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Winding up Alkynes: A Pd-Catalyzed Tandem-Domino Reaction to Chiral Biphenyls

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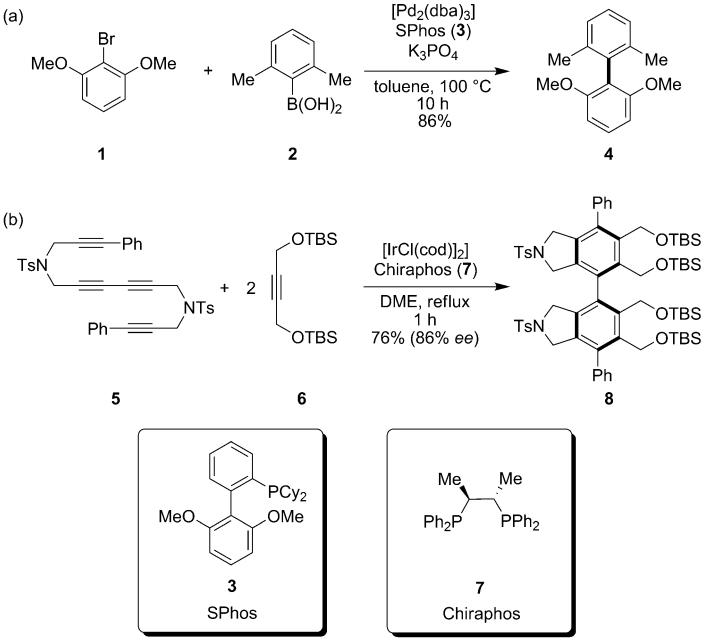
Dedicated to Professor Lutz F. Tietze on the occasion of his 70th birthday

The formation of biphenyls has comprised a pivotal part of C–C coupling chemistry since the seminal work of Ullmann in 1901.[1] The transformation using copper powder and aryl halides affords symmetrical biaryls and copper halide. Even sterically highly encumbered *o,o,o′,o′*-tetrasubstituted biaryls have been accessed using this old, but powerful synthetic procedure.[2] Studies with smaller chiral auxiliaries chelating the copper have led to a significant atroposelection and have been applied in various natural product syntheses.[3] Other methods to obtain *o,o,o′,o′*-tetrasubstituted biphenyls include oxidative couplings of highly functionalized phenol derivatives—a process that is similar to biochemical pathways furnishing biaryl-containing natural products.[4]

Modern techniques to reach biaryl cores rely on Pd-catalyzed Suzuki–Miyaura couplings to form the central C–C bond.[5,6] To couple sterically demanding substrates such as **1** and **2** is a particularly challenging issue. Tuning of steric and electronic properties of the ligands (e.g., **3**) proved to be necessary for a successful outcome (Scheme 1a).[7] Methods to generate chiral biaryl systems include enantioselective couplings employing chiral ligands; however, noteworthy are also diastereoselective procedures in which planar chirality (e.g., induced by $Cr(CO)_3$ complexes) or central chirality (e.g., induced by sulfoxides) is translated into the axial chirality of a biaryl axis.[8]

Another approach for the construction of biaryl systems takes a central diyne unit as starting point. Each of the two carbon–carbon triple bonds (e.g., of **5**) is reacted in a metal-catalyzed [2+2+2]-type cycloaddition (Scheme 1b) with an alkyne (e.g., **6**) or a nitrile.[9] In the former case chiral biphenyls such as **8** are formed, whereas the latter case gives 2,2′-bipyridines. The major difference to the above-mentioned coupling reactions is the construction of the aromatic core instead of the formation of the linking C–C bond between the arene units. For these cyclotrimerization reactions,



Scheme 1. (a) Suzuki–Miyaura coupling and (b) Ir-catalyzed [2+2+2]-cyclotrimerization to access *o,o,o′,o′*-tetrasubstituted biphenyls. The newly formed bonds are highlighted in bold.

cobalt and iridium catalysts have emerged as indispensable tools (Scheme 1b).[9,10]

Recently, we investigated a Pd-catalyzed domino process to access carbohydrate-derived chromans and isochromans.[11] The benzene annulation took place in such a way that oxidative addition of the catalytic Pd species into the C–Br bond of a bromo-olefin was followed by two subsequent carbopalladation steps and terminated by a cyclization step. This highly reliable, simple, and robust approach for the intra- and intermolecular annulation of persubstituted benzenes through a Pd-catalyzed domino reaction served as starting point when we sought for multiple carbopalladation processes leading to sterically encumbered biphenyls.

We intended to check our notion whether the same domino reactions might take place on both sides of a linear C_2 symmetric molecule. According to the nomenclature developed by Tietze, two domino processes at separate parts of the molecule are denominated as tandem-domino reactions.[12,13] In our case, the final cyclisation step of the

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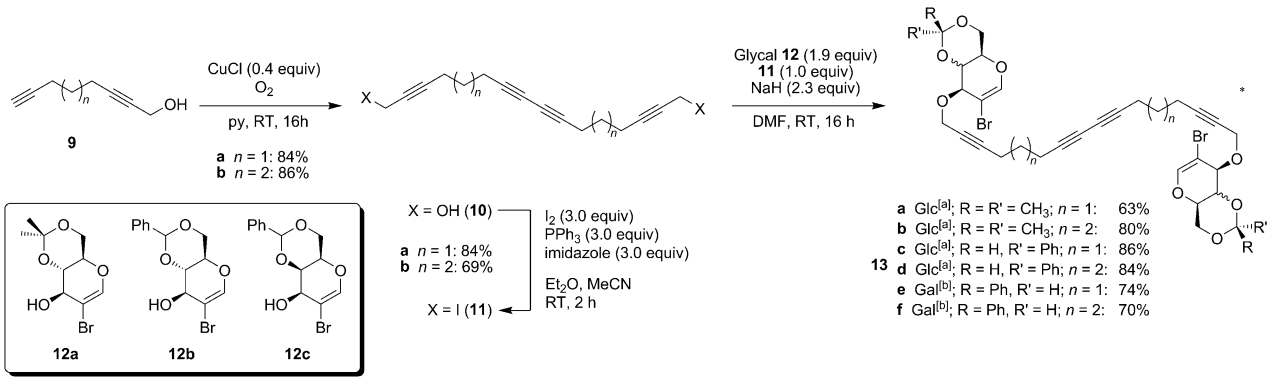


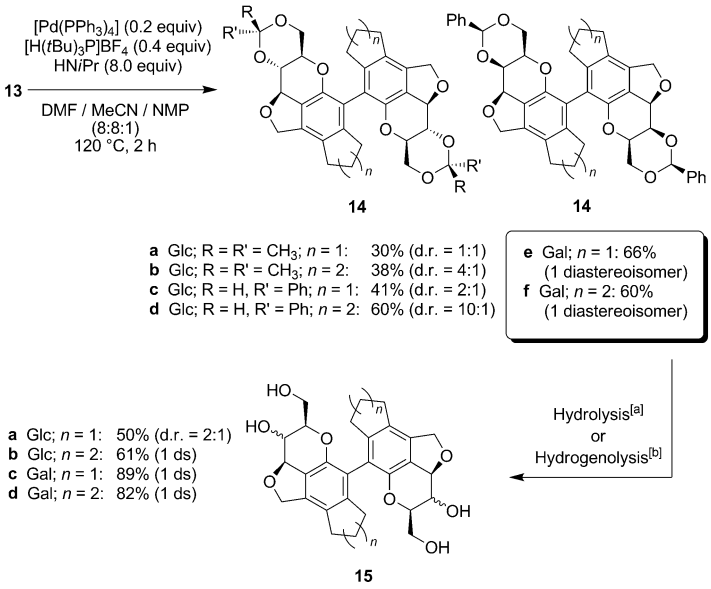
Scheme 2. Synthesis of disubstituted tetra-alkynes **13a–f** starting from octa-2,7-diyn-1-ol (**9a**) or nona-2,8-diyn-1-ol (**9b**). [a] Glc = glucose. [b] Gal = galactose.

second domino reaction would generate a chiral axis in a diastereoselective process.

The starting materials are easily obtained by using a facile synthetic strategy starting from 1,6-heptadiyne or 1,7-octadiyne (Scheme 2). After the conversion to the respective propargylic alcohol **9**,[14] easily obtained by the reaction of the monolithiated species with paraformaldehyde a copper-mediated Glaser–Hay coupling[15] by using atmospheric oxygen as oxidant results in the corresponding linear tetra-alkyne **10a** and **10b** in very good yields (84 and 86%, respectively). The two hydroxyl functionalities were converted into the iodides by a twofold Mukaiyama redox condensation reaction using iodine, triphenylphosphine, and imidazole. With the iodides as appropriate leaving groups in hand, the attachment of the tetra-alkyne chain to the carbohydrate derivatives was accomplished by a S_N2 reaction. As reaction partners, the suitably protected 2-bromoglycals **12**[11a] with a free hydroxyl group at C3 were employed for this step. To investigate the stereochemical and steric influences, two different 2-bromoglucals **12a** and **12b** (with isopropylidene and benzylidene protecting groups, respectively) and one 2-bromogalactal **12c** were used. Due to difficulties in preparing the 4,6-isopropylidene-protected bromogalactal we focused on the benzylidene protection in the latter case. Each of the three bromoglycals was combined with both the hexadecatetrayne **11a** and the octadecatetrayne **11b** to afford in total six different precursors **13a–13f**.

Next, we explored different reaction conditions for the anticipated tandem-domino process itself. The first attempts to use similar conditions as in the case of the intramolecular carbohydrate-derived chroman and isochroman formation were in vain. To our delight, it was possible to adjust the catalytic system we already developed for the intermolecular version of the chroman and isochroman formation. Optimal reaction conditions included the use of tetrakis(triphenylphosphine) palladium (20 mol%) as palladium source, tri(*tert*)butylphosphonium tetrafluoroborate (Fu's salt)[16] (40 mol%) as additional electron-rich and sterically encumbered ligand, and di-isopropylamine (8.0 equiv) as base in a mixture consisting of *N,N*-dimethylformamide, acetonitrile, and *N*-methylpyrrolidone (8:8:1) at 120°C.

We started our investigation of the anticipated tandem-domino sequence with the propano-tethered, isopropylidene-protected glucal derivative **13a** (Scheme 3). Unfortunately, we observed the desired biphenyl in only poor yield (30%) and without any diastereoselectivity of the resulting chiral axis (diastereomeric ratio (d.r.) = 1:1) to the desired biphenyl. By employing substrate **13b** with butano-tethers between the triple bonds, both the yield and diastereoselectivity could be slightly improved (38%, d.r. = 4:1). Changing the protecting group to the benzylidene acetal also improved the yield and the selectivity for both cases. Biphenyl **14c** was obtained in 41% yield and with a d.r. of 2:1. However, the improvement in the case of the butano-tethered biphenyl **14d** was significantly higher; the product was obtained in 60% yield and a diastereoselectivity of 10:1. Encouraged by these results, we examined the synthesis of bi-



Scheme 3. Tandem-domino reaction and corresponding deprotection to highly substituted chiral biphenyls. [a] Hydrolysis was performed for **15a** and **15b**. [b] Hydrogenolysis was performed for **15c** and **15d**, respectively.

phenyls with a galactal-derived backbone. Due to the orientation of all hydroxyls to the same side of the six-membered ring, even higher diastereoselectivities should be expected during this substrate-controlled process. Indeed, the anticipated products **14e** and **14f** were obtained in good yields (66 and 60%, respectively) and only one single diastereoisomer was formed. Converted to a single reaction step, such a yield means about 92% yield in every bond-forming transformation.

The cleavage of the protecting groups furnished the free hydroxyl functionalities of the native carbohydrate backbone. Palladium hydroxide on carbon (Pearlman's catalyst)[17] under atmospheric hydrogen pressure cleaved the benzylidene protecting group of the galactal-derived biphenyls **14e–14f**. The removal of the benzylidene-acetal in **14c–14d** proved to be a challenging task and could not be achieved by employing $Pd(OH)_2/C$. We found that acidic reaction conditions (by using trifluoroacetic acid) accomplished the hydrolysis of the acetals in moderate yield.[18] It is noteworthy that biphenyl **15b** was obtained as a single diastereoisomer after deprotection, although the protected biphenyl was used as a diastereomeric mixture of 10:1. Therefore we assume that the minor diastereoisomer is decomposed by the harsh reaction conditions.

For the mechanism of the domino transformation we propose a similar one as suggested in our previous work.[11] The domino sequence is initiated by an oxidative addition of the Pd^0 into the C–Br bond. Two subsequent carbopalladation reactions then lead to the formation of two rings and a 1,3,5-triene. The final cyclisation step affords the benzene unit and can be regarded either as disrotatory electrocyclic 6π-electron ring-closure or as C–H activation. A second cascade, independent from the first one, leads to the biphenyl in the same manner. Therefore, the process should be regarded as a tandem-domino reaction.

Our results show that the diastereoselectivity is controlled by the length of the tethering unit, the protecting group and, most importantly, the stereochemistry of the carbohydrate itself. Larger tethers as well as sterically more demanding protecting groups favour the formation of a single diastereoisomer. This effect is further enhanced by employing galactose-derived compounds, in which larger substituents point into the same direction. The assumption that the formation of the chiral axis is controlled by steric effects is depicted in Figure 1. We suggest that the S_a configuration of the chiral axis would cause a disfavoured arrangement. Both phenyl substituents point to each other and force strong steric repulsion. On the other hand, the R_a configuration would result in a less-hindered arrangement. The bulky phenyl groups do not face each other showing almost no interaction.

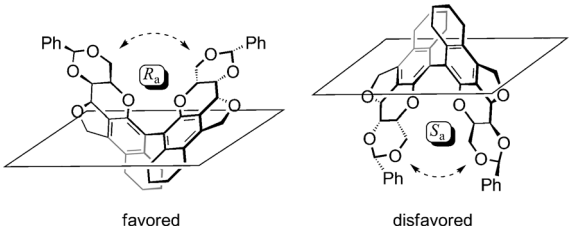


Figure 1. Proposal with respect to the steric interactions in the two possible biphenyl diastereoisomers (favoured and disfavoured scenario).

In conclusion, we have developed a Pd-catalyzed tandem-domino approach for the synthesis of highly substituted biphenyls. Two independent sequences consisting of a twofold carbopalladation and cyclization led to the desired products. Six carbon–carbon bonds, six rings, and one chiral axis are formed in one step. In several cases the axial chirality between both newly formed benzene units could be adjusted with high diastereomeric ratios. The stereogenic information is induced by the stereochemistry of the carbohydrate backbone and can further be increased by the use of bulky protecting groups. Such a Pd-catalyzed approach using tetraalkynes and terminal bromo-olefins might become a valuable tool for the preparation of complex biaryls.

Experimental Section

General procedure: The alkynylated bromoglycal **13** (0.10 mmol, 1.0 equiv) was dissolved in a mixture of DMF/MeCN/NMP (5.0 mL, 5.0 mL, 0.6 mL). $[Pd(PPh_3)_4]$ (20 μmol, 0.2 equiv), $[(tBu)_3PH]BF_4$ (40 μmol, 0.4 equiv) and diisopropylamine (0.80 mmol, 8.0 equiv) were then added. The reaction was stirred in a microwave reactor for 2 h at 120 °C. The absorption level was set to "very high" and the prestirring time to 10 s. The reaction was stopped by the addition of brine. The aqueous layer was extracted three times with EtOAc. The combined organic layers were washed with water and brine, and dried over Na_2SO_4. The solvent was removed by rotary evaporation and the residue was purified by silica gel column chromatography (pentane/EtOAc) to afford biphenyl **14** as a colorless to slightly yellow solid.

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Keywords: biphenyls · carbohydrates · chromans · domino reaction · palladium

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