PREPARATION OF SPIROCYCLIC POLYETHERS BY INTRAMOLECULAR HECK REACTIONS**

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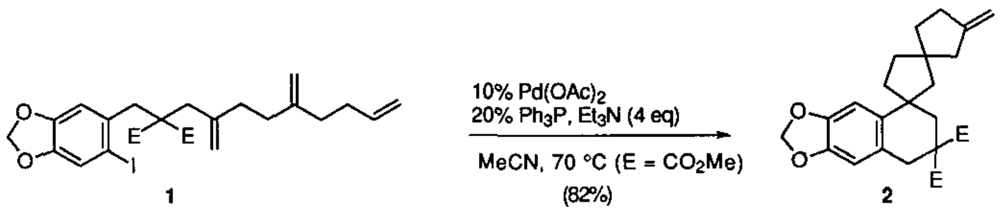
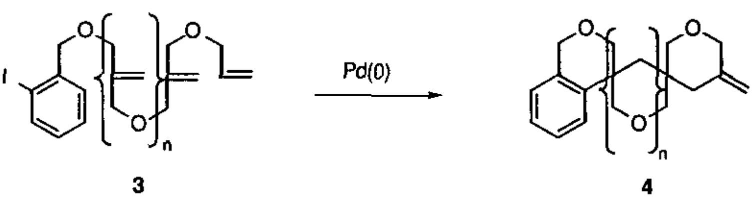
Abstract- The first examples of forming spirocyclic polyethers by multiple Heck cyclizations are reported.

The formation of carbon-carbon bonds is central to synthetic organic chemistry. In recent years, palladium catalyzed insertions of aryl and alkenyl halides and triflates (Heck reactions) have emerged as unusually versatile reactions for carbon-carbon bond formation.[1,2] Intramolecular insertions are particularly valuable, since they take place with a wide variety of substituted alkenes.[3] Work in this area from our laboratories has focused on the remarkable ability of intramolecular Heck reactions to forge quaternary carbon centers (e.g., **1** → **2**).[4]



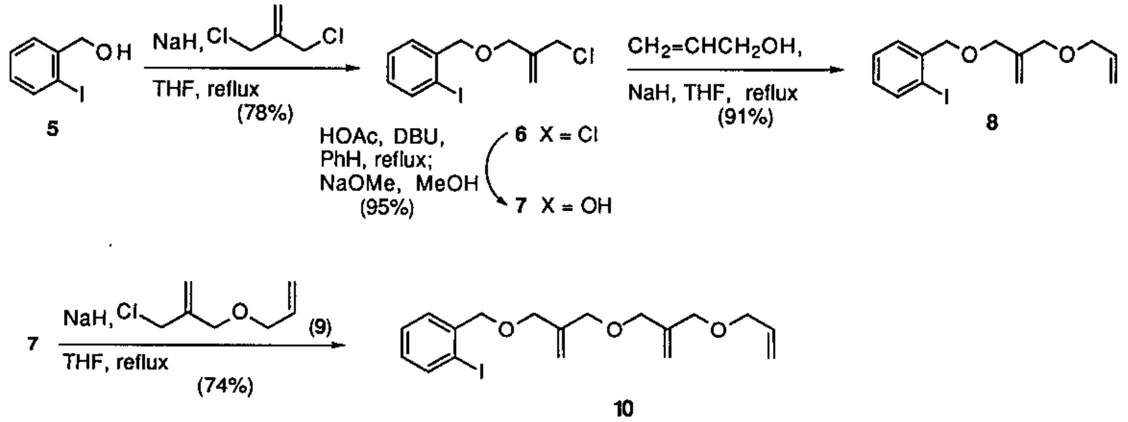
The power of intramolecular Heck reactions is highlighted by our recent use of this chemistry as the key strategic element of concise total syntheses of several structurally diverse natural products.[5] Since multiple cyclizations that proceed in a spirocyclic mode have proven to be particularly efficient,[2-4] we were interested in seeing if spiro heterocycles could be prepared also in this manner. Our initial investigations of this sequence for the synthesis of spirocyclic polyethers (**3** → **4**) are the subject of this report.



**Dedicated with respect to Dr. Arnold Brossi on the occasion of his 70th birthday.

The synthesis of the unsaturated polyether cyclization substrates is summarized in Scheme 1. Using straightforward chemistry that requires no further comment, the dienyl and trienyl polyethers (**8**) and (**10**) were prepared in good overall yields from *o*-iodobenzyl alcohol, methallyl dichloride and allyl alcohol.[6]

Scheme 1

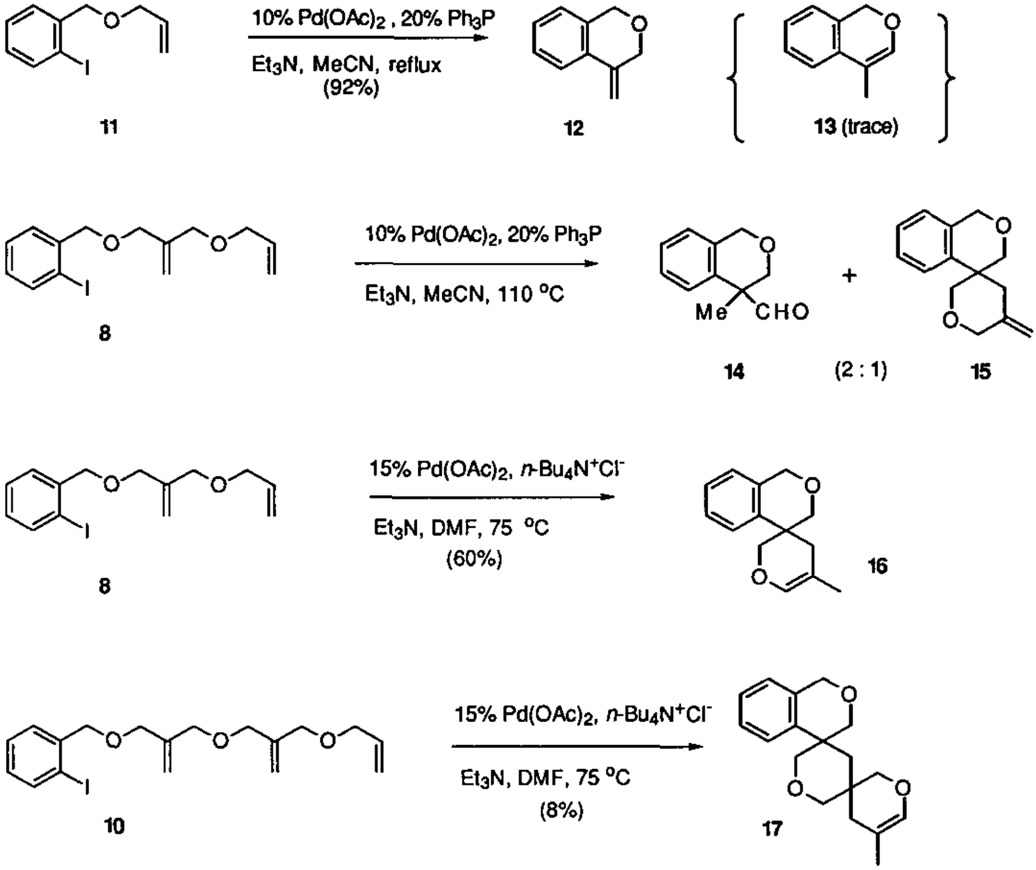


We initially examined simple cyclizations of allyl *o*-iodobenzyl ether (**11**), since Heck had earlier reported the cyclization of the corresponding bromide (Scheme 3).[7] In the presence of 10% $Pd(Ph_3P)_2$ (formed *in situ* from 10% $Pd(OAc)_2$ and 20% Ph_3P), iodo ether (**11**) cyclized in refluxing acetonitrile containing excess Et_3N to give the methylenedihydrobenzopyran (**12**) in 92% yield. In contrast to the earlier study of the bromo analog, only a trace of the double bond regioisomer (**13**) could be detected by 500 MHz ^1H nmr analysis of the crude cyclization product.

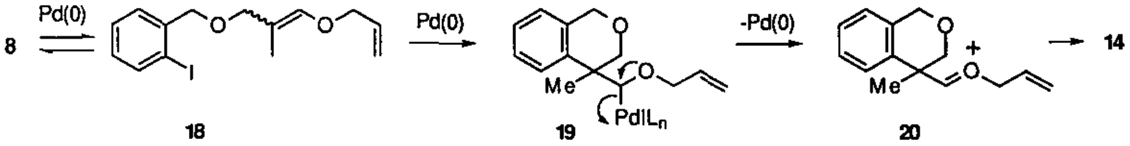
Attempted cyclization of the dienyl aryl iodide (**8**) under identical conditions returned only starting material. However, conducting this reaction in a sealed tube at 110 °C clearly led to the formation of two cyclization products (**14**) and (**15**), which were isolated in 49% yield and a 2:1 ratio after rapid chromatography on silica gel.[8] In order to optimize the formation of the biscyclization product (**15**), a wide variety of Heck cyclization conditions were examined. Best results were obtained using Jeffrey conditions,[9] which provided the regioisomeric spiro tricyclic diether (**16**) in 60% yield after purification on silica gel.[10] Unfortunately, cyclization of the trienyl iodide (**10**) under identical conditions provided the spiro tetracyclic triether (**17**) in low yield only.[11]

Not surprisingly, the side reaction that partially undermines Heck cyclizations of the polyethers (**8**) and (**10**) is palladium catalyzed rearrangement of the allylic ether to the more stable enol ether functionality.[12] In spite of intensive screening of palladium catalysts, amine bases and solvents, this competing process could never be completely suppressed. Such an event, in this case isomerization of **8** → **18**, is undoubtedly responsible for the formation of the dihydrobenzopyran aldehyde (**14**) from **8** (Scheme 3).

Scheme 2



Scheme 3



In summary, The first examples of forming spirocyclic polyethers by Heck cyclization cascades are reported. However, the utility of this chemistry is limited by palladium catalyzed isomerizations of the starting allylic polyether substrates.

ACKNOWLEDGMENTS

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6. Experimental details for these steps have been described, see: S. D. Knight, *Ph. D. Dissertation*, University of California, Irvine, 1994 (available from *Dissertation Abstracts*).
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8. Separation of this mixture by chromatography on silica gel was inefficient. Analytical samples of **14** and **15** were obtained by preparative glc (silylated 10% SP 2330 on 100/120 Supelcoport, He ~50 ml/min, 200 °C). Partial characterization data for aldehyde (**14**): ^{1}H Nmr (500 MHz) δ 9.75 (s, CHO), 7.22-7.29 (m, 3 H, ArH), 7.05 (d, 1 H, J = 6.9 Hz, ArH), 4.83 (s, $PhCH_2$), 4.26 (app d, 1 H, J = 11.7 Hz, OCH_2CCH_3), 3.66 (app d, 1 H, J = 11.7 Hz, OCH_2CCH_3), 1.39 (s, CH_3); ^{13}C nmr (125 MHz) 201.4, 134.7, 133.2, 127.4, 127.3, 124.6, 70.8, 68.5, 49.2, 18.4; ms (EI) m/z 176.0837 (176.0837 calcd for $C_{11}H_{12}O_2$). Partial characterization data for **15**: ^{1}H Nmr (500 MHz) δ 7.40 (d, J = 7.9 Hz, 1 H, ArH), 7.19-7.25 (m, 2 H, ArH), 7.01 (d, J = 7.0 Hz, 1 H, ArH), 4.94 (d, J = 1.5 Hz, 1 H, $C{=}CH_2$), 4.84 (s, 1 H, $C{=}CH_2$), 4.78 (s, 2 H, ArH), 4.06 and 4.25 (AB, J_{AB} = 12.2 Hz, 2 H, $OCH_2C{=}C$), 3.68 and 4.05 (AB,

J_{AB} = 11.6 Hz, 2 H, CH_2O), 3.65 and 3.89 (AB, J_{AB} = 11.3 Hz, 2 H, CH_2O), 2.40 and 2.77 (AB, J_{AB} = 14.6 Hz, 2 H, $CH_2C{=}C$), ms (EI) m/z 216.1147 (216.1150 calcd for $C_{14}H_{16}O_2$, 52%).

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10. Partial characterization data for **16**: ^1H Nmr (300 MHz) δ 7.00-7.30 (m, 4 H, ArH), 6.30 (br s, OC*H*=C), 4.80 (s, $ArCH_2$), 3.87-3.93 (m, OCH_2), 3.81 (app d, 1 H, J = 10.5 Hz, OCH_2), 3.67 (app d, 1 H, J = 11.5 Hz, OCH_2), 2.40 and 1.92 (AB, J_{AB} = 17.4 H_z $CH_2C{=}C$), 1.64 (s, $CH_3C{=}C$); ^{13}C nmr (75 MHz) 137.9, 134.9, 127.1, 126.5, 126.3, 124.3, 108.5, 105.1, 71.0, 70.1, 68.9, 35.6, 35.0, 18.2; IR (film) 3056, 3012, 2961, 2917, 2883, 2854, 1677, 1492, 1439, 1192, 1151, 1113, 1098, 1018, 762 cm^{-1}; ms (CI) m/z 217.1234 (217.1228 calcd for $C_{14}H_{17}O_2$).
11. Partial characterization data for **17**: ^1H Nmr (500 MHz) δ 7.38 (d, J = 7.9 Hz, 1 H, ArH), 7.24 (t, J = 7.9 Hz, 1 H, ArH), 7.18 (t, J = 7.4 Hz, 1 H, ArH), 6.99 (d, J = 7.4 Hz, 1 H, ArH), 6.20 (s, OC*H*=C), 4.78 (s, 2 H, $PhCH_2$), 3.70 and 4.43 (AB, J_{AB} = 11.4 Hz, 2 H), 3.42 and 4.06 (AB, J_{AB} = 11.8 Hz, 2 H), 3.30 and 4.01 (AB, J_{AB} = 11.4 Hz, 2 H) ,3.39 and 3.59 (AB, J_{AB} = 10.8 Hz, 2 H), 1.89 and 2.35 (AB, J_{AB} = 16.8 Hz, 2 H), 1.51 and 1.81 (AB, J_{AB} = 14.1 Hz, 2 H), 1.58 (s, 3 H, $C{=}CCH_3$); ms (CI) m/z 287.
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