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Rhodium(III)-Catalyzed Indazole Synthesis by C−H Bond Functionalization and Cyclative Capture

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Supporting Information

ABSTRACT: An efficient, one-step, and highly functional group-compatible synthesis of substituted *N*-aryl-2*H*-indazoles is reported via the rhodium(III)-catalyzed C−H bond addition of azobenzenes to aldehydes. The regioselective coupling of unsymmetrical azobenzenes was further demonstrated and led to the development of a new removable aryl group that allows for the preparation of indazoles without *N*-substitution. The 2-aryl-2*H*-indazole products also represent a new class of readily prepared fluorophores for which initial spectroscopic characterization has been performed.

Rhodium(III)-catalyzed addition of sp^2-hybridized C−H bonds to polarized π-bonds, including those present in aldehydes,[1] imines,[2] isocyanates,[3] aziridines,[4] carbon monoxide,[5] and isonitriles,[6] has proven to be a versatile and highly functional group-compatible synthetic approach.[7] Aldehydes are particularly attractive inputs because a vast number of derivatives are commercially available. However, the addition of C−H bonds to aldehydes is often reversible with the alcohol addition products typically favored when highly electron-deficient aldehydes are used.[1c,d,h] We have previously demonstrated that this inherent challenge can be overcome by cyclative capture of the hydroxyl group to obtain valuable heterocycle products (Figure 1).[1a,b,8] Herein, we introduce a new cyclative capture approach where the initially generated hydroxyl serves as a leaving group rather than a nucleophile to afford pharmaceutically important *N*-aryl-2*H*-indazoles by formal [4+1] annulation (Figure 1).[9,10] Substituents on unsymmetrical azobenzenes that effect a high level of regiocontrol have been established to significantly enhance the scope of the method. Moreover, by capitalizing on substituent control of regioselectivity, a readily cleavable 2-aryl substituent has been developed that provides straightforward access to indazoles lacking *N*-substitution. Finally, we have determined that appropriately substituted 2-aryl-2*H*-indazoles represent a new class of fluorophores that may find utility as fluorescent probes for biological study or as specialized materials. Initial spectroscopic characterization of representative derivatives has therefore been performed.

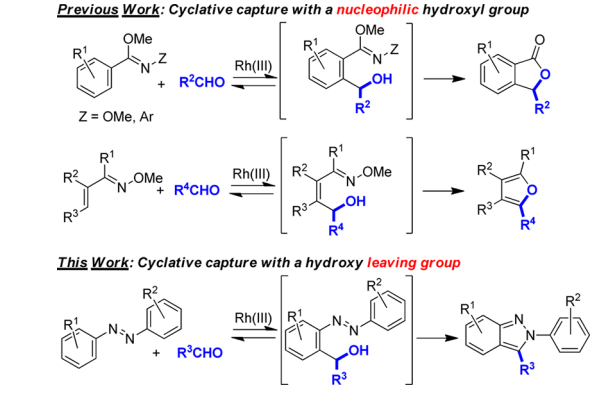
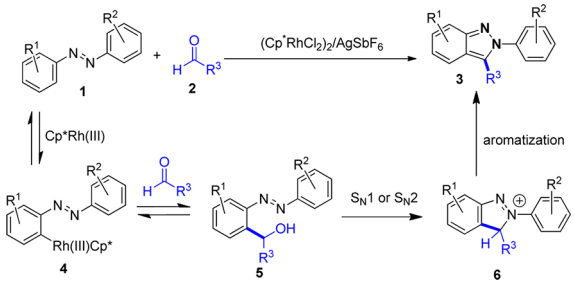


Figure 1. Two distinct approaches for cyclative capture.

Indazole is recognized as a privileged structure in the pharmaceutical industry with multiple drugs and drug candidates in clinical trials incorporating this pharmacophore.[11] The more difficult to prepare 2-substituted 2*H*-indazole class has in particular begun to attract the increased attention of the synthetic community due to the promise of drug candidates that contain this motif.[12,13] We envisioned that convergent entry to 2-substituted 2*H*-indazoles **3** should be possible by Rh(III)-catalyzed addition of azobenzenes **1** to aldehydes **2** (Scheme 1). We rationalized that the azo functional group would direct ortho C−H bond activation, followed by the reversible addition to aldehyde **2** to provide alcohol **5**. Cyclative capture by an intramolecular nucleophilic substitution to give **6** followed by rapid aromatization should provide the desired 2*H*-indazole **3**.

Scheme 1. Proposed Reaction Pathway for 2*H*-Indazole Synthesis



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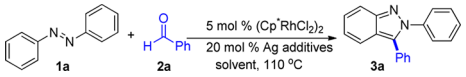
An enormous number of azobenzenes have been prepared due to their many applications in the chemical industry,[14] and it is therefore not surprising that the cyclometalation of azobenzene was one of first examples of this type of transformation.[15] Despite this, there have been few reports on the catalytic C−H functionalization of azobenzenes,[16] and none have relied on Rh(III) catalysis. Moreover, except for one substrate example,[16c] the regioselective functionalization of unsymmetrical azobenzenes is unexplored.

We first chose to evaluate azobenzene **1a** and benzaldehyde **2a** as model substrates and surveyed conditions that had previously been determined to be optimal for Rh(III) catalyzed additions to aldehydes (Table 1).[1a] The use of 5 mol% of $[Cp^*RhCl_2]_2$ and

Table 1. Optimization of Reaction Conditions[a]



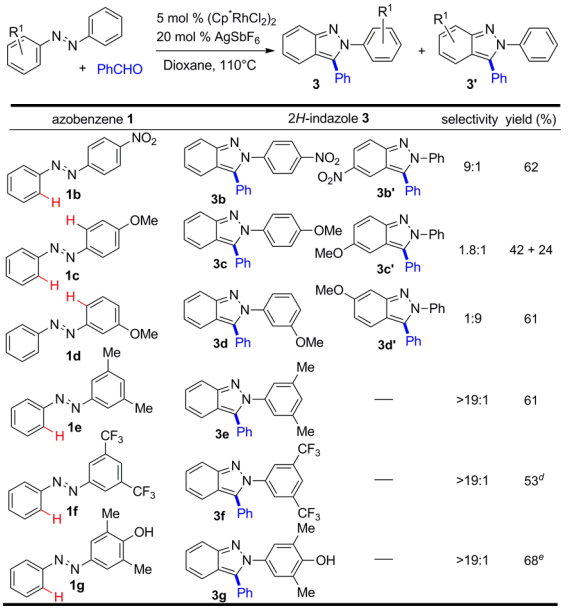
entry	solvent	Ag salt	yield (external)[b]
1	DCE	$AgSbF_6$	46
2	DCE	none	trace[c]
3	THF	$AgSbF_6$	46
4	HOAc	$AgSbF_6$	64
5	dioxane	$AgSbF_6$	81
6	dioxane	$AgBF_4$	52
7	dioxane	$AgPF_6$	15
8	dioxane	$AgBC_{24}F_{20}$	40
9	dioxane	none	0
10	dioxane	$AgSbF_6$	0[d]

[a]Conditions: **1** (0.10 mmol), **2** (0.20 mmol) in 0.5 mL of solvent for 24 h. [b]Determined by ^{1}H NMR relative to 2,6-dimethoxytoluene as external standard. [c]In place of $(Cp^*RhCl_2)_2$, $Cp^*Rh(CH_3CN)_3(SbF_6)_2$ was used. [d]No $(Cp^*RhCl_2)_2$ was added.

20 mol% of $AgSbF_6$ in DCE afforded the desired product **3a** in 46% yield (entry 1). The preformed cationic rhodium catalyst $[Cp^*Rh(CH_3CN)_3(SbF_6)_2]$ is often effective for aldehyde additions,[1c,g] but for this substrate combination this catalyst completely shut down the reaction (entry 2). Because solvent can play a key role in the reaction outcome,[1b] a variety of solvents were screened. THF maintained the same yield as DCE (entry 3), HOAc improved the yield to 64% (entry 4), and dioxane proved to be the most effective, affording the product in 81% yield (entry 5). Replacing $AgSbF_6$ with other silver salts reduced the yield of product (entries 6−8). Rationalizing the change in reaction yield upon variation of the counterion and solvent is complicated by the potential for differential effects upon C−H bond-functionalization and cyclization. No reaction was observed when either $[Cp^*RhCl_2]_2$ or $AgSbF_6$ alone was used (entries 9 and 10), which suggests that a cationic Rh(III) species is required for this C−H bond functionalization process.

Having defined an effective catalyst and reaction conditions for the synthesis of 2*H*-indazole **3a**, we next explored substrate scope for unsymmetrical azobenzenes. The 4-nitro-substituted azobenzene **1b** led to the indazole products in 62% combined yield with 9:1 regioselectivity favoring **3b** with C−H functionalization of the more electron-rich phenyl ring (Table 2). In contrast, the 4-methoxy-substituted azobenzene **1c** generated the regioisomeric products **3c** and **3c′** with low selectivity. The major product **3c** was obtained by C−H functionalization on the less electron-rich phenyl ring of the azobenzene, which is opposite to the selectivity observed with the 4-nitro derivative **1b**. For **3c′** the

Table 2. Electronic and Steric Effects on 2*H*-Indazole Regioselectivity[a,b,c]



[a]Conditions: azobenzene (0.20 mmol), benzaldehyde (0.40 mmol) in 1.0 mL of dioxane for 24 h. [b]Isolated yield. [c]Ratio was determined by crude ^{1}H NMR. [d]Reaction was conducted in 0.4 mL of dioxane. [e]Reaction was conducted in 1.0 mL of THF with 100 mg of $MgSO_4$.

methoxy group is meta to the site of reaction and therefore contributes an inductive effect but does not provide resonance stabilization. The inductive effect could either slow the rate of C−H functionalization or affect the rate of cyclative capture of the reversibly formed alcohol addition product. To test this assumption, the 3-methoxy substitution pattern in **1d** with the methoxy group capable of providing resonance stabilization was evaluated. As expected, the reaction favored **3d′** with a 9:1 regioselectivity for C−H functionalization occurring on the more electron-rich aromatic ring. The exclusive functionalization of azobenzene **1d** para rather than ortho to the methoxy group suggests that steric effects are important. For this reason, azobenzenes **1e** and **1f**, which are 3,5-disubstituted with electron-rich methyl or electron-deficient CF_3 groups, respectively, were evaluated, and each exclusively reacted at the less hindered ring to give indazoles **3e** and **3f** as single regioisomers.

The overriding importance of steric effects upon regioselectivity led to the design of azobenzene derivative **1g**. This approach provides 2-aryl-2*H*-indazoles with an electron-rich aryl substituent that can readily be cleaved by straightforward oxidative methods to provide indazole products lacking substitution on nitrogen. Specifically, coupling azobenzene **1g** with benzaldehyde smoothly afforded indazole **3g** as a single regioisomer in good yield. For this hydroxy-substituted azobenzene, addition of $MgSO_4$ as a drying agent was found to modestly improve the reaction yield. Moreover, THF provided a higher yield than dioxane, 68% vs 48%, respectively.

With an understanding of how electronic and steric effects control regioselectivity, we next explored substrate scope with a diverse set of azobenzenes **1** and aldehydes **2** (Table 3). We primarily focused on reactions of 4-hydroxy-3,5-dimethylphenyl derivatives of **1** because this group can be oxidatively removed from the 2*H*-indazole products **3** to provide the corresponding indazoles lacking *N*-substitution (vide infra). Both electron-poor and electron-rich aldehydes afforded the indazole products

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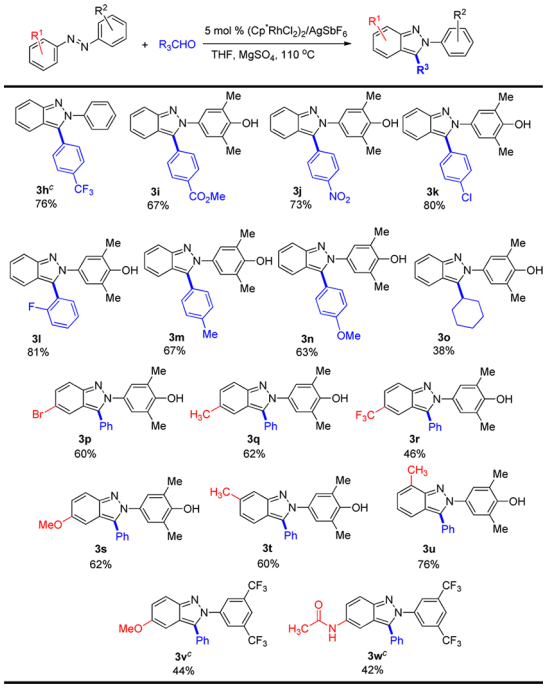
Table 3. Substrate Scope[a,b]



[a]Conditions: azobenzene (0.20 mmol), aldehyde (0.40 mmol), 100 mg of $MgSO_4$ in 1.0 mL of THF for 24 h. [b]Isolated yield. [c]Reaction was conducted in 0.4 mL of dioxane.

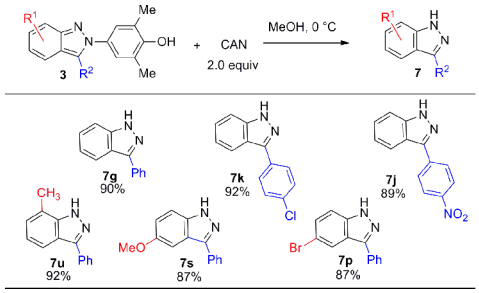
(**3h**−**3n**) in comparable yields, and ortho-substituents (**3l**) were also well tolerated. However, extension of the reaction to an aliphatic aldehyde (**3o**) resulted in a lower yield.

The reaction is sensitive to electronic effects introduced by substitution on azobenzenes **1**. Electron rich and neutral substituents led to indazole products in good yields (**3p**, **3q** and **3s** to **3u**), while the electron-deficient CF_3 group decreased the yield to 46% (**3r**). Consistent with the regiochemistry observed for *m*-methoxy substitution in **1d**, *m*-methyl substitution exclusively afforded the 2*H*-indazole functionalized at the less hindered C−H site (**3t**). It is also significant that even for an ortho-substituted azobenzene, the indazole product was obtained in high yield (**3u**). Azobenzenes **3v** and **3w** were prepared to evaluate substituent effects on fluorescence (vide infra), and were obtained in somewhat lower yield due to the electron-deficient 3,5-bis-trifluoromethyl groups (see **3v** vs **3s**). Excellent functional group compatibility was observed with bromo (**3p**), chloro (**3k**), fluoro (**3l**), ester (**3i**), nitro (**3j**), methyl (**3m**), methoxy (**3n**), acetamido (**3w**), trifluoromethyl (**3h**), and phenol groups (**3i**−**3u**) all tolerated for this one step 2*H*-indazole synthesis.

We hypothesized that indazoles lacking *N*-substitution should be accessible from those 2*H*-indazoles substituted with the *N*-4-hydroxy-3,5-dimethylphenyl group. Although oxidative cleavage of *N*-hydroxyphenyl groups from 2*H*-indazoles had not previously been reported, oxidation with ceric ammonium nitrate (CAN) in methanol provided the indazoles **7** in excellent yield (Table 4). Good functional group compatibility for the oxidation step was observed, with chloro, methyl, nitro, and methoxy groups all being well tolerated.

A number of the synthesized *N*-aryl-2*H*-indazoles were fluorescent. We therefore chose to characterize the fluorescence properties of representative derivatives (Table 5), in particular because our single-step synthesis strategy enables the preparation

Table 4. Oxidative Cleavage of Phenol by CAN[a,b]



[a]Conditions: azobenzene (0.10 mmol), CAN (0.20 mmol) in 4.0 mL of methanol at 0 °C for 10 min. [b]Isolated yield.

Table 5. Spectral Properties of Fluorophores[a]

compd	λ_{max} (nm)	λ_{em} (nm)	ε (M^{-1} cm^{-1})	Φ
3a	314	398	11700	0.08
3b	344	nd	15600	<0.01
3c	308	419	14700	0.10
3c′	331	420	9800	0.26
3d′	303	412	16800	0.06
3f	303	418	13400	0.17
3g	309	nd	15300	<0.01
3h	317	408	12600	0.11
3w	301	434	7700	0.14
3v	309, 351	438	14300, 8900	0.08

[a]Fluorescence measurements taken in 10 mM HEPES pH 7.3. Full spectra are given in the Supporting Information.

of a wide range of *N*-aryl 2*H*-indazoles with varied substitution patterns for facile optimization of fluorophore properties. The indazole fluorophores exhibited high extinction coefficients (~10^4 M^{-1} cm^{-1}) comparable to the widely used coumarin fluorophores.[17] These novel dyes also showed large Stokes shifts (~100 nm; Figure 2), which is an attractive property for

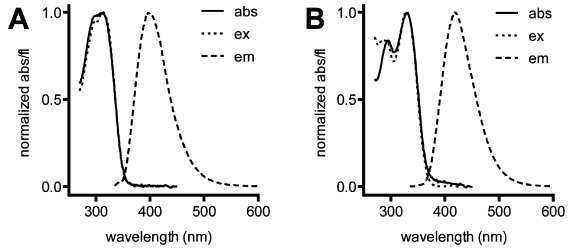


Figure 2. Absorbance (abs), fluorescence excitation (ex), and fluorescence emission (em) spectra for (A) **3a** and (B) **3c′**.

biological probes. Electron-donating substituents on the 5-position of the indazole ring (**3c′** and **3w**, Figure 2B) and 3,5-bis-trifluoromethyl groups on the *N*-phenyl ring (**3f**) resulted in bathochromic shifts in emission wavelength and increases in quantum yield. However, with either the 4-hydroxy-3,5-dimethyl (**3g**) or 4-nitro (**3b**) substitution patterns on the *N*-phenyl group, minimal fluorescence was observed. Replacement of the 3-phenyl group with a 3-(4-trifluoromethylphenyl) group on the indazole had only a modest effect on the fluorescent properties (see **3a** vs **3h**). Substitution on both the indazole and the *N*-phenyl group (**3v**) did not prove cumulative but instead resulted in a compound exhibiting complex optical properties and modest quantum yield.

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In summary, a formal [4+1] annulation for the preparation of *N*-aryl-2*H*-indazoles from azobenzenes and aldehydes has been developed. The reaction is initiated by Rh(III)-catalyzed direct addition of an azobenzene C−H bond to an aldehyde with subsequent cyclization and aromatization. In addition to enabling the Rh(III)-catalyzed activation of ortho-C−H bonds, the azo moiety serves as a nucleophile to trap the initial aldehyde addition product. A broad range of aldehydes and azobenzenes participate in the reaction to provide access to a large variety of differently substituted indazoles. Regioselective functionalization of unsymmetrical azobenzenes can be controlled by either electronic or steric effects. The *N*-4-hydroxy-3,5-dimethylphenyl substituent can readily be oxidatively cleaved from 2*H*-indazoles to provide indazoles lacking *N*-substitution. Moreover, *N*-aryl-2*H*-indazoles represent a new class of fluorophores with high extinction coefficients and large Stokes shifts. The preparation and evaluation of 2*H*-indazoles with extended chromophores for near-infrared applications[18] and with appropriate substitution for use as fluorogenic substrates[19] are under active investigation.

■ ASSOCIATED CONTENT

Supporting Information

Experimental procedures and spectral data. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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