ChemPubSoc Europe

DOI: 10.1002/cctc.201402715

Regioselective Direct Arylation of Fused 3-Nitropyridines and Other Nitro-Substituted Heteroarenes: The Multipurpose Nature of the Nitro Group as a Directing Group

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We report Pd- and Ni-catalysed, guided and regioselective C–H arylations of a series of fused 3-nitropyridines. The method described here is a facile tool for the chemical functionalisation of drug-like fused pyridines. The scope and limitations of the reaction, the chemical potential of the nitro group and a putative reaction mechanism are discussed.

Introduction

The formation of a single C–C bond by catalytic coupling reactions is a research area that has grown enormously in recent decades and contributes significantly to the production of both intermediates and fine chemicals.[1] As a result of their simplicity and efficiency, coupling strategies are uniquely amenable to modifications at the molecular level. However, during the last decade, direct transition-metal-catalysed C–H activation reactions by their virtue became one of the most prospective methodologies in modern organic chemistry.[2] Impressive amounts of applications in a relatively short period of time shows strong support for the importance and prospective of this method.[3] C–H activation became an important tool for the construction and side- and/or chemoselective functionalisation of many biologically active molecules and drug-like scaffolds.[3] C–H activation was also combined with many other classical chemical transformations, such as simultaneous additions to double and triple bounds,[4] additions to heteroatoms[5] and domino consecutive reactions.[6] Directing groups play an important role in the selective functionalisation of C–H bonds. Functionalised fragments contain potential donor atoms, such as N, O, P, S or others: that is, atoms able to be coordinated, even weakly, to the transition metal because of their strong Lewis base properties.[7] Nevertheless, sometimes these efficient moieties cannot be removed easily or they are not prone to undergo further functionalisation. Moreover, the need for greener reactants and reaction conditions to provide a high level of atom economy and minimise waste does not fit with the presence of non-convertible functional groups. As a result, extensive research into multi-functional directing groups is underway. That is, directing groups that can perform extra tasks, in addition to their directing purpose, are of considerable interest.[8] A clear example is the use of oxidising directing groups that contain a covalent bond responsible for the oxidation of the metal, which avoids the use of external oxidants that usually generate waste byproducts.[9] Another way to plan the multi-task character of the directing groups is the use of "removable" functional groups.[8] In this respect, cutting-edge innovations are the use of 2-pyridyl sulfoxide (A),[10a] 2-pyridyl ether (B),[10b,c] thioether (C),[10d] pyridyldiisopropylsilyl (D),[10e–g] nitrile (E),[10h] triazene (F),[10i] silanol (G)[10j] and carboxylates (H)[10k] as multi-functional and/or traceless directing groups (Scheme 1).

In this context, the nitro group is almost the paradigm of what a multi-purpose directing group could be. It can behave as a classical directing group[11] that selects the position in which the metal has to be incorporated and, typically, forms part of the target molecule by further functionalisation after the C–H activation step. This two-step approach undoubtedly has an enormous synthetic utility.[12,13]

The use of the nitro group as a regio-directing substituent in C–H activation has scarcely been reported to date (Scheme 2).[14] Examples include the Pd-catalysed *ortho*-arylation of nitrobenzene derivatives[14a] (A) and the C–H activation of the 4- and 5-positions of 3-nitropyridine (B).[14b] In spite of

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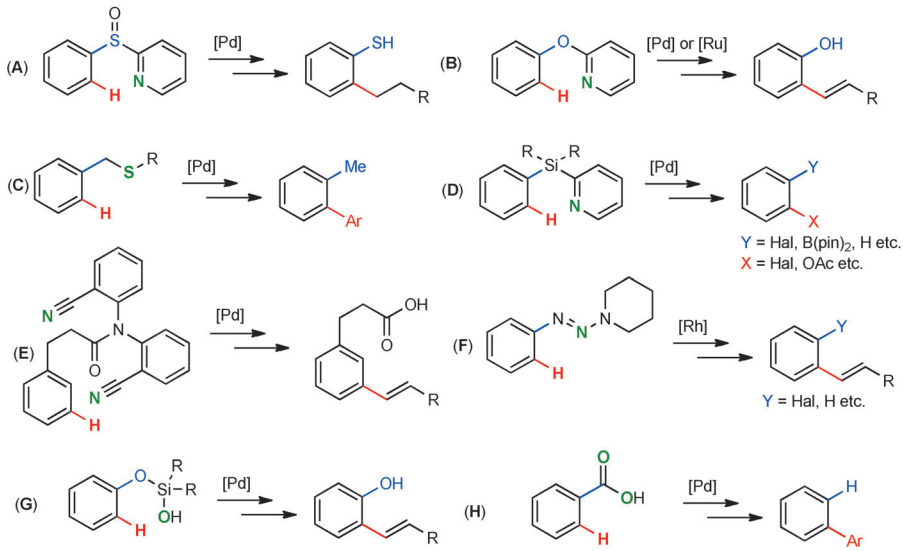
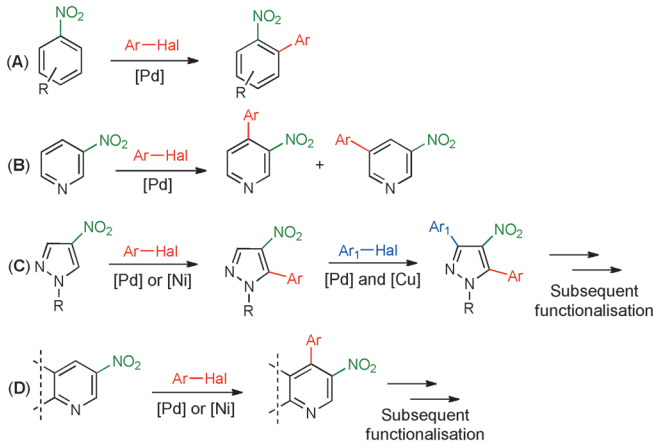
Supporting information for this article is available on the WWW under http://dx.doi.org/10.1002/cctc.201402715.



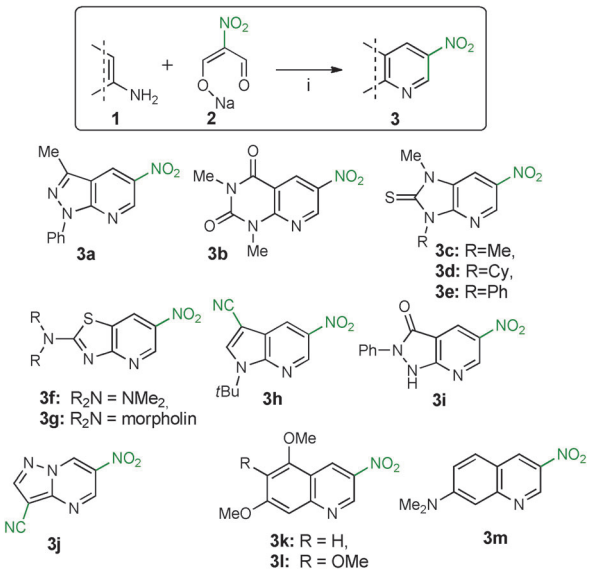
Scheme 1. Removable directing groups in directed C–H activation reactions. Hal = Halogen; pin = Pinacol.



Scheme 2. Reported use of the nitro group as a regio-directing substituent in C–H activation; A) see Ref. [14a], B) see Ref. [14b], C) see Ref. [14c], D) present study.

this, the authors did not demonstrate the vast chemical potential of the nitro group. In contrast, very recently we communicated the selective and guided functionalisation of 4-nitropyrazoles by Pd- and Ni-catalysed C–H arylation followed by a demonstration of the multi-purpose character of the nitro group as a directing group (Scheme 2 C).[14c]

In our present study, we continue to investigate the directing ability of the nitro group with the example of several fused 3-nitropyridines **3 a**–**m**, which represent an important class of purine-like compounds (Scheme 3).[15] The starting fused pyridines were prepared by the reaction of several electron-excessive aminoheterocycles **1** with the enolate of nitromalonaldehyde **2** in DMF in the presence of trimethylsilyl chloride (TMSCl) as a water scavenger (Scheme 3).[16a]



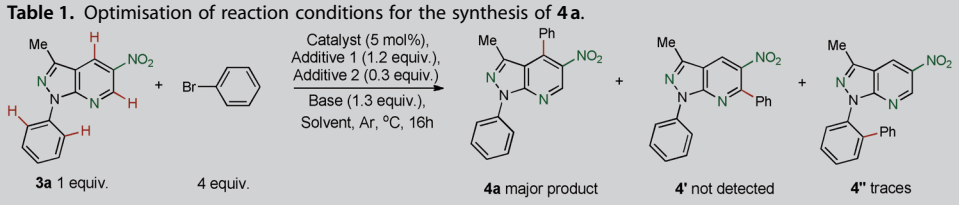
Scheme 3. Synthesis of fused pyridines i) DMF, TMSCl, Ar, 100 °C, 2–12 h. Cy = Cyclohexyl.

Results and Discussion

Based on our experience and following general movements in the field, to achieve the desired selective arylation, a number of crucial challenges had to be overcome: 1) the first challenge is the optimisation of reaction conditions so that only stoichiometric amounts of fused nitropyridines need to be used; 2) the second challenge is the investigation of regioselectivity in two potential active positions in the pyridine ring (α and γ); 3) among these, in most cases we have several functional groups that can in principle direct C–H arylation, hence we have several potentially active C–H bonds in most of the targets, which should be investigated; and 4) it is important to demonstrate the utility of the nitro group in follow-up chemistry and for downstream processes.

With the set of fused pyridines in hand, we focused on the optimisation of the reaction conditions. On the basis of our previous results, we considered Pd catalysts with CuI as an additive as the starting point in this study.[14c,17] Gratifyingly, pilot experiments indicated that the Pd/CuI system is efficient to activate the γ-C–H bond of the pyridine ring (Table 1, entries 2–8, 14, 17). The best catalyst for **3 a** is $[PdCl_2(PPh_3)_2]$, with which we obtained the desired product in 77% yield (entry 17). We found that the addition of phosphine ligands as well as biden-

Table 1. Optimisation of reaction conditions for the synthesis of **4a**.



3a 1 equiv. 4 equiv. **4a** major product **4'** not detected **4''** traces

Entry	Catalyst	Ligand	Additive 1	Additive 2	Base	Solvent	*T* [°C]	Yield [%]
1	$Pd(PPh_3)_4$	–	–	PivOH	K_2CO_3	DMF	130	–
2	$Pd(OAc)_2$	$Cy_3P{\cdot}HBF_4$	CuI	PivOH	K_2CO_3	DMF	130	48
3	$Pd(OAc)_2$	–	CuI	PivOH	K_2CO_3	DMF	130	52
4	$Pd(OAc)_2$	–	CuI	PivOH	Cs_2CO_3	DMF	130	43
5	$Pd(OAc)_2$	–	CuI	–	Cs_2CO_3	DMF	130	12
6	$Pd(OAc)_2$	–	CuI	–	K_2CO_3	DMF	130	15
7	$Pd(OAc)_2$	–	CuI	Ph_3CCO_2H	K_2CO_3	DMF	130	40
8	$Pd(OAc)_2$	–	CuI	PivOH	K_3PO_4	DMF	130	8
9	$Pd(OAc)_2$	–	CuI	–	KO*t*Bu	DMF	130	–
10	$Pd(OAc)_2$	–	Ag_2CO_3	PivOH	K_2CO_3	DMF	130	27
11	$Pd(OAc)_2$	–	CuI+Ag_2CO_3	PivOH	K_2CO_3	DMF	130	–
12	$Pd(OAc)_2$	–	AuCl	PivOH	K_2CO_3	DMF	130	–
13	–	–	CuI	PivOH	K_2CO_3	DMF	130	–
14	$Pd(OAc)_2$	–	CuI	PivOH	K_2CO_3	DMA	160	50
15	$Pd(OAc)_2$	–	CuI	PivOH	K_2CO_3	toluene	100	–
16	$Pd(OAc)_2$	–	CuI	–	K_2CO_3	TFA[a]	100	–
17	**$[PdCl_2(PPh_3)_2]$**	**–**	**CuI**	**PivOH**	**K_2CO_3**	**DMF**	**130**	**77**
18	**$[NiCl_2(PPh_3)_2]$**	**–**	**CuI**	**PivOH**	**K_2CO_3**	**DMF**	**130**	**43**
19	$RuCl_3{\cdot}H_2O$	$Cy_3P{\cdot}HBF_4$	CuI	PivOH	K_2CO_3	DMA	160	–
20	$[Ru(p\text{-cymene})Cl_2]_2$	–	– or CuI	PivOH	K_2CO_3	DMA	160	–
21	$[Rh(cod)Cl]_2$[b]	–	– or CuI	PivOH	K_2CO_3	DMA	160	–
22	$[Rh(OAc)_2]_2$	–	– or CuI	PivOH	K_2CO_3	DMA	160	–
23	$IrCl_3{\cdot}H_2O$	$Cy_3P{\cdot}HBF_4$	– or CuI	PivOH	K_2CO_3	DMA	160	–

[a] TFA = Trifluoroacetic acid. [b] cod = Cyclooctadiene.

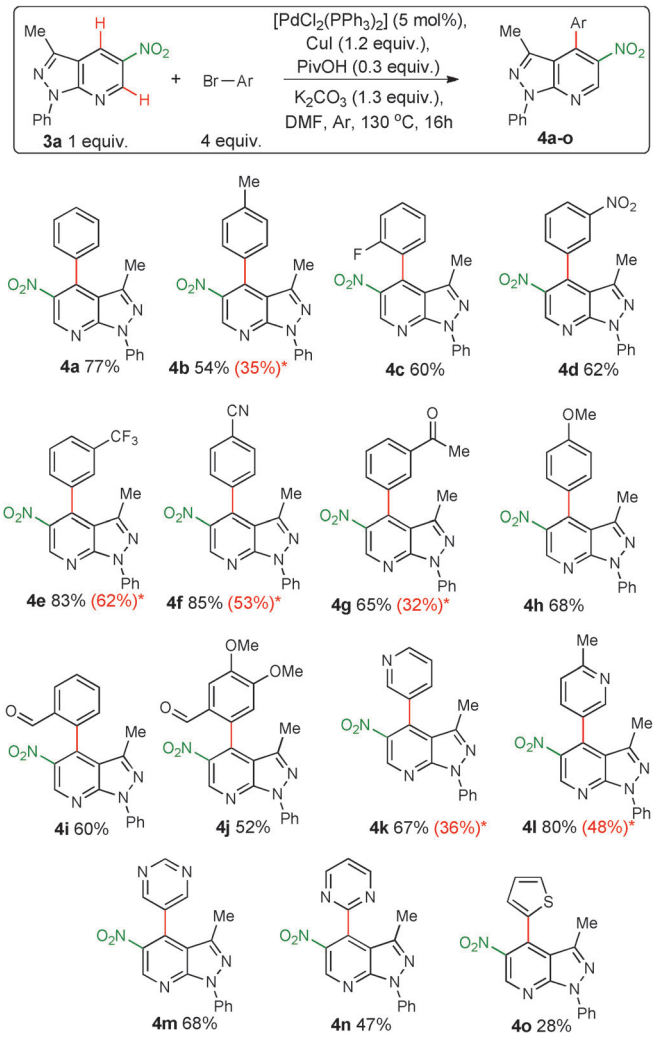
tate ligands such as 1,10-phenanthroline has no real impact on overall yield of the reaction (entries 2 and 3). Notably, the salts of coinage metals such as CuI and Ag_2CO_3 in stoichiometric amounts were necessary to achieve at least some conversion of fused pyridines, otherwise we obtained traces of **4''**. Interestingly, the use of Lewis acids such as CuI or Ag_2CO_3 blocks this pathway of the reaction. However, the mixture of CuI and Ag_2CO_3 produced an intensive reduction of Ag and oxidation of Cu without any conversion of reactants (entry 11). The best base for the reaction was the K_2CO_3/pivalic acid (PivOH) system, and any change in the system decreased the yield. The use of different solvents and temperatures showed that the reaction occurs only in DMF, dimethylacetamide (DMA) and *N*-methyl-2-pyrrolidone (NMP) without any notable differences in yields. Finally, the use of other catalysts to obtain another regioisomer and/or the same product with better yields was ineffective (entries 19–23). Among these, perhaps unsurprisingly, $[NiCl_2(PPh_3)_2]$ was active, although the conversion of reactants was not very high (entry 18).

With the optimised conditions in hand, we examined the scope of the reaction with respect to the aryl halide coupling partner (Scheme 4).

We demonstrated that aryl bromides substituted with Me, F, NO_2, CF_3, CN, Ac, formyl and OMe as well as heterocyclic bromides are compatible with the procedure and lead to the corresponding γ-C–H arylation products in good yields. Notably, $[NiCl_2(PPh_3)_2]$ was also active with the range of aryl bromides. In all cases the γ-arylated adduct was the only observed regioisomer. At the same time, the use of iodoarenes resulted in the formation of a great amount of biphenyls by homocoupling induced by CuI; this demanded a large excess of iodoarene, and the overall yields were visibly lower than that with aryl bromides. Together with this, aryl chlorides, in general, were not active enough, although in the case of electron-deficient 2-chloropyrimidine we obtained the corresponding heteroarylation product **4n** in a moderate yield of 48%. If 5-bromothiophene-2-carboxylic acid was used as the coupling partner, the C–H arylation reaction was followed by decarboxylation to form the arylation product **4o** in a low yield of 28%.

As a wide range of haloarenes was established, we examined the scope of fused nitropyridines. Gratifyingly, a wide range of substituents and substitution patterns are tolerated with no changes in the reaction conditions. That is, 1,3-dimethyl-6-nitropyrido[2,3-*d*]pyrimidine-2,4(1*H*,3*H*)-dione (**3b**), 6-nitro-1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thione derivatives **3c–e** and 6-nitrothiazolo[4,5-*b*]pyridine derivatives **3f** react uneventfully with the appropriate aryl bromides to lead to the corresponding γ-C–H arylation products in good yields (Scheme 5, **5**–**7**). Notably, in these cases the γ-arylated adduct was again the only observed regioisomer. Additionally the reactions can be catalysed by $[NiCl_2(PPh_3)_2]$, however, with a lower efficiency.

Of the target fused nitropyridines, pyrrolo[2,3-*b*]pyridine derivative **3h** stands out because it has two potentially active C–H bonds and directing groups.[18] Because the chemistry of indoles is somewhat similar to that of pyrrolo[2,3-*b*]pyridine derivatives, unsurprisingly, we obtained simultaneous C–H arylation at both rings.[19] As a result we isolated two isomers, namely, the C2 and C4 arylation products (Scheme 6, **8a–h**). We found that both positions are approximately equally active, that is, the addition of one equivalent of aryl bromide led to a mixture of products without the full conversion of reactant **3h**. A reduction of the amount of bromide as well as changing the reaction conditions does not change the regioselectivity of the reaction, or even in some cases, vice versa, the conversion of reactant decreased significantly. Good yields for both regioisomers can be achieved using similar conditions to those



Scheme 4. Scope of the reaction with respect to aryl bromides. * The yields of the C–H arylation catalysed by Ni are given in brackets in red.

used for other fused nitropyridines. Additionally, to avoid double arylation and/or a disastrous mixture of products, no more than two equivalents of aryl bromide should be used (see also Supporting Information Section B).

To extend our methodology, a number of variously nitro-substituted heteroarenes were investigated. Among others, 3-nitro-2*H*-chromen-2-one (**9a**), 3-nitro-4*H*-chromen-4-one (**9b**), 4-oxo-4*H*-chromene-3-carbonitrile (**9c**), 5-nitropyrimidine derivatives **9d**–**f**, 4-nitroisoxazole (**9g**) and methyl 4-nitrofuran-2-carboxylate (**9h**; Scheme 7) in addition to fused pyridines **3i** and **j** and quinolines **3k**–**m** (Scheme 3) were unreactive and/or unstable in our typical reaction protocol.

Gratifyingly, in contrast to these unsuccessful trials, 1-methyl-4-nitro-1*H*-pyrrole-2-carbonitrile (**9i**) and 2-nitrothiophene (**9j**) react readily with aryl bromides under standard conditions to lead to mono-arylated products **10a**–**c** in good yields (Scheme 7). In all cases, the product of the arylation of the β-C–H bond to the nitro group was the only observed regioisomer. Further optimisation of reaction conditions and exploration of new methods for C–H arylation of nitro-substituted heteroarenes is underway in our laboratory.

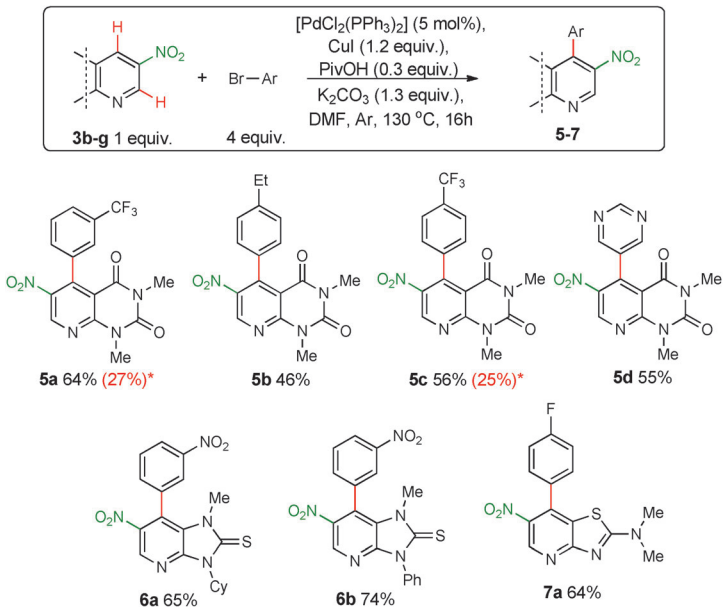
Next, we turned our attention to the possibility to introduce aryl groups at the α-position of fused nitropyridines (see also the scheme of Table 1, **4′**). Unfortunately, all our attempts to arylate the α-position of fused nitropyridines failed. Although a number of procedures were tested, in most cases we obtained complex mixtures and/or the poor conversion of reactants.

Thereby, to further extend the substrate scope, we synthesised nitro-substituted heteroarenes **11** and **12**, which already bear an aryl substituent at the α-position following a methodology we developed previously (Scheme 8).[16b]

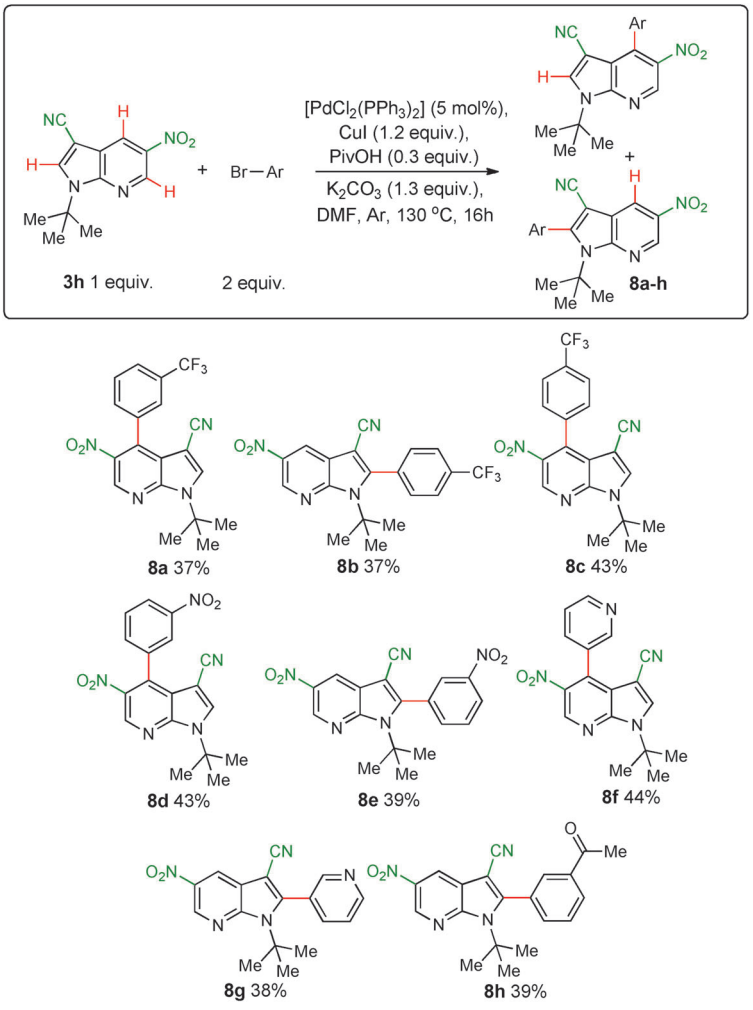
Although the chosen systems **11** and **12** have an OH group that can potentially lead to a C–O cross-coupling reaction: the reactions under standard conditions for C–H activation gave an unexpected result. In spite of a mixture of products, we could isolate two pure compounds, which were surprisingly **13b** and **14b** (Scheme 8). Further optimisation of the reaction conditions has shown that the reaction constitutes a two-step process. The first step is a type of intramolecular nucleophilic substitution reaction, which is followed by Pd-catalysed C–H activation. We found that the first step can occur in the absence of catalyst. Furthermore, we excluded reaction components successively to find that CuI and PivOH do not play decisive roles in this transformation and just base can initiate the cyclisation. Encouraged by these results, we substituted the nitro group successfully in a wide range of substrates; the only systems that were unreactive and/or unstable under basic conditions were pyrazoles **12b** and **c** and isoxazole **12d** (Scheme 8). With a number of fused furo[3,2-*b*]pyridine derivatives **13** in hand, we examined C–H arylation at the pyridine ring. Interestingly, C–H arylation can occur effectively under the standard conditions that were found to be optimal for fused nitropyridines. Fused furo[3,2-*b*]pyridine derivatives **13** react unprecedentedly with appropriate aryl bromides to lead to the corresponding γ-C–H arylation products in good yields (Scheme 8, **14a**–**d**). We demonstrated that the reaction can be performed either in one-pot or consecutively. Not surprisingly, the consecutive manner led to higher yields.

Eventually, to demonstrate the synthetic potential of this methodology fully, we explored the chemical versatility of the directing group briefly. The simple reduction of the nitro group was tested first (Scheme 9). Thus, the reduction of the C–H arylation products of fused nitropyridines **4**–**8** in methanol under typical conditions (Pd/C as the catalyst, normal pressure of H_2) resulted in the formation of amines **15a**–**c** in good yields (Scheme 9). Moreover, if the reduction was performed in the presence of an excess of formalin, the *N*,*N*-dimethylamine **16a** was obtained. Remarkably, if the amount of formalin was reduced to 1.5 equivalents, the reduction was followed by isoquinoline ring formation to give **17a**. In addition to this astonishing finding, **17a** can be prepared by the simple reduction of **4i** (Scheme 4) in a high yield. To summarise this with the substitution of nitro group described above, we have an easily modifiable directing group for the C–H functionalisation of heteroarenes.

The structure of the synthesised compounds was established mainly by 1D and 2D NMR spectroscopy (**10b**). The structures



Scheme 5. Scope of the reaction with respect to nitro-substituted pyrido[2,3-*d*]pyrimidine **3b**, 1*H*-imidazo[4,5-*b*]pyridine-2(3*H*)-thiones **3d** and **e** and thiazolo[4,5-*b*]pyridine **3f**. * The yields of the C–H arylation catalysed by Ni are given in brackets in red.



Scheme 6. Scope of the reaction with respect to nitro-substituted pyrrolo[2,3-*b*]pyridine **3h**.

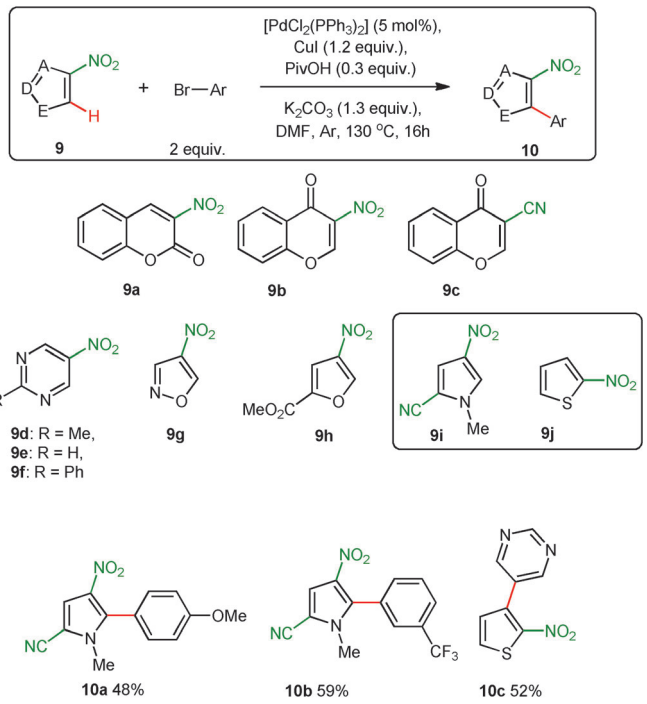
of **4a**, **h**, **l**, **5d**, **8h**, **13b**, **d** and **15c** were confirmed independently by single-crystal X-ray analyses (Figures S1–S8).[20]

To shed light on the directing ability of the nitro group and to obtain additional insights into the reaction mechanism, we designed substrates **18a–e**,[21] which were subjected to our standard Pd- and Ni-catalysed reaction conditions (Scheme 10). First the nitro group was changed into a polar substituent, namely, CN[21a] in **18a** and CO_2Et[21b] in **18b** (Scheme 10). However, to our astonishment, all attempts to perform the C–H arylation under standard conditions, elaborated for previous reactions, experienced a failure; substrates **18a** and **18b** were recovered completely. The same reactivity was observed for substrate **18c**.[21c] Additionally, the introduction of non-coordinating, bulky *p*-tolyl **18d**[16a] and CC-Ar **18e**[16a] substituents did not trigger the C–H activation. Compound **18d** was recovered fully, however, an intensive degradation was observed for **18e**, which might be because of the reactivity of the triple bond under transition-metal-catalysed conditions (Scheme 10).

However, in previous reports on imidazo[4,5-*b*]pyridines and related fused pyridines, we[17] and others[22] demonstrated that the pyridine ring remains intact under typical C–H activation protocols if the nitro group is replaced by H or the electron-withdrawing CF_3 group. In addition, the Pd-catalysed non-directed C–H arylation of unprotected simple pyridines leads to a mixture of isomers (C3/C4/C2) with predominant C(3)–H selectivity.[23] Notably, the reaction demands an excess of starting pyridine (solvent), which indicates the importance of directing groups.[14b,23]

Finally, the regioselectivity might be explained by the assumption that the free electron pair of the N atom of pyridine shields the 2-position (structure A in Scheme 11).[14b] Thus, intermediate B should be more favourable. However, pyridines have a tendency to adopt a non-productive N-bound coordination mode with metal centres (structure C or D in Scheme 11, similar considerations are appropriate for Ni as well).[24] In this respect, the protection of the N atom by conversion to N-oxides and *N*-iminopyridinium ylides has allowed the development of several C2-selective arylation reactions of pyridines.[25]

On this basis, we envisioned that high levels of reactivity with our catalytic system could be a result of the strong coordination of the N atom of the pyridine ring to Cu^{I} that would prevent the N-bound coordination mode of the pyridine substrates with Pd or Ni (C, D). Recently, in this context, two research groups found independently that the coordination of a strong and bulky Al-based Lewis acid with the pyridyl N atom not only activated the pyridyl rings but also favoured C(4)–H cleavage.[26] Hence, under these circumstances, it is possible that C4-selective C–H cleavage could take place if the appropriate orienta-



Scheme 7. Scope of the reaction with respect to nitro-substituted heteroarenes.

tion between the nitro group of the pyridine and Pd (Ni) is assembled (E).

Conclusions

We have studied in detail the transition-metal-catalysed arylation of fused nitropyridines by Pd and Ni using CuI as an additive. Pd was superior in terms of yields compared to Ni. Furthermore, we succeeded to activate the C–H bond using stoichiometric amounts of fused nitropyridines. The scope of the reaction with respect to the aryl halide coupling partner as well as for fused nitropyridines was examined. In all cases except pyrrolo[2,3-*b*]pyridine derivative **3h**, the reactions proceeded with exclusive γ regioselectivity. For the pyrrolo[2,3-*b*]pyridine derivative, we have shown that the C2 and C4 positions are almost equally active. Additionally, various nitro-substituted heteroarenes were investigated. During an investigation of the extension of substrate scope, a domino nitro group substitution–C–H arylation reaction was found. Within the course of this study the multi-purpose character of the nitro group was demonstrated. A mechanistic explanation of the results was proposed. The developed method shows a number of advantages, which include high experimental simplicity, catalyst efficiency, functional group compatibility and the low cost of the catalytic system. The products are purine-like compounds, which are of considerable pharmacological relevance. Further exploration of this chemistry is in progress in our laboratory.

Experimental Section

The dry solvents were purchased. Other solvents were purified by distillation. All reactions were performed under an inert atmosphere. For ^{1}H, ^{19}F and ^{13}C NMR spectra the deuterated solvents indicated were used. MS data were obtained by electron ionisation (EI, 70 eV), chemical ionisation (CI, isobutane) or ESI (mass analyser type was ESI-TOF/MS). For preparative-scale chromatography silica gel 60 (0.063–0.200 mm, 70–230 mesh) was used. The solvents for column chromatography were distilled before use.

General procedure for the synthesis of compounds 4a–o and 5–7

The corresponding fused 3-nitropyridine **3a–f** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.) and $[PdCl_2(PPh_3)_2]$ (or $[NiCl_2(PPh_3)_2]$; 0.05 equiv.) were weighed in air and placed successively in a Schlenk flask equipped with a magnetic stir bar, which was capped with a rubber septum. The reaction vessel was evacuated and back-filled with Ar (three times). Dry DMF (8 mL for 0.3 g of fused 3-nitropyridine) and aryl bromide (4 equiv.) were added with a syringe, and the reaction mixture was heated to 130 °C for 16 h. The reaction mixture was cooled to RT and concentrated under vacuum. The residue was purified by column chromatography typically using a heptane/ethyl acetate mixture to provide the desired arylated product.

General procedure for the synthesis of compounds 8a–h and 10a–c

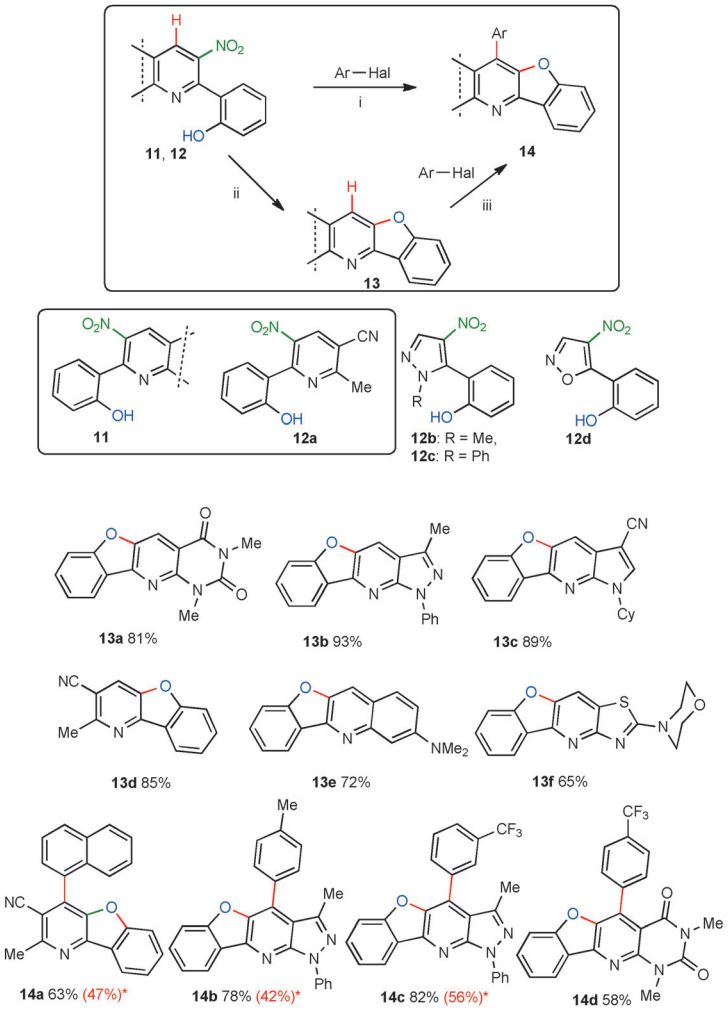
The corresponding nitro-substituted heteroarene **3h**, **9i** or **j** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.) and $[PdCl_2(PPh_3)_2]$ (0.05 equiv.) were weighed in air and placed successively into a Schlenk flask equipped with a magnetic stir bar, which was capped with a rubber septum. The reaction vessel was evacuated and back-filled with Ar (three times). Dry DMF (8 mL for 0.3 g of nitro-substituted heteroarene) and aryl bromide (2 equiv.) were added with a syringe, and the reaction was heated to 130 °C for 16 h. Upon completion, the reaction was cooled to RT and concentrated under vacuum. The residue was purified by column chromatography typically using a heptane/ethyl acetate mixture to provide the desired arylated product.

General procedure for the synthesis of compounds 11 and 12a–d

The corresponding 3-nitrochromone (1 equiv.) and the nucleophile (appropriate amino heterocyclic, 3-aminocrotononitrile, corresponding substituted hydrazine, hydroxylamine hydrochloride; 1.2 equiv.) were dissolved in acetic acid (20 mL for 1 g of nucleophile). The mixture was heated under reflux under an inert atmosphere for 8 h. Then the solution was evaporated under reduced pressure. The residue was purified by column chromatography typically using a heptane/ethyl acetate mixture.

General procedure for synthesis of compounds 13a–f

The corresponding fused 3-nitropyridine **11** or **12a** (1 equiv.) and K_2CO_3 (1.3 equiv.) were weighed in air and placed successively into a Schlenk flask equipped with a magnetic stir bar, which was capped with a rubber septum. The reaction vessel was evacuated and back-filled with Ar. Dry DMF (8 mL for 0.3 g of starting materi-



Scheme 8. The domino nitro group substitution–C–H arylation reaction; i) ArBr (4 equiv.), $[PdCl_2(PPh_3)_2]$ (5 mol%), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (2.3 equiv.), DMF, under Ar, 130 °C, 16 h; ii) K_2CO_3 (1.3 equiv.), DMF, under Ar, 130 °C, 16 h; iii) ArBr (4 equiv.), $[PdCl_2(PPh_3)_2]$ (5 mol%), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, under Ar, 130 °C, 16 h. * The yields of the one-pot C–H arylation are given in brackets in red.

al) was added with a syringe, and the reaction mixture was heated to 130 °C for 16 h. Upon completion, the reaction was cooled to RT and concentrated under vacuum. The residue was purified by column chromatography typically using a heptane/ethyl acetate mixture to provide the desired product.

General procedure for the synthesis of compounds 14 a–c

The corresponding fused 3-nitropyridine **11** or **12 a** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (2.3 equiv.) and $(CH_3)_3CCO_2H$ (0.3 equiv.) were weighed in air and placed successively into a Schlenk flask equipped with a magnetic stir bar, which was capped with a rubber septum. The reaction vessel was evacuated and back-filled with Ar (three times). Dry DMF (8 mL for 0.3 g of fused 3-nitropyridine) was added with a syringe, and the reaction mixture was heated to 130 °C for 6 h. The reaction was cooled to RT, and $[PdCl_2(PPh_3)_2]$ (0.05 equiv.) was weighed in air and placed into the Schlenk flask. The aryl bromide (4 equiv.) was added with a syringe, the reaction vessel was evacuated and back-filled with Ar, and the reaction mixture was heated to 130 °C for 10 h. Upon completion, the reaction was cooled to RT and concentrated under vacuum. The residue was purified by column chromatography typically using a heptane/ethyl acetate mixture to provide the desired arylated product.

General procedure for the synthesis of compounds 14 a–d

The corresponding fused furo[3,2-*b*]pyridine derivative **13** (1 equiv.), CuI (1.2 equiv.), K_2CO_3 (1.3 equiv.), $(CH_3)_3CCO_2H$ (0.3 equiv.) and $[PdCl_2(PPh_3)_2]$ (0.05 equiv.) were weighed in air and placed successively into a Schlenk flask equipped with a magnetic stir bar, which was capped with a rubber septum. The reaction vessel was evacuated and back-filled with Ar (three times). Dry DMF (8 mL for 0.3 g of fused furo[3,2-*b*]pyridine derivative) and aryl bromide (4 equiv.) were added with a syringe, and the reaction was heated to 130 °C for 16 h. Upon completion, the reaction was cooled to RT and concentrated under vacuum. The residue was purified by column chromatography typically using a heptane/ethyl acetate mixture to provide the desired arylated product.

General procedure for the synthesis of compounds 15 a–c and 17 a

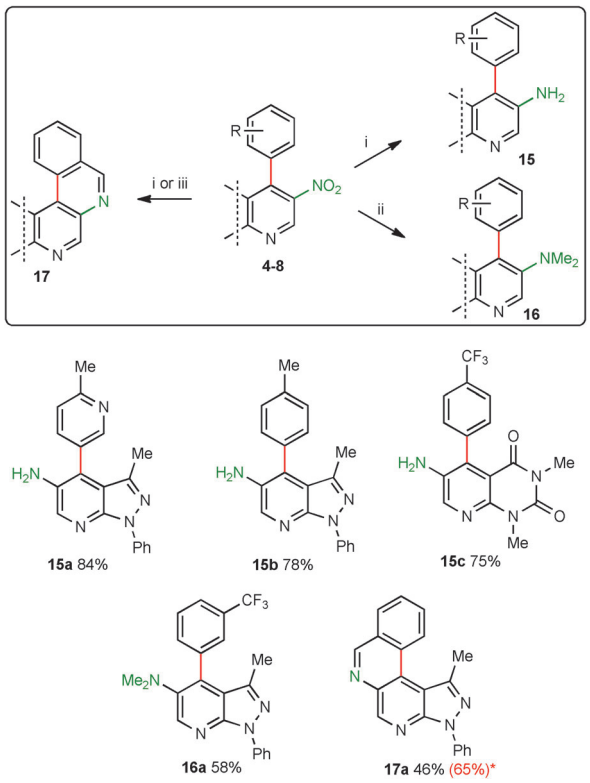
To a Schlenk flask equipped with a magnetic stir bar and filled with the corresponding fused 3-nitropyridine **4 b**, **l**, **i** or **5 c** (1 equiv.) was added 10% Pd/C (0.1 equiv.). The flask was fitted with a rubber septum and then held under vacuum for 3 min before it was filled with MeOH (25 mL for 0.3 g of fused 3-nitropyridine) and H_2. Holding under vacuum was repeated one more time, and after sequential filling with H_2, the reaction mixture was stirred for 5 h under a H_2 atmosphere. The reaction mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness or (if necessary) purified by column chromatography typically using a heptane/ethyl acetate mixture to provide the desired product.

General procedure for the synthesis of compound 16 a

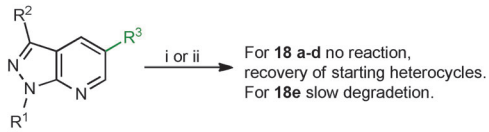
To a Schlenk flask equipped with a magnetic stir bar and filled with the fused 3-nitropyridine **4 e** (1 equiv.) was added 10% Pd/C (0.1 equiv.). The flask was fitted with a rubber septum and held under vacuum for 3 min before it was filled with MeOH (25 mL for 0.3 g of fused 3-nitropyridine), formaldehyde solution (6 equiv., 37 wt% in H_2O, contains 10–15% methanol as stabiliser), and H_2. Holding under vacuum was repeated one more time, and after sequential filling with H_2, the reaction mixture was stirred for 5 h under a H_2 atmosphere. The reaction mixture was filtered through a Celite pad, and the filtrate was evaporated to dryness. The residue was purified by column chromatography typically using a heptane/ethyl acetate mixture to provide the desired product.

General procedure for the synthesis of compound 17 a

To a Schlenk flask equipped with a magnetic stir bar and filled with the fused 3-nitropyridine **4 a** (1 equiv.) was added 10% Pd/C (0.1 equiv.). The flask was fitted with a rubber septum and held under vacuum for 3 min before it was filled with MeOH (25 mL for



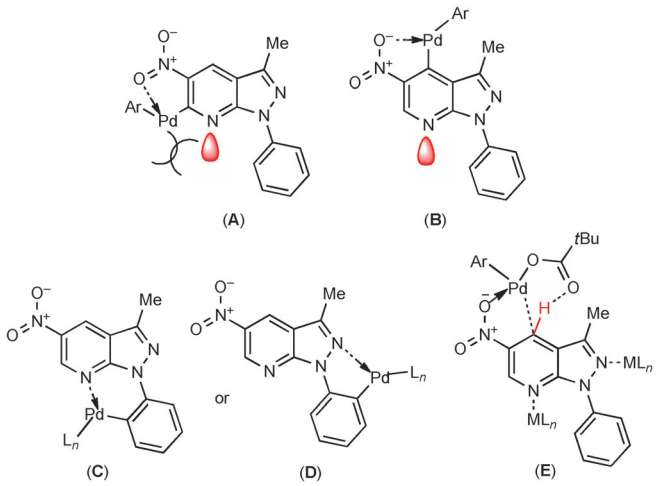
Scheme 9. Reduction of the nitro group; i) MeOH, H_2, Pd/C (10 mol%), 20 °C, 5 h. ii) MeOH, H_2, Pd/C (10 mol%), CH_2O in H_2O (37%, 6 equiv.), 20 °C, 5 h. iii) MeOH, H_2, Pd/C (10 mol%), CH_2O in H_2O (37%, 1.5 equiv.), 20 °C, 5 h. * The yield of the reduction of **4i** is given in brackets in red.



18a: R^1=Et, R^2=H, R^3=CN
18b: R^1=PMB, R^2=H, R^3=CO_2Et
18c: R^1=Ph, R^2=H, R^3=H
18d: R^1=Ph, R^2=Me, R^3=Tol
18e: R^1=Ph, R^2=Me, R^3=CC-4MeO-Ph

Scheme 10. Exploration of the directing ability of the nitro group; i) ArBr (4 equiv.), $[PdCl_2(PPh_3)_2]$. ii) $[NiCl_2(PPh_3)_2]$ (5 mol%), CuI (1.2 equiv.), PivOH (0.3 equiv.), K_2CO_3 (1.3 equiv.), DMF, under Ar, 130 °C, 16 h. PMB = *p*-Methoxybenzyl.

0.3 g of fused 3-nitropyridine), formaldehyde solution (1.5 equiv., 37 wt% in H_2O, contains 10–15% methanol as stabiliser), and H_2. Holding under vacuum was repeated one more time, and after sequential filling with H_2, the reaction mixture was stirred for 5 h under a H_2 atmosphere. The reaction mixture was filtered through Celite pad, and filtrate was evaporated to dryness. The residue was purified by column chromatography typically using a heptane/ethyl acetate mixture to provide the desired product.



Scheme 11. Proposed mechanistic explanation of the regioselectivity.

Acknowledgements

Financial support by the DAAD (scholarships for A.G. and S.M.) and by the State of Mecklenburg-Vorpommern is gratefully acknowledged. We are grateful to Enamine Ltd Company (Ukraine) for support.

Keywords: C–H activation · fused-ring systems · nickel · nitrogen heterocycles · palladium

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Received: September 7, 2014
Revised: October 12, 2014
Published online on ■■ ■■, 0000

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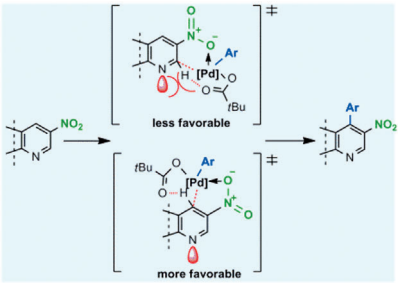
Regioselective Direct Arylation of Fused 3-Nitropyridines and Other Nitro-Substituted Heteroarenes: The Multipurpose Nature of the Nitro Group as a Directing Group



So nitro: We report Pd- and Ni-catalyzed, guided, and regioselective C–H arylations of a series of fused 3-nitropyridines. The method described here is a facile tool for the chemical functionalization of drug-like fused pyridines. The scope and limitations of the reaction, the chemical potential of the nitro group, and a putative reaction mechanism are discussed.