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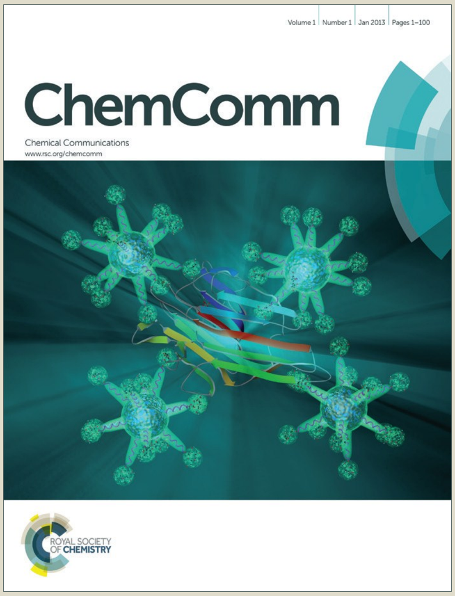

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Cobalt(III)-Catalyzed Annulation of Esters and Alkynes: A Facile Route to Indenones

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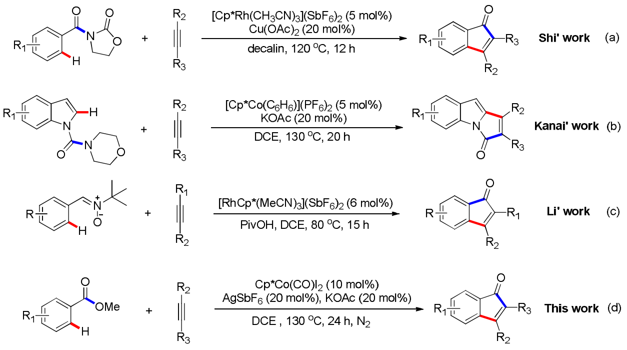
An efficient protocol for the synthesis of indenones has been developed from the annulation of benzoic esters and internal alkynes by exploiting cobalt catalyst.

Transition metal-catalyzed reactions involving C-H activation have attracted considerable interest because these transformations do not require the prefunctionalization of C-H bonds and thus change the way that chemists approach the complex molecules by allowing nontraditional retrosynthetic disconnections.[1] In particular, the C-M organometallic species generated from the direct metalation of C-H bonds is capable to undergo the nucleophilic addition reactions with polar multiple bonds to construct C-C and C-X bonds.[2] In the past decades, significant advances have been achieved for the additions of C-TM (TM = transition metal) upon aldehydes,[3] ketones,[4] imines,[5] amides,[6] and nitrile[3e,7] by using Pd,[5h,7] Rh,[3f-j,4c-d,5a-e,6a] Ru,[4e,6g]Re,[3c] Ir,[3a-b,4a-b] Mn,[3d-e] and Co catalysts.[3k,5f-g,6b-f] Ester is one of the most fundamental functional groups and has long been the subject of investigation in preparative organic chemistry.[8] However, the addition of C-TM species via C-H cleavage upon esters[9] remains the challenge due to the lower electrophilicity of esters.

Indenones are useful skeletons in pharmaceutical and material sciences, and much interest has focused on the development of approaches to indenones.[10] In 2012, Shi and coworkers demonstrated the rhodium-catalyzed annulation of benzimides and alkynes in the presence of 20 mol % $Cu(OAc)_2$ to give indenones (Scheme 1a).[6a] In this transformation, benzoic ester was sluggish to give the indenones in 42% GC yield. More recently, Kanai, Matsunaga, and coworkers reported the C2 site-selective annulation of N-carbamoylindoles with alkynes for the synthesis of the pyrroloindolones by the use of low cost cobalt catalyst (Scheme 1b).[6b] For the first time, they demonstrated the unique nucleophilic reactivity of organocobalt species toward the carbamoyl group. However, the addition of C-TM nucleophilic species to esters remains the challenge. Li and co-workers reported the rhodium-catalyzed annulations of *N*-tert-butyl-α-arylnitrones with internal alkynes(Scheme 1c).[5c] In this reaction, nitrone functions as an electrophile to capture the C-TM nucleophilic species. Herein, we report the cobalt-catalyzed annulation of benzoic esters with internal alkynes (Scheme 1d). It is found that the alkenyl-Co species, which is generated by insertion of alkyne into site-selective *ortho* C-H activation intermediate of benzoic esters, processes high nucleophilic activity to undergo the nucleophilic addition into the esters. This transformation provides a complementary route to important indenone motifs occurring prevalently in bioactive molecules, ligand scaffolds, and material science.



Scheme1. Transition metal-catalyzed annulation of alkynes and amides/esters via C-H activation.

We initially set out to optimize the reaction with methyl 4-methoxybenzoate (**1a**) and diphenylacetylene (**2a**) as model substrates and the results are summarized in Table 1. $[Cp^*RhCl_2]_2$ was firstly examined by using $Cu(OAc)_2$ or KOAc as additives in the presence of $AgSbF_6$ (20 mol%) in DCE (1 mL) at 130 °C for 24 h (entries 1-2). However, the expected indenone **3aa** was only obtained in trace. To our delight, the desired annulation product **3aa** was obtained in 32% (entry 3) by

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Electronic Supplementary Information (ESI) available: Condition screening, Generalprocedures, Mechanisticexperiments, characterization data and NMR spectra. See DOI: 10.1039/x0xx00000x

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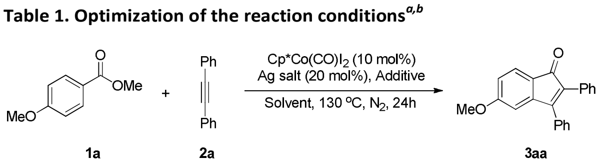
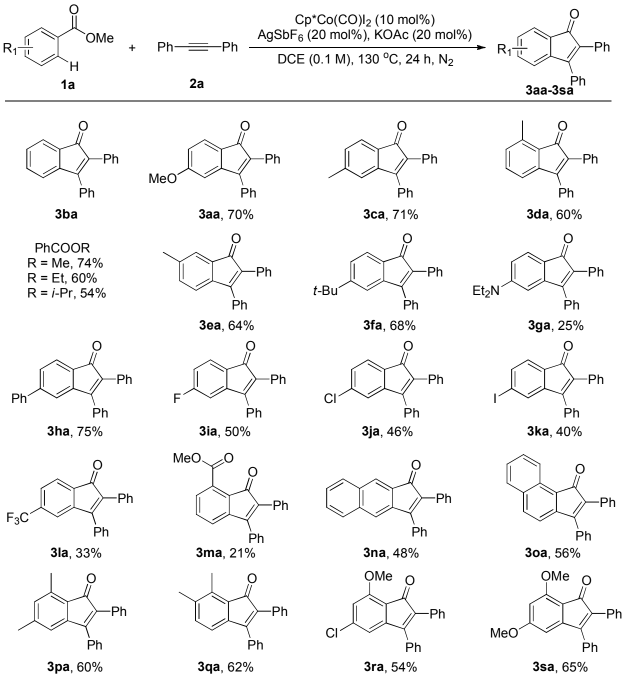
Table 1. Optimization of the reaction conditions[a,b]



Entry	Catalyst (mol%)	Ag salt	Additive (mol%)	Yield(%)[b]
1	$[Cp^*RhCl_2]_2$ (5)	$AgSbF_6$	KOAc (20)	NR
2[c]	$[Cp^*RhCl_2]_2$ (5)	$AgSbF_6$	$Cu(OAc)_2$ (20)	6
3	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$	$Cu(OAc)_2$ (20)	32
4	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$	AgOAc(20)	25
5	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$	NaOAc (20)	54
6	**$Cp^*Co(CO)I_2$ (10)**	**$AgSbF_6$**	**KOAc (20)**	**70**
7	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$	KOPiv (20)	65
8	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$	AdCOOK (20)	Trace
9	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$	MesCOOK(20)	40
10	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$	PhCOOK(20)	Trace
11	$Cp^*Co(CO)I_2$ (10)	$AgNTf_2$	KOAc (20)	50
12	$Cp^*Co(CO)I_2$ (10)	$AgBF_4$	KOAc (20)	NR
13	$Cp^*Co(CO)I_2$ (10)	$AgPF_6$	KOAc (20)	NR
14	$Cp^*Co(CO)I_2$ (10)	AgOTf	KOAc (20)	NR
15[d]	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$	KOAc (20)	trace
16	$Cp^*Co(CO)I_2$ (10)	none	KOAc (20)	NR
17	$Cp^*Co(CO)I_2$ (10)	$AgSbF_6$	none	NR
18	none	$AgSbF_6$	KOAc (20)	NR
19	$Co(OAc)_2$ (10)	$AgSbF_6$	KOAc (20)	NR
20	$CoCl_2$ (10)	$AgSbF_6$	KOAc (20)	NR

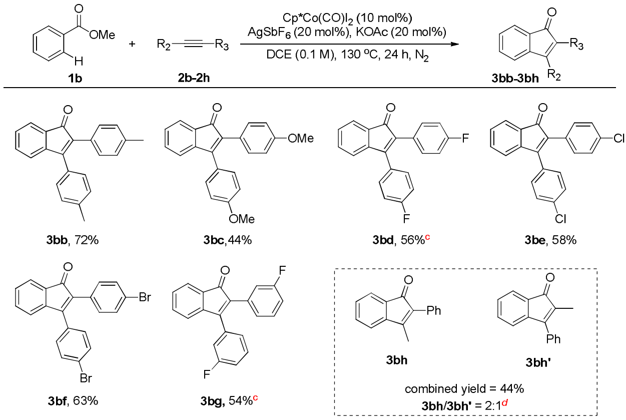
[a]Reaction conditions: substrate **1a** (0.1 mmol), diphenylacetylene**2a** (0.15 mmol), $Cp^*Co(CO)I_2$ (10 mol%), $AgSbF_6$ (20 mol%), KOAc (20 mol%), DCE (1 mL), 130 °C, N_2, 24 h. [b]Isolated yields. [c]determined by GC-MS. [d]Solvent was TFE (1 mL).

employing 10 mol % $Cp^*Co(CO)I_2$, showing the unique catalytic properties of cobalt catalyst over the rhodium catalysts in this reaction. Since the carboxylate anion accelerates the C-H metalation via a base-assisted concerted deprotonation,[11] we examined a series of carboxylate anions with different cation partners, and KOAc provided the optimal results (entries 3-10). It was found that Ag salts had a significant impact on the reaction.[12] No product was detected when AgOTf, $AgBF_4$, and $AgPF_6$ were employed (entries 12-14). The use of $AgNTf_2$ gave the yield to 50% (entry 11), and $AgSbF_6$ provided the highest yield (entry 6). The addition of Lewis acids such as $Cu(OTf)_2$, $Sc(OTf)_3$ and $Zn(OTf)_2$ was not capable to improve the reaction (See the ESI[†]).[13] Among the different solvents tested, DCE showed the best efficiency (See the ESI[†]). CF_3CH_2OH, a widely-used solvent in Co(III)-catalyzed C-H activation reactions, gave the desired product in trace (entry 15). No reaction was observed in the absence of cobalt catalyst or silver/carboxylate salts (entries 16-18). Simple cobalt salts were ineffective (entries 19-20).



Scheme 2. Scope of esters in the synthesis of substituted indenones[a,b] [a]Reaction conditions: substrate **1** (0.1 mmol), diphenylacetylene**2a** (0.15 mmol), $Cp^*Co(CO)I_2$ (10 mol%), $AgSbF_6$ (20 mol%), KOAc (20 mol%), DCE (1 mL), 130 °C, N_2, 24 h. [b]Isolated yields.

With the establishment of the optimized conditions, we first evaluated the scope of esters with diphenylacetylene **2a** as a counterpart (Scheme 2). It was found that the alkoxy part of esters had an obvious influence on the reaction efficiency. For example, the methyl benzoate gave the indenone **3ba** in 74% yield, but ethyl/isopropyl benzoates afforded the product **3ba** in the diminished yields. A significant electronic effect of arenes was observed in this annulations reaction. The esters with various electron-donating groups such as methoxyl (**3aa**), alkyl (**3ca, 3fa**), *N,N*-diethylamino (**3ga**) and phenyl (**3ha**) showed the good reactivity to give the desired products in moderate to good yields. However, the esters with electron-withdrawing groups such as halide (**3ia-3ka**) afforded the corresponding indenones in relatively lower yields. The strong electron-withdrawing substituents such as trifluoromethyl (**3la**) and ester (**3ma**) gave the desired indenones, but in low yields. Both *α*- and *β*-naphthylesters participated in the reaction smoothly to furnish the annulation products (**3na-3oa**) efficiently. The esters bearing the methyl groups at the *ortho* and *meta* positions gave the desired products in the slightly diminished yields, which might be attributed to the steric hindrance (**3da**, and **3ea** respectively). To our delight, this annulation reaction was not limited to monosubstituted esters.



Scheme3. Scope of alkynes in the synthesis of multisubstituetedindenones[a,b] [a]Reaction conditions: substrate **1a** (0.1 mmol), alkynes **2** (0.15 mmol), $Cp^*Co(CO)I_2$ (10 mol%), $AgSbF_6$ (20 mol%), KOAc (20 mol%), DCE (1 mL), 130 °C, N_2, 24 h. [b]Isolated yields. [c]140°C. [d]determined by ^{1}H-NMR.

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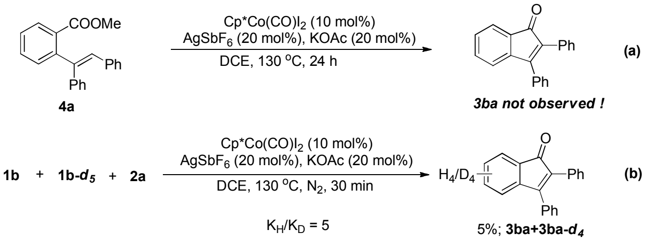
The disubstituted esters (**3pa-3sa**) were smoothly transformed into the corresponding products as well with acceptable yields under the optimized condition. The acrylate esters and heteroarene esters failed to give the desired products on the reaction conditions.

We next examined the scope of the alkynes in the coupling with methyl benzoate **1a** (Scheme 3). A variety of symmetrical internal alkynes reacted smoothly with the ester and provided the corresponding products in moderate to good yields (**3bb-3bg**). The halides such as bromide, chloride were well tolerated in the reaction, which provided ample opportunity for further derivatization of the obtained indenones (**3be, 3bf**). The unsymmetrical internal alkynes participated in the reaction smoothly to give the two regioisomers **3bh** and **3bh'** in a 2:1 ratio (**3bh/3bh'**). Terminal alkynes and symmetrical alkyl alkynes was inactive.



Scheme 4.Mechanistic studies.

In order to gain insights into the mechanism, the preliminary experiments were performed as shown in Scheme 4. The GC–MS analysis was performed with the reaction solution and the annulation product **3ba** was observed, accompanied with the formation of the hydroarylation product **4a**.[14] We supposed that the olefin **4a** might be the intermediate. To probe this, the olefin **4a** was synthesized and treated under the standard reaction condition. To our surprise, no desired product was observed. This result indicated that the olefin **4a** was not capable to cyclize under the reaction conditions.

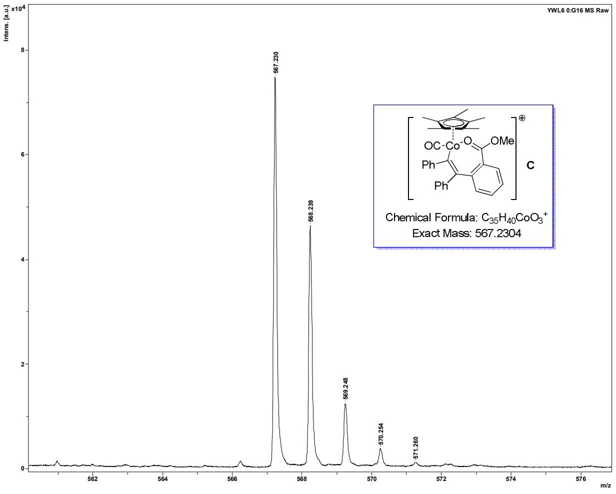
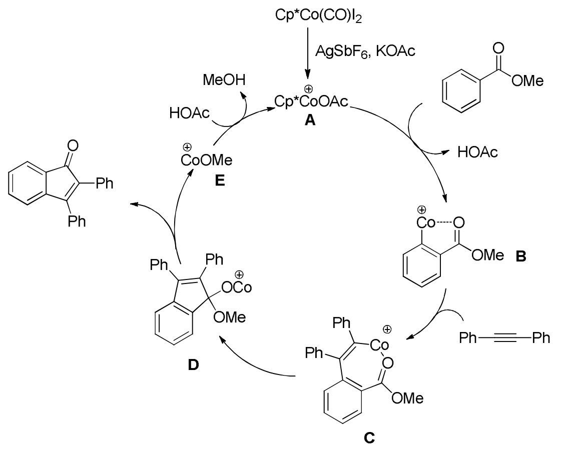


Fig. 1 Matrix-assisted laser desorption ionization time-of-flight mass spectroscopy (MALDI-TOF-MS) of **C** (exact mass: 567.2304) obtained from the reaction of **1b** and **2a** under standard conditions for 1h.

Furthermore, we measured the KIE in the intermolecular competitive experiment and a large KIE value of 5 was observed, suggesting that the initial C-H bond activation may be involved in the rate-limiting step. We also performed a MALDI-TOF analysis experiment using a mixture of the reaction solution reacted for 1 h. A series of signals identified with species **C** are detected as shown in **Fig. 1** (See the ESI[†]), displaying the possible presence of alkenyl-Co(III) species in the catalytic cycle.

Based on the our mechanistic studies and previous reports,[6,9] a plausible catalytic cycle is proposed as shown in Scheme 5. Iodide abstraction from precatalyst Cp*Co(CO)I$_2$ by AgSbF$_6$ and the subsequent ligand exchange generates the catalyst **A**, which undergoes the ester-assisted C-H metalation of to yield the cobaltacycle **B**. The migratory insertion of alkynes into cobaltacycle **B** forms the intermediate **C**, which was observed by MALDI-TOF as shown in **Fig. 1** (See the ESI[†]). The Co–C bond of intermediate **C** undergoes migratory insertion into the ester to form the intermediate **D**, which undergoes the elimination to give the product and produce the Co(III) alkoxide species **E**. The protonolysis of the metal alkoxide **E** regenerates Co(III) catalyst to fulfil the catalytic cycle.



Scheme 5. Proposed mechanism.

In conclusion, we have developed a cobalt(III)-catalyzed annulation of benzoate with internal alkynes for the facile synthesis of indenones. The reaction shows good functional group compatibility. Notably, cobalt catalyst displayed the unique catalytic reactivity over the rhodium catalyst to give the annulation products in high efficiency. Further studies to explore the cobalt(III)-catalyzed C-H functionalizations are ongoing in our lab.

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