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# Metal assisted synthesis of mono and diamino substituted pyridines

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ABSTRACT

A microwave assisted Buchwald–Hartwig amination protocol is reported for a series of dihalopyridine precursors. Using this procedure, selective substitution of one halogen by aryl or alkylamines is possible in very short time, usually 30 min. Mild base ($K_2CO_3$) can be used successfully, which broadens the substrate scope. The second halogen can then be substituted using alkylamines under nucleophilic substitution condition or via a Suzuki–Miyaura cross-coupling reaction. The target compounds are potential inducers of cardiomyogenesis as innovative approach in regenerative medicine.

## 1. Introduction

The pyridine ring system is generally considered as a most important heteroaromatic ring system due to its presence in numerous natural products and biologically active substances.[1] Amongst pyridine containing compounds *N*-aryl/alkyl amino substituted pyridines are interesting targets due to their presence in various bioactive compounds with diverse activity. For example, compounds of the general structure **1** were reported as a new class of antitumor agents,[2] substance **2** displayed inhibition of the vascular endothelial growth factor receptor (VEGFR-2) tyrosine kinase[3] and structure **3** was reported as a phosphodiesterase IV inhibitor (Fig. 1).[4] All of these compounds contain 4-arylamino substituted pyridine moieties. Compound **4** exhibits multiple and diverse activities, in particular it can be used in the treatment of hepatitis C[5a,b] as well as in the treatment of hypercholesterolemia.[5c]

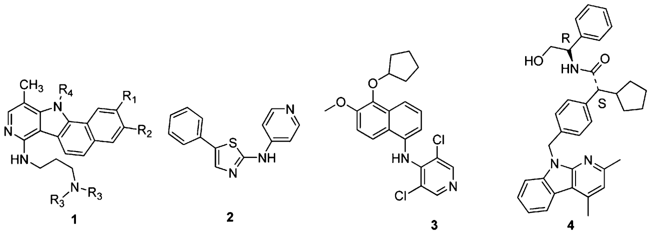

**Fig. 1.** Biologically active compounds containing the 4-aminopyridine moiety.

Consequently, the synthesis of *N*-aryl/alkyl pyridinamines has attracted much attention in recent years. The most frequently applied methods are nucleophilic substitution[6] and Buchwald–Hartwig amination.[7,8] Both methods yield the desired products and it depends on the specific problem, which one performs better. For instance, introduction of amines in 3-position of pyridine can be carried out successfully with Pd-catalyzed amination protocols, whereas nucleophilic substitution is extremely difficult. In 2- and 4-position both methods can be applied and again the specific problem often dictates the method of choice.

Buchwald–Hartwig aminations on a series of dihalopyridines (2,3-, 2,4-, 2,6-, and 3,5) are presented within this contribution. Another aim of the current contribution was the synthesis of aminopyridines, which resemble the structure of cardiogenols A–D (Fig. 2). These compounds were previously reported by Wu et al. to induce the growth of heart muscle cells from P19 stem cells.[9] This was the first report of synthetic small molecules with a cardiomyogenic effect, i.e., transformation of, e.g., a stem cell into cardiomyocytes. This is a very interesting novel biological activity, since the heart usually displays a very limited regenerative capacity after injury compared to other tissues,[10] and opens up novel perspectives for treatments in regenerative medicine.

The common structural feature of cardiogenols contains a pyrimidine core substituted with aryl- and alkylamines in positions 2 and 4. The present study aimed at developing a modular synthesis for structural analogs by applying the biomimetic strategy of heteroatom deletion, consequently, considering corresponding 2,6- or 2,4-diaminated pyridines (**I** and **II**) as target structure (Fig. 3).

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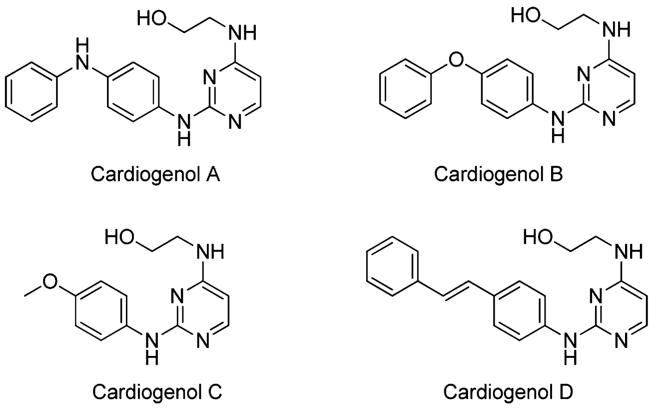


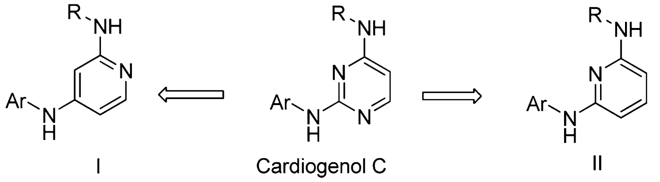
Cardiogenol A

Cardiogenol B

Cardiogenol C

Cardiogenol D

**Fig. 2.** Cardiogenols.



I

Cardiogenol C

II

**Fig. 3.** General structure of de-aza analogs to cardiogenols as target compounds.

## 2. Results and discussions

### 2.1. Buchwald–Hartwig coupling reactions on dihalopyridines

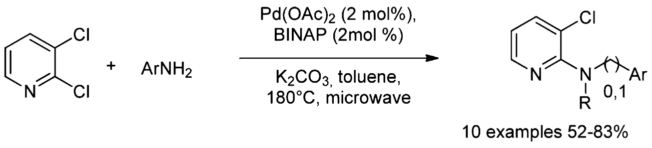
Among heterocycles, pyridine certainly represents a privileged scaffold and is present in many biological active compounds (e.g., alkaloids). Due to the prominent role of pyridine in medicinal chemistry, methods for efficiently decorating this heterocyclic scaffold are highly important and Buchwald–Hartwig reactions of pyridine halides have been investigated, in particular using chlorinated and brominated compounds.[8] However, only few examples of amination reactions on dihalogenated pyridines were reported in the literature using either palladium[11] or nickel catalysts.[12] 2,6-Dichloropyridine, 2,3-dichloropyridine, and 3,5-dichloropyridine were successfully applied in selective C–N cross-coupling reactions with aromatic amines.[13] In case of symmetric 2,6- and 3,5-dichloropyridine, only one C–N cross-coupling took place leading to a defined product, whereas 2,3-dichloropyridine reacted selectively at the more activated 2-position.

The most commonly used catalysts for Buchwald–Hartwig reactions are based on chelating phosphines, such as BINAP. Mixtures of $Pd_2(dba)_3$ or $Pd(OAc)_2$, and BINAP catalyze the cross-coupling of amines with a variety of aryl bromides.[8] In addition, aryl iodides, chlorides, and triflates can also be used as substrates. Recent reports have described the use of other bulky and more electron rich phosphine ligands.[8b,14] However, the BINAP catalyst system is still important as this is one of the most active and general catalysts for the coupling of aryl halides with primary amines.[15] Additionally, the BINAP catalyst system operates well in the presence of weak bases, such as cesium or even potassium carbonate allowing for a high level of functional group tolerance.[16] According to literature reports, the reactions of 2,3-dichloropyridine, 2,6-dichloropyridine, and 2,5-dichloropyridine with 2/3/4-aminopyridine proceeded smoothly ($Pd(OAc)_2$ (2 mol %), BINAP (2 mol %), $K_2CO_3$ (20 equiv) refluxing in toluene for 18 h), with yields between 48 and 93%.[13] Reaction of dichloropyrimidines with other substituted (electron donating and electron withdrawing) amines also proceeded smoothly with good yield.[13] Although regiospecific, this protocol has two major drawbacks: a large excess (usually approx. 20 equiv) of base ($K_2CO_3$) is required to achieve complete conversion and rather long reaction times (18 h typically) are necessary. The aforementioned protocol did not work for 3,5-dichloropyridine as precursor and more electron rich ligands and a longer reaction time (18–36 h) were necessary to accomplish the coupling step due to the unfavorable positions of chlorine atoms.

Finally, C–N coupling reactions at position 4 of pyridine are poorly covered in the literature[17,18] and the conversion of a 2,4-dihalopyridine was reported only briefly[19]; the selectivity and generality of this transformation was not further elaborated. We have recently disclosed a selective method for the C–N cross-coupling reaction in position 4 of 2-fluoro-4-iodopyridine within a preliminary study, which also allowed to decrease reaction time and amount of base employing the $Pd(OAc)_2$/BINAP system. This method was now investigated in the Buchwald–Hartwig coupling of other dihalopyridines in detail.

### 2.2. Buchwald–Hartwig coupling on 2,3-dichloropyridine

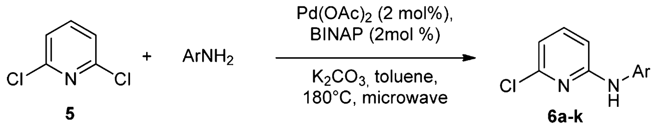
Recently, we reported on the Buchwald–Hartwig, Suzuki–Miyaura, and Liebeskind–Srogl coupling reactions of 2,3-dichloropyridine.[20] There, the optimized amination procedure[18] could be applied as well. In comparison to the previously disclosed literature protocol[13] requiring 20 equiv of base ($K_2CO_3$) and long reaction times (∼18 h) to obtain full conversion and good yields the reaction time could be significantly shortened with this microwave assisted[21] method (typically 30 min). Additionally, the amount of base could also be decreased to 3.5 equiv making the process much more efficient. Naturally, in case of 2,3-dichloropyridine, the C–N bond formation takes place in the more activated 2-position selectively (Scheme 1). The new protocol (2 mol % $Pd(OAc)_2$, 2 mol % (+/−) BINAP, 3.5 equiv $K_2CO_3$) was then applied to a series of dihalopyridines. BINAP was chosen as ligand since it gave good yields in all cases and is considerably cheaper than other ligands used for the Buchwald–Hartwig coupling reaction. It is also noteworthy that the widely applied stronger bases NaO$^t$Bu or KO$^t$Bu could be avoided. Although these stronger bases have been reported to give sometimes faster reactions,[16] their high basicity causes problems when base sensitive substrates are employed. An additional advantage of this protocol is that all reagents are not sensitive to air, hence, manipulation of all reaction partners could be conducted at ambient conditions avoiding troublesome handling in a glove box; simple flushing of the reaction vessel with argon before sealing was sufficient to ensure reproducible and good yields.



**Scheme 1.** Reaction of 2,3-dichloropyridine.

### 2.3. Buchwald–Hartwig coupling on 2,6-dichloropyridine

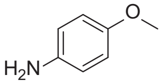
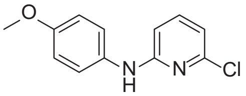
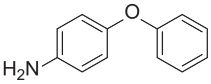
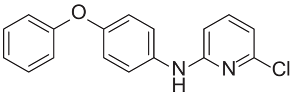
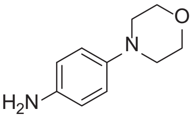
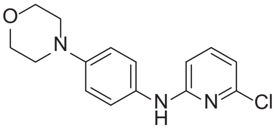
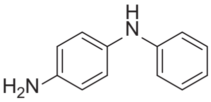
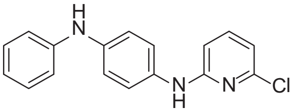
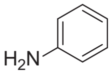
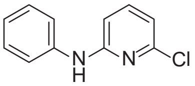
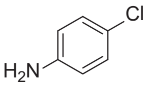
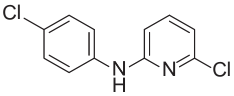
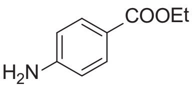
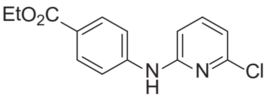
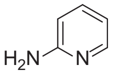
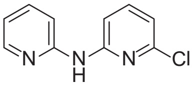
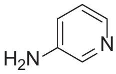
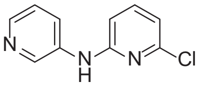
Also in the case of 2,6-dichloropyridine, the microwave assisted protocol performed well. Literature reports that only one C–N bond formation took place and no 2,6-diaminated products were observed under Buchwald–Hartwig conditions again using a large excess of base and long reaction times (∼24 h).[13] Our microwave assisted protocol worked well also on this starting material and a series of products was prepared in good yields within a short period of time (Scheme 2).



**Scheme 2.** Reaction of 2,6-dichloropyridine.

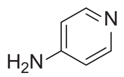
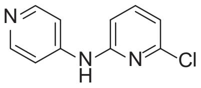
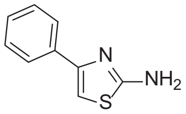
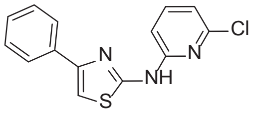
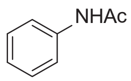
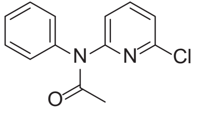
Table 1 summarizes the obtained results. Both, electron rich (entries 1–4) and electron poor (entries 6 and 7) anilines were easily introduced. Also, the presence of a base sensitive functional group was well tolerated (entry 7). An amide was also used to couple with the 2,6-dichloropyridine to investigate if this compound class can also be used as starting materials (entry 12), but in this case the yield of product was only 11%; even longer reaction time did not give an improved yield. Encouraged by the success of this amination protocol, some heteroaromatic amines were also

**Table 1**
Buchwald–Hartwig coupling on 2,6-dichloropyridine

| Entry | $RNH_2$ | Time (min) | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  | 30 |  **6a** | 72 |
| 2 |  | 30 |  **6b** | 77 |
| 3 |  | 30 |  **6c** | 77 |
| 4 |  | 30 |  **6d** | 79 |
| 5 |  | 30 |  **6e** | 76 |
| 6 |  | 30 |  **6f** | 53 |
| 7 |  | 30 |  **6g** | 66 |
| 8 |  | 30 |  **6h** | 58 |
| 9 |  | 30 |  **6i** | 71 |

(continued on next page)

**Table 1** (*continued*)

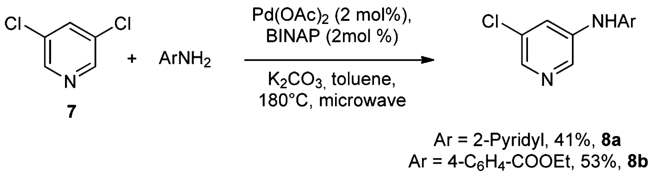
| Entry | $RNH_2$ | Time (min) | Product | Yield (%) |
|---|---|---|---|---|
| 10 |  | 30 | <br>**6j** | 65 |
| 11 |  | 45 | <br>**6k** | 73 |
| 12 |  | 45 | <br>**6l** | 11 |

used to couple with 2,6-dichloropyridines (Table 1). Aminopyridines bearing substituents in *o*, *m*, and *p*-position gave good yields (entries 8–10) and a similar result was obtained with 4-phenylthiazole-2-amine (entry 12).

Product **6a** carrying 4-methoxyaniline was of special interest as intermediate for the synthesis of the pyridine analog to Cardiogenol C, since substitution of the remaining chlorine at 6-position with ethanolamine will give the target compound.

## 2.4. Buchwald–Hartwig coupling on 3,5-dichloropyridine

Extending our investigations, symmetrical 3,5-dichloropyridine was used as starting material. According to literature reports more electron rich ligands and longer reaction times (18–36 h) were required for the coupling step due to the unfavorable positions of chlorine atoms;[13] no amination product was detected with 2-aminopyridine using BINAP as ligand. Several bulky and electron rich ligands, such as 1,3-bis(diphenylphosphino)propane, tricyclohexylphosphino and 2-(dicyclohexylphosphino)biphenyl (DCHPB) were tested and the best yield could be achieved using DCHPB as ligand.[13] In our hands, applying the above outlined conditions ($Pd(OAc)_2$, BINAP, $K_2CO_3$) under microwave irradiation on 3,5-dichloropyridine yielded the desired products without any problems in comparable yields to literature reports (employing more sophisticated and expansive ligands) (Scheme 3).[13]

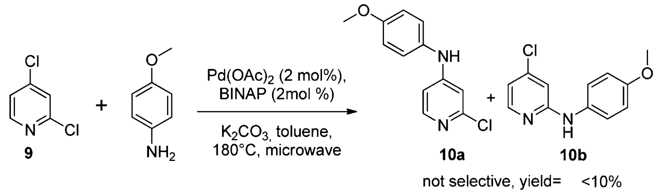


**Scheme 3.** Reaction of 3,5-dichloropyridine.

As only difference, extended microwave irradiation reaction times (2 h) were necessary and the conversion was not complete even after 2 h. The reaction time was not prolonged beyond 2 h due to partial decomposition of products. Compound **8a**, was synthesized in 41% yield (lit. 40%) and compound **8b** with 53% (lit. 56%).[13] Due to the much shorter reaction time and much cheaper ligand as well as much lower amounts of base these results represent a significant an improvement of the existing protocol.

## 2.5. Buchwald–Hartwig coupling on 2-fluoro-4-iodopyridine

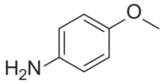
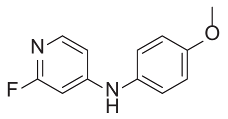
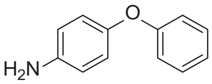
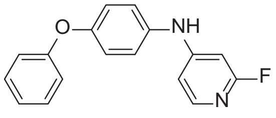
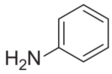
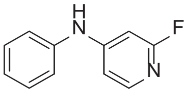
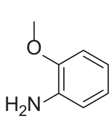
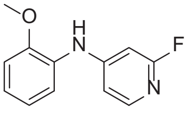
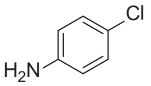
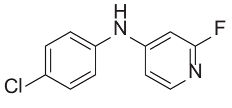
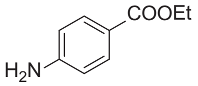
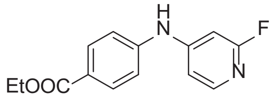
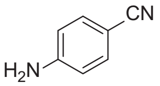
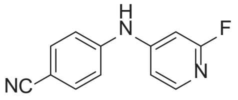
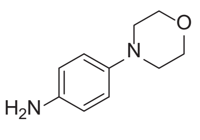
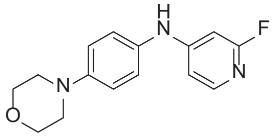
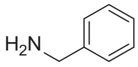
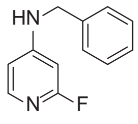
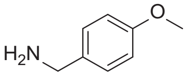
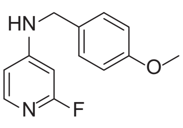
The formation of C–N bonds in 4-position of pyridine is an important topic from a synthetic point of view since 4-aminopyridines represent a frequently encountered structural motif in biologically active compounds (e.g., **1** and **2**). Recently, we have demonstrated the feasibility of microwave mediated amination in this position in a preliminary study.[18] For syntheses of 4-amino substituted pyridine derivatives, the most obvious and convenient 2,4-dihalopyridine starting material would be 2,4-dichloropyridine (**9**) (Scheme 4) as it is commercially available and cheap. However, in terms of reactivity the 2- and the 4-positions in pyridine are quite similar and mixture of products could be obtained. This was confirmed when the C–N cross-coupling reaction of 2,4-dichloropyridine (Scheme 4) was investigated. As could be expected, the reaction of **9** with *p*-anisidine provided both 2- and 4-amino substituted products **10a** and **10b** in approx. equimolar ratios (based on GC–MS), however, in less than 10% yield.



**Scheme 4.** Reaction of 2,4-dichloropyridine.

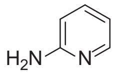
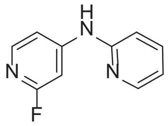
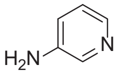
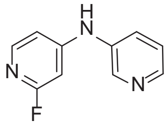
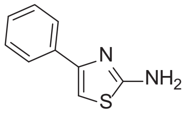
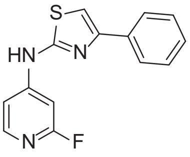
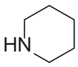
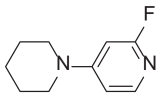
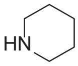
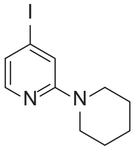
Consequently, two different halides need to be placed in positions 2 and 4 to facilitate selective substitution at C-4 by an increased reactivity of the halide at this site. In this regard, 2-fluoro-4-iodopyridine was chosen as substrate, which was prepared according to a literature protocol starting from commercially available and relatively cheap 2-fluoropyridine in high yield.[22] It was anticipated that amination will take place preferentially in 4-position under Pd-catalyzed reaction conditions. However, since high temperatures are used in the protocol developed within this work for the Buchwald–Hartwig step, a competing nucleophilic substitution in 2-position could be a possible side reaction. When carrying out the first experiment using *p*-anisidine as amine component, it was already found that neither nucleophilic substitution nor Buchwald–Hartwig coupling took place in 2-position and amination progressed exclusively in 4-position in 63% yield (Table 2, entry 1); no formation of 2,4-diaminated product was observed (Scheme 5).

**Table 2**
Amination of 2-fluoro-4-iodopyridine in position 4 via Buchwald–Hartwig amination

| Entry | $RNH_2$ | Time (min) | Product | Yield (%) |
|---|---|---|---|---|
| 1 |  | 30 |  **11a** | 63 |
| 2 |  | 30 |  **11b** | 75 |
| 3 |  | 30 |  **11c** | 65 |
| 4 |  | 30 |  **11d** | 83 |
| 5 |  | 30 |  **11e** | 52 |
| 6 |  | 45 |  **11f** | 69 |
| 7 |  | 45 |  **11g** | 78 |
| 8 |  | 30 |  **11h** | 84 |
| 9 |  | 45 |  **11i** | 52 |
| 10 |  | 45 |  **11j** | 56 |

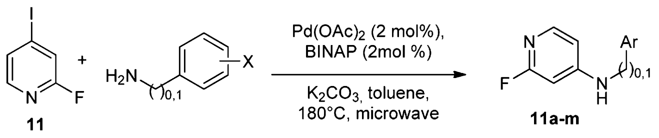
(continued on next page)

**Table 2** (*continued*)

| Entry | $RNH_2$ | Time (min) | Product | Yield (%) |
|---|---|---|---|---|
| 11 |  | 30 | <br>**11k** | 66 |
| 12 |  | 30 | <br>**11l** | 79 |
| 13 |  | 30 | <br>**11m** | 48 |
| 14 |  | 16 h[a] | <br>**11n** | 52 |
| 15 |  | 16 h[b] | <br>**11o** | 42 |

[a] Reaction was carried out at 100 °C for 16 h in a heating block.

[b] Reaction was carried out 130 °C for 16 h in a heating block.

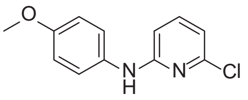
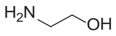
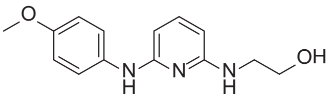
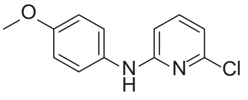
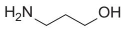
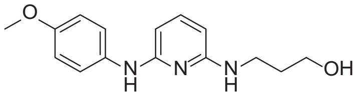
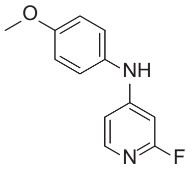
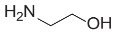
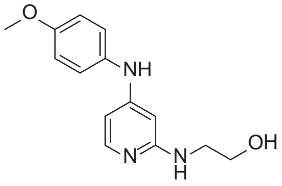
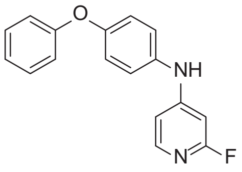
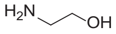
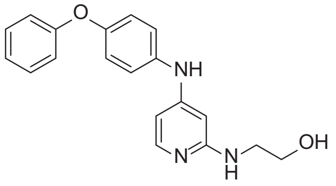


**Scheme 5.** Reaction of 2-fluoro-4-iodopyridine.

A series of substituted aniline derivatives were coupled employing the established conditions in order to assess the scope of the protocol. All reactions proceeded smoothly, affording the reaction products in good yields.[18] Product **11a** (entry 1, Table 2) carrying the 4-methoxyaniline substituent in position 4 is again of special interest since nucleophilic substitution of fluorine with ethanolamine will enable access to another pyridine derivative of Cardiogenol C important for structure–activity relationship studies.

This protocol was successful regardless of the nature of the amine used as coupling partner. Electron rich (entries 1, 2, 4, and 8) as well as electron poor (entries 5–7) anilines were well tolerated under the reaction conditions to produce the desired products in good yields. Base sensitive functional groups remained intact (entries 6, 7). Sterically demanding *o*-anisidine gave an excellent yield (83%, entry 4) indicating the applicability of sterically hindered amines in this transformation. Aliphatic amines were also used in this transformation. Benzylamine (entry 9) and 4-methoxybenzylamine (entry 10) both gave reasonable conversion and no other side products were isolated. However, in this case the yield was somewhat lower and longer reaction times were required (45 min). Additionally, the scope of heterocyclic amines as coupling partners in the C–N cross-coupling protocol was also investigated. All precursors provided access to C–N coupling products (entries 11–13, Table 3) upon selective reaction at position 4 in moderate to good yields. Also in the case of **11m** (entry 13) the reaction progressed smoothly and with complete conversion. However, a product and amine displayed similar $R_f$ values complicating chromatographic purification and decreasing the isolated yield. In another example, piperidine was investigated as example for a secondary aliphatic amine. The corresponding product **11n** was obtained in reasonable yield (entry 14) as well but different reaction conditions had to be applied. A lower temperature (100 °C) and conventional heating were necessary to give the 4-substituted product **11n**. It was found that temperatures above 130 °C promoted nucleophilic substitution at the fluorine in 2-position to become the predominant reaction pathway toward 2-substituted product **11o** (entry 15). A ratio of 5:1 (according to GC–MS) of 4-iodo-2-(piperidin-1-yl)pyridine (**11o**) and **11n** was obtained. It can be concluded that at higher temperatures the activation energy barrier for the nucleophilic substitution was exceeded and then the reaction rate of the nucleophilic substitution was higher compared

**Table 3**
Synthesis of pyridine analogs of the cardiogenols

| Entry | Py–ArNH | $RNH_2$ | Product | Yield (%) |
|---|---|---|---|---|
| 1 | <br>**6a** |  | <br>**12a** | 73 |
| 2 | <br>**6a** |  | <br>**12b** | 64 |
| 3 | <br>**11a** |  | <br>**12c** | 89 |
| 4 | <br>**11b** |  | <br>**12d** | 91 |

Reaction conditions: $RNH_2$ (8 equiv), 150 °C, 3 days, argon atmosphere.

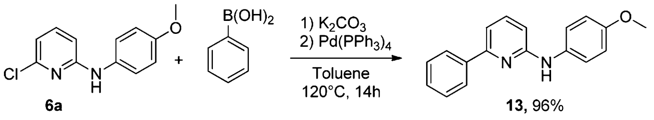
to the Buchwald–Hartwig cross-coupling process. This result is not unexpected according to literature reports, which stated that nucleophilic substitution of fluorine in 2-position of pyridine can occur even at rt without the presence of base.[23] Hence, it is rather remarkable that in all other cases no nucleophilic substitution of fluorine was observed.

### 2.6. Synthesis of 2,4 and 2,6-diamino substituted pyridines

In order to synthesize pyridine analogs of Cardiogenol C, a second amination reaction had to be carried out on either 2-arylamino-6-chloro- or 4-arylamino-2-fluoropyridine. For this purpose, a nucleophilic substitution of the remaining halide was carried out by using the aliphatic amines as solvents at high temperature (150 °C). Still, nucleophilic substitution of the halogen by aliphatic amines on arylamino substituted pyridines was very slow and it took 3 days to achieve complete conversion. As summarized in Table 3, the desired products were synthesized with good to excellent yields, demonstrating the principal applicability of the overall methodology to access pyridine analogs of cardiogenols.

### 2.7. Suzuki coupling on 2-amino substituted-6-chloropyridive derivatives

In addition to conventional nucleophilic substitutions, the remaining halide can also be used in C–C bond forming cross-coupling reactions. We have already investigated the scope of the Suzuki–Miyaura reaction in 3-position of 2-amino substituted pyridines in one of our recent publications.[20] To round up our investigations on Buchwald–Hartwig products obtained within this study, we tried to use the remaining chloride in 6-position for a subsequent Suzuki–Miyaura coupling reaction. Coupling at 6-position of pyridine is well explored[24] and there is also literature precedence for the coupling of 2-amino substituted-6-chloropyridines using $Pd(OAc)_2$ as catalyst and $K_3PO_4$ as base (three examples, yield 68%–83%).[25] Consequently, we conducted the Suzuki coupling with phenylboronic acid at 6-position utilizing $Pd(PPh_3)_4$ as catalyst and $K_2CO_3$ as base, which successfully produced the desired product in excellent yield (96%). Attempts to combine the Suzuki and Buchwald coupling steps in an one pot protocol were not successful, however (Scheme 6).



**Scheme 6.** Suzuki–Miyaura coupling on 2-aminosubstututed-6-chlopyridine.

## 3. Conclusions

In summary, the microwave assisted C–N cross-coupling protocol elaborated within this study is generally applicable to a number of dihalopyridines. This enables the synthesis of valuable building blocks for the preparation of biologically active compounds and pharmaceuticals. In comparison with previous protocols the method is superior due to more facile operation conditions (no glove box manipulation), much shorter reaction times due to the use of a microwave reactor, as well as substantially decreased amounts of base. The required base, $K_2CO_3$, is also very mild, which is advantageous in case of base sensitive substrates. By subsequently performing a nucleophilic substitution reaction of the remaining halide with ethanol- or propanolamine a set of pyridine analogs of the cardiogenols was obtained. Preliminary biological screenings on these compounds to assess their cardiomyogenesis inducing activity showed promising results in this regard.

## 4. Experimental section

### 4.1. General notes

Unless otherwise noted, chemicals were purchased from commercial suppliers and used without further purification. Microwave reactions were performed on a CEM Explorer PLS™ microwave unit. Flash column chromatography was performed on silica gel 60 from Merck (40–63 μm), whereas most separations were carried out using a Büchi Sepacore™ MPLC system with a 45 g column. For thin layer chromatography (TLC) aluminum backed silica gel was used. Melting points were determined using a Kofler-type Leica Galen III micro hot stage microscope and are uncorrected. HRMS were carried out by E. Rosenberg at Vienna University of Technology, Institute for Chemical Technologies and Analytics; all samples were analyzed by LC-IT-TOF-MS in only positive ion detection mode with the recording of MS and MS/MS spectra. NMR-spectra were recorded in $CDCl_3$ with TMS as internal standard or in DMSO-$d_6$ or $CD_3OD$ on a Bruker AC 200 (200 MHz) spectrometer and chemical shifts are reported in parts per million. Combustional Analyses were carried out in the Microanalytical Laboratory, Institute of Physical Chemistry, University of Vienna. GC–MS runs were performed on a Thermo Finnigan Focus GC/DSQ II using a standard capillary column BGB 5 (30m×0.32 mm ID). Either combustion analysis or HRMS are provided for compounds not previously reported in the literature. Characterization data of literature known compounds are available as in the Refs. 13,20,11c.

### 4.2. General procedure A

Dihalopyridine (1 equiv), amine (1.2 equiv), $K_2CO_3$ (3.5 equiv), $Pd(OAc)_2$ (2 mol %), and BINAP (2 mol %) were charged into a microwave vial and dry toluene was added. The vial was then sealed, evacuated, and flushed with argon. Then the reaction mixture was irradiated at 180 °C in a CEM Explorer™ microwave unit for 30 min (in few cases 45 min) with stirring. After cooling to rt, the solid material was removed by filtration and washed with 10 mL of EtOAc or $CH_2Cl_2$. The organic phases were combined and the solvent was evaporated. The resulting crude product was purified by flash column chromatography.

### 4.3. General procedure B

Compound **6a** (1 equiv) was mixed with appropriate amine (8 equiv) and heated in a screw cap vial under argon at 150 °C in a heating block for 3 days. After cooling to rt water (5 mL) was added and the mixture was extracted with EtOAc (5 mL) for three times. The EtOAc layer was then washed with brine and subsequently dried over $Na_2SO_4$. Evaporating the EtOAc layer gave the crude product, which was purified by flash column chromatography.

### 4.4. General procedure C

Compound **11a**/**11b** (1 equiv) was mixed with the appropriate amine (8 equiv) and heated in a screw cap vial under argon at 150 °C in a heating block for 3 days. After cooling to rt 2 N solution of NaOH (5 mL) was added and the mixture was extracted with EtOAc (15 mL) for three times. The EtOAc layer was then washed with brine and dried over $Na_2SO_4$. Evaporating the EtOAc layer gave the pure product.

*4.4.1. 6-Chloro-N-(4-methoxyphenyl)pyridin-2-amine (**6a**).* Prepared according to general procedure A. Column chromatography PE/EtOAc=4:3. Yield: 72% (115 mg, 0.49 mmol). Appearance: yellow solid. Mp: 74–76 °C. $R_f$=0.41 (PE/$CH_2Cl_2$=4:3). GC–MS: 219 (100), 234 ($M^+$, 234), 221 (32), 112 (30), 233 (27). $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$=3.81 (s, 3H), 6.52 (d, $J$=8.2 Hz, 1H), 6.65 (d, $J$=7.6 Hz, 1H), 6.74 (s, 1H), 6.89 (d, $J$=9.4 Hz, 2H), 7.19 (d, $J$=7.2 Hz, 2H), 7.34 (t, $J$=7.9 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$=54.6 (q), 103.8 (d), 112.4 (d), 113.8 (d), 123.7 (d), 131.1 (s), 139.1 (d), 148.5 (s), 155.9 (s), 156.4 (s). Combustion analysis: requires C 61.41%, H 4.72%, N 11.94%; found: C 61.42%, H 4.52%, N 11.78%.

*4.4.2. 6-Chloro-N-(4-phenoxyphenyl)pyridin-2-amine (**6b**).* Prepared according to general procedure A. Column chromatography 10% EtOAc in PE. Yield: 77% (154 mg, 0.52 mmol). Appearance: yellow crystals. Mp: 78–81 °C. $R_f$=0.51 (PE/EtOAc=10:1). GC–MS: 296 ($M^+$, 100), 77 (80), 295 (37), 51 (33), 298 (31). $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$=6.58–6.75 (q, $J$=7.2 Hz, 3H), 6.95–7.06 (m, 4H), 7.10 (d, $J$=7.4 Hz, 1H), 7.21–7.31 (m, 3H), 7.32–7.36 (m, 1H), 7.37–7.44 (m, 1H). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$=105.3 (d), 113.9 (d), 118.5 (d), 120.0 (d), 123.2 (d), 123.6(d), 129.8 (d), 134.8 (s), 140.0 (d), 149.7 (s), 153.5 (s), 156.7 (s), 157.5 (s). Combustion analysis: requires C 68.81%, H 4.42%, N 9.44%, found: C 68.60%, H 4.22%, N 8.92%.

*4.4.3. 6-Chloro-N-[(4-morpholinyl)phenyl]pyridin-2-amine (**6c**).* Prepared according to general procedure A. Column chromatography using PE/EtOAc=1:1. Yield: 77% (151 mg, 0.52 mmol). Appearance: light green crystal. Mp: 140–145 °C. $R_f$=0.46 (PE/EtOAc=1:1). GC–MS: 289 ($M^+$, 100), 231 (73), 230 (53), 291 (34), 232 (28). $^1$H NMR ($CD_3OD$, 200 MHz): $\delta$=2.92–3.20 (br s, 4H), 3.81–3.86 (m, 4H), 6.62 (t, $J$=7.7 Hz, 2H), 6.95 (d, $J$=8.0 Hz, 1H), 7.30–7.49 (m, 3H). $^{13}$C NMR ($CD_3OD$, 50 MHz): $\delta$=54.4 (q), 64.4 (q), 103.8 (d), 112.4 (d), 113.8 (d), 123.9 (d), 130.9 (s), 139.1 (d), 148.5 (s), 155.9 (s), 156.4 (s). Combustion analysis: requires C 62.18%, H 5.57%, N 14.50%, found: C 62.31%, H 5.15%, N 14.43%.

*4.4.4. $N^1$-(6-Chloropyridin-2-yl)-$N^4$-phenylbenzene-1,4-diamine (**6d**).* Prepared according to general procedure A. Column chromatography 15% EtOAc in PE. Yield: 79% (158 mg, 0.53 mmol). Appearance: brown oil. $R_f$=0.34 ($CH_2Cl_2$). GC–MS: 295 (100), 296 ($M^+$, 100), 297 (34), 167 (32), 169 (21). $^1$H NMR ($CD_3OD$, 200 MHz): $\delta$=6.52–6.67 (m, 2H), 6.71–6.82 (m), 6.95–7.09 (m, 4H), 7.10–7.22 (m, 2H), 7.30–7.44 (m, 3H). $^{13}$C NMR ($CD_3OD$, 50 MHz): $\delta$=108.2 (d), 113.4 (d), 117.4 (d), 120.1 (d), 120.5 (d), 122.8 (d), 130.1 (d), 135.0 (s), 140.3 (s), 140.8 (d), 146.1 (s) 150.3 (s), 158.4 (s, C2). HRMS: requires $[MH]^+$=296.0954; found 296.0949.

*4.4.5. 6-Chloro-N-(4-chlorophenyl)pyridin-2-amine (**6f**).* Prepared according to general procedure A. Column chromatography 10% EtOAc in PE. Yield: 53% (85 mg, 0.36 mmol). Appearance: orange solid. Mp: 95–96 °C. $R_f$=0.38 (PE/EtOAc=4:1). GC–MS: 237 (100), 238 (72), 239 ($M^+$, 100), 168 (61), 240 (46). $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$=6.59 (d, $J$=8.2 Hz, 1H), 6.66 (d, $J$=7.2 Hz, 2H), 7.19 (m, 4H), 7.33 (t, $J$=7.5 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$=106.2 (d), 114.6 (d), 121.9 (d), 128.4 (d), 129.3 (s), 138.2 (s), 140.1 (d), 149.7 (s), 155.7 (s). Combustion analysis: requires C 55.26%, H 3.37%, N 11.72%; found: C 55.31%, H 3.17%, N 11.43%.

*4.4.6. N-(6-Chloropyridin-2-yl)-4-phenylthiazol-2-amine (**6k**).* Prepared according to general procedure A. Column chromatography PE/EtOAc=2:1. Yield: 73% (142.5 mg, 0.50 mmol). Appearance: yellow solid. Mp: 167–170 °C. $R_f$=0.61 (PE/EtOAc=2:1). GC–MS: 287 ($M^+$, 100), 289 (39), 288 (25), 286 (21), 251 (19). $^1$H NMR

($CDCl_3$, 200 MHz): $\delta$=6.24 (d, *J*=8.0 Hz, 1H), 6.79 (d, *J*=7.4 Hz, 1H), 7.09 (s, 1H), 7.16–7.28 (m, 1H), 7.29–7.44 (m, 3H), 7.87 (d, *J*=6.9 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$=106.3 (d), 108.7 (d, C3), 115.7 (d), 126.2 (d), 128.0 (d), 128.8 (d), 134.4 (s), 139.5 (d), 148.4 (s), 149.2 (s), 151.1 (s), 161.2 (s). Combustion analysis: requires C 58.43%, H 3.50%, N 14.60%, S 11.14%; found: C 58.71% H 3.65%, N 14.30%, S 11.16%.

*4.4.7. N-(6-Chloropyridin-2-yl)-N-phenylacetamide (**6l**).* Prepared according to general procedure A. Column chromatography PE/EtOAc=1:1. Yield: 11% (18 mg, 0.07 mmol). Appearance: yellow oil. $R_f$=0.54 (PE/EtOAc=1:1). GC–MS: 202 (100), 204 (78), 205 (41), 206 (27), 246 ($M^+$, 3). $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$=2.12 (s, 3H), 7.14 (d, *J*=7.8 Hz, 1H), 7.23–7.32 (m, 2H), 7.33–7.49 (m, 4H), 7.64 (t, *J*=7.7 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$=24.4 (q), 118.9 (d), 121.6 (d), 128.0 (d), 128.6 (d), 129.5 (d), 140.1 (d), 141.4 (s), 149.6 (s), 154.7 (s), 171.0 (s). HRMS: requires $[MH]^+$=247.0638; found 247.0633.

*4.4.8. 2-(6-(4-Methoxyphenylamino)pyridin-2-ylamino)ethanol (**12a**).* Prepared according to general procedure B. Column chromatography (PE/EtOAc=3:1). Yield: 73% (153 mg, 0.59 mmol). Appearance: brown oil. $R_f$=0.37 (PE/EtOAc=3:1). $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$=3.35 (t, *J*=4.8 Hz, 2H), 3.80 (s, 3H), 3.84 (t, *J*=4.6 Hz, 2H), 5.80 (d, *J*=7.8 Hz, 1H), 5.92 (d, *J*=9.4 Hz, 1H), 6.89 (d, *J*=8.9 Hz, 2H), 7.17 (d, *J*=8.2 Hz, 2H), 7.32 (t, *J*=7.6 Hz, 1H). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$=45.3 (t), 55.5 (q), 61.0 (t), 94.4 (d), 114.7 (d), 125.7 (d), 131.0 (s), 143.0 (d), 153.4 (s), 154.6 (d), 157.3 (s), 177.7 (s). HRMS: requires $[MH]^+$=260.1394; found 260.1389.

*4.4.9. 3-[6-(4-Methoxyphenylamino)pyridin-2-ylamino]propan-1-ol (**12b**).* Prepared according to general procedure B. Yield: 64% (72 mg, 0.26 mmol). Appearance: Colorless oil. $R_f$=0.40 (EtOAc). $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$=1.65–1.83 (m, 2H), 3.29 (t, *J*=6.3 Hz, 2H), 3.64 (t, *J*=5.8 Hz, 2H), 3.71 (s, 3H), 5.72 (d, *J*=8.2 Hz, 1H,), 5.83 (d, *J*=8.2 Hz, 1H), 8.79 (d, *J*=8.9 Hz, 2H), 7.09 (d, *J*=8.8 Hz, 2H), 7.18 (d, *J*=8.02 Hz, 1H), 8.34 (s, 2H). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$=31.8 (t), 38.8 (t), 55.5 (q), 59.2 (t), 94.1 (d), 94.7 (s), 114.6 (d), 125.3 (d), 131.6 (s), 142.3 (s), 153.9 (d), 155.2 (s), 165.9 (d). HRMS: requires $[MH]^+$=274.1550; found 274.1555.

*4.4.10. 2-[4-(4-Methoxyphenylamino)pyridin-2-ylamino]ethanol (**12c**).* Prepared according to general procedure C. Yield: 89% (38 mg, 0.15 mmol). Appearance: brown solid. Mp: 164–165 °C. $R_f$=0.21(EtOAc/MeOH=10:1). $^1$H NMR (DMSO-$d_6$, 200 MHz): $\delta$=3.22 (m, 2H), 3.45 (m, 2H), 3.72 (s, 3H), 5.89 (s, 1H), 6.05 (m, 2H), 6.89 (d, *J*=8.8 Hz, 2H), 7.07 (d, *J*=8.8 Hz, 2H), 7.59 (d, *J*=5.7 Hz, 1H), 8.11 (s, 1H). $^{13}$C NMR (DMSO-$d_6$, 50 MHz): $\delta$=43.8 (t), 55.2 (q), 60.7 (t), 89.3 (d), 100.8 (d), 114.4 (d), 122.9 (d), 133.9 (s), 147.4 (d), 151.9 (s), 154.9 (s), 159.9 (s,). HRMS: requires $[MH]^+$=260.1394; found 260.1400.

*4.4.11. 2-[4-(4-Phenoxyphenylamino)pyridin-2-ylamino]ethanol (**12d**).* Prepared according to general procedure C. Yield: 91% (55 mg, 0.17 mmol). Appearance: brown solid. Mp: 166–169 °C. $R_f$=0.19 (EtOAc/MeOH 10:1). $^1$H NMR ($CD_3OD$, 200 MHz): $\delta$=3.33–3.37 (m, 2H), 3.68 (t, *J*=5.5 Hz, 2H), 6.05 (d, *J*=1.9 Hz, 1H), 6.20 (dd, $J_1$=6.1 Hz, $J_2$=2.2 Hz, 1H), 6.95 (s, 2H, ArH), 6.97–7.02 (m, 2H), 7.08 (t, *J*=7.3 Hz, 1H), 7.14–7.23 (m, 2H), 7.26–7.39 (m, 2H), 7.61 (d, *J*=6.1 Hz, 1H). $^{13}$C NMR ($CD_3OD$, 50 MHz): $\delta$=45.5 (t), 62.4 (t), 90.9 (d), 102.8 (d), 119.3 (d), 121.1 (d), 124.1 (d), 124.4 (d), 130.8 (d), 137.8 (s), 147.9 (d), 154.2 (d), 154.5 (s), 159.3 (s), 161.5 (s). HRMS: requires $[MH]^+$=322.1555; found 322.1545.

*4.4.12. N-(4-Methoxyphenyl)-6-phenylpyridin-2-amine (**13**).* 6-Chloro-*N*-(4-methoxyphenyl)pyridin-2-amine (105 mg, 0.45 mmol, 1 equiv), phenylboronic acid (82 g, 0.67 mmol, 1.5 equiv), $K_2CO_3$ (155 mg, 1.13 mmol, 2.5 equiv), $Pd(PPh_3)_4$ (23 mg, 0.02 mmol, 5 mol %) in dry toluene (2 mL) were charged into a screw cap vial. The vial was evacuated and back filled with argon. The reaction mixture was heated overnight (14 h) at 150 °C in the heating block. After cooling to rt, the solid material was removed by filtration and washed with EtOAc (10 mL). The solvent was evaporated and the resulting crude product was purified by flash column chromatography using DCM. Yield: 96% (119 mg, 0.43 mmol). Appearance: yellow oil. $R_f$=0.31 (DCM). GC–MS: 276($M^+$, 100), 261 (96), 275 (41), 277 (21), 127 (19). $^1$H NMR ($CDCl_3$, 200 MHz): $\delta$=3.73 (s, 3H), 6.41 (s, 1H), 6.54 (d, *J*=8.4 Hz, 1H), 6.77–6.88 (m, 2H), 7.06 (d, *J*=7.4 Hz, 1H), 7.15–7.25 (m, 2H), 7.29–7.49 (m, 4H), 7.90 (dd, $J_1$=7.8 Hz, $J_2$=1.6 Hz, 2H). $^{13}$C NMR ($CDCl_3$, 50 MHz): $\delta$=55.6 (q), 105.9 (d), 111.1 (d), 114.5 (d), 123.8 (d), 126.8 (d), 128.6 (d), 128.7 (d), 133.4 (s), 138.4 (d), 139.5 (s), 156.0 (s,), 156.1 (s, C6), 156.9 (s). HRMS: requires $[MH]^+$=277.1319; found 277.1319.

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## Supplementary data

Experimental details and NMR-spectra of the compounds are available as supplementary data. Supplementary data related to this article can be found online at doi:10.1016/j.tet.2011.04.060. These data include MOL files and InChiKeys of the most important compounds described in this article.

## References and notes

1. (a) O'Hagan, D. *Nat. Prod. Rep.* **2000**, *17*, 435–446; (b) Pinder, A. R. *Nat. Prod. Rep.* **1992**, *9*, 491–504; (c) Plunkett, A. O. *Nat. Prod. Rep.* **1994**, *11*, 581–590; (d) Pinder, A. R. *Nat. Prod. Rep.* **1989**, *4*, 527–537; (e) Pinder, A. R. *Nat. Prod. Rep.* **1987**, *4*, 527–537.
2. Riou, J. F.; Fosse, P.; Chi Hung, N.; Larsen, A. K.; Bissery, M. C.; Grondard, L.; Saucier, J. M.; Bisagni, E.; Lavelle, F. *Cancer Res.* **1993**, *53*, 5987–5993.
3. Peltason, L.; Bajorath, J. *J. Med. Chem.* **2007**, *50*, 5571–5578.
4. Chakraborti, A. K.; Gopalakrishnan, B.; Sobhia, M. E.; Malde, A. *Bioorg. Med. Chem. Lett.* **2003**, *13*, 2473–2749.
5. (a) Sasiela, W. J. PCT Int. Appl., WO 2008124384 A2 20081016 CAN 149:440328, 2008; (b) Ye, J.; Sun, F.; Huang, H.; Gale, M. J. PCT Int. Appl., WO 2008091763 A1 20080731 CAN 149:191978, 2008; (c) Iglesias, P.; Diez, J. J. *Expert Opin. Invest. Drugs* **2003**, *12*, 1777–1789.
6. Eicher, T.; Hauptmann, S. *The Chemistry of Heterocycles*; Wiley-VCH: Weinheim, 2003; 269.
7. (a) Guram, A. S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1994**, *116*, 7901–7902; (b) Paul, F.; Patt, J.; Hartwig, J. F. *J. Am. Chem. Soc.* **1994**, *116*, 5969–5970.
8. (a) Marcoux, J.-F.; Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1997**, *62*, 1568–1569; (b) Nishiyama, M.; Yamamoto, T.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 617–620; (c) Jaime-Figueroa, S.; Liu, Y.; Muchowski, J. M.; Putman, D. G. *Tetrahedron Lett.* **1998**, *39*, 1313–1316; (d) Marion, N.; Ecarnot, E. C.; Navarro, O.; Amoroso, D.; Bell, A.; Nolan, S. P. *J. Org. Chem.* **2006**, *71*, 3816–3821; (e) Lorimer, A. V.; O'Connor, P. D.; Brimble, M. A. *Synthesis* **2008**, 2764–2770.
9. (a) Wu, X.; Ding, S.; Ding, Q.; Gray, N. S.; Schultz, P. G. *J. Am. Chem. Soc.* **2004**, *126*, 1590–1591; (b) Wu, X.; Ding, S.; Schultz, P. G. PCT Int. Appl., WO 2005068437; CAN 143:172888, 2005.
10. (a) Urbanek, K.; Rota, M.; Cascapera, S.; Bearzi, C.; Nascimbene, A.; De Angelis, A.; Hosoda, T.; Chimenti, S.; Baker, M.; Limana, F.; Nurzynska, D.; Torella, D.; Rotatori, F.; Rastaldo, R.; Musso, E.; Quaini, F.; Leri, A.; Kajstura, J.; Anversa, P. *Circ. Res.* **2005**, *97*, 663–667; (b) Nagai, T.; Shiojima, I.; Matsuura, K.; Komuro, I. *Circ. Res.* **2005**, *97*, 615–617; (c) Barile, L.; Chimenti, I.; Gaetani, R.; Forte, E.; Milardi, F.; Frati, G.; Messina, E.; Giacomello, A. *Nat. Clin. Pract. Cardiovasc. Med.* **2007**, *4*, S9–S14.
11. (a) Wagaw, S.; Buchwald, S. L. *J. Org. Chem.* **1996**, *61*, 7240–7241; (b) Yin, J.; Zhao Matthew, M.; Huffman Mark, A.; McNamara James, M. *Org. Lett.* **2002**, *4*, 3481–3484; (c) Suzuki, T.; Igari, S.; Hirasawa, A.; Hata, M.; Ishiguro, M.; Fujieda, H.; Itoh, Y.; Hirano, T.; Nakagawa, H.; Ogura, M.; Makishima, M.; Tsujimoto, G.; Miyata, N. *J. Med. Chem.* **2008**, *51*, 7640–7644.
12. Desmarets, C.; Schneider, R.; Fort, Y. *Tetrahedron Lett.* **2001**, *42*, 247–250.
13. Jonckers, T. H. M.; Maes, B. U. W.; Lemiere, G. L. F.; Dommisse, R. *Tetrahedron* **2001**, *57*, 7027–7034.
14. (a) Yamamoto, T.; Nishiyama, M.; Koie, Y. *Tetrahedron Lett.* **1998**, *39*, 2367–2370; (b) Hamann, B. C.; Hartwig, J. F. *J. Am. Chem. Soc.* **1998**, *120*, 7369–7370; (c) Old, D. W.; Wolfe, J. P.; Buchwald, S. L. *J. Am. Chem. Soc.* **1998**, *120*, 9722–9723; (d) Wolfe, J. P.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **1999**, *38*, 2413–2416; (e) Wolfe, J. P.;

Tomori, H.; Sadighi, J. P.; Yin, J.; Buchwald, S. L. *J. Org. Chem.* **2000**, *65*, 1158–1174; (f) Shen, Q.; Ogata, T.; Hartwig, J. F. *J. Am. Chem. Soc.* **2008**, *130*, 6586–6596.

15. (a) Wolfe, J. P.; Wagaw, S.; Buchwald, S. L. *J. Am. Chem. Soc.* **1996**, *118*, 7215–7216; (b) Shekhar, S.; Ryberg, P.; Hartwig, J. F.; Mathew, J. S.; Blackmond, D. G.; Strieter, E. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2006**, *128*, 3584–3591.
16. Wolfe, J. P.; Buchwald, S. L. *Tetrahedron Lett.* **1997**, *38*, 6359–6362.
17. (a) Mack, A. G.; Suschitzky, H.; Wakefield, B. J. *J. Chem. Soc., Perkin Trans. 1* **1980**, 1682–1687; (b) Zhang, Q.; Liu, Y.; Gao, F.; Ding, Q.; Cho, C.; Hur, W.; Jin, Y.; Uno, T.; Joazeiro, C. A. P.; Gray, N. *J. Am. Chem. Soc.* **2006**, *128*, 2182–2183; (c) Grasa, G. A.; Viciu, M. S.; Huang, J.; Nolan, S. P. *J. Org. Chem.* **2001**, *66*, 7729–7737; (d) Shen, Q.; Hartwig, J. F. *J. Am. Chem. Soc.* **2007**, *129*, 7734–7735.
18. Koley, M.; Schnuerch, M.; Mihovilovic, M. D. *Synlett* **2010**, 1505–1510.
19. (a) Norman, M. H.; Zhu, J.; Fotsch, C.; Bo, Y.; Chen, N.; Chakrabarti, P.; Doherty, E. M.; Gavva, N. R.; Nishimura, N.; Nixey, T.; Ognyanov, V. I.; Rzasa, R. M.; Stec, M.; Surapaneni, S.; Tamir, R.; Viswanadhan, V. N.; Treanor, J. J. S. *J. Med. Chem.* **2007**, *50*, 3497–3514; (b) Ji, J.; Li, T.; Bunnelle, W. H. *Org. Lett.* **2003**, *5*, 4611–4614.
20. Koley, M.; Wimmer, l.; Schnürch, M.; Mihovilovic, M. D. *Eur. J. Org. Chem.* **2011**, 1972–1979.
21. Kappe, O. C.; Stadler, A. In *Microwaves in Organic and Medicinal Chemistry in 'Methods and Principles in Medicinal Chemistry'*; Mannhold, R., Kubinyi, H., Folkers, G., Eds.; Wiley-VCH: Weinheim, 2005; Vol. 25.
22. (a) Estel, L.; Marsais, F.; Queguiner, G. *J. Org. Chem.* **1988**, *53*, 2740–2744; (b) Rocca, P.; Chochennec, C.; Marsais, F.; Thomas-dit-Dumont, L.; Mallet, M.; Godard, A.; Queguiner, G. *J. Org. Chem.* **1993**, *58*, 7832–7838; (c) Stanetty, P.; Hattinger, G.; Schnürch, M.; Mihovilovic, M. D. *J. Org. Chem.* **2005**, *70*, 5215–5220.
23. Pasumansky, L.; Hernandez, A. R.; Gamsey, S.; Goralski, C. T.; Singaram, B. *Tetrahedron Lett.* **2004**, *45*, 6417–6420.
24. Billingsley, K. L.; Anderson, K. W.; Buchwald, S. L. *Angew. Chem., Int. Ed.* **2006**, *45*, 3484–3488.
25. Schneider, C.; Gueyrard, D.; Joseph, B.; Goekjian, P. G. *Tetrahedron* **2009**, *65*, 5427–5437.