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Design and Synthesis of Polycyclic Imidazole-Containing N-Heterocycles based on C–H Activation/Cyclization Reactions

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Abstract: A new strategy for the synthesis of polycyclic imidazole-containing N-heterocycles, based on the two general synthetic ways, namely the Pd(II)-catalyzed intramolecular arylation *via* CH/C–Hal and CH/CH coupling reactions, was developed. The method proposed here enables the synthesis of many fused N-heterocycles containing purine, 1-deazapurines and benzimidazole structural units.

Keywords: C–H activation; cyclization; fluorine; imidazoles; palladium

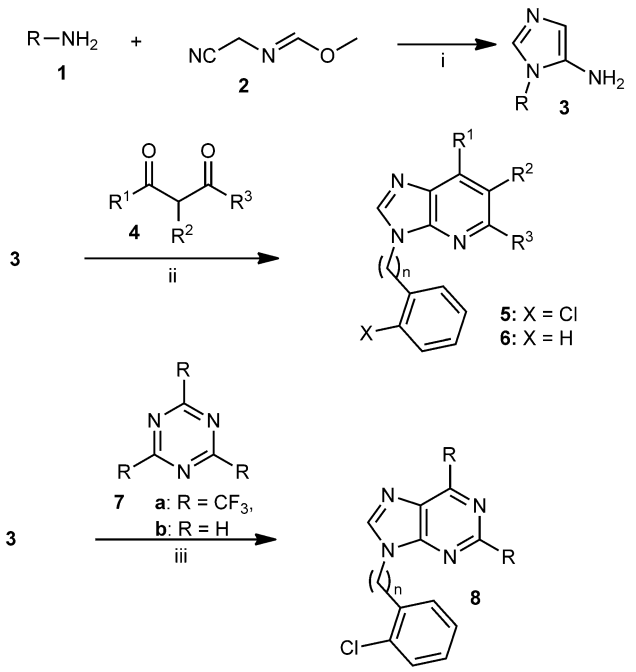
Introduction

Transition metal-catalyzed C–H activation reactions have recently found a tremendous number of novel applications (*ca.* 1000 publications) after the discovery and establishment of the methodology. In general, the C–H activation can be efficiently catalyzed by a number of transition metals, such as Pd,[1] Pt,[2] Rh,[3] Ru,[4] Ir[5] as well as Cu,[6] Co,[7] and Ni.[8] The most efficient and economical methods are considered to be Pd-catalyzed reactions, which, by their virtue, have opened many new synthetic ways to various heterocycles and carbocycles furnished with aromatic or aliphatic substituents as well as functional groups. In the same time the other transition metals are gaining relevance regarding their usage as catalytic systems for synthetic strategies related to C–H activation.[9]

Nowadays, functionalization of heterocycles by direct C–H bond activation is an important strategy for the derivatization of heterocyclic and carbocyclic compounds. Direct arylation,[10] alkylation,[1a,11] acylation,[12] sulfonation,[13] and halogenation[14] reactions of aromatic molecules were performed most of all by the application of Pd catalysts.

It is a well-known fact that azoles as well as fused azoles represent attractive targets for combinatorial library synthesis, due to their wide range of valuable biological activities. Many natural and synthetic azoles have occupied an important place in drug research as so-called privileged drug scaffolds.[15] More than 30 of the 200 worldwide best-selling drugs contain azole rings with two or more heteroatoms, both in the parent form as well as in the form of condensed systems or in a reduced state. About 20 of them contain an imidazole framework. Nevertheless, 6-trifluoromethylated purines, which were recently regarded as inhibitors of adenosine deaminase (ADA), are novel prospective drug-like scaffolds finding applications in the design and synthesis of pharmaceutically interesting compounds.[16] Very recently, Iaroshenko et al. have communicated the synthesis of 2- and 6-trifluoromethylated purines and 1-deazapurines as promising scaffolds for the design of adenosine deaminase (ADA) inhibitors.[17] The relevance of imidazoles and imidazole-containing scaffolds in medicinal chemistry and life sciences leads the way to the development of new methods for the functionalization of azole heterocycles.

Recent advances in C–H activation reactions of azoles[18] implicate several general methods which



Scheme 1. *Reaction conditions* (i): DCM, reflux, 1 h 20 min; (ii): DCM, reflux, 6 h; (iii): DCM, reflux, 7 h.

give rise, depending on the degree of substitution of the heterocyclic ring, to the possibility of selective introduction of new substituents into one of the hydrogen-substituted positions of the azole ring. Directing groups were used for the specific orientation of C–H activation reactions.[19] A number of methods for the synthesis of fused heterocycles have been reported,[20] including intramolecular cyclizations of *N*-alkylated imidazoles,[21] and purines[22a,b] by a C–H bond functionalization protocol.

On the other hand, the arylation of azoles by oxidative C–H bond activation can be also considered as a promising method for the synthesis of new azole derivatives as well as for the functionalization of the azole ring.[22]

The subject of the current study is the intermolecular Pd-catalyzed arylation of position 2 of benzimidazoles and fused heterocycles containing the imidazole moiety, namely purines and 1-deazapurines. The latter two systems were furnished with CF_3 groups as well as other electron-withdrawing groups, since this increases the acidity of proton 2-H of the imidazole ring and thus ensures a high activity in C–H activation reactions. The main concept of our study is the construction of new polyheterocyclic scaffolds containing an incorporated imidazole moiety.

Results and Discussion

Purines **8** and 1-deazapurines **5**, **6**, were prepared following the synthetic protocol recently developed by Iaroshenko's group based on the regioselective formal [3+3]-cyclization of *in situ* generated imidazole-5-amines **3** with a set of commercially available 1,3-dicarbonyl compounds **4**[17,23] and 1,3,5-triazines **7**[17,24] (Table 1 and Table 2).

Table 1. Yields of imidazo[4,5-*b*]pyridines **5** and **6**.

No.	n	R^1	R^2	R^3	Yield [%]
5a	2	CF_3	H	Me	80
5b	1	CF_3	H	Me	68
5c	2	CF_3	H	Ph	82
5d	1	CF_3	H	Ph	72
5e	2	CF_3	H	2-thienoyl	87
5f	1	CF_3	H	2-thienoyl	63
5g	2	CF_3	H	2-furyl	71
5h	1	CF_3	H	2-furyl	59
5i	2	CF_3	H	CF_3	55
5j	1	CF_3	H	CF_3	57
5k	2	CO_2Me	H	Me	61
5l	1	CO_2Me	H	Me	55
5m	2	CF_2Cl	H	Me	84
5n	1	CF_2Cl	H	Me	77
5o	2	H	NO_2	H	44
5p	1	H	NO_2	H	43
6a	2	CF_3	H	Me	72
6b	2	CF_3	H	Ph	68
6c	3	CF_3	H	Me	69
6d	3	CF_3	H	Ph	53

Table 2. Yields of *N*-substituted purines **8**.

No.	n	R	Yield [%]
8a	2	CF_3	68
8b	1	CF_3	69
8c	2	H	36[a]
8d	1	H	39

[a] Described in ref.[25]

Our initial experiments were mainly focused on the cyclization reaction of 1-deazapurines **5** and **6** by two general protocols, namely the direct Pd-catalyzed C–H arylation and oxidative C–H arylation.

At the beginning of this study, we probed a variety of bases and solvents for the desired direct intermolecular arylation of substrate **5a** which was taken as a model compound. The reactions were carried out in the absence of phosphine ligands (Table 3). We have found that the most effective transformations were accomplished using K_2CO_3 as the base and using DMF as the solvent (Scheme 1).

Treatment of 1-deazapurines **5a**, containing an *ortho*-halogenated aryl group attached by an alkyl-linker to position 9 of the 1-deazapurine moiety, with $Pd(OAc)_2$ (10 mol%) in DMF and K_2CO_3 (2 equiv.) resulted in formation of **9a** by intermolecular cyclization. However, the yields of the fused imidazole **9a**

Table 3. Optimization of the C–H activation, synthesis of compound **9a**.

Entry	Reaction conditions	Yield [%]
1	$Pd(OAc)_2$ (5 mol%), K_2CO_3 (2.5 equiv.), DMF, 140 °C, 15 h	8
2	$Pd(OAc)_2$ (5 mol%), K_3PO_4 (2.5 equiv.), DMF, 140 °C, 20 h	5
3	$Pd(OAc)_2$ (5 mol%), PPh_3 (10 mol%), K_2CO_3 (2.5 equiv.), DMF, 140 °C, 9 h	56
4	$Pd(OAc)_2$ (5 mol%), $P(Cy)_3{\cdot}HBF_4$ (10 mol%), K_2CO_3 (2.5 equiv.), DMF, 140 °C, 7 h	93
5	$Pd(OAc)_2$ (5 mol%), $P(tBu)_3$ (10 mol%), K_2CO_3 (2,5 equiv), DMF, 140 °C, 7 h	83

were rather low (less than 9%). Optimization of the conditions included mainly variation of ligands. The highest yields were obtained when $P(Cy)_3$ was employed which can be used directly or by generation *in situ* from the corresponding salt $P(Cy)_3{\cdot}HBF_4$. Under these optimal condition [$Pd(OAc)_2$ (5 mol%), $P(Cy)_3{\cdot}HBF_4$ (10 mol%), K_2CO_3 (2.5 equiv.), DMF, 140 °C], the reaction was completed within 7 h and afforded the desired fused imidazole **9a** in up to 93% yield. (Table 3, entry 4).

To study the scope and limitations of our synthetic methodology, the influence of substituents R and the length of the aliphatic linker were investigated. The reactions of a set 1-deazapurines **5b–p** were studied. We have found that the type as well as the position of the substituents R of the pyridine core had a dramatic influence on the yields. For instance, some illustrative trends in the chemical reactivity of adducts **5** are shown in Table 4. The reaction proceeded uneventfully and in high yields for 1-deazapurines furnished with a CF_3 substituent located at position 6 (products **9a–j**) (Scheme 2, Table 4).

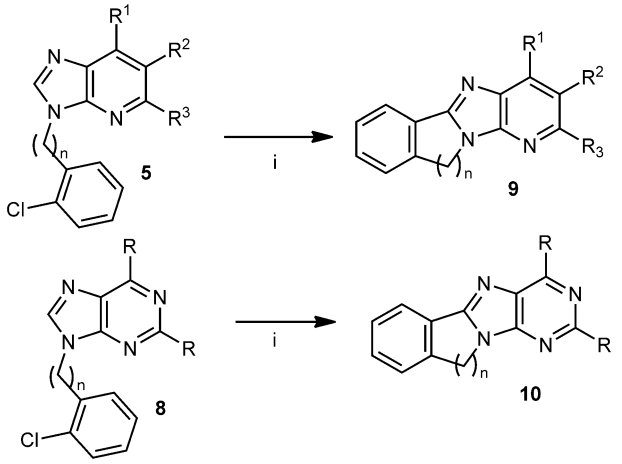
At the same time, the reaction of substrates **5m** and **5n**, bearing a CF_2Cl group, failed under various conditions (Table 4). In the case of NO_2 and CO_2Me substituted derivatives, the number n of CH_2 groups between the aryl substituent and the N-atom of the imidazole ring had an influence on the yields. We were able only in the case of $n=2$ to isolate products **9k** and **9o** in moderate yields. Moreover, in the case of **9j** and **9k**, the use of a more sterically encumbered ligand (XPhoS) was necessary. In general, the length of the linker was essential in terms of yield: compounds with $n=2$ show in all cases better yields than those with $n=1$ (Scheme 3, Table 4).

Thereafter, we have turned to the synthesis of structurally related fused purines **10** and have tested a set of purines **8a–d**. Using similar reaction conditions with some slight optimization (trifluoromethyl-containing purines were proven to be unstable in the case of temperatures higher than 100 °C and in presence of strong bases), it was possible to conduct the desired ring cyclization which delivered the fused purines **10a–d** in a yield range of 47–96%. In this case we have also observed a strong dependence of the yields on the length of the alkyl linker. The best yields were observed for $n=2$. At the same time, for

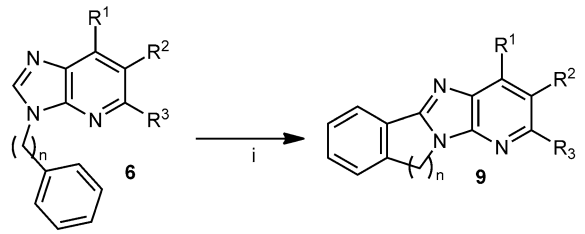
Table 4. Yields of fused imidazo[4,5-*b*]pyridines **9**.

No.	n	R^1	R^2	R^3	Yield [%] Scheme 2	Yield [%] Scheme 3
9a	2	CF_3	H	Me	93[a]	61[d]
9b	1	CF_3	H	Me	67[a]	
9c	2	CF_3	H	Ph	95[a]	62[d]
9d	1	CF_3	H	Ph	76[a]	
9e	2	CF_3	H	2-thienoyl	88[a]	
9f	1	CF_3	H	2-thienoyl	69[a]	
9g	2	CF_3	H	2-furyl	79[a]	
9h	1	CF_3	H	2-furyl	52[a]	
9i	2	CF_3	H	CF_3	88[a]	
9j	1	CF_3	H	CF_3	64[b]	
9k	2	CO_2Me	H	Me	39[c]	
9l	1	CO_2Me	H	Me	0[a–c]	
9m	2	CF_2Cl	H	Me	0[a–c]	
9n	1	CF_2Cl	H	Me	0[a–c]	
9o	2	H	NO_2	H	69[a]	
9p	1	H	NO_2	H	0[a–c]	
9q	3	CF_3	H	Me		57[d]
9r	3	CF_3	H	Ph		48[d]

[a] $Pd(OAc)_2$ (5 mol%), $P(Cy)_3{\cdot}HBF_4$ (10 mol%), K_2CO_3 (2.5 equiv.), DMF, 140 °C, 7 h.
[b] $Pd(OAc)_2$ (5 mol%), XPhoS (10 mol%), K_2CO_3 (2.5 equiv.), DMF, 120 °C, 6 h.
[c] $Pd(OAc)_2$ (5 mol%), XPhoS (10 mol%), KOAc (2 equiv.), DMF, 120 °C, 6 h.
[d] $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2.5 equiv.), HOAc, 110 °C, air, 8 h.



Scheme 2. *Reaction conditions*: (i) C–H activation, Table 4: conditions a–c; Table 6: conditions a and b.



Scheme 3. *Reaction conditions*: (i) oxidative C–H activation, Table 4: conditions d.

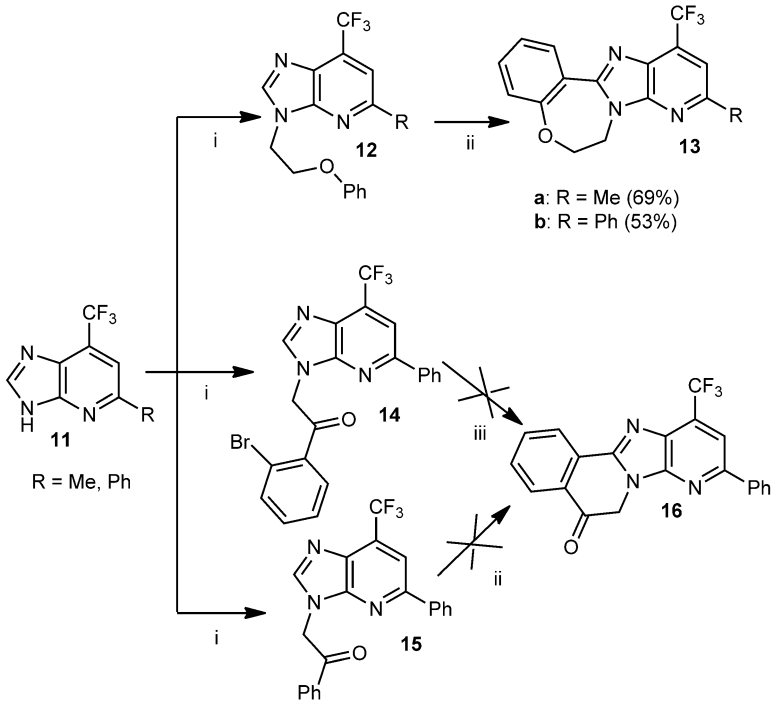
$n=1$, the yields were considerably lower or the reaction experienced failure.

We were also interested in the development of more economical methods for the synthesis of scaffolds **9**. We were aware of the possibility to use halogen-free analogues of **5**, which, in our opinion, should give rise to the desired fused imidazoles by oxidative C–H activation. As a starting point, we have applied the pioneering work of Desarbre et al.,[25] who reported a related methodology for the synthesis of novel indole derivatives.

After the optimization of the reaction conditions, we have found that the best results were obtained

Table 5. Optimization of the oxidative C-H activation, synthesis of compound **9a**.

Entry	Reaction conditions	Yield [%]
1	$Pd(OAc)_2$ (5 mol%)/$Cu(OAc)_2{\cdot}H_2O$ (2.5 equiv.)/K_2CO_3 (2 equiv.)/DMF/air/150 °C, 10 h	0
2	$Pd(OAc)_2$ (5 mol%)/$Cu(OAc)_2{\cdot}H_2O$ (2.5 equiv.)/AcOH/air/110 °C, 20 h	18
3	$Pd(OAc)_2$ (5 mol%)/$Cu(OAc)_2$ (2.5 equiv.)/K_2CO_3 (2 equiv.)/DMF/air/150 °C, 10 h	0
4	$Pd(OAc)_2$ (5 mol%)/$Cu(OAc)_2$ (2.5 equiv.)/K_2CO_3 (2 equiv.)/DMA/air/150 °C, 10 h	0
5	$Pd(OAc)_2$ (5 mol%)/$Cu(OAc)_2$ (2.5 equiv.)/K_2CO_3 (2 equiv.)/DMSO/air/160 °C, 10 h	0
6	$Pd(OAc)_2$ (5 mol%)/$Cu(OAc)_2$ (2.5 equiv.)/K_2CO_3 (2 equiv.)/PhMe:AcOH = 4:1/air/120 °C, 20 h	24
7	$Pd(OAc)_2$ (5 mol%)/$Cu(OAc)_2$ (2.5 equiv.)/K_2CO_3 (2 equiv.)/PhMe:PivOH = 4:1/air/130 °C, 20 h	34
8	$Pd(OAc)_2$ (5 mol%)/$Cu(OAc)_2$ (2.5 equiv.)/K_2CO_3 (2 equiv.)AcOH/air/110 °C, 20 h	42
9	$Pd(OAc)_2$ (5 mol%)/$Cu(OAc)_2$ (2.5 equiv.)/AcOH/air/110 °C, 20 h	42
10	$Pd(OAc)_2$ (10 mol%)/$Cu(OAc)_2$ (2.5 equiv.)/AcOH/air/110 °C, 8 h	61
11	$Pd(OAc)_2$ (10 mol%)/$Cu(OAc)_2$ (2.5 equiv.)/K_2CO_3 (2 equiv.)/PivOH/air/130 °C, 8 h	61
12	$Pd(OAc)_2$ (10 mol%)/$Cu(OAc)_2$ (2.5 equiv.)/AcOH/O_2/110 °C, 8 h	61

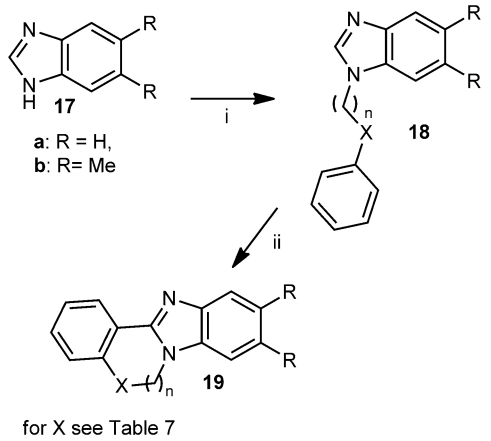


Scheme 4. *Reaction conditions*: (i): 1 equiv. of alkylating agent, 1,1 equiv. of NaH, DMF, 2 h; (ii): $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2,5 equiv.), HOAc, 110 °C, air, 8 h; (iii): $Pd(OAc)_2$ (5 mol%), XPhoS (10 mol%), KOAc (2 equiv.), DMF, 120 °C.

Table 6. Yields of fused purines **10**.

No.	n	R	Yield [%]
10a	2	CF_3	90[b]
10b	1	CF_3	47[b]
10c	2	H	96[a]
10d	1	H	0[a,b]

[a] $Pd(OAc)_2$ (5 mol%), $P(Cy)_3{\cdot}HBF_4$ (10 mol%), K_2CO_3 (2.5 equiv.), DMF, 140 °C, 14 h.
[b] $Pd(OAc)_2$ (5 mol%), XPhoS (10 mol%), KOAc (2 equiv.), DMF, 100 °C, 6 h.

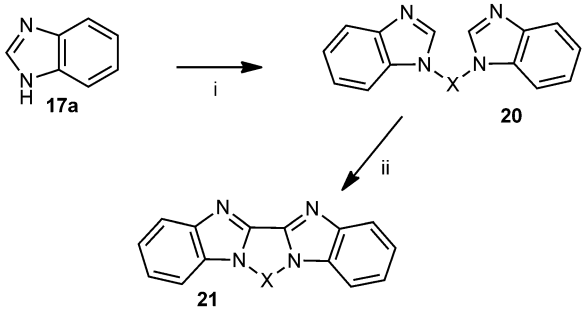


Scheme 5. *Reaction conditions:* (i): 1 equiv. of alkylating agent, 4 equiv. of K_2CO_3, DMF, 90 °C, air, 12 h; (ii): $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2.5 equiv.), K_2CO_3 (2 equiv.), PivOH, air, 130 °C, 14 h. For X, see Table 7.

Table 7. Yields of benzimidazole derivatives **18** and **19**.

No.	n	R	X	Yield [%]
18a	2	H	CH_2	79
18b	2	Me	CH_2	64
18c	3	H	CH_2	77
18d	3	H	–	69
19a	2	H	CH_2	58
19b	2	Me	CH_2	50
19c	3	H	CH_2	0
19d	3	H	–	0

using $Pd(OAc)_2$ in the presence of $Cu(OAc)_2$ as a sacrificial oxidant and air as co-oxidant; this transformation progressed under acidic conditions using acetic acid. Nevertheless, acetic acid as solvent has demonstrated the best yields for the reaction (Table 4, entry 10). Usage of pivalic acid as a solvent or pure oxygen as co-oxidant does not affect product outcome (Table 4, entries 11 and 12). As we have found, the quality of the $Cu(OAc)_2$ played a crucial role. The use of the hydrated form of the salt decreases drastically the overall yields (Table 5, entry 2).



Scheme 6. *Reaction conditions*: (i): 1 equiv. of alkylating agent, 4 equiv. of K_2CO_3, DMF, 90 °C, air, 12 h; (ii): $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2,5 equiv.), K_2CO_3 (2 equiv.), PivOH, air, 130 °C, 14 h.

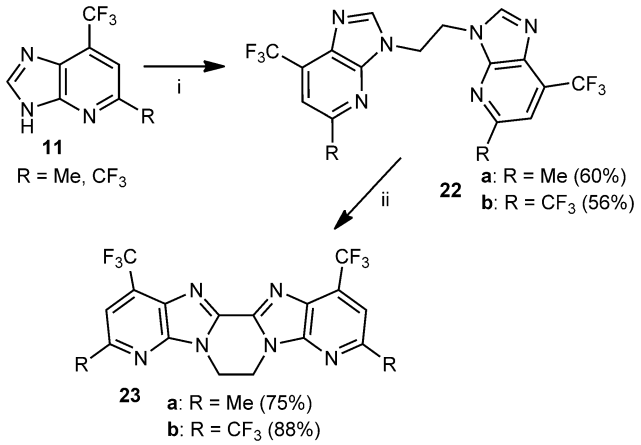
Motivated by our success, we decided to change the type of the linker. The direct base-mediated alkylation of 1-deazapurine **11** afforded compounds **12**, **14** and **15** in good yields (Scheme 4, Table 6). Using a subsequent C–H bond functionalization, we intended to access the fused imidazoles **13** and **16**. However, only substrates **12** could be converted into the corresponding products **13**. In the case of **14** and **15**, both C–H activation protocols mentioned above have experienced a failure.

In the same time, to obtain a complete profile of the reaction studied, we were interested in the behavior of the simple benzimidazole derivatives **18**. Indeed the oxidative C–H bond functionalization developed here can be also applied for the construction of the condensed benzimidazole scaffolds **19** (Scheme 5, Table 7), however some restrictions are present. In the case of benzimidazoles only methods with pivalic acid were efficient. Compound **19c** was partially formed after prolonged heating (40 h), but could not be isolated pure, and compound **19d** did not form at all.

After the general reaction conditions for both C–H bond activation strategies had been established and investigated in detail, we then switched to the direct intermolecular oxidative arylation of scaffolds containing two azole subunits which are linked by a spacer attached to both N-atoms. As model substrates for this study, we have chosen the benzimidazole derivatives **20** which were obtained by direct alkylation of benzimidazole **21** (Scheme 6). At the same time, we planned to investigate the influence of the length of the linker on the arylation reaction. Our attempt to use the same reaction conditions, as in the case of imidazo[4,5-*b*]pyridines surprisingly failed, despite the fact that simple benzimidazoles constitute a class of more electron-enriched heterocycles. In the current case, implementation of pivalic acid as a solvent and base is obligatory. It should be also noted that the reaction could be monitored by TLC and

Table 8. Yields of benzimidazole derivatives **20** and **21**.

No.	X	Yield [%]
20a	$(-CH_2-)_2$	60
20b	$(-CH_2-)_3$	76
20c	$(-CH_2-)_4$	69
20d	$(-CH_2-)_5$	67
20e	$-(CH_2)_2O(CH_2)_2-$	76
20f	1,2-phenylenedi(methylene)	83
21a	$(-CH_2-)_2$	52
21b	$(-CH_2-)_3$	58
21c	$(-CH_2-)_4$	39
21d	$(-CH_2-)_5$	31
21e	$-(CH_2)_2O(CH_2)_2-$	28
21f	1,2-phenylenedi(methylene)	42



Scheme 7. *Reaction conditions*: (i): 1 equiv. of alkylating agent, 1,1 equiv. of NaH, DMF, 2 h; (ii): $Pd(OAc)_2$ (10 mol%), $Cu(OAc)_2$ (2,5 equiv.), AcOH, air, 110 °C, 8 h (a); or $Pd(OAc)_2$ (10 mol%), AgOAc (2,5 equiv.)/AcOH, air, 110 °C, 8 h (b).

worked up only with preliminary treatment with NH_4Cl, possibly, due to the formation of stable complexes of benzimidazole-derived substrates with copper. As it is seen in Table 8, the length of the linker X has a great impact on the overall yields. The best yields were observed for imidazoles having a length of $n=2$ or 3. An increase of the length resulted in a decrease of the yields.

The next logical step was the synthesis of 1-deazapurines **22** and their cyclization to furnish the fused 1-deazapurines **23** (Scheme 7). In the case of the highly electron-poor bis-trifluoromethyl derivative (**22b**), oxidation with copper acetate does not take place. However, reaction proceeds smoothly when the stronger oxidant AgOAc is used.

The constitution of the synthesized fused imidazoles was mainly established by 1D and 2D NMR methods. Moreover, the structures of compounds **10b**, **13a**, and **23a** were independently established by X-ray single crystal analysis (Figure 1, Figure 2 and Figure 3).[26]

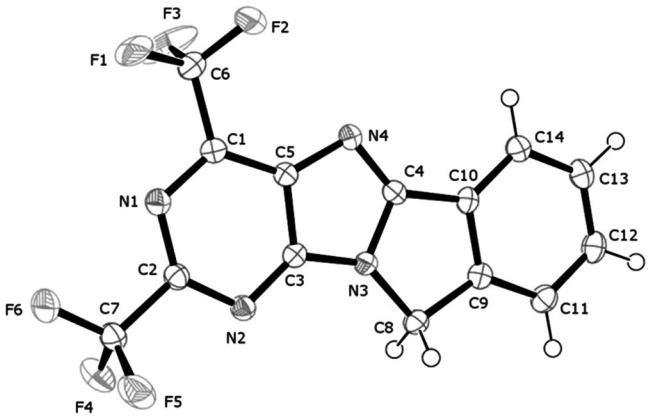


Figure 1. ORTEP plot of the structure **10b**.

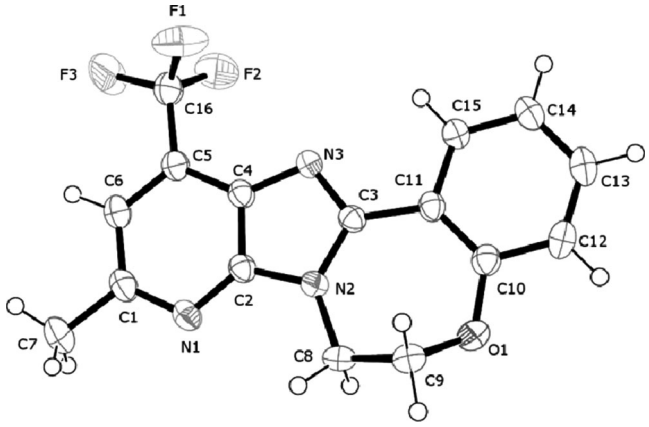


Figure 2. ORTEP plot of the structure **13a**.

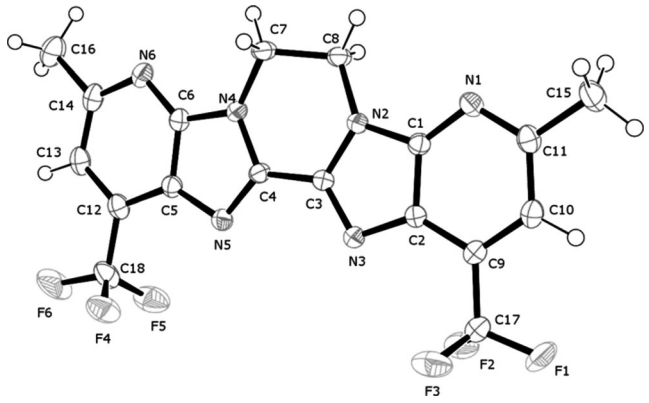


Figure 3. ORTEP plot of the structure **23a**.

Conclusions

In summary, we have developed a straightforward Pd-catalyzed reaction for the synthesis of fused purines

and 1-desazapurines furnished with a CF_3 group as well as of condensed benzimidazoles. An optimization study which implicated the development of many new reaction conditions, by the scanning of different type of ligands, catalyst systems, additives and bases was conducted. In the same time the nature of the alkyl linkers regarding the overall yields were studied.

Experimental Section

All solvents were purified and dried by standard methods. NMR spectra were recorded on a Bruker AVANCE 250 II and Bruker DPX 300. The following abbreviations were used to designate chemical shift multiplicities: s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet, br = broad. IR spectra were recorded on a Perkin–Elmer FT IR 1600 spectrometer (ATR). Mass spectra were obtained on a Hewlett–Packard HP GC/MS 5890/5972 instrument (EI, 70 eV) by GC inlet or on an MX-1321 instrument (EI, 70 eV) by direct inlet. Column chromatography was performed on silica gel (63–200 mesh, Merck). Silica gel Merck $60F_{254}$ plates were used for TLC.

General Procedure for the Synthesis of Imidazo[4,5-*b*]pyridines 5 and 6

To a Schlenk flask, set with reflux, CH_2Cl_2 (3 mL), corresponding amine (0.0055 mol), and methyl *N*-(cyanomethyl)-formimidate (0.005 mol) were added under an argon atmosphere at room temperature. The reaction mixture was refluxed during 1 h 20 min and after that, the mixture was cooled down to room temperature. 1,3-Dicarbonyl compound was added, and the mixture was further stirred at the same temperature for 15–20 min and then refluxed for 6 h. The solvent was evaporated to dryness and the residue was purified by column chromatography to give the desired compound.

General Procedure for the Synthesis of Purines 8

To a Schlenk flask, set with reflux, CH_2Cl_2 (3 mL), corresponding amine (0.0055 mol), and methyl *N*-(cyanomethyl)-formimidate (0.005 mol) were added under an argon atmosphere at room temperature. The reaction mixture was refluxed during 1 h 20 min and after that, the mixture was cooled down to room temperature, and then to 0 °C on an ice bath. Afterwards, corresponding 1,3,5-triazine was added, and the mixture was further stiredr at the same temperature for 15–20 min and then refluxed for 7 h. The solvent was evaporated to dryness and the residue was purified by column chromatography to give the desired compound.

General Procedure for Preparation of Fused Imidazo[4,5-*b*]pyridines and Purines 9a–p and 10

To an argon-purged pressure tube, filled with 200 mg of corresponding substrates **5** or **8**, $Pd(OAc)_2$ (5 mol%), ligand (10 mol%), and base (2 or 2.5 equiv.), 3,5 mL of dry DMF were added. Pressure tube was capped and reaction mixture was heated at the required temperature (mentioned in text). After the reaction is complete, the solution was diluted with 20 mL of chloroform, and liquid residues were evaporated under vacuum. The crude product was isolated *via* column chromatography.

General Procedure for Preparation of Alkylated Derivatives 12, 14, 15, 20a and 22

To the solution of -NH-containing heterocycle (300 mg, 1 equiv.) in dry DMF (4 mL) sodium hydride (1.1 equiv.) was added portionwise. After hydrogen evolution was over, corresponding alkylating agent (1 equiv.) was added. The mixture was stirred at room temperature during 2 h, and then was poured into water. The mixture was extracted with EtOAc (3 × 100 mL), organic layers were washed with water and dried over sodium sulfate. After evaporation of solvent, the residue was purified by column chromatography (in the case of **18a**, product was recrystallized from 60% aqueous ethanol).

General Procedure for Preparation of Fused Imidazo[4,5-*b*]pyridines 9a, 9c, 9q, 9r and 23 *via* Oxidative Arylation

200 mg (1 equiv.) of corresponding imidazo[4,5-*b*]pyridine was dissolved in 4 mL of acetic acid. Afterwards $Pd(OAc)_2$ (10 mol%) and anhydrous $Cu(OAc)_2$ (2.5 equiv.) or AgOAc (2.5 equiv.) (in the case of **21b**) were added and reaction mixture was heated up to 110 °C under air athmosphere during 8 h. As reaction is completed, the solvent was evaporated under vacuum, the residue was treated with water (30 mL). Organic residues were extracted with EtOAc (3 × 100 mL), washed with water and dried over sodium sulphate. After evaporation of solvent, the desired product was isolated by column chromatography.

General Procedure for Preparation of Alkylated Benzimidazole Derivatives 18 and 20b–f

To the solution of corresponding benzimidazole (300 mg, 1 equiv.) in 4 mL of DMF, K_2CO_3 (4 equiv.) and alkylating agent (1 equiv.) were added. Reaction mixture was stirred during 12 h at 90 °C, then poured into water. The mixture was extracted with EtOAc (3 × 100 mL), the organic layers were washed with water and dried over sodium sulfate. After evaporation of solvent, the residue was purified by column chromatography.

General Procedure for Preparation of Fused Benzimidazoles 19 and 21 *via* Oxidative Arylation

200 mg (1 equiv.) of corresponding benzimidazole was dissolved in 4 mL of pivalic acid. Afterwards $Pd(OAc)_2$ (10 mol%), anhydrous $Cu(OAc)_2$ (2,5 equiv.), K_2CO_3 (2 equiv.) were added and reaction mixture was heated up to 140 °C under air atmosphere during 14 h. When the reaction was completed, the crude mixture was threated with 20% aqueous NaOH, till the full neutralization of acid and then with concentrated aqueous NH_4Cl (50 mL) and left to stand for 1 hour (treatment with ammonium chloride is not necessary in the case of compounds **19**). Organic residues were extracted with EtOAc (3 × 150 mL), washed with water and dried over sodium sulfate. After evaporation of solvent,

the desired product was isolated by column chromatography.

References

[1] a) C. Verrier, C. Hoarau, F. Marsais, *Org. Biomol. Chem.* **2009**, *7*, 647–650; b) Y. H. Zhang, B. F. Shi, J. Q. Yu, *Angew. Chem.* **2009**, *121*, 6213–6216; *Angew. Chem. Int. Ed.* **2009**, *48*, 6097–6100; c) D. Lapointe, K. Fagnou, *Org. Lett.* **2009**, *11*, 4160–4163; d) L. Ackermann, S. Barfüßer, J. Pospech, *Org. Lett.* **2010**, *12*, 724–726; e) D. Shabashov, O. Daugulis, *J. Am. Chem. Soc.* **2010**, *132*, 3965–3972; f) T. Mukai, K. Hirano, T. Satoh, M. Miura, *Org. Lett.* **2010**, *12*, 1360–1363; g) T. Yao, K. Hirano, T. Satoh, M. Miura, *Chem. Eur. J.* **2010**, *16*, 12307–12311; h) L. Ackermann, S. Barfüßer, C. Kornhaaß, A. Kapdi, *Org. Lett.* **2011**, *13*, 3082–3085.

[2] a) M. Yamamoto, S. Matsubara, *Chem. Lett.* **2007**, *36*, 172–173; b) H. A. Zhong, J. A. Labinger, J. E. Bercaw, *J. Am. Chem. Soc.* **2002**, *124*, 1378–1399; c) A. C. Hutson, M. Lin, N. Basickes, A. Sen, *J. Organomet. Chem.* **1995**, *504*, 69–74; d) I. T. Horvath, R. A. Cook, J. M. Millar, G. Kiss, *Organometallics* **1993**, *12*, 8–10; e) C. S. Ellis, D. H. Ess, *J. Org. Chem.* **2011**, *76*, 7180–7718; f) G. B. Bajracharya, N. K. Pahadi, I. D. Gridnev, Y. Yamamoto, *J. Org. Chem.* **2006**, *71*, 6204–6621; g) M. Tobisu, H. Nakai, N. Chatani, *J. Org. Chem.* **2009**, *74*, 5471–5475.

[3] a) N. Umeda, K. Hirano, T. Satoh, N. Shibata, H. Sato, M. Miura, *J. Org. Chem.* **2011**, *76*, 13–24; b) F. W. Patureau, T. Besset, F. Glorius, *Angew. Chem.* **2011**, *123*, 1096–1099; *Angew. Chem. Int. Ed.* **2011**, *50*, 1064–1067; c) F. W. Patureau, F. Glorius, *J. Am. Chem. Soc.* **2010**, *132*, 9982–9983; d) T. K. Hyster, T. Rovis, *J. Am. Chem. Soc.* **2010**, *132*, 10565–10569; e) J. Chen, G. Song, C.-L. Pan, X. Li, *Org. Lett.* **2010**, *12*, 5426–5429; f) F. Wang, G. Song, X. Li, *Org. Lett.* **2010**, *12*, 5430–5433; g) D. R. Stuart, M. Bertrand-Laperle, K. M. N. Burgess, K. Fagnou, *J. Am. Chem. Soc.* **2008**, *130*, 16474–16475; h) L. Li, W. W. Brennessel, W. D. Jones, *J. Am. Chem. Soc.* **2008**, *130*, 12414–12419; i) K. Ueura, T. Satoh, M. Miura, *Org. Lett.* **2007**, *9*, 1407–1409; j) A. M. Berman, J. C. Lewis, R. G. Bergman, J. A. Ellman, *J. Am. Chem. Soc.* **2008**, *130*, 14926–14927.

[4] a) L. Ackermann, P. Novak, R. Vicente, N. Hofmann, *Angew. Chem.* **2009**, *121*, 6161–6164; *Angew. Chem. Int. Ed.* **2009**, *48*, 6045–6048; b) L. Ackermann, P. Novak, *Org. Lett.* **2009**, *11*, 4966–4969; c) L. Ackermann, N. Hofmann, R. Vicente, *Org. Lett.* **2011**, *13*, 1875–1877.

[5] a) E. Alvarez, S. Conejero, M. Paneque, A. Petronilho, M. L. Poveda, O. Serrano, E. Carmona, *J. Am. Chem. Soc.* **2006**, *128*, 13060–13061; b) K. Ueura, T. Satoh, M. Miura, *J. Org. Chem.* **2007**, *72*, 5362–5368; c) K.-I. Fujita, M. Nonogawa, R. Yamaguchi, *Chem. Commun.* **2004**, 1926–1927; d) B. De Boef, S. J. Pastine, D. Sames, *J. Am. Chem. Soc.* **2004**, *126*, 6556–6557; e) K. Tsuchikama, M. Kasagawa, K. Endo, T. Shibata, *Org. Lett.* **2009**, *11*, 1821–1823; f) Y. Guo, X. Zhao, D. Zhang, S.-I. Murahashi, *Angew. Chem.* **2009**, *121*, 2081–2083; *Angew. Chem. Int. Ed.* **2009**, *48*, 2047–2049.

[6] a) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2011**, *133*, 13577–13586; b) W. Xu, Y. Jin, H. Liu, Y. Jiang, H. Fu, *Org. Lett.* **2011**, *13*, 1274–1277; c) Y. Li, Y. Xie, R. Zhang, K. Jin, X. Wang, C. Duan, *J. Org. Chem.* **2011**, *76*, 5444–5449.

[7] a) N. Yoshikai, *Synlett* **2011**, 1047–1051; b) C. Zhao, F. D. Toste, R. G. Bergman, *J. Am. Chem. Soc.* **2011**, *133*, 10787–10789; c) J. M. Schomaker, W. C. Boyd, I. C. Stewart, F. D. Toste, R. G. Bergman, *J. Am. Chem. Soc.* **2008**, *130*, 3777–3779; d) J. M. Schomaker, F. D. Toste, R. G. Bergman, *Org. Lett.* **2009**, *11*, 3698–3700; e) W. C. Boyd, M. R. Crimmin, L. E. Rosebrugh, J. M. Schomaker, R. G. Bergman, F. D. Toste, *J. Am. Chem. Soc.* **2010**, *132*, 16365–16367.

[8] a) J. Guihaumé, S. Halbert, O. Eisenstein, R. N. Perutz, *Organometallics* **2012**, *31*, 1300–1314; b) E. Clot, O. Eisenstein, N. Jasim, S. A. Macgregor, J. E. McGrady, R. N. Perutz, *Acc. Chem. Res.* **2011**, *44*, 333–348.

[9] a) L. Ackermann, *Chem. Rev.* **2011**, *111*, 1315–1345; b) L. Ackermann, *Top. Organomet. Chem.* **2007**, *24*, 35–60; c) C.-L. Sun, B.-J. Li, Z.-J. Shi, *Chem. Rev.* **2011**, *111*, 1293–1314; d) T. Satoh, M. Miura, *Synthesis* **2010**, *20*, 3395–3409; e) F. Kakiuchi, T. Kochi, *Synthesis* **2008**, 3013–3039; f) L. Ackermann, *Angew. Chem.* **2011**, *123*, 3926–3928; *Angew. Chem. Int. Ed.* **2011**, *50*, 3842–3844.

[10] a) L. Ackermann, R. Vicente, A. Kapdi, *Angew. Chem.* **2009**, *121*, 9976–10011; *Angew. Chem. Int. Ed.* **2009**, *48*, 9792–9826; b) S. I. Gorelsky, D. Lapointe, K. Fagnou, *J. Am. Chem*, *Soc.*, **2008**, *130*, 10848–10849.

[11] a) L. Ackermann, *Chem. Commun.* **2010**, *46*, 4866–4877; b) R. N. Loy, M. S. Sanford, *Org. Lett.* **2011**, *13*, 2548–2551; c) A. Martins, M. Lautens, *J. Org. Chem.* **2008**, *73*, 8705–8710; d) A. Martins, M. Lautens, *J. Org. Chem.* **2008**, *73*, 8705–8710; e) S. Oi, Y. Tanaka, Y. Inoue, *Organometallics* **2006**, *25*, 4773–4778;.

[12] a) F. Xiao, Q. Shuai, F. Zhao, O. Basl, G. Deng, C.-J. Li, *Org Lett.* **2011**, *13*, 1614–1617; b) X. Jia, S. Zhang, W. Wang, L. F. Cheng, *J. Org. Lett.* **2009**, *11*, 3120–3123; c) Y. Fujiwara, I. Moritani, S. Danno, R. Asano, S. Teranishi, *J. Am. Chem. Soc.* **1969**, *91*, 7166–7172; d) T. Kochi, S. Urano, H. Seki, E. Mizushima, M. Sato, F. Kakiuchi, *J. Am. Chem. Soc.* **2009**, *131*, 2792–2793.

[13] X. Zhao, E. Dimitrijevic', V. M. Dong, *J. Am. Chem. Soc.* **2009**, *131*, 3466–3467.

[14] a) K. J. Stowers, M. S. Sanford, *Org. Lett.* **2009**, *11*, 4584–4587; b) N. R. Deprez, M. S. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 11234–11241; c) D. C. Powers, T. Ritter, *Nature Chem.* **2009**, *1*, 302–309; d) L. V. Desai, K. J. Stowers, M. S. Sanford, *J. Am. Chem. Soc.* **2008**, *130*, 13285–13293; e) X. Wang, T. S. Mei, J. Q. Yu, *J. Am. Chem. Soc.* **2009**, *131*, 7520–7524; f) T. Furuya, T. Ritter, *J. Am. Chem. Soc.* **2008**, *130*, 10060–10061; g) N. D. Ball, M. Sanford, *J. Am. Chem. Soc.* **2009**, *131*, 3796–3797.

[15] a) B. E. Evans, K. E. Rittle, M. G. Bock, R. M. DiPardo, R. M. Freidinger, W. L. Whitter, G. F. Lundell, D. F. Veber, P. S. Anderson, R. S. L. Chang, V. J. Lotti, D. J. Cerino, T. B. Chen, P. J. Kling, K. A. Kunkel, J. P. Springer, J. Hirshfield, *J. Med. Chem.* **1988**, *31*, 2235–2248; b) C. D. Duarte, E. J. Barreiro, C. Fraga, *Mini-Rev. Med. Chem.* **2007**, *7*, 1108–11019; c) R. W. DeSimone, K. S. Currie, S. A. Mitchell, J. W. Darrow, D. A.

Pippin, *Comb. Chem. High Throughput Screening* **2004**, *7*, 473–484; d) L. Costantino, D. Barlocco, *Curr. Med. Chem.* **2006**, *13*, 65–85.

[16] a) E. A. Veliz, O. M. Stephens, P. A. Beal, *Org. Lett.* **2001**, *3*, 2969–2972; b) M. Hocek, A. Holy, *Collect. Czech. Chem. Commun.* **1999**, *64*, 229–241; c) D. Hockova, M. Hocek, H. Dvorakova, I. Votruba, *Tetrahedron* **1999**, *55*, 11109–11118; d) P. Silhar, R. Pohl, I. Votruba, M. Hocek, *Synthesis* **2006**, 1848–1852.

[17] a) V. O. Iaroshenko, D. V. Sevenard, A. V. Kotljarov, D. M. Volochnyuk, A. O. Tolmachev, V. Ya. Sosnovskikh, *Synthesis* **2009**, 731–740; b) V. O. Iaroshenko, *Synthesis* **2009**, 3967–3974; c) V. O. Iaroshenko, D. Ostrovskyi, A. Petrosyan, S. Mkrtchyan, A. Villinger, P. Langer. *J. Org. Chem.* **2011**, 2899–2903.

[18] a) I. V. Seregin, V. Gevorgyan, *Chem. Soc. Rev.* **2007**, *36*, 1173–1193; b) H.-Q. Do, O. Daugulis, *J. Am. Chem. Soc.* **2007**, *129*, 12404–12405; c) F. Bellina, S. Cauteruccio, R. Rossi, *Eur. J. Org. Chem.* **2006**, 1379–1382.

[19] a) Y. Wu, B. Li, F. Mao, X. Li, F. Y. Kwong, *Org. Lett.* **2011**, *13*, 3258–3261; b) M. Seki, M. Nagahama, *J. Org. Chem.* **2011**, *76*, 10198–10206; c) G.-W. Wang, T.-T. Yuan, X.-L. Wu, *J. Org. Chem.* **2008**, *73*, 4717–4720; d) W. Li, Z. Yin, X. Jiang, P. Sun, *J. Org. Chem.* **2011**, *76*, 8543–8548; e) T. W. Lyons, K. L. Hull, M. S. Sanford, *J. Am. Chem. Soc.* **2011**, *133*, 4455–4464; f) L. Caron, L.-C. Campeau, K. Fagnou, *Org Lett.* **2008**, *10*, 4533–4536.

[20] a) Y.-S. Byun, C.-H. Jung, Y.-T. Park, *J. Heterocycl. Chem.* **1995**, *32*, 1835–1837; b) S. M. W. R. Allin, Bowman, M. R. J. Elsegood, V. McKee, R. Karim, S. S. Rahman, *Tetrahedron* **2005**, *61*, 2689–2696; c) M. A. Clyne, F. Aldabbagh, *Org. Biomol. Chem.* **2006**, *4*, 268–277; d) F. Bilodeau, M.-C. Brochu, N. Guimond, K. H. Thesen, P. Forgione, *J. Org. Chem.* **2010**, *75*, 1550–1560; e) S. Lage, U. Martinez-Estibalez, N. Sotomayor, E. Lete, *Adv. Synth. Catal.* **2009**, *351*, 2460–2468; f) A. P. Kozikowski, D. Ma, *Tetrahedron Lett.* **1991**, *32*, 3317–3320; g) E. Desarbre, J.-Y. Merour, *Heterocycles* **1995**, *41*, 1987–1998; h) L.-C. Campeau, M. Parisien, A. Jean, K. Fagnou, *J. Am. Chem. Soc.* **2006**, *128*, 581–590.

[21] a) C. Blaszykowski, E. Aktoudianakis, D. Alberico, C. Bressy, D. G. Hulcoop, F. Jafarpour, B. Laleu, M. Lautens, *J. Org. Chem.* **2008**, *73*, 1888–1897; b) J. K. Laha, G. D. Cuny, *J. Org. Chem.* **2011**, *76*, 8477–8482; c) A. P. Kozikowski, D. Ma, *Tetrahedron Lett.* **1991**, *32*, 3317–3320; d) T. Kuroda, F. Suzuki, *Tetrahedron Lett.* **1991**, *32*, 6915–6918; e) C. Blaszykowski, E. Aktoudianakis, C. Bressy, D. Alberico, M. Lautens, *Org. Lett.* **2006**, *8*, 2043–2045.

[22] a) I. Čerňa, R. Pohl, B. Klepetářová, M. Hocek, *Org. Lett.* **2006**, *8*, 5389–5392; b) B. Vanková, V. Krchnák, M, Soural, J. Hlavác, *ACS Comb. Sci.* **2011** 496–500; c) D. G. Pintori, M. F. Greaney, *J. Am. Chem. Soc.* **2011**, *133*, 1209–1211; d) L. Ackermann, R. Jeyachandran, H. K. Potukuchi, P. Nova'k, L. Büttner, *Org. Lett.* **2010**, *12*, 2056–2059.

[23] a) D. Ostrovskyi, V. O. Iaroshenko, A. Petrosyan, S. Dudkin, I. Ali, A. Villinger, A. Tolmachev, P. Langer, *Synlett* **2010**, 2299–2303; b) D. Ostrovskyi, V. O. Iaroshenko, I. Ali, S. Mkrtchyan, A. Villinger, A. Tolmachev, P. Langer, *Synthesis* **2011**, 133–141.

[24] V. O. Iaroshenko, A. Maalik, D. Ostrovskyi, A. Villinger, A. Spannenberg, P. Langer, *Tetrahedron* **2011**, *67*, 8321–8330.

[25] E. Desarbre, J.-Y. Merour, *Heterocycles* **1995**, *41*, 1987–1998.

[26] X-ray crystallographic data (excluding structure factors) for the structure **10b**, **13a** and **23a** reported in this paper have been deposited with the Cambridge Crystallographic Data Centre as supplementary publication nos. CCDC 865654, CCDC 865655 and CCDC 865656. These data can be obtained free of charge on application to CCDC, 12 Union Road, Cambridge CB2 1EZ, UK; Fax: +44-(1223)-336-033; E-mail: deposit@ccdc.cam.ac.uk, or *via* www.ccdc.cam.ac.uk/data_request/cif.

