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Solution to the C_3–Arylation of Indazoles: Development of a Scalable Method

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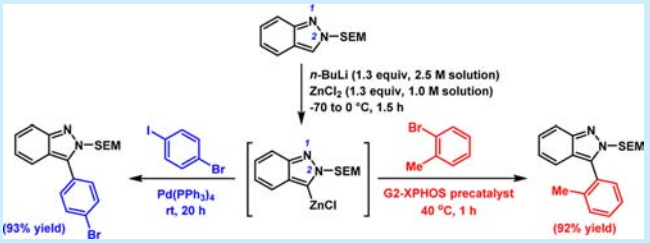
Supporting Information

ABSTRACT: 3-(Hetero)arylindazoles are important motifs in several biologically active compounds. Mild and flexible palladium-mediated Negishi reaction conditions are reported for the introduction of (hetero)aryl moieties at the 3-position of *N*(2)-SEM-protected indazoles in high yields. The requisite Zn-species are readily obtained via regioselective deprotonation and subsequent transmetalation. The methodology tolerates a variety of functional groups on both coupling partners and has been extended to bis-haloarene and heteroarene coupling partners where the most reactive halogen reacts first, leaving the second halogen for subsequent functionalization.



Indazoles represent a class of heterocycles that have gained tremendous popularity among medicinal chemists in recent years due to their growing applications in drug discovery.[1,2] These compounds perform as efficient isosteres for privileged structures such as indoles and benzimidazoles. While indazoles with different substitution patterns are well-known, indazoles with (hetero)aryl groups in the 3-position are of increasing interest (compound **1**, Figure 1). Unfortunately, access to this class of heterocycles is limited because of few general synthetic methods for their preparation.[3]

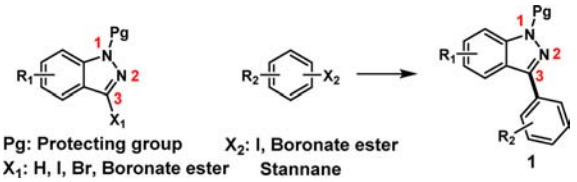
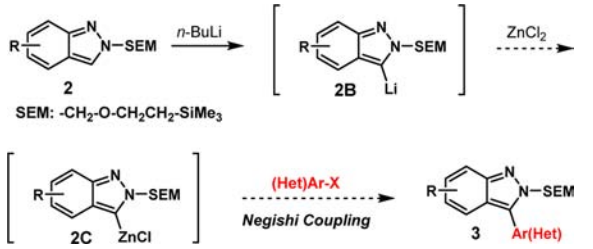


Figure 1. General strategy for C(3)-arylation of indazoles.

The most common methods for the direct introduction of (hetero)aryl moieties at C(3) of indazoles rely on Stille[4] or Suzuki–Miyaura[5] couplings. Key liabilities of these methods are the use of toxic tin reagents for the Stille coupling and competing proto-dehalogenation under standard Suzuki conditions. Recently, iridium,[6] copper,[7a] and palladium-mediated[7a,b] methods involving direct C–H activation reactions at the 3-position of indazoles have been described for the introduction of an aryl moiety. Unfortunately, these methods require high temperatures (100–165 °C) and may be incompatible with sensitive functionalities. As part of a drug discovery program, efficient access to 3-(hetero)aryl indazoles was required to enable the preparation of a range of substituted indazoles. Initial attempts employing both the Stille and Suzuki protocols met with limited success, thus necessitating the development of an alternative method. It was envisioned that Negishi cross-coupling could provide an attractive solution to this synthetic challenge. Knochel described such a strategy, coupling 3-indazolyl zinc species, generated by regioselective zincation using $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$, with a series of aryl iodides to furnish 3-arylindazoles.[8] While attractive, wide application of this methodology is restricted by the limited availability of aryl iodide coupling partners; aryl bromides and chlorides were unreactive under the reported conditions. Given the increasing number of applications of 3-arylindazoles in the pharmaceutical industry, a general method for the preparation of this synthetically challenging class of molecules is needed. In this letter, we report the development of a simple, mild, robust, and scalable method for the preparation of 3-arylindazoles that addresses each of these key criteria.

The regioselective 3-lithiation of *N*(2)-SEM-protected indazole employing *n*-butyllithium is known (Scheme 1).[9] We hypothesized that such a lithiated species (**2B**) could be transmetalated with $ZnCl_2$ to form an intermediate zinc-species (**2C**) *in situ*, which would participate in a palladium-catalyzed cross-coupling reaction with aryl halides. The strategy was

Scheme 1. Design Plan



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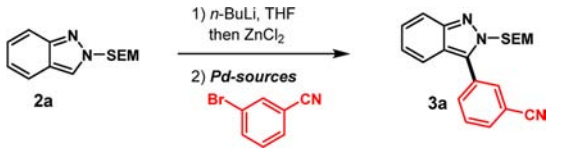
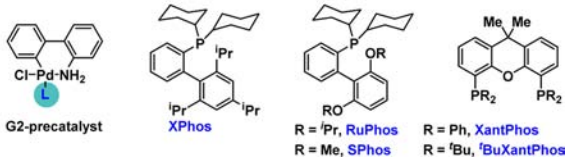
conceived with a desire to make use of cheap and readily available (hetero)aryl bromides and chlorides. In order to achieve this goal, we explored Pd-precatalysts that form reactive mono- or bisphosphine Pd species *in situ* due to their ability to oxidatively add to aryl bromides and chlorides, a feature we hoped we could exploit in developing this cross-coupling reaction.[10]

We began our investigation by probing the Negishi coupling between the Zn-species generated from indazole **2a** and 3-bromobenzonitrile (Table 1) mediated by a variety of palladium

Table 1. Catalyst Selection and Reaction Optimization[a]



entry	Pd-sources	temp (°C)	time (h)	conversion (%)
1	G2-XPhos precatalyst	rt	15	85
2	G2-RuPhos precatalyst	rt	15	85
3	G2-XantPhos precatalyst	rt	15	85
4	G2-SPhos precatalyst	rt	15	<10
5	G2-^{t}BuXantPhos precatalyst	rt	15	<10
6	G2-P(*o*-Tol)$_3$ precatalyst	rt	15	<10
7	G2-^{t}Bu$_3$P precatalyst	rt	15	<10
8	Pd(dppf)Cl$_2$	rt	15	<10
9	Pd(PPh$_3$)$_4$	rt	15	60
10	Pd(PPh$_3$)$_2$Cl$_2$	rt	15	<10
11	G2-XPhos precatalyst	40	1	>95
12	Pd(OAc)$_2$ + XPhos	rt	15	<10

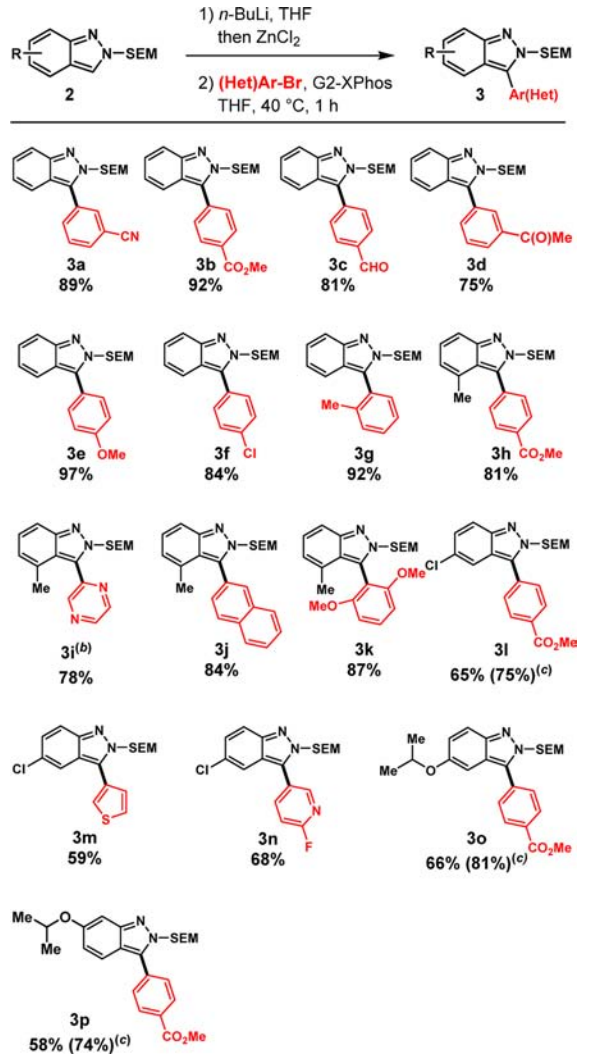


[a]Conversion based on HPLC area percent, uncorrected. Reaction conditions: *n*-BuLi (1.3 equiv, 2.5 M solution in hexane), THF, −70 °C, 45 min, $ZnCl_2$ (1.3 equiv, 1.0 M solution in THF), warm to 0 °C, 30 min, 3-bromobenzonitrile (1.0 equiv), Pd-catalyst (5 mol %), THF, rt, 15 h.

precatalysts. After carrying out the reactions at room temperature for 15 h, it was found that 5 mol % of G2-XPhos, RuPhos, and XantPhos precatalysts provided high conversions to product (85% by HPLC), while other G2-precatalysts (e.g., SPhos, ^{t}BuXantPhos, P(*o*-Tol)$_3$, ^{t}Bu$_3$P) resulted in low conversions (~10%). Interestingly, reactions catalyzed by Pd(PPh$_3$)$_4$ proceeded in 60% conversion after 15 h.[11] Other palladium sources such as Pd(PPh$_3$)$_2$Cl$_2$ and Pd(dppf)Cl$_2$ proved ineffective at catalyzing the cross-coupling reaction at room temperature (<10% conversion by HPLC). Additionally, the coupling reaction performed poorly in the presence of Pd(OAc)$_2$ (5 mol %) and XPhos (10 mol %) (entry 12). These observations suggested a poor reducing ability of the intermediate Zn-species to convert Pd(II) to Pd(0) under the reaction conditions. Given its ease of handling and superior catalytic activity, we selected the G2-XPhos precatalyst for further optimization. Higher temperature (40 °C) significantly improved the reaction kinetics, leading to the complete consumption of 3-bromobenzonitrile within 1 h. Employment of 5 mol % catalyst loading proved ideal for our application, whereas the use of lower catalyst loadings required extended reaction times to achieve full conversion.

Both electron-poor and electron-rich aromatic bromides were compatible coupling partners in this chemistry (Scheme 2). The

Scheme 2. Substrate Scope for C(3)-Arylation[a]



[a]Reaction conditions: *n*-BuLi (1.3 equiv, 2.5 M solution in hexane), THF, −70 °C, 45 min, $ZnCl_2$ (1.3 equiv, 1.0 M solution in THF), warm to 0 °C, 30 min, (Het)ArBr (1.0 equiv), G2-XPhos (5 mol %), THF, 40 °C, 1 h. [b]2-Chloropyrazine was used as coupling partner. [c]Yields in the parentheses are for reactions conducted at room temperature.

cross-coupling reaction was successfully extended to nucleophile- and base-sensitive aryl bromides, such as 4-bromobenzaldehyde and 3-bromoacetophenone, to produce **3c** and **3d** in high yields. Reactions with 4-bromochlorobenzene occurred exclusively at the bromo substituent, enabling the synthesis of compound **3f**, which is suitable for additional functionalization at the chloride. The presence of an *ortho* substituent on the aryl bromide substrate

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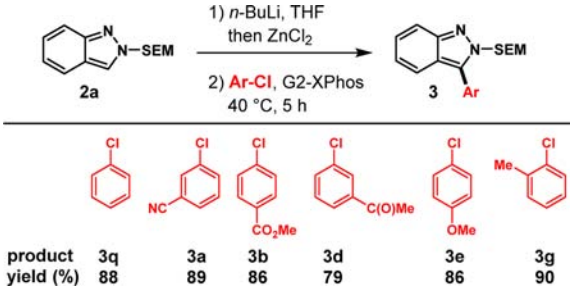
had no detrimental effect on the reaction, as illustrated by the high isolated yield of compound **3g** (92%).

We next turned our attention to the coupling reaction with substituted indazole derivatives. Reactions with sterically hindered 4-methylindazole provided compounds **3j** and **3k** in 84% and 87% isolated yields, a testament to the robustness of this newly developed method. 5-Chloroindazole derivatives (**3l**, **3m**, and **3n**) were produced in moderate to high yields (59−68%) when coupled at 40 °C. Products derived from electron-rich indazoles, (**3o** and **3p**) were also prepared, albeit in modest yields at 40 °C. Gratifyingly, the yields were improved significantly (81% and 74%, respectively) by carrying out the reactions at room temperature, demonstrating the sensitive nature of zinc species generated from electron-rich indazoles at higher temperatures.

In order to achieve a broader substrate scope for this transformation, we next explored the coupling reaction with aromatic chlorides (Scheme 3). To this end, we tested the

Scheme 3. Substrate Scope for C(3)-Arylation with Aryl Chlorides[a]



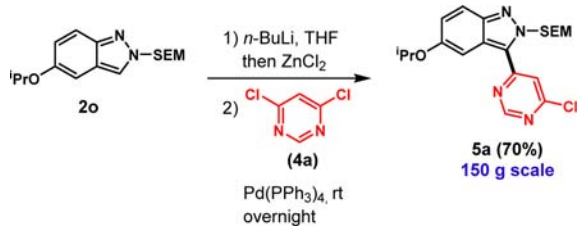
[a]Reaction conditions: *n*-BuLi (1.3 equiv, 2.5 M solution in hexane), THF, −70 °C, 45 min, $ZnCl_2$ (1.3 equiv, 1.0 M solution in THF), warm to 0 °C, 30 min, Ar−Cl (1.0 equiv), G2-XPhos (5 mol %), THF, 40 °C, 5 h.

reaction between chlorobenzene with the zinc species derived from indazole **2a** in the presence of G2-XPhos precatalyst at room temperature. This combination resulted in low conversion (<5%) after 24 h; however, the reaction proceeded to completion when carried out at elevated temperature (40 °C) for 5 h, furnishing the desired adduct **3q** in 88% isolated yield. These optimized conditions were then tested on other electron-deficient, base-sensitive, electron-rich and sterically demanding aryl chlorides to furnish the desired adducts in high isolated yields (Scheme 3).

As part of a medicinal chemistry program, we needed to synthesize multigram quantities of compound **5a**, where the chloride would be utilized as a handle for late-stage derivatization for rapid SAR development (Scheme 4). While Suzuki coupling reactions gave the product in low yield (20%), our newly optimized Negishi conditions described here resulted in an unselective reaction resulting in the formation of a number of undesired byproducts. The effects of temperature and concentration were briefly probed without much success, leading us to conclude that the high reactivity of the G2-XPhos precatalyst is detrimental to cross-coupling reactions with activated bis-halo aryl derivatives such as compound **4a**.

We hypothesized that a less active Pd-catalyst could provide the desired selectivity, and we turned our attention to $Pd(PPh_3)_4$, which had exhibited only modest reactivity in our original catalyst screening. Indeed, when the cross-coupling reaction was carried out with 1.1 equiv of 4,6-dichloropyrimidine (**4a**) in the presence of 5 mol % $Pd(PPh_3)_4$ at room temperature, the desired product

Scheme 4. Scale-up of a Key Intermediate[a]

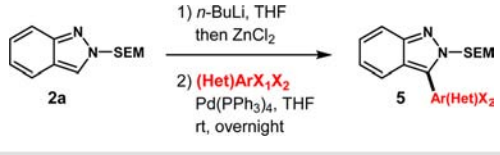


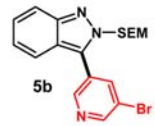
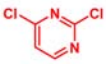
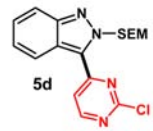
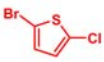
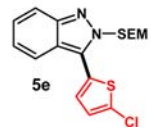
[a]Reaction conditions: *n*-BuLi (1.3 equiv, 2.5 M solution in hexane), THF, −70 °C, 45 min, $ZnCl_2$ (1.3 equiv, 1.0 M solution in THF), warm to 0 °C, 30 min, **4a** (1.0 equiv), $Pd(PPh_3)_4$ (5 mol %), rt, overnight.

5a was isolated in 70% yield (Scheme 4). Employing this protocol, we were able to prepare 150 g of **5a** in 70% yield, demonstrating the robustness and scalability of this strategy.

Extension of this observation to other activated dihalo-aryl derivatives is further illustrated in Table 2. The examples follow

Table 2. C(3)-Arylation of Indazoles with Dihalides[a]



entry	(Het)ArX_1X_2 (**4**)	product	yield (%)
1	 **4b**	 **5b**	78
2	 **4c**	 **5c**	93
3	 **4d**	 **5d**	75
4	 **4e**	 **5e**	88

[a]Reaction conditions: *n*-BuLi (1.3 equiv, 2.5 M solution in hexane), THF, −70 °C, 45 min, $ZnCl_2$ (1.3 equiv, 1.0 M solution in THF), warm to 0 °C, 30 min, **4** (1.0 equiv), $Pd(PPh_3)_4$ (5 mol %), rt, overnight.

the expected reactivity trend whereby the coupling occurs preferentially at the more reactive halogen, and the less reactive carbon−halogen bond remains intact. Reactions with aryl iodides **4b** and **4c** afforded **5b** and **5c** in 78% and 93% yields when using $Pd(PPh_3)_4$.[12] Given the collective results presented here, it is clear that this new protocol has broad applications for accessing chemical entities that are difficult to access by previous methods.

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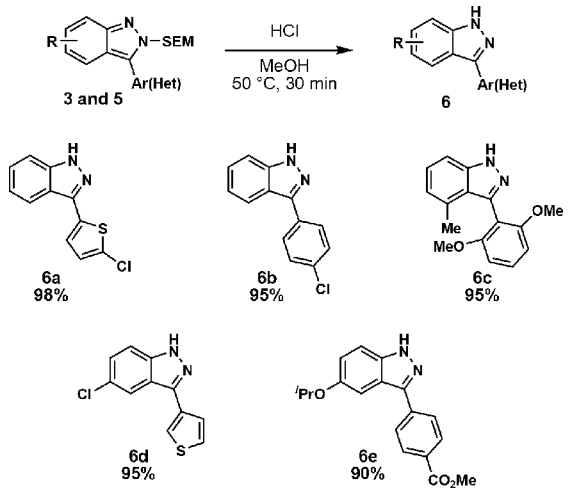
The SEM group in the resulting 3-arylindazoles can be easily removed in high yields by treatment with HCl in methanol at 50 °C for 30 min (Scheme 5) to reveal the unprotected indazole

Scheme 5. Removal of SEM Group[a]



[a]Reaction conditions: HCl (4.0 M solution in 1,4-dioxane, 1 equiv), MeOH, 50 °C, 30 min.

pharmacophores. Combined with its facile regioselective installation and the exquisitely selective C(3)-deprotonation it enables, this simple deprotection renders this strategy general for preparing this useful class of compounds.

In summary, a challenging problem associated with the direct introduction of (hetero)aryl moieties at the C(3) position of indazoles has been solved through the development of a mild, practical, robust, and scalable Negishi coupling protocol. This method exhibits high functional group tolerance and is operationally simple. While the use of the highly active G2-XPhos precatalyst provides convenient access to 3-arylindazoles within 1 h, the judicious choice of the less active $Pd(PPh_3)_4$ at room temperature provides access to halogenated indazole adducts in which the remaining halogen can be subjected to late-stage derivatization. Additionally, the successful coupling of aryl chlorides under these conditions provides a unique choice of coupling partners not previously demonstrated. The robustness and scalability of this methodology was demonstrated by the synthesis of 150 g of indazole **5a** in a single reaction. We anticipate rapid adoption of this methodology toward the preparation of 3-arylindazoles possessing a range of functionality and substitution patterns.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.orglett.6b01456.

Experimental data and characterization of all new compounds (PDF)

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Author Contributions

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Notes

The authors declare no competing financial interest.

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(11) This is in stark contrast to Knochels's finding where $Pd(PPh_3)_4$ failed to participate in the coupling reaction.

(12) Structure of **5d** was confirmed by 2D-NMR studies.

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