Article

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Cobalt(III)-Catalyzed Synthesis of Indazoles and Furans by C–H Bond Functionalization/Addition/Cyclization Cascades

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Supporting Information Placeholder

ABSTRACT: The development of operationally straightforward and cost effective routes for the assembly of heterocycles from simple inputs is important for many scientific endeavors, including pharmaceutical, agrochemical and materials research. In this Article we describe the development of a new air-stable cationic Co(III)-catalyst for convergent, one step bench-top syntheses of *N*-aryl-2*H*-indazoles and furans by C–H bond additions to aldehydes followed by in situ cyclization and aromatization. Only a sub-stoichiometric amount of AcOH is required as a low cost and convenient to handle additive. The syntheses of these heterocycles are the first examples of Co(III)-catalyzed additions to aldehydes, and reactions are demonstrated for a variety of aromatic, heteroaromatic, and aliphatic derivatives. The syntheses of both *N*-aryl-2*H*-indazoles and furans have been performed on 20 mmol scales and should readily be applicable to larger scales. The reported heterocycle syntheses also demonstrate the use of directing groups that have not previously been applied to Co(III)-catalyzed C–H bond functionalizations. Additionally, the synthesis of furans demonstrates the first example of cobalt(III)-catalyzed functionalization of alkenyl C–H bonds.

■ INTRODUCTION

Remarkable progress in transition-metal-catalyzed C–H bond functionalization has enabled the direct generation of nucleophilic partners without requiring pre-functionalization.[1,2] Strategies for the addition of C–H bonds to polarized π-bonds are particularly efficient and atom economical for the assembly of heteroatom substituted products.[3] Due to the vast number of diverse aldehydes that are commercially available, aldehydes potentially represent the most versatile of the polarized π-bond inputs. However, C–H bond additions to aldehydes are reversible with the alcohol products only favored when destabilized, highly electron-deficient aldehydes are used.[4] For typical aldehydes, good conversion to the alcohol product can only be achieved by trapping the alcohol to prevent reversibility, for example, through protection[5] or oxidation.[6] Recently, we have reported a general strategy to access important classes of heterocycles by cyclative capture of the initially formed alcohol intermediate via reaction with the directing group for C–H functionalization (Figure 1).[7] In this approach the alcohol can either react as a leaving group with the directing group serving as a nucleophile as represented by indazole synthesis, or the alcohol can act as a nucleophile with the directing group serving as an electrophile as depicted for furan synthesis.

While our cyclative capture approaches provide efficient and convergent access to heterocycles, this chemistry is limited by the expensive Rh(III) C–H functionalization catalysts that we have so far employed. Due to the high cost of the more extensively developed catalyst systems based upon the precious metals Rh, Pd, Ag, Ir, Pt and Au, it is not surprising that C–H bond functionalization using the earth abundant first row metals such as Mn,[8] Fe,[9] Co,[10–12] Ni[13] and Cu,[14] has increasingly been investigated as an attractive alternative based on availability and cost.[15]

In this Article we report the development of a new Co catalyst for the synthesis of 2-aryl indazoles and furans (Figure 1). These structural motifs are prevalent in drugs and natural products,[16–17] and for 2-aryl indazoles, exhibit interesting spectrophotometric properties.[7a] The transformations reported herein are the first

examples of Co-catalyzed additions of C–H bonds to carbonyl compounds and represent the first use of azo[18–19] and oxime directing groups with Co(III) catalysis (Figure 1). Moreover, the C–H bond functionalization of α,β-unsaturated oximes to give furans provides the first example of Co(III)-catalyzed functionalization of alkenyl C–H bonds.[20] Both heterocycle syntheses utilize the same air-stable cationic Co(III) catalyst, and reactions can be performed on the bench-top and on large scale.

Indazole synthesis: Cyclative capture with a hydroxyl leaving group
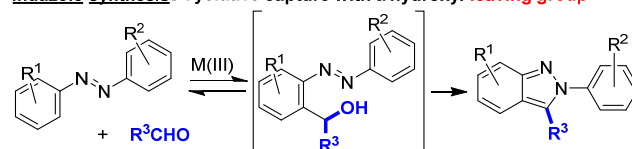
Furan synthesis: Cyclative capture with a hydroxyl nucleophile
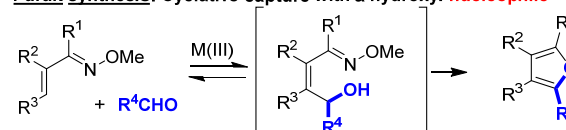
Previous work: Rh(III)
This work: Co(III)

Figure 1: Rhodium and cobalt-catalyzed heterocycle synthesis via aldehyde addition followed by cyclative capture.

■ RESULTS AND DISCUSSION

Seminal reports by Kanai, Matsunaga, and co-workers have established that the high-valent preformed cobalt complex [Cp*Co(C$_6$H$_6$)][PF$_6$]$_2$ (**4**) catalyzes the addition of 2-phenylpyridyl[11g] and indole[11f] C–H bonds to sulfonyl protected imines. We therefore envisioned that a cationic Cp*Co(III) system could also be designed for additions to aldehydes with cyclative capture to obtain heterocycles. To evaluate the potential of high valent Co-catalysts for these transformations, we chose to investigate the addition of azobenzene (**1a**) to benzaldehyde (**2a**) (Table 1). The initial attempt utilizing Kanai's and Matsunaga's

preformed catalyst [Cp*Co(C$_6$H$_6$)][PF$_6$]$_2$ (**4**) resulted in a poor yield of the desired product (entry 1).

We next evaluated a series of silver halide abstractors with [Cp*CoCl$_2$]$_2$ as the precatalyst to generate cationic Co(III) in situ. AgPF$_6$ provided similar results to those observed with the preformed catalyst (entry 2), and with AgSbF$_6$ or AgOAc little or no product was obtained (entries 3 and 4, respectively). However, switching to the non-coordinating AgB(C$_6$F$_5$)$_4$ significantly increased the yield (entry 5), and the addition of a slight excess of AgB(C$_6$F$_5$)$_4$ resulted in further improvement (entry 6). In previous reports on Co(III) catalysis the addition of catalytic amounts of acetate base was beneficial.[11d–f] During our optimization, we found that the addition of 20 mol % of AgOAc also proved to be advantageous to the reaction, resulting in a near quantitative yield (entry 7).[21] Furthermore, although lower concentrations were tolerated, high concentration (2.0 M) was selected for added convenience and efficiency.

Table 1. Optimization of Reaction Conditions for *N*-aryl-2*H*-Indazole Synthesis with [Cp*CoCl$_2$]$_2$ [a]
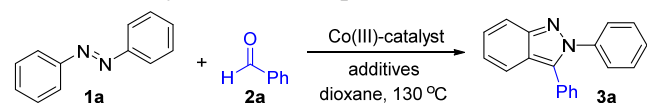
Entry	Co(III) source (mol %)	Ag salt (mol %)	Acetate additive (mol %)	Yield (%)[b]
1	**4** (10)	--	--	2
2	[Cp*CoCl$_2$]$_2$ (5)	AgPF$_6$ (20)	--	3
3	[Cp*CoCl$_2$]$_2$ (5)	AgSbF$_6$ (20)	--	1
4	[Cp*CoCl$_2$]$_2$ (5)	AgOAc (20)	--	--
5	[Cp*CoCl$_2$]$_2$ (5)	AgB(C$_6$F$_5$)$_4$ (20)	--	51
6	[Cp*CoCl$_2$]$_2$ (5)	AgB(C$_6$F$_5$)$_4$ (25)	--	61
7	[Cp*CoCl$_2$]$_2$ (5)	AgB(C$_6$F$_5$)$_4$ (25)	AgOAc (20)	97 (91)[c]
8	[Cp*CoCl$_2$]$_2$ (2.5)	AgB(C$_6$F$_5$)$_4$ (12.5)	AgOAc (10)	63
9	[Cp*CoCl$_2$]$_2$ (1)	AgB(C$_6$F$_5$)$_4$ (5)	AgOAc (4)	44
10	[Cp*CoCl$_2$]$_2$ (2.5)	AgB(C$_6$F$_5$)$_4$ (12.5)	KOAc (10)	54
11[d]	[Cp*CoCl$_2$]$_2$ (2.5)	AgB(C$_6$F$_5$)$_4$ (12.5)	AgOAc (10)	45
12	--	AgB(C$_6$F$_5$)$_4$ (25)	AgOAc (20)	--

[a] Conditions: **2a** (1.0 equiv), **1a** (2.0 equiv) in 1,4-dioxane (2.0 M) for 24 h. *[b]* Determined by GC analysis relative to tetradecane as an external standard. *[c]* Isolated yield at 0.20 mmol scale. *[d]* Reverse stoichiometry: **2a** (2.0 equiv), **1a** (1.0 equiv).

The application of lower catalyst loadings resulted in a reduced yield, providing 63% yield with 2.5 mol % of [Cp*CoCl$_2$]$_2$ (entry 8) and 44% yield when only 1 mol % [Cp*CoCl$_2$]$_2$ was employed (entry 9). We decided to continue evaluation at 2.5 mol % of [Cp*CoCl$_2$]$_2$ due to the difficulty in evaluating minor differences at the near quantitative yield observed at higher catalyst loading. The use of KOAc as an alternative to AgOAc resulted in a slightly lower yield (entries 8 vs. 10), as did the reversal of stoichiometry (entry 11). Finally, no reaction occurred when only Ag salts and no [Cp*CoCl$_2$]$_2$ was added (entry 12), indicating that Cp*Co(III) is essential for C–H bond functionalization.

Although a high yield of indazole **3a** was obtained under the optimized Co-catalyzed conditions (entry 7, Table 1), our goal of identifying a cost effective earth abundant catalyst system was only partially realized because a significant mol % of the precious metal silver was still required. In particular, 25 mol % of AgB(C$_6$F$_5$)$_4$ was necessary to abstract the chlorides to generate the cationic Co(III) catalyst, with 20 mol % more silver contributed by the AgOAc additive needed to achieve high yields.

As a first step to eliminating any use of Ag salts, we developed an independent synthesis of the optimal catalyst [Cp*Co(C$_6$H$_6$)][B(C$_6$F$_5$)$_4$]$_2$ (**5**) that avoids the use of costly metals. We selected [Cp*Co(C$_6$H$_6$)](PF$_6$)$_2$ (**4**) as a viable starting point because Kanai and Matsunaga had prepared this complex without the use of Ag salts or other expensive reagents.[11g] Anion metathesis of complex **4** and commercially available potassium

tetrakis(pentafluorophenyl)borate can be conveniently performed on a multi-gram scale to provide the desired catalyst **5** (Scheme 1). A biphasic mixture of benzene/H$_2$O was selected as the solvent of choice for this reaction to partition KPF$_6$ into the aqueous phase while avoiding any potential exchange of the benzene ligand on the parent [Cp*Co^{III}(C$_6$H$_6$)] complex.

Scheme 1. Synthesis of [Cp*Co(C$_6$H$_6$)][B(C$_6$F$_5$)$_4$]$_2$ (5)
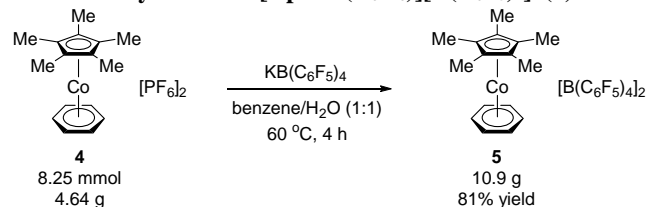
Preliminary evaluation of **5** in the C–H functionalization cascade to **3a** established a large increase in reactivity over **4** (Table 2, entries 1 vs. 2). In analogy to the observations for [Cp*CoCl$_2$]$_2$/AgB(C$_6$F$_5$)$_4$ in Table 1, the addition of silver acetate resulted in a dramatic improvement in the reaction yield (entries 3 and 4). We therefore sought to replace the precious metal additive AgOAc with earth abundant first row metal acetate salts.

We first investigated Cu(OAc)$_2$ because this additive had previously been observed to result in higher yields for Rh(III)-catalyzed transformations, including in transformations where Cu(II) did not serve as an oxidant.[22] While promising results were observed at 10 mol % (71%, entry 5), a significant reduction in yield was obtained at a higher loading (entry 6). Interestingly, although 10 mol % of Cu(OAc)$_2$(H$_2$O)$_4$ did not significantly influence reaction outcome (entry 7), at 20 mol % the tetrahydrate performed substantially better than anhydrous copper (II) acetate (entries 6 vs. 8). Based upon this observation, water was evaluated as an additive demonstrating that this transformation was not sensitive to moderate amounts of moisture (entries 9–11). In fact, water was slightly beneficial when 1.0 equivalent was employed providing **3a** in 53% yield. Turning our attention to other protic additives we found that AcOH proved highly effective (entry 12), and with these conditions achieved our goal of completely eliminating all precious metal additives from the reaction system.

Table 2. Optimization of Reaction Conditions for Indazole Synthesis with Catalyst 5 [a]
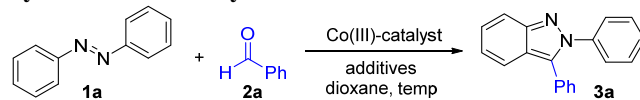
Entry	Preformed Co(III) catalyst (mol %)	Additive (mol %)	Temp (°C)	Yield (%)[b]
1	**4** (10)	--	130	2
2	**5** (10)	--	130	31
3	**5** (10)	AgOAc (10)	130	82
4	**5** (10)	AgOAc (20)	130	72
5	**5** (10)	Cu(OAc)$_2$ (10)	130	71
6	**5** (10)	Cu(OAc)$_2$ (20)	130	25
7	**5** (10)	Cu(OAc)$_2$(H$_2$O)$_4$ (10)	130	75
8	**5** (10)	Cu(OAc)$_2$(H$_2$O)$_4$ (20)	130	50
9	**5** (10)	H$_2$O (50)	130	45
10	**5** (10)	H$_2$O (1.0 equiv)	130	53
11	**5** (10)	H$_2$O (2.0 equiv)	130	27
12	**5** (10)	AcOH (10)	130	85
13	**5** (10)	AcOH (10)	100	87
14[c]	**5** (10)	AcOH (10)	100	90 (83)[d]
15	**5** (10)	AcOH (50)	130	71
16	**5** (10)	PivOH (10)	130	80
17	**5** (5)	AcOH (5)	130	67
18	**5** (5)	PivOH (5)	130	68

[a] Conditions: **2a** (1.0 equiv), **1a** (2.0 equiv) in 1,4-dioxane (2.0 M) for 24 h. *[b]* Determined by GC analysis relative to tetradecane as an external standard. *[c]* Reaction performed on the bench-top under nitrogen. *[d]* Isolated yield at 0.20 mmol scale.

Additional reaction parameters were investigated to enhance the practicality of the transformation. First, the reaction temperature was explored, and a comparable yield was observed at a temperature below the solvent boiling point (entries 13 and 14). Furthermore, rigorous glovebox conditions were not required, which allowed reactions to be conveniently set up on the bench-top (entry 14).

In previous reports of C–H functionalization, pivalic acid has proven to be superior to other organic acids.[23] However, when PivOH was used in place of AcOH, a similar yield was obtained (entries 12 vs. 16). This trend was also observed at lower acid and catalyst loading (entries 17 vs. 18). Ultimately, acetic acid was selected as the additive of choice due to lower cost.
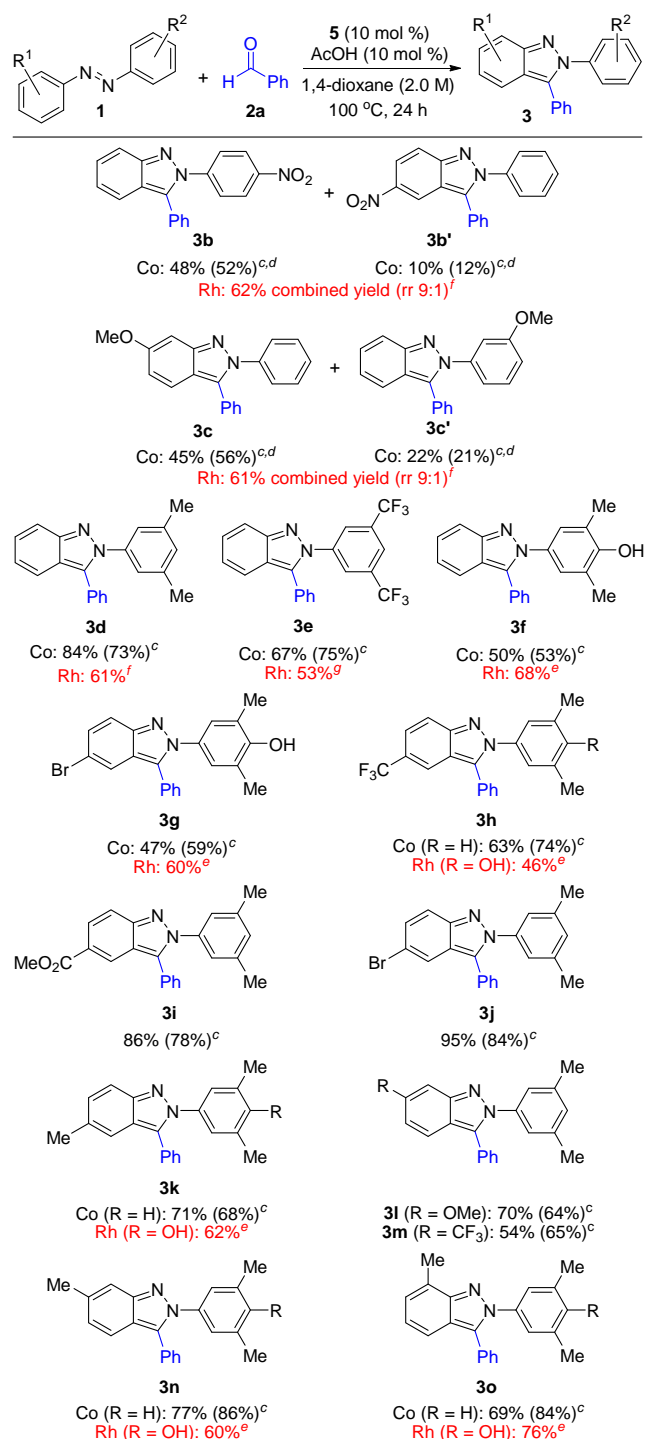
Having identified practical reaction conditions that were free of precious metals for the synthesis of **3a**, we next evaluated a series of unsymmetrical azobenzenes to determine the influence of steric and electronic parameters on the regioselectivity of this transformation (Table 3). In addition, the original conditions developed to generate cationic Cp*Co(III) in situ (Table 1) were also evaluated for each substrate to provide a comparative analysis of these two catalyst systems.

The major regioisomer obtained from the reaction of the para-nitro substituted azobenzene, (*E*)-1-(4-nitrophenyl)-2-phenyldiazene, resulted from C–H functionalization on the more electron-rich aromatic ring, providing fully separable regioisomers **3b** and **3b'** in a 4.6:1 ratio when the preformed catalyst **5** was used. Comparable results were seen when cationic Cp*Co(III) was generated in situ and the AgOAc additive was included, providing a 4.4:1 ratio of regioisomers **3b** and **3b'**. In a similar fashion, the meta-methoxy substituted azobenzene, (*E*)-1-(3-methoxyphenyl)-2-phenyldiazene, also underwent C–H functionalization on the more electron-rich aryl ring, furnishing products **3c** and **3c'** in 2.1:1 ratio of separable regioisomers with preformed catalyst **5**/AcOH and 2.7:1 ratio with [Cp*CoCl$_2$]$_2$/AgB(C$_6$F$_5$)$_4$/AgOAc. Notably, for both catalyst systems reaction on the meta-methoxy substituted aromatic ring only occurred at the less hindered of the two ortho sites to give regioisomer **3c**. These results are consistent with the yields and selectivity that we previously observed with Rh(III), although higher regioselectivities were observed with this precious metal catalyst.[7a]

Several 3,5-disubstituted azobenzenes containing both electron-withdrawing and electron-donating functionalities were also evaluated. Indazoles **3d** and **3e** were obtained as single regioisomers in good yield, establishing that steric effects dominate the regioselective outcome of this Cp*Co(III)-catalyzed reaction. With Rh(III) catalysis high regioselectivities albeit with slightly lower yields were previously observed for these substrates. In addition, a cleavable phenolic derivative was employed to access indazoles **3f** and **3g** in reasonable though lower yield than for the corresponding azobenzene lacking the hydroxyl substituent (see **3d**).[7a] For **3f** and **3g**, Rh(III) catalysts had previously provided somewhat higher yields.
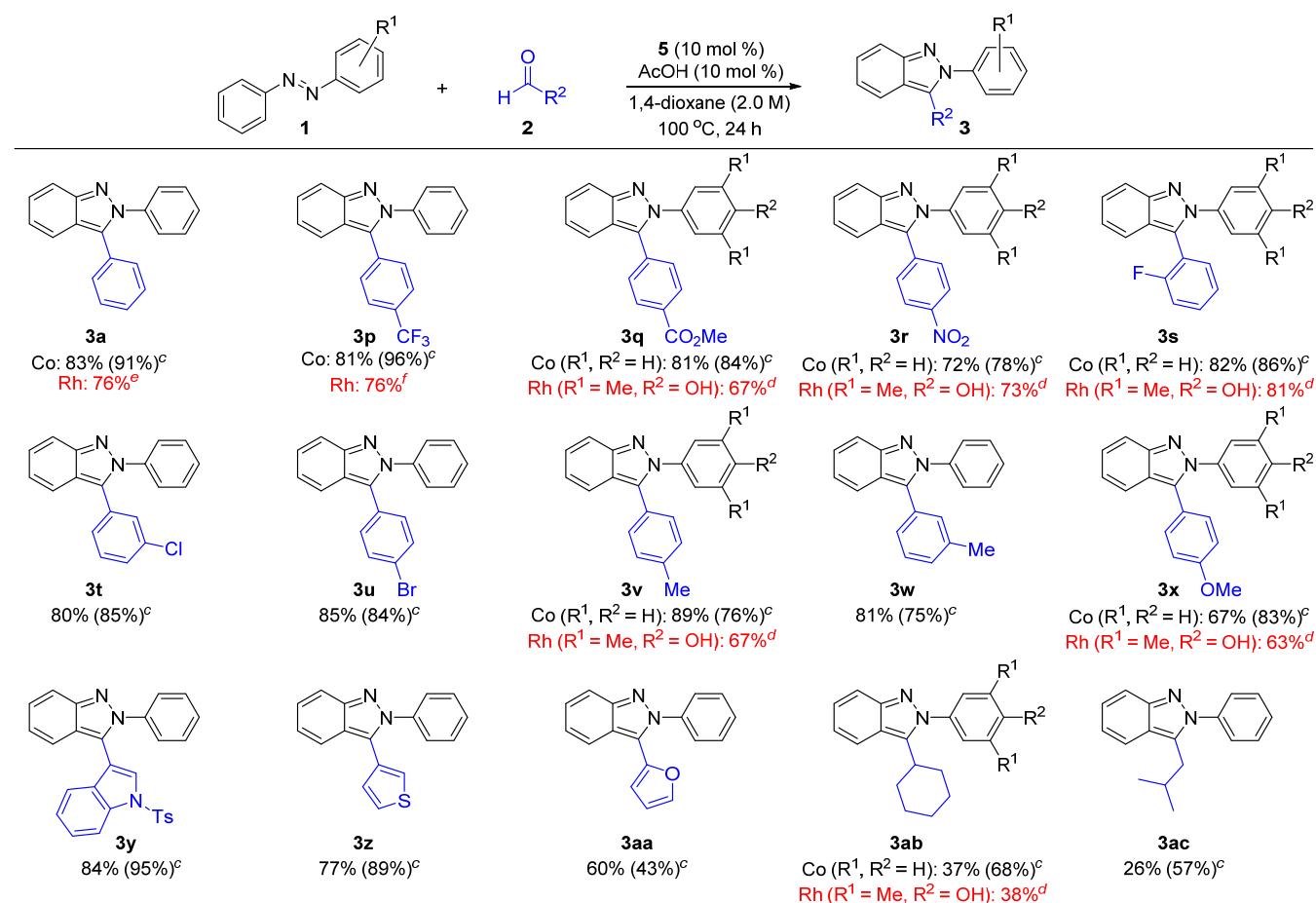
A series of 3,5-dimethyl substituted azobenzenes were then applied to the selective introduction of functionality to the indazole core (**3h**–**3o**, Table 3). Indazoles containing electron-poor (**3h**–**3i**, **3m**), electron-neutral (**3g**, **3j**–**3k**, **3n**–**3o**), and electron-rich (**3l**) substituents were all obtained in good yields. Moreover, functionality could be placed regiospecifically at the 5- (**3g**–**3k**), 6- (**3l**–**3n**) and 7-positions (**3o**) of the indazole ring. In cases where the same or closely related indazole products had previously been prepared using Rh(III) catalysis, comparable yields were observed (**3g**–**h**, **3k**, **3n**–**3o**).

Table 3. Azobenzene Substrate Scope [a,b]

3b
Co: 48% (52%)[c,d]

3b'
Co: 10% (12%)[c,d]

Rh: 62% combined yield (rr 9:1)[f]

3c
Co: 45% (56%)[c,d]

3c'
Co: 22% (21%)[c,d]

Rh: 61% combined yield (rr 9:1)[f]

3d
Co: 84% (73%)[c]
Rh: 61%[f]

3e
Co: 67% (75%)[c]
Rh: 53%[g]

3f
Co: 50% (53%)[c]
Rh: 68%[e]

3g
Co: 47% (59%)[c]
Rh: 60%[e]

3h
Co (R = H): 63% (74%)[c]
Rh (R = OH): 46%[e]

3i
86% (78%)[c]

3j
95% (84%)[c]

3k
Co (R = H): 71% (68%)[c]
Rh (R = OH): 62%[e]

3l (R = OMe): 70% (64%)[c]
3m (R = CF$_3$): 54% (65%)[c]

3n
Co (R = H): 77% (86%)[c]
Rh (R = OH): 60%[e]

3o
Co (R = H): 69% (84%)[c]
Rh (R = OH): 76%[e]

[a] *Co(III) conditions*: **2a** (0.20 mmol), azobenzene **1** (0.40 mmol), **5** (10 mol %) and AcOH (10 mol %) in 1,4-dioxane (2.0 M) at 100 °C for 24 h. [b] Isolated yields after silica gel chromatography. [c] *Co(III) in situ conditions:* **2a** (0.20 mmol), azobenzene **1** (0.40 mmol), [Cp*CoCl$_2$]$_2$ (5 mol % of Co dimer), AgB(C$_6$F$_5$)$_4$ (25 mol %), and AgOAc (20 mol %) in 1,4-dioxane (2.0 M) at 130 °C for 24 h. [d] Ratio of fully separable regioisomers. [e] *Rh(III) conditions:* azobenzene **1** (0.20 mmol), **2a** (0.40 mmol), [Cp*RhCl$_2$]$_2$ (5 mol % of Rh dimer), AgSbF$_6$ (20 mol %), and MgSO$_4$ (100 mg) in tetrahydrofuran (0.2 M) at 110 °C for 24 h. [f] Reaction was conducted in 1,4-dioxane (0.2 M). [g] Reaction was conducted in 1,4-dioxane (1.0 M).

Table 4. Aldehyde Substrate Scope for *N*-aryl-2*H*-Indazole Synthesis[a,b]

3a
Co: 83% (91%)[c]
Rh: 76%[e]

3p CF$_3$
Co: 81% (96%)[c]
Rh: 76%[f]

3q CO$_2$Me
Co (R^1, R^2 = H): 81% (84%)[c]
Rh (R^1 = Me, R^2 = OH): 67%[d]

3r NO$_2$
Co (R^1, R^2 = H): 72% (78%)[c]
Rh (R^1 = Me, R^2 = OH): 73%[d]

3s F
Co (R^1, R^2 = H): 82% (86%)[c]
Rh (R^1 = Me, R^2 = OH): 81%[d]

3t Cl
80% (85%)[c]

3u Br
85% (84%)[c]

3v Me
Co (R^1, R^2 = H): 89% (76%)[c]
Rh (R^1 = Me, R^2 = OH): 67%[d]

3w Me
81% (75%)[c]

3x OMe
Co (R^1, R^2 = H): 67% (83%)[c]
Rh (R^1 = Me, R^2 = OH): 63%[d]

3y N–Ts
84% (95%)[c]

3z S
77% (89%)[c]

3aa O
60% (43%)[c]

3ab
Co (R^1, R^2 = H): 37% (68%)[c]
Rh (R^1 = Me, R^2 = OH): 38%[d]

3ac
26% (57%)[c]

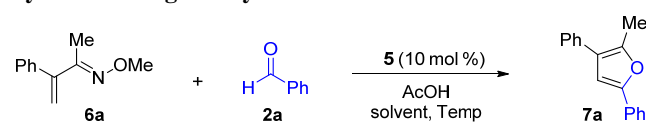[a] *Co(III) conditions:* aldehyde **2** (0.20 mmol), **1a** (0.40 mmol), **5** (10 mol %) and AcOH (10 mol %) in 1,4-dioxane (2.0 M) at 100 °C for 24 h. [b] Isolated yields after silica gel chromatography. [c] *Co(III) in situ conditions*: aldehyde **2** (0.20 mmol), **1a** (0.40 mmol), [Cp*CoCl$_2$]$_2$ (5 mol % of Co dimer), AgB(C$_6$F$_5$)$_4$ (25 mol %), and AgOAc (20 mol %) in 1,4-dioxane (2.0 M) at 130 °C for 24 h. [d] *Rh(III) conditions:* azobenzene **1** (0.20 mmol), aldehyde **2** (0.40 mmol), [Cp*RhCl$_2$]$_2$ (5 mol % of Rh dimer), AgSbF$_6$ (20 mol %), and MgSO$_4$ (100 mg) in tetrahydrofuran (0.2 M) at 110 °C for 24 h. [e] Reaction was conducted in 1,4-dioxane (0.2 M). [f] Reaction was conducted in 1,4-dioxane (1.0 M).

A variety of aldehydes were next evaluated (Table 4). Both electron-poor (**3p–t**) and electron-rich (**3v–x**) aldehydes coupled efficiently. Indazoles bearing diverse functionality such as trifluoromethyl (**3p**), methyl ester (**3q**), nitro (**3r**), fluoro (**3s**), chloro (**3t**), bromo (**3u**), methyl (**3v–3w**), and methoxy (**3x**) substituents were obtained in good to excellent yields. Moreover, ortho (**3s**), meta (**3t**, **3w**) and para (**3p–r**, **3u**, **3v**, **3x**) substitution patterns were well tolerated. Heterocycles such as an indole (**3y**), a thiophene (**3z**), and a furan (**3aa**) could be introduced in excellent to moderate yields. Even additions to the alkyl aldehydes cyclohexanecarboxaldehyde and isovaleraldehyde proceeded to give indazoles **3ab** and **3ac**, respectively, in reasonable yields. Notably, in the case of substrate **3aa** bearing a furanyl substituent, the Ag-free conditions developed for preformed catalyst **5** provided a noticeably higher yield. On the other hand, for substrates **3ab** and **3ac** derived from alkyl aldehydes, in situ preparation of the Co catalyst with use of the AgOAc additive gave better results, thus demonstrating the complementary nature of these two catalyst systems. We had previously evaluated many of these aldehydes for Rh(III)-catalyzed indazole synthesis (**3a**, **3p–3s**, **3v**, **3x**, **3ab**). Although a direct comparison cannot be made because different azobenzenes were employed in most cases, it is readily apparent that both Co(III) and Rh(III) catalysts show a comparable high level of functional group compatibility.
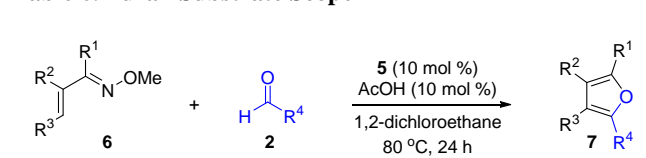
We next explored the possibility of extending this Co(III)-catalyzed aldehyde addition and cyclative capture approach to include the synthesis of highly functionalized furans **7** from α,β-unsaturated oximes **6** (Table 5). For the optimization studies we employed the oxime as the limiting reagent because aldehydes are generally readily available and inexpensive while the oxime must be prepared from the corresponding α,β-unsaturated ketone. For convenience and practicality, we also focused on preformed catalyst **5** and Ag free conditions. The use of 10 mol % of AcOH with 1,4-dioxane as the solvent was first employed because these conditions were optimal for indazole synthesis (entry 1). While a good yield was obtained, considerable improvement in yield to 83% was observed upon replacing 1,4-dioxane with THF (entry 2). A significant decrease in yield resulted when the reaction was conducted below the solvent boiling point (entries 3 and 4). However, use of DCE provided a comparable yield at both 100 °C and 80 °C (entries 5 and 6, respectively). The lower temperature was selected for further experiments to allow for large scale reactions to be conducted under reflux instead of in a sealed tube (vide infra). Finally, removing the AcOH catalyst resulted in much lower conversion (entry 7).

Table 5. Optimization of Reaction Conditions for Furan Synthesis using Catalyst 5[a]

Entry	Solvent	AcOH loading	Temp (°C)	Yield (%)[b]
1	Dioxane	10 mol %	100	64
2	THF	10 mol %	100	83
3	THF	10 mol %	80	74
4	THF	10 mol %	65	56
5	DCE	10 mol %	100	79
6	DCE	10 mol %	80	80 (67)[c]
7	DCE	--	80	25

[a] *Conditions:* **6a** (1.0 or 2.0 equiv), **2a** (1.0 or 2.0 equiv) in solvent (2.0 M) for 24 h. [b] Determined by GC analysis relative to tetradecane as an external standard. [c] Isolated yield at 0.20 mmol scale.

The substrate scope was explored with a range of α,β-unsaturated oximes **6** and aldehydes **2** (Table 6). Oximes lacking R^3 substitution resulted in trisubstituted furans **7a**–**7k** in good to excellent yields. Tetrasubstituted furan **7l** with a fused bicyclic framework was also prepared, albeit in lower yield. With respect

Table 6. Furan Substrate Scope[a,b]

[a] *Co(III) conditions: O*-methyl oxime **6** (0.20 mmol), aldehyde **2** (0.40 mmol), **5** (10 mol %) and AcOH (10 mol %) in 1,4-dichloroethane (2.0 M) for 24 h. [b] Isolated yields after silica gel chromatography. [c] *Rh(III) conditions: O*-methyl oxime **6** (0.20 mmol), aldehyde (0.40 mmol), [Cp*RhCl₂]₂ (5 mol % of Rh dimer), and AgSbF₆ (20 mol %) in tetrahydrofuran (0.3 M) at 90 °C for 24 h. [d] Reaction was conducted using [Cp*RhCl₂]₂ (10 mol % of Rh dimer) and AgSbF₆ (40 mol %).

to aromatic aldehydes, this transformation exhibited a broad scope and was compatible with fluoro (**7b**), chloro (**7c–7d**), bromo (**7e**), methyl ester (**7f**), methyl (**7g**), and trifluoromethyl (**7j–l**) functionality. Moreover, a good yield was obtained for sterically hindered ortho (**7b**) and meta (**7c**, **7g**) functionalities. Unactivated alkyl aldehydes were also tolerated affording furans **7h** and **7i** in moderate yield.

For almost all of the furans that we had previously prepared with Rh(III) catalysis, Co(III) provided comparable yields. The one exception is for tetrasubstituted furans such as **7l**, for which Rh(III)-catalysis provided considerably higher yields.[24]
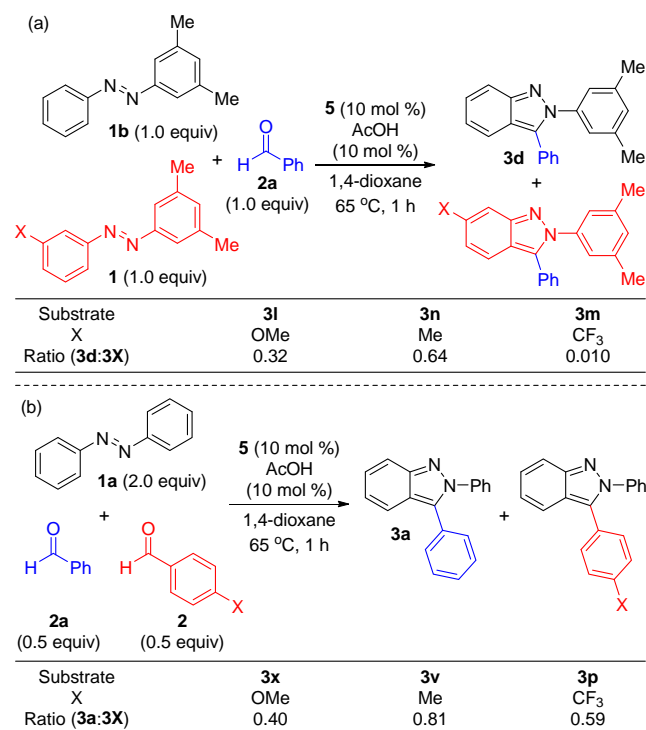
To evaluate the scalability these C–H functionalization cascades and to further demonstrate the robust nature of catalyst **5**, 20 mmol scale reactions were performed on the bench-top under reflux (Scheme 2). Indazole **3z** was accessed in 74% yield (4.08 g), comparable to the small-scale procedure (Table 3).[25] Additionally, furan **7j** was synthesized in 72% yield (4.34 g), which was a nearly identical yield to that obtained on smaller scale.

Scheme 2. Gram-Scale Indazole and Furan Synthesis using Catalyst 5
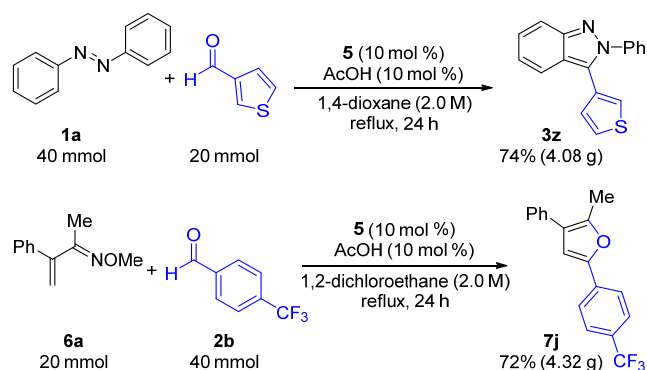
We performed several experiments to provide insight into the mechanism for aldehyde additions followed by cyclative capture and focused these studies on indazole synthesis. First, several competition experiments were performed at low conversion to determine the effect of electronics upon rate of conversion (Scheme 3).

Substituted azobenzenes were first explored (Scheme 3a) because this component is involved in each step of the catalytic cycle (vide infra). For all of the competition experiments, azobenzene **1b** proceeded to highest conversion affording indazole **3d**. Electron-rich methoxy and methyl-substituted azobenzenes (indazoles **3l** and **3n**, respectively) gave only modestly lower conversion than the unsubstituted derivative. In contrast, the azobenzene bearing a trifluoromethyl group, gave dramatically lower conversion to indazole **3m**. We hypothesize that two factors are primarily responsible for the dramatically lower conversion to **3m**. First, the electron-deficient trifluoromethyl group may slow the rate of C–H bond activation based upon studies on the effect of electronics on concerted-metallation-deprotonation for related Cp*Rh(III) complexes.[26] Second, the alcohol intermediate resulting from aldehyde addition cyclizes by intramolecular nucleophilic displacement of the hydroxyl group by either an S_N1 or S_N2 process. This cyclization would be expected to be slower when the electron-deficient trifluoromethyl group is present.

Scheme 3. Azobenzene and Aldehyde Competition Experiments to Analyze Electronic Effects

(a)

Substrate	3l	3n	3m
X	OMe	Me	CF₃
Ratio (**3d:3X**)	0.32	0.64	0.010

(b)

Substrate	3x	3v	3p
X	OMe	Me	CF₃
Ratio (**3a:3X**)	0.40	0.81	0.59

A series of aromatic aldehydes with different electronic properties were also subjected to competition experiments (Scheme 3b). Benzaldehyde (**2a**) gave higher conversion than both electron-rich (indazoles **3x** and **3v**) and -deficient (indazole **3p**) aldehydes. These results suggest that competing effects may lead to a substrate dependent change in the rate-limiting step. The electron-rich aldehyde 4-methoxybenzaldehyde has increased resonance stabilization, and therefore a lower equilibrium for the alcohol product resulting from C–H addition to the aldehyde. However, donating substituents would also be expected to facilitate cyclization by nucleophilic displacement of the hydroxyl group. On the other hand, the electron-deficient 4-trifluoromethylbenzaldehyde should result in a more favorable equilibrium for the alcohol product, but might also slow cyclization (vide supra). Regardless of electronic effects, it is important to note that good yields of indazoles **3** are obtained in nearly all cases (see Tables 3 and 4).

The reversibility of the cyclometallation step was next evaluated by subjecting site specifically deuterated azobenzene **1f** to the reaction conditions (Scheme 4a). After stopping the reaction at low conversion, a significant level of protio-deutero scrambling had occurred in both the recovered starting material and product.[27] A similar result was obtained for azobenzene **1g** deuterated solely on the aromatic ring with 3,5-dimethyl substitution (Scheme 4b). These results clearly indicate that while the steric hindrance introduced by 3,5-disubstitution completely prevents indazole formation on this disubstituted ring (see Table 3), cyclometallation readily occurs as evidenced by the extensive protio-deutero scrambling.

Scheme 4. Reversibility of Co(III)-Catalyzed C–H Functionalization using Deuterated Azobenzenes

(a)

(b)
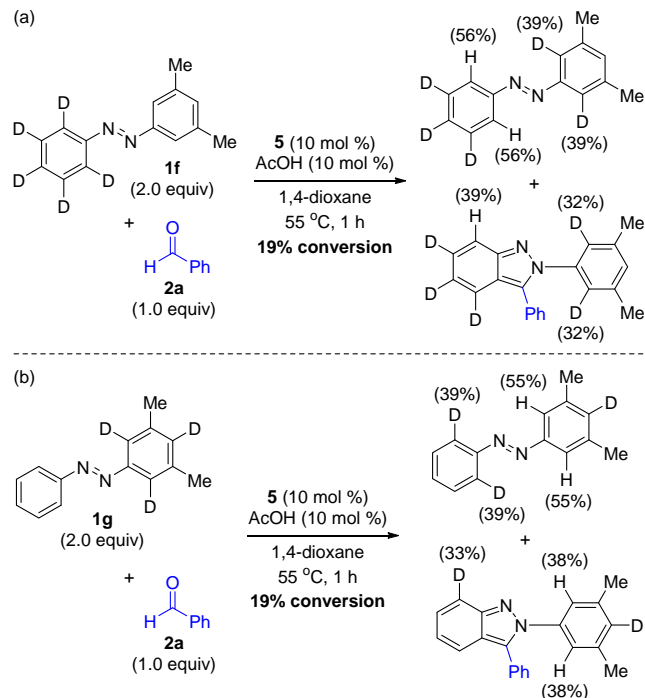
To assess the reversibility of Co(III)-catalyzed aldehyde insertion, the aldehyde addition product **8a** was prepared independently and then subjected to the reaction conditions in the presence of **2c** (Scheme 5). A mixture of indazoles **3a** and **3v** was obtained. Even though we had previously shown that 4-methylbenzaldehyde is converted to the product more slowly than benzaldehyde (see Scheme 3), a significant percentage of indazole **3v** is still produced. Furthermore, azobenzene (**1a**) was observed in the final reaction mixture, albeit in only 3% yield. These results conclusively indicate that the Co(III)-catalyzed C–H bond addition to aldehydes is reversible, which is consistent with other metal-catalyzed C–H bond additions to aldehydes.[28]

Scheme 5. Reversibility of Co(III)-Catalyzed Aldehyde Insertion using a Synthetic Intermediate
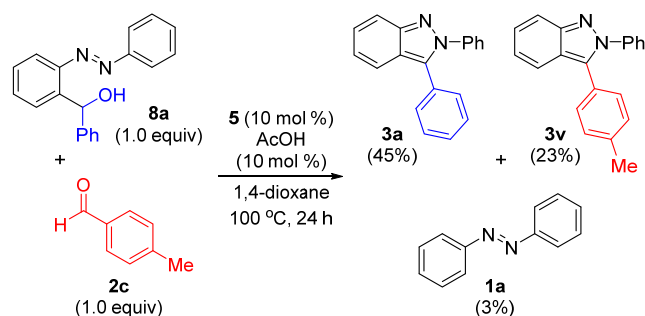
A potential mechanistic pathway for this C–H functionalization/addition/cyclization cascade is depicted in Scheme 6.[29] Thermal loss of the benzene from **5** provides the active catalyst. Coordination of azobenzene **1** is followed by reversible formation of cobaltacycle **9**.[30] Reversible aldehyde coordination and migratory insertion affords cobaltacycle **11**. Protonation of this metallacycle releases the alcohol intermediate **8** and regenerates the active catalyst. Cyclative capture of **8** then

proceeds via an intramolecular nucleophilic substitution reaction with concomitant release of H_2O to furnish **12**. This species then rearomatizes to afford the desired indazole **3**.

Scheme 6. Proposed Mechanism of Co(III)-Catalyzed C–H Functionalization/Addition/Cyclization Cascade
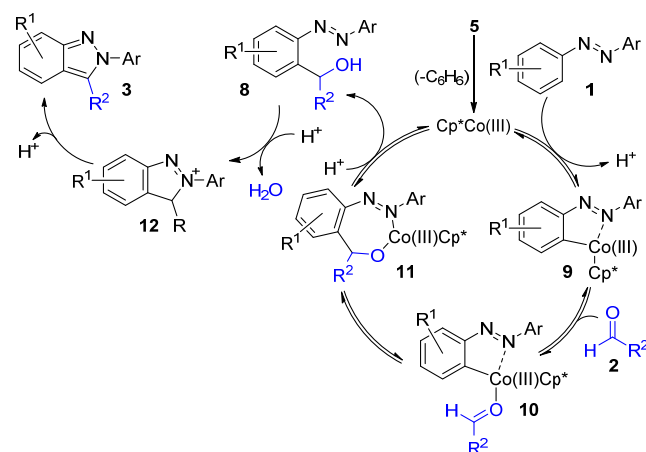
■ CONCLUSION

In summary, we have developed the first examples of cobalt-catalyzed C–H bond functionalization with additions to aldehydes. By employed azo and oxime directing groups, which have not previously been applied to Cp*Co(III)-catalyzed C–H bond functionalization, cyclative capture and aromatization is then achieved to enable the single step, convergent assembly of *N*-aryl-2*H*-indazoles and furans, respectively. A wide range of aryl, hetero, and alkyl aldehydes participate in these reactions to provide efficient access to highly substituted heterocycles. These transformations can be performed on the bench-top, under standard reflux conditions, and on large scale.

Successful implementation of these practical conditions necessitated that we develop a new air-stable cationic catalyst, $[Cp*Co(C_6H_6)][B(C_6F_5)_4]_2$ (**5**). Additionally, while AgOAc was initially identified as a key additive for obtaining acceptable reaction yields, after extensive evaluation we established that this precious metal additive could be replaced with sub-stoichiometric quantities of AcOH as a very low cost and simple to handle alternative. The air-stable cobalt catalyst and convenient bench-top reaction conditions should hopefully be applicable to other C–H bond functionalization reactions.

Supporting Information

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

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Notes

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(28) The reversibility of Rh(III)-catalyzed C–H bond addition to aldehydes has been previously demonstrated. (a) Chen, K.; Li, H.; Lei, Z.-Q.; Li, Y.; Ye, W.-H.; Zhang, L.-S.; Sun, J.; Shi, Z.-J. *Angew. Chem., Int. Ed.* **2012**, *51*, 9851. (b) Zhang, X.-S.; Li, Y.; Li, H.; Chen., K.; Lei, Z.-Q.; Shi, Z.-J. *Chem. Eur. J.* **2012**, *18*, 16214. (c) Li, H.; Li, Y.; Zhang, X.-S., Chen, K.; Wang, X.; Shi, Z.-J. *J. Am. Chem. Soc.* **2011**, *133*, 15244.

(29) For relevant mechanistic studies demonstrated for Rh(III)-catalysis, see: (a) reference 26; (b) Tauchert, M. E.; Incarvito, C. D.; Rheingold, A. L.; Bergman, R. G.; Ellman, J. A. *J. Am. Chem. Soc.* **2012**, *134*, 1482. (c) Li, Y.; Zhang, X.-S.; Li, H.; Wang, W.-H.; Chen, K.; Li, B.-J.; Shi, Z.-J. *Chem. Sci.* **2012**, *3*, 1634. (d) Li, L.; Brennessel, W. W.; Jones, W. D. *J. Am. Chem. Soc.*, **2008**, *130*, 12414.

(30) For an independent synthesis of a cobaltacycle, see reference 11e.

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R^1

N=N–Ar

H

+ **R^2CHO**

Cp*Co(III)

R^1

N=N

N–Ar

R^2

R^2 = aryl, heteroaryl, alkyl   29 examples

R^1

R^2

N–OMe

R^3

H

+ **R^4CHO**

Cp*Co(III)

R_1

R^2

O

R^3

R^4

R^4 = aryl, alkyl   12 examples