NIH Public Access
Author Manuscript
J Org Chem. Author manuscript; available in PMC 2012 November 4.

Published in final edited form as:
J Org Chem. 2011 November 4; 76(21): 8840–8851. doi:10.1021/jo201605v.

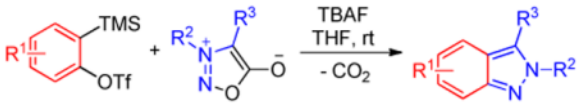
Synthesis of 2*H*-Indazoles by the [3 + 2] Dipolar Cycloaddition of Sydnones with Arynes

Yuesi Fang[†], **Chunrui Wu**[*,‡], **Richard C. Larock**[*,†], and **Feng Shi**[*,‡]

[†]Department of Chemistry, Iowa State University, Ames, IA 50011, U.S.A

[‡]Key Laboratory of Natural Medicine and Immuno-Engineering of Henan Province, Henan University, Jinming Campus, Kaifeng, Henan 475004, China PR

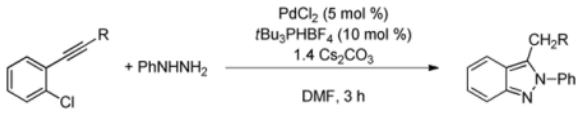
Abstract



A rapid and efficient synthesis of 2*H*-indazoles has been developed using a [3 + 2] dipolar cycloaddition of sydnones and arynes. A series of 2*H*-indazoles have been prepared in good to excellent yields using this protocol, and subsequent Pd-catalyzed coupling reactions can be applied to the halogenated products to generate a structurally diverse library of indazoles.

Introduction

The synthesis of heterocyclic compounds has attracted significant attention for decades. Among the various heterocycles, the indazole system has received significant attention due to its diverse bioactivity.[1] Although a number of methods for the preparation of indazoles are known, most methods target 1*H*-indazoles. Those focused on the selective and efficient preparation of 2*H*-indazoles, which also appear to have pharmaceutical promise,[2] remain limited. Recently, significant efforts have been devoted to the development of synthetic routes towards 2*H*-indazoles,[3] as highlighted by the elegant chemistry developed by Halland (eq 1)[3a] and Song (eq 2).[3b] However, it should be noted that most of these methods still have significant limitations. Thus, new routes are still desirable.



(1)

cwu@henu.edu.cn, larock@iastate.edu, fshi@henu.edu.cn.

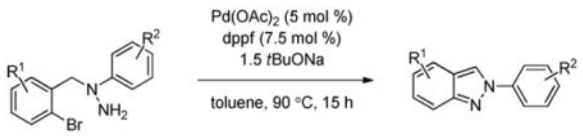
Supporting Information Available: Detailed computational results, and full ^{1}H and ^{13}C NMR spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

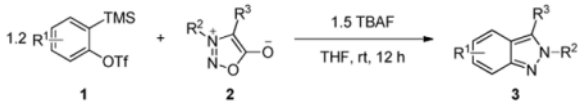
NIH-PA Author Manuscript



(2)

Our two groups have extensive ongoing research programs in aryne chemistry directed toward biologically important heterocycles, including approaches involving Pd-catalyzed annulation reactions,[4] electrophilic and nucleophilic reactions,[5] inter- or intramolecular annulation reactions,[6] and insertion reactions.[7] Aryne dipolar cycloadditions have provided synthetically useful methods for the synthesis of benzotriazoles,[8] indazoles,[9] and benzisoxazoles[10] by reactions with azides, diazo compounds, and nitrile oxides, respectively.

For the synthesis of 2*H*-indazoles, we have previously communicated a [3 + 2] cycloaddition approach involving arynes and readily accessible sydnones (eq 3).[11] This chemistry, which offers very mild reaction conditions, high yields, and no contamination by 1*H*-indazoles, presumably involves an initial [3 + 2] cycloaddition to afford a bicyclic adduct, followed by spontaneous extrusion of a molecule of CO_2 in a retro-[4 + 2] fashion. Herein, we wish to report the full details on this project, and demonstrate its potential application to the construction of a small library utilizing palladium-catalyzed cross-couplings of halogenated 2*H*-indazoles prepared by our methodology.



(3)

Results and Discussion

Preparation of the sydnones

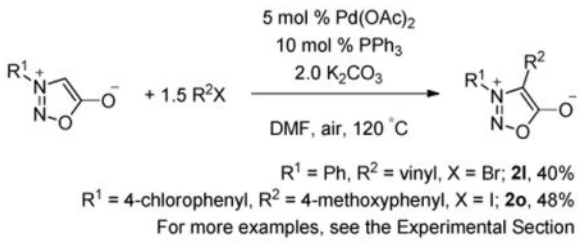
Sydnones are readily prepared from the corresponding amino acids[12] by a sequence which involves *N*-nitrosation/cyclodehydration. Three different protocols, namely Protocol 1A [1.5 equiv of $NaNO_2$, 0 °C, 1 h, then acidify], Protocol 1B [2.0 equiv of $NaNO_2$, HCl, then 0 °C, 1 h], and Protocol 1C [1.5 equiv of *i*-amyl nitrite, DME, rt, 2 d] have been used in the nitrosation step, and two other protocols, namely 2A [Ac_2O as solvent, 110 °C, 2 h] and 2B [2 equiv of TFAA, Et_2O, rt, 2 h] have been used for the cyclodehydration step. A variety of sydnones have been synthesized starting from readily available amino acids (Scheme 1, see the Experimental Section for details). However, preparation of some sydnones, especially those with an alkyl group at the *C*-4 position have not been successful.

Sydnones not readily derived from amino acids can be accessed by further functionalization of preformed monosubstituted sydnones. Thus, arylation and vinylation at the *C*-4 position of sydnones can be achieved from monosubstituted sydnones by Pd-catalyzed cross-coupling with aryl or vinylic halides using literature procedures (eq 4).[13] Alkynylation at the *C*-4 position can be performed using the same protocol or by oxidative coupling with terminal alkynes (eq 5).[14] Monosubstituted sydnones can also be iodinated[15] or acylated[16] at the *C*-4 position by reacting sydnones with ICl buffered with NaOAc/AcOH (eq 6) or acetic anhydride combined with NBS (eq 7) respectively.

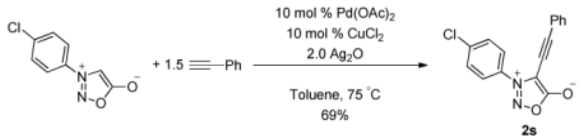
NIH-PA Author Manuscript

NIH-PA Author Manuscript

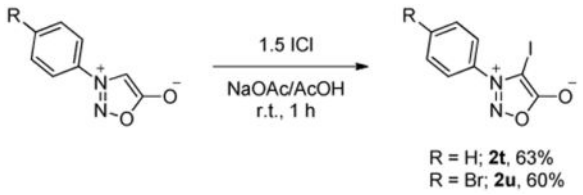
NIH-PA Author Manuscript



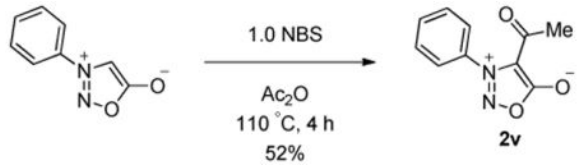
(4)



(5)



(6)



(7)

Reaction optimization

The reaction of *o*-(trimethylsilyl)phenyl triflate (**1a**) and *N*-phenylsydnone (**2a**) was investigated as the model reaction for optimization (Table 1). In the beginning, we found that using CsF in acetonitrile only afforded a 69% yield of **3aa** with incomplete conversion of **2a**, even upon a prolonged reaction time (entry 1). Running the reaction in THF led to complete conversion with a much improved 90% yield (entry 2). We quickly found that better results and shorter reaction times could be realized by changing the fluoride source from CsF to TBAF (entries 3 and 4). With this change, THF and acetonitrile exhibited no apparent difference in yields. However, THF is slightly preferred, because it appeared to afford a pure product (white vs. yellow in acetonitrile). In addition, when using THF as the solvent, the loadings of both **1a** and fluoride could be reduced while maintaining a near quantitative yield (entries 5 and 6). The reaction provides a clean, spot-to-spot transformation with perhaps only a trace of the starting material; no other spots were observed on TLC analysis. This sydnone-aryne cycloaddition appears to represent one of the

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

best approaches to 2*H*-indazoles in terms of efficiency and yield. The reaction conditions reported in Table 1, entries 5 and 6, which employ the same stoichiometry and concentration, but use of either solid TBAF or a THF solution of TBAF afford similar results. Thus, the procedures reported in entries 5 and 6 have been chosen as our standard reaction conditions for our study of additional substrates.

Scope and limitations

The scope and limitations of our approach to 2*H*-indazoles have been tested, first using a range of structurally diverse sydnones (Table 2). For monosubstituted sydnones with an aryl group, the reaction smoothly afforded excellent yields of the corresponding 2*H*-indazoles (entries 1-6), with a variety of functional groups tolerated, including halogens (entries 2 and 3), and alkyl (entry 4), ether (entry 5), and acetal (entry 6) groups. However, the electron deficient *N*-(4-nitrophenyl)sydnone **2g** (entry 7) was found to be unreactive. Even with the addition of a second batch of 1.2 equiv of **1a** after the first 1.2 equiv of **1a** was consumed, **2g** remained unreacted. *N*-Alkylsydnones (entries 8 and 9) also worked well under our reaction conditions, but in somewhat lower yields.

With substitution in the *C*-4 position of the sydnone, we have observed limited success with alkyl groups. Except for the proline-derived sydnone **2j** (entry 10), which has the 3- and 4-substitution tethered into a ring, other sydnones were found unstable under our reaction conditions and afforded a fairly complex reaction mixture in the end. For example, sydnone **2k** derived from leucine (entry 11) afforded only a 23% yield with ~10% recovery of the sydnone under our standard conditions, and 1.6 equiv of **1a** and 2.4 equiv of TBAF had to be employed for the full conversion of **2k**. On the other hand, sydnones with sp^2- or *sp*-carbon units in the *C*-4 position, including a vinyl group (entry 12), different aryl groups varying in their electronics (entries 13-16), different heterocyclic groups (entries 17 and 18), and an alkynyl group (entry 19), were all tolerated and the desired products were obtained in good to excellent yields, although in some cases (entries 18 and 19), incomplete conversion was observed. Successful substitution at the *C*-4 position of the sydnone has been extended to halogens, as illustrated in sydnones **2t** and **2u** (entries 20 and 21), where 88% and 90% yields have been obtained. However, substitution of other electron-withdrawing groups at the *C*-4 position has not been tolerated. For example, 4-acetylsydnone **2v** was found to be unreactive with benzyne under our standard conditions (entry 22), leading to complete recovery of the starting sydnone. The adverse effect of electron-withdrawing groups has also been observed in entry 13, where a lower yield was obtained.

Next, a variety of different aryne precursors have been tested under our optimized reaction conditions (Table 3). As can be seen, excellent yields can be achieved regardless of the aryne structure. Symmetrical aryne precursors **1b** and **1c** have been converted to the corresponding 2*H*-indazoles **3ba** (entry 1) and **3ca** (entry 2), respectively in almost quantitative yields. Unsymmetrical aryne precursor **1d**, which is neither electronically nor sterically biased, afforded mixtures of two possible regioisomers in nearly equal amounts (entry 3). Unsymmetrical aryne precursor **1e**, which is partially biased electronically, led to an inseparable mixture of two isomers in a 1 : 0.8 ratio (entry 4). Unsymmetrical aryne precursor **1f**, which is slightly biased by sterics, led to an inseparable mixture of two isomers in a 1 : 0.7 ratio (entry 5). An unsymmetrical naphthalyne precursor **1g** was also reactive and led to an inseparable mixture of two isomers in equal amounts (entry 6). However, 2,3-pyridyne precursor **1h**[17] proved unsuccessful using our standard reaction conditions. We observed that all sydnone starting material was recovered when compound **1h** was consumed (entry 7).

An interesting observation was made when we carried out the reaction using the unsymmetrical aryne precursor **1i**, which is both sterically and electronically biased. While

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

we isolated two products, we were only able to assign one as the 4-MeO isomer (**3ia**) (33% yield) through extensive NMR spectroscopic analysis and comparison with literature values.[11,18] We were unable to identify the other product. While HRMS suggested the identity as the desired regioisomeric product, the presence of extra aromatic protons, as well as two aliphatic methyl groups in the ^{1}H NMR spectrum, clearly suggested otherwise. It was not until we reacted **1i** with another sydnone **2d** that we realized what had happened. In the latter reaction, we again obtained two products. One was the desired 4-MeO isomer (**3id**) in a 44% yield, and the other product was again unidentified. However, we were able to observe exactly the same extra aromatic protons and exactly the same extra methyl signals that were observed in the previously unidentified product, but here the integration no longer involved integers. That clearly suggested that these "unidentified" products were in fact mixtures of two compounds. The mixture obtained from **1i** and **2a** involved approximately a 1:1 ratio of two products. Therefore, the HRMS information was correct. The "unidentified" product from **1i** and **2a** actually contained the 7-MeO isomer **3ia'**. The other component in the mixture was later attributed to *m*-anisidine based on ^{1}H NMR spectral analysis and comparison with literature values. The existence of *m*-anisidine was also confirmed by GC-MS. Thus, by stirring this "unidentified" product with an excess of acetic anhydride and pyridine, followed by a regular work-up and silica gel chromatography, the pure 7-MeO isomer (**3ia'**) could be obtained in a 40% yield. The ^{1}H NMR spectral data now matched the literature values.[18] Similarly, compound **3id'**, the 7-MeO isomer from the reaction of **1i** and **2d**, could be isolated pure in about a 42% yield.

The regioselectivity in this cycloaddition, especially with the aryne derived from **1i**, can be explained as shown in Scheme 2. For a sydnone, there are three resonance structures (**A**, **B**, and **C**, Scheme 2), and cycloaddition with the aryne should arise from the latter two. Since the aryne derived from **1i** is known to be attacked preferentially by nucleophiles at the meta position (with respect to the OMe group) for both electronic and steric reasons,[19] resonance structure **B** should lead to formation of the 7-OMe regioisomer **3ia'**, while resonance structure **C** should lead to formation of the 4-OMe regioisomer **3ia**. While we typically draw the structure of sydnones as either **A** or **B**, computational chemists long ago realized that despite the enolate nature and the observed nucleophilic reactivity of *C*-4, the *N*-2 position actually carries a significant negative charge[20] and may serve as the nucleophile in the aryne reaction. Although the charge distribution of sydnones has been controversial,[21] experimental results involving the cycloaddition of sydnones with unsymmetrical alkynes have clearly suggested that both *N*-2 and *C*-4 can react as the nucleophilic site.[22] Moreover, the molecular orbital analysis of sydnones indicates that the LUMO of sydnones has very similar coefficients for *N*-2 and *C*-4,[23] rendering the *N*-2 and *C*-4 positions of a sydnone similar in reactivity. All these literature results support the formation of both isomers **3ia** and **3ia'** through cycloaddition, and the side-product, *m*-anisidine, appears to arise from a separate path during the formation of isomer **3ia**. Possibly, due to steric hindrance of the methoxy group, the [3 + 2] cycloaddition to form **3ia** is partially disrupted and therefore occurs stepwise, which stops at betaine **D**.[24] The addition of water may lead to the formation of **E**, which is attacked by hydroxide to form a ring-opened intermediate **F**. Intermediate **F** can further decompose to nitroso compound **G**, which is then reduced to *m*-anisidine.

Mechanistic investigation

To gain further insight into this reaction, we conducted a brief Density Functional Theory and *ab initio* calculation of the reaction path using Gaussian 09. Geometry optimizations were performed with hybrid B3LYP functions in conjunction with the 6-31G(d) basis set. Higher-level relative energies were computed at the MP2/6-311+G(d,p) level based on the B3LYP/6-31G(d) optimized geometries. The schematic potential energy surface of the reaction with zero-point energy corrections is plotted in Figure 1. As can be seen, the initial

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

[3 + 2] cycloaddition is an exothermic step. A subsequent retro-[4 + 2] reaction is again exothermic. Since we were not able to find the transition states of these cycloaddition and cycloreversion processes, a relatively smooth potential energy surface may exist.

Elaboration of 2*H*-Indazoles

As our approach to 2*H*-indazoles tolerates halogen substituents, those halogen atoms offer an ideal site for further elaboration by subsequent Pd-catalyzed cross-couplings. Such a strategy can quickly afford a library of structurally diverse, highly functionalized 2*H*-indazoles. In this regard, we have demonstrated the feasibility of such elaborations by converting **3at** to the corresponding 3-aryl- and 3-(1-alkynyl)-2*H*-indazoles using Suzuki-Miyaura[25] and Sonogashira[26] reactions, respectively (Scheme 3).[27] By modifying the structure of the sydnones and arynes,[28] this approach can be easily exploited to provide more derivatives for potential biological activity screening. It should be noted that our direct new synthesis of alkynylsydnones[14] is unable to prepare indazoles like **5at**, and, therefore, the route described in Scheme 3 provides an effective route towards such compounds.

Conclusions

This work affords an efficient, new, synthetic route to 2*H*-indazoles by the [3 + 2] cycloaddition of arynes and sydnones. The reaction is applicable to a variety of sydnones and silylaryl triflates and affords the corresponding cycloadducts in moderate to excellent yields. Compared with literature protocols, our approach offers very mild reaction conditions, high yields, and no contamination by 1*H*-indazoles. The resulting halogen-substituted 2*H*-indazoles are readily elaborated to more complex products using known organopalladium chemistry. Thus, the versatility of the cycloaddition and the tolerance of halogen make this methodology ideal for pharmaceutical chemistry.

Experimental Section

General Information

All reagents purchased from commercial sources were used as received. The solvents THF and MeCN were distilled over Na/benzophenone and CaH_2, respectively. The aryne precursors were used as received; those not commercially available were prepared according to literature procedures.[29,17] The sydnones were prepared as outlined below. The silica gel for column chromatography was supplied as 300-400 mesh or 230-400 mesh.[30] Powdered CsF was used as received and stored in a desiccator. TBAF (either 1 M in THF solution or anhydrous solid) was used as received. The solid TBAF was stored in a desiccator as well.

All melting points were measured and are uncorrected. The ^{1}H and ^{13}C NMR spectra were recorded and are referenced to the residual solvent signals (7.26 ppm for ^{1}H in $CDCl_3$ and 77.2 ppm for ^{13}C in $CDCl_3$).

All aryne cycloaddition reactions were carried out in oven-dried glassware and were magnetically stirred. A nitrogen atmosphere was not used, except that a balloon of nitrogen was attached to the reaction flask for the ventilation of CO_2.

Computational methods

All electronic structure calculations involved in this work utilized the Gaussian 09 program package.[31] The geometries and frequencies of all the stationary points (including reactants, intermediates, and products) were calculated by Becke's three-parameter nonlocal-exchange functional with the nonlocal correlation functional of Lee-Yang-Parr (B3LYP) using the 6-31G(d) basis set. To get more reliable reaction energies, single-point corrections were

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

performed by restricted or unrestricted second-order Møller-Plesset perturbation theory (MP2) with the 6-311+G(d, p) basis set using the B3LYP optimized geometries.

Preparation of the sydnones

All the sydnones were prepared as follows. Due to long T1 relaxation times, the acquisition of ^{13}C NMR spectra for many sydnones could not be achieved, even after an overnight acquisition of 8000 scans on a 400 MHz instrument.

3-Phenylsydnone (2a)

[12a] To a suspension of 5.00 g of *N*-phenylglycine (33 mmol) in 60 mL of water at 0 °C was added dropwise a solution of 3.50 g of $NaNO_2$ (51 mmol, 1.5 equiv) in 20 mL of water. The mixture was stirred at 0 °C for an additional 20 min and the resultant clear red solution was filtered while cold. A scoop of activated charcoal (ca. 200-300 mg) was added and the mixture was stirred for a few minutes before being filtered again. The intermediate *N*-nitroso-*N*-phenylglycine was precipitated from the filtrate by the addition of 10 mL of concentrated HCl and was then collected by filtration. It was washed with cold water and dried overnight under a high vacuum. The resulting solid was then dissolved in 25 mL of acetic anhydride and the mixture was heated to 100 °C for 1.5 h. After being cooled to room temperature, the resulting mixture was poured into 300 mL of ice water. A yellow solid formed, which was triturated by stirring for a few minutes in this cold water. The solid was filtered, washed thoroughly with water until no smell of acetic acid remained, and dried under a high vacuum overnight to afford 3.37 g of product (63% yield) as off-white crystals. This representative procedure for preparing sydnones from the corresponding amino acid is identified as **Protocol 1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77-7.58 (m, 5 H), 6.75 (s, 1 H).

3-(4-Chlorophenyl)sydnone (2b)

A mixture of 5.10 g of 4-chloroaniline (40 mmol), 5.14 mL of ethyl chloroacetate (48 mmol, 1.2 equiv), and 6.53 g of NaOAc•$3H_2O$ (48 mmol, 1.2 equiv) in 10 mL of ethanol was refluxed in a 100 °C oil bath overnight. After being cooled to room temperature, the mixture was poured into ice water, and the precipitate was filtered and dried. The crude product, *N*-(4-chlorophenyl)glycine ethyl ester, after crystallization from ethanol (4.01 g, 47% yield), was an off-white solid. It is strongly suggested that this intermediate be purified, either through recrystallization or column chromatography. The resulting ester (3.00 g, 14 mmol) was stirred with 1.01 g of LiOH (3.0 equiv) in 30 mL of THF/water (1:1) at 0 °C. After 2 h at 0 °C, the reaction mixture was gradually warmed up to room temperature, where the pH was adjusted to 3-4 with concentrated HCl. The precipitate was filtered and dried to afford 2.53 g of *N*-(4-chlorophenyl)glycine (98% yield) as an off-white solid (62% overall yield). This representative procedure for preparing an amino acid is identified as **Route 1**.[32] Sydnone **2b** was then synthesized as an off-white solid (72% overall yield) from the resulting amino acid following **Protocol 1**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74-7.67 (m, 2H), 7.64-7.56 (m, 2H), 6.79 (s, 1H).

3-(4-Bromophenyl)sydnone (2c)

The corresponding amino acid was prepared from 4-bromoaniline following **Route 1** in a 65% overall yield. Sydnone **2c** was synthesized from this amino acid following **Protocol 1** as an off-white solid (50% overall yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, J = 8.4 Hz, 2 H), 7.62 (d, J = 8.8 Hz, 2 H), 6.73 (s, 1 H).

3-(4-Methylphenyl)sydnone (2d)

The corresponding amino acid was prepared from 4-methylaniline following **Route 1** in a 53% overall yield. Sydnone **2d** was synthesized from this amino acid following **Protocol 1**

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

as an off-white to cream solid (60% overall yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.61 (d, *J* = 8.5 Hz, 2 H), 7.42 (d, *J* = 8.2 Hz, 2 H), 6.72 (s, 1 H), 2.49 (s, 3 H).

3-(4-Methoxyphenyl)sydnone (2e)

The corresponding amino acid was prepared from 4-methoxylaniline following **Route 1** in a 50% overall yield. Sydnone **2e** was synthesized from this amino acid following **Protocol 1** as an off-white solid (78% overall yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 9.2 Hz, 2 H), 7.08 (d, *J* = 8.8 Hz, 2 H), 6.64 (s, 1 H), 3.91 (s, 3 H).

3-(3,4-Methylenedioxyphenyl)sydnone (2f)

The corresponding amino acid was prepared from 3,4-methylenedioxyaniline following **Route 1** in a 60% overall yield. Sydnone **2f** was synthesized from this amino acid following **Protocol 1** as a brown solid (27% overall yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.25-7.15 (m, 2 H), 6.96 (d, *J* = 8.3 Hz, 1 H), 6.64 (s, 1 H), 6.14 (s, 2 H).

3-(4-Nitrophenyl)sydnone (2g)

To 0.75 g of glycine (10 mmol) was added 10 mL of tetrabutylammonium hydroxide in methanol (1 M, 10 mmol, 1.0 equiv.); the solvent was removed under vacuum, and the residue was dissolved in 20 mL of DMSO. *p*-Fluoronitrobenzene (1.55 g, 11 mmol, 1.1 equiv) and 1.51 g of K_2CO_3 (11 mmol, 1.1 equiv) were added and the mixture was allowed to react under gentle warming (45 °C) with stirring until completion (monitored by TLC). The mixture was then poured into cold water, acidified with HCl, and extracted with ethyl acetate. The combined organic layers were evaporated under vacuum and the residue was purified by column chromatography (5:1 petroleum ether/EtOAc) to afford 1.2 g (65% yield) of the desired amino acid as a yellow solid.[33] Sydnone **2g** was then synthesized from this amino acid following **Protocol 1** as an off-white solid (36% overall yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.52 (d, *J* = 8.8 Hz, 2 H), 7,98 (d, *J* = 8.8 Hz, 2 H), 6.84 (s, 1 H).

3-Methylsydnone (2h)

To an ice-cold solution of 6.7 mL of conc. HCl and 3.56 g of sarcosine (40 mmol) in 10 mL of water, was added a saturated solution of 5.52 g of $NaNO_2$ (80 mmol) in water. The mixture was stirred at 0 °C for 1 h and then extracted with ethyl acetate three times. The combined organic layers were concentrated under a vacuum to obtain *N*-nitroso-*N*-methylglycine as a yellow oil. The resulting oil was dissolved in 4 mL of dry ether and charged dropwise with ~500 μL of trifluoroacetic anhydride (3.6 mmol, 1.8 equiv) at 0 °C. The reaction was stirred at 0 °C for a few minutes and gradually warmed to room temperature and stirred for another 1 h. The solvents were evaporated and the residue was dissolved in EtOAc. Solid $NaHCO_3$ was added to neutralize the excess acid and was removed by filtration. The EtOAc was evaporated and the residue was purified by chromatography (2:1 petroleum ether/EtOAc) to yield 300 mg of the desired sydnone (8 % overall yield) as a yellow oil. This representative precedure for preparing sydnones from the corresponding amino acid is identified as **Protocol 2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.32 (s, 1 H), 4.07 (s, 3 H).

3-Benzylsydnone (2i)

This sydnone was synthesized from *N*-benzylglycine as a white solid (39% overall yield) following **Protocol 2**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.45 (overlap, 3 H), 7.39 (overlap, 2 H), 6.21 (s, 1 H), 5.36 (s, 2 H).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

3,4-Cyclopenta[*c*]sydnone (2j)

This sydnone was prepared according to a literature procedure[34] as a brown oil (~11% overall yield).

3-(4-Chlorophenyl)-4-(isobutyl)-sydnone (2k)

To a round-bottom flask equipped with a stir bar, was added 1.32 g of L-leucine (10 mmol), followed by 190 mg of CuI (1 mmol, 10 mol %), 3.04 g of anhydrous K_2CO_3 (22 mmol, 2.2 equiv.), 2.87 g of 4-bromochlorobenzene (15 mmol, 1.5 equiv.), and 9 mL of undistilled DMSO. The reaction system was flushed with nitrogen. The flask was sealed with a Teflon stopper and placed in a 70 °C oil bath. The suspension was vigorously stirred. After 15 h, the stirring was found to be difficult, and another 4 mL of DMSO was added. The reaction was stopped at 40 h when the color changed from a purple-brown to blue. The reaction was poured into ice water and concentrated HCl was added until the pH reached 3-4. The precipitate was filtered, washed thoroughly with cold water (slightly acidified by HCl to pH ~4) and dried under a high vacuum to yield 2.6 g of crude *N*-(4-chlorophenyl)leucine as a slightly green solid (yield >100%).[12f,g] It should be noted that this method did not work for Met or Thr. This crude amino acid was used in the next step without further purification.

To a solution of 500 mg (~2 mmol considering possible impurities) of crude *N*-(4-chlorophenyl)leucine in 3 mL of undistilled DME was added dropwise ~400 μL of isoamyl nitrite (3 mmol, 1.5 equiv) at room temperature. The mixture was allowed to stir for 2 d before the solvent was removed under reduced pressure. The solid was triturated with petroleum ether and filtered. The cake was washed with petroleum ether and air dried. The solid was dissolved in 4 mL of dry ether and was charged dropwise with ~500 μL of trifluoroacetic anhydride (3.6 mmol, 1.8 equiv) at 0 °C. The reaction was stirred at 0 °C for a few minutes and gradually warmed to room temperature and stirred for another 1 h. The solvents were evaporated and the residue was dissolved in EtOAc. The excess acid present was neutralized by the addition of solid $NaHCO_3$, which was then removed by filtration. The EtOAc was evaporated and the residue was purified by chromatography (3:1 petroleum ether/EtOAc) to yield 130 mg of the desired sydnone (26% overall yield) as a light brown oil: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.62 (d, *J* = 8.6 Hz, 2 H), 7.46 (d, *J* = 8.7 Hz, 2 H), 2.37 (d, *J* = 7.4 Hz, 2 H), 1.88 (dt, *J* = 13.6, 6.8 Hz, 1 H), 0.80 (d, *J* = 6.6 Hz, 6 H).

3-(4-Chlorophenyl)-4-(4-methoxyphenyl)sydnone (2o)[13]

To a mixture of 197 mg of *N*-(4-chlorophenyl)sydnone (1.0 mmol), 351 mg of 4-iodoanisole (1.5 mmol, 1.5 equiv), 11 mg of $Pd(OAc)_2$ (0.05 mmol, 5 mol %), 26 mg of PPh_3 (0.1 mmol, 10 mol %), and 276 mg of anhydrous K_2CO_3 in a 10 mL round-bottom flask was added 2 mL of undistilled DMF. The flask was fitted with an air condenser and placed in a 120 °C oil bath overnight, during which time the reaction mixture was stirred open to the air. The mixture was cooled to room temperature, poured into 30 mL of water, and extracted three times with EtOAc. The combined extracts were washed once with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (petroleum ether/EtOAc) to afford 145 mg of **2o** as a yellow solid (48% yield). This representative procedure for preparing functionalized sydnones is identified as **Protocol 3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.57-7.51 (m, 2 H), 7.47-7.40 (m, 2 H), 7.24-7.17 (m, 2 H), 6.87-6.79 (m, 2 H), 3.79 (s, 3 H).

3-Phenyl-4-vinylsydnone (2l)

This sydnone was prepared from sydnone **2a** and vinyl bromide as a brown solid (40% yield) following **Protocol 3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.79-7.60 (m, 3 H), 7.59-7.50 (m, 2 H), 6.40-6.16 (m, 2 H), 5.41 (d, *J* = 10.6 Hz, 1 H).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

4-(4-Acetylphenyl)-3-phenylsydnone (2m)

This sydnone was prepared from sydnone **2a** and 4-bromoacetophenone as a yellow solid (30% yield) following **Protocol 3**: ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.7 Hz, 2 H), 7.76-7.56 (m, 3 H), 7.54-7.44 (m, 2 H), 7.43-7.33 (m, 2 H), 2.54 (s, 3 H).

4-(4-Methoxyphenyl)-3-phenylsydnone (2n)

This sydnone was prepared from sydnone **2a** and 4-iodoanisole as a yellow solid (46% yield) following **Protocol 3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.66 (t, *J* = 7.2 Hz, 1 H), 7.58 (t, *J* = 7.2 Hz, 2 H), 7.48 (d, *J* = 7.6 Hz, 2 H), 7.22 (d, *J* = 8.8 Hz, 2 H), 6.81 (d, *J* = 8.8 Hz, 2 H), 3.78 (s, 3 H).

3,4-*Bis*(4-chlorophenyl)sydnone (2p)

This sydnone was prepared from sydnone **2b** and 4-bromochlorobenzene as a brown solid (44% yield) following **Protocol 3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60-7.55 (m, 2 H), 7.47-7.42 (m, 2 H), 7.31-7.27 (m, 2 H), 7.24 7.20 (m, 2 H).

3-(4-Chlorophenyl)-4-(2-thiophenyl)sydnone (2q)

This sydnone was prepared from sydnone **2b** and 2-iodothiophene as a brown solid (50% yield) following **Protocol 3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (d, *J* = 8.4 Hz, 2 H), 7.53 (d, *J* = 8.4 Hz, 2 H), 7.35 (d, *J* = 3.7 Hz, 1 H), 7.28 (d, *J* = 5.0 Hz, 1 H), 7.02 (t, *J* = 4.5 Hz, 1 H).

3-(4-Chlorophenyl)-4-(2-pyridyl)sydnone (2r)

This sydnone was prepared from sydnone **2b** and 2-bromopyridine as a brown solid (60% yield) following **Protocol 3**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.25 (d, *J* = 4.6 Hz, 1 H), 8.11 (d, *J* = 8.0 Hz, 1 H), 7.75 (t, *J* = 7.8 Hz, 1 H), 7.52 (d, *J* = 8.7 Hz, 2 H), 7.45 (d, *J* = 8.7 Hz, 2 H), 7.13 (dd, *J* = 7.4, 4.9 Hz, 1 H).

3-(4-Chlorophenyl)-4-(phenylethynyl)sydnone (2s)[14]

A solution of 79 mg of sydnone **2b** (0.4 mmol) in 2 mL of toluene was charged with 4.5 mg of $Pd(OAc)_2$ (5 mol %), 6.8 mg of $CuCl_2$•$2H_2O$ (10 mol %), and 186 mg of Ag_2O (2.0 equiv), and then heated to 75 °C in an open flask. A solution of 88 μL of phenylacetylene (0.6 mmol) in 3 mL of toluene was added over 6 h using a syringe pump while the reaction was stirred open to the air. The reaction was allowed to stir for an additional 2 h after the addition, and then EtOAc and water were added. The layers were separated and the EtOAc was washed with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (petroleum ether/EtOAc) to afford 82 mg of **2s** as a yellow solid (69% yield): ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87-7.81 (m, 2 H), 7.67-7.61 (m, 2 H), 7.44-7.31 (m, 5 H).

4-Iodo-3-phenylsydnone (2t)[15]

To a solution of 243 mg of sydnone **2a** (1.5 mmol) in 2.5 mL of acetic acid was added 185 mg of NaOAc (2.25 mmol, 1.5 equiv.), followed by a solution of 366 mg of ICl (2.25 mmol, 1.5 equiv.) in 1.5 mL of acetic acid. The mixture was allowed to stir for 3 h, then quenched with water and the solid was collected by filtration. The cake was washed with drops of cold ethanol and dried under vacuum to afford 272 mg of product (63%) as a brown solid. This representative procedure for preparing functionalized sydnones is identified as **Protocol 4**: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (t, *J* = 7.2 Hz, 1 H), 7.67 (t, *J* = 7.6 Hz, 2 H), 7.60 (d, *J* = 7.6 Hz, 2 H).

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

3-(4-Bromophenyl)-4-iodosydnone (2u)

This sydnone was prepared from sydnone **2c** as a brown solid (60% yield) following **Protocol 4**: mp 160-162 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.81 (d, *J* = 8.8 Hz, 2 H), 7.50 (d, *J* = 8.8 Hz, 2 H); LRMS (ESI) 367 (M+H); HRMS (ESI) calcd for $C_8H_5BrIN_2O_2$ (M+H) 366.8574, found 366.8574.

4-Acetyl-3-phenylsydnone (2v)[16]

To a solution of 0.81 g of sydnone **2a** (5 mmol) in 5 mL of acetic anhydride was added 0.89 g of NBS (5 mmol). The mixture was allowed to stir for 4 h, poured into 20 mL of ice water, and extracted by EtOAc. The combined organic layers were washed with saturated $NaHCO_3$ solution, dried over Na_2SO_4, and evaporated under vacuum. The residue was purified by column chromatography (5:1 petroleum ether/EtOAc) to afford 529 mg of product (52% yield) as colorless crystals: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.83 (d, *J* = 7.6 Hz, 2 H), 7.43 (t, *J* = 8.0 Hz, 2 H), 7.23 (d, *J* = 7.6 Hz, 1 H).

General procedure for the synthesis of 2*H*-indazoles

To an oven-dried 10 mL round-bottom flask equipped with a stir bar were added 140 mg of benzyne precursor (~0.48 mmol, ~1.2 equiv) and 0.4 mmol of sydnone. THF (4 mL) was added and the mixture was stirred until all solid dissolved. To this solution was added TBAF (~160 mg of solid or ~630 μL of 1*M* THF solution, ~1.6 equiv) in one portion. The flask was sealed with a septum and a nitrogen balloon was attached. The reaction mixture was stirred at room temperature overnight. Upon completion, the reaction mixture was poured into saturated $NaHCO_3$ and extracted three times with EtOAc. The combined extracts were washed once with brine, dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (petroleum ether/EtOAc) to afford the 2*H*-indazole.

2-Phenyl-2*H*-indazole (3aa)

Following the general procedure, this product was isolated as a white solid: mp 79-81 °C (lit[35] 81-82 °C); R_f = 0.45 (6:1 petroleum ether/EtOAc);[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.41 (s, 1 H), 7.92-7.89 (m, 2 H), 7.81 (dd, *J* = 8.8, 0.9 Hz, 1 H), 7.72 (d, *J* = 8.5 Hz, 1 H), 7.56-7.50 (m, 2 H), 7.43-7.38 (m, 1 H), 7.34 (ddd, *J* = 8.8, 6.6, 1.1 Hz, 1 H), 7.12 (ddd, *J* = 8.4, 6.6, 0.8 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.7, 140.5, 129.5, 127.9, 126.8, 122.7, 122.4, 120.9, 120.40, 120.37, 117.9; LRMS (ESI): 217 (M+Na), 195 (M+H); HRMS (ESI): calcd for $C_{13}H_{11}N_2$ (M+H) 195.0917, found 195.0916.

2-(4-Chlorophenyl)-2*H*-indazole (3ab)

White solid: mp 141-143 °C; R_f = 0.50 (6:1 petroleum ether/EtOAc);[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.39 (s, 1 H), 7.89-7.84 (m, 2 H), 7.77 (d, *J* = 8.8 Hz, 1 H), 7.71 (d, *J* = 8.5 Hz, 1 H), 7.53-7.48 (m, 2 H), 7.33 (ddd, *J* = 8.6, 6.6, 0.8 Hz, 1 H), 7.17-7.09 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.8, 138.9, 133.5, 129.7, 127.1, 122.8, 122.7, 122.0, 120.35, 122.30, 117.8; LRMS (ESI) 251 (M+Na), 229 (M+H); HRMS (ESI) calcd for $C_{13}H_{10}ClN_2$ (M+H) 229.0527, found 229.0525.

2-(4-Bromophenyl)-2*H*-indazole (3ac)

Yellow solid: mp 146-148 °C; R_f = 0.38 (5:1 petroleum ether/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1 H), 7.79-7.75 (m, 3 H), 7.68 (d, *J* = 8.4 Hz, 1 H), 7.63 (d, *J* = 9.2 Hz, 2 H), 7.32 (dd, *J* = 7.6, 6.8 Hz, 1 H), 7.11 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 139.7, 132.8, 127.3, 123.1, 122.9, 122.4, 121.6, 120.6, 120.4, 118.1; LRMS (ESI) 273 (M+H); HRMS (ESI) calcd for $C_{13}H_{10}BrN_2$ (M+H) 273.0022, found 273.0030.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

2-(4-Tolyl)-2*H*-indazole (3ad)

White solid: mp 101-103 °C; R_f = 0.44 (6:1 petroleum ether/EtOAc);[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (d, *J* = 0.9 Hz, 1 H), 7.83-7.76 (m, 3 H), 7.71 (dt, *J* = 8.5, 1.0 Hz, 1 H), 7.38-7.29 (m, 3 H), 7.11 (ddd, *J* = 8.4, 6.6, 0.8 Hz, 1 H), 2.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 138.3, 137.9, 130.1, 126.6, 122.7, 122.3, 120.8, 120.30, 120.28, 117.9, 21.0; LRMS (ESI) 231 (M+Na), 209 (M+H); HRMS (ESI) calcd for $C_{14}H_{13}N_2$ (M+H) 209.1073, found 209.1072.

2-(4-Methoxyphenyl)-2*H*-indazole (3ae)

Yellow solid: mp 130-132 °C; R_f = 0.25 (5:1 petroleum ether/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.30 (s, 1 H), 7.79 (d, *J* = 8.8 Hz, 3 H), 7.69 (d, *J* = 8.4 Hz, 1 H), 7.31 (dd, *J* = 7.6, 7.2 Hz, 1 H), 7.10 (t, *J* = 7.4 Hz, 1 H), 7.01 (d, *J* = 8.8 Hz, 2 H), 3.85 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 149.7, 134.3, 126.7, 122.8, 122.6, 122.4, 120.5, 120.4, 117.9, 114.8, 55.8; LRMS (ESI) 257 (M+Na), 225 (M+H); HRMS (ESI) calcd for $C_{14}H_{13}N_2O$ (M+H) 225.1022, found 225.1026.

2-(3,4-Methylenedioxyphenyl)-2*H*-indazole (3af)

Pale white solid: mp 117-118 °C; R_f = 0.31 (6:1 petroleum ether/EtOAc);[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.29 (s, 1 H), 7.77 (dd, *J* = 8.8, 0.9 Hz, 1 H), 7.69 (d, *J* = 8.5 Hz, 1 H), 7.41 (d, *J* = 2.2 Hz, 1 H), 7.35-7.29 (m, 2 H), 7.11 (ddd, *J* = 8.4, 6.6, 0.8 Hz, 1 H), 6.91 (d, *J* = 8.4 Hz, 1 H), 6.07 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 148.4, 147.3, 135.2, 126.7, 125.6, 122.3, 120.5, 120.2, 117.7, 114.4, 108.4, 103.1, 101.9; LRMS (ESI) 261 (M+Na), 239 (M+H); HRMS (ESI) calcd for $C_{14}H_{11}O_2N_2$ (M+H) 239.0815, found 239.0812.

2-Methyl-2H-indazole (3ah)

Yellow oil: R_f = 0.21 (2:1 petroleum ether/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.88 (s, 1 H), 7.70 (d, *J* = 8.4 Hz, 1 H), 7.64 (d, *J* = 8.4 Hz, 1 H), 7.28 (t, *J* = 7.2 Hz, 1 H), 7.07 (t, *J* = 7.4 Hz, 1 H), 4.21 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.2, 126.0, 123.7, 122.3, 121.8, 120.1, 117.4, 40.5; LRMS (APCI) 133 (M+H); HRMS (APCI) calcd for $C_8H_9N_2$ (M+H) 133.0760, found 133.0762.

2-Benzyl-2*H*-indazole (3ai)

Yellow oil: R_f = 0.31 (5:1 petroleum ether/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.86 (s, 1 H), 7.73 (dd, *J* = 8.7, 0.9 Hz, 1 H), 7.61 (d, *J* = 8.4 Hz, 1 H), 7.34-7.30 (m, 3 H), 7.27-7.23 (m, 3 H), 7.06 (dd, *J* = 8.1, 7.5 Hz, 1 H), 5.57 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 135.9, 129.1, 128.5, 128.1, 126.2, 123.0, 122.2, 121.9, 120.3, 117.7, 57.6; LRMS (APCI) 209 (M+H); HRMS (APCI) calcd for $C_{14}H_{13}N_2$ (M+H) 209.1073, found 209.1078.

2,3-Dihydro-1*H*-pyrrolo[1,2-*b*]indazole (3aj)

Off-white solid: mp 99-100 °C; R_f = 0.31 (1:1 CH_2Cl_2/EtOAc);[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.67 (d, *J* = 8.7 Hz, 1 H), 7.57 (d, *J* = 8.3 Hz, 1 H), 7.26 (t, *J* = 7.6 Hz, 1 H), 7.03 (t, *J* = 7.5 Hz, 1 H), 4.42 (t, *J* = 7.3 Hz, 2 H), 3.18 (t, *J* = 7.2 Hz, 2 H), 2.84-2.63 (m, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.5, 138.8, 125.5, 120.3, 119.8, 117.6, 116.1, 48.9, 25.7, 23.0; LRMS (ESI) 181 (M+Na), 159 (M+H); HRMS (ESI) calcd for $C_{10}H_{11}N_2$ (M+H) 159.0917, found 159.0915.

2-(4-Chlorophenyl)-3-isobutyl-2*H*-indazole (3ak)

Slightly orange solid: mp 77-79 °C; R_f = 0.47 (6:1 petroleum ether/EtOAc);[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72-7.68 (m, 1 H), 7.65 (dt, *J* = 8.5, 1.0 Hz, 1 H), 7.55-7.44 (m, 4 H), 7.33 (ddd, *J* = 8.8, 6.6, 1.1 Hz, 1 H), 7.08 (ddd, *J* = 8.5, 6.6, 0.8 Hz, 1 H), 2.91 (d, *J* = 7.4 Hz, 2

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

H), 2.04-1.89 (m, 1 H), 0.83 (d, J = 6.6 Hz, 6 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.6, 138.7, 136.3, 134.8, 129.3, 127.6, 126.8, 121.5, 121.1, 120.4, 117.5, 34.1, 29.2, 22.5; LRMS (ESI) 307 (M+Na), 285 (M+H); HRMS (ESI) calcd for $C_{17}H_{18}ClN_2$ (M+H) 285.1153, found 285.1151.

2-Phenyl-3-vinyl-2*H*-indazole (3al)

Yellow gel: R_f = 0.18 (5:1 hexanes ether/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.92 (d, J = 8.5 Hz, 1 H), 7.79 (d, J = 8.7 Hz, 1 H), 7.64-7.48 (m, 5 H), 7.43-7.34 (m, 2 H), 7.23-7.15 (m, 1 H), 6.81 (dd, J = 17.8, 11.6 Hz, 1 H), 6.04 (dd, J = 17.8, 0.8 Hz, 1 H), 5.53 (dd, J = 11.6, 0.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.8, 139.6, 133.2, 129.1, 128.8, 126.7, 126.2, 124.9, 122.7, 120.6, 120.3, 118.0, 117.7; LRMS (EI) 220 (M), 219 (M-H); HRMS (EI) calcd for $C_{15}H_{12}N_2$ (M) 220.1000, found 220.0990.

3-(4-Acetylphenyl)-2-phenyl-2*H*-indazole (3am)

Yellow solid: mp 135-137 °C (lit[18] 136-138 °C); R_f = 0.36 (2:1 hexanes/EtOAc); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 8.1 Hz, 2 H), 7.82 (d, J = 8.8 Hz, 1 H), 7.72 (d, J = 8.5 Hz, 1 H), 7.47-7.36 (m, 8 H), 7.18 (t, J = 7.6 Hz, 1 H), 2.61 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 197.3, 149.0, 139.9, 136.2, 134.4, 133.9, 129.6, 129.1, 128.6, 128.6, 127.1, 125.9, 123.2, 121.8, 120.0, 117.9, 26.6; LRMS (EI) 312 (M); HRMS (EI) calcd for $C_{21}H_{16}N_2O$ (M) 312.1263, found 312.1262.

3-(4-Methoxyphenyl)-2-phenyl-2*H*-indazole (3an)

Yellow solid: mp 103-105 °C; R_f = 0.52 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.4 Hz, 1 H); 7.69 (d, J = 8.4 Hz, 1 H), 7.39 (d, J = 2.4 Hz, 2 H), 7.38-7.33 (m, 4 H), 7.27 (d, J = 8.8 Hz, 2 H), 7.12 (t, J = 7.6 Hz, 1 H), 6.91 (d, J = 8.8 Hz, 2 H); 3.82 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 149.0, 140.4, 135.5, 131.1, 129.1, 128.3, 127.1, 126.1, 122.4, 122.2, 121.7, 120.8, 117.8, 114.4, 55.4; LRMS (EI) 300 (M); HRMS (EI) calcd for $C_{20}H_{16}N_2O$ (M) 300.1263, found 300.1272.

2-(4-Chlorophenyl)-3-(4-methoxyphenyl)-2*H*-indazole (3ao)

Slightly brown solid: mp 122-124 °C; R_f = 0.39 (6:1 petroleum ether/EtOAc);[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.77 (d, J = 8.8 Hz, 1 H), 7.68 (d, J = 8.5 Hz, 1 H), 7.42-7.33 (m, 5 H), 7.30-7.26 (m, 2 H), 7.13 (ddd, J = 8.4, 6.6, 0.7 Hz, 1 H), 6.99-6.91 (m, 2 H), 3.86 (s, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.7, 149.0, 138.8, 135.4, 133.9, 130.9, 129.2, 127.2, 127.1, 122.4, 121.8, 121.7, 120.6, 117.6, 114.4, 55.3; LRMS (ESI) 357 (M+Na), 335 (M +H); HRMS (ESI) calcd for $C_{20}H_{16}ClN_2O$ (M+H) 335.0946, found 335.0942.

2,3-*Bis*(4-chlorophenyl)-2*H*-indazole (3ap)

Pale white solid: mp 126-129 °C; R_f = 0.52 (6:1 petroleum ether/EtOAc);[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.79 (d, J = 8.8 Hz, 1 H), 7.66 (d, J = 8.5 Hz, 1 H), 7.43-7.35 (m, 7 H), 7.32-7.27 (m, 2 H), 7.17 (ddd, J = 8.5, 6.6, 0.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 138.4, 134.7, 134.3, 134.1, 130.8, 129.35, 129.29, 128.0, 127.4, 127.1, 123.1, 121.8, 120.1, 117.8; LRMS (ESI) 361 (M+Na), 339 (M+H); HRMS (ESI) calcd for $C_{19}H_{13}Cl_2N_2$ (M+H) 339.0450, found 339.0448.

2-(4-Chlorophenyl)-3-(2-thiophenyl)-2*H*-indazole (3aq)

Yellow solid: mp 99-101 °C; R_f = 0.49 (6:1 petroleum ether/EtOAc).[36] The product spot overlapped with a highly fluorescent spot that immediately follows the product spot. Performing column chromatography with 8:1:0.4 petroleum ether/CH_2Cl_2/EtOAc offers some help in separation and purification of the desired product: ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.82 (d, J = 8.5 Hz, 1 H), 7.77 (d, J = 8.8 Hz, 1 H), 7.49-7.35 (m, 6 H), 7.19 (ddd,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

J = 8.4, 6.6, 0.8 Hz, 1 H), 7.10 (dd, *J* = 5.1, 3.6 Hz, 1 H), 7.03 (dd, *J* = 3.6, 1.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.9, 138.4, 134.7, 129.9, 129.6, 129.3, 128.4, 127.69, 127.65, 127.5, 127.3, 123.0, 121.9, 120.5, 117.7; LRMS (ESI) 333 (M+Na), 311 (M+H); HRMS (ESI) calcd for $C_{17}H_{12}ClSN_2$ (M+H) 311.0404, found 311.0404. The contaminant (the fluorescent spot) shows a series of non-overlapped signals as follows: 7.87 (d, *J* = 8.5 Hz), 7.50 (apparent t, *J* = 9.0 Hz), 7.13 (d, *J* = 3.8 Hz), 6.88 (d, *J* = 3.8 Hz).

2-(4-Chlorophenyl)-3-(2-pyridyl)-2*H*-indazole (3ar)

Slightly brown solid: mp 137-139 °C; R_f = 0.25 (6:1 petroleum ether/EtOAc);[36] ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.71-8.67 (m, 1 H), 7.93 (d, *J* = 8.5 Hz, 1 H), 7.81 (d, *J* = 8.8 Hz, 1 H), 7.71 (td, *J* = 7.8, 1.8 Hz, 1 H), 7.44-7.36 (m, 5 H), 7.32 (d, *J* = 7.9 Hz, 1 H), 7.29-7.24 (m, 1 H), 7.21 (ddd, *J* = 8.5, 6.6, 0.7 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.2, 149.2, 149.1, 139.1, 136.5, 134.3, 134.1, 129.2, 127.3, 127.1, 124.6, 123.6, 122.6, 122.3, 120.7, 117.8; LRMS (ESI) 328 (M+Na), 306 (M+H); HRMS (ESI) calcd for $C_{18}H_{13}ClN_3$ (M+H) 306.0793, found 306.0790.

2-(4-Chlorophenyl)-3-phenylethynyl-2*H*-indazole (3as)

Yellow solid: mp 141-144 °C; R_f = 0.50 (6:1 petroleum ether/EtOAc).[36] The product spot overlapped with some spots that have a long wavelength UV absorption. Performing column chromatography with 8:1:0.4 petroleum ether/CH_2Cl_2/EtOAc offers some help in separation and purification of the desired product. The impurities do not show more than minimum contamination by ^{1}H NMR spectroscopy: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01-7.95 (m, 2 H), 7.87-7.78 (m, 2 H), 7.58-7.49 (m, 4 H), 7.43-7.36 (m, 4 H), 7.25-7.21 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 138.6, 134.3, 131.3, 129.19, 129.14, 128.6, 127.6, 125.6, 125.5, 123.5, 121.9, 120.2, 118.2, 100.7, 77.7 (one overlapped signal); LRMS (ESI) 329 (M+H); HRMS (ESI) calcd for $C_{21}H_{14}ClN_2$ (M+H) 329.0840, found 329.0837.

3-Iodo-2-phenyl-2*H*-indazole (3at)

Off-white solid: mp 104-105 °C; R_f = 0.42 (5:1 petroleum ether/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.74 (d, *J* = 8.8 Hz, 1 H), 7.62 (d, *J* = 7.2 Hz, 2 H), 7.50 (m, 4 H), 7.36 (dd, *J* = 7.6, 6.8 Hz, 1 H), 7.16 (t, *J* = 7.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.1, 140.6, 129.4, 129.1, 128.4, 127.7, 126.8, 123.3, 121.2, 118.4, 76.2; LRMS (ESI) 321 (M+H); HRMS (ESI) calcd for $C_{13}H_{10}IN_2$ (M+H) 320.9883, found 320.9884.

2-(4-Bromophenyl)-3-iodo-2*H*-indazole (3au)

Yellow solid: mp 159-161 °C; R_f = 0.38 (5:1 petroleum ether/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.73 (d, *J* = 8.8 Hz, 1 H), 7.68 (d, *J* = 8.4 Hz, 2 H), 7.54 (d, *J* = 8.8 Hz, 2 H), 7.47 (d, *J* = 8.4 Hz, 1 H), 7.38 (t, *J* = 7.4 Hz, 1 H), 7.18 (t, *J* = 7.4 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.4, 139.6, 132.5, 132.4, 128.7, 128.4, 128.0, 123.6, 121.3, 118.5, 76.0; LRMS (ESI) 399 (M+H); HRMS (ESI) calcd for $C_{13}H_9BrIN_2$ (M+H) 398.8988, found 398.8988.

5,6-Dimethyl-2-phenyl-2*H*-indazole (3ba)

White solid: mp 133-135 °C; R_f = 0.24 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1 H), 7.87 (d, *J* = 7.8 Hz, 2 H), 7.56 (s, 1 H), 7.49 (t, *J* = 7.8 Hz, 2 H), 7.40 (s, 2 H), 7.36 (t, *J* = 7.4 Hz, 1 H), 2.39 (s, 3 H), 2.34 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.6, 140.5, 137.2, 132.3, 129.4, 127.3, 121.8, 120.5, 119.0, 118.6, 116.5, 21.1, 20.5; LRMS (EI) 222 (M), 207 (M-Me); HRMS (EI) calcd for $C_{15}H_{14}N_2$ (M) 222.1157, found 222.1155.

5,6-Dimethoxy-2-phenyl-2*H*-indazole (3ca)

White solid: mp 147-148 °C (lit[37] 149-150 °C); R_f = 0.26 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.21 (s, 1 H), 7.84 (d, *J* = 7.7 Hz, 2 H), 7.49 (t, *J* = 7.9 Hz, 2 H), 7.34

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

(t, *J* = 7.4 Hz, 1 H), 7.06 (s, 1 H), 6.89 (s, 1 H), 3.97 (s, 3 H), 3.93 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 152.0, 148.4, 146.6, 140.5, 129.5, 127.0, 120.0, 119.1, 117.4, 96.9, 95.8, 55.9; LRMS (EI) 254 (M); HRMS (EI) calcd for $C_{15}H_{14}N_2O_2$ (M) 254.1055, found 254.1059.

5-Methyl-2-phenyl-*2H*-indazole and 6-methyl-2-phenyl-*2H*-indazole (3da + 3da')

Slightly yellow solid: R_f = 0.26 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of isomers, two sets of signals) δ 8.32 (s, 1 H), 8.27 (s, 1 H), 7.89 (s, 2 H), 7.87 (s, 2 H), 7.71 (d, *J* = 8.9 Hz, 1 H), 7.59 (d, *J* = 8.6 Hz, 1 H), 7.53-7.47 (m, 4 H), 7.55 (s, 1 H), 7.43 (s, 1 H), 7.41-7.34 (m, 2 H), 7.17 (d, *J* = 8.6 Hz, 1 H), 6.96 (d, *J* = 8.5 Hz, 1 H), 2.48 (s, 3 H), 2.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of isomers) δ 150.3, 148.7, 140.5, 136.7, 131.7, 129.8, 129.4, 127.6, 125.4, 123.0, 121.1, 120.73, 120.70, 120.1, 119.8, 119.4, 118.3, 117.5, 116.1, 22.3, 21.8 (some overlap); LRMS (EI) 208 (M); HRMS (EI) calcd for $C_{14}H_{12}N_2$ (M) 208.1000, found 208.1003.

5-Methoxy-2-phenyl-2*H*-indazole and 6-Methoxy-2-phenyl-2*H*-indazole (3ea + 3ea')

Yellow solid: R_f = 0.25 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of isomers, two sets of signals) δ 8.27 (s, 1H), 8.22 (s, 0.8 H), 7.84 (d, *J* = 8.4 Hz, 3.6 H), 7.68 (d, *J* = 9.2 Hz, 0.8 H), 7.53 (d, *J* = 9.2 Hz, 1 H), 7.48 (t, *J* = 7.8 Hz, 3.6 H), 7.36-7.32 (m, 1.8 H), 7.04-7.02 (m, 1.8 H), 6.86 (d, *J* = 2.0 Hz, 0.8 H), 6.80 (dd, *J* = 8.8, 1.6 Hz, 1 H), 3.87 (s, 3 H), 3.82 (s, 2.4 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of isomers) δ 159.5, 155.6, 151.0, 146.9, 140.7, 140.6, 129.6, 127.6, 127.5, 122.9, 122.2, 121.4, 120.7, 120.53, 120.50, 119.46, 119.41, 118.7, 118.0, 96.4, 94.7, 55.5, 55.4 (one overlapped signal); LRMS (ESI) 225 (M+H); HRMS (ESI) calcd for $C_{14}H_{13}N_2O$ (M+H) 225.1022, found 225.1022.

4-Methyl-2-phenyl-*2H*-indazole and 7-methyl-2-phenyl-*2H*-indazole (3fa + 3fa')

Yellow oil: R_f = 0.35 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of isomers, two sets of signals) δ 8.35 (s, 1 H), 8.32 (s, 0.7 H), 7.88(dd, *J* = 8.4, 2.0 Hz, 3.4 H), 7.62 (d, *J* = 8.8 Hz, 1 H), 7.52-7.46 (m, 4.1 H), 7.37-7.34 (m, 1.7 H), 7.23-7.19 (m, 1 H), 7.07-6.98 (m, 1.4 H), 6.84 (d, *J* = 6.8 Hz, 1 H), 2.68 (s, 2.1 H), 2.54 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of isomers) δ 150.3, 150.0, 140.8, 140.7, 130.7, 129.7, 128.2, 127.93, 127.89, 127.4, 125.8, 124.3, 122.9, 122.7, 121.7, 121.3, 121.1, 120.9, 119.7, 117.9, 115.4, 19.3, 17.3; LRMS (ESI) 209 (M+H); HRMS (ESI) calcd for $C_{14}H_{13}N_2$ (M+H) 209.1073, found 209.1078.

2-Phenyl-2*H*-benzo[*g*]indazole and 2-phenyl-2*H*-benzo[*e*]indazole (3ga + 3ga')

Yellow gel: R_f = 0.42 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$, mixture of isomers, two sets of signals) δ 8.74 (d, *J* = 8.0 Hz, 1 H), 8.71 (s, 1 H), 8.33 (s, 1 H), 8.12 (d, *J* = 7.6 Hz, 1 H), 7.93 (t, *J* = 7.2 Hz, 4 H), 7.83 (d, *J* = 8.0 Hz, 2 H), 7.74 (d, *J* = 9.2 Hz, 1 H), 7.62 (m, 2 H), 7.52 (m, 8 H), 7.38 (m, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$, mixture of isomers) δ 148.9, 147.7, 140.7, 140.6, 132.9, 130.6, 129.72, 129.69, 129.3, 129.1, 128.6, 127.6, 127.5, 127.4, 127.2, 127.1, 126.9, 125.8, 125.6, 124.7, 123.6, 122.8, 121.2, 120.6, 120.5, 120.2, 120.0, 118.5, 117.9, 117.5; LRMS (ESI) 245 (M+H); HRMS (ESI) calcd for $C_{17}H_{13}N_2$ (M+H) 245.1073, found 245.1064.

4-Methoxy-2-phenyl-*2H*-indazole (3ia)

Following the general procedure, this product was isolated as a white gel by collecting the first spot: R_f = 0.24 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.48 (s, 1 H), 7.89 (d, *J* = 8.1 Hz, 2 H), 7.51 (t, *J* = 7.7 Hz, 2 H), 7.44-7.33 (m, 2 H), 7.31-7.18 (m, 1 H), 6.35 (d, *J* = 7.3 Hz, 1 H), 3.96 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.4, 151.2, 140.4, 129.5, 127.70, 127.65, 120.7, 119.0, 116.8, 110.3, 98.8, 55.2; LRMS (EI) 224 (M), 209 (M-

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

Me); HRMS (EI) calcd for $C_{14}H_{12}N_2O$ (M) 224.0950, found 224.0950. The 2D NMR spectra and the analysis are included in the SI.

7-Methoxy-2-phenyl-*2H*-indazole (3ia')

The second spot of the aforementioned column chromatography afforded a yellow gel: R_f = 0.12 (5:1 hexanes/EtOAc). This material was stirred with 1 mL of Ac_2O and 1 mL of pyridine at room temperature for 30 min. Then the volatiles were evaporated under a vacuum, and the product purified by column chromatography: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.36 (s, 1 H), 7.93 (d, *J* = 8.0 Hz, 2 H), 7.49 (t, *J* = 7.8 Hz, 2 H), 7.37 (t, *J* = 7.4 Hz, 1 H), 7.26 (d, *J* = 8.4 Hz, 1 H), 7.02 (dd, *J* = 8.4, 0.8 Hz, 1 H), 6.58 (d, *J* = 7.2 Hz, 1 H), 4.04 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.6, 143.5, 140.5, 129.6, 128.0, 124.5, 123.3, 121.2, 120.8, 112.5, 103.3, 55.7; LRMS (ESI) 225 (M+H), 247 (M+Na), 471 (2M+Na); HRMS (ESI) calcd for $C_{14}H_{13}N_2O$ (M+H) 225.1022, found 225.1024. This regioisomer matches the reported ^{1}H and ^{13}C NMR spectral data.[18]

4-Methoxy-2-(4-methylphenyl)-*2H*-indazole (3id)

Following the general procedure, this product was isolated as a white gel by collecting the first spot: R_f = 0.30 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.43 (s, 1 H), 7.76 (d, *J* = 7.6 Hz, 2 H), 7.36 (d, *J* = 8.4 Hz, 1 H), 7.29 (d, *J* = 7.6 Hz, 2 H), 7.24-7.20 (m, 1 H), 6.34 (d, *J* = 7.2 Hz, 1 H), 3.94 (s, 3 H), 2.40 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.6, 151.3, 138.3, 137.9, 130.2, 127.7, 120.8, 119.1, 116.9, 110.4, 98.9, 55.4, 21.2; LRMS (ESI) 239 (M+H); HRMS (ESI) calcd for $C_{15}H_{15}N_2O$ (M+H) 239.1179, found 239.1179.

7-Methoxy-2-(4-methylphenyl)-*2H*-indazole (3id')

The second spot of the aforementioned column chromatography afforded a yellow gel: R_f = 0.22 (5:1 hexanes/EtOAc). This material was stirred with 1 mL of Ac_2O and 1 mL of pyridine at room temperature for 30 min. Then the volatiles were evaporated under vacuum, and the product purified by column chromatography: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.31 (s, 1 H), 7.80 (d, *J* = 8.4 Hz, 2 H), 7.26 (t, *J* = 9.2 Hz, 3 H), 7.01 (t, *J* = 7.8 Hz, 1 H), 6.57 (d, *J* = 7.6 Hz, 1 H), 4.03 (s, 3 H), 2.39 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 150.5, 143.3, 138.3, 137.9, 130.0, 124.4, 123.1, 121.0, 120.6, 112.4, 103.1, 55.6, 21.2; LRMS (ESI) 239 (M+H), 261 (M+Na); HRMS (ESI) calcd for $C_{15}H_{14}N_2ONa$ (M+Na) 261.0998, found 261.0999.

Procedure for the Suzuki-Miyaura Coupling with Boronic Acids

To a 4 dram vial were added the starting material **3at** (~0.4 mmol), the boronic acid (1.5 equiv.), KOH (3.0 equiv.) and $Pd(PPh_3)_4$ (5 mol %) in 20 : 5 : 1 toluene/ethanol/H_2O (4 mL in total). The solution was vigorously stirred for 5 min at room temperature, flushed with argon and sealed, and then heated to 80 °C until TLC revealed complete conversion of the starting material. Upon cooling to room temperature, the resulting reaction mixture was diluted with water and extracted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by column chromatography to afford the following product.

3-(3,4-Methylenedioxyphenyl)-2-phenyl-2*H*-indazole (4at)

Following the general procedure, this product was isolated as a brown solid: mp 154-156 °C; R_f = 0.31 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.78 (d, *J* = 8.8 Hz, 1 H), 7.68 (d, *J* = 8.8 Hz, 1 H), 7.45 (d, *J* = 6.8 Hz, 2 H), 7.42-7.33 (m, 4 H), 7.12 (dd, *J* = 8.0, 7.2 Hz, 1 H), 6.87-6.81 (m, 2 H), 6.78 (s, 1 H), 5.98 (s, 2 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.0, 148.1, 147.9, 140.2, 135.3, 129.2, 128.4, 127.2, 126.1, 124.0, 123.5, 122.5, 121.8,

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

120.6, 117.8, 110.0, 108.9, 101.5; LRMS (ESI) 315 (M+H); HRMS (ESI) calcd for $C_{20}H_{15}N_2O_2$ (M+H) 315.1128, found 315.1125.

Procedure for the Sonogashira Coupling with a Terminal Alkyne

To a 4 dram vial was added the starting material **3at** (~0.4 mmol), the alkyne (1.2 equiv.), $PdCl_2(PPh_3)_2$ (3 mol %), CuI (3 mol %), DMF (1.5 mL) and Et_2NH (1.5 mL). The solution was stirred at room temperature, flushed with argon and sealed, and then heated to 60 °C until TLC analysis revealed complete conversion of the starting material. The solution was allowed to cool and diluted with EtOAc. The combined organic layers were dried over $MgSO_4$, concentrated, and purified by column chromatography to afford the following product.

3-(3-Methoxyprop-1-ynyl)-2-phenyl-2*H*-indazole (5at)

Yellow oil: R_f = 0.25 (5:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.91 (d, *J* = 7.6 Hz, 2 H), 7.78 (dd, *J* = 15.6, 8.8 Hz, 2 H), 7.53 (t, *J* = 7.8 Hz, 2 H), 7.46 (t, *J* = 7.2 Hz, 1 H), 7.36 (t, *J* = 7.6 Hz, 1 H), 7.20 (t, *J* = 7.4 Hz, 1 H), 4.41 (s, 2 H), 3.43 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 148.7, 140.2, 129.2, 128.9, 127.5, 126.1, 124.7, 123.6, 120.2, 118.5, 117.7, 96.7, 75.4, 60.7, 58.0; LRMS (ESI) 263 (M+H); HRMS (ESI) calcd for $C_{17}H_{15}N_2O$ (M+H) 263.1179, found 263.1180.

Supplementary Material

Refer to Web version on PubMed Central for supplementary material.

Acknowledgments

We thank the National Institutes of Health (GM070620 and GM079593 to R.C.L.), the National Institutes of Health Center for Chemical Methodology and Library Development at University of Kansas (P50 GM069663 to R.C.L.), the National Natural Science Foundation of China (No. 21002021 to F.S.), and the Key Project of the Chinese Ministry of Education (No. 210127 to F.S.) for their generous financial support, and the State Key Laboratory of Physical Chemistry of Solid Surfaces (Xiamen University) for providing computational resources. We also thank Mr. Donald C. Rogness (Iowa State University) for his help in preparation of the benzyne precursors, and Mr. Yong Wang (Henan University), Dr. Jiang Zhou (Peking University), Mr. Shu-Lun Tang and Dr. Kermal Harrata (both Iowa State University) for their help in the spectroscopic analysis.

References

1. (a) Schmidt A, Beutler A, Snovydovych B. Eur J Org Chem. 2008:4073.(b) Clutterbuck LA, Posada CG, Visintin C, Riddal DR, Lancaster B, Gane PJ, Garthwaite J, Selwood DL. J Med Chem. 2009; 52:2694. [PubMed: 19341281]
2. (a) Andreonati S, Sava V, Makan S, Kolodeev G. Pharmazie. 1999; 54:99. [PubMed: 10084155] (b) Paluchowska MH, Duszynska B, Klodzinska A, Tatarzynska E. Pol J Pharmacol. 2000; 52:209. [PubMed: 11055578] (c) Saczewski F, Saczewski J, Hudson AL, Tyacke RJ, Nutt DJ, Man J, Tabin P. Eur J Pharm Sci. 2003; 20:201. [PubMed: 14550886] (d) Angelis MD, Stossi F, Carlson KA, Katzenellenbogen BS, Katzenellenbogen JA. J Med Chem. 2005; 48:1132. [PubMed: 15715479]
3. (a) Halland N, Nazaré M, R'kyek O, Alonso J, Urmann M, Lindenschmidt A. Angew Chem Int Ed. 2009; 48:6879.(b) Song JJ, Yee NK. Org Lett. 2000; 2:519. [PubMed: 10814366] (c) Haag B, Peng Z, Knochel P. Org Lett. 2009; 11:4270. [PubMed: 19775181] (d) Taher A, Ladwa S, Rajan ST, Weaver GW. Tetrahedron Lett. 2000; 41:9893.(e) Varughese DJ, Manhas MS, Bose AK. Tetrahedron Lett. 2006; 47:6795.(f) Lee KY, Gowrisankar S, Kim JN. Tetrahedron Lett. 2005; 46:5387.(g) Kumar MR, Park A, Park N, Lee S. Org Lett. 2011; 13:3542. [PubMed: 21644532]
4. (a) Liu Z, Zhang X, Larock RC. J Am Chem Soc. 2005; 127:15716. [PubMed: 16277509] (b) Zhang X, Larock RC. Org Lett. 2005; 7:3973. [PubMed: 16119945] (c) Liu Z, Larock RC. Org Lett. 2004; 6:3739. [PubMed: 15469337] (d) Liu Z, Larock RC. Tetrahedron. 2007; 63:347. [PubMed: 18180808] (e) Henderson JL, Edwards AS, Greaney MF. J Am Chem Soc. 2006; 128:7426.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

[PubMed: 16756281] (f) Jayanth TT, Cheng CH. Chem Commun. 2006; 894(g) Peña D, Pérez D, Guitián E, Castedo L. Org Lett. 1999; 1:1555.(h) Radhakrishnan KV, Yoshikawa E, Yamamoto Y. Tetrahedron Lett. 1999; 40:7533.(i) Peña D, Pérez D, Guitián E, Castedo L. J Am Chem Soc. 1999; 121:5827.

5. (a) Yoshida H, Honda Y, Shirakawa E, Hiyama T. Chem Commun. 2001; 1880(b) Yoshida H, Shirakawa E, Honda Y, Hiyama T. Angew Chem Int Ed Engl. 2002; 41:3247. [PubMed: 12207403] (c) Liu Z, Larock RC. Org Lett. 2003; 5:4673. [PubMed: 14627412] (d) Liu Z, Larock RC. Org Lett. 2004; 6:99. [PubMed: 14703360] (e) Jeganmohan M, Cheng CH. Synthesis. 2005:1693.(f) Bhuvaneswari S, Jeganmohan M, Yang MC, Cheng CH. Chem Commun. 2008:2158.
6. (a) Raminelli C, Liu Z, Larock RC. J Org Chem. 2006; 71:4689. [PubMed: 16749809] (b) Feltenberger JB, Hayashi R, Tang Y, Babiash ESC, Hsung RP. Org Lett. 2009; 11:3430. [PubMed: 19591454] (c) Allan KM, Stoltz BM. J Am Chem Soc. 2008; 130:17270. [PubMed: 19035638] (d) Gilmore CD, Allan KM, Stoltz BM. J Am Chem Soc. 2008; 130:1558. [PubMed: 18193875] (e) Pérez D, Guitián E, Castedo L. J Org Chem. 1992; 57:5911.(f) Matsumoto T, Hosoya T, Suzuki K. J Am Chem Soc. 1992; 114:3568.(g) Hosoya T, Takashiro E, Matsumoto T, Suzuki K. J Am Chem Soc. 1994; 116:1004.(h) Hussain H, Kianmehr E, Durst T. Tetrahedron Lett. 2001; 42:2245.(I) Soorukram D, Qu T, Barrett AGM. Org Lett. 2008; 10:3833. [PubMed: 18672878]
7. (a) Liu Z, Larock RC. J Am Chem Soc. 2005; 127:13112. [PubMed: 16173716] (b) Tambar UK, Stoltz BM. J Am Chem Soc. 2005; 127:5340. [PubMed: 15826170]
8. Shi F, Waldo JP, Chen Y, Larock RC. Org Lett. 2008; 10:2409. [PubMed: 18476707]
9. Liu Z, Shi F, Martinez PDG, Raminelli C, Larock RC. J Org Chem. 2008; 73:219. [PubMed: 18067316]
10. Dubrovskiy AV, Larock RC. Org Lett. 2010; 12:1180. [PubMed: 20184347]
11. Wu C, Fang Y, Larock RC, Shi F. Org Lett. 2010; 12:2234. [PubMed: 20394430]
12. (a) Thoman CJ, Voaden DJ. Org Synth. 1965; 45:96.(b) Baker W, Ollis WD, Poole VD. J Chem Soc. 1950:1542.(c) Applegate J, Turnbull K. Synthesis. 1988:1011.(d) Azarifar D, Ghasemnejad-Borsa H. Synthesis. 2006:1123.(e) Azarifar D, Ghasemnejad-Borsa H, Tajbaksh M, Habibzadeh S. Heterocycles. 2007; 71:1815.(f) Ma D, Cai Q, Zhang H. Org Lett. 2003; 5:2453. [PubMed: 12841753] (g) Browne DL, Vivat JF, Plant A, Gomez-Bengoa E, Harrity JPA. J Am Chem Soc. 2009; 131:7762. [PubMed: 19449876]
13. Rodriguez A, Fennessy RV, Moran WJ. Tetrahedron Lett. 2009; 50:3942.
14. Wu C, Li P, Fang Y, Zhao J, Xue W, Li Y, Larock RC, Shi F. Tetrahedron Lett. 2011; 52:3797.
15. Browne DL, Taylor AP, Harrity JP. J Org Chem. 2010; 75:984. [PubMed: 20030356]
16. Ghasemnejad-Bosra H, Haghdadi M, Gholampour-Azizi I. Heterocycles. 2008; 75:391.
17. (a) Effenberger F, Daub W. Chem Ber. 1991; 124:2119.(b) Walters M, Shay J. Synth Commun. 1997; 27:3573.
18. Ohnmacht SA, Culshaw AJ, Greaney MF. Org Lett. 2010; 12:224. [PubMed: 20014781]
19. Kessar, SV. Comprehensive Organic Synthesis. Trost, BM.; Fleming, I., editors. Vol. 4. Pergamon Press; Oxford, England: 1991. p. 483-515.
20. (a) Hill R, Sutton LE, Longuet-Higgins C. J Chem Phys. 1949; 46:244.(b) Orgel LE, Cotterell TL, Dick W, Sutton LE. Trans Faraday Soc. 1951; 47:113.
21. Fan J, Wang Y, Ueng C. J Phys Chem. 1993; 97:8193.
22. For regioselectivities in favor of *C*-4 reacting as the nucleophilic site, see:(a) Padwa A, Burgess EM, Gingrich HL, Roush DM. J Org Chem. 1982; 47:786.(b) Chang E, Wong FF, Chen T, Chiang K, Yeh M. Heterocycles. 2006; 68:1007.(c) Fariña F, Fernández P, Fraile MT, Martín MV, Martín MR. Heterocycles. 1989; 29:967.(d) Harju K, Vesterinen J, Yli-Kauhaluoma J. Org Lett. 2009; 11:2219. [PubMed: 19419217] For regioselectivities in favor of *N*-2 reacting as the nucleophilic site, see(e) Hegde JC, Rai G, Puranik VG, Kalluraya B. Synth Commun. 2006; 36:1285.(f) Croce PD, Rosa CL, Zecchi G. J Chem Soc, Perkin Trans 1. 1985:2621.
23. (a) Padwa A, Burgess EM, Gingrich HL, Roush DM. J Org Chem. 1982; 47:786.(b) Houk KN, Sims J, Duke RE, Strozier RW, George JK. J Am Chem Soc. 1973; 95:7287.
24. The reaction between resonance structure **C** and aryne leads to a closer approximity between the carbonyl group of the sydnone and the OMe group of the aryne. Such steric repulsion does not exist if resonance structure **B** is reacting.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

25. Miyaura N, Suzuki A. Chem Rev. 1995; 95:2457.
26. (a) Negishi E, Anastasia L. Chem Rev. 2003; 103:1979. [PubMed: 12744698] (b) Miura M, Nomura M. Top Curr Chem. 2002; 219:211.
27. Cho C, Neuenswander B, Lushington GH, Larock RC. J Comb Chem. 2008; 10:941. [PubMed: 18937516]
28. For an improved synthesis of aryne precursors bearing diverse functional groups, see:(a) Kirkham JD, Delaney PM, Ellames GJ, Rowb EC, Harrity JPA. Chem Commun. 2010; 46:5154.(b) Crossley JA, Kirkham JD, Browne DL, Harrity JPA. Tetrahedron Lett. 2010; 51:6608.
29. (a) Peña D, Pérez D, Guitián E, Castedo L. J Am Chem Soc. 1999; 121:5827.(b) Peña D, Pérez D, Guitián E, Castedo L. J Org Chem. 2000; 65:6944. [PubMed: 11031014] (c) Yoshida H, Sugiura S, Kunai A. Org Lett. 2002; 4:2767. [PubMed: 12153230] (d) Liu Z, Zhang X, Larock RC. J Am Chem Soc. 2005; 127:15716. [PubMed: 16277509] (e) Peña D, Escudero S, Pérez D, Guitián E, Castedo L. Angew Chem, Int Ed Engl. 1998; 37:2659.(f) Yoshida H, Ikadai J, Shudo M, Ohshita J, Kunai A. J Am Chem Soc. 2003; 125:6638. [PubMed: 12769566] (g) Himeshima Y, Sonoda T, Kobayashi H. Chem Lett. 1983:1211.(h) Peña D, Cobas A, Pérez D, Guitian E. Synthesis. 2002:1454.
30. These two types of silica gel are noticeably different. We have observed that much higher R_f values are obtained using the 300-400 mesh silica gel.
31. Frisch, MJ.; Trucks, GW.; Schlegel, HB.; Scuseria, GE.; Robb, MA.; Cheeseman, JR.; Scalmani, G.; Barone, V.; Mennucci, B.; Petersson, GA.; Nakatsuji, H.; Caricato, M.; Li, X.; Hratchian, HP.; Izmaylov, AF.; Bloino, J.; Zheng, G.; Sonnenberg, JL.; Hada, M.; Ehara, M.; Toyota, K.; Fukuda, R.; Hasegawa, J.; Ishida, M.; Nakajima, T.; Honda, Y.; Kitao, O.; Nakai, H.; Vreven, T.; Montgomery, JA., Jr; Peralta, JE.; Ogliaro, F.; Bearpark, M.; Heyd, JJ.; Brothers, E.; Kudin, KN.; Staroverov, VN.; Kobayashi, R.; Normand, J.; Raghavachari, K.; Rendell, A.; Burant, JC.; Iyengar, SS.; Tomasi, J.; Cossi, M.; Rega, N.; Millam, NJ.; Klene, M.; Knox, JE.; Cross, JB.; Bakken, V.; Adamo, C.; Jaramillo, J.; Gomperts, R.; Stratmann, RE.; Yazyev, O.; Austin, AJ.; Cammi, R.; Pomelli, C.; Ochterski, JW.; Martin, RL.; Morokuma, K.; Zakrzewski, VG.; Voth, GA.; Salvador, P.; Dannenberg, JJ.; Dapprich, S.; Daniels, AD.; Farkas, Ö.; Foresman, JB.; Ortiz, JV.; Cioslowski, J.; Fox, DJ. Gaussian 09, Revision A.1. Gaussian, Inc.; Wallingford CT: 2009.
32. Rai NS, Kalluraya B, Lingappa B, Shenoy S, Puranic VG. Eur J Med Chem. 2008; 43:1715. [PubMed: 17923171]
33. Meo PL, D'Anna F, Riela S, Gruttadauria M, Noto R. Org Biomol Chem. 2003; 1:1584. [PubMed: 12926291]
34. (a) Ranganathan D, Bamezai S. Tetrahedron Lett. 1983; 24:1067.(b) Nikitenko AA, Winkley MW, Zeldis J, Kremer K, Chan AWY, Strong H, Jennings M, Jirkovsky I, Blum D, Khafizova G, Grosu GT, Venkatesan AM. Org Proc Res Dev. 2006; 10:712.
35. Cadogan JIG, Mackie RK. Org Synth. 1968; 48:113.
36. The underlined R_f values were obtained using the 300-400 mesh silica gel. The rest of the R_f values were obtained using the 230-400 mesh silica gel. These two types of silica gels behave quite differently.
37. Ina S, Inoue S, Noguchi I. Yakugaku Zasshi: J Pharm Soc Jpn. 1975; 95:1245.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

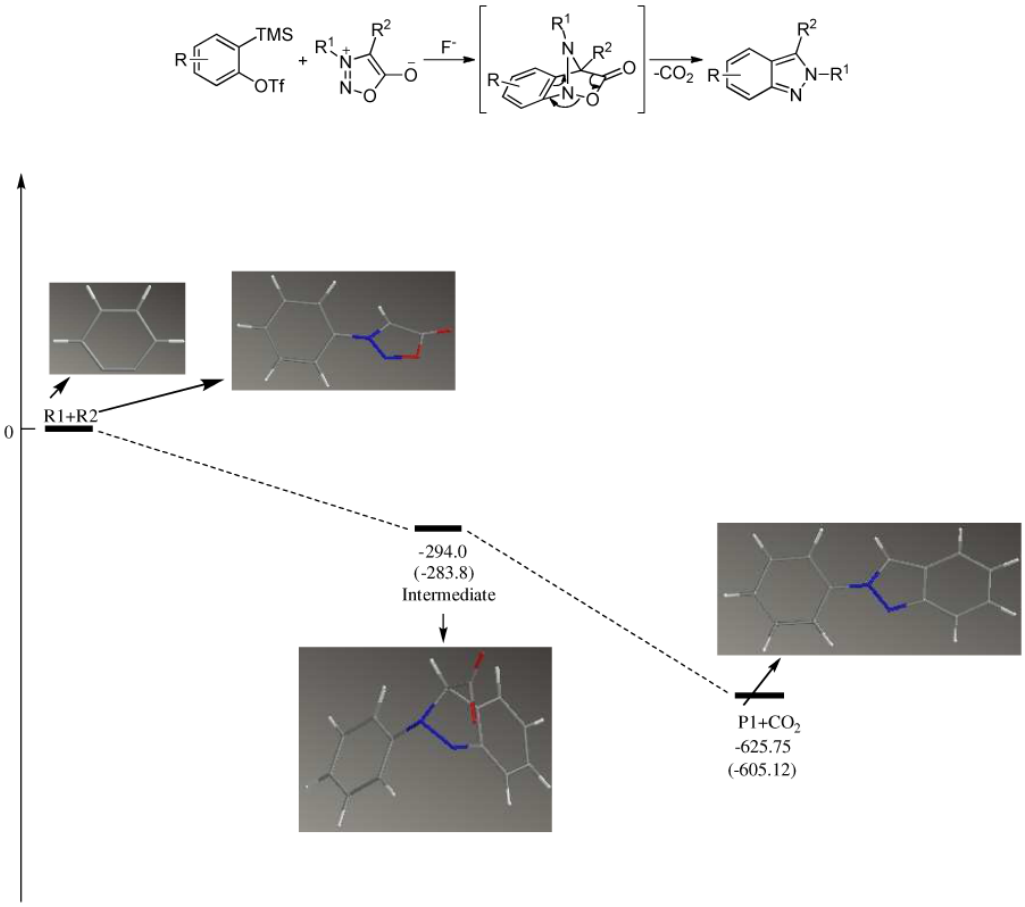


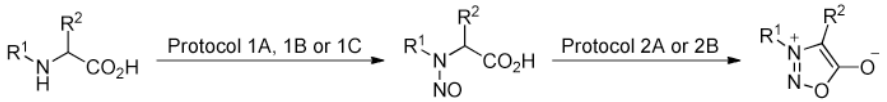
Figure 1.

Schematic potential energy surface with zero-point energy (ZPE) corrections at the MP2/6-311+G(d,p) level (units in kJ mol^{-1}). The values in parentheses are those obtained at the B3LYP/6-31G(d) level. The energy of the reactants is set to zero as a reference.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

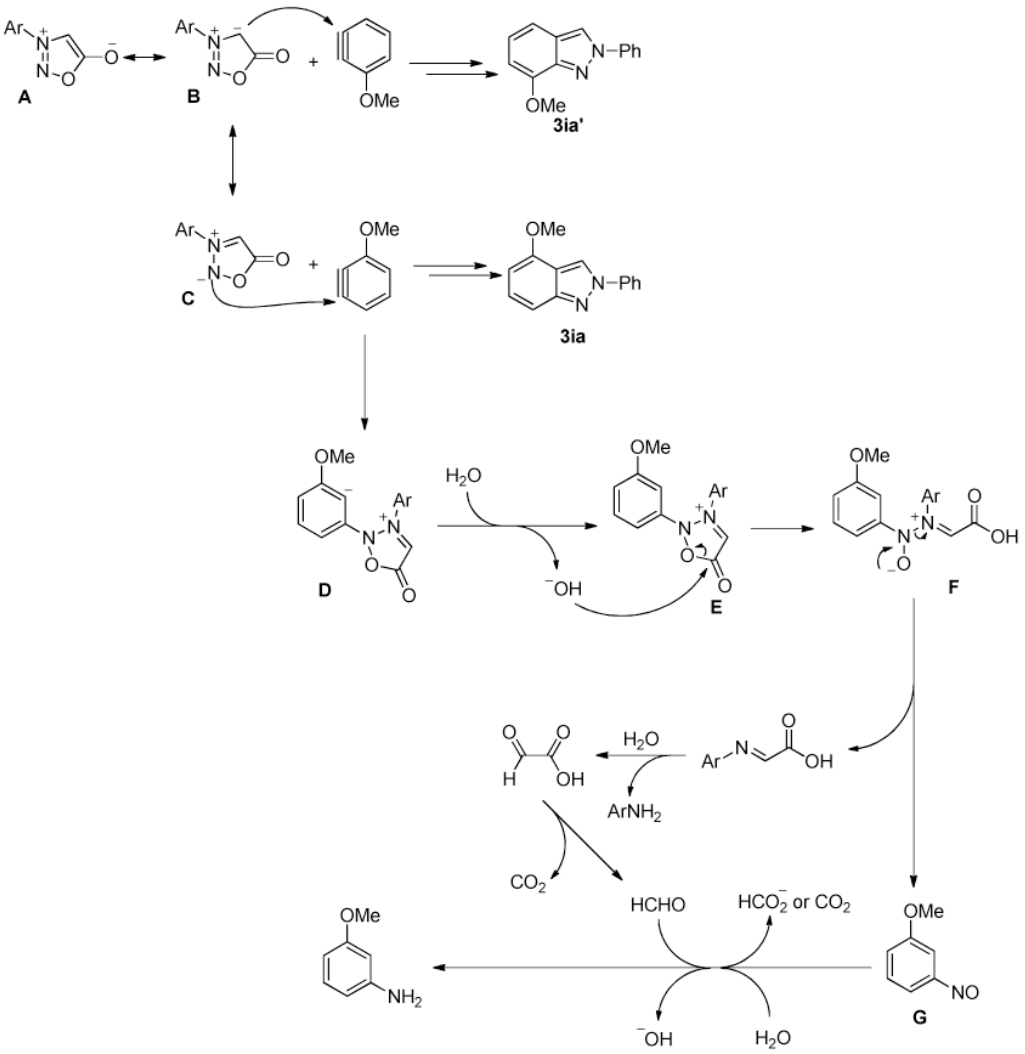


Scheme 1.
Synthesis of Sydnones.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript



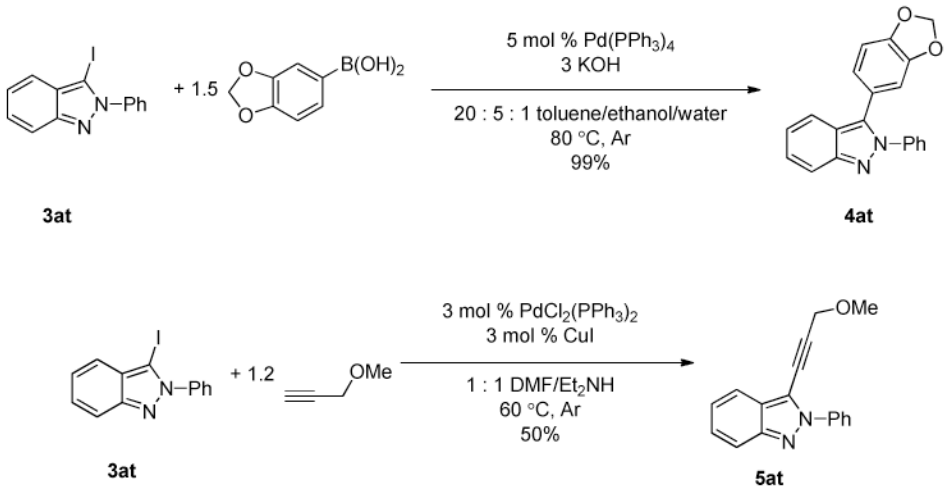
Scheme 2.

Regioselectivity in the Cycloaddition Reaction and Proposed Mechanism for the Formation of *m*-Anisidine.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

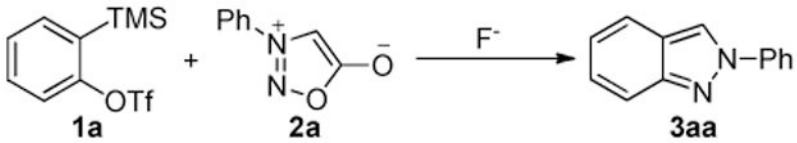


Scheme 3.
Suzuki-Miyaura and Sonogashira Coupling of 2*H*-Indazoles

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

Table 1

Reaction Optimization[a]



entry	1a (equiv)	fluoride source (equiv)	solvent	*T* (°C) /time (h)	yield[b] (%)
1	1.5	CsF (2.5)	MeCN	rt, 36	69[c]
2	1.5	CsF (2.5)	THF	70, 24	90
3[d]	1.5	TBAF (2.5)	MeCN	rt, 12	95[e]
4[d]	1.5	TBAF (2.5)	THF	rt, 12	94
5[d]	1.2	TBAF (1.5)	THF	rt, 12	98
6[f]	1.2	TBAF (1.5)	THF	rt, 12	97

[a] All reactions were carried out on a 0.4 mmol scale at 0.1 M concentration.

[b] Isolated yield.

[c] Incomplete conversion of **2a** even after 2 days.

[d] Solid anhydrous TBAF was used.

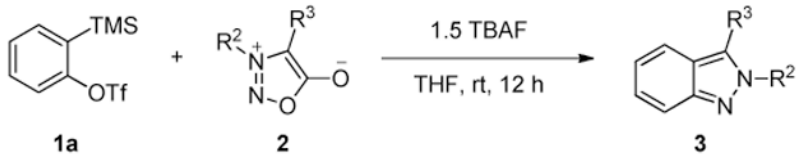
[e] The product is significantly yellow, although no apparent impurity was detected by ^{1}H NMR spectroscopy.

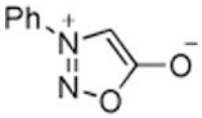
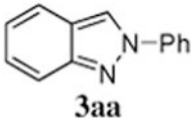
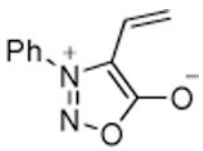
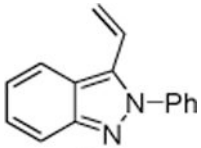
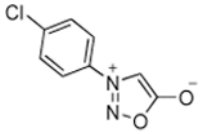
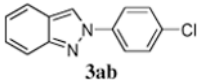
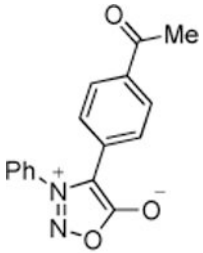
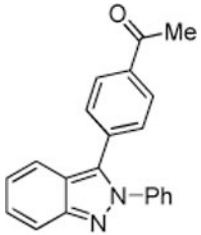
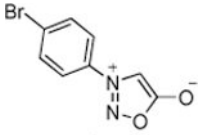
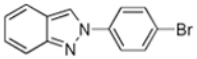
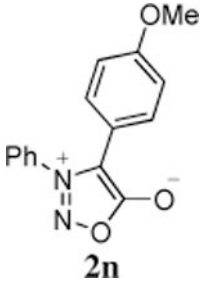
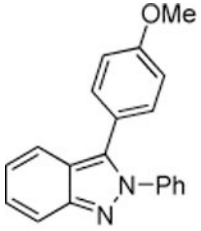
[f] A THF solution of TBAF (1 M) was used.

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript

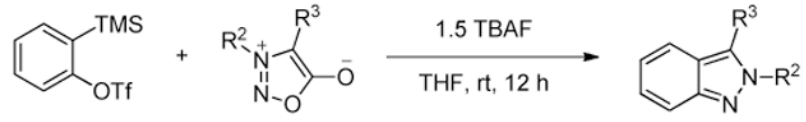
Table 2

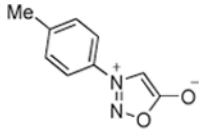
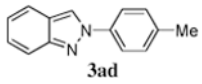
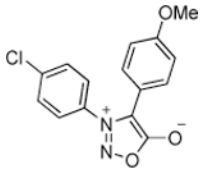
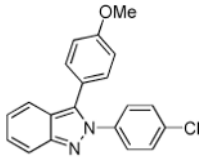
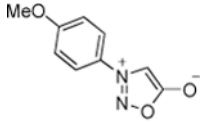
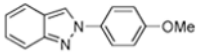
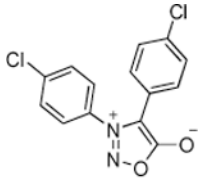
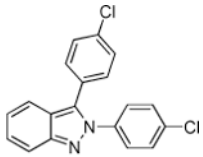
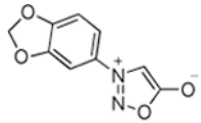
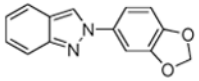
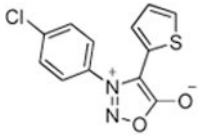
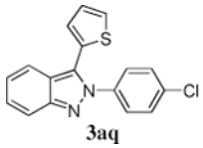
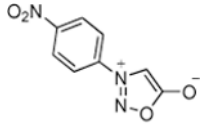
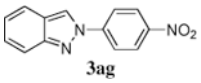
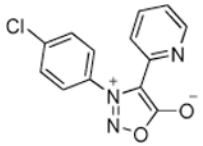
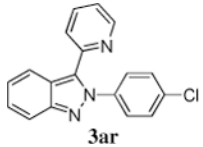
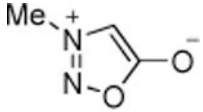
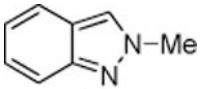
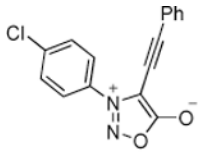
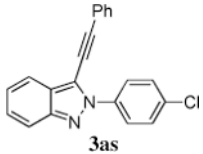
Synthesis of 2*H*-Indazoles from Benzyne and Sydnones[a]



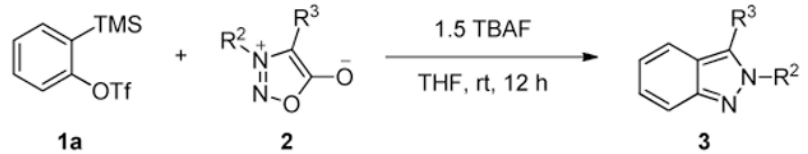
entry	sydnone	product	yield[b] (%)	entry	sydnone	product	yield[b] (%)
1	 2a	 3aa	98	12	 2l	 3al	79
2	 2b	 3ab	95	13	 2m	 3am	71
3	 2c	 3ac	93	14	 2n	 3an	90

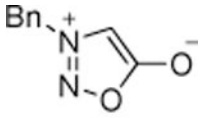
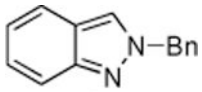
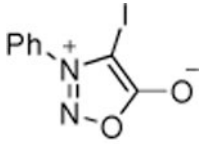
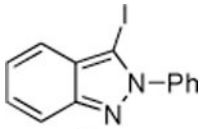
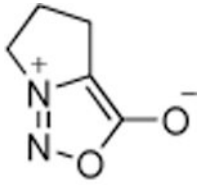
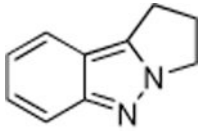
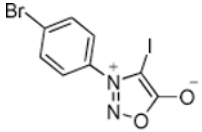
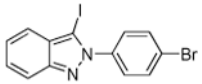
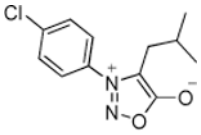
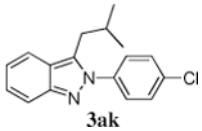
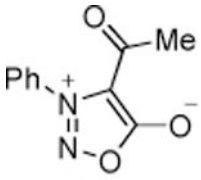
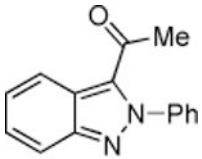
NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript



entry	sydnone	product	yield[b] (%)	entry	sydnone	product	yield[b] (%)
4	 2d	 3ad	94	15	 2o	 3ao	93
5	 2e	 3ae	92	16	 2p	 3ap	91
6	 2f	 3af	91	17	 2q	 3aq	~79[e]
7	 2g	 3ag	trace[c]	18	 2r	 3ar	72[f]
8	 2h	 3ah	77	19	 2s	 3as	70[g]

NIH-PA Author Manuscript
NIH-PA Author Manuscript
NIH-PA Author Manuscript



entry	sydnone	product	yield[b] (%)	entry	sydnone	product	yield[b] (%)
9	 2i	 3ai	70	20	 2t	 3at	88
10	 2j	 3aj	70	21	 2u	 3au	90
11	 2k	 3ak	63[d]	22	 2v	 3av	n.r.[h]

[a] All reactions were carried out on approximately 0.4 mmol of sydnone at a concentration of 0.1 M.

[b] Isolated yield.

[c] A trace amount of product was detected by GC-MS. Substrate **2g** was still unreactive upon heating.

[d] This reaction was performed with 1.6 equiv of **1a** and 2.4 equiv of TBAF.

[e] The reaction afforded a 52% yield of pure **3aq**, together with another fraction of impure **3aq** (32% by weight, approximately 80-85% purity) that was very hard to purify.

[f] With 15% recovery of **2r**.

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

[g]With 19% recovery of **2s**.

[h]With total recovery of **2v**, **1a** was consumed. Substrate **2v** was still unreactive upon heating.

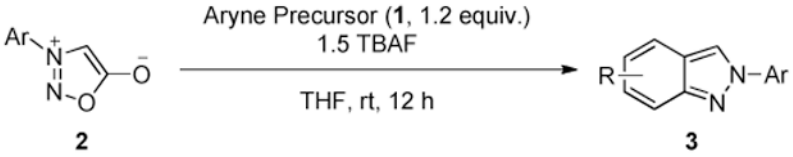
NIH-PA Author Manuscript

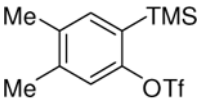
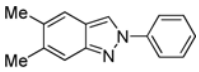
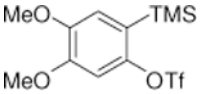
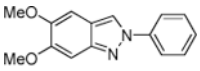
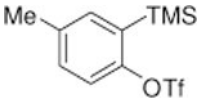
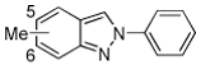
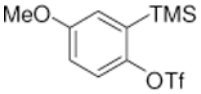
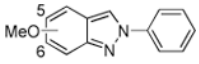
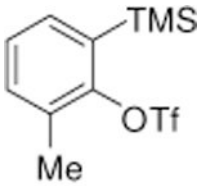
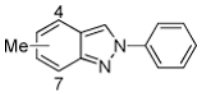
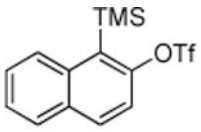
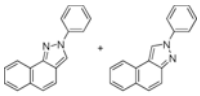
NIH-PA Author Manuscript

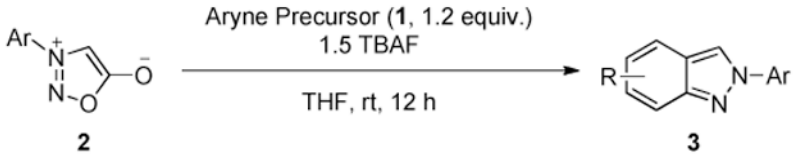
NIH-PA Author Manuscript

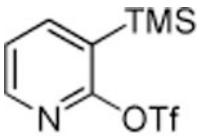
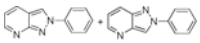
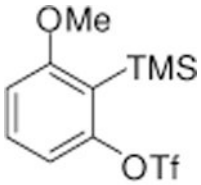
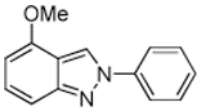
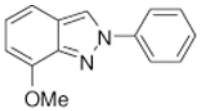
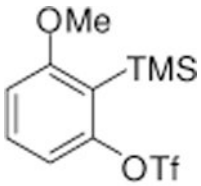
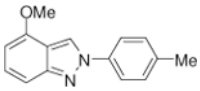
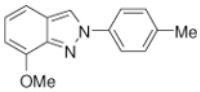
Table 3

Reaction with Other Aryne Precursors[a]



entry	sydnone	aryne precursor	product	yield[b] (%)
1	Ar=PH **2a**	 **1b**	 **3ba**	97
2		 **1c**	 **3ca**	95
3		 **1d**	 **3da + 3da'**	93[c]
4		 **1e**	 **3ea + 3ea'**	99[d]
5		 **1f**	 **3fa + 3fa'**	98[e]
6		 **1g**	 **3ga + 3ga'**	91[f]



entry	sydnone	aryne precursor	product	yield[b] (%)
7		 **1h**	 3ha + 3ha'	0[g]
8		 **1i**	 **3ia**  **3ia'**	33[h] 40
9	Ar=PH **2d**	 **1i**	 **3id**  **3id'**	44[i] 42[i]

[a] All reactions were carried out on 0.4 mmol of sydnone at a concentration of 0.1 M.

[b] Isolated yield.

[c] A 1:1 mixture of the 5-Me isomer and the 6-Me isomer was obtained.

[d] An inseparable 0.8:1 mixture of two isomers (5-MeO and 6-MeO) was obtained. The major isomer was not identified.

[e] A 0.7:1 mixture of two inseparable isomers (4-Me and 7-Me) was obtained. The major isomer was not identified.

NIH-PA Author Manuscript NIH-PA Author Manuscript NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

NIH-PA Author Manuscript

[f] A 1:1 mixture of **3ga** and **3ga'** was obtained.

[g] All sydnone starting material was recovered when precursor **1h** was consumed.

[h] See the Supporting Information for the structure assignment.

[i] The structures were assigned based on the polarity and ^{1}H NMR coupling pattern of the two isomers obtained from entry 6.