Organic & Biomolecular Chemistry

PAPER

View Article Online
View Journal | View Issue

Cite this: *Org. Biomol. Chem.*, 2014, **12**, 1475

Deproto-metallation using a mixed lithium–zinc base and computed CH acidity of 1-aryl 1*H*-benzotriazoles and 1-aryl 1*H*-indazoles†

Elisabeth Nagaradja,[a] Floris Chevallier,*[a] Thierry Roisnel,[b] Vincent Dorcet,[b] Yury S. Halauko,*[c] Oleg A. Ivashkevich,[c] Vadim E. Matulis[d] and Florence Mongin*[a]

Received 27th November 2013,
Accepted 20th December 2013

DOI: 10.1039/c3ob42380h

www.rsc.org/obc

1-Aryl-1*H*-benzotriazoles and -1*H*-indazoles were synthesized, and their deproto-metallation using the base prepared by mixing LiTMP with $ZnCl_2$·TMEDA (1/3 equiv.) was studied. In the indazole series, reactions occurring at the 3 position were followed by ring opening, and functionalization of the substrate was only found possible (on the sulfur ring) using 2-thienyl as aryl group. In the benzotriazole series, either mono- or bis-deprotonation (depending on the amount of base employed) was achieved with phenyl, 4-methoxyphenyl and 2-thienyl as aryl group, and bis-deprotonation in the case of 4-chlorophenyl and 4-trifluoromethylphenyl. The experimental results were analyzed with the help of the CH acidities of the substrates, determined in THF solution using the DFT B3LYP method.

Introduction

Di- and triazoles and their benzo analogues are key elements present in compounds of biological interest,[1] or in materials for a large range of applications.[1a,b,2]

Deprotonative lithiation[3] is an efficient tool to functionalize regioselectively aromatic heterocycles such as pyrroles,[4] indoles,[5] polyazoles,[6] furans,[7] thiophenes,[8] oxazoles,[9] thiazoles,[10] azines[11] and polyazines.[12]

Few examples concern the direct lithiation of benzotriazoles.[13] In 1995, Katritzky's team showed that, whereas benzotriazole can behave like a directing group for deproto-lithiation of a substituent connected to its N1 nitrogen,[14] further benzotriazole ring deprotonation is far less efficient (<20% yield).[15] After studies on the lateral dilithiation of *N*-Boc 1-amino-7-methylbenzotriazole,[16] Knight's group reported the double deproto-metallation of *N*-Boc 1-aminobenzotriazole using butyllithium in THF containing tetraglyme at −78 °C, affording after electrophilic trapping 7-substituted derivatives.[17] Katritzky and co-workers described in 1998 a few ring deproto-lithiation reactions followed by methylation starting from complexes between borane and 1-alkyl benzotriazoles (reaction at the 4 position).[18] One year later, Johnson and co-workers reported similar metallation at the 4 position, but this time from borane-free 1-(alkoxymethyl)benzotriazoles using lithium diisopropylamide at low temperature.[19] Katritzky and co-workers documented in 2003 dianion formations (metallation at both the 7 position and the lateral chain) from benzotriazoles bearing a vinyl chain using butyllithium in THF at −78 °C.[20]

In the indazole series, deproto-lithiation only proved possible in the case of 2-substituted 2*H*-indazoles for which ring opening of 3-lithio derivatives is unlikely.[6b]

For the functionalization of such substrates, monometal lithium bases are employed at very low temperatures and do not tolerate the presence of reactive functional groups.

Combinations of lithium reagents and softer metal compounds have recently emerged as efficient tools to deproto-metallate sensitive aromatic compounds.[21] In the framework of these studies, our group developed efficient pairs of metal amides which complement each other in deproto-metallation

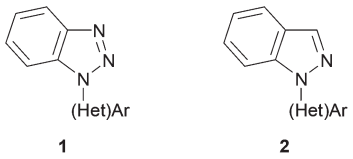
[a]*Equipe Chimie et Photonique Moléculaires, Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes 1, Bâtiment 10A, Case 1003, Campus Scientifique de Beaulieu, 35042 Rennes, France. E-mail: floris.chevallier@univ-rennes1.fr, florence.mongin@univ-rennes1.fr; Fax: +33-2-2323-6955*

[b]*Centre de Diffractométrie X, Institut des Sciences Chimiques de Rennes, UMR 6226 CNRS-Université de Rennes 1, Bâtiment 10B, Campus de Beaulieu, 35042 Rennes, France*

[c]*Department of Chemistry of Belarusian State University, 14 Leningradskaya Str., Minsk, 220030, Belarus. E-mail: hys@tut.by*

[d]*Research Institute for Physico-Chemical Problems of Belarusian State University, 14 Leningradskaya Str., Minsk, 220030, Belarus. Fax: +375-17-2264696*

†Electronic supplementary information (ESI) available: ^{1}H, ^{13}C and ^{19}F NMR spectra, crystal data, calculated values of the Gibbs energies $\Delta_{acid}G$ [kcal mol^{-1}] for deprotonation at the corresponding positions of the investigated heteroaromatic compounds, and selected Cartesian coordinates of molecular geometry for the most stable rotamer forms of the investigated heteroaromatics (on example of **1e**, **2e**) (neutral molecule, gas phase) optimized at B3LYP/6-31G(d) level of theory. CCDC 962368–962380. For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c3ob42380h



Scheme 1 Substrates for which the deproto-metallation was studied.

reactions. In particular, the TMP-based (TMP = 2,2,6,6-tetramethylpiperidino) lithium–zinc mixture, prepared by mixing $ZnCl_2$·TMEDA (TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) with LiTMP (3 equiv.), and supposed to be a 1 : 1 LiTMP·2LiCl(±TMEDA)–$Zn(TMP)_2$ mixture,[22] was identified as a synergic reagent (more efficient than separate LiTMP and $Zn(TMP)_2$) to functionalize sensitive aromatic compounds including heterocycles.[22a,23]

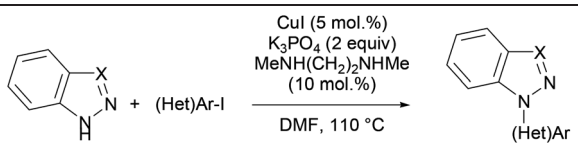
We herein describe our attempts to use such a lithium–zinc combination for the deproto-metallation of the azole substrates shown in Scheme 1. We earlier showed that the regioselectivity of the reaction for related substrates is partly determined by the acidity of the different hydrogens in their molecules.[23f,h,24] Similarly, we here tried to rationalize the reaction results using the CH acidities in THF of the heteroaromatic substrates calculated using the homodesmic reaction approach within the density functional theory (DFT) framework.

Results and discussion

Synthetic aspects

To reach the target substrates **1** and **2**, the unsubstituted azoles were treated with aryl and heteroaryl iodides under copper catalysis using the conditions reported by Buchwald and co-workers (Table 1).[25] Moderate to excellent yields were

Table 1 Synthesis of the azole substrates **1** and **2**



Entry	X	(Het)Ar	Product(s), Yield(s)[a] (%)
1	N	Ph	**1a**, 57
2	N	4-FC_6H_4	**1b**, 80 (**1b**′, 5)[b]
3	N	4-ClC_6H_4	**1c**, 78 (**1c**′, 9)[b]
4	N	4-$F_3CC_6H_4$	**1d**, 71
5	N	4-$MeOC_6H_4$	**1e**, 43 (**1e**′, 3)[b]
6	N	3-Pyridyl	**1f**, 69
7	N	2-Thienyl	**1g**, 41 (**1g**′, 5)[b]
8	CH	Ph	**2a**, 98
9	CH	4-$F_3CC_6H_4$	**2d**, 99
10	CH	4-$MeOC_6H_4$	**2e**, 79
11	CH	2-Thienyl	**2g**, 83

[a] After purification. [b] The isomeric 2-aryl derivatives **1**′ were isolated by column chromatography.

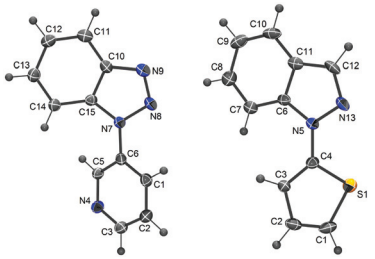


Fig. 1 ORTEP diagrams (50% probability) of **1f** and **2g**.

noted, with aryl iodides substituted by electron-withdrawing groups in general favouring the reaction. In the benzotriazole series, the isomeric 2-aryl derivatives **1**′, also formed in low yields, were discarded by column chromatography. The N-arylation site was confirmed for the derivatives **1f** and **2g** by X-ray diffraction analysis (Fig. 1).‡

As indicated by Buchwald and co-workers, the method is not suitable for N-arylation using aromatic bromides. Indeed, it failed to give efficiently N-heteroarylated products when 3-bromopyridine and 4-bromoisoquinoline were employed, even by trying to generate *in situ* the corresponding iodides.[26]

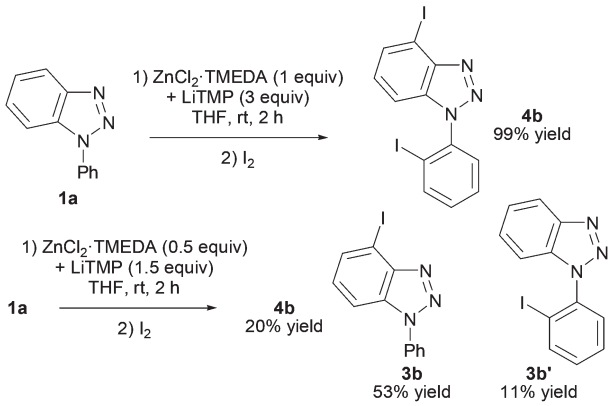
Concerning the deproto-metallation reaction using the TMP-based lithium–zinc mixture, optimization studies performed on different substrates showed that THF is the most suitable solvent, and 2 h a sufficient reaction time for a reaction performed at room temperature.[23a,b,e] Even if other kinds of trapping can be employed (interception with aldehydes, phenyl disulfide and allyl bromide, and palladium-catalyzed cross-coupling with aryl halides),[23d] we chose iodolysis because of its efficiency and since it is possible to involve the generated heterocyclic iodides in different transition metal-catalyzed coupling reactions.[23f]

Except for **1b** and **1f** from which complex mixtures were obtained, they led to interpretable results.

Upon treatment in THF for 2 h at room temperature with the lithium–zinc base, *in situ* prepared from $ZnCl_2$·TMEDA (0.5 equiv.) and LiTMP (1.5 equiv.), and subsequent interception with iodine, 1-phenyl-1*H*-benzotriazole (**1a**) was converted to a mixture containing the 4-iodo (**3b**, 53% yield), 2′-iodo (**3b**′, 11% yield) and 4,2′-diiodo (**4b**, 20% yield) derivatives in addition to the starting material (13% yield). The diiodide **4b** was isolated in 99% yield when 1 equiv. of $ZnCl_2$·TMEDA and 3 equiv. of LiTMP were employed (Scheme 2). All the products were identified unequivocally by X-ray diffraction (Fig. 2).‡

Starting from 1-(4-chlorophenyl)-1*H*-benzotriazole (**1c**), the use of 0.5 equiv. of $ZnCl_2$·TMEDA and 1.5 equiv. of LiTMP led to a complex mixture together with the starting material. The presence of the halogen, which is capable of acidifying the neighbouring hydrogens,[27] could be at the origin of a larger number of deprotonation sites. By increasing the amount of

‡CIF files available in the ESI:† CIF files of **1f** (CCDC 962368), **2g** (962369), **3b** (962370), **3b**′ (962371), **3e** (962372), **3g** (962373), **4b** (962374), **4c** (962375), **4c**′ (962376), **4d** (962377), **4e** (962378), **4e**′ (962379), and **4g** (962380).



Scheme 2 Deproto-metallation of **1a** followed by iodination.

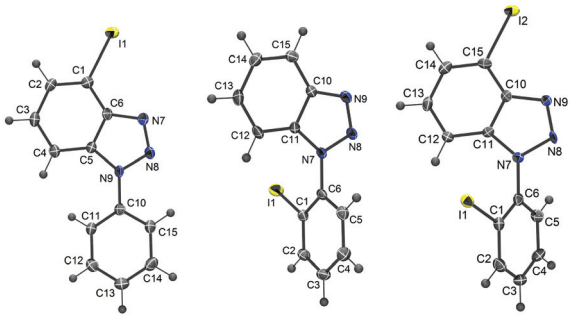
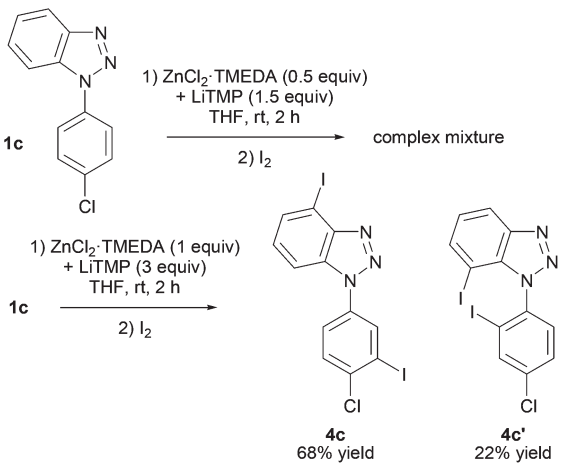


Fig. 2 ORTEP diagrams (50% probability) of **3b**, **3b′** and **4b**.



Scheme 3 Deproto-metallation of **1c** followed by iodination.

base (1 equiv. of $ZnCl_2$·TMEDA and 3 equiv. of LiTMP), the diiodides **4c** and **4c′** were obtained in 68 and 22% yield, respectively (Scheme 3), and their structure was identified unambiguously by X-ray diffraction (Fig. 3).‡

Using 1-(4-trifluoromethylphenyl)-1*H*-benzotriazole (**1d**) as the substrate similarly led to the formation of a complex

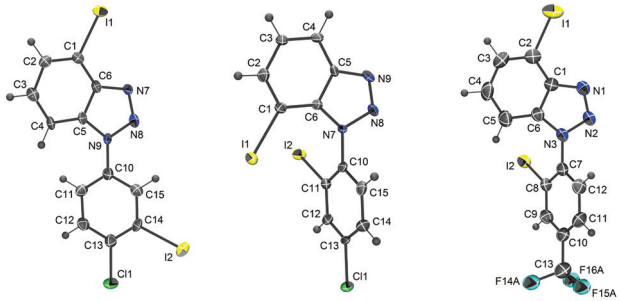
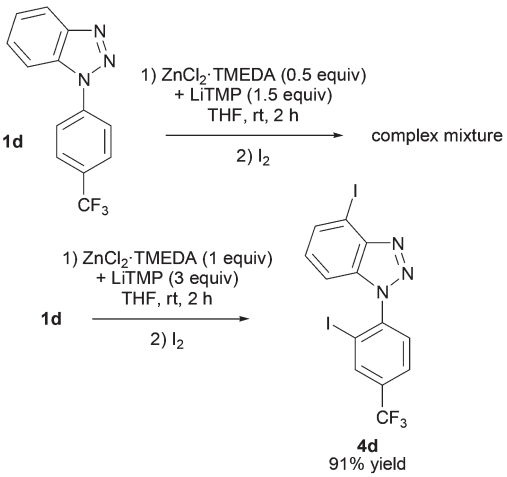


Fig. 3 ORTEP diagrams (50% probability) of **4c**, **4c′** and **4d**.

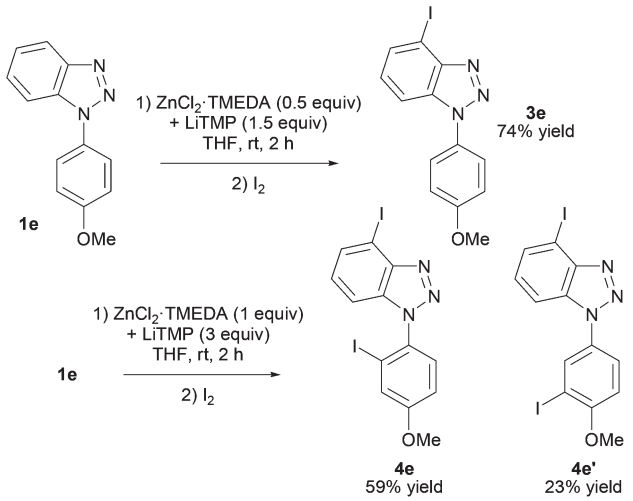


Scheme 4 Deproto-metallation of **1d** followed by iodination.

mixture in addition to the starting material upon treatment with a low amount of base. However, increasing the amount of base in this case only afforded the diiodide **4d**, isolated in 91% yield (Scheme 4 and Fig. 3).‡ The size of the trifluoromethyl group, together with its long range acidifying effect,[27] are both important factors that could explain why there is no metallation at its adjacent position.

Anisole being easily *ortho*-deprotonated under similar reaction conditions,[23d] it was interesting to involve in the deprotonation–iodination sequence 1-(4-methoxyphenyl)-1*H*-benzotriazole (**1e**). The monoiodide **3e** was obtained in 74% yield using 0.5 equiv. of $ZnCl_2$·TMEDA and 1.5 equiv. of LiTMP (together with the starting material). This reaction on the benzotriazole ring, similar to that observed using the benzotriazole **1a**, could be due to the lack of a long range acidifying effect of the methoxy group when compared with a chloro or a trifluoromethyl. As expected, doubling the amount of base resulted in the formation of the diiodides **4e** and **4e′**. All the iodides obtained were identified by X-ray diffraction from suitable crystals (Scheme 5, Fig. 4).‡

Finally,[28] the deproto-metallation of 1-(2-thienyl)-1*H*-benzotriazole (**1g**) was similarly performed to afford either the monoiodide **3g** resulting from a reaction next to sulfur, or the diiodide **4g** (minor other iodides were also noted) coming



Scheme 5 Deproto-metallation of **1e** followed by iodination.

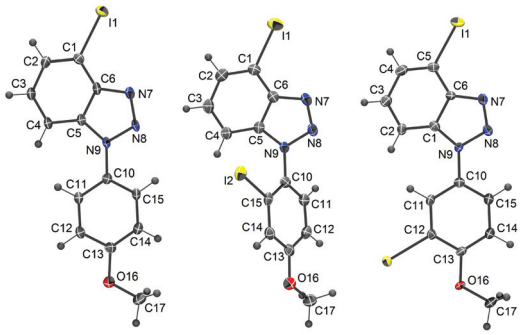
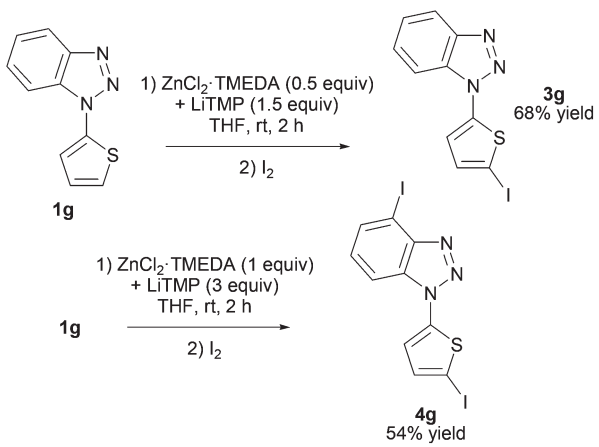


Fig. 4 ORTEP diagrams (50% probability) of **3e**, **4e** and **4e'**.



Scheme 6 Deproto-metallation of **1g** followed by iodination.

from an attack of both the 4 and 5′ positions (Scheme 6). The structures of the derivatives **3g** and **4g** were confirmed by X-ray analysis (Fig. 5).‡

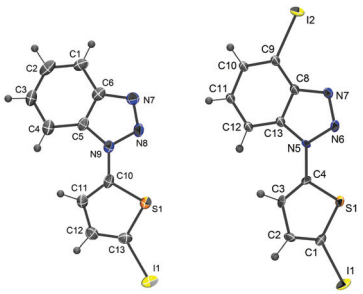
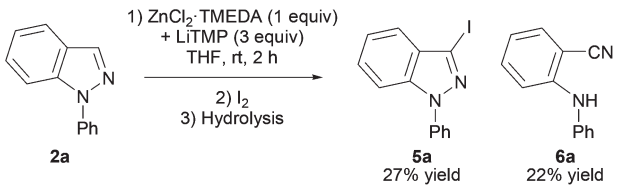


Fig. 5 ORTEP diagrams (50% probability) of **3g** and **4g**.



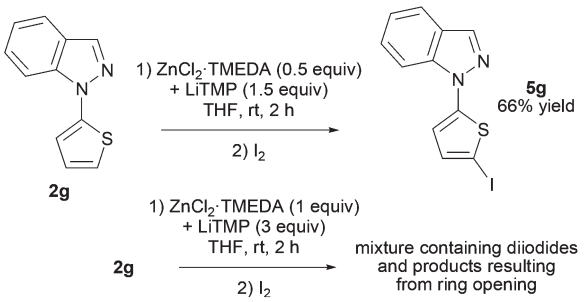
Scheme 7 Deproto-metallation of **2a** followed by iodination.

The deproto-metallation of the 1-substituted 1*H*-indazoles **2** was next attempted. To our knowledge, only diisopropylzinc in the presence of catalytic lithium acetylacetonate[29] and $Zn(TMP)_2$ [30] are capable of deprotonating 1-substituted 1*H*-indazoles at their 3 position. Using soft $Li(TMP)Zn(^tBu)_2$, deprotonation of **2a** in THF at temperatures between −78 and −40 °C for 1–2 h leads to the corresponding *N*-(2-cyanophenyl)anilide, coming from ring opening of the 3-metallated derivative.[31]

Upon treatment with 0.5 equiv. of each metal amide (LiTMP and $Zn(TMP)_2$), the substrates **2a**, **2d** and **2e** did not lead to efficient functionalization, and the starting material was the main compound recovered. Using 1 equiv. of each metal amide in the case of 1-phenyl-1*H*-indazole (**2a**) allowed us to obtain the expected 3-iodo derivative **5a**, but in a moderate 27% yield due to ring opening of the metallated species before quenching. Indeed, the formation of the nitrile **6a** (22% yield) was also observed (Scheme 7).

In the case of 1-(4-trifluoromethylphenyl)-1*H*-indazole (**2d**), using 1 equiv. of each metal amide (LiTMP and $Zn(TMP)_2$) led to the formation of a monoiodide (20% yield) coming from the deprotonation of the aryl group at the position *meta* to the trifluoromethyl. This monoiodide and the substrate **2d** (7% yield) were the only products obtained after reaction work-up. With 1-(4-methoxyphenyl)-1*H*-indazole (**2e**), metallation at the position adjacent to the nitrogen followed by ring opening took place under the same reaction conditions, as shown by the absence of hydrogen at the 3 position for some of the products contained in the complex mixture obtained.

From 1-(2-thienyl)-1*H*-indazole (**2g**), a reaction at the 5 position of the thienyl ring was observed using 0.5 equiv. of each metal amide, and the iodide **5g** was isolated in 66% yield (Scheme 8). Increasing the base amount in this case led to small quantities of diiodides together with ring opening.



Scheme 8 Deproto-metallation of **2g** followed by iodination.

Computational aspects

CH acidity of substances related to the investigated substrates has been the subject of few studies. A brief review of papers devoted to experimental and theoretical investigations of CH acidity of azoles is presented in our previous publication.[24a] One should especially mention pK_a values in THF experimentally found for benzofuran, benzothiophene, benzoxazole, benzothiazole, *N*-methylindole and alkylazoles.[32] The values obtained were correlated with semi-empirical AM1 gas-phase deprotonation energies,[33] and also with those estimated by means of DFT calculations recently.[34] Some experimental[35] and semi-empirical[36] gas-phase acidities of condensed heteroaromatics were also reported. In the present paper, the DFT calculations of CH acidity of the different *N*-aryl benzazoles, both in gas phase (see ESI†) and in THF solution (Scheme 9), are presented.

The gas phase acidities $\Delta_{acid}G$ and pK_a values in THF solution of all the substrates were calculated using the theoretical protocol described previously.[24]

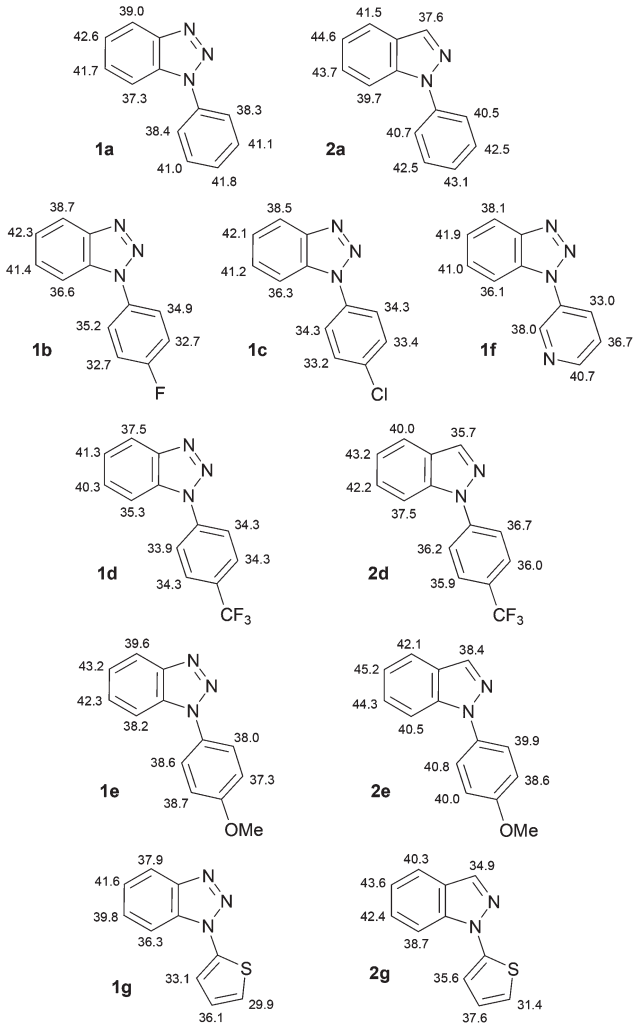
All the calculations were performed by using the DFT B3LYP method. The geometries were optimized using the 6-31G(d) basis set. No symmetry constraints were applied. In order to perform stationary point characterization and to calculate zero-point vibrational energies (ZPVE) and thermal corrections, vibrational 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 and tight convergence criteria. The gas phase Gibbs energies (G^0_{298}) were calculated for each isolated species using the following equation:

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

The gas phase acidities $\Delta_{acid}G$ were determined as the Gibbs energies of deprotonation of the substrates R – H ($\mathrm{R-H_{(g)} \rightarrow R^-_{(g)} + H^+_{(g)}}$) by the following formula:

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

The solvent influence was accounted for by using the polarized continuum model (PCM) with the default parameters for



Scheme 9 Calculated values of pK_a(THF) of the investigated compounds.

THF.[37] The cavity was built up using a united atom (UA) model, applied to 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:

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

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

$$\mathrm{R-H_{(s)} + Het^-{}_{(s)} \rightarrow R^-{}_{(s)} + Het - H_{(s)}},$$

where Het – H is an appropriate heterocycle with the experimentally known pK_a value. In this study, 1-propylpyrazole was chosen as a reference compound owing to its structural similarity and since its pK_a value in THF found by Fraser *et al.*,[32] 35.9, was supposed to be close to those for the investigated substrates.

It could be shown by a little algebra that the Gibbs energies of the homodesmic reactions ($\Delta_r G_s$) and the pK_a values are linked together by the following equations:

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

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

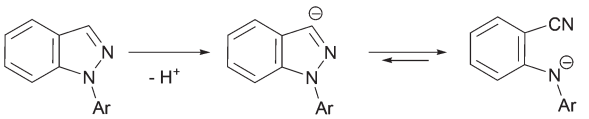
The CH acidity of the methoxy groups for the substrates **1e** and **2e** was not considered here since it was expected to be significantly lower and also because there was no sign of their deprotonation in the experiments.

It is obvious that some of the investigated compounds exist in the form of several rotamers due to sterical interaction with adjacent hydrogens and/or heteroatom lone pairs. In such cases, the data on Scheme 9 refer to the most stable ones. Moreover, among the molecules with several rotamers, the pyridyl benzotriazole **1f** is likely to exist in a form with remote heteroatoms (nitrogens) while for the sulfur-containing compounds **1g** and **2g** it is *vice versa*.

There are several potential deprotonation sites in the investigated substrates. When comparing the CH acidity in gas-phase (see ESI†) and in THF solution (Scheme 9), the correlation can be easily seen. The analysis of the obtained results shows that CH acidity increases logically with the introduction of electron-withdrawing groups, and decreases for electron-donating ones.

When analyzing the CH acidities distribution for a common structural motif, namely the benzocondensed part of the molecules, one can see some general trends. The most acidic hydrogen is at the 7 position followed by the 4 position.

For the benzotriazoles and indazoles bearing a 4-substituted phenyl group on N1, there is almost no difference in C–H acidity between the C2′ and C6′ sites, as well as between the C3′ and C5′ sites, a result in contrast with what was noticed earlier for *N*-arylpyrazoles.[23f] This difference between both series could be explained in terms of electronic and steric influence of the benzo part of the molecule.



Scheme 10 Possible side-reaction under equilibrium conditions.

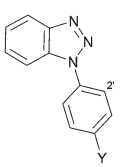
One distinct peculiarity for deprotonation at C3 of indazoles should be mentioned. Our calculations predict that these particular carbanions represent local shallow minima. Hence, under appropriate conditions, N–N bond cleavage can take place, leading to more stable 2-cyanoanilides (Scheme 10).

It is strongly desirable to evaluate the impact of the nature of the substituents (through their electronic effects) on the CH acidity (hence on their reactivity) in a series of related substrates. This could be achieved 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.[38] The linear free energy relationship (LFER) methodology can also be used to study the electronic effects of the substituents on the CH acidity.

We chose 1-substituted 1*H*-benzotriazoles for this purpose. The influence of the substituent on the reaction centre was tracked in relation to two aspects: (a) the influence of the X substituent nature of the heterocycle on the pK_a at the 4 position of the condensed system, which is rather acidic but free of steric hindrance (Table 2, entries 1–5), and (b) the influence of the Y substituent nature of the *N*-(4-substituted phenyl)benzotriazole on the pK_a at the 2′ position (Table 2, entries 6–10). The data obtained show that there is a correlation between the (electron-donating or electron-withdrawing) nature of the X or Y substituent and the pK_a change.

Unfortunately, this study was also restricted by lack of data on some LFER constants. As pure *ortho*-, *meta*- and *para*-positions cannot be found neither for five-membered rings nor for annelated systems, it is logical to use Jaffe's approach to describe the substituent effects in these 'unconventional'

Table 2 Calculated pK_a(THF) values for the heterocycles and substituent constants[38]

Entry	Compound, X or Y		pK_a (THF)	σ_m	σ_p	F	R
1		**1a**, Ph	39.0	0.06	−0.01	0.12	−0.13
2		**1b**, 4-FC_6H_4	38.7	0.12	0.06	0.17	−0.11
3		**1c**, 4-ClC_6H_4	38.5	0.15	0.12	0.18	−0.06
4		**1e**, 4-$MeOC_6H_4$	39.6	0.05	−0.08	0.13	−0.21
5		**1f**, 3-Pyridyl	38.1	0.23	0.25	0.24	0.01
6		**1a**, H	38.3	0.00	0.00	0.00	0.00
7		**1b**, F	34.9	0.34	0.06	0.45	−0.39
8		**1c**, Cl	34.3	0.37	0.23	0.42	−0.19
9		**1d**, CF_3	34.3	0.43	0.54	0.38	0.16
10		**1e**, OMe	38.0	0.12	−0.27	0.29	−0.56

rings according to:

$$\text{Property} = a_1 + a_2\sigma_m + a_3\sigma_p \text{ (where } a_i \text{ – fitted constants).}$$

The best equation within this approach for the position 4 of compounds (Table 2, entries 1–5) is as follows:

$$pK_a(\text{THF}) = 38.3 + 9.3\ \sigma_m - 9.7\ \sigma_p \quad (N = 5, r^2 = 0.975, \text{rmse} = 0.079)$$

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).[38] The best equation for the same compounds within this approach is:

$$pK_a(\text{THF}) = 38.0 + 0.50\ F - 7.0\ R \quad (N = 5, r^2 = 0.975, \text{rmse} = 0.079)$$

Thereby, both approaches give the equations for CH acidity prediction of comparable quality. The influence of a substituent on the forming carbanion center could be described in terms of a combination of inputs of both *meta*- and *para*-groups in the benzene ring while the resonance effects predominate over the inductive.

Concerning the CH acidity at the 2′ position of the compounds (Table 2, entries 6–10), the benzotriazole was treated as an ordinary substituent. This led to a good correlation even under one-parametric formalism:

$$pK_a(\text{THF}) = 38.7 - 10.8\ \sigma_m \quad (N = 5, r^2 = 0.954, \text{rmse} = 0.22)$$

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

$$pK_a(\text{THF}) = 38.5 - 10.7\ F - 3.8\ R \quad (N = 5, r^2 = 0.954, \text{rmse} = 0.27)$$

and

$$pK_a(\text{THF}) = 38.5 - 9.8\ \sigma_m - 0.8\ \sigma_p \quad (N = 5, r^2 = 0.960, \text{rmse} = 0.25)$$

So, the correlation between calculated and predicted pK_a values of investigated compounds using LFER equations gives the opportunity to predict their reactivity semi-quantitatively at low computational cost.

Discussion

The calculations of the CH acidities in THF (Scheme 9) allowed us to comment on the regioselectivities observed in the course of the reactions. However, it is worth noting that coordination of substrate heteroatoms (*e.g.* nitrogen, oxygen, *etc.*) to metals (*e.g.* of the base) can impact (reduce) the neighbouring pK_a values. In addition, it is important to keep in mind that the rationalization of the second deproto-metallation site using the substrate pK_a values is a rather oversimple approach since the first reaction (giving a lithium–zinc arylmetal species) will lead to a different distribution of acidities.

In the case of the substrates **1g** and **2g**, with a 2-thienyl group connected to the azole nitrogen, deproto-metallation at the 5 position of the thienyl substituent is the first reaction observed using the base prepared from $ZnCl_2$·TMEDA (0.5 equiv.) and LiTMP (1.5 equiv.) (Schemes 6 and 8). This result, evidenced by subsequent trapping with iodine, corresponds to a reaction at the most acidic site.

Upon treatment with 1 equiv. of each metal amide (LiTMP and $Zn(TMP)_2$), the phenyl-substituted indazole **2a** (and to a lesser extent its methoxy-substituted derivative **2e**) is similarly attacked at its most acidic site, at the indazole 3 position (Scheme 7). If an electron-withdrawing group such as a trifluoromethyl is connected to the 4 position of the phenyl substituent (substrate **2d**), competitive reaction on the benzene ring, at a position *meta* to the trifluoromethyl (which is a long range acidifying group)[27] and *ortho* to the 1*H*-1-indazolyl, is observed.

The calculations performed on the benzotriazole derivatives **1** show that the hydrogen at the 7 position is always more acidic than that at the 4 position. Nevertheless, reactions of the 1-substituted 1*H*-benzotriazoles **1a**, **1d**, **1e** and **1g** do not lead to any 7-iodo derivative, a result that could be due either to steric hindrance disfavouring a reaction at C7 or more probably to the presence of a nitrogen able to coordinate a metal favouring a reaction at C4. In the absence of an electron-withdrawing substituent on the phenyl ring 1-connected to 1*H*-benzotriazole, deprotonation first takes place at the 4 position of the heterocycle, as shown using 0.5 equiv. of each metal amide in the case of 1-phenyl-1*H*-benzotriazole (**1a**) and its methoxy derivative **1e** (Schemes 2 and 5). For the latter, such a result is surprising since there are more acidic sites on the phenyl ring, in particular *ortho* to the alkoxy group. Using the same reaction conditions with the substrates **1c** and **1d**, respectively bearing electron-withdrawing chloro and trifluoromethyl groups, leads to the formation of complex mixtures (Schemes 3 and 4).

Reacting the benzotriazole derivatives **1** with 1 equiv. of each metal amide furnishes diiodides, as previously noted with other azoles.[23f,h] From 1-phenyl-1*H*-benzotriazole (**1a**), the 1*H*-1-benzotriazolyl activates the neighboring site, and the second reaction occurs at the phenyl ring, affording after interception with iodine the 4,2′-diiodide **4b** (Scheme 2). Things are similar in the presence of a trifluoromethyl group at the 4 position of the phenyl ring (substrate **1d**, Scheme 4). When a methoxy group is introduced at the 4 position of the phenyl ring (substrate **1e**), the *ortho* sites are acidified by its inductive effect. As a consequence, not only the 4,2′-diiodide **4e** but also the 4,3′-diiodide **4e′** are produced (Scheme 5). As trifluoromethyl, the chloro group exhibits a strong acidifying effect,[27] leading in this case to the major formation of the 4,3′-diiodide **4c**. Curiously, the 7,2′-diiodo isomer **4c′** also forms from the substrate **1c** (Scheme 3). Finally, the role of the N3 heteroatom

in favouring the reaction at the 4 position is also evidenced in the case of **1g**, which is converted to the 4,5′-diiodide **4g** (Scheme 6).

Conclusions

Unlike 2-aryl 2*H*-1,2,3-triazoles for which ring opening is also possible after deproto-metallation, 1-aryl 1*H*-indazoles could not be functionalized efficiently at the position α to nitrogen by using the lithium–zinc base *in situ* prepared from $ZnCl_2$·TMEDA and LiTMP (3 equiv.) due to further easy ring opening.

The deproto-metallation of several 1-aryl 1*H*-benzotriazoles was also studied using this base. Interception of the metallated species by iodine led to mono- or di-iodides, depending on the amount of base employed. The CH acidities of the substrates in THF solution, which were calculated using a continuum solvation model, were used to rationalize the outcome of the reactions.

The iodo derivatives thus generated could be elaborated. For example, the monoiodides could be involved in Suzuki cross-coupling reactions, as shown recently in the pyrazole series.[23f] Concerning the diiodides, regioselective metal–halogen exchange[39] could be performed in order to functionalize, one after another, both iodinated sites.

Experimental

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. ^{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 are relative to the central peak of the solvent signal.[40] Mass spectra (HRMS) measurements were performed at the CRMPO (Centre Régional de Mesures Physiques de l'Ouest) of Rennes using a Waters Q-TOF 2 instrument in positive electrospray CI mode.

General procedure 1 for the synthesis of the 1-aryl 1*H*-benzotriazoles 1a–g and 2a,d,e,g[25]

A mixture of CuI (0.10 g, 0.50 mmol), the required azole (10 mmol), K_3PO_4 (4.4 g, 20 mmol), the required halide (12 mmol) and *N*,*N*′-dimethylethylenediamine (0.11 mL, 1.0 mmol) in DMF (5 mL) was degased and heated under argon at 110 °C for 72 h. After filtration over celite (washing using AcOEt) and removal of the solvents, the crude product was purified by chromatography over silica gel (the eluent is given in the product description).

1-Phenyl-1*H*-benzotriazole (**1a**) was prepared from benzotriazole (1.2 g) and iodobenzene (1.4 mL) using the general procedure 1, and was isolated (eluent: 4 : 1 heptane–AcOEt) in 57% yield (1.1 g) as an orange powder: mp 86 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.45 (dt, 1H, J = 8.2, 6.9 and 1.0 Hz), 7.49–7.65 (m, 4H), 7.75–7.82 (m, 3H), 8.16 (dt, 1H, J = 8.1 and 0.9 Hz); ^{13}C{1H} NMR ($CDCl_3$, 75 MHz) 110.5 (CH), 120.5 (CH), 123.1 (2CH), 124.5 (CH), 128.4 (CH), 128.8 (CH), 130.0 (2CH), 132.5 (C), 137.2 (C), 146.7 (C). The NMR data are analogous to those previously described.[41]

1-(4-Fluorophenyl)-1*H*-benzotriazole (**1b**) was prepared from benzotriazole (1.2 g) and 1-fluoro-4-iodobenzene (2.7 g) using the general procedure 1, and was isolated (eluent: 4 : 1 heptane–AcOEt) in 80% yield (1.7 g) as a yellow powder: mp 119 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.27–7.33 (m, 2H), 7.43 (ddd, 1H, J = 8.3, 7.0 and 1.0 Hz), 7.55 (ddd, 1H, J = 8.3, 6.9 and 1.1 Hz), 7.68 (dt, 1H, J = 8.4 and 0.9 Hz), 7.72–7.77 (m, 2H), 8.14 (ddd, 1H, J = 8.3, 1.0 and 0.9 Hz); ^{13}C{1H} NMR ($CDCl_3$, 75 MHz) 110.0 (CH), 116.9 (d, 2CH, J = 23 Hz), 120.3 (CH), 124.5 (CH), 124.8 (d, 2CH, J = 9 Hz), 128.4 (CH), 132.3 (C), 133.1 (d, C, J = 3 Hz), 146.4 (C), 162.3 (d, C, J = 249 Hz); ^{19}F{1H} NMR ($CDCl_3$, 282 MHz) −112. The NMR data are analogous to those previously described.[41] 2-(4-Fluorophenyl)-2*H*-benzotriazole (**1b′**) was also isolated (eluent: 4 : 1 heptane–AcOEt) in 5% yield (0.11 g) as a green powder: mp 92 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.21–7.24 (m, 2H), 7.41–7.44 (m, 2H), 7.91–7.94 (m, 2H), 8.32–8.37 (m, 2H); ^{13}C{1H} NMR ($CDCl_3$, 75 MHz) 116.5 (d, 2CH, J = 23 Hz), 118.4 (2CH), 122.5 (d, 2CH, J = 9 Hz), 127.4 (2CH), 136.7 (d, C, J = 3 Hz), 145.2 (2C), 162.9 (d, C, J = 249 Hz); ^{19}F{1H} NMR ($CDCl_3$, 282 MHz) −112.

1-(4-Chlorophenyl)-1*H*-benzotriazole (**1c**) was prepared from benzotriazole (1.2 g) and 1-chloro-4-iodobenzene (2.9 g) using the general procedure 1, and was isolated (eluent: 4 : 1 heptane–AcOEt) in 78% yield (1.8 g) as a yellow powder: mp 159 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.46 (ddd, 1H, J = 8.4, 6.9 and 1.0 Hz), 7.55–7.62 (m, 3H), 7.74 (ddd, 1H, J = 8.4, 1.0 and 0.9 Hz), 7.74–7.77 (m, 2H), 8.16 (ddd, 1H, J = 8.4, 1.0 and 0.9 Hz); ^{13}C{1H} NMR ($CDCl_3$, 75 MHz) 110.2 (CH), 120.5 (CH), 124.0 (2CH), 124.7 (CH), 128.6 (CH), 130.1 (2CH), 132.2 (C), 134.5 (C), 135.6 (C), 146.6 (C). The NMR data are analogous to those previously described.[41] 2-(4-Chlorophenyl)-2*H*-benzotriazole (**1c′**) was also isolated (eluent: 4 : 1 heptane–AcOEt) in 9% yield (0.21 g) as an orange powder: mp 175 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.39–7.45 (m, 2H), 7.48–7.54 (m, 2H), 7.89–7.93 (m, 2H), 8.28–8.32 (m, 2H); ^{13}C{1H} NMR ($CDCl_3$, 75 MHz) 118.5 (2CH), 121.9 (2CH), 127.6 (2CH), 129.7 (2CH), 134.9 (C), 139.0 (C), 145.2 (2C).

1-(4-Trifluoromethylphenyl)-1*H*-benzotriazole (**1d**) was prepared from benzotriazole (1.2 g) and 1-iodo-4-(trifluoromethyl)-benzene (1.8 mL) using the general procedure 1, and was isolated (eluent: 4 : 1 heptane–AcOEt) in 71% yield (1.9 g) as a white powder: mp 168 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.49 (ddd, 1H, J = 8.4, 7.0 and 0.9 Hz), 7.64 (ddd, 1H, J = 8.4, 7.0 and 1.0 Hz), 7.80 (dt, 1H, J = 8.4 and 0.9 Hz), 7.90 (d, 2H, J = 8.4 Hz), 7.99 (d, 2H, J = 8.4 Hz), 8.19 (ddd, 1H, J = 8.4, 1.0 and 0.9 Hz); ^{13}C{1H} NMR ($CDCl_3$, 75 MHz) 110.2 (CH), 120.7 (CH),

122.6 (2CH), 123.8 (q, CF_3, J = 272 Hz), 124.9 (CH), 127.3 (q, 2CH, J = 4 Hz), 129.0 (CH), 130.5 (C, J = 33 Hz), 132.0 (C), 140.0 (C), 146.8 (C); $^{19}F\{1H\}$ NMR ($CDCl_3$, 282 MHz) −63. The NMR data are analogous to those previously described.[41]

1-(4-Methoxyphenyl)-1*H*-benzotriazole (**1e**) was prepared from benzotriazole (1.2 g) and 4-iodoanisole (2.8 g) using the general procedure 1 but using CuI (0.20 g, 1.0 mmol) and *N*,*N*′-dimethylethylenediamine (0.22 mL, 2.0 mmol), and was isolated (eluent: 4 : 1 heptane–AcOEt) in 43% yield (0.97 g) as a yellow powder: mp 98 °C; ^1H NMR ($CDCl_3$, 300 MHz) 3.89 (s, 3H), 7.08–7.13 (m, 2H), 7.40 (ddd, 1H, J = 8.2, 6.9 and 1.0 Hz), 7.52 (ddd, 1H, J = 8.2, 6.9 and 1.0 Hz), 7.63–7.68 (m, 3H), 8.12 (dt, 1H, J = 8.1 and 0.9 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 55.8 (OMe), 110.4 (CH), 115.1 (2CH), 120.3 (CH), 124.3 (CH), 124.7 (2CH), 128.1 (CH), 130.1 (C), 132.7 (C), 146.4 (C), 159.9 (C). The NMR data are analogous to those previously described.[41] 2-(4-Methoxyphenyl)-2*H*-benzotriazole (**1e′**) was also isolated (eluent: 4 : 1 heptane–AcOEt) in 3% yield (68 mg) as a yellow powder: mp 102 °C; ^1H NMR ($CDCl_3$, 300 MHz) 3.90 (s, 3H), 7.04–7.07 (m, 2H), 7.39–7.43 (m, 2H), 7.91–7.94 (m, 2H), 8.26–8.29 (m, 2H). The ^1H NMR data are analogous to those previously described.[42] $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 55.8 (OMe), 114.6 (2CH), 118.3 (2CH), 122.2 (2CH), 127.0 (2CH), 134.1 (C), 145.0 (2C), 160.3 (C).

1-(3-Pyridyl)-1*H*-benzotriazole (**1f**) was prepared from benzotriazole (1.2 g) and 3-iodopyridine (2.5 g) using the general procedure 1, and was isolated (eluent: 9 : 1 CH_2Cl_2–AcOEt) in 69% yield (1.4 g) as a white powder: mp 142 °C; IR (ATR): 3087, 3053, 3024, 1579, 1495, 1457, 1427, 1287, 1265, 1192, 1065, 810, 731, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.47 (ddd, 1H, J = 8.2, 7.0 and 1.0 Hz), 7.56–7.63 (m, 2H), 7.76 (dt, 1H, J = 8.3 and 0.9 Hz), 8.14–8.18 (m, 2H), 8.76 (d, 1H, J = 4.2 Hz), 9.12 (s, 1H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 110.0 (CH), 120.7 (CH), 124.6 (CH), 124.9 (CH), 129.0 (CH), 130.3 (CH), 132.2 (C), 134.0 (C), 143.6 (CH), 146.7 (C), 149.8 (CH).

1-(2-Thienyl)-1*H*-benzotriazole (**1g**) was prepared from benzotriazole (1.2 g) and 2-iodothiophene (2.5 g) using the general procedure 1, and was isolated (eluent: 9 : 1 to 4 : 1 heptane–AcOEt) in 41% yield (0.83 g) as a yellow powder: mp 76 °C; IR (ATR): 3109, 1610, 1551, 1490, 1459, 1444, 1283, 1229, 1177, 1055, 962, 845, 782, 742, 696 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.15 (dd, 1H, J = 5.4 and 3.6 Hz), 7.34 (dd, 1H, J = 5.7 and 1.5 Hz), 7.39 (dd, 1H, J = 3.6 and 1.2 Hz,), 7.45 (ddd, 1H, J = 8.1, 6.9 and 0.9 Hz), 7.58 (ddd, 1H, J = 7.8, 6.9 and 0.9 Hz), 7.75 (dt, 1H, J = 8.4 and 0.9 Hz), 8.13 (dt, 1H, J = 8.4 and 1.0 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 110.4 (CH), 120.0 (CH), 120.5 (CH), 123.5 (CH), 124.8 (CH), 126.5 (CH), 128.9 (CH), 132.9 (C), 137.6 (C), 146.2 (C). HRMS (ESI/ASAP): calcd for $C_{10}H_8N_3S$ $[M + H]^+$ 202.0439, found 202.0437. 2-(2-Thienyl)-2*H*-benzotriazole (**1g′**) was also isolated (eluent: 9 : 1 to 4 : 1 heptane–AcOEt) in 5% yield (0.10 g) as a yellow powder: mp 114 °C; ^1H NMR ($CDCl_3$, 300 MHz) 7.08 (dd, 1H, J = 5.4 and 3.9), 7.24 (dd, 1H, J = 5.4 and 1.5 Hz), 7.42 (dd, 2H, J = 6.6 and 3.1 Hz), 7.77 (dd, 1H, J = 3.9 and 1.5 Hz), 7.89 (dd, 2H, J = 6.6 and 3.1 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 118.1 (2CH), 118.6 (CH), 123.4 (CH), 126.9 (CH), 127.6 (2CH), 143.1 (C), 145.1 (2C).

1-Phenyl-1*H*-indazole (**2a**) was prepared from indazole (1.2 g) and iodobenzene (1.4 mL) using the general procedure 1, and was isolated (eluent: 4 : 1 heptane–AcOEt) in 98% yield (1.9 g) as a green powder: mp 83 °C (lit.[43] 77–78 °C); IR (ATR): 3062, 1614, 1598, 1501, 1467, 1417, 1379, 1356, 1198, 1089, 1063, 978, 905, 838, 771, 741, 709, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.24 (ddd, 1H, J = 8.1, 6.9 and 0.9 Hz), 7.35 (tt, 1H, J = 7.5 and 1.2 Hz), 7.44 (ddd, 1H, J = 8.4, 6.9 and 1.2 Hz), 7.52–7.58 (m, 2H), 7.72–7.76 (m, 3H), 7.78–7.83 (m, 1H), 8.22 (d, 1H, J = 0.9 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 110.5 (CH), 121.4 (CH), 121.6 (CH), 122.8 (2CH), 125.4 (C), 126.7 (CH), 127.3 (CH), 129.6 (2CH), 135.5 (CH), 138.8 (C), 140.3 (C). The NMR data are in accordance with the literature.[43]

1-(4-Trifluoromethylphenyl)-1*H*-indazole (**2d**) was prepared from indazole (1.2 g) and 1-iodo-4-trifluoromethylbenzene (1.8 mL) using the general procedure 1, and was isolated (eluent: 4 : 1 heptane–AcOEt) in 99% yield (2.6 g) as a yellow powder: mp 68 °C; ^1H NMR ($CDCl_3$, 300 MHz) 7.28 (ddd, 1H, J = 7.8, 7.0 and 1.0 Hz), 7.49 (ddd, 1H, J = 8.4, 6.9 and 1.2 Hz), 7.82 (m, 4H), 7.91 (d, 2H, J = 8.4 Hz), 8.25 (d, 1H, J = 0.9 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 110.1 (CH), 121.7 (CH), 122.0 (2CH), 122.2 (CH), 124.1 (q, CF_3, J = 272 Hz), 126.7 (q, 2CH, J = 4 Hz), 127.8 (CH), 128.1 (q, C, J = 33 Hz), 136.6 (CH), 138.6 (C), 143.1 (C), 143.2 (C); $^{19}F\{1H\}$ NMR ($CDCl_3$, 282 MHz) −62.3. The mp and ^1H NMR data are in accordance with the literature.[43]

1-(4-Methoxyphenyl)-1*H*-indazole (**2e**) was prepared from indazole (1.2 g) and 4-iodoanisole (2.8 g) using the general procedure 1, and was isolated (eluent: 4 : 1 heptane–CH_2Cl_2) in 79% yield (1.8 g) as a yellow oil; ^1H NMR ($CDCl_3$, 300 MHz) 3.87 (s, 3H), 7.03–7.06 (m, 2H), 7.20 (ddd, 1H, J = 7.8, 6.9 and 0.9 Hz), 7.39 (ddd, 1H, J = 8.1, 6.9 and 0.9 Hz), 7.58–7.65 (m, 3H), 7.78 (dt, 1H, J = 8.1 and 1.0 Hz), 8.16 (d, 1H, J = 0.9 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 55.4 (OMe), 110.1 (CH), 114.5 (2CH), 121.1 (CH), 121.2 (CH), 124.3 (2CH), 124.9 (C), 126.8 (CH), 133.2 (C), 134.7 (CH), 138.8 (C), 156.2 (C). The ^1H NMR data are in accordance with the literature.[43]

1-(2-Thienyl)-1*H*-indazole (**2g**) was prepared from indazole (1.2 g) and 2-iodothiophene (2.5 g) using the general procedure 1, and was isolated (eluent: 4 : 1 heptane–AcOEt) in 83% yield (1.7 g) as a yellow powder: mp 86 °C; IR (ATR): 3104, 3079, 1613, 1549, 1497, 1468, 1417, 1369, 1358, 1350, 1185, 1086, 935, 842, 768, 740, 688 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.07 (dd, 1H, J = 5.5 and 3.7 Hz), 7.17 (dd, 1H, J = 5.5 and 1.4 Hz), 7.24 (dd, 1H, J = 3.7 and 1.4 Hz), 7.24–7.28 (m, 1H), 7.48 (ddd, 1H, J = 8.1, 6.9 and 1.2 Hz), 7.74–7.81 (m, 2H), 8.18 (d, 1H, J = 0.9 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 110.6 (CH), 117.0 (CH), 121.1 (CH), 121.5 (CH), 122.1 (CH), 125.3 (C), 126.1 (CH), 127.9 (CH), 136.1 (CH), 139.5 (C), 142.7 (C).

General procedure 2 for the deprotonative metallation followed by iodination

To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.50 mL, 3.0 mmol) in THF (5 mL) was added BuLi

(about 1.6 M hexanes solution, 3.0 mmol). After 15 min at 0 °C, $ZnCl_2$·TMEDA (0.25 g, 1.0 mmol) was added, and the mixture was stirred for 15 min at this temperature before introduction of the substrate (2.0 mmol). After 2 h at room temperature, a solution of I_2 (0.74 g, 3.0 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 CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure before purification by flash chromatography on silica gel.

4-Iodo-1-phenyl-1*H*-benzotriazole (**3b**) was obtained from 1-phenyl-1*H*-benzotriazole (**1a**, 0.39 g) using the general procedure 2 (eluent: 9 : 1 heptane–AcOEt) in 53% estimated yield. The analyses were obtained from a pure fraction: orange powder; mp 155 °C; IR (ATR): 3063, 2923, 2853, 1722, 1598, 1500, 1417, 1253, 1181, 1088, 1058, 930, 826, 779, 750, 693 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.21–7.26 (m, 1H), 7.47–7.71 (m, 6H), 7.80 (d, 1H, *J* = 7.2 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 85.9 (C), 110.5 (CH), 123.3 (2CH), 129.2 (CH), 129.5 (CH), 130.1 (2CH), 132.2 (C), 134.1 (CH), 137.0 (C), 148.1 (C).

1-(2-Iodophenyl)-1*H*-benzotriazole (**3b′**) was obtained from 1-phenyl-1*H*-benzotriazole (**1a**, 0.39 g) using the general procedure 2 (eluent: 9 : 1 heptane–AcOEt) in 11% estimated yield. The analyses were obtained from a pure fraction: white powder, mp 168 °C (lit.[44] 148–150 °C); IR (ATR): 3056, 1495, 1477, 1265, 1065, 894, 785, 733, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.29–7.36 (m, 2H), 7.42–7.62 (m, 4H), 8.10 (dd, 1H, *J* = 8.0 and 1.3 Hz), 8.17 (dt, 1H, *J* = 8.3 and 1.0 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 95.8 (C), 110.6 (CH), 120.4 (CH), 124.4 (CH), 128.3 (CH), 129.1 (CH), 129.6 (CH), 131.8 (CH), 133.6 (C), 139.3 (C), 140.6 (CH), 145.8 (C).

4-Iodo-1-(4-methoxyphenyl)-1*H*-benzotriazole (**3e**) was obtained from 1-(4-methoxyphenyl)-1*H*-benzotriazole (**1e**, 0.45 g) using the general procedure 2 (eluent: 95 : 5 CH_2Cl_2–MeOH) in 74% estimated yield. The analyses were obtained from a pure fraction: yellow powder; mp 120 °C; IR (ATR): 3053, 1591, 1516, 1264, 1181, 1072, 1033, 929, 834, 780, 732, 703, 667 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 3.91 (s, 3H), 7.10–7.13 (m, 2H), 7.29 (dd, 1H, *J* = 7.2 Hz), 7.61–7.65 (m, 3H), 7.85 (dd, 1H, *J* = 7.3 and 0.7 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 55.8 (OMe), 85.7 (C), 110.4 (CH), 115.1 (2CH), 124.9 (2CH), 129.3 (CH), 129.8 (C), 132.4 (C), 133.8 (CH), 147.8 (C), 160.1 (C).

1-(5-Iodo-2-thienyl)-1*H*-benzotriazole (**3g**) was prepared from 1-(2-thienyl)-1*H*-benzotriazole (**1g**, 0.40 g) using the general procedure 2 and was isolated (eluent: 4 : 1 heptane–AcOEt) in 68% yield (0.44 g) as a beige powder: mp 79 °C; IR (ATR): 3059, 1553, 1374, 1281, 1264, 1175, 1038, 1004, 964, 781, 764, 732, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.04 (d, 1H, *J* = 4.0 Hz), 7.30 (d, 1H, *J* = 4.0 Hz), 7.43 (ddd, 1H, *J* = 8.4, 7.0 and 1.1 Hz), 7.57 (ddd, 1H, *J* = 8.4, 6.9 and 1.0 Hz), 7.69 (ddd, 1H, *J* = 8.4, 1.0 and 0.9 Hz), 8.10 (ddd, 1H, *J* = 8.4, 1.0 and 0.9 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 71.5 (C), 110.1 (CH), 120.5 (CH), 120.9 (CH), 125.0 (CH), 129.1 (CH), 132.4 (C), 136.1 (CH), 141.9 (C), 146.1 (C).

1-(5-Iodo-2-thienyl)-1*H*-indazole (**5g**) was prepared from 1-(2-thienyl)-1*H*-indazole (**2g**, 0.40 g) using the general procedure 2 and was isolated (eluent: 4 : 1 heptane–AcOEt) in 66% yield (0.43 g) as a yellow oil: IR (ATR): 3045, 1612, 1552, 1497, 1467, 1417, 1361, 1263, 1183, 1075, 950, 921, 767, 732, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 6.91 (d, 1H, *J* = 4.0 Hz), 7.23 (d, 1H, *J* = 4.0 Hz), 7.26 (ddd, 1H, *J* = 7.9, 7.0 and 0.8 Hz), 7.48 (ddd, 1H, *J* = 8.5, 7.0 and 1.1 Hz), 7.69 (dd, 1H, *J* = 8.5 and 0.8 Hz), 7.78 (dt, 1H, *J* = 8.1 and 1.0 Hz), 8.16 (d, 1H, *J* = 0.9 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 68.2 (C), 110.2 (CH), 117.3 (CH), 121.4 (CH), 122.2 (CH), 125.1 (C), 127.9 (CH), 135.7 (CH), 136.3 (CH), 138.7 (C), 147.0 (C). HRMS (ESI): calcd for $C_{11}H_8N_2IS$ $[M + H]^+$ 326.9453, found 326.9456.

General procedure 3 for the deprotonative metallation followed by iodination

To a stirred, cooled (0 °C) solution of 2,2,6,6-tetramethylpiperidine (0.50 mL, 3.0 mmol) in THF (5 mL) was added BuLi (about 1.6 M hexanes solution, 3.0 mmol). After 15 min at 0 °C, $ZnCl_2$·TMEDA (0.25 g, 1.0 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 (0.74 g, 3.0 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 CH_2Cl_2 (3 × 20 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure before purification by flash chromatography on silica gel.

4-Iodo-1-(2-iodophenyl)-1*H*-benzotriazole (**4b**) was prepared from 1-phenyl-1*H*-benzotriazole (**1a**, 0.20 g) using the general procedure 3 and was isolated (eluent: 4 : 1 heptane–AcOEt) in 99% yield (0.44 g) as an orange powder: mp 149 °C; IR (ATR): 3060, 1599, 1576, 1489, 1442, 1264, 1180, 1069, 1056, 928, 827, 779, 749, 734 cm^{-1}; ^1H NMR (CD_3COCD_3, 300 MHz) 7.41 (dd, 1H, *J* = 8.3 and 7.0 Hz), 7.45–7.54 (m, 2H), 7.70–7.79 (m, 2H), 7.96 (dd, 1H, *J* = 6.9 and 1.2 Hz), 8.22 (ddd, 1H, *J* = 7.8, 1.2 and 0.6 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 85.8 (C), 95.7 (C), 110.7 (CH), 129.1 (CH), 129.6 (CH), 129.6 (CH), 132.1 (CH), 133.4 (C), 134.0 (CH), 139.1 (C), 140.6 (CH), 147.5 (C); MS (ESI): calcd for $C_{12}H_7I_2N_3$ $[M]^+$ 447, found 447.

4-Iodo-1-(3-iodo-4-chlorophenyl)-1*H*-benzotriazole (**4c**) was obtained from 1-(4-chlorophenyl)-1*H*-benzotriazole (**1c**, 0.23 g) using the general procedure 3 (eluent for preliminary purification: 4 : 1 heptane–AcOEt, eluent for final purification: 7 : 2 : 1 heptane–AcOEt–CH_2Cl_2) in 68% estimated yield. The analyses were obtained from a pure fraction: orange powder; IR (ATR): 3052, 2923, 2853, 1599, 1576, 1488, 1417, 1366, 1264, 1180, 1096, 1069, 1036, 928, 827, 778, 733, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.26–7.28 (m, 2H), 7.38 (d, 1H, *J* = 8.4 Hz), 7.56 (dd, 1H, *J* = 8.4 and 2.2 Hz), 7.86 (t, 1H, *J* = 4.0 Hz), 8.07 (d, 1H, *J* = 2.2 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 85.9 (C), 96.1 (C), 110.5 (CH), 129.5 (CH), 129.8 (CH), 129.9 (CH), 133.3 (C), 134.2 (CH), 137.4 (C), 137.8 (C), 140.0 (CH), 147.0 (C).

7-Iodo-1-(2-iodo-4-chlorophenyl)-1*H*-benzotriazole (**4c′**) was obtained from 1-(4-chlorophenyl)-1*H*-benzotriazole (**1c**, 0.23 g) using the general procedure 3 (eluent for preliminary

purification: 4 : 1 heptane–AcOEt, eluent for final purification: 7 : 2 : 1 heptane–AcOEt–CH_2Cl_2) in 22% estimated yield. The analyses were obtained from a pure fraction: orange powder; IR (ATR): 3084, 1599, 1575, 1488, 1416, 1366, 1264, 1180, 1096, 1069, 1050, 1036, 997, 928, 873, 827, 777, 733, 702 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.18 (dd, 1H, J = 8.3 and 7.5 Hz), 7.45 (d, 1H, J = 8.4 Hz), 7.57 (dd, 1H, J = 8.4 and 2.1 Hz), 7.97 (dd, 1H, J = 7.4 and 0.7 Hz), 8.03 (d, 1H, J = 2.2 Hz), 8.17 (dd, 1H, J = 8.3 and 0.7 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 71.7 (C), 100.9 (C), 120.7 (CH), 126.1 (CH), 129.2 (CH), 131.5 (CH), 137.7 (C), 138.8 (CH), 139.5 (CH), 3C not seen.

4-Iodo-1-(2-iodo-4-trifluoromethylphenyl)-1*H*-benzotriazole (**4d**) was prepared from 1-(4-trifluoromethylphenyl)-1*H*-benzotriazole (**1d**, 0.26 g) using the general procedure 3 and was isolated (eluent: 4 : 1 heptane–AcOEt) in 91% yield (0.47 g) as a yellow powder: mp 162 °C; IR (ATR): 3058, 1599, 1500, 1421, 1387, 1317, 1264, 1174, 1132, 1075, 1051, 1035, 929, 828, 738, 715 cm^{-1}; $^1H\{^{19}F\}$ NMR ($CDCl_3$, 300 MHz) 7.29–7.31 (m, 2H), 7.59 (d, 1H, J = 8.2 Hz), 7.84–7.91 (m, 2H), 8.33 (br s, 1H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 86.0 (C), 95.7 (C), 110.5 (CH), 122.4 (q, CF_3, J = 273 Hz), 126.8 (q, CH, J = 4 Hz), 129.3 (CH), 130.0 (CH), 133.0 (C), 133.9 (q, C, J = 33 Hz), 134.3 (CH), 137.8 (q, CH, J = 4 Hz), 142.4 (C), 147.6 (C); $^{19}F\{1H\}$ NMR ($CDCl_3$, 282 MHz) −63; MS (ESI): calcd for $C_{13}H_6F_3I_2N_3$ $[M]^+$ 515, found 515.

4-Iodo-1-(2-iodo-4-methoxyphenyl)-1*H*-benzotriazole (**4e**) was obtained from 1-(4-methoxyphenyl)-1*H*-benzotriazole (**1e**, 0.23 g) using the general procedure 3 (eluent: 95 : 5 CH_2Cl_2–MeOH) in 59% estimated yield. The analyses were obtained from a pure fraction: yellow powder; mp 178 °C; IR (ATR): 3079, 2933, 1722, 1593, 1498, 1296, 1270, 1236, 1181, 1071, 1031, 750, 736 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 3.90 (s, 3H), 7.07 (dd, 1H, J = 8.7 and 2.8 Hz), 7.24–7.27 (m, 2H), 7.34 (d, 1H, J = 8.7 Hz), 7.55 (d, 1H, J = 2.7 Hz), 7.85 (dd, 1H, J = 5.8 and 2.4 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 56.1 (OMe), 85.7 (C), 96.4 (C), 110.7 (CH), 115.2 (CH), 125.3 (CH), 129.5 (2CH), 132.0 (C), 133.8 (C), 133.9 (CH), 147.4 (C), 161.3 (C).

4-Iodo-1-(3-iodo-4-methoxyphenyl)-1*H*-benzotriazole (**4e′**) was obtained from 1-(4-methoxyphenyl)-1*H*-benzotriazole (**1e**, 0.23 g) using the general procedure 3 (eluent: 95 : 5 CH_2Cl_2–MeOH) in 23% estimated yield: ^1H NMR ($CDCl_3$, 300 MHz) 3.97 (s, 3H), 7.00 (d, 1H, J = 8.7 Hz), 7.27 (dd, 1H, J = 8.1 and 7.5 Hz), 7.60 (dd, 1H, J = 8.3 and 0.7 Hz), 7.67 (dd, 1H, J = 8.7 and 2.4 Hz), 7.84 (dd, 1H, J = 7.4 and 0.7 Hz), 8.11 (d, 1H, J = 2.7 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 56.9 (OMe), 85.9 (C), 86.5 (C), 110.2 (CH), 111.2 (CH), 124.8 (CH), 129.6 (CH), 130.8 (C), 132.3 (C), 134.1 (CH), 134.3 (CH), 147.9 (C), 158.9 (C).

4-Iodo-1-(5-iodo-2-thienyl)-1*H*-benzotriazole (**4g**) was prepared from 1-(2-thienyl)-1*H*-benzotriazole (**1g**, 0.20 g) using the general procedure 3 and was isolated (eluent: 9 : 1 heptane–AcOEt) in 54% yield (0.24 g) as a beige powder: mp 176 °C; IR (ATR): 3053, 1422, 1264, 1172, 1037, 896, 731, 703 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.07 (d, 1H, J = 4.0 Hz), 7.33 (dd, 1H, J = 8.4 and 7.4 Hz), 7.34 (d, 1H, J = 4.0 Hz), 7.66 (dd, 1H, J = 8.4 and 0.7 Hz), 7.87 (dd, 1H, J = 7.4 and 0.7 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 72.4 (C), 86.2 (C), 110.2 (CH), 122.1 (CH), 130.2 (CH), 132.5 (C), 134.6 (CH), 136.3 (CH), 141.6 (C), 147.8 (C).

3-Iodo-1-phenyl-1*H*-indazole (**5a**) was obtained from 1-phenyl-1*H*-indazole (**2a**, 0.19 g) using the general procedure 3 (eluent: 9 : 1 to 8 : 2 heptane–AcOEt) in 27% estimated yield: ^1H NMR ($CDCl_3$, 300 MHz) 6.97–7.03 (m, 3H), 7.20–7.31 (m, 3H), 7.47 (ddd, 1H, J = 8.3, 1.3 and 0.44 Hz), 7.53–7.57 (m, 1H), 7.66 (ddd, 1H, J = 7.7, 1.6 and 0.41 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 113.5 (C), 117.7 (C), 122.2 (2CH), 122.7 (CH), 126.0 (CH), 129.1 (2CH), 130.2 (CH), 133.9 (CH), 134.0 (CH), 147.0 (C), 149.4 (C).

2-(Phenylamino)benzonitrile (**6a**) was obtained from 1-phenyl-1*H*-indazole (**2a**, 0.19 g) using the general procedure 3 (eluent: 9 : 1 to 8 : 2 heptane–AcOEt) in 22% estimated yield. The analyses were obtained from a pure fraction: yellow oil; IR (ATR): 3343, 2929, 2217, 1726, 1594, 1575, 1515, 1497, 1473, 1457, 1318, 1292, 1163, 909, 732, 695 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 6.32 (br s, 1H), 6.81–6.87 (m, 1H), 7.13 (tt, 1H, J = 7.2 and 1.0 Hz), 7.15–7.21 (m, 3H), 7.34–7.40 (m, 3H), 7.50 (dd, 1H, J = 7.8 and 1.5 Hz); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 98.6 (C), 114.2 (CH), 117.7 (C), 119.4 (CH), 121.9 (2CH), 124.4 (CH), 129.8 (2CH), 133.2 (CH), 134.0 (CH), 140.0 (C), 147.4 (C). The NMR data are analogous to those previously described.[45]

1-(2-Iodo-4-trifluoromethylphenyl)-1*H*-indazole was obtained from 1-(4-trifluoromethylphenyl)-1*H*-indazole (**2d**, 0.26 g) using the general procedure 3 (eluent: 4 : 1 heptane–AcOEt) in 20% estimated yield: ^1H NMR ($CDCl_3$, 300 MHz) 7.22–7.26 (m, 1H), 7.27 (ddd, 1H, J = 7.9, 7.0 and 0.9 Hz), 7.43 (ddd, 1H, J = 8.3, 7.0 and 1.1 Hz), 7.54 (dd, 1H, J = 8.2 and 0.5 Hz), 7.75–7.80 (m, 1H), 7.84 (dt, 1H, J = 8.1 and 1.0 Hz), 8.27 (d, 1H, J = 1.0 Hz), 8.30 (d, J = 1.1 Hz, 1H); $^{13}C\{1H\}$ NMR ($CDCl_3$, 75 MHz) 96.1 (C), 110.4 (CH), 120.4 (q, C, J = 275 Hz), 121.5 (CH), 122.0 (CH), 124.7 (C), 126.3 (q, CH, J = 4 Hz), 127.5 (CH), 129.4 (CH), 132.2 (q, C, J = 33 Hz), 136.2 (CH), 137.6 (q, CH, J = 4 Hz), 139.9 (C), 145.3 (C); $^{19}F\{1H\}$ NMR ($CDCl_3$, 282 MHz) −63.

Acknowledgements

We are grateful to Région Bretagne and the Agence Nationale de la Recherche for financial support to E.N. E.N. and F.M. also thank the Institut Universitaire de France and Rennes Métropole for financial support. We gratefully acknowledge Thermo Fisher for generous gift of 2,2,6,6-tetramethylpiperidine.

Notes and references

1 (*a*) W.-Q. Fan and A. R. Katritzky, in *Comprehensive Heterocyclic Chemistry II*, ed. A. R. Katritzky, C. W. Rees, E. F. V. Scriven, Pergamon, Elsevier Science Ltd, Oxford, 1996, vol. 4; (*b*) T. Eicher, S. Hauptmann and A. Speicher, *The Chemistry of Heterocycles*, Wiley-VCH, New York, 2nd edn, 2003; (*c*) B. V. Suma, N. N. Natesh and V. Madhavan, *J. Chem. Pharm. Res.*, 2011, **3**, 375–381; (*d*) C. H. Zhou and Y. Wang, *Curr. Med. Chem.*, 2012, **19**, 239–280.

2 (*a*) G. Aromi, L. A. Barrios, O. Roubeau and P. Gamez, *Coord. Chem. Rev.*, 2011, **255**, 485–546; (*b*) D. Astruc, L. Liang, A. Rapakousiou and J. Ruiz, *Acc. Chem. Res.*, 2012, **45**, 630–640; (*c*) A. K. Verma, *Adv. Heterocycl. Chem.*, 2012, **107**, 101–132.

3 (*a*) H. W. Gschwend and H. R. Rodriguez, *Org. React.*, 1979, **26**, 1–360; (*b*) P. Beak and V. Snieckus, *Acc. Chem. Res.*, 1982, **15**, 306–312; (*c*) V. Snieckus, *Chem. Rev.*, 1990, **90**, 879–933; (*d*) T. G. Gant and A. I. Meyers, *Tetrahedron*, 1994, **50**, 2297–2360; (*e*) M. Schlosser, *Organometallics in Synthesis*, ed. M. Schlosser, Wiley, 2nd edn, 2002, ch. I.

4 T. L. S. Kishbaugh, *Top. Heterocycl. Chem.*, 2012, **29**, 1–46.

5 E. T. Pelkey, *Top. Heterocycl. Chem.*, 2010, **26**, 141–191.

6 (*a*) P. E. Alford, *Top. Heterocycl. Chem.*, 2012, **29**, 77–102; (*b*) S. Roy, S. Roy and G. W. Gribble, *Top. Heterocycl. Chem.*, 2012, **29**, 155–260; (*c*) J. M. Lopchuk, *Top. Heterocycl. Chem.*, 2012, **29**, 415–440.

7 K.-S. Yeung, *Top. Heterocycl. Chem.*, 2012, **29**, 47–76.

8 K. Smith and M. L. Barratt, *J. Org. Chem.*, 2007, **72**, 1031–1034.

9 (*a*) L. Fu, *Top. Heterocycl. Chem.*, 2012, **29**, 103–154; (*b*) J. C. Badenock, *Top. Heterocycl. Chem.*, 2012, **29**, 261–306.

10 (*a*) Y.-J. Wu, *Top. Heterocycl. Chem.*, 2012, **29**, 307–328; (*b*) C. F. Nutaitis, *Top. Heterocycl. Chem.*, 2012, **29**, 329–346.

11 (*a*) F. Mongin and G. Queguiner, *Tetrahedron*, 2001, **57**, 4059–4090; (*b*) M. Schlosser and F. Mongin, *Chem. Soc. Rev.*, 2007, **36**, 1161–1172; (*c*) M. Alessi, A. L. Larkin, K. A. Ogilvie, L. A. Green, S. Lai, S. Lopez and V. Snieckus, *J. Org. Chem.*, 2007, **72**, 1588–1594; (*d*) P. C. Gros and Y. Fort, *Eur. J. Org. Chem.*, 2009, 4199–4209; (*e*) H. K. Khartabil, P. C. Gros, Y. Fort and M. F. Ruiz-López, *J. Am. Chem. Soc.*, 2010, **132**, 2410–2416; (*f*) K. Smith, G. A. El-Hiti, A. Fekri and M. B. Alshammari, *Heterocycles*, 2012, **86**, 391–410; (*g*) F. Chevallier and F. Mongin, *Top. Heterocycl. Chem.*, 2013, **31**, 93–130; (*h*) M. Schlosser, *Top. Heterocycl. Chem.*, 2013, **31**, 171–222.

12 (*a*) A. Turck, N. Plé, F. Mongin and G. Queguiner, *Tetrahedron*, 2001, **57**, 4489–4505; (*b*) F. Chevallier and F. Mongin, *Chem. Soc. Rev.*, 2008, **37**, 595–609; (*c*) A. Kolarovič, *Top. Heterocycl. Chem.*, 2013, **31**, 21–64; (*d*) N. Plé and C. Fruit, *Top. Heterocycl. Chem.*, 2013, **31**, 131–170; (*e*) E. Horkel, *Top. Heterocycl. Chem.*, 2013, **31**, 223–268.

13 A. R. Katritzky, X. Lan, J. Z. Yang and O. V. Denisko, *Chem. Rev.*, 1998, **98**, 409–548.

14 See for example: A. R. Katritzky, J. Wu, W. Kuzmierkiewicz and S. Rachwal, *Liebigs Ann. Chem.*, 1994, 1–5.

15 (*a*) A. R. Katritzky, A. V. Ignatchenko and H. Lang, *Heterocycles*, 1995, **41**, 131–146; (*b*) A. R. Katritzky, D. C. Oniciu, L. Serdyuk and I. Ghiviriga, *J. Org. Chem.*, 1995, **60**, 1244–1249.

16 M. A. Birkett, D. W. Knight and M. B. Mitchell, *Tetrahedron Lett.*, 1993, **34**, 6935–6938.

17 S. K. Y. Li, D. W. Knight and P. B. Little, *Tetrahedron Lett.*, 1996, **37**, 5615–5618.

18 A. R. Katritzky, Y. Fang and S. A. Belyakov, *Org. Prep. Proced. Int.*, 1998, **30**, 325–330.

19 D. P. M. Pleynet, J. K. Dutton and A. P. Johnson, *Tetrahedron*, 1999, **55**, 11903–11926.

20 (*a*) A. R. Katritzky, S. Bobrov, K. Kirichenko, Y. Ji and P. J. Steel, *J. Org. Chem.*, 2003, **68**, 5713–5719; (*b*) A. R. Katritzky, S. Bobrov, H. Tao and K. Kirichenko, *Tetrahedron*, 2005, **61**, 3305–3309.

21 (*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; (*d*) B. Haag, M. Mosrin, H. Ila, V. Malakhov and P. Knochel, *Angew. Chem., Int. Ed.*, 2011, **50**, 9794–9824; (*e*) F. Mongin and M. Uchiyama, *Curr. Org. Chem.*, 2011, **15**, 2340–2361; (*f*) F. Mongin and A. Harrison-Marchand, *Chem. Rev.*, 2013, **113**, 7563–7727; (*g*) R. E. Mulvey, *Dalton Trans.*, 2013, **42**, 6676–6693.

22 (*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*) P. García-Álvarez, R. E. Mulvey and J. A. Parkinson, *Angew. Chem., Int. Ed.*, 2011, **50**, 9668–9671.

23 (*a*) 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; (*b*) A. Seggio, F. Chevallier, M. Vaultier and F. Mongin, *J. Org. Chem.*, 2007, **72**, 6602–6605; (*c*) G. Dayaker, A. Sreeshailam, F. Chevallier, T. Roisnel, P. Radha Krishna and F. Mongin, *Chem. Commun.*, 2010, **46**, 2862–2864; (*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*) F. Chevallier, Y. S. Halauko, C. Pecceu, I. F. Nassar, T. U. Dam, T. Roisnel, V. E. Matulis, O. A. Ivashkevich and F. Mongin, *Org. Biomol. Chem.*, 2011, **9**, 4671–4684; (*f*) G. Dayaker, D. Tilly, F. Chevallier, G. Hilmersson, P. C. Gros and F. Mongin, *Eur. J. Org. Chem.*, 2012, 6051–6057; (*g*) F. Chevallier, T. Blin, E. Nagaradja, F. Lassagne, T. Roisnel, Y. S. Halauko, V. E. Matulis, O. A. Ivashkevich and F. Mongin, *Org. Biomol. Chem.*, 2012, **10**, 4878–4885; (*h*) A. Sreeshailam, G. Dayaker, D. V. Ramana, F. Chevallier, T. Roisnel, S. Komagawa, R. Takita, M. Uchiyama, P. Radha Krishna and F. Mongin, *RSC Adv.*, 2012, **2**, 7030–7032; (*i*) D. Tilly, K. Snégaroff, G. Dayaker, F. Chevallier, P. C. Gros and F. Mongin, *Tetrahedron*, 2012, **68**, 8761–8766; (*j*) R. R. Kadiyala, D. Tilly, E. Nagaradja, T. Roisnel, V. E. Matulis, O. A. Ivashkevich, Y. S. Halauko, F. Chevallier, P. C. Gros and F. Mongin, *Chem.–Eur. J.*, 2013, **19**, 7944–7960.

24 (*a*) V. E. Matulis, Y. S. Halauko, O. A. Ivashkevich and P. N. Gaponik, *J. Mol. Struct. (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.

25 J. C. Antilla, J. M. Baskin, T. E. Barder and S. L. Buchwald, *J. Org. Chem.*, 2004, **69**, 5578–5587.

26 T. Furuyama, M. Yonehara, S. Arimoto, M. Kobayashi, Y. Matsumoto and M. Uchiyama, *Chem.–Eur. J.*, 2008, **14**, 10348–10356.
27 (*a*) F. Mongin and M. Schlosser, *Tetrahedron Lett.*, 1997, **38**, 1559–1562; (*b*) M. Schlosser, *Angew. Chem., Int. Ed.*, 1998, **37**, 1496–1513.
28 From **1b** and **1f**, the products obtained could not be identified.
29 L.-Z. Gong and P. Knochel, *Synlett*, 2005, 267–270.
30 A. Unsinn and P. Knochel, *Chem. Commun.*, 2012, **48**, 2680–2682.
31 V. L. Blair, D. C. Blakemore, D. Hay, E. Hevia and D. C. Pryde, *Tetrahedron Lett.*, 2011, **52**, 4590–4594.
32 R. R. Fraser, T. S. Mansour and S. Savard, *Can. J. Chem.*, 1985, **63**, 3505–3509.
33 I. F. Tupitsyn, A. S. Popov and A. Y. Shibaev, *Zh. Obshch. Khim.*, 1992, **62**, 2319–2328.
34 K. Shen, Y. Fu, J.-N. Li, L. Liu and Q.-X. Guo, *Tetrahedron*, 2007, **63**, 1568–1576.
35 M. Meot-Ner and S. A. Kafafi, *J. Am. Chem. Soc.*, 1988, **110**, 6297–6303.
36 J. C. Del Valle and J. L. G. De Paz, *J. Mol. Struct. (THEOCHEM)*, 1992, **86**, 481–491.
37 E. Cances, B. Mennucci and J. Tomasi, *J. Chem. Phys.*, 1997, **107**, 3032–3041.
38 (*a*) C. G. Swain and A. C. Lupton, *J. Am. Chem. Soc.*, 1968, **90**, 4328–4337; (*b*) C. Hansch, A. Leo and R. W. Taft, *Chem. Rev.*, 1991, **91**, 165–195.
39 D. Tilly, F. Chevallier, F. Mongin and P. C. Gros, *Chem. Rev.*, 2014, DOI: 10.1021/cr400367p.
40 H. E. Gottlieb, V. Kotlyar and A. Nudelman, *J. Org. Chem.*, 1997, **62**, 7512–7515.
41 V. Zimmermann and S. Bräse, *J. Comb. Chem.*, 2007, **9**, 1114–1137.
42 A. Maliakal, G. Lem, N. J. Turro, R. Ravichandran, J. C. Suhadolnik, A. D. DeBellis, M. G. Wood and J. Lau, *J. Phys. Chem. A*, 2002, **106**, 7680–7689.
43 A. Y. Lebedev, A. S. Khartulyari and A. Z. Voskoboynikov, *J. Org. Chem.*, 2005, **70**, 596–602.
44 C. Mukhopadhyay, P. K. Tapaswi and R. J. Butcher, *Org. Biomol. Chem.*, 2010, **8**, 4720–4729.
45 B. P. Fors, N. R. Davis and S. L. Buchwald, *J. Am. Chem. Soc.*, 2009, **131**, 5766–5768.