ORGANIC LETTERS

2012
Vol. 14, No. 1
346–349

A Ridge Walk between Reaction Modes: An Unprecedented Pd-Catalyzed Domino Sequence of Diynyl-Substituted Bromoarenes

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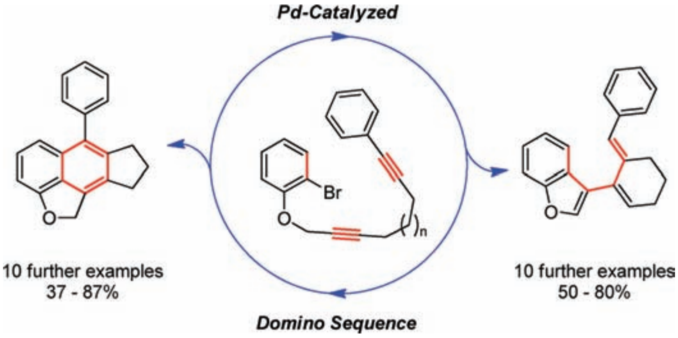
Received November 18, 2011

ABSTRACT



Diynyl-substituted bromoarenes underwent a novel Pd-catalyzed domino reaction to provide benzofurans, pyridinofurans, isochromenes, and indole derivatives. Slight changes of the substrate push the reaction in another direction resulting in benzene annulation.

Palladium-catalyzed transformations have emerged as some of the most powerful C–C coupling reactions during the past decades.[1] Commonly, catalytic cycles involve Pd(0)/Pd(II) species being easily converted into each other. The ability of Pd complexes to react with π systems leading to an insertion of either an alkene or an alkyne unit in the Pd–C bond (carbopalladation) sets the stage for a fast and efficient synthesis of a variety of complex target molecules.[2] Often the complexity gained in such a reaction can be further increased by offering several alkene or alkyne moieties resulting in multiple carbopalladation steps.[2] Depending on the substrate the species obtained during these processes might be prone to a variety of other reaction modes such as cross-coupling steps, pericyclic reactions, C–H activations, or CO insertions.[3] Commonly, the final step of such a Pd-catalyzed domino reaction[3–5] consists of a

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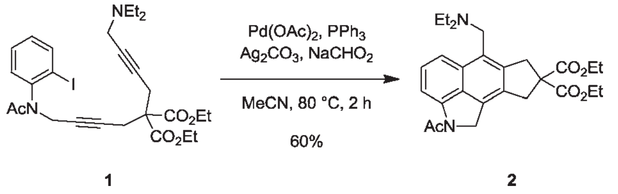
10.1021/ol2030923

reductive elimination of the Pd(II) species to regenerate the catalyst.[1,2]

Recently, we studied the formation of chromans and isochromans in a Pd-catalyzed domino reaction starting from carbohydrate derivatives.[6,7] To achieve this goal we utilized a twofold carbopalladation process followed by a ring closure and elimination of the Pd species. A similar annulation of a benzene ring was previously published by Grigg.[8] However, a very special pattern of heteroatoms proved to be the prerequisite for a successful outcome (see Scheme 1). Recently, also intermolecular twofold carbopalladations of diynes with aromatic cores were explored.[9]

We started our investigations with the diyne **3a** as a model compound to yield naphthalene derivatives similar to compounds obtained by Grigg. In contrast, our substrates consist of a butano tether between the two alkyne moieties. Furthermore, **3a** contains an *O*-linked diyne chain without any donor functionality at the terminus to force a ring closure by C–H activation.[10] While carrying out the reaction with **3a**, surprisingly, we detected as the only isolable product a molecule embodying a furan moiety and two alkene units. A benzene annulation, as originally anticipated, did not take place.

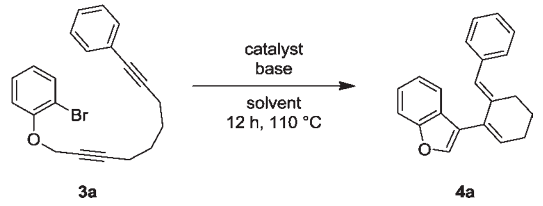
Scheme 1. Domino Reaction by Grigg et al.



Encouraged by this unexpected result we performed an intensive screening of various Pd sources, ligands, bases, and solvents. Some results of the optimization are compiled in Table 1. The most efficient catalytic system for the transformation of **3a** into **4a** turned out to be Pd(PPh$_3$)$_4$, CsF in toluene at 110 °C (entry 10).

With the optimal reaction conditions for **3a** in hand, the scope of this Pd-catalyzed domino process was explored with a variety of diynyl-substituted bromoarenes of type **3** (see Supporting Information for their syntheses). The arene was either a benzene or a pyridine derivative. The attachment of the diyne chain to the six-membered ring was optionally accomplished by a hydroxy functionality or an acetylated amine, but also hydroxymethyl groups were successfully employed. At the terminus of the diyne chain an aryl group, either electron-rich (with OMe groups) or electron-poor (with F substituents or even pyridine units), was installed. With the exception of one example (**3e**) the tether between the two triple bonds consisted of four methylene units. Our investigations revealed that the desired transformations proceeded smoothly and yielded the products in up to 80% yield. By utilizing this domino reaction we were able to access benzofurans **4a**–**4d**, isochromenes **4e**–**4f**, pyridinofurans **4g**–**4h**, and indoles **4i**–**4k** respectively (Scheme 2).[11] Limitations were observed in terms of terminal (H-substituted) diynes; in these cases no product formation was observed. With propano tethers between the alkyne moieties mostly inseparable mixtures of compounds were obtained (with the exception of **4e**).

Table 1. Optimization Studies for the Domino Reaction



Entry	Catalyst/ Ligand (mol %)	Base (equiv)	Solvent	Yield (%)
1	Pd(PPh$_3$)$_4$ (10)	HN*i*Pr (5)	MeCN	35
2	Pd(PPh$_3$)$_4$ (10)	HN*i*Pr (5)	dioxane	56[a]
3	Pd(PPh$_3$)$_4$ (10)	HN*i*Pr (5)	toluene	54
4	Pd(PPh$_3$)$_4$ (10)	LiOAc (5)	toluene	20
5	Pd(PPh$_3$)$_4$ (10)	Cs$_2$CO$_3$ (5)	toluene	75
6	Pd(PPh$_3$)$_4$ (10)	CsF (5)	toluene	75
7	Pd(OAc)$_2$ (10) PPh$_3$ (20)	Cs$_2$CO$_3$ (5)	toluene	52
8	Pd(OAc)$_2$ (10) dppe (20)	Cs$_2$CO$_3$ (5)	toluene	64
9	Pd(OAc)$_2$ (10) Josiphos (20)	Cs$_2$CO$_3$ (5)	toluene	62
10	Pd(PPh$_3$)$_4$ (10)	CsF (10)	toluene	80

[a] Inseparable impurities occurred.

To our delight, two structures of these domino products could also be proven unambiguously by X-ray

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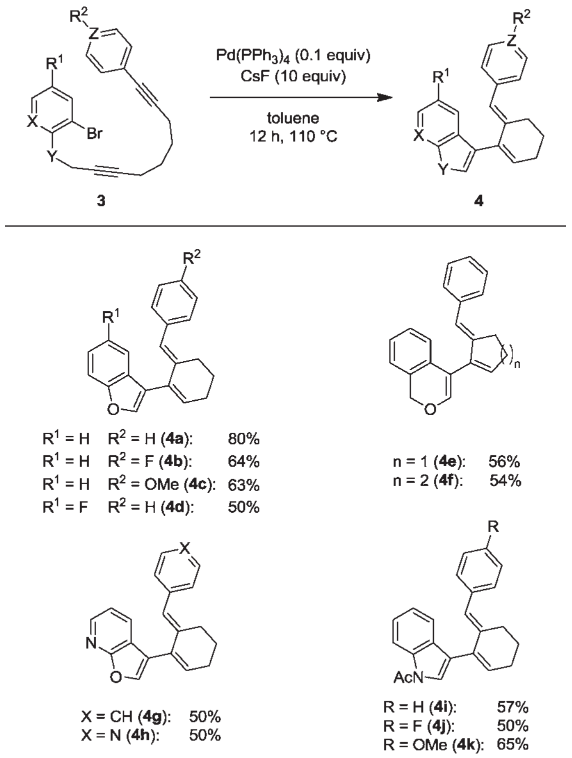
Scheme 2. Domino Reaction to Benzofurans **4a**−**4d**, Isochromenes **4e**−**4f**, Pyridinofurans **4g**−**4h**, and Indoles **4i**−**4k**



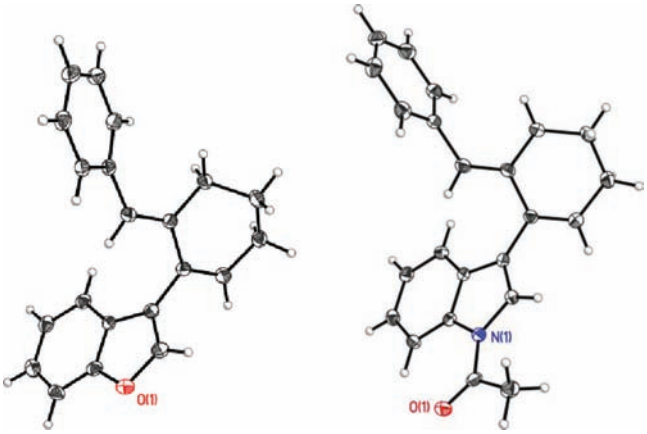
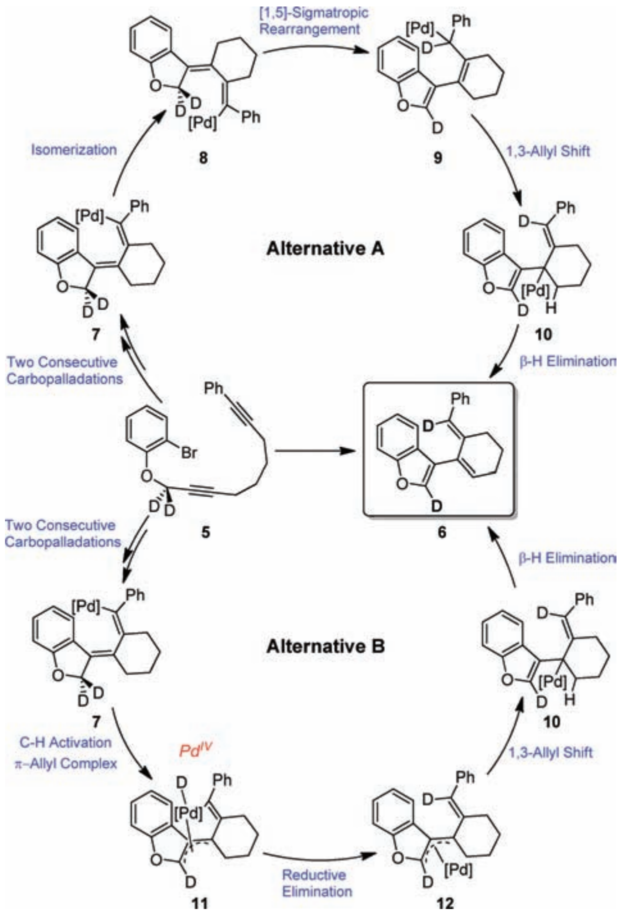


Figure 1. Crystal stucture of benzofuran **4a** (left) and indole derivative **4i** (right), depicted with anisotropic displacement parameters at the 50% probability level.

crystallographic analysis. Thermal ellipsoid plots of **4a** and **4i** are depicted in Figure 1.[12,13]

To elucidate the unusual outcome of this reaction mechanistically a deuterium-labeled diyne **5** was prepared. We were interested in whether the transfer of the deuterium from the deuterated methylene group next to the heteroatom takes place in an inter- or an intramolecular fashion. In total, 1 equiv of DBr or HBr is eliminated during the course of the reaction. In the case of an intermolecular reaction pathway a product mixture with D as well as H at the trisubstituted alkene would be the consequence. However, while carrying out the transformation with the deuterium-labeled analog **5** an entire transfer of deuterium from the methylene group to the alkene moiety in **6** was observed by NMR spectroscopy.

Scheme 3. Proposed Reaction Pathways for the Benzofuran Formation with Deuterated Substrate **5**: Alternatives A and B



Mechanistically, we suppose that the domino process is initiated by two consecutive carbopalladation steps following the oxidative addition of the Pd(0) species into the C−Br bond (Scheme 3). To explain the mechanistic outcome two different scenarios are conceivable: In the first one (Alternative A) a rotation of the tetrasubstituted double bond in intermediate **7** takes place. This assumption might be valid due to the strained geometry of the

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(13) The crystal data and experimental details for the X-ray measurements are listed in the Supporting Information. CCDC-849628 (**4a**), -849626 (**4i**), and -849625 (**14a**) contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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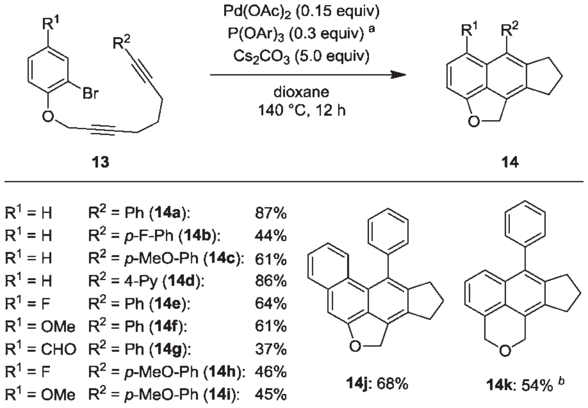
alkene and the temperature of 110 °C.[14] In the next step a [1,5]-sigmatropic rearrangement occurs affording **9**. A 1,3-allyl shift of the Pd and subsequent β-hydride elimination terminate the sequence. The distinct configuration of the exocyclic double bond in **6** might be attributed to the 1,3-allyl strain.

A second alternative would involve a Pd(IV) π allyl complex **11** being created by an oxidative addition into the C–D bond of **7**.[15–17] Reductive elimination would lead to a Pd(II) π allyl complex **12**. A migration of the Pd affords **10** consisting of benzofuran and a σ-bound Pd species. Finally, a β-hydride elimination would yield **6**.

Both scenarios are compatible with our observation that butano tethers yield the product whereas propano tethers are mostly associated only with traces of product. Because of the larger angle between the two exocyclic alkene units at a five-membered ring, the double bond, which has to change its configuration, is slightly less sterically hindered, thus less twisted and less prone to rotate. The same argument holds true for a Pd(IV) complex of type **11** which is more difficult to create in the case of a backbone consisting of a five-membered ring.

Scheme 4. Twofold Carbopalladation, C–H Activation Sequence To Yield Naphthalene Derivatives **14a**–**14k**[a,b]



R^1 = H	R^2 = Ph (**14a**):	87%
R^1 = H	R^2 = *p*-F-Ph (**14b**):	44%
R^1 = H	R^2 = *p*-MeO-Ph (**14c**):	61%
R^1 = H	R^2 = 4-Py (**14d**):	86%
R^1 = F	R^2 = Ph (**14e**):	64%
R^1 = OMe	R^2 = Ph (**14f**):	61%
R^1 = CHO	R^2 = Ph (**14g**):	37%
R^1 = F	R^2 = *p*-MeO-Ph (**14h**):	46%
R^1 = OMe	R^2 = *p*-MeO-Ph (**14i**):	45%

[a] $P(OAr)_3$: Tris(2,4-di-*tert*-butylphenyl)phosphite.[18] [b] Reaction conditions: Hermann-Beller catalyst (0.1 equiv),[19] Cs_2CO_3 (4.0 equiv), *n*Bu_4NOAc (3.0 equiv), DMF/MeCN/H_2O (5:5:1), 140 °C, 4 h, microwave irradiation.

Discouraged by the poor results with substrates embodying propano tethers we reinvestigated the reaction conditions. However, benzofuran derivatives could not be detected in significant amounts since the reaction pursues another path. With the use of a sterically highly encumbered phosphite ligand and $Pd(OAc)_2$ as a Pd source in dioxane at 140 °C the originally anticipated benzene annulation was observed in moderate to very good yields (Scheme 4). Electron-rich as well as electron-poor bromoarenes are suitable, and the same holds true for the aryl substituent attached to the terminal alkyne unit. Noteworthy, a bromonaphtalene derivative was successfully converted into the highly substituted phenanthrene **14j** demonstrating that also sterically hindered bromoarenes are appropriate starting materials for this domino reaction. The benzene annulation was also not hampered by the formation of a six-membered ring in the first carbopalladation as naphtalene derivative **14k** illustrates.

In summary, we found a novel domino reaction starting with diynyl-substituted bromoarenes. Benzofuran, pyridinofuran, indole, and isochromene systems were successfully obtained by this method in yields of 50–80%. The mechanistic scenario pursuing the two consecutive carbopalladation steps is not clear so far; either double bond isomerization followed by a sigmatropic rearrangement or the involvement of Pd(IV) species is assumed. A slight change of the substrates opened another reaction pathway resulting in the annulation of benzene moieties. Further investigations with respect to the underlying mechanism are underway.

Acknowledgment. This work was supported by the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie (Emmy Noether Fellowship and Dozentenstipendium to D.B.W.). M.L. thanks the State of Lower Saxony for a CaSuS Ph.D. Fellowship. D.S. thanks the DNSF for funding the CMC. The authors are grateful to Professor Dr. Lutz F. Tietze and Professor Dr. Armin de Meijere (both University of Göttingen) for helpful discussions.

Supporting Information Available. Experimental procedures, spectroscopic data, and NMR spectra for all new compounds. Cif files of **4a**, **4i**, and **14a**.[13] This material is available free of charge via the Internet at http://pubs.acs.org.

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