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Efficient synthesis of new 3-heteroaryl-1-functionalized 1*H*-indazoles

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ABSTRACT

The efficient synthesis of novel 3-heteroaryl *N*-1-functionalized indazoles, via palladium cross-coupling reactions of ethyl (3-iodo-1*H*-indazol-1-yl)acetate with 2- and 3-pyrrolylboronic acids, 2-, 4- and 5-thiazolylstannanes, and other heteroarylmetallated derivatives are reported.

1. Introduction

(Hetero)aryl groups directly connected by single Csp^2–Csp^2 bonds to heteroaryl moieties are present as core structures in many biologically active compounds,[1] naturally-occurring substances[2] and materials in polymer science.[3] As a consequence, particular interest has been paid to devise highly efficient, regio- and chemoselective methods to form heteroaryl–heteroaryl C–C bonds. Since the late 1980s, the transition metal-catalyzed cross-coupling reactions between heteroaryl halides and heteroarylmetal derivatives, represented the most effective methodology for the synthesis of unsymmetrical biheteroaryl.[4–7] Although natural products containing indazole moieties are rare,[8] indazoles play an increasingly important role in drug discovery (they act as an efficient isostere for privileged structures, such as indoles and benzimidazoles) and many synthetic indazoles are known and recognized by their pharmaceutical activity.[8,9] A SciFinder search of the indazole core structure returned 77,974 individual hits. A text search of indazole returned 5944 references; of them 2091 were patents (847 dated from 2005 to nowadays). We were interested on indazoles substituted at C-3 with azolyl nuclei because they are found in various biologically active compounds.[6a,c–e,10] After revision of the reported methods for synthesizing them,[6–8,10c,11] we realize that the use of cross-coupling procedures for joining their heterocyclic moieties is rather limited, because only some examples of coupling of the indazol at C-3 with furan and thiophene rings and some occasional example concerning pyridine and indol rings have been reported.[6a–d,10d] In this paper we describe a systematic study of the Pd-catalyzed coupling of **1**[12] (containing an N(1)–CH_2–CO_2Et group, susceptible of being further functionalized) with pyrrol and thiazol moieties, through their different positions, as well as with isoxazol-4-yl and oxazol-2-yl.

2. Results and discussion

The method used for performing different cross-coupling reactions was based on the commercial availability or simplicity for synthesizing the starting compounds. Thus, for assembling indazol-3-yl with 2- and 3-pyrrolyl moieties, the Suzuki reaction appeared to be the best choice because the required pyrrolboronic acids are scarcely toxic, stable and commercially available reagents. The reaction of 3-iodoindazole **1** with 1.5 equiv of boronic acid **2**, under conditions reported for the reactions of 3-iodoindazoles with 2-furyl- and 2-thienylboronic acids,[6b] involving the use of Pd$(PPh_3)_4$ (5 mol%) as catalyst, under reflux in a 2:1 mixture of DME and water, containing an excess of aq sodium bicarbonate (4 equiv), afford after 1 h compound **3** in 34% isolated yield (Table 1 entry 1). A notable increase in the yield was observed by decreasing the proportion of water in the solvent (12.5:1 mixture DME/water, entries 2 and 3).[13] Under the conditions of entry 3, the cross-coupling compound **3** was isolated in 89% yield. This improvement can be explained by assuming that the main competing side reaction, the deboronation of **2** to give *N*-(Boc) pyrrole, is slower when the proportion of water in the solvent becomes lower.

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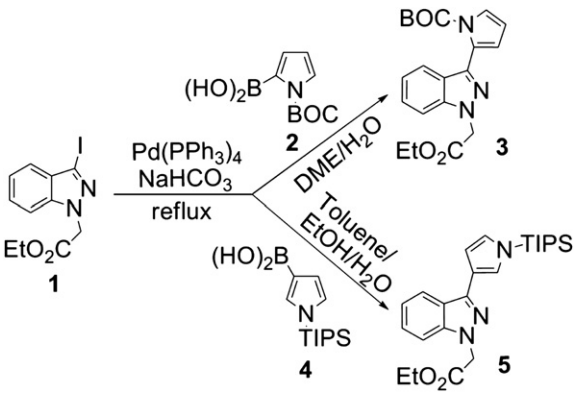
Table 1
Reactions of indazol **1** with pyrrolylboronic acids **2** or **4**



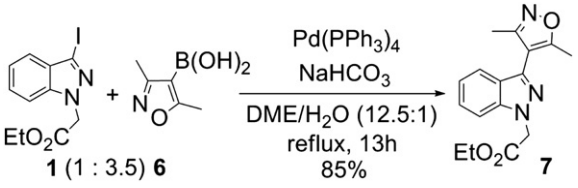
Entry	Boronic	DME/H_2O (toluene/EtOH/H_2O)	Time	Compound (% yield)[a]
1	**2**	2:1	1 h	**3** (34)
2	**2**	12.5:1	3 h[b]	**3** (65)
3	**2**	12.5:1	8.5 h	**3** (89)
4	**4**	12.5:1	13 h[b]	**5** (59)
5	**4**	12.5:1	16 h	**5** (56)
6	**4**	(19:1:1.6)	15 h	**5** (94)

[a] After column chromatography.
[b] Conversion (67%).

Reaction of indazol **1** with 2-pyrrolboronic acid **2** was also studied under $Pd(dba)_2$/[(*t*-Bu)$_3$PH]BF_4 catalysis under conditions reported by Fu for Suzuki cross coupling of aryl boronic acid and halides,[14] but it was not successful yielding a complex mixture.

Reactions of indazole **1** with 3-pyrrolboronic acid **4**, under conditions of the entry 3 in Table 1, also affords the expected cross-coupling biheterocyclic compound **5** in 59% yield after 13 h (Table 1, entry 4). The yield could not be improved by increasing the reaction time (entry 5). In this case, the best results were obtained by using a 19:1:1.6 mixture of toluene/EtOH/H_2O as solvent.[6b] In these conditions the degree of decomposition of **4** diminished, which determine a substantial improvement in the yield of **5** (94%, Table 1, entry 6). The use of these conditions in the reaction of **1** with **2** did not improve the results of the entry 3.

The cross-coupling reactions of **1** with the isoxazol-4-ylboronic acid **6** were studied under conditions of the entries 3 and 6 of Table 1. In this case, the use of a 19:1:1.6 mixture of toluene/EtOH/H_2O as solvent was completely unsuccessful, whereas under conditions of the entry 3 a 58:42 mixture of 3-isoxazolylindazol **7** and starting material was obtained after 21 h. The use of 3.5 equiv of the commercially available reagent **6** (instead of the 1.5 equiv) allowed to increases the yield of **7** up to 85% (after chromatographic purification, Scheme 1).

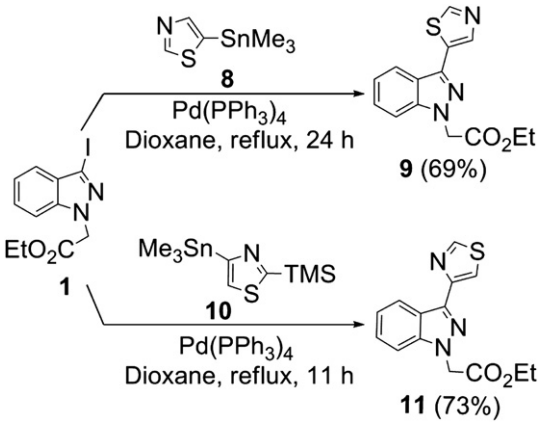


Scheme 1. Coupling of indazol **1** with isoxazol-4-ylboronic acid **6**.

These results evidence that the optimal experimental conditions for achieving the cross-coupling in each case depends on the nature of the heteroaryl partners.

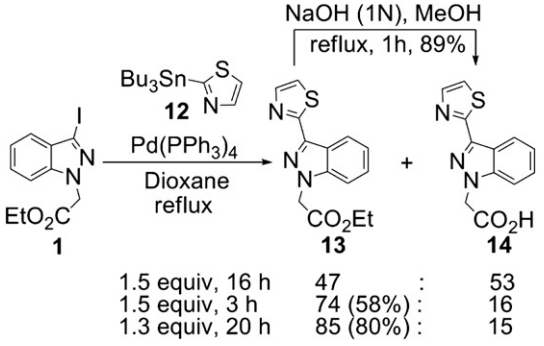
The use of the Suzuki's conditions for preparing the isomeric 3-(thiazolyl)indazoles had serious drawbacks. The first one was the high prize of the 2-, 4- and 5-thiazoleboronic acids, nowadays all of them commercially available.[15–17] Moreover, from a comparative study of Suzuki, Negishi, and Stille coupling, Stanetty[17] reported that the Stille coupling proved to be superior to the other methods with metal thiazoles. Since tin organyls are stable in the 2-, 4 or 5-position of thiazole and can easily be prepared[18] and stored for long periods of time, their Stille reactions with **1** were chosen for the preparation of the isomeric 3-(thiazolyl)indazoles.

Reactions of **1** with 1.5 equiv of 5-thiazolylstannane **8**[18,19] under $Pd(PPh_3)_4$ catalysis, in dry dioxane, afforded the ester **9** in 69% yield (after chromatographic purification) after 24 h (Scheme 2). Stannane **10**[18,20] is more reactive that **8**, and it evolves into the coupled product **11** (73% yield) in 11 h (Scheme 2). Longer reaction times reduce the yield, presumably due to the thermal unstability of **11**. Reactions conducted in toluene also gave worse results.



Scheme 2. Coupling of **1** with **8** and **10** under Stille conditions.

Reactions of 3-iodoindazole **1** with 1.5 equiv of stannane **12**, under similar conditions to those used in Scheme 2, ($Pd(PPh_3)_4$ as catalyst, reflux in dry dioxane) gave slightly different results (Scheme 3).



Scheme 3. Cross-coupling of indol **1** with 2-thiazolylstannane **12**.

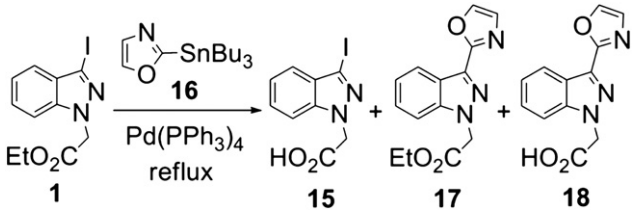
After 16 h, we obtained a 47:53 mixture of **13** (the expected coupling product) and **14** (the acid resulting in the hydrolysis of **13**). This mixture could be completely transformed into **14** (89% yield after purification) by dissolving the crude reaction in a 1 N NaOH methanolic solution and heating it at 45–50 °C for 1 h (Scheme 3).[21]

The ratio **14**/**13** can be reduced by decreasing the reaction time (58% of the ester **13** could be obtained after 3 h) and even better by decreasing the excess of the starting stannane (80% of **13** can be

isolated after 20 h when the reaction was made with 1.3 equiv of **12**), as it can be seen at Scheme 3. Taking into account the wide functional group tolerances of Stille reaction, that hydrolysis of the ester group was not observed in reactions of **1** with **8** and **10** (Scheme 2) and that in the Suzuki conditions (water is present) the acid of the coupled compound only was detected after 13 h, the result could be explained by the higher polarization of the C–Sn bond of **12**, that in presence of water traces would generate tributyltin hydroxide in equilibrium with bis(tributyltin) oxide, reagent used for hydrolysis of ester.[22]

Finally, we choose the Stille conditions for preparing the 3-(oxazol-2-yl)indazole derivatives because of stannane **16** is commercially available and the oxazolylstannanes have been successfully used as nucleophiles in Pd-catalyzed cross-coupling reactions.[4f,5h,23] We first performed the coupling of indazole **1** with **16** (1.5 equiv) under $Pd(PPh_3)_4$ catalysis at dioxane reflux (entry 1, Table 2). After 16 h, a 37:63 mixture of the acids **15** and **18** was obtained, resulting of hydrolysis of the esters **1** (starting product) and **17** (expected coupling product), respectively.

Table 2
Coupling of indazole **1** with oxazol-2-ylstannane **16**



Entry	Condition	Equiv **16**	Ratio (**1**:**15**):(**17**:**18**)
1	Dioxane, $Pd(PPh_3)_4$, 16 h	1.5	(0:37):(0:63)
2	Dioxane, $Pd(PPh_3)_4$, 32 h	2	(0:50):(0:50)
3	Dioxane, $Pd(PPh_3)_4$, 20 h	3	(0:50):(0:50)
4	$PhCH_3$, $Pd(PPh_3)_4$, 4 h	1.5	(15:11):(58:16)
5	$PhCH_3$, $Pd(PPh_3)_4$, 16 h	1.5	(18):(82)[a]
6	$PhCH_3$, $Pd(PPh_3)_4$, 24 h	3	(0:0):(47:53)[b]
7	Dioxane, $Pd(dba)_2/PCy_3$, 16 h	3	(0:87):(0:12)

[a] Ester **17** was isolated in 60% yield after chromatographic separation from this crude reaction.
[b] Acid **18** was isolated in 85% yield by treatment of this crude reaction with NaOH/EtOH.

Lower conversion of iodoindazoles was observed by increasing the equivalent of stannane (Table 2, entries 2 and 3), which must be a consequence of the formation of a higher amount of the acid resulting in the hydrolysis of **1**, which exhibits a very low ability for the coupling reactions. Hypothesis demonstrated because only 1% of acid **18** was obtained from reaction of iodoacid **15** with 1.5 equiv of stannane **16** in dioxane at reflux for 16 h.

The results indicated in Table 2, can be justified taking into account the following facts. First the oxazolyl stannane **16** is able to hydrolyze the ester group (like **12**, see above). Second, the ability for ester hydrolysis of **16** is lower than **12**,[24] as well as the reactivity of **16** towards **1**, which is also lower than that of **12**; this has been demonstrated with an experience of competence since after reflux for 16 h in toluene a mixture 1:1:1 of **1**/**12**/**16** and $Pd(PPh_3)_4$ a 79:21 mixture of 3-(thiazol-2-yl)indazoles (**13**+**14**)/3-(oxazol-2-yl)indazoles (**17**+**18**) was obtained. Third, to increase the reaction times (16 h, entry 1 Table 2, instead 3 h, Scheme 3) increase the extension of the hydrolysis. Finally, the lower reactivity of the iodoindazoleacetic acid **15** than the ester **1** (see before).

The higher ability of **12** (thiazol) than that **16** (oxazol) for hydrolysis of ester could be justified by higher stability of the cyclic intermediate generate along with tributyltin hydroxide in presence of water traces.

The addition of CuI in dioxane,[25] or the use of $Pd(dba)_2/PCy_3$ as catalyst (entry 7, Table 2) does not produce any improvement in the obtained results. The use of toluene as solvent increases the yield of coupling products (Table 2, entries 4–6). The best yield (60%) of ester **17** was obtained in toluene and 1.5 equiv of **16** (entry 5, Table 2). On the other hand, the acid **18** could be isolated in 85% yield by treatment with MeOH/NaOH of the reaction crude obtained under conditions of entry 6.

3. Conclusion

In conclusion, we have demonstrated that palladium-catalyzed heteroarylation of (3-iodoindol-1yl)acetate with heteroaryl boronic acids (pyrrole and isoxazole) and azolylstannanes are a practical method for introducing, in good or excellent yields, heteroaromatic diversity on the pyrazole ring of indazole.

4. Experimental section

4.1. General methods

All cross-coupling reactions were performed in flame-dried glassware under positive pressure of argon. Silica gel 60 (230–400 mesh ASTM) and DC-Alufolien 60 F_{254} were used for flash column chromatography and analytical TLC, respectively. Melting points were determined using a Gallenkamp apparatus in open capillary tubes and are uncorrected. The IR spectra were recorded on a Bruker Vector 22 spectrometer and the frequencies are given in cm^{-1}. NMR spectra were determined on Brucker AC-300 instrument in the solvent indicated in each case at 300 and 75.5 MHz for ^1H and ^{13}C NMR, respectively; chemical shifts were reported in parts per million and *J* values are given in hertz. Microanalyses were carried out on a LECO CHNS-932 in Laboratory of elemental analyses of SIDI of Universidad Autónoma de Madrid, and were in good agreement with the calculated values. High resolution mass spectrometry (HRMS), FAB: Waters, VG AutoSpec.

4.2. Synthesis of starting indazol: ethyl (3-iodo-1*H*-indazol-1-yl)acetate (1)

To a solution of 3-iodoindazole[6b] (3.94 g, 16.15 mmol) in THF (45 mL), cooled at 0 °C, was added potassium *tert*-butoxide (2.72 g, 24.24 mmol) in small portions. After 1 h at 0 °C, ethyl bromoacetate (5.39 g, 32.28 mmol) was added dropwise and the resulting mixture was stirred overnight at rt. The solvent was evaporated and the residue was dissolved in EtOAc (50 mL) and water (50 mL). The organic layer was separated and the aq layer was extracted with EtOAc (3×50 mL). The combined organic layers were dried ($MgSO_4$), filtered and the solvent evaporated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 7:1). Yield: 87%. Pale yellow solid mp 43–46 °C. IR (KBr): 1737, 1614, 1251, 1209, 1021, 763 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.48 (m, 2H), 7.27 (m, 2H), 5.15 (s, 2H), 4.22 (q, *J*=7.1 Hz, 2H), 1.25 (t, *J*=7.1, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.4, 140.7, 128.6, 127.9 (CH), 121.7 (2CH), 108.9 (CH), 93.0, 61.8 (CH_2), 50.5 (CH_2), 14.0. HRMS–FAB: *m*/*z* [M+H$^+$] calcd for $C_{11}H_{12}IN_2O_2$: 330.9944; found: 330.9943.

4.3. Suzuky coupling of indazole 1

*4.3.1. tert-Butyl 2-[1-(2-ethoxy-2-oxoethyl)-1H-indazol-3-yl]-1H-pyrrole-1-carboxylate (**3**).* To a mixture of 3-iodoindazole **1** (1.5 g, 4.54 mmol) and $Pd(PPh_3)_4$ (262 mg, 5 mol%) in DME (150 mL), boronic acid **2** (1.44 g, 6.82 mmol) was added followed by the addition of $NaHCO_3$ (1.53 g, 18.16 mmol) in water (12 mL). The reaction mixture was refluxed with vigorous stirring under argon atm for 8.5 h. After cooling to rt, water (250 mL) was added. The organic layer was separated and the aq layer was extracted with CH_2Cl_2

(4×100 mL). The combined organic layers were dried (Na_2SO_4), filtrated and the solvent evaporated. The crude products were purified by column chromatography on silica gel [1° CH_2Cl_2/Et_2O (99:1), 2° hexane/EtOAc (6:1)]. Yield: 89%. Colourless oil. IR (film): 1740, 1618, 1329, 1206, 734 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.57 (br d, J=8.1 Hz, 1H), 7.50 (dd, J=1.7 and 3.4 Hz, 1H), 7.41 (ddd, J=0.9, 6.7 and 8.3 Hz, 1H), 7.32 (br d, J=8.3 Hz, 1H), 7.17 (ddd, J=0.9, 6.7 and 8.1 Hz, 1H), 6.48 (dd, J=1.7 and 3.4 Hz, 1H), 6.32 (t, J=3.4 Hz, 1H), 5.16 (s, 2H), 4.23 (q, J=7.2 Hz, 2H), 1.27 (t, J=7.2 Hz, 3H), 1.12 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.7, 149.0, 140.5, 139.8, 126.6, 124.8, 124.5, 123.2, 121.4, 120.8, 116.5, 110.8, 108.7, 83.7, 61.6, 50.3, 27.1, 14.0. MS (FAB^+): m/z (%)=370 [MH^+] (61), 369 [M^+] (51), 269 (100), 196 (42), 57 (33). HRMS–FAB: m/z [M+H^+] calcd for $C_{20}H_{24}N_3O_4$: 370.1767; found: 370.1774.

*4.3.2. Ethyl 2-[3-(1-triisopropylsilyl-1H-pyrrol-3-yl)-1H-indazol-1-yl]acetate (**5**).* To a solution of 3-iodoindazole **1** (1.65 g, 5.0 mmol) and $Pd(PPh_3)_4$ (289 mg, 5 mol %) in a mixture of toluene (305 mL) and EtOH (16 mL), boronic acid **4** (2.00 g, 7.50 mmol) was added followed by the addition of $NaHCO_3$ (1.68 g, 20.00 mmol) in water (25.6 mL) and the reaction mixture was refluxed with vigorous stirring under argon atm for 15 h. After cooling to rt, water (250 mL) and KCN were added. The organic layer was separated and the aq layer was extracted with Et_2O (3×100 mL). The combined organic layers were dried ($MgSO_4$), filtered, and the solvent evaporated. The crude product was purified by column chromatography on silica gel (hexane/EtOAc 6:1). Yield: 94%. White solid. Mp 71–72 °C. IR (KBr): 1757, 1615, 1587, 1202 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.94 (br d, J=8.1 Hz, 1H), 7.40 (ddd J=1.0, 6.8 and 8.1 Hz, 1H), 7.35 (t, J=1.7 Hz, 1H), 7.29 (br d, J=8.4 Hz, 1H), 7.19 (m, 1H), 6.88 (m, 2H), 5.16 (s, 2H), 4.21 (q, J=7.2 Hz, 2H), 1.52 (sept, J=7.5 Hz, 3H), 1.24 (t, J=7.2 Hz, 3H), 1.15 (d, J=7.5 Hz, 18H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=168.2, 142.0, 141.4, 126.5, 124.9, 122.5, 122.3, 121.7, 120.5, 118.8, 109.7, 108.7, 61.5, 50.3, 17.8, 14.1, 11.7. MS (FAB^+): m/z (%)=426 [MH^+] (94), 425 [M^+] (100). HRMS–FAB: m/z [M^+] calcd for $C_{24}H_{35}N_3O_2Si$: 425.2499; found: 425.2505.

*4.3.3. Ethyl 2-[3-(3,5-dimethylisoxazol-4-yl)-1H-indazol-1-yl]acetate (**7**).* To a solution of 3-iodoindazole **1** (555 mg, 1.68 mmol), Pd(PPh_3)$_4$ (97 mg, 5 mol %) in DME (167 mL), were added boronic acid **6** (829 mg, 5.88 mmol) and $NaHCO_3$ (1.31 g, 15.62 mmol) in water (13.4 mL). The reaction mixture was refluxed with vigorous stirring under argon atm for 13 h. After cooling to rt, water (250 mL) was added. The organic layer was separated and the aq layer was extracted with CH_2Cl_2 (3×100 ml). The combined organic layers were dried ($MgSO_4$), filtrated and concentrated under reduced pressure. The crude products were purified by successive column chromatography on silica gel (hexane/EtOAc 6:1). Yield: 85%. White solid. Mp 128–130 °C. IR (KBr): 1744, 1647, 1647, 1220, 759 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=7.57 (br d, J=8.1 Hz, 1H), 7.46 (m, 1H), 7.39 (br d, J=8.4 Hz, 1H), 7.22 (m, 1H), 5.18 (s, 2H), 4.24 (q, J=7.1 Hz, 2H), 2.47 (s, 3H), 2.33 (s, 3H), 1.26 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.7, 167.4, 159.6, 141.1, 136.0, 127.1, 123.3, 121.4, 120.7, 109.2, 108.9, 61.8, 50.4, 14.1, 12.0, 10.8. Anal. Calcd for $C_{16}H_{17}N_3O_3$: C, 64.20; H, 5.72; N, 14.04. Found: C, 63.92; H, 5.77; N, 13.94.

4.4. Stille coupling of indazole 1

*4.4.1. Ethyl 2-[3-(1,3-thiazol-5-yl)-1H-indazol-1-yl]acetate (**9**).* A solution of 3-iodoindazole **1** (200 mg, 0.61 mmol), stannylthiazole **8** (291 mg, 0.91 mmol) and $Pd(PPh_3)_4$ (34 mg, 5 mol %) in dioxane (10 mL) was reflux with vigorous stirring under argon atm for 11 h. After cooling to rt, the reaction mixture was filtered through Celite and washed with abundant CH_2Cl_2. The solvent was removed under reduced pressure and the residue was purified by column chromatography on silica gel (CH_2Cl_2/Et_2O 9:1). Yield: 73%. Yellow solid of mp 104–106 °C. IR (KBr): 3078, 1737, 1616, 1587, 1316, 1211, 741 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.83 (d, J=0.5 Hz, 1H), 8.44 (d, J=0.5 Hz, 1H), 7.99 (dt, J=0.9 and 8.3 Hz, 1H), 7.48 (ddd J=0.9, 6.9 and 8.5 Hz, 1H), 7.37 (br d, J=8.5 Hz, 1H), 7.30 (ddd, J=0.9, 6.9 and 8.3 Hz, 1H), 5.18 (s, 2H), 4.24 (q, J=7.2 Hz, 2H), 1.26 (t, J=7.2 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.5, 152.1, 141.4, 140.2, 137.1, 130.8, 127.3, 122.0, 121.5, 120.7, 109.2, 61.8, 50.3, 14.0. Anal. Calcd for $C_{14}H_{13}N_3O_2S$: C, 58.52; H, 4.56; N, 14.62; O, 11.14; S, 11.16. Found: C, 58.66; H, 4.59; N, 14.56; S, 11.13.

*4.4.2. Ethyl [3-(1,3-thiazol-4-yl)-1H-indazol-1-yl]acetate (**11**).* A solution of 3-iodoindazole **1** (356 mg, 1.08 mmol), stannylthiazole **10** (400 mg, 1.62 mmol) and $Pd(PPh_3)_4$ (62 mg, 5 mol %) in dry dioxane (18 mL) was reflux with vigorous stirring under argon atm for 24 h. After cooling to rt, the reaction mixture was filtered through Celite and washed with abundant EtOAc. The solvent was evaporated and the crude reaction was purified by column chromatography on silica gel (hexane/Acetone 6:1). Yield: 69%. White solid. Mp 90–92 °C (Et_2O). IR (KBr): 3099, 3056, 1740, 1703, 1616, 1499, 1220, 1025, 879, 743 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.97 (d, J=2.1 Hz, 1H), 8.38 (dt, J=1.0 and 8.1 Hz, 1H), 7.91 (d, J=2.1 Hz, 1H), 7.45 (ddd J=1.0, 6.8 and 8.4 Hz, 1H), 7.35 (dt, J=1.0 and 8.4 Hz, 1H), 7.28 (ddd, J=1.0, 6.8 and 8.1 Hz, 1H), 5.21 (s, 2H), 4.23 (q, J=7.1 Hz, 2H), 1.25 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.8, 152.8, 150.2, 141.3, 140.1, 127.1, 122.6, 122.2, 121.7, 114.5, 108.8, 61.8, 50.5, 14.1. Anal. Calcd for $C_{14}H_{13}N_3O_2S$: C, 58.52; H, 4.56; N, 14.62; O, 11.14; S, 11.16. Found: C, 58.75; H, 4.59; N, 14.62; S, 11.06.

*4.4.3. 3-(1,3-Thiazol-2-yl)-1H-indazoles **13** and **14**.* A solution of 3-iodoindazole **1** (1.02 g, 3.10 mmol), stannylthiazole **12** (4.65 mmol for **14** and 4.03 mmol for **13**) and $Pd(PPh_3)_4$ (179 mg, 5 mol %) in dry dioxane (50 mL) was heated to reflux with vigorous stirring under argon atm for 16 h. After cooling to rt, the reaction mixture was filtered through Celite and the solid was washed with abundant EtOAc and the solvent of filtrate was removed under reduced pressure.

*4.4.3.1. Ethyl 2-[3-(1,3-thiazol-2-yl)-1H-indazol-1-yl]acetate (**13**).* It was isolated as white solid after two column chromatography (1° hexane/acetone 7:1 and 2° hexane/CH_2Cl_2/ether 60:35:5), from the crude reaction obtained following the above procedure using 1.3 equiv of stanname **12**. Yield 80%. Mp 95–97 °C IR (KBr): 1798, 1616, 1229, 750 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.51 (d, J=8.1 Hz, 1H), 7.96 (d, J=3.2 Hz, 1H), 7.48 (m, 1H), 7.34 (m, 3H), 5.21 (s, 2H), 4.23 (q, J=7.1 Hz, 2H), 125 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.3, 161.4, 143.4, 141.5, 139.8, 127.4, 122.7, 122.5, 121.6, 118.3, 108.8, 61.8, 50.5, 14.0. Anal. Calcd for $C_{14}H_{13}N_3O_2S$: C, 58.52; H, 4.56; N, 14.62; S, 11.16. Found: C, 58.34; H, 4.58; N, 14.63; S, 11.13. HRMS–FAB: m/z [M+H^+] calcd for $C_{14}H_{14}N_3O_2S$: 288.0807; found: 288.0798.

*4.4.3.2. 2-[3-(1,3-Thiazol-2-yl)-1H-indazol-1-yl]acetic acid (**14**).* It was isolated as white solid of mp 200–202 °C (decomposition), in 89% yield, when the crude reaction was dissolved in methanol (21 mL) and treated with 1 N aq NaOH (13.4 mL). The reaction mixture was heated to 45–50 °C for 1 h. After cooling to rt, the aq layer was washed with CH_2Cl_2 (3×25 mL), filtered and cooling at 0 °C. Then added 5% aq HCl until pH 2–3. The solid obtained was filtered and washed with ice-water until neutral pH. IR (KBr): 3500–2500, 1719, 1618, 1223, 1025, 740 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ=8.43 (d, J=8.1 Hz, 1H), 7.98 (d, J=3.1 Hz, 1H), 7.56 (m, 3H), 7.35 (t, J=7.3 Hz, 1H), 5.34 (s, 2H). ^{13}C NMR (75 MHz, CD_3OD): δ=171.3, 163.2, 144.4, 143.2, 140.4, 128.7, 123.7, 123.2, 122.4, 120.1, 110.8, 51.1. Anal. Calcd for $C_{12}H_9N_3O_2S$: C, 55.59; H, 3.50; N, 16.21; S, 12.37. Found: C, 55.48; H, 3.57; N, 16.05; S, 12.09.

*4.4.4. 3-(1,3-Oxazol-2-yl)-1H-indazoles (**17** and **18**).* A solution of 3-iodoindazole **1** (0.20 g, 0.61 mmol), stannyloxazole **16** (1.5 mmol for **17** and 1.82 mmol for **18**) and $Pd(PPh_3)_4$ (35 mg, 5 mol %) in dry toluene (10 mL) was heated to reflux with vigorous stirring under argon atm for 16 h or 24 h for ester **17** or acid **18**, respectively. After cooling to rt, the reaction mixture was filtered through Celite and the solid was washed with abundant CH_2Cl_2 and the solvent evaporated.

*4.4.4.1. Ethyl 2-[3-(1,3-oxazol-2-yl)-1H-indazol-1-yl]acetate (**17**).* The crude reaction was purified by two column chromatography (1° hexane/acetone 7:1 and 2° Hex/CH_2Cl_2/Et_2O 15:80:5). White solid of mp 114–116 °C. IR (KBr): 1748, 1620, 1597, 1316, 1174, 1113, 791, 765 cm^{-1}. ^1H NMR (300 MHz, $CDCl_3$): δ=8.39 (d, J=8.2 Hz, 1H), 7.79 (s, 1H), 7.49 (m, 1H), 7.33 (m, 3H), 5.25 (s, 2H), 4.22 (q, J=7.1 Hz, 1H), 1.24 (t, J=7.1 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ=167.3, 157.0, 141.2, 138.3, 134.1, 128.4, 127.6, 122.7, 122.24, 122.17, 109.1, 61.9, 50.8, 14.0. Anal. Calcd for $C_{14}H_{13}N_3O_3$: C, 61.99; H, 4.83; N, 15.49. Found: C, 61.60; H, 4.85; N, 15.43. HRMS–FAB: m/z [M+H$^+$] calcd for $C_{14}H_{14}O_3N_3$: 272.1035; found: 272.1041.

*4.4.4.2. 2-[3-(1,3-Oxazol-2-yl)-1H-indazol-1-yl]acetic acid (**18**).* The crude reaction was dissolved in MeOH (4.1 mL) and treated with 1 N aq NaOH (2.64 mL). The reaction mixture was heated to 45–50 °C for 1 h. After cooling to rt, the aq layer was washed with CH_2Cl_2 (3×10 mL), filtrated and cooling at 0 °C. Then, was added 5% aq HCl, until pH 2–3. The solid obtained was filtrated and washed with ice-water until neutral pH. Yield: 85%. White solid. Mp 227–229 °C (decomposition). IR (KBr): 3400–2450, 1709, 1594, 1264, 750 cm^{-1}. ^1H NMR (300 MHz, DMSO-d_6): δ=8.21 (d, J=8.1 Hz, 1H), 8.18 (s, 1H), 7.69 (d, J=8.1 Hz, 1H), 7.50 (t, J=7.6 Hz, 1H), 7.44 (s, 1H), 7.34 (t, J=7.6 Hz, 1H), 5.34 (s, 2H). ^{13}C NMR (75 MHz, DMSO-D6): δ=170.1, 156.9, 141.8, 140.3, 133.2, 129.1, 128.3, 123.6, 121.83, 121.77, 111.2, 51.0. MS (FAB$^+$): m/z (%)=244 [MH$^+$] (37). HRMS–FAB: m/z [M+H$^+$] calcd for $C_{12}H_{10}O_3N_3$: 244.0722; found: 244.0729.

4.5. (3-Iodo-1*H*-indazol-1-yl)acetic acid (15)

To a solution of ester **1** (0.250 g, 0.76 mmol) in MeOH (5 mL) was added 1 N aq NaOH solution (3.3 mL). The reaction mixture was heated to 45–50 °C for 1 h. The MeOH was evaporated and the aq residue cooling at 0 °C. Then 5 M HCl was added until pH 2–3. The precipitate was filtered and washed with ice-water until neutral pH. Yield: 98%. Mp 194–196 °C (with decomposition). IR (KBr): 3320–2500, 1769, 1731, 1616, 1321, 1222, 750 cm^{-1}. ^1H NMR (300 MHz, CD_3OD): δ=7.47 (m, 3H), 7.23 (m, 1H), 5.23 (s, 2H). ^{13}C NMR (75 MHz, CD_3OD): δ=171.2, 142.3, 129.8, 129.1, 122.9, 122.4, 110.7, 93.3, 50.9. Anal. Calcd for $C_9H_7IN_2O_2$: C, 35.79; H, 2.34; I, 42.01; N, 9.27. Found: C, 35.41; H, 2.34; N, 9.31. HRMS–FAB: m/z [M+H$^+$] calcd for $C_9H_8IN_2O_2$: 302.9631; found: 302.9636.

4.6. Reactions of 2-azolylstannanes (12 and 16) with ethyl (3-iodo-1*H*-indazol-1-yl)acetate (1). General procedure

A solution of ethyl (3-iodo-1*H*-indazol-1-yl)acetate (**1**) (0.061 mmol) and stannylazole **12** or **16** (0.091 mmol) in dry dioxane (1 mL) was heated to reflux with vigorous stirring under argon atm for 20 h. The solvent was removed under reduced pressure and the crude reaction analyzed by ^1H NMR.

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