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Palladium-Catalyzed Sequential Alkylation−Alkenylation Reactions: New Three-Component Coupling Leading to Oxacycles

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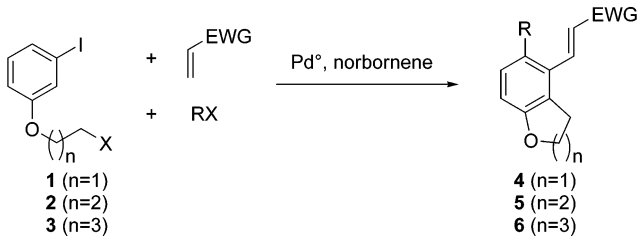
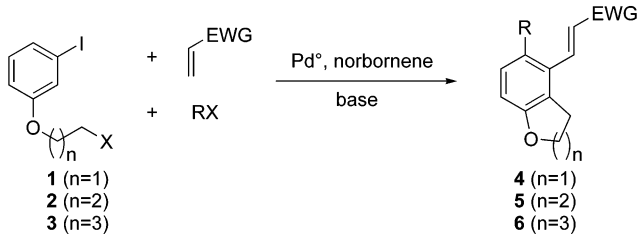
ABSTRACT



A new three-component domino reaction catalyzed by palladium was devised, producing polysubstituted bicyclic molecules in good yields from readily available substrates. The reaction conditions and the scope of the process were examined, and a possible mechanism is proposed.

Multicomponent reactions have proven to be a very elegant and rapid way to access complex structures from simple building blocks in a one-pot procedure.[1] Over the past few years, various sequential reactions have been developed using metal-catalyzed processes, most notably using palladium.[2] We became interested in this field and recently reported a modified Catellani method for the formation of fused aromatic rings from aryl iodides and bromoenoates under palladium catalysis in which two carbon−carbon bonds are formed in a one-pot process.[3,4] This procedure was extended to the formation of benzoxepines.[5] We now report a new three-component coupling using substrates **1**−**3**, an alkyl halide, and a Heck acceptor (Scheme 1), leading to heterocycles **4**−**6**.

Scheme 1. New Three-Component Coupling



This coupling is considerably more ambitious than the one previously described,[3,4] since both ortho positions of the iodoarene are to be functionalized by different alkyl halides,

(1) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136.
(2) Poli, G.; Giambastiani, G.; Heumann, A. *Tetrahedron* **2000**, *56*, 5959−5989.
(3) (a) Lautens, M.; Piguel, S. *Angew. Chem., Int. Ed.* **2000**, *39*, 1045−1046. (b) Lautens, M.; Paquin, J.-F.; Piguel, S.; Dahlmann, M. J. *Org. Chem.* **2001**, *66*, 8127−8134.
(4) This type of reaction was first reported by Catellani and co-workers: (a) Catellani, M.; Fagnola, M. C. *Angew. Chem.* **1994**, *106*, 2559−2561. Catellani, M.; Fagnola, M. C. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2421−2422. (b) Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem.* **1997**, *109*, 142−145. Catellani, M.; Frignani, F.; Rangoni, A. *Angew. Chem., Int. Ed. Engl.* **1997**, *36*, 119−122. (c) Catellani, M.; Mealli, C.; Motti, E.; Paoli, P.; Perez-Carreno, E.; Pregosin, P. S. *J. Am. Chem. Soc.* **2002**, *124*, 4336−4346. (d) Catellani, M. *Synlett* **2003**, 298−313.
(5) Lautens, M.; Paquin, J.-F.; Piguel, S. *J. Org. Chem.* **2002**, *67*, 3972−3974.

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and several byproducts (**A**, **B** and **C**) can be formed if the Heck reaction occurs before the catalytic cycle is completed (Figure 1). Oligomeric structures such as **D** and **E** can be

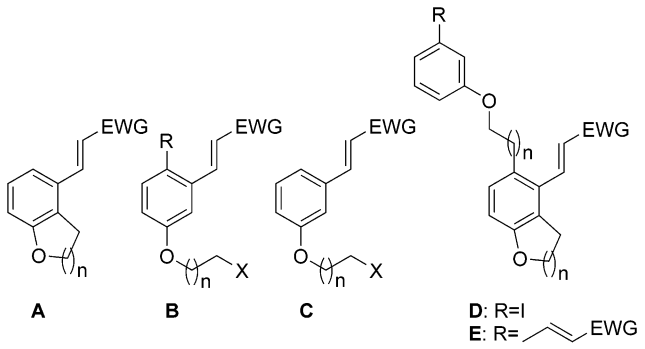
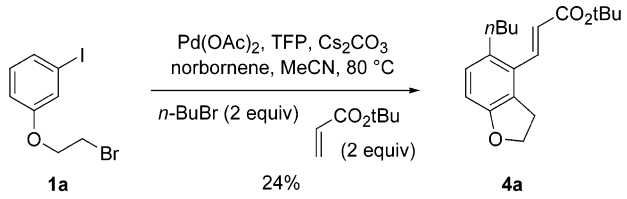


Figure 1. Possible byproducts.

generated if the substrate reacts with itself instead of reacting with the external alkyl halide. The value of this approach is in its brevity and ease of synthesis of the substrates, as well as the ease of variation of the external alkyl halide and the Heck acceptor. Access to five-, six-, and seven-membered oxacycles that are widely found in natural products and related compounds showing interesting biological and pharmaceutical properties[6,7] is now possible.

The first reaction was carried out on substrate **1a** using our previously optimized conditions:[3] $Pd(OAc)_2$ (10 mol %), 2-furylphosphine (20 mol %), norbornene (2 equiv), Cs_2CO_3 (2 equiv), *n*-BuBr (2 equiv), and *t*-Bu acrylate (2 equiv) in refluxing acetonitrile (Scheme 2). The desired product **4a**

Scheme 2

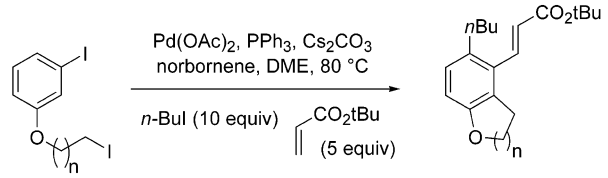


was obtained in 24% yield, showing that the reaction is viable and indeed highly selective. Trace amounts of compound **C** (where the Heck coupling occurs immediately) and of the oligomeric structures **D** and **E** were also observed.[8]

Many subtle factors influence the ratio and range of products, but the more important ones proved to be the phosphine ligand and the solvent. The use of alkylphosphine ligands or "naked" palladium species give only the Heck product **C**. With bidentate phosphines, **C** is still a major byproduct, but its formation can be greatly diminished using $Pd(OAc)_2$/PPh_3 in a ratio of 1:2.[9] **A** and **B** were never detected in the mixture, indicating that once carbopalladation of norbornene occurs, ortho alkylation is faster than decarbopalladation.[10]

Using iodoalkyl substrates[11] and the optimized conditions described in Scheme 3 ($Pd(OAc)_2$ (10 mol %), PPh_3 (20 mol

Scheme 3. Coupling Using Optimized Conditions



%), norbornene (5 equiv), Cs_2CO_3 (5 equiv), *n*-BuI (10 equiv), and *t*-Bu acrylate (5 equiv) in DME at 80 °C), the reaction gave the five-, six-, and seven-membered rings with good to excellent isolated yields.[12]

The proposed mechanism for this sequence is outlined in Scheme 4.[13] Pd(0) inserts into the Ar−I bond of **1** and then incorporates a norbornene and inserts into the most accessible ortho C−H aryl bond, forming a palladacycle. Elimination of HI by the base (here Cs_2CO_3) regenerates a tetracoordinated Pd(II). Oxidative addition of the external alkyl halide leads to a cyclic Pd(IV) species. A reductive elimination puts the alkyl group on the arene. An insertion into the second ortho C−H aryl bond occurs, followed by elimination of HX. Intramolecular oxidative addition of the alkyl halide present on the side chain takes place, followed by a reductive elimination that forms the five-membered oxacycle. Extrusion of norbornene, probably due to steric factors, gives an aryl-Pd(II) species. This intermediate undergoes a Heck reaction, leading to product **4**.

It is possible to envisage an alternative mechanism leading to **4**, where the first ortho alkylation would occur with the intramolecular alkyl halide and the second one with the

(6) (a) Fall, Y.; Vidal, B.; Alonso, D.; Gomez, G. *Tetrahedron Lett.* **2003**, *44*, 4467−4469. (b) Mukai, C.; Yamashita, H.; Hanaoka, M. *Org. Lett.* **2001**, *3*, 3385−3387. (c) Hoberg, J. O. *Tetrahedron* **1998**, *54*, 12631−12670. (d) Yasumoto, T.; Murata, M. *Chem. Rev.* **1993**, *93*, 1897−1909.

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(8) The moderate yield of **4a** can be explained by the instability of the substrate under the reaction conditions. Control experiments showed that after 24 h at 80 °C in the presence of Cs_2CO_3, 50% of the substrate **1a** is degraded, whereas **4a** is stable and can be recovered quantitatively.

(9) Furylphosphine and triphenylphosphine give comparable yields.

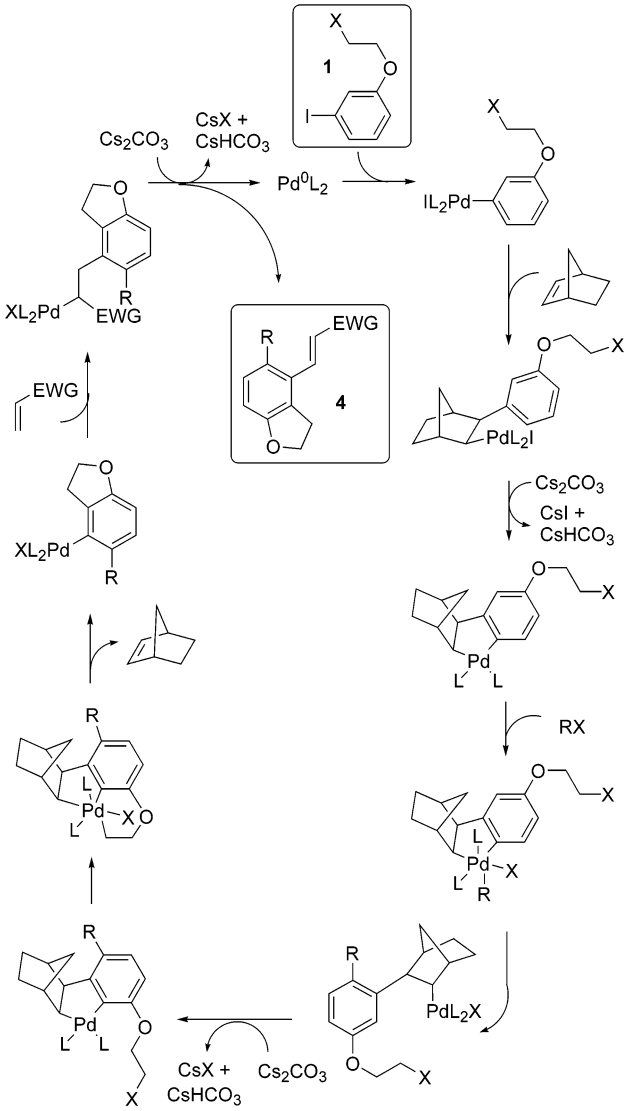
(10) Compounds **C**−**E** were isolated and characterized by ^{1}H NMR, mass spectrometry, HPLC, and UV. They are identical to the byproducts observed by HPLC of the crude reaction mixtures.

(11) Best yields were obtained with an alkyl iodide side chain. The bromo equivalent reacts more slowly, and part of the substrate decomposes before being transformed.

(12) Purity of the reagents proved to be important: the triphenylphosphine has to be recrystallized and the dimethoxyethane freshly distilled to obtain reproducible yields. Careful degassing of the reaction mixture prior to heating is necessary to avoid decomposition of the catalytic system before completion of the reaction.

(13) Proposed mechanism is based on mechanistic studies published by Catellani, Pregosin, and co-workers (see for example refs 4c and 4d) and on the byproducts that we observed in this reaction.

Scheme 4. Postulated Mechanism

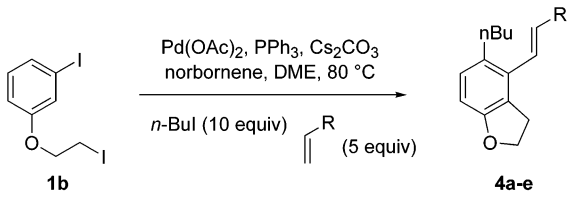


external alkyl halide. It seems difficult to distinguish between the mechanisms, and both pathways may be occurring simultaneously, but this alternative mechanism is less favorable because it requires the first C−H insertion to take place on the more hindered ortho position. The presence of small amounts of oligomeric compounds **D** and **E** (see Figure 1) in the reaction mixture, even when the reaction was done with a large excess of external alkyl halide, seems to indicate that the first ortho alkylation occurs very easily and on the less hindered position. This is also supported by the fact that the coupling conducted without external alkyl halide gives compounds **E** and **D** but no traces of **A**.

The generality of this sequence was demonstrated on the five-membered ring system, first by variation of the Heck acceptor, and then by variation of the external alkyl iodide.[14]

Changing from an ester (Table 1, entry 1) to an amide (entries 2 and 3) does not diminish the yield, even with a free NH present. However, the yield drops when a vinyl ketone with enolizable protons is used (entry 4). Using

Table 1. Variation of the Heck Acceptor

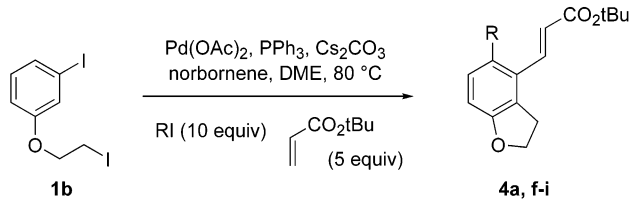


entry	R	product	yield (%)
1	CO_2tBu	**4a**	85
2	$C(O)NMe_2$	**4b**	60
3	C(O)NHtBu	**4c**	87
4	C(O)Et	**4d**	37
5	SO_2Ph		traces
6	CN	**4e**	40 (trans/cis 7:1)

acrylonitrile (entry 6) affords a nonseparable mixture of trans and cis isomers. The use of a sulfone (entry 5) totally inhibits the reaction, probably by coordination to palladium. Heck acceptors with additional α or *β* substituents on the double bond give poor yields and complex mixtures.

Variation on the alkyl iodide side chain is also possible. Iodides with a substituent in the α-position (*i*-PrI, entry 6) are too slow, but the reaction proceeds with substituents in the *β*-position (Table 2, entries 2 and 4). Chloride and oxygen

Table 2. Variation of External Alkyl Iodide



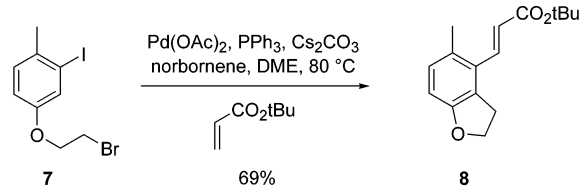
entry	RI	product	yield (%)
1	1-iodobutane	**4a**	85
2	1-iodo-2-methylpropane	**4f**	86
3	1-chloro-3-iodopropane	**4g**	53
4	2-iodomethyloxirane	**4h**	35
5	*tert*-butyl-(3-iodo-propoxy)-dimethylsilane	**4i**	60
6	2-iodopropane		mixture of products
7	iodomethane		

atoms on the chain are tolerated; even a sensitive functionality like an epoxide can be introduced, although with a lower

(14) **General Procedure for the Coupling Reaction.** 1-Iodo-3-(2-iodo-ethoxy)-benzene **1b** (75 mg, 0.2 mmol), the external alkyl iodide (2 mmol, 10 equiv), the Heck acceptor (1 mmol, 5 equiv), norbornene (96 mg, 1 mmol, 5 equiv), Cs_2CO_3 (326 mg, 1 mmol, 5 equiv), $Pd(OAc)_2$ (4.5 mg, 10 mol %), and PPh_3 (10.5 mg, 20 mol %) were dissolved in 2 mL of degassed dry dimethoxyethane. The mixture was flushed with N_2 and heated at 80 °C for 16 h. After cooling at room temperature, the mixture was diluted with diethyl ether, washed with water, dried over magnesium sufate, and purified by flash chromatography (silica, hexane/AcOEt).

yield. Introduction of a methyl group using MeI is not possible, but the methyl-substituted product can be obtained in good yield using substrate **7**[15] (Scheme 5).

Scheme 5. Ortho-Substituted Substrate



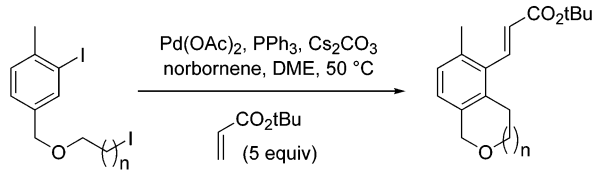
7 69% **8**

We extended the method to include a substrate based on a benzylic alcohol derivative instead of a phenol. Using our newly optimized catalytic system at a lower temperature of 50 °C, we were able to obtain cyclized products in satisfactory yields (Scheme 6).

In summary, we have shown that this new three-component coupling whereby three C−C bonds are formed in one pot is viable and tolerates a variety of functional groups. The palladium-catalyzed process efficiently produces interesting structures in only two steps from commercially available 3-iodo-phenol. Further exploration of this reaction is under way.

(15) Substrate **7** was obtained in good yield from the corresponding iodophenol. 3-Iodo-4-methyl phenol is not commercially available but can be obtained in two steps from 4-methyl-3-nitro phenol using literature procedures.

Scheme 6. Benzyl Alcohol Substrates



9 (n=1)
10 (n=2)

11 (n=1), 62%
12 (n=2), 61%

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Supporting Information Available: Experimental details and characterizations for substrates **1a**, **1b**, **2b**, **3b**, **7**, **9**, and **10**, for cyclized products **4a**−**i**, **5a**, **6a**, **8**, **11**, and **12**, and for byproducts **C**−**E** (with $n = 1$). This material is available free of charge via the Internet at http://pubs.acs.org.

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