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The Palladium(II)-Catalyzed Nazarov Reaction

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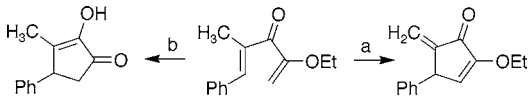
ABSTRACT

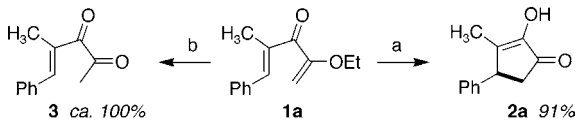


(a) $Pd(OAc)_2$; (b) $PdCl_2(MeCN)_2$

The $PdCl_2$-catalyzed cyclization of α-alkoxy dienones leads to 2-hydroxycyclopentenones, whereas the $Pd(OAc)_2$-catalyzed reaction leads to cross-conjugated cyclopentenones through an oxidative process.

During the course of a survey of Lewis acids for use in a catalytic asymmetric version[1] of the Nazarov reaction,[2] we examined the effect of $PdCl_2(MeCN)_2$ on dienone **1a**. Cyclization to 2-hydroxycyclopentenone **2a** took place in 91% yield in the presence of 1 mol % palladium at room temperature in acetone. An observation made by Kocienski suggests that the presence of the electron-donating alkoxy substituent in **1a** lowers the activation barrier for the proton-catalyzed Nazarov cyclization.[3] This presumably takes place because of the polarization of the enol ether and the resulting increase in electron density at the terminal sp^2-hybridized carbon atom. We were therefore concerned that small amounts of adventitious HCl might have catalyzed the conversion of **1a** to **2a**. To rule this out, **1a** was treated with 1 mol % 1 N HCl at room temperature in acetone. This led to α-diketone **3**, the product of enol ether hydrolysis, in nearly quantitative yield. None of the cyclic product **2a** was detected in the product mixture (Scheme 1). To determine whether the palladium-catalyzed reaction that we observed for **1a** is general, we examined the series of reactions summarized in Table 1. The dienone starting materials **1a**−**i** were prepared by adding 1-ethoxy-1-lithioethene or 2-lithiodihydropyran to the appropriate morpholino enamides. Dienones **1j**−**l** were prepared nonstereospecifically according to the method that is summarized in Scheme 2. In the case of **1j** and **1k**, the two geometric isomers were separated by flash column chromatography and cyclized independently. In the case of **1l**, the mixture of (*E*)- and (*Z*)-isomers was cyclized.

Scheme 1[a]



3 *ca. 100%* **1a** **2a** *91%*

[a] Conditions: (a) 1 mol % $PdCl_2(MeCN)_2$, acetone (H_2O), rt, 1 day, 91%; (b) 1 mol % 1 N HCl, acetone (H_20), rt, 3 days, ca. 100%.

(1) For examples of asymmetric Nazarov reactions, see: (a) Kerr, D. J.; Metje, C.; Flynn, B. L. *J. Chem. Soc., Chem. Commun.* **2003**, 1380−1381. (b) Pridgen, L. N.; Huang, K.; Shilcrat, S.; Tickner-Eldridge, A.; DeBrosse, C.; Haltiwanger, R. C. *Synlett* **1999**, *10*, 1612−1514. (c) Hu, H.; Smith, D.; Cramer, R. E.; Tius, M. A. *J. Am. Chem. Soc.* **1999**, *121*, 9895−9896. (d) Harrington, P. E.; Murai, T.; Chu, C., Tius, M. A. *J. Am. Chem Soc.* **2002**, *124*, 10091−10100.

(2) For a review of the Nazarov reaction, see: Habermas, K. L.; Denmark, S.; Jones, T. K. In *Organic Reactions*; Paquette, L. A., Ed.; John Wiley & Sons: New York, 1994; Vol. 45, pp 1−158.

(3) (a) Casson, S.; Kocienski, P. *J. Chem. Soc., Perkin Trans. 1* **1994**, 1187−1191. (b) Tius, M. A.; Kwok, C.-K.; Gu, X.-q.; Zhao, C. *Synth. Commun.* **1994**, *24*, 871−885.

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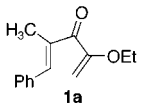
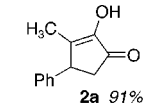
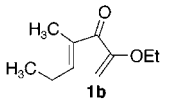
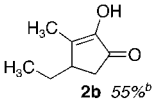
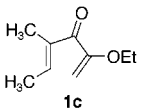
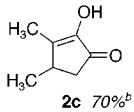
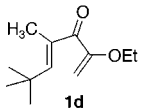
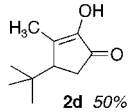
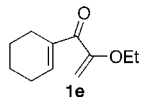
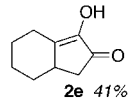
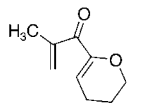
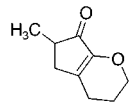
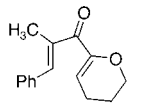
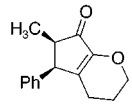
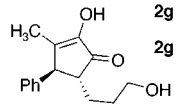
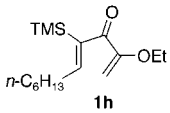
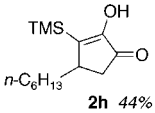
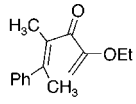
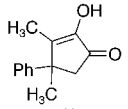
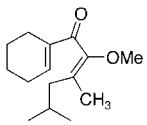
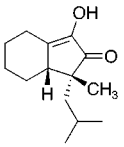
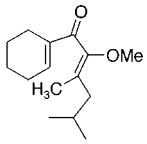
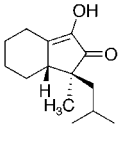
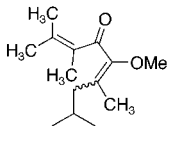
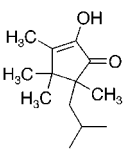
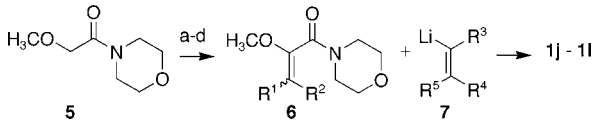
Table 1. 2-Hydroxycyclopentenones

 **1a**	 **2a** *91%*	1 mol%, 1 d
 **1b**	 **2b** *55%*[b]	5 mol%, 1 d
 **1c**	 **2c** *70%*[b]	2 mol%, 1 d
 **1d**	 **2d** *50%*	2 mol%, 1 d
 **1e**	 **2e** *41%*	2 mol%, 1 d
 **1f**	 **2f** *77%*	2 mol%, 1 d
 **1g**	 **2g**	1 mol%, 1 d or 20 mol%, 10 min
	 **4**	**2g**:**4**, 1:4, *88%* or **2g**:**4**, 3:1, *74%*
 **1h**	 **2h** *44%*	5 mol%, 3 h
 **1i**	 **2i** *92%*	4 mol%, 2 d
 **1j**	 **2j** *90%*	10 mol%, 14 h
 **1k**	 **2k** *74%*	10 mol%, 2 d
 **1l**	 **2l** *79%*	10 mol%, 2 d

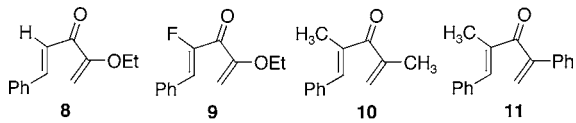
[a] All reactions were conducted in wet acetone at room temperature with the indicated quantity of $PdCl_2(MeCN)_2$. [b] These products were isolated as volatile solids.

Scheme 2[a]



[a] Conditions: (a) Cy_2NLi; (b) R^1COR^2; (c) $SOCl_2$, Et_3N; (d) *t*-BuOK.

The yields of cyclic products were generally good. Some of the results in Table 1 require some discussion. In the case of **1g**, the difference in the ratio of products **2g** and **4** that was observed under the two reaction conditions is a function of the reaction time. A low catalyst load (1 mol %) requires a longer reaction time (1 day vs 10 min) leading to a greater proportion of hydrolysate **4** in the product. The stereochemistry of **2g** is cis. Upon standing, slow isomerization to the trans isomer takes place.[4] Cyclopentenones **2i**−**l** show that quaternary carbon atoms can be incorporated into the cyclic products. It is noteworthy that **2l** bears two adjacent quaternary carbon atoms. The acid-catalyzed Nazarov reaction often fails in such cases and leads to mixtures of products resulting from Wagner−Meerwein rearrangement of the intermediate cation(s).[5] Cyclization of (*E*)- and (*Z*)-isomers **1j** and **1k**, respectively, was completely stereospecific and led to **2j** and **2k** in 90 and 74% yields, respectively. The relative stereochemistry in **2j** and **2k** was determined by NOE. The cyclization failed to take place in the case of dienones **8**−**11**.



Failure of the cyclization in the case of **8** can be rationalized in terms of conformational preferences, as has been done for the acid-catalyzed Nazarov reaction.[3b] Failure of **9** to undergo the cyclization is certainly due to the electron-withdrawing effect of the fluorine atom, whereas failure of **10** and **11** suggests that the α alkoxy group is required. The probable mechanism was suggested by these results, as well as by an observation that we made during our examination of $Pd(OAc)_2$ as a catalyst.

Exposure of **1a** to 20 mol % $Pd(OAc)_2$ in DMSO[6] under an oxygen atmosphere led to cross-conjugated cyclopentenone **12a** in 50% yield following flash column chromatography. The reaction was carried out with dienones **1b**, **1d**, **1e**, and **1i** with the results that are summarized in Figure 1. Product yields were lower for this process than for the $PdCl_2$-mediated process. This can be attributed in part to losses

(4) Stereochemistry was determined by NOE.

(5) (a) Motoyoshiya, J.; Yazaki, T.; Hayashi S. *J. Org. Chem.* **1991**, *56*, 735−740. (b) Morel-Fourrier, C.; Dulcere, J. P.; Santelli, M. *J. Am. Chem. Soc.* **1991**, *113*, 8062−8069. The rearrangement may be the desired process; see: Bender, J. A.; Arif, A. M.; West, F. G. *J. Am. Chem. Soc.* **1999**, *121*, 7443−7444.

(6) Toyota, M.; Sasaki, M.; Ihara, M. *Org. Lett.* **2003**, *5*, 1193−1195.

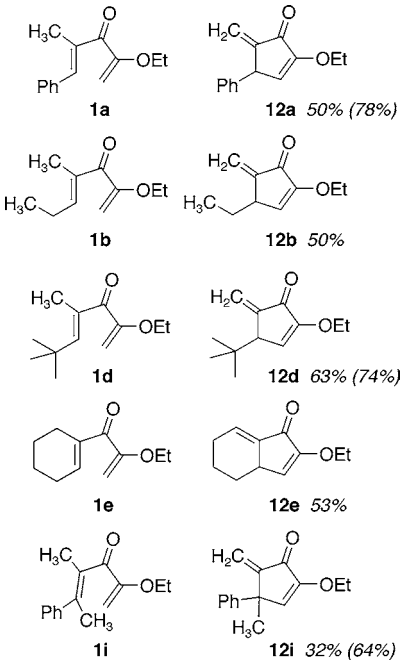


Figure 1. Cross-conjugated cyclopentenones. All reactions were performed with 20 mol % $Pd(OAc)_2$ in DMSO under an oxygen atmosphere at 80 °C for 24 h. Numbers in parentheses correspond to the yield of crude product. Crude product was obtained by evaporating the DMSO at 80 °C/1 mm Hg, dissolving the residue in toluene, filtering to remove solids, and stirring overnight at 80 °C with activated carbon.

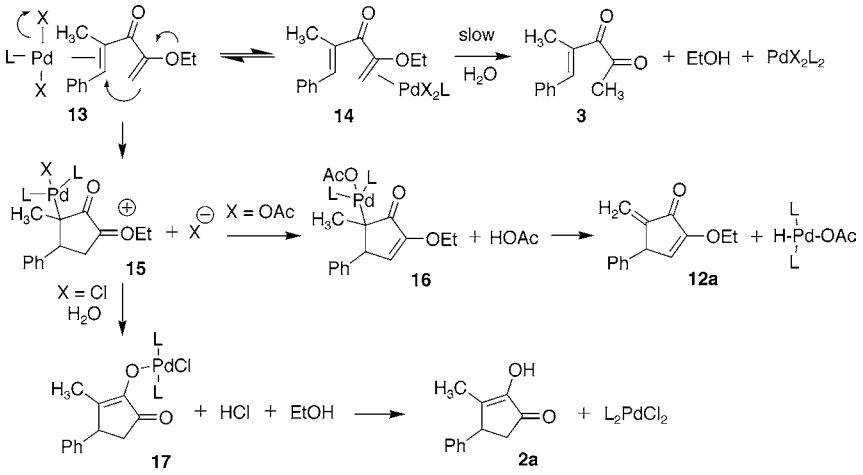
during purification, since the yield of crude products was much higher (see Figure 1, **12a**, **12d**, and **12i**). Many cross-conjugated cyclopentenones can be made from allenes; however, the products in Figure 1 cannot be made from allenes, since they are unsubstituted at the β endocyclic carbon atom. Moreover, the preparation of **12e** through our allene chemistry[7] would be very challenging, at best.

The observations suggest the mechanistic scheme that is summarized for **1a** (Scheme 3). Although the Nazarov reaction is initiated by activation of the carbonyl group by an acid, this seems unlikely in the present case. Instead, activation of the electron-poor olefin by complexation to palladium seems a more likely first step.[8] Complexation of the electrophilic palladium salt to the electron-rich enol ether (see **14**) is probably preferred but does not lead to cyclic product.[9] If the association of **1a** with palladium is reversible, π complex **13** can form and undergo intramolecular attack to produce palladium enolate **15**. When $Pd(OAc)_2$ is used, proton loss from **15** (X = OAc) leads to **16**, which undergoes β elimination to **12a**. In the absence of an oxidant, the palladium hydride that is also generated from reductive elimination leads to Pd(0) irreversibly. When $PdCl_2$ is used, **15** (X = Cl) undergoes hydrolysis with loss of ethanol to produce **17** and HCl. Decomposition of the palladium enolate by the strong acid regenerates the Pd(II) catalyst and leads to **2a**. The difference in reaction pathways between the $Pd(OAc)_2$- and the $PdCl_2$-catalyzed reactions may be due to the difference in basicity of the counterion. In the case of acetate, proton loss leading to **16** is fast. Failure of **9** to undergo cyclization in the presence of $PdCl_2$ can be understood in terms of an unfavorable equilibrium for the initial complexation of Pd(II). Failure of **10** and **11** underscores the critical role played by the enol ether. The stereochemical outcome in the case of **1j** and **1k** is consistent with attack of the enol ether anti to the palladium.

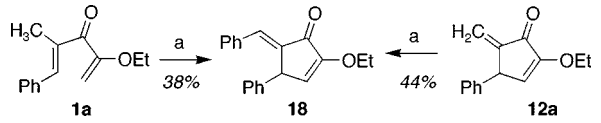
During our survey of reaction conditions for the $Pd(OAc)_2$-catalyzed reaction, PPh_3 was used as an additive. In the presence of a small molar excess of palladium and 0.5 equiv of PPh_3, the major reaction product (39% yield) from **1a** was **18**, in which the exocyclic alkene unexpectedly bears an (*E*)-phenyl substituent (Scheme 4). Exposure of **12a** to the same reaction conditions led to **18** in 44% yield, which suggests that the phenyl group was transferred from PPh_3. Insertion of palladium into the phosphorus−carbon bond of triarylphosphines is uncommon.[10]

In summary, two variants of a Pd(II)-catalyzed Nazarov cyclization have been described. The reaction takes place under mild conditions and, in the case of the $PdCl_2$-catalyzed

Scheme 3



Scheme 4[a]



[a] Conditions: 1.1 equiv of $Pd(OAc)_2$, 0.5 equiv of PPh_3, acetone, 3 days, rt.

process, with high efficiency. The reaction offers opportunities for asymmetric catalysis and for the formation of additional C−C bonds through cascade processes involving the intermediate palladium enolate.

Acknowledgment. We thank the National Institutes of Health (GM57873) for generous support and Professor Dirk Trauner for sharing his results with us.

Note Added after ASAP Posting. Conditions a and b of the abstract and TOC graphic were interchanged in the version posted ASAP November 25, 2003; the corrected version was posted December 3, 2003.

Supporting Information Available: General procedures for the synthesis of **1a**−**l**, **2a**−**l**, **12a**, **12b**, **12d**, **12e**, **12i**, and **18**; ^{1}H and ^{13}C NMR data for **1a**−**l**; and spectroscopic data and reproductions of ^{1}H NMR spectra for **2a**−**l**, **12a**, **12b**, **12d**, **12e**, **12i**, **18**. This material is available free of charge via the Internet at http://pubs.acs.org.

OL036017E

(7) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284−290.
(8) Hegedus, L. S. Transition Metals. In *Synthesis of Complex Organic Molecules*; University Science Books: Sausalito, 1999; Chapter 7.
(9) α-Diketone **3**, the product of enol ether hydrolysis, is the only significant byproduct of these reactions.
(10) (a) Kong, K.-C.; Cheng, C.-H. *J. Am. Chem. Soc.* **1991**, *113*, 6313−6315. (b) O'Keefe, D. F.; Dannock, M. C.; Marcuccio, S. M. *Tetrahedron Lett.* **1992**, *33*, 6679−6680. (c) Segelstein, B. E.; Butler, T. W.; Cherard, B. L. *J. Org. Chem.* **1995**, *12*, 12−13. (d) Moiseev, I. I.; Kozitsyna, N. Y.; Kochubey, D. I.; Kolomijchuk, V. N.; Zamaraev, K. I. *J. Organomet. Chem.* **1993**, *451*, 231−241. (e) Morita, D. K.; Stille, J. K.; Norton, J. R. *J. Am. Chem. Soc.* **1995**, *117*, 8576−8581.