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Dedicated to Professor Miha Tišler on the occasion of his 75th birthday

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Introduction.

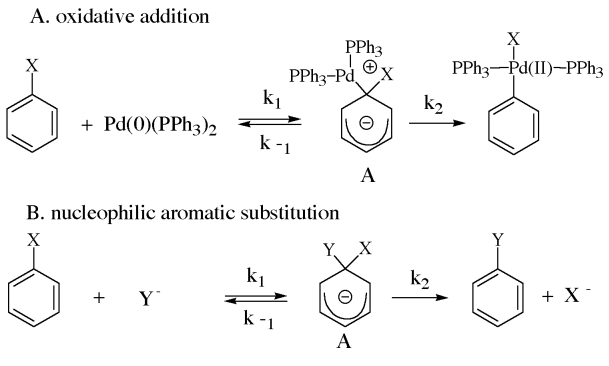
Our research group became interested in pyridazine chemistry for two reasons. First, many pyridazines are biologically active and the whole family of pyridazine derivatives shows a broad diversity of biological activities, useful for pharmaceutical [1-5] and agrochemical [1,2,5] applications. The second reason was our conviction that modern palladium-catalyzed reactions, such as the Stille reaction [6], the Suzuki reaction [7], *etc*., although not unknown in pyridazine chemistry, can be used much more for the synthesis of 'old' and well known pyridazine derivatives, as well as for completely new pyridazine containing structures, and this in a very efficient way. Especially we wanted to execute these reactions on chlorinated pyridazine derivatives for obvious reasons: chlorinated 1,2-diazines are cheaper than their brominated, iodinated or triflated counterparts, and they are easily accessible from syntheses [8,9], or from commercial sources [10]. But is this an accessible goal?

Oxidative Addition: a Nucleophilic Aromatic Substitution Model.

One of the fundamental steps in palladium-catalyzed reactions is the oxidative addition. Fitton *et al.*, [11] studied the oxidative addition of aromatic halogenides to $Pd(0)(PPh_3)_2$ [12] (Scheme 1.A) When comparing the oxidative addition of halobenzenes they found that iodobenzene reacts at room temperature and bromobenzene at 80 °C, but that chlorobenzene does not give any reaction even at 135 °C. The relative reactivities of halobenzenes are : iodobenzene > bromobenzene >> chlorobenzene. This observation is in agreement with a nucleophilic aromatic substitution (S_NAr) in which the second step of the substitution (Scheme 1.B), the breaking of the carbon-halogen bond, is the rate determining step [13].

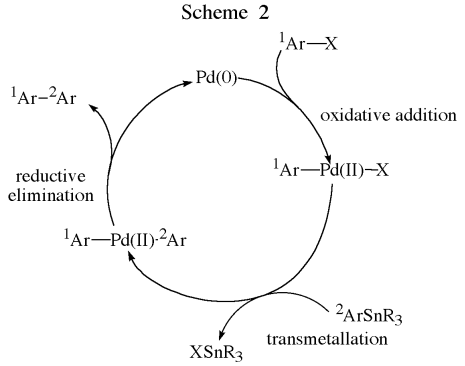
If the oxidative addition reaction indeed can be considered as an aromatic nucleophilic substitution reaction, all factors that promote the aromatic nucleophilic substitution will also promote the oxidative addition. One possibility to achieve this is to increase the nucleophilicity of the Pd-complex that is used as the catalyst. This can be done by using more electron rich ligands such as tricyclohexylphosphine [14], tri-*tert*.-butylphosphine [15], 2-(2'-dicyclohexylphosphinophenyl)-2-methyl-1,3-dioxolane [16], *o*-(di-*tert*-butylphosphino)biphenyl or *o*-(dicyclohexylphosphino)-biphenyl [17], and 1,3-bis-(2,4,6-trimethylphenyl)imidazol-2-ylidene or related bisimidazol-2-ylidene ligands [18] and has been proven to be very useful to perform palladium-catalyzed reactions with electron neutral and electron rich chlorobenzenes. However, if it is possible to replace these more electron rich ligands by ordinary triarylphosphines (*e.g.* PPh_3) this is desirable since the former are generally expensive. Another possibility to promote aromatic nucleophilic substitution is to decrease the electron density of the π-system of the aromatic ring. Indeed Fitton *et al.* [11] have shown that the indroduction of electron withdrawing substituents on chlorobenzene, makes oxidative addition possible with $Pd(0)(PPh_3)_2$ [12]. Moreover the stronger the electron withdrawing effect the faster is the oxidative addition reaction which is in agreement with the S_NAr-model. Since the incorporation of nitrogen in the benzene ring also decreases the electron density of the π-system, there is a good chance to perform palladium-catalyzed reactions on chloropyridazines with triarylphosphines (*e.g.*, PPh_3) as

Scheme 1



Oxidative addition *versus* nucleophilic aromatic substitution

Scheme 2



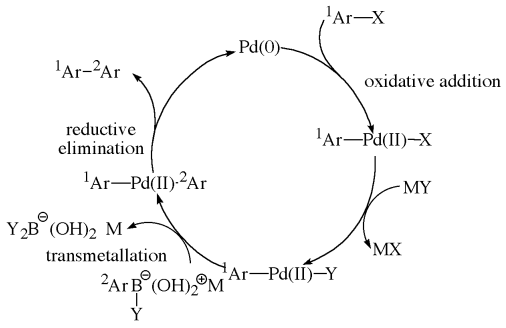
Stille arylation reaction

the ligands of the catalyst. In the literature examples of Suzuki-reactions on chlorinated pyridines [19], quinolines [20], pyrazines [21], triazines [22], and even on pyridazine derivatives [23,24], do support this idea.

Mechanism of the Suzuki, Stille and Buchwald-Hartwig Reaction.

The oxidative addition as described in the previous section is only one fundamental step in palladium-catalyzed reactions. Generally palladium-catalyzed cross-coupling reactions consist of three fundamental steps: the oxidative addition, the transmetallation and the reductive elimination (*e.g.,* Stille: Scheme 2 [6], Suzuki: Scheme 3 [7]). In contrast to the original palladium-catalyzed amination reactions with aminostannanes [25-27], in modern palladium-catalyzed aminations

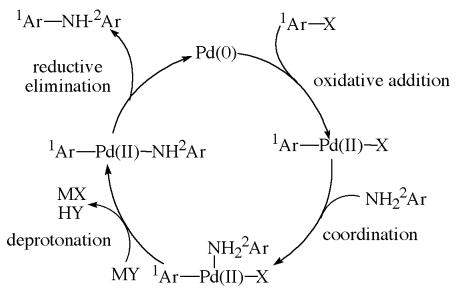
Scheme 3



Suzuki arylation reaction

amines can be used as such [28-31]. Here no transmetallation occurs but a direct coordination of the amine to the oxidative addition product followed by a deprotonation with base (Scheme 4) except when MOtBu is used. The success of these palladium-catalyzed reactions is highly dependent on the substrate, the organometallic reagent or amine, the base (if present) and the ligand that is used for the palladium catalyst. For example, we [32] and others [23,24,33] described smooth Suzuki arylations on chloropyridazines with *in situ* generated

Scheme 4



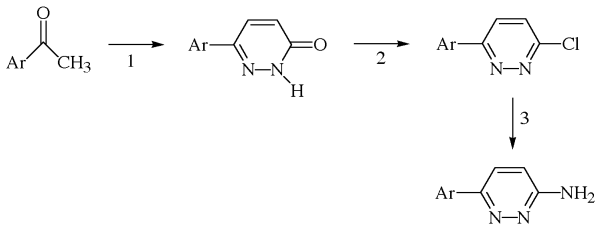
Buchwald-Hartwig amination reaction

$Pd(0)(PPh_3)_2$ catalyst, while the same substrates with the same catalytic system usually give moderate to bad results in the Sonogashira alkynylation [34-36].

Suzuki and Stille Arylation on 3-Amino-6-chloro- and 3-Amino-6-iodopyridazine: a Comparative Study [32].

First we explored the synthesis of 3-amino-6-arylpyridazines by palladium-catalyzed arylation of 3-amino-6-chloropyridazine. We chose this reaction for several reasons. The first reason is the fact that an amino group is a strong electron donating substituent and thus 3-amino-6-chloropyridazine is an electron rich chloropyridazine. We reasoned that if the palladium-catalyzed reactions on this pyridazine derivative were successful there is a good chance that similar reactions on chloropyridazines with substituents that are less electron donating, will also succeed. The second reason is that several important biologically active compounds have such a 3-amino-6-arylpyridazine substructure, for example the antidepressant Minaprine developed by Wermuth *et al.,* [37] and several other compounds which have been derived from it later [38], 6-arylimidazo[1,2-b]pyridazines [39,40], a neuroleptic compound synthesized in the group of Raviña *et al.* [41], *etc.*. The third reason is the fact that the classic way to prepare 3-amino-6-arylpyridazines is a multi-step pathway *via* a 6-aryl-3(2*H*)-pyridazinone. The most efficient way hitherto available to prepare 6-aryl-3(2*H*)-pyridazinones is a one-pot procedure developed by Coates *et al.* [42]: methylarylketones are condensed with glyoxylic acid; the condensation product is converted into an ammonium salt and the remaining ketone can be extracted from the reaction mixture; the γ-ketocarboxylic acid is further converted with hydrazine into a 6-aryl-3(2*H*)-pyridazinone (Scheme 5). These 6-aryl-3(2*H*)-pyridazinones can be converted with phosphorus oxychloride into the corresponding chloropyridazines from which the 3-amino-6-arylpyridazines can be prepared by a direct aminolysis [43,44]. Some authors state that the latter reaction is impractical [38,45]. An alternative is a two step procedure in which the chloropyridazine is converted with hydrazine into the corresponding hydrazinopyridazine which is further converted into the desired aminopyridazine by a hydrogenolysis reaction with Raney nickel [46]. Nevertheless also

Scheme 5



(1) (a) OHCCOOH•H_2O, solvent, (b) H_2O, NH_4OH to pH 8, (c) extraction of unreacted ketone, (d) N_2H_4•H_2O; (2) $POCl_3$; (3) (a) N_2H_4•H_2O, (b) Raney Nickel.

Classical synthesis of 3-amino-6-arylpyridazines

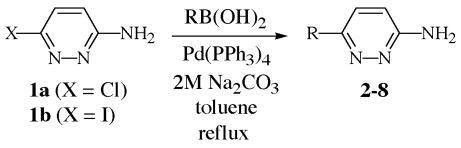
this procedure has its limitations since the hydrogenolysis reaction with RaNi is often incompatible with several functionalities, especially with sulphur containing structures [47].

Therefore we tried to replace this multi-step synthesis by a one-step arylation reaction starting from 3-amino-6-chloropyridazine (**1a**). Since there is a claim in the literature that iodopyridazines give better results than chloropyridazines in palladium-catalyzed reactions [36], although only evidence was given for the Sonogashira reaction, we decided to execute our arylation experiments as well on 3-amino-6-chloro- as on 3-amino-6-iodopyridazine (**1b**) under identical reaction conditions. 3-Amino-6-chloropyridazine is a commercially available product, but 3-amino-6-iodopyridazine is not. It can be prepared from the 6-chloro derivative by heating it under reflux in concentrated hydroiodic acid according to a procedure of Coad *et al.*, but the reported yield is less than 7% [48]. However we turned this procedure into a high yield synthesis (83%), mainly by increasing the reaction time.

Table 1 shows the results of our Suzuki arylation reactions on 3-amino-6-chloro- and 6-iodopyridazine. Several arylboronic acids have been used with both

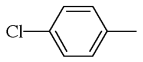
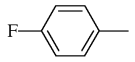
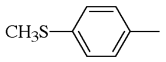
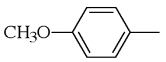
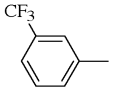
Table 1

Suzuki arylation on 3-amino-6-halopyridazines



1a (X = Cl)
1b (X = I)

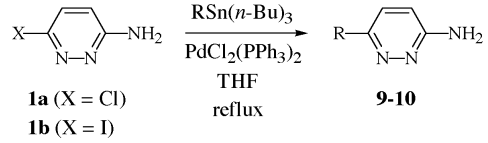
2-8

R	Reaction product	Yield from 1a (%) [a]	Yield from **1b** (%) [a]
	**2**	69	68
	**3**	70	68
	**4**	84	63
	**5**	75	73
	**6**	78	92
	**7**	81	80
	**8**	74	91

[a] Reaction conditions: **1a** or **1b** (2.55 mmol), boronic acid (3.83 mmol), $Pd(PPh_3)_4$ (3 mol %), Na_2CO_3 (2M, 2.7 mL), toluene (15 mL), 120°C (oil bath).

Table 2

Stille arylation on 3-amino-6-halopyridazines



1a (X = Cl)
1b (X = I)

9-10

R	Reaction product	Yield from **1a** (%) [a]	Yield from **1b** (%) [a]
	**9**	89	99
	**10**	96	87

[a] Reaction conditions: **1a** or **1b** (2.55 mmol), stannane (3.5 mmol), $PdCl_2(PPh_3)_2$ (9.4 mol %), THF (6 mL), 85°C (oil bath).

electron donating as well as electron withdrawing substituents. The yields are moderate to high. Sometimes the yields for both substrates are almost identical (**2**,**3**,**5**,**7**), sometimes they are in favor of the chloropyridazine (**4**), sometimes in favor of the iodopyridazine (**6**,**8**). But since the iodopyridazine is not commercially available and has to be synthesized from the chloropyridazine we concluded that there is no reason to start from 3-amino-6-iodopyridazine for the Suzuki arylation reaction. Wermuth *et al.*, [33] came to a similar conclusion for 3-chloro-6-methoxy- and 3-iodo-6-methoxypyridazine.

Parallel to the Suzuki reactions we also tried a couple of Stille reactions, again on 3-amino-6-chloro- and on 3-amino-6-iodopyridazine. As far as we know these are the first examples of Stille reactions on chloropyridazines. Table 2 shows that the yields of the reactions are high; one is in favor of the chloropyridazine (**10**), the other in favor of the iodopyridazine (**9**). In these reactions an additional aspect makes the reaction starting from the chloropyridazine more attractive than that starting from the iodopyridazine. For the latter substrate much longer reaction times are needed to complete the reaction. So in the case of the Stille arylation our conclusion is again that there is no reason to start from 3-amino-6-iodopyridazine.

More generally it can be concluded that the conviction that chloropyridazines can not be efficiently used for the Suzuki or Stille arylations of pyridazines has delayed for several years the use of these useful reactions in pyridazine chemistry. This conviction is most probably based on reports of Sonogashira reactions on chloropyridazines. Here generally, harsh conditions are necessary which often cause lower yields of alkynylpyridazines. Better results are obtained with iodopyridazines since milder reaction conditions can be used [36,49].

In the first part we presented predominantly Suzuki reactions and in the following topic we focus completely on this reaction for several reasons. The boronic acids used

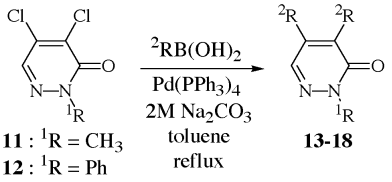
for the Suzuki arylation reactions are relatively non-toxic and environment friendly. The side products are non-toxic and can easily be separated from the reaction products. The organotin compounds used in the Stille reactions however are toxic and it is sometimes very hard to purify the reaction products from the tributyltinhalogenides formed during the reaction [50].

Suzuki Arylation on Chloro-3(2*H*)-pyridazinones [51].

We tried to expand the knowledge from the previous section to electronically different systems and became interested in 3(2*H*)-pyridazinones. In contrast to the pyridazine derivatives they are non-aromatic. Again it was our purpose to synthesize arylated products by palladium-catalyzed cross-coupling reactions, in this case starting from easily accessible and cheap chlorinated 3(2*H*)-pyridazinones. These pyridazinones are important intermediates in the synthesis of biologically active pyridazines such as the β-blocker Prizidilol [4,42,44]. But, also in the class of the pyridazinones themselves a lot of biologically active compounds can be found: 6-aryl-3(2*H*)-pyridazinones such as the cardiotonic agent Zardaverine [44], analgesic 4,6-diaryl-3(2*H*)-pyridazinones [52], and antihypertensive 5,6-diaryl-3(*2H*)-pyridazinones [53]. To the best of our knowledge in the literature only a few examples of 5-substituted 4-aryl-, 4-substituted 5-aryl- or 4,5-diaryl-3(2*H*)-pyridazinones can be found [5,54-57]. Therefore we focused on the synthesis of these products.

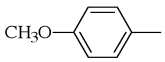
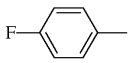
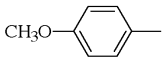
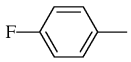
Table 3

Suzuki arylation on 4,5-dichloro-3(2*H*)-pyridazinones



11 : ^{1}R = CH_3
12 : ^{1}R = Ph

13-18

^{2}R	^{1}R	Reaction product	Yield (%) [a]
	CH_3	**13**	98
	CH_3	**14**	97
	CH_3	**15**	100
		**16**	97
		**17**	87
		**18**	100

[a] Reaction conditions: **11** or 1**2** (2.55 mmol), boronic acid (7.65 mmol), $Pd(PPh_3)_4$ (3 mol %), Na_2CO_3 (2M, 4 mL), toluene (15 mL), 120°C (oil bath).

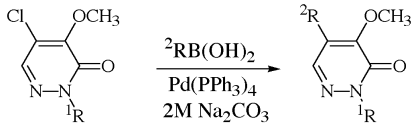
Table 3 shows our results on the Suzuki arylation of 4,5-dichloro-3(2*H*)-pyridazinones. Three equivalents of the boronic acids are used and both chlorine atoms are replaced smoothly by an aryl group. In all cases the yields are high to very high as well for 2-methyl (**11**) as for 2-phenyl-3(2*H*)-pyridazinone (**12**), and as well for phenylboronic acids with an electron donating as with an electron withdrawing substituent.

We have extended this method to other pyridazinone derivatives, first of all to 5-chloro-4-methoxy-3(2*H*)-pyridazinones with a 2-methyl (**19**) or a 2-phenyl substituent (**20**) (Table 4). Further a variety of boronic acids are used including a heterocyclic one. Again the arylations proceed smoothly giving very high yields, although the substrates contain a methoxy group that is an electron donating group.

We also used the isomeric 4-chloro-5-methoxy-3(2*H*)-pyridazinones (**29**,**30**) and again, not withstanding the strong electron donating methoxy group, the reactions proceed smoothly and the yields are high (Table 5). Also the steric hindrance of a carbonyl and a methoxy group in the *ortho* position of the reaction site does not seem to hamper the arylation reaction. Even a sterically more demanding *ortho*-tolyl

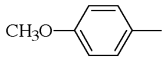
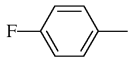
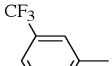
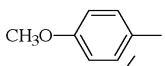
Table 4

Suzuki arylation on 5-chloro-4-methoxy-3(2*H*)-pyridazinones



19 : ^{1}R = CH_3
20 : ^{1}R = Ph

21-28

^{2}R	^{1}R	Reaction product	Yield (%) [a]
	CH_3	**21**	100
	CH_3	**22**	100
	CH_3	**23**	100
	CH_3	**24**	100
	CH_3	**25**	85
		**26**	100
		**27**	100
		**28**	100

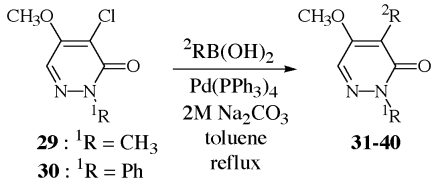
[a] Reaction conditions: **19** or **20** (1.28 mmol), boronic acid (1.92 mmol), $Pd(PPh_3)_4$ (3 mol %), Na_2CO_3 (2M, 1.4 mL), toluene (8 mL), 120°C (oil bath).

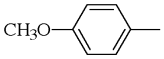
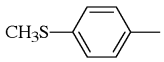
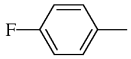
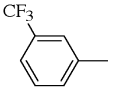
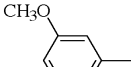
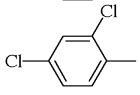
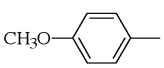
group could be introduced under our standard conditions (**37**). Only the introduction of a 2,4-dichlorophenyl (**38**) group gave an incomplete reaction even after two days of reflux under the same conditions. After testing several reaction conditions we found that two equivalents of the boronic acid were necessary to complete the reaction.

These arylations on 4,5-dichloro-, 5-chloro-4-methoxy- and 4-chloro-5-methoxy-3(2*H*)-pyridazinones show one common remarkable aspect. All the pyridazinone substrates are susceptible to alkaline hydrolysis. Nevertheless, although all our Suzuki reactions are executed in the presence of an aqueous 2 *M* sodium carbonate solution, the yields are high. Clearly, here no important losses by hydrolysis of the starting material occur.

Table 5

Suzuki arylation on 4-chloro-5-methoxy-3(2*H*)-pyridazinones



^{2}R	^{1}R	Reaction product	Yield (%) [a]
	CH_3	**31**	100
	CH_3	**32**	100
	CH_3	**33**	100
	CH_3	**34**	100
	CH_3	**35**	97
	CH_3	**36**	100
	CH_3	**37**	100
	CH_3	**38**	90
		**39**	100
		**40**	94

[a] Reaction conditions: **29** or **30** (1,28 mmol), boronic acid (**31**-**37**, **39**-**40**:1.92 mmol and **38**:3.2 mmol), $Pd(PPh_3)_4$ (3 mol %), Na_2CO_3 (2M, 1.4 mL), toluene (8 mL), 120°C (oil bath).

While our work was in progress a paper and a patent appeared dealing with palladium-catalyzed reactions on brominated and triflated 3(2*H*)-pyridazinones [57,58]. Raviña *et al.* studied Heck, Stille and Sonogashira reactions on MOM-protected 5-bromo-6-phenylpyridazinone. Li *et al.* synthesized 4,5-diaryl-3(2*H*)-pyridazinones with two different aryl groups starting from 4-bromo-5-trifluoromethylsulfonyloxy-3(2*H*)-pyridazinones. Attempts to execute selective Suzuki arylations on 4,5-dibromo-3(2*H*)-pyridazinones were unsuccessful. A mixture of 4-aryl-5-bromo-, 5-aryl-4-bromo- and 4,5-diaryl-3(2*H*)-pyridazinones was obtained. We also observed unselective behavior with 4,5-dichloro-3(2*H*)-pyridazinones.

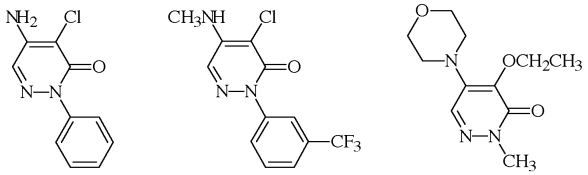
Buchwald-Hartwig Aminations on Chloro-3(2*H*)-pyridazinones [59].

In our work presented up to now, we only have executed palladium-catalyzed carbon-carbon forming reactions. But also other bonds such as carbon-nitrogen bonds can be formed by palladium-catalysis.

Since we know from the preceding work that chloro-3(2*H*)-pyridazinones undergo oxidative addition reactions, we hoped that these Pd-pyridazinone complexes would also react with amines. This means we hoped to extend our knowledge further to the palladium-catalyzed amination of chloro-3(2*H*)-pyridazinones. At the first sight there is no need for such a reaction. Many amino-3(2*H*)-pyridazinones are already known. Even several active amino-3(2*H*)-pyridazinones have been commercialized, such as the analgesic/anti-inflammatory Emorfazone [3,44] and the herbicides Chloridazon [44] and Norflurazon [44] (Scheme 6). However, as can be seen from these examples, the known products are primary amino, secondary alkylamino- and tertiary dialkylamino-3(2*H*)-pyridazinones. They can be prepared by simple nucleophilic substitution reactions with aliphatic amines [60-62]. However to the best of our knowledge only a few arylaminopyridazinones are known [63,64]. Arylamines are weak nucleophiles and nucleophilic substitutions can only be expected in the case of highly activated pyridazinones and arylamines.

Since almost no data on nucleophilic substitution reactions with arylamines on chloro-3(2*H*)-pyridazinones are available, we did some nucleophilic substitution test reactions [65]. For instance, refluxing 4-chloro-5-methoxy-2-methyl-3(2*H*)-pyridazinone (**29**) and an

Scheme 6



Chloridazon Norflurazon Emorfazone

Commercialized amino-3(2*H*)-pyridazinones

excess of *p*-toluidine (2.4 equivalents) for 24 hours in ethanol did not give any nucleophilic substitution product. Replacement of the pyridazinone by the less electron rich 4-chloro-5-methoxy-2-phenyl-3(2*H*)-pyridazinone (**30**) gave under the same reaction conditions and after 10 hours of reflux only a small amount of product in which the methoxy group was substituted by a 4-methylphenylamino group, as judged by DCI-MS. A similar investigation with the isomeric 5-chloro-4-methoxy-2-methyl-3(2*H*)-pyridazinone (**19**) and 5-chloro-4-methoxy-2-phenyl-3(2*H*)-pyridazinone (**20**) did not reveal any substitution with *p*-toluidine even after prolonged reflux in ethanol. 2-Benzyl-4-chloro-5-phenylamino-3(2*H*)-pyridazinone can be prepared from 2-benzyl-4,5-dichloro-3(2*H*)-pyridazinone and an excess of aniline (2.5 equivalents) in refluxing ethanol. However, a reaction time of 7 days is required to get 84 % yield. Using the weaker nucleophilic *p*-nitroaniline did not give any 2-benzyl-4-chloro-5-(4-nitrophenylamino)-3(2*H*)-pyridazinone. Attempts to prepare 4-arylamino-5-chloro-3(2*H*)-pyridazinones, in analogy with the preparation of 4-alkylamino-5-chloro- [66,67], 4-benzylamino-5-chloro- [62], and 4-dialkylamino-5-chloro-3(2*H*)-pyridazinones [67], by heating 4,5-dichloro-2-methyl-3(2*H*)-pyridazinone or 4,5-dichloro-2-phenyl-3(2*H*)-pyridazinone in toluene with 2.5 equivalents of aniline were unsuccessful. No substitution products could be detected by DCI-MS even after 24 hours of reflux. In such cases where amino compounds are hardly or not accessible, the palladium-catalyzed amination, which has been elaborated by Buchwald [30,31] and Hartwig [28,29], gains popularity.

In our first attempts to synthesize arylamino-3(2*H*)-pyridazinones *via* palladium-catalyzed cross-coupling reactions we selected 4-chloro-5-methoxy-2-methyl-3(2*H*)-pyridazinone (**19**) and *p*-fluoroaniline as test substrates. For the catalyst we chose the $Pd_2(dba)_3$/-BINAP combination together with sodium *t*-butoxide as the base, which according to Buchwald [30] gives the fastest reactions. However only a complex mixture of products was obtained. We realized that the strong base sodium *t*-butoxide is harmful for the pyridazinone, and we replaced it with the milder caesium carbonate. Using this catalyst-base combination the desired cross-coupling proceeded smoothly and the reaction product was obtained in very high yield. Similar results were obtained with *p*-toluidine and *p*-aminobenzonitrile (Table 6).

We were very encouraged by these results, but in our opinion the high loading of expensive catalyst is a drawback, and we tried to lower it. Disappointingly we learned that using only one fifth of the catalyst did not lead to a complete reaction: large amounts of starting material remained unconsumed, even after 48 hours of reflux. Instead decomposition products started to appear. To increase the reaction rate we tried several other reaction conditions: other bases, other palladium sources, other phosphine ligands, and phase transfer catalysis, but all without any positive result.

Recently, Watanabe *et al.* [68] reported that using a large excess of alkali metal carbonates accelerated palladium *N*-arylation of azoles. In consequence of this communication we replaced caesium carbonate with the cheaper potassium carbonate and found that using five equivalents in combination with 2 mol % of $Pd(OAc)_2$ and 2 mol % of BINAP in refuxing toluene gave optimal results. Larger excesses of the base did not further increase the reaction rate.

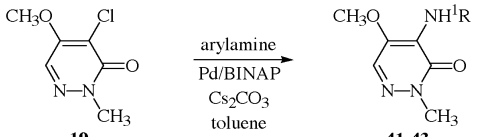
These reaction conditions were then applied for the reaction with several *p*-substituted anilines (Table 7). Both electron-rich and electron-poor anilines were successfully coupled within 3.5 to 31 hours giving the arylamino-3(2*H*)-pyridazinones in almost quantitative yield. We have run parallel reactions without palladium-catalyst, but even after prolonged reflux no desired product formation was observed. This proves that our reactions are palladium-catalyzed.

In testing the limits of this approach we examined 5-substituted 4-chloro-3(2*H*)-pyridazinones with increasing bulk of the 5-substituent (methoxy, ethylthio and phenoxy), and the heteroaromatic amine 2-aminopyridine and progressively deactivated and more sterically hindered anilines (Table 7). In all cases the yields are high to very high, even for the very sterically demanding coupling of 2-benzyl-4-chloro-5-phenoxy-3(2*H*)-pyridazinone (**45**) with 2-aminobenzonitrile (Table 7).

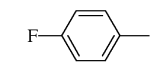
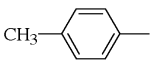
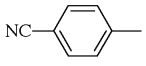
Finally we have coupled 4-chloro-5-methoxy-2-methyl-3(2*H*)-pyridazinone (**29**) with benzophenone imine [69]. Subsequent cleavage of the diphenyl ketimine with hydroxylamine gives the simple 4-amino-5-methoxy-2-methyl-3(2*H*)-pyridazinone **55**, which is nevertheless, as

Table 6

Synthesis of 4-arylamino-5-methoxy-2-methyl-3(2*H*)-pyridazinones

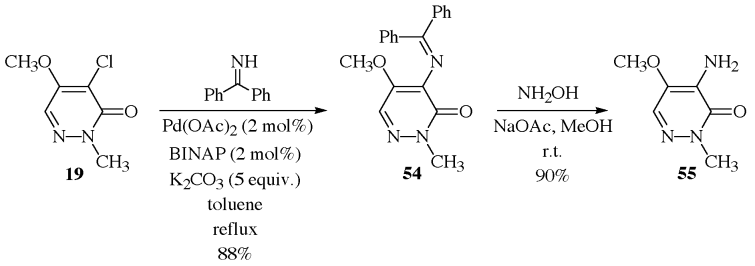


19 **41-43**

^{1}R	^{1} Reaction product	Time (h)	Yield from [a] (%)
	**41**	14	94
	**42**	12	92
	**43**	12	96

[a] Reaction conditions: amine (1.2 equiv.), Cs_2CO_3 (1.2 equiv.), $Pd_2(dba)_3$ (5 mol %), BINAP (10 mol %), toluene, 120°C (oil bath)

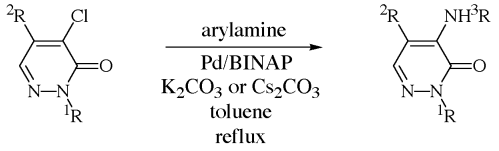
Scheme 7



Synthesis of 4-amino-5-methoxy-2-methyl-3(2*H*)-pyridazinone

Table 7

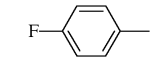
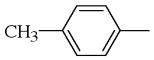
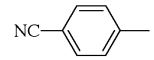
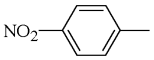
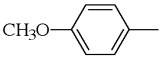
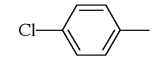
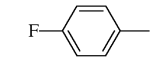
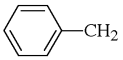
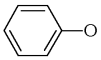
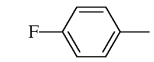
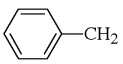
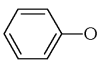
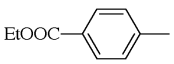
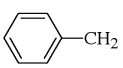
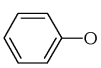
Synthesis of 2,5-disubstituted-4-arylamino-3(2*H*)-pyridazinones



19 : ^{1}R = CH_3, ^{2}R = CH_3O **41-43, 46-53**

44 : ^{1}R = Ph, ^{2}R = CH_3CH_2S

45 : ^{1}R = Bn, ^{2}R = PhO

^{1}R	^{2}R	^{3}R	Time (h)	Yield [a] (%)	Reaction product
CH_3	CH_3O		5	96	**41**
CH_3	CH_3O		31	96	**42**
CH_3	CH_3O		3.5	98	**43**
CH_3	CH_3O		7	100	**46**
CH_3	CH_3O		13.5	89	**47**
CH_3	CH_3O		3.5	95	**48**
CH_3	CH_3O		4	81	**49**
	CH_3CH_2S		11	93 [b]	**50**
			8	88	**51**
			2	97[c]	**52**
			11	91	**53**

[a] Reaction conditions: amine (1.2 equiv.), K_2CO_3 (5.0 equiv.), $Pd(OAc)_2$ (2 mol %), BINAP (2 mol %), toluene (9 mL), 120°C (oil bath). [b] 10 equiv. K_2CO_3 instead of 5 equiv. was required. [c] Cs_2CO_3 (5 equiv.) was used instead of K_2CO_3.

far as we could find, a new compound (Scheme 7). The yields of both reaction steps are high and this procedure can be a general alternative for the impractical direct aminolysis in a bomb tube.

Conclusion.

From all given examples on Suzuki, Stille and Buchwald-Hartwig reactions, we can conclude that palladium-catalyzed cross-coupling reactions on readily available and cheap chlorinated pyridazines and 3(*2H*)-pyridazinones are very efficient and generally applicable for the synthesis of pyridazine derivatives, which are sometimes hard to prepare *via* classical synthetic methods. Other examples will follow soon.

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REFERENCES AND NOTES

[*] Post-doctoral fellow from the University of Ljubljana, Slovenia.

[1] M. Tišler and B. Stanovnik, in Advances in Heterocyclic Chemistry, Vol **24**, A. J. Boulton and A. R. Katritzky, ed, Academic Press, New York, 1979, pp 363-456.

[2] M. Tišler and B. Stanovnik, in Advances in Heterocyclic Chemistry, Vol **49**, A. R. Katritzky, ed, Academic Press, New York, 1990, pp 385-474.

[3] H. Frank and G. Heinisch, in Progress in Medicinal Chemistry, Vol **27**, G. P. Ellis and G. B. West, ed, Elsevier Science Publishers, Amsterdam, 1990, pp 1-49.

[4] H. Frank and G. Heinisch, in Progress in Medicinal Chemistry, Vol **29**, G. P. Ellis and D. K. Luscombe, ed, Elsevier Science publishers, Amsterdam, 1992, pp 141-183.

[5] W. J. Coates, in Comprehensive Heterocyclic Chemistry, Vol **6**, A. R. Katritzky and C. W. Rees, ed., Pergamon Press, Oxford, 1996, pp 1-91.

[6] J. K. Stille, *Angew. Chem., Int. Ed. Engl.*, **25**, 508 (1986).

[7] N. Miyaura and A. Suzuki, *Chem.Rev.*, **95**, 2459 (1995).

[8] R. Schönbeck and E. Kloimstein, *Monatshefte Chem.*, **99**, 15 (1968).

[9] M. Tišler and B. Stanovnik, in Advances in Heterocyclic Chemistry, Vol **9**, A. R. Katritzky and A. J. Boulton, ed, Academic Press, New York, 1968, pp 211-320.

[10] Acros, Aldrich, Avocado, Lancaster and Maybridge.

[11] P. Fitton and E. A. Rick, *J. Organometal. Chem.*, **28**, 287 (1971).

[12] $Pd(0)(PPh_3)_2$ is formed *in situ*.

[13] J. March, Advanced Organic Chemistry (4th ed.), Wiley Interscience, New York, 1992, pp 641-644.

[14] W. Shen, *Tetrahedron Lett.*, **38**, 5575 (1997).

[15] A. F. Littke and G. C. Fu, *Angew. Chem., Int. Ed. Engl.*, **37**, 3387 (1998).

[16] X. Bei, H. W. Turner, W. H. Weinberg, A. S. Guram and J. F. Petersen, *J. Org. Chem.*, **64**, 6797 (1999).

[17] J. P. Wolfe, R. A. Singer, B. H. Yang and S. L. Buchwald, *J. Am. Chem. Soc.*, **121**, 9550 (1999).

[18] C. Zhang and M. L. Trudell, *Tetrahedron Lett.*, **41**, 595 (2000).

[19] H. Zhang and K. S. Chan, *Tetrahedron Lett.*, **37**, 1043 (1996).

[20] N. M. Ali, A. McKillop, M. B. Mitchell, R. A. Rebelo and P. J. Wallbank, *Tetrahedron*, **48**, 8117 (1992).

[21] W. J. Thompson, J. H. Jones, P. A. Lyle and J. E. Thies, *J. Org. Chem.*, **53**, 2052 (1988).

[22] D. Janietz and M. Bauer, *Synthesis*, 33 (1993).

[23] A. Turck, N. Plé, L. Mojovic, and G. Quéguiner, *Bull. Chem. Soc. Fr.*, **130**, 488 (1993).

[24] F. Trécourt, A. Turck, N. Plé, A. Paris and G. Quéguiner, *J. Heterocyclic Chem.*, **32**, 1057 (1995).

[25] M. Kosugi, M. Kameyama and T. Migita, *Chem. Lett.*, 927 (1983).

[26] F. Paul, J. Patt and J. F. Hartwig, *J. Am. Chem. Soc.*, **116**, 5969 (1994).

[27] A. S. Guram and S. L. Buchwald, *J. Am. Chem. Soc.*, **116**, 7901 (1994).

[28] J. F. Hartwig, *Angew. Chem., Int. Ed.*, **37**, 2047 (1998).

[29] J. F. Hartwig, M. Kawatsura, S. I. Hauck, K. H. Shaughnessy and L. M. Alcazar-Roman, *J. Org. Chem.*, **64**, 5575 (1999).

[30] J. P. Wolfe and S. L. Buchwald, *J. Org. Chem.*, **65**, 1144 (2000).

[31] J. P. Wolfe, H. Tomori, J. P. Sadighi, J. J. Yin and S. L. Buchwald, *J. Org. Chem.*, **65**, 1158 (2000).

[32] B. U. W. Maes, G. L. F. Lemière, R. Dommisse, K. Augustyns and A. Haemers, *Tetrahedron*, **56**, 1777 (2000).

[33] I. Parrot, Y. Rival, C.-G. Wermuth, *Synthesis*, 1163 (1999).

[34] Y. Abe, A. Ohsawa, H. Arai and H. Igeta, *Heterocycles*, **9**, 1397 (1978).

[35] A. Ohsawa, Y. Abe and H. Igeta, *Chem, Pharm. Bull.*, **28**, 3488 (1980).

[36] T. L. Draper and T. R. Bailey, *J. Org. Chem.*, **60**, 748 (1995).

[37] C.-G. Wermuth and A. Exinger, *Agressologie*, **13**, 285 (1972).

[38] C.-G. Wermuth, *J. Heterocyclic Chem.*, **35**, 1091 (1998).

[39] D. B. Moran, D. W. Powell and J. D. Allbright, US Patent 4569934A (1986); *Chem. Abstr.*, **106**, 50237k (1987).

[40] J.-J. Bourguignon, C.-G. Wermuth and P. Worms, EP Patent 306408 A1 (1989), US Patent 4910199 (1990); *Chem. Abstr.*, **111**, 97262h (1989).

[41] M. E. Castro, E. Rosa, J. A Osuna, T. Garciaferreiro, M. Loza, M. I. Cadavid, J. A. Fontenla, C. F. Masaguer, J. Cid, E. Raviña, G. Garciamera, J. Rodriguez and M.L. Deceballos, *Eur. J. Med. Chem.*, **29**, 831 (1994).

[42] W. J. Coates and A. McKillop, *Synthesis*, 334 (1993).

[43] T. Nakagone, in Pyridazines, R. N. Castle, ed, in The Chemistry of Heterocyclic Compounds, Vol **28**, A. Weisberger and E. C. Taylor, ed, John Wiley and Sons, New York (1973), pp. 463-627.

[44] D. J. Brown, in The Pyridazines, Supplement I, in The Chemistry of Heterocyclic Compounds, Vol **57**, E. C. Taylor, P. Wipf and A. Weissberger, ed, John Wiley and Sons, New York (2000).

[45] J.-P. Kan, K. Bizière, and C.-G. Wermuth, FR Patent 2539742A1 (1984), US Patent 4524070 (1985); *Chem. Abstr.*, **102**, 45967m (1985).

[46] J.-M. Sitamze, M. Schmitt and C.-G. Wermuth, *J. Org. Chem.*, **57**, 3257 (1992).

[47] L. K. Keefer and G. Lunn, *Chem. Rev.*, **89**, 459 (1989).

[48] P. Coad, R. A. Coad, S. Clough, J. Heypock, R. Salibury and C. Wilkins, *J. Org. Chem.*, **28**, 218 (1963).

[49] N. Haider and J. Käferböck, *Heterocycles*, **53**, 2527 (2000).

[50] D. P. Curran and M. Hoshino, *J. Org. Chem.*, **61**, 6480 (1996).

[51] B. U. W. Maes, O. R'kyek, J. Košmrlj, G. L. F. Lemière, E. Esmans, J. Rozenski, R. A. Dommisse and A. Haemers, *Tetrahedron*, **57**, 1323 (2001).

[52] F. Rohet, C. Rubat, P. Coudert, E. Albuisoon and J. Couquelet, *Chem. Pharm. Bull.*, **44**, 980 (1996).

[53] R. Buchman, J. A. Scozzie, Z. S. Ariyan, D. J. Rippin, W. J. Pyne, L. J. Powers and R. J. Matthews, *J. Med. Chem.*, **23**, 1398 (1980).

[54] K. U. Sadek, M. A. Selim and R. M. Abdel-Motaleb, *Bull. Chem. Soc. Jpn.*, **63**, 652 (1990).

[55] A. A. Elagamey, F. M. A. El-Taweel and M. N. M. Khodeir, *Pharmazie*, **47**, 418 (1992)

[56] J. Weismuller, P. Babczinski, K. Lurssen, H. J. Santel, R. R. Schmidt and B. Krauskopf, EP Patent 410238A2 (1991), US Patent 5097028 (1992); *Chem. Abstr.*, **115**, 29361x (1991).

[57] C. S. Li, J. Y. Gauthier, C. K. Lau and M. Therien, Patent WO/98/15548A1 (1998), US Patent 6004960 (1999); *Chem. Abstr.*, **128**, 282847s (1998).

[58] I. Estevez, A. Coelho and E. Raviña, *Synthesis*, 1666 (1999).

[59] J. Košmrlj, B. U. W. Maes, G. L. F. Lemière and A. Haemers, *Synlett*, 1581 (2000).

[60] S. Corsano, R. Scapicchi, G. Strappaghetti, G. Marucci, G. and F. Paparelli, *Eur. J. Med. Chem.*, **28**, 647 (1993).

[61] M. Takaya, M. Sato, K. Terashima, H. Tanizawa and Y. Maki, *J. Med. Chem.*, **22**, 53 (1979).

[62] P. Matyus, K. Fuji, K. Tanaka, J. Rohonczy, R. Hargitai and P. Sohar, *Heterocycles*, **38**, 1957 (1994).

[63] B. D. Schober, G. Megyeri and T. Kappe, *J. Heterocyclic Chem.*, **27**, 471 (1990).

[64] V. Dal Piaz, G. Ciciani, G. Turco, M. P. Giovannoni, M. Miceli, R. Pirisino and M. Perretti, *J. Pharm. Sci.*, **80**, 341 (1991).

[65] B. U. W. Maes, J. Košmrlj and Guy L. F. Lemière, unpublished results.

[66] K. H. Pilgram and G. E. Pollard, *J. Heterocyclic Chem.*, **14**, 1039 (1977).

[67] V. Konecny, S. Kovac and S. Varkonda, *Coll. Czech. Chem. Commun.*, **50**, 492 (1985).

[68] M. Watanabe, M. Nishiyama, T. Yamamoto and Y. Koie, *Tetrahedron Lett.*, **41**, 481 (2000).

[69] J. P. Wolfe, J. Ånman, J. P. Sadighi, R. A. Singer and S. L. Buchwald, *Tetrahedron Lett.*, **38**, 6367 (1997).