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Microwave-Accelerated Spiro-Cyclizations of *o*-Halobenzyl Cyclohexenyl Ethers by Palladium(0) Catalysis

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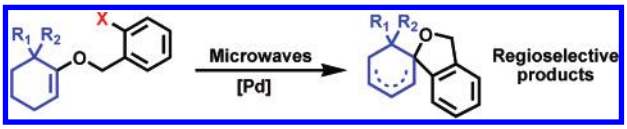


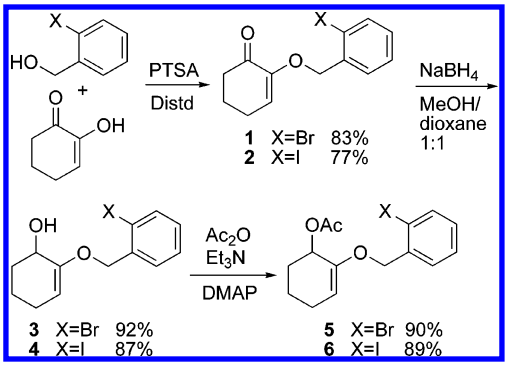
A number of new spiro[cyclohexane-1,1′-isobenzofuran]-based compounds was synthesized by palladium(0)-catalyzed 5-exo cyclization of a series of cyclohexenyl *o*-halobenzyl ethers. Controlled microwave heating was found to promote both product yield and reaction rate without compromising the selectivity. Heck cyclization of aryl iodide **6**, 2-(2-iodobenzyloxy)cyclohex-2-enyl acetate, proceeded selectively without involvement of the allylic acetate functionality.

New methods in preparation of constrained products are of importance in both natural product synthesis and in medicinal chemistry applications. In drug discovery, the use of restricted analogues serves as an important method to allow determination of bioactive conformations.[1] Palladium(0)-catalyzed Heck coupling reactions have emerged as one of the most versatile carbon−carbon bond forming processes.[2−6] The reaction is attractive for the synthetic chemist since (a) it provides a unique method for arylation or vinylation of double bonds, (b) it proceeds under mild conditions, and c) it tolerates the presence of a wide variety of functional groups. Although the traditional intermolecular Heck coupling has found wide utility, the intramolecular version of the Heck arylation constitutes perhaps the most important development of the Heck arylation reaction in recent times.[7,8] Unfortunately, the optimization of Heck reaction conditions is typically demanding and reaction times are generally long.[9]

Intramolecular Heck arylations proceed, when possible, with a preference for 5- and 6-exo cyclizations, except in a few cases where endo cyclizations have been reported.[7,10] As revealed by a large number of prominent chemists,[11−13] when operating under optimized conditions, this class of cyclization reactions has a remarkable ability to form congested quaternary centers.[14]

This report is part of an ongoing project toward the development of novel and robust metal-catalyzed transformations of fundamental importance with a special focus on microwave-enhanced protocols. Construction of rare spiro-compounds from *o*-halobenzyl cyclohexenyl ethers **1**−**8** was envisioned via 5-exo cyclization. Herein we report the discovery and examination of a series of microwave-accelerated intramolecular Heck reactions with controlled regioselectivity. The developed methodology allowed facile formation of new and restricted spiro[cyclohexane-1,1′-isobenzofuran] derivatives **9**−**12**.

SCHEME 1. Preparation of Heck Cyclizations Substrates 1−6



Preparation of Cyclization Precursors. The required ethers **1**−**6** were all prepared from commercially available 1,2-cyclohexanedione (Scheme 1). Ketones **1** and **2** were prepared by treating the appropriate *o*-halobenzyl alcohol with an excess of 1,2-cyclohexanedione and a catalytic amount of *p*-toluenesulfonic acid (PTSA). The condensation reaction was carried out in dry benzene, and the produced water was continuously removed via azeotropic distillation. This process afforded **1** and **2** in good yields (83% and 77%, respectively). Alcohols **3** and **4**, were smoothly synthesized by the sodium borohydride reduction of **1** and **2**, respectively. Finally, allylic esters **5** and **6** were prepared in 90% and 89% yield by acetylation of **3** and **4**, using acetic anhydride and 4-dimethylaminopyridine (DMAP).

Vinyl ethers **7** and **8** were synthesized via an acid-catalyzed transetherification reaction from methyl 1-cyclohexenyl ether and the appropriate *o*-halobenzyl alcohol (Scheme 2). The

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SCHEME 2. Preparation of Heck Cyclizations Substrates 7 and 8

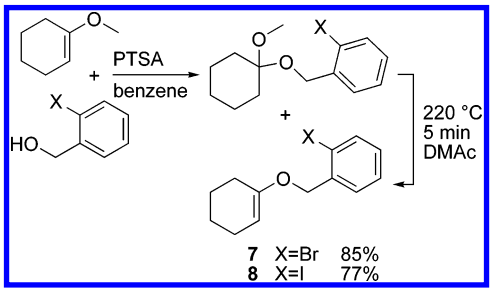
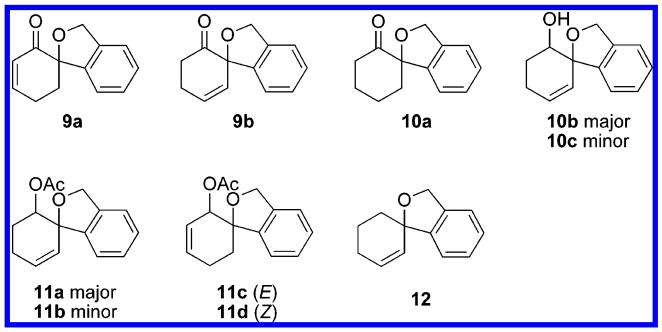


CHART 1. Heck Cyclization Products



equilibrium was driven toward the elimination products **7** and **8** by the continuous removal of methanol via azeotropic distillation. The remaining *o*-halobenzyl ketal was consumed by subjecting the crude product to 5 min of microwave irradiation (220 °C) in dimethylacetamide (DMAc).

Palladium-Catalyzed Spiro-Cyclizations. We have previously reported a number of very rapid microwave-accelerated palladium-catalyzed intermolecular Heck reactions.[15−17] However, this convenient superheating methodology has not been generally applied to intramolecular Heck processes.[18,19] Therefore, we decided to utilize controlled microwave irradiation for the fast spiro-cyclization of **1**−**8**, although for comparison and general usefulness we decided to also include examples with traditional heating.

Among the available reported protocols for Heck reactions with aryl bromides, we chose phosphine-free Jeffery type conditions with the addition of 2 equiv of tetrabutylammonium bromide (TBAB) for ring-closure of captodative olefin **1**.[20] Classical $Pd(OAc)_2$ (1%) was used as the palladium source, and pentamethylpiperidine (PMP)[12] was chosen as the amine base, since it was found to be superior to less hindered amines, e.g., triethylamine or diisopropylethylamine. In the initial microwave-mediated cyclization experiments we employed DMF or PEG, with or without addition of water, as reaction media in sealed vessels at 150−180 °C. Under these conditions, spiro-compound **9a** (Chart 1) was quickly formed although starting material **1** also underwent competing degradation by benzylic cleavage, generating *o*-bromotoluene as byproduct, together with other decomposition products. Employing considerably less polar toluene, as the solvent, furnished a significant improvement in both product selectivity and yield (Table 1). The best results with **1** were obtained after 10 min of microwave heating at 180 °C using sealed vessels (82% **9a**, entry 1), while the identical cyclization performed at 120 °C with classical heating delivered 71% of conjugated vinyl ketone **9a** after 18 h (entry 2). Addition of 5% v/v of water provided almost identical yields of **9a** (80% with microwave heating and 70% with oil-bath heating). Changing the ammonium salt additive to the halide free salts tetrabutylammonium hydrogen sulfate or tetrabutylammonium acetate severely diminished the isolated yield (22% and 9%, respectively). Regardless of the reaction system, full exo-selectivity and complete double-bond migration to give the α,β-unsaturated ketone was observed in all halide-containing reactions.

With the more exclusive aryl iodide substrate **2** in hand, we first explored similar nonaqueous toluene based conditions as developed for aryl bromide **1**. However, it was quickly realized that the ring-closure was promoted by the addition of 5% v/v of water.[3] With this aqueous solvent system, high yields of **9a** were smoothly obtained with both microwave and classical heating (entries 3 and 4, Table 1). The enhanced reactivity of **2** encouraged us to investigate the use of silver additives to inhibit double bond migration and thus the production of conjugated ketone **9a**.[12,21] In fact, predominant formation of regioisomer **9b** (Table 1, entry 5, Chart 1) could be accomplished by the addition of Ag_3PO_4 (0.6 equiv) and replacing TBAB and toluene with tetrabutylammonium hydrogen sulfate and dioxane. In addition to **9a** and **9b**, the corresponding 6-endo-arylation product (1,2-dihydrodibenzo[*b*,*d*]pyran-4(3*H*)-one) was also isolated (14%). Despite extensive tuning of several reaction parameters, full conversion of **2** was never obtained in presence of Ag_3PO_4.[12,21] We also investigated a number of additional silver(I)[22] and thallium(I)[23] salts, but they proved even less successful, typically affording yields below 10% of ring-closed products.

Switching our attention toward allyl alcohols **3** and **4**, as cyclization precursors, proved straightforward. Even though the allylic double bond is considered more electron-rich and thus slightly less reactive under the established neutral Heck conditions,[24] spiro-cyclohexanone product **10a** was directly obtained as the dominating product, regardless of the heating method (entries 6−8, Table 1). Double bond migration and subsequent Pd-enolate tautomerism explain the formation of the saturated ketone **10a**.[4,25] After chromatography, 51−59% of ketone **10a** and 7−15% of alcohols **10b**,**c** (*E*/Z-mixture) were isolated. The effect of solvent polarity was next studied with *n*-hexane−toluene−water mixtures as an alternative to the above utilized toluene−water system. In short, the selectivity for **10a** improved although the total yield diminished with increasing *n*-hexane content (entries 9 and 10).

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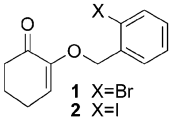
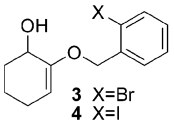
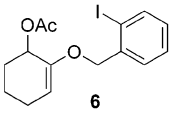
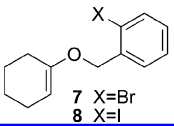
TABLE 1. Palladium Catalyzed Spiro-Cyclizations

Entry	Starting material		[Pd] (%)	Solvent	Conditions[a]	Temp (°C)	Heating Time	Isolated yields[b]	
								9a	**9b**
1		**1**	1%	Toluene	Microwave	180	10 min	82%	
2		**1**	1%	Toluene	Classical	120	18 h	71%	
3		**2**	1%	Toluene/water 19:1	Microwave	140	10 min	91%	
4		**2**	1%	Toluene/water 19:1	Classical	100	18 h	82%	
5[c]	**1** X=Br **2** X=I	**2**	1%	Dioxane/water 19:1	Classical	70	24 h	15%	26%[d]
								10a	**10b+c**
6		**3**	1%	Toluene	Microwave	180	10 min	51%	7%[e]
7		**4**	1%	Toluene/water 19:1	Microwave	140	10 min	59%	15%[e]
8		**4**	1%	Toluene/water 19:1	Classical	100	18 h	58%	12%[e]
9	**3** X=Br **4** X=I	**4**	1%	Toluene/hexane/ water 17:2:1	Microwave	140	10 min	44%	
10		**4**	1%	Toluene/hexane/ water 19:19:2	Microwave	140	10 min	20%	
								11a	
11	 **6**	**6**	1%	DMF	Microwave	140	10 min	54%	
								12	
12		**7**	10%	DMF	Microwave	180	10 min	63%	
13		**8**	1%	Toluene/water 19:1	Microwave	140	4 h	54%	
14		**8**	10%	DMF/water 19:1	Microwave	140	10 min	77%	
15	**7** X=Br **8** X=I	**8**	1%	DMF/water 1:1	Microwave	140	10 min	39%	

[a] Conditions: 0.50 mmol starting olefin, 0.005-0.05 mmol $Pd(OAc)_2$, 2.0 mmol PMP, 1.0 mmol TBAB, solvent added to provide a total volume of 3 mL. Reaction vessels were sealed under air. Entries 12 and 14 required 10 mol% $Pd(OAc)_2$ to give full conversion. [b] 95% purity by GC-MS and ^{1}H NMR. [c] 0.3 mmol of Ag_3PO_4 was added to the reaction mixture and TBAB was replaced by an equimolar amount of tetrabutylammonium hydrogen sulfate. [d] 14% of the corresponding product from arylation in the 3-position was isolated. [e] Combined isolated yield of **10b** and **10c**. Diastereomeric mixture 3:1.

In an attempt to inhibit the formation of the thermodynamically favored ketone **10a** via a repeated HPdX elimination−insertion sequence, the free hydroxy group of **4** was modified into the corresponding blocked *O*-acetyl compound **6** (Scheme 1). The hypothesis was first tested by subjecting **6** to the same conditions used for the spiroannulation of **4**. However, substantially higher yields were achieved when the reaction was performed in DMF. Four compounds of a reminiscent mass spectrometric fragmentation pattern were detected, although only the most abundant, **11a**, could be isolated in a pure state (54%, entry 11). According to ^{1}H NMR of the crude product mixture, the diastereomeric ratio of **11a**/**11b** was 2.5:1. Also, **11c** and **11d** were detected in minor amounts.

Starting from **5** or **6**, no side products from competing allylic substitutions were detected. Given the well-known reactivity of allylic acetates toward palladium(0) and the presence of 2 equiv of potentially nucleophilic bromide ions (from TBAB), we find the selective activation of the aryl−iodo bond at 140 °C noteworthy.[26] This selectivity may be due to a Pd(0)−vinyl group precoordination and subsequent presentation of the metal center to the halogen−carbon bond. The addition of dimethyl malonate to the reaction mixture did not give rise to any new products, and the only impact was a significantly reduced reaction rate. The attempted Heck cyclization starting from bromide precursor **5** was too sluggish to be preparatively useful, but GC-MS investigations revealed that the same product mixture (**11a**−**d**) resulted as when starting from **6**.

Finally, we turned our attention to exploring the cyclization of vinyl ethers **7** and **8**. Trying the toluene conditions previously found to be successful for the reaction of **1**−**4**, cyclization of **7** and **8** proved sluggish. In contrast, the use of more polar solvents such as aqueous DMF significantly promoted the reaction and, fortunately, electron-rich **7** and **8** did not decompose in this solvent system despite microwave heating to 140−180 °C. The highest yield of ring-closed allylic ether **12** (77%) was obtained with 10 mol% $Pd(OAc)_2$ (entry 14, Table 1). It is notable that no double bond isomerization seems to occur.

In summary, new, fast, and highly efficient intramolecular Heck methods for the generation of conformationally restricted spiro[cyclohexane-1,1′-isobenzofuran] derivatives have been established. The double bond position and oxidation state of the hexacycle was controlled by a careful choice of starting materials and reaction conditions. The presented reactions constitute an alternative to free radical protocols for construction of spirocyclic compounds.[27−29] In all investigated reactions, high-density microwave heating afforded shorter reaction times (10 min) and higher yields compared with classical heating.

Experimental Section

General Procedure for Preparation of 2-(2-Halobenzyloxy)-2-cyclohexenones (1 and 2). The following chemicals were added to a dry 100 mL three-necked round-bottomed flask: either *o*-bromobenzyl alcohol (4.68 g, 25 mmol) or *o*-iodobenzyl alcohol (5.85 g, 25 mmol), 1,2-cyclohexandione (4.20 g, 37.5 mmol), *p*-toluenesulfonic acid monohydrate (0.28 g, 1.25 mmol), and benzene (50 mL). A Soxhlet device filled with K_2CO_3 (s) was connected to the flask with a condenser on the top. Upon heating, condensed vapors rinsed through the Soxhlet device, trapping the released water. The contents of the flask were magnetically stirred and heated using an oil bath (120 °C) until no further conversion of the *o*-halobenzyl alcohol was detected. A second portion of 1,2-cyclohexandione (1.40 g, 12.5 mmol) was added, and the reaction

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was continued until not more than traces of *o*-halobenzyl alcohol remained in the reaction mixture. The reaction mixture was cooled to 0 °C, 0.5 M Na_2CO_3 (100 mL) was added, and the layers were separated. The organic phase was washed with additional portions of 0.5 M Na_2CO_3 until no trace of 1,2-cyclohexandione was left. The organic phase was dried ($MgSO_4$) and concentrated under reduced pressure. The crude product was purified by silica chromatography (ether/toluene) to give the title products.

2-(2-Bromobenzyloxy)-cyclohex-2-enone (1). The compound was prepared according to the General Procedure for Preparation of 2-(2-Halobenzyloxy)-2-cyclohexenones. White crystalline solid, 83% yield (5.83 g, 20.7 mmol, >95% by GC-MS), mp = 51 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.54−7.48 (m, 2H), 7.33−7.28 (m, 1H), 7.17−7.12 (m, 1H), 5.91 (t, J = 4.6 Hz, 1H), 4.90 (s, 2H), 2.53 (t, J = 6.7 Hz, 2H), 2.39 (td, J = 6.0, 4.6 Hz, 2H), 1.96 (tt, J = 6.7, 6.0 Hz, 2H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 194.2, 150.3, 136.0, 132.6, 129.4, 128.9, 127.8, 122.1, 119.8, 69.0, 39.1, 24.7, 23.1. IR (KBr) 1692 cm^{-1}. MS *m*/*z* (relative intensity 70 eV) 253 (10), 251 (10), 202 (16), 201 (100), 173 (19), 171 (98), 170 (13), 169 (94), 90 (38), 89 (37), 63 (23), 55 (24). Anal. Calcd for $C_{13}H_{13}BrO_2$: C, 55.54; H, 4.66. Found: C, 55.40; H, 4.56.

General Procedure for Preparation of 2-(2-Halobenzyloxy)-cyclohex-2-enol (3 and 4). 1 (7.03 g, 25 mmol) or **2** (8.20 g, 25 mmol) was dissolved in a mixture of THF (50 mL) and methanol (50 mL) in a 250 mL round bottomed flask and cooled to 0 °C. $NaBH_4$ (0.95 g, 25 mmol) was added in portions under continuous cooling and stirring. The mixture was allowed to stir for another 10 min before 0.5 M citric acid (50 mL) was added, and finally the mixture was concentrated to <20 mL under reduced pressure. The remaining mixture was extracted with diethyl ether, the combined ethereal phases were dried ($MgSO_4$) and concentrated, and the residue was purified by chromatography (aluminum oxide with 6% (w/w) water added, ether/toluene eluent) to furnish the title products.

2-(2-Bromobenzyloxy)-cyclohex-2-enol (3). The compound was prepared according to the General Procedure for Preparation of 2-(2-Halobenzyloxy)-2-cyclohexenol. White solid, 92% yield (6.51 g, 23.0 mmol, >95% by GC-MS), mp = 54 °C. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (dd, J = 8.0, 1.3 Hz, 1H), 7.46 (dd, J = 7.7, 1.8 Hz, 1H), 7.32 (ddd, J = 7.7, 7.5, 1.3 Hz, 1H), 7.17 (ddd, J = 8.0, 7.5, 1.8 Hz, 1H), 4.86−4.84 (m, 1H), 4.81 (s, 2H), 4.26−4.24 (m, 1H), 2.42 (s, 1H), 2.20−2.10 (m, 1H), 2.08−1.99 (m, 1H), 1.92−1.77 (m, 2H), 1.76−1.66 (m, 1H), 1.61−1.52 (m, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.6, 136.7, 133.0, 129.6, 129.5, 127.8, 123.1, 98.4, 68.7, 66.7, 31.3, 24.2, 19.0. IR (thin film) 3422, 3364 cm^{-1}. MS *m*/*z* (relative intensity 70 eV) 266 (12), 264 (12), 186 (11), 185 (18), 172 (11), 171 (100), 170 (12), 169 (93), 90 (30), 89 (34), 67 (11), 63 (14). Anal. Calcd for $C_{13}H_{15}BrO_2$: C, 55.14; H, 5.34. Found: C, 55.01; H, 5.21. Compound unstable in solution.

General Procedure for Spiro-Cyclizations (Table 1). The following chemicals were added to a thick-walled tube: $Pd(OAc)_2$, either as a 0.1 M stock solution (50 μL of solution containing 22.5 mg/mL $Pd(OAc)_2$ in acetonitrile, 0.005 mmol) or as solid (11.2 mg, 0.05 mmol); tetrabutylammonium bromide (322 mg, 1 mmol) or tetrabutylammonium hydrogen sulfate (340 mg, 1 mmol); either of the substrates: **1** (141 mg, 0.5 mmol), **2** (164 mg, 0.5 mmol), **3** (142 mg, 0.5 mmol), **4** (165 mg, 0.5 mmol), **5** (163 mg, 0.5 mmol), **6** (186 mg, 0.5 mmol), **7** (134 mg, 0.5 mmol), or **8** (157 mg, 0.5 mmol); in entry 5 only, Ag_3PO_4 (84 mg, 0.2 mmol); 3 mL of solvent and PMP (0.362 mL, 2 mmol). The reaction mixture was septum sealed in air and magnetically stirred and heated according to specifications. The reaction mixture was cooled, diluted (diethyl ether) and washed with water, dried (K_2CO_3), and concentrated under vacuum, and the residue was purified by chromatography (silica, ether/isohexane mobile phase) to yield products **9**−**12**.

***3′H*-Spiro[cyclohex-3-ene-1,1′-isobenzofuran]-2-one (9a).** Colorless oil, 91% yield (91.1 mg, 0.455 mmol, Table 1, entry 3, >95% by GC-MS). ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.27−7.21 (m, 1H), 7.20−7.15 (m, 2H), 7.11−7.08 (m, 1H), 7.01 (dtd, J = 10.1, 4.0, 0.7 Hz, 1H), 6.07 (dt, J = 10.1, 2.0 Hz, 1H), 5.19 (d, J = 12.2 Hz, 1H), 5.09 (d, J = 12.2 Hz, 1H), 2.58 (dddd, J = 6.7, 5.5, 4.0, 2.0 Hz, 2H), 2.31 (ddd, J = 13.6, 5.5, 0.7 Hz, 1H), 2.25 (dtd, J = 13.6, 6.7, 5.5 Hz, 1H). ^{13}C NMR (100 MHz, $CDCl_3$) δ 196.2, 150.7, 140.1, 139.6, 129.0, 128.7, 127.6, 121.9, 121.7, 89.5, 73.2, 34.4, 24.5. IR (thin film) 1682 cm^{-1}. MS *m*/*z* (relative intensity 70 eV) 200 (67), 182 (11), 133 (23), 132 (100), 131 (41), 115 (13), 104 (49), 103 (19), 90 (12), 89 (22), 78 (17), 77 (11), 63 (13), 50 (10). Anal. Calcd for $C_{13}H_{12}O_2$: C, 77.98; H, 6.04. Found: C, 77.75; H, 5.94.

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Supporting Information Available: Text giving full details of experimental procedures and spectroscopic data. This material is available free of charge via the Internet at http://pubs.acs.org.

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