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Cobalt(III)-catalyzed efficient synthesis of indenones through carboannulation of benzoates and alkynes†

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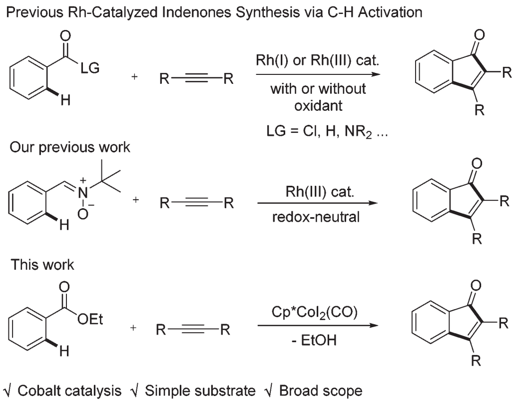
Cobalt(III)-catalyzed C–H activation of simple benzoate esters has been achieved, and redox-neutral annulative coupling with internal alkynes allowed efficient synthesis of indenones. The employment of the weak and simple ester directing group makes it an attractive protocol in carbocycle synthesis.

In the past few decades, transition metal-catalyzed C–H functionalization of arenes has been widely employed as an advantageous strategy to streamline chemical synthesis without prefunctionalization of arenes.[1] Among the transition metals, cobalt(III) has attracted increasing attention owing to its earth-abundance, low cost, low toxicity, and unique catalytic reactivity compared with heavy metal congeners such as Rh(III) and Ir(III).[2] Indeed, various types of C–C and C-heteroatom bond-forming reactions have been developed *via* cobalt-catalyzed C–H activation recently, as in the reports by Kanai/Matsunaga,[3] Glorius,[4] Ackermann,[5] Ellman,[6] Daugulis,[7] Chang,[8] and others.[9] However, compared to the well established Rh(III) catalysis,[10] only a handful examples of C–H activation systems have been realized *via* cobalt(III) catalysis that lead to construction of heterocycles,[11] and the construction of carbocycles is even unprecedented.

Indenones are important structural motifs that have found broad applications in synthetic chemistry, medicinal chemistry, and materials science.[12] Thus, the development of synthetic methods to access the indenone skeleton *via* an efficient C–H activation pathway has attracted increasing attention over the past few decades (Scheme 1).[13] For example, under rhodium catalysis the annulative couplings of aroyl chlorides,[14] benzaldehydes,[15] and benzamides[16] with internal alkynes delivered indenones as a result of *ortho*-functionalization. Recently, we reported mild indenone synthesis *via* Rh(III)-catalyzed carbocyclization between arylnitrones and alkynes under redox-neutral conditions.[17] In spite of the progress, these coupling systems mostly relied heavily on precious late metal catalysts and/or tediously synthesized substrates. Thus, the development of a more readily available substrate for the construction of the indenone framework in an efficient and atom-economical fashion using an inexpensive cobalt catalyst is highly desirable. We identified benzoate esters as a suitable candidate owing to their low cost and ready availability. While Shi and coworkers briefly demonstrated their application in Rh(III)-catalyzed indenone synthesis in one example, the efficiency was low.[16b] We reasoned that the weak directing effect of the ester group called for a more Lewis acidic metal. Therefore, Co(III) catalysts likely make efficient catalysts in that the stronger ligation of the ester directing group should favor the C–H activation. In addition, the stronger nucleophilicity of the cobalt alkenyl species should lead to more favorable interactions with the weakly electrophilic ester group. We now report cobalt(III) catalyzed C–H activation of benzoates with subsequent annulative coupling with internal alkynes, leading to efficient synthesis of indenones.



Scheme 1 Transition metal-catalyzed indenone synthesis.

We commenced our studies by examining the reaction parameters of the coupling between ethyl benzoate (**1a**) and diphenylacetylene (**2a**) in the presence of a cobalt(III) catalyst (Table 1). While traces of the product were detected using

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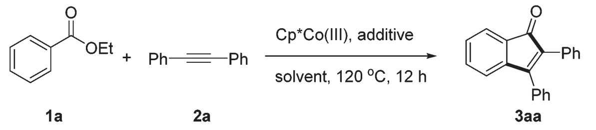
Table 1 Screening of reaction conditions[a]

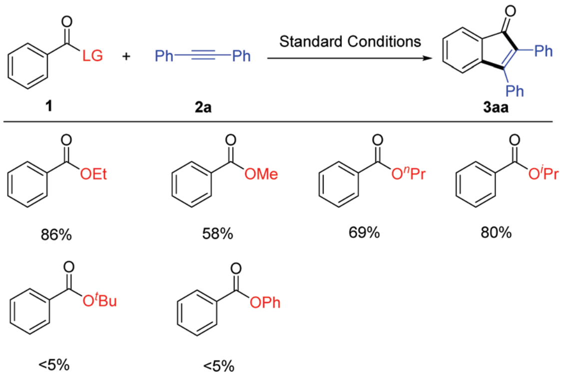


Entry	Cat. (mol%/20 mol%)	Additive	Solvent	Yield[b] (%)
1	$[Cp^*CoI_2]_2(5)/AgNTf_2$	—	HFIP[c]	<5
2	$[Cp^*CoI_2]_2(5)/AgNTf_2$	NaOAc	HFIP	<5
3	$[Cp^*CoI_2]_2(5)/AgNTf_2$	$Cu(OAc)_2$	HFIP	21
4	$[Cp^*CoI_2]_2(5)/AgOAc$	$Cu(OAc)_2$	HFIP	<5
5	$[Cp^*CoI_2]_2(5)/AgNTf_2$	$Zn(OAc)_2$	HFIP	46
6	$[Cp^*CoCl_2]_2(5)/AgNTf_2$	$Zn(OAc)_2$	HFIP	55
7	$Cp^*Co(CO)I_2(10)/AgNTf_2$	$Zn(OAc)_2$	HFIP	86
8	$Cp^*Co(CO)I_2(10)/AgSbF_6$	$Zn(OAc)_2$	HFIP	72
9	$Cp^*Co(CO)I_2(10)/AgNTf_2$	$Zn(OAc)_2$	TFE	76
10	$Cp^*Co(CO)I_2(10)/AgNTf_2$	$Zn(OAc)_2$	DCE	69

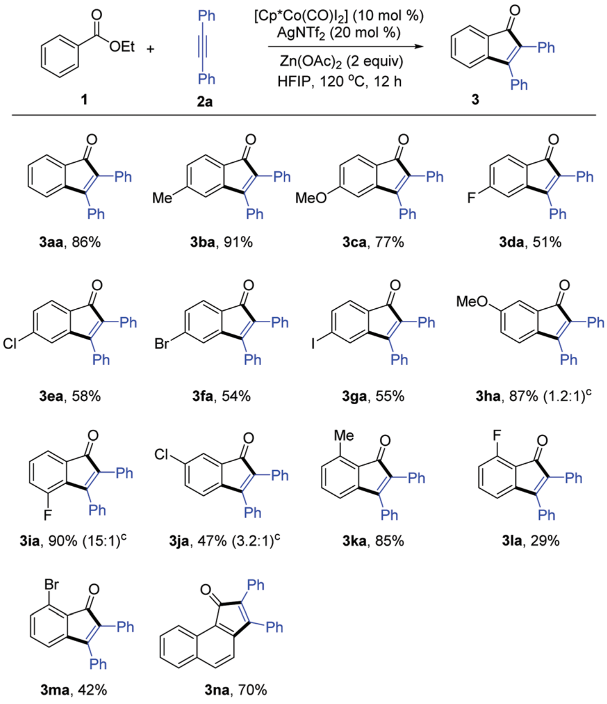
[a] Reaction conditions: ethyl benzoate (**1a**, 0.2 mmol), diphenylacetylene (**2a**, 0.24 mmol), catalyst/silver salt, additive (2.0 equiv.), solvent (2 mL),120 °C, 12 h, pressure tube under N_2. [b] Isolated yield after column chromatography. [c] HFIP = 1,1,1,3,3,3-hexafluoro-iso-propanol.

$[Cp^*CoI_2]_2/AgNTf_2$ as a catalyst with or without a NaOAc additive (Table 1, entries 1 and 2), switching the additive to $Cu(OAc)_2$ improved the efficiency and the desired indenone **3aa** was isolated in 21% yield using HFIP as a solvent (entry 3). No desired product was observed when AgOAc was used as an additive (entry 4). Various cobalt catalysts were then screened (entries 5 and 6) and $Cp^*Co(CO)I_2$ proved to be the optimal catalyst, affording product **3aa** in 86% isolated yield (entry 7). In contrast, a lower yield was obtained when $AgSbF_6$ was used as a halide scavenger (entry 8). Screening of the solvents revealed that other solvents tended to give inferior results (entries 9 and 10).

The effects of the ester group were further examined by following the optimized conditions (Scheme 2). It turned out that other esters such as methyl, *n*-propyl, and *i*-propyl esters were all applicable, affording the indenone product in 58–80% yield. In contrast, essentially no desired product was obtained when *t*-butyl or phenyl benzoate was used as an arene substrate, indicating that both steric and electronic effects of the leaving group played an important role.



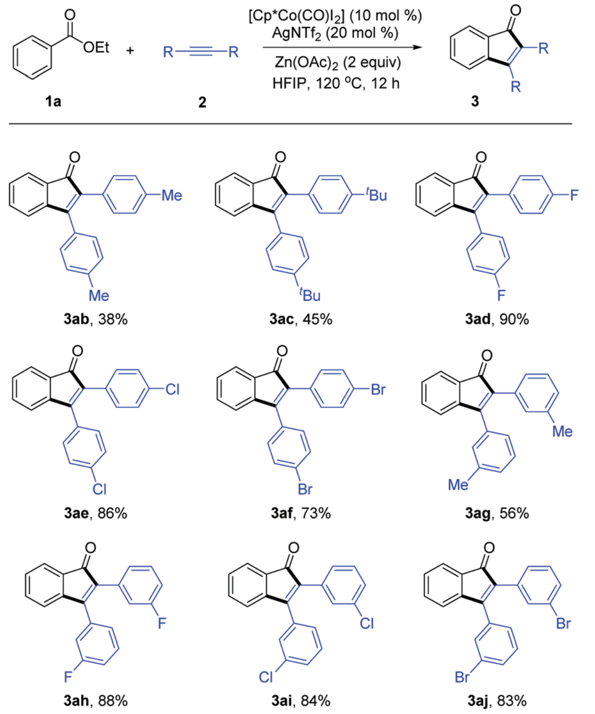
Scheme 2 Effects of the leaving group. Reaction conditions: benzoate esters (**1**, 0.2 mmol), diphenylacetylene (**2a**, 0.24 mmol), HFIP (2 mL), $Zn(OAc)_2$ (2.0 equiv.), 120 °C, 12 h, sealed tube under N_2. Isolated yield after column chromatography.



Scheme 3 Scope of ethyl esters. Reaction conditions: ethyl esters (**1**, 0.2 mmol), diphenylacetylene (**2a**, 0.24 mmol), HFIP (2 mL), $Zn(OAc)_2$ (2.0 equiv.), 120 °C, 12 h, sealed tube under N_2. Isolated yield after column chromatography. Regioselectivity ratio (determined by ^1H NMR spectroscopy).

With the optimized reaction conditions in hand, we first examined the scope and generality of the reaction (Scheme 3). A wide variety of ethyl benzoates bearing various electron-donating and halogen groups at the *para* position were compatible, giving the coupled products **3aa**–**3ga** in 51–91% yields. It was observed that introduction of an electron-withdrawing group caused a slight decrease of the reaction efficiency. Various *meta*-substituted substrates also proceeded efficiently at both the *ortho* positions with low to good regioselectivities (1.3–15 : 1). In contrast to the reactions of **3ha** and **3ja**, ethyl 3-fluorobenzoate reacted in high yield (90%) and excellent regioselectivity (15 : 1) at the more hindered *ortho* position (**3ia**) with the assistance of the ligating effect of the F atom and its reduced steric bulk.[18] Moreover, *ortho*-substituted ethyl benzoates were also tolerated (**3ka**–**3na**). The benzoates could also be extended to ethyl 1-naphthoate in good yield (**3oa**).

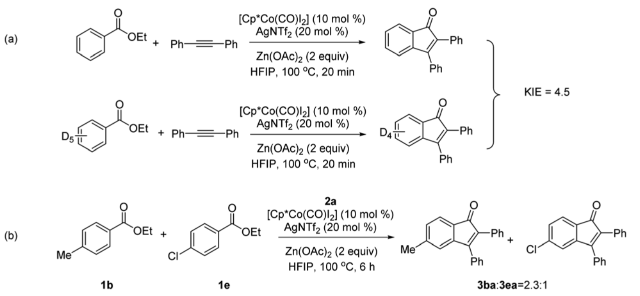
The scope of diarylacetylenes was next investigated (Scheme 4). The substituent in the diarylacetylene exhibited profound electronic effects, with a lower efficiency being observed for an EDG-functionalized diarylacetylene (**3ab** and **3ac**). Various diarylacetylenes with electron-withdrawing groups at the *para* position of the phenyl ring all reacted smoothly to give moderate to high yields (**3ad**–**3af**). In



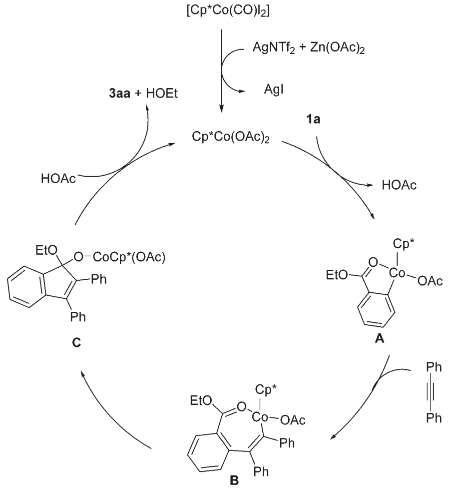
Scheme 4 Scope of the alkyne substrates. Reaction conditions: ethyl benzoate (**1a**, 0.2 mmol), diarylacetylenes (**2**, 0.24 mmol), HFIP (2 mL), $Zn(OAc)_2$ (2.0 equiv.), 120 °C, 12 h, sealed tube under N_2. Isolated yield after chromatography.

addition, diarylacetylenes with substituents such as methyl and halide groups at the *meta* position were also tolerated. In contrast, aryl-, alkyl- alkynes or internal aliphatic alkynes only reacted with poor efficiency under the standard conditions.

To gain some insights into the reaction mechanism, several experiments were conducted (Scheme 5). A kinetic isotope effect (KIE) value of 4.5 was obtained using **1a** and **1a**-d_5 by two side-by-side reactions in the coupling with **2a** at a low conversion. This result indicated that the C–H bond cleavage is likely involved in the turnover-limiting step. When an equimolar mixture of **1b** and **1e** was allowed to compete under the standard conditions in the coupling with diphenylacetylene **2a**, two indenones were obtained in 2.3 : 1 ratio, where an electron-rich benzoate reacted preferentially.



Scheme 5 Mechanistic studies.



Scheme 6 Proposed mechanism.

On the basis of our mechanistic experiments and previous reports,[11k] a plausible catalytic cycle is given in Scheme 6. An active catalyst $[Cp^*Co(OAc)_2]$ was generated from the ligand substitution between the cobalt catalyst precursor and $AgNTf_2$ and $Zn(OAc)_2$. C–H activation of ethyl benzoate gives a five-membered metallacyclic intermediate **A.** Alkyne insertion gives a seven-membered Co(III) alkenyl species **B**, which undergoes migratory insertion of the alkenyl group into the carbonyl group, affording a Co(III) alkoxide species **C**. Protonolysis of **C** by HOAc regenerates the active catalyst and releases the final product. The beneficial effect of $Zn(OAc)_2$ may originate from its role in enhancing the electrophilicity of the ester moiety though coordination with zinc(II), which facilitates insertion of the vinyl-Co bond into the carbonyl group.

Conclusions

In summary, a Cp*Co(III)-catalyzed annulation between benzoates and alkynes has been developed under redox-neutral conditions, which expands the applications of high valent cobalt(III) catalysts in the synthesis of diverse compounds. Starting from commercially available benzoates and their derivatives, a range of functionalized indenones were constructed with this protocol. Moreover, this catalytic system is highly efficient over a broad range of substrates with good functional group tolerance.

Acknowledgements

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