CARBOPALLADATION CASCADES TO ACCESS HETEROCYCLIC COMPOUNDS: OUR ENDEAVORS

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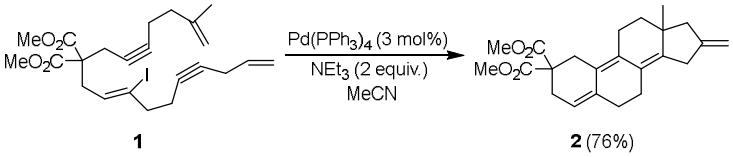
Abstract. *Carbopalladation cascades are well suited to create molecular complexity in a single reaction step. Alkyne moieties tethered by alkano units with embedded heteroatoms allow the formation of heterocyclic compounds by establishing carbon-carbon bonds during the carbopalladation process. Highly conjugated systems such as benzene rings, unsaturated dispiranes, dibenzopentafulvalenes are constructed by such an approach. Besides well-known syn-carbopalladations also formal anti-carbopalladations are discussed in which an alkyne moiety is formally attacked from opposite sides to yield a trans-substituted olefin.*

Contents

1. Introduction

Cantus firmus of this account is the carbopalladation of alkynes.[1] Starting from a CC triple bond the addition of an organopalladium species leads to a CC double bond while generating a new CC single bond and again an organometallic species with a Pd-C bond. A simple consideration of bond energies of CC single, CC double and CC triple bonds demonstrates that such a process releases about 35-40 kcal/mol. This relatively high thermodynamic driving force sets the basis for all carbopalladation cascades. It was the group of Ei-ichi Negishi in the late 1980s which first exploited this amazing chemistry.[2,3] They used acyclic precursors such as **1** which did undergo a carbopalladation cascade to afford tetracyclic steroid derivatives of type **2** (Scheme 1). Later on, the group of Armin de Meijere used similar cascades to generate arene units from acyclic molecules.[4] However, carbopalladation cascades using CC triple bonds are still a hot topic. The

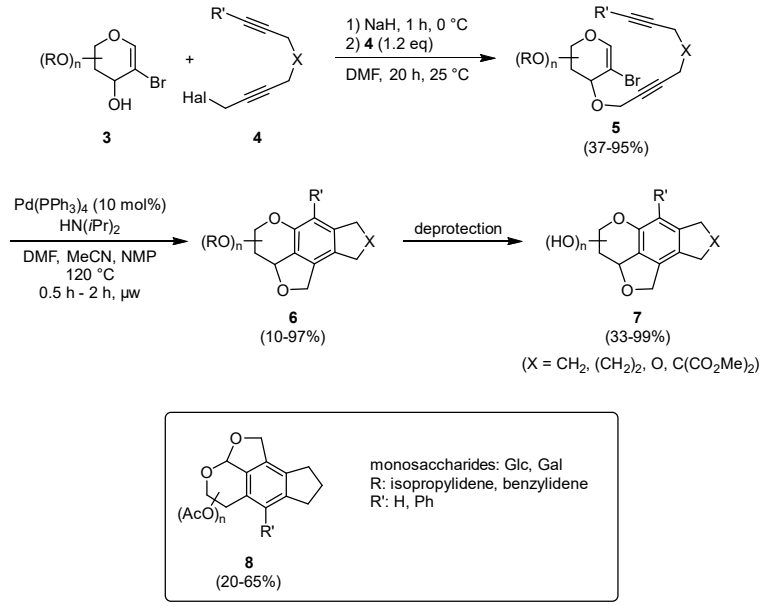
main protagonists in this field today are the groups of Jean Suffert,[5-7] Edward Anderson,[8-10] Lutz F. Tietze,[11,12] Bernd Schmidt[13] and X. Luan.[14,15] Although these reactions generate carbon-carbon single bonds they are ideally suited to access heterocyclic compounds when using heteroatoms in the chain connecting the alkyne units. In this personal account our endeavors in the area of cascade or domino reactions[16,17] which commenced in the field of carbohydrate chemistry are summarized.



Scheme 1. Negishi's synthesis of the steroid skeleton **2** starting from acyclic precursor **1**.

2. A carbohydrate-based chroman and isochroman synthesis

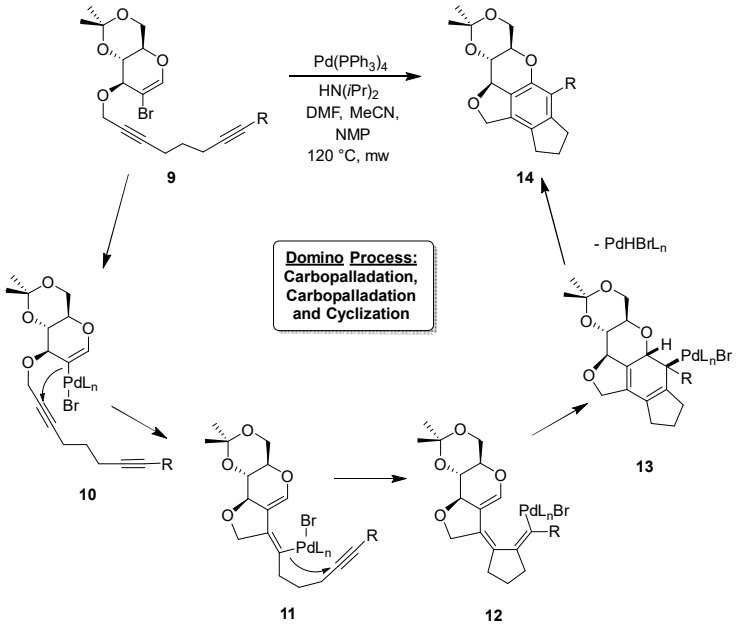
In 2009, because of a collaboration with medicinal chemists, we became interested in the synthesis of a library of enantiomerically pure chromans and isochromans. Commonly, chromans are accessed by starting from benzene derivatives annulating the pyran moiety in several steps. Of course, such a procedure sets the challenge to perform enantioselective reactions in case chiral and enantiomerically pure chromans are needed. To circumvent these obstacles our approach was to build up the benzene core instead of the pyrane core.[18] An appropriate pyrane core should be starting material. Since we wanted to have several stereochemically diverse target molecules modified monosaccharides would be the ideal precursors (Scheme 2).



Scheme 2. Chroman and isochroman synthesis via a carbopalladation cascade.

The modification should take place in such a way that there is a starting point for a carbopalladation cascade (e.g. a C-Br bond) and the possibility for an annulation. Therefore, easily available 2-bromoglycals **3** were employed as educts. They are accessed from commercially available glycals via a bromination-elimination procedure. After the installation of suitable protecting groups at 4- and 6-hydroxyls attachment of various dialkyne chains **4** was carried out affording a broad variety of different precursors **5** for the desired carbopalladation cascade (Scheme 2). The synthesis of the corresponding propargylic halides **5** was achieved starting from symmetrical dialkynes, e.g. from heptadiyne or octadiyne. The coupling was conducted either by nucleophilic substitution of the free 3-hydroxyl group with the propargylic halide or via Ferrier I reaction (in the case of isochroman precursors). Optimal conditions for the carbopalladation cascade comprise the use of a palladium(0) catalyst such as ($Pd(PPh_3)_4$) under microwave irradiation. To access analogous isochromans **8** a similar approach was followed. An S_N2' was employed to attach a diynol to the pseudoanomeric center of the 2-bromoglycal paving the way for the carbopalladation cascade.[18]

Starting point of the cascade is an oxidative addition of the Pd catalyst into the C-Br bond of **9** to form **10**. Two subsequent carbopalladations form a 1,3,5-triene system **12** being prone to 6π-electrocyclization which takes place in a disrotatory fashion, followed by β-hydride elimination. The latter reaction can easily take place since the electrocyclic ring-closure locates Pd and hydrogen on the same face of the six-membered ring. A mechanistic scenario is provided in Scheme 3.[18,19]



Scheme 3. Proposed mechanism of the carbopalladation cascade to yield chromans.

In almost all cases the domino reaction proceeded smoothly; different sugars were used as modified monosaccharide building blocks. Galactose, glucose, rhamnose and arabinose as well as various substituted diyne chains were employed. Alkyl-, aryl- and silyl-substituted alkyne moieties were successfully

incorporated and led to hexasubstituted benzene rings. But also terminal alkyne units allowed the reaction and led to pentasubstituted benzene moieties (Figure 1). The favorable type of attachment of the diyne chain was via an ether linkage, much poorer yields were obtained by an attachment via an ester linkage. A rationalization might be the reversal of polarity of the C-C triple bond disfavoring the first carbopalladation.

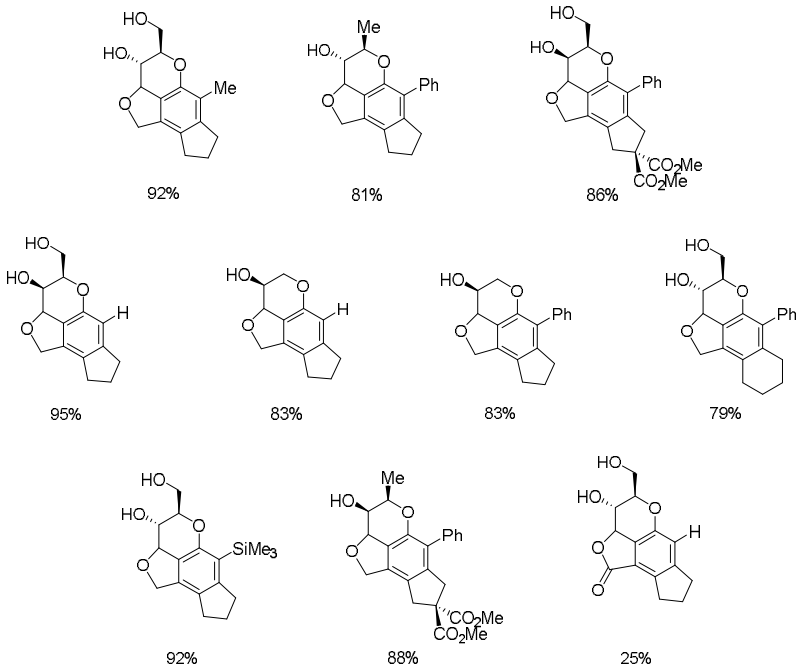
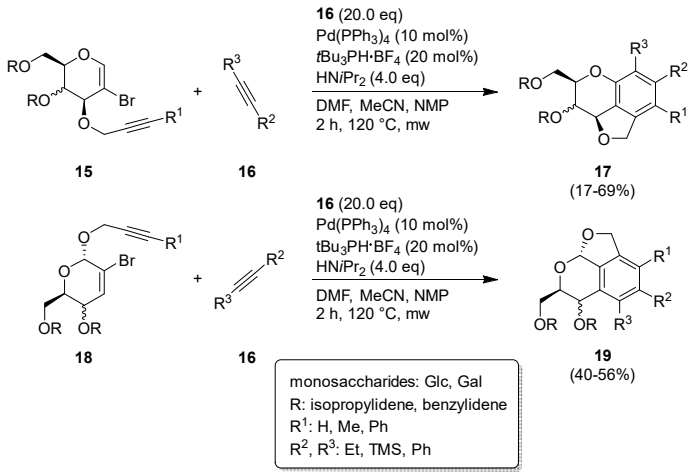


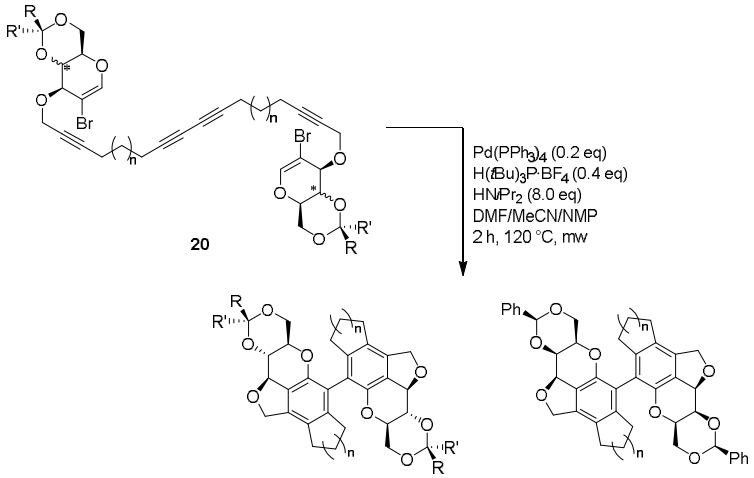
Figure 1. Some of the chromans (in deprotected form) being accessed by the carbopalladation cascade. Given are the yields of the domino sequence starting from the respective diynes.

A more modular approach is based on the respective intermolecular reaction. Instead of a diyne chain two separate alkynes might be used. The attachment of the first alkyne to the sugar moiety was performed as already described above by a simple propargylic substitution. Best results for the intermolecular carbopalladation cascade were obtained using a large excess (10-20-fold) of the external alkyne in a highly concentrated reaction mixture.[20] The addition of Fu' s salt generating in the presence of base the very electron-rich tris(*tert*-butyl)phosphine proved to be crucial; otherwise the yield of chromans was below 10%. The variation of the carbohydrate part and the differentiation of the attached alkyne as well as the external alkyne provided a broad range of different products. In order to demonstrate the generality and applicability of this approach both, chromans and isochromans, were synthesized in such a way (Scheme 4). Glucose- and galactose-derived carbohydrates moieties as well as alkynes with silyl-, alkyl- and aryl-substitution were utilized. We obtained good yields up to 60% for symmetrical external alkynes such as bis(trimethylsilyl)acetylene or 3-hexyne. The yield dramatically dropped down when sterically encumbered alkynes such as tolane were employed as external alkynes.[20]



Scheme 4. Intermolecular carbopalladation cascades to form chromans and isochromans.

A formal Glaser coupling of the H-terminated starting materials for the intramolecular version would yield compounds such as **20** with attached bromoglycals at both termini. Two independent carbopalladation cascades should lead to biphenyl structures with a chiral axis.[21] Thus, the respective linear C_2-symmetric precursor was subjected to similar reaction conditions. The anticipated process took place starting independently from both termini. The final cyclization step of the second carbopalladation cascade generates a chiral axis since persubstituted biphenyls are generated (Scheme 5). This type of biphenyl formation was investigated with glucose and galactose units as well as varying tether lengths.



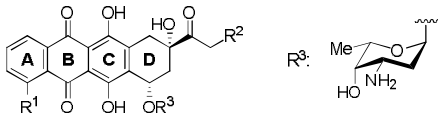
21a (Glc, R = R': CH_3, n: 1, 30%, *dr* = 1:1)
21b (Glc, R = R': CH_3, n: 2, 38%, *dr* = 4:1)
21c (Glc, R: H, R': Ph, n: 1, 44%, *dr* = 2:1)
21d (Glc, R: H, R': Ph, n: 2, 60%, *dr* = 10:1)
21e (Gal, n: 1, 66%)
(1 diastereoisomer)
21f (Gal; n: 2: 61%)
(1 diastereoisomer)

Scheme 5. Twofold carbopalladation cascade to access carbohydrate-derived biphenyls.

Best yields (61-66%) and diastereoselectivities (only one diastereoisomer) were obtained with galactose units bearing benzylidene protecting groups. In contrast, glucose units protected with isopropylidene groups afforded the desired compounds in only moderate yields and worse diastereoselectivities.

3. Towards the synthesis of anthracycline aglycone

The success of these carbopalladation cascades provoked us to investigate the synthesis of anthracycline mimics by a similar reaction design. Anthracyclines belong to the natural product class of aromatic polyketides. They were first isolated from the order of *Streptomycetales* by Brockmann in 1963, who described them as red to orange dyes.[22,23] Their structural features consist of a fourfold annulated ring system including two benzene moieties. The substitution of the D-ring bares several functional groups, i.e. two alcohol groups and a glycosylated 2,6-didesoxy sugar (Figure 2). These carbohydrates functionalities are of highest importance for the biological and pharmaceutical activity of these natural products.[24,25] Their main application relies on the treatment of different types of cancer such as leukemia, lymphomas, breast, uterine, ovarian and lung cancer.

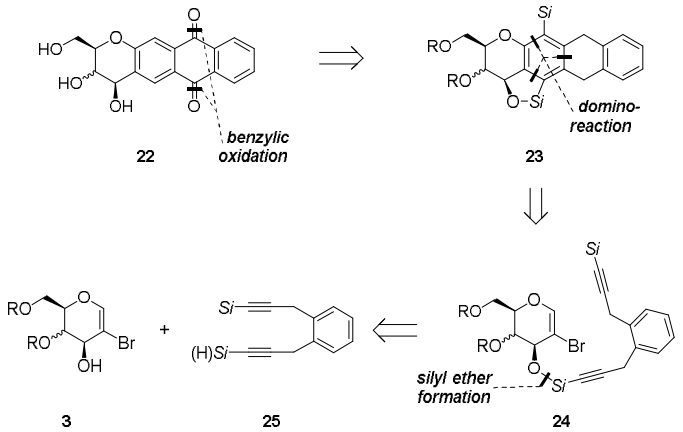


Daunomycin (**a**): R^1 = OMe, R^2 = H
Doxorubicin (**b**): R^1 = OMe, R^2 = OH
Idarubicin (**c**): R^1 = H, R^2 = H

Figure 2. Several naturally occurring anthracycline antibiotics.

To prepare respective mimics from monosaccharides, the D-ring was exchanged by a 2-bromoglycal and instead of an aliphatic dialkyne chain an aromatic diyne **25** was employed. Furthermore a silyl ether moiety should serve as tethering unit between both building blocks. The fourfold annulated ring system should be obtained in one single step, by making use of a carbopalladation cascade as in the synthesis of chromans.[26] This powerful transformation allows for the formation of the B- and C-ring in **22** and consequently the annulation of all four cycles as the retrosynthetic analysis depicted in Scheme 6 demonstrates.

Whereas the carbopalladation cascade as the key reaction did not cause any difficulties several other transformations proved to be rather challenging. In a very first step compounds of type **25** had to be synthesized (not shown). For this purpose, two different silylalkynyl groups were installed to appropriate benzylic iodides. In order to run an intramolecular and regiochemically defined carbopalladation process the 2-bromoglycal and the dialkyne have to be linked to each other. This transformation proved to be a highly demanding task; several different reaction conditions were explored, but only one afforded the desired product in sufficient yield. Thus, terminal silane **25** was transformed into the respective silabromide with a solution of elementary bromine in tetrachloromethane. The emerging reactive species was treated with the corresponding alcohol and triethylamine as base to furnish the coupling product **24**.



Scheme 6. Retrosynthetic analysis of anthracycline aglycone mimics. Si: any silyl group.

Utilization of the already known conditions for such a domino reaction provided the fourfold annulated ring system of type **23** in only one step and very good yield. The best yields were obtained for the TMS-substituted substrates.[26]

The silyl groups at the benzene ring were cleaved by the action of acetyl chloride in anhydrous methanol and tetrabutylammonium fluoride to afford **26** and **27**, respectively. A Tamao-Fleming like oxidation to generate the desired phenol derivatives did not take place. Commonly, these oxidative cleavage reactions require sp^3-hybridized carbon atoms which form the C-Si bond. To install the anthraquinone moiety by oxidation of the benzylic positions it was crucial to reprotect the alcohol functionalities. After TBS-protection of the hydroxyl moieties to furnish **28** an iron(III)-catalyzed benzylic oxidation proceeded smoothly with yields up to 70%. Finally, hydrolysis of the protecting groups generated the desired anthracycline derivatives **22** based on a carbohydrate skeleton (Scheme 7).[26]

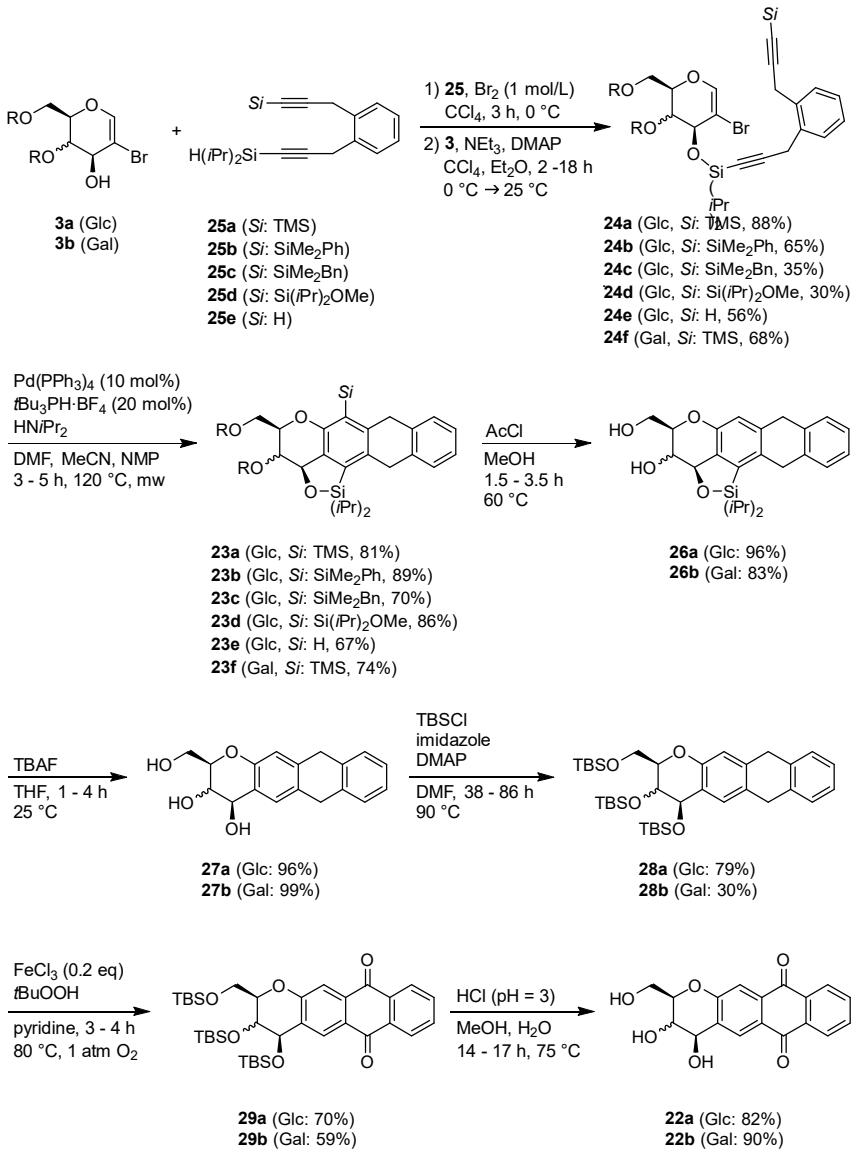
4. Dispiro compounds as unexpected products of helicene formation

The success in carbopalladation chemistry leading to benzene units led my group to develop carbopalladation cascades which should afford oligoene-based helicenes.[27]

Substrates such as **30** were in the focus which were envisioned to undergo a three-fold carbopalladation with the three alkyne units. A Stille cross-coupling reaction should terminate the process as fourth step of the cascade. However, after having conducted the transformation a dispiro compound **31** was obtained.

A fifth step after the carbopalladation/Stille cascade occurred: a 6π-electrocyclization (Scheme 8).[28] It is noteworthy that the product is the result of a conrotatory ring-closure being in contrast to the Woodward-Hoffmann rules which suggest a disrotatory process.

However, due to steric bulk a disrotatory process would be very unfavorable; thus, the system evades to a formally forbidden pathway. Respective oligoene-based helicenes were obtained by slightly changing the reaction design.[27] There are not discussed in this account since they do not comprise any heterocyclic entities.



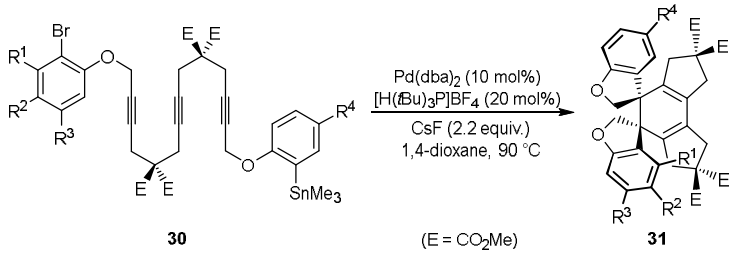
Scheme 7. Silyl ether coupling, carbopalladation cascade and derivatization into anthracycline derivatives.

5. Preparation of dibenzopentafulvalenes

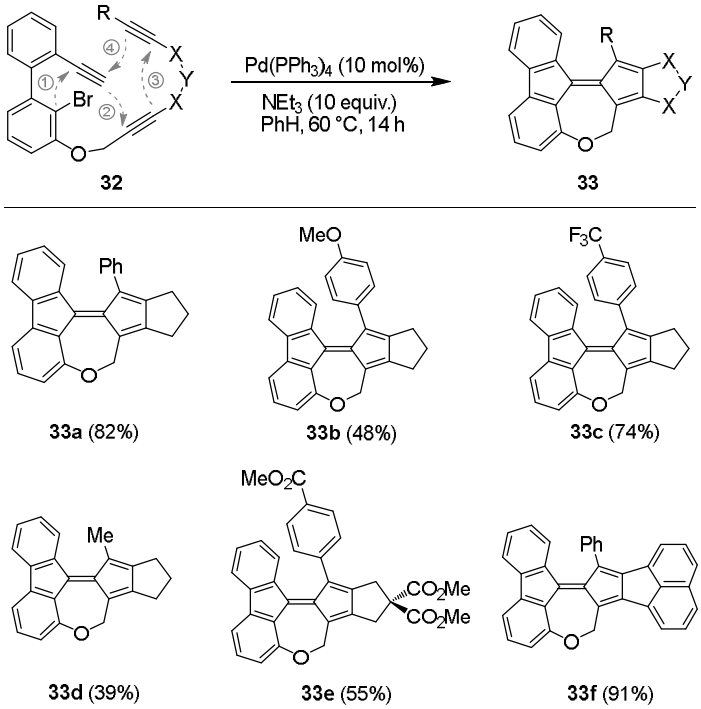
Whereas three alkyne units were linearly arranged to yield the dispiro compounds another arrangement as in **32** led to a novel synthesis of dibenzopentafulvalenes.[29] Such compounds have revealed great interest in recent years because of their electron-accepting properties (Scheme 9).

The retrosynthetic strategy used an easily available biphenylacetylene and two tethered alkyne moieties. The central dibenzopentafulvalene skeleton **33** is available in one synthetic step by a cascade

starting with an oxidative addition of Pd into the C-Br bond of **32** followed by three consecutive carbopalladation steps to form three C-C double bonds and a final attack of the emerging central CC double bond.



Scheme 8. Triple carbopalladation/Stille cascade followed by 6π-electrocyclization.



Scheme 9. Quadruple carbopalladation cascade to yield dibenzopentafulvalenes **33**.

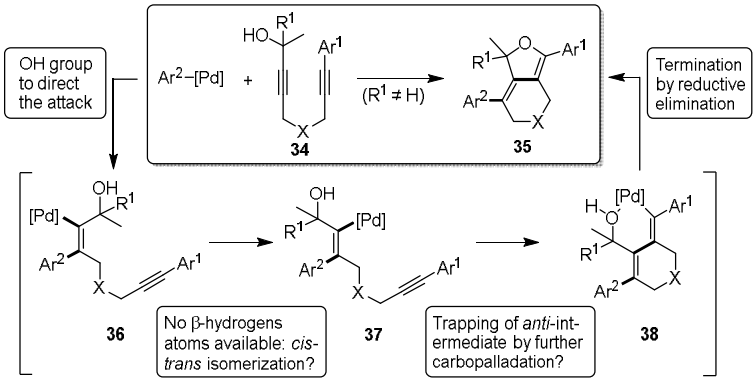
Grey arrows in Scheme 9 visualize the most probable mechanistic pathway. Why one initial 5-*exo*-dig cyclization is favored over another 5-*exo*-dig is not easy to be answered. We assume that the following two factors contribute: The conjugated double bond is activated for an attack of the Pd. In addition, it is much less flexible in its orientation than the propargylic one and should be reached more easily. As the compilation in Scheme 9 demonstrates electron-rich and electron-poor substituents at the terminal aryl

residue were tolerated. Since aliphatic residues offer a further possibility for side reactions by allowing a β-H elimination of the respective intermediate the yield decreases. A resulting diene-allene species would be relatively unstable and be prone to immediate decomposition. Also a modification of the tethers was possible. Ester substituents did not significantly affect the yield; the switch from an aliphatic to an aromatic tether even led to an increase. However, much longer reaction times (48 h) were required to transform the very rigid starting material into **33f**. As heterocyclic moieties a seven-membered oxygen-containing cycle is obtained in all cases.[29]

6. Formal *anti*-carbopalladation cascades

6.1. Reaction design

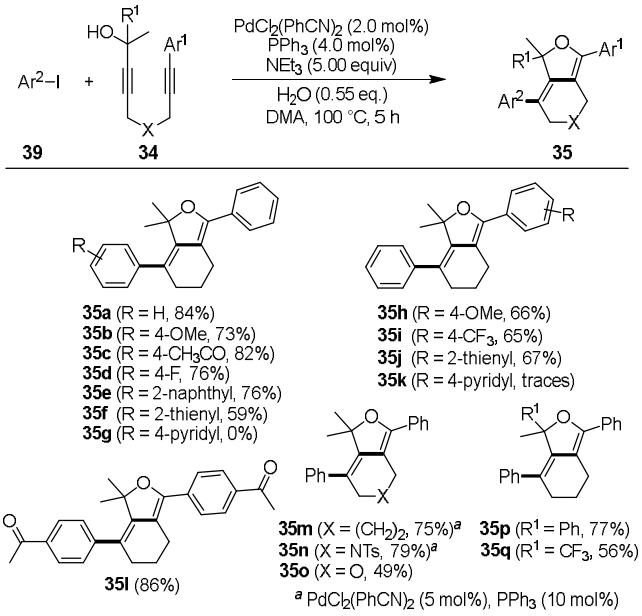
For decades, scientists used carbopalladation reactions with alkyne moieties which proceeded in a *syn*-like fashion. We became interested whether we could force systems to undergo a (formal) *anti*-carbopalladation process. Except of a very few earlier reports on random *cis-trans*-isomerization processes which relied on the use of extended π-systems[30,31] or α,β-unsaturated moieties[32] facilitating charge separation an in-depth study of (formal) *anti*-carbopalladation was not known when we raised this question. Our basic idea was to utilize diynes of type **34**.[33] One alkyne moiety is terminated by a tertiary alcohol which should lead to a regio- and chemoselective attack of an organopalladium species to afford vinyl palladium intermediate **36** (Scheme 10). The system was designed in such a way that neither β-hydrogen atoms are available nor a further carbopalladation can occur. Thus, a different mode of action should come into play. A β-hydroxy elimination might lead to an allene. The emerging palladium allene complex should have a relatively low barrier for the movement of the Pd to the other side of the allene. After the rearrangement, a hydroxypalladation would lead to the respective *anti*-carbopalladation intermediate **37**. After a second carbopalladation the cascade would be terminated by reductive elimination after nucleophilic attack of the hydroxyl group to the Pd species. As products electron-rich heterocyclic dienes **35** would be obtained.



Scheme 10. Reaction design of the formal *anti*-carbopalladation.

Optimization showed that the design was suitable to effect a (formal) *anti*-carbopalladation. There are three prerequisites for the desired process: a polar aprotic solvent such as DMF or DMA, elevated temperatures of 80-120 °C and monodentate phosphine ligands.[33] Chelating bisphosphines such as dppe or

BINAP shut down the reaction. Scheme 11 summarizes the reaction conditions and compiles some of the bicyclic dienol ethers which have been obtained. It is noteworthy that pyridine derivatives gave only trace amount of product (**35g** and **35k**).



Scheme 11. Optimized conditions and products obtained with the *anti*-carbopalladation/*syn*-carbopalladation cascade.

6.2. Mechanistic studies

In contrast to our original considerations mechanistic studies we performed showed that the original assumption assuming a palladium allene complex being a crucial intermediate was not tenable. We found that a 14 VE complex is the key intermediate for the respective *cis-trans*-isomerization resulting in the formal *anti*-carbopalladation intermediate.[33] Bidentate liganads hardly form such a 14 VE intermediate; thus the absence of any reactivity with dppe and BINAP is in line with this interpretation. Additional computations by DFT methods on a simple model system revealed a η^2-vinyl bound Pd complex for the transition state being in vacuo about 22 kcal/mol, in the preferred solvent DMA only about 18 kcal/mol higher in energy than the starting vinyl palladium species ***syn*-I**. However, one of the most important findings was that there is no interaction between the hydroxyl group and the palladium center (Figure 3).[33]

6.3. Different terminating processes

Encouraged by the computations which revealed no interaction between the hydroxyl group and the metal other residues at the terminus of the alkyne which do not allow a β-hydride elimination were tested. In addition, it should be also possible to terminate the cascade itself in other ways than described in Schemes 10 and 11.[34]

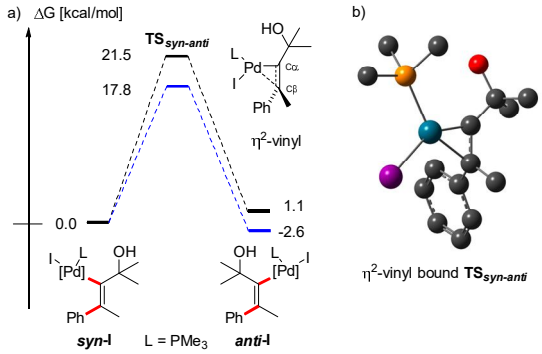
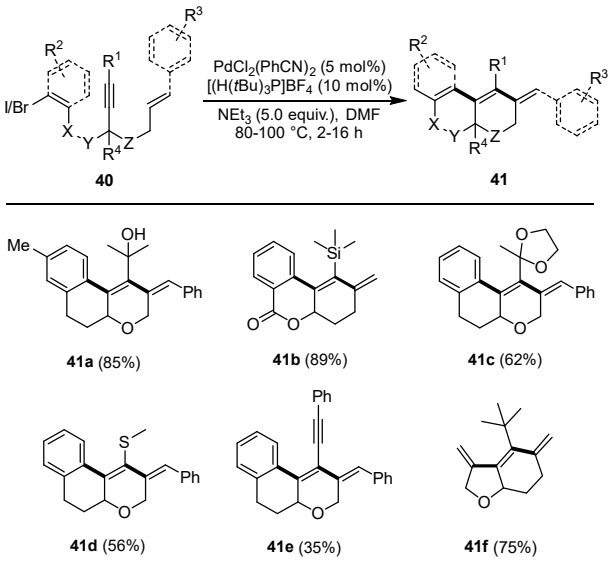


Figure 3. (a) Computed relative Gibbs energies for the *cis-trans*-isomerization of R-Pd(L)I. Gas phase (black), DMA (blue). (b) Computed structure of **TS**$_{syn\text{-}anti}$. Hydrogen atoms have been omitted for the sake of clarity; C (grey), Pd (blue), P (orange), I (purple), O (red).

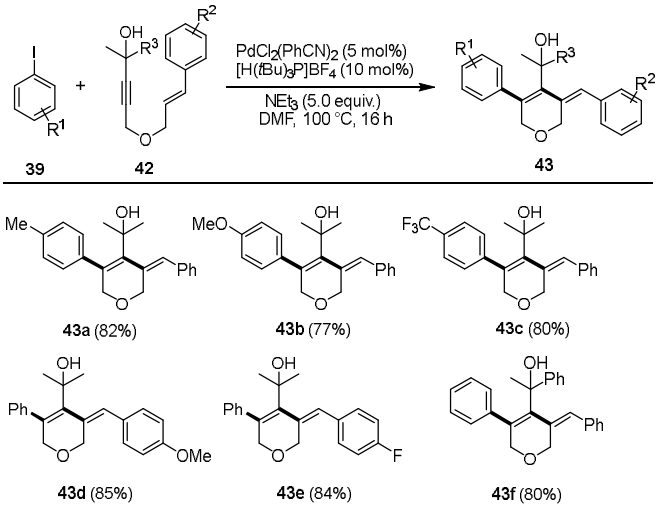
Numerous transformations known from Pd chemistry should be suitable such as Heck, Stille or Suzuki reactions. An intramolecular cascade starting from **40** terminated by a Heck reaction yielded products **41** which are compiled in Scheme 12. Besides the tertiary alcohol also *tert*-butyl, trimethylsilyl, acetal, divalent sulfur or a further carbon-carbon triple bond were tolerated. In contrary, the reaction does not work with electron-withdrawing groups such as esters, ketones, trifluoromethyl and aryl residues at the alkyne.



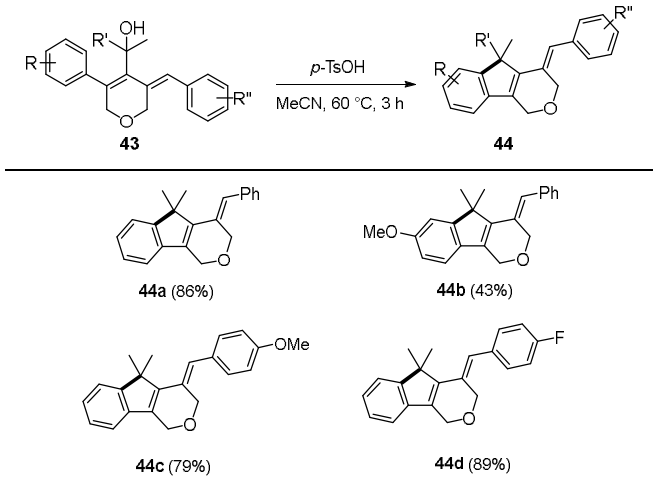
Scheme 12. Intramolecular *anti*-carbopalladation/Heck cascade.

An intramolecular variant of that transformation yielded highly substituted dienes **43** in good yields (Scheme 13).[35] The tertiary alcohol was used as directing group in order to achieve excellent chemo- and regioselectivity. Traces of acid such as *p*-TsOH allowed the tertiary alcohol to be transformed into a

carbocation which underwent Friedel-Crafts like chemistry which the adjacent phenyl residue. Indenes substituted with annelated heterocyclic motifs **44** were obtained in moderate to good yields (Scheme 14).

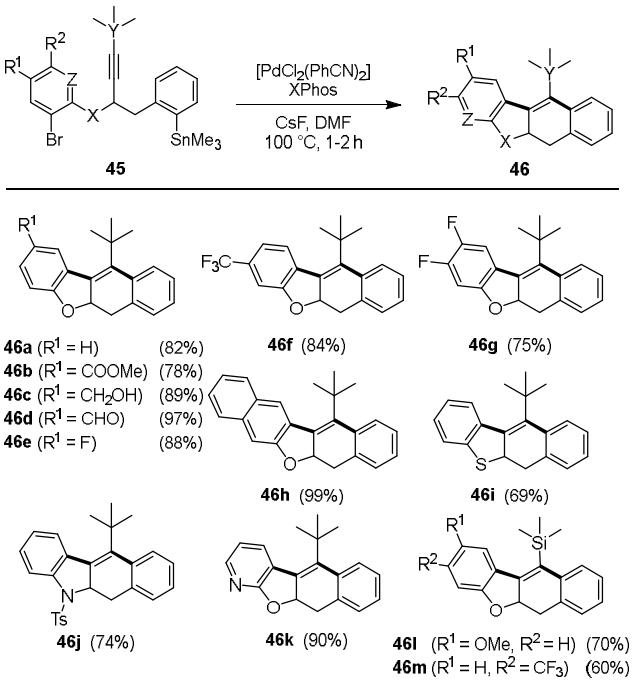


Scheme 13. Intermolecular *anti*-carbopalladation/Heck cascade.



Scheme 14. Acid-catalyzed ring-closure to heterocyclic indenes.

Besides the Heck reaction also a Stille reaction was employed to terminate the cascade after the formal *anti*-carbopalladation (Scheme 15).[36] Stannyl-substituted arenes **45** paved the way to another type of oligocyclic heterocycles **46**. The addition of caesium fluoride was essential to activate the C-Sn bond. The products were sensitive to acid and could be easily transformed into the respective furan derivatives by the use of *p*-TsOH.[36]



Scheme 15. Formal *anti*-carbopalladation/Stille cascade.

7. Conclusions

Although carbopalladation reactions are known to form C-C bonds they also demonstrate their utility in heterocycle synthesis. Our chroman and isochroman syntheses have shown that natural occurring heterocycles such as monosaccharides can be easily modified by a carbopalladation cascade generating an annelated benzene moiety. Other *syn*-carbopalladation reactions have led in our lab to dispiro compounds and dibenzopentafulvalenes. Besides cascades relying on *syn*-carbopalladations we also developed systems that have to undergo *anti*-carbopalladation processes by ruling out all other possible mechanistic pathways. After a *syn*-carbopalladation reaction a *cis-trans*-isomerization takes place in the coordination sphere of the metal. Crucial intermediate of that process is a 14 VE intermediate; thus, only monodentate phosphine ligands are tolerated. After the formal *anti*-carbopalladation process a variety of terminating reactions are possible leading to a plethora of different (hetero)cyclic scaffolds. Future research in this area will show that the *cantus firmus* of carbopalladation will be modulated and pave the way to new, elegant and efficient synthetic methods.

Acknowledgements

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