Ligand-free copper(I)-catalysed intramolecular direct C–H functionalization of azoles†

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The first examples of copper-catalysed intramolecular direct C-arylation of azaheterocycles for the synthesis of complex heterofused compounds is presented, featuring an unprecedented arylation *via* C–H activation of 9*H*-purine and 4-azabenzimidazole.

Introduction

Transition-metal-catalysed direct functionalization of C–H bonds has emerged over the past few years as an attractive alternative to the conventional cross-coupling reactions with organometallic reagents.[1] The main feature of these transformations is that the unactivated C–H bonds can be treated as a functional group, similar to the traditionally used C–halogen or C–metal bonds. These regioselective C(sp^2)–C(sp^2) bond formation processes are useful tools for the construction of highly functionalised molecules and display important synthetic features with attractive industrial prospects, particularly in terms of sustainable chemistry.[2] In this respect, they allow the direct conversion of non-activated arenes and generally exhibit high regioselectivity patterns among different C–H bonds circumventing the undesired formation of mixtures of regioisomers. Consequently, short reaction sequences and minor by-product waste (HX, with X = I, Br, Cl) are prime advantages of the latter processes. Traditionally, the regioselective formation of aryl–aryl bonds *via* C–H activation has been monopolised by the exclusive use of expensive transition metals such as Rh, Ru and Pd.[3,4] However, in recent years impressive progress has been made in the use of much cheaper and less toxic copper salts as convenient alternative catalysts to perform these challenging C–H functionalizations.[5,6] Herein, we present an efficient ligand-free intramolecular copper(I)-catalysed direct arylation of several electron-rich azoles with aryl iodides for the synthesis of a wide range of valuable heterofused molecules. As part of our ongoing interest in the assembly of therapeutically relevant heterocycles by means of copper-catalysed intramolecular ring closures,[7] we recently reported that the isoindolo[2,1-*a*]indole scaffold could be easily formed through an intramolecular copper-catalysed C–H functionalization process.[8] We were aware of the significant differences between indoles and other azoles like diazoles or triazoles, but the presence of azoles in a plethora of biologically active compounds[9] and other synthetic materials employed as dyes, electrostatographic toners and high-affinity ligands for numerous proteins (Fig. 1)[10] encouraged us to take a further step. We envisioned that a more general protocol for the preparation of heterocycle-fused azole derivatives could be based on such an advantageous direct arylation process.

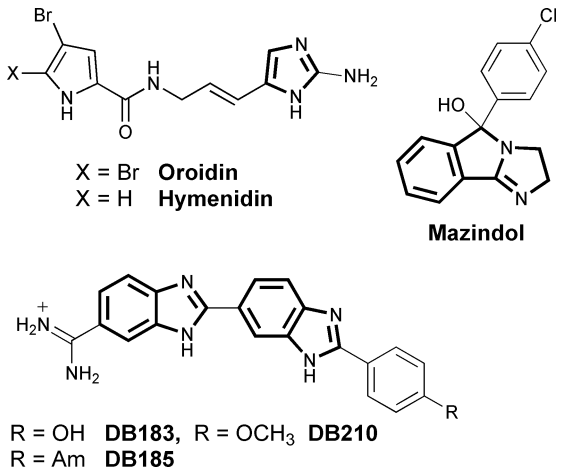

Fig. 1 Some relevant azole-containing natural products.

Results and discussion

Our preliminary studies focused on the conversion of 1-(2-iodobenzyl)-1*H*-benzo[*d*]imidazole **1a** into isoindolo[2,1-*a*]benzimidazole **2a** (see Table 1). After a first set of screening experiments of the copper source, base and solvent, it was found that the combination of 10 mol% of CuI along with 20 mol% of pyperazine 2-carboxylic acid (P2CA) as catalyst in the presence of 3 equiv. of LiO^{t}Bu in commercial *o*-xylene at 150 °C delivered the target product **2a** in 71% yield (entry 2). Curiously, the use of KO^{t}Bu or NaO^{t}Bu as base resulted always in lower conversions (~20%). It is known that the success of many C–H arylation reactions is strongly determined by the identity of the base employed. This effect might be related not only to the strength of the base but also to the solubility of both the base itself and the metal halides byproducts which are formed during the processes.[11]

Importantly, additional studies showed that the nature of the ligand did not affect the reaction outcome (Table 1, entries 2–7, yields ranging from 71–82%), which clearly evidenced its minor role in the process. To our delight, when a control experiment in the absence of any additional ligand was performed the target product **2a** was obtained as a sole product in 99% yield (entry 8). In fact, several benzotriazole and benzimidazole derivatives have

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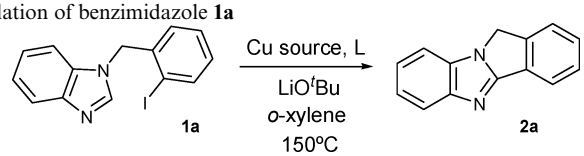
† Electronic supplementary information (ESI) available: Experimental procedures, characterization data, and ^{1}H and ^{13}C spectra of all new compounds. See DOI: 10.1039/b916549e

Table 1 Selected assays for the copper-catalysed intramolecular direct arylation of benzimidazole **1a**



Entry[a]	Cu	Ligand (L)[b]	Yield **2a**[c] (%)
1[d]	Cu bronze	PEG-400	0
2	CuI	P2CA	71 (100)
3	CuI	DMP	80 (100)
4	CuI	2AP	78 (100)
5	CuI	sarcosine	82 (100)
6	CuI	Py2CA	80 (100)
7	CuI	D-glucosamine	76 (100)
8	CuI	—	99 (100)
9	—	—	0 (0)
10	Cu_2O	—	91 (98)
11	Cu bronze	—	54 (55)
12[e]	CuI	—	98 (99)
13[f]	CuI	—	(62)
14[g]	CuI	—	(90)

[a] A sealed tube was charged with 10 mol% of Cu salt, 20 mol% of ligand (when it is added) and 3 equiv. of base. All reactions were run in commercial non-anhydrous *o*-xylene at 150 °C. [b] Phe: 1,10-phenanthroline; P2CA: piperazine-2-carboxylic acid; DMP: *N*,*N*′-dimethylpiperazine; 2AP: 2-aminopyridine; Py2CA: pyrrole-2-carboxylic acid; PEG-400: poly(ethylene glycol)-400. [c] Yield of isolated product. Conversion rate was calculated from ^{1}H-NMR spectra and is displayed in parentheses. [d] 2 equiv. of K_2CO_3 and PEG-400 as solvent were used. Only dehalogenated byproduct was formed [e] 5 mol% of CuI was used. [f] 2.5 mol% of CuI was used. [g] 5 mol% of CuI and 2.5 equiv. of LiO^{t}Bu were used.

been recently employed as ligands in copper-catalysed reactions.[12] As reasonably expected, no reaction was observed in the absence of copper source, thus highlighting the role of the metal (entry 9). Among the tested copper salts, CuI was identified as the catalyst of choice (entries 8 *vs.* 10–11). It is particularly noteworthy that on reducing the catalyst loading from 10 to 5 mol%, the target product was also obtained in an excellent 98% yield (entry 12 *vs.* 8). However, comparatively lower conversions were observed either using just 2.5 mol% of CuI (62%, entry 13) or less of the base (90%, entry 14). The use of DMF as solvent, as reported by Daugulis *et al.* for the intermolecular arylation of several azoles, afforded negligible results.[5b,13]

Additionally, six hours was determined as the optimal reaction time for the arylation to complete, as displayed by the kinetic sigmoidal curve of Fig. 2. This relatively long induction time suggests a prior complexation and formation of active copper species at the reaction temperature before the catalytic cycle takes place.

Therefore, the optimal conditions involved stirring the starting material in the presence of 5 mol% of CuI and 3 equiv. of LiO^{t}Bu in commercial grade *o*-xylene at 150 °C for 6 h. Unfortunately, when the bromo analogue 1-(2-bromobenzyl)-1*H*-benzo[*d*]imidazole was subjected to the optimal conditions no product was observed.

Given the excellent results obtained for the synthesis of isoindolo[2,1-*a*]benzimidazole **2a**, the scope of the process towards the preparation of analogous heterocyclic derivatives was next explored. Accordingly, a series of *N*-(2-iodobenzyl)substituted azoles **1a–h** were prepared by means of a simple benzylation of commercially available cheap heterocycles.[14] Symmetrically

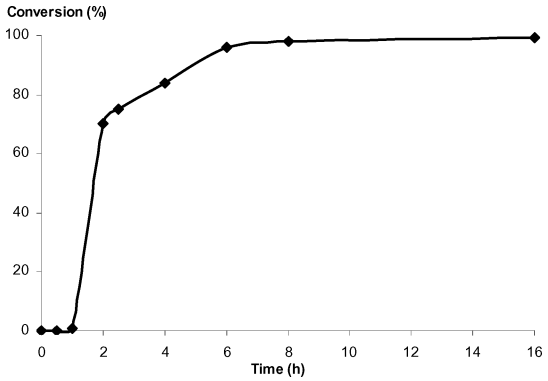


Fig. 2 Plot of conversion rate as a function of time.

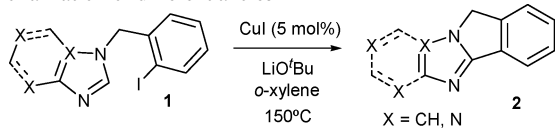
substituted azoles were employed as starting materials due to the fast tautomeric equilibrium they exhibit, otherwise an inseparable mixture of regioisomers is formed in the preliminary benzylation step. Interestingly, both 9*H*-purine and 4-azabenzimidazole underwent benzylation regioselectively at the N1 position, furnishing **1g** and **1h** as the only products. However, when 5-azabenzimidazole was subjected to the benzylation conditions a mixture of both N1 and N3-substituted products was observed.[15] This effect might be related to the fact that a nitrogen atom is located in the 4 position of 9*H*-purine and 4-azabenzimidazole, which may direct the benzylation preferentially towards the N1 position.

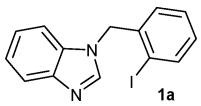
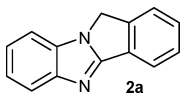
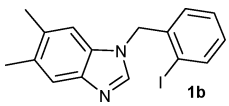
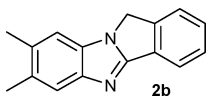
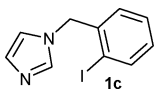
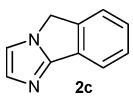
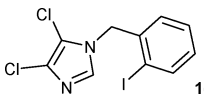
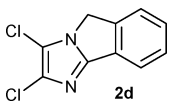
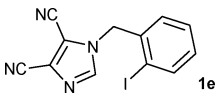
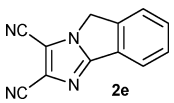
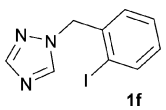
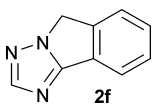
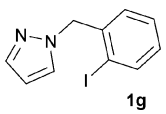
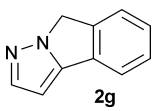
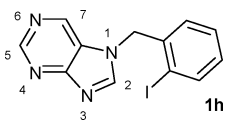
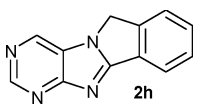
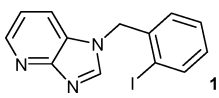
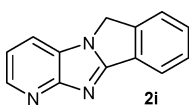
As displayed in Table 2, our simple ligand-free copper-catalysed protocol proved rather effective for the C–H functionalization of a wide variety of electron-rich nitrogen-containing heterocycles. In addition to various benzimidazoles (entries 1, 2), several imidazoles[16] (entries 3, 4) and 1,2,4-1*H*-triazole (entry 6) also reacted smoothly with the aryl iodide counterpart. In this context, it should be outlined that just a few reports on the intermolecular copper-catalysed direct *C*-arylation of triazoles have been reported thus far.[5a,6e] On the other hand, the lower reactivity of the C–H bond in the pyrazole core resulted in the recovery of the unreacted starting material (entry 7).

Notably, the presence of various halogens was well-tolerated (entry 4), which allows further synthetic manipulations of the resulting halogenated heterocycle. Unfortunately, the arylation was found incompatible with the presence of cyano groups and imidazole **1e** led to undesired decomposition processes (entry 5). Furthermore, when 4,5-diphenyl substituted imidazole **1j** (Fig. 3) was subjected to the optimised conditions many unidentified products were obtained, probably due to side-reactions between the aryl iodide counterpart and the two additional phenyl groups.

It is worth mentioning that these conditions were successfully applied to the arylation of less commonly employed motifs such as 9*H*-purine and 4-azabenzimidazole (entries 8, 9).[17] To the best of our knowledge, these examples indeed represent the first direct copper-catalysed C–H functionalizations of both 9*H*-purine (entry 8) and 4-azabenzimidazole (entry 9). The paramount importance of using these compounds relies on their cardiovascular properties and utility in the treatment of AIDS and HIV related diseases exhibited by some of them.[18] Besides, although substrate **1h** could theoretically undergo cyclization in two different positions (2 *vs.* 7), the reaction proceeded cleanly on the C-2 position leading to the selective formation of derivative **2h** (entry 8). In all cases the total consumption of the starting

Table 2 Scope of the ligand-less CuI catalysed intramolecular C–H functionalization of different azoles



Entry[a]	Substrate	Product	Yield (%)[b]
1			99
2			90
3			88
4			58
5			0
6			68
7			0
8			58
9			89

[a] A sealed tube was charged with substrate (1 equiv.), 5 mol% of CuI, 3 equiv. of LiO^{t}Bu and commercial non-anhydrous *o*-xylene at 150 °C. [b] Yield of isolated product. The yields were not improved when using dry *o*-xylene.

material was achieved, and formation of any undesired byproduct was not observed. Curiously, when the C-7 position was blocked with a chlorine atom the reaction did not work, instead undesired decomposition products were observed.

Unfortunately, when methoxy groups were incorporated into either the aryl iodide or the azole counterpart negligible results were obtained (Fig. 3). Subjecting substrate **1k** to the optimized conditions resulted in its decomposition, probably due to oxidative

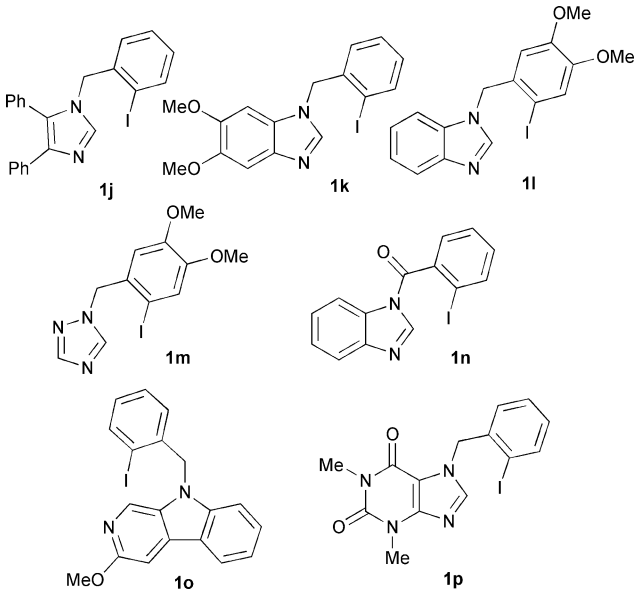


Fig. 3

side-reactions at the electron-rich arene moiety in the presence of a metal source.[19] The lack of reactivity of precursors **1l** and **1m** might be related to the deactivation towards the oxidative addition step exerted by the electron-donating methoxy groups.[20] However, the presence of an electron-withdrawing substituent does not ensure cyclization, since1-(2-iodophenylcarbonyl)-1*H*-benzo[*d*]imidazole **1n** was also unreactive under the same conditions.

The similarity between the imidazole core and the heterocyclic skeleton of substrates **1o** and **1p** encouraged us to check their reactivity under the optimised conditions (Fig. 3). Unfortunately, only starting materials were recovered in both cases. Interestingly, when our reported conditions for the intramolecular C-arylation of indoles (Cu bronze, K_2CO_3, PEG-400, 180 °C)[8] were tested, substrate **1o** reacted to provide the undesired dehalogenation product. These negligible results could be related not only to the presence of electron-donating methoxy groups in the azole counterpart of **1o**, but also to a poor metal coordination to the adjacent atom of nitrogen, thus hindering a subsequent metallation step.

Conclusions

In summary, we have developed a highly practical ligand-free copper-catalysed system for the intramolecular direct C–H arylation of several electron-rich azaheterocycles. The presented method is effective with just 5 mol% of catalyst and proved tolerant to the presence of additional halogens, allowing further synthetic manipulations. The reaction does not require anhydrous conditions, thus facilitating reagent manipulations and simplifying the whole process. Moreover, to best of our knowledge, this is the first example of copper-mediated C–H functionalization of both 9*H*-purine and 4-azabenzimidazole heterocycles. Indeed, this protocol provides a simple way to synthesize biologically relevant tri- and tetracyclic compounds.

Experimental section

General methods

All reagents were purchased and used as received. Chemical shifts (δ) are given in ppm downfield from Me_4Si and refer as internal standard to the residual solvent $CDCl_3$: ($\delta = 7.26$ for ^1H and 77.0 for ^{13}C). Coupling constants, J, are reported in hertz (Hz). Melting points were determined in a capillary tube and are uncorrected. TLC was carried out on SiO_2, and the spots were located with UV light. Flash chromatography was carried out on SiO_2. Drying of organic extracts during work-up of reactions was performed over anhydrous Na_2SO_4. Evaporation of solvents was accomplished with a rotary evaporator.

11*H*-Isoindolo[2,1-*a*]benzimidazole (2a). Typical procedure

A screw-capped tube (18 mL) was charged with 1-(2-iodobenzyl)-1*H*-benzo[*d*]imidazole **1a** (60.6 mg, 0.18 mmol), CuI (1.7 mg, 0.009 mmol), LiO^{t}Bu (43.2 mg, 0.54 mmol) and commercial non-anhydrous *o*-xylene (0.9 mL) at room temperature. After closing, it was heated at 150 °C for 6 h, allowed to cool and quenched with water. The aqueous layer was extracted three times with CH_2Cl_2 and organic layers were dried over anhydrous Na_2SO_4. The solvent was concentrated *in vacuo* and the resulting solid residue was redissolved and filtered through a short pad of silica gel. The solvent was evaporated to afford the target compound **2a** as a white solid (35.2 mg, 99%). Mp: 194–196 °C (from hexane); IR $_{max}$(KBr)/cm^{-1} 1467, 1537, 1619; ^1H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 4.98 (s, 2H, CH_2), 7.24–7.29 (m, 2H, H_7, H_8), 7.40 (dd, $J = 8.8$, 3.7 Hz, 1H, H_9), 7.45–7.54 (m, 3H, H_1, H_2, H_3), 7.76–7.90 (m, 1H, H_6), 8.04 (d, $J = 7.5$ Hz, 1H, H_4); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 47.2 (CH_2), 109.3 (C_9), 120.6 (C_6), 122.1 (C_4), 122.2. (C_7, C_8), 122.7 (C_8, C_7), 123.8 (C_1), 128.8 (C_2, C_3), 129.4 (C_{4a}, C_{11a}), 129.5 (C_3, C_2), 132.7 (C_{5a}), 143.5 (C_{11a}, C_{4a}), 148.4 (C_{9a}), 158.5 (C_{4b}); MS (CI) *m*/*z*: 208 (M + 2, 15), 207 (M + 1, 100), 206 (M$^+$, 59). HRMS (CI) [M + 1]: calculated for $C_{14}H_{11}N_2$, 207.0922; found, 207.0930.

By using the above procedure the following compounds were prepared:

7,8-Dimethyl-11*H*-isoindolo[2,1-*a*]benzimidazole (2b). Mp: 221–224 °C (from hexane); IR $_{max}$(KBr)/cm^{-1} 1314, 1437, 1537; ^1H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 2.37 (s, 6H, CH_3), 4.91 (s, 2H, CH_2), 7.17 (s, 1H, H_6, H_9), 7.40–7.53 (m, 3H, H_{arom}), 7.56 (s, 1H, H_9, H_6), 8.00 (d, $J = 7.0$ Hz, 1H, H_4); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 20.3, 20.5 (CH_3), 47.0 (CH_2), 109.6 (C_9), 120.5, 121.7, 123.7, 128.6, 129.0 (C_{arom}-H), 129.6, 130.9, 131.1, 131.8, 143.4, 146.8 (C_{arom}-C), 157.7 (C_{4b}); MS (CI) *m*/*z*: 236 (M + 2, 17), 235 (M + 1, 100), 234 (M$^+$, 55), 233 (13). HRMS (CI) [M + 1]: calculated for $C_{16}H_{15}N_2$, 235.1235; found, 235.1224.

5*H*-Imidazo[2,1-*a*]-isoindole (2c). The experimental data were compared to those reported in the bibliography.[21]

2,3-Dichloro-5*H*-imidazo[2,1-*a*]-isoindole (2d). Mp: 162–164 °C (from hexane); IR $_{max}$(KBr)/cm^{-1} 1214, 1437, 1472, 1537; ^1H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 4.78 (s, 2H, CH_2), 7.33–7.47 (m, 3H, H_{arom}), 7.73 (d, $J = 7.4$ Hz, 1H, H_9); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 48.8 (CH_2), 111.1 (C_{arom}-C), 119.9, 123.5, 128.1, 128.8 (C_{arom}-H), 129.1, 140.2 (C_{arom}-C), 149.2 (C_{9b}); MS (CI) *m*/*z*: 227 (M + 3, 60), 226 (M + 2, 32), 225 (M + 1, 100), 224 (M$^+$, 36). HRMS (CI) [M + 1]: calculated for $C_{10}H_7N_2Cl_2$, 224.9986; found, 224.9982. Found C 53.0, H 3.0, N 12.3%. Calculated for $C_{10}H_6N_2Cl_2$: C 53.3, H 2.7, N 12.4.

5*H*-[1,2,4]Triazolo[5,1-*a*]isoindole (2f). Mp: 98–101 °C (from hexane); IR $_{max}$(KBr)/cm^{-1} 1132, 1243, 1396, 1473, 1537; ^1H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 5.03 (s, 2H, CH_2), 7.44–7.53 (m, 3H, H_{arom}), 7.86 (dd, $J = 6.1$, 1.2 Hz, 1H, H_9), 8.05 (s, 1H, H_2); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 50.0 (CH_2), 121.4, 123.8, (C_{arom}-H), 127.1 (C_{5a}), 128.7, 129.3 (C_{arom}-H), 141.9 (C_{9b}), 155.9 (C_2), 160.1 (C_{9b}); MS (CI) *m*/*z*: HRMS (CI) [M + 1]: calculated for $C_9H_8N_3$ 158.0718, found 158.0711.

6*H*-Isoindolo[2,1-*f*]purine (2h). Mp: 239–241 °C (from hexane); IR $_{max}$(KBr)/cm^{-1} 1231, 1285, 1349, 1467, 1602; ^1H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 5.20 (s, 2H, CH_2), 7.58–7.67 (m, 3H, H_{arom}), 8.10–8.13 (m, 1H), 8.93 (s, 1H, H_2), 9.11 (s, 1H, H_4); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 46.9 (CH_2), 122.9, 124.3 (C_{arom}-H), 127.7 (C_{4a}), 129.2, 131.3 (C_{arom}-H), 139.2 (C_{6a}, C_{10a}), 144.1 (C_{10a}, C_{6a}), 147.8 (C_4), 150.4 (C_{11a}), 152 (C_2), 160.6 (C_{10b}); MS (CI) *m*/*z*: 210 (M + 2, 13), 209 (M + 1, 100), 208 (M$^+$, 18). HRMS (CI) [M + 1]: calculated for $C_{12}H_9N_4$, 209.0827; found, 209.0820.

6*H*-Pyrido[2′,3′,4,5]imidazo[2,1-*a*]isoindole (2i). Mp: 200–202 °C (from hexane); IR $_{max}$(KBr)/cm^{-1} 1373, 1449, 1531, 1602; ^1H NMR (300 MHz, $CDCl_3$, $SiMe_4$) (δ_H, ppm): 5.15 (s, 2H, CH_2), 7.20 (dd, $J = 8.0$, 4.9 Hz, 1H, H_{arom}), 7.49-7.52 (m, 2H, H_{arom}), 7.58–7.60 (m, 1H, H_{arom}), 8.03–8.05 (m, 2H, H_{arom}), 8.30 (d, $J = 4.7$ Hz, 1H, H_2); ^{13}C NMR (75 MHz, $CDCl_3$, $SiMe_4$) (δ_C, ppm): 46.8 (CH_2), 118.1, 122.2, 124.1, 127.7, 128.8, 130.2 (C_{arom}-H), 140.6 (C_{arom}-C), 143.3 (C_2), 143.8, 146.1, 159.3 (C_{arom}-C); MS (CI) *m*/*z*: 209 (M + 2, 13), 208 (M + 1, 100), 207 (M$^+$, 50). HRMS (CI) [M + 1]: calculated for $C_{13}H_{10}N_3$, 208.0875; found, 208.0865.

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Notes and references

1 For some recent reports, see: (*a*) D. Alberico, M. E. Scott and M. Lautens, *Chem. Rev.*, 2007, **107**, 174–238; (*b*) K. Godula and D. Sames, *Science*, 2006, **312**, 67–72; (*c*) F. Kakiuchi and N. Chatani, *Adv. Synth. Catal.*, 2003, **345**, 1077–1101; (*d*) V. Ritleng, C. Sirlin and M. Pfeffer, *Chem. Rev.*, 2002, **102**, 1731–1769; (*e*) J. Hassan, M. Sévignon, C. Gozzi, E. Schulz and M. Lemaire, M., *Chem. Rev.*, 2002, **102**, 1359–1469; (*f*) G. Dyker, *Angew. Chem., Int. Ed.*, 1999, **38**, 1698–1712; (*g*) I. V. Seregin and V. Gevorgyan, *Chem. Soc. Rev.*, 2007, **36**, 1173–1193; (*h*) M. Miura and M. Nomura, *Top. Curr. Chem.*, 2002, **219**, 211–241; (*i*) C. A. Zificsak and D. J. Hlasta, *Tetrahedron*, 2004, **60**, 8991–9016.

2 (*a*) R. G. Bergman, *Nature*, 2007, **446**, 391–393; (*b*) M. S. Chen and M. S. White, *Science*, 2007, **318**, 783–787; (*c*) A. R. Dick and M. S. Sanford, *Tetrahedron*, 2006, **62**, 2439–2463 and references cited therein; (*d*) L. Ackermann, A. Althammer and R. Born, *Tetrahedron*, 2008, **64**, 6115–6124; (*e*) J. C. Lewis, S. H. Wiedemann, R. G. Bergman and J. A. Ellman, *Org. Lett.*, 2004, **6**, 35–38.

3 (*a*) X. Chen, X.-S. Hao, C. E. Goodhue and J.-Q. Yu, *J. Am. Chem. Soc.*, 2006, **128**, 6790–6791; (*b*) C. H. Jun, H. Lee and J. B. Hong, *J. Org. Chem.*, 1997, **62**, 1200–1201; (*c*) C. P. Lenges and M. Brookhart, *J. Am. Chem. Soc.*, 1999, **121**, 6616–6623; (*d*) R. K. Thalji, K. A. Ahrendt, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2001, **123**, 9692–9693; (*e*) L. Ackermann, *Top. Organomet. Chem.*, N. Chatani, Ed.; Springer: Berlin, Heidelberg, New York, NY, 2007, Vol. 24, pp 35–60.

4 Ackermann and co-workers have reported impressive palladium- and rhodium-catalysed direct arylation methodologies employing the less reactive aryl bromides, chlorides, tosylates and mesylates as electrophiles *via* C–H functionalization. See: (*a*) L. Ackermann, R. Vicente and A. Althammer, A., *Org. Lett.*, 2008, **10**, 2299–2302; (*b*) L. Ackermann, R. Born and P. Álvarez-Bercedo, *Angew. Chem., Int. Ed.*, 2007, **46**, 6364–6367; (*c*) L. Ackermann, A. Althammer and R. Born, *Angew. Chem., Int. Ed.*, 2006, **45**, 2619–2622; (*d*) L. Ackermann, A. Althammer and S. Fenner, *Angew. Chem., Int. Ed.*, 2009, **48**, 201–204.

5 (*a*) H.-Q. Do, R. M. K. Khan and O. Daugulis, *J. Am. Chem. Soc.*, 2008, **130**, 15185–15192; (*b*) H.-Q. Do and O. Daugulis, *J. Am. Chem. Soc.*, 2007, **129**, 12404–12405; (*c*) T. Yoshizumi, H. Tsurugi, T. Satoh and M. Miura, *Tetrahedron Lett.*, 2008, **49**, 1598–1600; (*d*) A. K. Verma, T. Kesharwani, J. Singh, V. Tandon and R. C. Larock, *Angew. Chem., Int. Ed.*, 2009, **48**, 1138–1143; (*e*) S. Ueda and H. Nagasawa, *Angew. Chem., Int. Ed.*, 2008, **47**, 6411–6413; (*f*) S. Ueda and H. Nagasawa, *J. Org. Chem.*, 2009, **74**, 4272–4277.

6 (*a*) R. J. Phipps, N. P. Grimster and M. J. Gaunt, *J. Am. Chem. Soc.*, 2008, **130**, 8172–8174; (*b*) I. Ban, T. Sudo, T. Taniguchi and K. Itami, *Org. Lett.*, 2008, **10**, 3607–3609; (*c*) H.-Q. Do and O. Daugulis, *J. Am. Chem. Soc.*, 2008, **130**, 1128–1129; (*d*) G. Brasche and S. L. Buchwald, *Angew. Chem., Int. Ed.*, 2008, **47**, 1932–1934; (*e*) T. Kawano, T. Yoshizumi, K. Hirano, T. Satoh and M. Miura, *Org. Lett.*, 2009, **11**, 3072–3075; (*f*) T. Yoshizumi, T. Satoh, K. Hirano, D. Matsuo, A. Orita, J. Otera and M. Miura, *Tetrahedron Lett.*, 2009, **50**, 3273–3276.

7 (*a*) M. Carril, R. SanMartin and E. Domínguez, *Chem. Soc. Rev.*, 2008, **37**, 639–647 and references cited therein; (*b*) N. Barbero, R. SanMartin and E. Domínguez, *Tetrahedron*, 2008, **64**, 7283–7288; (*c*) N. Barbero, R. SanMartin and E. Domínguez, *Green Chem.*, 2009, **11**, 830–836; (*d*) N. Barbero, Carril, M. R. SanMartin and E. Domínguez, *Tetrahedron*, 2007, **63**, 10425–10432.

8 N. Barbero, R. SanMartin and E. Domínguez, *Tetrahedron Lett.*, 2009, **50**, 2129–2131.

9 For some recent reviews, see: (*a*) V. V. Lyaskovskyy, Z. V. Voitenko and V. A. Kovtunenko, *Chem. Heterocycl. Compd.*, 2007, **43**, 253–276 and references cited therein; (*b*) Z. V. Voitenko, T. V. Egorova and V. A. Kovtunenko, *Chem. Heterocycl. Compd.*, 2002, **38**, 1019–1039 and references cited therein; See also: (*c*) S. K. Meegalla, G. J. Stevens, C. A. McQueen, A. Y. Chen, C. Yu, L. F. Liu, L. R. Barrows and E. J. LaVoie, *J. Med. Chem.*, 1994, **37**, 3434–3439; Their potential activity as antibacterial, antitubercular and bronchodilator has also been evaluated, see: (*d*) B. P. V. Lingaiah, T. Yakaiah, P. S. Rao and B. Narsaiah, *Heterocycles*, 2005, **65**, 2329–2337 and references cited therein.

10 (*a*) K. M. Patel, V. H. Patel, M. P. Patel and R. G. Patel, *Dyes Pigm.*, 2002, **55**, 53–58; (*b*) A. P. Thomas, C. P. Allott, K. H. Gibson, J. S. Major, B. B. Masek, A. A. Oldham, A. H. Ratcliffe, D. A. Roberts, S. T. Russell and D. A. Thomason, *J. Med. Chem.*, 1992, **35**, 877–885.

11 See:(*a*) S. Pivsa-Art, T. Satoh, Y. Kawamura, M. Miura and M. Nomura, *Bull. Chem. Soc. Jpn.*, 1998, **71**, 467–473; (*b*) F. Besselièvre, S. Piguel, F. Mahuteau-Betzer and D. S. Grierson, *Org. Lett.*, 2008, **10**, 4029–4032.

12 For some recent examples on the use of benzotriazole, see: (*a*) A. K. Verma, J. Singh, V. K. Sankar, R. Chaudhary and R. Chandra, *Tetrahedron Lett.*, 2007, **48**, 4207–4210; (*b*) A. K. Verma, T. Kesharwani, J. Singh, V. Tandon and R. C. Larock, *Angew. Chem., Int. Ed.*, 2009, **48**, 1138–1143; For an example on the use of benzoimidazole-type ligands, see:; (*c*) V. O. Rodionov, S. I. Presolski, S. Gardinier, Y.-H. Lim and M. G. Finn, *J. Am. Chem. Soc.*, 2007, **129**, 12696–12704.

13 During the development of this work You *et al.* reported the direct arylation of several heterocycles with the less reactive aryl bromides. See: D. Zhao, W. Wang, F. Yang, J. Lan, L. Yang, G. Gao and J. You, *Angew. Chem., Int. Ed.*, 2009, **48**, 3296–3300.

14 R. Sanz, J. M. Ignacio, M. P. Castroviejo and F. J. Fañanas, *Arkivoc*, 2007, 84–91.

15 We subjected the mixture of regioisomers to the optimised cyclised conditions, but no product formation was observed.

16 For an alternative synthesis of 5*H*-imidazo[2,1-*a*]isoindole **2c** based on palladium catalysis, see: (*a*) R. Marcia de Figueiredo, S. Thoret, C. Huet and J. Dubois, *Synthesis*, 2007, 529–540; For a recently reported palladium-catalysed synthesis of isoindolo[2,1-*a*]benzimidazole **2a**, see:; (*b*) K. C. Majumdar, P. Debnath, A. Taher and A. K. Pal, *Can. J. Chem.*, 2008, **86**, 325–332.

17 Some examples of palladium- and rhodium-catalysed purine arylation can be found in: (*a*) K. L. Tan, R. G. Bergman and J. A. Ellman, *J. Am. Chem. Soc.*, 2002, **124**, 13964–13965; (*b*) K. L. Tan, S. Park, J. A. Ellman and R. G. Bergman, *J. Org. Chem.*, 2004, **69**, 7329–7335. To the best of our knowledge, the 4-azabenzimidazole framework has never been directly arylated through a metal-catalysed C–H functionalization.

18 (*a*) S. V. Goldstein, W. G. Stirtan, and B. A. Sherer, Patent US 2001, US 6242461; (*b*) T. Gungor, A. Fouquet, J. M. Teulon, D. Provost, M. Cazes and A. Cloarec, *J. Med. Chem.*, 1992, **35**, 4455–4463.

19 For a recent example, see: A. A. O. Sarhan and C. Bolm, *Chem. Soc. Rev.*, 2009, **38**, 2730–2744.

20 For some relevant reviews of copper-catalysed coupling reactions and the mechanism involved, see: (*a*) G. Evano, N. Blanchard and M. Toumi, *Chem. Rev.*, 2008, **108**, 3054–3131; (*b*) S. V. Ley and A. W. Thomas, *Angew. Chem., Int. Ed.*, 2003, **42**, 5400–5449; (*c*) I. P. Beletskaya and A. V. Cheprakov, *Coord. Chem. Rev.*, 2004, **248**, 2337–2369; (*d*) J. Hassan, M. Svignon, C. Gozzi, E. Schulz and M. Lemaire, *Chem. Rev.*, 2002, **102**, 1359–1470; (*e*) K. Kunz, U. Scholz and D. Ganzer, *Synlett*, 2003, 2428–2439; (*f*) F. Monnier and M. Taillefer, *Angew. Chem., Int. Ed.*, 2008, **47**, 3096–3099; (*g*) A. R. Muci and S. L. Buchwald, *Top. Curr. Chem.*, 2002, **219**, 131–209.

21 N. Arai, M. Takahashi, M. Mitani and A. Mori, *Synlett*, 2006, 3170–3172.