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Domino Reaction

Efficient Synthesis of Helical Tetrasubstituted Alkenes as Potential Molecular Switches: A Two-Component Palladium-Catalyzed Triple Domino Process**

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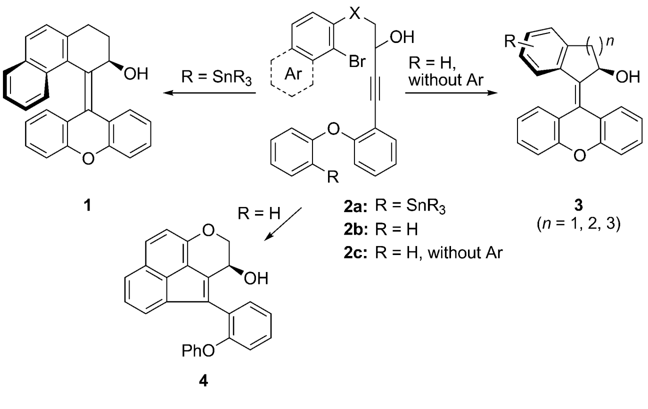
Dedicated to Professor Manfred Reetz on the occasion of his 70th birthday

The development of highly efficient ecologically and economically advantageous procedures for the synthesis of natural products and materials is a very important topic in organic chemistry. For this purpose we have utilized the domino concept, which allows the preparation of complex molecules starting from simple substrates in only a few steps.[1] The quality of a domino process can be correlated with the increase of complexity per step. Our research group and many others have used domino processes in the synthesis of numerous different compounds;[2] currently, the focus is on the use of catalytic reactions in these domino processes, especially transition-metal-catalyzed transformations, because classical cross-coupling reactions tolerate a variety of functional groups and reaction conditions.[3] However, one major drawback is the prerequisite for functionalization of one or both coupling partners. This issue could be avoided by using direct C–H functionalization of readily available substrates.[4] Thus, the design of novel domino reactions involving palladium-catalyzed transformations of unfunctionalized aromatic scaffolds is a promising approach.[5,14]

Herein, we describe a novel two-component Pd-catalyzed triple domino process, which includes a direct C–H functionalization as the last step, for the synthesis of helical tetrasubstituted alkenes. Helical alkenes, first described by Feringa and Wynberg,[6] represent a new class of compounds that has attracted great interest in the past decade owing to their high potential to act as analogues of mechanical machines and motors, as well as electronic devices, on the molecular level.[7] The reported structures are also of interest in the design of ligands for transition metals.[8] With respect to further applications as nanodevices the naphthalene part seems to be a key feature owing to its steric demand and its light-absorption properties.[9] A general and fast route to these compounds that allows diverse modifications is necessary for optimization of their properties; in this respect, domino reactions would be very suitable methods.

The first syntheses of tetrasubstituted alkenes by a domino process involving a C–H activation were described by the groups of Zhu[10] and Lautens.[11] We have prepared diastereo- and enantiopure tetrasubstituted alkenes (**1**) by a domino process consisting of a combination of a carbopalladation with a Heck[12] or a Stille reaction;[13] substrates of type **2a** were used for the domino process involving a Stille reaction. On the other hand, a carbopalladation/C–H activation domino process of substrates of type **2b** did not lead to the desired compounds but to acenaphthylenes **4** in excellent yield.[5b] This result can be explained by a proximity effect, that is, the hydrogen atom on the naphthalene moiety in **2b** is closer to the intermediately formed vinyl palladium moiety than the two *ortho*-hydrogen atoms on the phenyl ether group. By using substrates of type **2c**, in which the naphthalene moiety has been replaced by a phenyl ring, a carbopalladation/C–H activation domino process could be performed to give **3** in up to 94% yield (Scheme 1).[14] But the obtained alkenes are not suitable as potent molecular switches as their absorption spectrum does not cover a broad range of the wavelengths and they do not show bistability, owing to the lack of the naphthalene moiety.

We therefore investigated the use of substrates of type **5**, for which the undesired C–H activation cannot take place.



Scheme 1. Domino processes for the synthesis of **1**, **3**, and **4** from substrates **2**.

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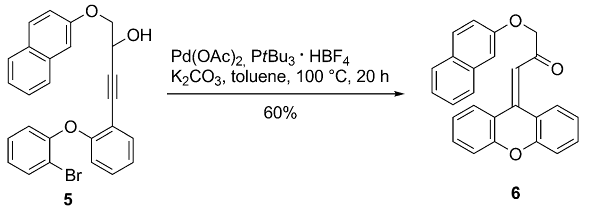
However, treatment of **5** with $Pd(OAc)_2$ in the presence of $PtBu_3{\cdot}HBF_4$ led to the ketone **6**; the vinyl palladium intermediate underwent a ß-hydride elimination and not the desired C–H activation (Scheme 2).



Scheme 2. Palladium-catalyzed transformation of **5** to give ketone **6**.

The problem could be solved by using alkynes of type **9** as substrates for the carbopalladation/C–H activation domino process, where a β-hydride elimination of the proposed vinyl palladium intermediate **10** could not take place. Thus, the desired helical alkene **11b** could be obtained in 31 % yield from alkyne **9a** in the presence of $Pd(OAc)_2$, PPh_3, and K_2CO_3. However, initial attempts to generate substrate **9a** by a Sonogashira reaction of the aryliodide **7b** and the alkyne **8a** under standard reaction conditions ($[PdCl_2(PPh_3)_2]$/CuI/NEt_3) led exclusively to the homocoupling product (Table 1, entry 1). Finally, by using a different base/solvent system we were able to obtain the desired product **9a** in good yield (Table 1, entry 2). But, when these reaction conditions were applied to substrates **7a** and **8d** the alkyne **9b** was formed in only 42 % yield; when standard reaction conditions were used the yield was 28 % (Table 1, entries 3 and 4). Fortunately, by applying copper-free conditions including a catalytic system consisting of $Pd(OAc)_2/PPh_3$ in the presence of nBu_4NOAc the alkyne **9b** was formed in 88 % yield (Table 1, entry 5).

As the yield of the domino process of **9a** was not satisfactory and to improve the efficiency of the whole reaction sequence we combined the carbopalladation/C–H activation domino process with the Sonogashira reaction to give a two-component triple domino process.[15–17] Pleasingly, reaction conditions similar to those employed for the Sonogashira reaction of **7a** and **8d** could be used for the domino transformations; the only changes required were a higher temperature and the use of DMF as the solvent. Under these reaction conditions a mixture of **7b** and **8a** gave the alkene **11b** in 67 % yield, and substrates **7a** and **8d** led to alkene **11j** in 77 % yield (Scheme 3).

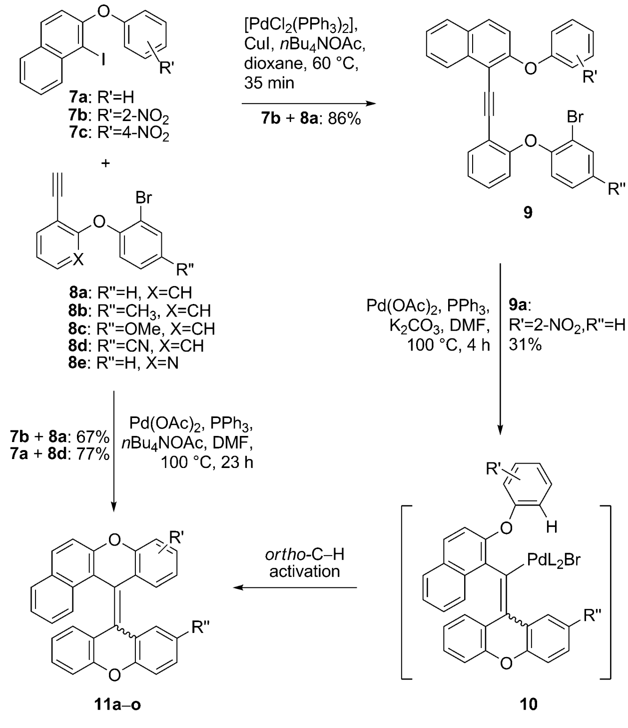
Table 1: Optimization of the coupling of aryl iodides **7** and alkynes **8** by a Sonogashira reaction.

Entry	Substrates	Reaction conditions	Result[a]
1	**7b**+**8a**	$[PdCl_2(PPh_3)_2]$, CuI, NEt_3, RT, 18 h	homocoupling product
2	**7b**+**8a**	$[PdCl_2(PPh_3)_2]$, CuI, nBu_4NOAc, 1,4-dioxane, 60 °C, 35 min	**9a** (86 %)
3	**7a**+**8a**	$[PdCl_2(PPh_3)_2]$, CuI, NEt_3, RT, 17 h	**9b** (28 %) + homocoupling product (46 %)
4	**7a**+**8d**	$[PdCl_2(PPh_3)_2]$, CuI, nBu_4NOAc, 1,4-dioxane, 60 °C, 19 h	**9b** (42 %) + homocoupling product
5	**7a**+**8d**	$Pd(OAc)_2$, PPh_3, nBu_4NOAc, 1,4-dioxane, 60 °C, 2.5 h	**9b** (88 %)

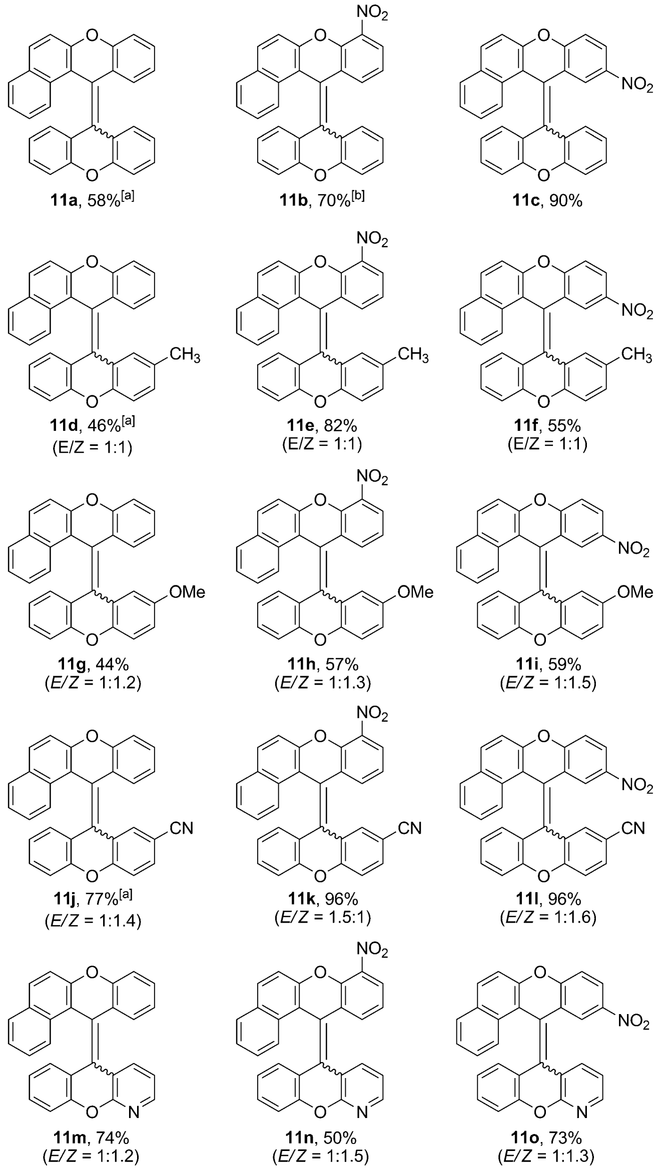
[a] Yield of the isolated product is given in parentheses.

To determine the scope and limitations of this reaction we used various aryliodides **7** bearing either a phenoxy (**7a**), a 2-nitrophenoxy (**7b**), or a 4-nitrophenoxy (**7c**) moiety to examine the influence of electronic and steric properties on the process (Scheme 4). Moreover, we also changed the substituents on the alkyne moiety (**8a–d**) and we even introduced a heterocyclic component (**8e**) in this part. In all cases we got good to excellent yields with up to 96 %, as found for **11k** and **11l**. In most of the examples the reaction mixtures were heated to 120 °C in a microwave reactor but, in a few cases, that is for the synthesis of **11a**, **11d**, and **11j**, the reaction mixtures were heated at 100 °C in an oil bath. Although it was our intention to keep the catalytic system as simple as possible, we also investigated the influence of other ligands; only in the reaction of aryliodide **7b** and alkyne **8a** to give **11b** was a slightly better yield achieved when 1,1′-bis(diphenylphosphanyl)ferrocene (dppf) was used as the ligand instead of PPh_3.

Products **11d–o** were obtained as mixtures of *E* and *Z* isomers, owing to fast isomerization of the double bond.[18] In most of the cases, the *Z* configuration, where the naphthalene moiety and the substituent on the lower part are opposite each other, is slightly preferred. Furthermore, the influence of the substituents on the lower and upper part of the substrates is not highly pronounced, although the use of substrates with electron-withdrawing groups, such as NO_2 and CN, seems to improve the yields, whereas the position of the



Scheme 3. Sonogashira reaction of aryl iodide **7b** and alkyne **8a** to give **9a** followed by a carbopalladation/C–H activation domino reaction (right). Triple domino process for the synthesis of helical alkenes **11** from aryl iodides **7** and alkynes **8** (left). DMF = *N*,*N*′-dimethylformamide.



11a, 58%[a]
11b, 70%[b]
11c, 90%
11d, 46%[a] (E/Z = 1:1)
11e, 82% (E/Z = 1:1)
11f, 55% (E/Z = 1:1)
11g, 44% (*E*/*Z* = 1:1.2)
11h, 57% (*E*/*Z* = 1:1.3)
11i, 59% (*E*/*Z* = 1:1.5)
11j, 77%[a] (*E*/*Z* = 1:1.4)
11k, 96% (*E*/*Z* = 1.5:1)
11l, 96% (*E*/*Z* = 1:1.6)
11m, 74% (*E*/*Z* = 1:1.2)
11n, 50% (*E*/*Z* = 1:1.5)
11o, 73% (*E*/*Z* = 1:1.3)

Scheme 4. Synthesis of alkenes **11a–o** by a Pd-catalyzed domino reaction of aryl iodides **7a–c** and alkynes **8a–e**. Reaction conditions: Aryl iodide (1.2 equiv), alkyne (1.0 equiv), Pd(OAc)$_2$ (20 mol%), PPh$_3$ (1.0 equiv), *n*Bu$_4$NOAc (3.0 equiv), dimethylformamide (1.0 mL, 0.03 mmol), microwave irradiation, 120 °C, 4 h. Yields given are of isolated products. [a] Reaction conducted at 100 °C in an oil bath. [b] The ligand dppf (1,1′-bis(diphenylphosphino)ferrocene) was used.

NO$_2$ group appears to be less important. Due to their instability a separation of the *E*/*Z* isomers was not possible; thus, by performing an EXSY-NMR experiment on compound **11e** the exchange rate between both isomers was measured to be $k = 0.06\,\mathrm{s}^{-1}$. With this data, the activation barrier of the isomerization could be calculated to $E_\mathrm{A} = 79.9\,\mathrm{kJ\,mol^{-1}}$.

Figure 1 shows the crystal structures of alkenes (*M*)-**11b** and (*P*,*Z*)-**11j**. Their folded conformation and helical shape around the central double bond is confirmed by single crystal X-ray analysis.[19,20]

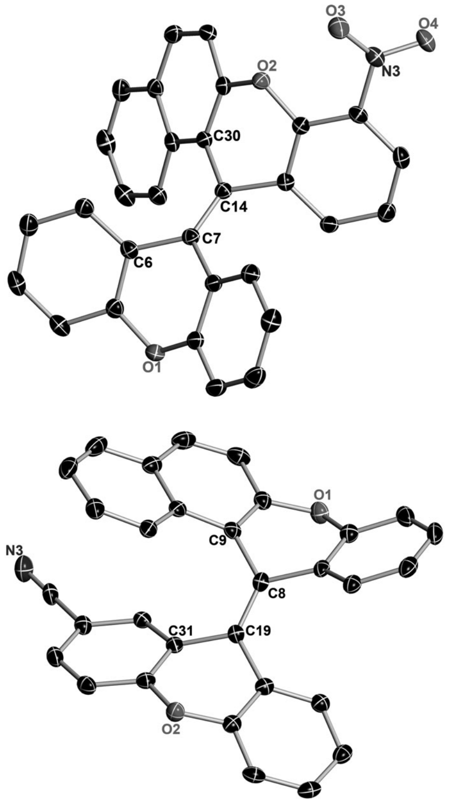


Figure 1. Crystal structures of alkenes **11b** (top) and **11j** (bottom). The hydrogen atoms are omitted for clarity and the anisotropic displacement parameters are depicted at the 50% probability level. Compounds **11b** (*M*/*P*) and **11j** (*M*/*P*,*Z*) crystallize as racemic mixtures in the solid state. Torsion angle for **11b** (C6-C7-C14-C30): 7.4(3)°. Torsion angle for **11j** (C9-C8-C19-C31): 6.9(3)°.

The synthesis of **7** and **8**, substrates for the triple domino process, could be achieved in a few steps. Aryliodide **7a** was prepared by a copper-catalyzed Chan–Lam-type coupling[21] of 2-iodo-1-naphthol and phenylboronic acid, whereas substrates **7b** and **7c** were synthesized from 2-iodo-1-naphthol and fluoronitrobenzene by a known aromatic substitution protocol to yield the corresponding aryliodides **7** in just one step.[22] The aromatic alkynes **8a–e** were obtained using procedures developed by us.[6b]

In conclusion we have developed a highly efficient and short route to various helical tetrasubstituted alkenes through a Pd-catalyzed domino process consisting of a Sonogashira reaction, a carbopalladation, and a direct C–H functionalization. Photochemical investigations of the synthesized alkenes are currently underway.

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Keywords: C–H activation · domino reactions · molecular switches · Sonogashira reaction · tetrasubstituted alkenes

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Communications

Domino Reaction

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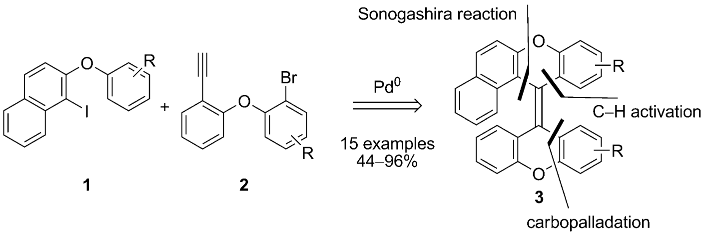
Efficient Synthesis of Helical Tetrasubstituted Alkenes as Potential Molecular Switches: A Two-Component Palladium-Catalyzed Triple Domino Process



1 **2** **3**

Fast and easy: Various helical tetrasubstituted alkenes were synthesized by a palladium-catalyzed domino process. The domino process consists of a Sonogashira reaction, a carbopalladation, and a direct C–H functionalization.