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

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A series of *N*-aryl and *N*-heteroaryl pyrazoles have been deproto-metallated 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 as pharmaceuticals and agrochemicals.[1] Among them, *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 on nitrogen an aromatic ring, 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)$_2$Mg·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 of new bimetallic combinations for deproto-metallation purpose,[6] we recently observed that the basic mixture obtained from ZnCl$_2$·TMEDA (TMEDA = *N*,*N*,*N'*,*N'*-tetramethylethylenediamine) and LiTMP (3 equiv), which proved to be 1:1 LiTMP-(TMP)$_2$Zn, could be used synergically to functionalize sensitive compounds such as functionalized or heterocyclic aromatics.[7]

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

Results and discussions

Synthetic aspects

Commercial 1-phenyl-1*H*-pyrazole could be deproto-metallated upon treatment by 1:1 LiTMP-(TMP)$_2$Zn (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 if not isolated, the 5,2'-diiodinated derivative was also present on the crude.[9] This prompted us to replace the phenyl group at 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).
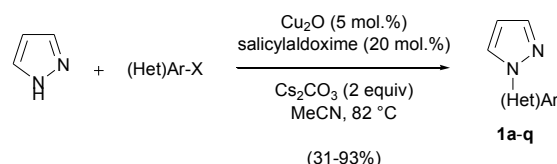
Scheme 1 Copper-catalyzed *N*-arylation of pyrazole.

The behaviour of the pyrazoles **1a-h** bearing a substituted phenyl group towards the lithium-zinc mixture was first studied (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)$_2$Zn (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'-diiodide[11] **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 nitrogen a 4-(dimethylamino)phenyl group[12] proved quite similar, giving either the monoiodide **2b** as the main derivative (54% yield) using LiTMP-(TMP)$_2$Zn (0.5 equiv each) or the diiodide **3b** (67% yield) turning to 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 Suzuki coupling to the corresponding phenyl derivative **4b** in 73% yield, and the crystal structure of the latter was also obtained (Figure 1).†

No reaction was observed starting from the 4-nitrophenyl substituted pyrazole **1c** (entry 3), probably due to competitive reaction of the base with the sensitive nitro group,[13] but using

1

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** and **3e** were already isolated in satisfying yields (65 and 84%, respectively) using 0.5 equiv of base (entries 4 and 5). The fluoro group proved to activate less strongly the 2' site than the cyano and trifluoromethyl groups, giving **3f** in a moderate 31% yield using 0.5 equiv of base. Turning 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]
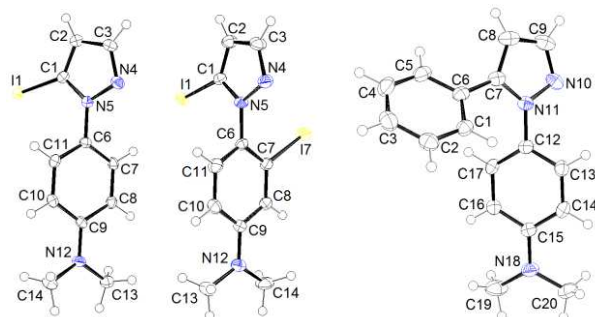

Figure 1 ORTEP diagrams (30% probability) of **2b** (left), **3b** (middle) and **4b** (right).

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).

**Table 1** Deprotonative metallation of **1a-h** followed by trapping with I₂
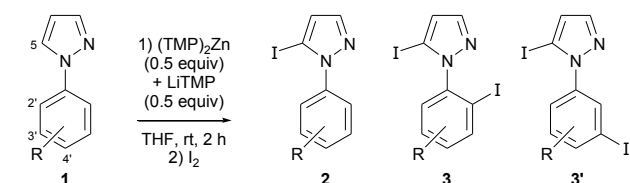
Entry	Substrate (R)	Products, Yields (%)		
		2	**3**	**3'**
1	**1a** (4-ᵗBu)	**2a**, 54 (4)[a]	**3a**, 28 (66)[a]	-[b]
2	**1b** (4-NMe₂)	**2b**, 54 (0)[a]	**3b**, 28 (67)[a]	-[b]
3	**1c** (4-NO₂)	-[c]	-[c]	-[c]
4	**1d** (4-CN)	-[b]	**3d**, 65	-[b]
5	**1e** (4-CF₃)	-[b]	**3e**, 84	-[b]
6	**1f** (4-F)	-[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).

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 nitrogen[16] (Scheme 2). The products being always iodinated at their 5 position, intramolecular deprotonation reactions from the pyrazolylzincates **A** seem more likely.
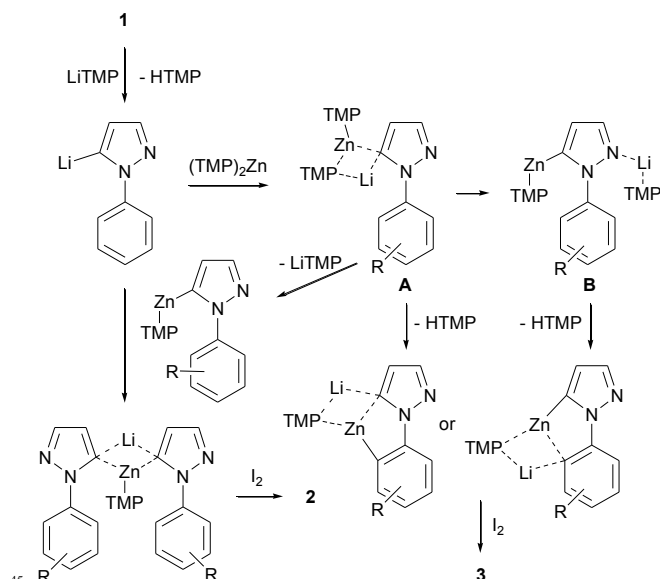

Scheme 2 Proposed pathways for the dimetallation of *N*-aryl pyrazoles using 1:1 LiTMP-(TMP)₂Zn.

In the search of other polymetallation reactions, we submitted 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 identified unequivocally by X-ray structure analysis (Scheme 3, Figure 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.

We then studied the behaviour of the pyrazoles **1k** and **1l** bearing a thiophenyl group (Scheme 4). Upon treatment by 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, respectively resulting from 5,3' and 5,5' dimetallation reactions. This result can be explained by the strong ability of sulphur to acidify the neighbouring hydrogen.[3h] In the case of **1l**, the acidifying effects of sulphur and pyrazole combine to allow the formation of the monoiodide **7'l** (30% yield) in addition to the

diiodide **8l** (41% yield, Figure 3†). Reducing the quantity of base to 0.33 equiv favoured the formation of **7'l**, which was isolated in 62% yield.
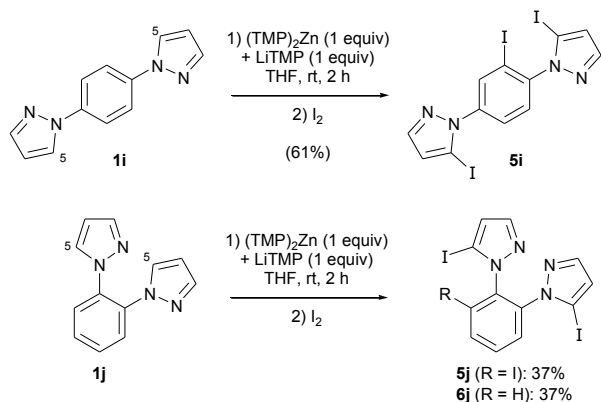
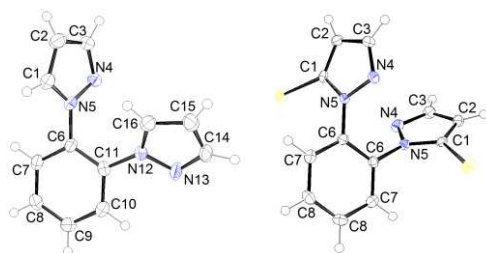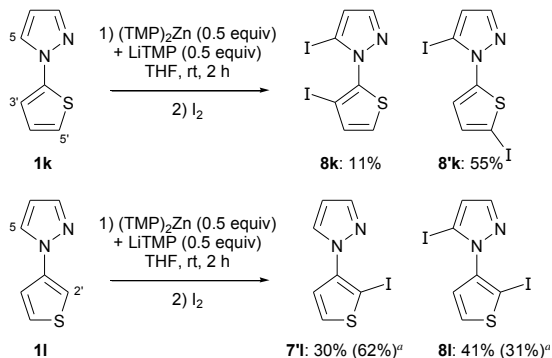**Scheme 3** Deprotonative metallation of **1i** and **1j** followed by trapping with I_2.

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

Scheme 4 Deprotonative metallation of **1k** and **1l** followed by trapping with I_2. [a] The deprotonation was performed using $(TMP)_2Zn$ (0.33 equiv) + LiTMP (0.33 equiv).
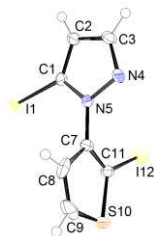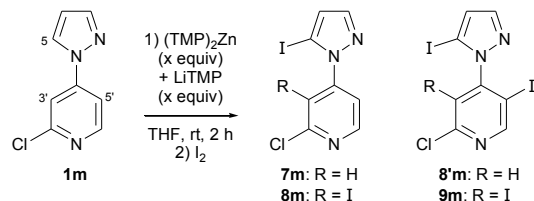

Figure 3 ORTEP diagrams (30% probability) of **8l**.

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 of the diiodides **8m** or **8'm**, but the triiodide **9m** was formed as the main product (48% yield, Figure 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.

Table 2 Deprotonative metallation of **1m** followed by trapping with I_2

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
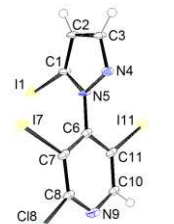
Figure 4 ORTEP diagrams (30% probability) of **9m**.

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'-diiodide **8n** was isolated in 60% yield (Table 3, entry 1, Figure 5†). The isomer **1o** gave a mixture of two iodides where the pyridine ring was substituted at C2 (**8o**, 28% yield, Figure 6†) and C4 (**8'o**, 30% yield) in a similar overall 58% yield (Table 3, entry 2).

Table 3 Deprotonative metallation of **1n**-**q** followed by trapping with I_2

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	**8p** (3'-I), 14
4	**1p**		1	**7p**, 0	**8p** (3'-I), 49
5	**1q**		0.5	**7q**, 60	

The substrate **1p** proved less prone to dideprotonation

either because of only one pyridine position 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 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 the diiodide **8p** in 49% yield (Table 3, entry 4). Finally it was possible to obtain exclusively the 5-iodo derivative **7q** (60% yield) starting from the pyrimidin-2-yl substituted pyrazole **1q** (Table 3, entry 5).

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

Figure 6 ORTEP diagrams (30% probability) of **1o** and **8o**.

Computational aspects

CH acidity of pyrazoles has been the subject of few studies. The value for 1-propyl-1H-pyrazole was experimentally found, and reported in 1985.[19] Substituent-CH acidities for methylpyrazoles[20] and ethynylpyrazoles[21] were respectively evaluated in liquid NH_3 and DMSO. In the last case, the results were proved by employi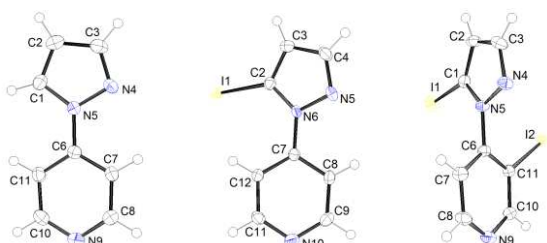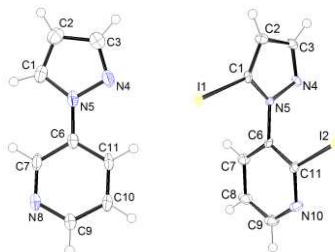ng the semi-empirical CNDO 2 method. In the present paper, the DFT calculations of CH acidity of the different N-aryl pyrazoles both in gas phase (Scheme 5) and in THF solution (Scheme 6) are presented.

The gas phase acidities $\Delta_{\mathrm{acid}}G$ and pK_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 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^0_{298}) were calculated for each species using the following equation:

$$G^0_{298} = E + \mathrm{ZPVE} + H_{0\rightarrow298} - TS^0_{298}.$$

The gas phase acidities $\Delta_{\mathrm{acid}}G$ were determined as the Gibbs energies of deprotonation of the substrates R−H (R−H$_{(g)}$ → R$^-_{(g)}$ + H$^+_{(g)}$) by the following formula:
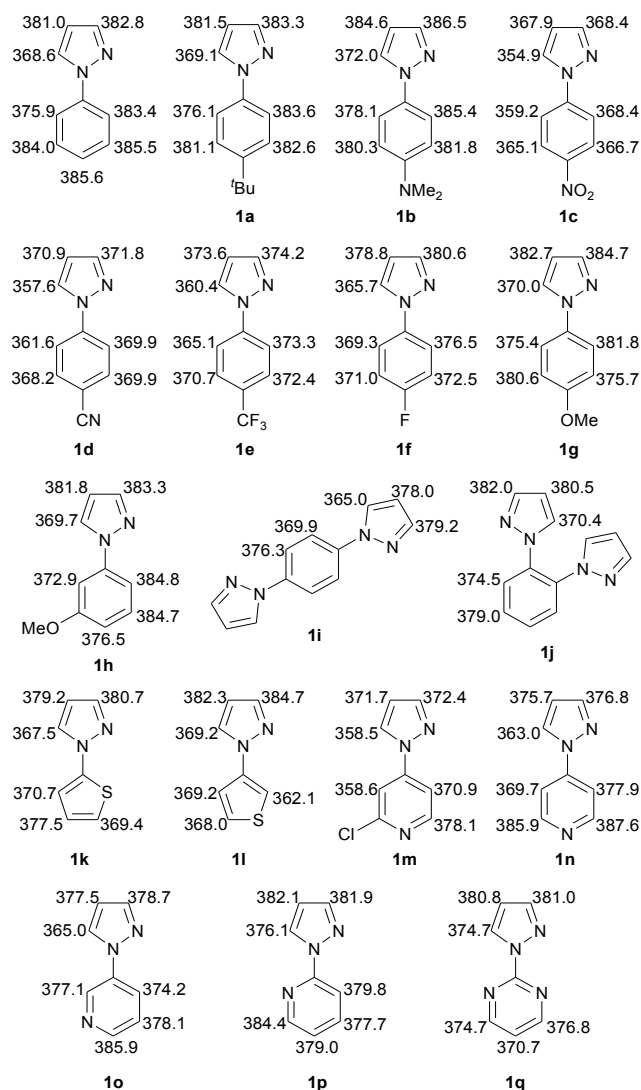
Scheme 5 Gas phase acidities ($\Delta_{\mathrm{acid}}G$, kcal·mol^{-1}) of the investigated pyrazoles.

$$\Delta_{\mathrm{acid}}G = G^0_{298}(\mathrm{R}^-) + G^0_{298}(\mathrm{H}^+) - G^0_{298}(\mathrm{RH}).$$

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 atomic radii of the UFF force field. The PCM energies E_{PCM} were calculated at the B3LYP/6-311+G(d,p) level using geometries optimized for isolated structures. The Gibbs energies in solution G_s were calculated for each species by the formula:

$$G_s = G^0_{298} + E_{\mathrm{PCM}} - E.$$

To cancel possible errors, the pK_a values were calculated by means of the following homodesmic reaction:

$$\mathrm{R-H}_{(s)} + \mathrm{Het}^-_{(s)} \rightarrow \mathrm{R}^-_{(s)} + \mathrm{Het-H}_{(s)},$$
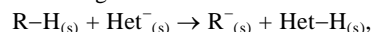
where Het−H is an appropriate five-membered heterocycle with experimentally known pK_a value. In the present work, 1-propyl-1H-pyrazole was chosen as reference compound since its pK_a value in THF found by Fraser et al.,[19] 35.9, was supposed to be close to those for the investigated substrates.

The Gibbs energies of the homodesmic reactions were respectively calculated using the following equations:

$$\Delta_r G_s = \sum_{products} G_s - \sum_{reactants} G_s$$

$$pK_a(\text{R-H}) = pK_a(\text{Het-H}) + \frac{\Delta_r G_s}{RT} \cdot \frac{1}{\ln 10}.$$

The CH acidity of side groups such as methoxy, dimethylamino and *tert*-butyl was expected to be significantly lower and hence was not considered.

It is obvious that some of the compounds under consideration exist in form of two or even more rotamers due to sterical interaction of adjacent hydrogens or/and heteroatom lone pairs. In such cases, the data on Schemes 5 and 6 refer to the most stable rotamers. According to our calculations for the investigated pyrazoles, the favoured rotamer form was determined substantially by intermolecular interactions.

1a (40.0, 40.3 / 33.9 / 40.2, 42.0 / 42.5, 42.9 / 43.3)

1a (40.1, 40.5 / 33.5 / 40.2, 42.2 / 44.6, 45.0 / tBu)

1b (42.2, 42.7 / 35.6 / 41.7, 43.3 / 43.2, 43.6 / NMe2)

1c (36.2, 35.5 / 28.8 / 31.9, 35.7 / 32.6, 33.0 / NO2)

1d (37.4, 36.7 / 30.0 / 33.5, 36.2 / 35.0, 35.5 / CN)

1e (37.9, 37.2 / 30.7 / 34.9, 37.4 / 36.1, 36.6 / CF3)

1f (39.2, 39.5 / 32.2 / 35.9, 37.7 / 34.1, 34.4 / F)

1g (40.4, 40.9 / 33.7 / 38.9, 40.5 / 40.1, 38.9 / OMe)

1h (39.8, 40.1 / 33.2 / 40.0, 38.7 / 42.4 / 39.6 / OMe)

1i (32.3, 39.3 / 39.5 / 36.9 / 38.8)

1j (41.3, 41.0 / 36.3 / 40.0 / 41.0)

1k (38.8, 39.0 / 32.0 / 35.0 / 38.2, 32.2 / S)
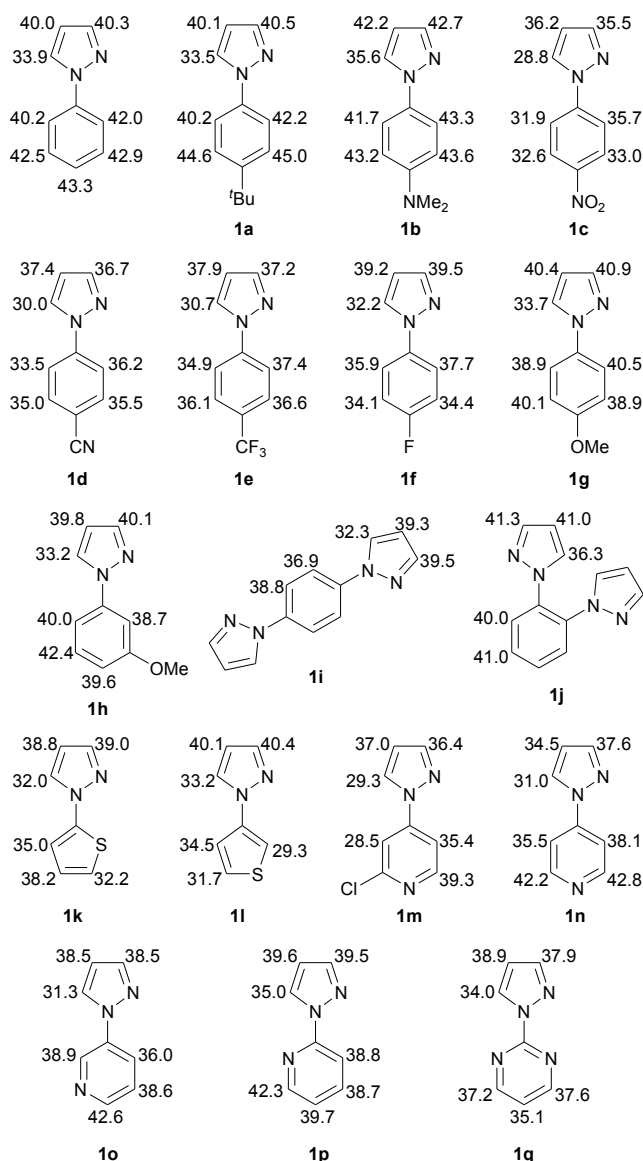
1l (40.1, 40.4 / 33.2 / 34.5, 29.3 / 31.7, S)

1m (37.0, 36.4 / 29.3 / 28.5, 35.4 / 39.3 / Cl, N)

1n (34.5, 37.6 / 31.0 / 35.5, 38.1 / 42.2, 42.8 / N)

1o (38.5, 38.5 / 31.3 / 38.9, 36.0 / 38.6 / 42.6 / N)

1p (39.6, 39.5 / 35.0 / 38.8 / 42.3, 38.7 / 39.7 / N)

1q (38.9, 37.9 / 34.0 / 37.2, 37.6 / 35.1 / N, N)

Scheme 6 Calculated values of pK_a(THF) of the investigated pyrazoles.

For the pyrazoles bearing a 4-substituted phenyl group, an inequality in C-H acidity (up to 4 logarithmic units) between the C2' and C6' sites, as well as between the C3' and C5' sites,

was noticed. This phenomenon could be explained by electron repulsion of syn-periplanar carbon and nitrogen lone pairs, and/or dipole moment direction.

Among the molecules with several rotamers, the pyridylpyrazoles are likely to exist in form with remote heteroatoms (nitrogens), while for the sulphur-containing compounds it is *vice versa*. For the *para*-bipyrazolyl **1i**, *anti*-disposition of heterocycles is much more favorable than *syn*-, while for the *ortho*-bipyrazolyl **1j**, the *anti*-form dominates over the *amphi*-, and the local minimum on the PES corresponding to the *syn*- form was not even located.

It is desirable to know the impact on the CH acidity of pyrazoles, and hence on their reactivity, of the electronic effects of substituents. This aim can be achieved by using the Hammett equation (or a similar approach), which is well-known as a powerful tool for the prediction of many important physico-chemical 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 study[8] 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, practical) 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, theoretical) 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.

Table 4 Calculated pK_a(THF) values for the pyrazoles and substituent constants[23]

Entry	Compound	X or Y	pK_a(THF)	σ_m	σ_p	F	R
1		Ph	33.9	0.06	-0.01	0.12	-0.13
2	**1a**	4-^{t}BuC$_6$H$_4$	33.5	0.07	0.01	0.12	-0.11
3	**1c**	4-O$_2$NC$_6$H$_4$	28.8	0.25	0.26	0.26	0.00
4	**1f**	4-FC$_6$H$_4$	32.2	0.12	0.06	0.17	-0.11
5	**1g**	4-MeOC$_6$H$_4$	33.7	0.05	-0.08	0.13	-0.21
6	**1n**	pyridin-4-yl	31.0	0.27	0.44	0.21	0.23
7	**1o**	pyridin-3-yl	31.3	0.23	0.25	0.24	0.01
8	**1p**	pyridin-2-yl	35.0	0.33	0.17	0.40	-0.23
9	**1q**	pyrimidin-2-yl	34.0	0.23	0.53	0.13	0.40
10		H	40.2	0.00	0.00	0.00	0.00
11	**1a**	^{t}Bu	40.2	-0.10	-0.20	-0.02	-0.18
12	**1b**	NMe$_2$	41.7	-0.16	-0.83	0.15	-0.98
13	**1c**	NO$_2$	31.9	0.71	0.78	0.65	0.13
14	**1d**	CN	33.5	0.56	0.66	0.51	0.15
15	**1e**	CF$_3$	34.9	0.43	0.54	0.38	0.16
16	**1f**	F	35.9	0.34	0.06	0.45	-0.39
17	**1g**	OMe	38.9	0.12	-0.27	0.29	-0.56

Unfortunately, this study was restricted by lacking 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 – fitted constants).

The best equation within the Jaffe's method for the most acidic 5 position of 1-phenyl-1H-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 splitted into a field/inductive component (F) and a resonance component (R).[23] The best equation for the same compounds within this approach is:

$$pK_a(\text{THF}) = 37.3 - 29.4\ F - 0.3\ R$$
$$(N = 7,\ r^2 = 0.902,\ \text{rmse} = 0.71)$$

Thereby, among the considered methods, the Jaffe's method gives the best equations for CH acidity prediction. The influence of a substituent on forming carbanion center is more similar to that for *meta*-group in benzene ring: 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:

$$pK_a(\text{THF}) = 39.8 - 11.4\ F - 3.7\ R$$
$$(N = 8,\ r^2 = 0.994,\ \text{rmse} = 0.34)$$
and
$$pK_a(\text{THF}) = 39.7 - 10.3\ \sigma_m - 0.5\ \sigma_p$$
$$(N = 8,\ r^2 = 0.991,\ \text{rmse} = 0.40)$$

So, the correlation between calculated and predicted pK_a values of pyrazoles using LFER equations (Figure 7) gives the 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. 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)-1H-pyrazole (**1l**) at least deproto-metallated 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)-1H-pyrazole (**1m**), which is not predominantly functionalized at its most acidic site, a result that could be in relation with the size of both the base and the chloro group.

Compared with 1-phenyl-1H-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 should disfavour it. The experimental results are rather in accordance with these predictions since the compounds **1a**,**b** behave as 1-phenyl-1H-pyrazole, mainly leading to the 5-iodo derivatives, whereas diiodides are obtained starting from the compounds **1d**-**h** (Table 1).

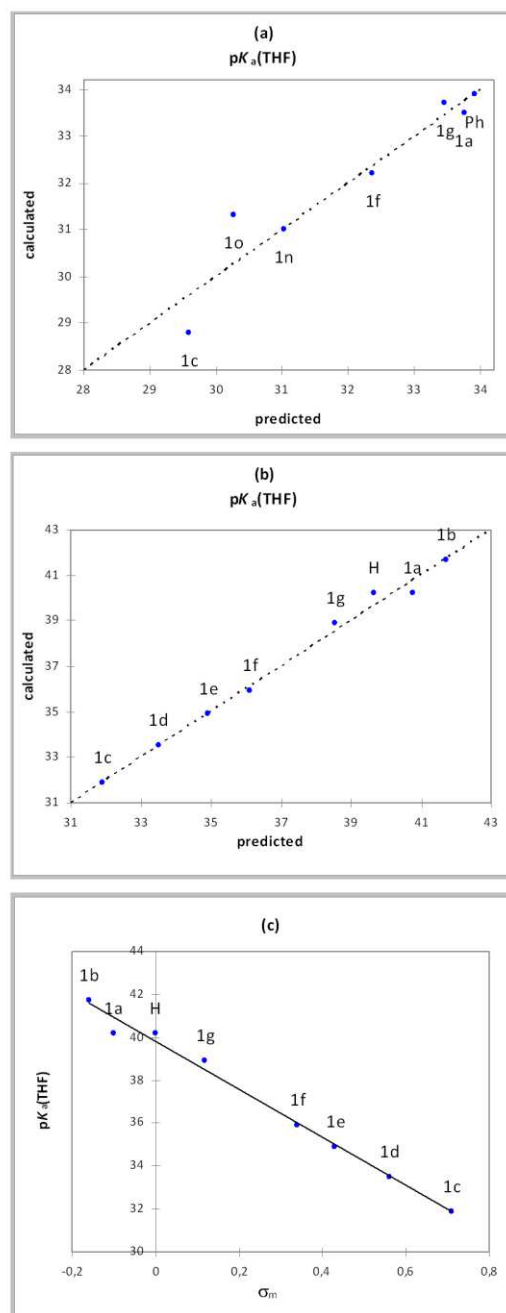**Figure 7** Correlation between calculated and predicted pK_a values of pyrazoles in THF solution using equations within Jaffe method for (a) Table 4, entries 1-7, and (b) Table 4, entries 10-17, and (c) regression of pK_a(THF) versus σ_m for Table 4, entries 10-17.

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 in relation with 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 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; second (and possibly third) metallation could then take place, according to the mechanism depicted in Scheme 2. Indeed, the second metallation does not necessarily takes 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 deproto-metallation 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 continuum solvation model. Even if the approach has limits, mainly due to the lack of mechanism information concerning such reactions, it proved efficient to predict in most cases studied the first deprotonation sites. In addition, the study carried out with *N*-(4-substituted phenyl) pyrazoles allowed both experimentally and theoretically the identification of a *meta* acidifying effect[12] from groups such as cyano, trifluoromethyl, fluoro and methoxy.

Experimental

Syntheses: general methods

Metallation reactions were performed under 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. [1]H and [13]C Nuclear Magnetic Resonance (NMR) spectra were recorded on a Bruker Avance III spectrometer at 300 and 75 MHz, respectively. [1]H chemical shifts (δ) are given in ppm relative to the solvent residual peak, and ^{13}C chemical shifts 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 elestrospray CI mode.

1-[4-(*tert*-Butyl)phenyl]-1*H*-pyrazole (1a) was prepared from 1-bromo-4-*tert*-butylbenzene using a described procedure[10] (reaction time: 115 h). Yield: 82%. Colourless liquid. IR (ATR): 2962, 2905, 2867, 1524, 1394, 1034, 937, 836, 746 cm^{-1}. [1]H (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 (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) was prepared from 1-bromo-4-(dimethylamino)benzene using a described procedure[10] (reaction time: 115 h). Yield: 45%. White solid (mp = 94 °C). IR (ATR): 1744, 1525, 1354, 1226, 936, 816, 754 cm^{-1}. [1]H (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 (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) was prepared from 1-bromo-4-nitrobenzene using a described procedure[10] (reaction time: 160 h). Yield: 42%. Yellow solid (mp = 174 °C). IR (ATR): 1740, 1366, 1239, 1217, 1205, 749 cm^{-1}. [1]H (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 (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) was prepared from 4-bromobenzonitrile using a described procedure[10] (reaction time: 144 h). Yield: 73%. White solid (mp = 86 °C). IR (ATR): 2971, 1738, 1366, 1217, 748 cm^{-1}. [1]H (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 (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) was prepared from 1-bromo-4-(trifluoromethyl)benzene using a described procedure[10] (reaction time: 94 h). Yield: 42%. White solid (mp = 96 °C). IR (ATR): 1739, 1217, 1106, 1068, 822, 755 cm^{-1}. [1]H (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 (CDCl$_3$, 75 MHz) 108.6, 118.9 (2C), 124.0 (q, J_F = 272), 126.8 (q, 2C, J_F = 4), 126.9, 128.3 (q, J_F = 33), 142.1, 142.6. [19]F (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) was prepared from 1-bromo-4-fluorobenzene using a described procedure[10] (reaction time: 24 h). Yield: 39%. White solid (mp < 50 °C). IR (ATR): 3124, 1741, 1521, 1508, 1394, 1218, 832, 747 cm^{-1}. [1]H (CDCl$_3$, 300 MHz) 6.47 (dd, 1H, *J* = 1.8 and 2.3), 7.15 (dd, 2H, *J* = 9.2 and J_F = 8.2), 7.66 (dd, 2H, *J* = 9.2 and J_F = 4.7), 7.72 (d, 1H, *J* = 1.8), 7.86 (d, 1H, *J* = 2.3). [13]C (CDCl$_3$, 75 MHz) 107.7, 116.1 (2C, d, J_F = 23), 120.9 (2C, d, J_F = 8), 126.9, 136.6, 141.1, 159.4 (d, J_F = 246). [19]F (CDCl$_3$, 282 MHz) -115.8. These values are consistent with those reported in the literature.[27]

1-(4-Methoxyphenyl)-1*H*-pyrazole (1g) was prepared from 4-iodoanisole using a described procedure[10] (reaction time: 42 h). Yield: 39%. Yellow solid (mp = 42 °C). IR (ATR): 1741, 1375, 1230, 830 cm^{-1}. ^{1}H (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 (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) was prepared from 3-iodoanisole using a described procedure[10] (reaction time: 91 h). Yield: 93%. Colourless liquid. IR (ATR): 3003, 2937, 2837, 1606, 1594, 1392, 1225, 1044, 946, 843, 746 cm^{-1}. ^{1}H (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 (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) was prepared from 1,4-diiodobenzene (5 equiv of pyrazole were employed) using a described procedure[10] (reaction time: 260 h). Yield: 31%. White solid (mp = 180 °C). IR (ATR): 1742, 1529, 1392, 1330, 1105, 936, 836, 757 cm^{-1}. ^{1}H (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 (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) was prepared from 1,2-diiodobenzene (3 equiv of pyrazole were employed) using a described procedure[10] (reaction time: 24 h). Yield: 76%. White solid (mp = 70 °C). IR (ATR): 1738, 1366, 1217, 759 cm^{-1}. ^{1}H (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 (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) was prepared from 2-bromothiophene using a described procedure[10] (reaction time: 24 h). Yield: 52%. Colourless liquid. IR (ATR): 3109, 1737, 1556, 1465, 1387, 1043, 918, 745 cm^{-1}. ^{1}H (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 (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) was prepared from 3-bromothiophene using a described procedure[10] (reaction time: 72 h). Yield: 64%. Colourless liquid. IR (ATR): 3111, 1740, 1557, 1397, 1035, 854, 767, 744 cm^{-1}. ^{1}H (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 (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)-1*H*-pyrazole (1m) was prepared from 4-bromo-2-chloropyridine using a described procedure[10] (reaction time: 24 h). Yield: 60%. White solid (mp = 112 °C). IR (ATR): 2971, 1740, 1595, 1570, 1381, 1217, 1084, 836, 750 cm^{-1}. ^{1}H (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 (CDCl$_3$, 75 MHz) 109.8, 111.5, 112.9, 126.9, 143.2, 148.0, 151.0, 153.1. HRMS (ESI): calcd for C$_8$H$_7$ClN$_3$ [M+H]$^+$ 180.0328, found 180.0321.

1-(Pyridin-4-yl)-1*H*-pyrazole (1n) was prepared from 4-bromopyridine hydrochloride (1 additional equivalent of Cs$_2$CO$_3$ was used) using a described procedure[10] (reaction time: 24 h). Yield: 61%. White solid (mp = 84 °C). IR (ATR): 2971, 1738, 1595, 1366, 1217, 1035, 817, 757 cm^{-1}. ^{1}H (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 (CDCl$_3$, 75 MHz) 109.1, 112.6 (2C), 126.6, 142.5, 145.9, 151.2 (2C). HRMS (ESI): calcd for C$_8$H$_8$N$_3$ [M+H]$^+$ 146.0718, found 146.0719.

1-(Pyridin-3-yl)-1*H*-pyrazole (1o) was prepared from 3-bromopyridine using a described procedure[10] (reaction time: 26 h). Yield: 67%. Yellow solid (mp < 50 °C). IR (ATR): 3115, 1739, 1586, 1521, 1391, 1045, 934, 748 cm^{-1}. ^{1}H (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 (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)-1*H*-pyrazole (1p) was prepared from 2-bromopyridine using a described procedure[10] (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}. ^{1}H (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 (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)-1*H*-pyrazole (1q) was prepared from 2-chloropyrimidine using a described procedure[10] (reaction time: 72 h). Yield: 73%. White solid (mp = 80 °C). IR (ATR): 2971, 1738, 1456, 1434, 1366, 1229, 1217, 931, 765 cm^{-1}. ^{1}H (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 (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 deproto-zincation 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, ZnCl$_2$·TMEDA (0.125 g, 0.5 mmol) was added, and the mixture was stirred for 15 min at this temperature before 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 $Na_2S_2O_3$ (10 mL) and extraction with Et_2O (3 x 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-1*H*-pyrazole (2a) 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 $ZnCl_2·TMEDA$). IR (ATR): 2962, 2905, 2868, 1511, 1385, 1079, 957, 917, 836, 773 cm^{-1}. ^{1}H (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 (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 $C_{13}H_{16}IN_2$ [M+H]$^+$ 327.0358, found 327.0354.

1-[4-(*tert*-Butyl)-2-iodophenyl]-5-iodo-1*H*-pyrazole (3a) 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 $ZnCl_2·TMEDA$). IR (ATR): 2962, 2925, 2870, 1600, 1517, 1392, 1364, 1202, 1109, 831 cm^{-1}. ^{1}H (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 (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 $C_{13}H_{15}I_2N_2$ [M+H]$^+$ 452.9325, found 452.9328.

1-[4-(Dimethylamino)phenyl]-5-iodo-1*H*-pyrazole (2b) 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}. ^{1}H (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 (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 $C_{11}H_{13}IN_3$ [M+H]$^+$ 314.0154, found 314.0152.

1-[4-(Dimethylamino)-2-iodophenyl]-5-iodo-1*H*-pyrazole (3b) 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 $ZnCl_2·TMEDA$; mp = 186 °C). IR (ATR): 2923, 2853, 1732, 1597, 1515, 1446, 1357, 1061, 1010, 954 cm^{-1}. ^{1}H (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 (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 $C_{11}H_{12}I_2N_3$ [M+H]$^+$ 439.9121, found 439.9124.

1-[4-(Dimethylamino)phenyl]-5-phenyl-1*H*-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 addition of Pd(dba)$_2$ (14 mg, 25 μmol), and PPh$_3$ (26 mg, 0.10 mmol). The resulting mixture was heated at 105 °C for 12 h, before cooling and dilution with Et_2O (30 mL), washing with H_2O, and extraction with CH_2Cl_2 (3

x 20 mL). After drying over Na_2SO_4, 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}. ^{1}H (CDCl$_3$, 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). ^{13}C (CDCl$_3$, 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 $C_{17}H_{18}N_3$ [M+H]$^+$ 264.1501, found 264.1499.

1-(4-Cyano-2-iodophenyl)-5-iodo-1*H*-pyrazole (3d) 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}. ^{1}H (CDCl$_3$, 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). ^{13}C (CDCl$_3$, 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 $C_{10}H_6I_2N_3$ [M+H]$^+$ 421.8651, found 421.8655.

5-Iodo-1-[2-iodo-4-(trifluoromethyl)phenyl]-1*H*-pyrazole (3e) 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}. ^{1}H (CDCl$_3$, 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). ^{13}C (CDCl$_3$, 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. ^{19}F (CDCl$_3$, 282 MHz) -62.6 (3F). HRMS (ESI): calcd for $C_{10}H_6F_3I_2N_2$ [M+H]$^+$ 464.8573, found 464.8572.

1-(4-Fluoro-2-iodophenyl)-5-iodo-1*H*-pyrazole (3f) 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 $ZnCl_2·TMEDA$; mp = 78 °C). IR (ATR): 3097, 1589, 1492, 1393, 1202, 1023, 958, 862 cm^{-1}. ^{1}H (CDCl$_3$, 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). ^{13}C (CDCl$_3$, 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). ^{19}F (CDCl$_3$, 282 MHz) -108.9. HRMS (ESI): calcd for $C_9H_6FI_2N_2$ [M+H]$^+$ 414.8605, found 414.8605.

1-(4-Fluoro-3-iodophenyl)-5-iodo-1*H*-pyrazole (3'f) 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 $ZnCl_2·TMEDA$; mp = 61 °C). IR (ATR): 3097, 2924, 1591, 1491, 1389, 1038, 965, 819 cm^{-1}. ^{1}H (CDCl$_3$, 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). ^{13}C (CDCl$_3$, 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). ^{19}F (CDCl$_3$, 282 MHz) -93.4. HRMS (ESI): calcd for $C_9H_6FI_2N_2$ [M+H]$^+$ 414.8605, found 414.8627.

5-Iodo-1-(2-iodo-4-methoxyphenyl)-1*H*-pyrazole (3g) 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}. ^{1}H (CDCl$_3$, 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). ^{13}C (CDCl$_3$, 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 C$_{10}$H$_9$I$_2$N$_2$O [M+H]$^+$ 426.8804, found 426.8811.

5-Iodo-1-(3-methoxyphenyl)-1*H*-pyrazole (2h) 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 ZnCl$_2$·TMEDA). IR (ATR): 2961, 2835, 1606, 1593, 1497, 1384, 1219, 1036, 971, 847 cm^{-1}. ^{1}H (CDCl$_3$, 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). ^{13}C (CDCl$_3$, 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 C$_{10}$H$_{10}$IN$_2$O [M+H]$^+$ 300.9838, found 300.9836.

5-Iodo-1-(2-iodo-3-methoxyphenyl)-1*H*-pyrazole (3h) 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 ZnCl$_2$·TMEDA; mp = 132 °C). IR (ATR): 3005, 2934, 2836, 1733, 1575, 1472, 1400, 1218, 1130, 971 cm^{-1}. ^{1}H (CDCl$_3$, 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). ^{13}C (CDCl$_3$, 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 C$_{10}$H$_9$I$_2$N$_2$O [M+H]$^+$ 426.8804, found 426.8810.

1,1'-[1,4-(2-Iodophenylene)bis-(1*H*-5-iodopyrazole)] (5i) 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 ZnCl$_2$·TMEDA; mp = 174 °C). IR (ATR): 3129, 2924, 2854, 1724, 1592, 1501, 1393, 1372, 954, 917 cm^{-1}. ^{1}H (CDCl$_3$, 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). ^{13}C (CDCl$_3$, 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 C$_{12}$H$_8$I$_3$N$_4$ [M+H]$^+$ 588.7883, found 588.7897.

1,1'-[1,2-(3-Iodophenylene)bis(1*H*-5-iodopyrazole) (5j) 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 ZnCl$_2$·TMEDA; mp = 214 °C). IR (ATR): 2924, 2853, 1731, 1485, 1455, 1405, 1382, 956, 917 cm^{-1}. ^{1}H (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 (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 C$_{12}$H$_8$I$_3$N$_4$ [M+H]$^+$ 588.7883, found 588.7904.

1,1'-(1,2-Phenylene)bis(1*H*-5-iodopyrazole) (6j) 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 ZnCl$_2$·TMEDA; mp = 182 °C). IR (ATR): 3129, 2924, 2854, 1515, 1405, 1384, 958, 917 cm^{-1}. ^{1}H (CDCl$_3$, 300 MHz) 6.45 (d, 2H, J = 1.9), 7.47 (d, 2H, J = 1.9), 7.59 (m, 4H). ^{13}C (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 C$_{12}$H$_9$I$_2$N$_4$ [M+H]$^+$ 462.8917, found 462.8939.

5-Iodo-1-(5-iodothiophen-2-yl)-1*H*-pyrazole (8'k) 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}. ^{1}H (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 C$_7$H$_5$I$_2$N$_2$S [M+H]$^+$ 402.8263, found 402.8272.

5-Iodo-1-(3-iodothiophen-2-yl)-1*H*-pyrazole (8k) was identified in an inseparable mixture with the starting material (11% estimated yield). ^{1}H (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)-1*H*-pyrazole (7'l) 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 ZnCl$_2$·TMEDA). IR (ATR): 3108, 2923, 2853, 1547, 1455, 1392, 1065, 1042, 853 cm^{-1}. ^{1}H (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 (CDCl$_3$, 75 MHz) 66.5, 106.7, 125.3, 130.0, 131.6, 140.9, 143.4. HRMS (ESI): calcd for C$_7$H$_6$IN$_2$S [M+H]$^+$ 276.9296, found 276.9301.

5-Iodo-1-(2-iodothiophen-3-yl)-1*H*-pyrazole (8l) 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 ZnCl$_2$·TMEDA; mp = 104 °C). IR (ATR): 3103, 2922, 2853, 1723, 1534, 1390, 987, 970, 917, 857 cm^{-1}. ^{1}H (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 (CDCl$_3$, 75 MHz) 77.9, 83.6, 116.5, 126.8, 131.1, 143.1, 143.2. HRMS (ESI): calcd for C$_7$H$_5$I$_2$N$_2$S [M+H]$^+$ 402.8263, found 402.8273.

1-(2-Chloropyridin-4-yl)-5-iodo-1*H*-pyrazole (7m) 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 ZnCl$_2$·TMEDA) and was identified in an inseparable mixture with the starting material. ^{1}H (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-1*H*-pyrazole (8m) 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 ZnCl$_2$·TMEDA; 5% using 3.0

mmol of 2,2,6,6-tetramethylpiperidine, 3.0 mmol of BuLi and 1.0 mmol of ZnCl$_2$·TMEDA) and was identified in an inseparable mixture with **8'm**. ^{1}H (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 (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) 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 ZnCl$_2$·TMEDA; 9% using 3.0 mmol of 2,2,6,6-tetramethylpiperidine, 3.0 mmol of BuLi and 1.0 mmol of ZnCl$_2$·TMEDA; mp = 118 °C). IR (ATR): 3127, 3069, 2922, 2854, 1560, 1532, 1407, 1388, 1107, 1015, 967, 917, 872 cm^{-1}. ^{1}H (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 (CDCl$_3$, 75 MHz) 82.0, 94.5, 117.7, 125.6, 144.1, 151.9, 152.3, 158.2. HRMS (ESI): calcd for C$_8$H$_5$ClI$_2$N$_3$ [M+H]$^+$ 431.8261, found 431.8260.

1-(2-Chloro-3,5-diiodopyridin-4-yl)-5-iodo-1H-pyrazole (9m) 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 ZnCl$_2$·TMEDA; mp = 184 °C). IR (ATR): 2923, 2854, 1724, 1562, 1531, 1451, 1399, 1194, 1109, 1029, 968, 917 cm^{-1}. ^{1}H (CDCl$_3$, 300 MHz) 6.72 (d, 1H, J = 1.9), 7.79 (d, 1H, J = 1.9), 8.75 (s, 1H). ^{13}C (CDCl$_3$, 75 MHz) 81.3, 95.1, 101.9, 117.7, 144.4, 154.7, 156.4, 156.5. HRMS (ESI): calcd for C$_8$H$_4$ClI$_3$N$_3$ [M+H]$^+$ 557.7228, found 557.7241.

5-Iodo-1-(pyridin-4-yl)-1H-pyrazole (7n) 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}. ^{1}H (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 (CDCl$_3$, 75 MHz) 79.0, 119.5 (2C), 119.7, 144.1, 146.9, 150.9 (2C). HRMS (ESI): calcd for C$_8$H$_7$IN$_3$ [M+H]$^+$ 271.9685, found 271.9690.

5-Iodo-1-(3-iodopyridin-4-yl)-1H-pyrazole (8n) 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}. ^{1}H (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 (CDCl$_3$, 75 MHz) 82.2, 96.8, 117.2, 124.5, 143.5, 149.8, 150.1, 158.7. HRMS (ESI): calcd for C$_8$H$_5$I$_2$N$_3$ [M+H]$^+$ 397.8651, found 397.8661.

5-Iodo-1-(2-iodopyridin-3-yl)-1H-pyrazole (8o) was prepared from **1o** following the general procedure and was obtained as a white solid (28% yield; mp = 138 °C). ^{1}H (CDCl$_3$, 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). ^{13}C (CDCl$_3$, 75 MHz) 83.8, 117.2, 122.2, 123.1, 137.0, 141.1, 143.6, 151.4. HRMS (ESI): calcd for C$_8$H$_5$I$_2$N$_3$ 396.8573, found 396.8547.

5-Iodo-1-(4-iodopyridin-3-yl)-1H-pyrazole (8'o) was prepared from **1o** following the general procedure and was obtained as a white solid (30% yield; mp = 175 °C). ^{1}H (CDCl$_3$, 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). ^{13}C (CDCl$_3$, 75 MHz) 83.7, 110.0, 117.1, 134.5, 140.7, 143.7, 149.5, 150.7. HRMS (ESI): calcd for C$_8$H$_5$I$_2$N$_3$ 396.8573, found 396.8564.

5-Iodo-1-(pyridin-2-yl)-1H-pyrazole (7p) 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}. ^{1}H (CDCl$_3$, 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). ^{13}C (CDCl$_3$, 75 MHz) 77.4, 118.3, 119.5, 123.1, 138.6, 143.5, 147.9, 152.4. HRMS (ESI): calcd for C$_8$H$_6$IN$_3$Na [M+Na]$^+$ 293.9504, found 293.9509.

5-Iodo-1-(3-iodopyridin-2-yl)-1H-pyrazole (8p) 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 ZnCl$_2$·TMEDA; mp = 238 °C). IR (ATR): 3126, 1590, 1565, 1470, 1445, 1403, 1377, 962, 785 cm^{-1}. ^{1}H (CDCl$_3$, 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). ^{13}C (CDCl$_3$, 75 MHz) 81.2, 93.7, 116.8, 126.2, 143.1, 148.7, 149.0, 150.6. HRMS (ESI): calcd for C$_8$H$_5$I$_2$N$_3$Na [M+Na]$^+$ 419.8471, found 419.8469.

5-Iodo-1-(pyrimidin-2-yl)-1H-pyrazole (7q) 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}. ^{1}H (CDCl$_3$, 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). ^{13}C (CDCl$_3$, 75 MHz) 77.7, 119.8, 121.0, 144.7, 156.9, 158.6 (2C). HRMS (ESI): calcd for C$_7$H$_6$IN$_4$ [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-Kα radiation (λ = 0.71073 Å). Except for **8o** (T = 100(2) K), X-ray diffraction data were collected at T = 150(2) K using 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. H atoms were finally included in their calculated positions. 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. C$_{12}$H$_{10}$N$_4$, M_r = 210.24, monoclinic, $P2_1/c$, a = 7.745(4), b = 12.472(6), c = 10.787(5) Å, β = 92.060(14)°, V = 1041.3(9) Å^3, Z = 4, ρ_{calcd} = 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 $\omega R(F^2) = 0.1467$ ($R(F) = 0.0685$) for 1062 observed reflections with $I > 2\sigma(I)$.

Crystal data for 1n. $C_8H_7N_3$, $M_r = 145.17$, monoclinic, $C2/c$, $a = 18.2414(9)$, $b = 5.4302(2)$, $c = 14.7271(7)$ Å, $\beta = 105.429(2)°$, $V = 1406.21(11)$ Å^3, $Z = 8$, $\rho_{calcd} = 1.371$ g cm^{-3}, $\mu = 0.088$ mm^{-1}. A final refinement on F^2 with 1599 unique intensities and 100 parameters converged at $\omega R(F^2) = 0.1059$ ($R(F) = 0.0397$) for 1382 observed reflections with $I > 2\sigma(I)$.

Crystal data for 1o. $C_8H_7N_3$, $M_r = 145.17$, monoclinic, $P2_1/a$, $a = 11.299(3)$, $b = 4.2309(9)$, $c = 14.743(3)$ Å, $\beta = 90.229(8)°$, $V = 704.8(3)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.368$ g cm^{-3}, $\mu = 0.088$ mm^{-1}. A final refinement on F^2 with 1606 unique intensities and 100 parameters converged at $\omega R(F^2) = 0.1401$ ($R(F) = 0.0565$) for 1174 observed reflections with $I > 2\sigma(I)$.

Crystal data for 2b. $C_{11}H_{12}IN_3$, $M_r = 313.14$, monoclinic, $P2_1/n$, $a = 7.3777(3)$, $b = 19.1576(9)$, $c = 8.7098(4)$ Å, $\beta = 111.017(2)°$, $V = 1149.14(9)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.81$ g cm^{-3}, $\mu = 2.758$ mm^{-1}. A final refinement on F^2 with 2611 unique intensities and 138 parameters converged at $\omega R(F^2) = 0.0509$ ($R(F) = 0.0221$) for 2432 observed reflections with $I > 2\sigma(I)$.

Crystal data for 3b. $C_{11}H_{11}I_2N_3$, $M_r = 439.03$, monoclinic, $P2_1/n$, $a = 6.9744(3)$, $b = 26.4537(12)$, $c = 7.2619(3)$ Å, $\beta = 90.717(2)°$, $V = 1339.71(10)$ Å^3, $Z = 4$, $\rho_{calcd} = 2.177$ g cm^{-3}, $\mu = 4.673$ mm^{-1}. A final refinement on F^2 with 3018 unique intensities and 148 parameters converged at $\omega R(F^2) = 0.0601$ ($R(F) = 0.0281$) for 2908 observed reflections with $I > 2\sigma(I)$.

Crystal data for 4b. $C_{17}H_{17}N_3$, $M_r = 263.34$, monoclinic, $P2_1/c$, $a = 6.3843(5)$, $b = 30.629(2)$, $c = 7.1492(6)$ Å, $\beta = 94.735(3)°$, $V = 1393.22(18)$ Å^3, $Z = 4$, $\rho_{calcd} = 1.255$ g cm^{-3}, $\mu = 0.076$ mm^{-1}. A final refinement on F^2 with 3171 unique intensities and 183 parameters converged at $\omega R(F^2) = 0.1439$ ($R(F) = 0.0683$) for 2759 observed reflections with $I > 2\sigma(I)$.

Crystal data for 6j. $C_{12}H_8I_2N_4$, $M_r = 462.02$, orthorhombic, $Pnab$, $a = 8.3852(3)$, $b = 10.2090(3)$, $c = 16.0643(5)$ Å, $V = 1375.18(8)$ Å^3, $Z = 4$, $\rho_{calcd} = 2.232$ g cm^{-3}, $\mu = 4.561$ mm^{-1}. A final refinement on F^2 with 1568 unique intensities and 83 parameters converged at $\omega R(F^2) = 0.0359$ ($R(F) = 0.017$) for 1406 observed reflections with $I > 2\sigma(I)$.

Crystal data for 8l. $C_7H_4I_2N_2S_1$, $M_r = 401.98$, monoclinic, $P2_1/n$, $a = 7.0510(2)$, $b = 20.8154(6)$, $c = 7.2666(2)$ Å, $\beta = 100.688(2)°$, $V = 1048.01(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 2.548$ g cm^{-3}, $\mu = 6.150$ mm^{-1}. A final refinement on F^2 with 2381 unique intensities and 109 parameters converged at $\omega R(F^2) = 0.0619$ ($R(F) = 0.0292$) for 2269 observed reflections with $I > 2\sigma(I)$.

Crystal data for 9m. $C_8H_3ClII_3N_3$, $M_r = 557.28$, monoclinic, $P2_1/n$, $a = 11.8807(5)$, $b = 7.3931(3)$, $c = 14.3980(6)$ Å, $\beta = 92.696(2)°$, $V = 1263.25(9)$ Å^3, $Z = 4$, $\rho_{calcd} = 2.93$ g cm^{-3}, $\mu = 7.606$ mm^{-1}. A final refinement on F^2 with 2882 unique intensities and 101 parameters converged at $\omega R(F^2) = 0.0924$ ($R(F) = 0.04$) for 2561 observed reflections with $I > 2\sigma(I)$.

Crystal data for 7n. $C_8H_6IN_3$, $M_r = 271.06$, monoclinic, $P2_1/c$, $a = 7.1532(3)$, $b = 14.7450(6)$, $c = 8.1035(4)$ Å, $\beta = 91.8830(10)°$, $V = 854.25(7)$ Å^3, $Z = 4$, $\rho_{calcd} = 2.108$ g cm^{-3}, $\mu = 3.692$ mm^{-1}. A final refinement on F^2 with 1957 unique intensities and 109 parameters converged at $\omega R(F^2) = 0.0504$ ($R(F) = 0.0207$) for 1824 observed reflections with $I > 2\sigma(I)$.

Crystal data for 8n. $C_8H_5I_2N_3$, $M_r = 396.95$, monoclinic, $P2_1/c$, $a = 7.1322(2)$, $b = 10.9173(3)$, $c = 13.3983(4)$ Å, $\beta = 99.7590(10)°$, $V = 1028.15(5)$ Å^3, $Z = 4$, $\rho_{calcd} = 2.564$ g cm^{-3}, $\mu = 6.075$ mm^{-1}. A final refinement on F^2 with 2357 unique intensities and 118 parameters converged at $\omega R(F^2) = 0.0445$ ($R(F) = 0.018$) for 2220 observed reflections with $I > 2\sigma(I)$.

Crystal data for 8o. $C_8H_5I_2N_3$, $M_r = 396.95$, monoclinic, $P2_1/n$, $a = 6.8316(4)$, $b = 13.4938(7)$, $c = 12.1649(7)$ Å, $\beta = 101.594(2)°$, $V = 1098.53(11)$ Å^3, $Z = 4$, $\rho_{calcd} = 2.4$ g cm^{-3}, $\mu = 5.685$ mm^{-1}. A final refinement on F^2 with 2499 unique intensities and 118 parameters converged at $\omega R(F^2) = 0.0675$ ($R(F) = 0.0291$) for 2315 observed reflections with $I > 2\sigma(I)$.

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Notes and references

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† Electronic supplementary information (ESI) available: 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). See DOI: 10.1039/b000000x/

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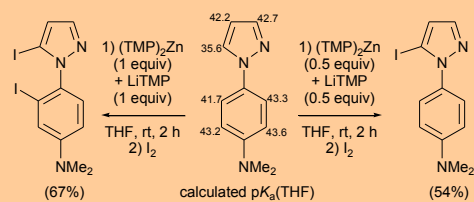
N-(hetero)arylpyrazoles have been deproto-metallated using 1:1 LiTMP-(TMP)$_2$Zn. The outcome of the reactions has been discussed in the light of DFT-calculated CH acidities (gas phase and THF solution).