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Cobalt-Catalyzed Hydroarylative Cyclization of 1,6-Enynes with Aromatic Ketones and Esters via C−H Activation

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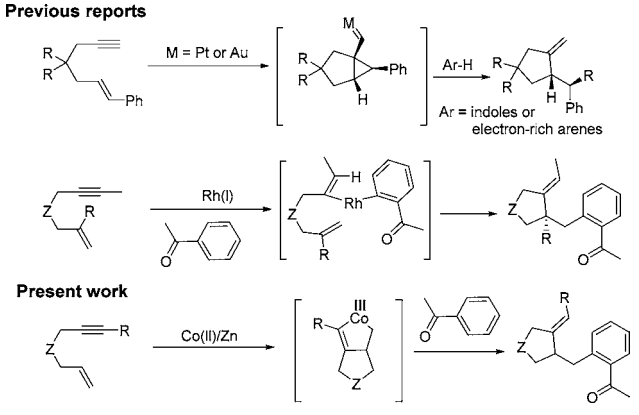
Supporting Information

ABSTRACT: A highly chemo- and stereoselective cobalt-catalyzed hydroarylative cyclization of 1,6-enynes with aromatic ketones and esters to synthesize functionalized pyrrolidines and dihydrofurans is described. A mechanism involving cobaltacycle triggered C−H activation of aromatic ketones and esters was proposed.

Transition-metal-catalyzed cyclization of 1,6-enynes has emerged as an efficient process to prepare cyclic skeletons with a broad range of functional moieties that are found in various natural products and bioactive molecules.[1,2] Among such reactions, the cyclization−coupling reaction of 1,6-enynes with main group organometallics is of high interest because they can afford the cyclic compounds with tri- or tetrasubstituted exocyclic double bonds in a highly stereoselective manner.[3,4] Many metal complexes including Pd, Rh, and Ni are known to catalyze these types of cyclization−coupling reactions, but only a few of them have been involved in the hydroarylative cyclization.[5,6] Representative examples include gold- and platinum-catalyzed cyclization of 1,6-enynes with electron-rich aromatic and heteroaromatic nucleophiles[5] and rhodium-catalyzed hydroarylative cyclization of 1,6-enynes with aromatic ketones[6] (Scheme 1). For the reactions catalyzed by gold and platinum complexes, a cyclopropyl metal carbene intermediate was proposed, whereas, for rhodium-catalyzed reactions, a carbonyl-directed C−H activation of aryl ketones[6c] was suggested as the initial key step (Scheme 1). These reactions, however, were limited to expensive second and third row transition metals, and thus the development of less expensive metal catalysts with a wide substrate scope is highly desirable.

Scheme 1. Metal-Catalyzed Hydroarylative Cyclization Reaction of 1,6-Enynes



Our continued interest in the metal-catalyzed reductive coupling[7] and C−H bond activation reactions[8] prompted us to explore the use of relatively inexpensive cobalt complexes as the catalysts for hydroarylative enyne cyclization reactions. Herein, we report a highly chemo- and stereoselective cobalt-catalyzed hydroarylative cyclization of 1,6-enynes with aromatic ketones or esters affording functionalized pyrrolidines and dihydrofurans in good to excellent yields. Unlike rhodium-, gold-, or platinum-catalyzed reactions, the reactions appear to proceed via a Co^{III} metallacycle[9] and carbonyl-directed *ortho* C−H activation (Scheme 1). Furthermore, the reaction was successfully extended to aromatic esters, which was not known in the previously reported hydroarylative cyclization reactions.

Cobalt complexes are well-known to catalyze enyne coupling reactions.[7b−d,10,11] In view of the catalytic ability of cobalt complexes in the enyne-coupling and C−H bond activation reactions,[12] we started to explore the possibility of using cobalt complexes for the hydroarylative enyne cyclization. Thus, treatment of enyne **1a** with acetophenone **2a** in the presence of $CoBr_2$ (5.0 mol %), dppp (5.0 mol %), Zn (0.10 mmol), ZnI_2 (0.20 mmol), and dichloromethane (DCM) at 40 °C for 2 h gave the hydroarylative cyclized product **3aa** in 96% yield (see the Supporting Information for details). The reaction is highly chemo- and stereoselective; the aryl group from the aromatic ketone adds exclusively to the alkene moiety of **1a**, and the exocyclic double bond of product **3aa** is in a *Z* configuration. Moreover, the C−H cleavage selectively occurs at the *ortho* position of the aromatic ketone. Solvent played a vital role in the success of the reaction. Chloro solvents such as DCM and $ClCH_2CH_2Cl$ were highly effective, affording the cyclized product in high yields, while 1,4-dioxane, THF, and CH_3CN were less effective, giving the cyclized product in only moderate

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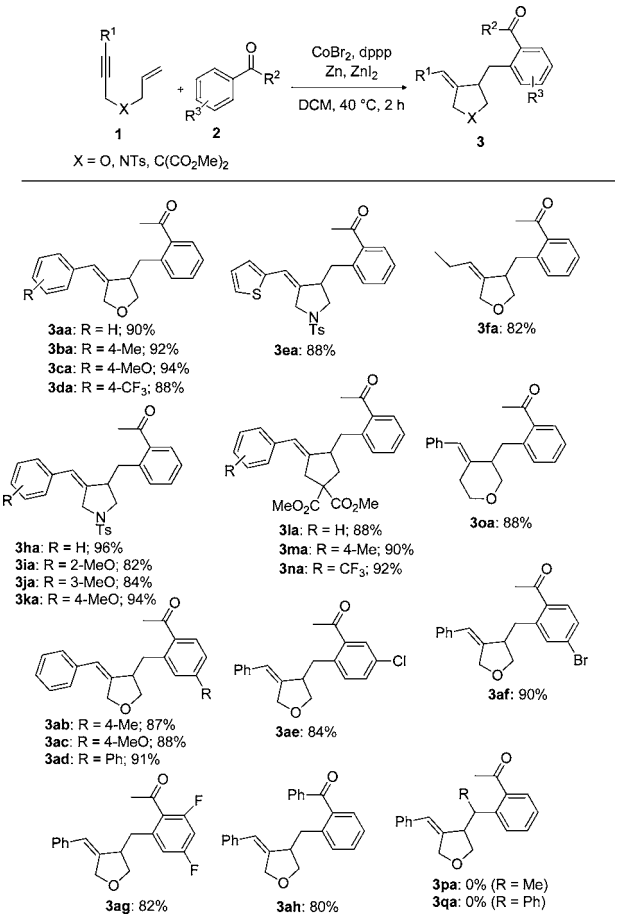
yields. On the other hand, toluene is ineffective as the solvent for the present catalytic reaction. Control experiments revealed that the reaction did not proceed without $CoBr_2$/dppp, Zn, or ZnI_2.

To understand the present catalytic conditions, we investigated the hydroarylative cyclization reaction of **1a** and **2a** in the presence of various cobalt complexes using DCM as the solvent. Among them, dppp and dppe complexes showed higher reactivity than other bidendate phosphine complexes such as dppm and dppb. Particularly, $CoBr_2$/dppp, $CoBr_2$/dppe, and CoI_2/dppp were effective, affording the cyclized product **3aa** in 96%, 85%, and 70% yields, respectively. Other cobalt complexes, including $CoBr_2$/dppm and $CoCl_2$/dppp, were also active but provided **3aa** in lower yields. A monodentate phosphine complex, $CoI_2(PPh_3)_2$, and bidentate nitrogen cobalt complex, Co(phen)Cl_2 (phen = 1,10-phenanthroline), were inactive for the present hydroarylative cyclization reaction.

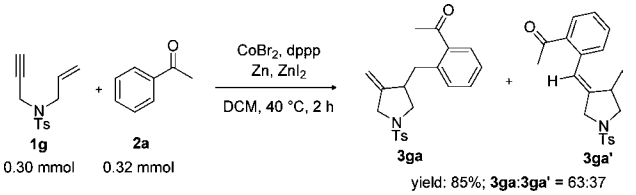
Under the optimized reaction conditions, we examined the hydroarylative cyclization of various enynes **1b**–**o** with **2a** (Scheme 2). The results revealed that substituents such as Me, MeO, and CF_3 on the aryl ring attached to the terminal carbon of the alkyne group are well-tolerated. For example, the substrates containing methyl (**1b**) and methoxy (**1c**) substituents at the *para* position of the benzene ring afforded products **3ba** and **3ca** in more than 90% yields. However, with the 4-CF_3 moiety, the cyclized product **3da** was obtained in 88% yield. Thiophen-2-yl-substituted alkyne **1e** was also suitable for the cyclization reaction to provide product **3ea** in high yield. Aliphatic alkyne **1f** also successfully underwent cyclization, providing **3fa** in 82% yield. Unlike enynes **1** with an internal alkynyl group that gives only one regioisomeric product, enyne **1g** containing a terminal alkyne gave regioisomeric products **3ga** and **3ga′** in a 63:37 ratio in an 85% combined yield (Scheme 3).

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



[a]All reactions were carried out using enyne **1** (0.30 mmol), aromatic ketone **2** (0.32 mmol), $CoBr_2$ (5 mol %), dppp (5 mol %), Zn (10 mol %), ZnI_2 (20 mol %) for 2 h. [b] Isolated yields.

Scheme 3. Result of Hydroarylative Cyclization of Terminal Enyne 1g and Acetophenone 2a



Next, we tested the reaction with various *N*- and *O*-tethered enynes **1h**–**o** (Scheme 2). Thus, *N*-tethered enynes **1h**–**k** containing aryl substituents at the alkyne terminus gave **3ha**–**ka** in 82–96% yields. In a similar manner, malonate-tethered enynes, **1l**–**n**, underwent tandem cyclization to provide the cyclic products **3la**–**na** in good to excellent yields. Finally, *O*-tethered 1,7-enyne **1o** also reacted effectively to deliver product **3oa** in 88% yield. It is noteworthy that enyne (**1p** and **1q**) bearing substitution at the alkene terminus did not afford the expected hydroarylative cyclization product (**3pa** and **3qa**).

To evaluate the scope of the reaction, various types of aromatic ketones were examined with **1a**. Thus, 4-methylacetophenone **2b** and electron-rich 4-methoxyacetophenone **2c** afforded **3ab** and **3ac** in good yields. Similarly, 4-phenyl substituted acetophenone **2d** provided **3ad** in 91% yield. The reaction was also compatible with halo substituents on the aromatic ring of acetophenone **2**. Thus, the reaction of 3-chloro-, 4-bromo-, and 2,4-difluoroacetophenones **2e**–**g** with **1a** gave the corresponding cyclized products **3ae**, **3af**, and **3ag** in 84%, 90%, and 82% yield, respectively. Finally, the bulkier benzophenone **2h** participated well, affording product **3ah** in good yield.

The present catalytic reaction was successfully extended to aromatic esters (Scheme 4). The reaction of methyl (**2i**) and ethyl benzoate (**2j**) with enyne **1h** afforded coupling products **3hi** and **3hj** in high yields. In a similar manner, halo substituted ethyl benzoates **2k**–**n** furnished **3hk**–**hn** in 71–82% yield. Gratifyingly, methyl 2,3-dimethoxybenzoate (**2o**) and phenyl benzoate (**2p**) reacted with **1h**, affording **3ho** and **3hp** in 89% and 84% yield, respectively. Likewise, *O*- and malonate tethered enynes **1a** and **1l** underwent cyclization and provided products **3aj** and **3lj** in good yields.

To understand the mechanism of the present catalytic reaction, we investigated the reaction of **1r** with deuterated aromatic ketone **2a**-d_5 (98% deuterium incorporation, Scheme 5). Delightfully, the desired hydroarylative product **3ra**-d_5 was obtained in 86% yield, in which a deuterium atom was transferred to the expected alkene carbon (96% deuterium incorporation) where the CF_3-aryl group was attached. To gain further insight, an intermolecular kinetic isotopic competition

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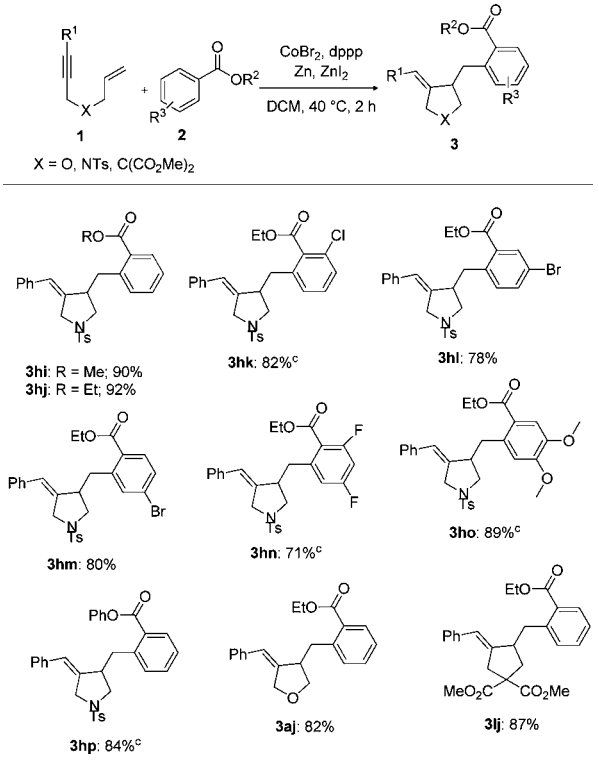
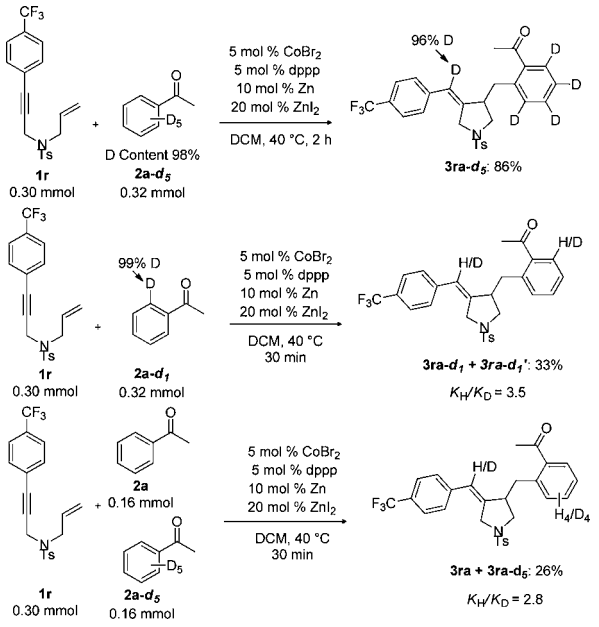
Scheme 4. Cobalt-Catalyzed Hydroarylative Cyclization of Enynes 1 and Aromatic Esters 2[a,b]



[a]All reactions were carried out using enyne **1** (0.30 mmol), aromatic ketone **2** (0.32 mmol), $CoBr_2$ (5 mol %), dppp (5 mol %), Zn (10 mol %), ZnI_2 (20 mol %) for 2 h. [b] Isolated yields. [c] $ClCH_2CH_2Cl$ at 80 °C.

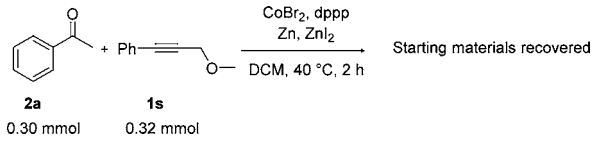
Scheme 5. Mechanistic Studies



experiment for the reaction of an equimolar amount of **2a** and **2a**-d_5 with enyne **1r** was performed. The reaction was quenched after 30 min affording a mixture of products **3ra** and **3ra**-d_5 in 26% yield. Analysis of the ratio of these two products shows a kinetic isotopic effect (KIE) of k_H/k_D = 2.8. In addition, the mono *ortho*-deuterated acetophenone **2a**-d_1 reacted with **1r** to give **3ra**-d_1 and **3ra**-d_1' in 33% yield with an intramolecular kinetic isotopic effect (KIE) of k_H/k_D = 3.5. These results suggest that sp^2 C−H activation of aromatic ketone occurred during the reaction, and the cleavage of the C−H bond is a product-determining step. Moreover, the observed similar values of inter- and intramolecular KIEs indicate that the complexation of ketone **2** to Co intermediate **6** to form **7** (see Scheme 7) is reversible.

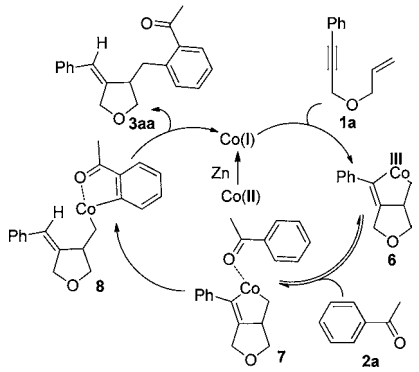
Next, we examined the reaction of **2a** with propargyl ether **1s** under the standard reaction conditions. The reaction did not afford any *ortho*-alkenylated product of **2a**. Instead, only the starting materials were recovered (Scheme 6). This result indicates that the C−H activation at the initial step is less likely but plausibly occurs after the formation of a cobaltacyclopentene intermediate (vide infra).

Scheme 6. Result of the Reaction of Propargyl Ether 1s with Acetophenone 2a



Based on these studies, we depict a plausible mechanism for the present catalytic reaction in Scheme 7. The catalytic cycle

Scheme 7. A Plausible Mechanism for the Cobalt-Catalyzed Hydroarylative Cyclization of 1a with 2a



begins by reducing Co(II) to Co(I) in the presence of Zn dust.[11] Enyne **1a** underwent oxidative cyclization in the presence of Co(I) to afford cobaltacyclopentene intermediate **6**.[1,7] After reversible complexation of ketone **2a** with **6**, *ortho* C−H metalation[12] occurs to afford intermediate **8**. Further reductive elimination of **8** affords **3aa** and regenerates a Co(I) species.[13,14]

In conclusion, we have successfully developed a highly step and atom economical cobalt-catalyzed hydroarylative cyclization of 1,6-enynes with aromatic ketones and esters. In the reaction, we demonstrated a novel cobaltacycle triggered C−H activation of aryl ketones and ester. The reaction is highly chemo- and stereoselective, affording functionalized pyrrolidines and dihydrofurans in good to excellent yields. Further extension of the reaction toward asymmetric synthesis is underway.

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■ ASSOCIATED CONTENT

Supporting Information

General experimental procedures, characterization details, and ^{1}H and ^{13}C NMR spectra of new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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