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COMMUNICATION

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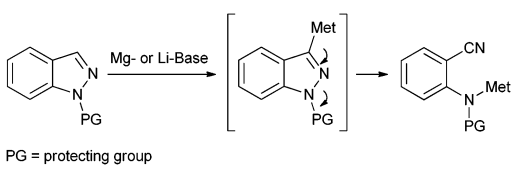
The metalation of various SEM-protected functionalized indazoles with TMP_2Zn provides 3-zincated indazoles which undergo palladium-catalyzed *Negishi* cross-couplings in good yields.

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 $(PhMe_2CCH_2)_2CuLi$[3] leading to stable 3-cuprated indazoles which can be readily acylated.[4] The lithiation,[5] magnesiation,[6] and zincation[7] of isoindazoles (2*H*-indazoles) have been reported. Also the direct arylation[8] 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 $TMP_2Zn{\cdot}2MgCl_2{\cdot}2LiCl$ (**1**; abbreviated TMP_2Zn; TMP = 2,2,6,6-tetramethylpiperidyl) which combines a high metalation activity with an excellent functional group tolerance.[12,13]

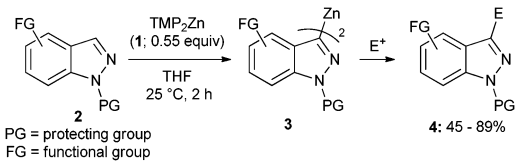
Herein, we wish to report that TMP_2Zn (**1**) allows for the first time a direct metalation of a range of *N*-protected indazoles of type **2** under mild conditions (without concomitant ring opening) leading to *bis*-indazolylzincs of type **3**. Their reaction with electrophiles (E) has been successfully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



Scheme 1

Ludwig Maximilians-Universität München, Department Chemie, Butenandtstraße 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

† Electronic supplementary information (ESI) available: Experimental procedures and NMR spectra of all products. See DOI: 10.1039/c2cc17804d

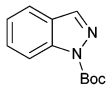
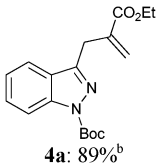
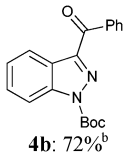
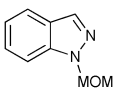
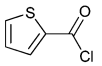
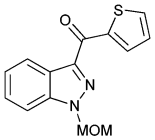
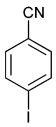
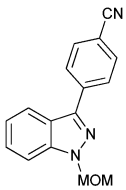
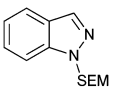
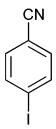
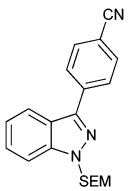
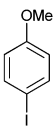
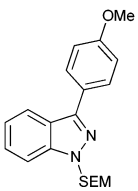
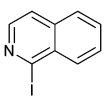
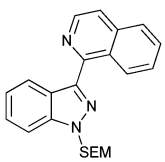
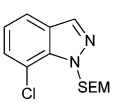
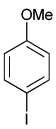
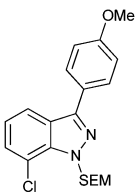
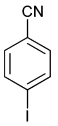
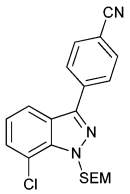
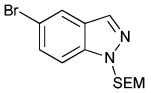
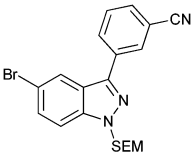
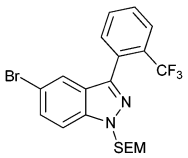
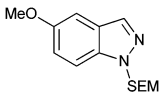
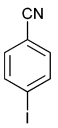
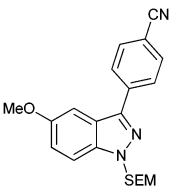
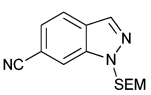
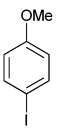
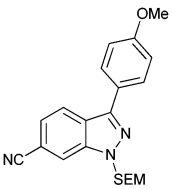
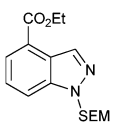
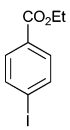
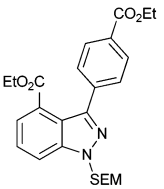
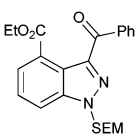
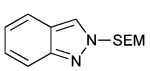
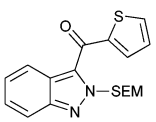


Scheme 2

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-couplings[14] 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)acrylate[15] 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% $Pd(dba)_2$ (dba = dibenzylideneacetone) and 4% tfp (tfp = tri-(2-furyl)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 systems[17] 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	 **2a**	 -40 to 25 °C, 2 h	 **4a**: 89%[b]
2	**2a**	PhCOCl -40 to 25 °C, 2 h	 **4b**: 72%[b]
3	 **2b**	 -40 to 25 °C, 2 h	 **4c**: 74%[b]
4	**2b**	 50 °C, 8 h	 **4d**: 76%[c]
5	 **2c**	 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	 **2d**	 50 °C, 12 h	 **4h**: 71%[c]
9	**2d**	 50 °C, 8 h	 **4i**: 86%[c]
10	 **2e**	 50 °C, 6 h	 **4j**: 62%[c]
11	**2e**	 50 °C, 10 h	 **4k**: 63%[c]
12	 **2f**	 50 °C, 6 h	 **4l**: 81%[c]
13	 **2g**	 50 °C, 10 h	 **4m**: 71%[c]
14	 **2h**	 50 °C, 24 h	 **4n**: 45%[c]
15	**2h**	PhCOCl -40 to 25 °C, 2 h	 **4o**: 77%[b]
16	 **2i**	 -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 CuCN·2LiCl[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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