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Optimization of Palladium-Catalyzed Polyene Cyclizations: Suppression of Competing Hydride Transfer from Tertiary Amines with Dabco and an Unexpected Hydride Transfer from 1,4-Dioxane

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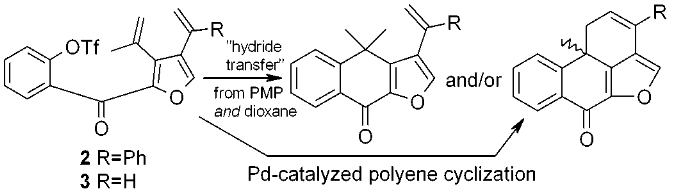
ABSTRACT



This paper demonstrates that both 1,2,2,6,6-pentamethylpiperidine (PMP) *and* 1,4-dioxane can act as hydride donors in palladium-catalyzed polyene cyclizations of 2 and 3. Studies using PMP-d_3 and dioxane-d_8 either incorporate a deuterium atom into the monosubstituted product or completely inhibit the hydride transfer so that the second ring closure occurs in high yield. Dabco is the best substitute for PMP.

In recent years palladium-catalyzed polyene cyclizations have proved to be a useful synthetic tool for the formation of several ring systems in a single transformation.[1,2] Our lab has been interested in its utility toward the synthesis of polycyclic natural products and, in particular, xestoquinone **1** (Scheme 1).[3] However, the key to polyene cyclizations is ensuring that all of the requisite bond-forming reactions take place. Recently,[4] while investigating the effect of remote substituents on the enantioselectivity of our polyene cyclization on a model system **2** (R = Ph), we reported the formation of geminal dimethyl byproduct **6**. However, when **3** (R = H) was treated under the same reaction conditions, only dicyclized product **9** was formed. Clearly two pathways are possible for intermediates **4** and **5** to follow. Pathway b results in the second ring being formed, while pathway c is preferred if a hydride transfer occurs faster than the second ring cyclization.

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(1) For recent reviews involving Pd-catalyzed polyene reactions, see: (a) de Meijere, A.; Brase, S. *J. Organomet. Chem.* **1999**, *576*, 88−110. (b) Grigg, R.; Sridharan, V. *J. Organomet. Chem.* **1999**, *576*, 65−87. (c) Larock, R. C. *J. Organomet. Chem.* **1999**, *576*, 111−124. (d) Takahasi, T.; Doi, T.; Yamamoto K. In *Transiton Metals for Organic Synthesis*; Beller, M., Bolm, C., Eds.; Wiley-VCH Verlag: Weinheim, 1998; Vol. 1, pp 265−274.

(2) For some recent examples of Pd-catalyzed polyene cyclizations, see:(a) Schweizer, S.; Song, Z.-Z.; Meyer, F. E.; Parsons, P. J.; de Meijere, A. *Angew. Chem. Int. Ed.* **1999**, *38*, 1452−1454. (b) Johnson, W. S.; Bartlett, W. R.; Czeskis, B. A.; Gautier, A.; Lee, C. H.; Lemoine, R.; Leopold, E. J.; Luedtke, G. R.; Bancroft, K. J. *J. Org. Chem.* **1999**, *64*, 9587−9595. (c) Xie, X.; Lu, X. *Tetrahedron Lett.* **1999**, *40*, 8415−8418. (d) Grigg, R.; Sridharan, V.; Zhang, J. *Tetrahedron Lett.* **1999**, *40*, 8277−8280. (e) Evans, P.; Grigg, R.; Ramzan, M. I.; Sridharan, V.; York, M. *Tetrahedron Lett.* **1999**, *40*, 3021−3024. (f) Coudanne, I.; Balme, G. *Synlett* **1998**, 998−1000. (g) Luo, F.-T.; Bajji, A. C.; Jeevanandam, A. *J. Org. Chem.* **1999**, *64*, 1738−1740.

(3) (a) Maddaford, S. P.; Andersen, N. G.; Cristofoli, W. A.; Keay, B. A. *J. Am. Chem. Soc.* **1996**, *118*, 10766−10773. (b) Keay, B. A.; Maddaford, S. P.; Cristofoli, W. A.; Andersen, N. G.; Passafaro, M. S.; Wilson, N. S.; Nieman, J. A. *Can. J. Chem.* **1997**, *75*, 1163−1171. (c) Cristofoli, W. A.; Keay B. A. *Synlett* **1994**, 625−627.

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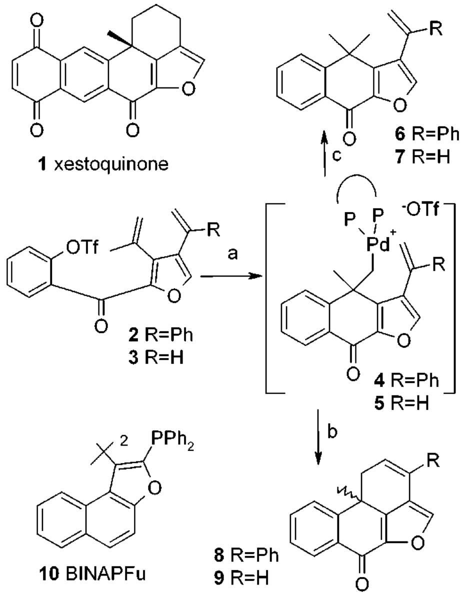
Scheme 1



a) $Pd_2(dba)_3$, (S)-BINAP, PMP, toluene, 110°C; b) 2nd cyclization; c) hydride transfer

Table 1. Deuteration Studies on the Cyclization of Substrate **3**

	ligand	solvent[a]	base	ratio **7**:**9**[b] (% yield)[c]	H or D transfer to **7**
1	(*S*)-**11**	tol	PMP	0:100 (83)	
2	(*S*)-**11**	diox	PMP	75:25 (85)	H
3	(*S*)-**10**	diox	PMP	100:0 (82)	H
4	(*S*)-**10**	diox	PMP-d_3	100:0 (72)	H
5	(*S*)-**10**	diox-d_8	PMP	10:90 (82)	H
6	(*S*)-**10**	diox-d_8	PMP-d_3	0:100 (61)	

[a] tol = toluene; diox = dioxane. [b] Ratio determined by GC−MS. [c] Combined isolated yield.

While the gem-dimethylated byproduct was never observed during our synthesis of (+)-xestoquinone,[3] Shibasaki and co-workers have reported observing trace amounts of the gem-dimethylated byproduct while repeating our synthesis.[5] This incomplete cyclization product was further observed when we attempted a polyene cyclization on **2** and **3** using the new chiral bidentate phosphine ligand BINAPFu **10**.[6] Interestingly, BINAPFu was found to outperform BINAP **11** in Hayashi's Heck arylation of 2,3-dihydrofuran[7] in a variety of solvents at high temperatures, of which one was dioxane. When the polyene cyclization on substrate **3** (Scheme 1) was attempted using (*S*)-BINAPFu *in dioxane* with 1,2,2,6,6-pentamethylpiperidine (PMP) as the base, the reduced monocyclized product **7** was obtained exclusively (entry 3, Table 1), while the same reaction using (*S*)-BINAP **11** formed a 75:25 mixture of **7** and **9** (entry 2, Table 1). Interestingly, when the same reaction with **3** ((*S*)-BINAP **11** and PMP) was performed *in toluene*, only the dicyclized product **9** was observed (entry 1, Table 1).[4] We herein report a detailed study that shows that both PMP *and dioxane* can transfer a hydride in these polyene cyclizations and that 1,4-diazabicyclo[2.2.2]octane (Dabco) can be used in place of PMP to inhibit the hydride transfers observed in toluene.[8]

As the choice of base[9] and solvent[9f,10] can play an important role in Heck reactions, we sought a method to prove if the base and/or solvent was the source of the hydride in these polyene cyclizations. Although some tertiary amine bases that contain α and *β* hydrogens have been reported to serve as hydride sources in palladium-catalyzed reactions through formation of an enamine,[11] PMP is incapable of forming an enamine as the methyl group attached to the nitrogen atom has no *β* hydrogen atoms and both adjacent carbon atoms in the ring have geminal dimethyl groups.[12] Therefore, if PMP is acting as a hydride source, the hydride must arise from a different mechanism. In addition, dioxane also influenced the outcome of the palladium-catalyzed polyene cyclization (hydride transfer vs second ring closure) when compared to toluene, so we wondered if dioxane might also be acting as a hydride source in these palladium-catalyzed reactions.[13]

To prove a hydride was being transferred from PMP and/or dioxane, we performed the cyclizations using deuterated

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(5) Miyazaki, F.; Uotso, K.; Shibasaki, M. *Tetrahedron* **1998**, *54*, 13073−13078.

(6) Andersen, N. G.; Parvez, M.; Keay, B. A. *Org. Lett.* **2000**, *2*, 2817−2820.

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(8) We are not the first to use Dabco to suppress the oxidation of amines to imines or enamines by Pd(0); see: Chen, C.; Lieberman, D. R.; Larsen, R. D.; Verhoeven, T. R.; Reider, P. J. *J. Org. Chem.* **1997**, *62*, 2676−2677.

(9) For some recent examples of the study of base in palladium-catalyzed Heck-type reactions, see: (a) Gurtler, C.; Buchwald, S. L. *Chem. Eur. J.* **1999**, *5*, 3107−3112. (b) Coudanne, I.; Castro, J.; Balme, G. *Synlett* **1998**, 995−997. (c) Kirschbaum, S.; Waldmann, H. *J. Org. Chem.* **1998**, *63*, 4936−4946. (d) Hagiwara, H.; Eda, Y.; Morohasi, K.; Suzuki, T.; Ando, M.; Ito, N. *Tetrahedron Lett.* **1998**, *39*, 4055−4058. (e) Jeffrey, T.; David, M. *Tetrahedron Lett.* **1998**, *39*, 5751−5754. (f) Ashimori, A.; Bachand, B.; Calter, M. A.; Govek, S. P.; Overman, L. E.; Poon, D. J. *J. Am. Chem. Soc.* **1998**, *120*, 6488−6499. (g) Shmidt, A. F.; Khalaika, A.; Vylkova, V. G. *Kinet. Catal.* **1998**, *39*, 194−199. (h) Beller; M.; Riermeier, T. H. *Eur. J. Inorg. Chem.* **1998**, 29−35.

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(11) (a) Clark, F. R. S.; Norman, R. O. C.; Thomas, C. B. *J. Chem. Soc. Perkin* Trans. *1* **1975**, 121−125. (b) Murahasi, S.-I.; Hirano, T.; Yano, T. *J. Am. Chem. Soc.* **1978**, *100*, 348−350. (c) Murahasi, S.-I.; Watanabe, T. *J. Am. Chem. Soc.* **1979**, *101*, 7429−7430; d) Stokker, G. E. *Tetrahedron Lett.* **1987**, *28*, 3179−3182. (d) Saá, J. M.; Dopico, M.; Martorell, G.; García-Raso, A. *J. Org. Chem.* **1990**, *55*, 991−995. (e) Cabri, W.; Candiani, I.; DeBernardinis, S.; Francalanci, F.; Penco, S. *J. Org. Chem.* **1991**, *56*, 5796−5800

(12) Overman and co-workers refer to PMP as a possible hydride source, although the papers cited make no direct reference to PMP: Laschat, S.; Narjes, F.; Overman, L. E. *Tetrahedron* **1994**, *50*, 347−358.

(13) To our knowledge dioxane has not been reported to transfer a hydride in palladium-catalyzed reactions; however, it is well-known that alkoxides can deliver a hydride during some palladium-catalyzed reactions. For more information, see: (a) Zask, A.; Helquist, P. *J. Org. Chem.* **1978**, *43*, 1619−1620. (b) Ben-David, Y.; Gozin, M.; Portnoy, M.; Milstein, D. *J. Mol. Catal.* **1992**, *73*, 173−180. (c) Tamaru, Y.; Yamamoto, Y.; Yamada, Y.; Yoshida, Z. *Tetrahedron Lett.* **1979**, *20*, 1401−1404.

base or solvent to try to trap a deuterium in the monocyclized product. The reaction of **3** with (*S*)-BINAPFu in dioxane in the presence of *N*-trideuteriomethyl-2,2,6,6-tetramethylpiperidine (PMP-d_3)[14] provided only monocyclized product **7** with no incorporation of a deuterium atom (entry 4, Table 1). When dioxane-d_8 was used with PMP a 10:90 mixture of **7**:**9** was obtained in which no deuterium was incorporated into monocyclized product **7** (entry 5, Table 1). Finally, the use of PMP-d_3 and dioxane-d_8 resulted in the exclusive formation of dicyclized product **9**. This result indicated that the only possible sources of hydride was PMP and/or dioxane and that no other species in the reaction mixture was capable of transferring a hydride (i.e., BINAPFu or unreacted starting material **3**). Moreover, Table 1 also shows that PMP can only account for ~10% of the hydride delivery in this cyclization (compare entries 4 and 5, Table 1) and *that dioxane must function as the major hydride source* even though compound **7** could not be isolated with a deuterium atom (entry 4, Table 1). Interestingly, the use of both PMP-d_3 and dioxane-d_8 completely reversed the ratio of **7**:**9** when compared to the use of PMP and dioxane (compare entries 3 and 6, Table 1). Thus the formation of **7** or **9** hinged on a delicate balance between the rate of a primary isotope effect for a hydride vs deuteride transfer (path b) and that of the subsequent cyclization (path c).

Direct proof of hydride transfer from PMP came from our cyclization studies with substrate **2** (R = Ph) in toluene with (*S*)-BINAP **11** where it had been observed that the second ring closure was much slower when compared with that of substrate **3** (R = H, compare entry 1 of both Tables 1 and 2). Cyclization using PMP-d_3 in toluene (or toluene-d_8) yielded a 54:46 mixture of **6**:**8** in which product **6** had complete incorporation of one deuterium atom (Table 2, entries 2 and 4). This indicated that PMP, which is unable to form an enamine, must transfer a hydride through iminium species **12** (Scheme 2, eq 1). It was possible that toluene could be the hydride source, but in a reaction with PMP and toluene-d_8, only a hydrogen atom was transferred into product **6** (Table 2, entry 3). It is interesting to note that the amount of gem-dimethylated product **6** formed was reduced when PMP-d_3 was used instead of PMP. This again can be attributed to a kinetic isotope effect (Table 2, entries 1 and 2).

Scheme 2

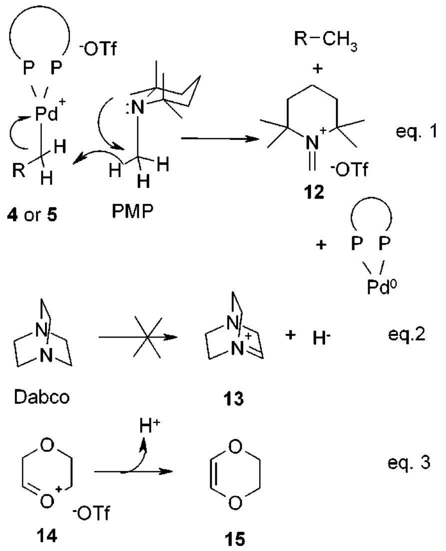

Table 2. Deuteration Studies on the Cyclization of Substrate **2** (R = Ph)

	ligand	solvent[a]	base	ratio **6**:**8**[b] (% yield)[c]	H or D transfer to **6**
1	(*S*)-**11**	tol	PMP	90:10 (91)	H
2	(*S*)-**11**	tol	PMP-d_3	54:46 (87)	D
3	(*S*)-**11**	tol-d_8	PMP	90:10 (94)	H
4	(*S*)-**11**	tol-d_8	PMP-d_3	55:45 (78)	D
5	(*S*)-**11**	diox-d_8	PMP	69:31 (73)	H
6	(*S*)-**11**	diox-d_8	Dabco	13:87 (59)	2:1 H:D
7	(S)-**10**	diox-d_8	Dabco	3:97 (73)	1:1 H:D
8	(S)-**11**	diox	Dabco	100:0 (69)	H
9	(*S*)-**10**	diox-d_8	PMP-d_3	0:100 (82)	
10	(S)-**11**	tol	Proton- Sponge	100:0 (88)	H

[a] tol = toluene; diox = dioxane. [b] Ratio determined by GC−MS. [c] Combined isolated yield.

Direct proof of a hydride transfer from dioxane was a more difficult task since most amine bases with α and *β* hydrogens could transfer a hydride faster than dioxane-d_8 could transfer a deuteride (Table 2, entry 5). We decided that Dabco might be an excellent substitute for PMP as it should not be able to transfer its α-H atom directly as a result of a violation of Bredt's rule through formation of the iminium species **13** (Scheme 2, eq 2).[8] Also if the rate in which a base like triethylamine is transformed into an enamine relies on precoordination of a palladium species to the N-atom before inserting into the α-C−H bond, then the rate of enamine formation with Dabco should also be retarded as the palladium atom would be further away from the α-C−H bond because of the bicyclic nature of Dabco. To our delight, the cyclization of **2** using Dabco in dioxane-d_8 gave 13:87 ratio of **6**:**8** in which monocyclized product **6** showed partial deuterium incorporation indicating that dioxane was capable of transferring a deuterium atom and that Dabco's ability to transfer a hydride was greatly reduced when compared to PMP (Table 2, entry 6). A deuterium kinetic isotope effect was also observed in this example as the major product from the reaction was the dicyclized product **8**. So the presence of dioxane-d_8 and Dabco resulted in a complete reversal of products observed when the reaction was run in toluene with PMP (Table 2, entry 1). When (*S*)-BINAP **11** was changed to (*S*)-BINAPFu (dioxane-d_8, Dabco), an even better ratio of **6**:**8** (3:97) was observed in which some deuterium was also transferred to the gem-dimethylated product **6** (Table 2, entry 7). Interestingly, we only observed gem-dimethylated product **6** when dioxane was used with Dabco and (*S*)-

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(14) PMP-d_3 was prepared by treating 2,2,6,6-tetramethylpiperidine with CD_3I (K_2CO_3, EtOH).

BINAP **11** (entry 8), which indicates the ease with which dioxane can transfer a hydride in these palladium-catalzyed reactions. Two other reactions were noteworthy. Only dicyclized product **8** was obtained if (*S*)-BINAPFu was used with dioxane-d_8 and PMP-d_3, again showing that the delicate balance between the two possible pathways (Scheme 1) can be tipped using deuterated species. Finally, the use of a more basic *N*-methylated base, such as *N*,*N*,*N′*,*N′*-tetramethyl-1,8-naphthalenediamine (Proton Sponge), resulted in only the gem-dimethylated compound **6** being formed (entry 10).[15] Therefore, PMP is not the only *N*-methylated base that can act as a hydride source. Presumably, dioxane can transfer a hydride directly to form an oxonium species **14** in a manner analogous to the PMP hydride transfer or form the enol ether **15** in an analogous mechanism for the enamine formation from amines with α and *β* hydrogens (Scheme 2, eq 3). Compound **15** can also be formed by loss of H^+ from **14**.[16]

We have demonstrated that Dabco is a poorer hydride transfer agent than PMP. In addition, Dabco is much less expensive than PMP.[17] The only factor remaining was to test whether Dabco would affect the % ee of the polyene cyclization. With substrate **3** (R = H), the % ee of the dicyclized product **9** was not significantly changed when Dabco was used instead of PMP (Table 3, entries 1 and 2). With substrate **2** (R = Ph), the use of Dabco in toluene greatly increased the amount of dicyclized product **8** obtained without significantly lowering the % ee (Table 3, entries 3 and 4).

Table 3. Comparison of Polyene Cyclization Results between PMP and Dabco[a]

substrate	base	ratio mono:di	% ee of **9** or **8**	isolated yield
3	PMP	**7**:**9** (0:100)	68	83%
3	Dabco	**7**:**9** (0:100)	65	82%
2	PMP	**6**:**8** (90:10)	80	91%
2	Dabco	**6**:**8** (4:96)	70	69%

[a] All reactions were done in toluene at 110 °C with (*S*)-BINAP **11**.

In conclusion, we have shown that both PMP and 1,4-dioxane can act as hydride sources in palladium-catalyzed polyene cyclizations. These compounds led to unwanted side products as a result of the inhibition of the second ring closure due to a preferential hydride transfer. To maxmize the formation of dicyclized products we recommend that Dabco be used in place of PMP and that the reaction be performed in toluene rather than dioxane.

Acknowledgment. We thank Natural Sciences and Engineering Research Council (NSERC) and the University of Calgary for financial support. NSERC is also thanked for postgraduate scholarships (to S.Y.W.L. and N.G.A.).

Supporting Information Available: Experimental details for the conversion of **2** to a mixture of **6** and **8** is provided. This material is available free of charge via the Internet at http://pubs.acs.org.

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[15] Non-amine bases such as potassium carbonate completely inhibited the polyene cyclization, and only unreacted starting material **2** or **3** was obtained.

[16] To date we have not been able to detect (by NMR) or isolate 2,3-dihydro-[1,4]-dioxine (**15**) in the reaction mixture. Work is continuing to determine the fate of dioxane in these systems.

[17] Dabco: $0.40 per g. PMP: $15.64 per g. Source: Aldrich Handbook of Fine Chemicals and Laboratory Equipment, 2000.