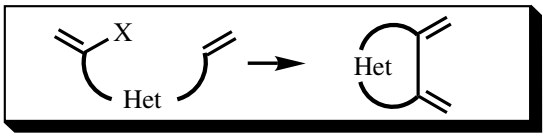


# IV.2.2.2 Synthesis of Heterocycles

GERALD DYKER

## A. INTRODUCTION

This section gives a concise overview on the construction of heterocycles by Heck-type reactions: all reactions covered here mechanistically start with an oxidative addition of a C–halide or another appropriate C–heteroatom bond to a Pd(0) species and go on either with a carbopalladation step (intramolecular in **Sect. B** and intermolecular in **Sect. C**) or a cyclopalladation step (**Sect. D**). The examples presented in the subsections are organized according to types of starting materials, since certain substructures turned out to be typical.

## B. HETEROCYCLES BY INTRAMOLECULAR CARBOPALLADATION

A starting material that is suitable for the direct construction of a heterocycle by an intramolecular Heck-type reaction has to fulfil some simple but fundamental requirements: there has to be the halide function or a triflate for the oxidative addition onto the Pd catalyst, a side chain with an unsaturated functionality such as an alkene or an alkyne in an appropriate distance, and of course the heteroatom in this side chain. **Figure 1** presents a substructure typical for very many starting materials, which were transformed to heterocycles by intramolecular Heck-type reactions (X = halide, Het = heteroatom). This type of substructure with an allylic side chain is easily accessible by derivatization of 2-bromo- and 2-iodo anilines, phenols, and thiophenols and leads to interesting heterocycles such as indoles and benzofurans, which are related to many natural products and other biological active compounds.

The Heck reaction with the simple representatives of this substructure shown in **Scheme 1** generally involves a double bond migration to give aromatized products in moderate to good yields.[1]–[4] The highest yield was achieved for 3-methylindole, because in this case the reaction was driven to completion by the addition of several portions of Pd catalyst. The presence of silver salts inhibits the migration of the double bond: as a result, products with an exocyclic methylene group can be isolated (**Scheme 1**).[5]

The construction of the indole nucleus is also possible with more highly substituted starting materials. Esters, nitriles, and various nitrogen functionalities do not disturb the reaction (**Scheme 2**), which was proved to be useful for natural product synthesis.[6]–[8]

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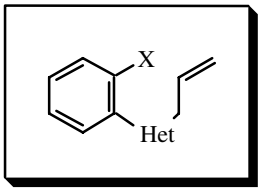
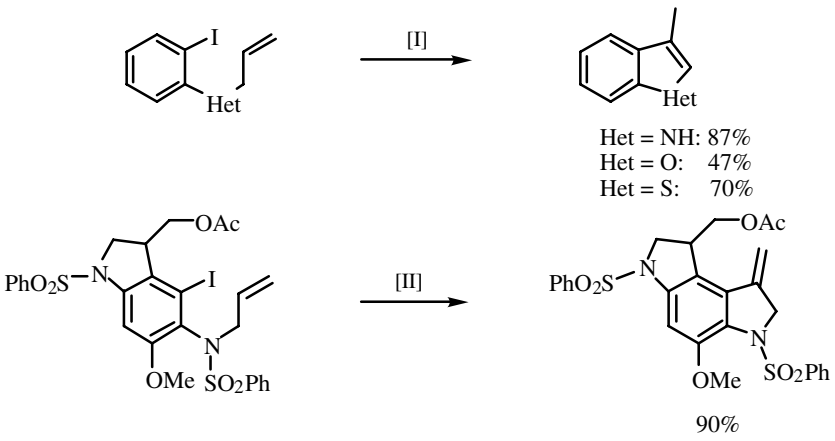
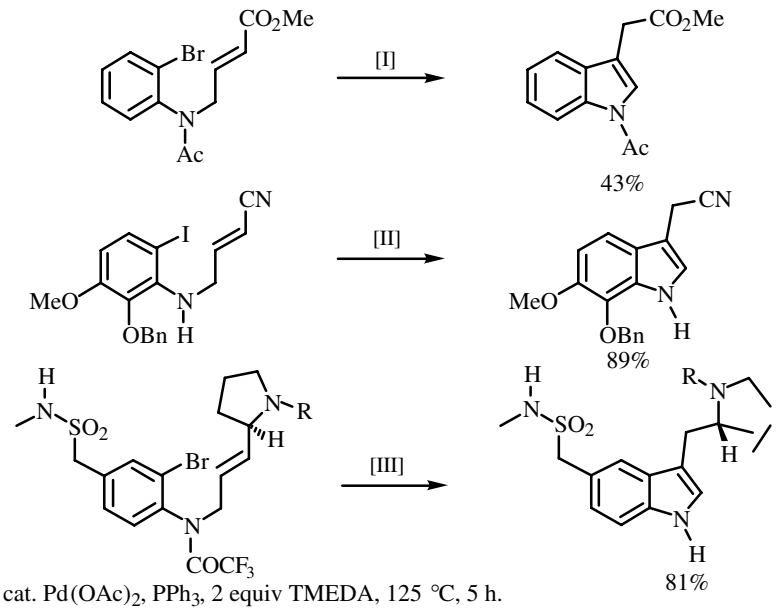



**Figure 1**




[I] = cat. $Pd(OAc)_2$, $Et_3N$ or $Na_2CO_3$, DMF or MeCN, 80–140 °C, 15–72 h.
[II] = 2 mol % $Pd(OAc)_2$, 1.5 equiv $Ag_2CO_3$, DMF, 20 °C, 2 h.

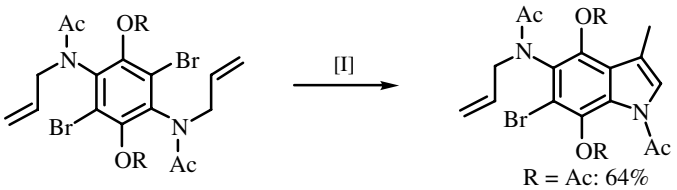
**Scheme 1**




[I] = cat. $Pd(OAc)_2$, $PPh_3$, 2 equiv TMEDA, 125 °C, 5 h.
[II] = 5 mol% $Pd(OAc)_2$, $P(o\text{-}Tol)_3$, $Et_3N$, MeCN, reflux, 3 h.
[III] = cat. $Pd(OAc)_2$, $Et_3N$, DMF, Δ.

**Scheme 2**

However, some cases are known in which electronic effects of substituents strongly influence the outcome of the intramolecular Heck reaction. The example presented in **Scheme 3** is especially illustrative: the bisamide underwent a monocyclization to give a highly substituted indole, whereas the corresponding dimethoxy-substituted starting material did not react at all.[9]

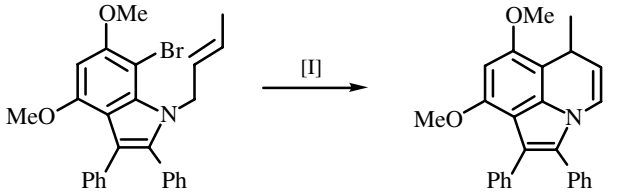



R = Ac: 64%
R = Me: 0%

[I] = cat. $Pd(OAc)_2$, P(*o*-Tol)$_3$, $Et_3N$, MeCN, 50–110 °C.

**Scheme 3**

In all these examples the ring closing carbopalladation step has to be classified as a 5-*exo-trig* reaction. Of course, there is no rule without exception: the cyclization of the indole derivative in **Scheme 4** obviously proceeds as a 6-*endo-trig* reaction, thereby avoiding the formation of a rather strained ring system with two annelated five-membered rings.[10] In order to achieve the rather high yield in this reaction a large amount of catalyst (43 mol %) had to be applied.

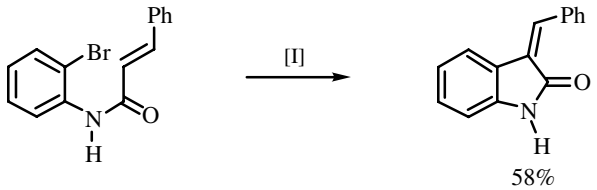



R = Me
94%

[I] = 43 mol % Pd $(OAc)_2$, 73 mol % P (*o*-Tol)$_3$, $Et_3N$, MeCN, 100 °C, 15 h.

**Scheme 4**

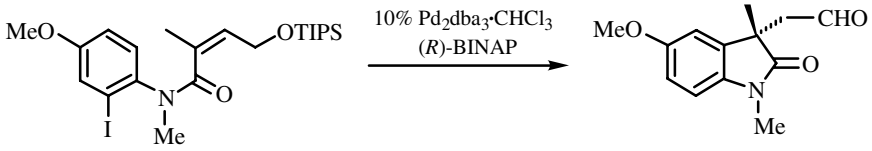
$\alpha,\beta$-Unsaturated amides as starting materials (**Schemes 5**, **6**, and **7**) are structurally closely related to the allylic amines discussed before and also match the substructure shown in **Figure 1**. The additional carbonyl group prevents aromatization and does not influence the regioselectivity of the carbopalladation step. The stereoselectivity observed for the product in **Scheme 5** is the result of the stereochemical requirements of the $\beta$-H-elimination step.[11]




58%

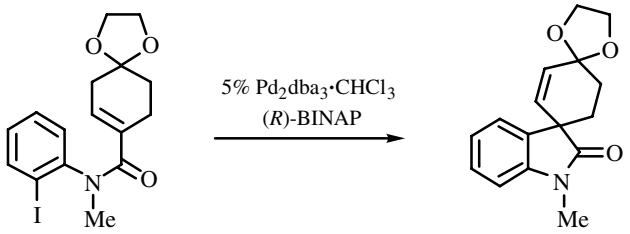
[I] = 1 mol % $Pd(OAc)_2$, 4 mol % P(*o*-Tol)$_3$, $Et_3N$, MeCN, 100 °C, 18 h.

**Scheme 5**




84% (95% ee)

**Scheme 6**




with $Ag_3PO_4$: *S*-enantiomer: 81% (71% ee)
without $Ag_3PO_4$: *R*-enantiomer: 77% (66% ee)

**Scheme 7**

Related substrates were repeatedly cyclized in an enantioselective fashion.[12],[13] For these examples the formation of a quaternary carbon as the chiral center is crucial. Very often BINAP has been applied as the chiral ligand: the synthesis of the chiral aldehyde in **Scheme 6** represents an important step in the synthesis of physostigmine.[14]

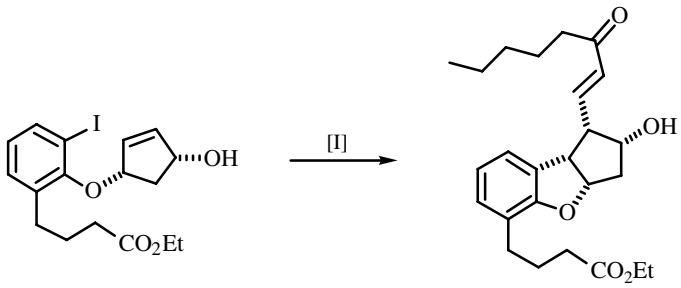
In certain cases the stereoselectivity of the cyclization reaction is rigorously influenced by the addition of silver salts[15]: using the same enantiomer of BINAP both enantiomers of a spiroannelated indole could be selectively obtained depending on the presence or absence of silver salts (**Scheme 7**).

Numerous examples of Heck-type reactions are known, where the common $\beta$-H-elimination usually following the carbopalladation step is inhibited because of structural or stereochemical reasons. Either the intermolecular reaction with an additional reagent or another cyclization reaction then terminates the Pd-catalyzed process. Such reactions are discussed below, again starting from substrates related to the substructure shown in **Figure 1**.

The product in **Scheme 8**, reminiscent of a prostaglandin, is the result of an intramolecular carbopalladation followed by an intermolecular Heck reaction, which becomes possible because the decisive intermediary alkylpalladium complex is lacking an appropriate hydrogen in synperiplanar position for the $\beta$-H-elimination.[16]

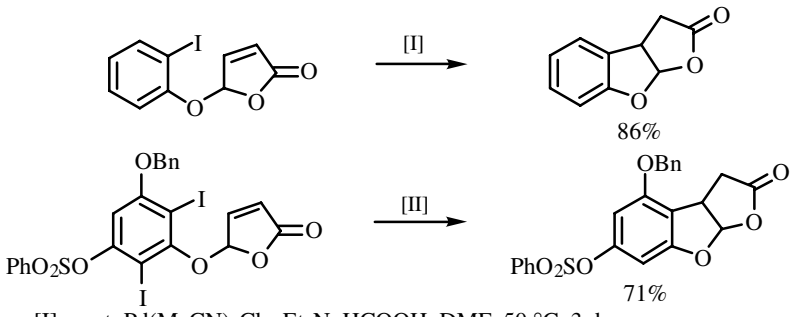
Similarly, the intermediary alkylpalladium complexes, which have to be assumed for the reactions in **Scheme 9**, have a sufficient lifetime to interact with an additional reagent: in these cases reduction by sodium formate takes place. The resulting furobenzofurans are model compounds for the synthesis of aflatoxines.[17],[18]

For the reactions presented in **Scheme 10** the catalytic cycle is terminated by a second ring-closing step, again becoming possible because of the inhibition of the $\beta$-H-elimination.[19]–[21] These examples illustrate the versatility of this type of domino processes. In view of the numerous possibilities for structural variation of the substrate and of additional reagents a broad variety of highly functionalized polycylic systems are easily accessible.[22],[23]



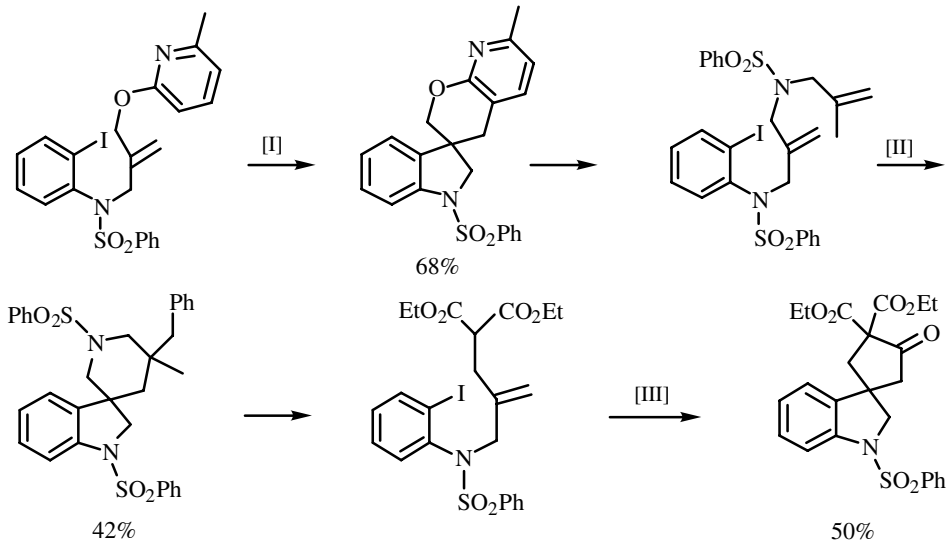
[I] = 5 mol % $Pd(OAc)_2$, 10 equiv 1-octen-3-one, 42%
*i*-$Pr_2Et$, *n*-$Bu_4NCl$, DMF, 50 °C.

**Scheme 8**



[I] = cat. $Pd(MeCN)_2Cl_2$, $Et_3N$, HCOOH, DMF, 50 °C, 3 d.
[II] = cat. $Pd(MeCN)_2Cl_2$, *n*-$Bu_4NCl$, $Et_3N$, HCOONa, DMF.

**Scheme 9**



[I] = 11 mol % $Pd(OAc)_2$, 25 mol % $PPh_3$, $Et_4NCl$, $K_2CO_3$, MeCN, reflux, 17 h.
[II] = 10 mol % $Pd(OAc)_2$, 20 mol % $PPh_3$, $Ph_4BNa$, $Et_4NCl$, $K_2CO_3$, MeCN.
[III] = 10 mol % $Pd(OAc)_2$, 25 mol % $PPh_3$, 1 atm CO, TlOAc, MeCN.

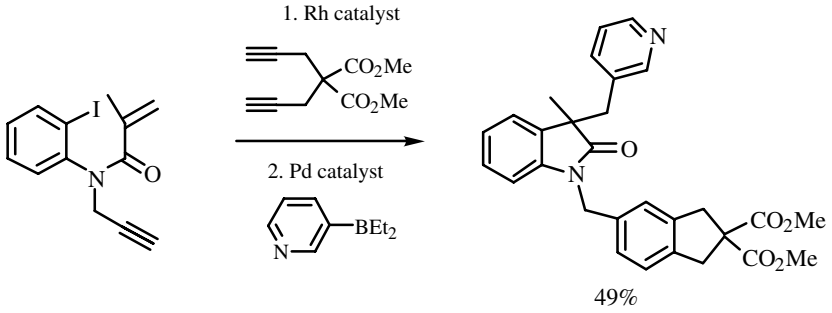
**Scheme 10**

The assembly of polyfunctional compounds is further illustrated by a recent example of a one-pot reaction (**Scheme 11**).[24] In the first reaction step a rhodium-catalyzed [2 + 2 + 2] cyclization of a bisalkyne with a monoalkyne takes place, building up a functionalized benzene nucleus. Subsequent addition of a palladium catalyst initiates the Heck-type heterocyclization, which is finally followed by the capturing of the intermediary alkyl–Pd complex with a boron-substituted pyridine.

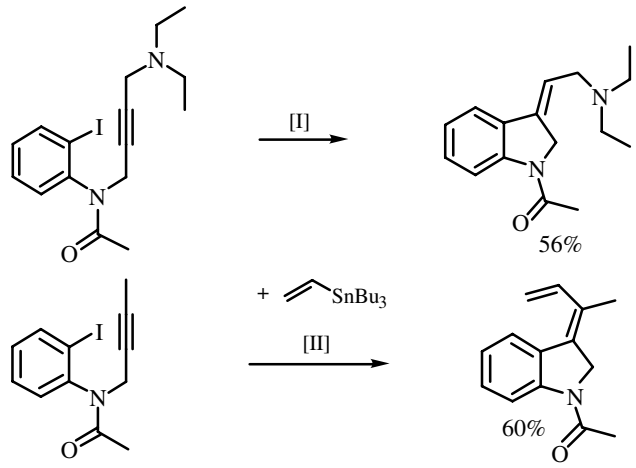
Closely related to the allyl-substituted starting materials discussed above are of course propargylic derivatives (**Scheme 12**).[25],[26] Since the carbopalladation of alkynes leads to alkenylpalladium species, which normally do not undergo $\beta$-H-elimination, additional reagents such as formic acid or a alkenyltin compound can take part in the process.

The ethenyl-substituted substructures in **Figure 2** are typical for a variety of substrates, which also lead to five-membered heterocycles. Compared to the structure in **Figure 1**, only the position of the heteroatom has changed in the case of the first structure. Generally, this does not significantly influence the reactivity or induce a change in mechanism.

The cyclization proceeds in the sense of a 5-*exo-trig* reaction in analogy to the processes discussed above for allylic substrates. Frequently, spirocyclic products are obtained as shown in **Scheme 13**.[26]–[28] Another prominent example is the final step in a total synthesis of camptothecin presented in **Scheme 14**.[29]




**Scheme 11**




[I] = 10 mol % $Pd(OAc)_2$, 20 mol % $PPh_3$, $Ag_2CO_3$, HCOONa, MeCN, 60 °C, 15h.
[II] = 10 mol % $Pd(OAc)_2$, 20 mol % $PPh_3$, MeCN, 5–25 °C, 2–6 h.

**Scheme 12**

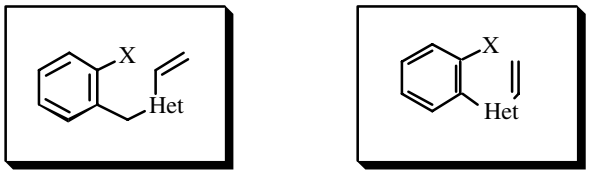
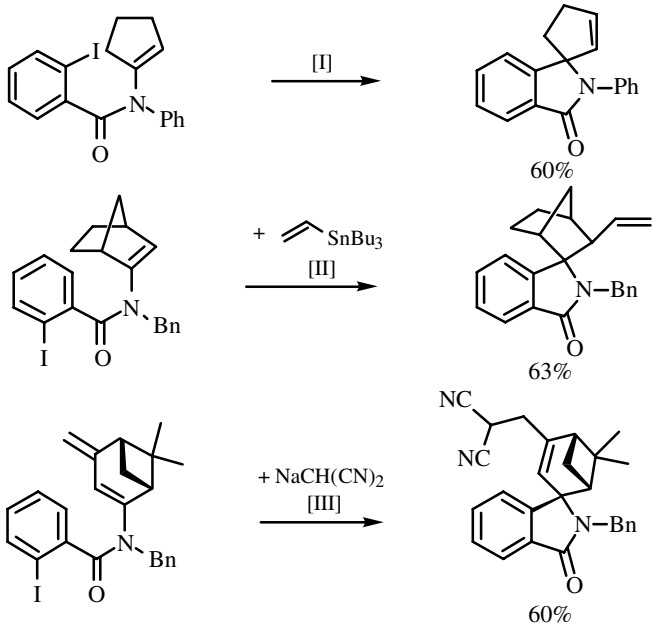
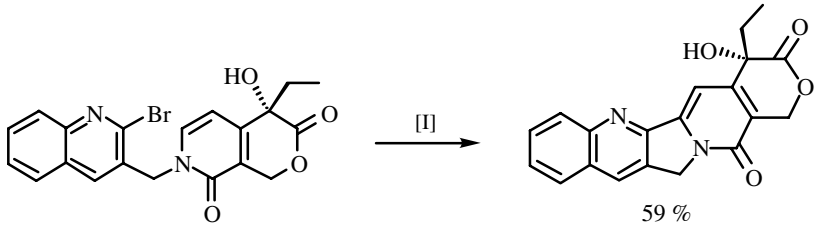



**Figure 2**




[I] = 10 mol % $Pd(OAc)_2$, 20 mol % $PPh_3$, $K_2CO_3$, $Et_4NCl$, MeCN, 80 °C, 2.5 h.
[II] = 10 mol % $Pd(OAc)_2$, 20 mol % $PPh_3$, MeCN, 80 °C, 1 h.
[III] = 10 mol % $Pd(OAc)_2$, 20 mol % $PPh_3$, MeCN, 80 °C.

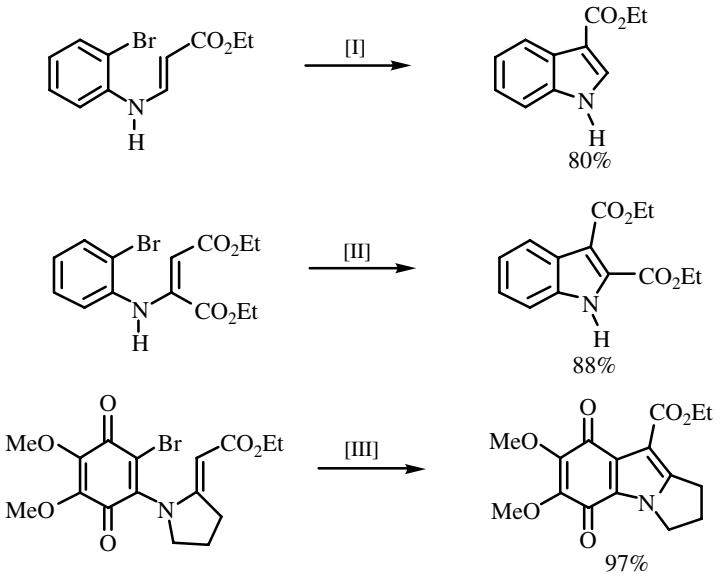
**Scheme 13**




[I] = cat. $Pd(OAc)_2$, AcOK, *n*-$Bu_4NBr$, DMF, 90 °C, 3 h.

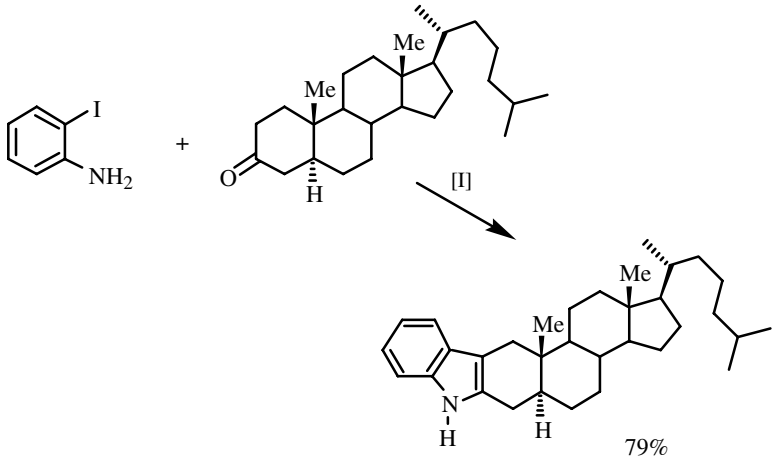
**Scheme 14**

The mechanism of the cyclization reactions in **Scheme 15** is yet unclear[30]–[32]: either an unusual 5-*endo-trig* carbopalladation takes place as key step or a cyclopalladation[33] followed by reductive elimination. More typical examples of the latter type of process are discussed in **Sect. D**. Whatever the mechanism, the yields achieved are good to excellent in every case. Moreover, this type of starting material is easy to build up, even *in situ* from aniline derivatives and suitable carbonyl compounds (**Scheme 16**).[34]




[I] = 5 mol % $Pd(OAc)_2$, 15 mol % P(*o*-Tol) , $Et_3N$, MeCN, 100 °C, 20 h.
[II] = 5 mol % $Pd(OAc)_2$, $Et_3N$, DMF, 120 °C, 3 h.
[III] = 6.8 mol % $Pd(OAc)_2$, $Et_3N$, MeCN, r.t., 2 h.

**Scheme 15**




[I] = 5 mol % $Pd(OAc)_2$, DABCO, DMF, 105 °C, 3 h.

**Scheme 16**

Compared to **Figure 1**, the substructures of **Figure 3** have side chains elongated by one carbon atom. Heck-type cyclization of substrates that match these substructures should lead to six-membered heterocycles because the intramolecular carbopalladation in the sense of a 6-*exo-trig* reaction should clearly be favored against the 7-*endo-trig* pathway.

The cyclization of the benzyl bromide in **Scheme 17** results in a tetrahydroquinoline derivative: variations of the final product are possible by the interaction with additional reagents such as sodium formate and sodium tetraphenylborate.[35]

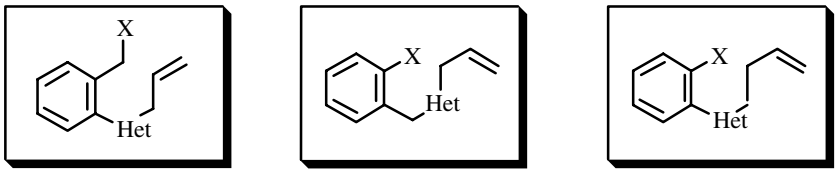
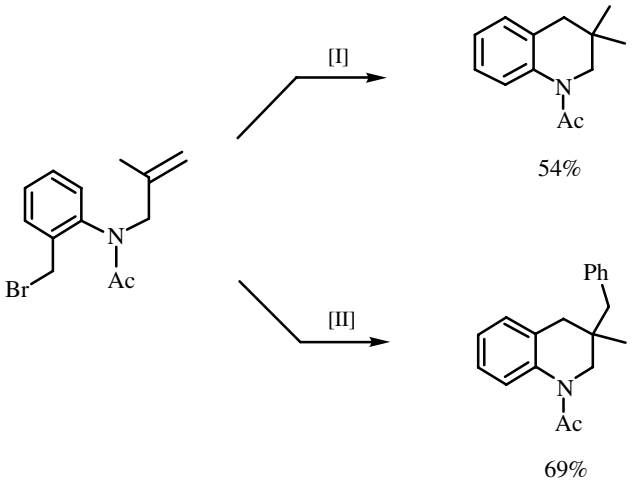



**Figure 3**




[I] = 10 mol % $Pd(OAc)_2$, 20 mol % $PPh_3$, HCOONa, MeCN, 80 °C, 4–6 h.
[II] = 10 mol % $Pd(OAc)_2$, 20 mol % $PPh_3$, $NaBPh_4$, anisole, 90 °C, 9 h.

**Scheme 17**

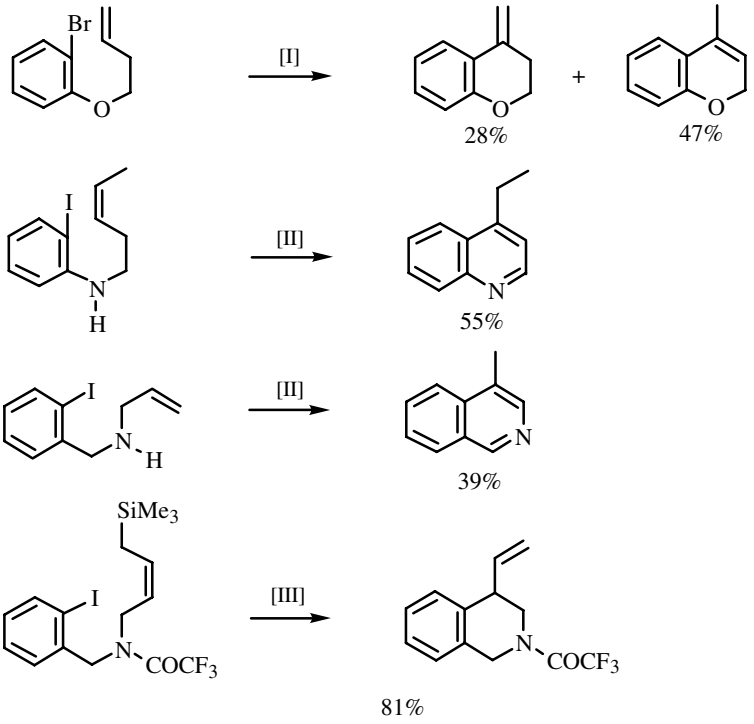
The homoallyl-substituted substrates of **Scheme 18** give benzopyrans and benzoquinolines, respectively.[36] The initially exocyclic double bond of the product tends to migrate into the ring, presumably by readdition of the intermediary hydridopalladium halide and subsequent $\beta$-H-elimination. In addition, for the *N*-heterocycle aromatization by dehydrogenation is observed. Similarly the 2-iodobenzylamine with the *N*-allyl substituent leads to the aromatized isoquinoline.[2] The fourth example of **Scheme 18** illustrates that a silyl substituent influences the regioselectivity of the $\beta$-H-elimination and that an acyl group at the nitrogen has some share in preventing aromatization.[37],[38]

Various functional groups are tolerated and especially electron-withdrawing groups on the aryl halide appear to have a beneficial effect on the yields achieved (**Scheme 19**).[39],[40]

Also, multiple annulated ring systems and spirocycles, which are related to drugs and natural products, are efficiently accessible by this methodology (**Schemes 20a** and **20b**).[41]–[43]

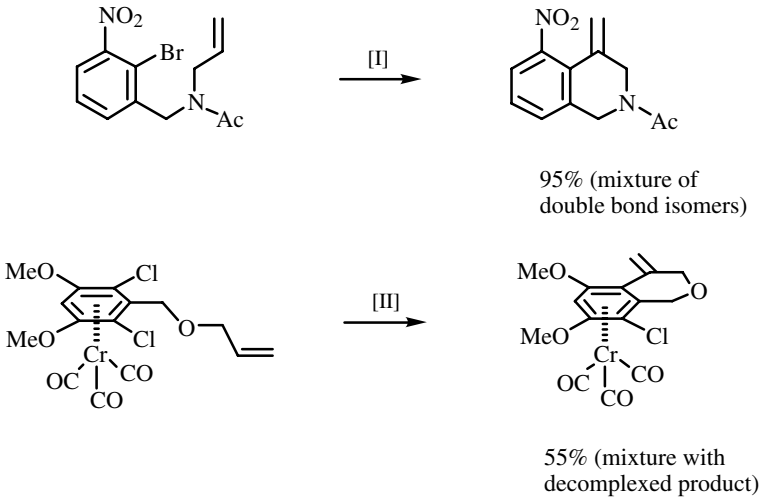
Similarly, oligocycles are obtained from appropriate allyl benzyl ethers as outlined with representative examples in **Scheme 21**.[44] Stereochemical aspects of Pd-catalyzed cyclizations in connection with the synthesis of pancratistatin and related natural products have been studied intensively (second reation in **Scheme 21**).[45],[46]

In the presence of an appropriate additional double bond, $\pi$-allylpalladium complexes are formed stereoselectively as intermediates, which subsequently undergo nucleophilic substitution, for instance, by a malonate (**Scheme 22**).[47]



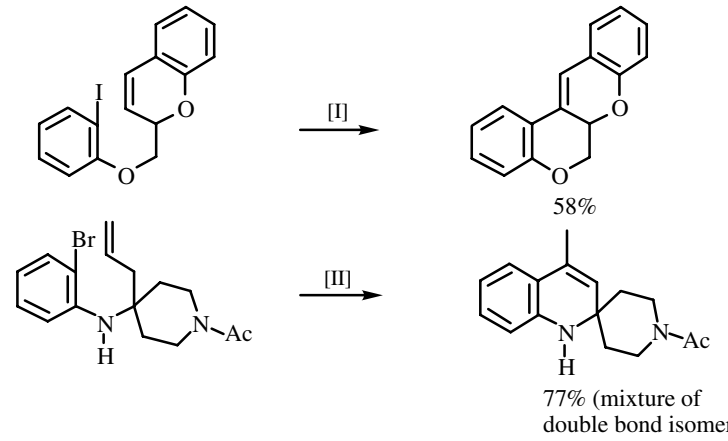

[I] = 1–2 mol % $Pd(OAc)_2$, 2–4 mol % P(*o*-Tol)$_2$, $Et_3N$, DMF, 100 °C, 2 d.
[II] = 2 mol % Pd $(OAc)_2$, $Na_2CO_3$ or NaOAc, *n*-$Bu_4NCl$, DMF, 80 °C, 1 d.
[III] = 5 mol % Pd $(OAc)_2$, 10 mol % $PPh_3$, KOAc, $Pr_4NBr$, DMF, 55 °C, 3 h.

**Scheme 18**

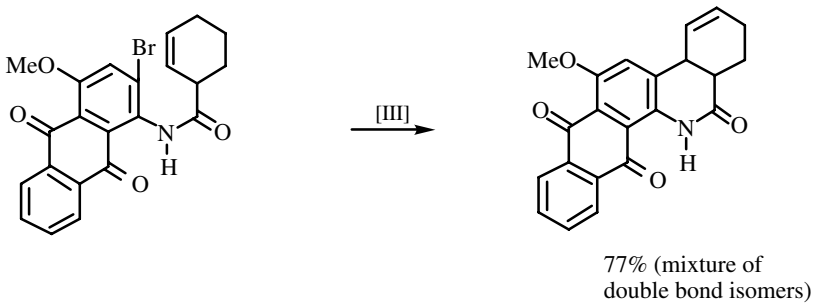



[I] = cat. $Pd(OAc)_2$, P(*o*-Tol)$_3$, $Et_3N$, 100 °C, 5 min.
[II] = cat. $Pd(OAc)_2$, $PPh_3$, $Et_3N$, DMF, 80 °C, 1 d.

**Scheme 19**

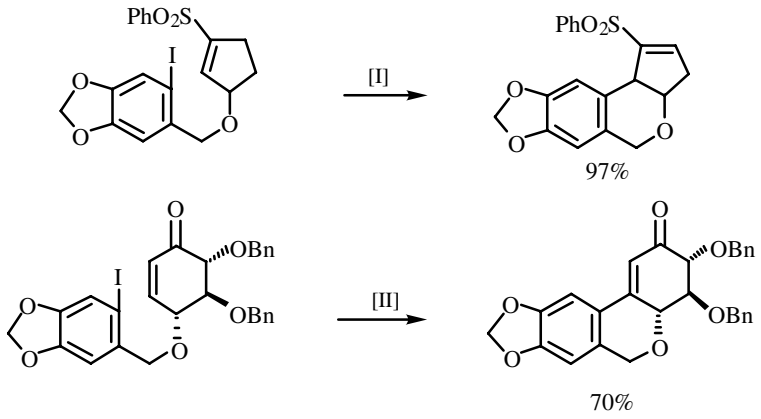



**Scheme 20a**



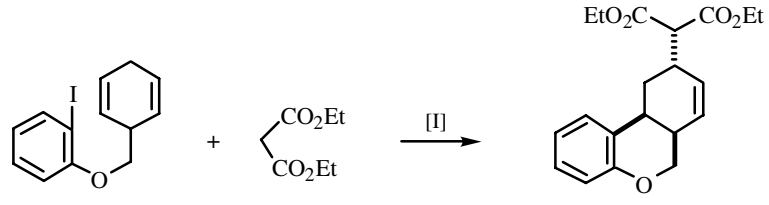

[I] = 50 mol % $Pd(OAc)_2$, $PPh_3$, $Et_3N$, MeCN, 70 °C, 12 h.
[II] = 5 mol % $Pd(OAc)_2$, 10 mol % $PPh_3$, $Et_3N$, MeCN, 80 °C, 3 d.
[III] = 10 mol % $Pd_2(dba)_3$, 20 mol % P(*o*-Tol)$_3$, *i*-$Pr_2$NEt, BSA/DMF 1:30, 70 °C, 1 h.

**Scheme 20b**




[I] = 5 mol % Pd $(PPh_3)_4$, $Et_3N$, $AgNO_3$, MeCN, reflux, 3.5 h.
[II] = cat. $Pd(OAc)_2$, $PPh_3$, $Et_3N$, $AgNO_3$, MeCN, reflux.

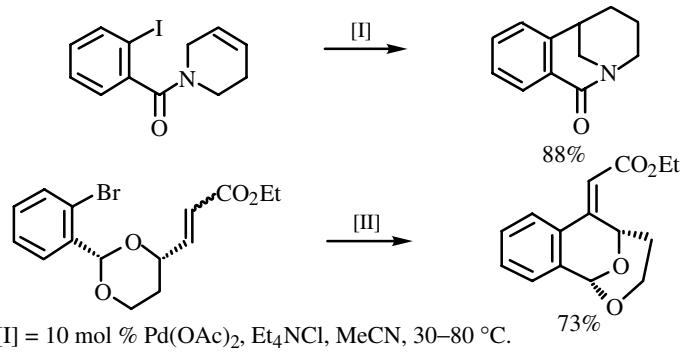
**Scheme 21**




[I] = 10 mol % $Pd(dba)_2$, $Na_2CO_3$, $Et_4NCl$, DMSO, 100 °C, 4 h.

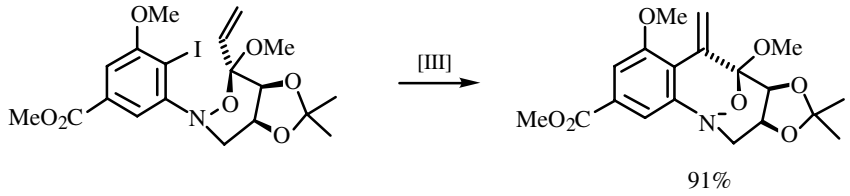
**Scheme 22**

In the first example of **Scheme 23a** the position of the double bond in the tetrahydropyridine moiety enables the formation of a bridged ring system with the nitrogen in a bridgehead position.[48] In principle, there is no limit for the structural complexity of heterocyclic products built up by intramolecular Heck-type reactions, as illustrated by the synthesis of chiral highly functionalized bridged systems in **Scheme 23b**.[49],[50]




[I] = 10 mol % $Pd(OAc)_2$, $Et_4NCl$, MeCN, 30–80 °C.
[II] = cat. $Pd(PPh_3)_4$, $Et_3N$, MeCN, 140 °C, 73 h; sealed tube.

**Scheme 23a**




[III] = 20 mol % $Pd(PPh_3)_4$, $Et_3N$, MeCN, 80 °C, 10 h, sealed tube.

**Scheme 23b**

Two examples for the formation of spirocyclic structures are presented in **Scheme 24**. The first one is a key step in the enantioselective total synthesis of the alkaloid (+)-tazettine.[51] The second is the result of a domino process with two subsequent carbopalladation steps[52]; numerous examples of this type of domino process are found in the literature and are discussed in other sections of this compendium.

Substrates that match the substructures shown in **Figure 4** are anticipated to lead to seven-membered heterocycles since the 7-*exo-trig* cyclization should generally be favored.

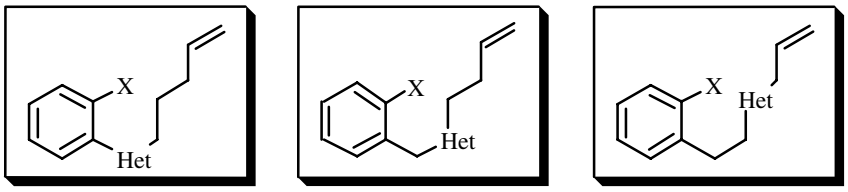
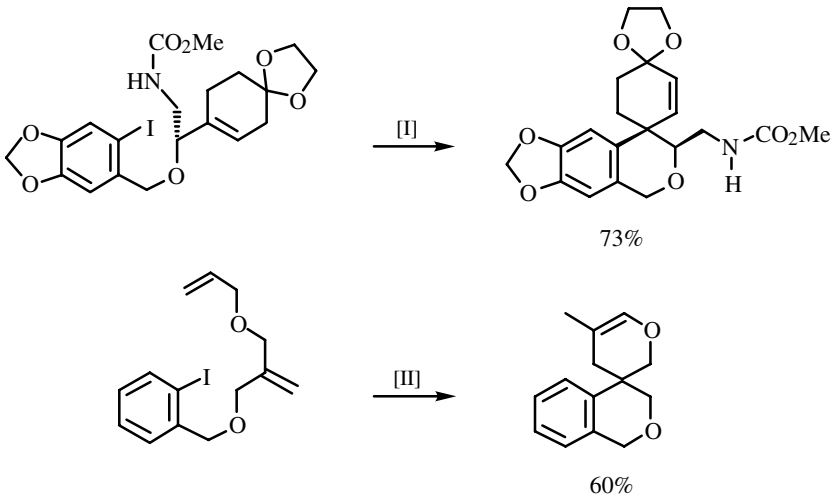


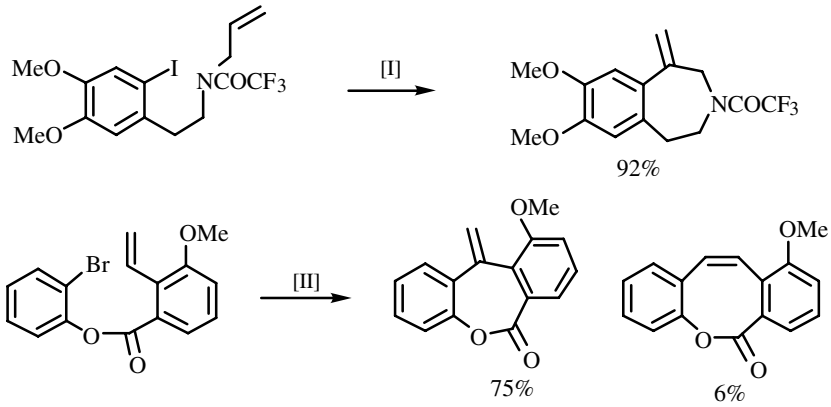

**Figure 4**




[I] = 10 mol % Pd $(OAc)_2$, 40 mol % $PPh_3$, $Ag_2CO_3$, THF, 56 °C.
[II] = 15 mol % Pd $(OAc)_2$, $Et_3N$, *n*-$Bu_4NCl$, DMF, 75 °C.

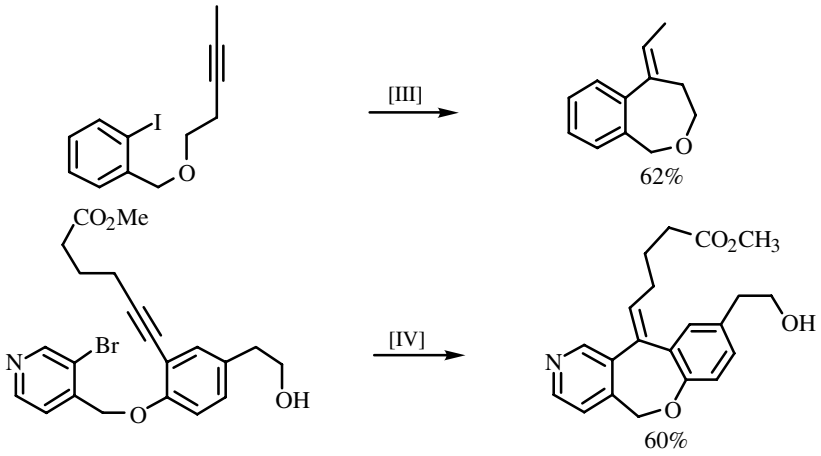
**Scheme 24**

This is indeed the case for the first two olefinic examples in **Scheme 25a**.[53],[54] In analogy, related alkynes cyclize exclusively in the sense of a 7-*exo-dig* reaction (**Scheme 25b**).[25],[55] Surprisingly, the very similar allene in **Scheme 26** reacts in an *endo* fashion resulting in an eight-membered heterocycle.[56]



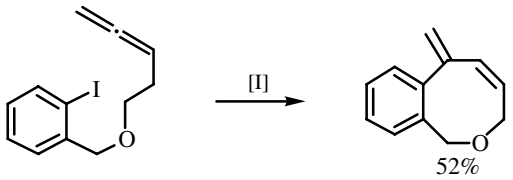

[I] = 1 mol % $Pd(OAc)_2$, $PPh_3$, KOAc, *n*-$Pr_4NBr$, DMF, 80 °C, 12 h.
[II] = 50 mol % $PdCl_2$ $(PPh_3)_2$ in several portions, NaOAc, MeCN, 90 °C, 2 d.

**Scheme 25a**




[III] = 10 mol % $Pd(OAc)_2$, $PPh_3$, piperidine, HCOOH, $Et_4NCl$, MeCN, 80 °C, 16 h.
[IV] = cat. $Pd(OAc)_2$, P(*o*-Tol)$_3$, piperidine, HCOOH, MeCN.

**Scheme 25b**

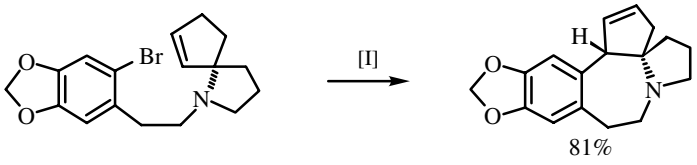



[I] = 5 mol % $PdCl_2(PPh_3)_2$, $K_2CO_3$, EtOH, DMF, 100 °C, 2 h.

**Scheme 26**

In the spirocyclic starting material of **Scheme 27** one can identify the third substructure of **Figure 4**. The Pd-catalyzed 7-*exo-trig* cyclization was the key step in the synthesis of cephalotoxine.[57]

The examples in **Scheme 28** further demonstrate the feasibility of the construction of medium-sized heterocycles. In these cases the *endo-type* cyclization is favored both by steric and by electronic factors.[58],[59]




[I] = 4 mol % $Pd(OAc)_2$/P(*o*-Tol)$_3$ cyclometallated complex, *n*-$Bu_4NOAc$, MeCN/DMF/$H_2O$, 110–120 °C.

**Scheme 27**

The starting materials discussed above were limited to aryl halides (with the exception in **Scheme 17**). Nevertheless, a broad variety of alkenyl halides are also suitable for the construction of heterocycles by Heck-type cyclizations. Some typical substructures, which can be identified as part of suitable substrates, are depicted in **Figures 5** and **6**.

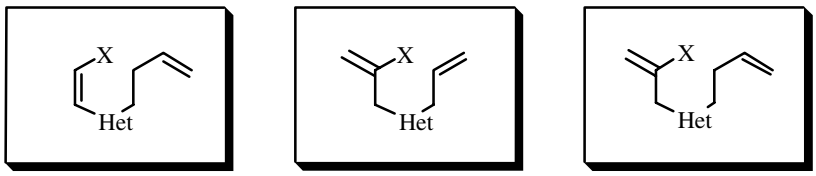



**Figure 5**

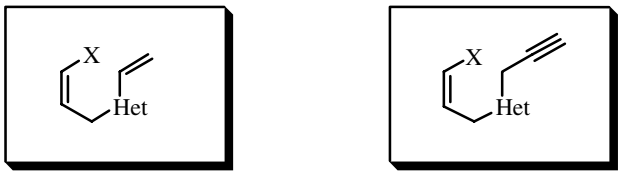
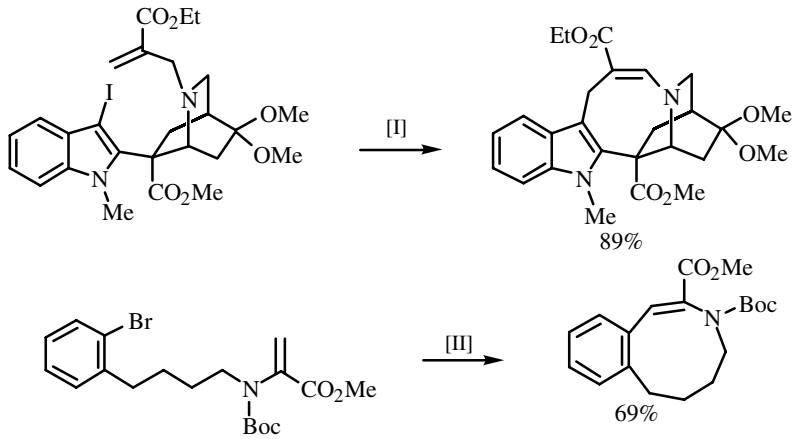


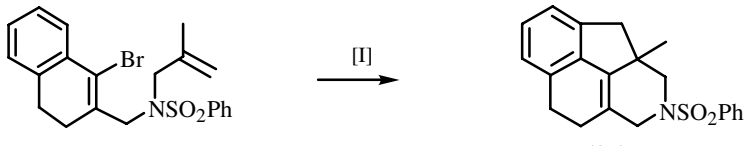

**Figure 6**




[I] = 6 mol % $Pd(OAc)_2$, KOAc, *n*-$Bu_4NCl$, DMF, 80 °C, 6 h.
[II] = 5 mol % $Pd(OAc)_2$, NaOAc, $Ph_4PCl$, DMF, 120 °C, 30 min.

**Scheme 28**

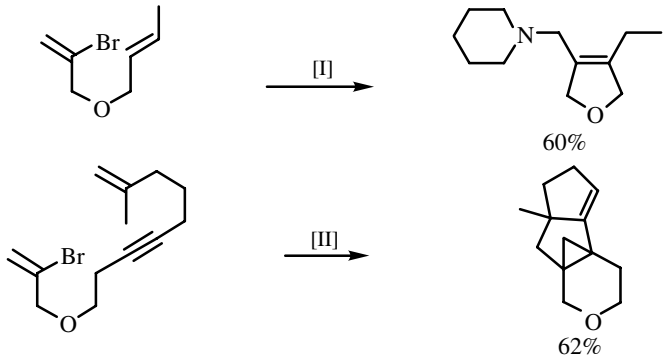
For the reaction in **Scheme 29** one can assume that the resulting double annelation starting from the dihydronaphthalene derivative should not differ from the one that would be achieved with the corresponding aromatic naphthalene.[60]




[I] = 10 mol % $Pd(OAc)_2$, 20 mol % $PPh_3$, AcOK, anisole, 140–150 °C, 18 h.

**Scheme 29**

However, in the case of the alkenyl bromides in **Scheme 30** the vinyl group is crucial for the resulting domino processes.[36],[61] In the first example, the initial carbopalladation leads to an allylpalladium complex, which is prone to react with the nucleophilic piperidine. The second example is explained by an unusual threefold carbopalladation, which becomes possible, because after each of the first two carbopalladation steps the $\beta$-H-elimination, normally terminating the process, is inhibited of structural reasons.

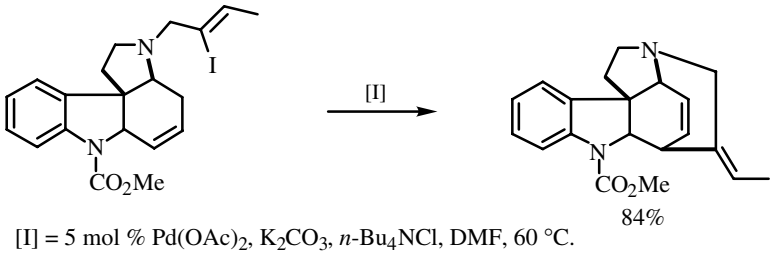



[I] =1–2 mol % $Pd(OAc)_2$, 2–4 mol % P(*o*-Tol)$_3$, piperidine, MeCN, 100 °C.
[II] = 3–5 mol % $Pd(PPh_3)_4$, $Ag_2CO_3$, MeCN, reflux, 3 d.

**Scheme 30**

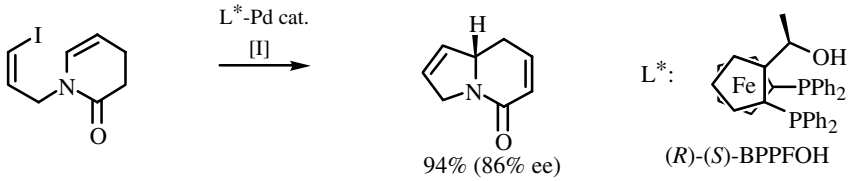
The starting material in **Scheme 31** matches the third substructure of **Figure 5**. This reaction is an impressive attempt to accomplish strychnos alkaloid synthesis by Heck-type reactions.[62]

Also interesting for alkaloid syntheses are substrates with substructures as those in **Figure 6**: **Schemes 32a** and **32b** demonstrate the synthesis of the indolizidine nucleus even in an enantioselective fashion.[63],[64]



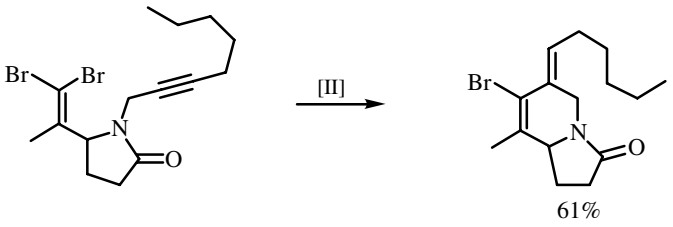

[I] = 5 mol % $Pd(OAc)_2$, $K_2CO_3$, *n*-$Bu_4NCl$, DMF, 60 °C.

**Scheme 31**




[I] = $Pd_2(dba)_3$ (4 mol % Pd), 9.6 mol % (*R*)-(*S*)-BPPFOH, Ag-exchanged zeolite, $CaCO_3$, DMSO/DMF, 0 °C.

**Scheme 32a**

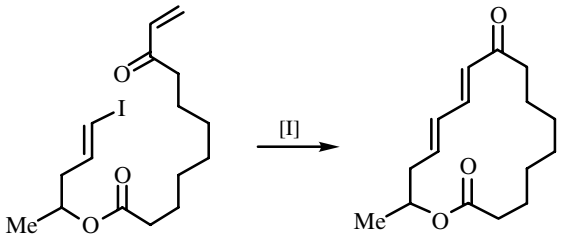



61%

[II] = 2 mol % $Pd(OAc)_2$, 4 mol % $PPh_3$, $HCOONH_4$ or $NH_4OAc$, MeCN, reflux.

**Scheme 32b**

In principle, the macrocyclization in Scheme 33 is catalytic in palladium. However, applying 1 equiv of the catalyst was one of the factors minimizing the competing intermolecular reaction and ensuring a rather high yield of the 16-membered lactone.[65]

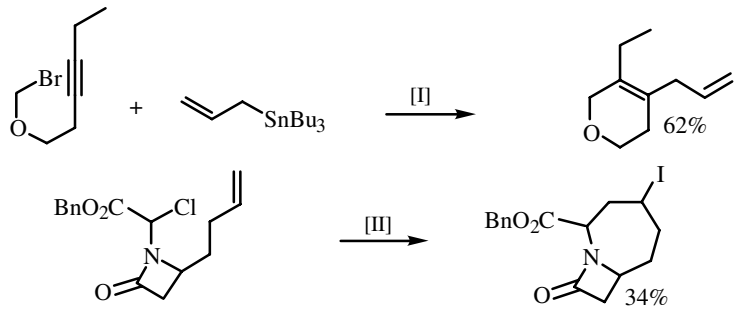



55%

[I] = 1 equiv $PdCl_2(MeCN)_2$, HCOOH, $Et_3N$, MeCN, 25 °C.

**Scheme 33**

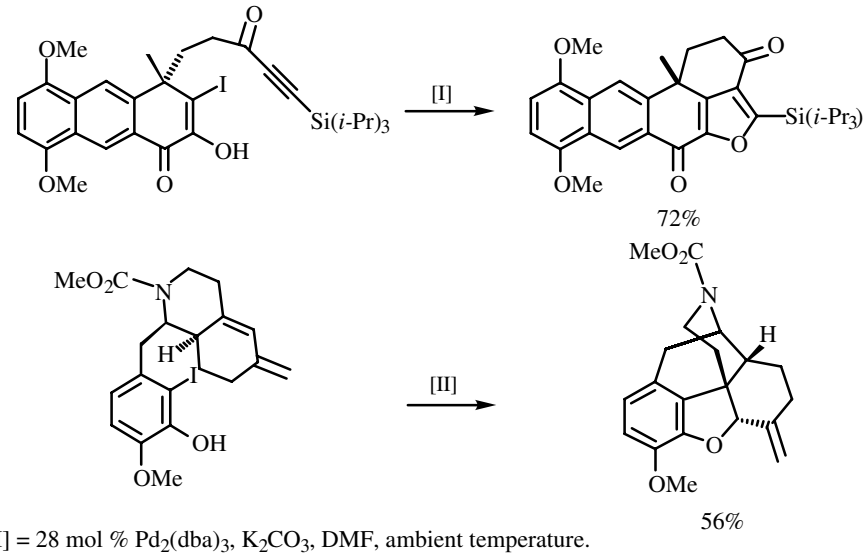
Although chloro- and bromomethyl substituents at a heteroatom represent sensitive functional groups, which tend to decompose under various conditions, the reactions in **Scheme 34** demonstrate that substrates of this kind are nevertheless suitable for Heck-type cyclizations[66],[67]: for the first example an intermediary alkenylpalladium species is assumed, which is trapped with an allylstannane, a reaction that has some precedent (e.g., **Schemes 12** and **13**). From a mechanistic point of view the net *trans*-addition to the alkyne is remarkable. On the other hand, the trapping of an alkylpalladium species with iodide anions as in the second reaction is also highly unusual.




[I] = 4 mol % $Pd(PPh_3)_4$.
[II] = 15 mol % $Pd(PPh_3)_4$, *i*-$Pr_2NEt$, *n*-$Bu_4NI$, dioxane.

**Scheme 34**

In all of the examples discussed so far, the heterocycle is directly formed in the carbopalladation step. In the following special examples the carbopalladation step provides a Pd functionality, which subsequently undergoes a heterocyclization.[68],[69] The first example of **Scheme 35** is best explained by the formation of an alkenylpalladium species by intramolecular carbopalladation of the alkyne followed by a cyclopalladation with the neighboring hydroxyl group, finally allowing reductive elimination to form the C—O bond. As a mechanistic alternative the complexation of the alkyne by the electrophilic arylpalladium iodide activates for the nucleophilic attack by the heterofunction (Wacker-type cyclization). In the second example the carbopalladation gives rise to an allylpalladium complex, which reacts intramolecularly with the nucleophilic phenolate. In any case, highly complex polycyclic compounds important for natural product synthesis are built up in a few steps.




[I] = 28 mol % $Pd_2(dba)_3$, $K_2CO_3$, DMF, ambient temperature.
[II] = 20 mol % $Pd(OCOCF_3)_2(PPh_3)_2$, 1,2,2,6,6-pentamethylpiperidine, toluene, 120 °C, 10 h.

**Scheme 35**

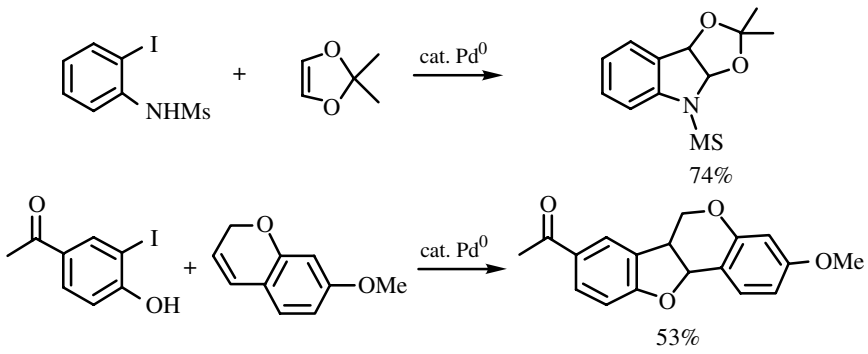
## C. HETEROCYCLE FORMATION INITIATED BY INTERMOLECULAR CARBOPALLADATION

Two types of reactions are summarized in this section: (i) the intermolecular carbopalladation leads to a Pd functionality such as alkyl-, alkenyl-, or allylpalladium complexes, which is intramolecularly trapped by a heteroatom (again Wacker-type processes are mechanistic alternatives); (ii) the palladium catalyst is not directly involved in the heterocyclization step, but the carbopalladation builds up a suitable functionality or changes bond angles so that the heterocyclization can take place.

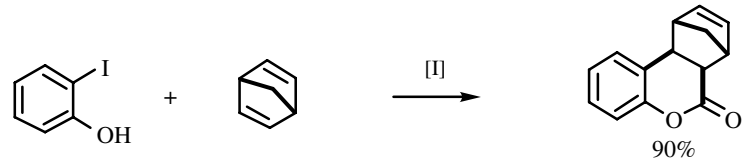
The first type is the intermolecular variant of the reactions in **Scheme 35** and has recently been thoroughly reviewed.[70] Alkenes, allenes, dienes, and alkynes are suitable unsaturated coupling components for the carbopalladation.

In **Scheme 36** two examples of electron-rich alkenes are presented.[70] In **Scheme 37** carbon monoxide takes part as a third component in the coupling process resulting in a lactone formation.[71]

The reactions in **Scheme 38** with allenes as coupling components proceed regioselectively with C—C bond formation at the central carbon and carbon–heteroatom bond formation at the more highly substituted terminal carbon atom.[72],[73] Reactions of this type have recently been performed enantioselectively.[74] Remarkably, for the macrocyclization in **Scheme 39** the carbon–heteroatom bond formation takes place at the unsubstituted terminal carbon atom.[75]

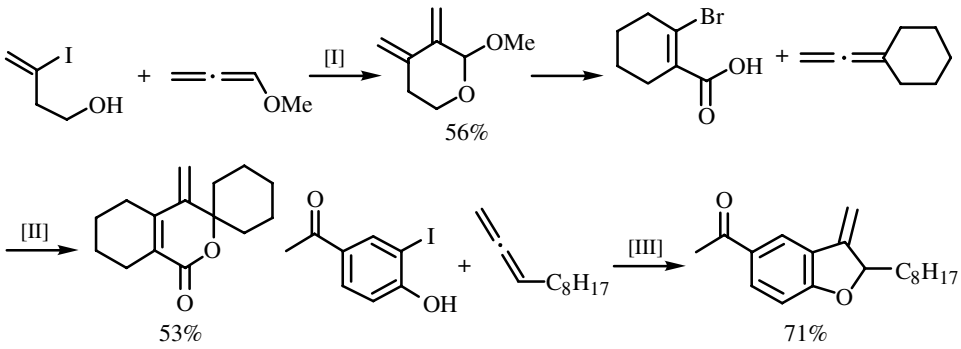



**Scheme 36**



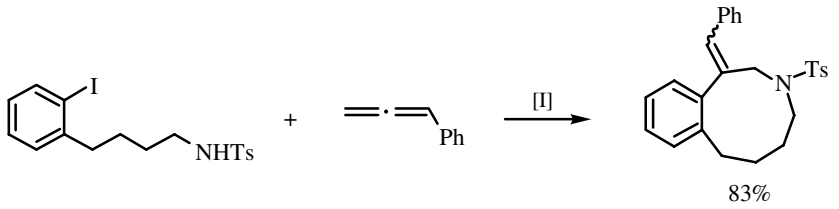

[I] = 15 mol % $Pd(PPh_3)_4$, $K_2CO_3$, 1 atm CO, anisole, 80 °C, 4 h.

**Scheme 37**




[I] = 5 mol % $Pd(OAc)_2$, 5 mol % $PPh_3$, $Na_2CO_3$, *n*-$Bu_4NCl$, DMF, 40 °C, 20 h.
[II] = 5 mol % $Pd(OAc)_2$, 5 mol % $PPh_3$, $Na_2CO_3$, *n*-$Bu_4NCl$, DMF, 25 °C, 3 d.
[III] = 5 mol % $Pd(OAc)_2$, 5 mol % $PPh_3$, $K_2CO_3$, *n*-$Bu_4NCl$, DMF, 100 °C, 1 d.

**Scheme 38**



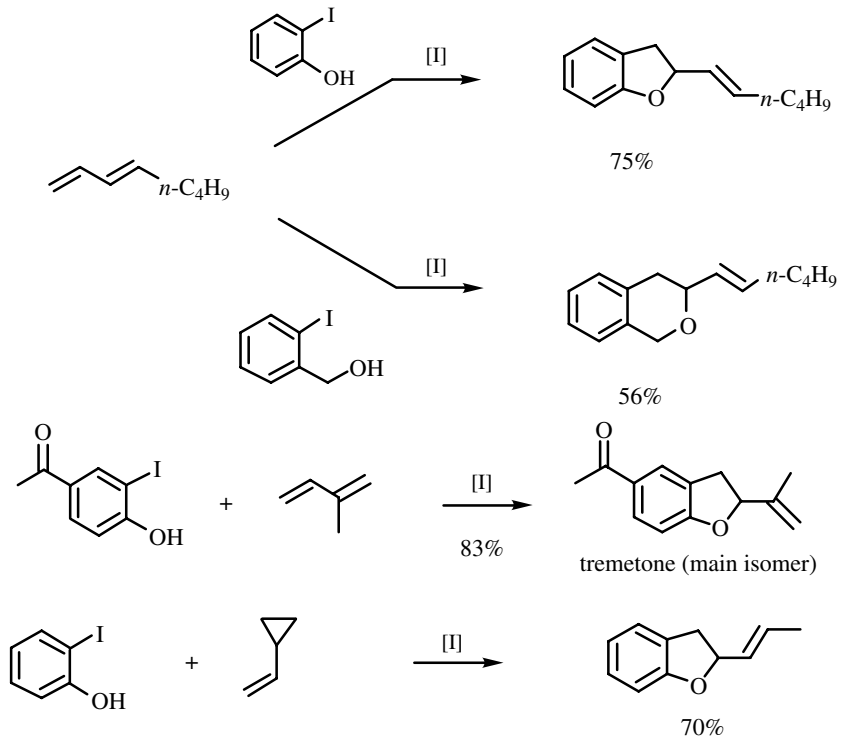

[I] = 5 mol % $Pd_2(dba)_3$, 5 mol % $PPh_3$, $Na_2CO_3$, *n*-$Bu_4NCl$, DMA, 100 °C, 3 d.

**Scheme 39**

The carbopalladation of 1,3-dienes as well as of vinylcyclopropanes (**Scheme 40**)[76],[77] leads to allylpalladium complexes, which are of course suitable for a subsequent heterocyclization (in comparison see second reaction in **Scheme 35**).

Cyclic dienes and 1,4-dienes react in the same way as proved by the synthesis of a tetrahydrocarbazole and a tetrahydroquinoline in **Scheme 41**.[78],[79]

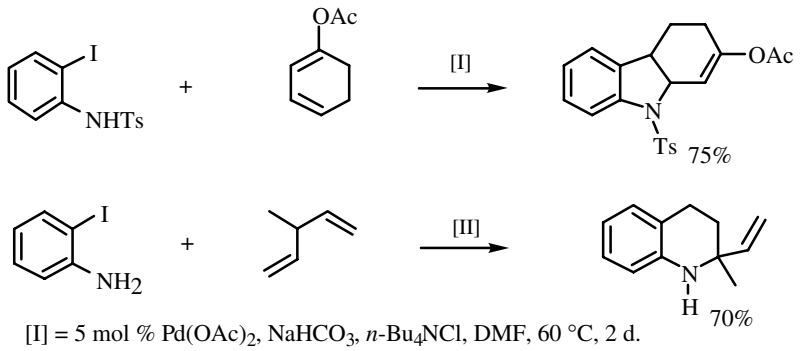
Representative for the numerous examples of analogous coupling reactions with alkynes as coupling components[80]–[83] are the syntheses of multiple functionalized nitrogen hetarenes shown in **Scheme 42**.[84]–[86] In order to avoid Sonogashira-type coupling reactions, the alkynes applied in this type of reaction have to be disubstituted; the




[I] = 5 mol % $Pd(OAc)_2$, $PPh_3$, NaOAc or KOAc, *n*-$Bu_4NCl$, DMF, 80–100 °C, 1–3 d.

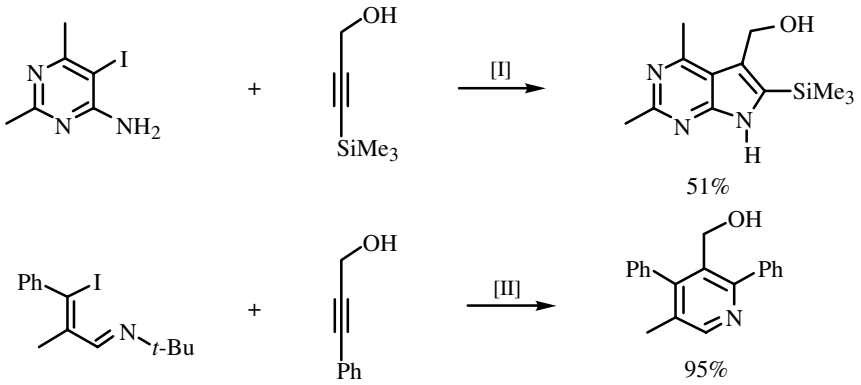
**Scheme 40**

trimethylsilyl group at the alkyne in the first reaction of **Scheme 42** therefore has to be understood as a protecting group. Similarly, an elegant synthesis of tryptophane was achieved starting from 2-iodoaniline and a silylalkynyl-functionalized amino acid.[87] In the second reaction of **Scheme 42** a *tert*-butyl-substituted imine illustrates the broad variability of the coupling components. In this case the *tert*-butyl group is eliminated as isobutene during the heterocyclization.[86]




[I] = 5 mol % $Pd(OAc)_2$, $NaHCO_3$, *n*-$Bu_4NCl$, DMF, 60 °C, 2 d.
[II] = 5 mol % $Pd(OAc)_2$, $K_2CO_3$, *n*-$Bu_4NCl$, DMF, 100 °C, 1.5 d.

**Scheme 41**

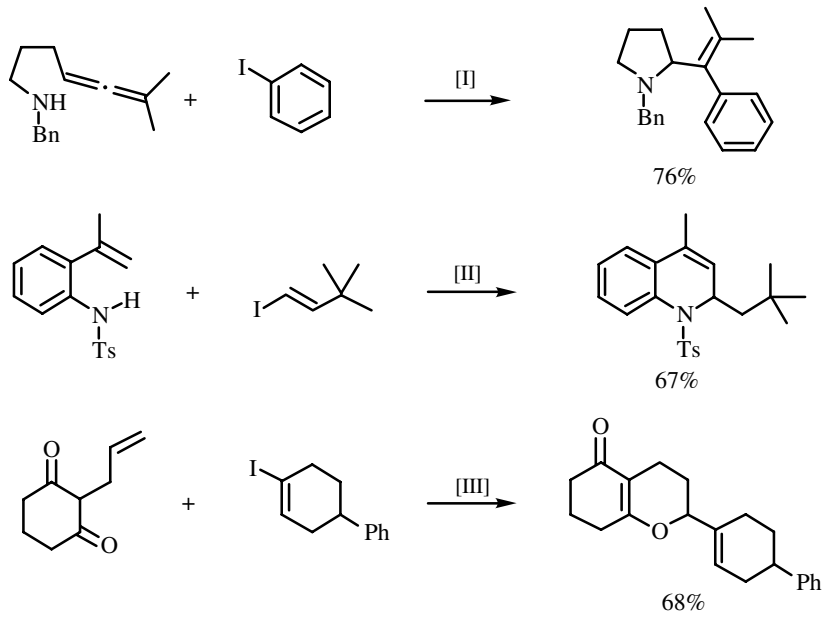



[I] = 5 mol % $Pd(OAc)_2$, $PPh_3$, $Et_3N$, *n*-$Bu_4NCl$, DMF, 90–100 °C, 19 h.
[II] = 5 mol % $Pd(OAc)_2$, $PPh_3$, $Na_2CO_3$, *n*-$Bu_4NCl$, DMF, 100 °C, 2 h.

**Scheme 42**

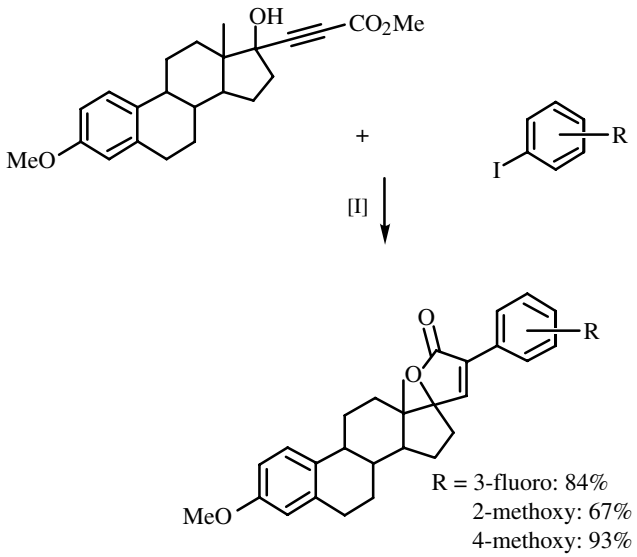
In the examples discussed so far, the halide and the heterofunction were part of the same coupling component. In contrast, for the reactions in **Scheme 43** the heterofunction is located as a neighboring group of the alkene moiety where the carbopalladation takes place.[88]–[92]

The reductive carbopalladation of the alkynyl-substituted steroid in **Scheme 44** changes the hybridization of two carbon atoms from sp to $sp^2$ and therefore bond angles from 180° to 120°, bringing the hydroxyl and the ester group into close proximity with each other as a prerequisite for the lactonization.[93]




[I] = 2–5 mol % $Pd(PPh_3)_4$ , $K_2CO_3$, DMF, 70 °C, 1–3 h.
[II] = 5 mol % $Pd(OAc)_2$, $Na_2CO_3$, *n*-$Bu_4NCl$, DMF, 100 °C, 6 h.
[III] = 5 mol % $Pd(OAc)_2$, $Na_2CO_3$, *n*-$Bu_4NCl$, DMF, 80 °C, 2 h.

**Scheme 43**

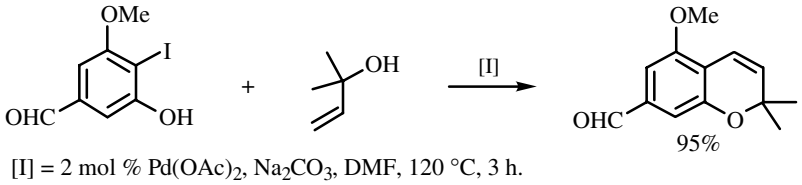



[I] = 5 mol % $Pd(OAc)_2(P(o\text{-}Tol)_3)_2$, *n*-$Bu_3N$, HCOOH, DMF, 60 °C, 6–9 h.

**Scheme 44**

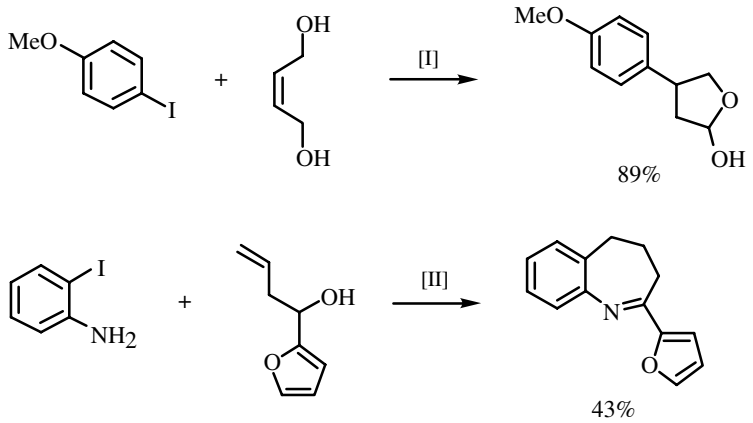
The construction of the benzopyran in **Scheme 45** is easily understood as a domino process consisting of a Heck reaction followed by a cyclocondensation with the allylic tertiary alcohol.[94]

Similarly, Heck reactions with allylic and homoallylic alcohols in **Scheme 46** lead to intermediary carbonyl compounds, which subsequently undergo heterocyclization either by formation of a hemiacetal (first example) or by cyclocondensation (second example).[95],[96] In both cases the palladium catalyst is not involved in the heterocyclization step.




[I] = 2 mol % $Pd(OAc)_2$, $Na_2CO_3$, DMF, 120 °C, 3 h.

**Scheme 45**




[I] = 10 mol % $Pd(OAc)_2$, $K_2CO_3$, $BnEt_3NBr$, DMF, 90 °C, 10 h.
[II] = 5 mol % $Pd(OAc)_2$, $K_2CO_3$, *i*-$Pr_2NEt$, LiCl, DMF, 120 °C, 2 d.

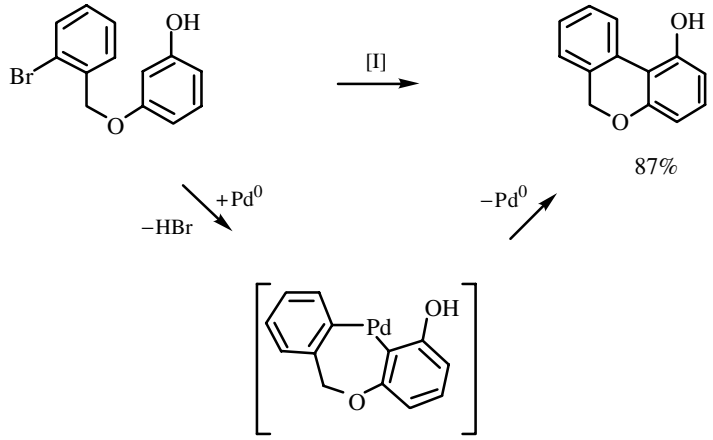
**Scheme 46**

## D. HETEROCYCLES BY CYCLOPALLADATION AS KEY STEP

Intramolecular Pd-catalyzed aryl–aryl coupling reactions under dehydrohalogenation are assumed to proceed via palladacycles as illustrated by the example in **Scheme 47**.[33],[97] Several mechanistic pathways may explain the cyclopalladation step including the C,H-activation; however, a reaction of an electrophilic arylpalladium bromide with the electron-rich phenolate in the sense of an electrophilic aromatic substitution is certainly a plausible explanation. C—C bond formation finally takes place by reductive elimination.

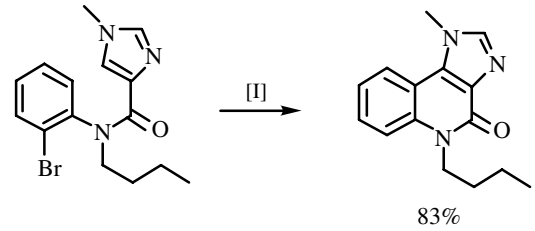
This type of aryl–aryl coupling reaction is equally possible on hetarenes such as indoles and imidazoles (**Scheme 48a**)[98],[99] and has been applied as a key step in natural product synthesis (**Scheme 48b**).[100]

The substituted dibenzopyran in **Scheme 49** is obviously formed from 3 equiv of starting material by a Pd-catalyzed coupling process involving C,H-activation at a $sp^3$-hybridized



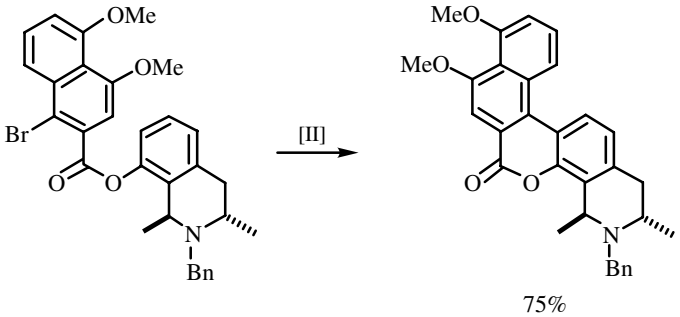

[I] = 20 mol % $Pd(PPh_3)_4$, KO*t*-Bu, DMA, 95 °C, 2 d.

**Scheme 47**




[I] = 10 mol % $Pd(OAc)_2$, $NaHCO_3$, *n*-$Bu_4NCl$, DMA, 150 °C, 1 d.

**Scheme 48a**

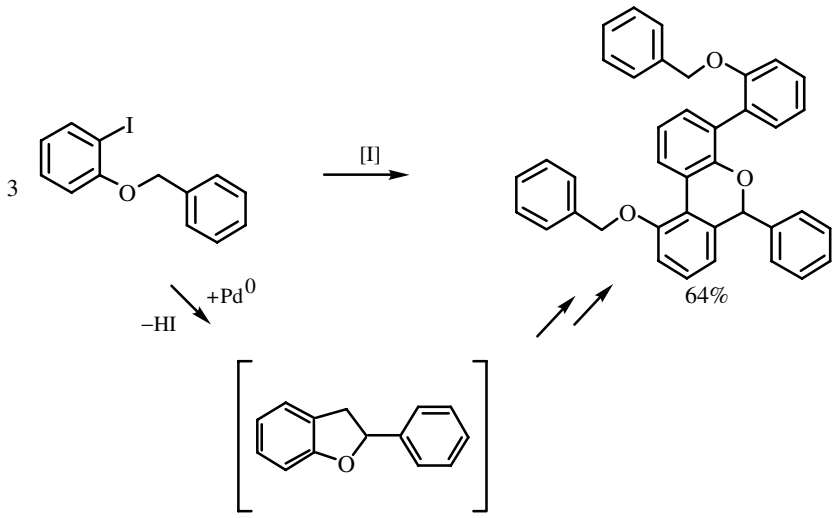



[II] = cat. $PdCl_2(PPh_3)_2$, AcONa, DMA, 130 °C.

**Scheme 48b**

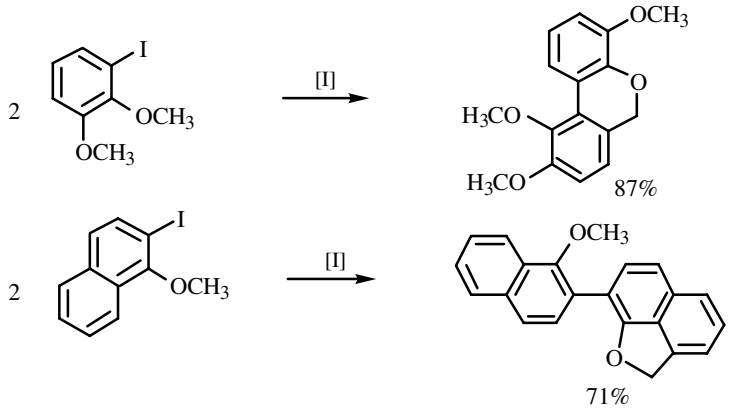
center. Five-membered oxapalladacycles are key intermediates in this process.[101] They can add aryl halides either directly to give $Pd^{IV}$ intermediates or by ligand exchange with arylpalladium halides. A number of structural variations of the starting material was studied (**Scheme 50**), opening up an easy access to various oxygen-containing heterocycles.[102] Especially, when neighboring groups are involved, which either block crucial positions or can react with $Pd^{II}$ functions, the domino process takes a short-cut and stops after the coupling of 2 equiv of the starting material (**Scheme 50**).

Based on this type of domino process with intermediary oxapalladacycles also cross-coupling reactions with vinyl bromides are possible as exemplified in **Scheme 51**.[103]



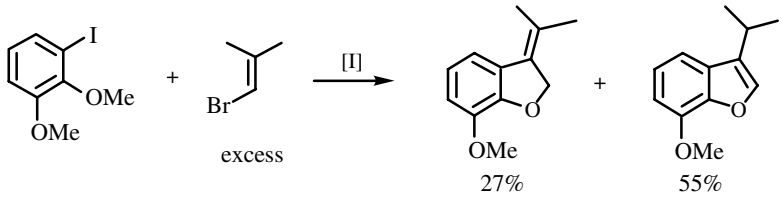

[I] = 4 mol % $Pd(OAc)_2$, $K_2CO_3$, *n*-$Bu_4NBr$, DMF, 100 °C, 3 d.

**Scheme 49**




[I] = 4 mol % $Pd(OAc)_2$, $K_2CO_3$, *n*-$Bu_4NBr$, DMF, 100 °C, 3 d.

**Scheme 50**




[I] = 10 mol % $Pd(OAc)_2$, $K_2CO_3$, *n*-$Bu_4NBr$, DMF, 100 °C, 3 d.

**Scheme 51**

## E. CONCLUSION

The synthesis of heterocycles making use of Heck-type reactions is obviously a growing field of current research, which takes advantage both of the broad applicability of palladium catalysis and of the outstanding importance of heterocycles. Palladium catalysis is even more useful for heterocyclic chemistry when taking into account that the Pd-catalyzed derivatization of heterocycles is not included in this overview.

## REFERENCES

[1] R. Odle, B. Blevins, M. Ratcliff, and L. S. Hegedus, *J. Org. Chem.*, **1980**, *45*, 2709.
[2] R. C. Larock and S. Babu, *Tetrahedron Lett.*, **1987**, *28*, 5291.
[3] R. C. Larock and D. E. Stinn, *Tetrahedron Lett.*, **1988**, *29*, 4687.
[4] N. Arnau, M. Moreno-Manas, and R. Pleixats, *Tetrahedron*, **1993**, *49*, 11019.
[5] L. F. Tietze and W. Buhr, *Angew. Chem. Int. Ed. Engl.*, **1995**, *34*, 1366.
[6] M. Mori, K. Chiba, and Y. Ban, *Tetrahedron Lett.*, **1977**, 1037.
[7] K. M. Aubart and C. H. Heathcock, *J. Org. Chem.*, **1999**, *64*, 16.
[8] J. E. Macor, D. H. Blank, R. J. Post, and K. Ryan, *Tetrahedron Lett.*, **1992**, *33*, 8011.
[9] L. S. Hegedus, T. A. Mulhern, and A. Mori, *J. Org. Chem.*, **1985**, *50*, 4282.
[10] I. St. C. Black, P. A. Keller, and N. Kumar, *Tetrahedron*, **1992**, *48*, 7601.
[11] M. O. Terpko and R. F. Heck, *J. Am. Chem. Soc.*, **1979**, *101*, 5281.
[12] M. Shibasaki and E. M. Vogl, *J. Organomet. Chem.*, **1999**, *576*, 1.
[13] S. E. Gibson and R. J. Middleton, *Contemp. Org. Synth.*, **1996**, *3*, 447.
[14] T. Matsuura, L. E. Overman, and D. J. Poon, *J. Am. Chem. Soc.*, **1998**, *120*, 6500.
[15] A. Ashimori and L. E. Overman, *J. Org. Chem.*, **1992**, *57*, 4571.
[16] R. C. Larock and N. H. Lee, *J. Org. Chem.*, **1991**, *56*, 6253.
[17] S. Wolff and H. M. R. Hoffmann, *Synthesis*, **1988**, 760.
[18] B. Schmidt and H. M. R. Hoffmann, *Tetrahedron*, **1991**, *47*, 9357.
[19] R. Grigg, P. Fretwell, C. Meerholtz, and V. Sridharan, *Tetrahedron*, **1994**, *50*, 359.
[20] R. Grigg, M. J. Dorrity, J. F. Malone, V. Sridharan, and S. Sukirthalingam, *Tetrahedron Lett.*, **1990**, *31*, 1343.
[21] R. Grigg and V. Sridharan, *Tetrahedron Lett.*, **1993**, *34*, 7471.
[22] R. Grigg and V. Sridharan, *J. Organomet. Chem.*, **1999**, *576*, 65.
[23] R. Grigg, J. P. Major, F. M. Martin, and M. Whittaker, *Tetrahedron Lett.*, **1999**, *40*, 7709.
[24] R. Grigg, V. Sridharan, and J. Zhang, *Tetrahedron Lett.*, **1999**, *40*, 8277.

[25] R. Grigg, V. Loganathan, V. Sridharan, P. Stevenson, S. Sukirthalingam, and T. Worakun, *Tetrahedron*, **1996**, *52*, 11479.

[26] B. Burns, R. Grigg, P. Ratananukul, V. Sridharan, P. Stevenson, S. Sukirthalingam, and T. Worakun, *Tetrahedron Lett.*, **1988**, *29*, 5565.

[27] R. Grigg, V. Sridharan, P. Stevenson, and S. Sukirthalingam, *Tetrahedron*, **1989**, *45*, 3557.

[28] R. Grigg, V. Sridharan, S. Sukirthalingam, and T. Worakun, *Tetrahedron Lett.*, **1989**, *30*, 1139.

[29] D. L. Comins, M. F. Baevsky, and H. Hong, *J. Am. Chem. Soc.*, **1992**, *114*, 10971.

[30] A. Kasahara, T. Izumi, S. Murakami, H. Yanai, and M. Takatori, *Bull. Chem. Soc. Jpn.*, **1986**, *59*, 927.

[31] T. Sakamoto, T. Nagano, Y. Kondo, and H. Yamanaka, *Synthesis*, **1990**, 215.

[32] J. R. Luly and H. Rapoport, *J. Org. Chem.*, **1984**, *49*, 1671.

[33] G. Dyker, *Chem. Ber./Recueil*, **1997**, *130*, 1567.

[34] C. Chen, D. R. Lieberman, R. D. Larsen, T. R. Verhoeven, and P. J. Reider, *J. Org. Chem.*, **1997**, *62*, 2676.

[35] R. Grigg, S. Sukirthalingam, and V. Sridharan, *Tetrahedron Lett.*, **1991**, *32*, 2545.

[36] L. Shi, C. K. Narula, K. J. Mak, L. Kao, Y. Xu, and R. F. Heck, *J. Org. Chem.*, **1983**, *48*, 3894.

[37] L. F. Tietze and R. Schimpf, *Angew. Chem. Int. Ed. Engl.*, **1994**, *33*, 1089.

[38] L. F. Tietze and R. Schimpf, *Chem. Ber.*, **1994**, *127*, 2235.

[39] B. C. Söderberg, S. R. Rector, and S. N. O'Neil, *Tetrahedron Lett.*, **1999**, *40*, 3657.

[40] S. Bräse, *Tetrahedron Lett.*, **1999**, *40*, 6757.

[41] S. A. Ahmad-Junan, P. C. Amos, and D. A. Whiting, *J. Chem. Soc. Perkin Trans., 1*, **1992**, 539.

[42] J. Cossy, C. Poitevin, D. Gomez Pardo, J.-L. Peglion, and A. Dessinges, *J. Org. Chem.*, **1998**, *63*, 4554.

[43] T. Okita and M. Isobe, *Tetrahedron*, **1994**, *50*, 11143.

[44] Z. Jin and P. L. Fuchs, *Tetrahedron Lett.*, **1993**, *34*, 5205.

[45] L. M. Grubb, A. L. Dowdy, H. S. Blanchette, G. K. Friestad, and B. P. Branchaud, *Tetrahedron Lett.*, **1999**, *40*, 2691.

[46] N. Chida, M. Ohtsuka, and S. Ogawa, *J. Org. Chem.*, **1993**, *58*, 4441.

[47] R. C. Larock and X. Han, *J. Org. Chem.*, **1999**, *64*, 1875.

[48] R. Grigg, V. Sridharan, P. Stevenson, and T. Worakun, *J. Chem. Soc. Chem. Commun.*, **1986**, 1697.

[49] B. Wünsch, H. Diekmann, and G. Höfner, *Tetrahedron: Asymmetry*, **1995**, *6*, 1527.

[50] K. F. McClure, S. J. Danishefsky, and G. K. Schulte, *J. Org. Chem.*, **1994**, *59*, 356.

[51] M. M. Abelman, L. E. Overman, and V. D. Tran, *J. Am. Chem. Soc.*, **1990**, *112*, 6959.

[52] S. D. Knight and L. E. Overman, *Heterocycles*, **1994**, *39*, 497.

[53] L. F. Tietze and R. Schimpf, *Synthesis*, **1993**, 876.

[54] M.-P. Denieul and T. Skrydstrup, *Tetrahedron Lett.*, **1999**, *40*, 4901.

[55] H. Finch, N. A. Pegg, and B. Evans, *Tetrahedron Lett.*, **1993**, *34*, 8353.

[56] S. Ma and E. Negishi, *J. Am. Chem. Soc.*, **1995**, *117*, 6345.

[57] L. F. Tietze and H. Schirok, *J. Am. Chem. Soc.*, **1999**, *121*, 10264.

[58] R. J. Sundberg and R. J. Cherney, *J. Org. Chem.*, **1990**, *55*, 6028.

[59] S. E. Gibson, J. O. Jones, R. McCague, M. J. Tozer, and N. J. Whitcombe, *Synlett*, **1999**, 954.

[60] R. Grigg, V. Sridharan, and S. Sukirthanlingam, *Tetrahedron Lett.*, **1991**, *32*, 3855.

[61] F. E. Meyer, P. J. Parsons, and A. de Meijere, *J. Org. Chem.*, **1991**, *56*, 6487.

[62] V. H. Rawal and C. Michoud, *J. Org. Chem.*, **1993**, *58*, 5583.

[63] Y. Sato, S. Nukui, M. Sodeoka, and M. Shibasaki, *Tetrahedron*, **1994**, *50*, 371.

[64] H. McAlonan, D. Montgomery, and P. J. Stevenson, *Tetrahedron Lett.*, **1996**, *37*, 7151.
[65] F. E. Ziegler, U. R. Chakraborty, and R. B. Weisenfeld, *Tetrahedron*, **1981**, *37*, 4035.
[66] R. K. Bhatt, S. D. Shin, J. R. Falck, and C. Mioskowski, *Tetrahedron Lett.*, **1992**, *33*, 4885.
[67] M. Mori, N. Kanda, and Y. Ban, *J. Chem. Soc. Chem. Commun.*, **1986**, 1375.
[68] A. Kojima, T. Takemoto, M. Sodeoka, and M. Shibasaki, *J. Org. Chem.*, **1996**, *61*, 4876.
[69] C. Y. Hong and L. E. Overman, *Tetrahedron Lett.*, **1994**, *35*, 3453.
[70] R. C. Larock, *J. Organomet. Chem.*, **1999**, *576*, 111.
[71] Z. W. An, M. Catellani, and G. P. Chiusoli, *J. Organomet. Chem.*, **1989**, *371*, C51.
[72] R. C. Larock, Y. He, W. W. Leong, X. Han, M. D. Refvik, and J. M. Zenner, *J. Org. Chem.*, **1998**, *63*, 2154.
[73] R. C. Larock, N. G. Berrios-Pena, and C. A. Fried, *J. Org. Chem.*, **1991**, *56*, 2615.
[74] J. M. Zenner and R. C. Larock, *J. Org. Chem.*, **1999**, *64*, 7314.
[75] R. C. Larock, C. Tu, and P. Pace, *J. Org. Chem.*, **1998**, *63*, 6859.
[76] R. C. Larock, N. G. Berrios-Pena, and K. Narayanan, *J. Org. Chem.*, **1990**, *55*, 3447.
[77] R. C. Larock and E. K. Yum, *Tetrahedron*, **1996**, *52*, 2743.
[78] R. C. Larock and L. Guo, *Synlett*, **1995**, 465.
[79] R. C. Larock, N. G. Berrios-Pena, C. A. Fried, E. K. Yum, C. Tu, and W. Leong, *J. Org. Chem.*, **1993**, *58*, 4509.
[80] R. C. Larock, M. J. Doty, and X. Han, *Tetrahedron Lett.*, **1998**, *39*, 5143.
[81] R. C. Larock, E. K. Yum, M. J. Doty, and K. K. C. Sham, *J. Org. Chem.*, **1995**, *60*, 3270.
[82] R. C. Larock, X. Han, and M. J. Doty, *Tetrahedron Lett.*, **1998**, *39*, 5713.
[83] N. Beydoun and M. Pfeffer, *Synthesis*, **1990**, 729.
[84] D. Wensbo, A. Eriksson, T. Jeschke, U. Annby, and S. Gronowitz, *Tetrahedron Lett.*, **1993**, *34*, 2823.
[85] F. Ujjainwalla and D. Warner, *Tetrahedron Lett.*, **1998**, *39*, 5355.
[86] K. R. Roesch and R. C. Larock, *J. Org. Chem.*, **1998**, *63*, 5306.
[87] T. Jeschke, D. Wensbo, U. Annby, S. Gronowitz, and L. S. Cohen, *Tetrahedron Lett.*, **1993**, *34*, 6471.
[88] I. W. Davies, D. I. C. Scopes, and T. Gallagher, *Synlett*, **1993**, 85.
[89] R. C. Larock, P. Pace, H. Yang, C. E. Russel, S. Cacchi, and G. Fabrizi, *Tetrahedron*, **1998**, *54*, 9961.
[90] S. Cacchi, G. Fabrizi, R. C. Larock, P. Pace, and V. Reddy, *Synlett*, **1998**, 888.
[91] S.-K. Kang, T.-G. Baik, and A. N. Kulak, *Synlett*, **1999**, 324.
[92] S.-K. Kang, T.-G. Baik, and Y. Hur, *Tetrahedron*, **1999**, *55*, 6863.
[93] A. Arcadi, B. Bernocchi, A. Burini, S. Cacchi, F. Marinelli, and B. Pietroni, *Tetrahedron*, **1988**, *44*, 481.
[94] X. Garcias, P. Ballester, and J. M. Saa, *Tetrahedron Lett.*, **1991**, *32*, 7739.
[95] T. Mandai, S. Hasegawa, T. Fujimoto, M. Kawada, and J. Tsuji, *Synlett*, **1990**, 85.
[96] G. Dyker and H. Markwitz, *Synthesis*, **1998**, 1750.
[97] D. D. Hennings, S. Iwasa, and V. H. Rawal, *J. Org. Chem.*, **1997**, *62*, 2.
[98] T. Kuroda and F. Suzuki, *Tetrahedron Lett.*, **1991**, *32*, 6915.
[99] A. P. Kozikowski and D. Ma, *Tetrahedron Lett.*, **1991**, *32*, 3317.
[100] G. Bringmann, J. R. Jansen, H. Reuscher, M. Rübenacker, K. Peters, and H. G. von Schnering, *Tetrahedron Lett.*, **1990**, *31*, 643.
[101] G. Dyker, *Angew. Chem. Int. Ed. Engl.*, **1992**, *31*, 1023.
[102] G. Dyker, *Chem. Ber.*, **1994**, *127*, 739.
[103] G. Dyker, *J. Org. Chem.*, **1993**, *58*, 6426.