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Article

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Unprotected Indazoles are Resilient to Ring-opening Isomerization: A Case Study on Catalytic C–S Couplings in the Presence of Strong Base

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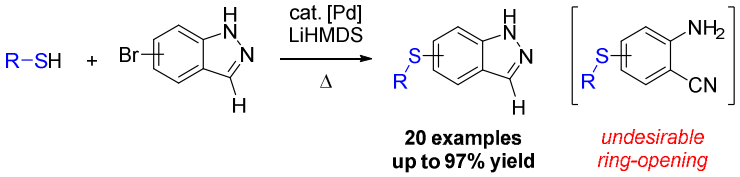


Abstract

Indazoles represent a privileged scaffold in medicinal chemistry. In the presence of strong base, however, *N*-protected indazoles are prone to an undesirable ring-opening reaction to liberate *ortho*-aminobenzonitriles. By employing unprotected indazoles with a free N–H bond, isomerization is averted since the heterocycle is deprotonated *in situ*. We herein report a functional group tolerant and robust C–S couplings of bromo-indazoles with thiols of varying electronic nature in the presence of lithium bis(trimethylsilyl)amide at elevated temperatures.

Introduction

Indazoles are an important heterocyclic scaffold in drug discovery, and these motifs often exhibit potent biological activities across a number of targets and therapeutic disease areas.[1,2,3] Due to their ubiquity in bioactive molecules and natural products, the synthesis of functionalized indazoles is an active area of research,[4,5] and indazoles bearing substitution on *N1* are common amongst this family of compounds.[6,7,8] One common strategy to promote productive bond

forming transformations on heterocycles is to introduce protecting groups, since unprotected heterocycles can often compromise synthetic routes, particularly in transition metal catalysis, due to unproductive reactivity of N–H bonds and/or catalyst deactivation.[9,10]

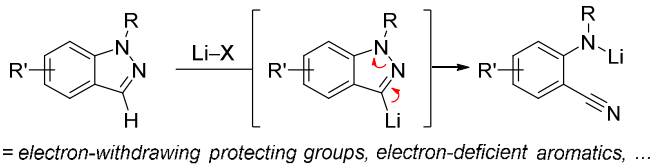


Figure 1. Kemp-type elimination of C3-unsubstituted indazoles.

In the case of indazoles, substitution of the acidic nitrogen can be detrimental to the success of certain reactions depending on the nature of the protecting group or functional group on *N1*.[11] During the course of an ongoing medicinal chemistry program, we observed an undesirable ring-opening isomerization reaction of *N1*-substituted indazoles. Presumably, basic organometallic reagents can rapidly deprotonate an acidic C–H bond at the C3 position,[12,13,14] and owing to the thermodynamic favorability of nitrile formation, these anions rapidly undergo Kemp-type eliminations to afford their corresponding ring-opened *ortho*-aminobenzonitrile by-products (**Figure 1**).[15,16] This reactivity is sparsely documented in the literature, *particularly in the context of modern transition metal catalysis wherein strong bases are frequently used and is underappreciated as a parasitic side-reaction*. Given the need to access indazoles bearing diverse functional groups, a synthetic approach that could circumvent ring-opening of the heterocyclic core would be of high utility to medicinal chemists.

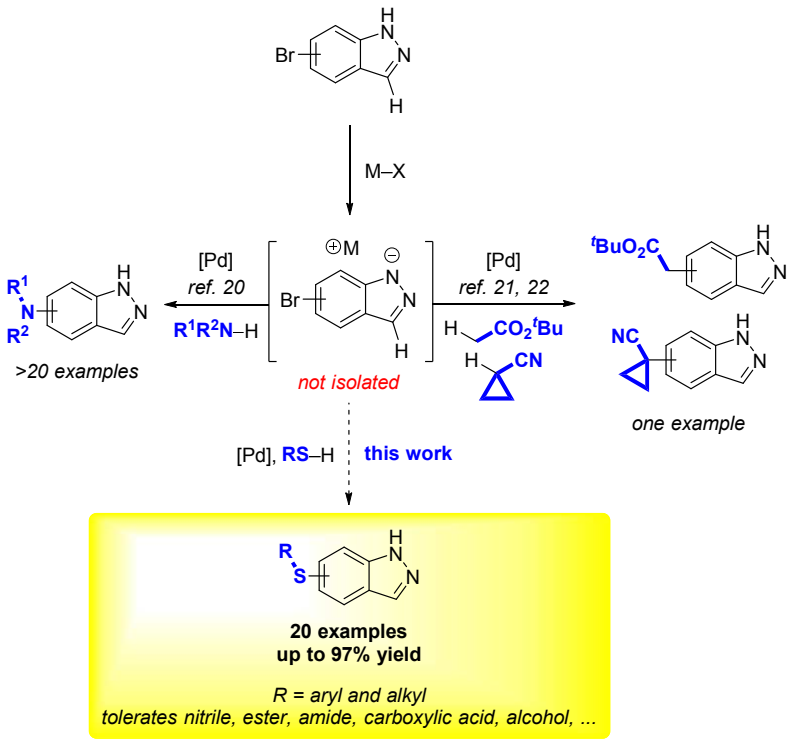


Figure 2. Palladium-catalyzed couplings of unprotected indazoles in the presence of strong base.

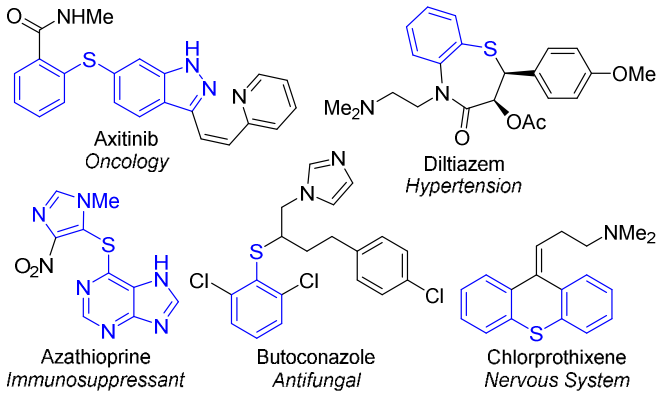
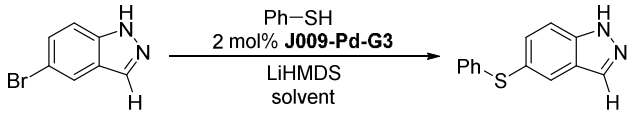


Figure 3. Therapeutic agents bearing aromatic thioethers.

Using unprotected indazoles provides a pathway for transient protection of the azole nucleus.[17] The indazole N–H bond can be readily deprotonated, and as a consequence, productive chemical transformations can take place, outcompeting the otherwise facile Kemp-type elimination and hence minimizing the formation of *ortho*-aminobenzonitriles. Indeed, Horner-Wadsworth-Emmons olefinations[18] and amide alkylations[19] have been documented using compounds containing an unprotected indazole. Additionally, catalytic C–N couplings[20] and the α-arylation of

aliphatic nitriles[21] and esters[22] are known. We selected aryl thioethers as a case study to illustrate the robustness of indazoles to ring-opening (**Figure 2**). Aryl thioethers are commonly found in biologically active, pharmaceutically relevant compounds (**Figure 3**),[23] and Pd-catalyzed cross-coupling of aryl halides with thiols can be achieved using strong bases such as lithium bis(trimethylsilyl)amide (LiHMDS).[24,25] Given the relevance of compounds such as axitinib and a dearth of general methods for thioetherifications using unprotected indazoles, we sought to identify a robust protocol for cross-coupling a diverse range of thiols and demonstrate functional group compatibility in the context of medicinal chemistry structure-activity relationship (SAR) support. In this manuscript, we highlight the resistance of unprotected indazoles to ring-opening reactions, and successfully achieve a broadly applicable palladium-catalyzed C–S coupling. Importantly, we demonstrate that the presence of free N–H bonds does not impede the success of the catalytic thioetherifications in a strongly basic medium and is, in fact, crucial to reaction success.

Results and Discussion



Entry	Solvent	Temperature	Conversion[a]
1	PhMe	100 °C	0% (0 mol% **J009-Pd-G3**)
2	PhMe	100 °C	54%
3	THF	100 °C	>99%
4	THF	120 °C	>99%

Table 1. Reaction optimization. *Conditions:* bromoindazole (0.5 mmol), thiol (0.6 mmol), **J009-Pd-G3** (*x* mol%), LiHMDS (1.2 mmol, 1.0 M in solvent), 16 h. [a] Determined by LCMS.

Palladium-catalyzed thioetherifications, in general, have not been extensively studied as their corresponding C–C, C–N, and C–O coupling counterparts.[24,25,26] We began our investigation using thiophenol and 5-bromoindazole as coupling partners with the goal of identifying a robust set of reaction conditions for rapid SAR evaluation on medicinal chemistry

programs (**Table 1**). Inspired by Hartwig's earlier accounts, we opted to use commercially available 3rd generation Buchwald precatalyst Josiphos-SL-J009-1-Pd-G3 (**J009-Pd-G3**, 2 mol%).[24, 25] In the presence of 2.4 equiv of LiHMDS, a modest 54% conversion was observed at 100 °C after 16 h as determined by chromatography (i.e., LCMS). The known properties of **J009-Pd-G3** as a strongly electron donating and bulky ligand presumably prevent the formation of parasitic Pd complexes that lie off the catalytic cycle. We were pleased to find that changing the solvent from toluene to tetrahydrofuran (THF) under otherwise identical conditions resulted in >99% conversion. A preliminary assessment of substrate scope identified that thiols containing trialkylamine functionalities were less reactive, and required a higher temperature of 120 °C. Of note, given the reactions scales on which we are operating, we opted to use pressure-resistant vials to minimize solvent evaporation since each vessel is designed to operate beyond 30 bar of pressure as set by the manufacturer's (Biotage) standard.

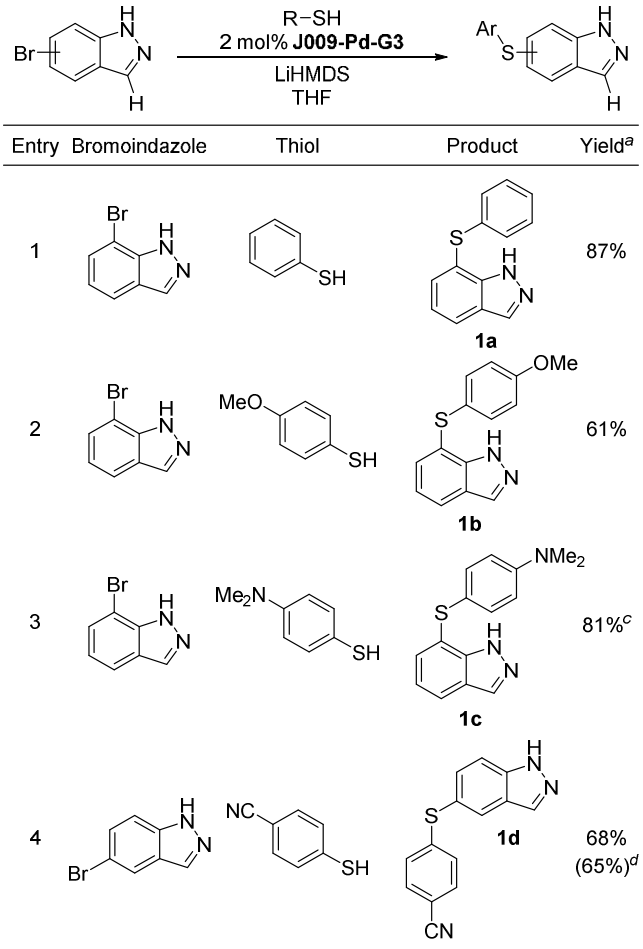
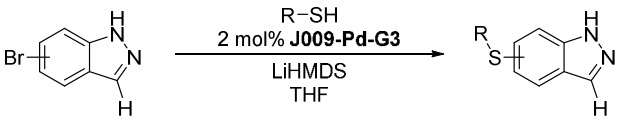


Table 2. Palladium-catalyzed thioetherification of unprotected indazoles with aromatic thiols. *Conditions:* bromoindazole (0.5 mmol), thiol (0.6 mmol), **J009-Pd-G3** (2 mol%), LiHMDS (1.2 mmol, 1.0 M in THF), 120 °C, 16 h. [a] Isolated yield. [b] Not determined. ~3:1 product/byproduct as determined by LCMS. [c] 0.25 mmol scale. [d] 5 mmol scale (~1 g).

Next, we subjected a number of thiol coupling partners to arylation with unprotected indazoles under palladium catalysis (**Tables 2–4**). Aromatic thiols of varying acidity underwent C–S coupling smoothly (**Table 2**). In the coupling between 7-bromoindazole and *para*-methoxythiophenol (entry 2), we observed complete consumption of the aryl bromide but a ~3:1 ratio of product to bis-indazole thioether dimer as indicated by LCMS. The observation of an "aryl-aryl scrambling" was previously reported by Hartwig in which large amounts of symmetrical bis-aryl thioethers were formed particularly when using electron-rich aromatic thiols.[24] Notably, ring-opening isomerization was not observed in our hands. Using *para*-cyanothiophenol (entry 3), we demonstrated scalability of this protocol to a 1 g scale (5 mmol) without significant changes in isolated yield (68% versus 65%).



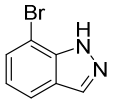
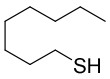
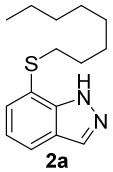
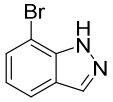
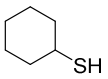
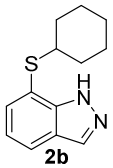
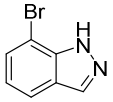
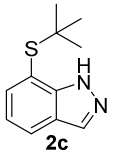
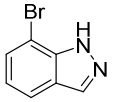
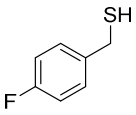
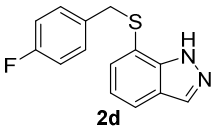
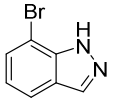
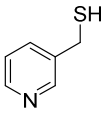
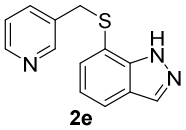
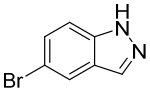
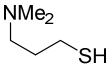
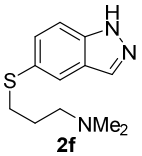
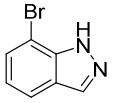
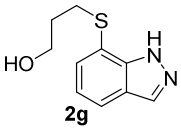
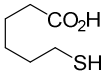
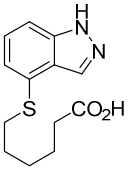
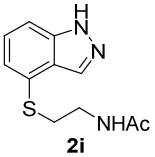
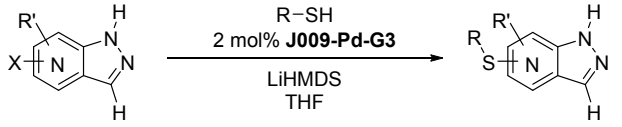
Entry	Bromoindazole	Thiol	Product	Yield[a]
1			 **2a**	93%[b]
2			 **2b**	95%
3			 **2c**	89%[b]
4			 **2d**	85%
5			 **2e**	73%[b]
6			 **2f**	97%
7			 **2g**	73%
8			 **2h**	86%[c]
9			 **2i**	73%[c]

Table 3. Palladium-catalyzed thioetherification of unprotected indazoles with aliphatic thiols. *Conditions:* bromoindazole (0.5 mmol), thiol (0.6 mmol), **J009-Pd-G3** (2 mol%), LiHMDS (1.2 mmol, 1.0 M in THF), 120 °C, 16 h. [a] Isolated yield. [b] 100 °C. [c] LiHMDS (1.7 mmol).

Aliphatic thiols were likewise competent coupling partners in catalytic C–S cross-couplings (**Table 3**). Although harsh basic conditions were used for these thioetherifications, the reaction exhibits broad functional group compatibility. Lewis-basic functional groups, including pyridine and alkylamines were tolerated (entries 5-6). Additionally, 3-mercaptopropan-1-ol gave the C–S coupling product exclusively, even in the presence of an unprotected alcohol (entry 7). Likewise, carboxylic acid (entry 8) and amide (entry 9) containing thiols generated the desired aryl thioether product in good yields. In all cases, no ring-opening to the *ortho*-aminobenzonitriles was observed, highlighting the robustness of this protocol and the use of indazoles directly for functionalization without the need for a protecting group at *N1*.



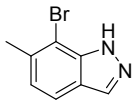
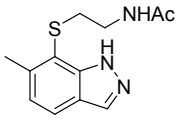
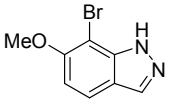
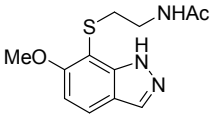
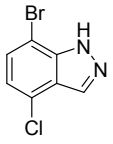
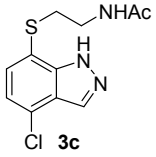
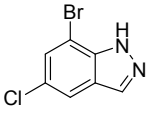
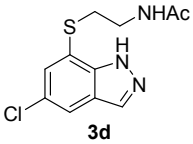
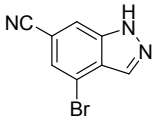
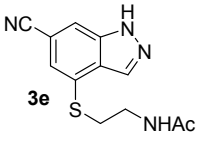
Entry	Bromoindazole	Thiol	Product	Yield[a]
1			 **3a**	48%
2			 **3b**	77%
3			 **3c**	66%
4			 **3d**	52%
5			 **3e**	54%

Table 4. Palladium-catalyzed thioetherification of substituted unprotected indazoles with aliphatic thiols. *Conditions:* bromoindazole (0.5 mmol), thiol (0.6 mmol), **J009-Pd-G3** (2 mol%), LiHMDS (1.7 mmol, 1.0 M in THF), 120 °C, 16 h. [a] Isolated yield.

With an excellent general scope of thiols and functional group compatibility for our C–S cross-couplings, we next evaluated a range of bromoindazoles (**Table 4**). Bromoindazoles bearing additional substitution on the ring underwent thioetherification in good yields. Methyl (entry 1), methoxy (entry 2), chloro (entries 3-4), and cyano (entry 5) functional

groups were all well tolerated. In the coupling of 4-chloro-7-bromoindazole and 5-chloro-7-bromoindazole, we observed thioetherification of both the C–Br and C–Cl bonds (~15–20% of the bis-thioether as determined by LCMS).

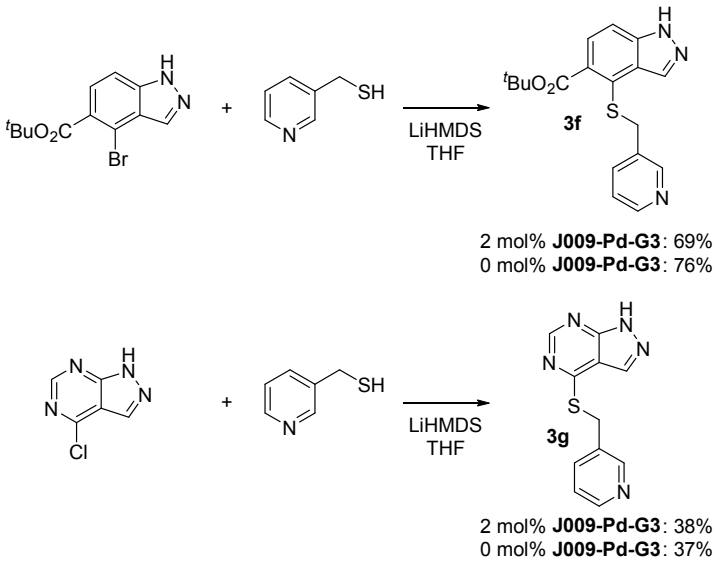


Figure 4. A S_NAr thioetherification of electron-deficient unprotected indazoles with aliphatic thiols. *Conditions:* bromoindazole (0.5 mmol), thiol (0.6 mmol), **J009-Pd-G3** (2 mol%), LiHMDS (1.2 mmol, 1.0 M in THF), 120 °C, 16 h.

In the course of our scope examination, we attempted to cross-couple electron-deficient indazole substrates such as *tert*-butyl 4-bromo-5-carboxylate and 4-chloro-*1H*-pyrazolo[3,4-d]pyrimidine with a thiol (**Figure 4**). Surprisingly, the reaction produced similar quantities of desired product in the absence of palladium, indicating that a facile S_NAr reaction may take place in specific instances provided that a suitable halide leaving group is present. It is significant that the deprotonation of the azole N–H does not impede the S_NAr reaction from proceeding. Importantly, this background activity is unique to electron-deficient indazoles, as electron-neutral and electron-rich substrates are unreactive (see **Table 1**).

Conclusion

We have demonstrated a robust protocol for functionalizing indazoles utilizing strongly basic reaction conditions. The Pd-catalyzed C–S coupling with thiols using unprotected indazoles as substrates proceeds with good to excellent yields, and these reactions exhibit a high degree of functional group tolerance. Together with the known C–N couplings, as reported by Buchwald,[20] and C–C couplings, as reported by the Merck Process[21] and University Health Network[22] groups, we anticipate that the guidance delineated in this manuscript will enable future medicinal chemistry efforts on bioactive indazoles.

Experimental Section

General Methods. All reactions were performed in scintillation or microwave vials under an atmosphere of nitrogen. All reagents and solvents were purchased from commercial sources and used without further purification. Reactions were monitored by LCMS or thin layer chromatography (TLC) on silica gel and visualized with UV light (254 nm). LCMS samples were run on an Agilent 1100 or 1200 system. Flash chromatography was performed using pre-packed RediSep R_f silica gel columns on a Teledyne Isco CombiFlash R_f automated chromatography system. Organic solutions were concentrated under reduced pressure on a Heidolph rotary evaporator. Reversed-phase high-performance liquid chromatography was carried out using an Agilent 1100 HPLC-MSD system consisting of a 6130B single quadrupole mass-selective detector (MSD), G1315B diode array detector, G2258A autosampler, two G1361A preparative pumps, one G1379A quaternary pump with degasser, one G1312A binary pump, and three G1364B fraction collectors from Agilent Technologies. System control and data analysis was performed using Agilent's ChemStation software, revision B.03.01-SR.1. A Waters XBridge C18 OBD Prep Column, 100Å, 5 μm, 19 mm X 150 mm column was used as the stationary phase (Waters Corporation). Gradient elution was carried out using water and acetonitrile as the mobile phase. An aqueous 10% ammonium hydroxide solution was teed into the mobile phase as a modifier using a static mixer prior to the column, pumped at 1% of the total mobile phase flow rate. ESI mass-triggered fraction collected was employed using positive ion polarity scanning to monitor for the target mass.

Proton nuclear magnetic resonance (^{1}H NMR) spectra and proton-decoupled carbon nuclear magnetic resonance (^{13}C{^{1}H} NMR) spectra were recorded on a Varian 500 (500 MHz) spectrometer at ambient temperature. All chemical shifts (δ) are reported in parts per million (ppm) and referenced to residual protium or the carbon resonance of the NMR solvent, respectively. Data are represented as follows: chemical shift, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet), coupling constants (*J*) in Hertz (Hz), integration. High-resolution mass spectrometry (HRMS) data were recorded on a Waters Xevo G2 QTof instrument in either ESI+ or ESI– (electrospray) ionization mode.

General Procedure. To a 5 mL microwave vial was added bromoindazole (0.5 mmol), Josiphos-SL-J009-1 Pd-G3 (9.2 mg, 0.05 mmol, 2 mol%), and thiol (0.6 mmol, 1.2 equiv.). Following a dropwise addition of LiHMDS (1.0 M in THF, 1.2 mL, 1.2 mmol, 2.4 equiv.), the resulting mixture was heated to 100–120°C for 16 h. After cooling to rt, the reaction mixture was quenched by the addition of 3 mL of MeOH, filtered through a bed of celite, and washed with

MeOH. The filtrate was concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel or mass-directed reversed-phase HPLC to give analytically pure product. *Note: caution should be taken due to the elevated internal pressure of each reaction vessel; we opted to use pressure-resistant vials to minimize solvent evaporation since each vessel is designed to operate beyond 30 bar of pressure as set by the manufacturer's (Biotage) standard.*

7-(Phenylthio)-1*H*-indazole (1a): 98.1 mg, 87%, 0–30% EtOAc/hexanes. Pale brown solid. ^{1}H NMR (500 MHz, MeOD) δ 8.12 (s, 1H), 7.84 (d, *J* = 8.1 Hz, 1H), 7.51 (d, *J* = 7.1 Hz, 1H), 7.27–7.12 (m, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 141.2, 135.7, 135.2, 133.0, 129.3 (2C), 128.3 (2C), 126.5, 123.9, 122.0, 121.8, 114.3. HRMS (ESI) *m/z* calc'd for $C_{13}H_{11}N_2S$ (M+H): 227.0643, found: 227.0647.

7-((4-Methoxyphenyl)thio)-1*H*-indazole (1b): 78.5 mg, 61%, 0–25% EtOAc/hexanes. Brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.12 (s, 1H), 7.71 (d, *J* = 8.0 Hz, 1H), 7.46 (d, *J* = 7.1 Hz, 1H), 7.32 (d, *J* = 8.1 Hz, 2H), 7.16 (t, *J* = 7.7 Hz, 1H), 6.84 (d, *J* = 8.1 Hz, 2H), 3.79 (s, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 159.4, 140.5, 135.6, 132.4 (2C), 130.5, 124.3, 123.9, 121.8, 120.8, 117.3, 115.2 (2C), 55.4. HRMS (ESI) *m/z* calc'd for $C_{14}H_{13}N_2OS$ (M+H): 257.0748, found: 257.0752.

4-((1*H*-Indazol-7-yl)thio)-*N*,*N*-dimethylaniline (1c): 54.8 mg (0.25 mmol scale), 81%, 0–25% EtOAc/DCM. Brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 10.35 (br s, 1H), 7.97 (s, 1H), 7.59 (d, *J* = 8.5 Hz, 1H), 7.44 (d, *J* = 8.3 Hz, 2H), 7.06 (s, 1H), 7.02 (d, *J* = 8.5 Hz, 1H), 6.75 (d, *J* = 8.3 Hz, 2H), 3.02 (s, 6H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 150.8, 140.8, 140.4, 136.5 (2C), 134.7, 121.1, 120.8, 120.8, 116.8, 113.1 (2C), 106.7, 40.3 (2C). HRMS (ESI) *m/z* calc'd for $C_{15}H_{16}N_3S$ (M+H): 270.1065, found: 270.1060.

4-((1*H*-Indazol-5-yl)thio)benzonitrile (1d): 85.6 mg, 68%, 0–20% EtOAc/DCM. Pale brown solid. ^{1}H NMR (500 MHz, MeOD) δ 8.12 (s, 1H), 8.08 (s, 1H), 7.66 (d, *J* = 8.6 Hz, 1H), 7.52 (d, *J* = 8.3 Hz, 2H), 7.49 (d, *J* = 8.4 Hz, 1H), 7.14 (d, *J* = 8.2 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 146.8, 140.3, 135.2, 133.5, 132.3 (2C), 129.0, 126.5 (2C), 124.6, 122.1, 118.9, 111.6, 108.4. HRMS (ESI) *m/z* calc'd for $C_{14}H_{10}N_3S$ (M+H): 252.0595, found: 252.0594.

7-(Octylthio)-1*H*-indazole (2a): 122.1 mg, 93%, 0–25% EtOAc/hexanes. Pale brown solid. ^{1}H NMR (600 MHz, $CDCl_3$) δ 8.16 (s, 1H), 7.69 (d, *J* = 8.1 Hz, 1H), 7.47 (d, *J* = 7.2 Hz, 1H), 7.27 (s, 1H), 7.17 (t, *J* = 7.6 Hz, 1H), 2.95 (t, *J* = 7.4 Hz, 2H), 1.63 (quin, *J* = 7.6 Hz, 2H), 1.41 (quin, *J* = 7.3 Hz, 2H), 1.35–1.19 (m, 8H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 141.4, 135.5, 130.3, 123.3, 121.5, 120.1, 117.4, 34.8, 31.8, 29.7, 29.2, 29.1, 28.7, 22.7, 14.1. HRMS (ESI) *m/z* calc'd for $C_{15}H_{23}N_2S$ (M+H): 263.1582, found: 263.1583.

7-(Cyclohexylthio)-1*H*-indazole (2b): 110.3 mg, 95%, 0–25% EtOAc/hexanes. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.18 (s, 1H), 7.73 (d, *J* = 8.0 Hz, 1H), 7.51 (d, *J* = 7.1 Hz, 1H), 7.16 (t, *J* = 7.6 Hz, 1H), 3.09 (t, *J* = 10.7 Hz, 1H), 1.94 (d, *J* = 11.7 Hz, 2H), 1.75 (d, *J* = 10.4 Hz, 2H), 1.67–1.51 (m, 1H), 1.39 (q, *J* = 11.0 Hz, 2H), 1.32–1.14 (m, 3H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 142.7, 135.7 133.4, 123.3, 121.5, 121.0, 115.1, 47.8, 33.7 (2C), 26.1 (2C), 25.6. HRMS (ESI) *m/z* calc'd for $C_{13}H_{17}N_2S$ (M+H): 233.1112, found: 233.1114.

7-(*tert*-Butylthio)-1*H*-indazole (2c): 91.7 mg, 89%, 0–25% EtOAc/hexanes. White solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.80 (d, *J* = 7.8 Hz, 1H), 7.54 (d, *J* = 6.9 Hz, 1H), 7.18 (t, *J* = 7.6 Hz, 1H), 1.33 (s, 9H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 144.0, 136.6, 135.6, 123.3, 122.1, 121.3, 113.9, 48.1, 31.2 (3 C). HRMS (ESI) *m/z* calc'd for $C_{11}H_{15}N_2S$ (M+H): 207.0956, found: 207.0952.

7-((4-Fluorobenzyl)thio)-1*H*-indazole (2d): 88.6 mg, 69%, 0–20% EtOAc/hexanes. Pale brown oil. ^{1}H NMR (500 MHz, CDCl3) δ 8.13 (s, 1H), 7.72 (d, *J* = 8.0 Hz, 1H), 7.35 (d, *J* = 7.1 Hz, 1H), 7.11 (t, *J* = 7.6 Hz, 1H), 7.06 (t, *J* = 8.3 Hz, 2H), 6.90 (t, *J* = 8.4 Hz, 2H), 4.04 (s, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 163.0, 161.1, 142.0, 135.6, 133.6, 132.8, 130.3, 130.3, 123.3, 121.8, 121.4, 115.5, 115.3, 39.6. HRMS (ESI) *m/z* calc'd for $C_{14}H_{12}FN_2S$ (M+H): 259.0705, found: 259.0702.

7-((Pyridin-3-ylmethyl)thio)-1*H*-indazole (2e): 88.6 mg, 73.4%, 5–95% MeCN/H_2O with 0.1% NH_4OH. Pale brown oil. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.49 (s, 1H), 8.43 (d, *J* = 4.9 Hz, 1H), 8.00 (s, 1H), 7.65–7.56 (m, 2H), 7.34 (s, 1H), 7.17 (d, *J* = 7.9 Hz, 1H), 7.07 (d, *J* = 8.4 Hz, 1H), 4.07 (s, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 149.0, 147.6, 140.6, 137.1, 134.3, 134.0, 133.4, 123.8, 123.6, 122.2, 121.3, 111.7, 36.5. HRMS (ESI) *m/z* calc'd for $C_{13}H_{12}N_3S$ (M+H): 242.0752, found: 242.0742.

3-((1*H*-Indazol-5-yl)thio)-*N*,*N*-dimethylpropan-1-amine (2f): 114.3 mg, 97%, 0–15% MeOH/DCM with 1% Et_3N. Brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 7.98 (s, 1H), 7.78 (s, 1H), 7.31 (d, *J* = 9.0 Hz, 1H), 7.26 (d, *J* = 9.0 Hz, 1H), 2.93 (t, *J* = 7.3 Hz, 2H), 2.47 (t, *J* = 7.3 Hz, 2H), 2.28 (s, 6H), 1.82 (quin, *J* = 7.3 Hz, 2H). ^{13}C{^{1}H} NMR (125 MHz, $CDCl_3$) δ 139.3, 134.0, 130.4, 127.0, 123.9, 123.7, 110.2, 58.3, 45.3, 33.6, 27.2. HRMS (ESI) *m/z* calc'd for $C_{12}H_{18}N_3S$ (M+H): 236.1221, found: 236.1225.

3-((1*H*-Indazol-7-yl)thio)propan-1-ol (2g): 76.1 mg, 73.1%, 0–5% MeOH/DCM. Pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.15 (s, 1H), 7.69 (d, *J* = 8.0 Hz, 1H), 7.49 (d, *J* = 7.1 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 3.92 (t, *J* = 5.8

Hz, 2H), 3.13 (t, *J* = 6.8 Hz, 2H), 1.88 (quin, *J* = 6.4 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 141.4, 135.2, 131.3, 123.3, 121.5, 120.8, 116.9, 60.4, 31.4, 31.4. HRMS (ESI) *m/z* calc'd for $C_{10}H_{13}N_2OS$ (M+H): 209.0748, found: 209.0745.

6-((1*H*-Indazol-4-yl)thio)hexanoic acid (2h): 100.7 mg, 76%, 5–95% MeCN/H_2O with 0.1% NH_4OH. White solid.^{1}H NMR (500 MHz, MeOD) δ 8.07 (s, 1H), 7.37 (d, *J* = 8.4 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.10 (d, *J* = 6.9 Hz, 1H), 3.08 (t, *J* = 7.3 Hz, 2H), 2.28 (t, *J* = 7.3 Hz, 2H), 1.70 (quin, *J* = 7.4 Hz, 2H), 1.62 (quin, *J* = 7.3 Hz, 2H), 1.52 (quin, *J* = 6.8 Hz, 2H). $^{13}C\{^{1}H\}$ NMR (125 MHz, MeOD) δ 176.4, 140.2, 132.1, 129.8, 126.8, 123.0, 119.7, 107.5, 33.7, 32.2, 28.6, 27.9, 24.3. HRMS (ESI) *m/z* calc'd for $C_{13}H_{17}N_2O_2S$ (M+H): 265.1010, found: 265.1013.

***N*-(2-((1*H*-Indazol-4-yl)thio)ethyl)acetamide (2i)**: 85.8 mg, 73%, 5–95% MeCN/H_2O with 0.1% NH_4OH. Pale brown solid. ^{1}H NMR (500 MHz, $CDCl_3$) δ 8.19 (s, 1H), 7.38 (d, *J* = 8.4 Hz, 1H), 7.33 (t, *J* = 7.7 Hz, 1H), 7.17 (d, *J* = 7.1 Hz, 1H), 5.94 (br s, 1H), 3.51 (q, *J* = 6.2 Hz, 2H), 3.21 (t, *J* = 6.3 Hz, 2H), 1.95 (s, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 170.3, 140.1, 133.7, 128.2, 127.2, 123.8, 121.2, 108.3, 38.8, 33.0, 23.2. HRMS (ESI) *m/z* calc'd for $C_{11}H_{14}N_3OS$ (M+H): 236.0857, found: 236.0863.

***N*-(2-((6-Methyl-1*H*-indazol-7-yl)thio)ethyl)acetamide (3a)**: 59.8 mg, 48%, 5–95% MeCN/H_2O with 0.1% NH_4OH. White solid. ^{1}H NMR (500 MHz, MeOD) δ 8.03 (s, 1H), 7.66 (d, *J* = 8.2 Hz, 1H), 7.12 (d, *J* = 8.2 Hz, 1H), 3.24 (t, *J* = 7.0 Hz, 2H), 2.92 (t, *J* = 6.9 Hz, 2H), 2.66 (s, 3H), 1.87 (s, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, MeOD) δ 172.0, 143.4, 141.7, 134.4, 123.9, 121.8, 120.9, 113.3, 39.4, 33.8, 21.0, 19.1. HRMS (ESI) *m/z* calc'd for $C_{12}H_{16}N_3OS$ (M+H): 250.1014, found: 250.1007.

***N*-(2-((6-Methoxy-1*H*-indazol-7-yl)thio)ethyl)acetamide (3b)**: 102.7 mg, 77%, 5–95% MeCN/H_2O with 0.1% NH_4OH. White solid. ^{1}H NMR (500 MHz, MeOD) δ 7.98 (s, 1H), 7.21 (d, *J* = 2.2 Hz, 1H), 7.14 (d, *J* = 2.2 Hz, 1H), 3.85 (s, 3H), 3.36 (t, *J* = 6.8 Hz, 2H), 3.09 (t, *J* = 6.8 Hz, 2H), 1.89 (s, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, $CDCl_3$) δ 170.7, 154.9, 137.7, 134.9, 123.6, 122.9, 110.0, 100.4, 55.9, 39.4, 35.6, 23.2. HRMS (ESI) *m/z* calc'd for $C_{12}H_{16}N_3O2S$ (M+H): 266.0963, found: 266.0962.

***N*-(2-((4-Chloro-1*H*-indazol-7-yl)thio)ethyl)acetamide (3c)**: 85.8 mg, 66%, 5–95% MeCN/H_2O with 0.1% NH_4OH. Pale brown solid. ^{1}H NMR (500 MHz, MeOD) δ 8.11 (s, 1H), 7.51 (d, *J* = 9.0 Hz, 1H), 7.27 (d, *J* = 9.0 Hz, 1H), 3.94 (s, 3H), 3.23 (t, *J* = 7.0 Hz, 2H), 3.05 (t, *J* = 6.9 Hz, 2H), 1.83 (s, 3H). $^{13}C\{^{1}H\}$ NMR (125 MHz, MeOD) δ 172.0, 141.8, 132.7, 131.1, 125.7, 122.2, 120.6, 115.5, 38.9, 33.2, 21.1. HRMS (ESI) *m/z* calc'd for $C_{11}H_{13}ClN_3OS$ (M+H): 270.0468, found: 270.0465.

***N*-(2-((5-Chloro-1*H*-indazol-7-yl)thio)ethyl)acetamide (3d)**: 70.1 mg, 52%, 5–95% MeCN/H_2O with 0.1% NH_4OH. Pale brown solid. ^1H NMR (500 MHz, MeOD) δ 8.07 (s, 1H), 7.72 (s, 1H), 7.51 (s, 1H), 3.38 (t, *J* = 6.8 Hz, 2H), 3.13 (t, *J* = 7.0 Hz, 2H), 1.89 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, MeOD) δ 172.1, 139.3, 133.9, 128.9, 126.1, 123.9, 118.8, 118.7, 38.8, 32.7, 21.0. HRMS (ESI) *m/z* calc'd for $C_{11}H_{13}ClN_3OS$ (M+H): 270.0468, found: 270.0464.

***N*-(2-((6-Cyano-1*H*-indazol-4-yl)thio)ethyl)acetamide (3e)**: 70.7 mg, 54%, 5–95% MeCN/H_2O with 0.1% NH_4OH. Brown solid. ^1H NMR (500 MHz, MeOD) δ 8.21 (s, 1H), 7.84 (s, 1H), 7.40 (s, 1H), 3.46 (t, *J* = 7.0 Hz, 2H), 3.28 (d, *J* = 6.7 Hz, 3H), 1.91 (s, 3H). $^{13}C\{^1H\}$ NMR (125 MHz, MeOD) δ 172.1, 132.5, 132.0, 124.5, 119.6, 118.5, 113.1, 110.0, 109.9, 38.5, 30.9, 21.0. HRMS (ESI) *m/z* calc'd for $C_{12}H_{13}N_4OS$ (M+H): 261.0810, found: 261.0807.

***tert*-Butyl 4-((pyridin-3-ylmethyl)thio)-1*H*-indazole-5-carboxylate (3f)**: 129.7 mg, 76%, 0–25% EtOAc/DCM. White solid. ^1H NMR (500 MHz, $CDCl_3$) δ 8.37 (s, 1H), 8.07 (d, *J* = 9.6 Hz, 2H), 7.61 (d, *J* = 8.7 Hz, 1H), 7.49 (d, *J* = 8.0 Hz, 1H), 7.29 (d, *J* = 8.7 Hz, 1H), 7.13 (t, *J* = 8.7 Hz, 1H), 4.17 (s, 2H), 1.61 (s, 9H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 167.0, 149.1, 147.9, 140.4, 136.7, 135.5, 134.2, 131.5, 127.8, 127.1, 126.8, 123.5, 110.2, 82.1, 38.2, 28.3 (3 C). HRMS (ESI) *m/z* calc'd for $C_{18}H_{20}N_3O_2S$ (M+H): 342.1276, found: 342.1275.

4-((Pyridin-3-ylmethyl)thio)-1*H*-pyrazolo[3,4-d]pyrimidine (3g): 45.5 mg, 37%, 5–95% MeCN/H_2O with 0.1% NH_4OH. Yellow solid. ^1H NMR (500 MHz, MeOD) δ 8.72 (s, 1H), 8.68 (s, 1H), 8.40 (d, *J* = 4.9 Hz, 1H), 8.14 (s, 1H), 7.98 (d, *J* = 7.9 Hz, 1H), 7.38 (dd, *J* = 8.0, 4.9 Hz, 1H), 4.69 (s, 2H). $^{13}C\{^1H\}$ NMR (125 MHz, $CDCl_3$) δ 164.2, 154.1, 152.5, 150.1, 148.5, 136.9, 133.5, 132.7, 123.6, 111.7, 30.1. HRMS (ESI) *m/z* calc'd for $C_{11}H_{10}N_5S$ (M+H): 244.0657, found: 244.0650.

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Supporting Information Statement

The Supporting Information is available free of charge on the ACS Publications website.

Copies of ^{1}H and $^{13}C\{^{1}H\}$ spectra of isolated compounds (PDF).

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