TANDEM ALKYNE CARBOPALLADATION/SUZUKI CROSS-COUPLING REACTION IN THE SYNTHESIS OF HETEROCYCLIC COMPOUNDS

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Abstract. *Palladium catalysis is a versatile strategy for the synthesis of many different kinds of compounds, including formation of heterocycles. Thanks to the possibility to combine more reactions catalysed by palladium complexes into a one-pot transformation, molecular complexity can be substantially increased in only one chemical step, which makes these transformations very efficient. In this chapter, the use of one particular combination of Pd-catalysed reactions, alkyne carbopalladation and Suzuki cross-coupling for the synthesis of heterocyclic compounds is reviewed.*

Contents

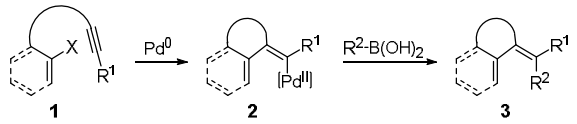
1. Introduction

Palladium-catalysed cross-coupling reactions have been extensively studied across the different fields of chemistry,[1] and applied in the synthesis of a wide range of organic compounds.[2-4] The pioneers in the field were deservedly awarded the 2010 Nobel Prize in Chemistry for this fundamental discovery.[5] Thanks to the great versatility of palladium chemistry, multiple Pd-catalysed reactions can be combined together into a one-pot transformation, which leads to higher efficiency and often better selectivity compared to the corresponding stepwise processes.[6] In this way, complex molecules can be prepared in one pot from simple starting materials. Most efficient of sequential transformations are those using only one catalyst for all the steps involved. We will use the term tandem reactions[7] for such transformations in this chapter, bearing in mind that the nomenclature is very inconsistent in the literature.

In general, such tandem reactions consist of at least two bond-forming transformations, both catalysed by the same palladium species. The organopalladium intermediate formed after the first reaction step (for example intermediate **2** in Scheme 1) is used as a starting material for the second bond-forming step, most often a cross-coupling reaction. In this chapter, we focus on combination of an intramolecular alkyne carbopalladation and a subsequent Suzuki cross-coupling. In such a process, two new C–C bonds are formed, together with a new (hetero)cyclic ring. Only examples leading to the formation of heterocyclic compounds are discussed here.

A general mechanism of a carbopalladation Suzuki cross-coupling reaction is depicted in Scheme 1. Oxidative addition of Pd^0 into a C–X bond of starting material **1** leads to a first organopalladium

intermediate (Pd^{II}), which is followed by insertion of the triple bond into the Pd–C bond, forming intermediate **2**. The intramolecular triple bond insertion takes place when its relative rate is higher than that of the following intermolecular reaction, which is usually the case, thus minimising the occurence of a direct cross-coupling reaction. Since the insertion proceeds as a *syn* addition, the reaction should lead stereoselectively to only one isomer of the coupling product (compound **3** in Scheme 1). However, depending on the substitution pattern of the the alkyne, the organopalladium intermediate **2** can isomerise during the reaction. The possible mechanisms by which this isomerization may take place were studied as early as in 1986 by Negishi:[8] formation of a zwitterionic metal carbene[9,10] or a η^2-vinylmetal complex has been suggested.[11]

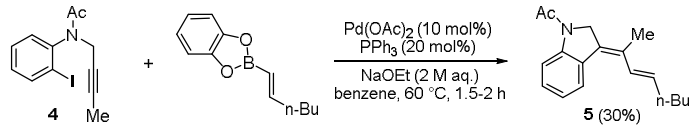


Scheme 1. General mechanism of the tandem alkyne carbopalladation/Suzuki cross-coupling reaction.

2. Formation of five-membered nitrogen heterocycles

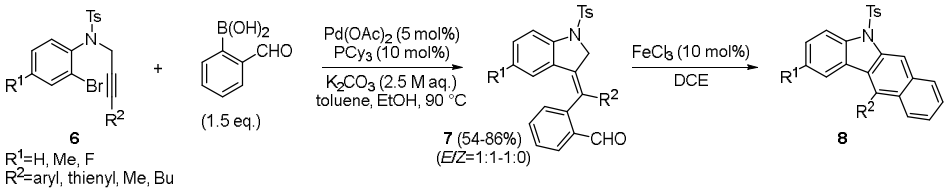
2.1. Synthesis of indolines

The first report of the tandem carbopalladation/Suzuki cross-coupling reaction was published by Grigg and co-workers in 1989.[12] During their previous work, they discovered that organopalladium intermediates formed by intramolecular carbopalladation of alkynes and alkenes can be intercepted by hydride ion sources[13] or organotin reagents.[14] In the mentioned publication, they managed to extend the scope to organozinc and organoboron compounds, achieving 5- and 6-*exo-dig* and -*trig* cyclisations, followed by C–C bond formation. By this means, various carbo- and heterocycles were prepared.[12] The reaction relevant for this chapter, in which indoline product **5** was formed in 30% yield from *o*-iodoaniline derivative **4**, is depicted in Scheme 2. Palladium acetate in combination with triphenylphosphine ligand was used as a catalyst, and an alkenylboronate ester as a coupling partner.



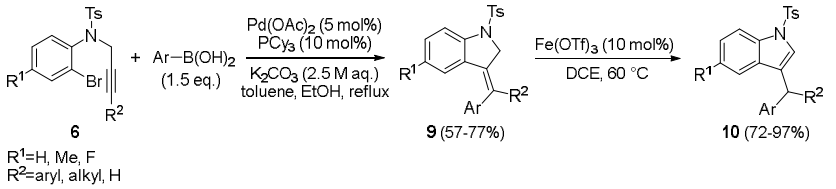
Scheme 2. First example of a carbopalladation/Suzuki cross-coupling reaction reported by Grigg.

Indolines are important building blocks which can be found in the structure of many natural products, and can be further modified to indoles[15] or other heterocycles. The group of Jana applied the Pd-catalysed tandem reaction of 2-bromo-*N*-propargylanilines **6** with 2-formylphenylboronic acid to get indoline products **7** that were then transformed into benzo[*b*]carbazoles **8** using iron catalysis (Scheme 3).[16] For the tandem reaction, $Pd(OAc)_2$ was employed in combination with tricyclohexylphosphine. Under the reported conditions (aqueous solution of K_2CO_3 in toluene/ethanol mixture), indolines **7** were obtained mostly as single isomers in 54-86% yields. A mixture of *E*/*Z* isomers was isolated only in a few cases: when R^2 was an electron poor aromatic ring, or when there was a fluorine substituent on the aniline ring (R^1=F).



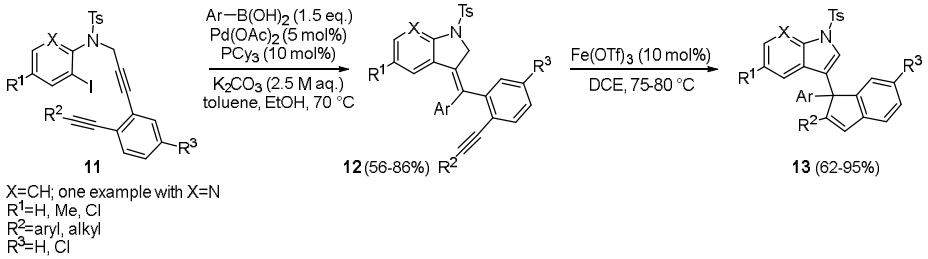
Scheme 3. Synthesis of indolines and their transformation into benzo[*b*]carbazoles.

The same research group published three additional reports on indoline synthesis in the following years.[17-19] In the first report, 3-methyleneindolines **9** were made from the same starting materials **6** and under similar conditions as above, but using different arylboronic acids (Scheme 4).[17] Products **9** were then converted to 3-alkylindoles **10** by a $Fe(OTf)_3$-catalysed isomerization. The tandem reaction gave yields around 70% and only a single isomer of the product was mentioned in all but one case. Notably, the reaction was also successfully performed with a terminal and alkyl-substituted alkyne **6** (R^2=H, Pr), albeit the corresponding products **9** were formed in lower yields (62 and 57%, respectively).



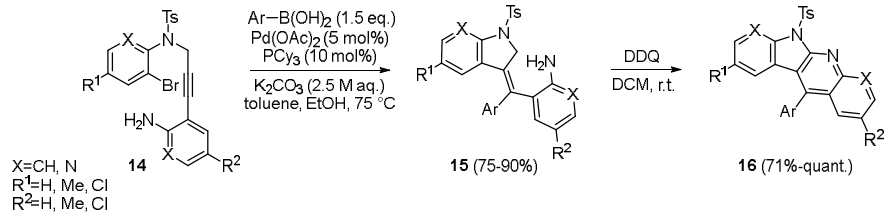
Scheme 4. Jana's synthesis of indolines, followed by isomerization to indols.

The next work of the group employed starting materials **11** with a 2-alkynyl-substituted aryl group on the triple bond, so it was possible to transform the indoline products **12** into 3-indenylindole derivatives **13** (Scheme 5).[18] Again, the same conditions were used for the Pd-catalysed tandem reaction, but at a lower temperature. The scope was extended by one example of azaindole product **12** (X=N), which was obtained in 70% yield.



Scheme 5. Synthesis 3-indenylindoles from indolines.

Lastly, from substrates **14** with a 2-aminoaryl substitution on the alkyne, indolo[2,3-*b*]quinolones **16** were synthesised through indolines **15** (Scheme 6).[19] The previously optimised conditions for the tandem reaction were suitable for these substrates as well, including aza and diaza analogues of **14**, which provided corresponding polyheterocyclic compounds **16** in good yields. Only in the case of arylboronic acids with strongly electron-withdrawing groups, namely aldehyde and cyanide group, it was difficult to purify the carbopalladation/Suzuki products **15**. Therefore, they were subjected to the following oxidation without purification, giving the indolo[2,3-*b*]quinolones **16** in 74 and 71% yield (two steps), respectively.

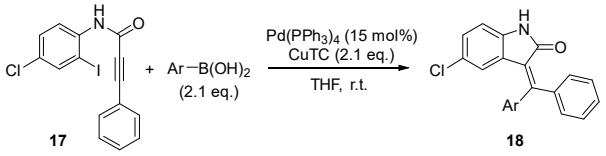


Scheme 6. Carbopalladation/Suzuki cross-coupling reaction in the synthesis of indolo[2,3-*b*]quinolones.

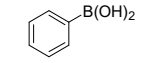
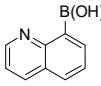
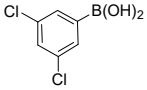
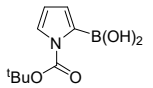
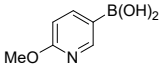
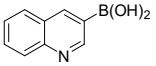
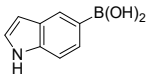
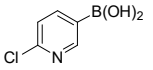
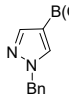
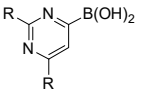
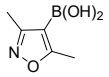
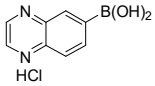
2.2. Synthesis of oxindoles

3-Alkylideneoxindoles occur widely in nature and many compounds with this core exhibit potent biological activities.[20] The use of the tandem carbopalladation/Suzuki cross-coupling reaction in the synthesis of oxindoles was first reported by Player in 2005.[21] A thorough optimisation of conditions was described in this work, with anilide **17** as starting material (Scheme 7). Firstly, different types of catalysts and ligands were screened with phenylboronic acid. It was found that while with $Pd(PPh_3)_4$ and K_2CO_3 in THF the reaction required heating to 100 °C under microwave irradiation (78% yield of **18**), with $Pd(OAc)_2$ and a carbene ligand the reaction proceeded at room temperature to give a similar yield (75%). However, the latter conditions were not suitable when electron-deficient, electron-rich or heterocyclic aromatic boronic acids were employed: they reacted sluggishly at room temperature and although elevating the temperature resulted in complete conversion to indolinone products **18**, it was only with modest and variable *E*/*Z* ratios. For that reason, the second best (69% yield with phenylboronic acid), base-free Suzuki conditions, with $Pd(PPh_3)_4$ and copper(I) thiophene-2-carboxylate (CuTC), were used to study the scope of the tandem reaction. A wide range of heteroarylboronic acids was tested in the reaction with anilide **17**, as shown in Scheme 7. The yields were generally high and in many cases exclusive formation of a single stereoisomer (the expected *E*-isomer) was observed.

For some of the boronic acids, however, the *E*/*Z* ratio was not optimal, therefore the effect of the solvent on selectivity was studied.



17 **18**

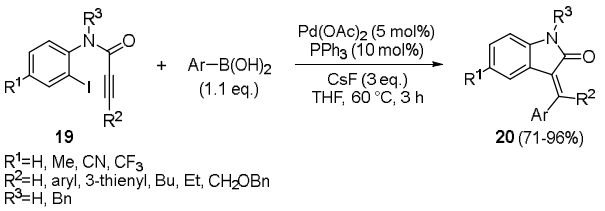
Boronic acid	Yield (*E*/*Z* ratio)	Boronic acid	Yield (*E*/*Z* ratio)
	69% 95%[a]		85% (15:1)
	93%[b] (1:0)		87% (25:1)
	96% (1:0)		62% (4:1) 57%[a] (1:0)
	91% (1:0)		85% (5:1) 93%[a] (27:1)
	93% (1:0)		R=Cl 93% (6.3:1) 84%[a] (1:0) R=H 42%[c] (23:1)
	R=OMe 82% (1:0) R=H 80% (1:0)		86% (6.5:1) 82%[a] (12:1)
	83% (13:1)		0%[c]

[a] With 10 mol% of $Pd(PPh_3)_4$ in THF/DMF (4:1). [b] With 20 mol% of $Pd(PPh_3)_4$. [c] Reaction performed at 40 °C.

Scheme 7. Scope of the tandem reaction forming oxindoles, as reported by Player.

The best isomer ratio was observed for a mixture of THF and DMF (4:1), as a significant increase in the formation of *E*-isomer was achieved in all the experiments conducted in this solvent system (see Scheme 7, note[a]). The chlorine substituent in **17** was originally present only to assist in the stereochemical assignment of isomers by NOE experiments. It was found that its absence had almost no effect on the reaction (94% yield with phenylboronic acid), as had the presence of a methoxy substituent in position 5 (92% yield). On the other hand, exchanging the iodine in **17** for bromine reduced the yield to 56%, due to the less efficient oxidative addition.

A similar approach to the synthesis of 3-alkylideneoxindoles was published by Takemoto in the same year.[22] Substrates **19** differed from those used in Player's work by the alkyne substitution (Scheme 8, R^2) and mainly arylboronic acids were studied as coupling partners. As for the catalytic system, combination of $Pd(OAc)_2$ with triphenylphosphine was used. With sodium hydroxide as a base and a terminal alkyne starting material **19** (R^2=H), the corresponding oxindole **20** was formed in 92% yield as a mixture of *E*/*Z* isomers (22:1). When the base was changed for CsF, the yield increased to 95% and *E*-isomer of the product was formed exclusively. The conditions with CsF were thus used for the investigation of scope, by which means oxindoles **20** were obtained in high yields for both benzylated (R^3=Bn) and *N*-free (R^3=H) anilides **19**, and with both electron-rich and electron-poor arylboronic acids (Scheme 8). As for the substitution on the anilide ring of **19**, the CF_3 substitution (R^1=CF_3) slowed the reaction down (71% yield in 10 hours), but methyl and cyano substitutents had almost no effect on the reaction outcome. Besides arylboronic acids, two experiments with butylboronic acid were performed, providing oxindole product **20** in lower yields compared to other experiments (45% for R^2=Ph; 70% for R^2=H).

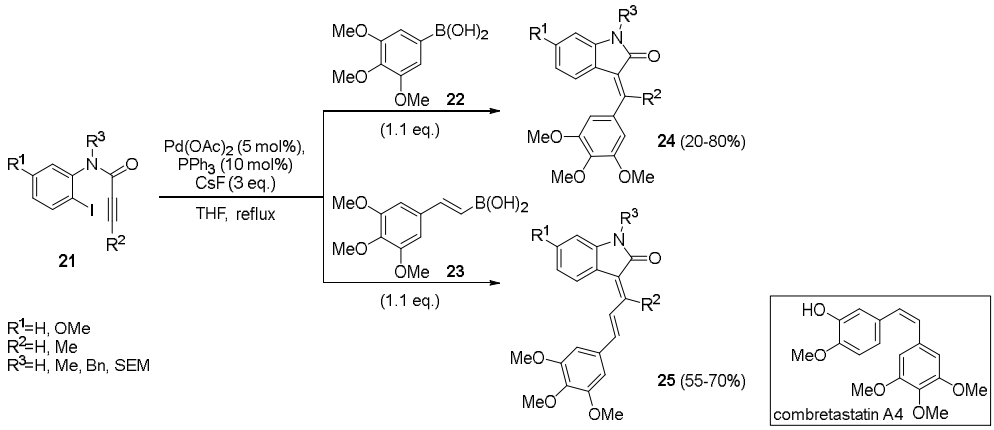


Scheme 8. Takemoto's synthesis of oxindoles.

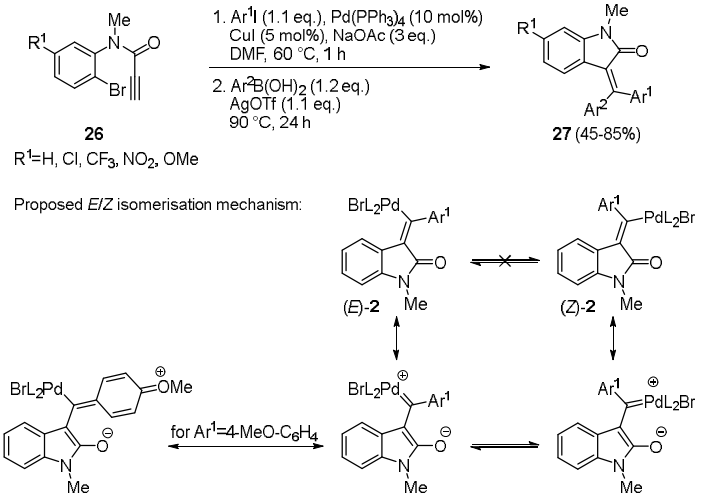
Takemoto's conditions for the tandem carbopalladation/Suzuki cross-coupling reaction were later applied by Pontikis in the synthesis of constrained analogues of combretastatin A4, a natural product with a potent antitumour activity (Scheme 9).[23] The same type of starting material **21** as in above-mentioned syntheses was employed, together with two trimethoxy-substituted boronic acids **22** and **23**, yielding oxindole products **24** and **25**, respectively. Conditions with aqueous NaOH and with CsF were tested, the latter of which provided better *E*/*Z* selectivity (32:1 *E*/*Z* ratio in one reaction, pure *E*-isomer in all the other experiments) in the range of yields shown in Scheme 9. In the reactions with aqueous NaOH, the *E*/*Z* ratio varied with substrates, the most striking example being the preferential formation of the undesired *Z*-isomer as a major stereoisomer (*E*/*Z*=1:4) in the reaction of **21** (R^1, R^2=H, R^3=Me) with the styrylboronic acid **23**. Notably, substrate **21** combining *N*-free amide with a terminal alkyne (R^1, R^2, R^3=H) failed to undergo the tandem reaction completely, whereas all other substituent combinations lead to the desired products. It was found that a bigger substituent on nitrogen is beneficial for the reaction outcome (20% yield of **24** for R^3=Me versus 50% for R^3=Bn), which was rationalised by steric interactions that might favour the reactive rotamer of **21**. The authors also studied *in vitro* antivascular activity of their products **24** and **25** on cancer cell lines, and found that the properties of one of the tested compounds (**24**; R^1=OMe, R^2=Me, R^3=H) were comparable with combretastatin A4.[24] The results were further supported by molecular docking studies.

In 2013, Seo and co-workers published synthesis of oxindoles, in which they managed to combine the discussed tandem reaction with a preceding Sonogashira cross-coupling step.[25] A similar process, but involving C–H activation, was published by Zhu previously.[26] In Seo's work, terminal alkynes **26** were subjected to Sonogashira reaction conditions with aryl iodides, and after the first step was complete, boronic acid was added and the temperature increased to 90 °C, to achieve the subsequent tandem carbopalladation/Suzuki cross-coupling reaction (Scheme 10). The final products **27** were formed in

moderate to good yields for both symmetrically (Ar^1=Ar^2) and unsymmetrically substituted compounds, nonetheless, the *E*/*Z* selectivity was low in the case of unsymmetrical ones.



Scheme 9. Synthesis of combretastatin A4 analogues.

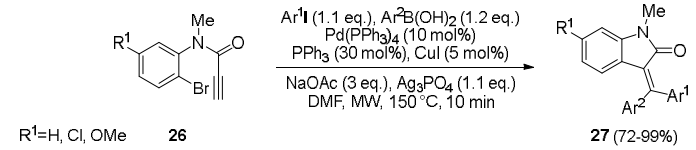


Scheme 10. Synthesis of oxindoles by combining Sonogashira cross-coupling with the tandem reaction, and the proposed mechanism of *E*/*Z* isomerization.

The best *E*/*Z* ratio (1:10) was achieved for 4-nitrophenyl iodide followed by phenylboronic acid (Ar^1=4-NO_2-C_6H_4, Ar^2=Ph). On the contrary, using 4-methoxyphenyl iodide and the same boronic acid resulted unexpectedly in the formation of product **27** with the *E*-isomer, which would formally result from *anti* addition on the double bond, as a major component (*E*/*Z*=1.6:1). Control experiments with two differently substituted compounds **27** showed that isomerization of products is possible but minimal (less than 20% of isomerised products were observed when pure isomers were subjected to reaction conditions). It was thus concluded that the stereochemical result arises from the reaction at the level of intermediate **2**, which can undergo isomerization. The authors proposed a plausible mechanism for *E*/*Z* isomerization based on the zwitterionic metal carbene route, which is consistent with the observed stereochemical outcomes and explains the effect of substituents of aryl iodides on *E*/*Z* ratios (Scheme 10). In the case of 4-methoxyphenyl iodide (Ar^1=4-$MeOC_6H_4$), the corresponding vinylpalladium intermediate **2** has an

additional resonance structure, which stabilises the zwitterionic state, thus facilitating interconversion between (*E*)-**2** and (*Z*)-**2**. To increase stereoselectivity of the reaction, the effect of silver additives, known for changing the catalytic cycle to a cationic pathway, was explored. The best results were achieved with AgOTf, which reversed the stereochemical outcome of the mentioned reaction with 4-methoxyphenyl iodide, slightly favouring the expected *Z*-isomer (*E*/*Z*=1:1.2). Addition of AgOTf improved the *E*/*Z* ratios in all the performed experiments, but the authors were unable to achieve excellent stereoselectivities as described in oxindole syntheses above.

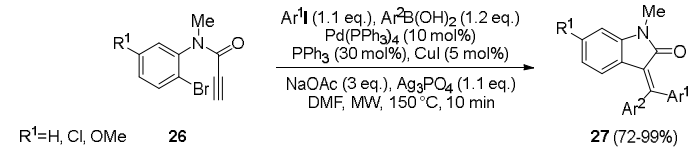
Two years later, the same group published an additional study of the same reaction, further demonstrating the effect of silver additives.[27] Compared to their previous work, both the yields and *E*/*Z* ratios of products **27** were improved (up to 99% and 26:1 ratio), together with shortening the time to only 10 minutes under microwave irradiation (Scheme 11). Ag_3PO_4 was used as an additive and PPh_3 as a ligand, while all the reagents, including the boronic acid, were combined at the outset of the reaction.



Scheme 11. Seo's synthesis of oxindoles under the improved conditions.

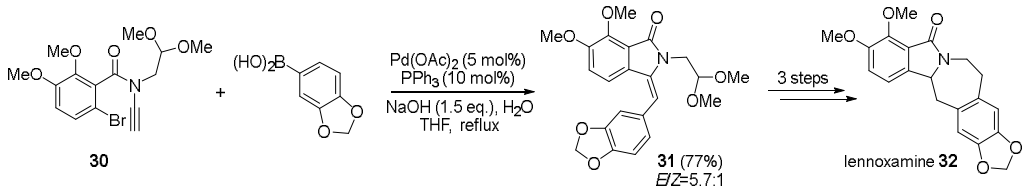
2.3. Synthesis of isoindolinones

The discussed tandem reaction can also be used to prepare isomeric isoindolinones from ynamide starting materials. Such approach was explored by Cossy (Scheme 12).[28] Out of the tested conditions, the combination of $Pd(OAc)_2$ and triphenylphosphine with aqueous NaOH as a base provided highest, but still rather moderate, yields of isoindolinone products **29**. In all the reactions, a single *E*-isomer of **29** was formed. A bromopyridin substrate **28** (Z=N, X=Br) was found to be similarly reactive as aryliodides at these conditions, providing the corresponding pyrrolopyridinone products in comparable yields. It was also shown that the silyl-protected ynamides **28** (R^2=$SiMe_3$) can be used directly in the tandem reaction, yielding the same products **29**, since the trimethylsilyl group is cleaved in situ under the reported conditions.



Scheme 12. Synthesis of isoindolinones from ynamides as reported by Cossy.

The developed method was later applied in the synthesis of lennoxamine **32** by the same research group using substrate **30** in the tandem reaction (Scheme 13).[29] In contrast to their previous work, isoindolinone **31** was isolated as a mixture of *E*/*Z* isomers in 5.7:1 ratio. This was not a problem in the synthesis, though, since the double bond was reduced in the following step, and in two more steps the target compound **32** was obtained.

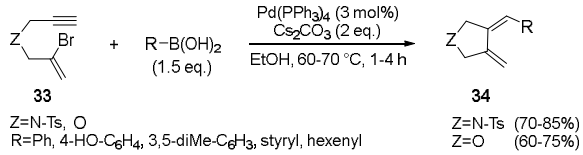


Scheme 13. Synthesis of lennoxamine using the Pd-catalysed tandem reaction.

3. Synthesis of five-membered heterocycles from alkenyl halides

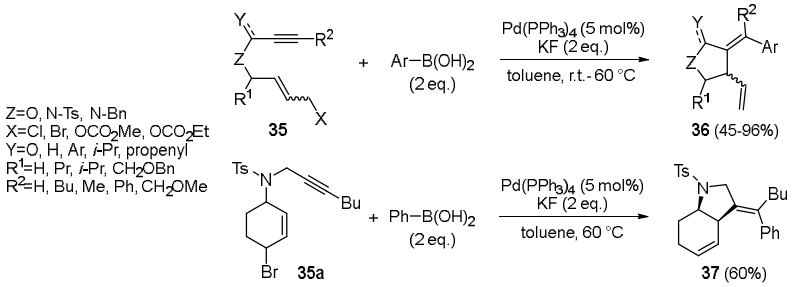
All of the heterocycle syntheses using the Pd-catalysed tandem carbopalladation/Suzuki cross-coupling reaction mentioned so far started by oxidative addition into an (aryl)C–X bond of aryl halides. There are also a few examples in the literature of these reactions employing aliphatic halides as starting materials and they all involve a 5-*exo*-dig cyclisation to form both nitrogen- and oxygen-containing heterocyclic compounds. These reactions will be discussed in this section for both the heteroatoms.

The first study using vinyl halides as starting materials, in particular 2-bromo-1,6-enynes **33**, was published by Oh in 2003 (Scheme 14).[30] During the optimisation, it was found that $Pd(PPh_3)_4$ provided higher yields of products **34** than $Pd(OAc)_2$, and that ethanol was a solvent of choice for this reaction. Three aromatic and two alkenylboronic acids underwent the reaction successfully with both tested substrates **33**, yielding nitrogen- and oxygen-containing compounds **34** with slightly better yields of pyrrolidines compared to tetrahydrofuran derivatives. The stereochemistry of the products was determined by NOE NMR experiments, and was consistent with the expected *syn* addition to the triple bond, as shown in Scheme 14.



Scheme 14. First example of the tandem carbopalladation/Suzuki cross-coupling reaction starting from alkenyl halides as reported by Oh.

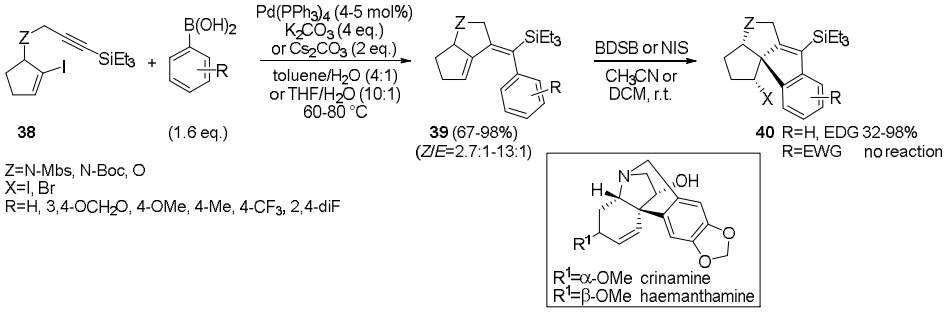
Zhang *et al.* employed allylic halides **35** as starting materials for the tandem cyclisation/Suzuki cross-coupling reaction (Scheme 15).[31,32] The mechanism of this reaction does not start with an oxidative addition to the C–X bond. The authors proposed that the reaction begins by forming a π-allylpalladium complex (the X group leaves), followed by insertion of the alkyne to form an intermediate of the type **2**, which then reacts in a Suzuki cross-coupling reaction with an arylboronic acid. The authors also performed several experiments that supported this π-allylpalladium pathway. The optimised conditions involved the use of $Pd(PPh_3)_4$ with KF in toluene, and produced variously substituted pyrrolidines and tetrahydrofurans **36** (Y=H), as well as pyrrolidinones and tetrahydrofuranones **36** (Y=O) mostly in more than 75% yields. Lower yields were obtained in case of a terminal alkyne (R^2=H, 21%) and for a *N*-benzyl substituted starting material without a carbonyl group (Z=N-Bn, Y=H, 38%). In addition, a bicyclic product **37**, with exclusively *cis* stereochemistry between the rings, was successfully prepared using the same conditions from alkyne **35a**.



Scheme 15. Zhang's synthesis starting from allylic halides.

Our research group contributed to this topic by performing the Pd-catalysed tandem reaction with alkenyl halides **38**, thereby forming both nitrogen- and oxygen-containing products **39** (Scheme 16).[33] The advantage of using alkenyl halides in this transformation was that compounds **39** with an aliphatic double bond could be utilised in a subsequent halocarbocyclisation to form polycyclic products **40** containing quaternary carbon centres (their relative stereochemistry is shown in the Scheme), which are structurally related to Amaryllidaceae alkaloids. As to the tandem reaction, standard Suzuki conditions were used,

providing good to excellent yields of compounds **39** with both electron-rich and electron-poor arylboronic acids. However, all of the products were formed as mixtures of *Z*/*E* isomers, with the ratios being generally better for nitrogen-containing products (*Z*/*E*=7.3:1 to 13:1) than for their oxygen congeners (*Z*/*E*=2.7:1 to 10:1). We assume that the formation of the undesired *E*-isomer was due to the presence of the silicon substituent, which enables a push-pull interaction between Si and Pd atoms in the intermediate **2**.[8] The following halocarbocyclisation was performed with two different reagents generating an electrophilic halogen, *N*-iodosuccinimide or BDSB (bromodiethylsulphonium bromopentachloroantimonate), providing products **40** in good yields for methoxy- and methylenedioxy-substituted compounds and moderate yields of products with phenyl and tolyl substituents. Compounds **39** containing electron-withdrawing groups on the aromatic ring did not undergo the reaction. On the other hand, high stereocontrol was achieved in the reaction sequence, enabling enantioselective synthesis of quaternary carbon centres: two products **40** were prepared with 87 and 94% ee for an oxygen- and nitrogen-containing compound, respectively.



Scheme 16. Our application of the tandem carbopalladation/Suzuki cross-coupling reaction followed by halocarbocyclisation in the synthesis of quaternary carbon centres.

Apart from the above-mentioned synthesis of quaternary carbon centres, we also applied the discussed tandem reaction in the synthesis of naphthalene-containing compounds (Scheme 17).[34] Both oxygen- and nitrogen-containing substrates **41** were treated with variously substituted 2-bromophenylboronic acids and two heteroaromatic boronic acids, providing dienes **42** in good yields and mostly as single isomers. Only arylboronic acids with a 6-fluoro substituent did not react at these conditions. The exception from the single isomer formation were nitrogen derivatives **42** bearing a phenyl substituent on the alkyne (R^1=Ph), which were formed as *E*/*Z* mixtures in reactions with three arylboronic acids out of the four tested, with ratios ranging from 2.4:1 to 3.2:1. As regards the other products, isomer formation (in 9.7:1 ratio) was observed in only one reaction of a nitrogen-containing compound **41** with a methyl group (R^1=Me).

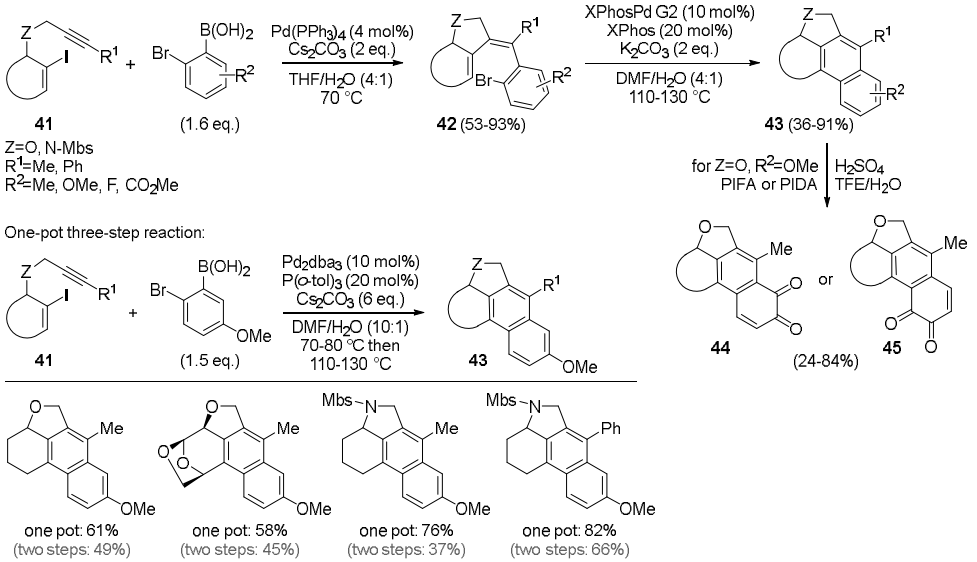
Products **42** were then subjected to an intramolecular Heck reaction, which proceeded in a 6-*endo*-*trig* fashion to form naphthalenes **43**. Moreover, we succeeded in combining all the three Pd-catalysed reactions into a one-pot transformation, giving better yields of products **43** than by the stepwise process (Scheme 17, lower part). The catalytic system had to be changed for the combination of carbopalladation/Suzuki and Heck reactions because under the previous conditions only small amounts of naphthalene products were formed. $Pd_2(dba)_3$ with tri(*o*-tolyl)phosphine in aqueous DMF were found to be the most suitable conditions, providing full conversion of intermediate **42**. We also showed that the methoxy-substituted products **43** can be oxidised in one-step to *o*-naphthoquinones **44** and **45** using hypervalent iodine reagents. The quinone products were subjected to cytotoxicity screening and were found to have activities in μM concentrations.

4. Formation of six-membered nitrogen heterocycles

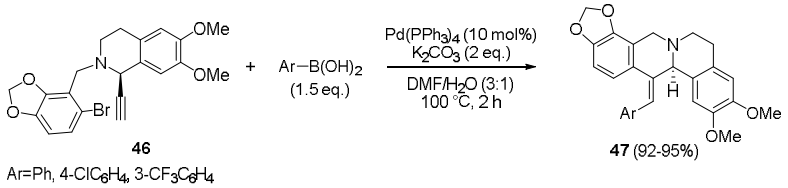
4.1. Synthesis of tetrahydroisoquinolines and tetrahydroquinolines

The alkyne carbopalladation can also be performed as a 6-*exo*-*dig* cyclisation to form six-membered heterocycles. This strategy was employed by Tong to prepare 13-substituted analogues of protoberberine alkaloids (Scheme 18).[35] Starting aryl bromide **46** was subjected to the reaction with three differently substituted arylboronic acids and provided excellent yields of the corresponding polycyclic products **47**. On

the other hand, butylboronic acid did not react under these conditions. The utility of the described transformation was shown on the synthesis of a potential anti-ulcerative colitis agent, which was prepared from compound **47** (Ar=3-$CF_3C_6H_4$) by a PtO_2-catalysed hydrogenation of the double bond.



Scheme 17. Synthesis of naphthalenes and naphthoquinones using the Pd-catalysed tandem reaction combined with Heck reaction reported by our research group.

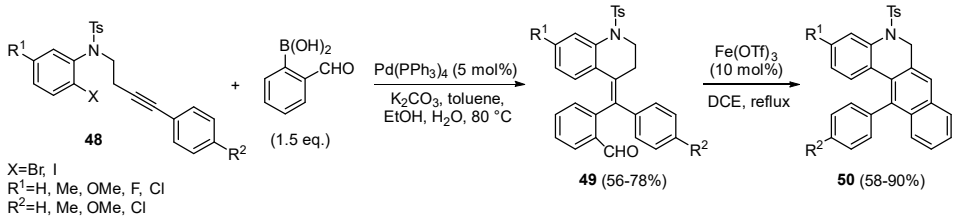


Scheme 18. Tong's synthesis of protoberberine alkaloid analogues.

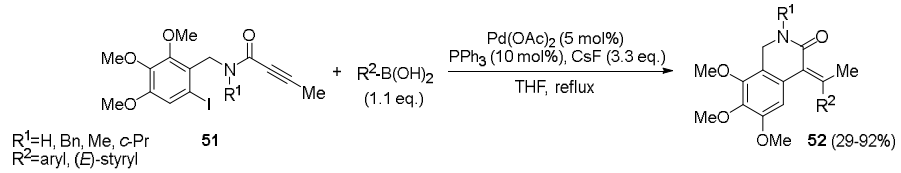
Jana *et al.* reported synthesis of tetrahydroquinolines[36] by using similar conditions already developed for their five-membered congeners (see Scheme 3). The tandem reaction of substrates **48** was performed with $Pd(PPh_3)_4$ as a catalyst and 2-formylphenylboronic acid, yielding tetrahydroquinoline products **49** in moderate yields (Scheme 19).[36] The subsequent iron-catalysed isomerization/cyclodehydration led to dihydrobenzo[*j*]phenanthridines **50**.

4.2. Synthesis of dihydroisoquinolinones

Formation of six-membered lactams **52** was reported by Pontikis in 2009 (Scheme 20)[37] as a means to prepare another series of combretastatin A4 analogues. Under the previously developed conditions (see Scheme 9), alkynes **51** with substituted nitrogen underwent the reaction smoothly providing dihydroisoquinolinones **52** in 65-92% yields as single stereoisomers. A substrate with a free nitrogen (R^1=H), however, was not suitable for the reaction and gave only 29% yield of the corresponding product. Similarly, a strongly electron-deficient 4-trifluoromethylphenylboronic acid, as well as arylboronic acid with a bulky 3-OTBS substituent, were less reactive, yielding products **52** (R^1=Me) in 48% and 30% yield, respectively. In contrast to their five-membered analogues, compounds **52** did not show any significant tubulin polymerisation inhibitory activity.[24]

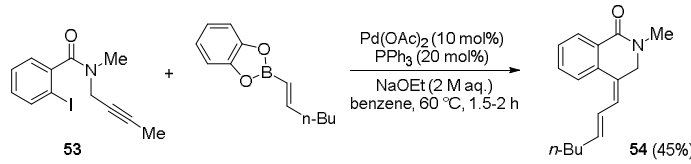


Scheme 19. Synthesis of tetrahydroquinolines and their further cyclisation catalysed by $Fe(OTf)_3$.



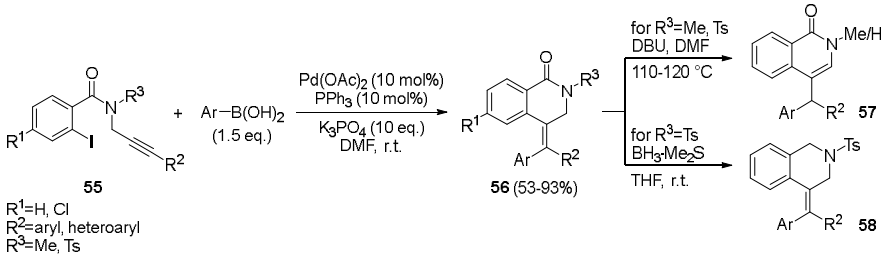
Scheme 20. Synthesis of the second series of combretastatin A4 analogues.

In the pioneering publication of Grigg and co-workers,[12] one example of a six-membered ring formation using the tandem carbopalladation/Suzuki cross-coupling reaction was also shown (Scheme 21). Starting from amide **53**, the corresponding dihydroisoquinolin-1-one **54** was isolated in 45% yield.



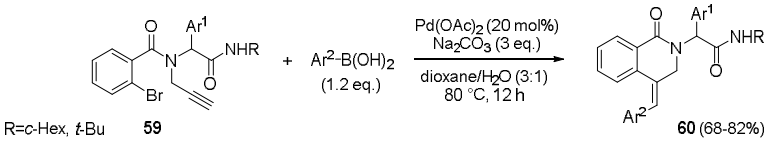
Scheme 21. Example of a 6-*exo*-dig cyclisation reported by Grigg in 1989.

Recently, several publications dealing with the synthesis of dihydroisoquinolin-1-ones have appeared. In 2018, variously substituted compounds **56** were prepared from benzamides **55** (Scheme 22).[38] The best results were obtained using a combination of $Pd(OAc)_2$ catalyst with a triphenylphosphine ligand, and using K_3PO_4 as a base in dry DMF. Formation of a single stereoisomer was observed in all the cases. A reaction of a terminal alkyne **55** (R^2=H) was also performed at the same conditions, but lead only to decomposition. However, when an aqueous base was used, the corresponding dihydroisoquinolinone **56** (R^2=H) was formed in 44% yield. The utility of the method was proved by further modifications of products **56** either by isomerization to compounds **57** (together with detosylation for R^3=Ts), or by reduction to products **58**, that can be transformed even further to isoquinolines by heating with *t*-BuOK.



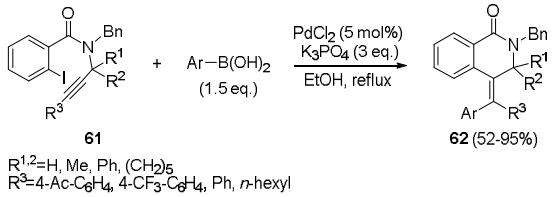
Scheme 22. Synthesis and further transformations of dihydroisoquinolinones.

In another report, a series of Ugi products **59** was subjected to the tandem reaction, catalysed by $Pd(OAc)_2$ without any additional ligand, to form products **60** stereoselectively and in good yields (Scheme 23).[39] The authors also managed to perform the same transformation with palladium immobilised on pyridine-imidazolium ionic-liquid-supported magnetic nanoparticles (Pd@Py-IL-SPION) as the catalyst,[40] which gave products **60** in similar yields (65-85%). Recyclability of the catalyst was demonstrated as well in the report.



Scheme 23. Synthesis of dihydroisoquinolinones from Ugi products.

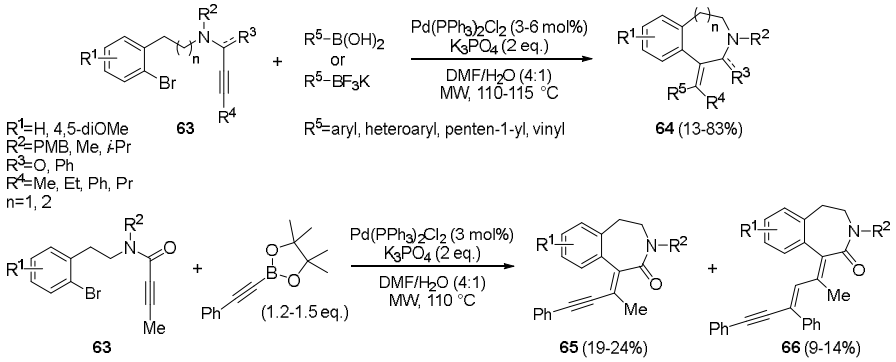
Marinelli *et al.* extended the scope of the reaction to substrates **61** substituted at propargylic position (Scheme 24).[41] Notably, ligand-free conditions with $PdCl_2$ provided the best results out of the tested catalysts, yielding compounds **62** in a stereoselective fashion.



Scheme 24. Marinelli's synthesis of dihydroisoquinolinones.

5. Formation of medium-sized nitrogen heterocycles

Only one report of application of the tandem carbopalladation/Suzuki cross-coupling reaction to the synthesis of medium-sized nitrogen-containing rings, can be found in the literature. It was published in 2015 by Peshkov and Van der Eycken.[42] They used variously substituted propargyl amides **63** (R^3=O) as starting materials and the tandem reaction was performed under microwave irradiation (Scheme 25). By this method, they successfully prepared a large series of benzazepines **64**, together with two examples of benzazocines (n=2). Propargyl amine **63** (R^3=Ph) was also reactive at these conditions but gave rather low yields. Several different organoboron reagents were tested for the reaction, out of which boronic acids provided the best results.



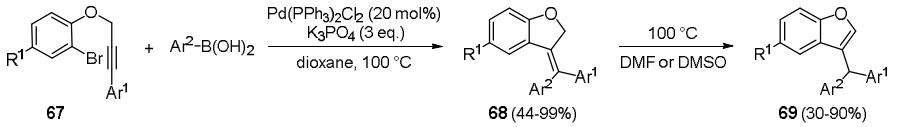
Scheme 25. Method for the preparation of seven- and eight-membered nitrogen heterocycles.

The authors also investigated reactions with (phenylethynyl)boronic acid pinacol ester, in which case mixtures of anticipated products **65** with compounds **66**, resulting from double incorporation of the boron reagent, were obtained in low yields (Scheme 25).

6. Formation of oxygen heterocycles

6.1. Using starting materials with an ether linker

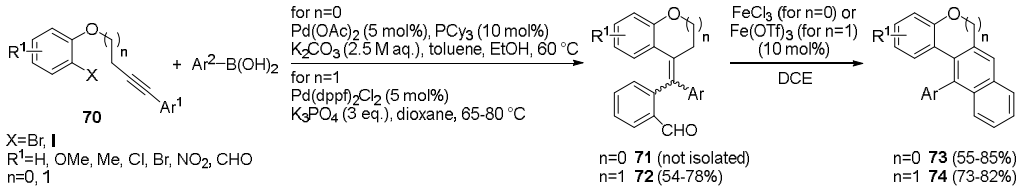
Along with nitrogen heterocycles, the palladium-catalysed tandem reaction discussed herein was also exploited in the synthesis of oxygen-containing heterocyclic compounds, although less frequently. Cyclisation of aryl-substituted propargylic aryl ethers **67** in a 5-*exo-dig* mode, combined with a Suzuki reaction with arylboronic acids was reported in 2013 by Arcadi *et al.* (Scheme 26).[43] The used conditions were quite general and stereoselective, affording dihydrobenzofurans **68** in moderate to excellent yields. Neither electron-withdrawing nor -donating groups on both substrates and boronic acids had much influence on the results. A reaction with a potassium *trans-β*-styryltrifluoroborate reagent was also attempted, and the desired product was formed, albeit in a lower yield (45%) than with arylboronic acids. Isomerization of the tandem products to benzofurans **69** was achieved by heating in DMF or DMSO.



Scheme 26. Synthesis of dihydrobenzofurans and their further isomerization to benzofurans.

A similar approach towards the synthesis of benzofurans was also explored in the group of Jana, using the conditions they developed for indoles[17] (see Scheme 4). Hence, the dihydrobenzofuran derivatives were prepared in 74-82% yields, and the following aromatisation was performed at 60-80 °C with a $Fe(OTf)_3$ catalyst in 70-96% yields.

Furthermore, the same group studied the synthesis of fused five- and six-membered heterocycles, based on their results with nitrogen derivatives[16,36] (compare with Schemes 3 and 15). Thus, they developed a method for the synthesis of naphtho[2,3-*b*]benzofurans **73**[44] and naphtho[2,3-*c*]chromenes **74**[36] (Scheme 27). The Pd-catalysed tandem reaction provided products **71** or **72** bearing an aldehyde group, which originated either from the substrate **70** or the 2-formylphenylboronic acid. The presence of the aldehyde group then enabled the following cycloaromatisation with an iron catalyst.

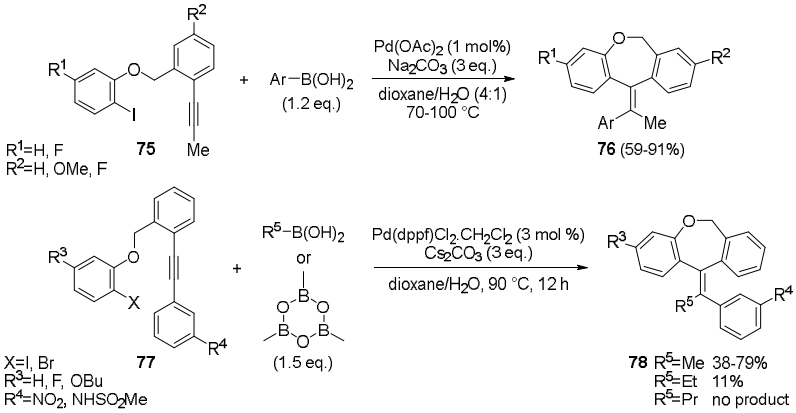


Scheme 27. Jana's synthesis of polycyclic oxygen heterocycles.

Researchers from Eli-Lilly laboratories applied the tandem reaction in the synthesis of seven-membered heterocycles, namely dibenzo[*b*,*e*]oxepine derivatives **76** and **78** (Scheme 28).[45,46] In their first report, methyl-substituted alkynes **75** were used as starting materials in combination with differently substituted arylboronic acids and $Pd(OAc)_2$ (1 mol%) as a catalyst, affording the desired products **76** stereoselectively and in good yields. Only traces of direct coupling products were observed. One example of an isomeric product was also prepared, in which case the starting material had the linker with CH_2 and O groups exchanged.

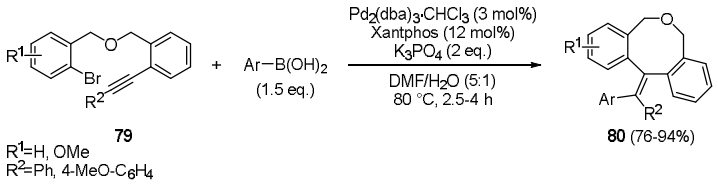
In the second publication,[46] reactions with alkylboronic acids were explored, yielding products **78** (Scheme 28). A palladium catalyst with a bis(diphenylphosphino)ferrocene ligand was found suitable for the

reactions with methylboronic acid or trimethylboroxine, giving good yields (65-79%) of nitro-substituted compounds **78** (R^4=NO_2) as single stereoisomers. A less satisfactory result was achieved with a sulphonamide **77** (R^4=$NHSO_2Me$), yielding to only 38% of the corresponding product containing a significant amount of the wrong stereoisomer. The yield and *E*/*Z* ratio of this product were improved to 58% and 24:1 when K_2CO_3 was used as a base in non-aqueous dioxane. Alkylboronic acids with a longer chain, on the other hand, were not very reactive: product **78** was isolated in 11% yield with ethylboronic acid, while no product at all was observed in the reaction with propylboronic acid.



Scheme 28. Synthesis of dibenzoxepine derivatives.

Synthesis of eight-membered homologues of products above has also been achieved by this strategy.[47] After an initial catalyst and ligand screening, combination of a Pd^0 precatalyst with Xantphos ligand was chosen for investigation of the scope of the tandem reaction of alkynes **79** (Scheme 29). All the tested arylboronic acids (Ar=phenyl, nitrophenyl and methoxyphenyl) were tolerated, providing the corresponding heterocyclic products **80** in good yields. Small amounts of direct Suzuki cross-coupling products were mentioned to be formed in some cases.

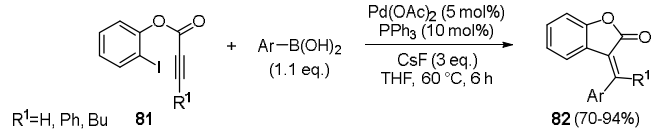


Scheme 29. Formation of eight-membered oxygen heterocycles.

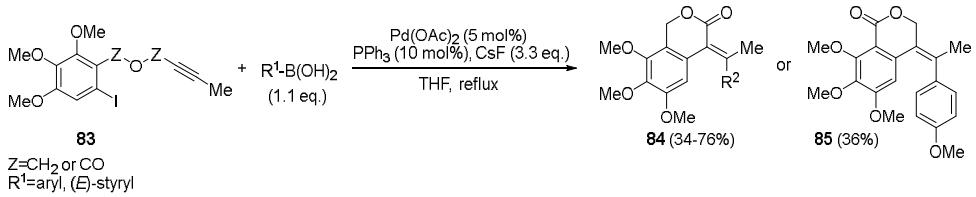
6.2. Using starting materials with an ester linker

Takemoto applied the conditions developed for the synthesis of oxindoles (see Scheme 8) to their oxygen congeners as well,[22] starting from compounds **81**, thereby preparing benzofuranones **82** (Scheme 30). All the performed experiments provided products **82** in high yields, which were only slightly lower than for the corresponding oxindoles. Similarly, Pontikis *et al.* used these conditions for substrates **81**, together with the two trimethoxy-substituted boronic acids **22** and **23**[24] (see Scheme 9), to prepare two oxygen-containing analogues of combretastatin A4 in 44 and 47% yields.

In the same manner, six-membered combretastatin analogues were also prepared, again using the same conditions as for the nitrogen-containing compounds[37](see Scheme 20). The reaction proceeded smoothly with substrates **83**, yielding isochromanones **84**, and one example of isomeric compound **85**, in moderate yields (Scheme 31). Interestingly, the exchange of the nitrogen atom in compounds **52** for oxygen in **84** considerably enhanced biological activity of these compounds.[24]



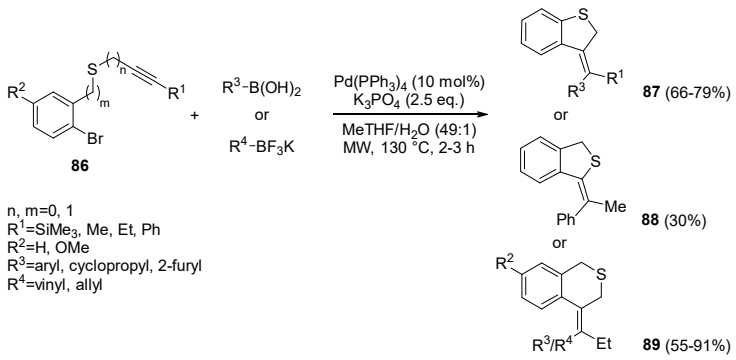
Scheme 30. Synthesis of 3-alkylidenebenzofuran-2-ones by Takemoto.



Scheme 31. Synthesis of six-membered lactones using the discussed tandem reaction.

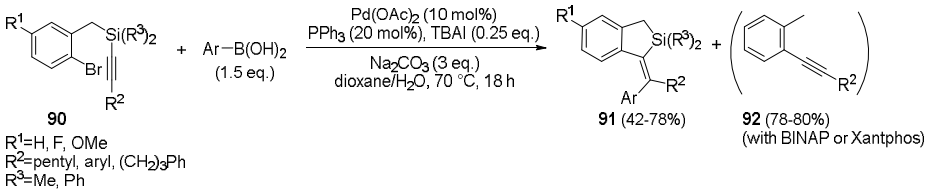
7. Formation of heterocycles with other heteroatoms

The number of Pd-catalysed reactions with sulphur-containing substrates is limited due to thiophilicity of palladium, which can lead to deactivation of the catalyst. Nevertheless, Gulea and Suffert succeeded in using the tandem alkyne carbopalladation/Suzuki cross-coupling reaction in the synthesis of both five- and six-membered sulphur heterocycles.[48] Starting alkynes **86** were subjected to the reaction with $Pd(PPh_3)_4$ and K_3PO_4 under microwave irradiation, providing dihydrobenzo[*b*]thiophenes **87**, a dihydrobenzo[*c*]thiophene **88**, and six-membered isothiochromanes **89** (Scheme 32). Out of the different starting materials, the ones with a propargyl benzyl thioether linker were found to give the best results. In all the performed reactions, however, products of the direct Suzuki cross-coupling were formed as minor products, along with the desired cyclised compounds **87**-**89**. In several cases, the resulting mixtures of cyclisation and direct coupling products were inseparable due to their similar polarity.



Scheme 32. Synthesis of sulphur-containing heterocycles.

The same research group also synthesised five-membered silicon-containing heterocycles **91** by the carbopalladation/Suzuki cross-coupling reaction sequence (Scheme 33).[49] 2-Bromobenzyl silylalkynes **90**, which were used as starting materials, were reacted with both electron-rich and electron-poor arylboronic acids, as well as two heteroaromatic boronic acids (2-furyl and 3-pyridyl), providing compounds **91** in moderate yields. Dimethyl, diphenyl and methylphenyl substituents on the silicon atom were well tolerated in the reaction conditions, only a siletane substrate (R^3=$(CH_2)_3$) did not undergo the reaction. Interestingly, when bisphosphine ligands such as BINAP or Xantphos were used in the reaction, the migration of the alkyne, together with the silyl group cleavage was observed, and product **92** was formed in good yields.



Scheme 33. Synthesis of silicon-containing heterocycles.

8. Conclusions

Since the first published experiments in the late 1980s, the palladium-catalysed tandem alkyne carbopalladation/Suzuki cross-coupling reaction has become a powerful method for the synthesis of different types of heterocycles. Over the years, the results in terms of yields and *E*/*Z* selectivity have been significantly improved, and the mechanism has been well studied. From nitrogen and oxygen heterocycles, the scope was extended to sulphur- and silicon-containing compounds as well. Moreover, the discussed tandem reaction was successfully employed in the synthesis of biologically active compounds. While most of the reactions used aryl halides as starting materials, giving rise to heterocycles fused with aromatic ring(s), the method is also applicable to alkenyl halides, which opens up new possibilities for the synthesis of heterocyclic compounds, as we demonstrated by the preparation of heterocycles containing quaternary carbon centres or naphthoquinone cores. It has also been shown that the process can be effectively combined with other catalytic transformations, in some cases even in one pot, which makes such processes truly efficient. Thus, as can be seen from this example, the development of new types of tandem reactions can still be an important goal for the synthetic community.

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