Pure Appl. Chem., Vol. 82, No. 7, pp. 1375–1392, 2010.
doi:10.1351/PAC-CON-09-12-10

Multiple Pd-catalyzed reactions in the synthesis of natural products, drugs, and materials*

Lutz F. Tietze‡ and Alexander Düfert

Institute of Organic and Biomolecular Chemistry, Georg-August-University, D-37077 Göttingen, Germany

Abstract: The efficient synthesis of natural products, drugs, and materials with economical and ecological advantages is a very important goal in modern synthetic chemistry. In such an approach, toxic substrates as well as reagents have to be avoided, the amount of waste has to be reduced, and the exploitation of our resources has to be diminished. In this respect, the use of catalytic processes is highly advantageous; however, even more beneficial is the combination of several catalytic processes either in a sequential or, more efficiently, in a domino mode. In this article, the synthesis of several natural products, drugs, and materials is described, employing multiple Pd-catalyzed processes either in a sequential or a domino fashion. Based on a double-Heck reaction developed by us for the preparation of estradiol, the efficient synthesis of the highly potent contraceptive desogestrel is discussed; for the synthesis of α-tocopherol and diversonol an enantioselective domino-Wacker/Heck reaction was utilized, whereas in the case of diversonol, a domino-Wacker/carbonylation was even more effective, and several molecular switches containing a helical tetrasubstituted double bond were prepared employing a domino-carbopalladation/Stille reaction. Finally, acenaphthylenes could be obtained by a domino-carbopalladation/C–H-activation.

Keywords: 2,2'-bis(oxazolin-2-yl)-1,1'-binaphthyl; carbopalladation; C–H activation; chromanes; desogestrel; diversonol; domino reaction; estradiol; Heck reaction; molecular switches; Pd-catalyzed transformations; Stille reaction; vitamin E; Wacker oxidation.

INTRODUCTION

In modern synthesis, a paradigm shift has occurred in recent years; whereas, over the last decades the main focus was on stereoselectivity, nowadays the efficiency of chemical procedures, which can be defined as increase in complexity per transformation, the preservation of the natural resources, and the ecological benefits combined with economical advantages are the objectives in modern synthesis. Such an approach is not only valuable for our environment but also for industrial processes and will have a great impact on production. As a recent example I would like to mention the efficient synthesis of Tamiflu, an important antiviral drug, by a domino process [1].

A general approach to address the above-mentioned challenges is the development and use of catalytic transformations with the focus on multiple or domino-catalyzed transformations [2]. For the C–C, C–O, and C–N bond formation, Pd-catalyzed processes such as the Heck, Negishi, Stille, Suzuki, Sonogashira, and the Tsuji–Trost reaction as well as the Wacker oxidation have been shown to be highly

*Paper based on a presentation at the 15th International Conference on Organometallic Chemistry Directed Towards Organic Synthesis (OMCOS-15), 26–31 July 2009, Glasgow, UK. Other presentations are published in this issue, pp. 1353–1568.
‡Corresponding author

valuable. Though several other transition metals have also been used for these bond formations, Pd has the broadest scope due its high selectivity and the exceedingly mild reaction conditions. Further recent improvements by using special ligands allowed bond formation to take place with an unprecedented substrate range of formerly unreactive or problematic compounds, e.g., aryl chlorides or alkyl halides and the formation of highly enantio-enriched compounds [2b,3].

Usually, the "normal" procedure for the synthesis of organic compounds has been a stepwise formation of individual bonds in the target molecules, with work-up stages after each transformation. In contrast, modern synthesis management must seek procedures that allow the formation of several bonds, whether C–C, C–O, or C–N in one process. In an ideal procedure, the entire transformation should be run without the addition of any further reagents or catalysts, and without changing the reaction conditions. We have defined this type of transformation as a "domino reaction" or "domino process" [2]. Such a process would be the *transformation of two or more bond-forming reactions under identical reaction conditions in which the latter transformations take place at the functionalities obtained in the former transformations*. In the processes one, two, three, or more compounds can be involved. Thus, multicomponent reactions are usually domino reactions.

The advantages of such a process lie not only in its elegance and high efficiency—both bond-forming efficiency as well as atom-efficiency—but also in the saving of resources as well as time, and the reduction of chemical waste, thus making these syntheses economically and ecologically beneficial. By combining the two concepts—domino reactions and Pd-catalyzed transformations—efficient, selective, and elegant assemblies of complex natural products, drugs, and materials are feasible.

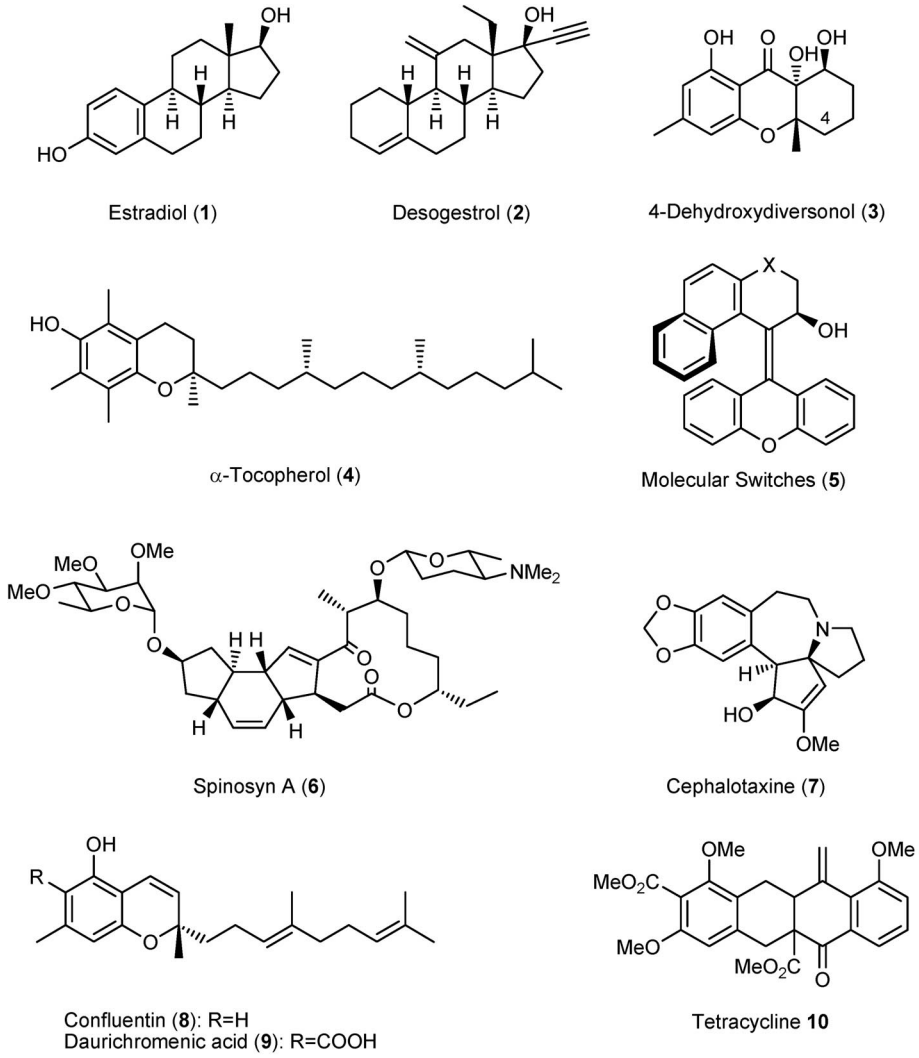
For the reason of comparison and the development of new domino processes, we have created a classification of these transformations. As an obvious characteristic, we used the mechanism of the different bond-forming steps. In this classification, we differentiate between cationic, anionic, radical, pericyclic, photochemical, transition-metal-catalyzed, oxidative or reductive, and enzymatic reactions. An overview of the possible combinations of reactions of up to three steps is shown in Table 1.

Table 1 Classification of domino reactions.

I. Transformation	II. Transformation	III. Transformation
Cationic	Cationic	Cationic
Anionic	Anionic	Anionic
Radical	Radical	Radical
Pericyclic	Pericyclic	Pericyclic
Photochemical	Photochemical	Photochemical
Transition-metal-catalyzed	Transition-metal-catalyzed	Transition-metal-catalyzed
Oxidative or reductive	Oxidative or reductive	Oxidative or reductive
Enzymatic	Enzymatic	Enzymatic

As can be seen from the different possible combinations in Table 1, taking into account only two steps we have 64 new reaction types, and by including a third step the number increases to 512. However, it should be noted that three steps in a domino process is by far not the limit. The described classification allows not only a clear overview of the existing domino reactions, but also helps to develop new domino reactions and to initiate ingenious independent research projects in this important field of synthetic organic chemistry.

In this short overview of parts of our work, we would like to demonstrate the usefulness of multiple Pd-catalyzed transformations by presenting the enantioselective total synthesis of the contraceptive desogestrel (**2**) based on our synthesis of the natural steroid estradiol (**1**) [4,5], 4-dehydroxydiversonol (**3**) [6], where we used a similar approach as in the enantioselective synthesis α-tocopherol (**4**) [7], and molecular switches (**5**) (Scheme 1) [8].



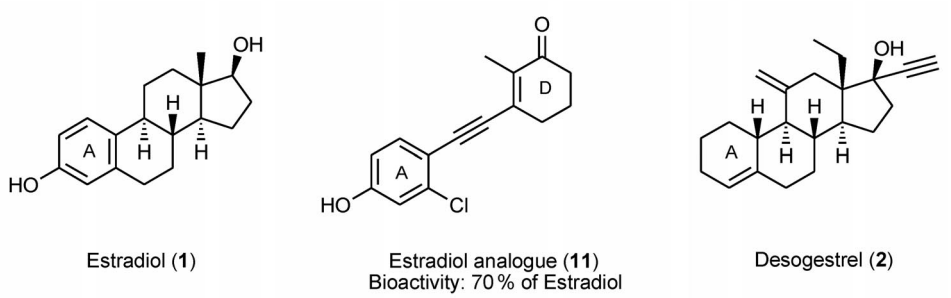
Scheme 1 Synthesis of natural products, drugs, and materials using multiple Pd-catalyzed transformations.

Several other syntheses of natural products and their analogs have also been developed by us using this approach as the enantioselective synthesis of analogs of the highly potent insecticide spinosyn A (**6**) [9], the alkaloid cephalotaxine (**7**) [10], the chromanes confluentin (**8**) [11], as well as daurichromenic acid (**9**) [11], and the tetracycline **10** [12], whereas in the syntheses of **1**, **2**, **6**, and **7** a successive approach of two Pd-catalyzed transformations was used, **3**, **4**, **5**, and **7–10** were prepared in a domino-Pd process.

ESTRADIOL (1) AND DESOGESTREL (2)

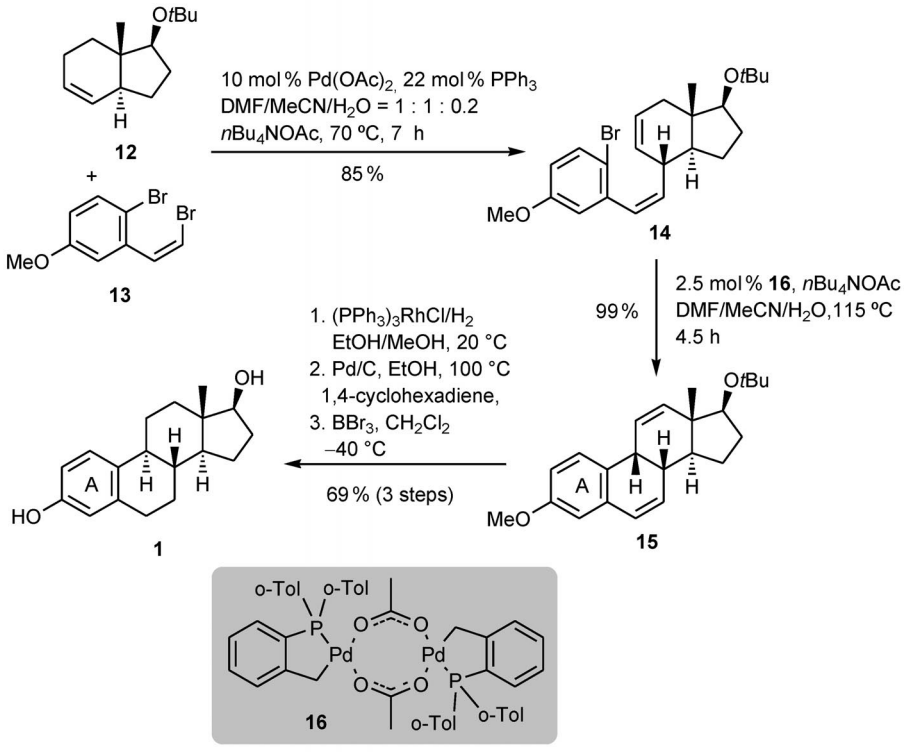
Steroids play an important role in the therapy of different diseases as well as in birth control. The female sex hormone estradiol (**1**) is one of the most important natural estrogens, and besides our approach using two Pd-catalyzed transformations [4a,b] several other syntheses of this compound have been published [13]. While **1** was recognized as a sex hormone quite early, more recent investigations have

shown a much broader spectrum of its biological activity. Based on estradiol, we have also designed novel adjustable analogs for the use as biological switches [14]. Astoundingly, the simple alkyne **11**, prepared again by two successive Pd-catalyzed transformations, shows approximately 70 % of the bioactivity of estradiol. The key transformation in the enantioselective syntheses of desogestrel (**2**) and estradiol (**1**) is the combination of two Heck reactions for the formation of ring B. Bioactivity studies have revealed desogestrel to be one of the most potent contraceptives (Scheme 2) [14].



Scheme 2 Steroids and analogs.

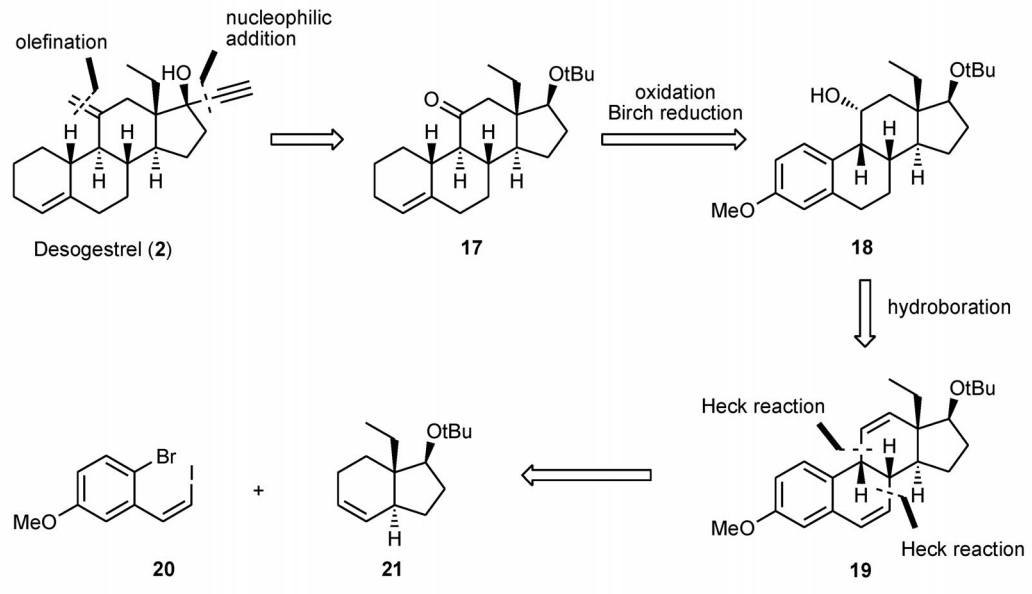
In the synthesis of estradiol (**1**), the hydrinden **12** and the bromovinylbromoarene **13** were used as substrates. In the first intermolecular Heck reaction employing Pd acetate compound **14** is formed exclusively in 85 % yield by a selective reaction at the vinyl bromide moiety of **13** at C-4 of **12** from the α-face *anti* to the angular methyl group (Scheme 3).



Scheme 3 Synthesis of estradiol (**1**).

For the second—this time intramolecular—Heck reaction of **14** to give **15**, a variety of catalyst systems were employed. However, only the Pd compound **16**, developed by Herrmann and Beller [15], allowed this transformation leading to **15** with the unnatural *cis*-orientation of rings B and C in 99 % yield as a single diastereomer. To complete the synthesis of estradiol (**1**), first the double bond in ring B in **15** was hydrogenated selectively using the Wilkinson catalyst, secondly the double bond in ring C was isomerized in situ to the C_9-C_{11} position and then reduced using Pd/C with 1,4-cyclohexadiene in a transfer hydrogenation and finally the *t*butyl- and the methyl ether were cleaved using BBr_3 to give **1** in 69 % over three steps.

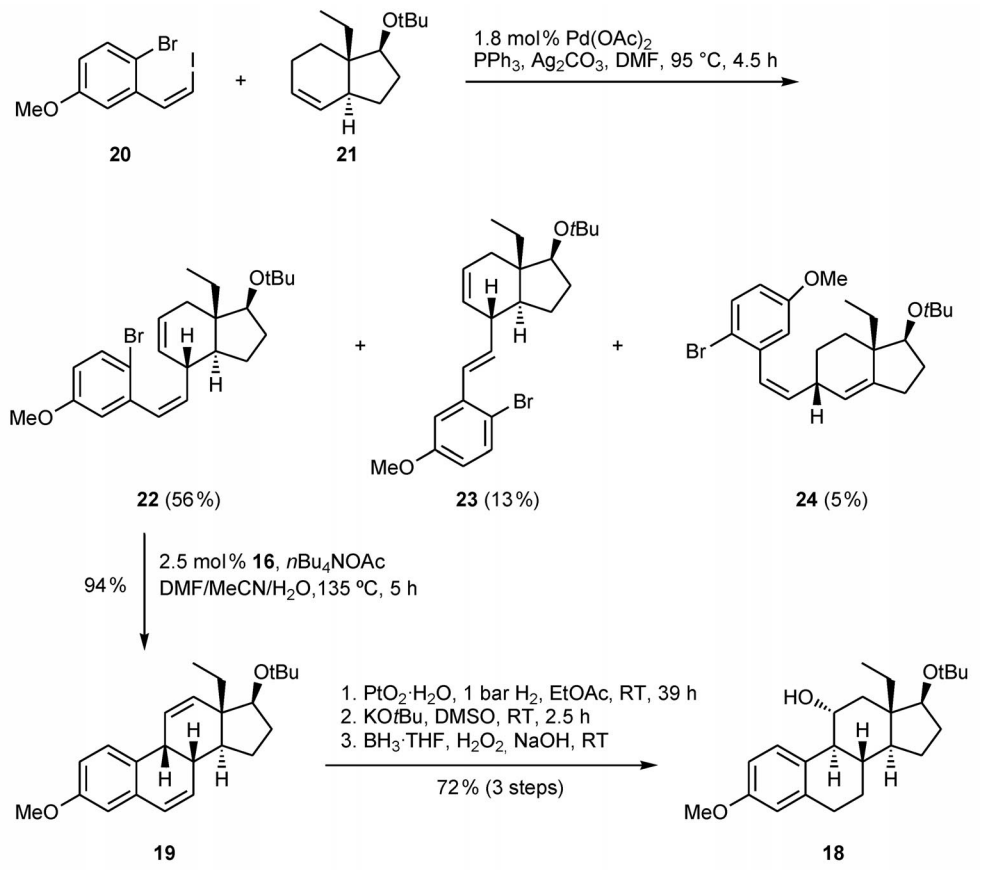
A similar approach was used for the synthesis of the tetracylic skeleton of desogestrel (**2**). Thus, the retrosynthesis of **2** leads via **17** and **18** to **19**, which could be obtained by two successive Heck reactions starting from **20** and **21** (Scheme 4). In contrast to the hydrinden **12** with an angular methyl group used in the synthesis of **1**, substrate **21** contains an angular ethyl group, which causes a reduction in reactivity probably due to an increased steric hindrance.



Scheme 4 Retrosynthesis of desogestrel (**2**).

Thus, the first Heck reaction had to be performed at a higher temperature using the vinyl iodide **20** in the presence of Ag_2CO_3, which caused a partial isomerization of the (*Z*)- to an (*E*)-double bond in **20** and probably also in the product **22**. Thus, reaction of **20** and **21** using $Pd(OAc)_2$ as Pd source and PPh_3 as ligand led to **22** in 56 % isolated yield and in addition to the corresponding (*E*)-isomer **23** in 13 % yield. Furthermore, small amounts of the regioisomer **24** and probably its double-bond isomer were also formed. Transformation of **22** in the presence of catalytic amounts of **16** led to formation of **19** in which the rings B and C are *cis*-fused with 94 % yield. For the selective hydrogenation of the double bond in the B ring, platinum could be used as catalyst as the double bond in ring C is much more shielded compared to **15**. The isomerization of the double bond in ring C was performed using KO*t*Bu, and it followed a hydroboration with BH_3·THF and H_2O_2 in basic medium to give the intermediate **18** in 72 % over 3 steps with the correct stereochemistry of the tetracyclic skeleton (Scheme 5).

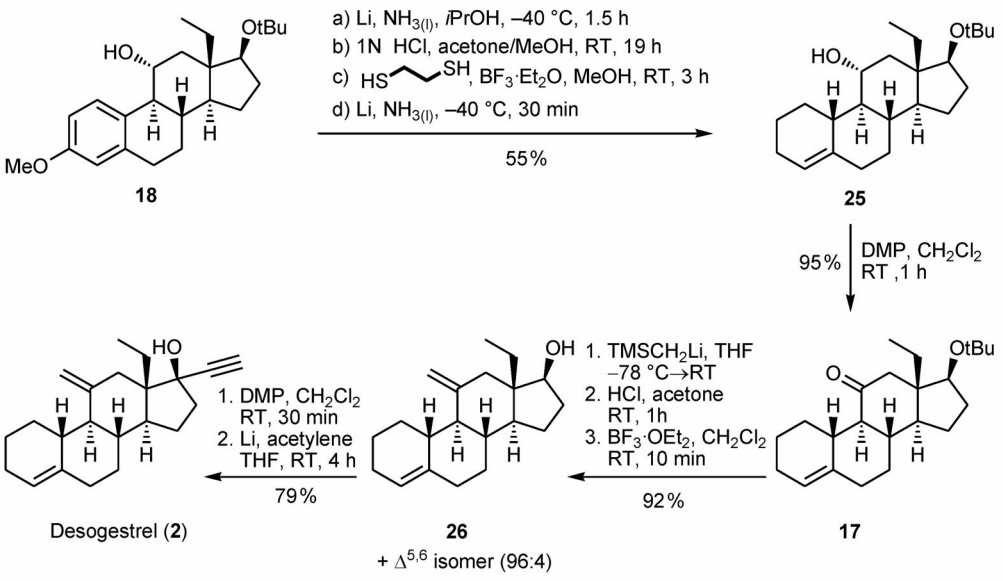
In the following steps, the aromatic ring A in **18** had to be reduced to give a cyclohexene ring and the hydroxyl group had to be transformed into a methylene moiety. The first task was accomplished by a Birch reduction with Li in liquid ammonia followed by work-up with HCl to give an α,β-unsaturated



Scheme 5 Synthesis of **18** via a double Heck reaction.

ketone, which was transformed into an α,β-unsaturated thioacetal. The final step in this sequence was the reductive removal of the thioacetal to afford **25** (Scheme 6).

It followed an oxidation of the secondary hydroxyl group into a ketone using the Dess–Martin procedure. The transformation of the keto moiety in the formed product **17** into the required *exo*-methylene group caused some difficulties at the beginning. Both a Wittig as well as a Lombardo reaction were not successful. However, formation of a β-hydroxysilane by nucleophilic attack of lithium-methyltrimethylsilane to the keto moiety followed by an acid-catalyzed Peterson elimination and the cleavage of the *t*butyl ether using $BF_3{\cdot}OEt_2$ led to the desired compound **26** in 92 % yield. The final steps in the synthesis of desogestrel (**2**) were the oxidation of the secondary alcohol moiety in **26** using the Dess–Martin procedure and the addition of lithium acetylide. Unfortunately, the cleavage of the *t*butyl ether moiety resulted in a partial isomerization of the double bond in ring A to the $\Delta^{5,6}$-position to give a 96:4 mixture in favor of the desired product. A separation at this stage was not possible, and even performing the reaction at lower temperature and for a shorter time did not prevent the isomerization. Fortunately, the final product desogestrel (**2**) is crystalline and a recrystallization allowed us to remove the undesired isomer.

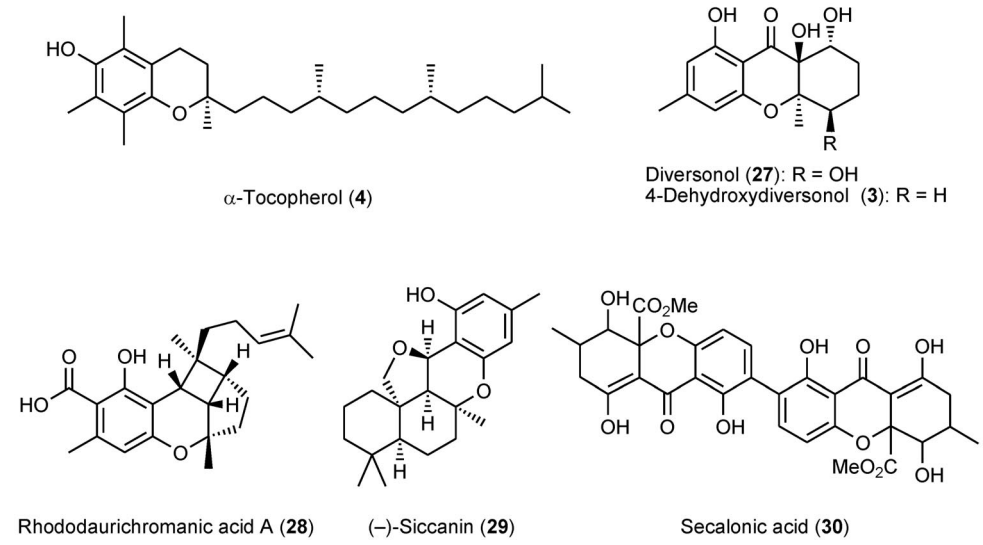


Scheme 6 Synthesis of desogestrel (**2**).

DIVERSONOL AND α-TOCOPHEROL

Natural products containing a chromane skeleton are widespread in nature with α-tocopherol (**4**) as the most prominent example. Other compounds containing such a structural motif are diversonol (**27**), confluentin (**8**), daurichromenic acid (**9**), the dimer rhododaurichromenic acid (**28**), and siccanin (**29**) [16].

Moreover, a collection of other natural products as the secalonic acids (**30**), complex polyketides originally isolated from the fungus *Claviceps purpurea*, can be counted to this group [17]. The compounds exhibit a widespread biological activity that includes antioxidant as well as antibacterial, cytostatic, and anti-HIV properties [18]. Despite their interesting profile, synthetic efforts toward their synthesis, with the exception of α-tocopherol, have only recently been made (Scheme 7) [19,20].

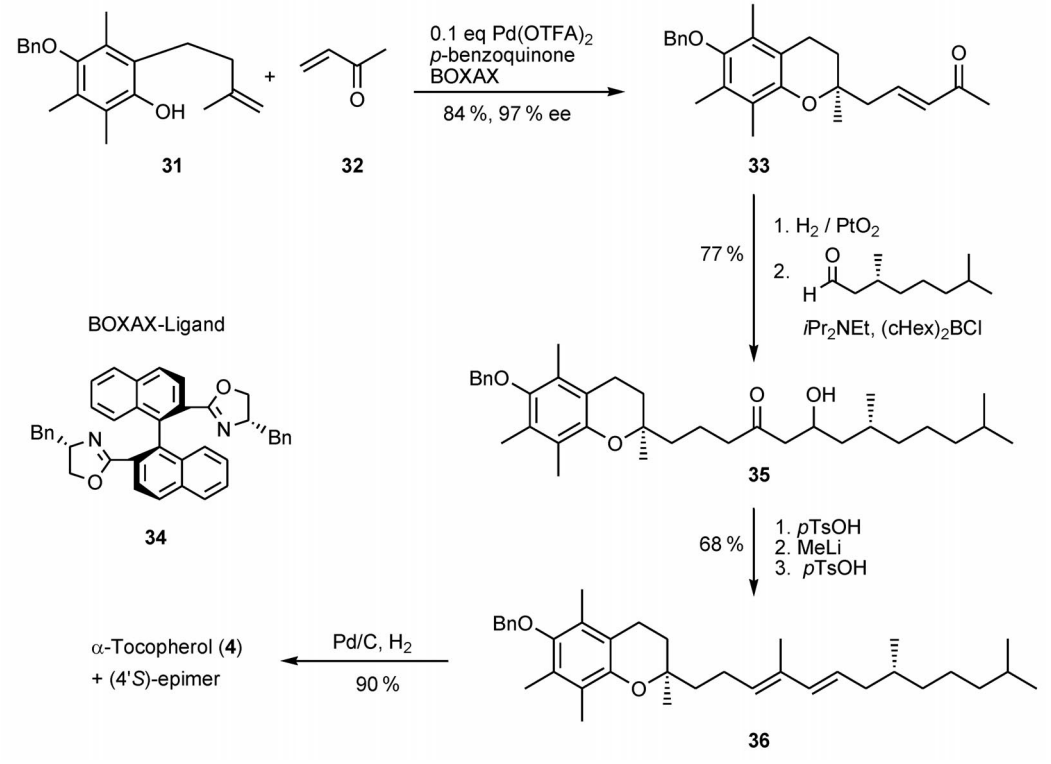


Scheme 7 Natural chromanes.

For the enantioselective synthesis of α-tocopherol (**4**), we have developed a new enantioselective domino-Pd-catalyzed process consisting of an intramolecular Wacker oxidation in the presence of a chiral BOXAX ligand and an intermolecular Heck-type reaction of the intermediately formed Pd-alkyl moiety with methyl vinyl ketone. This concept was also employed for the enantioselective synthesis of diversonol (**27**), but the enantioselectivity of the reaction was only 85 % ee; in contrast, a domino-Wacker/carbonylation reaction in the presence of a chiral 2,2'-bis(oxazolin-2-yl)-1,1'-binaphthyl (BOXAX) ligand gave the desired structure with excellent enantioselectivity.

α-Tocopherol belongs to the family of vitamin E together with β-tocopherol, γ-tocopherol, and δ-tocopherol with three stereogenic centers and the corresponding α-, β-, γ-, and δ-tocotrienols with only one stereogenic center. α-Tocopherol (**4**) is the most potent compound of this family, which acts as an antioxidant and is the essential protective factor against lipid oxidation by capturing highly reactive free radicals formed in the body within the normal oxidative metabolism. For activity it is essential that the stereogenic center at the chromane moiety has the (*R*)-configuration, since the (*S*)-enantiomer is not accepted as substrate by the tocopherol transfer protein, which is responsible for the transport of vitamin E into the tissue. Commercially, α-tocopherol is produced as a mixture of all eight stereoisomers.

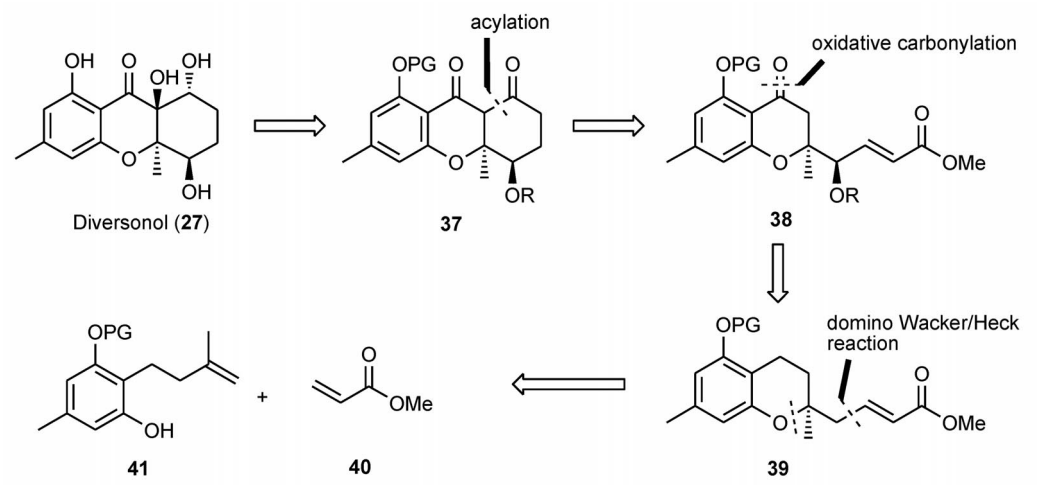
For the efficient enantioselective synthesis of α-tocopherol (**4**) we used **31** as substrate containing a phenolic hydroxyl group and an alkene moiety. Treatment of a mixture of **31** and methyl vinyl ketone (**32**) in the presence of 10 mol % palladium trifluoroacetate and the ligand (*S*,*S*)-Bn-BOXAX (**34**) [21] as well as benzoquinone led to the desired chromane **33** in 84 % yield and an excellent enantioselectivity of 97 % (Scheme 8). It followed a hydrogenation of the double bond and an aldol reaction of the boron enolate of the formed saturated ketone with an enantiopure C_{10}-aldehyde obtained from enantiopure (*R*)-citronellol to give **35** [22]. The last steps in the synthesis of α-tocopherol (**4**) were an



Scheme 8 Efficient enantioselective synthesis of α-tocopherol (**4**) using a domino-Wacker/Heck reaction.

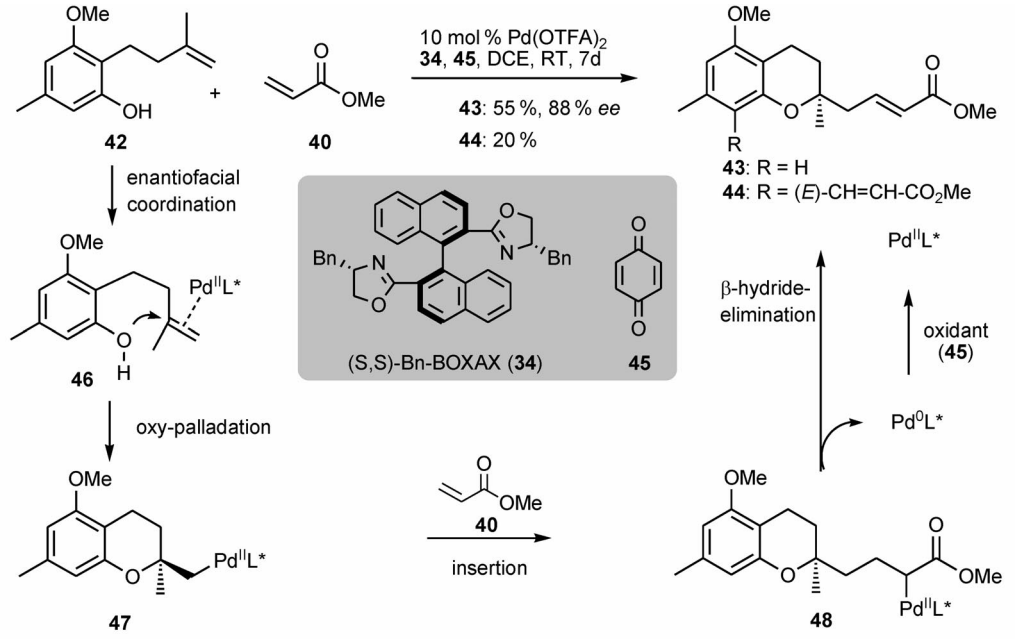
acid-catalyzed elimination of water, addition of methyl lithium to the carbonyl moiety, as well as a concluding acid-catalyzed elimination of water to afford **36**. Finally, hydrogenation of **36** containing a butadiene moiety yielded α-tocopherol (**4**) and its (4'*S*)-epimer, which has the same antioxidant activity as α-tocopherol in 61 % yield over 4 steps.

For the enantioselective synthesis of diversonol **27**, a metabolite from *Penicillium diversum*, we wanted to apply the same approach as described for the synthesis of α-tocopherol, which follows from the retrosynthesis described in Scheme 9. The main intermediate would be via **37** and **38** the chromane **39**, which should be accessible by an enantioselective domino-Wacker/Heck reaction of the phenol **41** and methyl acrylate **40**. Indeed, reaction of **42** and **40** in the presence of catalytic amounts of $Pd(OTFA)_2$ and the chiral ligand Bn-BOXAX (**34**) as well as benzoquinone **45** as gave the desired chromane **43** in 55 % yield and 88 % ee (Scheme 10). In addition, compound **44** was formed probably via a CH activation in 20 % yield.



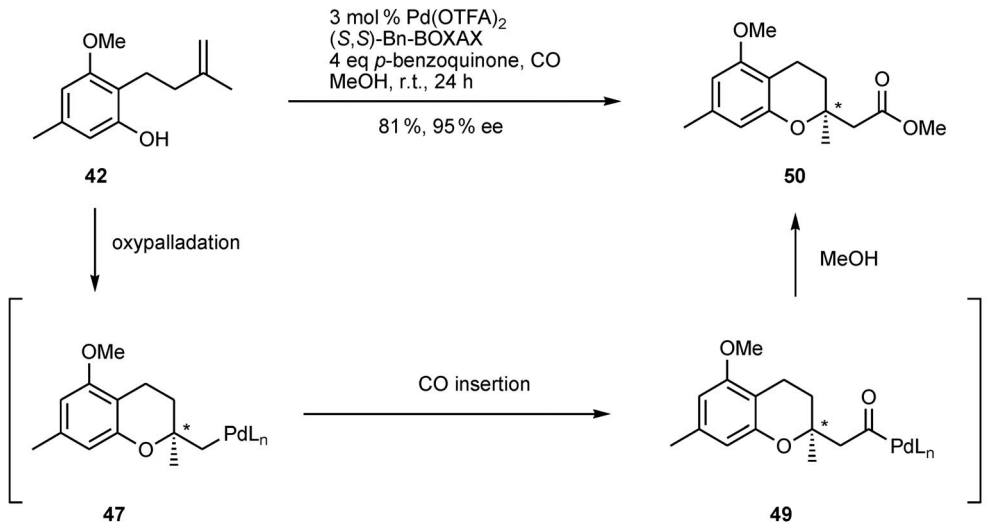
Scheme 9 Retrosynthesis of diversonol (**27**).

Mechanistically, the enantiodiscriminating step is the enantiofacial coordination of the chiral Pd catalyst. It follows an oxypalladation to give the σ-Pd-species **47**, which cannot undergo a β-hydride elimination but instead reacts with methyl acrylate present in the reaction mixture in a Heck transformation to form **48**. After the ensuing β-hydride elimination, the chromane **43** and Pd^0 are generated, which is reoxidized by *p*-benzoquinone to reenter the catalytic cycle (Scheme 10).



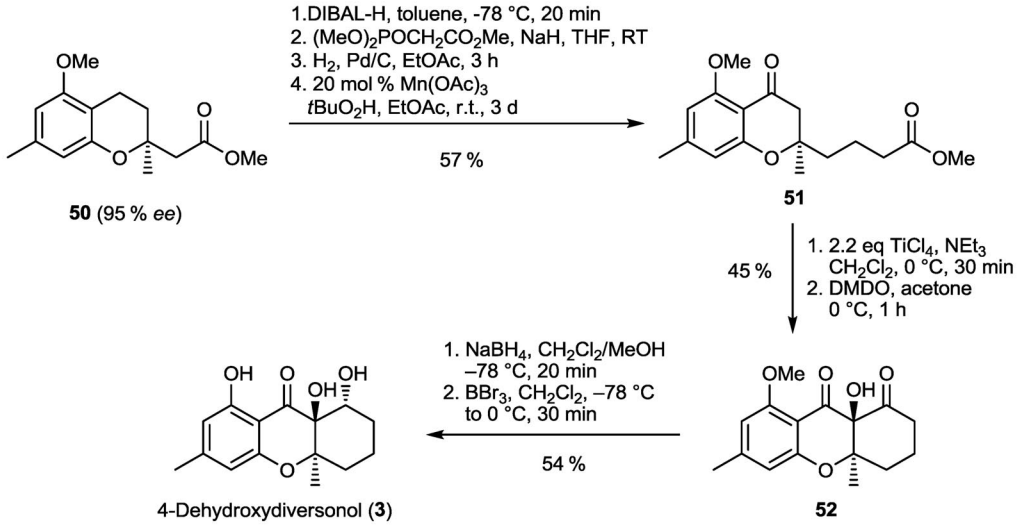
Scheme 10 Mechanism of the domino Wacker/Heck reaction of **40** and **42**.

However, for an efficient synthetic approach toward diversonol (**27**), the obtained yields and the rather low enantioselectivity were not sufficient. We therefore developed an enantioselective domino-Wacker/carbonylation reaction in methanol as solvent using again **42** as substrate to give the chromane **50** in 81 % yield with an enantioselectivity of 95 % ee (Scheme 11).



Scheme 11 Enantioselective formation of the chromane **50**.

We assume that also in this transformation the σ-Pd species **47** is an intermediate, which then undergoes an insertion into CO to form the CO-Pd species **49**, which reacts with methanol to give the methyl ester **50**. Reduction of the ester moiety in **50** with diisobutylaluminum hydride (DIBAL-H) leads the corresponding aldehyde, which can be transformed into the α,β-unsaturated ester **43** using a Wittig–Horner procedure (Scheme 12).



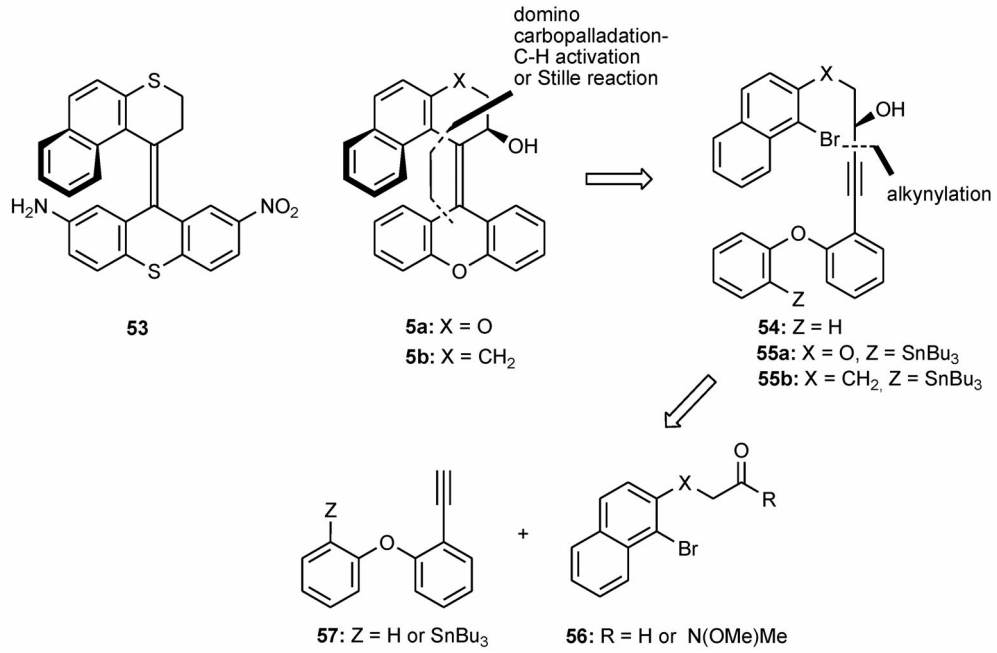
Scheme 12 Synthesis of 4-dehydroxydiversonol (**3**).

43 was then selectively hydrogenated and the carbonyl functionality introduced by using *t*butylhydroperoxide in the presence of catalytic amounts of $Mn(OAc)_3$, to give **51** in 57 % yield over 4 steps. It followed a ring closure with formation of the corresponding 1,3-diketone by acylation using titanium tetrachloride at 0 °C and an oxidative introduction of a hydroxyl group with dimethyldioxirane. It can be assumed that first an epoxidiation of the β-keto enol tautomer of the 1,3-diketone takes place, which is followed by a ring opening to yield **52** in 45 % yield over 2 steps. To complete the synthesis of 4-dehydroxydiversonol (**3**), the ketone at C-1 in **52** was selectively reduced with $NaBH_4$ and the methyl ether cleaved with BBr_3. So far, we were not able to introduce the missing hydroxyl group at C-4 without racemization.

The procedures could also be employed for the synthesis of simpler differently substituted chromanes and dioxines [23].

MOLECULAR SWITCHES

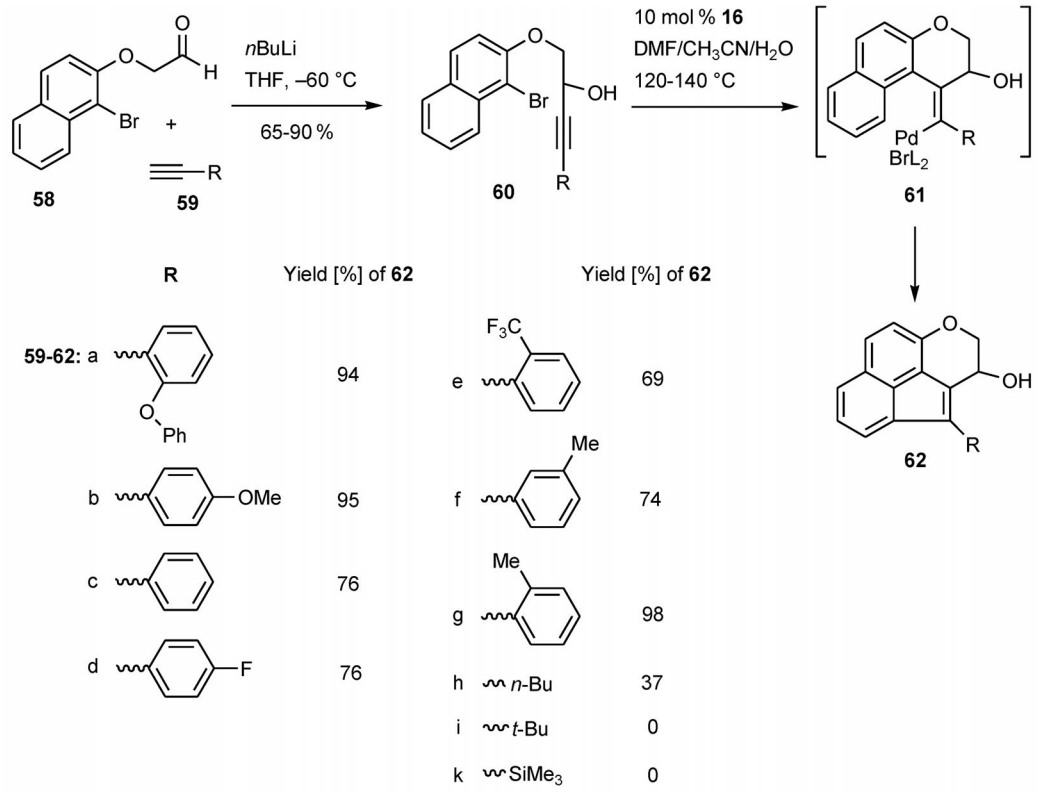
The development of organic compounds that allow a controlled motion at the molecular level is an important prerequisite for the construction of nanoswitches and nanomotors. Based on today's requirements in the miniaturization of data storage devices and the concomitant success of digital optical data systems, in which recording and read-out of information is carried out by light, the shift from classic electronic semiconductor elements to light-driven molecular switches has gained great impetus [24,25]. Based on tetrasubstituted helical alkenes as **53**, which were introduced by Feringa and Wynberg, this type of molecular switch is particularly promising since its stable states can be accessed using circularly polarized light (Scheme 13) [26].



Scheme 13 Retrosynthesis of molecular switches of type **5**.

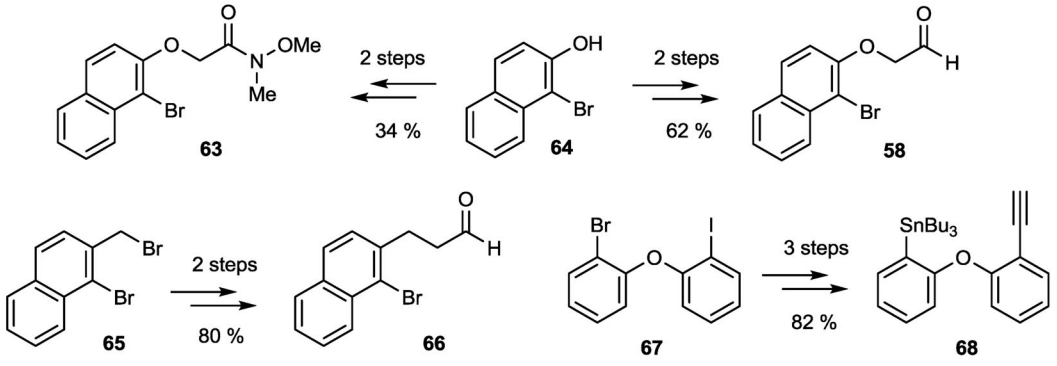
Our first attempts to synthesize tetrasubstituted alkenes of type **5** was based on a domino-carbopalladation/C–H-activation according to the retrosynthetic analysis in Scheme 13 with **54** as intermediate, which should be accessible by a addition of the alkyne **57** (Z = H) to the aldehydes **56**. However, this approach did not lead to the desired compounds **5** but to the acenaphthylenes **62**; on the other hand, molecular switches of type **5** could be obtained highly successfully by the Pd-catalyzed domino-carbopalladation/Stille reaction of compounds of type **55** containing a $Sn(Bu)_3$ substituent. Compounds **55** were accessible by reaction of the metallated alkyne **57** [Z = $Sn(Bu_3)$] and the aldehydes **56** (R = H) or the Weinreb amides **56** [R = N(OMe)Me] followed by reduction.

For our approach toward the synthesis of molecular switches **5** using a domino-carbopalladation/C–H-activation the alkyne **59a** was deprotonated using *n*-butyllithium and afterwards added to the aldehydes **58** to give the alcohol **60a**, which could be resolved into the two enantiomers using chromatography on chiral support. Reaction with catalytic amounts of the Pd catalyst **16**, however, did not lead to desired compound **5** but to the acenaphthylene **62a** probably via **61a**. The reaction could be exploited for synthesis of differently substituted acenaphthylenes **62b–h**. Good yields were obtained, when the alkyne **59** was substituted with an aromatic rest. Simple aliphatic alkynes as **59h** gave lower yields and bulky rests as *t*butyl or trimethylsily at the alkyne moiety (**59i** and **59k**) prohibited the transformation (Scheme 14).



Scheme 14 Domino-carbapalladation/C–H-activation for the synthesis of acenaphthylenes **62**.

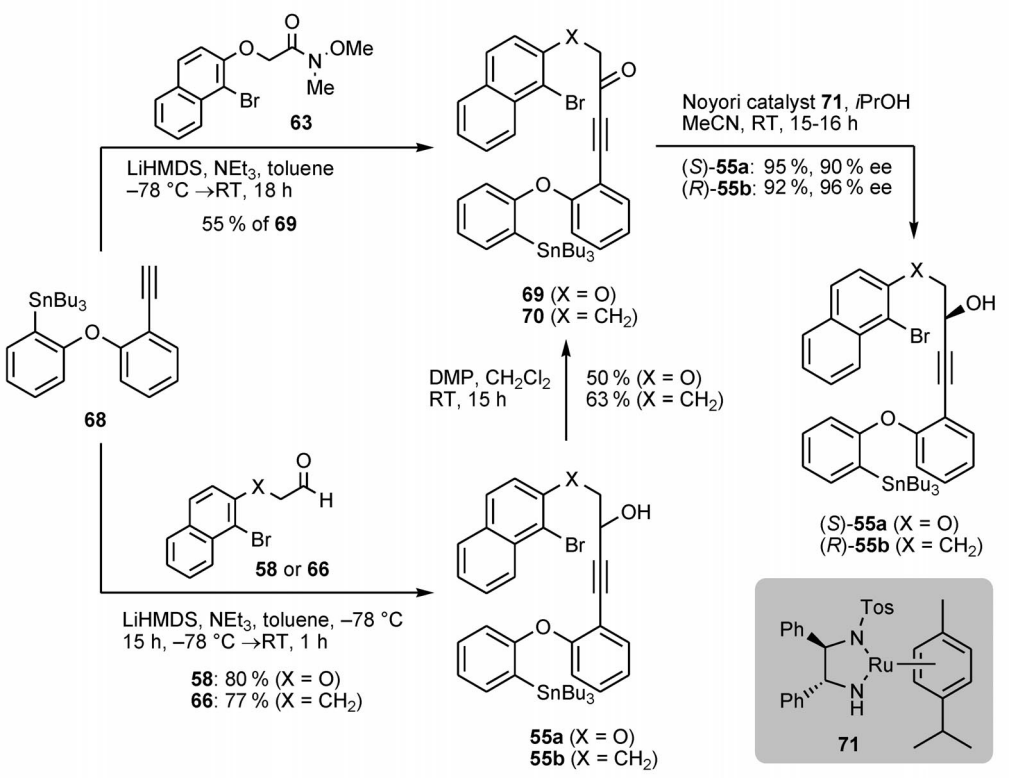
We therefore developed another approach for the construction of **5**, employing a domino-carbopalladation/Stille reaction as the key step, closing the upper and lower ring while forming the tetrasubstituted double bond. The necessary substrates **55** for the domino reaction could be obtained in a few steps from the commercially available compounds bromonaphthol **64**, bromomethylnaphthalene **65**, and the diphenyl ether **67**, which were transformed into the Weinreb amide **63**, the aldehydes **58** and **66** and the stannane **68**, respectively, in acceptable to good yields (Scheme 15).



Scheme 15 Synthesis of intermediates for the domino reaction.

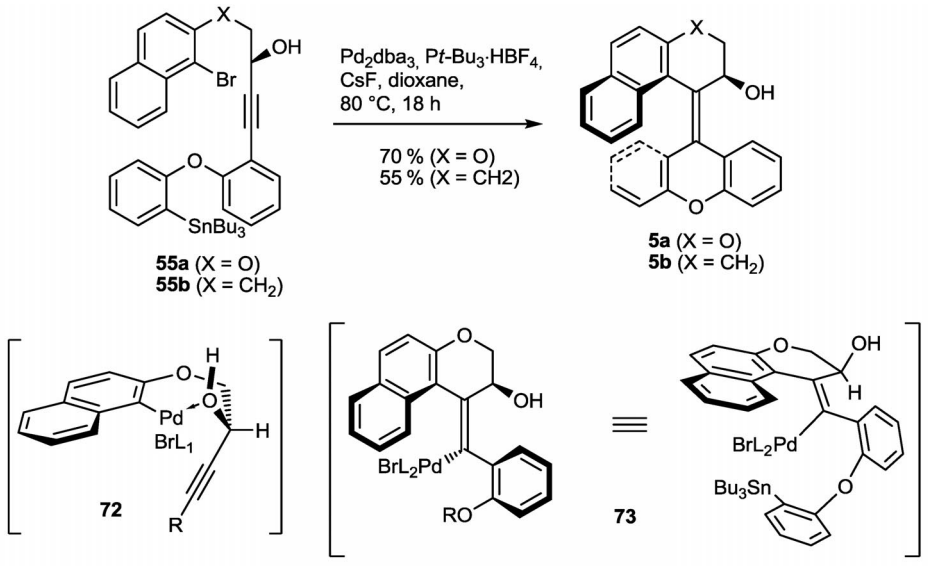
The alkynylation of aldehyde **58** and **66**, respectively, with the alkyne **68** could be accomplished by very slow addition of the aldehyde to the lithiated alkyne via syringe pump. The combination of LiHMDS with the unusual solvent system (toluene/NEt_3) proved to be the most effective for receiving the corresponding propargylic alcohols **55**. Employing other bases did not give the product. The high base/solvent dependence in this reaction is attributed to the aggregation behavior of organolithium compounds, while the slow addition of the aldehyde prevents an aldol condensation. In this sequence, the propargylic alcohols **55** were obtained as racemic mixtures. However, they could be resolved by chromatography on a chiral phase to give both almost pure enantiomers of **55a** and **55b** (ee >99.6 %).

However, besides the chromatographic resolution we also developed an enantioselective synthesis of **55**. On the one hand, Dess–Martin oxidation of racemic **55a** and **55b** furnished the ketones **69** and **70** in 50 and 63 % yield, respectively. On the other hand, reaction of the Weinreb amide **63** with litiated acetylide **68** at –78 °C led to the ketone **69** in 55 % yield. Reduction of the ketones **69** and **70** using the chiral Noyori catalyst **71** [27] in a transfer hydrogenation gave (*S*)-**55a** and (*R*)-**55b**, respectively, with excellent yield and very good enantioselectivities of 90 and 96 % ee (Scheme 16).



Scheme 16 Enantioselective synthesis of propargylic alcohols **55**.

Once the enantioenriched propargylic alcohols **55a** and **55b** were in hand, the domino carbopalladation/Stille reaction could be conducted. The domino reaction of (*S*)-**55a** and (*R*)-**55b** with Pd_2dba_3 in the presence of $PtBu_3 \cdot HBF_4$ afforded the helical alkenes (*S*,*P*)-**5a** and (*R*,*P*)-**6b** in 70 and 55 % yield, respectively, as single diastereomers (Scheme 17). Use of the enantiomers of **55** leads to the opposite helicity. Thus, the configuration of the helical structure in the products **5** of the Pd-catalyzed domino reaction of **55a** and **55b** is controlled by the stereogenic center in the starting materials, whereby for **55a** the (*S*)-enantiomer exclusively leads to (*P*)-helicity and the (*R*)-enantiomer to (*M*)-he-

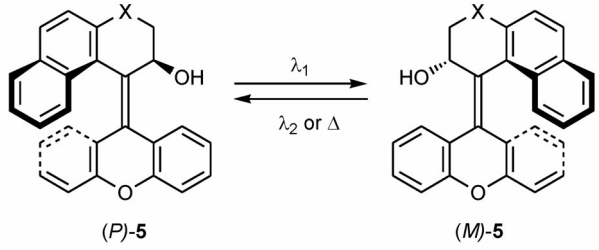


Scheme 17 Pd-catalyzed domino reaction of **55a** and **55b** with proposed intermediates explaining the stereoselectivity.

licity. For **55b**, it is the opposite due to a change of the priority of the substituents at the stereogenic center.

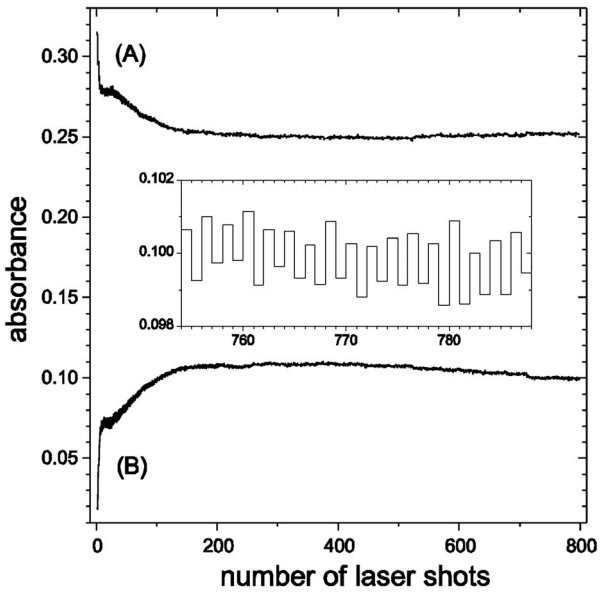
The induced diastereoselectivity can be explained by an interaction of the Pd atom and the hydroxyl group in the primarily assembled Pd intermediate **72**, which forces the alkyne moiety to lie below the naphthalene skeleton and thus controls the selective insertion into the triple bond to give intermediate **73** (Scheme 17).

Reversible optical switching was confirmed for both **5a** and **5b** from the thermally stable **P**-form to the less stable **M**-form by irridiaton. The thermal back-conversion of (*M*)-**5b** takes several hours; (*M*)-**5a** shows a lower thermal stability compared to (*M*)-**5b** with a thermal **M** → **P** back-switching in the order of minutes (Scheme 18).



Scheme 18 Light-induced switching process.

To assess the possibility of a fast optical switching, **5b** was subjected to alternate nanosecond laser excitation. An instantaneous **P** to **M** conversion was achieved by an excimer laser (308 nm, 15 ns pulse length) and the reverse process was initiated by an excimer-pumped dye laser (390 nm, 15 ns pulse length). With this set-up, over 3000 switching cycles were conducted without notable loss of its switching ability (Scheme 19).



Scheme 19 Photochemical switching experiment for **5b** employing alternate laser pulses at 308 and 390 nm. Curve (A) shows the **P**-form, whereas (B) corresponds to the **M**-form. The inset shows a magnification of the late part of the curve (B).

ACKNOWLEDGMENTS

We thank the Deutsche Forschungsgemeinschaft and the Fonds der Chemischen Industrie for generous support. A. D. is highly grateful to the Studienstiftung des Deutschen Volkes and the Fonds der Chemischen Industrie for a Ph.D. scholarship.

REFERENCES

1. (a) H. Ishikawa, T. Suzuki, Y. Hayashi. *Angew. Chem*. **121**, 1330 (2009); (b) H. Ishikawa, T. Suzuki, Y. Hayashi. *Angew. Chem., Int. Ed.* **48**, 1304 (2009).
2. (a) L. F. Tietze, G. Brasche, K. Gericke. *Domino Reactions in Organic Synthesis*, Wiley-VCH, Weinheim (2006); (b) L. F. Tietze, U. Beifuss. *Angew. Chem.* **105**, 137 (1993); (c) L. F. Tietze, U. Beifuss. *Angew. Chem., Int. Ed. Engl*. **32**, 131 (1993); (d) L. F. Tietze. *Chem. Rev*. **96**, 115 (1995); (e) L. F. Tietze, N. Rackelmann. In *Multicomponent Reactions*, J. Zhu (Ed.), Wiley-VCH, Weinheim (2005); (f) L. F. Tietze, L. Levy. In *The Mizoroki-Heck Reaction*, M. Oestreich (Ed.), Wiley-VCH, Chichester (2009); (g) L. F. Tietze, D. A. Spiegl, C. C. Brazel. In *Experiments in Green and Sustainable Chemistry*, H. W. Roesky, D. K. Kennepohl (Eds.), Wiley-VCH, Weinheim (2009); (h) L. F. Tietze, A. Düfert. In *Catalytic Asymmetric Conjugate Reactions*, A. Cordóva (Ed.), Wiley-VCH, Weinheim (2010); (i) L. F. Tietze, N. Rackelmann. *Pure Appl. Chem*. **76**, 1967 (2004); (j) L. F. Tietze, T. Kinzel. *Pure Appl. Chem*. **79**, 629 (2007); (k) L. F. Tietze, T. Kinzel, C. Brazel. *Acc. Chem. Res*. **42**, 367 (2009).
3. (a) A. C. Frisch, M. Beller. *Angew. Chem*. **117**, 680 (2005); (b) A. C. Frisch, M. Beller. *Angew. Chem., Int. Ed.* **44**, 674 (2005); (c) A. Rudolph, M. Lautens. *Angew. Chem.* **121**, 2694 (2009); (d) A. Rudolph, M. Lautens. *Angew. Chem., Int. Ed.* **48**, 2656 (2009); (e) G. C. Fu. *Acc. Chem. Res.* **41**, 1555 (2008); (f) L. F. Tietze, I. Hiriyakkanavar, H. P. Bell. *Chem. Rev*. **104**, 3453 (2004).

4. (a) L. F. Tietze, T. Nöbel, M. Spescha. *Angew. Chem., Int. Ed. Engl.* **35**, 2259 (1996); (b) L. F. Tietze, T. Nöbel, M. Spescha. *J. Am. Chem. Soc.* **120**, 8971 (1998); (c) L. F. Tietze, S. Petersen. *Eur. J. Org. Chem.* 1619 (2001).
5. L. F. Tietze, I. Krimmelbein. *Chem.—Eur. J.* **14**, 1541 (2008).
6. L. F. Tietze, D. A. Spiegl, F. Stecker, J. Major, C. Raith, C. Grosse. *Chem.—Eur. J.* **14**, 8956 (2008).
7. (a) L. F. Tietze, K. M. Sommer, J. Zinngrebe, F. Stecker. *Angew. Chem.* **117**, 262 (2005); (b) L. F. Tietze, K. M. Sommer, J. Zinngrebe, F. Stecker. *Angew. Chem., Int. Ed.* **44**, 257 (2005); (c) L. F. Tietze, F. Stecker, J. Zinngrebe, K. M. Sommer. *Chem.—Eur. J.* **12**, 8770 (2006).
8. L. F. Tietze, A. Düfert, F. Lotz, L. Sölter, K. Oum, T. Lenzer, T. Beck, R. Herbst-Irmer. *J. Am. Chem. Soc.* **131**, 17879 (2009).
9. (a) L. F. Tietze, G. Brasche, C. Stadler, A. Grube, N. Böhnke. *Angew. Chem., Int. Ed.* **45**, 5015 (2006); (b) L. F. Tietze, G. Brasche, A. Grube, N. Böhnke, C. Stadler. *Chem.—Eur. J.* **13**, 4396 (2007).
10. (a) L. F. Tietze, H. Schirok. *Angew. Chem.* **109**, 1159 (1997); (b) L. F. Tietze, H. Schirok. *Angew. Chem., Int. Ed. Engl.* **36**, 1124 (1997); (c) L. F. Tietze, H. Schirok. *J. Am. Chem. Soc.* **121**, 10264 (1999); (d) L. F. Tietze, H. Schirok, M. Wöhrmann. *Chem.—Eur. J.* **6**, 510 (2000); (e) L. F. Tietze, H. Schirok, M. Wöhrmann, K. Schrader. *Eur. J. Org. Chem.* 2433 (2000); (f) L. F. Tietze, H. Braun, P. L. Steck, S. A. A. El Bialy, N. Tölle, A. Düfert. *Tetrahedron* **63**, 6437 (2007).
11. L. F. Tietze, F. Stecker. Unpublished material.
12. L. F. Tietze, T. Redert, H. P. Bell, S. Hellkamp, L. M. Levy. *Chem.—Eur. J.* **14**, 2527 (2008).
13. (a) J. H. Rigby, N. C. Warshakoon, A. J. Payen. *J. Am. Chem. Soc*. **121**, 8237 (1999); (b) F. Zeelen. *Nat. Prod. Rep.* **11**, 607 (1994).
14. (a) K. M. D. Islam, M. Dilcher, C. Thurow, C. Vock, I. K. Krimmelbein, L. F. Tietze, V. Gonzalez, H. Zhao, C. Gatz. *PEDS* **22**, 45 (2009); (b) L. F. Tietze, C. A. Vock, I. K. Krimmelbein, L. Nacke. *Synthesis* 2040 (2009); (c) L. F. Tietze, C. A. Vock, I. K. Krimmelbein, J. M. Wiegand, L. Nacke, T. Ramachandar, K. M. D. Islam, C. Gatz. *Chem.—Eur. J.* **14**, 3670 (2008).
15. (a) W. A. Herrmann, C. Broßmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer. *Angew. Chem*. **107**, 1989 (1995); (b) W. A. Herrmann, C. Broßmer, K. Öfele, C.-P. Reisinger, T. Priermeier, M. Beller, H. Fischer. *Angew. Chem., Int. Ed. Engl*. **34**, 1844 (1995); (c) W. A. Herrmann, C. Broßmer, K. Öfele, C. P. Reisinger, T. Priermeier, M. Beller, H. Fischer. *Chem.—Eur. J.* **3**, 1357 (1997).
16. Y. Kashiwada, K. Yamazaki, Y. Ikeshiro, T. Yamagashi, T. Fujioka, K. Mihashi, K. Mizuki, L. K. Cosentino, K. Fowke, S. L. Morris-Natschke, K.-H. Lee. *Tetrahedron* **57**, 1559 (2001).
17. F. Kraft. *Arch. Pharm.* **244**, 336 (1906).
18. (a) A. Stoll, J. Renz, A. Brack. *Helv. Chim. Acta* **35**, 2022 (1952); (b) I. Kurobane, S. Iwahashi, A. Fukuda. *Drugs Exp. Clin. Res*. **13**, 339 (1987); (c) F. McPhee, P. S. Caldera, G. W. Bemis, A. F. McDonagh, I. D. Kuntz. *Biochem. J.* **320**, 681 (1996).
19. Racemic approaches: (a) K. C. Nicolaou, A. Li. *Angew. Chem., Int. Ed*. **47**, 6579 (2008); (b) C. F. Nising, A. Friedrich, S. Bräse. *Synlett* 2987 (2007); (c) C. F. Nising, U. K. Ohnemüller, A. Friedrich, B. Lesch, J. Steiner, H. Schnöckel, M. Nieger, S. Bräse. *Chem.—Eur. J.* **12**, 3647 (2006); (d) U. K. Ohnemüller, C. F. Nising, M. Nieger, S. Bräse. *Eur. J. Org. Chem.* 1535 (2006); (e) C. F. Nising, U. K. Ohnemüller, S. Bräse. *Angew. Chem.* **118**, 313 (2006); (f) C. F. Nising, U. K. Ohnemüller, S. Bräse. *Angew. Chem., Int. Ed.* **45**, 307 (2006); (g) Y.-L. Shi, M. Shi. *Synlett* 2623 (2005); (h) K. Y. Lee, J. M. Kim, J. N. Kim. *Bull. Korean Chem. Soc.* **24**, 17 (2003); (i) C. D. Gabbutt, J. D. Hepworth, M. W. J. Urquhart, L. M. Vazquez de Miguel. *J. Chem. Soc., Perkin Trans. 1* 1819 (1997); (j) B. Franck, J. Stöckigt, U. Zeidler, G. Franckowiak. *Chem. Ber.* **106**, 1198 (1973).
20. Enantioselective approaches: (a) U. K. Ohnemüller, C. F. Nising, A. Encinas, S. Bräse. *Synthesis* 2175 (2007); (b) R. Rios, H. Sundén, I. Ibrahem, A. Córdova. *Tetrahedron Lett.* **48**, 2181 (2007).

21. (a) H. Hocke, Y. Uozumi. *Tetrahedron* **59**, 619 (2003); (b) H. Hocke, Y. Uozumi. *Synlett* 2049 (2002); (c) Y. Uozumi, H. Kyota, K. Kato, M. Ogasawara, T. Hayashi. *J. Org. Chem.* **64**, 1620 (1999); (d) Y. Uozumi, K. Kato, T. Hayashi. *J. Org. Chem*. **63**, 5071 (1998); (e) Y. Uozumi, K. Kato, T. Hayashi. *J. Am. Chem. Soc*. **119**, 5063 (1997); (f) M. B. Andrus, D. Asgari, J. A. Sclafani. *J. Org. Chem*. **62**, 9365 (1997); (g) Y. Uozumi, H. Kyota, E. Kishi, K. Kitayama, T. Hayashi. *Tetrahedron: Asymmetry* **7**, 1603 (1996); (h) T. D. Nelson, A. I. Meyers. *J. Org. Chem*. **59**, 2655 (1994).
22. R. Noyori. *Green Chem*. **5**, G37 (2003).
23. (a) L. F. Tietze, J. Zinngrebe, D. A. Spiegl, F. Stecker. *Heterocycles* **74**, 473 (2007); (b) L. F. Tietze, A. Heins, M. Soleiman-Beigi, C. Raith. *Heterocycles* **77**, 1123 (2008); (c) L. F. Tietze, K. F. Wilckens, S. Yilmaz, F. Stecker, J. Zinngrebe. *Heterocycles* **70**, 309 (2006).
24. (a) V. Balzani, M. Venturi, A. Credi. *Molecular Devices and Machines: A Journey into the Nanoworld*, Wiley-VCH, Weinheim (2003); (b) Special issue on "Molecular machines": *Acc. Chem. Res.* **34**, 409 (2001).
25. (a) B. L. Feringa (Ed.). *Molecular Switches*, Wiley-VCH, Weinheim (2001); (b) J. C. Crano, R. J. Guglielmetti. *Organic Photochromic and Thermochromic Compounds*, Vols. 1–3, Springer, New York (1999); (c) B. L. Feringa, R. A. van Delden, N. Koumura, E. M. Geertsema. *Chem. Rev*. **100**, 1789 (2000); (d) Y.-L. Huang, W.-C. Hung, C.-C. Lai, Y.-H. Liu, S.-M. Peng, S.-H. Chiu. *Angew. Chem.* **119**, 6749 (2007); (e) Y.-L. Huang, W.-C. Hung, C.-C. Lai, Y.-H. Liu, S.-M. Peng, S.-H. Chiu. *Angew. Chem., Int. Ed*. **46**, 6629 (2007).
26. (a) B. L. Feringa. *J. Org. Chem*. **72**, 6635 (2007); (b) B. L. Feringa, H. Wynberg. *J. Am. Chem. Soc*. **99**, 602 (1997); (c) W. F. Jager, B. de Lange, A. M. Schoevaars, B. L. Feringa. *Tetrahedron: Asymmetry* **4**, 1481 (1993).
27. (a) K. Matsumura, S. Hashiguchi, T. Ikariya, R. Noyori. *J. Am. Chem. Soc*. **119**, 8738 (1997); (b) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori. *Angew. Chem*. **109**, 297 (1997); (c) K.-J. Haack, S. Hashiguchi, A. Fujii, T. Ikariya, R. Noyori. *Angew. Chem., Int. Ed. Engl*. **36**, 285 (1997).

