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Iodoindazoles with Selective Magnesiation at Position 3: A Route to Highly Functionalized Indazoles

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Abstract: A unique route to highly functionalized indazoles is described. A regioselective magnesiation at position 3 of 4-, 5-, 6- and 7-iodo-2-THP-indazoles (THP = tetrahydropyranyl) has been developed using TMPMgCl·LiCl (TMP = 2,2,6,6-tetramethylpiperidyl). The obtained magnesiate can be trapped by different electrophiles to introduce a wide range of functional groups including halogens, thioalkyls, alcohols, aldehydes, ketones, amides, or esters at position 3. Once this position is functionalized, the iodine atoms can be further reacted through metal–halogen exchange or cross-coupling strategies. Finally, N-substitution reactions allow the synthesis of a variety of highly functionalized indazoles giving access to these valuable scaffolds through a simple and unique route.

Indazole or 2-azaindole is an heteroaromatic nucleus that can be found in only few natural products isolated from plants of the genus *Nigella*,[1] for example, nigellicine,[2] nigellidine[3] and nigeglanine.[4] Indazole is found in many synthetic derivatives, particularly in the field of medicinal chemistry, in which it is generally used as an isostere of indole.[5] Therefore, this scaffold was successfully used in drug development programs to afford anti-HIV[6] or anti-tumor agents,[7,8,9] cannabinoid,[10] 5-HT_2,[11] 5-HT_3[12] or 5-HT_4[13,14] receptors ligands, kinase[15–18] or NO-synthase inhibitors.[19,20] Several indazole derivatives are now available as marketed drugs: granisetron, bendazac, benzydamine, or axitinib.

Thus, many efforts have been made to develop valuable synthetic tools to obtain diversely substituted indazoles. Among these, intramolecular cyclization from *ortho*-substituted aniline derivatives such as hydrazines, hydrazones, azo-, and diazo compounds is a very popular method but is generally hampered by harsh conditions and limited availability of starting materials.[21] Recently, the use of transition metal-catalyzed C–H activation reactions has extended the scope of these ring-closure reactions to non-*ortho*-substituted aromatic compounds bearing hydrazo,[22–25] diazo,[26,27] and imidate[28] functional groups.

The direct functionalization of the indazole ring using cross-coupling reactions or metal–halogen exchange from variously substituted N-protected haloindazoles is an attractive alternative to cyclization reactions to obtain functionalized indazoles.[29–35] However, in the case of direct metalation at position 3 of 1-substituted indazoles, ring-opening issues remain a strong limitation.[36,37] Recently, two methods in the literature describing the selective functionalization of substituted indazoles at position 3 using direct metalation reactions have attracted our attention.[38,39] First, Yu reported the selective 3-arylation of 1-methyl or 1-THP indazoles by palladium-catalyzed C–H activation (Figure 1 A).[38] Although this strategy allows the use of substituted indazoles in position 4, 5, 6, and 7, it remains restricted to functionalization with aromatic groups. Second, using TMP_2Zn as a base, Knochel was able to selectively deprotonate diversely substituted N-protected indazoles at position 3. Therefore, the obtained organozinc intermediates were further transmetalated with palladium and used in a Negishi cross-coupling reaction or with copper and reacted with

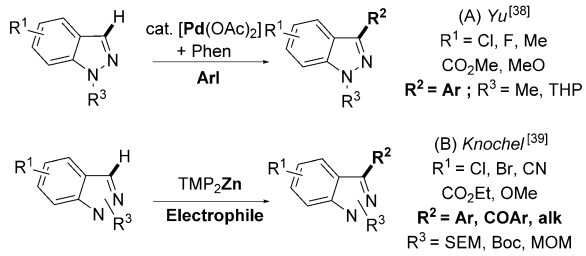

Figure 1. Previous work, synthesis of polyfunctional indazoles through palladation or zincation at position 3.

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acyl chlorides or allylbromides to give 3-arylated, -acylated or -alkylated indazoles, respectively (Figure 1 B).[39]

Taking into account these latter results, we were interested in extending the scope of these metalation strategies to further functionalize position 3 and promote higher molecular diversity in the other positions (Figure 2). For this purpose, in

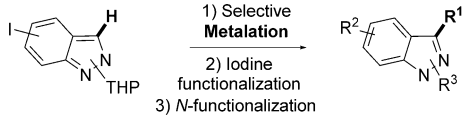


Figure 2. This work: synthesis of polyfunctional indazoles through metalation of iodoindazoles at position 3.

this work, we decided to investigate the selective metalation of iodo-*N*-THP-indazoles followed by electrophilic trapping. Therefore, using a three-step synthesis including metalation at position 3, iodine functionalization and *N*-functionalization, we wish to obtain polyfunctionalized indazoles. This new route will allow late-stage diversification of the indazole ring, thus providing highly functionalized and valuable scaffolds through a simple and unique route.

Results and Discussion

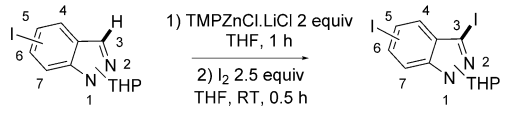
Starting from Knochel's results, we decided to first investigate selective zincation at position 3 using THP-protected indazoles. Our first experiments performed with TMPZnCl·LiCl and I_2 showed that only 2-THP protection[40] and microwave heating produced the expected 3-iodoindazoles **2n** and **2a** (Table 1).

However, attempts to obtain 3-functionalized indazoles with these zincation conditions with carbon dioxide, benzyl isocyanate or 2-chlorobenzoyl chloride were not successful due to the weak nucleophilicity of the organozinc intermediate (Table 2).

These results led us to choose a new approach based on organomagnesium species. Therefore, investigation using 7-iodoindazoles **1a** and **1b**, respectively, protected with THP at position 1 and 2 was initiated (Table 3). Two equivalents of TMPMgCl·LiCl were used for the deprotonation at 0 °C, and trapping of the Grignard reagent with I_2 was observed solely with **1b** bearing THP at position 2 to give 3,7-diiodo-2-THP-indazole **2a** isolated in 67% yield. Optimization of reaction conditions was then pursued with **1b**, Me_2S_2 as the electrophile and 1.5 equivalents of TMPMgCl·LiCl. The room-temperature deprotonation was found detrimental with only 42% yield, whereas performing the reaction at −10 °C led to 7-iodo-3-(methylsulfanyl)-2-THP-indazole **2b** in 87% yield. Using these best conditions with I_2 as the electrophile, the desired product **2a** was thus isolated in 85% yield.

We then explored the reactivity of the three other iodoindazole isomers **1c–h** (Table 4). The same conditions were efficient for the 6-iodo and 5-iodo-2-THP-indazole **1d** and **1f** as the 3-iodoindazoles **2h** and **2n** were isolated in 83 and 87% yield, respectively. Finally, using 4-iodo-2-THP-indazole **1h** as the starting material, the combined steric hindrance of both the THP in position 2 and iodine in position 4, led to a slight decrease of reactivity, and the magnesiation conditions had to be modified to improve the yield of the isolated product. Therefore, using a shorter metalation time (0.5 h) and a higher temperature (−10 °C to RT), electrophilic trapping with I_2 provided the expected 3-iodo-2-THP-indazole **2r** in 69% yield.

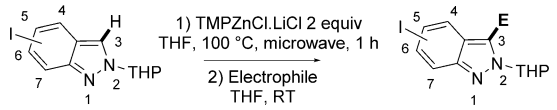
Table 1. 5- and 7-Iodoindazoles functionalization at position 3 using TMPZnCl·LiCl and I_2.



Starting material	Iodine position	THP position	*T* [°C]	Product [%][a]
1e	5	1	RT	–
1f	5	2	RT	–
1e	5	1	100[b]	–[c]
1f	5	2	100[b]	**2n** (62)
1a	7	1	100[b]	–[c]
1b	7	2	100[b]	**2a** (85)

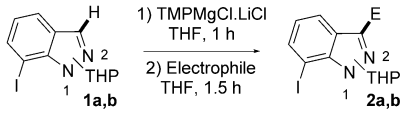
[a] Yield of the isolated products. [b] Using microwave heating. [c] Trace amounts of the product were detected by LCMS.

Table 2. 5- and 7-Iodoindazoles functionalization at position 3 using TMPZnCl·LiCl and various electrophiles.



Starting material	Iodine position	Electrophile and condition	Product [%]
1f	5	CO_2 gas, excess, 2 h	–
1f	5	BnNCO 2.1 equiv, 2 h	–
1b	7	BnNCO 2.1 equiv, 2 h	–
1b	7	2-ClPhCOCl 2 equiv, 3 h	–

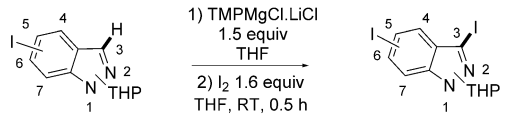
Table 3. 7-Iodoindazole functionalization at position 3 using TMPMgCl·LiCl.



Starting material	THP position	Base [equiv]	*T* [°C]	Electrophile [equiv]	Product [%][a]
1a	1	2	0	I_2 (2.1)	–
1b	2	2	0	I_2 (2.1)	**2a** (67)
1b	2	1.5	0	Me_2S_2 (1.6)	**2b** (63)
1b	2	1.5	RT	Me_2S_2 (1.6)	**2b** (42)
1b	2	1.5	−10	Me_2S_2 (1.6)	**2b** (87)
1b	2	1.5	−10	I_2 (1.6)	**2a** (85)

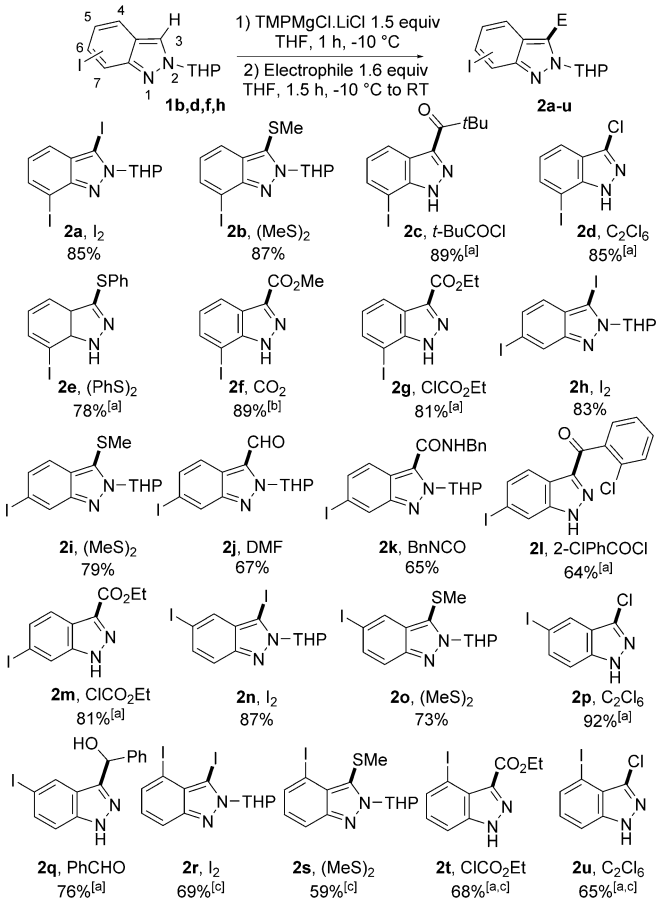
[a] Yield of the isolated product.

Table 4. 4-, 5- and 6-Iodoindazoles functionalization at position 3 using TMPMgCl·LiCl and I_2.



Starting material	Iodine position	THP position	Magnesiation conditions	Product [%][a]
1c	6	1	−10 °C, 1 h	–
1d	6	2	−10 °C, 1 h	**2h** (83)
1e	5	1	−10 °C, 1 h	–
1f	5	2	−10 °C, 1 h	**2n** (87)
1g	4	1	−10 °C, 1 h	–
1h	4	2	−10 °C, 1 h	**2r** (44)
1h	4	2	−10 °C to RT, 0.5 h	**2r** (69)

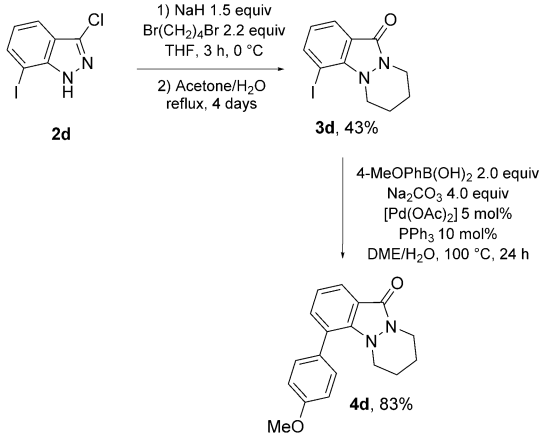
[a] Yield of the isolated product.



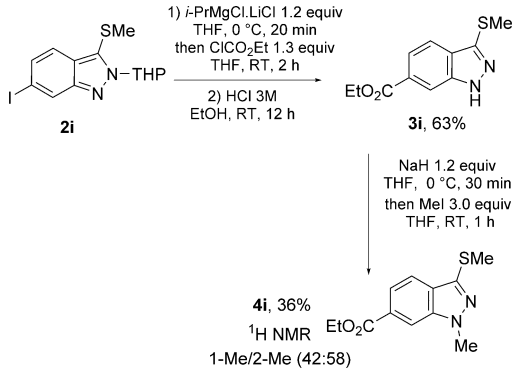
Scheme 1. Iodoindazoles functionalization at position 3. Yields are of the isolated products. [a] Followed by deprotection, the reaction was quenched with 1 M HCl and stirred for 2 h. [b] Followed by esterification, the reaction was solubilized in MeOH and heated at reflux with H_2SO_4 (cat.) for 16 h. [c] Magnesiation conditions: 0.5 h, −10 °C to RT.

With these conditions in hand, the scope of the reaction was further evaluated (Scheme 1). Using *t*BuCOCl as the electrophile followed by the acidic deprotection of the THP group, ketone **2c** was obtained in an overall 89% yield. Following the same sequence, 3-chloro-7-iodoindazole **2d** was obtained in 85% yield using C_2Cl_6 as the electrophile. $(PhS)_2$ reacted smoothly to afford the 3-phenylsulfanyl derivative **2e** in 78% yield, whereas esters in position 3 were obtained according to two routes: either by trapping with CO_2 followed by esterification or directly by trapping with ethyl chloroformate leading to the methyl and ethyl esters **2f** and **2g**, respectively. We then explored the reactivity of the three other iodoindazole isomers. The same conditions were found to be efficient for the 6-iodo and 5-iodo-2-THP-indazole **1d** and **1f.** Therefore using Me_2S_2, 2-chlorobenzoyl chloride, ethyl chloroformate or C_2Cl_6 under the same conditions, selectively functionalized indazoles at position 3 **2i,l,m,o,p** were obtained in good yields. Interestingly, the use of DMF as the electrophile promoted the formation of aldehyde **2j**, whereas the use of benzyl isocyanate or benzaldehyde gave carboxamide **2k** and alcohol **2q**, respectively. Finally, using 4-iodo-2-THP-indazole **1h** as the starting material, and the shorter metalation time (0.5 h) at higher temperature (−10 °C to RT) previously discovered, electrophilic trapping with Me_2S_2 provided the expected 3-thiomethylindazole **2s** in 59% yield. Accordingly, ethyl 4-iodoindazole-3-carboxylate **2t** and 3-chloro-4-iodoindazole **2u** were obtained after reaction with ethyl chloroformate and C_2Cl_6 followed by acidic work-up in 68 and 65% yields, respectively. Therefore, the combination of magnesiation and trapping with diverse electrophiles allow a large diversity of functional groups to be introduced in position 3 including halogens, thioalkyls, alcohols, aldehydes, ketones, esters, or amides. Moreover, the deprotection of the THP group can be easily done following the trapping of the electrophile without purifying the intermediate.

We then turned our attention to the further functionalization of 3-substituted iodoindazoles (Scheme 2). Therefore, double alkylation of 3-chloro-7-iodoindazole **2d** with 1,4-dibromobutane followed by hydrolysis provided the tricyclic pyridazino[1,2-*a*]indazolone **3d** in a moderate yield. This heterocycle was further functionalized through a Suzuki cross-coupling affording the 7-arylated derivative **4d** in 83% yield. This provides



Scheme 2. 3-Chloro-7-iodoindazole **2d** polyfunctionalization. Yields are of the isolated products.

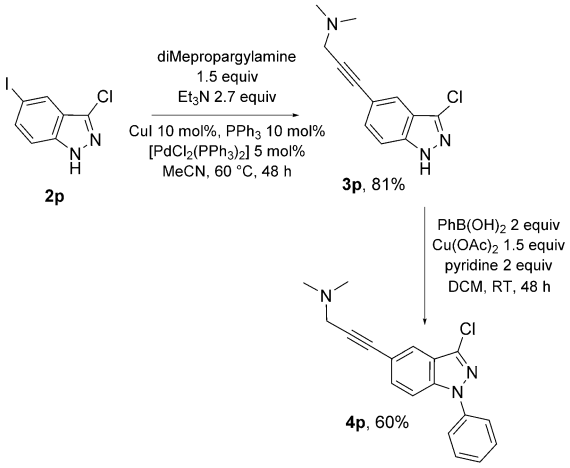


Scheme 3. 6-Iodo-3-(methylsulfanyl)-2-THP-indazole **2i** polyfunctionalization. Yields are of the isolated products.

a straightforward access to the natural product backbone isolated from *Nigella sativa*.[1]

Magnesium-iodine exchange was then evaluated (Scheme 3) starting from 6-iodo-3-(methylsulfanyl)-2-THP-indazole **2i** with *i*PrMgCl·LiCl, which gave ethyl 3-(methylsulfanyl)-1H-indazole-6-carboxylate **3i** in 63% yield after trapping with ethyl chloroformate followed by THP deprotection. *N*-Alkylation was then attempted using MeI and NaH as the base to afford a 42:58 mixture of 1-methyl and 2-methylindazole derivatives from which 1-methyl isomer **4i** was isolated in 36% yield.

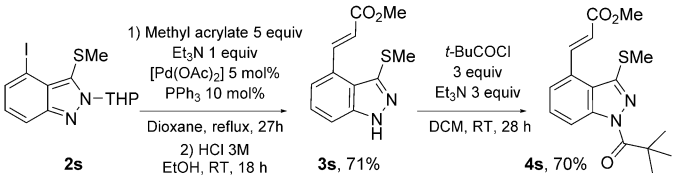
The Sonogashira cross-coupling reaction using 3-chloro-5-iodoindazole **2p** and *N*,*N*-dimethylpropargylamine afforded the alkyne **3p** in 81% yield (Scheme 4). The latter was then further



Scheme 4. 3-Chloro-5-iodoindazole **2p** polyfunctionalization. Yields are of the isolated products.

N-arylated using the Chan–Lam procedure to afford the *N*-phenylindazole **4p** in 60% yield.

Finally, 4-iodo-3-(methylsulfanyl)-2-THP-2H-indazole **2s** was successively alkenylated using a Heck cross-coupling reaction with methyl acrylate, followed by *N*-acylation with pivaloyl chloride, affording the trisubstituted indazole **4s** in 49% overall yield (Scheme 5).



Scheme 5. 3-Chloro-5-iodoindazole **2s** polyfunctionalization. Yields are of the isolated products.

Conclusion

We have established a new method to selectively synthesize magnesiated indazoles at position 3. Application of this methodology to 4-, 5-, 6-, and 7-iodoindazoles followed by electrophilic trapping provided a library of 3-substituted iodoindazoles in good yields. These iodoindazoles can be the source of a high molecular diversity through further iodine and nitrogen functionalization procedures. Therefore, as demonstrated, we were able to synthesize highly functionalized indazoles in only three steps using a unique route.

Experimental Section

Preparation of TMPMgCl·LiCl

A nitrogen-flushed round bottom flask, equipped with a magnetic stirrer was charged with freshly titrated *i*PrMgCl·LiCl[41] (10 mmol, 1 equiv, 1 M in THF). 2,2,6,6-Tetramethylpiperidine (TMPH) (10.5 mmol, 1.05 equiv) was added dropwise at 25 °C. The complete formation of the base was checked by quenching an aliquot with benzaldehyde (until signals of 2-methyl-1-phenylpropan-1-ol disappeared in ^{1}H NMR spectrum, ca. 48 h). The TMPMgCl·LiCl solution was titrated by using benzoic acid (61 mg, 0.5 mmol) in dry THF (1 mL) and 4-(phenylazo)diphenylamine (3 mg) as an indicator (colour changes from orange to purple). A concentration of 1.05 M in THF was obtained.

Typical procedure for magnesiation and electrophilic trapping of 2-THP-protected indazoles 1b,d,f

A nitrogen-flushed 10 mL vial was charged the chosen iodoindazole compound (1 equiv, 0.3 M in THF). The solution was cooled to −10 °C, then TMPMgCl·LiCl (1.5 equiv) was added dropwise. The mixture was stirred for 1 h and the chosen electrophile (1.6 equiv) was slowly added at −10 °C. After stirring for 5 min, the reaction was allowed to warm to 25 °C and stirred for indicated time (Scheme 1).

Typical procedure for magnesiation and electrophilic trapping of 2-THP-protected 4-iodoindazole 1h

A nitrogen-flushed 10 mL vial was charged with 4-iodoindazole **1h** (1 equiv, 0.3 M in THF). The solution was cooled to −10 °C, then TMPMgCl·LiCl (1.5 equiv) was added dropwise. The reaction mixture was allowed to warm to RT and stirred for 0.5 h. The chosen electrophile (1.6 equiv) was slowly added and the resulting mixture was stirred for the indicated time (Scheme 1).

3,7-Diiodo-2-(tetrahydro-2*H*-pyran-2-yl)-2*H*-indazole 2a

Following typical magnesiation procedure, metalation of **1b** (100 mg, 0.3 mmol) was completed within 1 h at −10 °C. A solution of I_2 (116 mg, 0.46 mmol) in dry THF (1 mL) was added and the resulting mixture was stirred for 0.5 h at RT. The reaction mixture was quenched with a saturated aqueous $Na_2S_2O_3$, extracted with EtOAc and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (cyclohexane/EtOAc 12:1) to afford **2a** as a white solid (118 mg, 85%). M.p. = 111–113 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.79 (d, J = 7.0 Hz, 1H), 7.41 (d, J = 8.3 Hz, 1H), 6.85 (dd, J = 8.3, 7.0 Hz, 1H), 5.83 (dd, J = 9.2, 2.9 Hz, 1H), 4.11–4.06 (m, 1H), 3.78–3.74 (m, 1H), 2.78–2.70 (m, 1H), 2.28–2.70 (m, 1H), 2.10–2.07 (m, 1H), 1.85–1.71 (m, 2H), 1.70–1.60 ppm (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 149.7, 137.1, 126.7, 124.3, 121.4, 88.4, 85.0, 77.0, 67.8, 29.4, 24.8, 22.2 ppm; HRMS/ESI calcd for $C_{12}H_{13}I_2N_2O$ $[M+H]^+$ 454.9112; found: 454.9109.

3-(2-Chlorobenzoyl)-6-iodo-1*H*-indazole 2l: Following typical magnesiation procedure, the metalation of **1d** (100 mg, 0.3 mmol) was completed within 1 h at −10 °C. 2-Chlorobenzoyl chloride (0.06 mL, 0.46 mmol) was added dropwise and the resulting mixture was stirred for 1.5 h at RT. Then 1 M HCl (1 mL) was added and the reaction mixture was stirred overnight. THF was removed in vacuo and the residue was partitioned between water and EtOAc. The organic layer was separated, washed with a saturated $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (cyclohexane/EtOAc 8:1) to afford **2l** as a white solid (73 mg, 64%). M.p. = 261–263 °C; ^{1}H NMR (400 MHz, DMSO): δ = 14.6 (m, 1H) 8.14 (s, 1H), 8.03 (d, J = 8.4 Hz, 1H), 7.68 (d, J = 8.4 Hz, 1H), 7.61 (d, J = 7.4 Hz, 1H), 7.60–7.53 (m, 2H), 7.51–7.45 ppm (m, 1H); ^{13}C NMR (100 MHz, DMSO): δ = 189.6, 142.7, 142.4, 138.9, 132.6, 131.6, 130.2, 129.8, 129.8, 127.0, 123.1, 121.2, 120.2, 93.5 ppm; HRMS/ESI calcd for $C_{14}H_9ClIN_2O$ $[M+H]^+$ 382.9443; found: 382.9439.

4-Iodo-6,7,8,9-tetrahydro-11*H*-pyridazino[1,2-*a*]indazol-11-one 3d: A nitrogen-flushed 10 mL vial was charged with **2d** (100 mg, 0.36 mmol, 1 equiv) in THF (10 mL). NaH (22 mg, 0.54 mmol, 1.5 equiv) was added slowly at 0 °C and the reaction mixture was stirred for 1 h. 1,4-Dibromobutane (128 μL, 1.08 mmol, 3.0 equiv) was added at 0 °C and the mixture was stirred for 2 h. THF was removed in vacuo and the residue was heated at reflux in a mixture of acetone/H_2O (9:1) (4 mL) for 4 days. The solvent was removed in vacuo and the residue was extracted with CH_2Cl_2. The organic layer was collected, dried over $MgSO_4$, filtered and concentrated. The residue was purified by column chromatography on silica gel (cyclohexane/EtOAc 9:1 to 7:3) to afford **3d** as a colourless oil (49 mg, 43%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.93 (dd, J = 7.7, 1.1 Hz, 1H), 7.85 (dd, J = 7.7, 1.1 Hz, 1H), 6.98 (t, J = 7.7 Hz, 1H), 3.97 (m, 2H), 3.75 (m, 2H), 2.07–2.02 (m, 2H), 1.82–1.76 ppm (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 151.1, 142.8, 125.3, 124.1, 123.3, 77.3, 51.2, 40.8, 23.4, 22.9 ppm; HRMS/ESI calcd for $C_{11}H_{12}IN_2O$ $[M+H]^+$ 314.9989; found: 314.9988.

Ethyl 3-(methylsulfanyl)-1*H*-indazole-6-carboxylate 3i: In a nitrogen-flushed 10 mL vial was added **2i** (207 mg, 0.56 mmol, 1 equiv) in THF (2 mL). The solution was cooled to 0 °C and *i*PrMgCl·LiCl (593 μL, 0.67 mmol, 1.2 equiv, 1.13 M in THF) was added dropwise. The mixture was stirred for 20 min at 0 °C. Ethyl choroformate (124 μL, 0.73 mmol, 1.3 equiv) was slowly added. After stirring for few minutes at 0 °C, the reaction mixture was allowed to warm to 25 °C and stirred for 1.5 h. The reaction mixture was quenched with H_2O, and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was dissolved in EtOH (4 mL), 1 M HCl (4 mL) was added and the reaction mixture was stirred for 3 days. The mixture was quenched with a saturated $NaHCO_3$ solution (7 mL) and extracted with EtOAc. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (cyclohexane/EtOAc 95:5) to afford **3i** as a pale-yellow gum (83 mg, 59%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 11.24 (s, 1H), 8.28 (s, 1H), 7.84 (d, J = 8.5 Hz, 1H), 7.74 (d, J = 8.5 Hz, 1H), 4.43 (q, J = 7.1 Hz, 2H), 2.66 (s, 3H), 1.43 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 166.9, 142.4, 141.2, 129.6, 125.7, 121.4, 120.2, 112.7, 61.5, 16.0, 14.6 ppm; HRMS/ESI calcd for $C_{11}H_{13}N_2O_2S$: 237.0692 $[M+H]^+$; found: 237.0693.

3-(3-Chloro-1*H*-indazol-5-yl)-*N*,*N*-dimethylprop-2-yn-1-amine 3p: 3-Chloro-5-iodo-1*H*-indazole **2p** (500 mg, 1.8 mmol, 1 equiv), $[PdCl_2(PPh_3)_2]$ (63 mg, 0.09 mmol, 0.05 equiv), PPh_3 (47 mg, 0.18 mmol, 0.1 equiv), CuI (34 mg, 0.18 mmol, 0.1 equiv), and triethylamine (0.75 mL, 5 mmol, 3 equiv) were introduced in a nitrogen-flushed round bottom flask. The flask was evacuated and backflushed with nitrogen. Acetonitrile (20 mL, degassed under nitrogen during 15 min) and 3-dimethylaminoprop-1-yne (0.3 mL, 2.7 mmol, 1.5 equiv) were then added and the resulting mixture was stirred at 60 °C for 48 h. The solvent was evaporated and the crude was purified by column chromatography on silica gel (CH_2Cl_2 to CH_2Cl_2/MeOH 95:5) to afford **3p** as a brown solid (342 mg, 81%). M.p. = 145–147 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.76 (s, 1H), 7.44 (d, J = 8.7 Hz, 1H), 7.40 (dd, J = 8.7, 1.0 Hz, 1H), 3.59 (s, 2H), 2.49 ppm (s, 6H). Signal due to NH is missing. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 140.9, 134.9, 131.4, 123.5, 120.5, 116.2, 110.9, 85.9, 82.9, 48.6, 44.1 (2C) ppm; HRMS/ESI calcd for $C_{12}H_{13}ClN_3$: 234.0792 $[M+H]^+$; found: 234.0794.

(*E*)-Methyl 3-(3-(methylsulfanyl)-1*H*-indazol-4-yl)acrylate 3s: PPh_3 (21 mg, 0.08 mmol, 0.1 equiv), $[Pd(OAc)_2]$ (9 mg, 0.04 mmol, 0.05 equiv) and triethylamine (0.11 mL, 0.8 mmol, 1 equiv) in dioxane (2 mL) were added in a nitrogen-flushed round bottom flask. The mixture was stirred at room temperature for 10 min. A solution of **2s** (300 mg, 0.8 mmol, 1 equiv) in dioxane (9 mL) and methyl acrylate (0.36 mL, 4 mmol, 5 equiv) was then added, and the reaction mixture was stirred at 100 °C for 27 h. H_2O (10 mL) was added and the mixture was extracted with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated in vacuo. The residue was then solubilized in a mixture of EtOH (20 mL) and HCl (37% in water, 3 mL).The resulting mixture was stirred at 25 °C for 18 h. After neutralization with a 2 M NaOH solution, the solvent was evaporated. The crude was then extracted with EtOAc. The organic layer was separated, washed with water, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (cyclohexane/EtOAc 8:1 to 4:1) to afford **3s** as a yellow solid (141 mg, 71%). M.p. = 156–158 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.77 (d, J = 15.8 Hz, 1H), 7.53 (dd, J = 7.4, 1.7 Hz, 1H), 7.42–7.35 (m, 2H), 6.52 (d, J = 15.8 Hz, 1H), 3.86 (s, 3H), 2.65 ppm (s, 3H). Signal due to NH is missing. ^{13}C NMR (100 MHz, $CDCl_3$): δ = 167.4, 142.4, 141.8, 141.5, 129.2, 127.6, 121.0, 120.2, 119.1, 111.9, 52.0, 16.6 ppm; HRMS/ESI calcd for $C_{12}H_{13}N_2O_2S$: 249.0692 $[M+H]^+$; found: 249.0692.

4-(4-Methoxyphenyl)-6,7,8,9-tetrahydro-11*H*-pyridazino[1,2-*a*]indazol-11-one 4d: Compound **3d** (16 mg, 0.05 mmol, 1 equiv), $[Pd(OAc)_2]$ (3 mg, 0.0025 mmol, 0.05 equiv), PPh_3 (1 mg, 0.005 mmol, 0.10 equiv), Na_2CO_3 (21 mg, 0.2 mmol, 4.0 equiv) and 4-methoxyphenylboronic acid (11 mg, 0.075 mmol, 1.5 equiv) in a 1:1 mixture of DME/H_2O (6 mL) were added in a sealed tube, evacuated and backfilled with nitrogen. The mixture was stirred for 22 h at 100 °C, cooled to 25 °C, filtered through a pad of Celite,

and extracted with EtOAc. The organic layer was washed with water and dried over $MgSO_4$. After filtration, the solvent was removed in vacuo and the residue was purified by column chromatography on silica gel (cyclohexane/EtOAc 12:1) to afford **4d** as a white solid (13 mg, 83%). M.p. = 208–210 °C; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.82 (dd, J = 7.7, 1.3 Hz, 1H), 7.55–7.50 (m, 2H), 7.42 (dd, J = 7.4, 1.2 Hz, 1H), 7.30–7.26 (m, 1H), 7.03–6.96 (m, 2H), 4.02–3.94 (m, 2H), 3.87 (s, 3H), 2.94–2.86 (m, 2H), 1.84–1.64 ppm (m, 4H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 160.5, 159.4, 147.9, 132.5, 130.2, 129.4 (2C), 127.6, 123.7, 122.3, 121.4, 114.2 (2C), 55.3, 50.8, 40.4, 23.4, 22.9 ppm; HRMS/ESI calcd for $C_{18}H_{19}N_2O_2$ 295.1441 $[M+H]^+$; found: 295.1441.

Ethyl 1-methyl-3-(methylsulfanyl)-1*H*-indazole-6-carboxylate 4i: A nitrogen-flushed round bottom flask was charged with a solution of **3i** (50 mg, 0.21 mmol, 1.0 equiv) in dry THF (2 mL). The solution was cooled to 0 °C, NaH (8.3 mg, 0.25 mmol, 1.2 equiv) was added and the reaction was stirred for 30 min at 0 °C. Methyl iodide (40 μL, 0.63 mmol, 3.0 equiv) was added at 0 °C and the mixture was slowly allowed to warm to 25 °C and stirred for 1 h. The reaction was quenched with H_2O and extracted with EtOAc. The organic layer was dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (cyclohexane/EtOAc 9:1) to give **4i** as an orange oil (19 mg, 36%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.49 (t, J = 1.2 Hz, 1H), 7.78 (dd, J = 8.8, 1.2 Hz, 1H), 7.73 (dd, J = 8.8, 1.2 Hz, 1H), 4.41 (q, J = 7.1 Hz, 2H), 4.32 (s, 3H), 2.40 (s, 3H), 1.42 ppm (t, J = 7.1 Hz, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ = 167.1, 147.4, 128.7, 128.1, 127.3, 122.2, 121.6, 119.9, 61.2, 38.4, 19.8, 14.5 ppm; HRMS/ESI calcd for $C_{12}H_{15}N_2O_2S$: 251.0849 $[M+H]^+$; found: 251.0848.

3-(3-Chloro-1-phenyl-1*H*-indazol-5-yl)-*N*,*N*-dimethylprop-2-yn-1-amine 4p: In a round bottom flask, a mixture of **3p** (100 mg, 0.43 mmol, 1 equiv), phenylboronic acid (104 mg, 0.86 mmol, 2 equiv), $[Cu(OAc)_2]$ (117 mg, 0.64 mmol, 1.5 equiv), pyridine (0.07 mL, 0.86 mmol, 2 equiv) and activated molecular sieves 4 Å (600 mg) in CH_2Cl_2 (7 mL) were stirred under air atmosphere at 25 °C for 48 h. The reaction completion was monitored by TLC. After filtration through a pad of Celite, the filtrate was concentrated in vacuo. The crude was purified by column chromatography on silica gel (CH_2Cl_2/MeOH 98:2 to 95:5) to give **4p** as a brown oil (79 mg, 60%). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.84 (s, 1H), 7.71–7.59 (m, 3H), 7.55–7.51 (m, 2H), 7.51–7.48 (m, 1H), 7.41–7.34 (m, 1H), 3.49 (s, 2H), 2.39 ppm (s, 6H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 139.4, 139.1, 136.2, 132.0, 129.7 (2C), 127.4, 123.8, 122.7 (2C), 122.5, 117.4, 111.0, 84.8, 84.5, 48.7, 44.4 ppm (2C); HRMS/ESI calcd for $C_{18}H_{17}ClN_3$: 310.1106 $[M+H]^+$; found: 310.1106.

(*E*)-Methyl 3-(3-(methylsulfanyl)-1-pivaloyl-1*H*-indazol-4-yl)acrylate 4s: A round bottom flask was charged with a solution of **3s** (112 mg, 0.45 mmol, 1 equiv) in dry CH_2Cl_2 (5 mL) and placed under nitrogen. The solution was cooled to 0 °C, triethylamine (0.19 mL, 1.35 mmol, 3 equiv) and pivaloyl chloride (0.17 mL, 1.35 mmol, 3 equiv) were successively added. The reaction mixture was allowed to warm to 25 °C and stirred for 18 h. A saturated $NaHCO_3$ solution (15 mL) was then added and the mixture was extracted with CH_2Cl_2. The organic layer was separated, washed with brine, dried over $MgSO_4$ and concentrated in vacuo. The residue was purified by column chromatography on silica gel (cyclohexane/EtOAc 12:1) to give **4s** as a white solid (105 mg, 70%). M.p. = 153–155 °C. ^{1}H NMR (400 MHz, $CDCl_3$): δ = 8.56–8.45 (m, 2H), 7.56–7.49 (m, 2H), 6.49 (d, J = 15.7 Hz, 1H), 3.85 (s, 3H), 2.75 (s, 3H), 1.56 ppm (s, 9H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 177.5, 166.9, 147.9, 142.3, 140.7, 129.9, 129.0, 122.9, 122.1, 121.5, 117.9, 52.1, 41.9, 27.8 (3C), 14.9 ppm; HRMS/ESI calcd for $C_{17}H_{21}N_2O_3S$: 333.1267 $[M+H]^+$; found: 333.1266.

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