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Cobalt-Catalyzed Carbocyclization of *o*-Iodobenzaldehydes and *o*-Iodophenylketones with Alkynes

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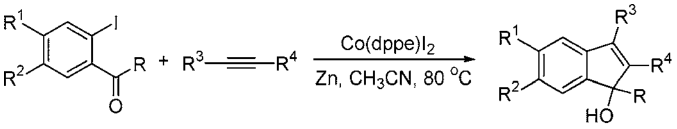
ABSTRACT



1a-g **2a-h** **3a-s**

Treatment of various *o*-iodobenzaldehydes and *o*-iodophenyl ketones with alkynes in the presence of Co(dppe)I_2 and Zn powder in acetonitrile at 80 °C afforded the corresponding indenols in moderate to excellent yields with exceedingly high regioselectivity. For most unsymmetrical alkynes tested, the carbocyclization gave a single regioisomer.

Transition metal-mediated transformation of aryl halides into various organic compounds has become an exceedingly powerful method in organic synthesis.[1,2] Palladium and nickel complexes are generally the catalysts for these reactions due to the facile oxidative addition of aryl halides to Pd and Ni(0) metal complexes. On the other hand, cobalt complexes are well-known catalysts for $[2 + 2 + 2]$[3,4] and $[2 + 2]$[5] cycloaddition reactions, Pauson−Khand reaction,[6] hydroformylation,[7] and en-yne reductive coupling.[8] The use of the cobalt complexes as catalysts for the activation of aryl and alkyl halides has started to draw attention only very recently.[9] Oshima et al. described a cobalt-catalyzed Heck-type reaction of alkyl halides with styrenes via a single electron-transfer mechanism.[9a] Cahiez and Knochel reported cobalt-catalyzed coupling reactions of alkenyl halides with organozinc[9b] and organomagnesium[9c] reagents. Gosmini et al. reported the synthesis of arylzinc compounds from aryl bromides catalyzed by $CoBr_2$ (10−20 mol %) in the presence of $ZnBr_2$ and zinc dust.[9d] Activation of zinc dust by CF_3COOH was needed, and a catalytic amount of ArBr (10 mol %) was used to avoid the formation of ArH.

Indenols[10−13] are an important class of organic compounds known for several important biological activities such as analgesic and insecticidal properties.[14,15] Palladium complexes were shown to catalyze the carbocyclization of disubstituted alkynes with *o*-bromobenzaldehydes and *o*-

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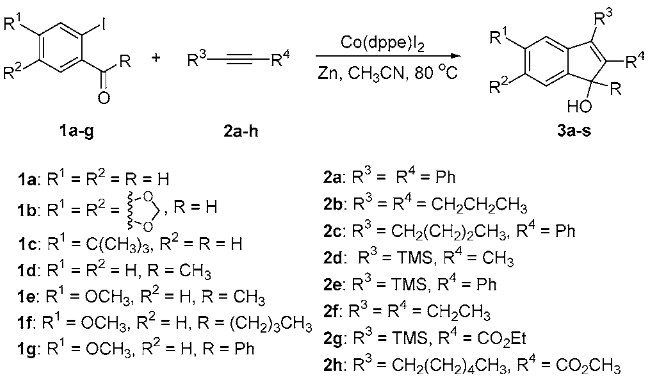
bromophenyl ketones to give indenols.[12] We also reported that nickel complexes exhibit similar catalytic properties for the carbocyclization of propiolates with *o*-iodophenyl ketones.[16] Our interest in cobalt-catalyzed reactions[4,5,8] and the recent attention of activation of aryl halides by complexes of the cobalt family[9] have prompted us to investigate the catalytic activity of cobalt complexes for the carbocyclization of *o*-iodobenzaldehydes and *o*-iodophenyl ketones with alkynes. Herein, we report for the first time that cobalt phosphine complexes successfully catalyze the reaction under mild conditions to afford indenol derivatives with excellent regioselectivity and in high yields. Surprisingly, the present cobalt catalyst system is more competitive than the palladium and nickel system for the synthesis of indenols. This result opens a new direction for the activation of Ar-X bond with cobalt complexes.

The reaction of 2-iodobenzaldehyde (**1a**) with diphenylacetylene (**2a**) in the presence of $Co(PPh_3)_2I_2$ and zinc metal powder in acetonitrile at 80 °C for 3 h proceeded to give indenol **3a** in 22% yield (Scheme 1). The yield of **3a** was greatly improved to 85%, when $Co(dppe)I_2$ (dppe = bis(diphenylphosphino)ethane) was used as the catalyst. The structure of **3a** was established on the basis of its ^1H and ^{13}C NMR and mass data. Control experiments indicated that in the absence of either $Co(dppe)I_2$ or zinc metal, no desired product was observed in the reaction.

Scheme 1



Similarly, various iodobenzaldehydes (**1a**−**c**) and alkynes (**2a**−**e**) undergo carbocyclization in the presence of $Co(dppe)I_2$ and zinc powder to give the corresponding indenols **3a**−**h** in 54~85% yields. A small amount of reduction products *o*-iodobenzyl alcohols was observed for these reactions. The results are summarized in Table 1 (entries 1−8). For unsymmetrical alkynes, the regioselectivity is generally excellent. Two regioisomers **3e** and **3e′** with a ratio of 88/12 were obtained for 1-phenyl-1-hexyne, but only one regioisomer was detected for MeC≡CTMS (**2d**, entry 6) and PhC≡CTMS (**2e**, entries 7−8). The regiochemistry of these products as shown in Table 1 was carefully assigned on the basis of NOE experiments. The major isomer **3e** from **1a** and **2c** has the phenyl group next to the hydroxy moiety, while for products **3f**−**h**, the TMS group is away from the hydroxy moiety.

The carbocyclization of *o*-iodophenyl ketones with alkynes also proceeds smoothly to furnish the corresponding indenols. As shown in Table 1 (entires 9−19), the reaction of 2-iodoacetophenone (**2d**) with alkynes **2a**−**g** afforded the corresponding indenols **3i**−**p** in excellent yields. The carbocyclization of **2d** with unsymmerical alkynes is highly regioselective. For alkyne **2c**, regioisomers **3k**/**3k′** were obtained in a 89/11 ratio, while for trimethylsilyl alkynes **2d** and **2e**, only one regioisomer was found. The regiochemistry of **3k**−**m** is similar to that of *o*-iodobenzaldehyde reaction. For propiolates **2g** and **2h**, the cyclization also proceeds smoothly to afford single regioisomers **3o** and **3p**, respectively (Table 1). Similarly, the reaction of substituted iodophenyl ketones **1e**−**g** with **2a** produced substituted indenol in good to excellent yields (entries 17−19).

Scheme 2

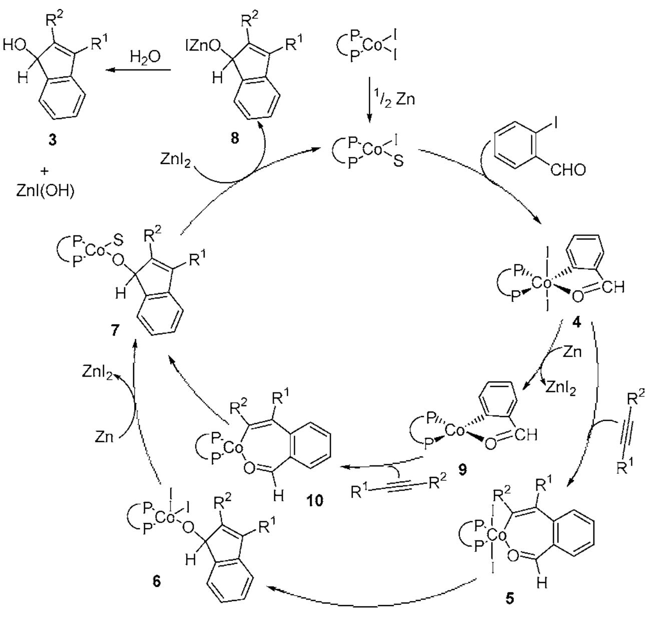


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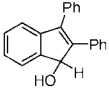
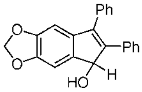
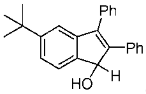
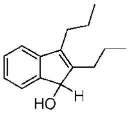
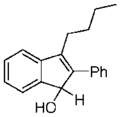
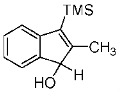
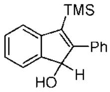
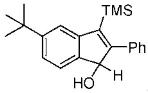
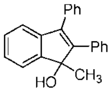
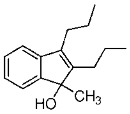
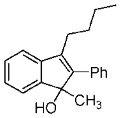
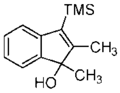
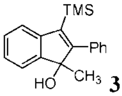
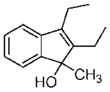
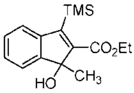
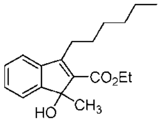
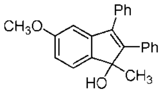
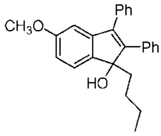
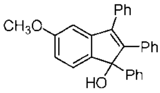
Table 1. Results of Cobalt-Catalyzed Carbocyclization of *o*-Iodobenzaldehydes and Iodophenyl Ketone (**1**) with Alkynes (**2**)[a]

Entry	1	2	Product	Yield (%)[b]
1	**1a**	**2a**	 **3a**	85
2	**1b**	**2a**	 **3b**	70
3	**1c**	**2a**	 **3c**	82
4	**1a**	**2b**	 **3d**	54
5	**1a**	**2c**	 **3e/3e'**	80 (88:12)
6	**1a**	**2d**	 **3f**	60
7	**1a**	**2e**	 **3g**	58
8	**1c**	**2e**	 **3h**	57
9	**1d**	**2a**	 **3i**	93
10	**1d**	**2b**	 **3j**	99
11	**1d**	**2c**	 **3k/3k'**	95 (89:11)
12	**1d**	**2d**	 **3l**	95
13	**1d**	**2e**	 **3m**	89
14	**1d**	**2f**	 **3n**	99
15	**1d**	**2g**	 **3o**	95
16	**1d**	**2h**	 **3p**	97
17	**1e**	**2a**	 **3q**	99
18	**1f**	**2a**	 **3r**	76
19	**1g**	**2a**	 **3s**	85

[a] Reaction conditions: *o*-iodobenzaldehyde or *o*-iodophenyl ketone (1.00 mmol), alkyne (1.50 mmol), Co(dppe)I_2 (0.050 mmol; 5.0 mol %), Zn (2.75 mmol), CH_3CN (3.0 mL) at 80 °C for 3 h. [b] Isolated yields; isomeric ratios are in parentheses.

Compared with the corresponding palladium- and nickel-catalyzed reactions, the present cobalt-catalyzed carbocyclization shows several advantages. The reactions conditions are mild, and a very short reaction time (only 3 h) is needed for completion. Moreover, the yields are generally excellent (entries 9−19) and obtained with very high regioselectivity for the unsymmetrical alkynes used.

The exact mechanism for the present catalytic reaction is not yet clear, but on the basis of the known cobalt chemistry, the following pathway (Scheme 2) is proposed. Reduction of Co(II) to Co(I) by zinc dust initiates the catalysis. Oxidative addition of *o*-iodobenzaldehyde to Co(I) species affords an *o*-metalated benzaldehyde cobalt complex **4** with both the *o*-carbon and the aldehyde oxygen bonded to the cobalt(III) center. Intermediate **4** undergoes insertion with an alkyne to generate a seven-membered cobaltacycle **5**. Intramolecular nucleophilic addition of the cobalt−carbon bond in **5** to the aldehyde group leads to the formation of cobalt alkoxide **6**. Reduction of the latter by zinc powder affords a Co(I) alkoxide **7**. Transmetalation of **7** with ZnI_2 generates the active Co(I) species and the corresponding zinc alkoxide **8**, which is converted to the final product **3** after hydrolysis. Oxidative addition of aryl halides to cobalt(I) has been proposed in a cobalt-mediated reaction,[9d] although no such oxidative additon product has been isolated previously. An alternative pathway involving the reduction of Co(III) species **4** by zinc metal to Co(I) intermediate **9**, followed by insertion of an alkyne to give **10**, cannot be totally excluded.

In summary, we have demonstrated that the Co(dppe)I_2/Zn system successfully catalyzed the carbocyclization reaction of *o*-iodobenzaldehydes and *o*-iodophenyl ketones with alkynes to afford indenols in high regioselectivity and excellent yields. The cobalt system appears to be more efficient than the palladium and nickel catalysts for this carbocyclization reaction. The success of this cobalt-catalyzed carbocyclization certainly will encourage more research on the reaction of aryl or alkenyl halides with unsaturated carbon−carbon bonds using complexes of the cobalt family as the catalyst. Further work in this direction is underway.

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Supporting Information Available: Preparation details, characterization data, and ^{1}H NMR spectra of all compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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