The Suzuki Reaction Applied to the Synthesis of Novel Pyrrolyl and Thiophenyl Indazoles

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Abstract: The paper describes the Suzuki cross-coupling of a variety of N and C-3 substituted 5-bromoindazoles with N-Boc-2-pyrrole and 2-thiopheneboronic acids. The reactions, performed in the presence of K2CO3, dimethoxyethane and Pd(dppf)Cl2 as catalyst, gave the corresponding adducts in good yields. The methodology allows the facile production of indazole-based heteroaryl compounds, a unique architectural motif that is ubiquitous in biologically active molecules.

Keywords: indazoles; pyrrole; thiophene; Suzuki cross-coupling; heterobiaryl compounds

1. Introduction

Indazole, the indole bioisoster, is a highly utilized pharmacophore [1] found in many biologically active compounds such as lonidamine (1) [2], a molecule with anticancer activity, or the Akt1 inhibitor 2 (Figure 1) [3].

Due to the broad variety of their biological activities, the synthesis of indazole derivatives as well as the functionalization of the indazole ring system have recently been reviewed [4–12], especially in the context of drug development. During the last years, indazole derivatives bearing aryl groups on the 5 or 6 position have been prepared and identified as potent, selective glucocorticoid receptor agonists and antagonists [13] or inhibitors of protein kinase c-zeta [14]. Conversely, to the best of our
knowledge, the functionalization of the indazole ring with aromatic heterocycles like pyrrole and thiophene has been less explored. Among the very few reported examples, some recent patents have described 3-substituted-5-thienyl-1H-indazole as ligands for nicotinic acetylcholine receptors [15] or inhibitors of kinase activity [16,17]. Likewise, only 6-pyrrolyl-indazoles have recently been disclosed for their inhibitory activity of glycogen synthase kinase-3, and their synthesis was performed starting from pyrrolylbenzonitriles [18].

Figure 1. Relevant molecules with an indazole moiety.

As part of the effort to discover novel indazole derivatives as valuable building blocks in medicinal chemistry [19], we were looking for an efficient and effective synthetic protocol of wide applicability towards 5-(pyrrol-2-yl)- and 5-(thiophen-2-yl)-1H-indazoles. The Suzuki reaction provides a very reliable method for the preparation of biaryl derivatives [20]. However, although simple aryl halides and aryl boronic acids are widespread employed coupling partners, the corresponding reactions involving their heteroaryl analogues are noticeably fewer [21–28]. Herein, we report our initial investigations on the Suzuki cross-coupling between differently N-substituted 5-bromo-indazoles and pyrrole- or thiopheneboronic acids.

2. Results and Discussion

In order to determine the optimal reaction conditions we began by studying the cross-coupling of 5-bromo-1-ethyl-1H-indazole (3a) with N-Boc-2-pyrroleboronic acid (4) [29] as a pilot reaction (Scheme 1). Indazole 3a was prepared by the alkylation of the 5-bromo-1H-indazole with ethyl bromide [30]. In the presence of cesium carbonate (Cs₂CO₃), a 1.2:1 ratio of 3a and the N-2 isomer 3g was obtained. The two regioisomers were purified and identified by comparison of their spectral data with that reported for similar N-alkylated indazoles [31].

Scheme 1. Suzuki cross-coupling of 5-bromo-1-ethyl-1H-indazole and N-Boc-2-pyrroleboronic acid.
The Suzuki reaction was carried out by employing K$_2$CO$_3$ as base, dimethoxyethane as solvent and heating the reaction mixture at 80 °C. As shown in Table 1, we examined four palladium catalysts and found that [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride [Pd(dppf)Cl$_2$] [32] was the best choice, affording the coupling product in high yield after only two hours. Interestingly, bis(tricyclohexylphosphine)palladium [Pd(PC$_y$$_3$)$_2$] yielded the product in modest yield, although generally the electron richness and the sterical hindrance of the phosphinic ligands make it an efficient palladium source for cross-coupling reaction [33,34]. The commonly used tetrakis(triphenylphosphine)palladium [Pd(PPh$_3$)$_4$] and bis(triphenylphosphine)palladium(II) dichloride [Pd(PPh$_3$)$_2$Cl$_2$] were less effective than [Pd(dppf)Cl$_2$] for this transformation, affording the final product after longer reaction times and in lower yields.

Table 1. Screening of palladium catalysts for the Suzuki coupling of 5-bromo-1-ethyl-1H-indazole and N-Boc-2-pyrroleboronic acid.

| Entry | Pd catalyst      | Reaction Time | 5a Yield |
|-------|------------------|---------------|----------|
| 1     | Pd(PPh$_3$)$_4$  | 4 h           | 22%      |
| 2     | Pd(PPh$_3$)$_2$Cl$_2$ | 4 h           | 75%      |
| 3     | Pd(PC$_y$$_3$)$_2$ | 2 h           | 57%      |
| 4     | Pd(dppf)Cl$_2$  | 2 h           | 84%      |

Having identified Pd(dppf)Cl$_2$ as the most suitable catalyst, in order to explore the versatility of this type of Suzuki coupling, a series of 5-bromoindazoles bearing alkyl or acyl groups on the N-1 or N-2 positions were prepared [30,35–38] and tested with Boc-protected-2-pyrroleboronic acid 4 (Scheme 2).

Scheme 2. Synthesis of 5-(pyrrol-2-yl)-1H-indazoles by the Suzuki cross-coupling.

In all cases the expected coupling products were obtained in very modest to quite good yields and fully characterized (Table 2). The lower yields registered for the N-acyl-indazoles 3e and 3f may be a consequence of the facile deacylation of these substrates under basic conditions [39]. This is confirmed by the isolation of 5c (30% yield) as an additional product in their reaction mixtures. The reaction was also performed on the unsubstituted 5-bromoindazole 3c and afforded the corresponding product 5c in 50% yield, due to the likely formation of side-products, not further investigated. Moreover, it is worthy to note that the N-Boc-indazole 3d resulted to be a very good substrate for the cross-coupling. The
easy removal of the Boc group would make the coupling product 5d a valuable building block in the synthesis of new interesting indazole-based molecules.

On the basis of these positive results, we extended the scope of the Suzuki cross-coupling to the synthesis of 5-(thiophen-2-yl)-1H-indazoles. Thiophene, like pyrrole, is found in a variety of natural products and pharmaceutically interesting compounds [40]. In addition, polythiophenes, which are often prepared via Suzuki-Miyaura processes, are highly conducting polymers that possess good processing qualities [41].

The coupling with 2-thiopheneboronic acid (6) was carried out under the same reaction conditions previously employed and gave the expected 5-(thiophen-2-yl)-1H-indazoles 7a–g (Scheme 3).

Scheme 3. Synthesis of 5-(thiophen-2-yl)-1H-indazoles by the Suzuki cross-coupling.

With respect to the corresponding coupling reactions with 2-pyrroleboronic acid 4, the products were obtained in lower yields (Table 2), due to the tendency of thiopheneboronic acids to undergo protodeboronation and the formation of a side-product identified as the thiophene dimer [22].

Table 2. Suzuki cross-coupling reaction for the synthesis of 5-(pyrrol-2-yl)- and 5-(thiophen-2-yl)-1H-indazoles.

| Entry | Products 5 | Yield 5 [a] | Products 7 | Yield 7 [a] |
|-------|------------|-------------|------------|-------------|
| a     | ![Product 5a](image1) | 84% | ![Product 7a](image2) | 60% |
| b     | ![Product 5b](image1) | 74% | ![Product 7b](image2) | 62% |
| c     | ![Product 5c](image1) | 50% | ![Product 7c](image2) | traces |
| d     | ![Product 5d](image1) | 81% | ![Product 7d](image2) | 70% |
Table 2. Cont.

| Entry | Products 5 | Yield 5 \[^{a}\] | Products 7 | Yield 7 \[^{a}\] |
|-------|------------|----------------|------------|----------------|
| e     | ![Image]   | 45%            | ![Image]   | 30%            |
| f     | ![Image]   | 30%            | ![Image]   | 35%            |
| g     | ![Image]   | 92%            | ![Image]   | 87%            |

\[^{a}\] Isolated Yields.

On the bases of the described successful results and in view of the interest in C-3 substituted indazole derivatives reported in the literature [5], a preliminary study for the extension of the above reaction to C-3 substituted indazoles has been also initiated. To this purpose, 5-bromo-1H-indazole-3-carboxylic acid methyl ester (8, Scheme 4) was prepared by a known esterification of 5-bromo-1H-indazole-3-carboxylic acid, reported to afford 8 as the unique product [42]. However, in our hands, the protocol gave a 1:1 mixture of two products identified as 8 and the corresponding unprecedented 1-methyl derivative 9, respectively.

Therefore, both substrates 8 and 9 were reacted with the Boc-protected-2-pyrroleboronic acid 4 (Scheme 4) and gave the corresponding 3-substituted-(5-pyrrol-2-yl)-indazoles 10 and 11, thus indicating that the C-3 substituent doesn’t invalidate the success of the Suzuki reaction. The extension of this methodology to variously C-3 functionalized indazole derivatives by using pyrrole and thiophene boronic acids is currently under investigation.

Scheme 4. Synthesis of 3-substituted-(5-pyrrol-2-yl)-indazoles by the Suzuki cross-coupling.

3. Experimental

3.1. General Experimental Methods

Solvents and common reagents were purchased from a commercial source and used without further purification. N-Boc-2-pyrroleboronic acid 4 was prepared according to the literature procedure [29].
2-Thiopheneboronic acid 6 and 5-bromo-1H-indazole-3-carboxylic acid were purchased from a commercial source. All reactions were monitored by thin layer chromatography (TLC) carried out on Merck F-254 a silica glass plates and visualized with UV light. The resulting mixtures were purified by flash column chromatography on silica gel by eluting, unless otherwise stated, with hexane/ethyl acetate, 8:2. 1H-NMR spectra were recorded on Varian Gemini 300 (300 MHz) instrument. Chemical shifts are expressed in parts per million (δ scale) and are referenced to the residual protons of the NMR solvent (CHCl3: δ 7.26); (s) = singlet; (d) = doublet; (t) = triplet; (q) = quartet; (dd) = double doublet; (ddd) = double double doublet; (dt) = double triplet; (dq) = double quartet; (m) = multiplet. Coupling constants (J) are expressed in Hz. 13C-NMR spectra were recorded on Varian Gemini 300 (75 MHz). Chemical shifts are expressed in parts per million (δ scale) and are referenced to the residual carbons of the NMR solvent (CHCl3: δ 77.0). Infrared Spectra (IR) were obtained using a Perkin-Elmer 1600 (FT-IR, Walthman, MA, USA); data are presented as the frequency of absorption (cm⁻¹). HRMS Spectra were recorded with Micromass Q-TOF micro Mass Spectrometer (Waters, Milford, MA, USA).

**5-Bromo-1-ethyl-1H-indazole 3a** [30]. To a solution of 5-bromo-1H-indazole (500 mg, 2.55 mmol) in anhydrous DMF (8 mL), ethyl bromide (3.85 mmol, 0.60 mL) was added at room temperature, followed by an excess of Cs₂CO₃ (2.5 g, 7.65 mmol). After stirring the reaction mixture at room temperature for 3 h, 2 N HCl was added until a neutral pH was reached. The aqueous layer was extracted with ethyl acetate and the combined organic extracts were dried over anhydrous Na₂SO₄. After filtration, the solvent was removed in vacuo and the residue was purified by flash column chromatography. Yield: 227 mg (1 mmol, 40%); dark orange viscous liquid; Rf = 0.47. 1H-NMR: δ = 1.45 (t, 3H, CH₃, J = 7.3 Hz), 4.35 (q, 2H, CH₂, J = 7.3 Hz), 7.21 (d, 1H, ArH, J = 8.9 Hz), 7.36 (dd, 1H, ArH, J = 1.8 Hz, J = 8.9 Hz), 7.77–7.81 (m, 1H, ArH), 7.88 (s, 1H, ArH) ppm. 13C-NMR: δ = 15.1, 44.1, 110.5, 113.7, 123.7, 125.8, 129.3, 132.2, 137.9 ppm. HRMS: calcd. for C₉H₁₀BrN₂ 225.0027; found 225.0032.

**5-Bromo-2-ethyl-2H-indazole (3g)** [30,43]. This compound was obtained in the alkylation of 5-bromo-1H-indazole with ethyl bromide together with 3a (3a/3g = 1.2/1). Yield: 178 mg (0.80 mmol, 31%); dark orange viscous liquid; Rf = 0.12. 1H-NMR: δ = 1.62 (t, 3H, CH₃, J = 7.3 Hz), 4.45 (q, 2H, CH₂, J = 7.3 Hz), 7.32 (dd, 1H, ArH, J = 1.8 Hz, J = 9.1 Hz), 7.58 (dd, 1H, ArH, J = 0.8 Hz, J = 9.1 Hz), 7.77–7.80 (m, 1H, ArH), 7.85 (s, 1H, ArH) ppm. 13C-NMR: δ = 15.1, 44.1, 110.5, 113.7, 123.7, 125.8, 129.3, 132.2, 137.9 ppm. HRMS: calcd. for C₉H₁₀BrN₂ 225.0027; found 225.0032.

**5-Bromo-1-(3-chloro-propyl)-1H-indazole (3b)** [44]. Compound 3b was prepared from 5-bromo-1H-indazole (500 mg, 2.55 mmol) and 1-bromo-3-chloropropane (3.85 mmol, 0.40 mL) according to the procedure described for 3a. After solvent evaporation, the crude mixture was chromatographed over silica gel. Yield: 352 mg (1.3 mmol, 50%); dark orange viscous liquid; Rf = 0.62. 1H-NMR: δ = 2.35–2.43 (m, 2H, CH₂CH₂CH₂CH₃), 3.46 (t, 2H, CH₂Cl, J = 5.8 Hz), 4.54 (t, 2H, CH₂N, J = 6.0 Hz), 7.38 (dd, 1H, ArH, J = 0.8 Hz, J = 8.9 Hz), 7.46 (dd, 1H, ArH, J = 1.8 Hz, J = 8.9 Hz), 7.84–7.88 (m, 1H, ArH), 7.95 (s, 1H, ArH) ppm. 13C-NMR: δ = 32.6, 42.0, 45.7, 110.6, 113.9, 123.7, 125.6, 129.7, 132.9, 138.8 ppm. HRMS: calcd. for C₁₀H₁₀BrClN₂ 272.9794; found 272.9800. The N-2 isomer was isolated as minor product. Yield: 69 mg (0.25 mmol, 10%); dark orange viscous liquid; Rf = 0.47.
$^1$H-NMR: $\delta = 2.42$–$2.50$ (m, 2H, CH$_2$CH$_2$CH$_2$), 3.42 (t, 2H, CH$_2$Cl, $J = 5.8$ Hz), 4.59 (t, 2H, CH$_2$N, $J = 6.4$ Hz), 7.34 (dd, 1H, ArH, $J = 1.8$ Hz, $J = 9.1$Hz), 7.57 (dd, 1H, ArH, $J = 0.8$ Hz, $J = 9.1$Hz), 7.79–$7.83$ (m, 1H, ArH), 7.92 (s, 1H, ArH) ppm. $^{13}$C-NMR: $\delta = 32.9$, $41.6$, $50.6$, $110.3$, $115.4$, $119.4$, $122.5$, $123.3$, $129.9$, $147.8$ ppm. HRMS: calcld. for C$_{10}$H$_{11}$BrClN$_2$ 272.9794; found 272.9792.

5-Bromo-indazole-1-carboxylic acid tert-butyl ester (3d). Compound 3d was prepared from 5-bromo-1H-indazole (500 mg, 2.55 mmol) and Boc$_2$O (583 mg, 2.68 mmol) according to the literature procedure and the spectral data were in agreement with those reported in the literature [36]. Yield: 558 mg (1.89 mmol, 74%).

1-(5-Bromo-indazol-1-yl)-2-phenyl-ethanone (3e). Compound 3e was prepared from 5-bromo-1H-indazole (500 mg, 2.55 mmol) and phenylacetyl chloride (3.85 mmol, 0.50 mL) according to the procedure described for 3a. After solvent evaporation, the crude mixture was chromatographed over silica gel. Yield: 360 mg (1.15 mmol, 45%); dark orange viscous liquid; $R_f = 0.85$. $^1$H-NMR: $\delta = 4.52$ (s, 2H, CH$_2$C=O), 7.25–$7.50$ (m, 5H, ArH), 7.63 (dd, 1H, ArH, $J = 1.8$, $J = 8.8$ Hz), 7.86–$7.89$ (m, 1H, ArH), 8.08 (s, 1H, ArH), 8.34 (dd, 1H, ArH, $J = 0.7$ Hz, $J = 8.8$ Hz) ppm. $^{13}$C-NMR: $\delta = 41.7$, $117.1$, $117.9$, $120.3$, $123.8$, $127.5$, $128.2$, $128.9$, $129.9$, $132.7$, $133.9$, $139.0$, $171.6$ ppm. IR (CHCl$_3$): $\tilde{\nu} = 1728$ cm$^{-1}$. HRMS: calcld. for C$_{15}$H$_{11}$BrN$_2$NaO 336.9952; found 336.9949.

1-(5-Bromo-indazol-1-yl)-ethanone (3f) [38]. To a solution of 5-bromo-1H-indazole (500 mg, 2.55 mmol) in anhydrous DCM (48 mL) was added acetic anhydride (0.45 mL, 5.10 mmol), pyridine (403 mg, 0.40 mL, 5.10 mmol) and dimethylaminopyridine (DMAP) in a catalytic amount. The solution was stirred at 40 °C overnight. The organic phase was washed with water (2 × 50 mL), 1N HCl (2 × 50 mL), NaHCO$_3$ (aq) (2 × 50 mL) and brine (2 × 50 mL) and then dried over anhydrous Na$_2$SO$_4$. The solvent was removed in vacuo to give 3f. Yield: 833 mg (3.50 mmol, 70%); dark orange viscous liquid; $R_f = 0.87$. $^1$H-NMR: $\delta = 2.81$ (s, 3H, CH$_3$), 7.65 (dd, 1H, ArH, $J = 1.8$, $J = 8.8$ Hz), 7.87–$7.90$ (m, 1H, ArH), 8.08 (s, 1H, ArH), 8.34 (dd, 1H, ArH, $J = 0.7$ Hz, $J = 8.8$ Hz) ppm. $^{13}$C-NMR: $\delta = 22.9$, $115.8$, $116.6$, $122.4$, $126.8$, $131.4$, $136.7$, $137.5$, $169.9$. IR (CHCl$_3$): $\tilde{\nu} = 1726$ cm$^{-1}$. HRMS: calcld. for C$_9$H$_7$BrN$_2$NaO 260.9639; found 260.9644.

5-Bromo-1H-indazole-3-carboxylic acid methyl ester (8) and 5-Bromo-1-methyl-1H-indazole-3-carboxylic acid methyl ester (9). Compounds 8 and 9 were obtained from 5-bromo-1H-indazole-3-carboxylic acid (160 mg, 0.66 mmol) by applying an esterification procedure reported to afford 8 as the unique product [42]. However, in our hands, the protocol gave a 1:1 mixture of two products that were separated by chromatography. The first compound was identified as 8 and showed spectral data in agreement with those reported in literature [42]. Yield: 61 mg (0.24 mmol, 36%). The second compound was identified as 9. Yield: 59 mg (0.22 mmol, 34%); $R_f = 0.7$ (hexane/ethyl acetate, 1:1). $^1$H-NMR: $\delta = 4.03$ (s, 3H, CO$_2$CH$_3$), 4.48 (s, 3H, NCH$_3$), 7.41 (dd, 1H, ArH, $J = 1.8$ Hz, $J = 9.1$ Hz), 7.63 (dd, 1H, ArH, $J = 0.7$ Hz, $J = 9.1$ Hz), 8.13–$8.15$ (m, 1H, ArH) ppm. $^{13}$C-NMR: $\delta = 41.8$, $52.3$, $119.3$, $119.9$, $123.7$, $127.3$, $128.9$, $131.4$, $145.9$, $161.0$ ppm. HRMS: calcld. for C$_{10}$H$_{10}$BrN$_2$O$_2$ 268.9926; found 268.9930.
3.2. General Procedure for the Suzuki Coupling Reaction

A solution of bromo indazole 3 (1 mmol) and [1,1'-bis(diphenylphosphino)ferrocene]palladium(II) dichloride [Pd(dppf)Cl2] (10%) in anhydrous DME (10 mL) was stirred under a flow of argon for 1 h. To the solution were added sequentially 1-(tert-butoxycarbonyl)pyrrole-2-boronic acid (4) or 2-thiopheneboronic acid (6) (2 mmol) in anhydrous DME (2.6 mL) and potassium carbonate (2 mmol) in water (2.5 mL). The mixture was heated to 80 °C for 2 h and allowed to cool. The reaction mixture was then poured into aqueous saturated NaHCO3 solution and extracted with ethyl acetate. The organic layers were combined, washed with brine and dried over Na2SO4. The solution was concentrated in vacuo and the residue was purified by flash column chromatography on silica gel to give the desired product.

2-(1-Ethyl-1H-indazol-5-yl)-pyrrole-1-carboxylic acid tert-butyl ester (5a). Yield: 261 mg (0.84 mmol, 84%); dark orange viscous liquid; Rf = 0.28. 1H-NMR: δ = 1.34 (s, 9H, CH3), 1.52 (t, 3H, CH3, J = 7.3 Hz), 4.44 (q, 2H, CH2, J = 7.3 Hz), 6.19–6.25 (m, 2H, ArH), 7.25–7.26 (m, 1H, ArH), 7.34–7.36 (m, 1H, ArH), 7.38 (s, 1H, ArH), 7.69 (m, 1H, ArH), 7.99 (s, 1H, ArH) ppm. 13C-NMR: δ = 15.2, 27.9, 44.3, 83.7, 108.2, 110.5, 114.4, 121.2, 122.4, 123.7, 127.3, 129.1, 133.8, 135.2, 139.1, 149.6 ppm. IR (CHCl3): ν = 1733 cm⁻¹. HRMS: calcd. for C18H21N3NaO2 334.1531; found 334.1526.

2-(2-Ethyl-2H-indazol-5-yl)-pyrrole-1-carboxylic acid tert-butyl ester (5g). Yield: 286 mg (0.92 mmol, 92%); dark orange viscous liquid; Rf = 0.32 (hexane/ethyl acetate, 7:3). 1H-NMR: δ = 1.33 (s, 9H, CH3), 1.61 (t, 3H, CH3, J = 7.3 Hz), 4.46 (q, 2H, CH2, J = 7.3 Hz), 6.18–6.23 (m, 2H, ArH), 7.25 (dd, 1H, ArH, J = 1.8 Hz, J = 8.9 Hz), 7.35–7.36 (m, 1H, ArH), 7.60 (m, 1H, ArH), 7.65 (dd, 1H, ArH, J = 0.8 Hz, J = 8.9 Hz), 7.99 (s, 1H, ArH) ppm. 13C-NMR: δ = 16.1, 27.9, 48.7, 83.7, 110.7, 114.5, 116.3, 119.6, 121.6, 122.4, 122.5, 128.1, 128.8, 135.8, 148.2, 149.6 ppm. IR (CHCl3): ν = 1725 cm⁻¹. HRMS: calcd. for C18H21N3NaO2 334.1531; found 334.1536.

2-[1-(3-Chloro-propyl)-1H-indazol-5-yl]-pyrrole-1-carboxylic acid tert-butyl ester (5b). Yield: 267 mg (0.74 mmol, 74%); dark orange viscous liquid; Rf = 0.62. 1H-NMR: δ = 1.34 (s, 9H, CH3), 2.37–2.46 (m, 2H, CH2CH2CH2), 3.49 (t, 2H, CH2Cl, J = 6.3 Hz), 4.57 (t, 2H, CH2N, J = 6.3 Hz), 6.19–6.25 (m, 2H, ArH), 7.35–7.41 (m, 2H, ArH), 7.43–7.49 (m, 1H, ArH), 6.79 (m, 1H, ArH), 8.01 (s, 1H, ArH) ppm. 13C-NMR: δ = 27.9, 32.7, 42.1, 45.6, 83.7, 108.0, 110.8, 114.7, 121.3, 122.5, 123.8, 127.5, 129.1, 133.9, 135.3, 139.3, 149.6 ppm. IR (CHCl3): ν = 1725 cm⁻¹. HRMS: calcd. for C19H22ClN3NaO2 382.1299; found 382.1299.

2-(1H-Indazol-5-yl)-pyrrole-1-carboxylic acid tert-butyl ester (5c). Yield: 141 mg (0.50 mmol, 50%); dark orange viscous liquid; Rf = 0.28 (hexane/ethyl acetate, 7:3). 1H-NMR: δ = 1.34 (s, 9H, CH3), 6.21–6.27 (m, 2H, ArH), 7.37–7.49 (m, 3H, ArH), 7.74 (s, 1H, ArH) ppm. 13C-NMR: δ = 27.9, 83.8, 109.0, 110.8, 114.8, 121.0, 122.5, 123.0, 127.7, 129.5, 135.0, 135.4, 139.6, 149.6 ppm. IR (CHCl3): ν = 1734, 3469 cm⁻¹. HRMS: calcd. for C16H17N3NaO2 306.1223; found 306.1223.

5-(1-tert-Butoxycarbonyl-1H-pyrrol-2-yl)-indazole-1-carboxylic acid tert-butyl ester (5d). Yield: 310 mg (0.81 mmol, 81%); dark orange viscous liquid; Rf = 0.67 (hexane/ethyl acetate, 7:3). 1H-NMR:
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δ = 1.35 (s, 9H, CH3), 1.73 (s, 9H, CH3), 6.26–6.21 (m, 2H, ArH), 7.38–7.36 (m, 1H, ArH), 7.52 (dd, 1H, ArH, J = 1.6 Hz, J = 8.7 Hz), 7.70–7.69 (m, 1H, ArH), 8.14 (dd, 1H, ArH, J = 0.7 Hz, J = 8.7 Hz), 8.17 (s, 1H, ArH) ppm. 13C-NMR: δ = 27.9, 28.4, 83.8, 85.2, 108.2, 111.3, 118.4, 119.0, 123.6, 124.5, 128.7, 130.3, 135.2, 135.4, 139.3, 149.3, 149.7 ppm. IR (CHCl3): ν = 1736, 1737 cm⁻¹. HRMS: calcd. for C21H25N3NaO4 406.1743; found 406.1740.

2-(1-Phenylacetyl-1H-indazol-5-yl)-pyrrole-1-carboxylic acid tert-butyl ester (5e). Yield: 180 mg (0.45 mmol, 45%); yellow viscous liquid; Rf = 0.42. 1H-NMR: δ = 1.35 (s, 9H, CH3), 4.54 (s, 2H, CH2), 6.21–6.27 (m, 2H, ArH), 7.26–7.44 (m, 6H, ArH), 7.52 (dd, 1H, ArH, J = 1.6 Hz, J = 8.7 Hz), 7.71 (m, 1H, ArH), 8.17 (s, 1H, ArH), 8.41 (dd, 1H, ArH, J = 0.7 Hz, J = 8.7 Hz) ppm. 13C-NMR: δ = 27.9, 41.6, 83.8, 108.9, 112.2, 116.2, 118.3, 119.3, 123.9, 124.5, 127.4, 128.3, 129.0, 129.7, 133.4, 135.9, 138.2, 140.8, 149.7, 171.6 ppm. IR (CHCl3): ν = 1731, 1739 cm⁻¹. HRMS: calcd. for C24H23N3NaO3 424.1637; found 424.1632.

2-(1-Acetyl-1H-indazol-5-yl)-pyrrole-1-carboxylic acid tert-butyl ester (5f). Yield: 97.5 mg (0.30 mmol, 30%); yellow viscous liquid; Rf = 0.79 (hexane/ethyl acetate, 9:1). 1H-NMR: δ = 1.35 (s, 9H, CH3), 2.83 (s, 3H, CH3), 6.22–6.26 (m, 2H, ArH), 7.36–7.38 (m, 1H, ArH), 7.55 (dd, 1H, ArH, J = 1.6 Hz, J = 8.7 Hz), 7.70–7.71 (m, 1H, ArH), 8.13 (s, 1H, ArH), 8.41 (dd, 1H, ArH, J = 0.7 Hz, J = 8.7 Hz) ppm. 13C-NMR: δ = 23.2, 27.9, 84.0, 110.9, 114.7, 115.3, 120.9, 122.9, 126.2, 128.7, 131.3, 131.7, 134.4, 140.8, 149.7, 171.3 ppm. IR (CHCl3): ν = 1719, 1778 cm⁻¹. HRMS: calcd. for C18H19N3NaO3 348.1324; found 348.1320.

1-Ethyl-5-thiophen-2-yl-1H-indazole (7a). Yield: 137 mg (0.60 mmol, 60%); brown solid, m.p. 104–106 °C; Rf = 0.55 (hexane/ethyl acetate, 6:4). 1H-NMR: δ = 1.59 (t, 3H, CH3, J = 7.3 Hz), 4.43 (q, 2H, CH2, J = 7.3 Hz), 7.07–7.10 (m, 1H, ArH), 7.25–7.30 (m, ArH), 7.39 (d, 1H, ArH, J = 8.7 Hz), 7.65 (dd, 1H, ArH, J = 1.6 Hz, J = 8.7 Hz), 7.94 (m, 1H, ArH), 8.01 (s, 1H, ArH) ppm. 13C-NMR: δ = 15.2, 44.1, 109.7, 118.3, 121.1, 124.4, 124.8, 125.7, 127.6, 128.2, 133.4, 138.5, 145.1 ppm. IR (CHCl3): ν = 2988, 3002 cm⁻¹. HRMS: calcd. for C13H13N2S 229.0799; found 229.0803.

2-Ethyl-5-thiophen-2-yl-2H-indazole (7g). Yield: 198 mg (0.87 mmol, 87%); brown solid, m.p. 100–103 °C; Rf = 0.42. 1H-NMR: δ = 1.63 (t, 3H, CH3, J = 7.3 Hz), 4.46 (q, 2H, CH2, J = 7.3 Hz), 7.06–7.09 (m, 1H, ArH), 7.25 (m, 1H, ArH), 7.30 (m, 1H, ArH), 7.58 (dd, 1H, ArH, J = 1.6 Hz, J = 8.7 Hz), 7.73 (m, 1H, ArH), 7.86 (m, 1H, ArH), 7.91 (s, 1H, ArH) ppm. 13C-NMR: δ = 16.2, 48.8; 109.7, 116.8, 118.1, 121.5, 122.5, 122.6, 122.9, 124.3, 125.7, 128.2, 145.5 ppm. IR (CHCl3): ν = 2978, 3037 cm⁻¹. HRMS: calcd. for C13H13N2S 229.0799; found 229.0803.

1-(3-Chloro-propyl)-5-thiophen-2-yl-1H-indazole (7b). Yield: 171 mg (0.62 mmol, 62%); brown solid, m.p. 105–107 °C; Rf = 0.75 (hexane/ethyl acetate, 7:3). 1H-NMR: δ = 1.63 (t, 3H, CH3, J = 7.3 Hz), 4.46 (q, 2H, CH2, J = 7.3 Hz), 7.06–7.09 (m, 1H, ArH), 7.25 (m, 1H, ArH), 7.30 (m, 1H, ArH), 7.58 (dd, 1H, ArH, J = 1.6 Hz, J = 8.7 Hz), 7.73 (m, 1H, ArH), 7.86 (m, 1H, ArH), 7.91 (s, 1H, ArH) ppm. 13C-NMR: δ = 16.2, 48.8; 109.7, 116.8, 118.1, 121.5, 122.5, 122.6, 122.9, 124.3, 125.7, 128.2, 145.5 ppm. IR (CHCl3): ν = 2978, 3037 cm⁻¹. HRMS: calcd. for C14H14ClN2S 277.0566; found 277.0567.
5-Thiophen-2-yl-indazole-1-carboxylic acid tert-butyl ester (7d). Yield: 210 mg (0.70 mmol, 70%); brown solid, m.p. 112–113 °C; R_f = 0.39 (hexane/ethyl acetate, 9:1). ^1H-NMR: δ = 1.73 (s, 9H, CH_3), 7.11 (m, 1H, ArH), 7.30 (m, 1H, ArH), 7.33 (dd, 1H, ArH, J = 1.6 Hz, J = 8.7 Hz), 7.79 (dd, 1H, ArH, J = 0.7 Hz, J = 8.7 Hz), 7.92 (m, 1H, ArH), 8.17 (m, 2H, ArH) ppm. ^13C-NMR: δ = 28.4, 85.2, 115.2, 118.0, 123.6, 125.2, 126.7, 127.8, 128.4, 130.7, 139.3, 139.8, 144.0, 149.3 ppm. IR (CHCl_3): ˜= 1743 cm\(^{-1}\). HRMS: calcd. for C_{16}H_{16}N_2NaO_2S 323.0830; found 323.0827.

2-Phenyl-1-(5-thiophen-2-yl-indazol-1-yl)-ethanone (7e). Yield: 95 mg (0.30 mmol, 30%); brown solid, m.p. 114–116 °C; R_f = 0.49. ^1H-NMR: δ = 4.54 (s, 2H, CH_2), 7.11 (m, 2H, ArH), 7.29–7.45 (m, 6H, ArH), 7.81 (dd, 1H, ArH, J = 1.6 Hz, J = 8.7 Hz), 7.92 (m, 1H, ArH), 8.17 (s, 1H, ArH), 8.43 (dd, 1H, ArH, J = 0.7 Hz, J = 8.7 Hz) ppm. ^13C-NMR: δ = 41.8, 116.2, 117.8, 123.8, 125.3, 127.3, 128.3, 128.5, 128.6, 128.8, 130.2, 130.8, 131.6, 135.2, 140.3, 171.6 ppm. IR (CHCl_3): ˜= 1713 cm\(^{-1}\). HRMS: calcd. for C_{19}H_{14}N_2NaOS 341.0724; found 341.0727.

1-(5-Thiophen-2-yl-indazol-1-yl)-ethanone (7f). Yield: 85 mg (0.35 mmol, 35%); brown solid, m.p. 116–117 °C; R_f = 0.37 (hexane/ethyl acetate, 9:1). ^1H-NMR: δ = 2.79 (s, 3H, CH_3), 7.09–7.12 (m, 1H, ArH), 7.30–7.36 (m, 2H, ArH), 7.81 (dd, 1H, ArH, J = 1.7 Hz, J = 8.7 Hz), 7.92–7.94 (m, 1H, ArH), 8.13 (s, 1H, ArH), 8.43 (d, 1H, ArH, J = 8.7 Hz) ppm. ^13C-NMR: δ = 23.2, 116.1, 117.8, 123.8, 125.3, 127.2, 128.3, 128.4, 131.5, 138.5, 139.9, 143.8, 171.5 ppm. IR (CHCl_3): ˜= 1713 cm\(^{-1}\). HRMS: calcd. for C_{13}H_{10}N_2NaOS 265.0411; found 265.0412.

5-(1-tert-Butoxycarbonyl-1H-pyrrol-2-yl)-1H-indazole-3-carboxylic acid methyl ester (10). Compound 10 was prepared from 5-bromo-1H-indazole-3-carboxylic acid methyl ester 8 (61 mg, 0.24 mmol) and 2-pyrroleboronic acid 4 (99 mg, 0.47 mmol) according to the general procedure for the Suzuki coupling reaction. Yield: 57 mg (0.17 mmol, 70%); orange viscous liquid; R_f = 0.27 (hexane/ethyl acetate, 1:1). ^1H-NMR: δ = 1.34 (s, 9H, CH_3), 4.05 (s, 3H, OCH_3), 6.26–6.29 (m, 2H, ArH), 7.37–7.41 (m, 1H, ArH), 7.48 (dd, 1H, ArH, J = 1.5 Hz, J = 8.8 Hz), 7.67 (d, 1H, ArH, J = 8.8 Hz), 8.17–8.20 (m, 1H, ArH) ppm. ^13C-NMR: δ = 27.9, 51.3, 83.8, 108.8, 110.7, 114.6, 115.0, 122.6, 123.0, 123.6, 129.1, 134.9, 140.5, 141.7, 150.2, 171.0 ppm. IR (CHCl_3): ˜= 1728, 1774 cm\(^{-1}\). HRMS: calcd. for C_{18}H_{19}N_3NaO_4 364.1273; found 364.1270.

5-(1-tert-Butoxycarbonyl-1H-pyrrol-2-yl)-1-methyl-1H-indazole-3-carboxylic acid methyl ester (11). Compound 11 was prepared from 5-bromo-1-methyl-1H-indazole-3-carboxylic acid methyl ester 9 (59 mg, 0.22 mmol) and 2-pyrroleboronic acid 4 (91 mg, 0.43 mmol) according to the general procedure for the Suzuki coupling reaction. Yield: 58 mg (0.16 mmol, 75%); brown solid, m.p. 102–104 °C; R_f = 0.35 (hexane/ethyl acetate, 1:1). ^1H-NMR: δ = 1.32 (s, 9H, CH_3), 4.01 (s, 3H, OCH_3), 4.52 (s, 3H, NCH_3), 6.22–6.31 (m, 2H, ArH), 7.30–7.43 (m, 1H, ArH), 7.69–7.75 (m, 1H, ArH), 7.67 (d, 1H, ArH, J = 8.8 Hz), 8.17–8.20 (m, 1H, ArH) ppm. ^13C-NMR: δ = 27.9, 42.6, 51.5, 83.8, 108.3, 110.4, 114.3, 115.0, 122.5, 123.6, 124.0, 128.9, 134.1, 139.7, 141.8, 150.1, 171.1 ppm. IR (CHCl_3): ˜ = 1716, 1774 cm\(^{-1}\). HRMS: calcd. for C_{19}H_{21}N_3NaO_4 378.1430; found 378.1434.
4. Conclusions

In summary, this work establishes that indazoles bearing alkyl or acyl groups at either the $N$-1 or $N$-2 positions are suitable substrates for Suzuki cross-coupling reactions with pyrrole- and thiophene-boronic acids. We found that in the presence of Pd(dppf)Cl$_2$ as palladium catalyst, the Suzuki reactions proceed in relatively short times (2 h) and in good yields. The best results were obtained when $N$-alkyl and $N$-Boc indazoles were employed as starting materials. Moreover, it was demonstrated that even bromoindazoles bearing a carbomethoxy group on C-3 are good coupling partners in these reactions. To the best of our knowledge, this is the first systematic study of Suzuki reactions between various 5-bromoindazoles and 2-pyrrole- or 2-thiopheneboronic acids. This could provide a promising access to new heterobiaryl compounds, valuable building blocks for use in medicinal chemistry.

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*Sample Availability:* Samples of the compounds 7a, 7b and 7g are available from the authors.

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