Organic & Biomolecular Chemistry

Accepted Manuscript

This article can be cited before page numbers have been issued, to do this please use: C. Wiethan, C. Lavoie, A. Borzenko, J. Clark, H. G. Bonacorso and M. Stradiotto, *Org. Biomol. Chem.*, 2017, DOI: 10.1039/C7OB00841D.

ROYAL SOCIETY OF CHEMISTRY

rsc.li/obc

View Article Online
DOI: 10.1039/C7OB00841D

Journal Name

ARTICLE

Ni and Cu-Catalyzed One Pot Synthesis of Unsymmetrical 1,3-Di(hetero)aryl-1H-indazoles from Hydrazine, o-Chloro (hetero)benzophenones, and (Hetero)aryl Bromides

Received 00th January 20xx,
Accepted 00th January 20xx

DOI: 10.1039/x0xx00000x

www.rsc.org/

Carson Wiethan,[a] Christopher M. Lavoie,[b] Andrey Borzenko,[b] Jillian S. K. Clark,[b] Helio G. Bonacorso*[a] and Mark Stradiotto*[b]

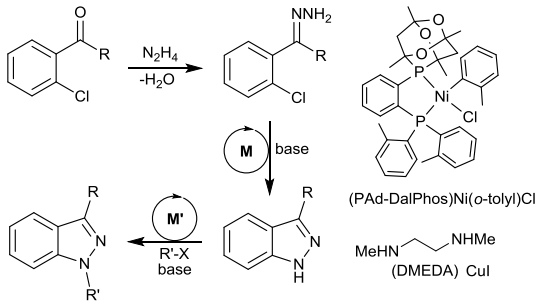
The nickel-catalyzed cyclization of in situ generated *ortho*-chlorobenzophenone hydrazone derivatives, to afford 3-(hetero)aryl-1*H*-indazoles, is documented for the first time. The product 1*H*-indazoles can be transformed subsequently in a one-pot procedure into 1,3-di(hetero)aryl-1*H*-indazoles via copper-catalyzed *N*-arylation with (hetero)aryl bromides.

Introduction

1*H*-Indazole derivatives have been shown to exhibit useful pharmacological properties in a range of applications; the 1,3-disubstituted 1*H*-indazole core structure in particular is found in several commercialized pharmaceuticals, including but not limited to granisetron (antiemetic) and benzydiamine (anaesthetic/analgesic).[1] It is not surprising that there is considerable interest in the establishment of new and/or improved synthetic routes to substituted 1*H*-indazoles. In moving beyond the diazotization or nitrosation of 2-alkyl substituted anilines, which commonly require harsh reaction conditions,[1-2] recent focus has been directed toward the development of alternative routes to substituted 1*H*-indazoles that make use of relatively inexpensive and abundant starting materials, and which can be conducted under comparatively mild reaction conditions.[3]

In this context, the cyclization of hydrazones derived from ortho-(pseudo)haloaryl carbonyl compounds represents a conceptually attractive route to substituted 1*H*-indazoles. While some reactions of this type have been shown to proceed either uncatalyzed[4] or base-catalyzed,[5] in the case of electronically unactivated (hetero)aryl hydrazones the application of palladium, copper, or iron catalysts has proven useful in enabling intramolecular C-N bond formation that affords the 1*H*-indazole core.[6] Notwithstanding such progress, the vast majority of these transformations employ pre-formed substituted/protected hydrazones, with no examples involving substrates derived from ortho-chlorobenzophenones in combination with parent hydrazine.

Building on this theme, we became interested in addressing such synthetic challenges by developing new modular one-pot routes to 1,3-di(hetero)aryl substituted 1*H*-indazoles as outlined in Scheme 1, whereby hydrazones prepared in situ from the condensation of parent hydrazine and ortho-chloro(hetero)benzophenones could be C-N cross-coupled to give 3-substituted-1*H*-indazoles, that in turn could be subjected to *N*-arylation leading to 1,3-disubstituted 1*H*-indazoles. Given the high cost and relative rarity of the platinum group metals, our aim was to employ only base-metal catalysis;[7] we were particularly attracted to the use of nickel[8] and/or copper[9] catalysts, in light of their utility in C-N cross-coupling of (hetero)aryl electrophiles. Herein we disclose our success in this effort, whereby unsymmetrical 1,3-di(hetero)aryl-1*H*-indazoles are assembled in a one-pot fashion via intramolecular (PAd-DalPhos)Ni(*o*-tolyl)Cl[10]-catalyzed C-N cross-coupling, followed by (DMEDA)/CuI-catalyzed *N*-(hetero)arylation.



Scheme 1 Proposed one-pot, base metal-catalyzed route to 1,3-disubstituted 1*H*-indazoles, and the catalysts employed successfully herein for these transformations (M = Ni; M' = Cu).

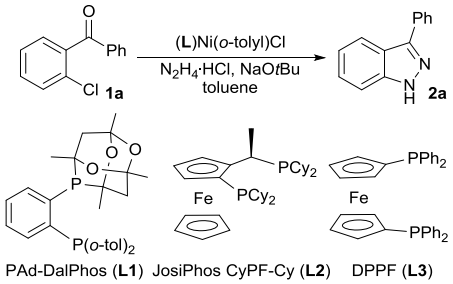
Results and discussion

Our initial efforts were directed toward the identification of an effective nickel pre-catalyst for the intramolecular C-N cross-

[a] Departamento de Química, Universidade Federal de Santa Maria, 97105-900 Santa Maria, Brazil. helio.bonacorso@ufsm.br
[b] Department of Chemistry, Dalhousie University Halifax, NS, B3H 4R2 Canada. mark.stradiotto@dal.ca
[c] Electronic Supplementary Information (ESI) available: Copies of NMR spectra. See DOI: 10.1039/x0xx00000x

coupling of the hydrazone derived in situ from the condensation of parent hydrazine and ortho-chlorobenzophenone (**1a**), leading to 3-phenyl-1*H*-indazole (**2a**). From the outset we viewed transformations of this type as presenting a challenge, given both the potential of nickel to effect undesired N-N bond cleavage of hydrazine derivatives,[11] and the absence of reports documenting the nickel-catalyzed C-N cross-coupling of (hetero)benzophenone hydrazones with aryl chlorides.[12] Encouraged by the catalytic utility of (PAd-DalPhos)Ni(*o*-tolyl)Cl[10] in ammonia monoarylation employing (hetero)aryl chlorides, this pre-catalyst was selected for our preliminary catalytic screen (Table 1). We were pleased to observe that this PAd-DalPhos (**L1**)-derived pre-catalyst afforded high conversion to the desired indazole **2a**, (entry 1) under relatively mild conditions (5 mol% Ni, 16 h, 60 °C). Whereas analogous reactions conducted at 25 °C were unsuccessful (entry 2), the application of a shorter reaction time was tolerated (entry 3). Conversely, negligible conversion to **2a** was achieved (24 h, 60 °C) when using related pre-catalysts featuring either JosiPhos CyPF-Cy (**L2**)[13] or DPPF (**L3**)[14] (entries 4 and 5), or in the absence of a nickel pre-catalyst (entry 6).

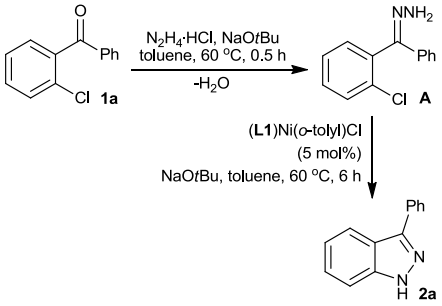
Table 1. Optimization studies for 3-phenyl-1*H*-indazole (**2a**) formation.[a]



Entry	Ligand (**L**)	Time (h)	T (°C)	Conversion to **2a**[b]
1	**L1**	16	60	>90
2	**L1**	16	25	<10
3	**L1**	12	60	90
4	**L2**	24	60	<10
5	**L3**	24	60	<10
6	no-precatalyst	24	60	not detected

[a] Reaction conditions: 2-Chlorobenzophenone (**2a**) (0.2 mmol), hydrazine monohydrochloride (0.24 mmol, 1.2 eq.), (**L**)Ni(*o*-tolyl)Cl (5 mol%), NaO*t*Bu (0.48 mmol, 2.4 eq.), toluene (2 mL). [b] Estimated on the basis of calibrated gas chromatographic data.

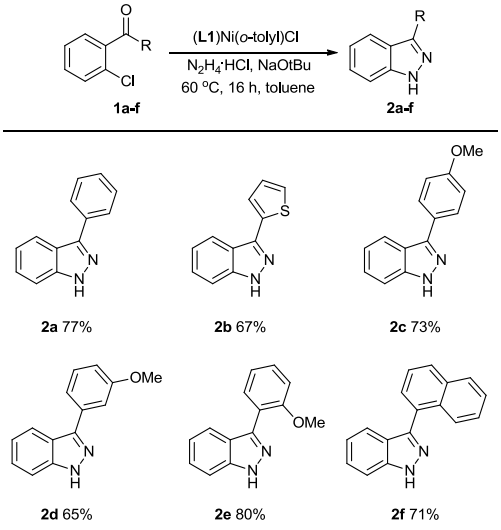
In an effort to gain insight regarding the order of events leading from **1a** to **2a**, the reaction between **1a** and hydrazine under catalytic conditions, but in the absence of the nickel pre-catalyst, was examined by use of calibrated GC methods (Scheme 2). A substantial quantity of the anticipated hydrazone intermediate **A** was detected after only 5 minutes; after 0.5 h clean conversion of **1a** to **A** was observed. Subsequent addition of (PAd-DalPhos)Ni(*o*-tolyl)Cl (5 mol%) and base (in keeping with the stoichiometry of the catalytic reaction) resulted in the formation of **2a** (70%) after 6 h. Moreover, in monitoring the progress of the catalytic reaction (as in Table 1, entry 1), the build-up of **A** is rapid, followed by the slow conversion to **2a**. Collectively, these qualitative observations suggest that nickel-catalyzed intermolecular cross-coupling of **1a** with free hydrazine is unlikely. Rather, a reaction scheme such as that outlined in Scheme 1 appears to be operational, whereby fast condensation affords the hydrazone, which in turn undergoes nickel-catalyzed intramolecular C-N cross-coupling to afford the target indazole.



Scheme 2 Step-wise conversion of **1a** into the hydrazone intermediate **A**, followed by nickel-catalyzed ring-closure to afford **2a**.

The generality of this transformation leading to 3-substituted-1*H*-indazoles was examined briefly (Table 2). A series of substituted ortho-chloro(hetero) benzophenones featuring electron-donating, electron-withdrawing and ortho-substitution were employed successfully, leading to **2a-f** (65-80% yield). Our efforts to extend this methodology to ortho-chloro(hetero)acetophenone derivatives were unsuccessful, likely owing in part to the instability of the putative aryl alkyl hydrazone intermediate (analogous to **A**, Scheme 2).[15]

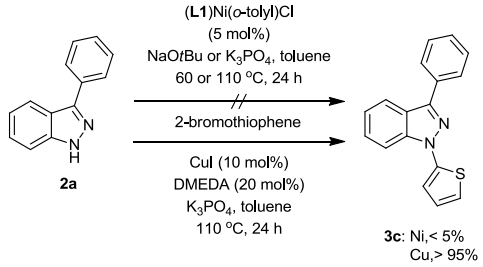
Table 2. Synthesis of 3-(hetero)aryl-1*H*-indazoles.[a]



[a] Reaction conditions: ketone **1a-f** (0.5 mmol), hydrazine monohydrochloride (0.6 mmol, 1.2 eq.), NaO*t*Bu (1.2 mmol, 2.4 eq.), (PAd-DalPhos)Ni(*o*-tolyl)Cl (5 mol%), toluene (2 mL).

Having established a successful nickel-catalyzed route to 3-(hetero)aryl-1*H*-indazoles (Tables 1 and 2), we then sought to extend this protocol to a one-pot synthesis of unsymmetrical 1,3-di(hetero)aryl-1*H*-indazoles as outlined generically in Scheme 1; notably this would require hitherto unknown nickel-catalyzed indazole C-N cross-coupling with a (hetero)aryl

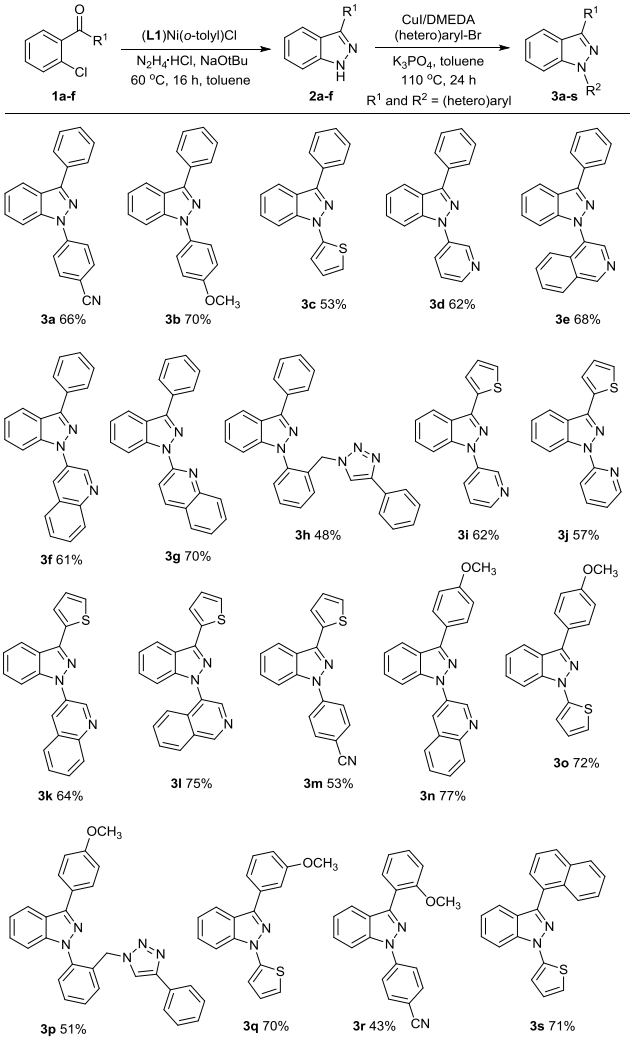
electrophile. To test the feasibility of this latter transformation, the C-N cross-coupling of **2a** with 2-bromothiophene (1.4 eq) in the presence of (PAd-DalPhos)Ni(*o*-tolyl)Cl (5 mol%) and base (NaO*t*Bu or K_3PO_4, 2.4 eq.) was explored (24 h, 60 °C or 110 °C). Unfortunately, under all conditions tested, no appreciable amount of the target *N*-arylated indazole (**3c**) was detected on the basis of NMR spectroscopic or gas chromatographic analysis (Scheme 3). With an aim toward employing an alternative base metal catalyst for the indazole *N*-arylation step, we turned our attention to the use of catalytic CuI/DMEDA under conditions described by Buchwald and co-workers[16] for the *N*-arylation of azoles. Gratifyingly, high conversion to **3c** was achieved under the conditions outlined in Scheme 3. Subsequently, efforts were made to employ CuI/DMEDA (10 and 20 mol%, respectively) for the transformation of **1a** into **2a**. However, the use of CuI/DMEDA in place of the nickel catalyst, either under the conditions outlined in Table 2 (NaO*t*Bu, 16 h, 60 °C) or using K_3PO_4 (24 h, 110 °C), proved ineffective for the synthesis of **2a**.



Scheme 3 Screening of nickel and copper catalysis for the *N*-arylation of **2a** with 2-bromothiophene to give **3c** (2.4 eq. base used throughout).

Collectively, these observations established nickel as being optimal for the initial indazole ring-closure and copper as being optimal for the subsequent indazole *N*-arylation within our reactivity survey, thereby forming the basis for a one-pot, two-step protocol for the assembly of unsymmetrical 1,3-di(hetero)aryl-1*H*-indazoles (Table 3). In this regard, 3-(hetero)aryl-1*H*-indazoles **2a-f** derived from **1a-f** were generated in situ and subjected to CuI/DMEDA-catalyzed *N*-arylation to afford a series of structurally diverse unsymmetrical 1,3-di(hetero)aryl-1*H*-indazoles **3a-s**. We were pleased to find that electron-rich, electron-poor, and ortho-substituted bromides, including heteroaryl variants (thiophenyl, pyridyl, quinolyl, and appended triazole), were each successfully employed in this one-pot protocol. The average overall isolated yield of **3** (63%, 19 examples; most of which are reported here for the first time) is notable in that this value corresponds to approximately 85% yield for each of the three one-pot steps leading from **1** to **3** (i.e., condensation of hydrazine and ortho-chloro(hetero)benzophenones; nickel-catalyzed ring-closure to give 3-substitued-1*H*-indazoles **2**; and copper-catalyzed *N*-arylation leading **3**).

Table 3. One-pot synthesis of unsymmetrical 1,3-di(hetero)aryl-1*H*-indazoles.[a]



[a] Reaction conditions: Step 1: ketone **1a-e** (0.5 mmol), hydrazine monohydrochloride (0.6 mmol, 1.2 eq.), NaO*t*Bu (1.2 mmol, 2.4 eq.), (PAd-DalPhos)Ni(*o*-tolyl)Cl (5 mol%), toluene (2 mL). Step 2: (hetero)aryl bromide (0.7 mmol, 1.4 eq.), K_3PO_4 (1.2 mmol, 2.4 eq.), CuI (10 mol%), DMEDA (20 mol%), toluene (1 mL). Note that no workup was carried out between Steps 1 and 2.

Conclusions

In summary, we have developed the first nickel-catalyzed cyclization of in situ-generated *ortho*-chlorobenzophenone hydrazone derivatives, to afford 3-(hetero)aryl-1*H*-indazoles, and have demonstrated that the derived 1*H*-indazoles can be transformed subsequently in a one-pot procedure into 1,3-di(hetero)aryl-1*H*-indazoles via copper-catalyzed *N*-arylation with (hetero)aryl bromides. This modular new route to 1,3-di(hetero)aryl-1*H*-indazoles is attractive in that it makes use of parent hydrazine monohydrochloride without prior functionalization/protection, and circumvents the use of platinum-group metal catalysis. Encouraged by these results, we are currently exploring the extension of these reactivity concepts to the assembly and functionalization of other sought-after heterocyclic structures.

Experimental Section

General considerations. Unless otherwise indicated, all reactions were setup inside a nitrogen-filled inert atmosphere glovebox and worked up in air using benchtop procedures. Toluene was deoxygenated by sparging with nitrogen followed by passage through an mBraun double column solvent purification system packed with alumina and copper-Q5 reactant and storage over activated 4 Å molecular sieves. Synthesis and characterization of the ketones **1b-f** are provided in the Supporting Information. The pre-catalysts (**L**)Ni(*o*-tolyl)Cl (PAd-DalPhos, **L1**;[10] JosiPhos CyPF-Cy, **L2**;[13b] or DPPF, **L3**[14]) were prepared by use of literature procedures. Otherwise, all reagents including **1a** were obtained from commercial sources and used without further purification. Column chromatography was performed on silica gel (230−400 mesh). All NMR spectra were acquired on a 300 or 500 MHz spectrometer with samples dissolved in $CDCl_3$ or DMSO-d_6, and with signals referenced accordingly. Data are reported as follows: Chemical shift (δ) (multiplicity, coupling constant, integration). Splitting patterns are indicated as follows: s = singlet, d = doublet, t = triplet, q = quartet, qui = apparent quintet, dd = doublet of doublets, td = triplet of doublets, m = multiplet, b = broad. All coupling constants (J) are reported in Hertz (Hz). High resolution mass spectrometry data (HRMS) were obtained using ion trap (ESI) instruments operating in positive ion mode.

General procedure for the synthesis of 3-(hetero)aryl-1*H*-indazoles (2a-f). Ketone (0.5 mmol), hydrazine monohydrochloride (0.6 mmol), NaO*t*Bu (1.2 mmol), (PAd-DalPhos)Ni(*o*-tolyl)Cl (5 mol%), and toluene (2 mL) were added to a screw capped vial containing a magnetic stir bar. The vial was sealed with a cap containing a PTFE septum, placed in a temperature-controlled aluminum heating block set at 60 °C, and magnetic stirring was initiated. After 16 h, product workup was carried out; the crude reaction mixture was filtered over a silica plug, followed by rinsing of the plug with EtOAc (60 mL). The combined eluent was collected, concentrated on the rotary evaporator, and the crude product thus obtained was purified by use of column chromatography.

General procedure for the one-pot synthesis of unsymmetrical 1,3-di(hetero)aryl-1*H*-indazoles (3a-s). Products **2a-f** were generated as outlined above. However, instead of conducting product workup, under inert atmosphere the reaction vial was opened and (hetero)aryl bromide (0.7 mmol), K_3PO_4 (1.2 mmol), CuI (10 mol%), DMEDA (20 mol%), and toluene (1 mL) were added. The vial was re-sealed with a cap containing a PTFE septum, placed in a temperature-controlled aluminum heating block set at 110 °C, and magnetic stirring was initiated. After 24 h, the crude reaction mixture was filtered over a silica plug, followed by rinsing of the plug with EtOAc (60 mL). The combined eluent was collected, concentrated on the rotary evaporator, and the crude product thus obtained was purified by use of column chromatography.

3-Phenyl-1*H*-indazole (2a): Eluted with 20% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 75 mg – 77%. NMR: ^{1}H (500 MHz, $CDCl_3$): δ = 11.18 (b, 1H), 8.08 – 8.04 (m, 3H), 7.58 (t, J = 7.5, 2H), 7.49 – 7.46 (m, 1H), 7.43 – 7.37 (m, 2H), 7.29 – 7.25 (m, 1H); ^{13}C{^{1}H} (125 MHz, $CDCl_3$): δ = 145.8, 141.7, 133.6, 128.9, 128.2, 127.7, 126.8, 121.4, 121.1, 121.0, 110.2. Data agree with literature.[17]

3-(Thiophen-2-yl)-1*H*-indazole (2b): Eluted with 20% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 67 mg – 67%. NMR: ^{1}H (500 MHz, $CDCl_3$, 25 °C) δ = 10.41 (b, 1H), 8.06 (d, J = 8.2, 1H), 7.69 (dd, J = 3.5, 0.8, 1H), 7.46 – 7.41 (m, 2H), 7.39 (dd, J = 5.1, 0.9, 1H), 7.28 – 7.25 (m, 1H), 7.20 (dd, J = 5.1, 3.6, 1H). ^{13}C{^{1}H} (125 MHz, $CDCl_3$, 25 °C) δ = 141.6, 140.8, 135.8, 127.7, 127.2, 125.2, 124.9, 121.6, 120.9, 120.5, 110.1. Data agree with literature.[18]

3-(4-Methoxyphenyl)-1*H*-indazole (2c): Eluted with 20% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 82 mg – 73%. NMR: ^{1}H (300 MHz, $CDCl_3$): δ = 11.61 (b, 1H), 8.03 – 7.96 (m, 3H), 7.38 – 7.32 (m, 1H), 7.26-7.18 (m, 2H), 7.11 – 7.06 (m, 2H), 3.90 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$): δ = 159.7, 145.7, 141.8, 128.9, 126.6, 126.2, 121.1, 121.1, 114.4, 110.3, 55.4 Data agree with literature.[18]

3-(3-Methoxyphenyl)-1*H*-indazole (2d): Eluted with 20% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 73 mg – 65%. NMR: ^{1}H (300 MHz, $CDCl_3$): δ = 10.05 (b, 1H), 8.05 (d, J = 8.2, 1H), 7.62 – 7.56 (m, 2H), 7.45 (t, J = 7.9, 1H), 7.40 – 7.36 (m, 2H), 7.26 – 7.21 (m, 1H), 7.02 – 6.99 (m, 1H), 3.89 (s, 3H).^{13}C{^{1}H} (75 MHz, $CDCl_3$): δ = 160.1, 145.7, 141.8, 134.8, 130.0, 126.8, 121.4, 121.1, 120.2, 114.2, 112.9, 110.4, 55.3. Data agree with literature.[19]

3-(2-Methoxyphenyl)-1*H*-indazole (2e): Eluted with 20% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 90 mg – 80%. NMR: ^{1}H (300 MHz, $CDCl_3$): δ = 10.64 (b, 1H), 7.80 – 7.73 (m, 2H), 7.50 – 7.44 (m, 1H), 7.34 – 7.29 (m, 1H), 7.20 – 7.15 (m, 2H), 7.11 (d, J = 7.8, 2H), 3.84 (s, 3H). ^{13}C{^{1}H} (75 MHz, $CDCl_3$): δ = 157.4, 143.1, 141.4, 131.4, 129.7, 126.4, 122.2, 122.0, 120.9, 120.6, 111.4, 110.4, 55.5. Data agree with literature.[20]

3-(Naphthalen-1-yl)-1*H*-indazole (2f): Eluted with 10% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 87 mg – 71%. NMR: ^{1}H (500 MHz, $CDCl_3$): δ = 12.25 (b, 1H), 8.32 – 8.31 (m, 1H), 8.01 – 7.98 (m, 2H), 7.79 – 7.67 (m, 2H), 7.57 – 7.52 m, 2H), 7.48 – 7.39 (m, 2H), 7.21 (t, J = 6.7, 1H), 6.93 – 6.92 (m, 1H). ^{13}C{^{1}H} (125 MHz, $CDCl_3$): δ = 143.4, 134.1, 131.9, 131.3, 128.8, 128.2, 128.1, 126.7, 126.4, 126.3, 126.1, 125.4, 121.9, 121.3, 110.9. HRMS (ESI): $C_{17}H_{12}N_2Na$ (M + Na) requires 267.0898 / Found: 267.0893.

4-(3-Phenyl-1*H*-indazol-1-yl)benzonitrile (3a): Eluted with 10% EtOAc in hexanes solution. Physical aspect: Yellow solid. Yield: 97 mg – 66%. NMR: ^{1}H (500 MHz, $CDCl_3$, 25 °C) δ = 8.11 (d, J = 8.1, 1H), 8.04 – 8.00 (m, 4H), 7.87 – 7.83 (m, 3 H), 7.57 – 7.53 (m, 3H), 7.48 (tt, J = 7.4, 1.5, 1H), 7.36 (t, J = 7.5, 1H). ^{13}C{^{1}H} (125 MHz, $CDCl_3$, 25 °C) δ = 147.9, 143.8, 140.0, 133.5, 132.4, 128.9, 128.8, 128.0, 127.9, 124.1, 122.9, 122.1, 122.0, 118.6, 110.7, 109.2. HRMS (ESI): $C_{20}H_{13}N_3Na$ (M + Na) requires 318.1007 / Found: 318.0988. Data agree with literature.[21]

1-(4-Methoxyphenyl)-3-phenyl-1*H*-indazole (3b): Eluted with 5% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 105 mg – 70%. NMR: ^{1}H (300 MHz, $CDCl_3$, 25 °C) δ = 8.08 – 8.01 (m, 3H), 7.69 – 7.64 (m, 3H), 7.54 – 7.49 (m, 2H), 7.45 – 7.38 (m, 2H), 7.28 – 7.23 (m, 1H), 7.09 – 7.03 (m, 2H), 3.87 (s, 3H). ^{13}C {^{1}H} (75 MHz, $CDCl_3$, 25 °C) δ = 158.5, 145.5, 140.6, 133.4, 133.3, 128.8, 128.1, 127.7, 126.9, 124.8, 122.7, 121.7, 121.5, 114.6, 110.5, 55.6. HRMS (ESI): $C_{20}H_{17}N_2O$ (M + H) requires 301.1341 / Found: 301.1338.

3-Phenyl-1-(thiophen-2-yl)-1*H*-indazole (3c): Eluted with 2% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 73 mg – 53%. NMR: ^{1}H (300 MHz, $CDCl_3$, 25 °C) δ = 8.07 (dt, J = 8.1, 0.9, 1H), 8.05 – 8.01 (m, 2H), 7.79 (dt, J = 8.5, 0.8, 1H), 7.57 – 7.42 (m, 4H), 7.34 –

7.29 (m, 2H), 7.19 (dd, *J* = 5.5, 1.4, 1H), 7.09 (dd, *J* = 5.5, 3.7, 1H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$, 25 °C) δ = 146.6, 142.4, 140.9, 132.7, 128.8, 128.5, 127.9, 127.6, 126.0, 123.0, 122.3, 121.6, 121.1, 117.3, 110.7 HRMS (ESI): $C_{17}H_{12}N_2SNa$ (M + Na) requires 299.0619 / Found: 299.0606.

3-Phenyl-1-(pyridin-3-yl)-1*H*-indazole (3d): Eluted with 10% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 84 mg – 62%. NMR: ^1H (500 MHz, DMSO-d_6, 25 °C) δ = 9.13 (s, 1H), 8.65 (d, *J* = 4.3, 1H), 8.32 – 8.30 (m, 1H), 8.20 (d, *J* = 8.2, 1H), 8.08 – 8.06 (m, 2H), 7.96 (d, *J* = 8.5, 1H), 7.67 (dd, *J* = 8.2, 4.7, 1H), 7.61 – 7.58 (m, 3H), 7.50 (t, *J* = 7.4, 1H), 7.41 (t, *J* = 7.5, 1H). $^{13}C\{^1H\}$ (125 MHz, DMSO-d_6, 25 °C) δ = 147.5, 145.9, 143.3, 139.8, 136.1, 132.1, 129.6, 128.9, 128.6, 127.9, 127.3, 124.3, 122.7, 122.4, 121.4, 110.7. HRMS (ESI): $C_{18}H_{14}N_3$ (M + H) requires 272.1188 / Found: 272.1182.

4-(3-Phenyl-1*H*-indazol-1-yl)isoquinoline (3e): Eluted with 10% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 109 mg – 68%. NMR: ^1H (300 MHz, $CDCl_3$, 25 °C) δ = 9.39 (s, 1H), 8.82 (s, 1H), 8.19 – 8.09 (m, 4H), 7.88 – 7.85 (m, 1H), 7.75 – 7.68 (m, 2H), 7.59 – 7.54 (m, 2H), 7.49 – 7.41 (m, 2H), 7.38 – 7.32 (m, 2H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$, 25 °C) δ = 152.9, 146.9, 142.8, 140.9, 133.0, 132.5, 131.4, 131.0, 129.4, 128.8, 128.4, 128.0, 127.8, 127.7, 127.3, 122.8, 122.4, 122.1, 121.6, 110.3. HRMS (ESI): $C_{22}H_{16}N_3$ (M + H) requires 322.1344 / Found: 322.1334.

3-(3-Phenyl-1*H*-indazol-1-yl)quinoline (3f): Eluted with 15% EtOAc in hexanes solution. Physical aspect: off-white solid. Yield: 98 mg – 61%. NMR: ^1H (300 MHz, $CDCl_3$, 25 °C) δ = 9.50 (d, *J* = 2.4, 1H), 8.50 (d, *J* = 2.4, 1H), 8.21 (d, *J* = 8.5, 1H), 8.13 (d, *J* = 8.2, 1H), 8.09 – 8.05 (m, 2H), 7.93 (dd, *J* = 8.1, 1.0, 1H), 7.87 (d, *J* = 8.5, 1H), 7.79 – 7.74 (m, 1H), 7.66 – 7.45 (m, 5H), 7.39 – 7.33 (m, 1H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$, 25 °C) δ = 147.4, 146.5, 146.1, 140.6, 133.7, 132.8, 129.5, 129.4, 128.9, 128.6, 127.9, 127.8, 127.8, 127.6, 127.1, 123.5, 122.5, 121.9, 110.3. HRMS (ESI): $C_{22}H_{16}N_3$ (M + H) requires 322.1344 / Found: 322.1341.

2-(3-Phenyl-1*H*-indazol-1-yl)quinoline (3g): Eluted with 4% EtOAc in hexanes solution. Physical aspect: white solid. Yield: 112 mg – 70%. NMR: ^1H (300 MHz, $CDCl_3$, 25 °C) δ = 9.30 (d, *J* = 8.5, 1H), 8.44 (d, *J* = 8.9, 1H), 8.27 (d, *J* = 8.9, 1H), 8.15 (d, *J* = 8.4, 1H), 8.12 – 8.07 (m, 3H), 7.84 (dd, *J* = 8.1, 1.2, 1H), 7.78 – 7.72 (m, 1H), 7.67 – 7.62 (m, 1H), 7.61 – 7.55 (m, 2H), 7.53 – 7.46 (m, 2H), 7.43 – 7.37 (m, 1H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$, 25 °C) δ = 153.0, 147.4, 146.7, 140.5, 138.2, 132.9, 129.9, 128.8, 128.7, 128.3, 128.0, 128.0, 127.6, 126.1, 125.3, 124.3, 123.2, 121.0, 116.4, 113.7. HRMS (ESI): $C_{22}H_{16}N_3$ (M + H) requires 322.1344 / Found 322.1329.

3-Phenyl-1-(2-((4-phenyl-1*H*-1,2,3-triazol-1-yl)methyl)phenyl)-1*H*-indazole (3h): Eluted with 15% EtOAc in hexanes solution. Physical aspect: off-white solid. Yield: 103 mg – 48%. NMR: ^1H (300 MHz, $CDCl_3$, 25 °C) δ = 8.14 (dt, *J* = 8.2, 0.8, 1H), 8.07 – 8.03 (m, 2H), 7.76 (s, 1H), 7.68 – 7.64 (m, 2H), 7.61 – 7.28 (m, 13H), 5.62 (s, 2H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$, 25 °C) δ = 147.7, 146.5, 142.1, 137.5, 132.9, 132.3, 131.1, 130.5, 129.7, 129.3, 129.0, 128.7, 128.6, 128.0, 127.6, 126.9, 125.6, 122.3, 122.2, 121.6, 120.3, 110.2, 50.0. HRMS (ESI): $C_{28}H_{21}N_5Na$ (M + Na) requires 450.1695 / Found 450.1678.

1-(Pyridin-3-yl)-3-(thiophen-2-yl)-1*H*-indazole (3i): Eluted with 15% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 86 mg – 62%. NMR: ^1H (300 MHz, $CDCl_3$, 25 °C) δ = 9.15 (s, 1H), 8.64 (d, *J* = 3.4, 1H), 8.15 (d, *J* = 8.1, 2H), 7.80 – 7.76 (m, 2H), 7.56 – 7.51 (m, 2H), 7.45 (dd, *J* = 5.1, 1.1, 1H), 7.39 – 7.34 (m, 1H), 7.24 (dd, *J* = 5.1, 3.6, 1H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$, 25 °C) δ = 147.5, 143.7, 142.3, 140.2, 136.8, 134.9, 129.9, 128.0, 127.7, 125.9, 125.6, 124.1, 122.9, 122.6, 121.6, 110.3. HRMS (ESI): $C_{16}H_{11}N_3SNa$ (M + Na) requires 300.0571 / Found: 300.0569.

1-(Pyridin-2-yl)-3-(thiophen-2-yl)-1*H*-indazole (3j): Eluted with 15% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 79 mg – 57%. NMR: ^1H (300 MHz, $CDCl_3$, 25 °C) δ = 8.92 (dt, *J* = 8.6, 0.9, 1H), 8.53 (ddd, *J* = 4.9, 1.8, 0.8, 1H), 8.15 (dt, *J* = 8.4, 0.9, 1H), 8.09 (dt, *J* = 8.1, 1.0, 1H), 7.86 – 7.80 (m, 1H), 7.78 (dd, *J* = 3.6, 1.1, 1H), 7.59 – 7.53 (m, 1H), 7.44 (dd, 5.1, 1.1, 1H), 7.39 – 7.34 (m, 1H), 7.22 (dd, *J* = 7.1, 3.6, 1H), 7.15 (ddd, *J* = 7.3, 4.9, 1.0, 1H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$, 25 °C) δ = 154.1, 147.6, 142.0, 140.2, 138.2, 135.3, 128.1, 127.7, 126.0, 125.8, 123.4, 123.0, 120.7, 119.8, 115.7, 113.7. HRMS (ESI): $C_{16}H_{11}N_3SNa$ (M + Na) requires 300.0571 / Found: 300.0562.

3-(3-(Thiophen-2-yl)-1*H*-indazol-1-yl)quinoline (3k): Eluted with 15% EtOAc in hexanes solution. Physical aspect: white solid. Yield: 105 mg – 64%. NMR: ^1H (300 MHz, $CDCl_3$, 25 °C) δ = 9.46 (d, *J* = 2.3, 1H), 8.49 (d, *J* = 2.4, 1H), 8.22 (d, *J* = 8.3, 1H), 8.17 (dt, *J* = 8.2, 1.0, 1H), 7.94 (dd, *J* = 8.1, 1.2, 1H), 7.84 (dt, *J* = 8.5, 0.8 1H), 7.80 – 7.74 (m, 2H), 7.67 – 7.62 (m, 1H), 7.58 – 7.52 (m, 1H), 7.45 (dd, *J* = 5.1, 1.1, 1H), 7.41 – 7.36 (m, 1H), 7.23 (dd, *J* = 5.1, 3.6). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$, 25 °C) δ = 146.4, 145.9, 142.4, 140.5, 134.9, 133.6, 129.5, 129.4, 128.1, 127.9, 127.8 (two signals), 127.7, 127.3, 126.0, 125.7, 123.0, 122.7, 121.7, 110.3. HRMS (ESI): $C_{20}H_{14}N_3S$ (M + H) requires 328.0908 / Found: 328.0892.

4-(3-(Thiophen-2-yl)-1*H*-indazol-1-yl)isoquinoline (3l): Eluted with 15% EtOAc in hexanes solution. Physical aspect: off-white solid. Yield: 122 mg – 75%. NMR: ^1H (300 MHz, $CDCl_3$, 25 °C) δ = 9.38 (s, 1H), 8.79 (s, 1H), 8.19 (d, *J* = 8.0, 1H), 8.14 – 8.10 (m, 1H), 7.84 – 7.78 (m, 2H), 7.74 – 7.68 (m, 2H), 7.47 – 7.41 (m, 2H), 7.38 – 7.31 (m, 2H), 7.23 (dd, *J* = 5.1, 3.6, 1H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$, 25 °C) δ = 153.0, 142.7, 142.0, 141.0, 135.3, 132.6, 131.5, 130.8, 129.4, 128.1, 127.8, 127.7, 127.6, 125.7, 125.4, 122.8, 122.4, 121.9, 121.3, 110.4. HRMS (ESI): $C_{20}H_{14}N_3S$ (M + H) requires 328.0908 / Found: 328.0896.

4-(3-(Thiophen-2-yl)-1*H*-indazol-1-yl)benzonitrile (3m): Eluted with 15% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 80 mg – 53%. NMR: ^1H (300 MHz, $CDCl_3$, 25 °C) δ = 8.14 (dt. *J* = 8.1, 0.9, 1H), 8.0 – 7.96 (m, 2H), 7.85 – 7.81 (m, 3H), 7.76 (dd. *J* = 3.6, 1.1, 1H), 7.57 – 7.52 (m, 1H), 7.45 (dd, *J* = 5.1, 1.1, 1H), 7.41 – 7.36 (m, 1H), 7.22 (dd, *J* = 5.1, 3.6, 1H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$, 25 °C) δ = 143.5, 142.8, 139.9, 134.6, 133.5, 128.3, 127.8, 126.3, 125.9, 123.5, 123.1, 122.0, 121.9, 118.5, 110.8, 109.3. HRMS (ESI): $C_{18}H_{11}N_3SNa$ (M + Na) requires 324.0571 / Found: 324.0554.

3-(3-(4-Methoxyphenyl)-1*H*-indazol-1-yl)quinolone (3n): Eluted with 15% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 135 mg – 77%. NMR: ^1H (300 MHz, $CDCl_3$, 25 °C) δ = 9.50 (d, *J* = 2.5, 1H), 8.49 (d, *J* = 2.3, 1H), 8.21 (d, *J* = 8.4, 1H), 8.10 (d, *J* = 8.2, 1H), 8.03 – 7.99 (m, 2H), 7.92 (dd, *J* = 8.1, 0.9, 1H), 7.86 (d, *J* = 8.5, 1H), 7.78 – 7.73 (m, 1H), 7.66 – 7.60 (m, 1H), 7.55 – 7.50 (m, 1H), 7.37 – 7.31 (m, 1H), 7.12 – 7.07 (m, 2H), 3.90 (s, 3H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$, 25 °C) δ = 160.1, 147.3, 146.4, 146.1, 140.5, 133.8, 129.5, 129.3, 129.1, 128.0, 127.8, 127.7, 127.6, 126.8, 125.4, 123.5, 122.3, 122.0, 114.4, 110.2, 55.4. HRMS (ESI): $C_{23}H_{18}N_3O$ (M + H) requires 352.1450 / Found: 352.1451.

3-(4-Methoxyphenyl)-1-(thiophen-2-yl)-1*H*-indazole (3o): Eluted with 4% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 110 mg – 72%. NMR: ^1H (300 MHz, $CDCl_3$, 25 °C) δ = 8.06 – 7.97 (m, 3H), 7.78 (d, *J* = 8.4, 1H), 7.50 (t, *J* = 7.5, 1H), 7.33 – 7.28 (m, 2H),

7.18, (d, *J* = 5.1, 1H), 7.09 – 7.07 (m, 3H), 3.90 (s, 3H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$, 25 °C) δ = 159.9, 146.3, 142.5, 140.7, 129.0, 127.5, 125.9, 125.2, 122.9, 122.1, 121.6, 120.8, 116.9, 114.3, 110.6, 55.3. HRMS (ESI): $C_{18}H_{14}N_2OSNa$ (M + Na) requires 329.0725 / Found 329.0715.

3-(4-Methoxyphenyl)-1-(2-((4-phenyl-1H-1,2,3-triazol-1-yl) methyl) phenyl)-1*H*-indazole (3p): Eluted with 15% EtOAc in hexanes solution. Physical aspect: off-white solid. Yield: 117 mg – 51%. NMR: ^1H (300 MHz, $CDCl_3$, 25 °C) δ = 8.11 (d, *J* = 8.1, 1H), 7.99 (d, *J* = 8.7, 2H), 7.75 (s, 1H), 7.67 (d, *J* = 7.2, 2H), 7.60 – 7.28 (m, 10H), 7.08 (d, *J* = 8.7, 2H), 5.62 (s, 2H), 3.90 (s, 3H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$, 25 °C) δ = 160.0, 147.7, 146.3, 142.0, 137.6, 132.2, 131.1, 130.5, 129.6, 129.1, 128.8, 128.6, 127.9, 127.5, 126.8, 125.6, 125.4, 122.1 (two signals), 121.6, 120.4, 114.4, 110.2, 55.4, 50.1. HRMS (ESI): $C_{29}H_{23}N_5ONa$ (M + Na) requires 480.1800 / Found 480.1793.

3-(3-methoxyphenyl)-1-(thiophen-2-yl)-1*H*-indazole (3q): Eluted with 4% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 107 mg – 70%. NMR: ^1H (500 MHz, $CDCl_3$, 25 °C) δ = 8.09 (d, *J* = 8.2, 1H), 7.78 (d, *J* = 8.5, 1H), 7.65 (d, *J* = 7.6, 1H), 7.63 – 7.62 (m, 1H), 7.52 – 7.49 (m, 1H), 7.47 (t, *J* = 7.9, 1H), 7.33 – 7.30 (m, 2H), 7.19 (dd, *J* = 5.5, 1.3, 1H), 7.09 (dd, *J* = 5.5, 3.7, 1H), 7.04 – 7.02 (m, 1H), 3.93 (s, 3H). $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$, 25 °C) δ = 159.9, 146.4, 142.3, 140.9, 133.9, 129.8, 127.6, 125.9, 123.0, 122.3, 121.6, 121.1, 120.3, 117.3, 114.4, 113.1, 110.7, 55.3. HRMS (ESI): $C_{18}H_{14}N_2OSNa$ (M + Na) requires 329.0725 / Found 329.0718.

4-(3-(2-Methoxyphenyl)-1*H*-indazol-1-yl)benzonitrile (3r): Eluted with 10% EtOAc in hexanes solution. Physical aspect: White solid. Yield: 70 mg – 43%. NMR: ^1H (300 MHz, $CDCl_3$): δ = 8.03 – 7.98 (m. 2H), 7.85 – 7.79 (m, 4H), 7.68 (dd, *J* = 7.5, 1.7, 1H), 7.54 – 7.45 (m, 2H), 7.31 – 7.26 (m, 1H), 7.15 – 7.09 (m, 2H), 3.88 (s, 3H). $^{13}C\{^1H\}$ (75 MHz, $CDCl_3$): δ = 157.4, 146.8, 143.8, 139.3, 133.4, 131.5, 130.5, 127.7, 125.5, 123.4, 122.1, 121.8, 121.2, 120.9, 118.6, 111.3, 110.3, 109.9, 108.8, 55.5. HRMS (ESI): $C_{21}H_{15}N_3ONa$ (M + Na) requires 348.1113 / Found 348.1099.

3-(Naphthalen-1-yl)-1-(thiophen-2-yl)-1*H*-indazole (3s): Eluted with 10% EtOAc in hexanes solution. Physical aspect: yellow solid. Yield: 115 mg – 71%. NMR: ^1H (500 MHz, $CDCl_3$): δ = 8.33 – 8.30 (m, 1H), 8.00 – 7.94 (m, 2H), 7.89 – 7.83 (m, 2H), 7.71 (dt, *J* = 8.1, 1.0, 1H), 7.65 – 7.60 (m, 1H), 7.57 – 7.52 (m, 2H), 7.50 – 7.47 (m, 1H), 7.36 (dd, *J* = 3.7, 1.4, 1H), 7.29 – 7.24 (m, 1H), 7.20 (dd, J = 5.5, 1.4, 1H), 7.11 (dd, *J* = 5.5, 3.7, 1H). $^{13}C\{^1H\}$ (125 MHz, $CDCl_3$): δ = 146.6, 142.6, 140.2, 134.0, 131.8, 130.3, 129.2, 128.4, 128.3, 127.8, 126.5, 126.2, 126.0, 126.0, 125.3, 124.9, 122.1, 121.9, 120.8, 116.9, 110.6. HRMS (ESI): $C_{21}H_{14}N_2SNa$ (M + Na) requires 349.0775 / Found: 349.0765.

Acknowledgements

We are appreciative of the generous financial support of this work from the Conselho Nacional de Desenvolvimento Científico e Tecnológico (CNPq) and the Natural Sciences and Engineering Research Council of Canada (NSERC Canada).

Notes and references

1. (a) G. A. Bistocchi, G. Demeo, M. Pedini, A. Ricci, H. Brouilhet, S. Boucherie, M. Rabaud, P. Jacquignon, *Farmaco Ed. Sci.* **1981**, *36*, 315-333; (b) W. Stadlbauer, *Sci. Synth*. **2002**, *12*, 227-324; (c) H. Cerecetto, A. Gerpe, M. Gonzalez, V. J. Aran, C. O. de Ocariz, *Mini-Rev. Med. Chem.* **2005**, *5*, 869-878; (d) A. Thangadurai, M. Minu, S. Wakode, S. Agrawal, B. Narasimhan, *Med. Chem. Res*. **2012**, *21*, 1509-1523; (e) D. D. Gaikwad, A. D. Chapolikar, C. G. Devkate, K. D. Warad, A. P. Tayade, R. P. Pawar, A. J. Domb, Eur. *J. Med. Chem.* **2015**, *90*, 707-731.

2. (a) P. Jacobson, L. Huber, *Ber. Dtsch. Chem. Ges.* **1908**, *41*, 660-671; (b) C. Ruchardt, V. Hassmann, *Liebigs Ann. Chem.* **1980**, 908-927; (c) T. Yoshida, N. Matsuura, K. Yamamoto, M. Doi, K. Shimada, T. Morie, S. Kato, *Heterocycles* **1996**, *43*, 2701-2712; (d) F. Crestey, V. Collot, S. Stiebing, S. Rault, *Tetrahedron* **2006**, *62*, 7772-7775.

3. For selected recent examples involving uncatalyzed aryne cycloaddition or employing arylamino oxime synthons, see: (a) T. Jin, Y. Yamamoto, *Angew. Chem. Int. Ed.* **2007**, *46*, 3323-3325; (b) B. C. Wray, J. P. Stambuli, *Org. Lett.* **2010**, *12*, 4576-4579; (c) C. Spiteri, S. Keeling, J. E. Moses, *Org. Lett.* **2010**, *12*, 3368-3371.

4. For selected examples, see: (a) G. M. Shutske, R. C. Allen, M. F. Forsch, L. L. Setescak, J. C. Wilker, *J. Med. Chem.* **1983**, *26*, 1307-1311; (b) B. R. Henke, C. J. Aquino, L. S. Birkemo, D. K. Croom, R. W. Dougherty, G. N. Ervin, M. K. Grizzle, G. C. Hirst, M. K. James, M. F. Johnson, K. L. Queen, R. G. Sherrill, E. E. Sugg, E. M. Suh, J. W. Szewczyk, R. J. Unwalla, J. Yingling, T. M. Willson, *J. Med. Chem.* **1997**, *40*, 2706-2725; (c) S. Caron, E. Vazquez, *Synthesis* **1999**, 588-592; (d) V. Leroy, G. E. Lee, J. Lin, S. H. Herman, T. B. Lee, *Org. Process Res. Dev.* **2001**, *5*, 179-183; (e) J. R. J. Cui, G. L. Araldi, J. E. Reiner, K. M. Reddy, S. J. Kemp, J. Z. Ho, D. V. Siev, L. Mamedova, T. S. Gibson, J. A. Gaudette, N. K. Minami, S. M. Anderson, A. E. Bradbury, T. G. Nolan, J. E. Semple, *Bioorg. Med. Chem. Lett.* **2002**, *12*, 2925-2930; (f) J. Witherington, V. Bordas, A. Gaiba, A. Naylor, A. D. Rawlings, B. P. Slingsby, D. G. Smith, A. K. Takle, R. W. Ward, *Bioorg. Med. Chem. Lett.* **2003**, *13*, 3059-3062; (g) T. J. Watson, T. A. Ayers, N. Shah, D. Wenstrup, M. Webster, D. Freund, S. Horgan, J. P. Carey, *Org. Process Res. Dev.* **2003**, *7*, 521-532; (h) K. Lukin, M. C. Hsu, D. Fernando, M. R. Leanna, *J. Org. Chem.* **2006**, *71*, 8166-8172.

5. I. Thome, C. Besson, T. Kleine, C. Bolm, *Angew. Chem. Int. Ed.* **2013**, *52*, 7509-7513.

6. For selected representative examples including variations on this reaction theme, see: (a) J. J. Song, N. K. Yee, *Org. Lett.* **2000**, *2*, 519-521; (b) J. J. Song, N. K. Yee, *Tetrahedron Lett.* **2001**, *42*, 2937-2940; (c) K. Inamoto, M. Katsuno, T. Yoshino, I. Suzuki, K. Hiroya, T. Sakamoto, *Chem. Lett.* **2004**, *33*, 1026-1027; (d) D. K. O'Dell, K. M. Nicholas, *Heterocycles* **2004**, *63*, 373-382; (e) C. S. Cho, D. K. Lim, N. H. Heo, T.-J. Kim, S. C. Shim, *Chem. Commun.* **2004**, 104-105; (f) A. Y. Lebedev, A. S. Khartulyari, A. Z. Voskoboynikov, *J. Org. Chem.* **2005**, *70*, 596-602; (g) C. Pabba, H. J. Wang, S. R. Mulligan, Z. J. Chen, T. M. Stark, B. T. Gregg, *Tetrahedron Lett.* **2005**, *46*, 7553-7557; (h) K. Inamoto, M. Katsuno, T. Yoshino, Y. Arai, K. Hiroya, T. Sakamoto, *Tetrahedron* **2007**, *63*, 2695-2711; (i) K. Inamoto, T. Saito, M.

Katsuno, T. Sakamoto, K. Hiroya, *Org. Lett.* **2007**, 9, 2931-2934; (j) D. Vina, E. del Olmo, J. L. Lopez-Perez, A. San Feliciano, *Org. Lett.* **2007**, *9*, 525-528; (k) B. J. Stokes, C. V. Vogel, L. K. Urnezis, M. Pan, T. G. Driver, *Org. Lett.* **2010**, *12*, 2884-2887; (l) X. Xiong, Y. Jiang, D. Ma, *Org. Lett.* **2012**, *14*, 2552-2555; (m) X. Li, L. He, H. Chen, W. Wu, H. Jiang, *J. Org. Chem.* **2013**, *78*, 3636-3646; (n) T. Zhang, W. Bao, *J. Org. Chem.* **2013**, *78*, 1317-1322; (o) M. Tang, Y. F. Kong, B. J. Chu, D. Feng, *Adv. Synth. Catal.* **2016**, 358, 926-939.

7. R. M. Bullock, *Catalysis Without Precious Metals*, Wiley-VCH, Weinheim, Germany, **2010**.

8. M. Marín, R. J. Rama, M. C. Nicasio, *Chem. Rec.* **2016**, *16*, 1819-1832.

9. F. Monnier, M. Taillefer, Top. *Organomet. Chem.* **2013**, *46*, 173-204.

10. C. M. Lavoie, P. M. MacQueen, N. L. Rotta-Loria, R. S. Sawatzky, A. Borzenko, A. J. Chisholm, B. K. V. Hargreaves, R. McDonald, M. J. Ferguson, M. Stradiotto, *Nat. Commun.* **2016**, *7*, 11073.

11. F. Alonso, G. Radivoy, M. Yus, *Tetrahedron* **2000**, *56*, 8673-8678.

12. The intermolecular nickel-catalyzed cross-coupling of parent benzophenone hydrazone with aryl bromides, but not chlorides, has been reported: W. Wu, X. H. Fan, L. P. Zhang, L. M. Yang, *RSC Adv.* **2014**, *4*, 3364-3367.

13. (a) A. Borzenko, N. L. Rotta-Loria, P. M. MacQueen, C. M. Lavoie, R. McDonald, M. Stradiotto, *Angew. Chem. Int. Ed.* **2015**, *54*, 3773-3777; (b) J. S. K. Clark, C. M. Lavoie, P. M. MacQueen, M. J. Ferguson, M. Stradiotto, *Organometallics* **2016**, *35*, 3248-3254.

14. N. H. Park, G. Teverovskiy, S. L. Buchwald, *Org. Lett.* **2014**, *16*, 220-223.

15. (a) H. H. Szmant, C. Mcginnis, *J. Am. Chem. Soc.* **1950**, *72*, 2890-2892; (b) S. Wagaw, B. H. Yang, S. L. Buchwald, *J. Am. Chem. Soc.* **1998**, *120*, 6621-6622.

16. J. C. Antilla, J. M. Baskin, T. E. Barder, S. L. Buchwald, *J. Org. Chem.* **2004**, *69*, 5578-5587.

17. C. M. Counceller, C. C. Eichman, B. C. Wray, J. P. Stambuli, *Org. Lett.* **2008**, *10*, 1021-1023.

18. P. Li, J. J. Zhao, C. R. Wu, R. C. Larock, F. Shi, *Org. Lett.* **2011**, *13*, 3340-3343.

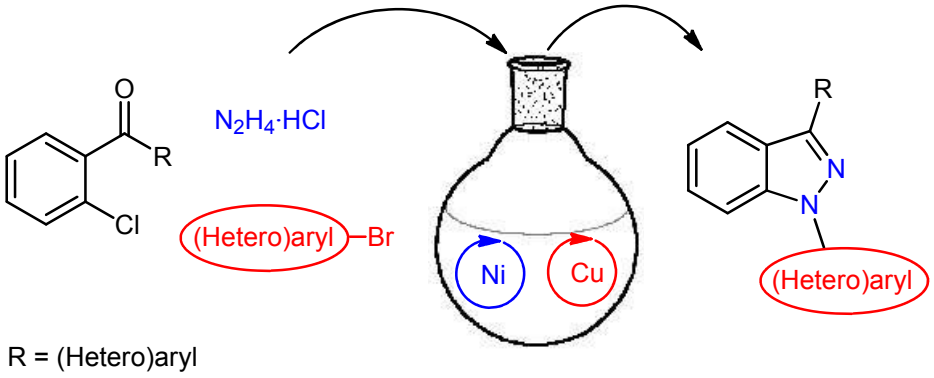
19. W. Youngsaye, C. L. Hartland, B. J. Morgan, A. Ting, P. P. Nag, B. Vincent, C. A. Mosher, J. A. Bittker, S. Dandapani, M. Palmer, L. Whitesell, S. Lindquist, S. L. Schreiber, B. Munoz, *Beilstein J. Org. Chem.* **2013**, *9*, 1501-1507.

View Article Online
DOI: 10.1039/C7OB00841D

20. R. Albers, S. S. Bhagwat, C. A. Buhr, Q. Chao, R. Ferri, V. Plantevin, K. Sahasrabudhe, S. T. Sakata, J. Sapienza, Y. Satoh. U.S. Patent 7,211,594.

21. J. T. Hu, H. C. Xu, P. J. Nie, X. B. Xie, Z. X. Nie, Y. Rao, *Chem. Eur. J.* **2014**, *20*, 3932-3938.

View Article Online
DOI: 10.1039/C7OB00841D



A new nickel-catalyzed cyclization of *ortho*-chlorobenzophenone hydrazones, to afford 3-(hetero)aryl-1*H*-indazoles, is developed and applied in a one-pot synthesis of 1,3-di(hetero)aryl-1*H*-indazoles.