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Synthesis of 5*H*-pyridazino[4,5-*b*]indoles and their benzofurane analogues utilizing an intramolecular Heck-type reaction

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Cordially dedicated to Professor Sándor Antus on the occasion of his 60th birthday and to Professor Herman Desseyn on the occasion of his 65th birthday

Abstract—The title ring systems were prepared from pyridazin-3(2*H*)-one precursors in novel, efficient pathways. 2-Methylbenzo[*b*]furo[2,3-*d*]pyridazin-1(2*H*)-one was synthesized via a regioselective nucleophilic substitution reaction of a 2-methyl-4,5-dihalopyridazin-3(2*H*)-one with phenol followed by an intramolecular Heck-type reaction. The same molecule and its 6-phenyl analogue were also prepared via reaction of 2-methyl-5-iodopyridazin-3(2*H*)-one or 2-methyl-5-chloro-6-phenylpyridazin-3(2*H*)-one, respectively, with 2-bromophenol or 2-iodophenol followed by Pd-catalyzed cyclodehydrohalogenation. Moreover, a new approach for the synthesis of 2-methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-ones was also elaborated utilizing a Heck-type ring closure reaction on 5-[(2-bromophenyl)amino]-2-methylpyridazin-3(2*H*)-ones which were obtained via Buchwald–Hartwig amination of 2-methyl-5-halopyridazin-3(2*H*)-ones with 2-bromoaniline.

1. Introduction

The 5*H*-pyridazino[4,5-*b*]indole skeleton, an aza-analogue of β-carboline, is well known for its interesting pharmacological properties. For instance, 5*H*-pyridazino[4,5-*b*]indole derivatives show a wide variety of cardiovascular activities such as inhibition of blood platelet aggregation, thromboxane synthetase and phosphodiesterase as well as inotropic and antihypertensive activity.[1a–k] Interestingly, the structurally closely related benzo[*b*]furo[2,3-*d*]pyridazine ring system has been far less investigated.[1l,m] Encouraged by the pharmacological value of these ring systems, we decided to probe a new and short approach towards the synthesis of 5*H*-pyridazino[4,5-*b*]indoles and benzo[*b*]furo[2,3-*d*]pyridazines. Recently, our laboratories published several examples on the synthesis of diazino-fused polycyclic heteroaromatic compounds based on the Suzuki coupling of a (pseudo)halopyridazin-3(2*H*)-one with *ortho* substituted arylboronic acids.[2] In this paper we describe an entirely new methodology for the synthesis of pyridazino-annelated ring systems based on an intramolecular Heck-type reaction with a π-system of the pyridazin-3(2*H*)-one core.

Of the target ring systems, only the synthesis of 5*H*-pyridazino[4,5-*b*]indoles has been thoroughly studied.[2a,e,3,4] The oldest and standard procedure is based on the reaction of a 2,3-dicarbonylated indole with a hydrazine.[3a–c] More recently, an inverse electron demand Diels–Alder reaction of indoles with 1,2,4,5-tetrazines was utilized for the preparation of 5*H*-pyridazino[4,5-*b*]indoles.[4] In 2001, we reported the first pyridazine-based approach, providing the first example for a palladium-catalyzed strategy for the synthesis of this skeleton.[2a] This approach relies on a Suzuki cross-coupling of easily accessible 5-iodo-2-methylpyridazin-3(2*H*)-one[5] (**1**) with a protected 2-aminophenylboronic acid (**2**) (Scheme 1). Subsequent deprotection and diazotization of amine **4** followed by an in situ S_N1 reaction with sodium azide yielded arylazide **5**. The thermal reaction of this compound, presumably via an electrocyclic reaction of a nitrene intermediate, led to the tricyclic fused ring system. The latter approach is totally different from the two other strategies since the pyridazino-indole core is built up starting from a pyridazin-3(2*H*)-one rather than from an indole moiety.

Keywords: Palladium; Buchwald–Hartwig amination; Intramolecular Heck-type reaction; Pyridazinone; Aza-β-carboline.
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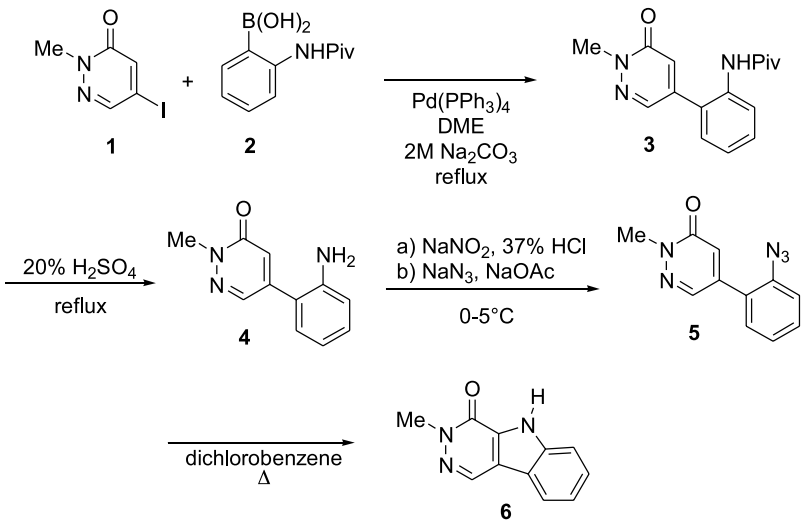
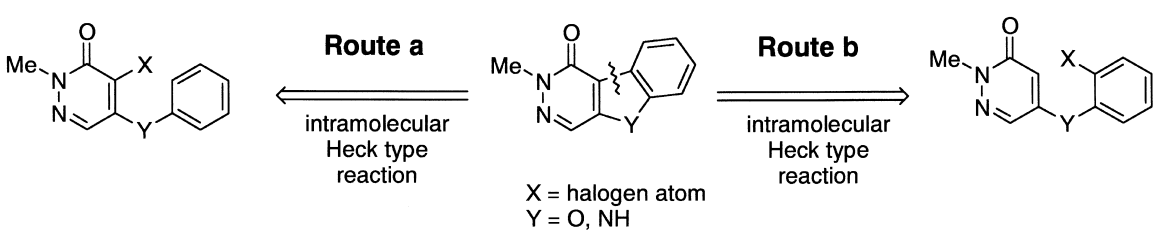


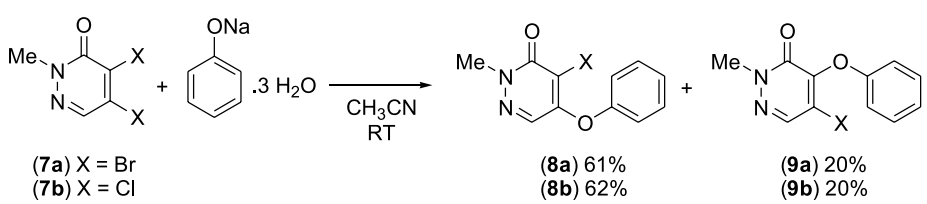
Scheme 1.

Although, our earlier developed palladium-catalyzed procedure could in principle be extended to the preparation of 5*H*-pyridazino[4,5-*b*]indoles substituted at the benzene ring, and furthermore a modified route using protected 2-hydroxyphenylboronic acids could be developed for the synthesis of their furo analogues, this type of Suzuki based methodology has a serious drawback since it requires (at least) equimolar amounts of substituted 2-amino- or 2-hydroxyphenylboronic acids which are not commercially available. Therefore, we decided to develop a new palladium-catalyzed approach, based on easily available halogenated pyridazin-3(2*H*)-ones, via a combination of a substitution and an intramolecular Heck-type reaction.[6,7] The 5-phenoxypyridazin-3(2*H*)-ones, required for the benzofuropyridazines, are easily available through a nucleophilic substitution reaction on halopyridazin-3(2*H*)-ones with phenol whereas the 5-phenylaminopyridazin-3(2*H*)-ones, required for the pyridazinoindoles, were thought to be conveniently accessible via a Buchwald–Hartwig amination reaction.[8,9f–j]

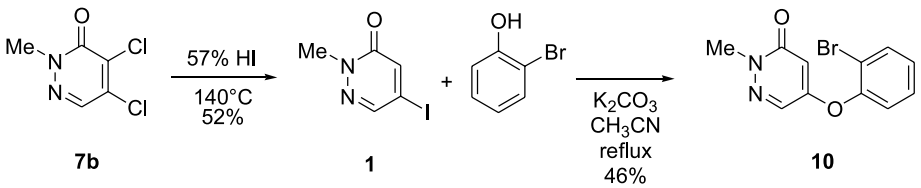
For the subsequent ring closure step two routes can be considered: the halogen atom participating in the intramolecular Heck-type reaction can be present either at the pyridazinone (route a) or at the attached phenoxy- or phenylamino-ring (route b) (Scheme 2). To determine which route gives the best result, we decided to explore the above-mentioned strategies in the synthesis of the benzo[*b*]furo[2,3-*d*]pyridazine skeleton. As reported in the literature 4-bromo-2-methyl-5-phenoxypyridazin-3(2*H*)-one (**8a**) and 4-chloro-2-methyl-5-phenoxypyridazin-3(2*H*)-one (**8b**) can be obtained via phenolysis of the corresponding 4,5-dibromo- (**7a**) and 4,5-dichloro-2-methylpyridazin-3(2*H*)-one (**7b**) in refluxing acetonitrile using potassium carbonate as the base.[9g] However, we found that 2-methyl-4,5-diphenoxypyridazin-3(2*H*)-one was also formed under these reaction conditions. Therefore, in analogy to the room temperature monoalkoxylation of 2-substituted 4,5-dihalopyridazin-3(2*H*)-ones with sodium alkanolates, we tried to perform phenolysis of 4,5-dibromo- (**7a**) and 4,5-dichloro-2-methylpyridazin-3(2*H*)-one (**7b**) in acetonitrile at room temperature with 1 equivalent of commercially available sodium phenolate trihydrate (Scheme 3). After 19 h stirring at room temperature we obtained 61% of 4-bromo-2-methyl-5-phenoxypyridazin-3(2*H*)-one (**8a**) and 62% of 4-chloro-2-methyl-5-phenoxypyridazin-3(2*H*)-one (**8b**). Interestingly, in these reaction mixtures we also found 20% of the



Scheme 2.

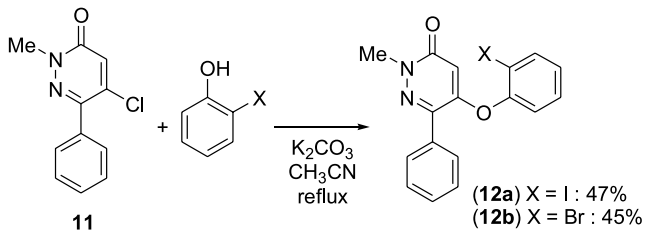


Scheme 3.



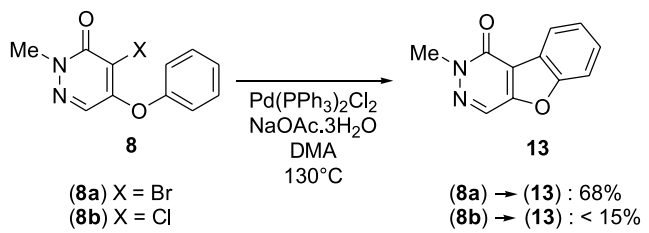
Scheme 4.

isomeric 5-halo-2-methyl-4-phenoxypyridazin-3(2*H*)-ones (**9a** and **9b**).[10,11] To the best of our knowledge, the formation of 2-substituted 5-halo-4-phenoxypyridazin-3(2*H*)-ones from the corresponding 2-substituted 4,5-dihalopyridazin-3(2*H*)-ones and phenol has not yet been reported. The 5-(2-bromophenoxy)-2-methylpyridazin-3(2*H*)-one (**10**), required for the other route, was obtained in a moderate yield from 5-iodo-2-methylpyridazin-3(2*H*)-one (**1**), under the reaction conditions reported for the synthesis of 2-substituted 4-halo-5-phenoxypyridazin-3(2*H*)-ones from 2-substituted 4,5-dihalopyridazin-3(2*H*)-ones (Scheme 4).[9g] Similarly, 5-(2-iodophenoxy)- (**12a**) and 5-(2-bromophenoxy)-2-methyl-6-phenylpyridazin-3(2*H*)-one (**12b**) were prepared by phenolysis of 5-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one[12] (**11**) (Scheme 5).



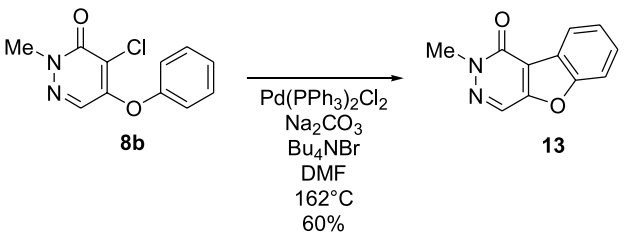
Scheme 5.

Intramolecular Heck-type reaction of **8a** was carried out under the reaction conditions ($Pd(PPh_3)_2Cl_2$, $NaOAc.3H_2O$, DMA, 130 °C)[13] we recently published for the construction of angularly annelated pyridazine ring systems, and afforded the desired 2-methylbenzo[*b*]furo[2,3-*d*]pyridazin-1(2*H*)-one (**13**) in 68% yield (Scheme 6).[2f,14] Since compound **8b** contains an activated carbon chlorine bond the same reaction conditions were tested for the cyclodehydrochlorination of this substrate (Scheme 6).[15] Unfortunately, less than 15% of **13** was obtained from **8b** and a lot of starting material remained unreacted in the crude reaction mixture, as judged by TLC and MS analysis. After some optimization work we found that compound **13** could be obtained in a similar yield as starting from **8a** when DMF was used as solvent, Na_2CO_3 as base and Bu_4NBr as additive (compare Schemes 6 and 7).[14,16–18] Interestingly, under the same reaction conditions as used for the cyclization of **8a**, the

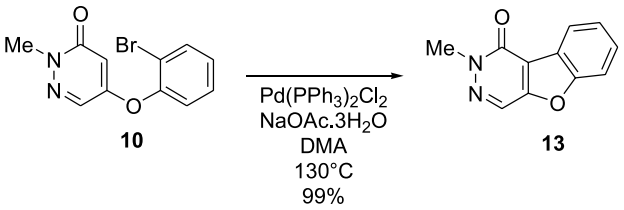


Scheme 6.

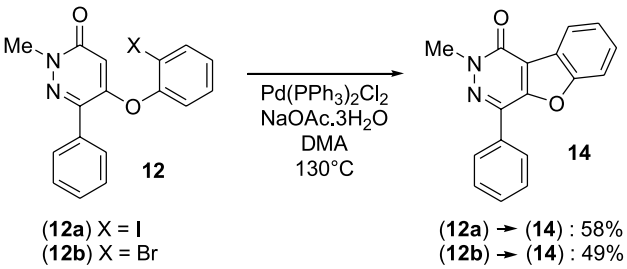
intramolecular Heck-type reaction of the isomeric derivative **10** afforded **13** in excellent yield (99%) (Scheme 8). Disappointingly, and unexpectedly, the presence of a 6-phenyl group in **12** has apparently a strong effect on the yield of cyclization since 2-methyl-4-phenylbenzo[*b*]-furo[2,3-*d*]pyridazin-1(2*H*)-one (**14**) was isolated in only 49% yield (Scheme 9). The use of 5-(2-iodophenoxy)-2-methyl-6-phenylpyridazin-3(2*H*)-one (**12a**), the iodo analogue of **12b**, gave **14** in a slightly higher yield (58%) (Scheme 9).



Scheme 7.

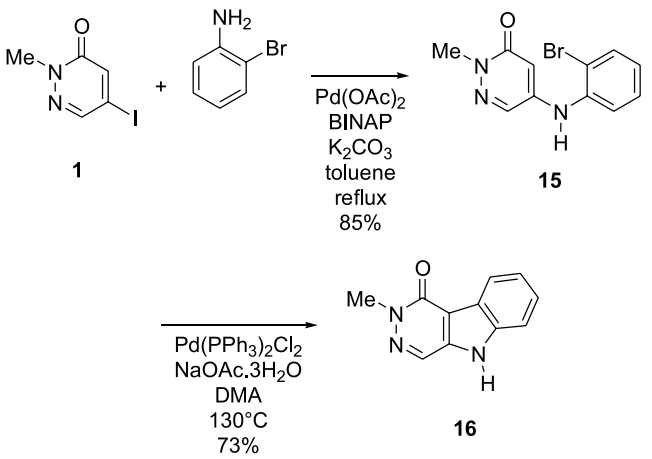


Scheme 8.



Scheme 9.

These results clearly indicate that, for the synthesis of the benzo[*b*]furo[2,3-*d*]pyridazine skeleton, the intramolecular Heck-type reaction of 5-(2-halophenoxy)pyridazin-3(2*H*)-ones (route b) is superior to that of 4-halo-5-phenoxypyridazin-3(2*H*)-ones (route a).[19] Therefore, we decided to explore a reaction pathway similar to the former route for the synthesis of the 5*H*-pyridazino[4,5-*b*]indole skeleton by utilizing 5-(2-bromophenylamino)-2-methylpyridazin-3(2*H*)-one (**15**), easily available from 5-iodo-2-methylpyridazin-3(2*H*)-one (**1**) (Scheme 10). Nucleophilic



Scheme 10.

substitution of the iodine atom of **1** via an addition–elimination mechanism with 2-bromoaniline did not occur as expected.[20] Buchwald–Hartwig amination with 2-bromoaniline seemed therefore to be worth trying.

We recently reported on the Pd-catalyzed amination of 4-chloropyridazin-3(2*H*)-ones with substituted anilines.[21b] When we applied these reaction conditions for the amination of **1** with 2-bromoaniline, **15** was obtained in excellent yield (85%) (Scheme 10). Although the amination reaction of **1** using 5 equiv.[21b] of K_2CO_3 was considerably faster than using only 1 equiv., the same yield could be obtained in an overnight reaction.[21,22] In the final step of the synthesis of the pyridazinoindole system, Pd-catalyzed cyclodehydrobromination of **15** was carried out under the conditions used for cyclization of **8a**, giving the desired 2-methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (**16**) in 73% yield (Scheme 10).

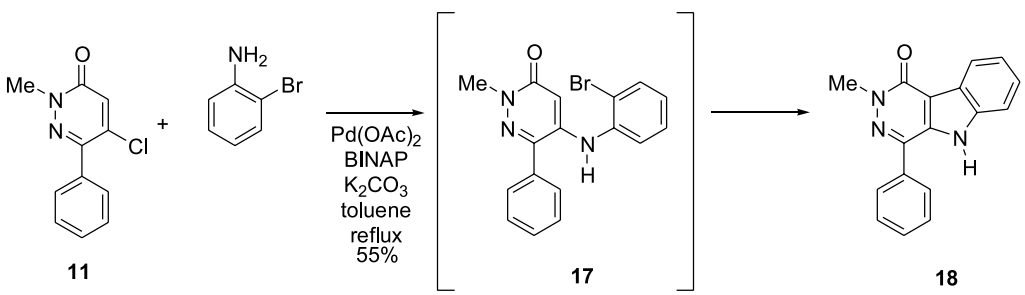
In analogy to the synthesis of 2-methyl-4-phenylbenzo[*b*]-furo[2,3-*d*]pyridazin-1(2*H*)-one (**14**) we attempted to prepare the nitrogen analogue 2-methyl-4-phenyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (**18**) from the same starting material. Remarkably, Buchwald–Hartwig reaction of 5-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one (**11**) with 2-bromoaniline worked smoothly and no homocoupling of the bromoaniline was observed (Scheme 11). The C–Cl bond of **11** seems to be more reactive in the oxidative addition step than the C–Br bond of 2-bromoaniline. The preferential reaction of the C–Cl bond of **11** can be explained by taking into account that this C–Cl bond is part of a vinylogous carbamoyl chloride which dramatically increases its reactivity for oxidative addition to Pd(BINAP) in comparison with unactivated C–Cl bonds.[15] In addition, the amino substituent of 2-bromoaniline sterically and electronically deactivates the C–Br bond for the oxidative addition to Pd(BINAP) catalyst.[23] Interestingly, the reaction did not end up with the formation of **17**. In a one pot process the intermediately formed **17** cyclized via an intramolecular Heck-type reaction yielding 2-methyl-4-phenyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (**18**) in 55% overall yield (Scheme 11).

In conclusion, we have studied the synthesis of the benzo[*b*]furo[2,3-*d*]pyridazine and 5*H*-pyridazino[4,5-*b*]indole ring systems via a new approach by combination of a nucleophilic substitution reaction or a selective Buchwald–Hartwig reaction on a 5-halopyridazin-3(2*H*)-one with an intramolecular Heck-type reaction. These syntheses represent the first report of Heck-type reactions with C–H activation on a pyridazin-3(2*H*)-one core. The presented Pd-catalyzed strategy is especially useful for the synthesis of benzo[*b*]furo[2,3-*d*]pyridazines and 5*H*-pyridazino[4,5-*b*]indoles substituted in the benzene ring since it only requires easily accessible substituted 2-bromophenols and 2-bromoanilines, respectively.

2. Experimental

2.1. General

All melting points were determined on a Kofler apparatus, except for the melting points of compounds **8a**, **8b**, **9a**, **9b**, and **18** which were determined on a Büchi apparatus. All the reported melting points are uncorrected. The IR spectra of compounds **10**, **12a**, **12b** and **13–16** were recorded on a Perkin–Elmer 1600 FT-IR instrument in potassium bromide pellets. The IR spectra of compounds **1**, **8a**, **8b**, **9a**, **9b** and **18** were recorded on a Bruker Vector 22 spectrometer in potassium bromide pellets. The ^{1}H- and ^{13}C NMR spectra of compounds **10**, **12a**, **12b** and **13–16** were recorded on a Bruker AM 200 MHz spectrometer in the solvent indicated using TMS as the internal standard. The assignments of ^{13}C NMR spectra of **10**, **12a**, **12b** and **13–16** were supported by DEPT-135 spectra. The ^{1}H and ^{13}C NMR spectra of compounds **1**, **8a**, **8b**, **9a**, **9b** and **18** were recorded on a Varian Unity 400 spectrometer in the solvent indicated with TMS as the internal standard. All coupling constants are given in Hz and chemical shifts are given in ppm. The numbering used for the assignment of NMR-signals is as follows for non-cyclized compounds: pyridazinone ring simple figures, 5-substituents primed figures and 4- or



Scheme 11.

6-substituents double primed figures. For the cyclized compounds, the IUPAC numbering was followed. For mass-spectrometric analysis, samples were dissolved in CH_3OH containing 0.1% formic acid and diluted to a concentration of approximately 10^{-5} mol/L. 1 μL injections were directed to the mass spectrometer at a flow rate of 5 μL/min CH_3OH (0.1% formic acid), using a CapLC HPLC system (Waters, Millford). Product ion spectra and accurate mass data were acquired on a quadrupole-time-of-flight mass spectrometer (QTofII, Micromass, Manchester, UK) equipped with a standard electrospray ionisation (ESI) interface. Cone voltage (approx. 35 V) and capillary voltage (approx. 3.3 kV) were optimised on one compound and used for all others. For the determination of the high-resolution *m/z*-values of the molecular ion $[M+H]^+$, a solution of polyethylene glycol 300 in CH_3OH/H_2O with 1 mmol ammonium acetate, was added just before the mass spectrometer (at a rate of 1 μL/min) to the mobile phase. The calculated masses of PEG $[M+H]^+$ and $[M+NH_4]^+$ ions were used as lock mass for the measurement of the accurate mass values of the samples. For the product ion experiments (MS) the mass of the $[M+H]^+$ was used as lock mass for the fragments. Fragmentation was induced by low energy collisional activation using different collision energies between 20 and 30 eV. Product ion spectra were recorded using data-dependant acquisition selecting automatically the parent ion, as it is the most abundant ion upon injection of the sample. This automation reduced the programming of the product ion acquisition. Parent ions were selected with low resolution ($[M+H]^+$ ±2 Da) unless otherwise stated. Therefore compounds containing chlorine and bromine show the presence of isotopes. All signals with a signal to noise ratio ≥5/1 were reported. For column chromatography of compounds **10**, **12a**, **12b** and **13**–**16** Kieselgel 60 (Aldrich, 0.063–0.2 mm silica gel) was used, while for compounds **1**, **8a**, **8b**, **9a**, **9b** and **18** Kieselgel 60 (ROCC, 0.040–0.063 mm) was used. The starting compounds 4,5-dibromo-2-methylpyridazin-3(2*H*)-one[9j,k] (**7a**), 4,5-dichloro-2-methylpyridazin-3(2*H*)-one[9j,k] (**7b**) and 5-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one[12] (**11**) were prepared according to known literature procedures. 2-Bromophenol (Aldrich), 2-iodophenol (Aldrich), 2-bromoaniline (Aldrich), $Pd(OAc)_2$ (Fluka), racemic BINAP (Strem), $Pd(PPh_3)_2Cl_2$ (Acros and Aldrich), sodium phenolate trihydrate (Aldrich) and tetrabutylammonium bromide (Acros) were obtained from commercial sources. For the Buchwald–Hartwig aminations anhydrous p.a. K_2CO_3 (Acros) and p.a. toluene (Acros) were used.

2.2. Synthesis of 5-iodo-2-methylpyridazin-3(2*H*)-one[5] (1)

A round-bottom flask was charged with 4,5-dichloro-2-methylpyridazin-3(2*H*)-one (6.50 mmol) and 57% HI (10.7 mL). The mixture was heated at 140 °C for 25 h. After cooling to room temperature, crushed ice (100 g) and water (50 mL) were added and the mixture was cautiously neutralized with potassium carbonate. Subsequently, small portions of solid sodium thiosulfate were added until the suspension turned yellow. Then, the water phase was extracted with CH_2Cl_2 (3×100 mL). The combined organic layers were dried on $MgSO_4$ and evaporated in vacuo. The crude product was purified with column chromatography using heptane–diethyl ether (1:1) as the eluent to yield the title compound (1.135 g, 74%); mp 182–183 °C; R_f (heptane–diethyl ether 1:1): 0.28; IR (KBr): ν_{max}: 2926, 1642, 1568, 1503, 1451, 1413, 1368, 1310, 1285, 1244, 1164, 1008, 917, 871, 744, 638, 618, 592, 492 cm^{-1}; δ_H ($CDCl_3$): 7.90 (d, *J*=2.05 Hz, 1H, H-6), 7.46 (d, *J*=2.05 Hz, 1H, H-4), 3.72 (s, 3H, CH_3); δ_C ($CDCl_3$): 159.05 (C-3), 141.62 (C-4 or C-6), 137.89 (C-4 or C-6), 102.26 (C-5), 39.91 (CH_3); MS (ESI): 237, 110; HRMS (ESI) for $C_5H_5N_2OI$ $[M+H]^+$: calcd: 236.9525, found: 236.9513.

2.3. General procedure for the reaction of 7a or 7b with sodium phenolate trihydrate

A mixture of 4,5-dihalo-2-methylpyridazin-3(2*H*)-one (5 mmol) and sodium phenolate trihydrate (5 mmol) in acetonitrile (50 mL) was stirred at room temperature for 19 h. Then water was added (70 mL) and the mixture was extracted with CH_2Cl_2 (3×70 mL). The combined organic layers were dried over $MgSO_4$ and evaporated in vacuo. The crude product contains two isomers, which were separated via column chromatography on silica gel using hexane–ethyl acetate (8:2) as the eluent.

The following compounds were prepared in this manner.

2.3.1. 4-Bromo-2-methyl-5-phenoxypyridazin-3(2*H*)-one (8a). Yield: 0.860 g, 61%; mp 141–142 °C; R_f (hexane–ethyl acetate 8:2): 0.17; IR (KBr): ν_{max}: 3051, 2925, 1644, 1600, 1581, 1484, 1453, 1418, 1382, 1315, 1275, 1218, 1167, 1146, 1062, 1012, 896, 822, 782, 738, 693, 635, 455 cm^{-1}; δ_H ($CDCl_3$): 7.44 (dd, *J*=8.6, 7.3 Hz, 2H, H-3′, -5′), 7.35 (s, 1H, H-6), 7.28 (tt, *J*=7.4, ≈1.2 Hz, 1H, H-4′), 7.09 (dd, *J*=8.7, ≈1.1 Hz, 2H, H-2′,-6′) 3.82 (s, 3H, CH_3); δ_C ($CDCl_3$): 159.06 (C-3), 155.66 and 153.88 (C-1′ or C-5), 130.42 (C-3′,-5′), 128.99 (C-6), 125.90 (C-4′), 119.57 (C-2′,-6′), 111.45 (C-4), 40.88 (CH_3); MS (ESI): 283, 281, 207, 205, 201, 77; HRMS (ESI) for $C_{11}H_{10}N_2O_2Br$ (^{79}Br) $[M+H]^+$: calcd: 280.9926, found: 280.9918.

2.3.2. 5-Bromo-2-methyl-4-phenoxypyridazin-3(2*H*)-one (9a). Yield: 0.281 g, 20%; mp 113–114 °C; R_f (hexane–ethyl acetate 8:2): 0.21; IR (KBr): ν_{max}: 3057, 1649, 1587, 1491, 1480, 1472, 1429, 1278, 1241, 1222, 1183, 1170, 1151, 1076, 1044, 973, 937, 916, 776, 753, 689, 528 cm^{-1}; δ_H ($CDCl_3$): 7.89 (s, 1H, H-6), 7.32 (dd, *J*=8.7, 7.5 Hz, 2H, H-3″,-5″), 7.12 (tt, *J*=7.5, 1.1 Hz, 1H, H-4″), 6.96 (dd, *J*=8.7, 1.1 Hz, 2H, H-2″,-6″), 3.75 (s, 3H, CH_3); δ_C ($CDCl_3$): 156.28 and 155.59 and 149.59 (C-3, C-4 or C-1″), 138.25 (C-6), 129.59 (C-3″,-5″), 123.97 (C-4″), 117.09 (C-5), 116.45 (C-2″,-6″), 39.99 (CH_3); MS (ESI): 283, 281, 207, 205, 175, 95, 77; HRMS (ESI) for $C_{11}H_{10}N_2O_2Br$ (^{79}Br) $[M+H]^+$: calcd: 280.9926, found: 280.9912.

2.3.3. 4-Chloro-2-methyl-5-phenoxypyridazin-3(2*H*)-one (8b). Yield: 0.738 g, 62%; mp 131 °C; R_f (hexane–ethyl acetate 8:2): 0.20; IR (KBr): ν_{max}: 3057, 1649, 1603, 1583, 1486, 1454, 1382, 1320, 1279, 1220, 1171, 1154, 1074, 1015, 898, 875, 836, 784, 741, 694, 651, 522, 461 cm^{-1}; δ_H ($CDCl_3$): 7.45 (s, 1H, H-6), 7.44 (m, 2H, H-3′,-5′), 7.27 (tt, *J*=7.5, ≈1.2 Hz, 1H, H-4′), 7.09 (dd, *J*=8.6, ≈1.2 Hz, 2H, H-2′,6′), 3.82 (s, 3H, CH_3); δ_C ($CDCl_3$): 158.80 (C-3),

153.95 and 153.51 (C-1′ or C-5), 130.44 (C-3′,-5′), 129.38 (C-6), 125.87 (C-4′), 120.16 (C-4), 119.45 (C-2′,-6′), 40.73 (CH_3); MS (ESI): 239, 237, 163, 161, 95, 77; HRMS (ESI) for $C_{11}H_{10}N_2O_2Cl$ (^{35}Cl) $[M+H]^+$: calcd: 237.0431, found: 237.0432.

2.3.4. 5-Chloro-2-methyl-4-phenoxypyridazin-3(2*H*)-one (9b). Yield: 0.232 g, 20%; mp 119–120 °C; R_f (hexane–ethyl acetate 8:2): 0.31; IR (KBr): ν_{max}: 3060, 2924, 1649, 1589, 1484, 1471, 1430, 1282, 1227, 1185, 1170, 1151, 1076, 1048, 1022, 963, 918, 897, 823, 777, 754, 732, 689, 627, 531 cm^{-1}; δ_H ($CDCl_3$): 7.80 (s, 1H, H-6), 7.32 (dd, J=7.3, 8.8 Hz, 2H, H-3″,-5″), 7.12 (tt, J=7.5, ≈1.2 Hz, 1H, H-4″), 6.96 (dd, J=8.7, ≈1.1 Hz, 2H, H-2″,-6″), 3.76 (s, 3H, CH_3); δ_C ($CDCl_3$): 156.59 and 155.66 and 147.57 (C-3 or C-4 or C-1″), 136.58 (C-6), 129.59 (C-3″,-5″), 127.56 (C-5), 123.97 (C-4″), 116.45 (C-2″-6″), 40.08 (CH_3); MS (ESI): 239, 237, 161, 131, 95, 77; HRMS (ESI) for $C_{11}H_{10}N_2O_2Cl$ (^{35}Cl) $[M+H]^+$: calcd: 237.0431, found: 237.0435.

2.4. General procedure for the reaction of 1 or 11 with 2-halophenols

A round-bottom flask equipped with a reflux condenser and a drying tube was charged with **1** (2.12 mmol) or **11** (2.26 mmol for **12a**; 2.12 mmol for **12b**), K_2CO_3 (1.2 equiv.), dry acetonitrile (10.0 mL for **10** and **12a**; 15 mL for **12b**) and 2-halophenol (1.2 equiv.). The mixture was refluxed until the starting material had been consumed as judged by TLC analysis. The solid K_2CO_3 was removed by filtration and the filtrate was subsequently concentrated. Then water (25 mL) was added to the residue and the mixture was extracted with chloroform (4×25 mL). The combined organic phases were dried over $MgSO_4$. The solvent was evaporated in vacuo, and the compounds were purified by column chromatography.

The following compounds were prepared in this manner.

2.4.1. 5-(2-Bromophenoxy)-2-methylpyridazin-3(2*H*)-one (10). Reaction time: 40 h; eluent for flash column chromatography: toluene–ethyl acetate (8:2); yield: 0.276 g, 46% as white prisms; mp 98–100 °C; R_f (ethyl acetate–chloroform 9:1): 0.68; IR (KBr) ν_{max}: 3015, 1659, 1604, 1574, 1542, 1475, 1393, 1338, 1278, 1207, 1188, 1157, 1021, 853 cm^{-1}; δ_H ($CDCl_3$): 7.81 (d, J=2.8 Hz, 1H, H-6), 7.14–7.70 (m, 4H, phenyl aromatic protons), 5.84 (d, 1H, H-4), 3.75 (s, 3H, CH_3); δ_C ($CDCl_3$): 161.8 (C-3), 158.9 (C-1′), 149.4 (C-5), 134.4 (C-6), 131.3 (C-3′), 129.3 (C-5′), 128.1 (C-4), 123.0 (C-4′), 115.9 (C-2′), 106.8 (C-6′), 54.5 (CH_3); MS (ESI): 281, 201, 155, 127, 110 (precursor monoisotopic); HRMS (ESI) for $C_{11}H_{10}BrN_2O_2$ (^{79}Br) $[M+H]^+$: calcd: 280.9926, found: 280,9926.

2.4.2. 5-(2-Iodophenoxy)-2-methyl-6-phenylpyridazin-3(2*H*)-one (12a). Reaction time: 21 h; eluent for flash column chromatography: toluene–acetone (7:3); yield: 0.430 g, 47% as white cubes; mp 174–175 °C; R_f (toluene–acetone): 0.50; IR (KBr): ν_{max}: 3059, 1655, 1596, 1505, 1464, 1405, 1327, 1273, 1210, 1150, 1057, 1019, 991, 851, 777, 738, 690, 595, 569 cm^{-1}; δ_C ($CDCl_3$): 7.87–7.97 (m, 3H, H-2″,-6″,-3′), 7.26–7.51 (m, 4H, H-3″, -4″,-5″,-5′), 6.99–7.09 (m, 2H, H-4′,-6′), 5.88 (s, 1H, H-4), 3.83 (s, 3H, 2-CH_3); δ_C ($CDCl_3$): 167.7 and 157.9 (C-3, C-5), 152.5 (C-1′), 140.6 (C-6), 140.5 (C-3′), 132.7 (C-1″), 130.4 and 129.3 and 128.3 (C-4″,-4′,-5′), 129.1 and 128.3 (C-2″,-3″,-5″,-6″), 122.4 (C-6′), 107.2 (C-4), 89.9 (C-2′), 39.8 (CH_3); MS (ESI): 405, 277; HRMS (ESI) for $C_{17}H_{14}IN_2O_2$ $[M+H]^+$: calcd: 405.0100, found: 405.0080.

2.4.3. 5-(2-Bromophenoxy)-2-methyl-6-phenylpyridazin-3(2*H*)-one (12b). Reaction time: 38 h; eluent for flash column chromatography: toluene–acetone (7:3); yield: 0.342 g, 45% as white prisms; mp 146–147 °C; R_f (toluene–acetone): 0.32; IR (KBr): ν_{max} 3061, 1661, 1598, 1512, 1467, 1413, 1327, 1262, 1213, 1145, 1058, 991, 944, 922, 854, 782, 745, 697, 574 cm^{-1}; δ_H ($CDCl_3$): 7.88–7.93 (m, 2H, H-2″,-6″), 7.68 (d, J=9.6 Hz, 1H, H-3′), 7.34–7.51 (m, 4H, H-5′,-3″,-4″,-5″), 7.01–7.26 (m, 2H, H-4′,-6′), 5.89 (s, 1H, H-4), 3.83 (s, 3H, 2-CH_3); δ_C ($CDCl_3$): 161.7 and 157.9 (C-3, C-5), 149.5 (C-1′), 140.6 (C-6), 134.4 (C-3′), 132.7 (C-1″), 129.4 and 129.3 and 128.1 (C-4″, -4′, -5′), 128.9 and 128.3 (C-2″,-3″ -5″,-6″), 123.3 (C-6′), 115.9 (C-2′), 107 (C-4), 38.8 (CH_3); MS (ESI): 357, 277, 129, 128; 82 (precursor monoisotopic); HRMS (ESI) for $C_{17}H_{14}BrN_2O_2$ (^{79}Br) $[M+H]^+$: calcd: 357.0239, found: 357.0233.

2.4.4. Synthesis of 5-[(2-bromophenyl)amino]-2-methylpyridazin-3(2*H*)-one (15). A round-bottom flask was purged with Ar and charged with $Pd(OAc)_2$ (0.03 mmol), racemic BINAP (0.03 mmol) and toluene (5 mL). While stirring, the mixture was flushed with Ar for approximately 10 min. In another flask 5-iodo-2-methylpyridazin-3(2*H*)-one (**1**) (1.5 mmol), 2-bromoaniline (1.2 equiv.) and K_2CO_3 (1 equiv.) were weighed. Subsequently, the catalyst solution was added and the flask rinsed well with an additional amount of toluene (5 mL). The resulting mixture was flushed with Ar for a few minutes under magnetic stirring and subsequently heated in an oil bath (oil bath temperature 120 °C, Ar atmosphere) until the starting material had been consumed as judged by TLC and MS analysis. The reaction mixture was filtered over celite and rinsed well with dichloromethane (200 mL). The solvent was evaporated in vacuo and the residue purified by column chromatography using ethyl acetate–chloroform (9:1) as the eluent. Reaction time: 24 h; yield: 0.357 g, 85% as white prisms; mp 193–195° C; R_f (ethyl acetate–chloroform 9:1): 0.39; IR (KBr): ν_{max}: 3214, 1625, 1589, 1521, 1439, 1341, 1278, 1026, 846, 754 cm^{-1}; δ_H ($CDCl_3$): 7.58 (d, J=2.8 Hz, 1H, H-6), 7.01–7.70 (m, 4H, phenyl aromatic protons), 6.31 (br s, 1H, NH), 6.26 (d, 1H, H-4), 3.72 (s, 3H, CH_3); δ_C ($CDCl_3$): 161.8 (C-3), 145.2 (C-1′), 136.4 (C-5), 133.6 (C-6), 130.8 (C-3′), 128.5 (C-5′), 126.4 (C-4), 123.2 (C-4′), 117.5 (C-2′), 101.9 (C-6′), 39.5 (CH_3); MS (ESI): 282, 280, 200, 171, 158, 145, 142, 130, 117, 57; HRMS (ESI) for $C_{11}H_{11}BrN_3O$ (^{79}Br) $[M+H]^+$: calcd: 280.0085, found: 280.0092.

2.5. General procedure for the Pd-catalyzed cyclodehydrohalogenation of 8a, 10, 12a, 12b and 15

A mixture of the appropriate halocompound **8a** (0.60 mmol), **10**, **15** (0.71 mmol), **12a** (0.87 mmol), or **12b** (1.00 mmol), bis(triphenylphosphine)palladium dichloride (20 mol%) and $NaOAc·3H_2O$ (2.5 equiv.) in

dimethyl acetamide (10 mL for **8a**, **10**, **12b** and **15**; 6 mL for **12a**) was stirred at 130 °C under Ar atmosphere for the reaction times indicated below. The mixture was then evaporated to dryness in vacuo. Water (10 mL) was added and the mixture was subsequently extracted with chloroform (3×10 mL). The combined organic phases were dried over $MgSO_4$. The solvent was evaporated in vacuo, and the compounds were purified by column chromatography.

The following compounds were prepared in this manner.

2.5.1. 2-Methylbenzo[*b*]furo[2,3-*d*]pyridazin-1(2*H*)-one (13). (a) *When started from* **8a**. Reaction time: 22 h; eluent for flash column chromatography: hexane–ethyl acetate (8:2); yield: 0.082 g, 68%.

(b) *When started from* **10**. Reaction time: 6 h; eluent for flash column chromatography: toluene–ethyl acetate (8:2); yield: 0.140 g, 99%.

White needles; mp 148–150 °C; R_f (ethyl acetate–chloroform 9:1): 0.82; IR (KBr): ν_{max}: 3094, 1669, 1578, 1444, 1377, 1331, 1189, 1058, 880, 752 cm^{-1}; δ_H ($CDCl_3$): 8.32 (s, 1H, H-4); 8.26 (m, 1H, H-9), 7.45–7.67 (m, 3H, aromatic protons), 3.96 (s, 3H, CH_3); δ_C ($CDCl_3$): 159.0 (C-1), 154.4 and 155.8 (C-4a,-5a), 128.6 (C-4), 125.0 and 126.3 (C-7, -9), 123.3 (C-8), 117.6 and 122.2 (C-9a,-9b), 112.0 (C-6), 39.7 (CH_3). MS (ESI): 201, 144, 116, 89; HRMS (ESI) for $C_{11}H_9N_2O_2$ $[M+H]^+$: calcd: 201.0664, found: 201.0658.

2.5.2. 2-Methyl-4-phenylbenzo[*b*]furo[2,3-*d*]pyridazin-1(2*H*)-one (14). (a) *When started from* **12a**. Reaction time: 10 h; eluent for flash column chromatography: toluene–acetone (7:3) mixture. After column chromatography the product was crystallized from acetone. Yield: 0.140 g, 58%.

(b) *When started from* **12b**. Reaction time: 11 h; eluent for flash column chromatography: petroleum ether [bp 40–70°]-ethyl acetate (2:1) mixture. Yield: 0.136 g, 49%.

Beige needles; mp 154–155 °C; R_f (toluene/acetone 7:3): 0.69; (petroleum ether [bp 40–70°]-ethyl acetate 2:1): 0.55; IR (KBr): ν_{max}: 1662, 1574, 1508, 1443, 1377, 1323, 1271, 1181, 1111, 1057, 1019, 890, 786, 748, 697, 599 cm^{-1}; δ_H ($CDCl_3$): 8.32 (d, J=7.4 Hz, 1H, H-9), 8.16–8.20 (m, 2H, H-2″,-6″), 7.68 (d, J=7.4 Hz, 1H, H-6), 7.45–7.61 (m, 5H, H-3″,-4″,-5″,-7,-8), 4.03 (s, 3H, 2-CH_3); δ_C ($CDCl_3$):158.8 (C-1), 155.6 and 153.1 (C-4a,-5a), 135.7 (C-4), 132.3 (C-1″), 129.7 and 128.5 and 124.9 and 123.2 (C-7,-8,-9,-4″), 128.7 and 127.6 (C-2″,-3″,-5″,-6″), 122.3 (C-9a), 117.7 (C-9b), 111.9 (C-6), 39.8 (CH_3); MS (ESI): 277, 220, 77; HRMS (ESI) for $C_{17}H_{13}N_2O_2$ $[M+H]^+$: calcd: 277.0977, found: 277.0965.

2.5.3. 2-Methyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (16). Reaction time: 3 h; eluent used for flash column chromatography: ethyl acetate–chloroform (9:1) mixture; yield: 0.103 g, 73% as white cubes; mp >250 °C; R_f (ethyl acetate–chloroform 9:1): 0.55; IR (KBr): ν_{max}: 3177, 1629, 1548, 1448, 1383, 1330, 1234, 1074, 996, 735 cm^{-1}; δ_H (DMSO-d_6): 12.23 (br s, 1H, NH), 8.39 (s, 1H, H-4), 8.19 (d, J=7.6 Hz, 1H, H-9), 7.66 (d, J=8.2 Hz, 1H, H-6), 7.29–7.53 (m, 2H, H-7,8), 3.79 (s, 3H, CH_3); δ_C (DMSO-d_6): 158.3 (C-1), 138.3 (C-4a), 136.6 (C-5a), 126.3 and 126.9 (C-4 and C-9), 122.1 (C-9a), 121.5 and 121.6 (C-7 and C-8), 112.6 (C-6), 111.3 (C-9b), 38.5 (CH_3). MS (ESI): 200, 143, 116; HRMS (ESI) for $C_{11}H_{10}N_3O$ $[M+H]^+$: calcd: 200.0824, found: 200.0823.

2.6. Pd-catalyzed cyclodehydrohalogenation of 8b

A mixture of the halocompound **8b** (1.0 mmol), bis(triphenyl phosphine)palladium dichloride (0.234 mmol), Na_2CO_3 (2.5 mmol) and Bu_4NBr (1.0 mmol) in DMF (4 mL) was stirred at 162 °C under N_2 atmosphere for 20 h. The mixture was then evaporated to dryness in vacuo. Water (20 mL) was added and it was extracted with chloroform (3×20 mL). The combined organic phases were dried over $MgSO_4$. The solvent was evaporated in vacuo, and the compounds were purified by column chromatography, using heptane–ethyl acetate (8:2) as the eluent, to yield **13** (0.119 g; 60%).

2.7. Synthesis of 2-methyl-4-phenyl-2,5-dihydro-1*H*-pyridazino[4,5-*b*]indol-1-one (18) via a one-pot Pd-catalyzed amination—Pd-catalyzed cyclodehydrohalogenation reaction

A round-bottom flask was purged with Ar and charged with $Pd(OAc)_2$ (0.20 mmol), racemic BINAP (0.20 mmol) and toluene (6 mL). While stirring, the mixture was flushed with Ar for approximately 10 min. In another flask 5-chloro-2-methyl-6-phenylpyridazin-3(2*H*)-one (**11**) (1.0 mmol), 2-bromoaniline (1.2 equiv.) and K_2CO_3 (10 equiv.) were weighed. Subsequently, the catalyst solution was added and the flask was rinsed well with an additional amount of toluene (6 mL). The resulting mixture was flushed with Ar for a few minutes under magnetic stirring and subsequently heated in an oil bath (oil bath temperature 120 °C, Ar atmosphere) until the starting material had been consumed as judged by TLC and MS analysis. The reaction mixture was evaporated to dryness in vacuo. Then water (50 mL) was added to the residue and the mixture was extracted with chloroform (3×50 mL). The combined organic phases were dried over $MgSO_4$. The solvent was evaporated in vacuo and the residue purified by flash column chromatography, using a 1:1 mixture of ethyl acetate and heptane as the eluent. Reaction time: 27 h; yield: 0.153 g, 55%; mp >250 °C (decomp.); R_f (ethyl acetate–heptane 1:1): 0.41; IR (KBr): ν_{max}: 3063, 2943, 1623, 1581, 1549, 1494, 1448, 1380, 1324, 1278, 1247, 1215, 1071, 1018, 789, 754, 702, 604 cm^{-1}; δ_H ($CDCl_3$): 8.78 (br s, 1H, NH), 8.49 (br d, J=7.9 Hz, 1H, H-9), 7.80 (dd, J=8.24, 1.37 Hz, 2H, Ph-2,6), 7.60–7.48 (m, 5H, Ph-3,4,5 and H-6 and H-7 or H-8), 7.40 (ddd, J=8.09, 6.87, 1.37 Hz, 1H, H-7 or H-8), 4.01 (s, 3H, CH_3); δ_C ($CDCl_3$): 159.04 (C-1), 137.99 and 136.45 and 135.33 and 134.26 (C_{Ph}-1, C-4, C-4a, C-5a), 129.57 (C_{Ph}-4), 129.45 (C_{Ph}-2,6), 127.66 (C_{Ph}-3,5), 127.01 (C-9), 123.36 (C-9a), 123.18 and 122.52 (C-7, C-8), 113.60 (C-9b), 111.54 (C-6), 39.30 (CH_3); MS (ESI): 276, 219, 144; HRMS (ESI) for $C_{17}H_{14}N_3O$ $[M+H]^+$: calcd: 276.1137, found: 276.1139.

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10. Identification of the 4-halo-2-methyl-5-phenoxypyridazin-3(2*H*)-one (**8**) and 5-halo-2-methyl-4-phenoxypyridazin-3(2*H*)-one (**9**) isomers has been done via comparison of the ^{1}H NMR spectra ($CDCl_3$) of the hydrogenolysis reaction products of **8** and **9** (Pd/C, H_2, NEt_3, CH_3OH, room temperature). We observed in each case, starting from the bromo- as well as from the chloro-phenoxypyridazin-3(2*H*)-ones, a coupling constant of 4.7 Hz for the hydrogenolysed halo-phenoxypyridazin-3(2*H*)-one isomer with the higher R_f value on TLC (eluent: hexane–ethyl acetate: 80–20) and a coupling constant of 2.8 Hz for the isomer with the lower Rf value on TLC (eluent: hexane–ethyl acetate: 80–20). A coupling constant of 2.8 Hz is typical for a 4,6 relation on a pyridazin-3(2*H*)-one core whereas a value of 4.7 Hz is consistent with a 5,6 relation. For typical $J_{4,6}$ and $J_{5,6}$ values on mono-substituted pyridazin-3(2*H*)-ones see: (a) Katz, D. Z.; Wise, D. S.; Townsend, L. B. *J. Heterocycl. Chem.* **1983**, *20*, 369–379. (b) See Ref. 9g.
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12. Estévez, I.; Raviña, E.; Sotelo, E. *J. Heterocycl. Chem.* **1998**, 1421–1428.
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14. The most important side reaction observed in the Pd-catalyzed cyclodehydrohalogenation of **8a** and **8b** is hydrodehalogenation. The formation of 2-methyl-5-phenoxypyridazin-3(2*H*)-one has been proven by NMR analysis of the column chromatography fractions that revealed the presence of a compound with a molecular mass of 202.
15. The rate of oxidative addition of aryl halogenides to a $Pd(PPh_3)_2$ or Pd(BINAP) catalyst is ArI>ArBr≫ArCl. However, the presence of electron withdrawing groups on, as well as the incorporation of nitrogen atoms in the benzene ring of the aryl chloride makes oxidative addition of aryl chlorides to palladium catalysts with traditional triarylphosphane ligands possible: (a) Fitton, P.; Rick, E. A. *J. Organomet. Chem.* **1971**, *28*, 287–291. (b) See Ref. 8g.
16. As a model compound for the optimisation of the Pd-catalyzed cyclodehydrochlorination of **8b** we used 2-benzyl-4-chloro-5-phenoxypyridazin-3(2*H*)-one. Several reaction conditions have been tried for the cyclization of this substrate: (1) $Pd(OAc)_2$, Na_2CO_3 (2.5 equiv.), DMF, reflux: starting material and hydrodechlorinated substrate, (2) $Pd(OAc)_2$, Na_2CO_3 (2.5 equiv.), DMF, Bu_4NBr (1 equiv.), reflux: mainly hydrodechlorinated substrate and only traces of the desired reaction product, (3) $Pd(PPh_3)_2Cl_2$, Na_2CO_3 (2.5 equiv.), DMF, Bu_4NBr (1 equiv.), reflux (Jefferey's conditions):[17] 37% hydrodechlorinated substrate and 42% of the desired cyclodehydrochlorinated reaction product, (4) $Pd(PPh_3)_2Cl_2$, Na_2CO_3 (2.5 equiv.), toluene, Bu_4NBr (1 equiv.): no reaction.
17. $Pd(PPh_3)_2X_2$, M_2CO_3 and Bu_4NY in DMF are the Jefferey's reaction conditions. For intermolecular Heck reactions under Jefferey's conditions see: Jefferey, T. *Tetrahedron* **1996**, *52*, 10113–10130.
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22. When 5 equiv. of K_2CO_3 were used 40% of 5-[(2-bromophenyl)amino]-2-methylpyridazin-3(2*H*)-one (**15**) and a recovery of 52% of 5-iodo-2-methylpyridazin-3(2*H*)-one (**1**) were obtained after refluxing for 3 h, whereas the use of 1 equiv. of the same base under the same reaction conditions gave a yield of 30% of **15** and a recovery of 63% of **1** in the same reaction time.
23. A similar selective behaviour has recently been reported by us for the Suzuki reaction of **11** with 2-bromophenylboronic acid. In this case the conjugate base of 2-bromophenylboronic acid probably sterically and electronically retards oxidative addition of the *ortho* C–Br bond to the Pd(0) catalyst: see Ref. 2e. Interestingly, also Armin de Meijere's group reported selectivity when using 2-bromophenylboronic acid in the Suzuki cross-coupling reaction with 1-bromonaphthalene: Wegner, H. A.; Scott, L. T.; de Meijere, A. *J. Org. Chem.* **2003**, *68*, 883–887.