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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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 deprotonetalations 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
1. Introduction

Di- and triazoles are key elements present in compounds of biological interest or in materials for a wide range of applications. Aromatic deprotonative lithiation is an efficient tool to functionalize regioselectively heterocycles. Concerning 1-substituted 1,2,3- and 1,2,4-1H-triazoles, such a possibility has been developed, affording after subsequent trapping 5-substituted derivatives.

Combinations of lithium reagents and softer metal compounds have recently emerged as efficient tools to deprotometalate sensitive aromatic compounds. 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, prepared by mixing LiTMP with ZnCl₂·TMEDA (1/3 equiv, TMEDA = N,N,N',N'-tetramethylethylenediamine) and supposed to be a 1:1 Zn(TMP)₂-LiTMP-2LiCl(±TMEDA) mixture, 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 and 4 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.
2. Results and Discussion

2.1. Synthetic aspects

1-Phenyl-1H-1,2,3-triazole (1a) was prepared by adapting a procedure described. 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). Moderate to excellent yields were noted, with aryl iodides favoring the reaction as observed previously.

![Scheme 1](image)

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

![Scheme 2](image)

**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 ZnCl₂·TMEDA (x equiv) and LiTMP (3x equiv), 1-phenyl-1H-pyrazole (3a) is mainly deprotonated at its 5 position (x = 0.5), a result evidenced by subsequent interception with iodine. In addition, 2-phenyl-2H-1,2,3-triazole (4a) mainly led to the 4-iodo derivative under the same reaction conditions. It was thus of interest to attempt the reaction from 1-phenyl-1H-1,2,3-triazole (1a) and 1-phenyl-1H-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 =
(80% yield) from 1a after carrying out the reaction using LiTMP (1.5 equiv) in THF, but using a lower (-20 °C) reaction temperature.

\[
\text{ZnCl}_2 \cdot \text{TMEDA} (x \text{ equiv}) + \text{LiTMP} (3x \text{ equiv}) \quad \text{THF, rt, 2 h}
\]

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 ZnCl₂·TMEDA and 2.25 equiv of LiTMP instead of 0.5 equiv of ZnCl₂·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. 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).
The triazole moiety is a well-known bioisostere of amide and ester groups and a linker replacement of double bonds. Moreover, resveratrol is a compound with a versatile biological activity. 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. 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. Unfortunately, treatment of 8 by the base (0.5 equiv of ZnCl₂·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
be isolated. Analyzing the crude showed, besides the monoiodide 9a (estimated 25% yield), the formation of the diiodide 10 and the monoiode 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 monoiode 4b and diiodide 4b' as described previously. The monoiode 4b was first reacted with arylboronic acids (stoichiometric amount) in a Suzuki-type cross-coupling procedure 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.
For easier purification, we turned to a dba-free reported procedure\(^\text{15}\) using catalytic PdCl\(_2\) and triphenylphosphine, a biphasic medium and Na\(_2\)CO\(_3\) 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.](image)

**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).
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. Fraser reported the pKₐ value (26.2) of 1-propyl-1H-1,2,4-triazole in THF solution. Gas-phase deprotonation energies for several triazoles were estimated by means of semi-empirical calculations. We also recently contributed to this field by DFT computed values for substituted triazoles, N-aryl triazoles, N-aryl pyrazoles and N-aryl benzotriazoles.

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 Δacid G and pKₐ values were obtained by using the theoretical protocol described thoroughly previously.

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

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

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

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

Whereas the solvent influence was treated by using the polarized continuum model (PCM) with the default parameters for THF, the PCM energies $E_{\text{PCM}}$ 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:

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

The $pK_a$ values were calculated by means of the following homodesmic reaction:

$$\text{R–H}_{\text{g}} + \text{Het}^-_{\text{g}} \rightarrow \text{R}^-_{\text{g}} + \text{Het–H}_{\text{g}},$$

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., 35.9, was supposed to be close to those for the investigated substrates.

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

$$pK_a(R-H) = pK_a(\text{Het–H}) + \frac{\Delta G_s}{RT} \times \frac{1}{\ln 10}. $$
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 pKₐ 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 pKₐ 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 pKₐ 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 pKₐ values of 32.6 and 30.2, respectively at the 3 and 5 position of the 2-thienyl group.
To rationalize the formation of a mixture from 8 using the base prepared from ZnCl₂·TMEDA (0.5 equiv) and LiTMP (1.5 equiv), the pKᵦ 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). When 4-substituted by a strongly electron-withdrawing trifluoromethoxy group, which is known to exhibit a long range effect, 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 pKᵦ(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 μg.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
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 μg.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 (μg.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)

<table>
<thead>
<tr>
<th>Bacteria</th>
<th>4c</th>
<th>4d</th>
<th>4e</th>
<th>4f</th>
<th>4c’</th>
<th>4d’</th>
<th>4e’</th>
<th>4f’</th>
<th>4g’</th>
<th>8</th>
<th>ATB</th>
</tr>
</thead>
<tbody>
<tr>
<td><em>Escherichia coli</em> ATCC 25922</td>
<td>128</td>
<td>128</td>
<td>128</td>
<td>128</td>
<td>256</td>
<td>256</td>
<td>128</td>
<td>128</td>
<td>128</td>
<td>128</td>
<td>4a</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> ATCC 25923</td>
<td>256</td>
<td>256</td>
<td>128</td>
<td>256</td>
<td>256</td>
<td>256</td>
<td>128</td>
<td>64</td>
<td>128</td>
<td>256</td>
<td>&lt;1b</td>
</tr>
<tr>
<td><em>Staphylococcus aureus</em> ATCC 29213</td>
<td>&gt;256</td>
<td>128</td>
<td>64</td>
<td>256</td>
<td>128</td>
<td>256</td>
<td>128</td>
<td>256</td>
<td>256</td>
<td>&lt;1b</td>
<td></td>
</tr>
<tr>
<td><em>Enterococcus faecalis</em> ATCC 29212</td>
<td>128</td>
<td>128</td>
<td>64</td>
<td>128</td>
<td>128</td>
<td>256</td>
<td>128</td>
<td>256</td>
<td>128</td>
<td>128</td>
<td>&lt;1c</td>
</tr>
<tr>
<td><em>Pseudomonas aeruginosa</em> ATCC 27853</td>
<td>128</td>
<td>128</td>
<td>128</td>
<td>64</td>
<td>128</td>
<td>256</td>
<td>64</td>
<td>128</td>
<td>128</td>
<td>128</td>
<td>8d</td>
</tr>
</tbody>
</table>

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. 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
hydroxy analogue 4e'. Moreover, the effect of the trifluoromethyl group of 8, highlighted by Pagliai et al., 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 (IC₅₀) 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, 4e'-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).

<table>
<thead>
<tr>
<th>Compound</th>
<th>4c</th>
<th>4d</th>
<th>4e</th>
<th>4f</th>
<th>4c'</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 24 h</td>
<td>85.5 ± 4.9</td>
<td>94.0 ± 0.0</td>
<td>102.0 ± 0.0</td>
<td>66.0 ± 1.4</td>
<td>49.0 ± 0.0</td>
</tr>
<tr>
<td>After 48 h</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>nd</td>
<td>23.0 ± 1.4</td>
</tr>
</tbody>
</table>

<table>
<thead>
<tr>
<th>Compound</th>
<th>4d'</th>
<th>4e'</th>
<th>4f'</th>
<th>4g'</th>
<th>8</th>
<th>Resveratrol</th>
</tr>
</thead>
<tbody>
<tr>
<td>After 24 h</td>
<td>75.0 ± 4.2</td>
<td>54.5 ± 0.7</td>
<td>44.0 ± 4.2</td>
<td>40.5 ± 4.5</td>
<td>58.5 ± 2.5</td>
<td>93.4 ± 2.9</td>
</tr>
<tr>
<td>After 48 h</td>
<td>nd</td>
<td>11.0 ± 1.4</td>
<td>2.5 ± 1.5</td>
<td>11.0 ± 4.2</td>
<td>24.0 ± 0.0</td>
<td>60.3 ± 6.4</td>
</tr>
</tbody>
</table>

### Table 3. Half maximal inhibitory concentration (IC₅₀) 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).

<table>
<thead>
<tr>
<th>Compound</th>
<th>4c'</th>
<th>4e'</th>
<th>4f'</th>
<th>4g'</th>
<th>8</th>
<th>Resveratrol</th>
</tr>
</thead>
<tbody>
<tr>
<td>IC₅₀ (µM)</td>
<td>52.0 ± 5.7</td>
<td>40.0 ± 2.8</td>
<td>17.5 ± 0.7</td>
<td>45.5 ± 2.1</td>
<td>67.0 ± 1.4</td>
<td>129.9 ± 3.6</td>
</tr>
</tbody>
</table>

### 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.
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. 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, and then refined with full-matrix least-square methods based on $F^2$ (SHELX-97) with the aid of the WINGX program. 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).
4.2. 1-Phenyl-1H-1,2,3-triazole (1a). Compound 1a was prepared by adapting a procedure described.\(^8\) A mixture of Cu\(_2\)O (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\(_2\)Cl\(_2\) (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\(_2\)Cl\(_2\)/heptane 1:1 to CH\(_2\)Cl\(_2\)/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 1H-1,2,4-triazoles 2a,b.\(^9\) A mixture of CuI (0.10 g, 0.50 mmol), the required azole (10 mmol), K\(_3\)PO\(_4\) (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-1H-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)-1H-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
(ATR): 3440, 3110, 1781, 1556, 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 (CH), 142.0 (CH), 152.6 (CH). HRMS (ASAP): calcd for C\(_6\)H\(_6\)N\(_3\)S [M+H]\(^+\) 152.0282, found 152.0284.

4.3.3. 2-(4-Trifluoromethoxyphenyl)-2H-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 \(\mu\)mol) 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\(_3\)PO\(_4\) (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\(_2\)Cl\(_2\) (30 mL) was added, the organic phase was washed with NH\(_4\)Cl-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), 183.4 (C), 148.3 (C); \(^{19}\)F NMR (CDCl\(_3\), 282 MHz) -58.0.

4.4. General procedure 2 for the deprotonative metalation followed by iiodolysis. 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\(_2\)S\(_2\)O\(_3\) (10 mL) and extraction with
CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure before purification by flash chromatography on silica gel.

4.4.1. 5-Iodo-1-phenyl-1H-1,2,4-triazole (6a). Compound 6a was prepared from 1-phenyl-1H-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 (CDCl₃, 300 MHz) 7.54 (br s, 5H), 8.10 (s, 1H); ¹³C NMR (CDCl₃, 75 MHz) 99.8 (C), 126.1 (2CH), 129.4 (2CH), 129.8 (CH), 137.5 (C), 155.0 (CH). HRMS (ASAP): calcd for C₈H₇IN₃ [M+H]⁺ 271.9685, found 271.9684. Crystal data for 6a (CCDC 1058467). C₈H₆IN₃, M = 271.06, monoclinic, P 2₁/c, a = 6.7529(2), b = 7.2343(2), c = 18.0011(6) Å, β = 95.0770(10)°, V = 875.95(5) Å³, Z = 4, d = 2.055 g cm⁻³, μ = 3.600 mm⁻¹. A final refinement on F² with 2000 unique intensities and 109 parameters converged at ω(R) = 0.0636 (R(F) = 0.0252) for 1886 observed reflections with I > 2σ(I).

4.4.2. 5-Iodo-1-(2-thienyl)-1H-1,2,4-triazole (6b). Compound 6b was prepared from 1-(2-thienyl)-1H-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, 2930, 1593, 1511, 1495, 1410, 699, 676 cm⁻¹; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 75 MHz) 102.5 (C), 124.9 (CH), 125.7 (CH), 125.9 (CH), 137.6 (C), 155.0 (CH). HRMS (ASAP): calcd for C₆H₅IN₃S [M+H]⁺ 277.9249, found 277.9247.

4.4.3. 2-(2-Iodo-4-trifluoromethoxyphenyl)-2H-1,2,3-triazole (9a). Compound 9a was formed (23% estimated yield) from 2-(4-trifluoromethoxyphenyl)-2H-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,
4.4. 4-Iodo-2-(2-iodo-4-trifluoromethoxyphenyl)-2H-1,2,3-triazole (10). Compound 10 was formed (19% estimated yield) from 2-(4-trifluoromethoxyphenyl)-2H-1,2,3-triazole (8) using the general procedure 2 and was identified by its 1H NMR spectra: 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃, 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); 19F NMR (CDCl₃, 282 MHz) -57.9.

4.4.5. 4-Iodo-2-(4-trifluoromethoxyphenyl)-2H-1,2,3-triazole (9b). Compound 9b was formed (6% estimated yield) from 2-(4-trifluoromethoxyphenyl)-2H-1,2,3-triazole (8) using the general procedure 2 and was identified by its 1H NMR spectra: 1H NMR (CDCl₃, 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, ZnCl₂·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 I₂ (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 Na₂S₂O₃ (10 mL) and extraction with CH₂Cl₂ (3 x 20 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure before purification by flash chromatography on silica gel.

4.5.1. 5-Iodo-1-phenyl-1H-1,2,3-triazole (5a). Compound 5a was prepared from 1-phenyl-1H-1,2,3-triazole (1a) using the general procedure 3 and was isolated (eluent: CH₂Cl₂) in 89% yield as a white powder: mp 134 °C; 1H NMR (CDCl₃, 300 MHz) 7.53-7.59 (m, 5H), 7.87 (s, 1H); 13C NMR (CDCl₃, 75 MHz) 78.7 (C), 125.9 (2CH), 129.3 (2CH), 130.1 (CH), 962, 952, 884, 823, 736, 671 cm⁻¹; 1H NMR (CDCl₃, 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); 13C NMR (CDCl₃, 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); 19F NMR (CDCl₃, 282 MHz) -57.9.
136.5 (C), 141.8 (CH). HRMS (ASAP): calcd for C₈H₇IN₃ [M+H]⁺ 271.9685, found 271.9690.

**Crystal data for 5a** (CCDC 1058464). C₈H₇IN₃, M = 271.06, monoclinic, P 2₁/n, a = 5.11980(10), b = 33.1939(9), c = 5.15960(10) Å, β = 91.3720(10) °, V = 876.60(3) Å³, Z = 4, d = 2.054 g cm⁻³, μ = 3.598 mm⁻¹. A final refinement on F² with 2015 unique intensities and 145 parameters converged at ω(R(F²) = 0.091 (R(F) = 0.0441) for 1980 observed reflections with I > 2σ(I).

4.5.2. 5-Iodo-1-(2-iodo-5-thienyl)-1H-1,2,4-triazole (7b). Compound 7b was obtained from 1-(2-thienyl)-1H-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; ¹H NMR (CDCl₃, 300 MHz) 7.01 (d, 1H, J = 4.0 Hz), 7.24 (d, 1H, J = 4.0 Hz), 8.03 (s, 1H); ¹³C NMR (CDCl₃, 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). C₆H₃IN₂S, 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) Å³, Z = 8, d = 2.785 g cm⁻³, μ = 6.710 mm⁻¹. A final refinement on F² with 2201 unique intensities and 109 parameters converged at ωR(F²) = 0.0709 (R(F) = 0.0289) for 1955 observed reflections with I > 2σ(I).

4.5.3. 5-Iodo-1-(3-iodo-2-thienyl)-1H-1,2,4-triazole (7b'). Compound 7b' was obtained from 1-(2-thienyl)-1H-1,2,4-triazole (2b) using the general procedure 3 (eluent: heptane/AcOEt 9:1 to 7:3) in 28% estimated yield: ¹H NMR (CDCl₃, 300 MHz) 7.14 (d, 1H, J = 5.7 Hz), 7.47 (d, 1H, J = 5.7 Hz), 8.10 (s, 1H); ¹³C NMR (CDCl₃, 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. A degassed solution of 4-iodo-2-phenyl-2H-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 PPh₃ (13 mg, 50
μmol, 10 mol.%) in dioxane (10 mL) was heated at 105 °C for 18 h. The reaction mixture was then diluted with Et₂O (50 mL) and washed with H₂O (2 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure before purification by flash chromatography on silica gel.

4.6.1. 2,4-Diphenyl-2H-1,2,3-triazole (4c). Compound 4c was prepared from phenylboronic acid (61 mg) using the general procedure 4 and was isolated (elucent: 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 (CDCl₃, 300 MHz) 7.33-7.54 (m, 6H), 7.89-7.93 (m, 2H), 8.06 (s, 1H), 8.13-8.17 (m, 2H); ¹³C NMR (CDCl₃, 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-2H-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 (elucent: heptane/AcOEt/Et₂O 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 (CDCl₃, 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); ¹³C NMR (CDCl₃, 75 MHz) 56.0 (CH₃), 56.2 (CH₃), 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). C₁₆H₁₅N₃O₂, M = 281.31, monoclinic, P 2₁/n, a = 15.2065(19), b = 4.8810(6), c = 19.365(2) Å, β = 104.952(5) °, V = 1388.7(3) Å³, Z = 4, d = 1.346 g cm⁻³, μ = 0.091 mm⁻¹. A final refinement on F² with 3180 unique intensities and 192 parameters converged at ω(F²) = 0.1327 (R(F) = 0.0459) for 2105 observed reflections with I > 2σ(I).
4.7. General procedure 5 for the Suzuki-type mono-coupling. A degassed solution of 4-iodo-2-phenyl-2H-1,2,3-triazole (4b, 0.14 g, 0.5 mmol) and the required boronic acid (0.5 mmol), Na₂CO₃ (0.12 g, 1.1 mmol), PdCl₂ (2 mg, 10 μmol, 2 mol.%), PPh₃ (8 mg, 30 μmol, 6 mol.%), in H₂O (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 H₂O (10 mL) and extracted with CH₂Cl₂ (3 x 10 mL). The combined organic layers were dried over Na₂SO₄ and concentrated under reduced pressure before purification by flash chromatography on silica gel.

4.7.1. 4-(4-Hydroxyphenyl)-2-phenyl-2H-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 (CDCl₃, 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; ¹³C NMR (CDCl₃, 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). C₁₄H₁₁N₃O, 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) Å³, Z = 8, d = 1.383 g cm⁻³, μ = 0.091 mm⁻¹. A final refinement on F² with 2591 unique intensities and 166 parameters converged at ω(R(F²)) = 0.0954 (R(F) = 0.0394) for 2092 observed reflections with J > 2σ(I).

4.7.2. 4-(4-Aminophenyl)-2-phenyl-2H-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: CH₂Cl₂/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 (CDCl₃, 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-
7.52 (m, 2H), 7.69-7.72 (m, 2H), 7.95 (s, 1H), 8.09-8.13 (m, 2H); $^1$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$_2$CO$_3$ (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$_2$O (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$_2$O (10 mL) and extracted with CH$_2$Cl$_2$ (3 x 10 mL). The combined organic layers were dried over Na$_2$SO$_4$ 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); $^1$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,
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): calcld for C$_{22}$H$_{19}$N$_3$NaO$_2$ [M+Na]$^{+}$ 380.1375, found 380.1378.

4.8.3. 2-(4'-Hydroxy-1,1'-(2-biphenyl))-4-(4-hydroxyphenyl)-2H-1,2,3-triazole (4e'). Compound 4e' was prepared from 4-hydroxyphenylboronic acid (0.28 g) using the general procedure 6 and was isolated (elucent: 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): calcld for C$_{20}$H$_{15}$N$_3$NaO$_2$ [M+Na]$^{+}$ 352.1062, found 352.1064.

4.8.4. 2-(4'-Amino-1,1'-(2-biphenyl))-4-(4-aminophenyl)-2H-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 (elucent: 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): calcld for C$_{20}$H$_{15}$N$_5$ [M+H]$^{+}$ 328.1562, found 328.1561.
4.8.5. 2-(3’-Chloro-1,1’-(2-biphenyl))-4-(3-chlorophenyl)-2H-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; ¹H NMR (CDCl₃, 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); ¹³C NMR (CDCl₃, 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 C₂₀H₁₄Cl₂N₃ [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/xxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxxx. It contains ¹H, ¹³C (and ¹⁹F) 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).

References and notes


