JACS
JOURNAL OF THE AMERICAN CHEMICAL SOCIETY
Article
pubs.acs.org/JACS

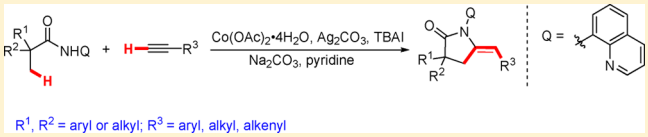
Cobalt-Catalyzed Cyclization of Aliphatic Amides and Terminal Alkynes with Silver-Cocatalyst

Jitan Zhang,[†,∥] Hui Chen,[†,∥] Cong Lin,[†] Zhanxiang Liu,[†] Chen Wang,[§] and Yuhong Zhang*[,†,‡]

[†]Department of Chemistry, Zhejiang University, Hangzhou 310027, China
[‡]State Key Laboratory of Applied Organic Chemistry, Lanzhou University, Lanzhou 730000, China
[§]Zhejiang Key Laboratory of Alternative Technologies for Fine Chemicals Process, Shaoxing University, Shaoxing 312000, China

Supporting Information

ABSTRACT: A new method of cobalt-catalyzed synthesis of pyrrolidinones from aliphatic amides and terminal alkynes was discovered through a C−H bond functionalization process on unactivated sp^3 carbons with the silver cocatalyst using a bidentate auxiliary. For the first time, a broad range of easily accessible alkynes are exploited as the reaction partner in $C(sp^3)$−H bond activation to give the important 5-ethylidene-pyrrolidin-2-ones in a site-selective fashion. The reaction tolerates a wide variety of functional groups including −F, −Cl, −Br, $-CF_3$, ether, cyclopropane, and thiophene. Both pyridine ligand and aromatic solvent play the important role for the promotion of reactivity. This cobalt-catalyzed cyclization reaction can be successfully extended to a variety of aromatic amides to afford a variety of isoindolinones. Attractive features of this catalytic system include its low cost, easy operation, and convenient access to a wide range of pyrrolidinones and isoindolinones.



INTRODUCTION

Transition metal-catalyzed C−H bond activations, which provide the attractive alternatives for traditional cross-coupling reactions without the need for prefunctionalization, have long been one of the most important research objectives in organic chemistry.[1] Significant advances have been made with catalysts based on precious metal catalysts such as Pd, Rh, Ru, and Ir.[2] However, with the increasing interest in sustainable catalysis, considerable effort in this area has been directed toward the new reactions by utilizing low cost and environmentally benign first-row transition metals in place of noble transition metals currently. In this regard, cobalt catalysts in various oxidation states have attracted particular attention due to their unique properties demonstrated in $C(sp^2)$−H activation as new catalytic systems,[3] and pioneering progress has been made by Nakamura,[4] Daugulis,[5] and Kanai.[6] Following these fundamental paradigms, a series of novel cobalt-catalyzed organic transformations of arenes and alkenes have been developed by the groups of Glorious,[7] Ellman,[8] Yoshikai,[9] Song,[10] and Ackermann[11] recently.

In contrast to the direct functionalization of $C(sp^2)$−H bond, the use of cobalt catalysts in the transformations of unactivated sp^3 C−H bond cleavage is extremely underdeveloped.[12] Because the $C(sp^3)$−H bonds lack π electrons that can readily interact with transition metals, most transformations of $C(sp^2)$−H bonds are quite difficult to achieve for a sp^3 C−H bond. Cenini[12a,b] and Zhang[12f,h] have demonstrated the cobalt-catalyzed functionalization of relatively reactive sp^3 C−H bonds, and an unusual cobalt-catalyzed activation of $C(sp^3)$−H bond adjacent to nitrogen was reported by Brookhart.[12d,g] Very recently, Ge and co-workers reported an elegant example of cobalt-catalyzed intra- and intermolecular amination of unactivated sp^3 C−H bonds.[13] One of the key points of this successful reaction is the utilization of a bidentate chelating auxiliary, which is proven to be the powerful strategy for the activation of sp^3 C−H bonds.[14,15]

The pivotal role of terminal alkynes as outstanding building blocks has attracted considerable attention of both industrial and academic laboratories for decades because of their prominent reactivity and vast number that are commercially available. A number of new transformations for applying terminal alkynes in the $C(sp^2)$−H bond functionalizations as the reaction partners have been reported.[16,17] However, this chemistry is limited to the fuctionalization of $C(sp^2)$−H bonds, and the use of terminal alkynes in unactivated sp^3 C−H bond fuctionalizations is still not achieved yet.[18] It has been widely considered that the terminal alkynes interference the C−H activation step potentially and the homocoupling of the terminal alkynes along with the main reaction product decelerate the efficacy of its cross-coupling with inert C−H bond under oxidative reaction conditions. To overcome these problems, bromoalkyne was successfully explored as a preactivated alkynes in the palladium-catalyzed alkynylation of unactivated $C(sp^3)$−H bonds by Chatani and Yu.[19] From the viewpoint of atom and step economy, the direct use of terminal alkynes as coupling partner is more appealing. In the present study, we wish to disclose a cobalt-catalyzed transformation of unactivated $C(sp^3)$−H bonds with terminal alkynes with the assistance of 8-aminoquinolyl group to access the important pyrrolidinones, which are prevalent motifs in drugs and natural products.[20,21] Superior reactivity is demonstrated by this cobalt

Received: July 16, 2015
Published: September 21, 2015

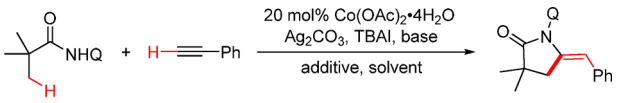
DOI: 10.1021/jacs.5b07424
J. Am. Chem. Soc. 2015, 137, 12990−12996

catalytic system and the homocoupling of terminal alkynes is suppressed. The reaction can be successfully extended to a variety of aromatic amides to afford a variety of isoindolinones. This transformation not only represents a significant step forward for implementing alkynes as privileged counterparts in C(sp^3)−H activation endeavors, but also provides useful insight into the catalytic C(sp^3)−H bond functionalization by cobalt catalysis.

RESULTS AND DISSCUSION

Our investigation to explore the cobalt-catalyzed sp^3 C−H activation began with the reaction of propioamide **1a** and phenylacetylene (**2a**) in the presence of $Co(OAc)_2$ and selected additives as shown in Table 1. Initial observations revealed that

Table 1. Optimization of Reaction Conditions[a]



1a **2a** **3a**

entry	reaction conditions	yield (%)[b]
1	$Co(OAc)_2$, TFB	trace
2	$Co(OAc)_2$, TBAI (TBAB), TFB	73 (71)
3	$Co(OAc)_2$, TBAI, toluene	57
4	$Co(OAc)_2$, TBAI, PhCl	51
5	$Co(OAc)_2$, TBAI, PhBr	26
6	$Co(OAc)_2$, TBAI, PhF	70
7	$Co(OAc)_2$, TBAI, NaOAc, TFB	N.R.
8	$Co(OAc)_2$, TBAI, KOAc, TFB	N.R.
9	$Co(OAc)_2$, TBAI,K_2CO_3, TFB	52
10	$Co(OAc)_2$, TBAI, $NaHCO_3$, TFB	66
11	$Co(OAc)_2$, TBAI, $KHCO_3$, TFB	40
12	$Co(OAc)_2$, TBAI, Na_2CO_3, TFB	82
13	$Co(OAc)_2$, TBAI, Na_2CO_3, pyridine, TFB	95
14	$Co(OAc)_2$, TBAI, pyridine, TFB	60
15	$Co(OAc)_2$, TBAI, Na_2CO_3, bipy, TFB	trace
16	$Co(OAc)_2$, TBAI, Na_2CO_3, *o*-phen, TFB	trace
17	TBAI, Na_2CO_3, pyridine, TFB	N.R.
18[c]	$Co(OAc)_2$, TBAI, Na_2CO_3, *o*-phen, TFB	N.R.
19	$Mn(OAc)_2$, TBAI, Na_2CO_3, pyridine, TFB	N.R.
20	$Fe(acac)_3$, TBAI, Na_2CO_3, pyridine, TFB	N.R.
21	$Ni(OAc)_2$, TBAI, Na_2CO_3, pyridine, TFB	59

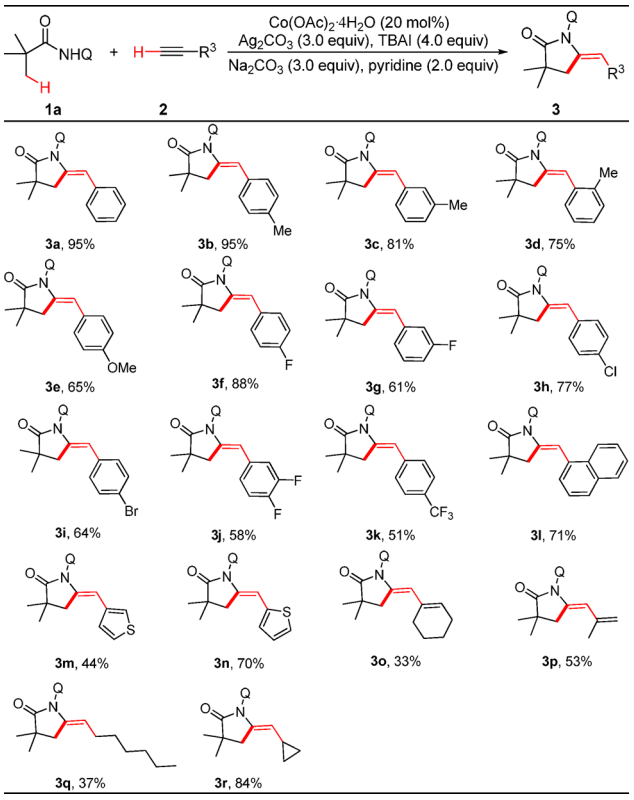
[a]Reaction conditions: **1a** (0.2 mmol), **2a** (0.4 mmol), $Co(OAc)_2$·$4H_2O$ (0.04 mmol), Ag_2CO_3 (0.6 mmol), TBAI (0.8 mmol), base (0.6 mmol), additive (0.4 mmol), TFB (0.6 mL), N_2, 22 h at 150 °C. [b]Isolated yield of **3a** by flash column chromatography. [c]A total of 0.2 equiv bipy or *o*-phen was added. TFB = trifluoromethylbenzene, Bipy =2,2′-bipyridine, *o*-phen =1,10-phenanthroline. Q = Quinolin-8-yl, TBAI = Tetrabutylammonium Iodide, TBAB = Tetrabutylammonium Bromide.

the dimmer of alkyne was the major product and only a trace of pyrrolidinone **3a** was observed (Table 1, entry 1). Gratifyingly, the combination of cobalt catalyst with tetrabutylammonium iodide (TBAI) resulted in the isolation of **3a** in 73% yield with absolute *E*-configuration (Table 1, entry 2), and the homocoupling reaction was suppressed apparently. It was observed that the *Z*-configuration product **3a**′ was initially formed and gradually changed into the *E*-configuration product **3a** under the reaction conditions (see Supporting Information). The replacement of TBAI with tetrabutylammonium bromide (TBAB) gave a slightly lower yield (Table 1, entry 2, in parentheses). However, the promotional effect of tetrabutylammonium chloride (TBACl), tetraethylammonium bromide (TEAB) and tetraethylammonium iodide (TEAI) decreased drastically (see Supporting Information). These results implicate that the main role of TBAI in this transformation may be the phase transfer catalyst. A remarkable solvent effect was observed. No reaction took place in the common solvents, such as DMF, DMSO, TFEtOH, and DCE (see Supporting Information). An exception was the use of toluene, which generated pyrrolidinone **3a** in 57% yield (Table 1, entry 3). The subsequent studies revealed that the use of other aromatic solvents, such as chlorobenzene, bromobenzene, and fluorobenzene, resulted in pyrrolidinone **3a** as well (Table 1, entries 4−6), but superior reaction outcome was obtained by trifluoromethylbenzene which gave a 73% yield (Table 1, entry 2). We hypothesize that the enhanced reactivity with aromatic solvent arises in part from its coordination with cobalt catalyst, which would facilitate the formation of Co π-arene intermediate.[22] A number of bases were also examined, and the nature of bases, as well as their counterions, influenced the catalytic reactivity. For example, NaOAc and KOAc stopped the reaction (Table 1, entries 7 and 8). K_2CO_3, $NaHCO_3$ and $KHCO_3$ gave inferior reactivity (Table 1, entries 9−11), but Na_2CO_3 showed significant effect on the reaction to give the product in 82% yield (Table 1, entry 12). To further improve the conversion, several ligands were screened and application of pyridine showed an enhancement of reactivity to give a 95% yield (Table 1, entry 13), albeit low background reaction rate in the presence of its analogous 2,2′-bipyridine and 1,10-phenanthroline was observed (Table 1, entries 15−18). Various cobalt sources, such as $CoBr_2$, $CoCl_2$, CoI_2, and $Co(acac)_2$, were examined (see Supporting Information). The other metal catalysts such as $Mn(OAc)_2$·$4H_2O$, $Fe(acac)_3$, $Ni(OAc)_2$ were examined. We found that $Mn(OAc)_2$·$4H_2O$ and $Fe(acac)_3$ failed to promote the reaction, but 20 mol % $Ni(OAc)_2$ catalyzed the reaction under the reaction conditions to give the same product in 59% yield (Table 1, entries 19−21). These studies reconfirm that $Co(OAc)_2$ is the optimal cobalt catalyst source. No reaction was observed in the absence of the cobalt catalyst or silver salt (see Supporting Information).

To explore the scope and limitation of this cobalt-catalyzed cyclization reaction, a number of alkynes were applied under the optimal reaction conditions as shown in Scheme 1. In general, both electron-rich and electron-deficient alkynes were compatible with the reaction conditions (**3a**−**3k**). For example, 1-ethynyl-4-methylbenzene reacted smoothly to give the desired product in 95% yield (**3b**). Its analogues 1-ethynyl-3-methylbenzene and 1-ethynyl-2-methylbenzene gave the products in good yields (**3c** and **3d**). However, 1-ethynyl-4-methoxylbenzene was less active to give the product in 65% yield (**3e**). The electron-deficient acetylenes showed similar reactivity and afforded the corresponding pyrrolidinones in moderate to good yields (**3f**−**3i**). Notably, the strong electron-deficient 4-ethynyl-1,2-difluorobenzene and 1-ethynyl-4-(trifluoromethyl)benzene could be tolerated in the reaction, although the corresponding pyrrolidinones were provided in moderate yields (**3j** and **3k**). 1-Ethynylnaphthalene participated in the reaction smoothly to give the product in 71% yield (**3l**). The employment of 2- and 3-ethynylthiophene as substrates afforded the desired pyrrolidinones with the comparable yields (**3m** and **3n**), although 2-ethynylthiophene showed better reactivity partially due to the more efficient conjugated system of 2-ethynylthiophene. The conjugated eneynes participated in

DOI: 10.1021/jacs.5b07424
J. Am. Chem. Soc. 2015, 137, 12990−12996

Scheme 1. Substrate Scope of Alkynes[a,b]



[a]Reaction conditions: **1a** (0.2 mmol), **2** (0.4 mmol), $Co(OAc)_2{\cdot}4H_2O$ (0.04 mmol), Ag_2CO_3 (0.6 mmol), Na_2CO_3 (0.6 mmol), pyridine (0.4 mmol), TBAI (0.8 mmol), TFB (0.6 mL), N_2, 22 h at 150 °C. [b]Isolated yield of **3** by flash column chromatography. TFB = Trifluoromethylbenzene, Q = Quinolin-8-yl, TBAI = Tetrabutylammonium Iodide.

the reaction to afford the pyrrrolidones containing conjugated diene (**3o** and **3p**), which may allow the synthesis of more complex molecules. It should be noted that aliphatic alkynes, which are relatively less active in many coupling reactions, showed comparable reactivity to afford the corresponding pyrrolidinones (**3q** and **3r**). However, relatively lower yields were obtained with these substrates, which might be attributed to their lower stability comparing with the extended conjugation of aromatic alkynes. The regioselectivity of the reaction is always such that C−N bond formation takes place on the terminal carbon atom. In all cases the *E*-isomers are afforded. The structure of the pyrrolidinone **3a** was confirmed by X-ray crystallography (Figure 1).

The scope of the aliphatic amides was investigated as displayed in Scheme 2. Depending on the substituent at α-carbon, a mixture of diasteroisomers was obtained, albeit the ratio of the diastereoisomers was close. Theoretical calculations were carried out to determine the relative stability of different configurations of **4a** (see Supporting Information). Two racemic pairs of enantiomers were located, and the results showed that the configurations in which the ethyl on C3 and quinolin-8-yl lie on the same side of the lactam were slightly more stable than the configurations in which the methyl on C3 and quinolin-8-yl lie on the same side of the lactam. High selectivity of the β-methyl groups over the methylene groups was observed (**4a**−**4l**), and the coupling of γ- or δ-methyl group C−H bonds with phenylacetylene was not observed. The

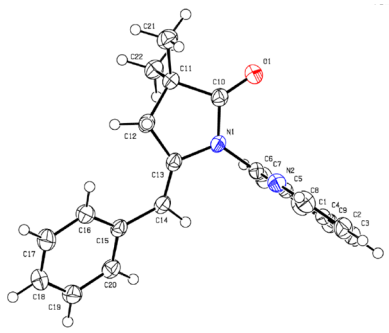
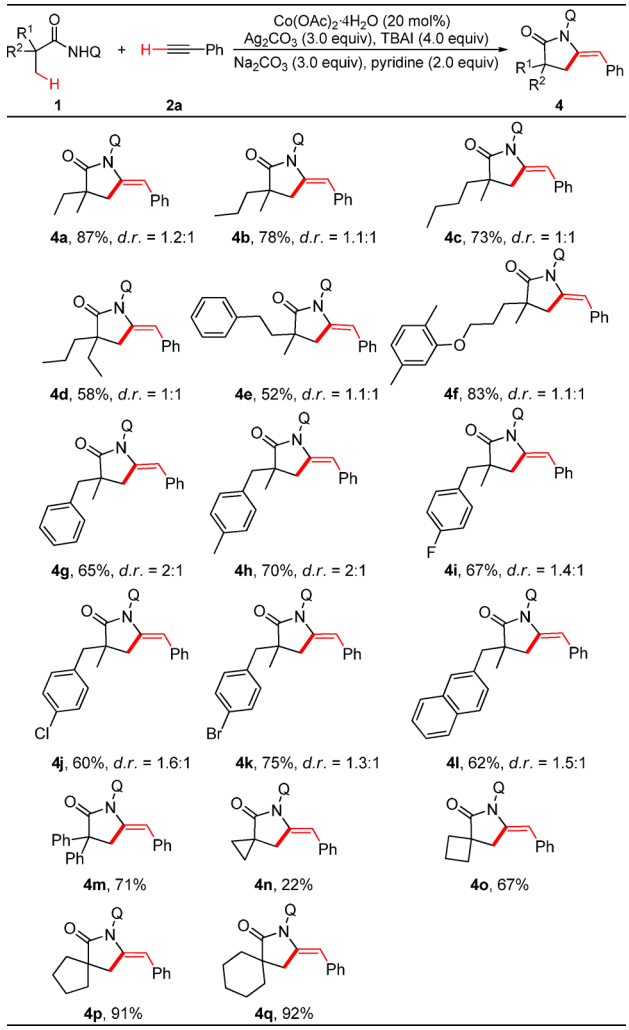


Figure 1. ORTEP drawing of pyrrolidinone **3a**.

Scheme 2. Substrate Scope of Aliphatic Amides[a,b]



[a]Reaction conditions: **1** (0.2 mmol), **2a** (0.4 mmol), $Co(OAc)_2{\cdot}4H_2O$ (0.04 mmol), Ag_2CO_3 (0.6 mmol), Na_2CO_3 (0.6 mmol), pyridine (0.4 mmol), TBAI (0.8 mmol), TFB (0.6 mL), N_2, 22 h at 150 °C. [b]Isolated yield of **4** by flash column chromatography. TFB = trifluoromethylbenzene, Q = Quinolin-8-yl, TBAI = Tetrabutylammonium Iodide.

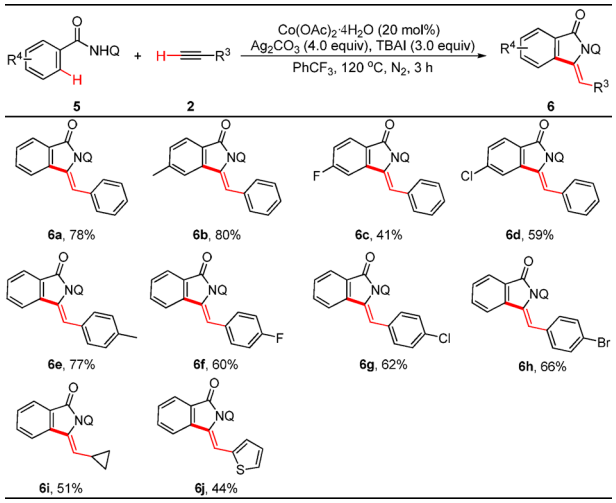
substituents at the α-position of the amide slightly influenced the reactivity: the yield was decreased with the increasing of the alkyl chain (**4a**−**4e**). A variety of functionalities, including methyl, bromide, chloride, fluoride, aryloxyl, and naphthyl, were well tolerated (**4f** and **4h**−**4l**). Notably, the Sonogashira

DOI: 10.1021/jacs.5b07424
J. Am. Chem. Soc. 2015, 137, 12990−12996

reaction of aryl bromide and aryl chloride was suppressed thoroughly using this cobalt catalytic system and the cyclization products were delivered smoothly (**4j** and **4k**). Substrate bearing sterically hindered substituents at α-carbon can be converted into the corresponding product in 71% yield (**4m**). This cobalt-catalyzed reaction was found to be powerful enough to create the valuable spiro-γ-lactam product (**4n**) with an amide bearing the alicyclic group at α-position. Interestingly, along with the enlargement of the ring at α-position of amides, the enhanced reactivity was obtained and the diverse spiro-γ-lactam products were obtained in higher yields (**4o**-**4q**), which is owing in part to the more suitable angle for the formation of metallacycle intermediate.[23]

In light of the importance of isoindolinones as the biologically active molecules and natural products,[24] we studied the use of aromatic amides as coupling partners (Scheme 3).

Scheme 3. Reactions of Aromatic Amides and Terminal Alkynes[a,b]



[a]Reaction conditions: **5** (0.2 mmol), **2** (0.4 mmol), $Co(OAc)_2{\cdot}4H_2O$ (0.04 mmol), Ag_2CO_3 (0.8 mmol), TBAI (0.6 mmol), $PhCF_3$ (1.0 mL), N_2, 3 h at 120 °C. [b]Isolated yield of **6** by flash column chromatography. Q = Quinolin-8-yl, TBAI = Tetrabutylammonium Iodide.

After slight modification of the reaction conditions, this cobalt-catalyzed cyclization reaction can be successfully extended to a variety of aromatic amides as shown in Scheme 3. A variety of aromatic amides bearing either electron-withdrawing or electron-donating groups were applicable to give the diverse isoindolinones in moderate to good yields (**6b**−**6d**), albeit electron-deficient aromatic amides gave the lower yields (**6c**).

For the aryl acetylene derivatives, we found that electron-rich aryl acetylene was more reactive and gave slightly higher yields (**6e**) than electron-deficient aryl acetylenes (**6f**−**6g**). The isoindolinone **6j** was obtained in 44% yield from 2-ethynylthiophene. The structure of the isoindolinone **6f** was confirmed by X-ray crystallography (Figure 2).

To gain insight into the reaction mechanism, GC−MS analysis was performed with the reaction solution for 5 h and the trace of alkynylated product **9** was detected with the formation of the pyrrolidinone **3a** in 89% (Scheme 4, eq 1, see Supporting Information). This result indicates that the cyclization may proceed in two steps: first the alkynylation of sp^3 C−H bond, and second the cyclization of alkynylated

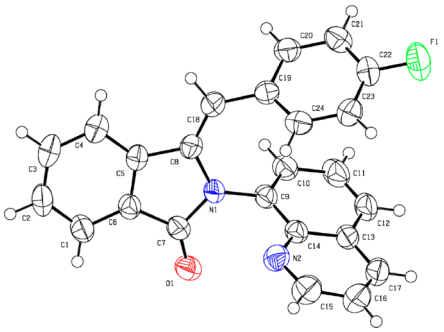
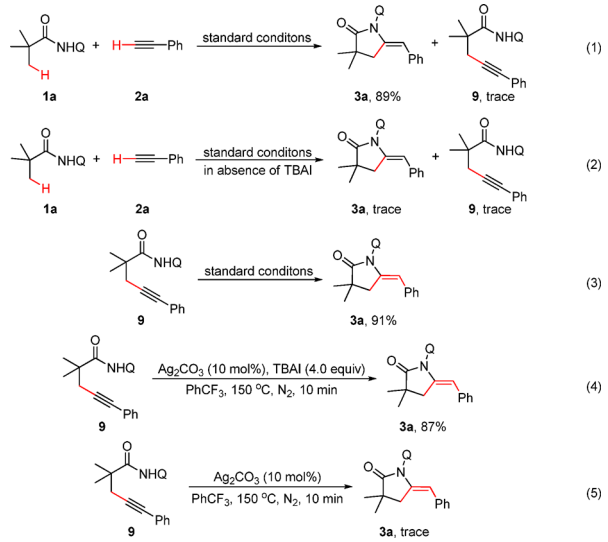


Figure 2. ORTEP drawing of pyrrolidinone **6f**.

Scheme 4. Investigation of the Possible Intermediate



product **9** under the reaction conditions. When the reaction was performed in the absence of TBAI, the trace of alkynylated product **9** was still detected, but the amount of pyrrolidinone **3a** drastically decreased (Scheme 4, eq 2). Using a literature method,[25] we synthesized compound **9** which was subjected to the standard reaction conditions. Surprisingly, the cyclization took place very rapidly and the reaction completed in 10 min (Scheme 4, eq 3). Further study revealed that the use of catalytic amount of Ag_2CO_3 (10 mol %) and stoichiometric TBAI was acquired for the cyclization (Scheme 4, eq 4). The cyclization was sluggished in the absence of TBAI (Scheme 4, eq 5).

In contrast to our previous methods of nickel-catalyzed thioetherfication[26] and copper-mediated aryloxylation[27] of unactivated sp^3 C−H bonds, this cobalt catalytic system is very sensitive to the solvent and only aromatic solvents give the comparable yields (Table 1, entries 2−6). In accordance with known coordination properties of Co(III) with arenes,[22] we hypothesize that the aromatic solvent may coordinate with Co(III) and influence the reactivity. To support this hypothesis, we performed a MALDI-TOF analysis experiment using a mixture of the reaction solution which reacted for 5 h. Indeed, a series of signals identified with species **A** are detected as shown in Figure 3 (see Supporting Information), displaying that both pyridine and aromatic solvent coordinated with Co(III) center. This result suggests that pyridine and aromatic solvent might be implicated with the formation of metallacycle intermediate and influence the reactivity. In addition, the reaction is inhibited

DOI: 10.1021/jacs.5b07424
J. Am. Chem. Soc. 2015, 137, 12990−12996

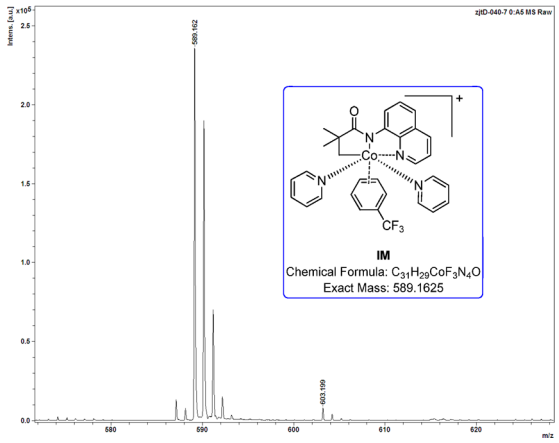
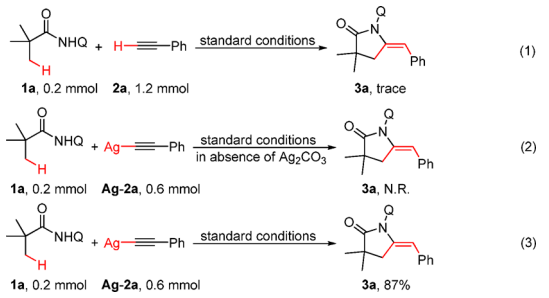


Figure 3. Matrix-assisted laser desorption ionization time-of-flight mass spectroscopy (MALDI-TOF-MS) of **IM** (exact mass: 589.1625) obtained from the reaction of **1a** and **2a** under standard conditions for 5 h.

thoroughly during the course of catalysis with 6 equiv of phenylacetylene (Scheme 5, eq 1). The large excess of

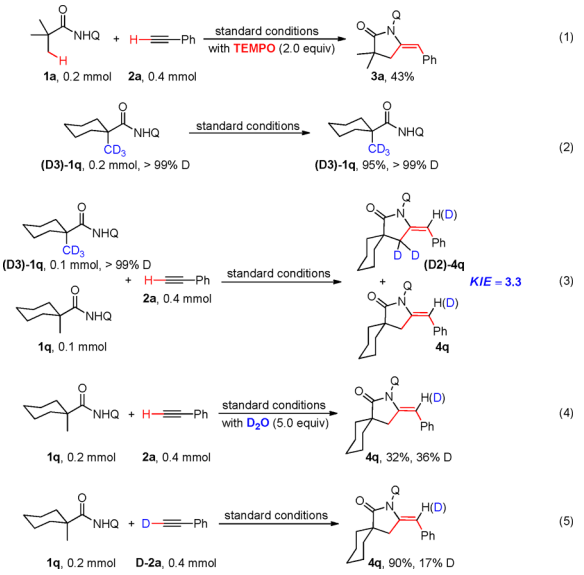
Scheme 5. Investigation of the Possible Co(III) Intermediate



phenylacetylene is supposed to diminish Ag_2CO_3 oxidant by formation of silver(I) phenylacetylide[17i,28] and hence stop the oxidation of Co(II) to Co(III). To further confirm the role of Ag_2CO_3, the reaction of silver(I) phenylacetylide with the amide substrate **1a** by the use of Co(II) was performed in the presence or absence of silver carbonate (Scheme 5, eqs 2 and 3). We found that the reaction failed in the absence of silver carbonate, and in contrast, the desired reaction for the pyrrolidinone **3a** carried out smoothly in the presence of silver carbonate. These findings demonstrate the pivotal role of Co(III) species in the activation of the inert sp^3 C−H bond.

The addition of 2,2,6,6-tetramethylpiperidine (TEMPO, 2 equiv) as a radical quencher drastically decreased the yield to 43%, implying that a radical pathway may involve in the reaction process (Scheme 6, eq 1). In order to trap the possible formed alkynyl radical[29] in the reaction, the electron-rich 1,1-diphenylethene was subjected to the reaction and the expected $C(sp^2)$−C(sp) coupling product was observed (see the Supporting Information for details). This result supports the existence of the alkynyl radical during the reaction. On the other hand, we performed the reaction with the deuterium-labeled compound **(D3)-1q** in the absence of phenylacetylene under the standard reaction conditions. In this case, the deuterium-proton exchange was not observed (Scheme 6, eq 2), indicating that the activation of sp^3 C−H bond is irreversible. An intermolecular kinetic isotope effect experiment was performed by the treatment of equivalent amide **1q** and its

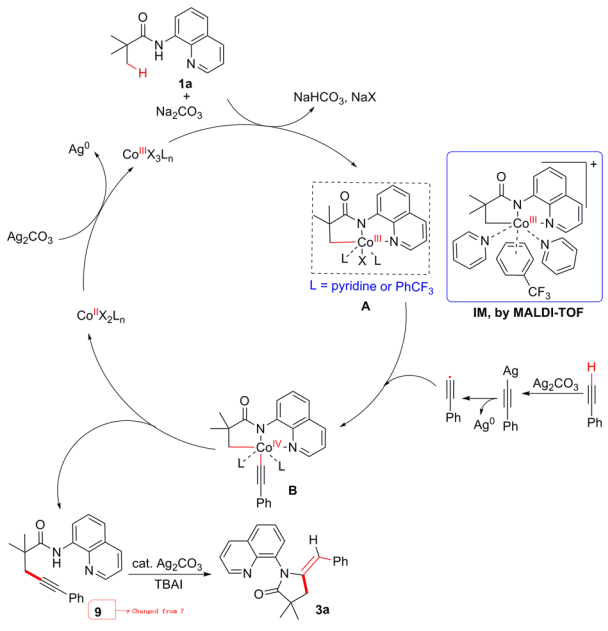
Scheme 6. Radical and Deuterium-Labeling Experiments



deuterated analogues **(D3)-1q** under the reaction conditions (Scheme 6, eq 3). A kinetic isotope effect (KIE) of 3.3 was disclosed, suggesting that the cleavage of C−H bond may be involved in the rate-determining step. The incorporation of deuterium on the alkenyl carbon was always observed in the presence of deuterium sources. For example, the deuterium-labeled product on the alkenyl carbon was detected in the reaction of eqs 3−5 (Scheme 6). This result is reasonable because the deuterition occurs during the final protonation of C−M bond of the cyclization intermediate.[30]

On the basis of these experiments and previous reports,[13,30,31] a catalytic cycle outlined in Scheme 7 is proposed. The first step of the catalytic reaction is the oxidation of Co(II) by Ag_2CO_3 to give Co(III) species, which activates the inert sp^3 C−H bond to form the key intermediate **A**. Both pyridine ligand and trifluoromethylbenzene might be

Scheme 7. Tentative Reaction Mechanism

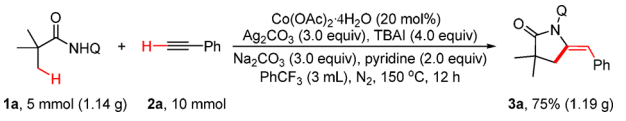


DOI: 10.1021/jacs.5b07424
J. Am. Chem. Soc. 2015, 137, 12990−12996

involved in the formation of intermediate **A** and promote the reaction (Figure 3). The attack of alkyne radical into Co(III) gives the species **B**, which undergoes the reductive elimination to give the alkynylated product and liberate the Co(II) species. The oxidation of Co(II) to Co(III) by silver salts continues the cycle. The subsequent catalytic cyclization occurs rapidly in the presence of 10 mol % Ag_2CO_3 and TBAI to give the pyrrolidinone products. Another possible pathway is through the ion exchange of intermediate **A** with alkynyl anion and subsequent reductive elimination to give the alkynylated product **9** through a Co(III)/Co(I) mechanism.[10b]

This protocol is readily scalable, and when the reaction was scaled up to 5 mmol with a gram scale, the pyrrolidinone product **3a** was isolated in 75% yield (Scheme 8).

Scheme 8. Gram-Scale Reaction of 1a



1a, 5 mmol (1.14 g) **2a**, 10 mmol **3a**, 75% (1.19 g)

CONCLUSIONS

The cobalt catalyst demonstrated promising catalytic property for the cyclization of aliphatic amides with terminal alkynes. For the fist time, terminal alkyne was exploited as the coupling partner of sp^3 C−H bond to give the useful pyrrolidinones. The cobalt catalytic system can be successfully extended to the aromatic amides and thus diverse isoindolinones can be accessed. This new transformation demonstrates good functional group tolerance, excellent reactivity, and high yields. MALDI-TOF analysis and related experiments evidence that the coordination of both ligand and solvent toward cobalt serve as critical factors for ensuring reactivity of this sp^3 C−H functionalization reaction. On the basis of the insights provided in this study, efforts are currently on the way for the exploration of other cobalt-catalyzed sp^3 C−H bond functionalizations.

ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b07424.

Crystallographic data (CIF)
Detailed experimental procedures and characterization data for new compounds (PDF)

AUTHOR INFORMATION

Corresponding Author

*yhzhang@zju.edu.cn

Author Contributions

‖Jitan Zhang and Hui Chen contributed equally.

Notes

The authors declare no competing financial interest.

ACKNOWLEDGMENTS

Funding from Natural Science Foundation of China (No. 21272205, 21472165), National Basic Research Program of China (No. 2011CB936003), and the Program for Zhejiang Leading Team of S&T Innovation (2011R50007) is acknowledged.

REFERENCES

(1) For selected reviews of C−H functionalizations: (a) Giri, R.; Shi, B.-F.; Engle, K. M.; Maugel, N.; Yu, J.-Q. *Chem. Soc. Rev.* **2009**, *38*, 3242. (b) Chen, X.; Engle, K. M.; Wang, D.-H.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2009**, *48*, 5094. (c) Colby, D. A.; Bergman, R. G.; Ellman, J. A. *Chem. Rev.* **2010**, *110*, 624. (d) Wang, D.-H.; Engle, K. M.; Shi, B.-F.; Yu, J.-Q. *Science* **2010**, *327*, 315. (e) McMurray, L.; O'Hara, F.; Gaunt, M. J. *Chem. Soc. Rev.* **2011**, *40*, 1885. (f) Gutekunst, W. R.; Baran, P. S. *Chem. Soc. Rev.* **2011**, *40*, 1976. (g) Baudoin, O. *Chem. Soc. Rev.* **2011**, *40*, 4902. (h) Hartwig, J. F. *Chem. Soc. Rev.* **2011**, *40*, 1992. (i) Zhang, C.; Tang, C.; Jiao, N. *Chem. Soc. Rev.* **2012**, *41*, 3464. (j) Rouquet, G.; Chatani, N. *Angew. Chem., Int. Ed.* **2013**, *52*, 11726. (k) Hashmi, A. S. K. *Acc. Chem. Res.* **2014**, *47*, 864.

(2) (a) Lyons, T. W.; Sanford, M. S. *Chem. Rev.* **2010**, *110*, 1147. (b) Wencel-Delord, J.; Dröge, T.; Liu, F.; Glorius, F. *Chem. Soc. Rev.* **2011**, *40*, 4740. (c) Kwak, J.; Ohk, Y.; Jung, Y.; Chang, S. *J. Am. Chem. Soc.* **2012**, *134*, 17778. (d) Li, G.; Leow, D.; Wan, L.; Yu, J.-Q. *Angew. Chem., Int. Ed.* **2013**, *52*, 1245. (e) Liu, B.; Fan, Y.; Gao, Y.; Sun, C.; Xu, C.; Zhu, J. *J. Am. Chem. Soc.* **2013**, *135*, 468. (f) Ackermann, L. *Acc. Chem. Res.* **2014**, *47*, 281. (g) Cho, S. H.; Hartwig, J. F. *Chem. Sci.* **2014**, *5*, 694. (h) Liu, B.; Zhou, T.; Li, B.; Xu, S.; Song, H.; Wang, B. *Angew. Chem., Int. Ed.* **2014**, *53*, 4191.

(3) (a) Hess, W.; Treutwein, J.; Hilt, G. *Synthesis* **2008**, *2008*, 3537. (b) Kulkarni, A. A.; Daugulis, O. *Synthesis* **2009**, 4087. (c) Ackermann, L. *Chem. Commun.* **2010**, *46*, 4866. (d) Yoshikai, N. *Synlett* **2011**, *2011*, 1047. (e) Yao, T.; Hirano, K.; Satoh, T.; Miura, M. *Angew. Chem., Int. Ed.* **2012**, *51*, 775. (f) Ackermann, L. *J. Org. Chem.* **2014**, *79*, 8948. (g) Fallon, B. J.; Derat, E.; Amatore, M.; Aubert, C.; Chemla, F.; Ferreira, F.; Perez-Luna, A.; Petit, M. *J. Am. Chem. Soc.* **2015**, *137*, 2448.

(4) (a) Ilies, L.; Chen, Q.; Zeng, X.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 5221. (b) Chen, Q.; Ilies, L.; Nakamura, E. *J. Am. Chem. Soc.* **2011**, *133*, 428. (c) Chen, Q.; Ilies, L.; Yoshikai, N.; Nakamura, E. *Org. Lett.* **2011**, *13*, 3232.

(5) (a) Grigorjeva, L.; Daugulis, O. *Angew. Chem., Int. Ed.* **2014**, *53*, 10209. (b) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2014**, *16*, 4684. (c) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2014**, *16*, 4688. (d) Grigorjeva, L.; Daugulis, O. *Org. Lett.* **2015**, *17*, 1204.

(6) (a) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Angew. Chem., Int. Ed.* **2013**, *52*, 2207. (b) Yoshino, T.; Ikemoto, H.; Matsunaga, S.; Kanai, M. *Chem. - Eur. J.* **2013**, *19*, 9142. (c) Sun, B.; Yoshino, T.; Matsunaga, S.; Kanai, M. *Adv. Synth. Catal.* **2014**, *356*, 1491. (d) Ikemoto, H.; Yoshino, T.; Sakata, K.; Matsunaga, S.; Kanai, M. *J. Am. Chem. Soc.* **2014**, *136*, 5424. (e) Suzuki, Y.; Sun, B.; Yoshino, T.; Kanai, M.; Matsunaga, S. *Tetrahedron* **2015**, *71*, 4552.

(7) (a) Yu, D. G.; Gensch, T.; de Azambuja, F.; Vasquez-Cespedes, S.; Glorius, F. *J. Am. Chem. Soc.* **2014**, *136*, 17722. (b) Zhao, D.; Kim, J. H.; Stegemann, L.; Strassert, C. A.; Glorius, F. *Angew. Chem., Int. Ed.* **2015**, *54*, 4508.

(8) (a) Hummel, J. R.; Ellman, J. A. *J. Am. Chem. Soc.* **2015**, *137*, 490. (b) Hummel, J. R.; Ellman, J. A. *Org. Lett.* **2015**, *17*, 2400.

(9) (a) Gao, K.; Yoshikai, N. *Acc. Chem. Res.* **2014**, *47*, 1208. (b) Gao, K.; Lee, P.-S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2010**, *132*, 12249. (c) Lee, P. S.; Fujita, T.; Yoshikai, N. *J. Am. Chem. Soc.* **2011**, *133*, 17283. (d) Ding, Z.; Yoshikai, N. *Org. Lett.* **2010**, *12*, 4180. (e) Gao, K.; Yoshikai, N. *J. Am. Chem. Soc.* **2013**, *135*, 9279. (f) Lee, P.-S.; Yoshikai, N. *Org. Lett.* **2015**, *17*, 22. (g) Yang, J.; Seto, Y. W.; Yoshikai, N. *ACS Catal.* **2015**, *5*, 3054.

(10) (a) Zhang, L. B.; Hao, X. Q.; Zhang, S. K.; Liu, Z. J.; Zheng, X. X.; Gong, J. F.; Niu, J. L.; Song, M. P. *Angew. Chem., Int. Ed.* **2015**, *54*, 272. (b) During the submission of this manuscript, a cobalt(II)-catalyzed Csp^2−H alkynylation/annulation with terminal alkynes was reported. Zhang, L.-B.; Hao, X.-Q.; Liu, Z.-J.; Zheng, X.-X.; Zhang, S.-K.; Niu, J.-L.; Song, M.-P. *Angew. Chem., Int. Ed.* **2015**, *54*, 10012.

(11) (a) Song, W.; Ackermann, L. *Angew. Chem., Int. Ed.* **2012**, *51*, 8251. (b) Punji, B.; Song, W.; Shevchenko, G. A.; Ackermann, L. *Chem. - Eur. J.* **2013**, *19*, 10605. (c) Ma, W.; Ackermann, L. *ACS Catal.* **2015**, *5*, 2822. (d) Li, J.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 3635. (e) Li, J.; Ackermann, L. *Chem. - Eur. J.* **2015**, *21*, 5718.

DOI: 10.1021/jacs.5b07424
J. Am. Chem. Soc. 2015, 137, 12990−12996

(f) Moselage, M.; Sauermann, N.; Richter, S. C.; Ackermann, L. *Angew. Chem., Int. Ed.* **2015**, *54*, 6352.
(12) (a) Cenini, S.; Tollari, S.; Penoni, A.; Cereda, C. *J. Mol. Catal. A: Chem.* **1999**, *137*, 135. (b) Ragaini, F.; Penoni, A.; Gallo, E.; Tollari, S.; Gotti, C. L.; Lapadula, M.; Mangioni, E.; Cenini, S. *Chem.- Eur. J.* **2003**, *9*, 249. (c) Dick, A. R.; Sanford, M. S. *Tetrahedron* **2006**, *62*, 2439. (d) Bolig, A. D.; Brookhart, M. *J. Am. Chem. Soc.* **2007**, *129*, 14544. (e) Boutadla, Y.; Davies, D. L.; Macgregor, S. A.; Poblador-Bahamonde, A. I. *Dalton Trans.* **2009**, 5820. (f) Lu, H.-J.; Zhang, X. P. *Chem. Soc. Rev.* **2011**, *40*, 1899. (g) Lyons, T. W.; Brookhart, M. *Chem. - Eur. J.* **2013**, *19*, 10124. (h) Lu, H.-J.; Li, C.-Q.; Jiang, H.-L.; Lizardi, C. L.; Zhang, X. P. *Angew. Chem., Int. Ed.* **2014**, *53*, 7028.
(13) Wu, X.; Yang, K.; Zhao, Y.; Sun, H.; Li, G.; Ge, H. *Nat. Commun.* **2015**, *6*, 6462.
(14) (a) Zaitsev, V. G.; Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2005**, *127*, 13154. (b) Daugulis, O.; Do, H.-Q.; Shabashov, D. *Acc. Chem. Res.* **2009**, *42*, 1074.
(15) For recent examples of C(sp^3)−H bonds functionalization by using bidentate directing groups, see: (a) Shabashov, D.; Daugulis, O. *J. Am. Chem. Soc.* **2010**, *132*, 3965. (b) Hasegawa, N.; Charra, V.; Inoue, S.; Fukumoto, Y.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 8070. (c) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. (d) Nadres, E. T.; Daugulis, O. *J. Am. Chem. Soc.* **2012**, *134*, 7. (e) He, G.; Zhao, Y.; Zhang, S.; Lu, C.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 3. (f) Zhang, S. Y.; He, G.; Zhao, Y.; Wright, K.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2012**, *134*, 7313. (g) Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030. (h) Zhang, S. Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 12135. (i) Zhang, S. Y.; He, G.; Nack, W. A.; Zhao, Y.; Li, Q.; Chen, G. *J. Am. Chem. Soc.* **2013**, *135*, 2124. (j) Zhang, Q.; Chen, K.; Rao, W.; Zhang, Y.; Chen, F.-J.; Shi, B.-F. *Angew. Chem., Int. Ed.* **2013**, *52*, 13588. (k) Chen, F.-J.; Zhao, S.; Hu, F.; Chen, K.; Zhang, Q.; Zhang, S.-Q.; Shi, B.-F. *Chem. Sci.* **2013**, *4*, 4187. (l) Shan, G.; Yang, X.; Zong, Y.; Rao, Y. *Angew. Chem., Int. Ed.* **2013**, *52*, 13606. (m) Wang, C.; Chen, C.; Zhang, J.; Han, J.; Wang, Q.; Guo, K.; Liu, P.; Guan, M.; Yao, Y.; Zhao, Y. *Angew. Chem., Int. Ed.* **2014**, *53*, 9884. (n) Wang, Z.; Ni, J.; Kuninobu, Y.; Kanai, M. *Angew. Chem., Int. Ed.* **2014**, *53*, 3496. (o) Wu, X.; Zhao, Y.; Zhang, G.; Ge, H. *Angew. Chem., Int. Ed.* **2014**, *53*, 3706. (p) Wu, X.; Zhao, Y.; Ge, H. *Chem. - Eur. J.* **2014**, *20*, 9530. (q) Li, M.; Dong, J.; Huang, X.; Li, K.; Wu, Q.; Song, F.; You, J. *Chem. Commun.* **2014**, *50*, 3944. (r) Gu, Q.; Al Mamari, H. H.; Graczyk, K.; Diers, E.; Ackermann, L. *Angew. Chem., Int. Ed.* **2014**, *53*, 3868. (s) Aihara, Y.; Chatani, N. *J. Am. Chem. Soc.* **2014**, *136*, 898. (t) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2014**, *136*, 1789. (u) Zhang, S. Y.; Li, Q.; He, G.; Nack, W. A.; Chen, G. *J. Am. Chem. Soc.* **2015**, *137*, 531. (v) Li, M.; Yang, Y.; Zhou, D.; Wan, D.; You, J. *Org. Lett.* **2015**, *17*, 2546. (w) Wu, X.; Zhao, Y.; Ge, H. *J. Am. Chem. Soc.* **2015**, *137*, 4924.
(16) For C−H bond alkynylation, see: (a) Brand, J. P.; Waser, J. *Chem. Soc. Rev.* **2012**, *41*, 4165. (b) Kobayashi, K.; Arisawa, M.; Yamaguchi, M. *J. Am. Chem. Soc.* **2002**, *124*, 8528. (c) Seregin, I. V.; Ryabova, V.; Gevorgyan, V. *J. Am. Chem. Soc.* **2007**, *129*, 7742. (d) Tobisu, M.; Ano, Y.; Chatani, N. *Org. Lett.* **2009**, *11*, 3250. (e) Matsuyama, N.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2009**, *11*, 4156. (f) Besselivre, F.; Piguel, S. *Angew. Chem., Int. Ed.* **2009**, *48*, 9553. (g) Kim, S. H.; Chang, S. *Org. Lett.* **2010**, *12*, 1868. (h) Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2010**, *49*, 7304. (i) Ano, Y.; Tobisu, M.; Chatani, N. *Org. Lett.* **2012**, *14*, 354. (j) Ano, Y.; Tobisu, M.; Chatani, N. *Synlett* **2012**, *23*, 2763. (k) Li, Y.; Brand, J. P.; Waser, J. *Angew. Chem., Int. Ed.* **2013**, *52*, 6743. (l) Xie, F.; Qi, Z.; Yu, S.; Li, X. *J. Am. Chem. Soc.* **2014**, *136*, 4780. (m) Feng, C.; Loh, T.-P. *Angew. Chem., Int. Ed.* **2014**, *53*, 2722. (n) Xu, Y.-H.; Zhang, Q.-C.; He, T.; Meng, F.-F.; Loh, T.-P. *Adv. Synth. Catal.* **2014**, *356*, 1539.
(17) (a) Li, Z.; Li, C.-J. *J. Am. Chem. Soc.* **2004**, *126*, 11810. (b) Cheng, K.; Yao, B.; Zhao, J.; Zhang, Y. *Org. Lett.* **2008**, *10*, 5309. (c) de Haro, T.; Nevado, C. *J. Am. Chem. Soc.* **2010**, *132*, 1512. (d) Yang, L.; Zhao, L.; Li, C. J. *Chem. Commun.* **2010**, *46*, 4184. (e) Matsuyama, N.; Kitahara, M.; Hirano, K.; Satoh, T.; Miura, M. *Org. Lett.* **2010**, *12*, 2358. (f) Wei, Y.; Zhao, H.; Kan, J.; Su, W.; Hong, M. *J. Am. Chem. Soc.* **2010**, *132*, 2522. (g) Kim, S. H.; Yoon, J.; Chang, S. *Org. Lett.* **2011**, *13*, 1474. (h) Kim, S. H.; Park, S. H.; Chang, S. *Tetrahedron* **2012**, *68*, 5162. (i) Jie, X.; Shang, Y.; Hu, P.; Su, W. *Angew. Chem., Int. Ed.* **2013**, *52*, 3630. (j) Zhou, B.; Chen, H.; Wang, C. *J. Am. Chem. Soc.* **2013**, *135*, 1264. (k) Shang, M.; Wang, H. L.; Sun, S. Z.; Dai, H. X.; Yu, J.-Q. *J. Am. Chem. Soc.* **2014**, *136*, 11590. (l) Dong, J.; Wang, F.; You, J. *Org. Lett.* **2014**, *16*, 2884. (m) Liu, Y. J.; Liu, Y. H.; Yin, X. S.; Gu, W. J.; Shi, B. F. *Chem. - Eur. J.* **2015**, *21*, 205.
(18) For first examples of gold-catalyzed alkyl-C,H-insertions involving alkynes, both intra- and intermolecular, see: (a) Hashmi, A. S. K.; Braun, I.; Nösel, P.; Schädlich, J.; Wieteck, M.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 4456. (b) Hashmi, A. S. K.; Wieteck, M.; Braun, I.; Rudolph, M.; Rominger, F. *Angew. Chem., Int. Ed.* **2012**, *51*, 10633. (c) Hansmann, M. M.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2013**, *52*, 2593. (d) Hashmi, A. S. K.; Lauterbach, T.; Nösel, P.; Vilhelmsen, M. H.; Rudolph, M.; Rominger, F. *Chem. - Eur. J.* **2013**, *19*, 1058. (e) Nösel, P.; Lauterbach, T.; Rudolph, M.; Rominger, F.; Hashmi, A. S. K. *Chem. - Eur. J.* **2013**, *19*, 8634.
(19) (a) Ano, Y.; Tobisu, M.; Chatani, N. *J. Am. Chem. Soc.* **2011**, *133*, 12984. (b) He, J.; Wasa, M.; Chan, K. S. L.; Yu, J.-Q. *J. Am. Chem. Soc.* **2013**, *135*, 3387. (c) Al-Amin, M.; Arisawa, M.; Shuto, S.; Ano, Y.; Tobisu, M.; Chatani, N. *Adv. Synth. Catal.* **2014**, *356*, 1631.
(20) (a) Robson, R. H.; Prescott, L. F. *Br. J. Clin. Pharmacol.* **1979**, *7*, 81. (b) Ward, J. W.; Gilbert, D. L.; Franko, B. V.; Woodard, G.; Mann, G. T. *Toxicol. Appl. Pharmacol.* **1968**, *13*, 242. (c) Isolation: Rainey, D. P.; Smalley, E. B.; Crump, M. H.; Strong, F. M. *Nature* **1965**, *205*, 203. (d) Isolation: Issa, H. H.; Tanaka, J.; Rachmat, R.; Setiawan, A.; Trianto, A.; Higa, T. *Mar. Drugs* **2005**, *3*, 78. (e) Ye, L.-W.; Shu, C.; Gagosz, F. *Org. Biomol. Chem.* **2014**, *12*, 1833.
(21) (a) Snyder, H. L.; Hamlin, E. *J. Am. Chem. Soc.* **1950**, *72*, 5082. (b) Berlin, S.; Ericsson, C.; Engman, L. *J. Org. Chem.* **2003**, *68*, 8386. (c) Westermann, B. *Angew. Chem., Int. Ed.* **2003**, *42*, 151. (d) Xu, F.; Corley, E.; Murry, J. A.; Tschaen, D. M. *Org. Lett.* **2007**, *9*, 2669. (e) Jakubec, P.; Helliwell, M.; Dixon, D. J. *Org. Lett.* **2008**, *10*, 4267. (f) He, G.; Zhang, S.-Y.; Nack, W. A.; Li, Q.; Chen, G. *Angew. Chem., Int. Ed.* **2013**, *52*, 11124.
(22) (a) Fagan, P. J.; Ward, M. D.; Calabrese, J. C. *J. Am. Chem. Soc.* **1989**, *111*, 1698. (b) Schneider, J. J.; Denninger, U.; Heinemann, O.; Krüger, C. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 592. (c) Hung-Low, F.; Bradley, C. A. *Organometallics* **2011**, *30*, 2636. (d) Hung-Low, F.; Krogman, J. P.; Tye, J. W.; Bradley, C. A. *Chem. Commun.* **2012**, *48*, 368. (e) Yoshikai, N.; Asako, S.; Yamakawa, T.; Ilies, L.; Nakamura, E. *Chem. - Asian J.* **2011**, *6*, 3059.
(23) Shang, R.; Ilies, L.; Matsumoto, A.; Nakamura, E. *J. Am. Chem. Soc.* **2013**, *135*, 6030.
(24) (a) Kato, Y.; Ebiike, H.; Achiwa, K.; Ashizawa, N.; Kurihara, T.; Kobayashi, F. *Chem. Pharm. Bull.* **1990**, *38*, 2060. (b) Lamblin, M.; Couture, A.; Deniau, E.; Grandclaudon, P. *Org. Biomol. Chem.* **2006**, *5*, 1466.
(25) Witham, C. A.; Mauleón, P.; Shapiro, N. D.; Sherry, B. D.; Toste, F. D. *J. Am. Chem. Soc.* **2007**, *129*, 5838.
(26) Lin, C.; Yu, W.; Yao, J.; Wang, B.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 1340.
(27) Zhang, J.; Chen, H.; Wang, B.; Liu, Z.; Zhang, Y. *Org. Lett.* **2015**, *17*, 2768.
(28) Viterisi, A.; Orsini, A.; Weibel, J.-M.; Pale, P. *Tetrahedron Lett.* **2006**, *47*, 2779.
(29) (a) Martelli, G.; Spagnolo, P.; Tiecco, M. *J. Chem. Soc. B* **1970**, 1413. (b) Xie, J.; Shi, S.; Zhang, T.; Mehrkens, N.; Rudolph, M.; Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2015**, *54*, 6046.
(30) (a) Fang, G.; Bi, X. *Chem. Soc. Rev.* **2015**, DOI: 10.1039/C5CS00027K. (b) Gainer, M. J.; Bennett, N. R.; Takahashi, Y.; Looper, R. E. *Angew. Chem., Int. Ed.* **2011**, *50*, 684.
(31) Liu, J.-B.; Chen, C.; Chu, L.; Chen, Z.-H.; Xu, X.-H.; Qing, F.-L. *Angew. Chem., Int. Ed.* **2015**, *54*, 11839.

DOI: 10.1021/jacs.5b07424
J. Am. Chem. Soc. 2015, 137, 12990−12996