

N-aryl pyrazoles: DFT calculations of CH acidity and deprotonative metallation using a combination of lithium and zinc amides†

Floris Chevallier,^{*a} Yury S. Halauko,^{*b} Christelle Pecceu,^a Ibrahim F. Nassar,^a To Uyen Dam,^a Thierry Roisnel,^c Vadim E. Matulis,^d Oleg A. Ivashkevich^d and Florence Mongin^{*a}

Received 18th February 2011, Accepted 23rd March 2011

DOI: 10.1039/c1ob05267e

A series of *N*-aryl and *N*-heteroaryl pyrazoles have been deprotonated using a 2,2,6,6-tetramethylpiperidino-based mixed lithium–zinc combination. Mono-, di-, and tri-iodides have been obtained after subsequent trapping with iodine, depending on the substrate and on the quantity of base used. The results have been discussed in the light of the CH acidities of the substrates, determined both in the gas phase and in THF solution using the DFT B3LYP method.

Introduction

Pyrazoles belong to the most important heterocycles containing nitrogen. They have attracted considerable interest because of their long history of applications in pharmaceuticals and agrochemicals.¹ Among them, the *N*-aryl derivatives have been shown to exhibit a broad spectrum of biological activities.²

Lithium (or magnesium) monometal bases have been employed to perform deprotonative metallation reactions of pyrazoles bearing an aromatic ring on a nitrogen, allowing their subsequent functionalization.³ Nevertheless, low temperatures are required to perform these reactions.⁴

In 2009, Knochel and co-workers showed that mixed lithium–magnesium bases, such as TMPMgCl·LiCl and (TMP)₂Mg·2LiCl (TMP = 2,2,6,6-tetramethylpiperidino), were suitable reagents to allow chemoselective reactions of SEM-protected and *N*-methyl pyrazoles.⁵

In the search for new bimetallic combinations for deprotonation purposes,⁶ we recently observed that the basic mixture obtained from ZnCl₂·TMEDA (TMEDA = *N,N,N',N'*-tetramethylethylenediamine) and LiTMP (3 equiv.), which proved

to be 1 : 1 LiTMP–(TMP)₂Zn, could be used synergistically to functionalize sensitive compounds, such as functionalized or heterocyclic aromatics.⁷

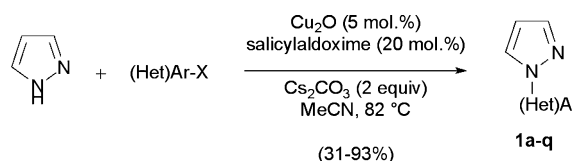
In the continuation of this study, herein we describe the use of this lithium–zinc base in a series of *N*-aryl and *N*-heteroaryl pyrazoles. As an attempt to rationalize the regioselectivity of the reactions, the CH acidities of the pyrazole substrates in THF were calculated within the density functional theory (DFT) framework using a homodesmic reaction approach described previously.⁸

Results and discussions

Synthetic aspects

Commercial 1-phenyl-1*H*-pyrazole could be deprotonated upon treatment with 1 : 1 LiTMP–(TMP)₂Zn (0.5 equiv. each) in tetrahydrofuran (THF) at room temperature for 2 h to afford, after subsequent trapping with iodine, the 5-substituted derivative in 56% yield.^{7a} Even when not isolated, the 5,5'-diiodinated derivative was also present in the crude.⁹ This prompted us to replace the phenyl group at the nitrogen with different aryl and heteroaryl groups to see the impact on the outcome of the reaction.

To this purpose, pyrazole was treated with aryl and heteroaryl halides (iodides, bromides, or even chlorides) under copper catalysis using the conditions reported by Cristau, Taillefer and co-workers,¹⁰ to afford the derivatives **1a–q** in moderate to high yields (Scheme 1).



Scheme 1 Copper-catalyzed *N*-arylation of pyrazole.

^aChimie et Photonique Moléculaires, UMR 6510 CNRS, Université de Rennes 1, Bâtiment 10A, Case 1003, Campus Scientifique de Beaulieu, 35042, Rennes, France. E-mail: floris.chevallier@univ-rennes1.fr, florence.mongin@univ-rennes1.fr; Fax: +33-2-2323-6955

^bDepartment of Electrochemistry of Belarusian State University, 14 Leningradskaya Str., Minsk, 220030, Belarus. E-mail: hys@tut.by, halauko@bsu.by

^cCentre de Diffractométrie X, Sciences Chimiques de Rennes, UMR 6226 CNRS, Université de Rennes 1, Bâtiment 10B, Case 1003, Campus Scientifique de Beaulieu, 35042, Rennes, France

^dResearch Institute for Physico-Chemical Problems of Belarusian State University, 14 Leningradskaya Str., Minsk, 220030, Belarus; Fax: +375-17-2264696

† Electronic supplementary information (ESI) available: ¹H and ¹³C NMR spectra and Cartesian coordinates of molecular geometries for the most stable rotamer forms of studied pyrazoles. CCDC reference numbers 800823–800832, 813448, 813449. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c1ob05267e

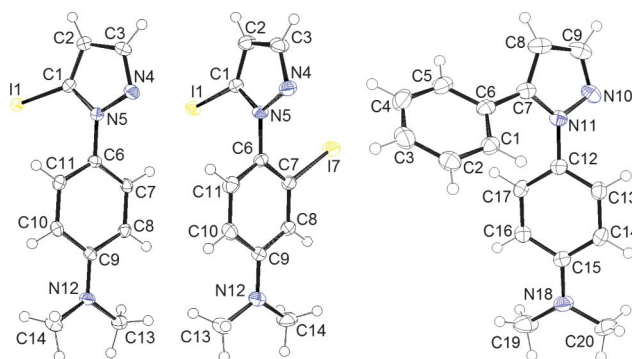
Table 1 Deprotonative metallation of **1a–h** followed by trapping with I₂

Entry	Substrate (R)	Products, Yields (%)
1	1a (4- <i>t</i> -Bu)	2a , 54 (4) ^a 3a , 28 (66) ^a — ^b
2	1b (4-NMe ₂)	2b , 54 (0) ^a 3b , 28 (67) ^a — ^b
3	1c (4-NO ₂)	— ^c — ^c — ^c
4	1d (4-CN)	— ^b 3d , 65 — ^b
5	1e (4-CF ₃)	— ^b 3e , 84 — ^b
6	1f (4-F)	— ^b 3f , 31 (57) ^a 3'f , 0 (22) ^a
7	1g (4-OMe)	— ^b 3g , 60 — ^b
8	1h (3-OMe)	2h , 12 (70) ^d 3h , 61 (7) ^d — ^b

^a The deprotonation was performed using (TMP)₂Zn (1 equiv.) + LiTMP (1 equiv.). ^b Not obtained. ^c No reaction. ^d The deprotonation was performed using (TMP)₂Zn (0.33 equiv.) + LiTMP (0.33 equiv.).

The behaviour of the pyrazoles **1a–h** bearing a substituted phenyl group towards the lithium–zinc mixture was studied first (Table 1). As previously observed with 1-phenyl-1*H*-pyrazole, the reaction of the 4-*tert*-butylated derivative **1a** with 1 : 1 LiTMP–(TMP)₂Zn (0.5 equiv. each) in THF for 2 h followed by trapping with iodine led to two derivatives, the 5-substituted derivative **2a**, obtained in 54% yield, and the 5,2'-diiodide¹¹ **3a**, isolated in 28% yield. The formation of the diiodide **3a** was favoured (66%) by increasing the base quantity to 1 equiv. (entry 1).

The behaviour of the pyrazole **1b** bearing, at the nitrogen, a 4-(dimethylamino)phenyl group¹² proved to be quite similar, giving either the monoiodide **2b** as the main derivative (54% yield) using LiTMP–(TMP)₂Zn (0.5 equiv. each) or the diiodide **3b** (67% yield) with a larger amount of base (entry 2). Both the mono- and the diiodide **2b** and **3b** were identified unequivocally by X-ray structure analysis. The iodide **2b** was converted by a Suzuki coupling to the corresponding phenyl derivative **4b** in 73% yield, and the crystal structure of the latter was also obtained (Fig. 1).[‡]

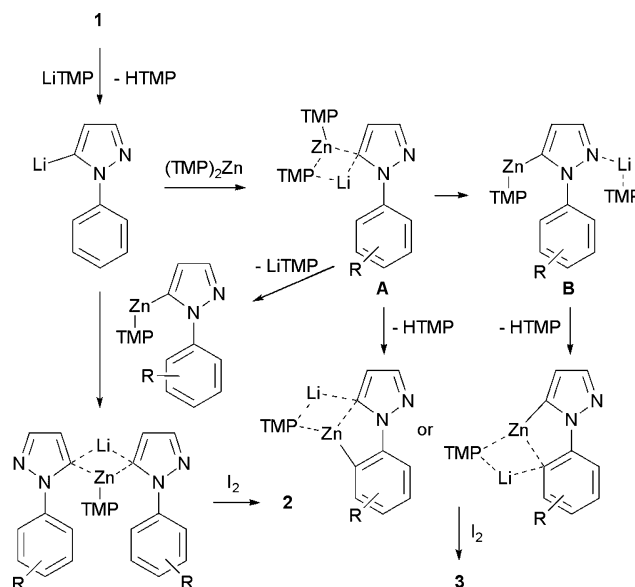
**Fig. 1** ORTEP diagrams (30% probability) of **2b** (left), **3b** (middle) and **4b** (right).

[‡] CIF files available in the electronic supplementary information (ESI): CIF files of **1j** (CCDC 813449), **1n** (800823), **1o** (813448), **2b** (800829), **3b** (800830), **4b** (800832), **6j** (800831), **8l** (800824), **9m** (800828), **7n** (800826), **8n** (800827) and **8o** (800825).

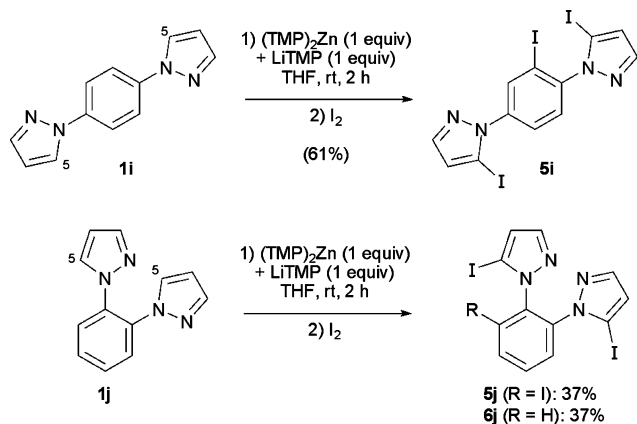
No reaction was observed when starting from the 4-nitrophenyl substituted pyrazole **1c** (entry 3), probably due to a competitive reaction of the base with the sensitive nitro group,¹³ but using other electron-withdrawing R groups the reactions proceeded satisfactorily. In the case of pyrazoles **1d** (4-cyanophenyl substituted) and **1e** (4-(trifluoromethyl)phenyl substituted), the 5,2'-diiodides **3d,e** were already isolated in satisfactory yields (65 and 84%, respectively) using 0.5 equiv. of base (entries 4 and 5). The fluoro group proved to activate the 2' site less strongly than the cyano and trifluoromethyl groups, giving **3f** in a moderate 31% yield using 0.5 equiv. of base. Changing to 1 equiv. of base led to the formation of the two diiodides **3f** and **3'f**, a result probably due to the strong ability of the fluoro group to direct the metallation to the *ortho* site (entry 6).¹⁴

With *N*-(4-methoxyphenyl)pyrazole (**1g**), we turned to an electron-donating group renowned for being less *ortho*-directing than fluoro.¹⁵ Surprisingly, the corresponding 5,2'-diiodide **3g** was isolated in 60% yield using 0.5 equiv. of base (entry 7). By moving the methoxy group from the 4' to the 3' position (substrate **1h**), the diiodide **3h** was formed in a similar 61% yield but the monoiodide **2h** was concomitantly formed in 12% yield. A metallation occurring first at the 5 position was evidenced using 0.33 equiv. of base; under the same reaction conditions, the iodide **2h** was obtained in 70% yield (entry 8).

A reaction pathway where the deprotonation proceeds with LiTMP and the resultant aryllithium intermediate converts by *in situ* trapping with (TMP)₂Zn (or ArZnTMP) to the more stabilized arylzinc species was assumed to explain the synergy of the metallation reactions using 1 : 1 LiTMP–(TMP)₂Zn.^{7a} To rationalize the dimetallation easily observed with the *N*-aryl pyrazoles involved in the reaction, one can consider a proximity effect, either with a lithium pyrazolylzincate **A** or with a pre-metallation complex **B** between LiTMP and the pyrazole-complexing nitrogen¹⁶ (Scheme 2). As the products are always iodinated at their 5 position, intramolecular deprotonation reactions from the pyrazolylzincates **A** seem more likely.

**Scheme 2** Proposed pathways for the dimetallation of *N*-aryl pyrazoles using 1 : 1 LiTMP–(TMP)₂Zn.

In the search for other polymetallation reactions, we added 1,1'-(1,4-phenylene)bis(1*H*-pyrazole) (**1i**)¹⁷ to LiTMP–(TMP)₂Zn (1 equiv. each) in THF for 2 h before interception with iodine. Under these conditions, the triiodide **5i** was isolated in 61% yield. When 1,1'-(1,2-phenylene)bis(1*H*-pyrazole) (**1j**) was similarly treated, the corresponding triiodide **5j** was also obtained but in a lower 37% yield. Indeed, a less iodinated derivative **6j** resulting from a deprotonation at the 5 position of both pyrazole rings was also formed in 37% yield, and was unequivocally identified by X-ray structure analysis (Scheme 3, Fig. 2).[‡] These results tend to show that the deprotonation at the phenylene ring is less favoured when the pyrazole ring does not belong to the same plane.



Scheme 3 Deprotonative metallation of **1i** and **1j**, followed by trapping with I₂.

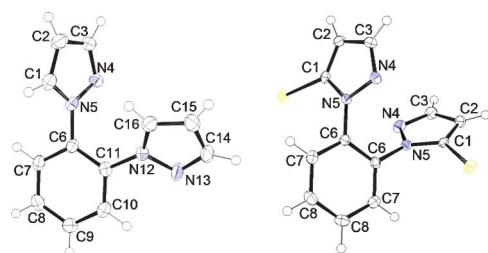
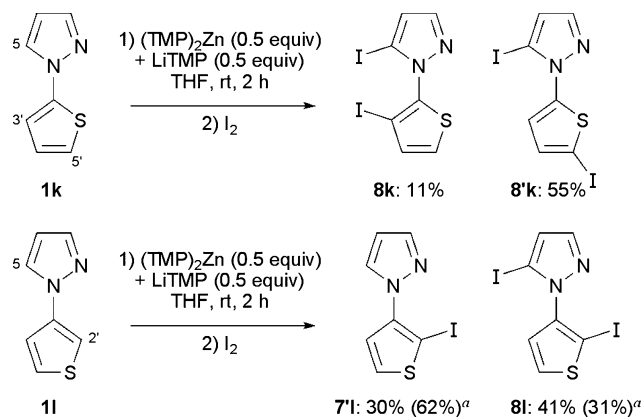


Fig. 2 ORTEP diagrams (30% probability) of **1j** and **6j**.

We then studied the behaviour of the pyrazoles **1k** and **1l** bearing a thiophenyl group (Scheme 4). Upon treatment with 1 : 1 LiTMP–(TMP)₂Zn (0.5 equiv. each), followed by quenching with iodine, the *N*-thiophenyl pyrazole **1k** provided both diiodides **8k** and **8'k** in 11 and 55% yield *via* a 5,3' and 5,5' dimetallation reaction, respectively. This result can be explained by the strong ability of sulfur to acidify the neighbouring hydrogen.^{3h} In the case of **1l**, the acidifying effects of sulfur and pyrazole combine to allow the formation of the monoiodide **7l** (30% yield) in addition to the diiodide **8l** (41% yield, Fig. 3[‡]). Reducing the quantity of base to 0.33 equiv. favoured the formation of **7l**, which was isolated in 62% yield.

The pyrazole **1m**, benefitting from a doubly activated position, was next considered. However, whatever the quantity of base employed (0.33, 0.5 or 1 equiv.), mixtures were obtained (Table 2). It was not possible to favour the formation of the monoiodide **7m** by reducing the amount of base, nor the formation of one



Scheme 4 Deprotonative metallation of **1k** and **1l**, followed by trapping with I₂.^a The deprotonation was performed using (TMP)₂Zn (0.33 equiv.) + LiTMP (0.33 equiv.).

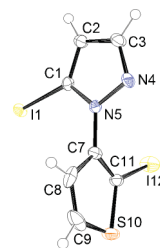


Fig. 3 ORTEP diagram (30% probability) of **8l**.

Table 2 Deprotonative metallation of **1m** followed by trapping with I₂

Entry	x	Products, yields (%)			
1	0.33	7m , 8	8m , 11	8'm , 26	9m , 0
2	0.5	7m , 0	8m , 18	8'm , 34	9m , 12
3	1	7m , 0	8m , 5	8'm , 9	9m , 48

of the diiodides **8m** or **8'm**, but the triiodide **9m** was formed as the main product (48% yield, Fig. 4[‡]) employing 1 equiv. of base. These results could be due to the long range acidifying effect of the chloro group,¹⁸ not only activating the *ortho*, but also the *para* site.

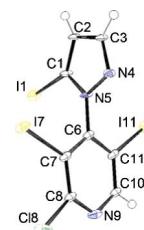




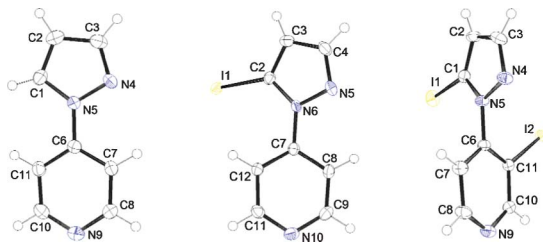
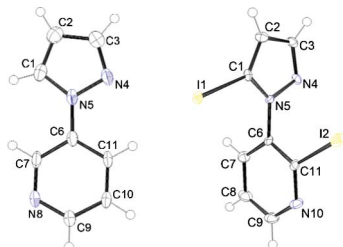


Fig. 4 ORTEP diagram (30% probability) of **9m**.

Table 3 Deprotonative metallation of **1n–q**, followed by trapping with I₂

Entry	1	x	Products, Yields (%)
1	1n 	0.5	7n , 8 8n (3'-I), 60
2	1o 	0.5	8o (2'-I), 28 8'o (4'-I), 30
3	1p 	0.5	7p , 45
4		1	7p , 0 8p (3'-I), 49
5	1q 	0.5	7q , 60

Fewer derivatives are formed in the case of **1n**, which is symmetrical due to the removal of the chloro group. In addition to the 5-iodo derivative **7n**, which was formed in 8% yield, the 5,3'-diodide **8n** was isolated in 60% yield (Table 3, entry 1, Fig. 5†). The isomer **1o** gave a mixture of two iodides where the pyridine ring was substituted at C2 (**8o**, 28% yield, Fig. 6†) and C4 (**8'o**, 30% yield) in a similar overall 58% yield (Table 3, entry 2).

**Fig. 5** ORTEP diagrams (30% probability) of **1n** (left), **7n** (middle) and **8n** (right).**Fig. 6** ORTEP diagrams (30% probability) of **1o** and **8o**.

The substrate **1p** proved less prone to dideprotonation, either because only one pyridine position was activated by the pyrazole nitrogen instead of two in the previous examples, or because the

pyrazole ring hardly belongs to the plane of the pyridine because of repulsion between the nitrogens. Indeed, the monoiodide **7p** was the main product (45% yield) under the conditions used before (Table 3, entry 3). Increasing the base quantity to 1 equiv. led to production of the diiodide **8p** in 49% yield (Table 3, entry 4). Finally, it was possible to exclusively obtain the 5-iodo derivative **7q** (60% yield) starting from the pyrimidin-2-yl substituted pyrazole **1q** (Table 3, entry 5).

Computational aspects

The CH acidity of pyrazoles has been the subject of few studies. The value for 1-propyl-1*H*-pyrazole was experimentally found and reported in 1985.¹⁹ Substituent–CH acidities for methylpyrazoles²⁰ and ethynylpyrazoles²¹ were respectively evaluated in liquid NH₃ and DMSO. In the last case, the results were proved by employing the semi-empirical CNDO 2 method. In the present paper, the DFT calculations of the CH acidity of the different *N*-aryl pyrazoles, both in the gas phase (Scheme 5) and in THF solution (Scheme 6), are presented.

The gas phase acidities ΔG_{acid} and $\text{p}K_{\text{a}}$ values in THF solution of all the pyrazole substrates were calculated using a theoretical approach related to the one previously described.⁸

All the calculations were carried out using the DFT B3LYP method. The geometries were optimized using the 6-31G(d) basis set. No symmetry constraints were imposed. In order to perform stationary points characterization and to calculate zero-point vibrational energies (ZPVE) and thermal corrections to the Gibbs free energy, vibrational frequencies were calculated at the same level of theory. The single point energy calculations were performed using the 6-311+G(d,p) basis set. The gas phase Gibbs energies (G_{298}^0) were calculated for each species using the following equation:

$$G_{298}^0 = E + \text{ZPVE} + H_{0 \rightarrow 298} - TS_{298}^0$$

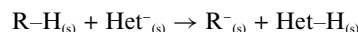
The gas phase acidities ΔG_{acid} were determined as the Gibbs energies of deprotonation of the substrates R–H (R–H_(g) → R[−]_(g) + H⁺_(g)) by the following formula:

$$\Delta G_{\text{acid}} = G_{298}^0(\text{R}^-) + G_{298}^0(\text{H}^+) - G_{298}^0(\text{RH})$$

The solvent effects were evaluated using the polarized continuum model (PCM) with the default parameters for THF.²² The cavity was built up using a united atom (UA) model, applied on the atomic radii of the UFF force field. The PCM energies E_{PCM} were calculated at the B3LYP/6-311+G(d,p) level using the geometries optimized for isolated structures. The Gibbs energies in solution G_{s} were calculated for each species using the formula:

$$G_{\text{s}} = G_{298}^0 + E_{\text{PCM}} - E$$

To cancel out possible errors, the $\text{p}K_{\text{a}}$ values were calculated by means of the following homodesmotic reaction:



where Het–H is an appropriate five-membered heterocycle with an experimentally known $\text{p}K_{\text{a}}$ value. In the present work, 1-propyl-1*H*-pyrazole was chosen as the reference compound, since its $\text{p}K_{\text{a}}$ value in THF, found by Fraser *et al.*,¹⁹ 35.9, was supposed to be close to those for the investigated substrates.

characteristics of substances.²³ Linear free energy relationship (LFER) methodology can also be used to study the electronic effects of the substituents on the CH acidity.

In a previous study⁸ the peculiarities concerned with the application of LFER methodology to heterocycles were briefly discussed. In this paper, the heterocycle was considered to this purpose as a single system, in which the substituent and the reaction centre interact. The main points of interest are: (i) practically, the influence of the X substituent nature of *N*-substituted pyrazoles on the pK_a at the most acidic 5 position (Table 4, entries 1–9), and (ii) theoretically, the influence of the Y substituent nature of *N*-(4-substituted phenyl)pyrazoles on the pK_a at the 2' position (Table 4, entries 10–17). The data show that there is a correlation between the nature (electron-donating or electron-withdrawing) of the substituent X or Y and the pK_a change.

Unfortunately, this study was restricted by a lack of data on LFER constants.²³ As pure *ortho*-, *meta*- and *para*-positions do not exist for five-membered rings, the Jaffe's approach was employed to describe the substituent effects in these "unconventional" five-membered rings according to:

Property = $a_1 + a_2 \sigma_m + a_3 \sigma_p$ (where a_i are fitted constants).

The best equation within the Jaffe's method for the most acidic 5 position of 1-phenyl-1*H*-pyrazole and the compounds **1a**, **1c**, **1f**, **1g**, **1n** and **1o** is as follows (compounds **1p** and **1q** with strong steric interactions were excluded as outliers):

$$pK_a(\text{THF}) = 36.5 - 40.6\sigma_m + 12.5\sigma_p$$

($N = 7$, $r^2 = 0.911$, $\text{rmse} = 0.67$)

According to Swain and Lupton, the electronic effects of a substituent can be split into a field/inductive component (F) and a resonance component (R).²³ The best equation for the same compounds within this approach is:

$$pK_a(\text{THF}) = 37.3 - 29.4 F - 0.3R$$

($N = 7$, $r^2 = 0.902$, $\text{rmse} = 0.71$)

Thereby, among the considered methods, the Jaffe's method gives the best equations for CH acidity prediction. The influence of a substituent on forming the carbanion center is more similar to that for a *meta*-group in a benzene ring as the inductive effects predominate over the resonance effects; a result in agreement with that found earlier for triazoles.^{8b}

Concerning the CH acidity at the 2' position of the compounds **1a–g**, the pyrazole was treated as an ordinary substituent. This led to an excellent correlation, even under one-parametric formalism:

$$pK_a(\text{THF}) = 39.8 - 11.1\sigma_m$$

($N = 8$, $r^2 = 0.990$, $\text{rmse} = 0.38$)

The best equations within the Swain's and Jaffe's approaches proved to be respectively:

$$pK_a(\text{THF}) = 39.8 - 11.4F - 3.7R$$

($N = 8$, $r^2 = 0.994$, $\text{rmse} = 0.34$)

$$pK_a(\text{THF}) = 39.7 - 10.3\sigma_m - 0.5\sigma_p$$

($N = 8$, $r^2 = 0.991$, $\text{rmse} = 0.40$)

So, the correlation between the calculated and predicted pK_a values of pyrazoles using LFER equations (Fig. 7) gives us the

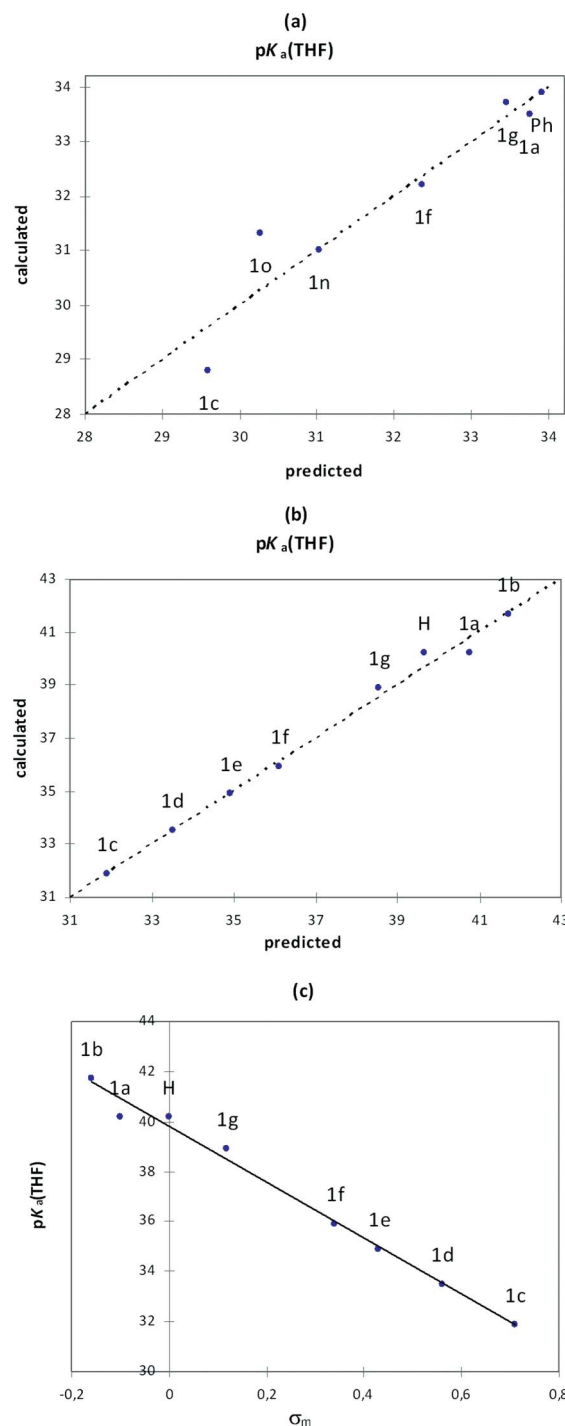


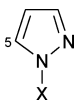
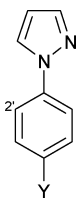
Fig. 7 The correlation between the calculated and predicted pK_a values of pyrazoles in THF solution using equations within the Jaffe method for (a) Table 4, entries 1–7, and (b) Table 4, entries 10–17, and (c) regression of $pK_a(\text{THF})$ versus σ_m for Table 4, entries 10–17.

opportunity to predict their reactivity semi-quantitatively at low computational cost.

Discussion

The calculations show that the investigated *N*-aryl and *N*-heteroaryl pyrazoles possess several deprotonation sites.

Table 4 Calculated $pK_a(\text{THF})$ values for the pyrazoles and substituent constants²³

Entry	Compound	X or Y	$pK_a(\text{THF})$	σ_m	σ_p	F	R	
1		1a	Ph	33.9	0.06	-0.01	0.12	-0.13
2		1c	4- ^t BuC ₆ H ₄	33.5	0.07	0.01	0.12	-0.11
3		1f	4-O ₂ NC ₆ H ₄	28.8	0.25	0.26	0.26	0.00
4		1g	4-FC ₆ H ₄	32.2	0.12	0.06	0.17	-0.11
5		1n	4-MeOC ₆ H ₄	33.7	0.05	-0.08	0.13	-0.21
6		1o	pyridin-4-yl	31.0	0.27	0.44	0.21	0.23
7		1p	pyridin-3-yl	31.3	0.23	0.25	0.24	0.01
8		1q	pyridin-2-yl	35.0	0.33	0.17	0.40	-0.23
9			pyrimidin-2-yl	34.0	0.23	0.53	0.13	0.40
10		1a	H	40.2	0.00	0.00	0.00	0.00
11		1b	^t Bu	40.2	-0.10	-0.20	-0.02	-0.18
12		1c	NMe ₂	41.7	-0.16	-0.83	0.15	-0.98
13		1d	NO ₂	31.9	0.71	0.78	0.65	0.13
14		1e	CN	33.5	0.56	0.66	0.51	0.15
15		1f	CF ₃	34.9	0.43	0.54	0.38	0.16
16		1g	F	35.9	0.34	0.06	0.45	-0.39
17		1g	OMe	38.9	0.12	-0.27	0.29	-0.56

Nevertheless, except when thiophen-3-yl and 2-chloropyridin-4-yl are grafted on the pyrazole 1 position, the most acidic site corresponds to the 5 position of the pyrazole ring. When the gas phase and THF solution CH acidities of the pyrazoles are compared, a correlation can be easily found and the most acidic position remains the same. These results are in good agreement with the corresponding experimental data. Indeed, 1-(thiophen-3-yl)-1*H*-pyrazole (**1l**) is at least deprotonated at its most acidic C2' position, and all the other compounds studied are at least iodinated at C5. The exception is 1-(2-chloropyridin-4-yl)-1*H*-pyrazole (**1m**), which is not predominantly functionalized at its most acidic site, a result that could be related to the size of both the base and the chloro group.

Compared with 1-phenyl-1*H*-pyrazole, the derivatives bearing a nitro, a cyano, a trifluoromethyl and, to a lesser extent, a fluoro group at the 4 position of the phenyl ring (compounds **1c–f**) have a higher CH acidity in THF solution at C5; the *tert*-butyl and methoxy group (compounds **1a**, **1g** and **1h**) have nearly no effect, and the dimethylamino group (compound **1b**) decreases this acidity (Scheme 6). Thus, according to calculations, electron-withdrawing groups are expected to favour the deprotonation on the pyrazole ring, whereas the electron-donating groups should disfavour it. The experimental results are in accordance with these predictions, since the compounds **1a**, **b** behave as 1-phenyl-1*H*-pyrazole, mainly leading to the 5-iodo derivatives, whereas diiodides are obtained when starting from the compounds **1d–h** (Table 1).

It can also be deduced from the calculations that the CH acidity at C5 increases with the introduction of a pyridin-4-yl (compounds **1m** and **1n**), a pyridin-3-yl (compound **1o**) and, to a lesser extent, a thiophen-2-yl group (compound **1k**) on its 1 position. No change is observed with a thiophen-3-yl group (compound **1l**). In contrast, when a pyridin-2-yl (compound **1p**) or a pyrimidin-2-yl (compound **1q**) is present, this acidity decreases, a result that could be related to the presence of the nitrogen(s) of these groups at a position close to the C5 site (Scheme 6). Experimentally, diiodides are more easily obtained from the compounds **1m–o** and **1k**, which have a stronger CH acidity at C5, whereas monoiodides

are formed as the main products from the compounds **1p** and **1q**, which have a weaker CH acidity at C5 (compound **1h** has an intermediate behaviour) (Table 2 and 3).

These results tend to show that metallation at C5 occurs first; a second (and possibly a third) metallation could then take place, according to the mechanism depicted in Scheme 2. Indeed, the second metallation does not necessarily take place at the second most acidic position. One example is the reaction of 1-(4-fluorophenyl)-1*H*-pyrazole (**1f**), for which the second most acidic phenyl site is C3' and the main product the 5,2'-diiodinated derivative **3f** (Table 1, entry 6).

Conclusions

Attempts to rationalize the outcome of the deprotonation reactions of *N*-aryl and *N*-heteroaryl pyrazoles using the TMP-based mixed lithium–zinc combination were performed using the CH acidities of the substrates in THF solution, calculated using a continuum solvation model. Even if the approach has limits, mainly due to the lack of mechanistic information concerning such reactions, in most cases it proved to be efficient in predicting the first deprotonation sites. In addition, the study carried out with *N*-(4-substituted phenyl) pyrazoles allowed the identification, both experimentally and theoretically, of a *meta* acidifying effect,¹² from groups such as cyano, trifluoromethyl, fluoro and methoxy.

Experimental

Syntheses: general methods

Metallation reactions were performed under an argon atmosphere. THF was distilled over sodium/benzophenone. Column chromatography separations were achieved on silica gel (40–63 μm). Melting points were measured on a Kofler apparatus. IR spectra were taken on a Perkin–Elmer Spectrum 100 spectrometer. ¹H and ¹³C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer at 300 and 75 MHz,

respectively. ^1H chemical shifts (δ) are given in ppm relative to the solvent residual peak, ^{13}C chemical shifts are relative to the central peak of the solvent signal,²⁴ and coupling constants (J) are given in Hz. Mass spectra (HRMS) measurements were performed at the CRMPO (Centre Régional de Mesures Physiques de l'Ouest) of Rennes using either a Waters Q-TOF 2 or a Bruker micrOTOF Q II instrument in positive electrospray CI mode.

1-[4-(*tert*-Butyl)phenyl]-1*H*-pyrazole (1a). This was prepared from 1-bromo-4-*tert*-butylbenzene using a described procedure¹⁰ (reaction time: 115 h). Yield: 82%. Colourless liquid. IR (ATR): 2962, 2905, 2867, 1524, 1394, 1034, 937, 836, 746 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 1.40 (s, 9H), 6.49 (dd, 1H, $J = 1.5$ and 2.0), 7.51 and 7.67 (AB, d, 4H, $J = 8.8$), 7.78 (d, 1H, $J = 1.5$), 7.94 (d, 1H, $J = 2.0$). ^{13}C NMR (CDCl_3 , 75 MHz) 31.4 (3C), 34.6, 107.4, 119.0 (2C), 126.3 (2C), 126.8, 137.9, 140.9, 149.6. These values are consistent with those reported in the literature.²⁵

1-[4-(Dimethylamino)phenyl]-1*H*-pyrazole (1b). This was prepared from 1-bromo-4-(dimethylamino)benzene using a described procedure¹⁰ (reaction time: 115 h). Yield: 45%. White solid (mp = 94 °C). IR (ATR): 1744, 1525, 1354, 1226, 936, 816, 754 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 2.98 (s, 6H), 6.41 (dd, 1H, $J = 1.6$ and 2.3), 6.77 and 7.51 (AB, d, 4H, $J = 9.1$), 7.67 (d, 1H, $J = 1.6$), 7.79 (d, 1H, $J = 2.3$). ^{13}C NMR (CDCl_3 , 75 MHz) 40.8 (2C), 106.8, 112.8 (2C), 120.8 (2C), 126.7, 130.8, 140.2, 149.4. These values are consistent with those reported in the literature.²⁶

1-(4-Nitrophenyl)-1*H*-pyrazole (1c). This was prepared from 1-bromo-4-nitrobenzene using a described procedure¹⁰ (reaction time: 160 h). Yield: 42%. Yellow solid (mp = 174 °C). IR (ATR): 1740, 1366, 1239, 1217, 1205, 749 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.55 (dd, 1H, $J = 1.8$ and 2.6), 7.79 (d, 1H, $J = 1.8$), 7.88 and 8.33 (AB, d, 4H, $J = 9.3$), 8.04 (d, 1H, $J = 2.6$). ^{13}C NMR (CDCl_3 , 75 MHz) 109.5, 118.7 (2C), 125.5 (2C), 127.2, 142.9, 144.5, 145.5. These values are consistent with those reported in the literature.¹⁰

1-(4-Cyanophenyl)-1*H*-pyrazole (1d). This was prepared from 4-bromobenzonitrile using a described procedure¹⁰ (reaction time: 144 h). Yield: 73%. White solid (mp = 86 °C). IR (ATR): 2971, 1738, 1366, 1217, 748 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.52 (dd, 1H, $J = 1.8$ and 2.6), 7.73 and 7.83 (AB, d, 4H, $J = 9.0$), 7.76 (d, 1H, $J = 0.5$ and 1.8), 7.99 (dd, 1H, $J = 0.5$ and 2.6). ^{13}C NMR (CDCl_3 , 75 MHz) 109.2, 109.6, 118.5, 119.0 (2C), 126.9, 133.8 (2C), 142.5, 143.0. These values are consistent with those reported in the literature.¹⁰

1-[4-(Trifluoromethyl)phenyl]-1*H*-pyrazole (1e). This was prepared from 1-bromo-4-(trifluoromethyl)benzene using a described procedure¹⁰ (reaction time: 94 h). Yield: 42%. White solid (mp = 96 °C). IR (ATR): 1739, 1217, 1106, 1068, 822, 755 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.52 (dd, 1H, $J = 1.8$ and 2.5), 7.72 and 7.84 (AB, d, 4H, $J = 8.5$), 7.77 (dd, 1H, $J = 0.5$ and 1.8), 7.99 (dd, 1H, $J = 0.5$ and 2.5). ^{13}C NMR (CDCl_3 , 75 MHz) 108.6, 118.9 (2C), 124.0 (q, $J_{\text{F}} = 272$), 126.8 (q, 2C, $J_{\text{F}} = 4$), 126.9, 128.3 (q, $J_{\text{F}} = 33$), 142.1, 142.6. ^{19}F NMR (CDCl_3 , 282 MHz) -62.3 (3F). These values are consistent with those reported in the literature.¹⁰

1-(4-Fluorophenyl)-1*H*-pyrazole (1f). This was prepared from 1-bromo-4-fluorobenzene using a described procedure¹⁰ (reaction

time: 24 h). Yield: 39%. White solid (mp < 50 °C). IR (ATR): 3124, 1741, 1521, 1508, 1394, 1218, 832, 747 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.47 (dd, 1H, $J = 1.8$ and 2.3), 7.15 (dd, 2H, $J = 9.2$ and $J_{\text{F}} = 8.2$), 7.66 (dd, 2H, $J = 9.2$ and $J_{\text{F}} = 4.7$), 7.72 (d, 1H, $J = 1.8$), 7.86 (d, 1H, $J = 2.3$). ^{13}C NMR (CDCl_3 , 75 MHz) 107.7, 116.1 (2C, d, $J_{\text{F}} = 23$), 120.9 (2C, d, $J_{\text{F}} = 8$), 126.9, 136.6, 141.1, 159.4 (d, $J_{\text{F}} = 246$). ^{19}F NMR (CDCl_3 , 282 MHz) -115.8. These values are consistent with those reported in the literature.²⁷

1-(4-Methoxyphenyl)-1*H*-pyrazole (1g). This was prepared from 4-iodoanisole using a described procedure¹⁰ (reaction time: 42 h). Yield: 39%. Yellow solid (mp = 42 °C). IR (ATR): 1741, 1375, 1230, 830 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 3.83 (s, 3H), 6.43 (dd, 1H, $J = 1.9$ and 2.3), 6.96 and 7.58 (AB, d, 4H, $J = 9.1$), 7.69 (dd, 1H, $J = 0.5$ and 1.9), 7.82 (dd, 1H, $J = 0.5$ and 2.3). ^{13}C NMR (CDCl_3 , 75 MHz) 55.7, 107.3, 114.6 (2C), 121.0 (2C), 126.9, 134.1, 140.7, 158.3. These values are consistent with those reported in the literature.¹⁰

1-(3-Methoxyphenyl)-1*H*-pyrazole (1h). This was prepared from 3-iodoanisole using a described procedure¹⁰ (reaction time: 91 h). Yield: 93%. Colourless liquid. IR (ATR): 3003, 2937, 2837, 1606, 1594, 1392, 1225, 1044, 946, 843, 746 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 3.80 (s, 3H), 6.41 (dd, 1H, $J = 1.8$ and 2.5), 6.79 (ddd, 1H, $J = 1.0$, 2.5 and 8.1), 7.19 (ddd, 1H, $J = 1.0$, 2.0 and 8.0), 7.30 (m, 2H), 7.70 (dd, 1H, $J = 0.5$ and 1.8), 7.87 (dd, 1H, $J = 0.5$ and 2.5). ^{13}C NMR (CDCl_3 , 75 MHz) 55.5, 105.0, 107.7, 111.1, 112.4, 127.0, 130.2, 141.1, 141.3, 160.5. These values are consistent with those reported in the literature.²⁸

1,1'-(1,4-Phenylene)bis(1*H*-pyrazole) (1i). This was prepared from 1,4-diiodobenzene (5 equiv. of pyrazole were employed) using a described procedure¹⁰ (reaction time: 260 h). Yield: 31%. White solid (mp = 180 °C). IR (ATR): 1742, 1529, 1392, 1330, 1105, 936, 836, 757 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.49 (dd, 2H, $J = 1.9$ and 2.4), 7.74 (dd, 2H, $J = 0.4$ and 1.9), 7.78 (s, 4H), 7.94 (dd, 2H, $J = 0.4$ and 2.4). ^{13}C NMR (CDCl_3 , 75 MHz) 108.0 (2C), 120.1 (4C), 126.8 (2C), 138.4 (2C), 141.4 (2C). These values are consistent with those reported in the literature.¹⁰

1,1'-(1,2-Phenylene)bis(1*H*-pyrazole) (1j). This was prepared from 1,2-diiodobenzene (3 equiv. of pyrazole were employed) using a described procedure¹⁰ (reaction time: 24 h). Yield: 76%. White solid (mp = 70 °C). IR (ATR): 1738, 1366, 1217, 759 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.29 (dd, 2H, 1.9 and 2.4), 7.00 (dd, 2H, 0.5 and 2.4), 7.51 (m, 2H), 7.68 (m, 2H), 7.70 (dd, 2H, 0.5 and 1.9). ^{13}C NMR (CDCl_3 , 75 MHz) 107.6 (2C), 127.1 (2C), 129.0 (2C), 130.6 (2C), 134.7 (2C), 141.3 (2C). These values are consistent with those reported in the literature.²⁹

1-(Thiophen-2-yl)-1*H*-pyrazole (1k). This was prepared from 2-bromothiophene using a described procedure¹⁰ (reaction time: 24 h). Yield: 52%. Colourless liquid. IR (ATR): 3109, 1737, 1556, 1465, 1387, 1043, 918, 745 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.41 (dd, 1H, $J = 1.6$ and 2.4), 6.93 (dd, 1H, $J = 4.6$ and 4.6), 7.02 (d, 2H, $J = 4.6$), 7.66 (d, 1H, $J = 0.5$ and 1.6), 7.79 (dd, 1H, $J = 0.5$ and 2.4). ^{13}C NMR (CDCl_3 , 75 MHz) 107.8, 114.0, 120.2, 126.1, 128.1, 141.2, 143.8. These values are consistent with those reported in the literature.¹⁰

1-(Thiophen-3-yl)-1*H*-pyrazole (1l). This was prepared from 3-bromothiophene using a described procedure¹⁰ (reaction time:

72 h). Yield: 64%. Colourless liquid. IR (ATR): 3111, 1740, 1557, 1397, 1035, 854, 767, 744 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.41 (dd, 1H, $J = 1.9$ and 2.4), 7.34–7.40 (m, 3H), 7.67 (dd, 1H, $J = 1.9$ and 0.6), 7.80 (dd, 1H, $J = 0.6$ and 2.4). ^{13}C NMR (CDCl_3 , 75 MHz) 107.0, 110.5, 120.2, 126.5, 127.4, 139.8, 140.6. These values are consistent with those reported in the literature.¹⁰

1-(2-Chloropyridin-4-yl)-1H-pyrazole (1m). This was prepared from 4-bromo-2-chloropyridine using a described procedure¹⁰ (reaction time: 24 h). Yield: 60%. White solid (mp = 112 °C). IR (ATR): 2971, 1740, 1595, 1570, 1381, 1217, 1084, 836, 750 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.55 (dd, 1H, $J = 1.8$ and 2.6), 7.56 (dd, 1H, $J = 1.8$ and 5.6), 7.71 (d, 1H, $J = 1.8$), 7.79 (d, 1H, $J = 1.8$), 8.0 (d, 1H, $J = 2.6$), 8.42 (d, 1H, $J = 5.6$). ^{13}C NMR (CDCl_3 , 75 MHz) 109.8, 111.5, 112.9, 126.9, 143.2, 148.0, 151.0, 153.1. HRMS (ESI): calcd for $\text{C}_8\text{H}_7\text{ClN}_3$ [$\text{M} + \text{H}$]⁺ 180.0328, found 180.0321.

1-(Pyridin-4-yl)-1H-pyrazole (1n). This was prepared from 4-bromopyridine hydrochloride (1 additional equivalent of Cs_2CO_3 was used) using a described procedure¹⁰ (reaction time: 24 h). Yield: 61%. White solid (mp = 84 °C). IR (ATR): 2971, 1738, 1595, 1366, 1217, 1035, 817, 757 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.48 (dd, 1H, $J = 1.7$ and 2.6), 7.59 (br d, 2H, $J = 5.5$), 7.73 (dd, 1H, $J = 1.7$ and 0.4), 8.00 (dd, 1H, $J = 2.6$ and 0.4), 8.61 (br d, 2H, $J = 5.5$). ^{13}C NMR (CDCl_3 , 75 MHz) 109.1, 112.6 (2C), 126.6, 142.5, 145.9, 151.2 (2C). HRMS (ESI): calcd for $\text{C}_8\text{H}_8\text{N}_3$ [$\text{M} + \text{H}$]⁺ 146.0718, found 146.0719.

1-(Pyridin-3-yl)-1H-pyrazole (1o). This was prepared from 3-bromopyridine using a described procedure¹⁰ (reaction time: 26 h). Yield: 67%. Yellow solid (mp < 50 °C). IR (ATR): 3115, 1739, 1586, 1521, 1391, 1045, 934, 748 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.53 (dd, 1H, $J = 1.8$ and 2.5), 7.44 (dd, 1H, $J = 4.7$ and 8.3), 7.78 (dd, 1H, $J = 0.4$ and 1.8), 7.97 (dd, 1H, $J = 0.4$ and 2.5), 8.07 (ddd, 1H, $J = 1.3$, 2.6 and 8.3), 8.55 (dd, 1H, $J = 1.3$ and 4.7), 9.00 (d, 1H, $J = 2.6$). ^{13}C NMR (CDCl_3 , 75 MHz) 108.5, 124.1, 126.6, 126.9, 136.6, 140.6, 142.1, 147.6. These values are consistent with those reported in the literature.¹⁰

1-(Pyridin-2-yl)-1H-pyrazole (1p). This was prepared from 2-bromopyridine using a described procedure¹⁰ (reaction time: 24 h). Yield: 76%. White solid (mp < 50 °C). IR (ATR): 3127, 3093, 2971, 1738, 1590, 1453, 1388, 1198, 936, 759 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.46 (dd, 1H, $J = 1.7$ and 2.6), 7.17 (br dd, 1H, $J = 4.9$ and 7.3), 7.73 (dd, 1H, $J = 0.7$ and 1.7), 7.80 (br ddd, 1H, $J = 1.8$, 7.3 and 8.3), 7.98 (br d, 1H, $J = 8.3$), 8.40 (br dd, 1H, $J = 1.8$ and 4.9), 8.57 (dd, 1H, $J = 0.7$ and 2.6). ^{13}C NMR (CDCl_3 , 75 MHz) 107.9, 112.5, 121.5, 127.1, 138.9, 142.1, 148.1, 151.7. These values are consistent with those reported in the literature.³⁰

1-(Pyrimidin-2-yl)-1H-pyrazole (1q). This was prepared from 2-chloropyrimidine using a described procedure¹⁰ (reaction time: 72 h). Yield: 73%. White solid (mp = 80 °C). IR (ATR): 2971, 1738, 1456, 1434, 1366, 1229, 1217, 931, 765 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.50 (dd, 1H, $J = 1.6$ and 2.7), 7.20 (t, 1H, $J = 4.8$), 7.82 (dd, 1H, $J = 0.6$ and 0.9), 8.59 (dd, 1H, $J = 0.6$ and 2.7), 8.74 (d, 2H, $J = 4.8$). ^{13}C NMR (CDCl_3 , 75 MHz) 108.6, 118.6, 129.0, 143.5, 155.8, 158.7 (2C). These values are consistent with those reported in the literature.³¹

General procedure for the deprotonation followed by iodination. To a stirred, cooled (0 °C) solution of 2,2,6,6-

tetramethylpiperidine (0.25 mL, 1.5 mmol) in THF (5 mL) was added BuLi (about 1.6 M hexanes solution, 1.5 mmol). After 15 min at 0 °C, $\text{ZnCl}_2 \cdot \text{TMEDA}$ (0.125 g, 0.5 mmol) was added, and the mixture was stirred for 15 min at this temperature before the introduction of the substrate (1.0 mmol). After 2 h at room temperature, a solution of I_2 (0.37 g, 1.5 mmol) in THF (5 mL) was added. The mixture was stirred overnight before addition of an aqueous saturated solution of $\text{Na}_2\text{S}_2\text{O}_3$ (10 mL) and extraction with Et_2O (3×20 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4 , filtered and concentrated under reduced pressure before purification by flash chromatography on silica gel.

1-[4-(*tert*-Butyl)phenyl]-5-iodo-1H-pyrazole (2a). This was prepared from **1a** following the general procedure and was obtained as a yellow liquid (54% yield; 4% using 3.0 mmol of 2,2,6,6-tetramethylpiperidine, 3.0 mmol of BuLi and 1.0 mmol of $\text{ZnCl}_2 \cdot \text{TMEDA}$). IR (ATR): 2962, 2905, 2868, 1511, 1385, 1079, 957, 917, 836, 773 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 1.36 (s, 9H), 6.61 (d, 1H, $J = 1.9$), 7.34 and 7.49 (AB, d, 4H, $J = 9.0$), 7.67 (d, 1H, $J = 1.9$). ^{13}C NMR (CDCl_3 , 75 MHz) 31.4 (3C), 34.9, 80.8, 117.3, 125.7 (2C), 125.8 (2C), 137.7, 142.6, 151.8. HRMS (ESI): calcd for $\text{C}_{13}\text{H}_{16}\text{IN}_2$ [$\text{M} + \text{H}$]⁺ 327.0358, found 327.0354.

1-[4-(*tert*-Butyl)-2-iodophenyl]-5-iodo-1H-pyrazole (3a). This was prepared from **1a** following the general procedure and was obtained as a yellow liquid (28% yield; 66% using 3.0 mmol of 2,2,6,6-tetramethylpiperidine, 3.0 mmol of BuLi and 1.0 mmol of $\text{ZnCl}_2 \cdot \text{TMEDA}$). IR (ATR): 2962, 2925, 2870, 1600, 1517, 1392, 1364, 1202, 1109, 831 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 1.35 (s, 9H), 6.62 (d, 1H, $J = 1.9$), 7.26 (d, 1H, $J = 8.2$), 7.47 (dd, 1H, $J = 2.1$ and 8.2), 7.69 (d, 1H, $J = 1.9$), 7.92 (d, 1H, $J = 2.1$). ^{13}C NMR (CDCl_3 , 75 MHz) 31.3 (3C), 35.0, 83.6, 98.2, 116.3, 126.2, 129.1, 136.8, 140.5, 142.8, 155.1. HRMS (ESI): calcd for $\text{C}_{13}\text{H}_{15}\text{I}_2\text{N}_2$ [$\text{M} + \text{H}$]⁺ 452.9325, found 452.9328.

1-[4-(Dimethylamino)phenyl]-5-iodo-1H-pyrazole (2b). This was prepared from **1b** following the general procedure and was obtained as a white solid (54% yield; mp = 140 °C). IR (ATR): 2925, 1728, 1609, 1535, 1370, 1187, 959, 808, 784 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 3.02 (s, 6H), 6.57 (d, 1H, $J = 1.9$), 6.74 and 7.31 (AB, d, 4H, $J = 9.1$), 7.64 (d, 1H, $J = 1.9$). ^{13}C NMR (CDCl_3 , 75 MHz) 40.6 (2C), 82.2, 111.7 (2C), 116.5, 127.4 (2C), 129.5, 142.2, 150.5. HRMS (ESI): calcd for $\text{C}_{11}\text{H}_{13}\text{IN}_3$ [$\text{M} + \text{H}$]⁺ 314.0154, found 314.0152.

1-[4-(Dimethylamino)-2-iodophenyl]-5-iodo-1H-pyrazole (3b). This was prepared from **1b** following the general procedure and was obtained as a white solid (28% yield; 67% using 3.0 mmol of 2,2,6,6-tetramethylpiperidine, 3.0 mmol of BuLi and 1.0 mmol of $\text{ZnCl}_2 \cdot \text{TMEDA}$; mp = 186 °C). IR (ATR): 2923, 2853, 1732, 1597, 1515, 1446, 1357, 1061, 1010, 954 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 3.01 (s, 6H), 6.59 (d, 1H, $J = 1.9$), 6.69 (dd, 1H, $J = 2.8$ and 8.8), 7.13 (d, 1H, $J = 8.8$), 7.15 (d, 1H, $J = 2.8$), 7.67 (d, 1H, $J = 1.9$). ^{13}C NMR (CDCl_3 , 75 MHz) 40.4 (2C), 85.1, 99.3, 111.5, 115.8, 121.5, 129.3, 131.4, 142.4, 151.5. HRMS (ESI): calcd for $\text{C}_{11}\text{H}_{12}\text{I}_2\text{N}_3$ [$\text{M} + \text{H}$]⁺ 439.9121, found 439.9124.

1-[4-(Dimethylamino)phenyl]-5-phenyl-1H-pyrazole (4b). A solution of **2b** (0.16 g, 0.5 mmol), phenylboronic acid (0.30 g,

2.5 mmol), and CsF (0.15 g, 1.0 mmol) in dioxane (5 mL) was degassed with Ar for 30 min before the addition of Pd(dba)₂ (14 mg, 25 μmol), and PPh₃ (26 mg, 0.10 mmol). The resulting mixture was heated at 105 °C for 12 h, before cooling and dilution with Et₂O (30 mL), washing with H₂O and extraction with CH₂Cl₂ (3 × 20 mL). After drying over Na₂SO₄, the solvent was evaporated under reduced pressure, and the coupled product **4b** was isolated by purification by flash chromatography on silica gel as a white solid (73% yield; mp = 140 °C). IR (ATR): 2891, 2805, 1624, 1524, 1361, 1068, 924, 803 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) 2.96 (s, 6H), 6.48 (d, 1H, *J* = 1.4), 6.65 (d, 2H, *J* = 8.8), 7.15 (d, 2H, *J* = 8.8), 7.25–7.29 (m, 5H), 7.68 (d, 1H, *J* = 1.4). ¹³C NMR (CDCl₃, 75 MHz) 40.8 (2C), 107.1, 112.4 (2C), 126.3 (2C), 128.0, 128.5 (2C), 128.8 (2C), 131.0, 132.4, 139.7, 142.8, 149.6. HRMS (ESI): calcd for C₁₇H₁₈N₃ [M + H]⁺ 264.1501, found 264.1499.

1-(4-Cyano-2-iodophenyl)-5-iodo-1H-pyrazole (3d). This was prepared from **1d** following the general procedure and was obtained as a white solid (65% yield; mp = 112 °C). IR (ATR): 2924, 2852, 2230, 1608, 1525, 1493, 1389, 1026, 957, 837 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) 6.67 (d, 1H, *J* = 1.7), 7.45 (d, 1H, *J* = 8.1), 7.73 (d, 1H, *J* = 1.8), 7.79 (dd, 1H, *J* = 1.8 and 8.1), 8.25 (d, 1H, *J* = 1.7). ¹³C NMR (CDCl₃, 75 MHz) 82.8, 98.8, 115.2, 116.2, 117.1, 130.3, 132.6, 142.9, 143.5, 146.7. HRMS (ESI): calcd for C₁₀H₆I₂N₃ [M + H]⁺ 421.8651, found 421.8655.

5-Iodo-1-[2-iodo-4-(trifluoromethyl)phenyl]-1H-pyrazole (3e). This was prepared from **1e** following the general procedure and was obtained as a yellow liquid (84% yield). IR (ATR): 1604, 1501, 1397, 1383, 1317, 1169, 1126, 1070, 957, 709 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) 6.65 (d, 1H, *J* = 1.8), 7.46 (d, 1H, *J* = 8.2), 7.72 (d, 1H, *J* = 1.7), 7.76 (dd, 1H, *J* = 1.7 and 8.2), 8.21 (d, 1H, *J* = 1.8). ¹³C NMR (CDCl₃, 75 MHz) 83.0, 98.6, 116.7, 122.3 (q, *J*_F = 273), 125.9 (q, *J*_F = 4), 130.1, 132.9 (q, *J*_F = 33), 136.6 (q, *J*_F = 4), 143.1, 146.0. ¹⁹F (CDCl₃, 282 MHz) -62.6 (3F). HRMS (ESI): calcd for C₁₀H₆F₃I₂N₂ [M + H]⁺ 464.8573, found 464.8572.

1-(4-Fluoro-2-iodophenyl)-5-iodo-1H-pyrazole (3f). This was prepared from **1f** following the general procedure and was obtained as a yellow solid (31% yield; 57% using 3.0 mmol of 2,2,6,6-tetramethylpiperidine, 3.0 mmol of BuLi and 1.0 mmol of ZnCl₂·TMEDA; mp = 78 °C). IR (ATR): 3097, 1589, 1492, 1393, 1202, 1023, 958, 862 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) 6.63 (d, 1H, *J* = 1.9), 7.19 (ddd, 1H, *J* = 2.7, 8.7 and *J*_F = 7.7), 7.32 (dd, 1H, *J* = 8.7 and *J*_F = 5.3), 7.67 (dd, 1H, *J* = 2.7 and *J*_F = 7.7), 7.70 (d, 1H, *J* = 1.9). ¹³C NMR (CDCl₃, 75 MHz) 83.7, 98.6 (d, *J*_F = 9), 116.0 (d, *J*_F = 23), 116.5, 126.5 (d, *J*_F = 25), 130.6 (d, *J*_F = 9), 139.4, (d, *J*_F = 4), 143.0, 162.2 (d, *J*_F = 255). ¹⁹F NMR (CDCl₃, 282 MHz) -108.9. HRMS (ESI): calcd for C₉H₆FI₂N₂ [M + H]⁺ 414.8605, found 414.8605.

1-(4-Fluoro-3-iodophenyl)-5-iodo-1H-pyrazole (3'f). This was prepared from **1f** following the general procedure and was obtained as a brown solid (22% yield using 3.0 mmol of 2,2,6,6-tetramethylpiperidine, 3.0 mmol of BuLi and 1.0 mmol of ZnCl₂·TMEDA; mp = 61 °C). IR (ATR): 3097, 2924, 1591, 1491, 1389, 1038, 965, 819 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) 6.62 (d, 1H, *J* = 1.8), 7.16 (dd, 1H, *J* = 8.9 and *J*_F = 7.3), 7.51 (ddd, 1H, *J* = 2.7, 8.9 and *J*_F = 4.5), 7.67 (d, 1H, *J* = 1.8), 7.93 (dd, 1H, *J* =

2.7 and *J*_F = 5.4). ¹³C NMR (CDCl₃, 75 MHz) 81.0 (d, *J*_F = 28), 81.1, 115.5 (d, *J*_F = 26), 118.0, 128.1 (d, *J*_F = 8), 137.3 (d, *J*_F = 3), 143.2, 143.3, 161.7 (d, *J*_F = 248). ¹⁹F NMR (CDCl₃, 282 MHz) -93.4. HRMS (ESI): calcd for C₉H₆FI₂N₂ [M + H]⁺ 414.8605, found 414.8627.

5-Iodo-1-(2-iodo-4-methoxyphenyl)-1H-pyrazole (3g). This was prepared from **1g** following the general procedure and was obtained as a white solid (60% yield; mp = 98 °C). IR (ATR): 3005, 2925, 2852, 1592, 1567, 1496, 1396, 1384, 1291, 1231, 1221, 1027, 1017, 957, 917 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) 3.86 (s, 3H), 6.61 (d, 1H, *J* = 1.9), 6.98 (dd, 1H, *J* = 2.8 and 8.7), 7.25 (d, 1H, *J* = 8.7), 7.45 (d, 1H, *J* = 2.8), 7.71 (d, 1H, *J* = 1.9). ¹³C NMR (CDCl₃, 75 MHz) 56.0, 84.4, 98.8, 114.6, 116.2, 124.4, 130.0, 136.1, 142.8, 160.6. HRMS (ESI): calcd for C₁₀H₉I₂N₂O [M + H]⁺ 426.8804, found 426.8811.

5-Iodo-1-(3-methoxyphenyl)-1H-pyrazole (2h). This was prepared from **1h** following the general procedure and was obtained as a yellow liquid (12% yield; 70% using 1.0 mmol of 2,2,6,6-tetramethylpiperidine, 1.0 mmol of BuLi and 0.33 mmol of ZnCl₂·TMEDA). IR (ATR): 2961, 2835, 1606, 1593, 1497, 1384, 1219, 1036, 971, 847 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) 3.85 (s, 3H), 6.62 (d, 1H, *J* = 1.9), 6.98 (ddd, 1H, *J* = 0.9, 2.4 and 8.2), 7.06 (dd, 1H, *J* = 2.0 and 2.4), 7.11 (ddd, 1H, *J* = 0.9, 2.0 and 7.9), 7.38 (dd, 1H, *J* = 7.9 and 8.2), 7.68 (d, 1H, *J* = 1.9). ¹³C NMR (CDCl₃, 75 MHz) 55.7, 80.8, 111.8, 115.0, 117.6, 118.6, 129.6, 141.2, 142.7, 159.9. HRMS (ESI): calcd for C₁₀H₁₀IN₂O [M + H]⁺ 300.9838, found 300.9836.

5-Iodo-1-(2-iodo-3-methoxyphenyl)-1H-pyrazole (3h). This was prepared from **1h** following the general procedure and was obtained as a yellow solid (61% yield; 7% using 1.0 mmol of 2,2,6,6-tetramethylpiperidine, 1.0 mmol of BuLi and 0.33 mmol of ZnCl₂·TMEDA; mp = 132 °C). IR (ATR): 3005, 2934, 2836, 1733, 1575, 1472, 1400, 1218, 1130, 971 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) 3.96 (s, 3H), 6.63 (d, 1H, *J* = 1.9), 6.93 (dd, 1H, *J* = 1.2 and 8.4), 6.99 (dd, 1H, *J* = 1.2 and 7.8), 7.44 (dd, 1H, *J* = 7.8 and 8.4), 7.70 (dd, 1H, *J* = 1.9). ¹³C NMR (CDCl₃, 75 MHz) 57.0, 83.4, 91.3, 111.9, 116.5, 122.1, 129.7, 139.8, 142.7, 159.4. HRMS (ESI): calcd for C₁₀H₉I₂N₂O [M + H]⁺ 426.8804, found 426.8810.

1,1' [1,4-(2-Iodophenylene)bis-(1H-5-iodopyrazole)] (5i). This was prepared from **1i** following the general procedure and was obtained as a white solid (61% yield using 3.0 mmol of 2,2,6,6-tetramethylpiperidine, 3.0 mmol of BuLi and 1.0 mmol of ZnCl₂·TMEDA; mp = 174 °C). IR (ATR): 3129, 2924, 2854, 1724, 1592, 1501, 1393, 1372, 954, 917 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) 6.64 (d, 1H, *J* = 1.8), 6.65 (d, 1H, *J* = 1.8), 7.44 (d, 1H, *J* = 8.4), 7.70 (dd, 1H, *J* = 2.3 and 8.4), 7.71 (d, 1H, *J* = 1.8), 7.72 (d, 1H, *J* = 1.8), 8.17 (d, 1H, *J* = 2.3). ¹³C NMR (CDCl₃, 75 MHz) 80.6, 83.6, 98.1, 116.7, 118.7, 126.3, 129.6, 136.7, 141.4, 142.8, 143.1, 143.6. HRMS (ESI): calcd for C₁₂H₈I₃N₄ [M + H]⁺ 588.7883, found 588.7897.

1,1' [1,2-(3-Iodophenylene)bis(1H-5-iodopyrazole)] (5j). This was prepared from **1j** following the general procedure and was obtained as a white solid (37% yield using 3.0 mmol of 2,2,6,6-tetramethylpiperidine, 3.0 mmol of BuLi and 1.0 mmol of ZnCl₂·TMEDA; mp = 214 °C). IR (ATR): 2924, 2853, 1731, 1485,

1455, 1405, 1382, 956, 917 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.44 (d, 1H, $J = 1.9$), 6.45 (d, 1H, $J = 1.9$), 7.37 (dd, 1H, $J = 7.9$ and 8.0), 7.43 (d, 1H, $J = 1.9$), 7.52 (d, 1H, $J = 1.9$), 7.53 (dd, 1H, $J = 1.4$ and 7.9), 8.11 (dd, 1H, $J = 1.4$ and 8.0). ^{13}C NMR (CDCl_3 , 75 MHz) 83.4, 84.4, 100.8, 116.4, 116.8, 129.7, 131.4, 139.3, 140.6, 140.7, 142.8, 143.0. HRMS (ESI): calcd for $\text{C}_{12}\text{H}_8\text{I}_3\text{N}_4$ [$\text{M} + \text{H}$] $^+$ 588.7883, found 588.7904.

1,1'-(1,2-Phenylene)bis(1H-5-iodopyrazole) (6j). This was prepared from **1j** following the general procedure and was obtained as a white solid (37% yield using 3.0 mmol of 2,2,6,6-tetramethylpiperidine, 3.0 mmol of BuLi and 1.0 mmol of $\text{ZnCl}_2 \cdot \text{TMEDA}$; mp = 182 °C). IR (ATR): 3129, 2924, 2854, 1515, 1405, 1384, 958, 917 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.45 (d, 2H, $J = 1.9$), 7.47 (d, 2H, $J = 1.9$), 7.59 (m, 4H). ^{13}C NMR (CDCl_3 , 75 MHz) 82.9 (2C), 116.7 (2C), 129.7 (2C), 129.8 (2C), 137.0 (2C), 142.8 (2C). HRMS (ESI): calcd for $\text{C}_{12}\text{H}_8\text{I}_2\text{N}_4$ [$\text{M} + \text{H}$] $^+$ 462.8917, found 462.8939.

5-Iodo-1-(5-iodothiophen-2-yl)-1H-pyrazole (8'k). This was prepared from **1k** following the general procedure and was obtained as a white solid (55% yield; mp = 64 °C). IR (ATR): 3107, 2923, 1552, 1403, 1364, 1205, 945, 906 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.60 (d, 1H, $J = 1.8$), 6.94 (d, 1H, $J = 4.0$), 7.20 (d, 1H, $J = 4.0$), 7.66 (d, 1H, $J = 1.8$). ^{13}C (CDCl_3 , 75 MHz) 72.6, 83.1, 118.1, 124.7, 135.3, 143.6, 145.7. HRMS (ESI): calcd for $\text{C}_7\text{H}_5\text{I}_2\text{N}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 402.8263, found 402.8272.

5-Iodo-1-(3-iodothiophen-2-yl)-1H-pyrazole (8k). This was identified in an inseparable mixture with the starting material (11% estimated yield). ^1H NMR (CDCl_3 , 300 MHz) 6.64 (d, 1H, $J = 1.9$), 7.10 (d, 1H, $J = 5.7$), 7.40 (d, 1H, $J = 5.7$), 7.73 (d, 1H, $J = 1.9$).

1-(2-Iodothiophen-3-yl)-1H-pyrazole (7l). This was prepared from **1l** following the general procedure and was obtained as a yellow liquid (30% yield; 62% using 1.0 mmol of 2,2,6,6-tetramethylpiperidine, 1.0 mmol of BuLi and 0.33 mmol of $\text{ZnCl}_2 \cdot \text{TMEDA}$). IR (ATR): 3108, 2923, 2853, 1547, 1455, 1392, 1065, 1042, 853 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.46 (dd, 1H, $J = 1.5$ and 2.0), 7.10 (d, 1H, $J = 5.7$), 7.53 (d, 1H, $J = 5.7$), 7.73 (d, 1H, $J = 1.5$), 7.96 (d, 1H, $J = 2.0$). ^{13}C NMR (CDCl_3 , 75 MHz) 66.5, 106.7, 125.3, 130.0, 131.6, 140.9, 143.4. HRMS (ESI): calcd for $\text{C}_7\text{H}_6\text{IN}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 276.9296, found 276.9301.

5-Iodo-1-(2-iodothiophen-3-yl)-1H-pyrazole (8l). This was prepared from **1l** following the general procedure and was obtained as a white solid (41% yield; 31% using 1.0 mmol of 2,2,6,6-tetramethylpiperidine, 1.0 mmol of BuLi and 0.33 mmol of $\text{ZnCl}_2 \cdot \text{TMEDA}$; mp = 104 °C). IR (ATR): 3103, 2922, 2853, 1723, 1534, 1390, 987, 970, 917, 857 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.63 (d, 1H, $J = 1.8$), 6.96 (d, 1H, $J = 5.6$), 7.57 (d, 1H, $J = 5.6$), 7.71 (d, 1H, $J = 1.8$). ^{13}C NMR (CDCl_3 , 75 MHz) 77.9, 83.6, 116.5, 126.8, 131.1, 143.1, 143.2. HRMS (ESI): calcd for $\text{C}_7\text{H}_5\text{I}_2\text{N}_2\text{S}$ [$\text{M} + \text{H}$] $^+$ 402.8263, found 402.8273.

1-(2-Chloropyridin-4-yl)-5-iodo-1H-pyrazole (7m). This was formed from **1m** following the general procedure (8% estimated yield using 1.0 mmol of 2,2,6,6-tetramethylpiperidine, 1.0 mmol of BuLi and 0.33 mmol of $\text{ZnCl}_2 \cdot \text{TMEDA}$) and was identified in an inseparable mixture with the starting material. ^1H NMR (CDCl_3 , 300 MHz) 6.71 (d, 1H, $J = 1.8$), 7.63 (dd, 1H, $J = 1.9$ and

5.5), 7.73 (dd, 1H, $J = 0.5$ and 1.9), 7.74 (d, 1H, $J = 1.8$), 8.50 (dd, 1H, $J = 0.5$ and 5.5).

1-(2-Chloro-3-iodopyridin-4-yl)-5-iodo-1H-pyrazole (8m).

This was formed from **1m** following the general procedure (18% estimated yield; 11% using 1.0 mmol of 2,2,6,6-tetramethylpiperidine, 1.0 mmol of BuLi and 0.33 mmol of $\text{ZnCl}_2 \cdot \text{TMEDA}$; 5% using 3.0 mmol of 2,2,6,6-tetramethylpiperidine, 3.0 mmol of BuLi and 1.0 mmol of $\text{ZnCl}_2 \cdot \text{TMEDA}$) and was identified in an inseparable mixture with **8'm**. ^1H NMR (CDCl_3 , 300 MHz) 6.69 (d, 1H, $J = 1.9$), 7.20 (d, 1H, $J = 5.0$), 7.75 (d, 1H, $J = 1.9$), 8.49 (d, 1H, $J = 5.0$). ^{13}C NMR (CDCl_3 , 75 MHz) 86.2, 100.5, 117.5, 123.0, 141.8, 149.6, 157.2, 159.1.

1-(2-Chloro-5-iodopyridin-4-yl)-5-iodo-1H-pyrazole (8'm).

This was prepared from **1m** following the general procedure and was obtained as a white solid (34% yield; 26% using 1.0 mmol of 2,2,6,6-tetramethylpiperidine, 1.0 mmol of BuLi and 0.33 mmol of $\text{ZnCl}_2 \cdot \text{TMEDA}$; 9% using 3.0 mmol of 2,2,6,6-tetramethylpiperidine, 3.0 mmol of BuLi and 1.0 mmol of $\text{ZnCl}_2 \cdot \text{TMEDA}$; mp = 118 °C). IR (ATR): 3127, 3069, 2922, 2854, 1560, 1532, 1407, 1388, 1107, 1015, 967, 917, 872 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.67 (d, 1H, $J = 1.9$), 7.38 (s, 1H), 7.73 (d, 1H, $J = 1.9$), 8.86 (s, 1H). ^{13}C NMR (CDCl_3 , 75 MHz) 82.0, 94.5, 117.7, 125.6, 144.1, 151.9, 152.3, 158.2. HRMS (ESI): calcd for $\text{C}_8\text{H}_5\text{ClI}_2\text{N}_3$ [$\text{M} + \text{H}$] $^+$ 431.8261, found 431.8260.

1-(2-Chloro-3,5-diiodopyridin-4-yl)-5-iodo-1H-pyrazole (9m).

This was prepared from **1m** following the general procedure and was obtained as a white solid (12% yield; 48% using 3.0 mmol of 2,2,6,6-tetramethylpiperidine, 3.0 mmol of BuLi and 1.0 mmol of $\text{ZnCl}_2 \cdot \text{TMEDA}$; mp = 184 °C). IR (ATR): 2923, 2854, 1724, 1562, 1531, 1451, 1399, 1194, 1109, 1029, 968, 917 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.72 (d, 1H, $J = 1.9$), 7.79 (d, 1H, $J = 1.9$), 8.75 (s, 1H). ^{13}C NMR (CDCl_3 , 75 MHz) 81.3, 95.1, 101.9, 117.7, 144.4, 154.7, 156.4, 156.5. HRMS (ESI): calcd for $\text{C}_8\text{H}_4\text{ClI}_3\text{N}_3$ [$\text{M} + \text{H}$] $^+$ 557.7228, found 557.7241.

5-Iodo-1-(pyridin-4-yl)-1H-pyrazole (7n). This was prepared from **1n** following the general procedure and was obtained as a brown solid (8% yield; mp = 122 °C). IR (ATR): 3120, 3095, 3051, 2923, 2853, 1587, 1575, 1498, 1403, 1403, 1373, 1211, 1074, 1022, 962, 915, 825 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.70 (d, 1H, $J = 1.8$), 7.64 (dd, 2H, $J = 1.6$ and 4.6), 7.74 (d, 1H, $J = 1.8$), 8.74 (dd, 2H, $J = 1.6$ and 4.6). ^{13}C NMR (CDCl_3 , 75 MHz) 79.0, 119.5 (2C), 119.7, 144.1, 146.9, 150.9 (2C). HRMS (ESI): calcd for $\text{C}_8\text{H}_7\text{IN}_3$ [$\text{M} + \text{H}$] $^+$ 271.9685, found 271.9690.

5-Iodo-1-(3-iodopyridin-4-yl)-1H-pyrazole (8n). This was prepared from **1n** following the general procedure and was obtained as a brown solid (60% yield; mp = 115 °C). IR (ATR): 3127, 3041, 1567, 1487, 1395, 1376, 1016, 961, 917, 833 cm^{-1} . ^1H NMR (CDCl_3 , 300 MHz) 6.62 (d, 1H, $J = 1.9$), 7.29 (d, 1H, $J = 5.0$), 7.68 (d, 1H, $J = 1.9$), 8.64 (d, 1H, $J = 5.0$), 9.07 (s, 1H). ^{13}C NMR (CDCl_3 , 75 MHz) 82.2, 96.8, 117.2, 124.5, 143.5, 149.8, 150.1, 158.7. HRMS (ESI): calcd for $\text{C}_8\text{H}_5\text{I}_2\text{N}_3$ [$\text{M} + \text{H}$] $^+$ 397.8651, found 397.8661.

5-Iodo-1-(2-iodopyridin-3-yl)-1H-pyrazole (8o). This was prepared from **1o** following the general procedure and was obtained

as a white solid (28% yield; mp = 138 °C). ¹H NMR (CDCl₃, 300 MHz) 6.68 (d, 1H, *J* = 1.8), 7.43 (dd, 1H, *J* = 4.7 and 7.8), 7.61 (dd, 1H, *J* = 1.9 and 7.8), 7.74 (d, 1H, *J* = 1.8), 8.51 (dd, 1H, *J* = 1.9 and 4.7). ¹³C NMR (CDCl₃, 75 MHz) 83.8, 117.2, 122.2, 123.1, 137.0, 141.1, 143.6, 151.4. HRMS (ESI): calcd for C₈H₅I₂N₃ 396.8573, found 396.8547.

5-Iodo-1-(4-iodopyridin-3-yl)-1H-pyrazole (8'o). This was prepared from **1o** following the general procedure and was obtained as a white solid (30% yield; mp = 175 °C). ¹H NMR (CDCl₃, 300 MHz) 6.68 (d, 1H, *J* = 1.9), 7.75 (d, 1H, *J* = 1.9), 7.95 (d, 1H, *J* = 5.2), 8.32 (d, 1H, *J* = 5.2), 8.50 (s, 1H). ¹³C NMR (CDCl₃, 75 MHz) 83.7, 110.0, 117.1, 134.5, 140.7, 143.7, 149.5, 150.7. HRMS (ESI): calcd for C₈H₅I₂N₃ 396.8573, found 396.8564.

5-Iodo-1-(pyridin-2-yl)-1H-pyrazole (7p). This was prepared from **1p** following the general procedure and was obtained as a colourless liquid (45% yield). IR (ATR): 3059, 3016, 1588, 1577, 1468, 1442, 1404, 1373, 960, 916, 778 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) 6.69 (d, 1H, *J* = 1.6), 7.33 (ddd, 1H, *J* = 1.1, 4.9 and 7.3), 7.71 (d, 1H, *J* = 1.6), 7.77 (br d, 1H, *J* = 8.1), 7.86 (ddd, 1H, *J* = 1.9, 7.3 and 8.1), 8.56 (br d, 1H, *J* = 4.9). ¹³C NMR (CDCl₃, 75 MHz) 77.4, 118.3, 119.5, 123.1, 138.6, 143.5, 147.9, 152.4. HRMS (ESI): calcd for C₈H₆IN₃Na [M+Na]⁺ 293.9504, found 293.9509.

5-Iodo-1-(3-iodopyridin-2-yl)-1H-pyrazole (8p). This was prepared from **1p** following the general procedure and was obtained as a yellow solid (14% yield; 49% using 3.0 mmol of 2,2,6,6-tetramethylpiperidine, 3.0 mmol of BuLi and 1.0 mmol of ZnCl₂·TMEDA; mp = 238 °C). IR (ATR): 3126, 1590, 1565, 1470, 1445, 1403, 1377, 962, 785 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) 6.66 (d, 1H, *J* = 1.8), 7.20 (dd, 1H, *J* = 4.7 and 7.9), 7.73 (d, 1H, *J* = 1.8), 8.33 (dd, 1H, *J* = 1.6 and 7.9), 8.61 (dd, 1H, *J* = 1.6 and 4.7). ¹³C NMR (CDCl₃, 75 MHz) 81.2, 93.7, 116.8, 126.2, 143.1, 148.7, 149.0, 150.6. HRMS (ESI): calcd for C₈H₅I₂N₃Na [M+Na]⁺ 419.8471, found 419.8469.

5-Iodo-1-(pyrimidin-2-yl)-1H-pyrazole (7q). This was prepared from **1q** following the general procedure and was obtained as a white solid (60% yield; mp = 100 °C). IR (ATR): 3127, 1569, 1427, 1402, 964, 915, 813, 740 cm⁻¹. ¹H NMR (CDCl₃, 300 MHz) 6.75 (d, 1H, *J* = 1.6), 7.33 (t, 1H, *J* = 4.8), 7.80 (d, 1H, *J* = 1.6), 8.84 (d, 2H, *J* = 4.8). ¹³C NMR (CDCl₃, 75 MHz) 77.7, 119.8, 121.0, 144.7, 156.9, 158.6 (2C). HRMS (ESI): calcd for C₇H₆IN₄ [M + H]⁺ 272.9637, found 272.9631.

Crystallography

Single crystals suitable for X-ray diffraction were grown after slow evaporation of solutions of **1j**, **1n**, **1o**, **2b**, **3b**, **4b**, **6j**, **8l**, **9m**, **7n**, **8n** and **8o** in dichloromethane at room temperature.

The samples were studied with graphite monochromatized Mo-K α radiation (λ = 0.71073 Å). Except for **8o** (*T* = 100(2) K), X-ray diffraction data were collected at *T* = 150(2) K using an APEXII Bruker-AXS diffractometer. The structure was solved by direct methods using the SIR97 program,³² and then refined with full-matrix least-square methods based on *F*² (SHELX-97)³³ with the aid of the WINGX program.³⁴ All non-hydrogen atoms were refined with anisotropic thermal parameters. Except *N*-linked

hydrogen that was introduced in the structural model through Fourier difference maps analysis, H atoms were finally included in their calculated positions. Molecular diagrams were generated by ORTEP-3 (version 2.02).³⁵

Crystal data for 1j. C₁₂H₁₀N₄, *M_r* = 210.24, monoclinic, *P*₂₁/*c*, *a* = 7.745(4), *b* = 12.472(6), *c* = 10.787(5) Å, β = 92.060(14)°, *V* = 1041.3(9) Å³, *Z* = 4, ρ_c = 1.341 g cm⁻³, μ = 0.086 mm⁻¹. A final refinement on *F*² with 2360 unique intensities and 146 parameters converged at *wR*(*F*²) = 0.1467 (*R*(*F*) = 0.0685) for 1062 observed reflections with *I* > 2 σ (*I*).

Crystal data for 1n. C₈H₇N₃, *M_r* = 145.17, monoclinic, *C*2/*c*, *a* = 18.2414(9), *b* = 5.4302(2), *c* = 14.7271(7) Å, β = 105.429(2)°, *V* = 1406.21(11) Å³, *Z* = 8, ρ_c = 1.371 g cm⁻³, μ = 0.088 mm⁻¹. A final refinement on *F*² with 1599 unique intensities and 100 parameters converged at *wR*(*F*²) = 0.1059 (*R*(*F*) = 0.0397) for 1382 observed reflections with *I* > 2 σ (*I*).

Crystal data for 1o. C₈H₇N₃, *M_r* = 145.17, monoclinic, *P*₂₁/*a*, *a* = 11.299(3), *b* = 4.2309(9), *c* = 14.743(3) Å, β = 90.229(8)°, *V* = 704.8(3) Å³, *Z* = 4, ρ_c = 1.368 g cm⁻³, μ = 0.088 mm⁻¹. A final refinement on *F*² with 1606 unique intensities and 100 parameters converged at *wR*(*F*²) = 0.1401 (*R*(*F*) = 0.0565) for 1174 observed reflections with *I* > 2 σ (*I*).

Crystal data for 2b. C₁₁H₁₂IN₃, *M_r* = 313.14, monoclinic, *P*₂₁/*n*, *a* = 7.3777(3), *b* = 19.1576(9), *c* = 8.7098(4) Å, β = 111.017(2)°, *V* = 1149.14(9) Å³, *Z* = 4, ρ_c = 1.81 g cm⁻³, μ = 2.758 mm⁻¹. A final refinement on *F*² with 2611 unique intensities and 138 parameters converged at *wR*(*F*²) = 0.0509 (*R*(*F*) = 0.0221) for 2432 observed reflections with *I* > 2 σ (*I*).

Crystal data for 3b. C₁₁H₁₁I₂N₃, *M_r* = 439.03, monoclinic, *P*₂₁/*n*, *a* = 6.9744(3), *b* = 26.4537(12), *c* = 7.2619(3) Å, β = 90.717(2)°, *V* = 1339.71(10) Å³, *Z* = 4, ρ_c = 2.177 g cm⁻³, μ = 4.673 mm⁻¹. A final refinement on *F*² with 3018 unique intensities and 148 parameters converged at *wR*(*F*²) = 0.0601 (*R*(*F*) = 0.0281) for 2908 observed reflections with *I* > 2 σ (*I*).

Crystal data for 4b. C₁₇H₁₇N₃, *M_r* = 263.34, monoclinic, *P*₂₁/*c*, *a* = 6.3843(5), *b* = 30.629(2), *c* = 7.1492(6) Å, β = 94.735(3)°, *V* = 1393.22(18) Å³, *Z* = 4, ρ_c = 1.255 g cm⁻³, μ = 0.076 mm⁻¹. A final refinement on *F*² with 3171 unique intensities and 183 parameters converged at *wR*(*F*²) = 0.1439 (*R*(*F*) = 0.0683) for 2759 observed reflections with *I* > 2 σ (*I*).

Crystal data for 6j. C₁₂H₈I₂N₄, *M_r* = 462.02, orthorhombic, *Pnab*, *a* = 8.3852(3), *b* = 10.2090(3), *c* = 16.0643(5) Å, *V* = 1375.18(8) Å³, *Z* = 4, ρ_c = 2.232 g cm⁻³, μ = 4.561 mm⁻¹. A final refinement on *F*² with 1568 unique intensities and 83 parameters converged at *wR*(*F*²) = 0.0359 (*R*(*F*) = 0.017) for 1406 observed reflections with *I* > 2 σ (*I*).

Crystal data for 8l. C₇H₄I₂N₂S₁, *M_r* = 401.98, monoclinic, *P*₂₁/*n*, *a* = 7.0510(2), *b* = 20.8154(6), *c* = 7.2666(2) Å, β = 100.688(2)°, *V* = 1048.01(5) Å³, *Z* = 4, ρ_c = 2.548 g cm⁻³, μ = 6.150 mm⁻¹. A final refinement on *F*² with 2381 unique intensities and 109 parameters converged at *wR*(*F*²) = 0.0619 (*R*(*F*) = 0.0292) for 2269 observed reflections with *I* > 2 σ (*I*).

Crystal data for 9m. C₈H₃ClI₃N₃, *M_r* = 557.28, monoclinic, *P*₂₁/*n*, *a* = 11.8807(5), *b* = 7.3931(3), *c* = 14.3980(6) Å,

$\beta = 92.696(2)^\circ$, $V = 1263.25(9) \text{ \AA}^3$, $Z = 4$, $\rho_c = 2.93 \text{ g cm}^{-3}$, $\mu = 7.606 \text{ mm}^{-1}$. A final refinement on F^2 with 2882 unique intensities and 101 parameters converged at $wR(F^2) = 0.0924$ ($R(F) = 0.04$) for 2561 observed reflections with $I > 2\sigma(I)$.

Crystal data for 7n. $\text{C}_8\text{H}_6\text{IN}_3$, $M_r = 271.06$, monoclinic, $P2_1/c$, $a = 7.1532(3)$, $b = 14.7450(6)$, $c = 8.1035(4) \text{ \AA}$, $\beta = 91.8830(10)^\circ$, $V = 854.25(7) \text{ \AA}^3$, $Z = 4$, $\rho_c = 2.108 \text{ g cm}^{-3}$, $\mu = 3.692 \text{ mm}^{-1}$. A final refinement on F^2 with 1957 unique intensities and 109 parameters converged at $wR(F^2) = 0.0504$ ($R(F) = 0.0207$) for 1824 observed reflections with $I > 2\sigma(I)$.

Crystal data for 8n. $\text{C}_8\text{H}_5\text{I}_2\text{N}_3$, $M_r = 396.95$, monoclinic, $P2_1/c$, $a = 7.1322(2)$, $b = 10.9173(3)$, $c = 13.3983(4) \text{ \AA}$, $\beta = 99.7590(10)^\circ$, $V = 1028.15(5) \text{ \AA}^3$, $Z = 4$, $\rho_c = 2.564 \text{ g cm}^{-3}$, $\mu = 6.075 \text{ mm}^{-1}$. A final refinement on F^2 with 2357 unique intensities and 118 parameters converged at $wR(F^2) = 0.0445$ ($R(F) = 0.018$) for 2220 observed reflections with $I > 2\sigma(I)$.

Crystal data for 8o. $\text{C}_8\text{H}_5\text{I}_2\text{N}_3$, $M_r = 396.95$, monoclinic, $P2_1/n$, $a = 6.8316(4)$, $b = 13.4938(7)$, $c = 12.1649(7) \text{ \AA}$, $\beta = 101.594(2)^\circ$, $V = 1098.53(11) \text{ \AA}^3$, $Z = 4$, $\rho_c = 2.4 \text{ g cm}^{-3}$, $\mu = 5.685 \text{ mm}^{-1}$. A final refinement on F^2 with 2499 unique intensities and 118 parameters converged at $wR(F^2) = 0.0675$ ($R(F) = 0.0291$) for 2315 observed reflections with $I > 2\sigma(I)$.

Acknowledgements

We thank Sarah Lévêque for her contribution to this study. We are grateful to Région Bretagne for financial support to C.P. and to Ambassade de France en République Arabe d'Égypte for financial support to I.F.N. We also thank the Institut Universitaire de France and Rennes Métropole (financial support to F.M.).

Notes and references

- (a) J. Elguero, *Comprehensive Heterocyclic Chemistry II* (ed.: A. R. Katritzky, C. W. Rees, E. F. V. Scriven), Pergamon, Elsevier Science Ltd., Oxford, 1996, Vol. 3; (b) T. Eicher, S. Hauptmann and A. Speicher, *The Chemistry of Heterocycles*, 2nd ed., Wiley-VCH, New York, 2003.
- See for example: S. Peruncheralathan, A. K. Yadav, H. Ila and H. Junjappa, *J. Org. Chem.*, 2005, **70**, 9644–9647, and references therein.
- (a) H. R. Snyder, F. Verbanac and D. B. Bright, *J. Am. Chem. Soc.*, 1952, **74**, 3243–3246; (b) P. W. Alley and D. A. Shirley, *J. Am. Chem. Soc.*, 1958, **80**, 6271–6274; (c) A. Marxer and M. Siegrist, *Helv. Chim. Acta*, 1974, **57**, 1988–2000; (d) S. Iwata, C.-P. Qian and K. Tanaka, *Chem. Lett.*, 1992, 357–360; (e) G. W. Rewcastle and A. R. Katritzky, *Adv. Heterocycl. Chem.*, 1993, **56**, 155–302; (f) M. R. Grimmett and B. Iddon, *Heterocycles*, 1994, **37**, 2087–2147; (g) M. Schlosser, J.-N. Volle, F. Leroux and K. Schenk, *Eur. J. Org. Chem.*, 2002, 2913–2920; (h) M. Schlosser, *Organometallics in Synthesis*, 2nd ed. (Ed.: M. Schlosser), Wiley, 2002, Chapter I; (i) A. Mukherjee, U. Subramanyam, V. G. Puranik, T. P. Mohandas and A. Sarkar, *Eur. J. Inorg. Chem.*, 2005, 1254–1263; (j) G. P. Lahm, T. M. Stevenson, T. P. Selby, J. H. Freudenberger, D. Cordova, L. Flexner, C. A. Bellin, C. M. Dubas, B. K. Smith, K. A. Hughes, J. G. Hollingshaus, C. E. Clark and E. A. Benner, *Bioorg. Med. Chem. Lett.*, 2007, **17**, 6274–6279; (k) J. Pu, A. F. Kreft, S. H. Aschmies, K. P. Atchison, J. Berkowitz, T. J. Caggiano, M. Chlenov, G. Diamantidis, B. L. Harrison, Y. Hu, D. Huryn, J. Steven Jacobsen, M. Jin, K. Lipinski, P. Lu, R. L. Martone, K. Morris, J. Sonnenberg-Reines, D. R. Riddell, J. Sabalski, S.-C. Sun, E. Wagner, Y. Wang, Z. Xu, H. Zhou and L. Resnick, *Bioorg. Med.*

- Chem.*, 2009, **17**, 4708–4717; (l) K. M. Clapham, A. S. Batsanov, M. R. Bryce and B. Tarbit, *Org. Biomol. Chem.*, 2009, **7**, 2155–2161.
- For basicity-driven ring opening reactions, see for example: M. Takahashi, T. Mamiya, H. Hasegawa, T. Nagai and H. Wakita, *J. Heterocycl. Chem.*, 1986, **23**, 1363–1366.
- C. Despotopoulou, L. Klier and P. Knochel, *Org. Lett.*, 2009, **11**, 3326–3329.
- (a) R. E. Mulvey, *Organometallics*, 2006, **25**, 1060–1075; (b) R. E. Mulvey, F. Mongin, M. Uchiyama and Y. Kondo, *Angew. Chem., Int. Ed.*, 2007, **46**, 3802–3824; (c) R. E. Mulvey, *Acc. Chem. Res.*, 2009, **42**, 743–755.
- (a) J.-M. L'Helgoual'ch, A. Seggio, F. Chevallier, M. Yonehara, E. Jeanneau, M. Uchiyama and F. Mongin, *J. Org. Chem.*, 2008, **73**, 177–183; (b) A. Seggio, M. I. Lannou, F. Chevallier, D. Nobuto, M. Uchiyama, S. Golhen, T. Roisnel and F. Mongin, *Chem.–Eur. J.*, 2007, **13**, 9982–9989; (c) A. Seggio, F. Chevallier, M. Vaultier and F. Mongin, *J. Org. Chem.*, 2007, **72**, 6602–6605; (d) K. Snégaroff, S. Komagawa, F. Chevallier, P. C. Gros, S. Golhen, T. Roisnel, M. Uchiyama and F. Mongin, *Chem.–Eur. J.*, 2010, **16**, 8191–8201; (e) G. Dayaker, A. Sreeshailam, F. Chevallier, T. Roisnel, P. R. Krishna and F. Mongin, *Chem. Commun.*, 2010, **46**, 2862–2864.
- For previous studies in azole series, see: (a) V. E. Matulis, Y. S. Halauko, O. A. Ivashkevich and P. N. Gaponik, *THEOCHEM*, 2009, **909**, 19–24; (b) Y. S. Halauko, V. E. Matulis, O. A. Ivashkevich, Y. V. Grigoriev and P. N. Gaponik, *Tetrahedron*, 2010, **66**, 3415–3420.
- Major metallation at C5 and minor dimetallation at C5 and C2' take place using butyllithium (see Ref. 3b). In contrast, metallation occurs regioselectively at C2' employing ethylmagnesium bromide (see Ref. 3c).
- H.-J. Cristau, P. P. Cellier, J.-F. Spindler and M. Taillefer, *Eur. J. Org. Chem.*, 2004, 695–709.
- A dideprotonation-diiodination has recently been described in the indazole series using $(\text{TMP})_2\text{Zn}\cdot 2\text{MgCl}_2\cdot 2\text{LiCl}$: B. Haag, Z. Peng and P. Knochel, *Org. Lett.*, 2009, **11**, 4270–4273.
- For a metallation similarly *meta* to a dimethylamino group, see: D. R. Armstrong, W. Clegg, S. H. Dale, E. Hevia, L. M. Hogg, G. W. Honeyman and R. E. Mulvey, *Angew. Chem., Int. Ed.*, 2006, **45**, 3775–3778.
- (a) W. C. Black, B. Guay and F. Scheuermeyer, *J. Org. Chem.*, 1997, **62**, 758–760; (b) M. Mosrin and P. Knochel, *Org. Lett.*, 2009, **11**, 1837–1840.
- Concerning the *ortho*-directing power of fluorine, see: F. Faigl, K. Fogassy, Z. Szanto, A. Lopata and L. Toke, *Tetrahedron*, 1998, **54**, 4367–4374.
- Concerning the relative *ortho*-directing power of fluoro and methoxy, see: D. C. Furlano, S. N. Calderon, G. Chen and K. L. Kirk, *J. Org. Chem.*, 1988, **53**, 3145–3147.
- Concerning the ability of pyrazole to complex metals, see: R. Mukherjee, *Coord. Chem. Rev.*, 2000, **203**, 151–218.
- Concerning the lithiation of 1,1'-(1,4-phenylene)bis(1H-pyrazole) (**11**), see: H. Laxy and T. Kauffmann, *Chem. Ber.*, 1980, **113**, 2749–2754.
- M. Schlosser, *Angew. Chem., Int. Ed.*, 1998, **37**, 1496–1513.
- R. R. Fraser, T. S. Mansour and S. Savard, *Can. J. Chem.*, 1985, **63**, 3505–3509.
- A. N. Sinyakov and M. S. Shvartsberg, *Bull. Acad. Sci. USSR, Div. Chem. Sci. (Engl. Transl.)*, 1979, **28**, 1053–1054.
- A. I. Belov, M. I. Terekhova, E. S. Petrov, S. F. Vasilevskii and M. S. Shvartsberg, *Russ. Chem. Bull.*, 1992, **41**, 398–402.
- E. Cancès, B. Mennucci and J. Tomasi, *J. Chem. Phys.*, 1997, **107**, 3032–3041.
- C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165–195.
- H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512–7515.
- K. Swapna, A. Vijay Kumar, V. Prakash Reddy and K. Rama Rao, *J. Org. Chem.*, 2009, **74**, 7514–7517.
- T. Asaumi, T. Matsuo, T. Fukuyama, Y. Ie, F. Kakiuchi and N. Chatani, *J. Org. Chem.*, 2004, **69**, 4433–4440.
- Y.-C. Teo, F.-F. Yong, C.-Y. Poh, Y.-K. Yan and G.-L. Chua, *Chem. Commun.*, 2009, 6258–6260.

-
- 28 M. Taillefer, N. Xia and A. Ouali, *Angew. Chem., Int. Ed.*, 2007, **46**, 934–936.
- 29 O. Ivashchuk and V. I. Sorokin, *Lett. Org. Chem.*, 2009, **6**, 57–59.
- 30 D. Zhu, R. Wang, J. Mao, L. Xu, F. Wu and B. Wan, *J. Mol. Catal. A: Chem.*, 2006, **256**, 256–260.
- 31 Y.-J. Cherng, *Tetrahedron*, 2002, **58**, 887–890.
- 32 A. Altomare, M. C. Burla, M. Camalli, G. L. Cascarano, C. Giacovazzo, A. Guagliardi, A. G. G. Moliterni, G. Polidori and R. Spagna, *J. Appl. Crystallogr.*, 1999, **32**, 115–119.
- 33 G. M. Sheldrick, *Acta Crystallogr., Sect. A: Found. Crystallogr.*, 2008, **64**, 112–122.
- 34 L. J. Farrugia, *J. Appl. Crystallogr.*, 1999, **32**, 837–838.
- 35 L. J. Farrugia, *J. Appl. Crystallogr.*, 1997, **30**, 565.