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Efficient, Regioselective Palladium-Catalyzed Tandem Heck-Isomerization Reaction of Aryl Bromides and Non-Allylic Benzyl Alcohols

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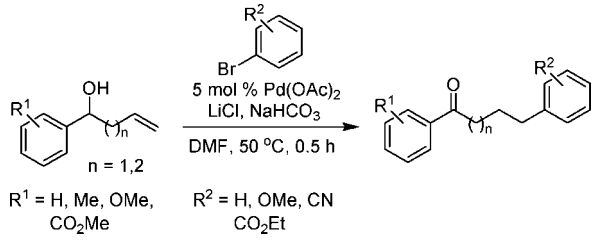
ABSTRACT



An efficient and mild method to couple aryl bromides and activated non-allylic alcohols in a Heck reaction with tandem isomerization to selectively afford high yields of 1,5-diarylalkan-1-ones has been developed. Mechanistic insight was gained through NMR studies of products derived from deuterium-labeled intermediates.

Development of palladium-catalyzed coupling reactions has allowed access to diverse arrays of complex, biologically important molecules that would have otherwise been difficult to synthesize.[1] In this class of transformations, the Heck reaction has become a widely utilized method for the formation of carbon−carbon bonds.[2] When used in tandem with other reactions, such as subsequent palladium-catalyzed transformations, rearrangements, or isomerizations, the power of this approach is magnified.[3]

During our investigations of nonsteroidal agonists of the farnesoid X receptor (FXR), we attempted to employ a Heck reaction to couple our functionalized heteroaryl core scaffold appended with γ-hydroxy alcohol **1** to generate an intermediate styrene derivative **3** (eq 1). Much to our surprise, the only product isolated, albeit in low yield, was ketone **4**. While tandem Heck-isomerization reactions are well documented with allylic alcohols[4] and homoallylic alcohols[5] with aryl iodides, the few reports with longer chain lengths or aryl

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(1) For selected reviews, see: (a) Tietz, L. F.; Ila, H.; Bell, H. P. *Chem. Rev.* **2004**, *104*, 3453. (b) Trost, B. M.; Crawley, M. L. *Chem. Rev.* **2003**, *103*, 2921. (c) Miyaura, N.; Suzuki, A. *Chem. Rev.* **1995**, *95*, 2457.

(2) For selected reviews, see: (a) Beletskaya, I. P.; Cheprakov, A. V. *Chem. Rev.* **2000**, *100*, 3909. (b) Dounay, A. B.; Overman, L. E. *Chem. Rev.* **2003**, *103*, 2945.

(3) Recent represenative reviews and examples: (a) Muzart, J. *Tetrahedron* **2005**, *61*, 4179. (b) Alberico, D.; Rudolph, A.; Lautens, M. *J. Org. Chem.* **2007**, *72*, 775. (c) Cheung, W. S.; Patch, R. L.; Player, M. R. *J. Org. Chem.* **2005**, *70*, 3741. (d) Artman, G. D.; Weinreb, S. M. *Org. Lett.* **2003**, *9*, 1523. (e) Pinho, P.; Minnaard, A. J.; Feringa, B. L. *Org. Lett.* **2003**, *5*, 259.

(4) Classic examples: (a) Melpoder, J. B.; Heck, R. F. *J. Org. Chem.* **1976**, *41*, 265. (b) Chalk, A. J.; Magennis, S. A. *J. Org. Chem.* **1976**, *41*, 273.

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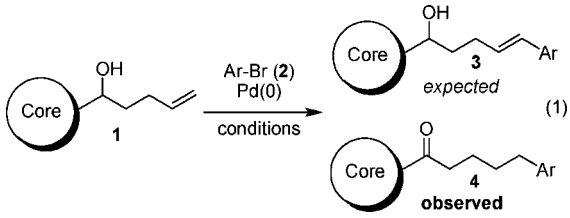
bromides require either forcing conditions, long time periods, or unusual ligands and in all cases give mixtures of regioisomeric and intermediate products, including cyclized adducts.[6] In fact, some research groups have deliberately taken advantage of the cyclized "side products" to synthesize a variety of tetrahydrofurans from γ-hydroxy terminal alkenes.[7] Additionally, under mild conditions reactions of homoallyl alcohols have been exclusive for aryl iodides in the presence aryl bromides, as is the case with 2-iodobromobenzene and pent-4-en-2-ol.[5b]



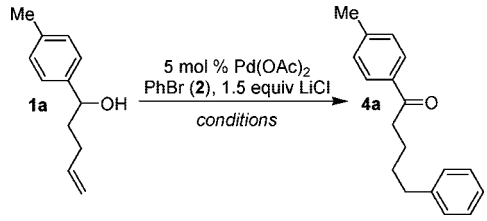
To better understand the scope and limitations of the process we observed and whether it was specific to our unusual system, we attempted to optimize the reaction conditions on the simple γ-hydroxy alkene derivative **1a** (Table 1). Starting with the same conditions as applied to our hydroxy alkene fragment, compound **1a** was successfully reacted with bromobenzene to give ketone **4a** (Table 1, entry 1). When the reaction was run for only half the time (1 h) under these conditions, conversion was still complete and the isolated yield improved to 44% (Table 1, entry 2).

An examination of reaction progress at different temperatures and times (Table 1, entries 2−6) revealed that an improved yield (72%) of product was possible at a lower temperarture (50 °C). However, at room temperature the reaction did not reach full conversion even after 24 h had elapsed. Changing the base from potassium carbonate to triethylamine or cesium carbonate resulted in lower conversion and higher formation of side products (Table 1, entries 7 and 8). Notably, the use of sodium bicarbonate as a base allowed complete conversion to product in 3 h and high yield of product in only 0.5 h at 50 °C (Table 1, entries 9 and 10). Further optimization of conditions was not achieved by variation of the solvent (Table 1, entries 12−14). As expected, the reaction did not proceed in the absence of lithium chloride (Table 1, entry 11), confirming its role as a ligand.

A small array of electron-rich and electron-poor fragments were coupled under the optimized conditions (Table 2). A range of substituents gave moderate to high yields of targets under optimized conditions when $n = 2$ (Table 2, entries 1−7). Notably, there was not any obvious trend or difference in reactivity between the systems of varied electronics. However, surprisingly, when smaller homoallyl substrates **1h**−**1j** ($n = 1$) were utilized, the yields fell significantly and the reaction produced traditional isomeric side products (Table 2, entries 8−10).

The rapid and efficient nature of the transformation when $n = 2$ coupled with the low yield and generation of isomers when $n = 1$ caused us to wonder if a mechanism other than the traditional palladium-catalyzed olefin migration[8] was needed

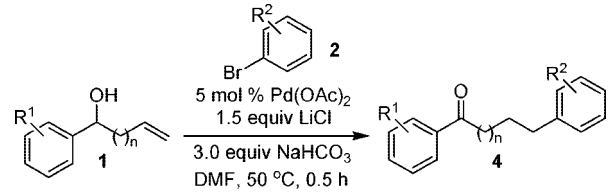
Table 1. Optimization of Reaction Conditions[a]



entry	ArBr equiv	time (h)	temp (°C)	base[b] (3 equiv)	solvent	yield % (convn)[c]
1	**1.2**	**2**	**100**	**K_2CO_3**	**DMF**	**34 (100)**
2	2.5	1	100	K_2CO_3	DMF	44 (100)
3	3.0	1	50	K_2CO_3	DMF	(90)
4	3.0	3	50	K_2CO_3	DMF	(>95)
5	**2.5**	**5**	**50**	**K_2CO_3**	**DMF**	**72 (100)**
6	2.5	24	25	K_2CO_3	DMF	(76)
7	2.5	3	50	TEA	DMF	(88)[d]
8	2.5	3	50	Cs_2CO_3	DMF	71 (95)
9	2.5	3	50	$NaHCO_3$	DMF	(>95)
10	**2.5**	**0.5**	**50**	**$NaHCO_3$**	**DMF**	**87 (100)**
11	2.5	0.5	50	$NaHCO_3$	DMF	(0)[e]
12	2.5	3	50	$NaHCO_3$	CH_3CN	(35)[d]
13	3.0	24	50	$NaHCO_3$	CH_3CN	(40)[d]
14	2.5	3	50	$NaHCO_3$	THF	(71)

[a] All reactions were run with alkene **1a** as the limiting reagent on a 1.00 mmol scale under N_2 atmosphere. [b] All bases and solvents used were anhydrous unless other specified. [c] The conversion was determined by LCMS monitoring using UV detection at 220 nM. [d] Significant amounts of side products formed. [e] LiCl was not added to the reaction.

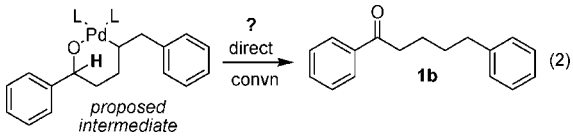
Table 2. Pd-Cataylzed Tandem Heck-Isomerization Reactions[a]



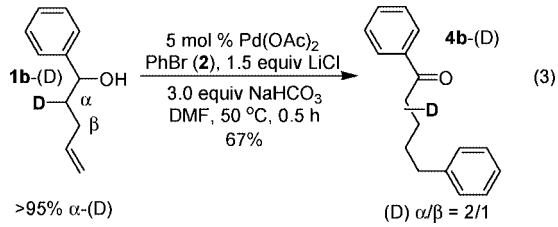
entry	R^1	R^2	n	product	yield %
1	4-Me	H	2	**4a**	87
2	H	H	2	**4b**	82
3	4-OMe	H	2	**4c**	71
4	4-CO_2Me	H	2	**4d**	59
5	H	4-OMe	2	**4e**	75
6	H	3-CN	2	**4f**	88
7	H	4-CO_2Et	2	**4g**	67
8	H	H	1	**4h**	21[c]
9	4-OMe	H	1	**4i**	23[c]
10	4-CO_2Me	H	1	**4j**	45

[a] All reactions were run with alkene as the limiting reagent on a 1.00 mmol scale under N_2 atmosphere. [b] All bases and solvents used were anhydrous. [c] Significant amounts of side products formed.

to rationalize the results when $n = 2$. One idea considered was whether or not some type of direct C−H abstraction or other process terminated the Heck addition, possibly stabilized through a six-membered palladacycle, facilitating the transposition of the olefin to the ketone (eq 2).

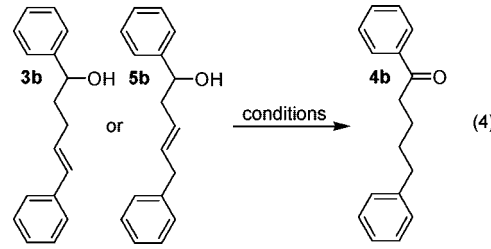


To test this hypothesis, deuterium-labeled substrate **1b** was synthesized and subjected to reaction conditions (eq 3).[9] Migration of the deuterium was observed yielding a 2:1 mixture of isomers of **4b**. If a direct C−H activation was the active pathway, the deteurium label should have remained unaffected. This result is consistent with formation of a traditional Heck adduct containing an olefin, followed by reversible hydropalladation−dehydropalladation as the mechanism of migration. This would eventually lead to enol formation (which is a thermodynamic sink as the enol tautomerizes to and is trapped as the ketone).



Although the deteurium labeling result was consistent with a stepwise isomerization mechanism, additional information was needed to support this result. When adducts **3b** and **5b**,[10] presumably initial adducts formed from the Heck reaction, were subjected to the optimized reaction conditions, less than 5% migration product (**4b**) was observed after 30 min (Table 3, entries 1 and 2). Prolonged reaction time did not significantly increase migration and resulted in the formation of multiple products (Table 3, entries 3 and 4). This result was not unexpected as the requisite palladium hydride would likely not be generated without the initial aryl bromide present. Attempts to apply modified conditions, whereby a palladium hydride−iminium complex is generated in situ,[11] still did not produce isomerization of **3b** to **4b**. These conditions did cause **5b** to isomerize to some extent, albeit with a complex mixture of side products. When a 1:1 ratio of aryl bromide versus palladium catalyst was added, no appreciable isomerization occurred (Table 3, entry 7). Addition of tetrabutylammonium bromide to the reaction also had no effect (Table 3, entry 8). The combination of these results suggest that although clearly olefin migration may be part of the mechanism, there must be additional nonclassical factors in the reaction at work to facilitate this relatively facile transformation.

Table 3. Probe of the Tandem Heck-Isomerization Mechanism



entry	reagent	conditions	convn (%)
1	**3b**	5 mol % $Pd(OAc)_2$, 1.5 equiv LiCl, $NaHCO_3$, DMF, 50 °C, 0.5 h	0
2	**5b**	5 mol % $Pd(OAc)_2$, 1.5 equiv LiCl, $NaHCO_3$, DMF, 50 °C, 0.5 h	0
3	**3b**	5 mol % $Pd(OAc)_2$, 1.5 equiv LiCl, $NaHCO_3$, DMF, 50 °C, 24 h	<5
4	**5b**	5 mol % $Pd(OAc)_2$, 1.5 equiv LiCl, $NaHCO_3$, DMF, 50 °C, 24 h	<5
5	**3b**	10 mol % Et_3N, 10 mol % Pd/C (5 mol % Pd), toluene, 80 °C	<5
6	**5b**	10 mol % Et_3N, 10 mol % Pd/C (5 mol % Pd), toluene, 80 °C	20[c]
7	**5b**	5 mol % $Pd(OAc)_2$, 5 mol % PhBr, 1.5 equiv LiCl, $NaHCO_3$, DMF, 50 °C, 1 h	~5
8	**5b**	5 mol % $Pd(OAc)_2$, 1.5 equiv LiCl, $NaHCO_3$, Bu_4NBr, DMF, 50 °C, 1 h,	<5

[a] All bases and solvents used were anhydrous unless otherwise specified, and reactions were run on 0.500 mmol scale under N_2 atmosphere. [b] The conversion to **4b** was determined by LCMS monitoring using UV detection at 220 nM. [c] A complex mixture of several adducts and starting material formed.

In conclusion, we have developed mild and efficient conditions that led in high yields to functionalized 1,5-diarylalkanone products. Notably, this protocol avoids the use of phosphine ligands and the formation of regioisomeric and cyclized products that are common during this type of transformation. We were able to apply this route to synthesize several arrays of otherwise difficult to access medicinal chemistry targets, the results of which will be reported in due course.

Supporting Information Available: Experimental details; ^1H and ^{13}C NMR, HRMS, and HPLC results for selected products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) Hay, M. B.; Hardin, A. R.; Wolfe, J. P. *J. Org. Chem.* **2005**, *70*, 3099.

(8) Migration by sequential hydropalladation−dehydropalladation.

(9) **1b**-(D) was synthesized with >95% incorporation of deuterium in four steps from benzaldehyde (see Supporting Information).

(10) Adduct **5b** was prepared by the procedure of Kimura, M.; Matsuo, S.; Shibata, K.; Tamaru, Y. *Angew. Chem., Int. Ed.* **1999**, *38*, 3386.

(11) Recently reported conditions to isomerize allyl alcohols to the corresponding carbonyl compounds: Coquerel, Y.; Bremond, P.; Rodriguez, J. *J. Organomet. Chem.* **2007**, 4805.