

Synthesis of 3-aryl-1*H*-indazoles via iridium-catalysed C–H borylation and Suzuki–Miyaura coupling†

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The regioselective iridium-catalysed C3-borylation of 1*H*-indazoles has been achieved. Subsequent Suzuki–Miyaura coupling of the boronate esters with aryl chlorides, bromides and iodides affords 3-aryl-1*H*-indazoles in good yields.

Indazoles are rare in nature but are an important class of heterocycles in medicinal and agrochemical discovery programs due to their isosterism with indoles.¹ In particular, 3-aryl-1*H*-indazoles feature in the estrogen receptor agonist **1**,² the anti-fungal agent **2** (ref. 3) and the antibiotic teloxantrone (**3**) (Fig. 1).

Previously reported approaches to 3-aryl-1*H*-indazoles include the condensation of hydrazines with fluorobenzo-phenones,^{2–4} diazomethane cycloaddition with benzyne,⁵ C–H amidation of aryl hydrazones⁶ or catalytic N–N bond formation.⁷ However, these methods all suffer from requiring the use of either explosive or toxic reagents. In addition, the diversity of substitution on both the indazole and the aryl group must be introduced relatively early on in the synthetic sequence when employing these conditions.

The synthesis of 3-aryl-1*H*-indazoles via the cross coupling of 1*H*-indazoles metalated in the 3-position to aryl halides is particularly attractive from a discovery-chemistry viewpoint because it enables the late-stage attachment of an indazole moiety to an aryl halide intermediate, thus allowing the rapid access to a variety of substitution patterns. However, this reaction is hampered by the propensity of a 3-metallated, 1*H*-indazole **4** to undergo ring-opening to the corresponding 2-aminophenyl nitrile **5** (Scheme 1).

Knochel and co-workers reported an elegant solution to this problem in 2012 by zincation at the 3-position of 1-alkyl-1*H*-indazoles employing TMPZnCl, followed by subsequent Negishi cross-coupling with aryl iodides.⁸ Subsequent reports from the Itami, Yu and Guillaumet groups have demonstrated the direct

C–H arylation of 1*H*-indazoles with aryl iodides.^{9–11} However, the conditions reported require high temperatures (up to 150 °C) and they fail when the cheaper and more readily available aryl chlorides are used as the coupling partner. Furthermore, the examples of aryl halides reported are limited to those unsubstituted at the *ortho* positions.

In an attempt to broaden the substrate-scope of 1*H*-indazole C3-arylation to include both aryl chlorides and bromides and also aryl halides that possess one or two *ortho* substituents, we turned to the Ir-catalysed C–H borylation reaction,¹² followed by Suzuki–Miyaura cross coupling. The results of this investigation are reported herein.

Our initial investigations were focussed on the borylation of 1-methyl-1*H*-indazole **6** employing the [Ir(OMe)(COD)]₂/di-*tert*-butyl bipyridine (dtbpy) catalyst system pioneered by Ishiyama, Takagi, Hartwig and Miyaura and subsequently applied by other researchers to the C–H borylation of a wide variety of aromatics and heteroaromatics over the last decade.^{12–15} We were pleased to observe that when employing 0.5 equivalents of bis(pinacolato)diboron (B₂Pin₂) in *tert*-butyl methyl ether (TBME) at 55 °C for 1.5 h, selective borylation at the 3-position of **6** gave **7** in 50% yield after chromatographic purification (Scheme 2). Boronate **7** was stored in a freezer without evidence of degradation for 6 months. The high C3-regioselectivity can be attributed to a

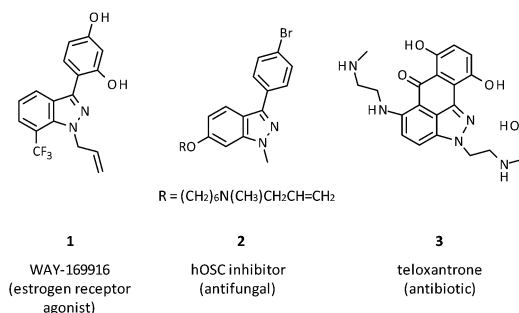
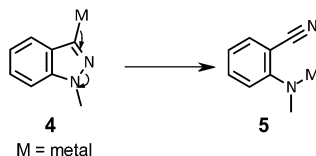


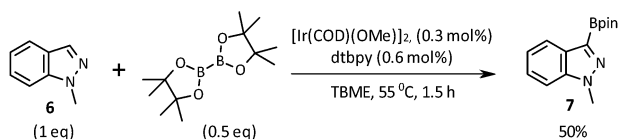
Fig. 1 Bioactive 3-aryl-1*H*-indazoles.

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Scheme 1 Fragmentation of 3-metallated 1H-indazoles.

Scheme 2 Borylation of 1-Me-1H-indazole with B₂Pin₂.

combination of steric factors and the C–H acidity at this position.¹⁶ To the best of our knowledge, 3-boronic esters of 1-alkyl-1H-indazoles have not previously been reported in the literature.¹⁷

A short screen of conditions for the Suzuki–Miyaura arylation of boronic ester **7** was concluded with the discovery that the Buchwald second-generation XPhos precatalyst **8** in TBME and aqueous potassium phosphate effects the cross coupling with most of the aryl halides we tried (Table 1).¹⁸ This cross coupling could be performed thermally (55 °C for 16 h, conditions A) or under microwave irradiation (100 °C for 20 min, conditions B).

As shown in Table 1, aryl iodides, chlorides and bromides all react in good yields (entries 1–3). The coupling is tolerant of electron donating substituents (entries 6 and 7). Highly hindered electrophiles such as 2,6-diethylphenyl bromide also perform well (entry 5). The reaction is also tolerant of free alcohols (entry 8) and will work on 2-pyridinyl and 2-pyrimidinyl halides (entries 9 and 10).

We next turned our attention to combining the indazole borylation and Suzuki–Miyaura coupling into a one-pot procedure.¹⁹ We were pleased to find that this was possible without a work-up or solvent swap.²⁰ It was possible to simply monitor the borylation by GCMS and, once this indicated the consumption of starting material, the palladium precatalyst **8**, the aryl halide, potassium phosphate and water could be added to the reaction mixture (Scheme 3).

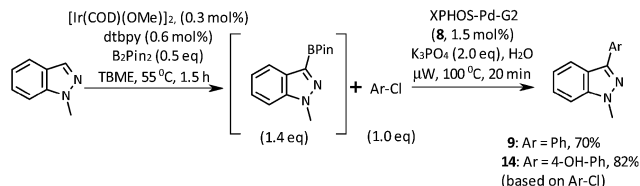
We next investigated varying the substitution on the indazole employing this one-pot procedure (Table 2). The commercially available indazole bearing a methyl ester at the 5-position (entry 1) was smoothly borylated using the conditions described in Scheme 3. When using more highly functionalised indoles, we found it preferential to use 1 equivalent of B₂Pin₂ for the borylation, as doing so increased the reaction rate (entries 1, 2, 3 and 5). When a methyl ester is in the 4-position, borylation is instead directed to the 6-position (entry 5), presumably due to the steric bulk of the 4-substituent. 1*N*-methoxymethyl protected indazole also performs well in the 3-borylation–Suzuki sequence (entries 2 and 3). Furthermore, the azaindazole in entry 4 is well tolerated.²¹

Finally, the borylation of the isomeric 2-methyl-2H-indazole **22** was attempted (Scheme 4). Despite smooth borylation at the

Table 1 Suzuki–Miyaura coupling of boryl-indazole **7**^b

Entry	Ar-X	Product	Yield ^a (%)
1			72 (A), 74 (B)
2			71 (A), 66 (B)
3			86 (A), 68 (B)
4			63 (A), 97 (B)
5			90 (B)
6			76 (B)
7			91 (B)
8			84 (B)
9			87 (B)
10			97 (B)

^a Isolated yields after chromatography. ^b Reaction conditions: a solution of the aryl halide (1.0 eq., typically 0.50 mmol), **7** (1.3 eq.), XPhos-Pd-G2 (0.015 eq.) and K₃PO₄ (2.0 eq.) in TBME–H₂O (10 : 1, typically 0.1 M) was heated in a RBF at 55 °C for 16 h (conditions A) or in a microwave reactor at 100 °C for 20 min (conditions B).

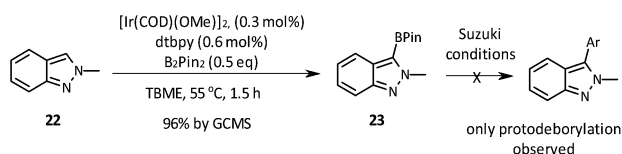


Scheme 3 One pot borylation/Suzuki sequence.

Table 2 One-pot indazole borylation and Suzuki–Miyaura coupling

Entry	Indazole	Ar-X ^a	Product
1			17 (65%)
2			18 (70%)
3			19 (78%)
4 ^b			20 (71%)
5			21 (89%)

^a Isolated yields are after chromatography and are based on Ar-X. ^b 0.5 eq of B₂Pin₂ used. 4 h for borylation step.



Scheme 4 Borylation of 2-methyl-2H-indazole 22.

3-position, the resulting pinacol boronate 23 proved to be unstable in our hands. All attempts to employ it in a Suzuki–Miyaura reaction employing either the Pd–XPhos precatalyst or other standard catalysts for this reaction (e.g. PdCl₂(dppf)/CsF or Pd(OAc)₂/SPhos/K₃PO₄) resulted in proto-deborylation and no desired product formation.

In conclusion, we have demonstrated a novel route to 3-aryl-1H-indazoles employing Ir-catalysed C–H borylation at the 3-position, followed by Suzuki–Miyaura coupling with aryl halides. In particular, the wide substrate scope of the aryl halide coupling partner in combination with the high yielding and operationally simple procedure allows a diverse selection of 3-aryl-1H-indazoles to be rapidly furnished as part of a discovery chemistry program.

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