–C bond. Thus, sequential application of the titanium-mediated cyclopropanation of esters and the palladium-mediated ring opening of the resulting cyclopropanols provides a convenient method for functionalizing monosubstituted olefins.

The unique reactivity of cyclopropanes due to the high level of strain offers considerable utility in organic synthesis. Many imaginative applications of cyclopropanes as useful building blocks have been predicated on regio- and stereocontrolled ring-opening reactions of substituted cyclopropanes.[1] Typically, electrophilic opening has been achieved by transition metals (Pd, Pt, Rh, and Ir), halogens (Cl^+ and Br^+), and soft Lewis acids (Hg^{2+} and Tl^{3+}).[2] The electron donor (particularly, alkoxy, siloxy, and arylthio) substituted cyclopropanes have found increasing use, primarily due to facile and regiocontrolled ring opening.[3] Surprisingly, ring opening of unprotected hydroxycyclopropanes has been little explored. Herein we report the palladium-mediated regioselective ring opening of substituted cyclopropanols.

The starting cyclopropanols were readily prepared by the titanium-mediated cyclopropanation of carboxylic esters.[4,5] The presence of the free alcohol on the cyclopropane ring was anticipated to facilitate ring opening due to the intermediacy of the metal alkoxide.[6] Indeed, treatment of **1a** and **1b** with $Pd(OAc)_2$ in the presence of pyridine under an atmosphere of oxygen gave the ring-opened products **2a** and **2b** in 55% and 88% yields, respectively (Table 1, entries 1 and 2).

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(3) (a) Kuwajima, I.; Nakamura, E. *Top. Curr. Chem.* **1990**, *155*, 1. (b) Ikura, K.; Ryu, I.; Kambe, N.; Sonoda, N. *J. Am. Chem. Soc.* **1992**, *114*, 1520. (c) Ryu, I.; Ikura, K.; Tamura, Y.; Maenaka, J.; Ogawa, A.; Sonoda, N. *Synlett* **1994**, 941. (d) Sugimura, T.; Futagawa, T.; Mori, A.; Ryu, I.; Sonoda, N.; Tai, A. *J. Org. Chem.* **1996**, *61*, 6100. (e) Hoberg, J. O.; Jennings, P. W. *Organometallics* **1996**, *15*, 3902. (f) Beyer, J.; Madsen, R. *J. Am. Chem. Soc.* **1998**, *120*, 12137. (g) Ito, Y.; Fujii, S.; Nakatsuka, M.; Kawamoto, F.; Saegusa, T. In *Organic Synthesis*; Norland, W. E., Ed.; Wiley: New York, 1988; Collect. Vol. 6, p 327. (h) Booker-Milburn, K. I.; Thompson, D. F. *J. Chem. Soc., Perkin Trans. 1* **1995**, 2315. (i) Hoberg, J. O. *J. Org. Chem.* **1997**, *62*, 6615. (j) Reference 1e. (k) Cohen, T.; Brockunier, L. *Tetrahedron* **1989**, *45*, 2917 and references therein.

(4) (a) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Prityts-kaya, T. S. *Zh. Org. Khim.* **1989**, *25*, 2244. (b) Kulinkovich, O. G.; Sviridov, S. V.; Vasilevskii, D. A.; Savchenko, A. I.; Prityts-kaya, T. S. *Zh. Org. Khim.* **1991**, *27*, 294. (c) Kulinkovich, O. G.; Sorokin, V. L.; Kel'in, A. V. *Zh. Org. Khim.* **1993**, *29*, 66.

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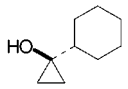
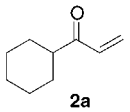
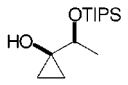
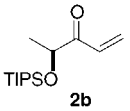
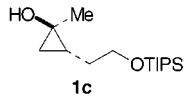
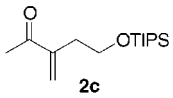
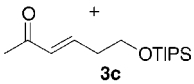
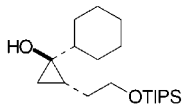
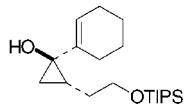
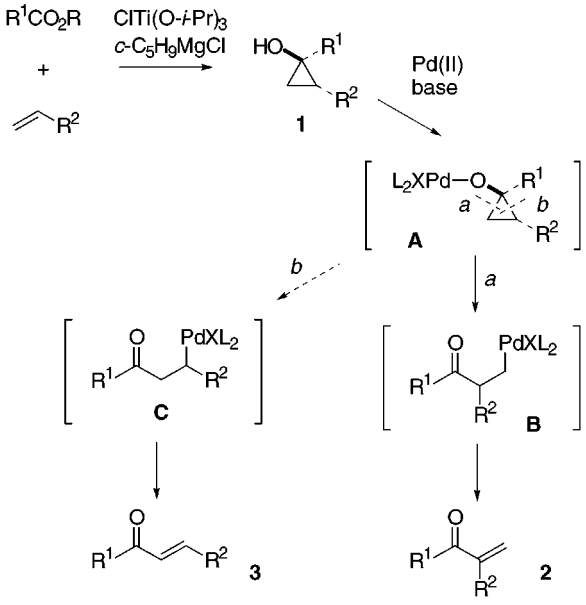
Table 1. Pd(II)-Mediated Ring Opening of Cyclopropanols

entry	substrate	conditions[a]/ time	product(s)/ selectivity and yield
1	 **1a**	A 4 h	 **2a** 55%
2	 **1b**	A 4 h	 **2b** 88%
3	 **1c**	A 4 h	 **2c** +  **3c** **2c** : **3c** = 3.9 : 1 (87%)
4		B 1.5 h	**2c** : **3c** = 4.2 : 1 (93%)
5		C 1 h	**2c** : **3c** = 3.5 : 1 (77%)
6		D 1 h	**2c** : **3c** = 1 : 0 (79%)
7	 **1d**	B[b] 4 h	**2d** and **3d**: R^1 = *c*-C_6H_{11} R^2 = CH_2CH_2OTIPS **2d** : **3d** = 6.8 : 1 (84%)[b]
8		D 1 h	**2d** : **3d** = 1 : 0 (76%)
9	 **1e**	B[b] 4 h	**2e** and **3e**: R^1 = 1-cyclohexenyl R^2 = CH_2CH_2OTIPS **2e** : **3e** = 7.5 : 1 (59%)[b]
10		D 1 h	**2e** : **3e** = 4.2 : 1 (73%)

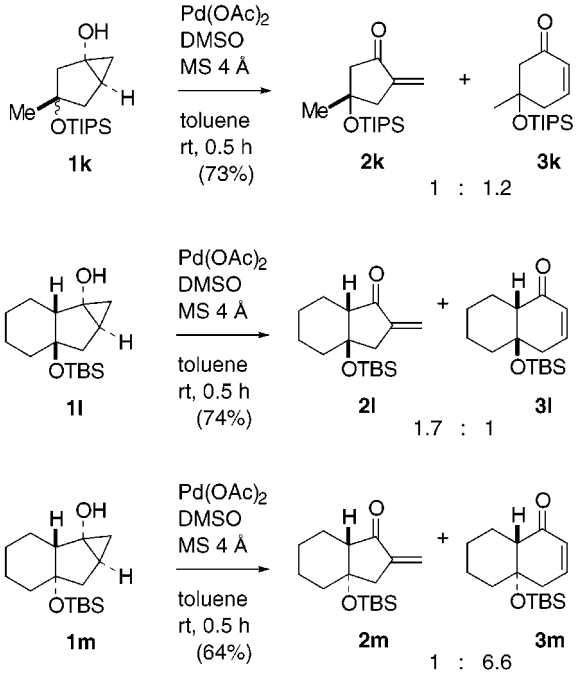
a. Reaction conditions:
(A) $Pd(OAc)_2$ (0.1 equiv), pyridine (2 equiv), MS 4 Å, toluene, 80 °C, O_2.
(B) $Pd(OAc)_2$ (0.1 equiv), DMSO (2 equiv), MS 4 Å, toluene, 80 °C, O_2.
(C) $Pd_2(dba)_3$ (0.1 equiv), DMSO (2 equiv), MS 4 Å, toluene, 80 °C, O_2.
(D) $Pd_2(dba)_3$ (0.1 equiv), *p*-benzoquinone (2 equiv), MS 4 Å, toluene, 80 °C, O_2.
b. 0.2 equiv catalyst under an atmosphere of N_2 instead of oxygen.

We next examined the regioselectivity of Pd(II)-mediated ring-opening reactions of substituted cyclopropanols (Scheme 1). Under identical reaction conditions, the cyclopropanol **1c** afforded a 3.9:1 mixture of the two regioisomers **2c** and **3c** in 87% yield (Table 1, entry 3). From the examination of different conditions (such as use of DMSO[7]) and catalysts (entries 4−6), exclusive formation of **2c** was achieved by employing $Pd_2(dba)_3$ and *p*-benzoquinone as a reoxidant (entry 6). Similar results were also obtained for cyclopropanols **1d** (entries 7 and 8) and **1e** (entries 9 and 10), although ring opening of **1e** was found to proceed with only modest regioselectivity. At lower temperatures (e.g., 50 °C),

Scheme 1



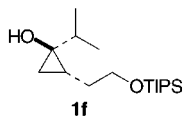
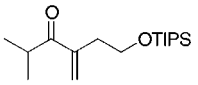
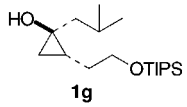
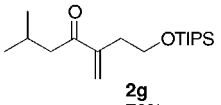
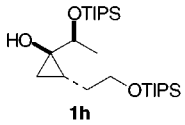
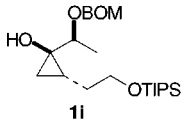
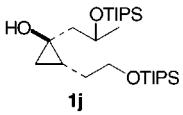
Scheme 2



(7) For a unique role of DMSO, see: (a) Kagan, H. B.; Ronan, B. *Rev. Heteroat. Chem.* **1992**, *1*, 92. (b) Larock, R. C.; Hightower, T. R. *J. Org. Chem.* **1993**, *58*, 5298. (c) Semmelhack, M. F.; Kim, C. R.; Dobler, W.; Meier, M. *Tetrahedron Lett.* **1989**, *30*, 4925.

(8) For example, treatment of **2e** with anhydrous $FeCl_3$ at −20 °C (20 min) resulted in a Nazarov reaction to afford the fused cyclopentenone product in 61% yield.

Table 2

entry	substrate	conditions[a]/ time	product(s)/ selectivity and yield
1	 **1f**	D 1 h	 **2f** 71%
2	 **1g**	D 1 h	 **2g** 70%
3	 **1h**	D 3 d	N. R.
4		A 4 h	**2h** and **3h**: R^1 = (*S*)-CH(OTIPS)Me R^2 = CH_2CH_2OTIPS **2h** : **3h** = 4.1 : 1 (84%)
5		B[b] 4 h	**2h** : **3h** = 7.0 : 1 (60%)[b]
6	 **1i**	D 3 d	**2i** and **3i**: R^1 = (*S*)-CH(OBOM)Me R^2 = CH_2CH_2OTIPS **2i** : **3i** = 1 : 0 (37%)
7		B 1 h	**2i** : **3i** = 2.5 : 1 (74%)
8	 **1j**	D 1 h	**2j**: R^1 = $CH_2CH(OTIPS)Me$ R^2 = CH_2CH_2OTIPS (78%)

a. Reaction conditions and *b*.: See the footnotes for Table 1.

ring opening took place more slowly and with insubstantial enhancement in regioselectivity. Mechanistically, the Pd(II)−alkoxide intermediate **A** undergoes ring opening of the less substituted C−C bond (bond a) to produce an alkylpalladium species **B** in preference to **C** (from scission of bond b). Subsequent β-hydride elimination then affords the products **2c**−**e** and **3c**−**e**. Finally, the Pd(II)−hydride or Pd(0) species formed is converted to active Pd(II) by a reoxidant. The pivotal role of the Pd(II)−alkoxide intermediate **A** was demonstrated in a control experiment employing the *tert*-butyldimethylsilyl ether (structure not shown) of **1c**, which was recovered unreacted.

Additional examples, mainly containing α- or β-substituents adjacent to the cyclopropanol functionality, are shown in Table 2. While the palladium-mediated ring-opening reaction of cyclopropanols appears to be general, α-alkoxy-substituted compounds (Table 2, entries 3−7) proved to be sensitive to the catalyst and the reaction conditions.

On cursory examination, ring opening of bicyclic or tricyclic cyclopropanols **1k**−**m** revealed a preference for cleavage of the more substituted C−C bond (bond b in Scheme 1). The product distributions given in Scheme 2 are kinetic in origin, since no changes were observed upon resubjecting **2k**−**m** or **3k**−**m** to the identical reaction conditions. Higher levels of ring strain associated with these substrates can account for rapid ring opening and the opposite regioselectivity.

It should be noted that the present method nicely complements Pt(II)-catalyzed isomerization of siloxycyclopropanes to allyl silyl ethers by means of a 1,2-hydrogen shift.[3b] Sequential application of the titanium-mediated cyclopropanation of esters and the palladium-mediated ring opening of the resulting cyclopropanols should be of utility in organic synthesis.[8]

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