Deprotometalation-iodolysis and computed CH acidity of 1,2,3- and 1,2,4-triazoles. Application to the synthesis of resveratrol analogues

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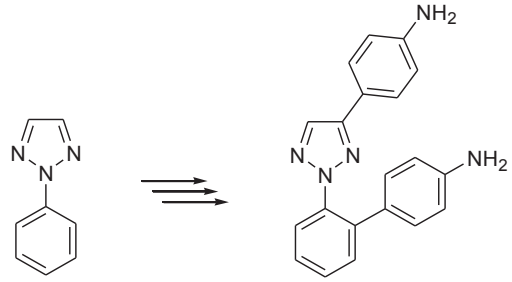
Graphical Abstract



Deprotometalation-iodolysis and computed CH acidity of 1,2,3- and 1,2,4-triazoles. Application to the synthesis of resveratrol analogues

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Abstract:

1-Aryl- and 2-aryl-1,2,3-triazoles were synthesized by *N*-arylation of the corresponding azoles using aryl iodides. The deprotometalations of 1-phenyl-1,2,3-triazole and -1,2,4-triazole were performed using a 2,2,6,6-tetramethylpiperidino-based mixed lithium-zinc combination and occurred at the most acidic site, affording by iodolysis the 5-substituted derivatives. Dideprotonation was noted from 1-(2-thienyl)-1,2,4-triazole by increasing the amount of base. From 2-phenyl-1,2,3-triazoles, and in particular from 2-(4-trifluoromethoxy)phenyl-1,2,3-triazole, reactions at the 4 position of the triazolyl, but also ortho to the triazolyl on the phenyl group, were observed. The results were analyzed with the help of the CH acidities of the substrates, determined in THF solution using the DFT B3LYP method. 4-Iodo-2-phenyl-1,2,3-triazole and 4-iodo-2-(2-iodophenyl)-1,2,3-triazole were next involved in Suzuki coupling reactions to furnish the corresponding 4-arylated and 4,2'-diarylated derivatives. When evaluated for biological activities, the latter (which are resveratrol analogues) showed moderate antibacterial activity and promising antiproliferative effect against MDA-MB-231 cell line.

Keywords: triazole, deprotonative metalation, CH-acidity, resveratrol analogue, antiproliferative activity

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1. Introduction

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

Aromatic deprotonative lithiation[3] is an efficient tool to functionalize regioselectively heterocycles.[4] Concerning 1-substituted 1,2,3- and 1,2,4-1*H*-triazoles, such a possibility has been developed, affording after subsequent trapping 5-substituted derivatives.[4q]

Combinations of lithium reagents and softer metal compounds have recently emerged as efficient tools to deprotometalate sensitive aromatic compounds.[5] In the framework of these studies, we developed efficient pairs of metal amides which complement each other in deprotometalation reactions. In particular, the TMP-based (TMP = 2,2,6,6-tetramethylpiperidino) lithium-zinc mixture,[6] prepared by mixing LiTMP with $ZnCl_2$·TMEDA (1/3 equiv, TMEDA = *N*,*N*,*N*′,*N*′-tetramethylethylenediamine) and supposed to be a 1:1 $Zn(TMP)_2$-LiTMP·2LiCl(±TMEDA) mixture,[7] was identified as a suitable reagent to functionalize sensitive aromatic compounds including heterocycles.

We herein describe our attempts to use the lithium-zinc combination above mentioned for the deprotometalation (followed by iodolysis) of the azole substrates **1** and **2** shown in Scheme 1. Earlier we have shown that the regioselectivity of the same reaction for the related substrates **3**[6f] and **4**[6h] is partly determined by the acidity of the different hydrogens in their molecules. As a consequence, we similarly tried to rationalize the reaction results using the CH acidities in THF of the heteroaromatic substrates calculated by using the homodesmic reaction approach within the density functional theory (DFT) framework. Finally, iodides generated by deprotometalation-iodolysis were involved in palladium-catalyzed Suzuki cross-coupling reactions, and the resulting arylated triazoles (which are resveratrol analogues) were evaluated for their biological activity.

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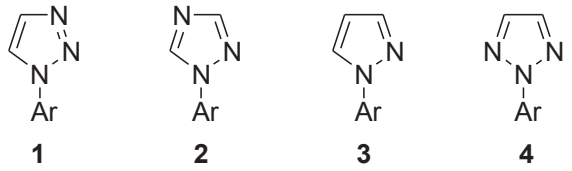
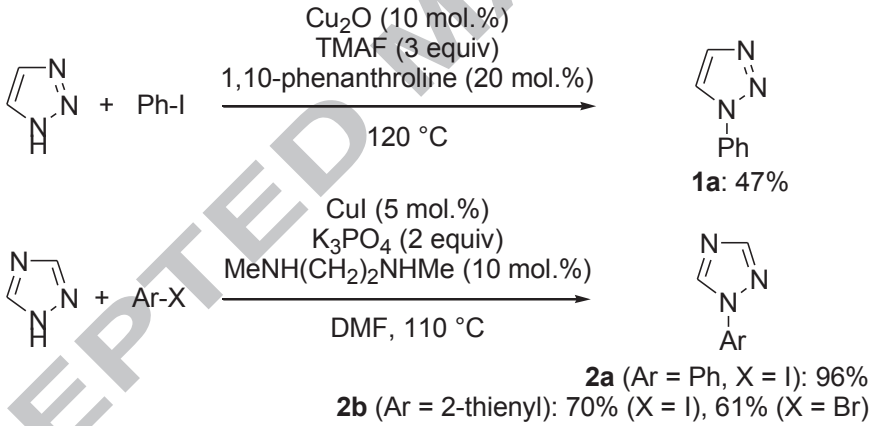


Scheme 1. Substrates for which the deprotometalation has been studied.

2. Results and Discussion

2.1. Synthetic aspects

1-Phenyl-1*H*-1,2,3-triazole (**1a**) was prepared by adapting a procedure described.[8] To reach the target substrates **2**, the unsubstituted azoles were treated with aryl and heteroaryl halides under copper catalysis using the conditions reported by Buchwald and co-workers (Scheme 2).[9] Moderate to excellent yields were noted, with aryl iodides favoring the reaction as observed previously.[6l]



Scheme 2. Synthesis of **1a**, **2a** and **2b**.

Upon treatment in THF for 2 h at room temperature with the lithium-zinc base, *in situ* prepared from $ZnCl_2$·TMEDA (x equiv) and LiTMP (3x equiv), 1-phenyl-1*H*-pyrazole (**3a**) is mainly deprotonated at its 5 position (x = 0.5), a result evidenced by subsequent interception with iodine.[6c,6f] In addition, 2-phenyl-2*H*-1,2,3-triazole (**4a**) mainly led to the 4-iodo derivative under the same reaction conditions.[6h] It was thus of interest to attempt the reaction from 1-phenyl-1*H*-1,2,3-triazole (**1a**) and 1-phenyl-1*H*-1,2,4-triazole (**2a**). In both cases, the reaction took place at the 5 position of the triazolyl group, and the iodides **5a** (x = 0.75) and **6a** (x =

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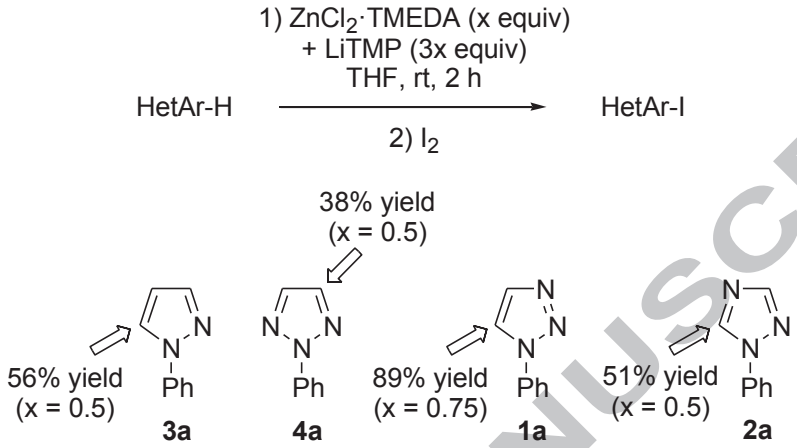
0.5) were isolated in 89 and 51% yield, respectively (Scheme 3). The iodide **5a** was also isolated (80% yield) from **1a** after carrying out the reaction using LiTMP (1.5 equiv) in THF, but using a lower (-20 °C) reaction temperature.



Scheme 3. Deprotometalation followed by iodolysis on *N*-phenylpyrazole and different *N*-phenyltriazoles.

By replacing the phenyl group connected to the 1,2,4-triazole by a 2-thienyl group (substrate **2b**), a reaction at the 5 position of the aza-heterocycle was still observed, as demonstrated by the isolation of the corresponding iodide **6b** in 95% yield. By increasing the amount of base (0.75 equiv of $ZnCl_2$·TMEDA and 2.25 equiv of LiTMP instead of 0.5 equiv of $ZnCl_2$·TMEDA and 1.5 equiv of LiTMP), the iodide **6b** became the minor product formed (8% yield) due to competitive dideprotometalation, as previously noted in the other azole series.[6f,6h] Indeed, the diiodides **7b** and **7b'** were obtained in 59 and 28% yield, respectively (Scheme 4). The iodides **5a** and **6a**, as well as the major isomer **7b**, were identified unequivocally by X-ray structure analysis (Figure 1).

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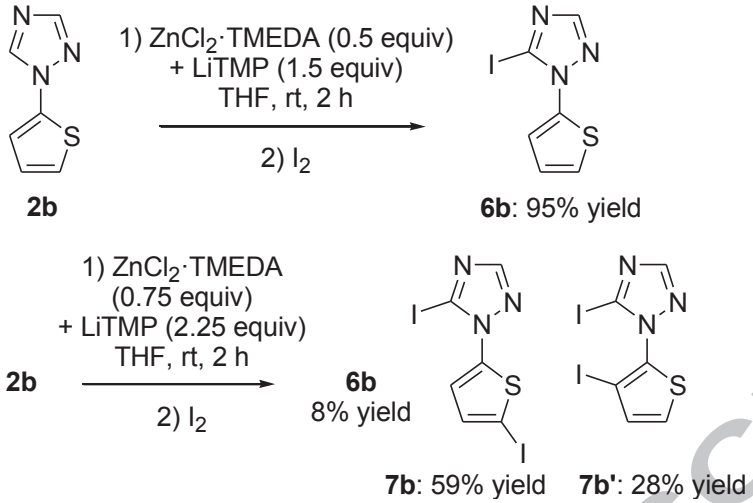
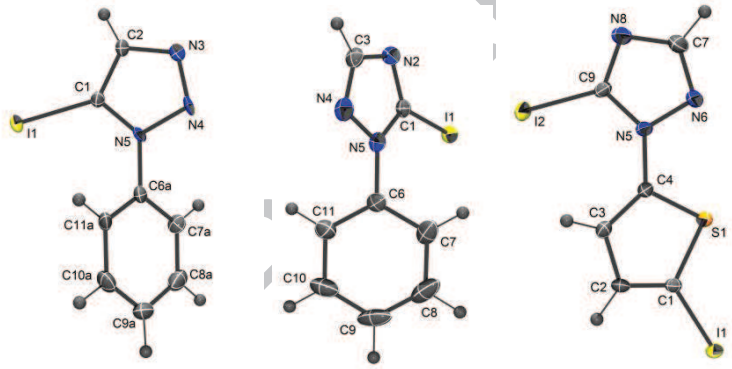


Scheme 4. Deprotometalation of **2b** followed by iodolysis.

Figure 1. ORTEP diagram (50% probability) of **5a**, **6a** and **7b**.



The triazole moiety is a well-known bioisostere of amide and ester groups and a linker replacement of double bonds.[10] In addition, resveratrol is a compound with a versatile biological activity.[11] In order to progress towards triazole-modified resveratrol analogues (Scheme 5, **A**), 2-(4-trifluoromethoxyphenyl)-1,2,3-triazole (**8**) was identified as a good precursor due to the impact of the trifluoromethoxy group on the biological activity of the derivatives.[12] It was synthesized by regioselective palladium-catalysed *N*-arylation of 1,2,3-triazole at its N2 position using 1-bromo-4-(trifluoromethoxy)benzene under conditions described by Buchwald and co-workers.[13] Unfortunately, treatment of **8** by the base (0.5 equiv of $ZnCl_2$·TMEDA and 1.5 equiv of LiTMP) as before led, after addition of iodine, to a mixture from which only pure 2-(2-iodo-4-trifluoromethoxyphenyl)-1,2,3-triazole (**9a**) could

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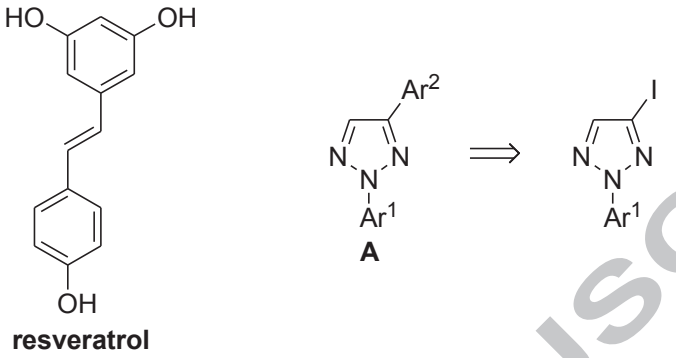
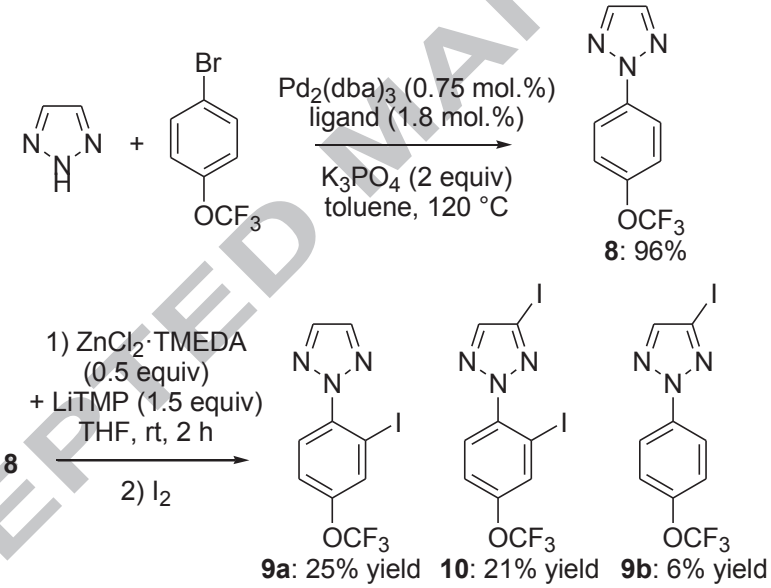
be isolated. Analyzing the crude showed, besides the monoiodide **9a** (estimated 25% yield), the formation of the diiodide **10** and the monoiodide **9b** (in estimated 21 and 6% yield, respectively) and the recovery of substrate (about 33% yield) (Scheme 6).



Scheme 5. Resveratrol and planned analogues (**A**).



Scheme 6. Deprotometalation of **8** followed by iodolysis.

This disappointing result led us to rather consider the synthesis of targets without trifluoromethoxy group. We thus chose 2-phenyl-1,2,3-triazole (**4a**), and synthesized the monoiodide **4b** and diiodide **4b'** as described previously.[6h] The monoiodide **4b** was first reacted with arylboronic acids (stoichiometric amount) in a Suzuki-type cross-coupling procedure[14] using catalytic $Pd(dba)_2$ (dba = dibenzylidene acetone) and triphenylphosphine, dioxane as solvent and CsF instead of a base to afford the compounds **4c**,**d** in 54-70% yields.

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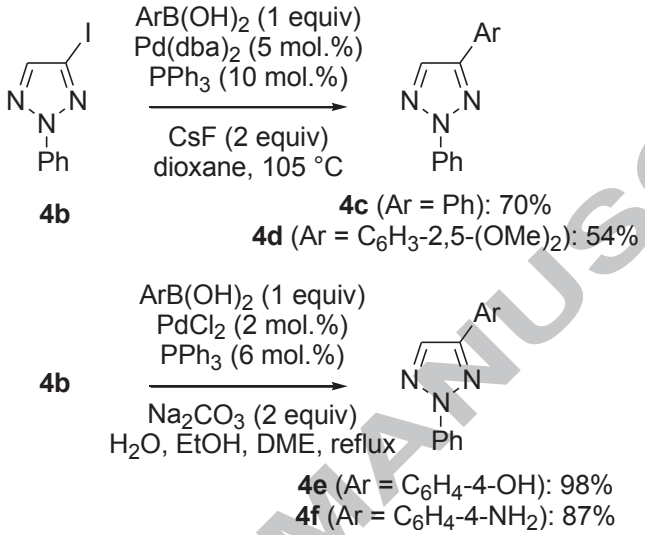
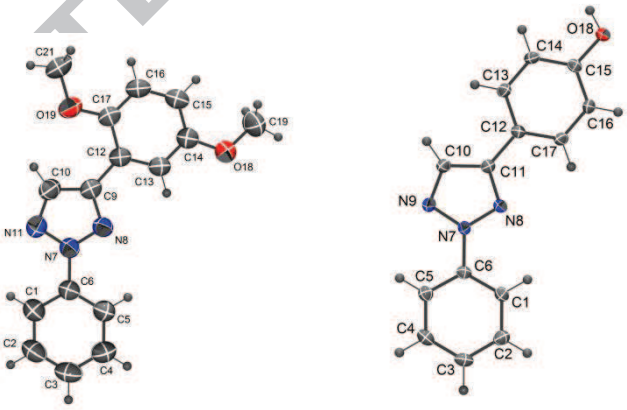
For easier purification, we turned to a dba-free reported procedure[15] using catalytic $PdCl_2$ and triphenylphosphine, a biphasic medium and Na_2CO_3 as a base, and isolated the arylated compounds **4e**,**f** in 87-98% yields (Scheme 7). The structures of the compounds **4d** and **4e** were confirmed by X-ray diffraction (Figure 2).



Scheme 7. Suzuki-type cross-coupling from **4b**.

Figure 2. ORTEP diagram (50% probability) of **4d** and **4e**.



When involved in the reaction, the diiodide **4b'** led to a complex mixture due to unselective mono-coupling. We decided to employ the arylboronic acid in excess (4 equiv) in order to synthesize the bis-coupling products. Thus, the bis-arylated derivatives were obtained in yields ranging from 73 to 92% (Scheme 8).

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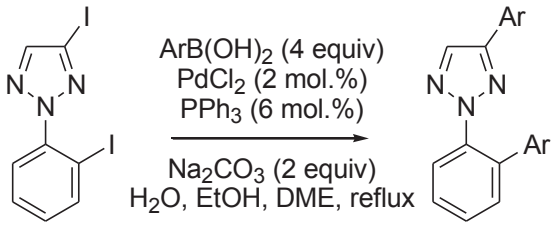


4b'

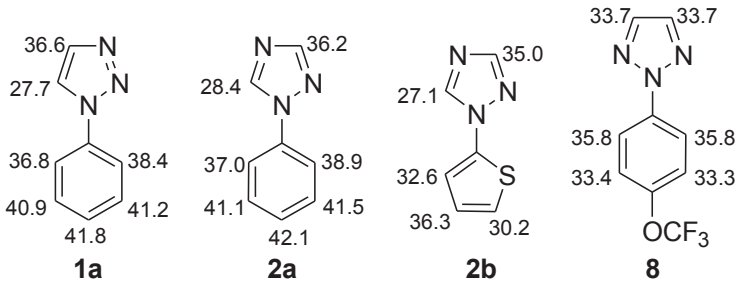
4c' (Ar = Ph): 90%
4d' (Ar = C_6H_4-4-OMe): 75%
4e' (Ar = C_6H_4-4-OH): 92%
4f' (Ar = C_6H_4-4-NH_2): 73%
4g' (Ar = C_6H_4-3-Cl): 83%

Scheme 8. Suzuki-type cross-coupling from **4b'**.

2.2. Computational aspects

The studies on CH acidity of triazoles and their derivatives are not numerous. A brief review of papers devoted to experimental and theoretical investigation of CH acidity of azoles is presented in our previous publication.[16] Fraser reported the pK_a value (26.2) of 1-propyl-1*H*-1,2,4-triazole in THF solution.[17] Gas-phase deprotonation energies for several triazoles were estimated by means of semi-empirical calculations.[18] We also recently contributed to this field by DFT computed values for substituted triazoles,[19] *N*-aryl triazoles,[6h] *N*-aryl pyrazoles[6f] and *N*-aryl benzotriazoles.[6l]

In the present paper, the DFT calculated CH acidities of several *N*-aryl triazoles, both in gas phase (see Supplementary data) and in THF solution (Scheme 9), are presented. These $\Delta_{acid}G$ and pK_a values were obtained by using the theoretical protocol described thoroughly previously.[16]



1a **2a** **2b** **8**

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

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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 points 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:

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

Whereas the solvent influence was treated by using the polarized continuum model (PCM) with the default parameters for THF,[20] 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 equation:

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

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 experimentally known pK_a value. In this study, 1-propylpyrazole was chosen as reference compound since its pK_a value in THF found by Fraser et al,[17] 35.9, was supposed to be close to those for the investigated substrates.

Within this approach the Gibbs energy of the homodesmic reaction ($\Delta_r G_s$) and the pK_a value are linked together by the following equation:

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

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It is obvious that the compounds **2b** and **8** exist in form of several rotamers due to sterical interaction between adjacent hydrogens or/and heteroatom lone pairs. In such cases, the data on Scheme 9 (and Supplementary data) refer to the most stable ones.

There are several potential deprotonation sites in the investigated substrates. When comparing the CH acidity in gas-phase (see Supplementary data) and in THF solution (Scheme 9), the correlation can be easily seen. Investigation of gas-phase CH acidity (see Supplementary data) is of a great importance because these values are free of solvent influence and can be used for acidity scale development. The calculated values of gas-phase acidity of the investigated compounds lie within the range of 360 to 381 kcal mol^{-1}, which is typical for weak CH acids.

When analyzing the pK_a values distribution for the substrates, one can notice that the 5 position of the triazole ring is clearly the most acidic for **1a**, **2a** and **2b**. According to our previous experience, these absolute pK_a values below 30 should hint the regioselectivities unequivocally. In contrast, for **8**, CH acidities of the same magnitude should lead to poor selectivity.

2.3. Discussion

The calculations of the CH acidities in THF (Scheme 9) allowed us to comment the regioselectivities observed in the course of the reactions.

When treated with the lithium-zinc base, the substrates **1a**, **2a** and **2b** were first attacked at the 5 position of the triazole ring. This could be easily rationalized since the 5 position is clearly the most acidic of these substrates, with pK_a values of 27.7, 28.4 and 27.1, respectively. Using the base in excess with the substrate **2b** led to the formation of the diiodides **7b** and **7b'**, a result that could be due to rather low pK_a values of 32.6 and 30.2, respectively at the 3 and 5 position of the 2-thienyl group.

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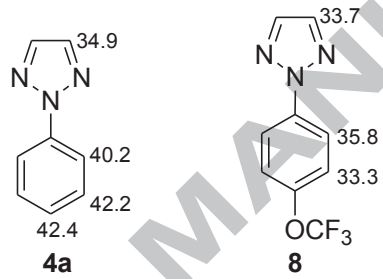
To rationalize the formation of a mixture from **8** using the base prepared from $ZnCl_2$·TMEDA (0.5 equiv) and LiTMP (1.5 equiv), the pK_a values in THF solution of **8** were compared with those of 2-phenyl-1,2,3-triazole (**4a**), which was deprotometalated at its 4 position under the same reaction conditions (Scheme 10).[6h] When 4-substituted by a strongly electron-withdrawing trifluoromethoxy group, which is known to exhibit a long range effect,[21] the phenyl group becomes more prone to deprotonation and can compete with the triazolyl ring. Such an effect could be at the origin of the observed formation of a mixture of iodides from **8**.



Scheme 10. Comparison of pK_a(THF) values of **4a** vs **8**.

2.4. Biological evaluation

Due to their structural similarity with the resveratrol skeleton, most of the synthesized derivatives were biologically evaluated. As a preliminary screening, ten of these triazoles (the compounds **4c-f**, **4c'-g'** and **8**) were assessed for their antibacterial activities against a representative sample of the bacterial species, the most frequently encountered at the Hospital and responsible of healthcare-associated infections (HAI): *Escherichia coli*, *Pseudomonas aeruginosa*, *Staphylococcus aureus* and *Enterococcus faecalis* (Table 1). Bacteria were treated with different concentrations of compounds (range 1 to 256 $\mu g.mL^{-1}$). For all the bacteria tested, both Gram-positive and Gram-negative, we were able to determine antibacterial activities (i.e. determination of the Minimum Inhibitory Concentration). More interesting, even if we observe globally a weak antibacterial activity for these compounds, all of them have an antibacterial activity, and to our knowledge, this is the first time that this kind

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of antibacterial activity is described against these pathogens. On particular interest, the 4,2'-diaryl derivatives **4e'** and **4f'** as well as the 4-aryl derivatives **4e** and **4f** showed higher antibacterial activities (with MICs = 64 $\mu g.mL^{-1}$). Nevertheless, at this stage it is difficult to speculate on the possibility to have promising antibacterial candidates. But we believe that this triazole derivatives could be of interest, and it is necessary to have more data (for example, synthesize other derivatives, or to conduct Structure Activity Relationships studies) to be able to obtain or identify potent antibacterial candidates.

Table 1. Antibacterial activity MICs ($\mu g.mL^{-1}$) of the compounds **4c-f**, **4c'-g'**, **8** and **ATB** (reference antibiotic) obtained by broth microdilution method, according to CLSI guidelines (n = 2, see Supplementary data)

Bacteria	**4c**	**4d**	**4e**	**4f**	**4c'**	**4d'**	**4e'**	**4f'**	**4g'**	**8**	**ATB**
Escherichia coli ATCC 25922	128	128	128	128	256	256	128	128	128	256	4[a]
Staphylococcus aureus ATCC 25923	256	256	128	256	256	256	128	**64**	128	256	<1[b]
Staphylococcus aureus ATCC 29213	>256	128	**64**	256	128	256	128	128	256	256	<1[b]
Enterococcus faecalis ATCC 29212	128	128	**64**	128	128	256	128	128	256	128	<1[c]
Pseudomonas aeruginosa ATCC 27853	128	128	128	**64**	128	256	**64**	128	128	128	8[d]

[a] Amoxicillin.
[b] Oxacillin.
[c] Vancomycin.
[d] Ticarcillin.

Ten of these triazoles were also assessed for their antiproliferative activities against MDA-MB-231 cell line. Indeed, MDA-MB-231 is an estrogen-receptor negative human breast adenocarcinoma cell line currently used as model for antiproliferative assays with resveratrol analogues.[22] Cells were treated with different concentrations of compounds (ranging from 1 to 150 μM). The discrimination was done at 100 μM. After 24 h treatment, some compounds were found of particular interest (Table 2). The 4,2'-diaryl derivatives **4c'**, **4e'**, **4f'** and **4g'** showed higher antiproliferative activities than the 4-aryl derivatives **4c**, **4d**, **4e** and **4f**. The methoxy-substituted derivative **4d'** displayed a weaker effect on the viability than the

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hydroxy analogue **4e'**. Moreover, the effect of the trifluoromethyl group of **8**, highlighted by Pagliai et al,[12] seems to be confirmed in this experiment. The antiproliferative evaluation of the five molecules **4c'**, **4e'-g'** and **8** was pursued by using a 48 h treatment time. Cell survival continued to decrease, and less than 5% of the cells treated with 100 μM of **4f'** survived after 48 h. More interestingly, treatment with 25 μM of **4f'** still led to a strong antiproliferative effect with 22.0% ±1.4% after the same duration (data not shown). Half maximal inhibitory concentrations (IC_{50}) were measured and proved to be 17.5 ±0.7 μM for **4f'** and 67.0 ±1.4 μM for **8** (Table 3).

Table 2. Antiproliferative activity of the compounds **4c-f**, **4c'-g'**, **8** and resveratrol (reference compound) against MDA-MB-231 cell line (results are expressed as a percentage of survival determined by the MTT assay after 24 or 48 h of treatment at a concentration of 100 μM; results are mean ± SEM of two independent experiments; nd: not determined).

Compound	**4c**	**4d**	**4e**	**4f**	**4c'**	
After 24 h	85.5 ± 4.9	94.0 ± 0.0	102.0 ± 0.0	66.0 ± 1.4	49.0 ± 0.0	
After 48 h	nd	nd	nd	nd	23.0 ± 1.4	
Compound	**4d'**	**4e'**	**4f'**	**4g'**	**8**	**resveratrol**
After 24 h	75.0 ± 4.2	54.5 ± 0.7	44.0 ± 4.2	40.5 ± 4.5	58.5 ± 2.5	93.4 ± 2.9
After 48 h	nd	11.0 ± 1.4	2.5 ± 1.5	11.0 ± 4.2	24.0 ± 0.0	60.3 ± 6.4

Table 3. Half maximal inhibitory concentration (IC_{50}) of MDA-MB-231 cells proliferation treated by the compounds **4c'**, **4e'-g'**, **8** and resveratrol (reference compound) (the cells were treated with different concentrations of the compounds during 48 h, and survival was assessed by the MTT assay; results are mean ± SEM of two determinations).

Compound	**4c'**	**4e'**	**4f'**	**4g'**	**8**	**resveratrol**
IC_{50} (μM)	52.0 ± 5.7	40.0 ± 2.8	17.5 ± 0.7	45.5 ± 2.1	67.0 ± 1.4	129.9 ± 3.6

3. Conclusions

The different 1-aryl triazoles involved in the deprotometalation-iodolysis sequence were functionalized at their most acidic site, which is the 5 position of the aza-ring. By increasing the amount of base, it proved possible to also deprotonate the aryl group connected to the azole.

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In the case of 2-phenyl-1,2,3-triazole, the 4-iodo and 4,2'-diiodo derivatives were involved in Suzuki coupling to afford 4-aryl and 4,2'-diaryl compounds, which were evaluated for biological activities. This synthesis of triazole derivatives is promising for the generation of potent antiproliferative compounds.

4. Experimental

4.1. General

Metalation 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, ^{13}C chemical shifts are relative to the central peak of the solvent signal.[23] 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.

4.1.1. Crystallography

The samples were studied with graphite monochromatized Mo-Kα radiation (λ = 0.71073 Å). X-ray diffraction data were collected at T = 150(2) K (compounds **4e**, **5a**, **6a**, **7b**) or 294(2) K (compound **4d**) using APEXII Bruker-AXS diffractometer. The structure was solved by direct methods using the SIR97 program,[24] and then refined with full-matrix least-square methods based on F^2 (SHELX-97)[25] with the aid of the WINGX program.[26] All non-hydrogen atoms were refined with anisotropic atomic displacement parameters. Except oxygen linked hydrogen atom that was introduced in the structural model through Fourier difference maps analysis (**4e**), H atoms were finally included in their calculated positions. Molecular diagrams were generated by ORTEP-3 (version 2.02).[26]

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4.2. 1-Phenyl-1*H*-1,2,3-triazole (1a). Compound **1a** was prepared by adapting a procedure described.[8] A mixture of Cu_2O (0.12 g, 0.80 mmol), 1,2,3-triazole (0.48 mL, 8.0 mmol), 1,10-phenanthroline (0.29 g, 1.6 mmol), iodobenzene (1.1 mL, 9.6 mmol) and tetramethylammonium fluoride (2.2 g, 24 mmol) was heated under argon at 120 °C for 48 h. CH_2Cl_2 (10 mL) was added to the residue. After filtration over celite, the organic phase was washed with brine (2 x 5 mL) and the solvent was evaporated. The crude product was purified by chromatography over silica gel (eluent: CH_2Cl_2/heptane 1:1 to CH_2Cl_2/AcOEt 1:1) to afford the pure compound in 47% yield as an orange powder: mp 58 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.42-7.49 (m, 1H), 7.51-7.58 (m, 2H), 7.74-7.78 (m, 2H), 7.88 (br s, 1H), 8.03 (d, 1H, *J* = 0.9 Hz). The ^{1}H NMR data are in accordance with those previously described.[27] ^{13}C NMR ($CDCl_3$, 75 MHz) 120.8 (2CH), 121.9 (CH), 129.0 (CH), 129.9 (2CH), 134.6 (CH), 137.2 (C).

4.3. General procedure 1 for the synthesis of the 1-aryl 1*H*-1,2,4-triazoles 2a,b.[9] 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 is purified by chromatography over silica gel (the eluent is given in the product description).

4.3.1. 1-Phenyl-1*H*-1,2,4-triazole (2a). Compound **2a** was prepared from 1,2,4-triazole (0.69 g) and iodobenzene (1.4 mL) using the general procedure 1, and was isolated (eluent: heptane/AcOEt 7:3) in 96% yield as a yellow powder: mp 48 °C (lit.[28] 46 °C); ^{1}H NMR ($CDCl_3$, 300 MHz) 7.42 (m, 1H), 7.53 (m, 2H), 7.71 (m, 2H), 8.15 (s, 1H), 8.74 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 120.1 (2CH), 128.3 (CH), 129.9 (2CH), 137.1 (C), 140.9 (CH), 152.7 (CH).

4.3.2. 1-(2-Thienyl)-1*H*-1,2,4-triazole (2b). Compound **2b** was prepared from 1,2,4-triazole (0.69 g) and 2-iodothiophene (1.3 mL) using the general procedure 1, and was isolated (eluent: heptane/AcOEt 4:1) in 70% yield as a pale yellow powder: mp 62 °C; IR

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(ATR): 3440, 3110, 1781, 1556, 1497, 1464, 1403, 1355, 1272, 1221, 1199, 1141, 1028, 1012, 942, 845, 733, 699, 670 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.02 (dd, 1H, J = 5.4 and 3.9 Hz), 7.19 (dd, 1H, J = 3.6 and 1.2 Hz), 7.21 (dd, 1H, J = 5.4 and 1.5 Hz), 8.07 (s, 1H), 8.45 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 117.8 (CH), 122.8 (CH), 126.4 (CH), 138.8 (C), 142.0 (CH), 152.6 (CH). HRMS (ASAP): calcd for $C_6H_6N_3S$ $[M+H]^+$ 152.0282, found 152.0284.

4.3.3. 2-(4-Trifluoromethoxyphenyl)-2*H*-1,2,3-triazole (8). Compound **8** was prepared by adapting a procedure described.[13] A degased solution of $Pd_2(dba)_3$ (20 mg, 90 μmol) and 2-di-*tert*-butylphosphino-3,4,5,6-tetramethyl-2′,4′,6′-triisopropyl-1,1′-biphenyl (104 mg, 0.22 mmol) in toluene (6 mL) was heated at 120 °C for 5 min and transferred to a degased mixture of K_3PO_4 (5.1 g, 24 mmol), 1,2,3-triazole (0.83 mL, 14 mmol) and 1-bromo-4-(trifluoromethoxy)benzene (1.8 mL, 12 mmol) in toluene (6 mL). The resulting mixture was heated under argon at 120 °C for 24 h. CH_2Cl_2 (30 mL) was added, the organic phase was washed with NH_4Cl-saturated water (10 mL) and brine (10 mL), and the solvent was evaporated. The crude product was purified by chromatography over silica gel (eluent: heptane/AcOEt 95:5) to afford the pure compound in 96% yield as a beige powder: mp < 50 °C; IR (ATR): 1606, 1511, 1411, 1386, 1251, 1207, 1193, 1152, 1100, 1084, 1056, 962, 949, 921, 852, 821, 731, 664 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.32-7.36 (m, 2H), 7.82 (s, 2H), 8.11-8.15 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 120.4 (2CH), 120.6 (q, C, J = 256 Hz), 122.0 (2CH), 136.0 (2CH), 138.4 (C), 148.3 (C); ^{19}F NMR ($CDCl_3$, 282 MHz) -58.0.

4.4. General procedure 2 for the deprotonative metalation followed by iodolysis. 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

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CH_2Cl_2 (3 x 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.

4.4.1. 5-Iodo-1-phenyl-1*H*-1,2,4-triazole (6a). Compound **6a** was prepared from 1-phenyl-1*H*-1,2,4-triazole (**2a**) using the general procedure 2 and was isolated (eluent: heptane/AcOEt 4:1) in 51% yield as a white powder: mp 109 °C; IR (ATR): 3066, 2244, 1598, 1499, 1475, 1364, 1323, 1273, 1165, 994, 908, 761, 730, 693, 666 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.54 (br s, 5H), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 99.8 (C), 126.1 (2CH), 129.4 (2CH), 129.8 (CH), 137.5 (C), 155.0 (CH). HRMS (ASAP): calcd for $C_8H_7IN_3$ $[M+H]^+$ 271.9685, found 271.9684. **Crystal data for 6a** (CCDC 1058467). $C_8H_6IN_3$, M = 271.06, monoclinic, $P\ 2_1/c$, a = 6.7529(2), b = 7.2343(2), c = 18.0011(6) Å, β= 95.0770(10) °, V = 875.95(5) $Å^3$, Z = 4, d = 2.055 g cm^{-3}, μ = 3.600 mm^{-1}. A final refinement on F^2 with 2000 unique intensities and 109 parameters converged at $\omega R(F^2)$ = 0.0636 ($R(F)$ = 0.0252) for 1886 observed reflections with $I > 2\sigma(I)$.

4.4.2. 5-Iodo-1-(2-thienyl)-1*H*-1,2,4-triazole (6b). Compound **6b** was prepared from 1-(2-thienyl)-1*H*-1,2,4-triazole (**2b**) using the general procedure 2 and was isolated (eluent: heptane/AcOEt 4:1) in 95% yield as a yellow powder: mp 66 °C; IR (ATR): 3465, 3101, 2643, 1549, 1474, 1323, 1267, 1247, 1160, 1031, 945, 847, 699, 676 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.07 (dd, 1H, J = 5.5 and 3.8 Hz), 7.32 (dd, 1H, J = 3.8 and 1.4 Hz), 7.38 (dd, 1H, J = 5.5 and 1.4 Hz), 8.06 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 102.5 (C), 124.9 (CH), 125.7 (CH), 125.9 (CH), 137.6 (C), 155.0 (CH). HRMS (ASAP): calcd for $C_6H_5IN_3S$ $[M+H]^+$ 277.9249, found 277.9247.

4.4.3. 2-(2-Iodo-4-trifluoromethoxyphenyl)-2*H*-1,2,3-triazole (9a). Compound **9a** was formed (23% estimated yield) from 2-(4-trifluoromethoxyphenyl)-2*H*-1,2,3-triazole (**8**) using the general procedure 2 and a pure fraction was isolated (eluent: heptane) as a yellow powder: mp < 50 °C; IR (ATR): 2930, 1593, 1511, 1495, 1410, 1252, 1217, 1200, 1171, 1065, 1026,

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962, 952, 884, 823, 736, 671 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.35 (ddq, 1H, *J* = 8.7, 2.7 and 0.9 Hz), 7.52 (d, 1H, *J* = 8.7 Hz), 7.85-7.87 (m, 1H), 7.89 (s, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 92.8 (C), 120.4 (q, C, *J* = 258 Hz), 121.3 (CH), 128.6 (CH), 132.7 (CH), 136.0 (2CH), 141.9 (C), 149.4 (C); ^{19}F NMR ($CDCl_3$, 282 MHz) -57.9.

4.4.4. 4-Iodo-2-(2-iodo-4-trifluoromethoxyphenyl)-2*H*-1,2,3-triazole (10). Compound **10** was formed (19% estimated yield) from 2-(4-trifluoromethoxyphenyl)-2*H*-1,2,3-triazole (**8**) using the general procedure 2 and was identified by its ^{1}H NMR spectra: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.33-7.36 (m, 1H), 7.51 (d, 1H, *J* = 9.0 Hz), 7.85-7.86 (m, 1H), 7.93 (s, 1H).

4.4.5. 4-Iodo-2-(4-trifluoromethoxyphenyl)-2*H*-1,2,3-triazole (9b). Compound **9b** was formed (6% estimated yield) from 2-(4-trifluoromethoxyphenyl)-2*H*-1,2,3-triazole (**8**) using the general procedure 2 and was identified by its ^{1}H NMR spectra: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.33-7.36 (m, 2H), 7.86 (s, 1H), 8.07-8.10 (m, 2H).

4.5. General procedure 3 for the deprotonative metalation followed by iodolysis. 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 (1.3 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 x 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.

4.5.1. 5-Iodo-1-phenyl-1*H*-1,2,3-triazole (5a). Compound **5a** was prepared from 1-phenyl-1*H*-1,2,3-triazole (**1a**) using the general procedure 3 and was isolated (eluent: CH_2Cl_2) in 89% yield as a white powder: mp 134 °C; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.53-7.59 (m, 5H), 7.87 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 78.7 (C), 125.9 (2CH), 129.3 (2CH), 130.1 (CH),

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136.5 (C), 141.8 (CH). HRMS (ASAP): calcd for $C_8H_7IN_3$ $[M+H]^+$ 271.9685, found 271.9690. **Crystal data for 5a** (CCDC 1058464). $C_8H_6IN_3$, M = 271.06, monoclinic, $P\ 2_1/n$, a = 5.11980(10), b = 33.1939(9), c = 5.15960(10) Å, β= 91.3720(10) °, V = 876.60(3) Å^3, Z = 4, d = 2.054 g cm^{-3}, μ = 3.598 mm^{-1}. A final refinement on F^2 with 2015 unique intensities and 145 parameters converged at $\omega R(F^2)$ = 0.091 ($R(F)$ = 0.0441) for 1980 observed reflections with $I > 2\sigma(I)$.

4.5.2. 5-Iodo-1-(2-iodo-5-thienyl)-1*H*-1,2,4-triazole (7b). Compound **7b** was obtained from 1-(2-thienyl)-1*H*-1,2,4-triazole (**2b**) using the general procedure 3 (eluent: heptane/AcOEt 9:1 to 7:3) in 59% estimated yield. The analyses were obtained from a pure fraction: beige powder; mp 142 °C; IR (ATR): 3056, 2923, 1552, 1474, 1369, 1331, 1265, 1160, 953, 795, 734, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.01 (d, 1H, J = 4.0 Hz), 7.24 (d, 1H, J = 4.0 Hz), 8.03 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 74.4 (C), 101.8 (C), 126.1 (CH), 135.7 (CH), 142.0 (C), 155.3 (CH). **Crystal data for 7b** (CCDC 1058468). $C_6H_3I_2N_3S$, M = 402.97, orthorhombic, $P\ c\ a\ b$, a = 7.5513(4), b = 11.9393(5), c = 21.3208(9) Å, V = 1922.22(15) Å^3, Z = 8, d = 2.785 g cm^{-3}, μ = 6.710 mm^{-1}. A final refinement on F^2 with 2201 unique intensities and 109 parameters converged at $\omega R(F^2)$ = 0.0709 ($R(F)$ = 0.0289) for 1955 observed reflections with $I > 2\sigma(I)$.

4.5.3. 5-Iodo-1-(3-iodo-2-thienyl)-1*H*-1,2,4-triazole (7b'). Compound **7b'** was obtained from 1-(2-thienyl)-1*H*-1,2,4-triazole (**2b**) using the general procedure 3 (eluent: heptane/AcOEt 9:1 to 7:3) in 28% estimated yield: ^{1}H NMR ($CDCl_3$, 300 MHz) 7.14 (d, 1H, J = 5.7 Hz), 7.47 (d, 1H, J = 5.7 Hz), 8.10 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 84.8 (C), 105.1 (C), 129.0 (CH), 134.0 (CH), 155.8 (CH), 1C not seen.

4.6. General procedure 4 for the Suzuki-type mono-coupling.[14] A degassed solution of 4-iodo-2-phenyl-2*H*-1,2,3-triazole (**4b**, 0.14 g, 0.5 mmol) and the required boronic acid (0.5 mmol), CsF (0.15 g, 1.0 mmol), $Pd(dba)_2$ (13 mg, 25 µmol, 5 mol.%) and PPh_3 (13 mg, 50

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μmol, 10 mol.%) in dioxane (10 mL) was heated at 105 °C for 18 h. The reaction mixture was then diluted with Et_2O (50 mL) and washed with H_2O (2 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure before purification by flash chromatography on silica gel.

4.6.1. 2,4-Diphenyl-2*H*-1,2,3-triazole (4c). Compound **4c** was prepared from phenylboronic acid (61 mg) using the general procedure 4 and was isolated (eluent: heptane/AcOEt 9.5:0.5) in 70% yield as a yellow powder: mp < 50 °C; IR (ATR): 3040, 2925, 1598, 1498, 1480, 1460, 1395, 1343, 978, 964, 845, 766, 753, 710, 687, 660 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 7.33-7.54 (m, 6H), 7.89-7.93 (m, 2H), 8.06 (s, 1H), 8.13-8.17 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 118.9 (2CH), 126.3 (2CH), 127.5 (CH), 128.9 (CH), 129.1 (2CH), 129.4 (2CH), 130.2 (C), 132.7 (CH), 140.0 (C), 149.0 (C).

4.6.2. 4-(2,5-Dimethoxyphenyl)-2-phenyl-2*H*-1,2,3-triazole (4d). Compound **4d** was prepared from 2,5-dimethoxyphenylboronic acid (182 mg) using the general procedure 4, but using 2 equiv of boronic acid, and was isolated (eluent: heptane/AcOEt/Et_2O 98:1:1) in 54% yield as a yellow powder: mp 68-70 °C; IR (ATR): 2940, 2835, 1724, 1598, 1526, 1489, 1465, 1436, 1382, 1335, 1313, 1270, 1222, 1172, 1074, 1044, 1023, 992, 965, 859, 801, 754, 734, 704, 689, 661 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 3.87 (s, 3H), 3.92 (s, 3H), 6.89-6.97 (m, 2H), 7.35 (tt, 1H, J = 7.3 and 1.2 Hz), 7.47-7.53 (m, 2H), 7.74 (dd, 1H, J = 2.7 and 0.6 Hz), 8.15-8.19 (m, 2H), 8.32 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 56.0 (CH_3), 56.2 (CH_3), 112.8 (CH), 113.4 (CH), 115.5 (CH), 118.9 (2CH), 119.7 (C), 127.4 (CH), 129.4 (2CH), 136.2 (CH), 140.0 (C), 145.6 (C), 151.5 (C), 154.0 (C). **Crystal data for 4d** (CCDC 1058466). $C_{16}H_{15}N_3O_2$, M = 281.31, monoclinic, $P\,2_1/n$, a = 15.2065(19), b = 4.8810(6), c = 19.365(2) Å, β = 104.952(5) °, V = 1388.7(3) $Å^3$, Z = 4, d = 1.346 g cm^{-3}, μ = 0.091 mm^{-1}. A final refinement on F^2 with 3180 unique intensities and 192 parameters converged at $\omega R(F^2)$ = 0.1327 ($R(F)$ = 0.0459) for 2105 observed reflections with $I > 2\sigma(I)$.

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4.7. General procedure 5 for the Suzuki-type mono-coupling. A degassed solution of 4-iodo-2-phenyl-2*H*-1,2,3-triazole (**4b**, 0.14 g, 0.5 mmol) and the required boronic acid (0.5 mmol), Na_2CO_3 (0.12 g, 1.1 mmol), $PdCl_2$ (2 mg, 10 µmol, 2 mol.%) and PPh_3 (8 mg, 30 µmol, 6 mol.%), in H_2O (6 mL), EtOH (5 mL) and 1,2-dimethoxyethane (8 mL), was heated at 90 °C for 24 h. The reaction mixture was then diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure before purification by flash chromatography on silica gel.

4.7.1. 4-(4-Hydroxyphenyl)-2-phenyl-2*H*-1,2,3-triazole (4e). Compound **4e** was prepared from 4-hydroxyphenylboronic acid (69 mg) using the general procedure 5 and was isolated (eluent: heptane/AcOEt 4:1) in 98% yield as a beige powder: mp 178-179 °C (lit.[29] 177-179 °C); IR (ATR): 3306, 3044, 2926, 2853, 1713, 1615, 1595, 1497, 1461, 1390, 1265, 1224, 1200, 1174, 979, 966, 835, 752, 736, 705, 661 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 6.91-6.95 (m, 2H), 7.32-7.38 (m, 1H), 7.47-7.53 (m, 2H), 7.78-7.81 (m, 2H), 7.98 (s, 1H), 8.10-8.14 (m, 2H), OH not seen; ^{13}C NMR ($CDCl_3$, 75 MHz) 116.0 (2CH), 118.9 (2CH), 123.0 (C), 127.4 (CH), 127.9 (2CH), 129.4 (2CH), 132.2 (CH), 140.1 (C), 148.8 (C), 156.4 (C). **Crystal data for 4e** (CCDC 1058465). $C_{14}H_{11}N_3O$, M = 237.26, orthorhombic, *P c a n*, a = 7.5313(3), b = 17.1106(9), c = 17.6845(10) Å, V = 2278.9(2) $Å^3$, Z = 8, d = 1.383 g cm^{-3}, μ = 0.091 mm^{-1}. A final refinement on F^2 with 2591 unique intensities and 166 parameters converged at $\omega R(F^2)$ = 0.0954 ($R(F)$ = 0.0394) for 2092 observed reflections with $I > 2\sigma(I)$.

4.7.2. 4-(4-Aminophenyl)-2-phenyl-2*H*-1,2,3-triazole (4f). Compound **4f** was prepared from 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.11 g) using the general procedure 5 and was isolated (eluent: CH_2Cl_2/heptane 8:2) in 87% yield as a white powder: mp 134-136 °C; IR (ATR): 3438, 3420, 3355, 2925, 2855, 1730, 1622, 1609, 1596, 1497, 1488, 1459, 1392, 1342, 1285, 1183, 1073, 977, 967, 832, 753, 692, 657 cm^{-1}; ^1H NMR ($CDCl_3$, 300 MHz) 3.8 (br s, 2H), 6.75-6.79 (m, 2H), 7.33 (tt, 1H, J = 7.5 and 1.2 Hz), 7.45-

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7.52 (m, 2H), 7.69-7.72 (m, 2H), 7.95 (s, 1H), 8.09-8.13 (m, 2H); ^{13}C NMR ($CDCl_3$, 75 MHz) 115.4 (2CH), 118.8 (2CH), 120.5 (C), 127.2 (CH), 127.5 (2CH), 129.3 (2CH), 132.0 (CH), 140.1 (C), 147.3 (C), 149.3 (C). HRMS (ESI): calcd for $C_{14}H_{13}N_4$ $[M+H]^+$ 237.1140, found 237.1137.

4.8. General procedure 6 for the Suzuki-type bis-coupling. A degassed solution of 4-iodo-2-(2-iodophenyl)-2*H*-1,2,3-triazole (**4b'**, 0.20 g, 0.5 mmol) and the required boronic acid (2.0 mmol), Na_2CO_3 (0.12 g, 1.1 mmol), $PdCl_2$ (2 mg, 10 µmol, 2 mol.%) and PPh_3 (8 mg, 30 µmol, 6 mol.%), in H_2O (6 mL), EtOH (5 mL) and 1,2-dimethoxyethane (8 mL), was heated at 90 °C for 24 h. The reaction mixture was then diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure before purification by flash chromatography on silica gel.

4.8.1. 2-(1,1'-(2-Biphenyl))-4-phenyl-2*H*-1,2,3-triazole (4c'). Compound **4c'** was prepared from phenylboronic acid (0.24 g) using the general procedure 6 and was isolated (eluent: heptane/AcOEt 100:0 to 95:5) in 90% yield as a yellow oil: IR (ATR): 3053, 1599, 1506, 1485, 1458, 1440, 1392, 1265, 1092, 1074, 978, 969, 847, 766, 757, 732, 694 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 7.13-7.16 (m, 2H), 7.26-7.29 (m, 3H), 7.35-7.43 (m, 3H), 7.49-7.56 (m, 3H), 7.69-7.74 (m, 3H), 7.90 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 126.3 (2CH), 126.5 (CH), 127.5 (CH), 128.4 (CH), 128.4 (2CH), 128.6 (2CH), 128.8 (CH), 129.1 (2CH), 129.6 (CH), 130.3 (C), 131.5 (CH), 132.3 (CH), 137.9 (C), 138.7 (C), 138.9 (C), 148.6 (C). HRMS (ASAP): calcd for $C_{20}H_{16}N_3$ $[M+H]^+$ 298.1344, found 298.1340.

4.8.2. 2-(4'-Methoxy-1,1'-(2-biphenyl))-4-(4-methoxyphenyl)-2*H*-1,2,3-triazole (4d'). Compound **4d'** was prepared from 4-methoxyphenylboronic acid (0.30 g) using the general procedure 6 and was isolated (eluent: heptane/AcOEt 100:0 to 7:3) in 75% yield as a yellow oil: IR (ATR): 2940, 2938, 1613, 1519, 1488, 1456, 1290, 1246, 1177, 1033, 979, 969, 832, 765, 732, 703, 665 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 3.77 (s, 3H), 3.84 (s, 3H), 6.79-6.83 (m, 2H), 6.93-6.97 (m, 2H), 7.04-7.08 (m, 2H), 7.43-7.53 (m, 3H), 7.66-7.70 (m, 3H), 7.84 (s,

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1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 55.3 (CH_3), 55.4 (CH_3), 113.8 (2CH), 114.4 (2CH), 122.9 (C), 126.6 (CH), 127.5 (2CH), 127.8 (CH), 129.4 (CH), 129.6 (2CH), 131.1 (C), 131.3 (CH), 131.7 (CH), 137.5 (C), 138.6 (C), 148.3 (C), 159.0 (C), 160.1 (C). HRMS (ESI): calcd for $C_{22}H_{19}N_3NaO_2$ $[M+Na]^+$ 380.1375, found 380.1378.

4.8.3. 2-(4'-Hydroxy-1,1'-(2-biphenyl))-4-(4-hydroxyphenyl)-2*H*-1,2,3-triazole (4e'). Compound **4e'** was prepared from 4-hydroxyphenylboronic acid (0.28 g) using the general procedure 6 and was isolated (eluent: heptane/AcOEt 100:0 to 0:1) in 92% yield as a yellow oil: IR (ATR): 3054, 1707, 1615, 1594, 1516, 1489, 1456, 1367, 1265, 1223, 1173, 1105, 971, 836, 732, 703 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 6.62-6.66 (m, 2H), 6.79-6.82 (m, 2H), 6.90-6.93 (m, 2H), 7.39-7.48 (m, 3H), 7.52-7.56 (m, 2H), 7.62 (d, 1H, J = 7.2 Hz), 7.81 (s, 1H), 2 OH not seen; ^{13}C NMR ($CDCl_3$, 75 MHz) 115.4 (2CH), 116.0 (2CH), 122.3 (C), 126.7 (CH), 127.7 (2CH), 127.8 (CH), 129.6 (CH), 129.7 (2CH), 130.6 (C), 131.3 (CH), 131.6 (CH), 137.7 (C), 138.3 (C), 148.6 (C), 155.6 (C), 156.8 (C). HRMS (ESI): calcd for $C_{20}H_{15}N_3NaO_2$ $[M+Na]^+$ 352.1062, found 352.1064.

4.8.4. 2-(4'-Amino-1,1'-(2-biphenyl))-4-(4-aminophenyl)-2*H*-1,2,3-triazole (4f'). Compound **4f'** was prepared from 4-(4,4,5,5-tetramethyl-1,3,2-dioxaborolan-2-yl)aniline (0.44 g) using the general procedure 6 and was isolated (eluent: heptane/MeOH 100:0 to 0:1) in 73% yield as a pink oil: IR (ATR): 3360, 1622, 1515, 1488, 1454, 1388, 1287, 1181, 971, 830, 766, 736 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 3.7 (br s, 4H), 6.54-6.58 (m, 2H), 6.70-6.74 (m, 2H), 6.89-6.92 (m, 2H), 7.41 (ddd, 1H, J = 7.5, 5.7 and 3.3 Hz), 7.47-7.51 (m, 2H), 7.55-7.58 (m, 2H), 7.59-7.64 (m, 1H), 7.79 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 114.9 (2CH), 115.2 (2CH), 120.6 (C), 126.6 (CH), 127.3 (CH), 127.3 (2CH), 128.8 (C), 129.2 (CH), 129.3 (2CH), 131.0 (CH), 131.2 (CH), 137.9 (C), 138.4 (C), 145.6 (C), 146.9 (C), 148.6 (C). HRMS (ESI): calcd for $C_{20}H_{18}N_5$ $[M+H]^+$ 328.1562, found 328.1561.

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4.8.5. 2-(3'-Chloro-1,1'-(2-biphenyl))-4-(3-chlorophenyl)-2*H*-1,2,3-triazole (4g'). Compound **4g'** was prepared from 3-chlorophenylboronic acid (0.31 g) using the general procedure 6 and was isolated (eluent: heptane/AcOEt 100:0 to 4:1) in 83% yield as a yellow oil: IR (ATR): 3061, 1564, 1500, 1470, 1453, 1411, 1264, 1099, 1081, 994, 968, 887, 847, 804, 787, 763, 735, 703, 695, 683 cm^{-1}; ^{1}H NMR ($CDCl_3$, 300 MHz) 6.94 (dt, 1H, J = 7.5 and 1.5 Hz), 7.17 (d, 1H, J = 7.8 Hz), 7.19-7.25 (m, 2H), 7.32-7.35 (m, 2H), 7.49-7.59 (m, 4H), 7.68-7.76 (m, 2H), 7.83 (s, 1H); ^{13}C NMR ($CDCl_3$, 75 MHz) 124.3 (CH), 126.3 (CH), 126.3 (CH), 126.7 (CH), 127.6 (CH), 128.8 (CH), 128.9 (CH), 128.9 (CH), 129.5 (CH), 129.7 (CH), 130.3 (CH), 131.4 (CH), 131.8 (C), 132.5 (CH), 134.2 (C), 135.0 (C), 136.3 (C), 138.4 (C), 140.6 (C), 147.5 (C). HRMS (ASAP): calcd for $C_{20}H_{14}{}^{35}Cl_2N_3$ $[M+H]^+$ 366.0565, found 366.0561.

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Supplementary data

Supplementary data associated with this article can be found, in the online version, at http://dx.doi.org/10.1016/xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. It contains ^{1}H, ^{13}C (and ^{19}F) NMR spectra, gas phase acidities of the investigated compounds, Cartesian coordinates of molecular geometry for the most stable rotamer form of the triazoles **1a**, **2a**,**b** and **8** (neutral molecule, gas phase) optimized at B3LYP/6-31G(d) level of theory, biological evaluation, and crystallographic data (CIF files).

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