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Regioselective zincation of indazoles using TMP_2Zn and *Negishi* cross-coupling with aryl and heteroaryl iodides†

Andreas Unsinn and Paul Knochel*

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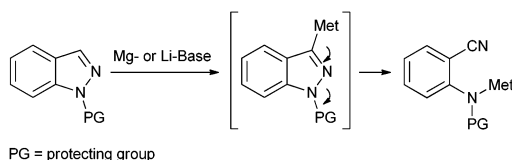
The metalation of various SEM-protected functionalized indazoles with TMP_2Zn provides 3-zincated indazoles which undergo palladium-catalyzed *Negishi* cross-couplings in good yields.

Indazoles are an important class of *N*-heterocycles which have found numerous pharmaceutical applications.¹ The direct lithiation or magnesiation of indazoles at position 3 is difficult due to a facile fragmentation of these heterocycles leading to aminonitriles (Scheme 1).²

Alternatively, 3-iodoindazoles undergo a selective I/Cu-exchange with $(\text{PhMe}_2\text{CCH}_2)_2\text{CuLi}$ ³ leading to stable 3-cuprated indazoles which can be readily acylated.⁴ The lithiation,⁵ magnesiation,⁶ and zincation⁷ of isoindazoles (2*H*-indazoles) have been reported. Also the direct arylation⁸ of 2*H*-indazoles as well as the use of 3-iodoindazoles in *Suzuki*-⁹ or *Stille*¹⁰ cross-couplings is known.

However, the direct metalation and transition metal catalyzed arylation of 1*H*-indazoles has not been reported. This reaction is especially interesting due to the potential pharmaceutical activity of 3-arylated indazoles.^{1,11} Recently, we have described the synthesis of a kinetically highly active zinc base $\text{TMP}_2\text{Zn}\cdot 2\text{MgCl}_2\cdot 2\text{LiCl}$ (**1**; abbreviated TMP_2Zn ; $\text{TMP} = 2,2,6,6$ -tetramethylpiperidyl) which combines a high metalation activity with an excellent functional group tolerance.^{12,13}

Herein, we wish to report that TMP_2Zn (**1**) allows for the first time a direct metalation of a range of *N*-protected indazoles of type **2** under mild conditions (without concomitant ring opening) leading to *bis*-indazolylzincs of type **3**. Their reaction with electrophiles (E) has been successfully accomplished, leading to products of type **4** (Scheme 2).

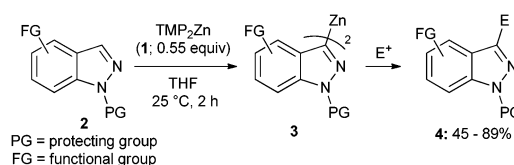


Scheme 1

Ludwig Maximilians-Universität München, Department Chemie, Butenandtsstraße 5-13, Haus F, 81377 München, Germany.
E-mail: paul.knochel@cup.uni-muenchen.de;

Fax: +49 089 2180 77680; Tel: +49 089 2180 77681

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Scheme 2

Zinc reagents (**3**) react well with various electrophiles like allylic bromides and acid chlorides, but we have also found reaction conditions to perform direct arylations *via Negishi* cross-couplings¹⁴ with various aryl iodides.

Thus, preliminary experiments performed in order to find the optimal protecting group (PG) of indazole (**2**) showed that both a *tert*-butoxycarbonyl- (Boc; **2a**) and a methoxymethyl protected indazole (MOM; **2b**) readily react with TMP_2Zn (**1**; THF, 25 °C, 2 h) to produce the expected *bis*(3-indazolyl)zinc reagents (**3a–b**). Copper-catalyzed trapping with various electrophiles such as ethyl 2-(bromomethyl)acrylate¹⁵ or acid chlorides provides the desired 3-functionalized indazoles (**4a–c**) in 72–89% yield (entries 1–3 of Table 1). A 3-arylation could be realized for the first time with the MOM-protected *bis*-indazolylzinc reagent (**3b**). Its reaction with 4-iodobenzonitrile (1.2 equiv) in the presence of 2% $\text{Pd}(\text{dba})_2$ ($\text{dba} = \text{dibenzylideneacetone}$) and 4% tfp ($\text{tfp} = \text{tri}(2\text{-furyl})\text{phosphine}$)¹⁶ at 50 °C for 8 h leads to the desired 3-arylated indazole (**4d**) in 76% yield. Attempts to couple bromoarenes with other catalytic systems¹⁷ were not successful. Furthermore these *Negishi* cross-couplings had to be performed at 50 °C. This elevated temperature proved to be a problem for the cross-coupling of further functionalized indazoles leading to partial ring opening byproducts. By switching to SEM-protected indazoles (SEM = 2-(trimethylsilyl)ethoxymethyl)¹⁸ the corresponding zinc reagents undergo Pd-catalyzed cross-couplings in high yields. Thus, the arylation of SEM-protected indazole (**2c**) with 4-iodobenzonitrile gives the cross-coupling product (**4e**) in 76% yield (entry 5). Less reactive aryl iodides, such as 4-iodoanisole (50 °C, 12 h), react now very well leading to the 3-arylated indazole (**4f**) in 81% yield (entry 6). A heterocyclic iodide, such as 2-iodoisoquinoline, undergoes the cross-coupling smoothly, affording the desired product (**4g**) in 62% yield (entry 7). This cross-coupling reaction could be extended to functionalized indazoles bearing a chlorine substituent (**2d**, entries 8 and 9), a bromine substituent (**2e**, entries 10 and 11), a methoxy group (**2f**, entry 12), as well as sensitive functions

Table 1 Direct zincations of protected indazoles and subsequent reactions with various electrophiles

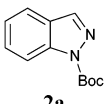
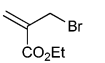
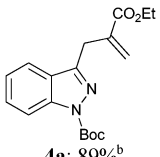
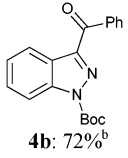
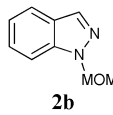

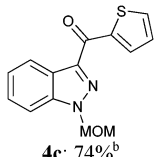
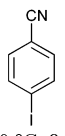
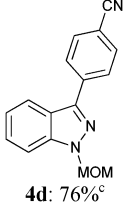
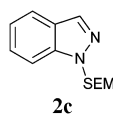
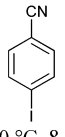
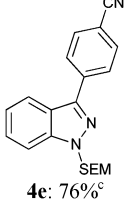
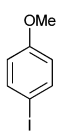
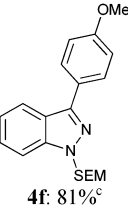
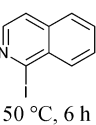
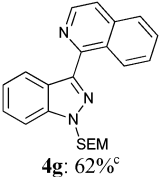

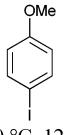
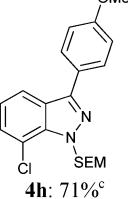
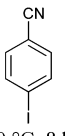
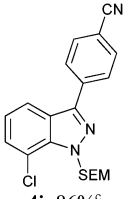
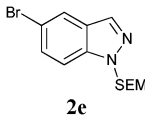
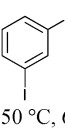
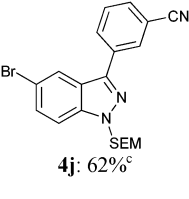
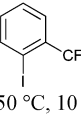
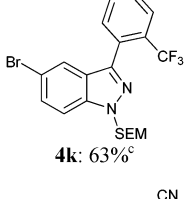
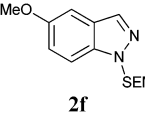
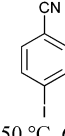
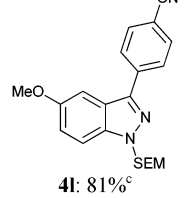
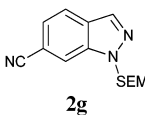
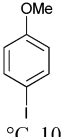
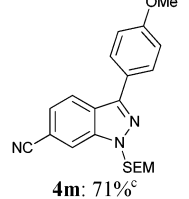
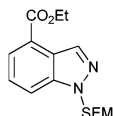
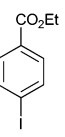
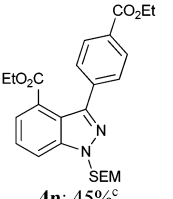
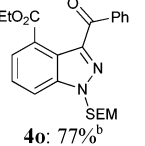
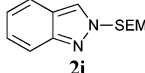

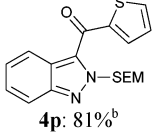
Entry	Indazole	Electrophile/conditions	Product/Yield ^a (%)
1		 -40 to 25 °C, 2 h	 4a : 89% ^b
2	2a	PhCOCl -40 to 25 °C, 2 h	 4b : 72% ^b
3		 -40 to 25 °C, 2 h	 4c : 74% ^b
4	2b	 50 °C, 8 h	 4d : 76% ^c
5		 50 °C, 8 h	 4e : 76% ^c
6	2c	 50 °C, 12 h	 4f : 81% ^c
7	2c	 50 °C, 6 h	 4g : 62% ^c
8		 50 °C, 12 h	 4h : 71% ^c

Table 1 (continued)

Entry	Indazole	Electrophile/conditions	Product/Yield ^a (%)
9	2d	 50 °C, 8 h	 4i : 86% ^c
10		 50 °C, 6 h	 4j : 62% ^c
11	2e	 50 °C, 10 h	 4k : 63% ^c
12		 50 °C, 6 h	 4l : 81% ^c
13		 50 °C, 10 h	 4m : 71% ^c
14		 50 °C, 24 h	 4n : 45% ^c
15	2h	PhCOCl -40 to 25 °C, 2 h	 4o : 77% ^b
16		 -40 to 25 °C, 2 h	 4p : 81% ^b

^a Yield of isolated analytically pure product. ^b A transmetalation with CuCN·2LiCl (1.1 equiv) was performed. ^c Obtained by a palladium-catalyzed cross-coupling (2% Pd(dba)₂; 4% tfp; 50 °C, 6–24 h).

like a nitrile (**2g**, entry 13) and an ester group (**2h**, entry 14). The desired 3-arylated indazoles (**4h–n**) are produced in 45–86% yield. We verified also that these SEM-protected indazoles undergo acylation reactions. Thus, the ester substituted indazole (**2h**) after zincation with TMP_2Zn (**1**) and transmetalation with $\text{CuCN}\cdot 2\text{LiCl}$ ¹⁹ reacts with benzoyl chloride leading to the 3-benzoylated indazole (**4o**) in 77% yield (entry 15).

We have also found that the SEM protected 2*H*-indazole (**2i**) was metalated with TMP_2Zn (**1**) under similar conditions (25 °C, 2 h) leading after copper-catalyzed acylation with thiophene-2-carbonyl chloride to the desired ketoindazole (**4p**) in 81% yield (entry 16).²⁰

In summary we have reported a simple, mild and efficient method for the metalation of 1*H*-indazoles at position 3 with TMP_2Zn (**1**). The resulting indazolylzincs could be arylated *via* Negishi cross-couplings with various aryl iodides. Applications towards the synthesis of biologically active molecules are currently being investigated in our laboratories.

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- This shows that it is in principle unnecessary to separate the isomeric 1*H*- and 2*H*-indazoles that are usually obtained as mixtures in several preparation methods.