JOC The Journal of Organic Chemistry

Article

pubs.acs.org/joc

Synthesis of Substituted 1*H*-Indazoles from Arynes and Hydrazones

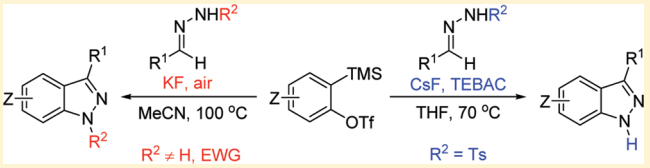
Pan Li,[†] Chunrui Wu,*[,†] Jingjing Zhao,[†] Donald C. Rogness,[‡] and Feng Shi*[,†]

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

[‡]Department of Chemistry, Iowa State University, Ames, Iowa 50011, United States

Supporting Information

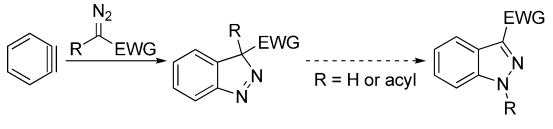
ABSTRACT: The 1*H*-indazole skeleton can be constructed by a [3 + 2] annulation approach from arynes and hydrazones. Under different reaction conditions, both *N*-tosylhydrazones and *N*-aryl/alkylhydrazones can be used to afford a variety of indazoles. The former reaction affords 3-substituted indazoles either via *in situ* generated diazo compounds or through an annulation/elimination process. The latter reaction leads to 1,3-disubstituted indazoles likely through an annulation/oxidation process. The reactions operate under mild conditions and can accommodate aryl, vinyl, and less satisfactorily, alkyl groups.



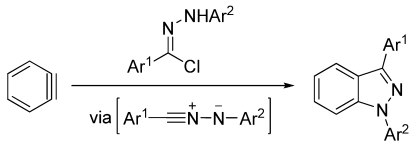
INTRODUCTION

The indazole unit is an important heterocyclic privileged structure.[1] Derivatives of indazoles exhibit a broad spectrum of bioactivities including anti-inflammatory,[2] anti-tumor,[3] anti-HIV,[4] anti-cancer,[5] anti-platelet,[6] and serotonin 5-HT3 receptor antagonist activities.[7] With the growing interest in indazole derivatives, preparation of the indazole skeleton has been pursued for a long time by synthetic organic chemists, and recent developments have allowed for indazoles to be accessed from easily obtained starting materials under milder conditions in fewer steps.[8−11]

Among the different approaches, those involving arynes as a starting material have gained increasing attention in the past five years. Yamamoto, Larock, and their co-workers have independently reported the [3 + 2] cycloaddition reaction of arynes with diazo compounds (eq 1),[12] and Moses and co-workers have disclosed a [3 + 2] cycloaddition with nitrile imides (eq 2).[13] Nonetheless, both routes have limitations in a synthetic perspective. The diazo route is effective only for indazoles with electron-withdrawing groups at the 3-position, and the nitrile imide route is effective only for 1,3-diaryl indazoles. Thus, developing a more general aryne approach that accommodates a wider combination of aryl, alkyl, and vinyl groups at the 1- and/or 3-positions is still needed.[14]



(1)



(2)

To address these issues, we thought to introduce the easily obtained hydrazone as an alternative substrate. Hydrazones can be used as precursors for *in situ* generation of a number of 1,3-dipoles for the subsequent aryne cycloaddition, including nitrile imides (oxidation of *N*-monosubstituted hydrazones,[15] path A, Scheme 1), azomethine imines (thermal H-shift of *N*-monosubstituted hydrazones,[16] path B, Scheme 1), and diazo compounds (base-promoted elimination of *N*-tosylhydrazones, path C, Scheme 1).[17,18] They can also independently react with arynes in a nucleophilic attack−nucleophilic cyclization fashion[19,20] to afford indazolines (path D, Scheme 1),[21] which can be readily transformed to indazoles under various conditions depending on the exact substitution. These possibilities inspired us to study the reactivity of hydrazones in aryne chemistry, and herein we wish to disclose our full results that extend the scope of our earlier communication.[22]

RESULTS AND DISCUSSION

Reaction of *N*-Tosylhydrazones To Prepare 3-Substituted Indazoles. We first examined the possibility of path C or path D1 using *N*-tosylhydrazones as a substrate. The reaction of benzyne precursor **1a** and anisaldehyde *N*-tosylhydrazone (**2a**) was studied as a model (Table 1). Through our survey of reaction conditions, a phase transfer catalyst[23] such as TEBAC ($Et_3NBn^+Cl^-$) and a proper dilution proved effective for a good yield (entries 1−4). THF was a superior solvent compared to MeCN. Moreover, at least 2 equiv of CsF was needed (entry 5) since 1 equiv was used to eliminate the Ts^-.[24] Gratifyingly, no further *N*-arylation of **3a** was observed under these reaction conditions.[12]

The scope of this reaction was then studied (Table 2). Different arynes reacted smoothly (entries 1 and 2). *N*-

Received: December 17, 2011
Published: March 13, 2012

Scheme 1. Possible Reactivities of Hydrazones with Arynes To Afford Indazoles

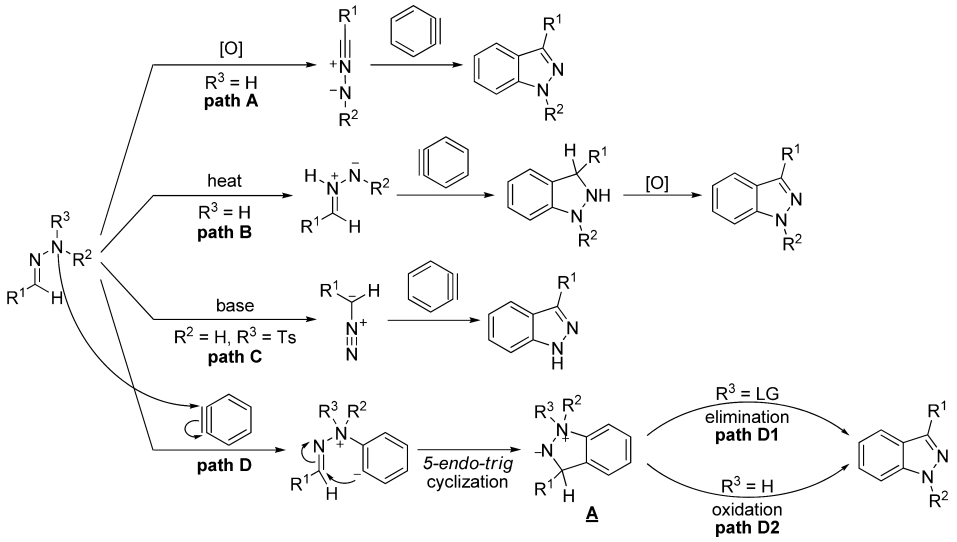
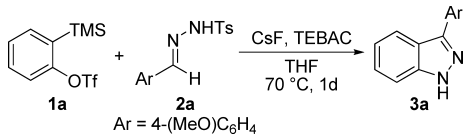


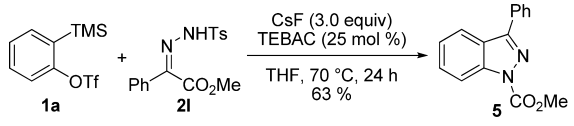
Table 1. Optimization of the Reaction with *N*-Tosylhydrazones[a]



entry	CsF (equiv)	THF (mL)	TEBAC (mol %)	yield[b] (%)
1	**3**	**10**	**25**	**87**
2	3	10	10	77
3	3	5	10	61
4	3	5	0	38[c]
5	1.5	10	25	40

[a]All reactions were carried out on 0.4 mmol of **2a** with 1.2 equiv of **1a**. [b]Isolated yield. [c]59% of **2a** was recovered.

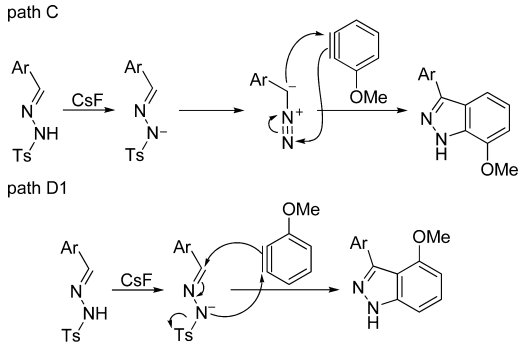
Tosylhydrazones derived from aromatic (entries 3–8) and heteroaromatic aldehydes (entries 9 and 10) were all successfully transformed to the desired indazoles, despite the lower yields for the latter. Hydrazones derived from primary or secondary aliphatic aldehydes afforded only complex mixtures. Nonetheless, **2j** derived from a tertiary aldehyde allowed for a marginal success (entry 11). Unsuccessful substrates also include **2k** with a vinylic R^1 group (entry 12), which underwent an apparent 1,5-dipolar cyclization to form **4** instead of reaction with benzyne.[23d,25] Ketone-derived hydrazones generally resulted in complex mixtures, regardless of the type of ketone (aliphatic, aromatic, acyclic, or cyclic),[26] but **2l** derived from an α-dicarbonyl compound was reactive to afford **5** in a 63% yield after an acyl migration[12a] (eq 3).



(3)

As to the mechanism of this approach, we tend to consider that both path C and path D1 (see Scheme 1, *vide supra*) were involved. The former pathway can be supported by a strong IR absorption at 2053 cm^{-1} when **2a** and CsF were mixed in the absence of **1**, which is characteristic for diazo compounds.[27] The latter pathway can be supported by the formation of the *N*-arylation side product. The regioselectivity of the reaction involving 3-methoxybenzyne (entry 2, Table 2) brought further evidence. Path C, according to previous reports,[12a] should afford the 7-methoxy isomer, but path D1, as a result of the favorable distal attack of the nucleophile to the OMe group,[28–30] should lead to the 4-methoxy isomer (Scheme 2).

Scheme 2. Regioselectivity and Mechanistic Insights for the Unsymmetrical Benzyne



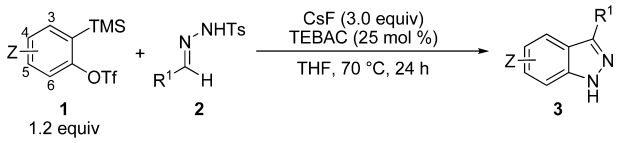
The resultant 4.8:1 ratio again suggested that the diazo route (path C) was likely a major route for this specific benzyne.

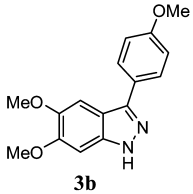
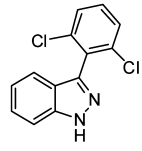
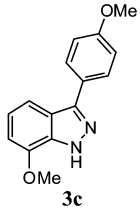
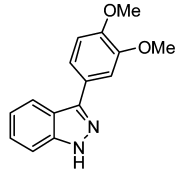
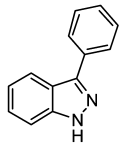
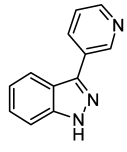
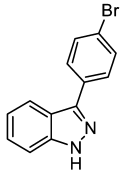
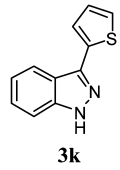
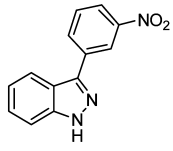
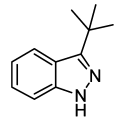
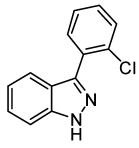
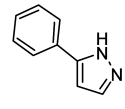
Reaction of *N*-Aryl/Alkylhydrazones To Prepare 1,3-Disubstituted Indazoles. Since the *N*-tosylhydrazone route turned out to be effective only for 3-arylindazoles, our next effort was to seek alternative substrates that could potentially lead to indazoles with a more general substitution pattern, especially to accommodate vinyl and alkyl groups. Thus, the oxidative variant was sought using *N*-monosubstituted hydrazones **6** as the substrate,[31] in light of possible mechanistic paths A, B, and D2 (see Scheme 1, *vide supra*). Air was chosen as the oxidant.[32] As such, the model reaction of hydrazone **6a** and benzyne precursor **1a** was first attempted (Table 3).

The optimization endeavor revealed a set of best conditions employing a less-soluble KF as the fluoride source at 100–120 °C in MeCN (sealed-tube conditions,[33] entries 1 and 2). Yields

dx.doi.org/10.1021/jo202598e | J. Org. Chem. 2012, 77, 3149–3158

Table 2. Scope of *N*-Tosylhydrazones[a]



entry	1 (Z)	2 (R^1)	product	yield[b] (%)	entry	1 (Z)	2 (R^1)	product	yield[b] (%)
1	**1b** 4,5-$(MeO)_2$	**2a** 4-$(MeO)C_6H_4$	 **3b**	56	7	**1a**	**2f** 2,6-$Cl_2C_6H_3$	 **3h**	75
2	**1c** 3-MeO	**2a**	 **3c**	60[c]	8	**1a**	**2g** 3,4-$(MeO)_2C_6H_3$	 **3i**	84
3	**1a** H	**2b** Ph	 **3d**	82	9	**1a**	**2h** 3-pyridyl	 **3j**	68
4	**1a**	**2c** 4-BrC_6H_4	 **3e**	85	10	**1a**	**2i** 2-thiophenyl	 **3k**	36
5	**1a**	**2d** 3-$(O_2N)C_6H_4$	 **3f**	55	11	**1a**	**2j** *t*-Bu	 **3l**	33
6	**1a**	**2e** 2-ClC_6H_4	 **3g**	77	12	**1a**	**2k** PhCH=CH	 **4**	99

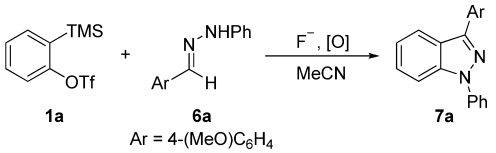
[a]All reactions were carried out on approximately 0.4 mmol of **2** in 10 mL of THF. [b]Isolated yield. [c]A mixture of 4.8:1 regioisomers in favor of the one shown, combined yield. The major isomer was assigned by NOESY experiment.

were lower when KF was replaced with CsF or with a decrease in temperature (entries 3 and 4). THF proved ineffective as a solvent, and DME was inferior to MeCN. We tend to consider that this combination of fluoride source, temperature, and solvent is associated with the desired kinetics of the aryne generation to match the subsequent cycloaddition or annulation steps. In addition, a Ce(IV) oxidant (entry 6) was ineffective. The conditions described in entry 2 were chosen as the standard conditions for subsequent studies.

We next examined the scope and limitations of this approach (Table 4). Again, different arynes reacted smoothly (entries 1 and 2), and the unsymmetrical 3-methoxybenzyne resulted in a 9:1 mixture of regioisomers now favoring the 4-OMe isomer (entry 2). This different regioselectivity (from the one depicted in entry 2, Table 2) clearly suggests different mechanisms. Hydrazones derived from aromatic aldehydes (entries 3–6) showed a general success. Steric factors proved irrelevant in this context (entries 5 and 6), while electron-negative R^1 groups tend to give higher yields (compare entries 3–6 with entry 2, Table 3). Hydrazones derived from a heteroaromatic aldehyde (entry 7) and an α,β-unsaturated aldehyde (entry 8) were successfully employed, thus allowing for indazoles to bear heteroaryl and vinyl groups at the 3-position. The hydrazine moiety, namely, the R^2 group of **6**, can cover phenyl groups

dx.doi.org/10.1021/jo202598e | J. Org. Chem. 2012, 77, 3149–3158

Table 3. Optimization of the Reaction with *N*-Phenylhydrazones[a]



entry	fluoride	oxidant	T (°C)	time (h)	yield[b] (%)
1	KF	air, sealed tube	120	16	63
2	**KF**	**air, sealed tube[c]**	**100**	**16**	**62**
3	CsF	air, sealed tube	100	8	49
4	CsF	air, open flask	80	8	46
5	CsF	air, open flask	rt	24	tr
6	KF	$Ce(NO_3)_4{\cdot}6H_2O$ (2 equiv)	100	16	0

[a]All reactions were carried out on a 0.3 mmol scale in 3 mL of solvent open to air. **1a**:**6a**:fluoride =1.2:1:2. [b]Isolated yield. [c]See the Supporting Information for the effects of the size of the tube.

with different electronic properties (entries 9 and 10), but a nitro group was not tolerated (entry 11). Interestingly, *N*,*N*-dibenzylhydrazone **6l′** worked smoothly to afford **7m** in a moderate yield (entry 12), where one of the benzyl groups was presumably scavenged by the second equivalent of fluoride.[21b] In contrast, *N*,*N*-dimethylhydrazone did not follow the same path but instead afforded 2-dimethylaminophenyl ketone in a moderate yield.[21a]

Other than *N*-arylhydrazones (R^2 = Ar), reaction of *N*-unsubstituted hydrazones (R^2 = H) resulted in the incorporation of two molecules of benzyne to afford *N*-phenylindazole instead of indazoles with free NH groups. Substrates with R^2 being electron-withdrawing groups, including acyl, alkoxycarbonyl, and sulfonyl groups, were not compatible under the oxidative conditions. Thus, hydrazones **2** could not be used to afford 1-tosylindazoles. In addition, hydrazones derived from aliphatic aldehydes (R^1 = alkyl) were found to be much less stable and quickly deteriorated upon standing. These hydrazones could be prepared *in situ* by mixing the aldehyde and the hydrazine in the flask 5 min before **1a** and KF were added (Scheme 3). Under these conditions, hydrazones with R^1 being tertiary, secondary, or primary alkyl groups were all welcome, albeit in lower yields.

It is difficult to differentiate the three mechanistic paths, namely, A, B, and D2 (see Scheme 1, *vide supra*), in this approach, since they share not only the same substrate and reaction conditions but also the same regioselectivity with the reaction of **1c**. We tend to think that among the three possibilities, path B was the most doubtful, as formation of azomethine imines from **6** typically requires acidic or at least neutral conditions, which are in contrast to our basic conditions. To date, all efforts to trap intermediate **A** (see Scheme 1, *vide supra*) in path D by external electrophiles such as Ac_2O or $(MeO)_2CO$ have been unsuccessful, even with ketone-derived hydrazones. In addition, the reaction failed to afford indazolines in the absence of any oxidant but resulted in the recovery of **6**. These two observations made us unable to rule out path A, despite the dramatic difference in our reaction conditions and Moses' conditions.[13] Whatever mechanism is operative, use of hydrazones **6** clearly provides a wider scope of indazoles where vinyl and, less satisfactorily, alkyl groups can be accommodated.

CONCLUSIONS

In summary, we have developed aryne reactions to prepare 3-substituted and 1,3-disubstituted 1*H*-indazoles using hydrazones as inexpensive and readily available starting materials. Specifically, *N*-tosylhydrazones can afford 3-substituted indazoles, and *N*-monosubstituted hydrazones can lead to 1,3-disubstituted indazoles. Compared with the early discoveries in aryne reactions to indazoles, our methods allow for indazoles bearing more diverse combination of substitutions at the 1- and 3-positions. Introduction of aryl and vinyl groups have been successful, and the introduction of alkyl groups has been partially resolved. With the rapid development of aryne chemistry, construction of more heterocyclic scaffolds through aryne processes can be expected in the future.

EXPERIMENTAL SECTION

General Considerations. All reagents purchased from commercial sources were used as received. The solvents THF and MeCN were distilled from Na/benzophenone and CaH_2, respectively. The silica gel for column chromatography was supplied as 300−400 meshes.[34] Powdered CsF was used as received and stored in a desiccator. All melting points are uncorrected. The ^1H and ^{13}C NMR spectra are referenced to the residual solvent signals (7.26 ppm for ^1H and 77.0 ppm for ^{13}C in $CDCl_3$; 2.05 ppm for ^1H and 29.8 ppm for ^{13}C in acetone-d_6). All aryne reactions were carried out in oven-dried glassware and were magnetically stirred.

General Procedure To Prepare *N*-Tosylhydrazones (2).[27] To a solution of *p*-toluenesulfonyl hydrazide (1.02 g, 5.5 mmol, 1.1 equiv) in 5 mL of MeOH was added an aldehyde (5 mmol) slowly (liquid aldehyde was added dropwise, and solid aldehyde was added in small portions). The mixture was stirred at room temperature for 2 h. MeOH was evaporated *in vacuo*, and the residue was recrystallized from MeOH to afford the *N*-tosylhydrazones, which were used directly to the aryne reactions.

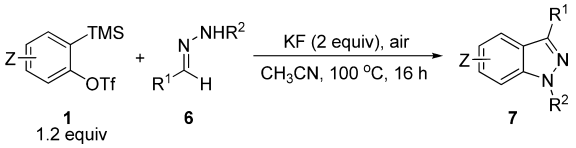
Hydrazone ***2a***. The general procedure was applied to 680 mg of 4-methoxybenzaldehyde to afford 1.37 g of **2a** (90%) as white solid, mp 105−106 °C (lit.[23d] 110−111 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 8.01 (s, 1 H), 7.87 (d, J = 8.3 Hz, 2 H), 7.73 (s, 1 H), 7.55−7.47 (m, 2 H), 7.30 (d, J = 8.1 Hz, 2 H), 6.87−6.85 (m, 2 H), 3.81 (s, 3 H), 2.40 (s, 3 H).

Hydrazone ***2b***. The general procedure was applied to 530 mg of benzaldehyde to afford 0.70 g of **2b** (51%) as white solid, mp 120−121 °C (lit.[23d] 127−128 °C); ^1H NMR (400 MHz, $CDCl_3$) δ 7.94 (s, 1 H), 7.88 (d, J = 8.3 Hz, 2 H), 7.75 (s, 1 H), 7.59−7.57 (m, 2 H), 7.38−7.34 (m, 3 H), 7.31 (d, J = 8.1 Hz, 2 H), 2.41 (s, 3 H).

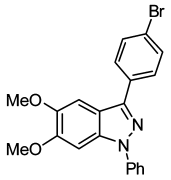
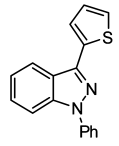
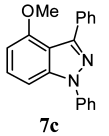
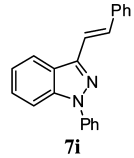
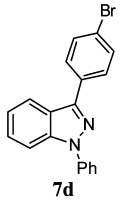
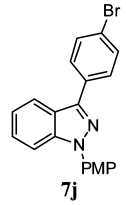
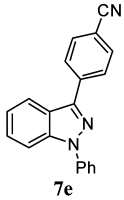
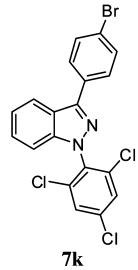
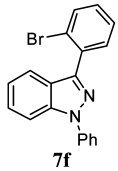
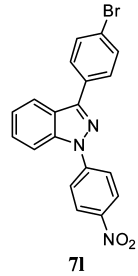
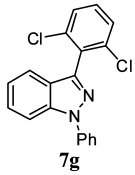
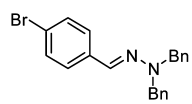
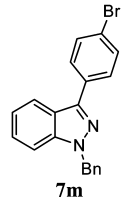
Hydrazone ***2c***. The general procedure was applied to 925 mg of 4-bromobenzaldehyde to afford 1.60 g of **2c** (91%) as white solid, mp 171−171.5 °C; ^1H NMR (400 MHz, $CDCl_3$) δ 7.89 (s, 1 H), 7.86 (d,

dx.doi.org/10.1021/jo202598e | J. Org. Chem. 2012, 77, 3149−3158

Table 4. Scope of *N*-Monosubstituted Hydrazones[a]



1 1.2 equiv + **6** → **7**

entry	1	6 (R^1, R^2)	product	yield[b] (%)	entry	1	6 (R^1, R^2)	product	yield[b] (%)
1	**1b**	**6b** R^1 = 4-BrC_6H_4, R^2 = Ph	 **7b**	89	7	**1a**	**6g** R^1 = 2-thiophenyl, R^2 = Ph	 **7h**	70
2	**1c**	**6c** R^1 = Ph, R^2 = Ph	 **7c**	78[c]	8	**1a**	**6h** R^1 = styrenyl, R^2 = Ph	 **7i**	64
3	**1a**	**6b**	 **7d**	82	9	**1a**	**6i** R^1 = 4-BrC_6H_4, R^2 = 4-(MeO)C_6H_4	 **7j**	56
4	**1a**	**6d** R^1 = 4-(NC)C_6H_4, R^2 = Ph	 **7e**	80	10	**1a**	**6j** R^1 = 4-BrC_6H_4, R^2 = 2,4,6-$Cl_3C_6H_2$	 **7k**	72
5	**1a**	**6e** R^1 = 2-BrC_6H_4, R^2 = Ph	 **7f**	86	11	**1a**	**6k** R^1 = 4-BrC_6H_4, R^2 = 4-(O_2N)C_6H_4	 **7l**	mixture
6	**1a**	**6f** R^1 = 2,6-$Cl_2C_6H_3$, R^2 = Ph	 **7g**	94	12	**1a**	**6l'** 	 **7m**	54[d]

[a]All reactions were carried out on a 0.3 mmol scale in 3 mL of solvent in a 15 mL sealed tube. [b]Isolated yield. [c]A mixture of 9:1 regioisomers in favor of the one shown, combined yield. [d]Reaction was carried out using 1.6 equiv of **1a** and 2.6 equiv of KF.

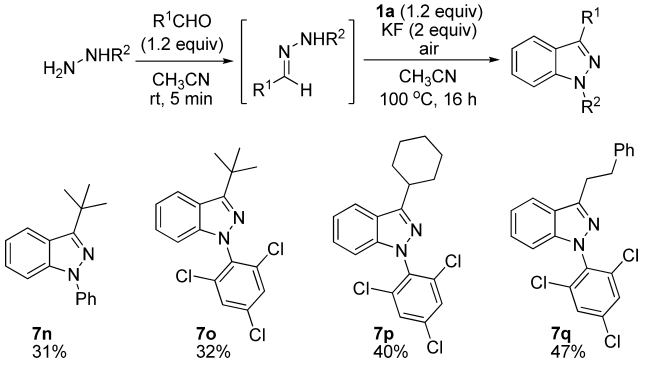
J = 8.3 Hz, 2 H), 7.69 (s, 1 H), 7.51−7.42 (m, 4 H), 7.32 (d, *J* = 8.1 Hz, 2 H), 2.41 (s, 3 H).

Hydrazone ***2d.*** The general procedure was applied to 755 mg of 3-nitrobenzaldehyde to afford 0.70 g of **2d** (44%) as white solid, mp 153−154 °C (lit.[23d] 154−156 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.37 (t, *J* = 1.8 Hz, 1 H), 8.28 (s, 1 H), 8.21 (ddd, *J* = 8.2, 2.2, 1.0 Hz, 1 H), 7.93 (d, *J* = 7.8 Hz, 1 H), 7.90 (d, *J* = 8.3 Hz, 2 H), 7.82 (s, 1 H), 7.55 (t, *J* = 8.0 Hz, 1 H), 7.35 (d, *J* = 8.1 Hz, 2 H), 2.42 (s, 3 H).

Hydrazone ***2e.*** The general procedure was applied to 700 mg of 2-chlorobenzaldehyde to afford 1.30 g of **2e** (84%) as white solid, mp

dx.doi.org/10.1021/jo202598e | *J. Org. Chem.* 2012, 77, 3149−3158

Scheme 3. Scope of the One-Pot Protocol with Hydrazones Generated *in Situ* from Aliphatic Aldehydes[a]



[a]All reactions were carried out on a 0.3 mmol scale in 3 mL of solvent in a sealed tube.

137−138 °C (lit.[35] 154−156 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.16 (s, 1 H), 7.95−7.90 (m, 2 H), 7.88 (d, J = 8.3 Hz, 2 H), 7.34−7.31 (m, 3 H), 7.30−7.24 (m, 2 H), 2.42 (s, 3 H).

Hydrazone ***2f***. The general procedure was applied to 875 mg of 2,6-dichlorobenzaldehyde to afford 1.58 g of **2f** (92%) as white solid, mp 182−182.5 °C; ^{1}H NMR (400 MHz, acetone-d_6) δ 10.7 (s, 1 H), 8.16 (s, 1 H), 7.84 (d, J = 8.3 Hz, 2 H), 7.46−7.36 (m, 5 H), 2.41 (s, 3 H).

Hydrazone ***2g***. The general procedure was applied to 830 mg of 3,4-dimethoxybenzaldehyde to afford 1.25 g of **2g** (75%) as white solid, mp 129−130 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87−7.85 (m, 2 H), 7.70 (s, 1 H), 7.31 (d, J = 7.9 Hz, 2 H), 7.26 (s, 1 H), 7.24 (d, J = 1.8 Hz, 1 H), 7.01 (dd, J = 8.2, 1.9 Hz, 1 H), 6.82 (d, J = 8.2 Hz, 1 H), 3.91 (s, 3 H), 3.89 (s, 3 H), 2.41 (s, 3 H)

Hydrazone ***2h***. The general procedure was applied to 535 mg of nicotinaldehyde to afford 0.82 g of **2h** (60%) as brown solid, mp 154−155 °C (lit.[36] 155−156 °C); ^{1}H NMR (400 MHz, acetone-d_6) δ 10.48 (s, 1 H), 8.74 (d, J = 1.9 Hz, 1 H), 8.56 (dd, J = 4.8, 1.7 Hz, 1 H), 8.03 (s, 1 H), 8.01 (dt, J = 8.1, 1.9 Hz, 1 H), 7.87−7.81 (m, 2 H), 7.42−7.38 (m, 3 H), 2.39 (s, 3 H).

Hydrazone ***2i***. The general procedure was applied to 560 mg of thiophene-2-carbaldehyde to afford 1.10 g of **2i** (79%) as brown solid, mp 134−135 °C (lit.[37] 140−141 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1 H), 7.85 (d, J = 8.3 Hz, 2 H), 7.77 (s, 1 H), 7.36 (d, J = 5.0 Hz, 1 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.20 (dd, J = 3.6, 0.7 Hz, 1 H), 7.01 (dd, J = 5.0, 3.7 Hz, 1 H), 2.41 (s, 3 H).

Hydrazone ***2j***. The general procedure was applied to 430 mg of pivalaldehyde to afford 0.35 g of **2j** (28%) as white solid, mp 107−108 °C (lit.[38] 110−112 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.80 (d, J = 8.3 Hz, 2 H), 7.34 (s, 1 H), 7.31 (d, J = 8.0 Hz, 2 H), 7.06 (s, 1 H), 2.43 (s, 3 H), 1.00 (s, 9 H).

Hydrazone ***2k***. The general procedure was applied to 660 mg of cinnamaldehyde to afford 0.70 g of **2k** (47%) as white solid, mp 156−156.5 °C (lit.[39] 158−159 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.86−7.84 (m, 2 H), 7.54 (d, J = 8.6 Hz, 1 H), 7.41−7.39 (m, 2 H), 7.36−7.30 (m, 5 H), 6.87−6.84 (m, 3 H), 2.41 (s, 3 H).

Hydrazone ***2l***. The general procedure was applied to 820 mg of methyl 2-oxo-2-phenylacetate to afford 1.25 g of **2l** as a mixture of two geometric isomers in a 3.4:1 ratio (75% combined). Major isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.62 (s, 1 H), 7.88−7.86 (m, 2 H), 7.50−7.48 (m, 2 H), 7.41−7.30 (m, 5 H), 3.87 (s, 3 H), 2.42 (s, 3 H). Minor isomer: ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.12 (s, 1 H), 7.86−7.84 (m, 2 H), 7.20−7.18 (m, 2 H), 3.82 (s, 3 H), 2.45 (s, 3 H), other signals are overlapping with the major isomer.

General Procedure To Prepare 3-Substituted Indazoles (3) from *N*-Tosylhydrazones (2). To an oven-dried 25 mL round-bottom flask equipped with a stirrer bar was added 0.4 mmol of *N*-tosylhydrazone **2**, followed by the aryne precursor (0.48 mmol, 1.2 equiv). THF (10 mL) was added, followed by TEBAC (23 mg, 0.1 mmol, 0.25 equiv) and CsF (ca. 180−185 mg, 1.2 mmol, 3 equiv). The flask was topped with a refluxing condenser, and the reaction mixture was stirred at 70 °C for 24 h, cooled to room temperature, poured into brine, and extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (petroleum ether/EtOAc) to afford the indazoles **3**.

3-(4-Methoxyphenyl)-1H-indazole ***(3a)***. The general procedure was applied to 122 mg of **2a** and 143 mg of **1a** to afford 78 mg of **3a** (87%) as slightly yellow solid, mp 85−86 °C (lit.[40] 88−90 °C); R_f = 0.30 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.01 (d, J = 8.2 Hz, 1 H), 7.95−7.89 (m, 2 H), 7.46−7.35 (m, 2 H), 7.22 (dt, J = 7.2, 1.6 Hz, 1 H), 7.10−7.01 (m, 2 H), 3.89 (s, 3 H), NH not observed; ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 145.1, 141.4, 128.9, 126.8, 125.9, 121.13, 121.07, 120.7, 114.4, 110.4, 55.3; HRMS (ESI) calcd for $C_{14}H_{13}N_2O$ (M + H) 225.1022, found 225.1020.

5,6-Dimethoxy-3-(4-methoxyphenyl)-1H-indazole ***(3b)***. The general procedure was applied to 122 mg of **2a** and 172 mg of **1b** to afford 64 mg of **3b** (56%) as white solid, mp 209−210 °C; R_f = 0.45 (EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.66 (s, 1 H), 7.93 (d, J = 8.6 Hz, 2 H), 7.20 (s, 1 H), 7.08 (d, J = 8.7 Hz, 2 H), 6.38 (s, 1 H), 3.94 (s, 3 H), 3.87 (s, 3 H), 3.70 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.4, 150.8, 146.4, 144.4, 137.4, 128.9, 126.5, 114.5, 113.6, 99.8, 91.5, 55.1, 55.8, 55.3; HRMS (ESI) calcd for $C_{16}H_{17}N_2O_3$ (M + H) 285.1234, found 285.1231.

7-Methoxy-3-(4-methoxyphenyl)-1H-indazole ***(3c)***. The general procedure was applied to 122 mg of **2a** and 158 mg of **1c** to afford 61 mg of **3c** (60%) as white solid. The major isomer can be separated: mp 149−151 °C; R_f = 0.35 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.22 (s, 1 H), 7.92 (d, J = 8.7 Hz, 2 H), 7.58 (d, J = 8.1 Hz, 1 H), 7.14 (t, J = 7.8 Hz, 1 H), 7.05 (d, J = 8.7 Hz, 2 H), 6.77 (d, J = 7.5 Hz, 1 H), 4.01 (s, 3 H), 3.88 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 159.6, 145.7, 145.3, 133.8, 128.7, 126.3, 122.4, 121.9, 114.3, 113.2, 105.0, 55.5, 55.3; HRMS (ESI) calcd for $C_{15}H_{15}N_2O_2$ (M + H) 255.1128, found 255.1126. The regiochemistry is assigned by the NOESY experiment, where the H at the 4-position of the indazole shows a correlation with the H's at the 2′-position of the 3-aryl group.

3-Phenyl-1H-indazole ***(3d)***. The general procedure was applied to 110 mg of **2b** and 143 mg of **1a** to afford 64 mg of **3d** (82%) as white solid, mp 116−117 °C (lit.[41] 115−116 °C); R_f = 0.43 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 12.53 (s, 1 H), 8.08 (d, J = 7.5 Hz, 2 H), 8.05 (d, J = 8.4 Hz, 1 H), 7.59 (t, J = 7.4 Hz, 2 H), 7.50 (t, J = 7.2 Hz, 1 H), 7.33 (t, J = 7.6 Hz, 1 H), 7.22 (t, J = 7.5 Hz, 1 H), 7.09 (d, J = 8.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 145.5, 141.6, 133.5, 129.0, 128.2, 127.8, 126.7, 121.2, 120.9, 120.8, 110.4; HRMS (ESI) calcd for $C_{13}H_{11}N_2$ (M + H) 195.0917, found 195.0915.

3-(4-Bromophenyl)-1H-indazole ***(3e)***. The general procedure was applied to 142 mg of **2c** and 143 mg of **1a** to afford 92 mg of **3e** (85%) as slightly yellow solid, mp 135−137 °C; R_f = 0.42 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.40 (s, 1 H), 8.00 (d, J = 8.2 Hz, 1 H), 7.91−7.82 (m, 2 H), 7.68−7.61 (m, 2 H), 7.50 (t, J = 8.4 Hz, 1 H), 7.44 (dd, J = 8.0, 7.1 Hz, 1 H), 7.29−7.22 (m, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 144.6, 141.6, 132.4, 132.1, 129.1, 127.0, 122.3, 121.7, 120.8, 120.7, 110.2; HRMS (ESI) calcd for $C_{13}H_{10}BrN_2$ (M + H) 273.0022, found 273.0020.

3-(3-Nitrophenyl)-1H-indazole ***(3f)***. The general procedure was applied to 128 mg of **2d** and 143 mg of **1a** to afford 53 mg of **3f** (55%) as glassy yellow solid, mp 188−189 °C; R_f = 0.33 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, acetone-d_6) δ 12.78 (s, 1 H), 8.88 (t, J = 1.9 Hz, 1 H), 8.54−8.51 (m, 1 H), 8.27 (ddd, J = 8.2, 2.3, 0.9 Hz, 1 H), 8.18 (d, J = 8.3 Hz, 1 H), 7.85 (t, J = 8.0 Hz, 1 H), 7.71 (d, J = 8.4 Hz, 1 H), 7.48 (dt, J = 7.5, 0.8 Hz, 1 H), 7.32 (dt, J = 7.6, 0.8 Hz, 1 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 149.7, 143.1, 142.7, 136.8, 133.6, 131.1, 127.4, 122.9, 122.7, 122.0, 121.3, 121.1, 111.6; HRMS (ESI) calcd for $C_{13}H_{10}N_3O_2$ (M + H) 240.0768, found 240.0764.

3-(2-Chlorophenyl)-1H-indazole ***(3g)***. The general procedure was applied to 124 mg of **2e** and 143 mg of **1a** to afford 70 mg of **3g** (77%) as white solid, mp 140−141 °C; R_f = 0.38 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1 H), 7.72 (d, J = 8.2 Hz, 1 H), 7.63−7.62 (m, 1 H), 7.60−7.56 (m, 1 H), 7.47−7.37 (m, 4 H), 7.21 (ddd, J = 7.9, 6.4, 1.3 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 143.8, 140.8, 133.8, 132.4, 132.2, 130.2, 129.7, 126.9, 126.7, 121.9, 121.4,

dx.doi.org/10.1021/jo202598e | J. Org. Chem. 2012, 77, 3149−3158

121.0, 110.2; HRMS (ESI) calcd for $C_{13}H_{10}ClN_2$ (M + H) 229.0527, found 229.0524.

*3-(2,6-Dichlorophenyl)-1H-indazole (**3h**).* The general procedure was applied to 138 mg of **2f** and 143 mg of **1a** to afford 79 mg of **3h** (75%) as white solid, mp 160−161 °C; R_f = 0.47 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.71 (s, 1 H), 7.53−7.47 (m, 4 H), 7.45−7.40 (m, 1 H), 7.37 (dd, J = 8.7, 7.4 Hz, 1 H), 7.20 (ddd, J = 7.9, 6.8, 0.9 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.4, 140.6, 136.7, 131.2, 130.5, 128.2, 126.9, 122.1, 121.2, 120.6, 110.2; HRMS (ESI) calcd for $C_{13}H_9Cl_2N_2$ (M + H) 263.0137, found 263.0136.

*3-(3,4-Dimethoxyphenyl)-1H-indazole (**3i**).* The general procedure was applied to 134 mg of **2g** and 143 mg of **1a** to afford 86 mg of **3i** (84%) as white solid, mp 147−149 °C; R_f = 0.13 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.44 (s, 1 H), 8.03 (d, J = 8.2 Hz, 1 H), 7.57−7.53 (m, 2 H), 7.45−7.40 (m, 2 H), 7.26−7.22 (m, 1 H), 7.03 (d, J = 8.1 Hz, 1 H), 3.98 (s, 3 H), 3.97 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.4, 149.2, 145.5, 141.7, 126.8, 126.4, 121.2, 121.1, 120.8, 120.2, 111.4, 110.7, 110.2, 56.0, 55.9; HRMS (ESI) calcd for $C_{15}H_{15}N_2O_2$ (M + H) 255.1128, found 255.1125.

*3-(Pyridin-3-yl)-1H-indazole (**3j**).* The general procedure was applied to 110 mg of **2h** and 143 mg of **1a** to afford 53 mg of **3j** (68%) as brown solid, mp 184−185 °C; R_f = 0.40 (10:1 CH_2Cl_2/MeOH); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.55 (s, 1 H), 9.27 (d, J = 1.0 Hz, 1 H), 8.70−8.68 (m, 1 H), 8.29 (dt, J = 7.9, 1.7 Hz, 1 H), 8.03 (d, J = 8.2 Hz, 1 H), 7.56 (d, J = 8.4 Hz, 1 H), 7.48−7.45 (m, 2 H), 7.31−7.26 (m, 1 H); ^{13}C NMR (100 MHz, acetone-d_6) δ 149.6, 148.8, 142.9, 142.2, 134.7, 130.9, 127.3, 124.6, 122.3, 121.5, 121.3, 111.4; HRMS (ESI) calcd for $C_{12}H_{10}N_3$ (M + H) 196.0869, found 196.0866.

*3-(Thiophen-2-yl)-1H-indazole (**3k**).* The general procedure was applied to 112 mg of **2i** and 143 mg of **1a** to afford 29 mg of **3k** (36%) as brown solid, mp 151−153 °C (lit.[42] 137 °C); R_f = 0.47 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 10.06 (s, 1 H), 8.07 (dt, J = 8.2, 0.9 Hz, 1 H), 7.68 (dd, J = 3.6, 1.1 Hz, 1 H), 7.51 (dt, J = 8.4, 0.9 Hz, 1 H), 7.46−7.42 (m, 1 H), 7.38 (dd, J = 5.1, 1.1 Hz, 1 H), 7.29−7.25 (m, 1 H), 7.19 (dd, J = 5.1, 3.6 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 141.5, 140.7, 135.8, 127.7, 127.1, 125.2, 124.9, 121.6, 120.8, 120.4, 110.3; HRMS (ESI) calcd for $C_{11}H_9N_2S$ (M + H) 201.0481, found 201.0478.

*3-tert-Butyl-1H-indazole (**3l**).* The general procedure was applied to 102 mg of **2j** and 143 mg of **1a** to afford 23 mg of **3l** (33%) as white solid, mp 152−154 °C; R_f = 0.46 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 9.72 (s, 1 H), 7.91 (d, J = 8.2 Hz, 1 H), 7.45 (d, J = 8.4 Hz, 1 H), 7.36 (dt, J = 7.4, 0.9 Hz, 1 H), 7.13 (J = 7.6, 0.9 Hz, 1 H), 1.54 (s, 9 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 154.5, 141.8, 126.2, 122.1, 120.5, 119.8, 110.0, 33.7, 30.0; HRMS (ESI) calcd for $C_{11}H_{15}N_2$ (M + H) 175.1230, found 175.1227.

*5-Phenyl-1H-pyrazole (**4**).* The general procedure was applied to 120 mg of **2k** and 143 mg of **1a** to afford 45 mg of **4** (99%) as white solid, mp 75−76 °C (lit.[43] 76−77 °C); R_f = 0.24 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 11.09 (s, 1 H), 7.77 (d, J = 7.8 Hz, 2 H), 7.61 (d, J = 2.1 Hz, 1 H), 7.41 (t, J = 7.6 Hz, 2 H), 7.34 (t, J = 7.3 Hz, 1 H), 6.62 (d, J = 2.1 Hz, 1 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 149.1, 133.2, 132.1, 128.8, 128.0, 125.9, 102.6; HRMS (ESI) calcd for $C_9H_9N_2$ (M + H) 145.0760, found 145.0758.

*Methyl 3-Phenyl-1H-indazole-1-carboxylate (**5**).* The general procedure was applied to 133 mg of **2l** and 143 mg of **1a** to afford 63 mg of **5** (63%) as white solid, mp 112−114 °C; R_f = 0.48 (2:1 hexanes/EtOAc); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.32 (d, J = 8.3 Hz, 1 H), 7.98−7.96 (m, 3 H), 7.60 (t, J = 7.7 Hz, 1 H), 7.56−7.45 (m, 3 H), 7.40 (t, J = 7.5 Hz, 1 H), 4.15 (s, 3 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 151.3, 150.8, 141.2, 131.4, 129.5, 129.2, 128.8, 128.3, 124.3, 124.2, 121.4, 114.7, 54.5; HRMS (ESI) calcd for $C_{15}H_{13}N_2O_2$ (M + H) 253.0972, found 253.0969.

General Procedure To Prepare Hydrazones (6). To a solution of a hydrazine (5.5 mmol, 1.1 equiv) in 5 mL of MeOH was added an aldehyde (5 mmol) slowly (liquid aldehyde was added dropwise, and solid aldehyde was added in small portions). The mixture was stirred at room temperature for 2 h. MeOH was evaporated *in vacuo*, and the residue was recrystallized from MeOH to afford the *N*-alkyl/arylhydrazones.

*Hydrazone **6a**.* The general procedure was applied to 680 mg of 4-methoxybenzaldehyde and 594 mg of phenylhydrazine to afford 0.75 g of **6a** (66%) as white solid, mp 119−120 °C (lit.[44] 121 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.64 (s, 1 H), 7.60 (d, J = 8.7 Hz, 2 H), 7.30−7.26 (m, 2 H), 7.10 (d, J = 7.8 Hz, 2 H), 6.91 (d, J = 8.7 Hz, 2 H), 6.86 (t, J = 7.1 Hz, 1 H), 3.84 (s, 3 H), NH not observed.

*Hydrazone **6b**.* The general procedure was applied to 925 mg of 4-bromobenzaldehyde and 594 mg of phenylhydrazine to afford 1.02 g of **6b** (74%) as white solid, mp 123−124 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.65 (br, 1 H), 7.61 (s, 1 H), 7.53−7.48 (m, 4 H), 7.29 (t, J = 7.9 Hz, 2 H), 7.11 (d, J = 7.9 Hz, 2 H), 6.90 (t, J = 7.3 Hz, 1 H).

*Hydrazone **6c**.* The general procedure was applied to 530 mg of benzaldehyde and 594 mg of phenylhydrazine to afford 0.80 g of **6c** (82%) as white solid, mp 161−162 °C (lit.[44] 158 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.68−7.66 (m, 3 H), 7.59 (br, 1 H), 7.39 (t, J = 7.4 Hz, 2 H), 7.33−7.26 (m, 3 H), 7.13 (d, J = 7.9 Hz, 2 H), 6.90 (t, J = 7.3 Hz, 1 H).

*Hydrazone **6d**.* The general procedure was applied to 655 mg of 4-formylbenzonitrile and 594 mg of phenylhydrazine to afford 0.70 g of **6d** (63%) as bright yellow solid, mp 153−154 °C (lit.[44] 144 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.93 (s, 1 H), 7.73−7.71 (m, 2 H), 7.64−7.62 (m, 3 H), 7.31 (t, J = 7.9 Hz, 2 H), 7.14 (d, J = 7.8 Hz, 2 H), 6.94 (t, J = 7.3 Hz, 1 H).

*Hydrazone **6e**.* The general procedure was applied to 925 mg of 2-bromobenzaldehyde and 594 mg of phenylhydrazine to afford 0.71 g of **6e** (51%) as yellow solid, mp 70−71 °C (lit.[8c] 68−70 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.09−8.06 (m, 1 H), 7.85 (s, 1 H), 7.54 (d, J = 8.0 Hz, 1 H), 7.34−7.28 (m, 3 H), 7.17−7.13 (m, 3 H), 6.91 (t, J = 7.3 Hz, 1 H), NH not observed.

*Hydrazone **6f**.* The general procedure was applied to 875 mg of 2,6-dichlorobenzaldehyde and 594 mg of phenylhydrazine to afford 0.35 g of **6f** (26%) as sight yellow solid, mp 66−67 °C (lit.[45] 59−61 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.98 (s, 1 H), 7.91 (s, 1 H), 7.36 (d, J = 8.1 Hz, 2 H), 7.29 (t, J = 7.9 Hz, 2 H), 7.15−7.11 (m, 3 H), 6.91 (t, J = 7.3 Hz, 1 H).

*Hydrazone **6g**.* The general procedure was applied to 560 mg of thiophene-2-carbaldehyde and 594 mg of phenylhydrazine to afford 0.35 g of **6g** (35%) as yellow solid, mp 137−138 °C (lit.[46] 138−139 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.87 (s, 1 H), 7.29−7.25 (m, 4 H), 7.09−7.07 (m, 3 H), 7.02−7.00 (m, 1 H), 6.87 (t, J = 7.3 Hz, 1 H).

*Hydrazone **6h**.* The general procedure was applied to 660 mg of cinnamaldehyde and 594 mg of phenylhydrazine to afford 0.65 g of **6h** (59%) as bright yellow solid, mp 173−174 °C (lit.[47] 167−169 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.56 (br, 1 H), 7.54 (d, J = 9.2 Hz, 1 H), 7.47−7.45 (m, 2 H), 7.35 (t, J = 7.5 Hz, 2 H), 7.30−7.26 (m, 3 H), 7.06−6.99 (m, 3 H), 6.88 (t, J = 7.3 Hz, 1 H), 6.69 (d, J = 16.0 Hz, 1 H).

*Hydrazone **6i**.* The general procedure was applied to 925 mg of 4-bromobenzaldehyde and 760 mg of (4-methoxyphenyl)hydrazine to afford 0.52 g of **6i** (34%) as yellow solid, mp 132−133 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.60 (br, 2 H), 7.51−7.46 (m, 4 H), 7.06 (br, 2 H), 6.86 (d, J = 8.9 Hz, 2 H), 3.79 (s, 3 H).

*Hydrazone **6j**.* The general procedure was applied to 925 mg of 4-bromobenzaldehyde and 1.16 g of (2,4,6-trichlorophenyl)hydrazine to afford 1.04 g of **6j** (55%) as pale-white solid, mp 126−127 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.72 (s, 1 H), 7.62 (s, 1 H), 7.49 (s, 4 H), 7.35 (s, 2 H).

*Hydrazone **6k**.* The general procedure was applied to 925 mg of 4-bromobenzaldehyde and 840 mg of (4-nitrophenyl)hydrazine to afford 0.38 g of **6k** (24%) as yellow solid, mp 210−211 °C (lit.[48] 138−139 °C); ^{1}H NMR (400 MHz, $CDCl_3$) δ 8.20 (d, J = 9.1 Hz, 2 H), 8.07 (s, 1 H), 7.75 (s, 1 H), 7.60−7.50 (m, 4 H), 7.13 (d, J = 9.1 Hz, 2 H).

*Hydrazone **6l′**.* This compound was prepared using *N*,*N*-dibenzylhydrazine as a starting material. *N*,*N*-Dibenzylhydrazine was obtained as the exclusive product while we were attempting to prepare *N*-benzylhydrazine by the reaction of 855 mg of benzyl bromide (5 mmol) with 300 mg of hydrazine monohydrate (6 mmol) under

dx.doi.org/10.1021/jo202598e | J. Org. Chem. 2012, 77, 3149−3158

literature conditions[49] (we obtained 400 mg of *N,N*-dibenzylhydrazine, 75%). The general procedure was applied to 505 mg of 4-bromobenzaldehyde (2.7 mmol, 1.5 equiv) and 400 mg of *N,N*-dibenzylhydrazine (1.9 mmol) to afford 0.38 g of **6l′** (53%) as white solid, mp 134 °C; ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.41−7.24 (m, 14 H), 7.08 (s, 1 H), 4.53 (s, 4 H).

General Procedure To Prepare 1,3-Disubstituted Indazoles (7) from *N*-Aryl/Alkylhydrazones (6). To an oven-dried seal tube equipped with a stirrer bar was added 0.3 mmol of hydrazone **6**, followed by the aryne precursor (0.36 mmol, 1.2 equiv). CH_3CN (3 mL) was added, followed by KF (ca. 34−37 mg, 0.6 mmol, 2 equiv). The tube was sealed and heated to 100 °C for 16 h. Upon completion, the reaction mixture was cooled to room temperature, poured into brine, and extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (petroleum ether/DCM) to afford the indazoles **7**.

*3-(4-Methoxyphenyl)-1-phenyl-1H-indazole (**7a**).* The general procedure was applied to 68 mg of **6a** and 108 mg of **1a** to afford 56 mg of **7a** (62%) as white solid, mp 121−122 °C (lit.[13] 128−129 °C); R_f = 0.45 (1:1 petroleum ether/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (d, J = 8.2 Hz, 1 H), 8.04−7.98 (m, 2 H), 7.84−7.78 (m, 3 H), 7.59−7.54 (m, 2 H), 7.49−7.43 (m, 1 H), 7.40−7.35 (m, 1 H), 7.31−7.26 (m, 1 H), 7.11−7.08 (m, 2 H), 3.90 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 159.7, 145.9, 140.2, 140.1, 129.4, 128.9, 127.0, 126.5, 125.8, 123.0, 122.8, 121.7, 121.6, 114.2, 110.6, 55.3; HRMS (ESI) calcd for $C_{20}H_{17}N_2O$ (M + H) 301.1335, found 301.1335.

*3-(4-Bromophenyl)-5,6-dimethoxy-1-phenyl-1H-indazole (**7b**).* The general procedure was applied to 83 mg of **6b** and 129 mg of **1b** to afford 110 mg of **7b** (89%) as slightly yellow solid, mp 146−147 °C; R_f = 0.30 (1:1 petroleum ether/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.85 (d, J = 8.4 Hz, 2 H), 7.75 (d, J = 7.8 Hz, 2 H), 7.64 (d, J = 8.4 Hz, 2 H), 7.56 (t, J = 7.8 Hz, 2 H), 7.38 (t, J = 7.4 Hz, 1 H), 7.28 (s, 1 H), 7.12 (s, 1 H), 3.98 (s, 3 H), 3.96 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 151.0, 146.9, 144.2, 140.0, 135.9, 132.3, 131.8, 129.4, 128.8, 126.6, 122.7, 121.9, 115.7, 100.3, 92.0, 56.2, 56.0; HRMS (ESI) calcd for $C_{21}H_{18}BrN_2O_2$ (M + H) 409.0546, found 409.0552.

*4-Methoxy-1,3-diphenyl-1H-indazole (**7c**).* The general procedure was applied to 59 mg of **6c** and 119 mg of **1c** to afford 70 mg of **7c** (78%) as yellow oil; R_f = 0.41 (1:1 petroleum ether/DCM); ^{1}H NMR (major isomer, 300 MHz, $CDCl_3$) δ 8.03−8.00 (m, 2 H), 7.82−7.78 (m, 2 H), 7.58−7.36 (m, 8 H), 6.64−6.57 (m, 1 H), 3.92 (s, 3 H); ^{13}C NMR (major isomer, 75 MHz, $CDCl_3$) δ 154.6, 146.7, 142.3, 140.1, 133.7, 129.8, 129.3, 128.4, 127.9, 127.7, 126.7, 123.3, 114.1, 103.2, 100.9, 55.4; HRMS (ESI) calcd for $C_{20}H_{17}N_2O$ (M + H) 301.1335, found 301.1337. This compound has been accessed before by Moses,[13] and the spectroscopic data are identical with the reported regioisomer.

*3-(4-Bromophenyl)-1-phenyl-1H-indazole (**7d**).* The general procedure was applied to 83 mg of **6b** and 108 mg of **1a** to afford 86 mg of **7d** (82%) as white solid, mp 155−156 °C (lit.[13] 154−157 °C); R_f = 0.45 (2:1 petroleum ether/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.04 (d, J = 8.2 Hz, 1 H), 7.97−7.91 (m, 2 H), 7.83−7.75 (m, 3 H), 7.71−7.64 (m, 2 H), 7.63−7.53 (m, 2 H), 7.47 (dt, J = 1.0, 6.9 Hz, 1 H), 7.40 (tt, J = 1.1, 7.4 Hz, 1 H), 7.31 (dt, J = 0.7, 7.1 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.8, 140.3, 139.9, 132.2, 131.9, 129.5, 129.1, 127.2, 126.8, 123.0, 122.8, 122.3, 122.1, 121.2, 110.8; HRMS (ESI) calcd for $C_{19}H_{14}BrN_2$ (M + H) 349.0335, found 349.0334.

*4-(1-Phenyl-1H-indazol-3-yl)benzonitrile (**7e**).* The general procedure was applied to 67 mg of **6d** and 108 mg of **1a** to afford 71 mg of **7e** (80%) as yellow solid, mp 141−142 °C; R_f = 0.33 (1:1 petroleum ether/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.18 (d, J = 8.5 Hz, 2 H), 8.06 (d, J = 8.2 Hz, 1 H), 8.81−7.77 (m, 5 H), 7.61−7.55 (m, 2 H), 7.49 (dt, J = 0.9, 6.9 Hz, 1 H), 7.43 (tt, J = 1.0, 7.4 Hz, 1 H), 7.34 (dt, J = 0.6, 7.5 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.6, 140.4, 139.6, 137.7, 132.5, 129.5, 127.8, 127.4, 127.2, 123.0, 122. 7, 122.6, 120.9, 118.9, 111.3, 111.0; HRMS (ESI) calcd for $C_{20}H_{14}N_3$ (M + H) 296.1182, found 296.1182.

*3-(2-Bromophenyl)-1-phenyl-1H-indazole (**7f**).* The general procedure was applied to 83 mg of **6e** and 108 mg of **1a** to afford 90 mg of **7f** (86%) as orange oil; R_f = 0.35 (2:1 petroleum ether/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.87−7.82 (m, 3 H), 7.81−7.74 (m, 2 H), 7.66 (dd, J = 7.6, 1.7 Hz, 1 H), 7.62−7.53 (m, 2 H), 7.52−7.43 (m, 2 H), 7.42−7.38 (m, 1 H), 7.37−7.34 (m, 1 H), 7.28 (ddd, J = 7.9, 6.9, 0.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.2, 140.0, 139.4, 133.8, 133.3, 132.4, 130.0, 129.4, 127.3, 127.1, 126.6, 123.9, 123.4, 122.8, 122.1, 121.6, 110.5; HRMS (ESI) calcd for $C_{19}H_{14}BrN_2$ (M + H) 349.0335, found 349.0335.

*3-(2,6-Dichlorophenyl)-1-phenyl-1H-indazole (**7g**).* The general procedure was applied to 80 mg of **6f** and 108 mg of **1a** to afford 96 mg of **7g** (94%) as orange oil; R_f = 0.35 (2:1 petroleum ether/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.88−7.85 (m, 3 H), 7.60−7.55 (m, 3 H), 7.53−7.46 (m, 3 H), 7.43−7.32 (m, 2 H), 7.31−7.24 (m, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 142.3, 140.0, 139.3, 136.6, 130.9, 130.4, 129.4, 128.2, 127.3, 126.7, 124.2, 122.9, 121.8, 121.1, 110.7; HRMS (ESI) calcd for $C_{19}H_{13}Cl_2N_2$ (M + H) 339.0450, found 339.0452.

*1-Phenyl-3-(thiophen-2-yl)-1H-indazole (**7h**).* The general procedure was applied to 61 mg of **6g** and 108 mg of **1a** to afford 58 mg of **7h** (70%) as slightly yellow oil; R_f = 0.36 (2:1 petroleum ether/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.13 (dt, J = 8.2, 0.9 Hz, 1 H), 7.85−7.74 (m, 4 H), 7.61−7.53 (m, 2 H), 7.47 (ddd, J = 8.5, 5.1, 1.1 Hz, 1 H), 7.44−7.36 (m, 2 H), 7.32 (ddd, J = 7.9, 6.9, 0.8 Hz, 1 H), 7.23 (dd, J = 5.1, 3.6 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 141.0, 140.1, 139.8, 135.4, 129.4, 127.6, 127.3, 126.7, 125.4, 125.1, 122.9, 122.5, 122.1, 121.3, 110.7; HRMS (ESI) calcd for $C_{17}H_{13}N_2S$ (M + H) 277.0794, found 277.0787.

*1-Phenyl-3-styryl-1H-indazole (**7i**).* The general procedure was applied to 67 mg of **6h** and 108 mg of **1a** to afford 57 mg of **7i** (64%) as slightly yellow oil; R_f = 0.51 (1:1 petroleum ether/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.11 (d, J = 8.1 Hz, 1 H), 7.80−7.75 (m, 3 H), 7.68−7.63 (m, 3 H), 7.60−7.54 (m, 3 H), 7.50−7.39 (m, 4 H), 7.37−7.30 (m, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 144.2, 140.1, 139.9, 137.2, 131.6, 129.4, 128.7, 127.9, 127.2, 126.7, 126.6, 123.4, 122.9, 121.9, 121.1, 119.6, 110.7; HRMS (ESI) calcd for $C_{21}H_{17}N_2$ (M + H) 297.1386, found 297.1383.

*3-(4-Bromophenyl)-1-(4-methoxyphenyl)-1H-indazole (**7j**).* The general procedure was applied to 92 mg of **6i** and 108 mg of **1a** to afford 64 mg of **7j** (56%) as slightly yellow solid, mp 169−170 °C; R_f = 0.41 (1:1 petroleum ether/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.03 (d, J = 8.2 Hz, 1 H), 7.96−7.89 (m, 2 H), 7.70−7.62 (m, 5 H), 7.44 (ddd, J = 1.0, 6.9, 8.0 Hz, 1 H), 7.29 (ddd, J = 0.8, 7.0, 8.0 Hz, 1 H), 7.12−7.03 (m, 2 H), 3.89 (s, 3 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 158.6, 144.3, 140.5, 133.0, 132.3, 131.9, 129.1, 127.0, 124.8, 122.4, 122.1, 121.9, 121.1, 114.6, 110.6, 55.6; HRMS (ESI) calcd for $C_{20}H_{16}BrN_2O$ (M + H) 379.0441, found 379.0430.

*3-(4-Bromophenyl)-1-(2,4,6-trichlorophenyl)-1H-indazole (**7k**).* The general procedure was applied to 114 mg of **6j** and 108 mg of **1a** to afford 98 mg of **7k** (72%) as slightly yellow oil; R_f = 0.49 (2:1 petroleum ether/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.07 (dt, J = 8.6, 0.8 Hz, 1 H), 7.94−7.91 (m, 2 H), 7.67−7.65 (m, 2 H), 7.57 (s, 2 H), 7.47 (ddd, J = 8.1, 7.0, 1.0 Hz, 1 H), 7.33 (ddd, J = 8.0, 7.0, 0.9 Hz, 1 H), 7.13 (dt, J = 8.4, 0.8 Hz, 1 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 146.0, 142.0, 136.3, 136.2, 133.4, 132.0, 131.9, 129.2, 128.9, 127.6, 122.7, 122.3, 121.7, 121.3, 109.9; HRMS (ESI) calcd for $C_{19}H_{11}BrCl_3N_2$ (M + H) 450.9166, found 450.9159.

*1-Benzyl-3-(4-bromophenyl)-1H-indazole (**7m**).* The general procedure was applied to 87 mg of **6l′** (0.23 mmol), 108 mg of **1a** (0.36 mmol, 1.57 equiv), and 35 mg of KF (0.6 mmol, 2.6 equiv) to afford 45 mg of **7m** (54%) as slightly yellow solid, mp 78−79 °C; R_f = 0.49 (1:1 petroleum ether/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 8.01−7.97 (m, 1 H), 7.94−7.85 (m, 2 H), 7.67−7.61 (m, 2 H), 7.38−7.37 (m, 2 H), 7.32−7.20 (m, 6 H), 5.66 (s, 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 143.0, 141.1, 136.7, 132.6, 131.9, 128.9, 128.7, 127.8, 127.1, 126.5, 121.9, 121.4, 121.1, 109.8, 53.0 (1 overlapped signal); HRMS (ESI) calcd for $C_{20}H_{16}BrN_2$ (M + H) 363.0491, found 363.0492.

General Procedure To Prepare Indazoles 7n−7q from *in Situ* Prepared Hydrazones. To an oven-dried seal tube equipped with a stirrer bar were added 0.3 mmol of hydrazine and CH_3CN (1 mL). A solution of an aliphatic aldehyde (0.36 mmol, 1.2 equiv) in CH_3CN (2 mL) was added dropwise. The mixture was stirred at room

temperature for 5 min before being charged with the aryne precursor **1a** (88 μL, 0.36 mmol, 1.2 equiv) and KF (ca. 34−37 mg, 0.6 mmol, 2 equiv). The tube was sealed and heated to 100 °C for 16 h. Upon completion, the reaction mixture was cooled to room temperature, poured into brine, and extracted with EtOAc. The combined extracts were dried over $MgSO_4$, filtered, and evaporated. The residue was purified by column chromatography (petroleum ether/DCM) to afford the indazole.

*3-tert-Butyl-1-phenyl-1H-indazole (**7n**).* The general procedure was applied to 31 mg of pivaldehyde and 33 mg of phenylhydrazine to afford 23 mg of **7n** (31%) as slightly yellow oil; R_f = 0.28 (2:1 petroleum ether/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.97 (d, J = 8.2 Hz, 1 H), 7.76−7.74 (m, 3 H), 7.57−7.48 (m, 2 H), 7.40 (ddd, J = 8.2, 7.0, 0.9 Hz, 1 H), 7.32 (tt, J = 7.4, 1.0 Hz, 1 H), 7.23−7.15 (m, 1 H), 1.62 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 155.0, 140.4, 140.3, 129.3, 126.4, 126.0, 122.8, 122.7, 122.5, 120.3, 110.5, 33.9, 30.0; HRMS (ESI) calcd for $C_{17}H_{19}N_2$ (M + H) 251.1543, found 251.1539.

*3-tert-Butyl-1-(2,4,6-trichlorophenyl)-1H-indazole (**7o**).* The general procedure was applied to 31 mg of pivaldehyde and 64 mg of (2,4,6-trichlorophenyl)hydrazine to afford 34 mg of **7o** (32%) as slightly yellow solid, mp 133−134 °C; R_f = 0.26 (2:1 petroleum ether/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.98 (dt, J = 8.2, 0.9 Hz, 1 H), 7.52 (s, 2 H), 7.37 (ddd, J = 8.2, 7.0, 1.0 Hz, 1 H), 7.20 (ddd, J = 8.0, 7.0, 0.9 Hz, 1 H), 7.03 (dt, J = 8.4, 0.8 Hz, 1 H), 1.59 (s, 9 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 156.1, 141.9, 136.6, 135.6, 133.9, 128.9, 126.6, 122.5, 121.6, 120.5, 109.7, 34.0, 30.0; HRMS (ESI) calcd for $C_{17}H_{16}Cl_3N_2$ (M + H) 353.03736, found 353.03658.

*3-Cyclohexyl-1-(2,4,6-trichlorophenyl)-1H-indazole (**7p**).* The general procedure was applied to 41 mg of cyclohexanecarbaldehyde and 64 mg of (2,4,6-trichlorophenyl)hydrazine to afford 46 mg of **7p** (40%) as yellow oil; R_f = 0.23 (2:1 petroleum ether/DCM); ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.85 (d, J = 8.1 Hz, 1 H), 7.52 (s, 2 H), 7.39−7.36 (m, 1 H), 7.21 (t, J = 7.5 Hz, 1 H), 7.03 (d, J = 8.4 Hz, 1 H), 3.15 (tt, J = 11.8, 3.4 Hz, 1 H), 2.17−2.14 (m, 2 H), 1.93−1.89 (m, 2 H), 1.83−1.79 (m, 2 H), 1.54−1.32 (m, 4 H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 153.3, 141.3, 136.5, 135.6, 133.9, 128.8, 127.1, 122.4, 121.0, 120.7, 109.5, 37.6, 32.5, 26.6, 26.2; HRMS (ESI) calcd for $C_{19}H_{18}Cl_3N_2$ (M + H) 379.0530, found 379.0522.

*3-Phenethyl-1-(2,4,6-trichlorophenyl)-1H-indazole (**7q**).* The general procedure was applied to 49 mg of 3-phenylpropanal and 64 mg of (2,4,6-trichlorophenyl)hydrazine to afford 56 mg of **7q** (47%) as colorless oil; R_f = 0.43 (1:1 petroleum ether/DCM); ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.70 (d, J = 8.1 Hz, 1 H), 7.53 (s, 2 H), 7.43−7.38 (m, 1 H), 7.29−7.18 (m, 6 H), 7.04 (d, J = 8.4 Hz, 1 H), 3.43−3.33 and 3.27−3.17 (A_2B_2, 2 + 2 H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 148.1, 141.4, 141.2, 136.5, 135.8, 133.7, 128.8, 128.5, 128.4, 127.3, 126.0, 123.2, 121.0, 120.5, 109.5, 35.3, 29.1; HRMS (ESI) calcd for $C_{21}H_{16}Cl_3N_2$ (M + H) 401.0374, found 401.0375.

■ ASSOCIATED CONTENT

Supporting Information

Full ^{1}H and ^{13}C NMR spectra of the final products **3**, **4**, **5**, and **7**, including the NOESY spectrum for compound **3c**. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: cwu@henu.edu.cn; fshi@henu.edu.cn.

Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

This project is financially supported by the National Natural Science Foundation of China (No. 21002021 to F.S.), the Key Project of the Chinese Ministry of Education (No. 210127 to F.S.), and start-up funds from Henan University (to F.S. and C.W.). We thank Mr. Lei Liu, Prof. Shrong-Shi Lin, Dr. Jiang Zhou (all of Peking University), Mr. Huaiqiu Wang, Mr. Weining Zhao, Prof. Zheng Duan (all of Zhengzhou University), and Mr. Yong Wang and Dr. Li Yu (both of Henan University) for their help in the spectroscopic analysis.

■ REFERENCES

(1) For excellent reviews of indazoles' activity and synthesis, see: (a) Cerecetto, H.; Gerpe, A.; González, M.; Arán, V. J.; de Ocáriz, C. O. *Mini-Rev. Med. Chem.* **2005**, *5*, 869. (b) Stadlbauer, W. In *Science of Synthesis*; Georg Thieme: Stuttgart, 2002; Vol. *12*, pp 227−324.

(2) (a) Runti, C.; Baiocchi, L. *Int. J. Tissue React.* **1985**, *7*, 175. (b) Bistochi, G. A.; De Meo, G.; Pedini, M.; Ricci, A.; Brouilhet, H.; Bucherie, S.; Rabaud, M.; Jacquignon, P. *Farmaco, Ed. Sci.* **1981**, *36*, 315. (c) Picciola, G.; Ravenna, F.; Carenini, G.; Gentili, P.; Riva, M. *Farmaco, Ed. Sci.* **1981**, *36*, 1037.

(3) Keppler, B. K.; Hartmann, M. *Met.-Based Drugs* **1994**, *1*, 145.

(4) (a) Sun, J.-H.; Teleha, C. A.; Yan, J.-S.; Rodgers, J. D.; Nugiel, D. A. *J. Org. Chem.* **1997**, *62*, 5627. (b) Rodgers, J. D.; Johnson, B. L.; Wang, H.; Greenberg, R. A.; Erickson-Viitanen, S.; Klabe, R. M.; Cordova, B. C.; Rayner, M. M.; Lam, G. N.; Chang, C.-H. *Bioorg. Med. Chem. Lett.* **1996**, *6*, 2919.

(5) De Lena, M.; Lorusso, V.; Latorre, A.; Fanizza, G.; Gargano, G.; Caporusso, L.; Guida, M.; Catino, A.; Crucitta, E.; Sambiasi, D.; Mazzei, A. *Eur. J. Cancer* **2001**, *37*, 364.

(6) Lee, F.-Y.; Lien, J.-C.; Huang, L.-J.; Huang, T.-M.; Tsai, S.-C.; Teng, C.-M.; Wu, C.-C.; Cheng, F.-C.; Kuo, S.-C. *J. Med. Chem.* **2001**, *44*, 3747.

(7) Harada, H.; Morie, T.; Hirokawa, Y.; Terauchi, H.; Fujiwara, I.; Yoshida, N.; Kato, S. *Chem. Pharm. Bull.* **1995**, *43*, 1912.

(8) (a) Viña, D.; del Olmo, E.; López-Pérez, J.; San Feliciano, A. *Org. Lett.* **2007**, *9*, 525. (b) Inamoto, K.; Katsuno, M.; Takashi, Y.; Arai, Y.; Hiroya, K.; Sakamoto, T. *Tetrahedron* **2007**, *63*, 2695. (c) Lebedev, A. Y.; Khartulyari, A. S.; Voskoboynikov, A. Z. *J. Org. Chem.* **2005**, *70*, 596.

(9) Inamoto, K.; Saito, T.; Katsuno, M.; Sakamoto, T.; Hiroya, K. *Org. Lett.* **2007**, *9*, 2931.

(10) (a) Counceller, C. M.; Eichman, C. C.; Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2008**, *10*, 1021. (b) Wray, B. C.; Stambuli, J. P. *Org. Lett.* **2010**, *12*, 4576.

(11) Huang, L.-J.; Shih, M.-L.; Chen, H.-S.; Pan, S.-L.; Teng, C.-M.; Lee, F.-Y.; Kuo, S.-C. *Bioorg. Med. Chem.* **2006**, *14*, 528.

(12) (a) Liu, Z.; Shi, F.; Martinez, P. D. G.; Raminelli, C.; Larock, R. C. *J. Org. Chem.* **2008**, *73*, 219. (b) Jin, T.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2007**, *46*, 3323.

(13) Spiteri, C.; Keeling, S.; Moses, J. E. *Org. Lett.* **2010**, *12*, 3368.

(14) Harrity and co-workers have developed methods to prepare diverse substituted aryne precursors, which would allow for halogens, ester, and cyano groups present on the 4−7 positions of the final indazole, see: (a) Kirkham, J. D.; Delaney, P. M.; Ellames, G. J.; Rowb, E. C.; Harrity, J. P. A. *Chem. Commun.* **2010**, *46*, 5154. (b) Crossley, J. A.; Kirkham, J. D.; Browne, D. L.; Harrity, J. P. A *Tetrahedron Lett.* **2010**, *51*, 6608.

(15) Padwa, A.; Pearson, W. H. *Synthetic Applications of 1,3-Dipolar Cycloaddition Chemistry toward Heterocycles and Natural Products*; Wiley: New York, Chichester, 2002; pp 494−495 and references therein.

(16) (a) Presset, M.; Mohanan, K.; Hamann, M.; Coquerel, Y.; Rodriguez, J. *Org. Lett.* **2011**, *13*, 4124. (b) Arrieta, A.; Carrillo, J. R.; Cossio, F. P.; Diaz-Ortiz, A.; JoseGomez-Escalonilla, M.; de la Hoz, A.; Langa, F.; Moreno, A. *Tetrahedron* **1998**, *54*, 13167. (c) Shimizu, T.; Hayashi, Y.; Miki, M.; Teramura, K. *J. Org. Chem.* **1987**, *52*, 2277.

(17) For applications in [3 + 2] cycloaddition, see: (a) Taber, D. F.; Guo, P. *J. Org. Chem.* **2008**, *73*, 9479. (b) Wu, L.; Shi, M. *J. Org. Chem.* **2010**, *75*, 2296. (c) For a comprehensive review of processes generating diazo compounds from *N*-tosylhydrazones, see: Fulton, J. R.; Aggarwal, V. K.; de Vicente, J. *Eur. J. Org. Chem.* **2005**, 1479.

(18) (a) Zhou, L.; Ye, F.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2010**, *132*, 13590. (b) Xiao, Q.; Ma, J.; Yang, Y.; Zhang, Y.; Wang, J. *Org. Lett.* **2009**, *11*, 4732. (c) Barluenga, J.; Moriel, P.; Valdés, C.; Aznar, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 5587. (d) Zhao, X.; Lu, K.; Zhang, Y.; Wang, J. *Chem. Commun.* **2010**, *46*, 1724. (e) Zhao, X.; Wu, G.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 3296. (f) Xiao, Q.; Xia, Y.; Li, H.; Zhang, Y.; Wang, J. *Angew. Chem., Int. Ed.* **2011**, *50*, 1114. (g) Zhou, L.; Shi, Y.; Xiao, Q.; Liu, Y.; Ye, F.; Zhang, Y.; Wang, J. *Org. Lett.* **2011**, *13*, 968. (h) Barluenga, J.; Tomás-Gamasa, M.; Aznar, F.; Valdés, C. *Nat. Chem.* **2009**, *1*, 494.

(19) For similar aryne reactions with nucleophiles tethered with electrophiles, see: (a) Okuma, K.; Nojima, A.; Matsunaga, N.; Shioji, K. *Org. Lett.* **2009**, *11*, 169. (b) Zhao, J.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 583. (c) Rogness, D. C.; Larock, R. C. *J. Org. Chem.* **2011**, *76*, 4980. (d) Okuma, K.; Matsunaga, N.; Nagahora, N.; Shiji, K.; Yokomori, Y. *Chem. Commun.* **2011**, *47*, 5822. (e) Chai, G.; Qiu, Y.; Fu, C.; Ma, S. *Org. Lett.* **2011**, *13*, 5196. (f) Rogness, D. C.; Larock, R. C. *Tetrahedron Lett.* **2009**, *50*, 4003. (g) Rogness, D. C.; Larock, R. C. *J. Org. Chem.* **2010**, *75*, 2289. (h) Gilmore, C. D.; Allan, K. M.; Stoltz, B. M. *J. Am. Chem. Soc.* **2008**, *130*, 1558. (i) Huang, X.; Zhang, T. *J. Org. Chem.* **2010**, *75*, 506.

(20) Aryne reactions with nucleophiles tethered with electrophiles can also lead to σ-bond cleavage; see: (a) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2010**, *12*, 3117. (b) Laczkowski, K. Z.; Garcia, D.; Pena, D.; Cobas, A.; Perez, D.; Guitian, E. *Org. Lett.* **2011**, *13*, 960. (c) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 6638. (d) Yoshioka, E.; Kohtani, S.; Miyabe, H. *Org. Lett.* **2010**, *12*, 1956. (e) Yoshida, H.; Watanabe, M.; Morishita, T.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 1505. (f) Yoshida, H.; Mimura, Y.; Ohshita, J.; Kunai, A. *Chem. Commun.* **2007**, 2405. (g) Yoshida, H.; Ito, Y.; Yoshikawa, Y.; Ohshita, J.; Takaki, K. *Chem. Commun.* **2011**, 8664. (h) Liu, Y.-L.; Liang, Y.; Pi, S.-F.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 5691. (i) Biswas, K.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 4946. (j) Pintori, D. G.; Greaney, M. F. *Org. Lett.* **2010**, *12*, 168. (k) Huang, X.; Xue, J. *J. Org. Chem.* **2007**, *72*, 3965. (l) For a recent review, see: Pena, D.; Perez, D.; Guitian, E. *Angew. Chem., Int. Ed.* **2006**, *45*, 3579.

(21) This strategy has been used by Larock and co-workers: (a) Dubrovskiy, A. V.; Larock, R. C. *Org. Lett.* **2011**, *13*, 4136. (b) Markina, N. A.; Dubrovskiy, A. D.; Larock, R. C. *Org. Biomol. Chem.* **2012**, *10*, 2409.

(22) Li, P.; Zhao, J.; Wu, C.; Larock, R. C.; Shi, F. *Org. Lett.* **2011**, *13*, 3340.

(23) (a) Aggarwal, V. K.; de Vicente, J.; Bonnert, R. V. *J. Org. Chem.* **2003**, *68*, 5381. (b) Aggarwal, V. K.; Fulton, J. R.; Sheldon, C. G.; de Vicente, J. *J. Am. Chem. Soc.* **2003**, *125*, 6034. (c) Aggarwal, V. K.; Patel, M.; Studley, J. *Chem. Commun.* **2002**, 1514. (d) Aggarwal, V. K.; Alonso, E.; Bae, I.; Hynd, G.; Lydon, K. M.; Palmer, M. J.; Patel, M.; Porcelloni, M.; Richardson, J.; Stenson, R. A.; Studley, J. R.; Vasse, J. L.; Winn, C. L. *J. Am. Chem. Soc.* **2003**, *125*, 10926. (e) Zhang, Z.; Liu, Y.; Ling, L.; Li, Y.; Dong, Y.; Gong, M.; Zhao, X.; Zhang, Y.; Wang, J. *J. Am. Chem. Soc.* **2011**, *133*, 4330.

(24) For an example in aryne chemistry where Ts serves as a leaving group, see: (a) Zhao, J.; Wu, C.; Li, P.; Ai, W.; Chen, H.; Wang, C.; Larock, R. C.; Shi, F. *J. Org. Chem.* **2011**, *76*, 6837. (b) Zhao, J.; Li, P.; Wu, C.; Chen, H.; Ai, W.; Sun, R.; Ren, H.; Larock, R. C.; Shi, F. *Org. Biomol. Chem.* **2012**, *10*, 1922.

(25) (a) Doyle, M. P.; Yan, M. *J. Org. Chem.* **2002**, *67*, 602. (b) For a review, see: Taylor, E. C.; Turchi, I. J. *Chem. Rev.* **1979**, *79*, 181.

(26) Greaney and co-workers have reported a benzyne Fischer-indole reaction using ketone-derived *N*-tosylhydrazones as a starting material; see: McAusland, D.; Seo, S.; Pintori, D. G.; Finlayson, J.; Greaney, M. F. *Org. Lett.* **2011**, *13*, 3667.

(27) Creary, X.; Tam, W. W.; Albizati, K. F.; Stevens, R. V. *Org. Synth.* **1990**, *64*, 207.

(28) For explanation of this regioselectivity, see: (a) Sanz, R. *Org. Prep. Proc. Int.* **2008**, *40*, 215. (b) Tadross, P. M.; Gilmore, C. D.; Bugga, P.; Virgil, S. C.; Stoltz, B. M. *Org. Lett.* **2010**, *12*, 1224.

(29) One reviewer suggested that the anion of the *N*-tosylhydrazone may react as an aza enolate so that the C can attack the aryne as the nucleophile. While this may theoretically be true, it has never been observed. A good example can be found in ref 26, where the N attacked the benzyne exclusively. Similar arguments may be applied to *N*-aryl/alkyl hydrazones, where the hydrazones may theoretically react as an enamine resulting in the C serving as the nucleophile. Again, as demonstrated in ref 21 and in our later results in this disclosure, this was much less relevant.

(30) It has been suggested to carry out a Hammett study by using different 4-substituted phenyl groups as Ar (cf. Scheme 2) so that the electronic property can be systematically varied, and a change in slope in the Hammett plot can be expected. Regretfully, only when Ar was a 4-methoxyphenyl group could we isolate the two regioisomers separately in reasonable yields. Substrates with all other substituted phenyl groups resulted in lowered yields and inseparable mixtures of regioisomers where unambiguous assignment of regioisomers was difficult (most of 3-aryl-4-methoxyindazoles and 3-aryl-7-methoxyindazoles are unknown compounds and comparison with literature data is also difficult).

(31) For successful benzyne reactions under oxidative conditions, see: (a) Huang, X.; Zhang, T. *Tetrahedron Lett.* **2009**, *50*, 208. (b) Shen, Y.-M.; Grampp, G.; Leesakul, N.; Hu, H.-W.; Xu, J.-H. *Eur. J. Org. Chem.* **2007**, 3718.

(32) Because of the innate reactivity of benzynes, a lot of common oxidants are not compatible. For example, BQ and DDQ will generate phenolic products upon reduction, which are reactive with benzynes.

(33) Since the temperature was above the boiling point of the solvent, the reaction has to be performed in the sealed tube. The air in the head space was the actual oxidant. However, we have found that excessive dioxygen adversely affects the yield. See the Supporting Information for an estimation of O_2 quantity dependence of this reaction.

(34) The silica gel supplied in the Chinese market exhibits differences from that in the US market. The same compounds are retarded less.

(35) McMahon, R. J.; Abelt, C. J.; Chapman, O. L.; Johnson, J. W.; Kreil, C. L.; LeRoux, J.-P.; Mooring, A. M.; West, P. R. *J. Am. Chem. Soc.* **1987**, *109*, 2456.

(36) Sartorelli, A. C.; Agrawal, K. C.; Booth, B. A.; Pittman, J.; Bartholomew, D. G.; Broom, A. D. *J. Med. Chem.* **1976**, *19*, 830.

(37) Juneau, R.; Mitchell, S.; Wolgamott, G. *J. Pharm. Sci.* **1979**, *68*, 930.

(38) Cacchi, S.; Torre, F. L.; Misiti, D. *Synthesis* **1977**, *5*, 301.

(39) Kabalka, G. W.; Summers, S. T. *J. Org. Chem.* **1981**, *46*, 1217.

(40) Adger, B. M.; Bradbury, S.; Keating, M.; Rees, C. W.; Storr, R. C.; Williams, M. T. *J. Chem. Soc., Perkin Trans. 1* **1975**, 31.

(41) Wentrup, C.; Damerius, A.; Reichen, W. *J. Org. Chem.* **1978**, *43*, 2037.

(42) Servi, S.; Akgun, Z. R. *Synth. Commun.* **2002**, *32*, 3399.

(43) Um, I.-K.; Lee, E.-J.; Seok, J.-A.; Kim, K.-H. *J. Org. Chem.* **2005**, *70*, 7530.

(44) Pratapan, S.; Scaria, P. M.; Bhattacharyya, K.; Das, P. K.; George, M. V. *J. Org. Chem.* **1986**, *51*, 1972.

(45) Dadiboyena, S.; Valente, E. J.; Hamme, A. T. *Tetrahedron Lett.* **2009**, *50*, 291.

(46) Frolova, N. A.; Vatsadze, S. Z.; Vetokhina, N. Y.; Zavodnik, V. E.; Zyk, N. V. *Mendeleev Commun.* **2006**, *16*, 251.

(47) Hearn, M. J.; Lebold, S. A.; Sinha, A.; Sy, K. *J. Org. Chem.* **1989**, *54*, 4188.

(48) Shoppee, C. W. *J. Chem. Soc.* **1931**, 1225.

(49) Sidique, S.; Shiryaev, S. A.; Ratnikov, B. I.; Herath, A.; Su, Y.; Strongin, A. Y.; Cosford, N. D. P. *Bioorg. Med. Chem. Lett.* **2009**, *19*, 5773.