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Ligand-Controlled Divergent C—H Functionalization of Aldehydes with Enynes by Cobalt Catalysts

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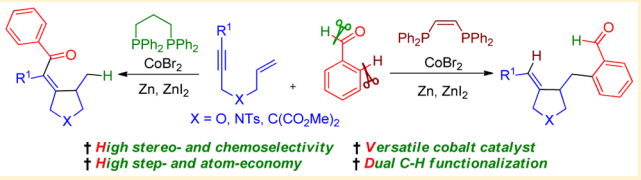
Supporting Information

ABSTRACT: We describe a highly step and atom economical cobalt-catalyzed cyclization of 1,6-enynes with aldehydes to synthesize functionalized pyrrolidines and dihydrofurans with high chemo- and stereoselectivity. The catalytic reaction plausibly proceeds via the cobaltacycle intermediate generated from the reaction of enyne substrate with cobalt catalyst, followed by switchable C—H functionalization of weakly coordinating aldehydes depending on the electronic nature of the ligand.



1. INTRODUCTION

Catalytic and selective functionalization of the C—H bond to more versatile functional groups has become a viable strategy for step- and atom-economical C—C bond formation.[1] Among the elegant methods available, directing group-assisted transition-metal-catalyzed selective C—H functionalization reaction provides a powerful and convenient route to construct C—C and C—X (X = hetero atoms) bonds.[2] Despite the fact that a number of valuable directing groups have been used, the weekly coordinating aldehyde-assisted C—H bond activation is highly challenging due to the overoxidation of aldehyde under strong oxidizing reaction conditions in most of the methodologies. Moreover, a number of competitive reactions including decarbonylation[3] and hydroacylation of alkenes and alkynes with aldehyde[4] are also possible in the presence of metal complexes as the catalyst. Hence, aldehyde-directed ortho arylation,[5] alkenylation,[6] and oxygenation[7] were only established using Ru or Pd as the catalyst. Notably, these types of C—H activations are underdeveloped with more abundant first-row transition metals.

Recently, cobalt-catalyzed directing group assisted C—H functionalization has received greater attention due to its intriguing reactivity and selectivity.[8] However, until now, only nitrogen atom-based directing groups such as imine, pyridine, and amide were employed and studied extensively. The *ortho*-C—H functionalization reactions of weakly coordinating carbonyl compounds are rather limited.[2s,9] In this context, we recently reported a cobalt-catalyzed *ortho*-C—H functionalization of aryl ketones and esters with enynes.[10] In this reaction, a Co(III) metallacycle generated from enyne and Co(I) is proposed to be an active intermediate for the *ortho*-C—H functionalization. During this study, we found that the reaction of benzaldehyde with enyne **1a** predominately gave a hydroacylation product **4aa**. To our surprise, the *ortho*-C—H functionalized hydroarylation product was obtained only in trace. This unexpected result is also attractive because the hydroacylation reaction of aldehyde with enynes is hardly studied.[12e]

Our continuous interest in metal-catalyzed C—H functionalization and enyne coupling reactions[11] prompted us to develop a reliable method that can selectively give hydroarylation or hydroacylation product. Here, we present a ligand controlled highly chemo- and stereoselective cobalt-catalyzed hydro-acylation and -arylation reactions of enynes with aldehydes affording functionalized pyrrolidines and dihydrofurans in good to excellent yields.

2. RESULTS AND DISCUSSION

2.1. Cobalt-Catalyzed *ortho*-C—H Functionalization of Aldehydes. Our initial investigation focused on the search for suitable reaction conditions for the hydroarylation of enyne **1a** with benzaldehyde **2a**. Nevertheless, the hydroacylative cyclized product **4aa** was obtained in good yield in the presence of $CoBr_2$ (5.0 mol %), Zn (10.0 mol %), ZnI_2 (10.0 mol %), and 1,2-bis(diphenylphosphino)propane (dppp) (5.0 mol %) in dichloromethane at 40 °C for 12 h (Table 1, entry 1). The reaction is highly chemo- and stereoselective; the carbonyl insertion takes place at the alkyne moiety of **1a** and the exocyclic double bond of product **4aa** is in *E* configuration. While changing the ligand from dppp to dppe, the reaction gave a mixture of hydroarylative and hydroacylative cyclized products with a **3aa**/**4aa** ratio of 81:19 in 70% combined yield (Table 1, entry 2). These results encouraged us to investigate the influence of different ligands in the enyne cyclization reaction. It is noteworthy that the monodentate phosphine and bidentate nitrogen ligands were completely ineffective for both cyclization reactions (Table 1, entries 3−5).

Next, we further screened the commonly used bidentate phosphine ligands. The smaller-bite-angle dppm (Table 1, entry 6) as well as larger-bite-angle diphosphines such as dppb (entry

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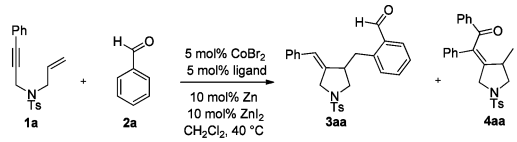
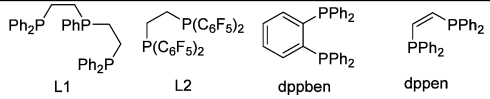
Table 1. Optimization Studies[a,b]



Entry	ligand	3aa:4aa	Yield (%)[b]
1	dppp	1:99	78
2	dppe	81:19	70
3	PPh_3	--	--
4	Bipy	--	--
5	1,10-Phen	--	--
6	dppm	--	--
7	dppb	--	--
8	dppf	0:100	13
9	L1	88:12	27
10	dppben	94:6	53
11	L2	--	--
12	dppen	98:2	70
13[c]	dppen	99:1	84
14[d]	dppp	1:99	86

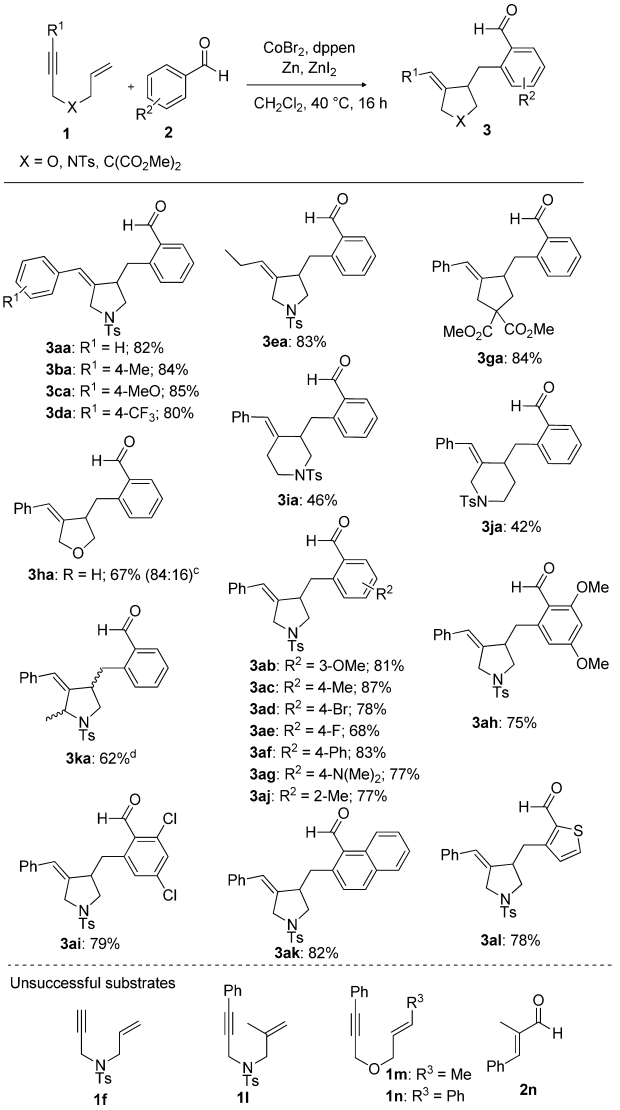


[a]Unless otherwise mentioned, all reactions were carried out with enyne **1a** (0.10 mmol), aromatic aldehyde **2a** (0.11 mmol), $CoBr_2$ (5 mol %), ligand (5 mol %), Zn (10 mol %), ZnI_2 (10 mol %) at 40 °C for 12 h. [b]Yields were measured from the crude mixture by ^1H NMR integration method using mesitylene as an internal standard. [c]Reaction for 16 h. [d]Reaction for 18 h.

7) and BINAP did not give the desired hydroarylative product, whereas 1,1′-bis(diphenylphosphino)ferrocene (dppf) (entry 8) afforded only hydroacylation product **4aa**, albeit in lower yield. However, high selectivity for the hydroarylation of enyne **1a** by benzaldehyde (**2a**) was observed with tridentate phosphine **L1** and dppben giving **3aa**/**4aa** in a 9:1 ratio in moderate yields (entries 9−10). Finally, the use of *cis*-1,2-bis(diphenylphosphino)ethylene (dppen) led to hydroarylative cyclized product with a **3aa**/**4aa** ratio of 99:1 in 84% combined yield (entry 13).

With this optimized protocol, we explored the hydroarylation of various enynes **1a-i** with benzaldehyde (**2a**) (Scheme 1). *N*-Tethered enyne containing electron-withdrawing and electron-donating groups at the para position of the phenyl ring **1a-d** underwent the hydroarylative cyclization to afford **3aa-da** in 80−85% yields. Likewise, aliphatic alkyne **1e** reacted effectively to provide the cyclic product **3ea** in good yield. *O*- and malonate-tethered enynes **1g-h** were also suitable for the reaction giving the corresponding products **3ga-ha** in 84% and 67% yields. Notably, the reaction of 1,7-enynes **1i-j** with benzaldehyde gave product **3ia-ja** in lower yield, along with a nearly equal amount of exocyclic diene product from enyne coupling of **1i-j**. The enyne **1k** containing methyl substitution at propargylic position also provided the hydroarylation product **3ka** in 62% yield with a diastereomeric ratio (dr) of 1:0.7. This reaction condition is not suitable for the terminal enyne **1f** and enynes (**1l-n**) containing 1,1- and 1,2-disubstituted alkenes.

Scheme 1. Cobalt-Catalyzed Hydroarylative Cyclization of Enynes 1 with Aromatic Aldehydes 2[a,b]



[a]Enyne **1** (0.20 mmol), aromatic aldehyde **2** (0.22 mmol), $CoBr_2$ (5 mol %), dppen (5 mol %), Zn (10 mol %), ZnI_2 (10 mol %) for 16 h. [b]Isolated yields (**3**:**4** ratio >98:2). [c]Ratio of **3**:**4**. [d]dr 1:0.7

This present catalytic reaction was successfully extended to various aromatic aldehydes **2b-l** with enyne **1a**. Thus, treatment of 3-methoxy benzaldehyde with **1a** resulted in the selective C−H activation at less-hindered position of the **2b**, providing **3ab** in 81% yield. Electron-donating groups substituted benzaldehydes **2c**, **2g**, and **2h** were converted to the corresponding cyclized product **3ac**, **3ag**, and **3ah** in good to excellent yields. Furthermore, we were delighted to find that halide functional groups (**2d**, **2e**, and **2i**) were well tolerated in this reaction, affording **3ad**, **3ae**, and **3ai** in moderate yields. The structure of ortho-functionalized aldehyde **3ai** was unambiguously determined by X-ray crystallographic analysis (Figure 1). The more sterically hindered 2-methy benzaldehyde (**2j**) also participated well in the hydroarylative cyclization to deliver **3aj** in 77% yield. Gratifyingly, 1-naphthaldehyde (**2k**) and thiophene-2-carbaldehyde (**2l**) furnished the respective hydroarylative cyclized products in good yields. It is noteworthy that the vinylic C—H

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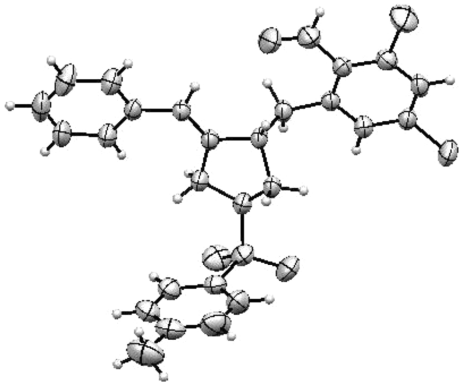


Figure 1. ORTEP diagram of **3ai**.

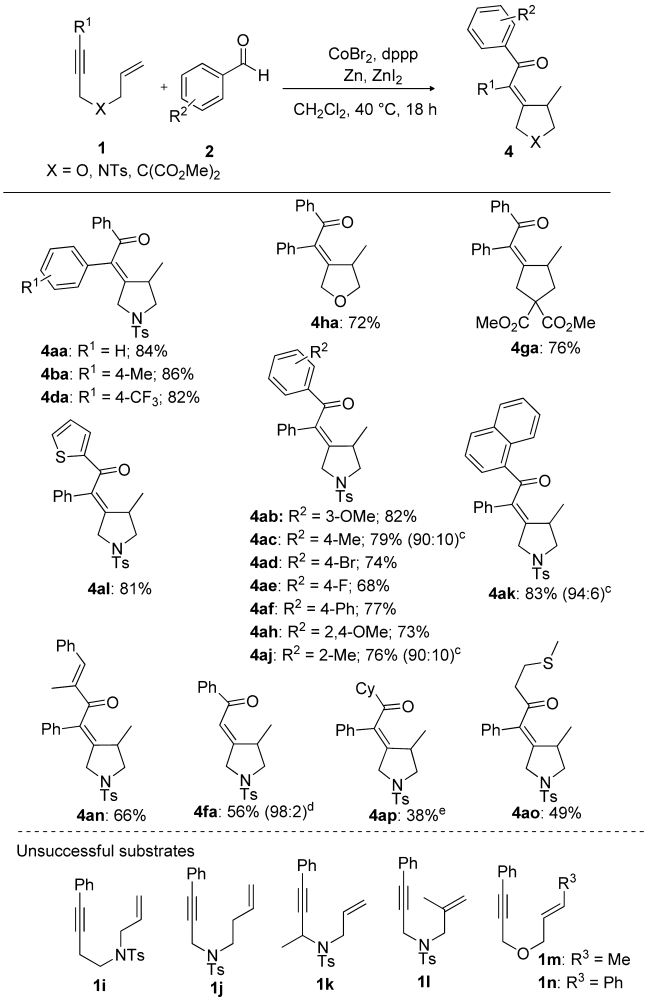
activation (**2n**) did not occur under the standard reaction conditions.

2.2. Cobalt-Catalyzed Hydroacylation of Enynes with Aldehydes. After successfully examining the hydroarylation reaction, we next investigate the hydroacylation reaction. Metal-catalyzed hydroacylation is one of the efficient method for the synthesis of carbonyl compounds with high atom efficiency.[4,12] Extensive studies had been devoted to rhodium catalysts. Moreover, aldehydes were limited to chelating aldehydes such as β-sulfur aldehydes,[13] salicylaldehydes,[14] and aldimines[15] to achieve high regioselectivity and suppress the competitive decarbonylation. Due to more abundance, low cost and homologous reactivity, cobalt is an ideal alternative to rhodium. Nevertheless, cobalt-catalyzed hydroacylation strategies are seldom known.[16] Herein, we explore the possibility of cobalt-catalyzed hydroacylation reaction of aldehyde with 1,6-enyne.

The scope of the hydroacylation reaction is demonstrated in Scheme 2. The reaction of various *N*-tethered enynes bearing different substituents at the para position of benzene ring (**1a-d**), *O*- and malonate-tethered enynes (**1g,h**) all proceded well. Benzaldehydes with electron-rich methoxy (**2b**, **2h**), methyl (**2c**, **2j**), and phenyl (**2f**) groups provided the corresponding cyclized product in moderate yields. Particularly, the methyl substitution at the ortho and para positon of the arene ring of **2c** and **2j** shows slightly low chemoselectivity for the corresponding carbonyl insertion products **4ac** and **4aj**. This is probably owing to the poorer electrophilicity of carbonyl carbon in the electron rich aromatic aldehydes, **2c** and **2j**, which might decrease the carbonyl insertion rate and provide the chance for C—H metalation. Heterocyclic aldehyde **2l** is also proved to be a viable substrate, affording **4al** in 81% yield. In a similar manner, 1-naphthaldehyde (**2k**) was also amenable to the reaction conditions giving mainly the hydroacylation product **4ak** with a **4ak**/**3ak** ratio of 94:6 in 83% combined yield. It should be noted that 1,7-enynes, **1i-j**, were not suitable for this reaction, providing trace amounts of exocyclic dienes only. Likewise, enynes, **1l-n**, containing 1,1- and 1,2-disubstituted alkenes did not give the desired products.

The present hydroacylation reaction was not limited to aromatic aldehydes; it was compatible with vinyl and aliphatic aldehydes. Thus, treatment of α-methyl cinnamaldehyde (**2n**) with **1a** afforded **4an** in 66% yield. Likewise, aliphatic aldehydes **2o,p** participated in the reaction, providing **4ao-ap** in slightly lower yields. Enyne **2f** containing terminal alkyne also successfully underwent the cyclization to deliver regioisomeric product **4fa** in a ratio of 98:2.

Scheme 2. Cobalt-Catalyzed Hydroacylative Cyclization of Enynes 1 with Aldehydes 2[a,b]



[a]Enyne **1** (0.20 mmol), aldehyde **2** (0.22 mmol), $CoBr_2$ (5 mol %), dppp (5 mol %), Zn (10 mol %), and ZnI_2 (10 mol %) for 18 h. [b]Isolated yields (**4**:**3** ratio > 97:3). [c]Ratio of **4**:**3**. [d]Ratio of regioisomers. [e]Enyne **1** (0.20 mmol), aldehyde **2** (1.0 mmol), $CoBr_2$ (10 mol %), dppp (10 mol %), Zn (20 mol %), and ZnI_2 (20 mol %).

2.3. Mechanistic Studies. In order to gain preliminary insight into the mechanism for the cobalt-catalyzed dual functionalization of aldehydes with enynes, deuterium kinetic isotopic effects (KIE) were examined (Scheme 3). The reaction of enyne **1a** with aldehyde **2a-d$_5$** gave the hydroarylation product **3aa-d$_5$**, in which a deuterium atom was transferred to the expected alkene carbon. Likewise, the reaction of enyne **1a** with aldehyde **2a-d′** afforded hydroacylation product **4aa-d′**, the D atom on the aldehyde group of **2a-d′** was transferred to the methyl position of the product. In addition, the reaction of enyne **1a** with ethanol gave reductive coupling product **3a** conforming that these reactions proceed via a common cobaltacycle **A** (Scheme 4). Then, the competition reaction using an equimolar mixture of **2a** and **2a-d$_5$** with enyne **1a** under the hydroarylation conditions was conducted, an intramolecular KIE of 3.0 was observed at early conversion stage. However, the parallel reactions of **2a** or **2a-d$_5$** with enyne **1a** provided a KIE of 1.4 (see Supporting Information for details). Similarly, a significant KIE of ~3.5 was obtained, when *ortho*-deuterated benzaldehyde **2a-d$_1$** was treated with enyne **1a**

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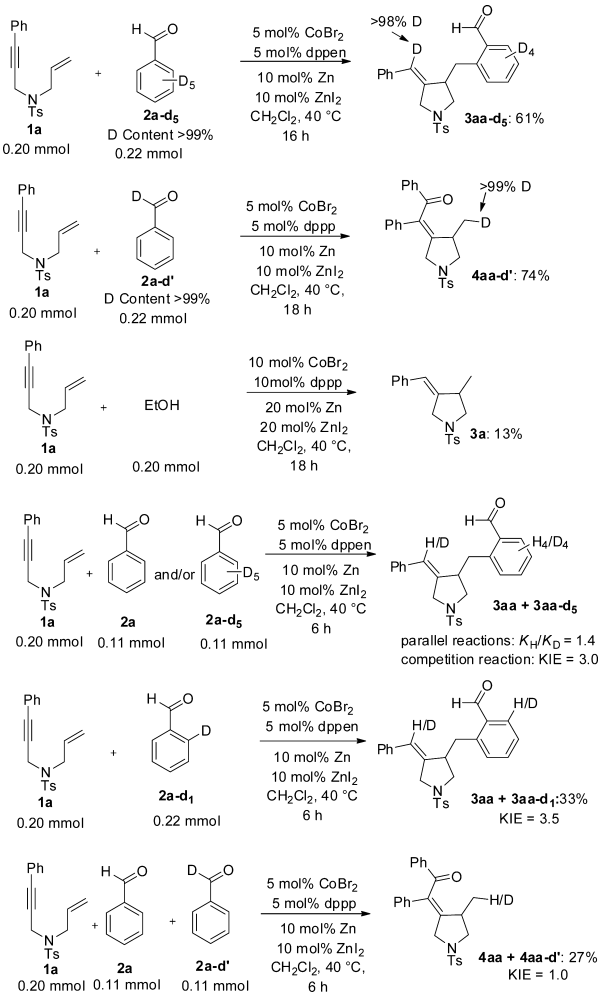
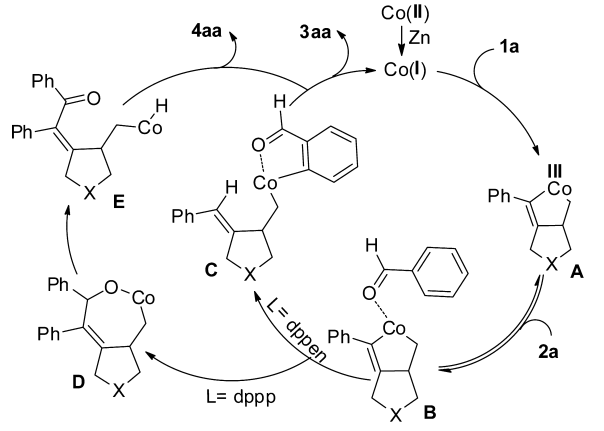
Scheme 3. Mechanistic Studies



Scheme 4. Plausible Mechanism for the Cobalt-Catalyzed Cyclization of Enynes with Aldehydes



under the hydroarylation conditions. These results indicate that the C—H metalation may be the rate-determining step for the hydroarylation reaction of **2a** with **1a**. The considerably similar inter- and intramolecular KIEs suggest that the complexation of aldehyde with cobaltacycle **A** is reversible (Scheme 4). Finally, an intramolecular KIE of ∼1.0 was observed for the hydroacylation reaction which suggests that the C—H cleavage may not be the product-determining step.

Considering our preliminary mechanistic studies and literature precedence,[10,17] we propose a plausible mechanism for the underlying reaction as shown in Scheme 4. Oxidative cyclization of enyne **1a** forms a five-membered cobaltacycle A as the first step after the generation of Co(I) by reducing Co(II) in the presence of zinc dust. The reversible complexation (B) of aldehyde **2a** followed by C—H metalation affords the intermediate C, when dppen is used as the ligand. Subsequently, reductive elimination provides the hydroarylative cyclized product **3aa**. Alternatively, the carbonyl insertion into the bicyclic cobaltacycle provides intermediate D in the presence of dppp ligand, which is capable of β-hydride elimination[16c] to deliver a cobalt hydride species E. Further C—H bond formation furnishes the product **4aa** and regenerates the catalyst for the next catalytic cycle. Although the origin of this divergence remains unclear, we speculate that the selectivity is possibly controlled by electronic nature of the cobaltacycle. Thus, slightly electron-rich cobaltacycle B with dppp ligand favors the insertion of aldehyde into the metal–carbon bond of the cobaltacycle, whereas mild electron-deficient ligands such as ethylene and benzene diphosphines reduce the nucleophilicity of the cobaltacycle leading to *ortho*-C—H metalation.

The reason for the observed regioselectivity of the present Co-catalyzed hydroacylation and hydroarylation is not entirely clear. It is probably that in the cobaltacycle **B**, the Co-attached sp^2 carbon has slightly higher electron density than the sp^3 carbon (Scheme 4) due to higher electronegativity of sp^2 carbon than sp^3 carbon resulting in protonation or carbonyl insertion preferentially at the sp^2 carbon.

3. CONCLUSIONS

In summary, we have successfully demonstrated an atom economical cobalt-catalyzed switchable C—H functionalization of weakly coordinating aldehydes with enynes, affording functionalized pyrrolidines and dihydrofurans in good to excellent yields with high chemo- and stereoselectivity. The reaction plausibly proceeds via a novel cobaltacycle intermediate followed by insertion or C—H metalation of aldehydes depending on the electronic nature of the ligands on the cobaltacycle. Further investigation on cobalt-catalyzed atom economical synthetic approach is underway.

■ ASSOCIATED CONTENT

Supporting Information

This material is available free of charge on ACS publication Web site at The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10447.

General experimental procedures, characterization details, and copies of ^{1}H and ^{13}C NMR spectra of new compounds (PDF)

X-ray data (CIF)

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Notes

The authors declare no competing financial interest.

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