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Effect of ether versus ester tethering on Heck cyclizations

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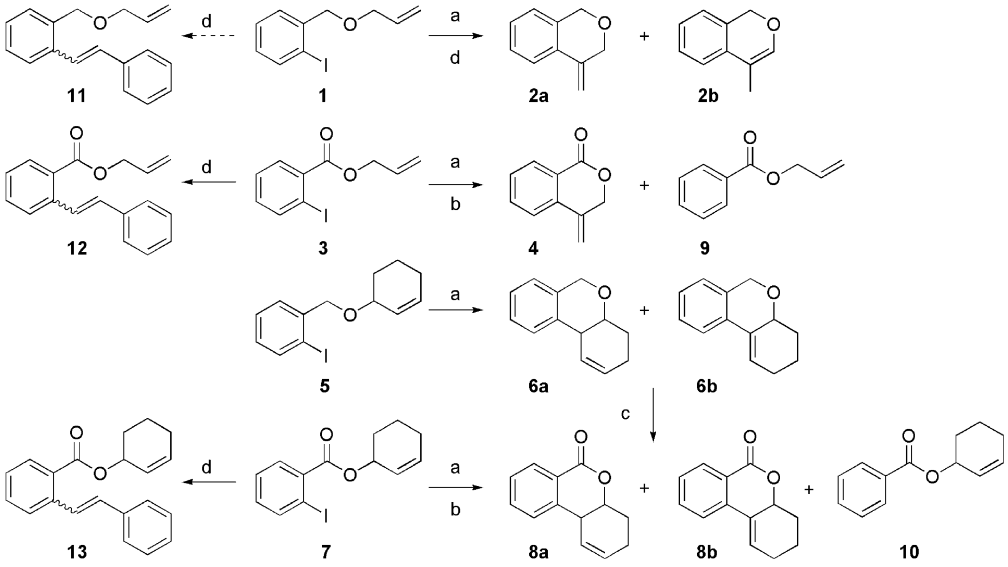
Abstract—Ether tethers allow Heck cyclizations to proceed in high yields. Ester tethers lead to low yields. Styrene trapping experiments indicate that ester reactions form viable organopalladium intermediates that cannot cyclize efficiently.

Heck cyclizations[1] to form a six-membered ring were investigated for the synthesis of the phenanthridone alkaloid (+)-pancratistatin and analogs.[2] Model ether-tethered and ester-tethered cyclizations were studied (Scheme 1). Allyl 2-iodobenzyl ether (**1**),[3] allyl 2-iodobenzoate (**3**),[4] cyclohexenyl 2-iodobenzyl ether (**5**),[5] and cyclohexenyl 2-iodobenzoate (**7**)[6] were subjected to previously-studied Heck conditions [$Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Et_3N (2 equiv), $AgNO_3$ (1 equiv), MeCN, 80 °C],[2] and the products were isolated by flash chromatography. For ether-tethered aryl iodides **1** and **5**, cyclization gave high yields of products **2a**+**2b**[7] and **6a**+**6b**[8] (Table 1). Ester-tethered aryl iodides **3** and **7** gave only unreacted starting material and deiodinated, uncyclized products **9** and **10**. Ester-tethered cyclization products **4**[9] and **8a**+**8b**[8] were produced in trace amounts. Oxidation[10] of cyclic ethers **6a**+**6b** with PCC provided cyclic esters **8a**+**8b** in good yield (59%).



Scheme 1. Reagents and conditions: (a) $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Et_3N (2 equiv), $AgNO_3$ (1 equiv), MeCN, 80 °C. (b) $Pd(OAc)_2$ (10 mol %), KOAc (2 equiv), Bu_4NBr (1 equiv), 4 Å MS, DMF, 80 °C. (c) PCC, Celite, CH_2Cl_2, rt. (d) Styrene (3 equiv), $Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol %), Et_3N (2 equiv), $AgNO_3$ (1 equiv), MeCN, 80 °C.

Keywords: Heck cyclization; Tethered cyclization; Ester rotation barrier.
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Table 1. Reaction of tethered substrates in Scheme 1

Substrate	Conditions[a]/time	Product yield[b] (%)			Isomer ratio[c]
1	a/8 h	**2a**+**2b** (81)[c]			**2a/2b**: 82/18
3	a/8 h	**4** (3)[c]	**3** (22)[d]	**9** (2)[d]	
3	b/24 h	**4** (0)	**3** (0)[d]		
5	a/8 h	**6a**+**6b** (93)[c]			**6a/6b**: 77/23
7	a/8 h	**8a**+**8b** (0)	**7** (64)[d]	**10** (13)[d]	
7	a/24 h	**8a**+**8b** (13)[c]	**7** (50)[d]	**10** (14)[d]	**8a/8b**: 59/41
7	b/24 h	**8a**+**8b** (34)[c]	**7** (0)		**8a/8b**: 78/22
6a+**6b**	c/5 d	**8a**+**8b** (59)			
1	d/24 h	**11** (0)	**2a**+**2b** (56)		
3	d/24 h	**12** (45)			
7	d/24 h	**13** (82)			

[a] See Scheme 1 for reagents and conditions.
[b] Isolated yields after column chromatography.
[c] Note, double-bond rearrangements in cyclized products; isomer ratio determined by ^{1}H NMR.
[d] Starting material isolated; yield of deiodinated material determined by ^{1}H NMR.

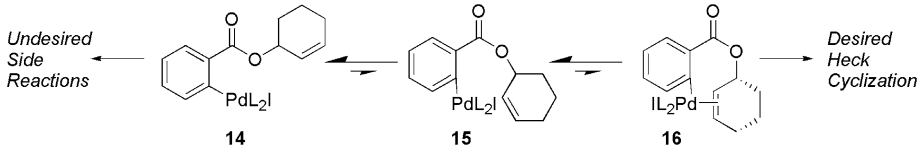

Figure 1. Proposed unproductive intermediate, with favored conformer **14** and unfavored conformers **15** and **16**.

Jeffery conditions [$Pd(OAc)_2$ (10 mol %), KOAc (2 equiv), Bu_4NBr (1 equiv), 4 Å MS, DMF, 80 °C] improve intermolecular and intramolecular Heck reactions.[11] The Jeffery modification differs from standard Heck-type conditions in the use of tetraalkylammonium salts, and in some cases the absence of a phosphine ligand. Jeffery conditions promoted the cyclization of ester **7** to esters **8a**+**8b** in modest yield (34%). For ester **3** under Jeffery conditions no significant formation of ester **4** was observed but starting material was consumed and a mixture of incompletely-characterized materials was isolated indicating several side reactions including either ester hydrolysis and/or palladative ester deallylation.[12] Previously suggested reasons for the success of the Jeffery conditions include assisted regeneration of zero-valent palladium catalyst,[11] smaller coordination sphere about the palladium[13] and accelerated reactivity of an anionic palladyl intermediate.[14]

One plausible explanation of the ester versus ether results is that oxidative addition of palladium to the aryl iodide bond occurs in all cases but only ether-tethered compounds cyclize efficiently. Styrene trapping experiments were performed to test for the formation of cyclization-impaired ester intermediates such as **14**, **15**, and **16** shown in Figure 1.[15] Compounds **1**, **3**, and **7** were treated to standard (non-Jeffery) Heck conditions with an excess of styrene[16] (Scheme 1). Allyl ether **1** cyclized to **2** with no incorporation of styrene. Esters **3** and **7** again gave no cyclization products. Instead, high yields of styrene-inserted ester products **12** and **13**[17] were formed. This indicates that competent palladium intermediates are formed in all cases, but only ether-tethered compounds cyclize efficiently. Ester-tethered compounds in the absence of the styrene trap get stuck at the palladium–aryl intermediate which presumably decomposes, either slowly or on workup, to produce deiodinated uncyclized **9** or **10**.

Ester conformational effects provide a plausible explanation for the inefficient cyclizations of ester-tethered compounds. An ether tether has a rotation barrier comparable to an aliphatic chain, only 3–5 kcal/mol. Thus, it is easy for the palladium–aryl intermediate in an ether-tethered compound to find the alkene and complete a cyclization reaction. In contrast, ester C–O single bonds are rotationally restricted, with possible *Z* conformations (such as **14**) and *E* conformations (such as **15**).[18] The *Z* conformation is preferred—for example, the *Z* conformation for phenyl benzoate is favored over the *E* by 5–6 kcal/mol, with a rotation barrier of 10–13 kcal/mol.[19] Thus, the conformational equilibrium of intermediates such as **14** and **15** (Fig. 1) strongly favors **14**, which cannot cyclize. In addition, conformer **15** may be further disfavored due to the steric effect of bulky ligands on the palladium. Finally, the alkene complex **16** may be strained, further disfavoring cyclization.

Acknowledgements

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References and notes

1. Brasë, S.; de Meijere, A. In *Metal-Catalyzed Cross-Coupling Reactions*; de Meijere, A., Diederich, F., Eds., 2nd ed.; Wiley-VCH: Weinheim, 2004, pp 217–315.
2. Grubb, L. M.; Dowdy, A. L.; Blanchette, H. S.; Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1999**, *40*, 2691–

2694; Friestad, G. K.; Branchaud, B. P. *Tetrahedron Lett.* **1995**, *36*, 7047–7050.
3. Beckwith, A. L. J.; Gara, W. B. *J. Chem. Soc., Perkin Trans. 2* **1975**, 795–802.
4. Iyer, S.; Raimesh, C.; Ramani, A. *Tetrahedron Lett.* **1997**, *38*, 8533–8536.
5. Negishi, E.-i.; Nguyen, T.; O'Connor, B.; Evans, J. M.; Silviera, A., Jr. *Heterocycles* **1989**, *28*, 55–58.
6. Spectroscopic data for **7**: ^{1}H NMR (300 MHz, $CDCl_3$): 7.94 (d, 1H), 7.75 (d, 1H), 7.36 (t, 1H), 7.10 (t, 1H), 5.98 (m, 1H), 5.86 (m, 1H), 5.50 (m, 1H), 2.2–1.6 (m, 6H). ^{13}C NMR (75 MHz, $CDCl_3$): 166.4, 141.2, 135.7, 133.3, 132.5, 130.9, 127.9, 125.3, 94.0, 69.7, 28.3, 25.0, 18.9. IR (KBr, cm^{-1}) 2937, 1716, 1429, 1248.
7. Shi, L.; Narula, C. K.; Mak, K. T.; Kao, L.; Xu, Y.; Heck, R. F. *J. Org. Chem.* **1983**, *48*, 3894–3900.
8. Spectroscopic data for **6a**: ^{1}H NMR (300 MHz, $CDCl_3$): 7.3–7.2 (m, 3H), 7.01 (d, 1H), 5.78 (m, 1H), 5.66 (d, 1H), 4.87 (s, 2H), 4.08 (br s, 1H), 3.33 (br s, 1H) 2.4–1.8 (m, 4H). ^{13}C NMR (75 MHz, $CDCl_3$): 136.8, 134.5, 129.0, 128.9, 127.0, 126.5, 126.2, 124.3, 71.4, 68.0, 37.7, 27.2, 20.0. IR (KBr, cm^{-1}) 2922, 2841, 1490, 1448, 1099. APCI MS m/z (M−1) calcd 185.1, obsd 185.0. Spectroscopic data for **8a**: ^{1}H NMR (300 MHz, $CDCl_3$): 8.10 (d, 1H), 7.55 (t, 1H), 7.40 (t, 1H), 7.29 (d, 1H), 5.79 (m, 1H), 5.68 (d, 1H), 4,82 (s, 1H), 2.98 (m, 1H) 2.55 (s, 2H), 2.4–1.8 (m, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): 166.2, 133.9, 130.9, 127.9, 126.6, 125.9, 123.1, 75.3, 35.6, 30.2, 28.8. IR (KBr, cm^{-1}) 2917, 1724, 1270, 1115. APCI MS m/z (M+1) calcd 201.1, obsd 201.0.
9. Beautement, K.; Clough, J. M. *Tetrahedron Lett.* **1984**, *25*, 3025–3028.
10. Corey, E. J.; Suggs, J. W. *Tetrahedron Lett.* **1975**, *16*, 2647–2650.
11. Jeffery, T. *Tetrahedron* **1996**, *52*, 10113–10130.
12. Deziel, R. *Tetrahedron Lett.* **1987**, *28*, 4371–4372.
13. Rigby, J. H.; Hughes, R. C.; Heeg, M. J. *J. Am. Chem. Soc.* **1995**, *117*, 7834–7835.
14. Amatore, C.; Azzabi, M.; Jutand, A. *J. Am. Chem. Soc* **1991**, *113*, 8375–8384.
15. Brown, J. M.; Perez-Torrente, J. J.; Alcock, N. W.; Clase, H. J. *Organometallics* **1995**, *14*, 207–213.
16. Pampin, C.; Estevez, J. C.; Castedo, L.; Estevez, R. J. *Tetrahedron Lett.* **2002**, *43*, 4551–4553.
17. Spectroscopic data for **12**: ^{1}H NMR (300 MHz, $CDCl_3$): 7.98 (dd, 2H), 7.84 (d, 1H), 7.72 (d, 1H), 7.54 (m, 2H), 7.5–7.2 (m, 3H), 7.15 (t, 1H), 7.02 (d, 1H), 6.05 (m, 1H), 5.46 (d, 1H), 5.32 (m, 1H), 4.84 (d, 2H). IR (KBr, cm^{-1}) 2942, 1727, 1248, 1131. APCI MS m/z (M+1) calcd 265.1, obsd 265.0, 265.2. Spectroscopic data for **13**: ^{1}H NMR (300 MHz, $CDCl_3$): 7.98 (d, 1H), 7.92 (d, 1H), 7.71 (d, 1H), 7.6–7.5 (m, 3H), 7.4–7.2 (m, 4H), 6.99 (d, 1H), 6.03 (d, 1H), 5.80 (m, 1H), 5.53 (d, 1H) 2.1–1.6 (m, 6H). IR (KBr, cm^{-1}) 2940, 1708, 1246, 1131. APCI MS m/z (M+1) calcd 305.2, obsd 305.0.
18. Eliel, E. L.; Wilen, S. H. In *Stereochemistry of Organic Compounds*, 2nd ed.; Wiley-Interscience: New York, 1994, pp 618–619, and references cited therein.
19. Imase, T.; Kawauchi, S.; Watanabe, J. *Macromol. Theory Simul.* **2001**, *10*, 434–440.