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Cobalt-Catalyzed gem-Cross-Dimerization of Terminal Alkynes

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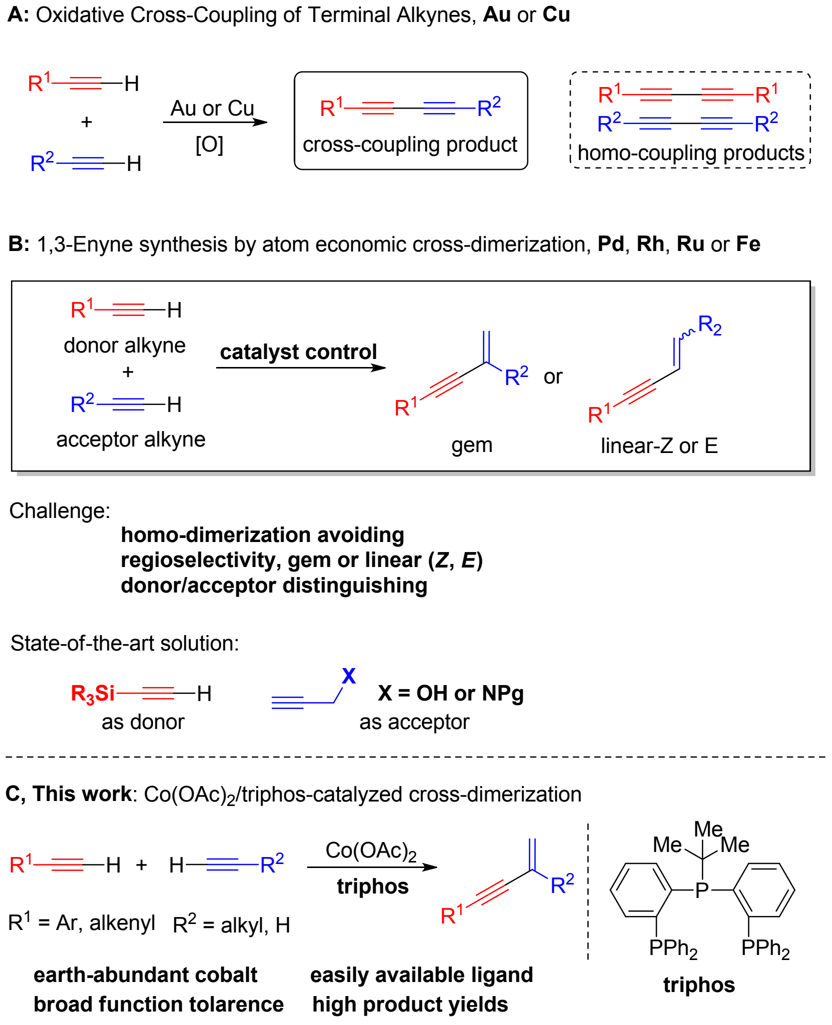
KEYWORDS. Terminal Alkynes, Cross-dimerization, Cobalt, Triphos, 1,3-enynes

ABSTRACT. Transition-metal-catalyzed dimerization of two different terminal alkynes provides an atom-economic synthesis of valuable conjugated 1,3-enynes. Despite many catalyst systems developed, the state-of-the-art solutions are still limited to special alkynes. A practical catalyst, which could be used to cross-dimerize general aryl alkynes and aliphatic alkynes, is still highly desired. Herein we present the earth-abundant Co(II)-catalyzed highly gem-selective cross-dimerization of aryl alkynes and aliphatic alkynes or gas acetylene under mild reaction conditions. Conjugated 1,3-enynes with various useful functional groups can be prepared in high yields. The applying of $Co(OAc)_2$ and t-butyl group substituted triphos ligand is essential to distinguish the alkynes at different steps and realize the gem-selectivity.

INTRODUCTION

The cross-coupling of two molecules with similar reactivities is a big challenge in organic synthesis. An extremely sophisticated distinguishing between the two reaction partners has to be designed to achieve the cross-coupling over homo-coupling.[1] Terminal alkynes are very versatile building blocks in organic synthesis, which could be used to prepare a variety of important organic molecules.[2] However, the precise control in the coupling of terminal alkynes is very challenging. The oxidative cross-coupling of aryl alkynes and aliphatic alkynes has only been reported recently with gold or Cu complexes, in which a discrimination of the acidities of alkynes by the catalysts is the key for the cross-selectivity (scheme 1, **A**).[3] Conjugated 1,3-enynes are not only found in many natural products and biologically active molecules,[4] but also very useful intermediates to prepare aromatic rings, heteocycles, allenes and other structures.[5] Among the many synthetic methods, transition-metal-catalyzed dimerization of terminal alkynes provides an efficient and atom-economic synthetic route to 1,3-enynes. The cross-dimerization of two different terminal alkynes is more complicated than the oxidative cross-coupling.[6] Besides the donor/acceptor selection processes, the control of regioselectivity is another concern. Although several transition-metals have been reported to catalyze the cross-dimerization of terminal alkynes, the state-of-the-art solution is that only very special substrates can be utilized. Bulky silyl-group substituted terminal alkynes as donor alkynes[7] and propargylic alcohols or amines as better acceptor alkynes[8] have to be applied to realize the cross-selectivity, but the scope of the alkynes is limited accordingly (scheme 1, **B**). A practical cross-dimerization of more general aryl alkynes and aliphatic alkynes is highly desirable.[9] Herein, we report an earth-abundant-metal cobalt-catalyzed highly selective cross-dimerization of sterically and electronically unremarkable aryl or alkenyl alkynes and aliphatic alkynes to prepare a variety of gem-1,3-enynes with useful functional groups in high yields under mild reaction conditions (scheme 1, **C**). Moreover, simple gas acetylene could be utilized in this transformation.

Scheme 1. The Cross-coupling of Two Different Terminal Alkynes.



To develop a selective cross-dimerization of two different terminal alkynes, the catalyst has to control three processes in case of metal acetylide mechanism: 1) selective metal-acetylide formation with one of the two terminal alkynes; 2) coordination of metal-acetylide with only the other alkyne to avoid homo-dimerization; 3) regioselectivity in the acceptor alkyne (gem or linear) (Figure 1). During our investigation on the Co(I)-catalyzed enol ester formation between alkynes and carboxylic acids,[10] we observed the 1,3-enyne formation from phenylacetylene with $Co(OAc)_2$/triphos when no reducing Zn was added. We were aware that the OAc ligand in the Co(II)/triphos complex may function as an internal base to promote the cobalt-acetylide formation. The weakly basic acetate may help distinguish between two different terminal alkynes by the acidity difference. The steric hindrance in the $Co(OAc)_2$/triphos complexes could control the coordination of the second alkynes. Bulky groups at phosphorus atoms as well as the backbone structure in the triphos ligands are able to help select smaller aliphatic alkynes. The regioselectivity of the products could be controlled by the steric factors in the ligands. Accordingly, $Co(OAc)_2$/triphos combination might be used to catalyze the selective cross-dimerization of aryl alkynes and aliphatic alkynes.

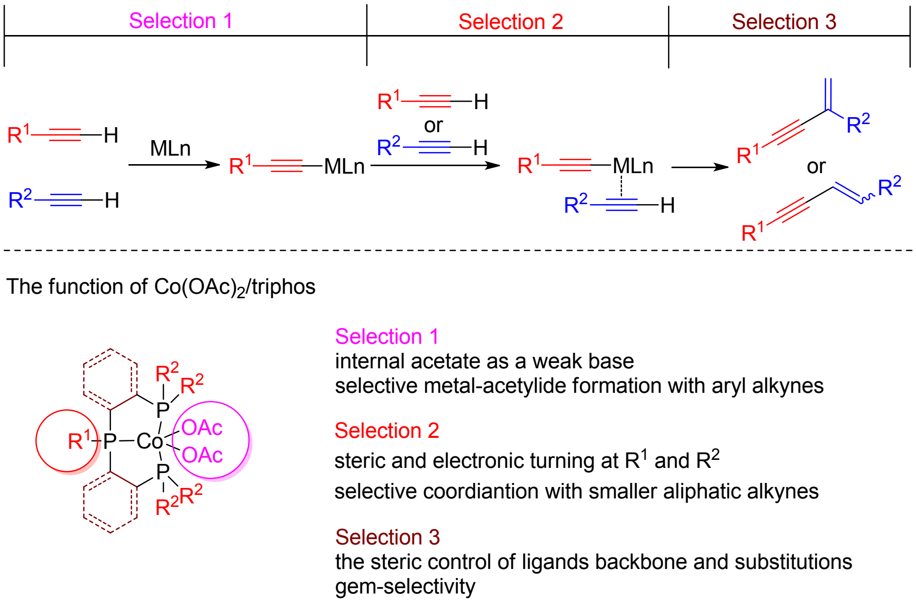


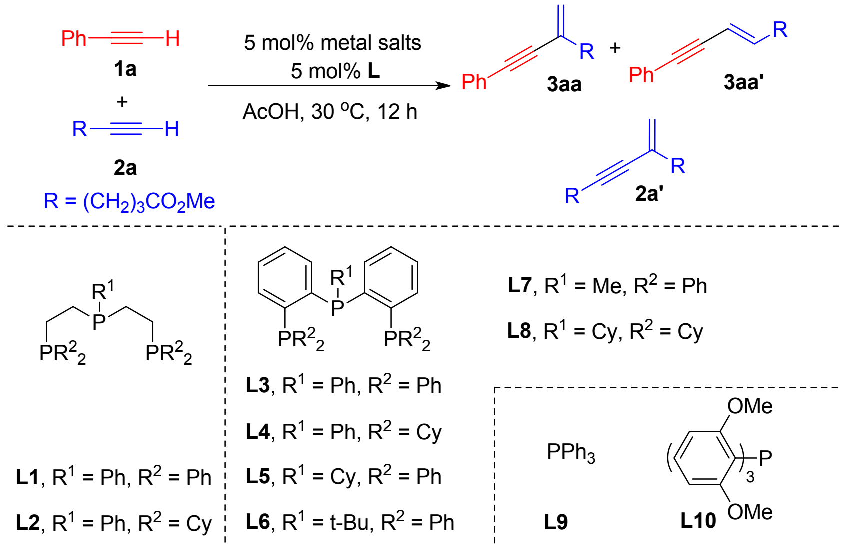
Figure 1. The Selective Processes and the Requirements for Selective Catalyst.

RESULTS AND DISCUSSION

Condition Optimization

To test our hypothesis, we started the study with phenylacetylene **1a** and ester-functionalized aliphatic alkyne **2a** as the model substrates with 1.3 : 1 ratio (Table 1). With $Co(OAc)_2 \cdot 4H_2O$ and triphos **L1** as catalyst, cross-dimerization product **3aa** was isolated in 79% yield. Protic solvent acetic acid was proven to be the key to avoid the oligomers formation. Small amount of head-to-head regiomer **3aa'** and homo-dimer **2a'** were detected by comparation with samples synthesized independently. To improve the selectivity, seven other triphos ligands (**L2** to **L8**) were synthesized and examined. When **L2** with four Cy groups was used, the reaction becomes much slower, while better regioselectivity was observed (entry 2). **L3** with two phenyl rings in the skeleton leads to higher regioselectivity than **L1** (entry 3). However, the amount of homo-dimer **2a'** increases. The Cy groups in **L4** slow down the reaction (61 % yield) and give better selectivity. The influence of substitution at the middle P atom is also examined. Bulkier Cy and t-butyl groups in the triphos ligand **L5** and **L6** lead to inhibition of undesired linear regiomer and homo-dimerization products (entries 5 and 6). Nevertheless, more **3aa'** and **2a'** were obtained in case **L7** with a smaller methyl group was applied. Finally, **L8** with five Cy groups makes this reaction be less reactive (entry 8). The investigation of the homo-dimerization of **1a** and **2a** independently with different triphos ligands further supports this trend (see SI). In the comparing experiments, $[Rh(cod)Cl]_2$/**L9**[8c] and $Pd(OAc)_2$/**L10**[8b], which are selective catalysts to cross-dimerize aryl alkyne (alkenyl alkyne) with propargyl alcohols, are not able to cross-dimerize aryl alkyne and simple aliphatic alkynes selectively (entries 9 and 10). The yield of cross-dimerization product **3aa** could be further improved to 90% when a 1 : 1 mixture of THF and acetic acid was used as the solvent, and 2.5 mol % of cobalt catalyst does not decrease the efficiency (entry 11).

Table 1. Optimization of The Co(II)-Catalyzed Cross-dimerization Reaction of Terminal Alkynes[a]



entry	catalyst	L	yield(**3aa**) (%)[b]	**3aa/3aa'/2a'**[c]
1	$Co(OAc)_2.4H_2O$	**L1**	79	23/4/1
2	$Co(OAc)_2.4H_2O$	**L2**	30	37/0/1
3	$Co(OAc)_2.4H_2O$	**L3**	70	30/1/6
4	$Co(OAc)_2.4H_2O$	**L4**	61	68/0/1
5	$Co(OAc)_2.4H_2O$	**L5**	80	12/0/1
6	$Co(OAc)_2.4H_2O$	**L6**	83	25/0/1
7	$Co(OAc)_2.4H_2O$	**L7**	52	24/3/8
8	$Co(OAc)_2.4H_2O$	**L8**	10	45/0/1
9[d]	$[Rh(cod)Cl]_2$	**L9**	25	9/2/1
10[e]	$Pd(OAc)_2$	**L10**	13	10/1/8
11[f]	$Co(OAc)_2.4H_2O$	**L6**	90	25/0/1

[a]Conditions: **1a** (0.65 mmol, 1.3 equiv), **2a** (0.5 mmol, 1.0 equiv), AcOH (1.0 mL).

[b]Isolated yield. [c]The ratio of **3aa**/ **3aa'**/**2a'** was determined with crude ^{1}H NMR analysis.

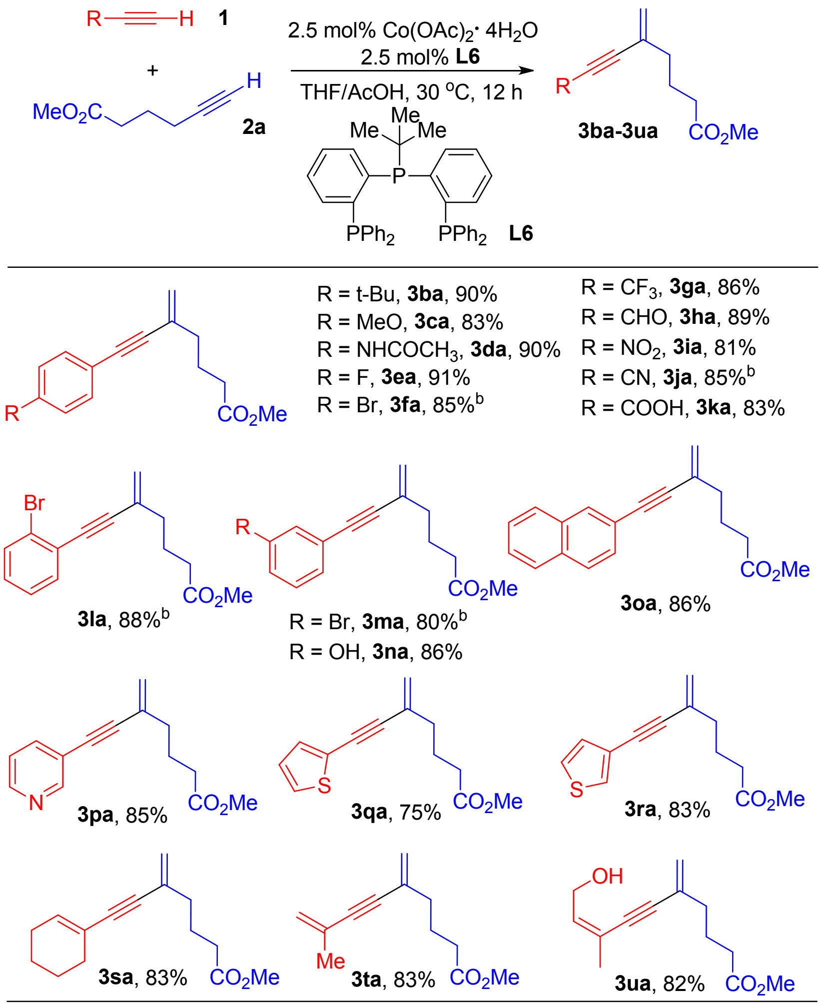
[d]in dichloromethane at 40 °C. [e]in benzene at rt. [f]2.5 mol% $Co(OAc)_2.4H_2O$ in 1: 1 THF/AcOH

Scope of Alkynes

With the optimized reaction condition in hand, the scope of the donor aryl alkynes was examined (Scheme 2). A variety of aryl alkynes with functional groups at para-position on the phenyl ring were checked firstly. Electron-rich t-Bu, MeO, and $NHCOCH_3$ could be tolerated as shown in **3ba** to **3da**. Halogen-substituted aryl alkynes react smoothly to give the cross-dimerization products **3ea** to **3ga** in high yields. Strong electron-withdrawing aldehyde, nitro, cyano and carboxylic acid functions have no negative effect to the yields of the reactions (**3ha** to **3ka**). Bromide at ortho- or meta and free hydroxyl group at meta position can also be tolerated (**3la**, **3ma** and **3na**). Terminal alkynes with 1-naththyl, 2 or 3-thiophenyl and 3-pyridyl groups were all transformed to the enynes **3oa** to **3ra** in high yields. Alkenyl alkynes could also react with aliphatic alkyne **2a** to give the dienynes **3sa** to **3ua**.

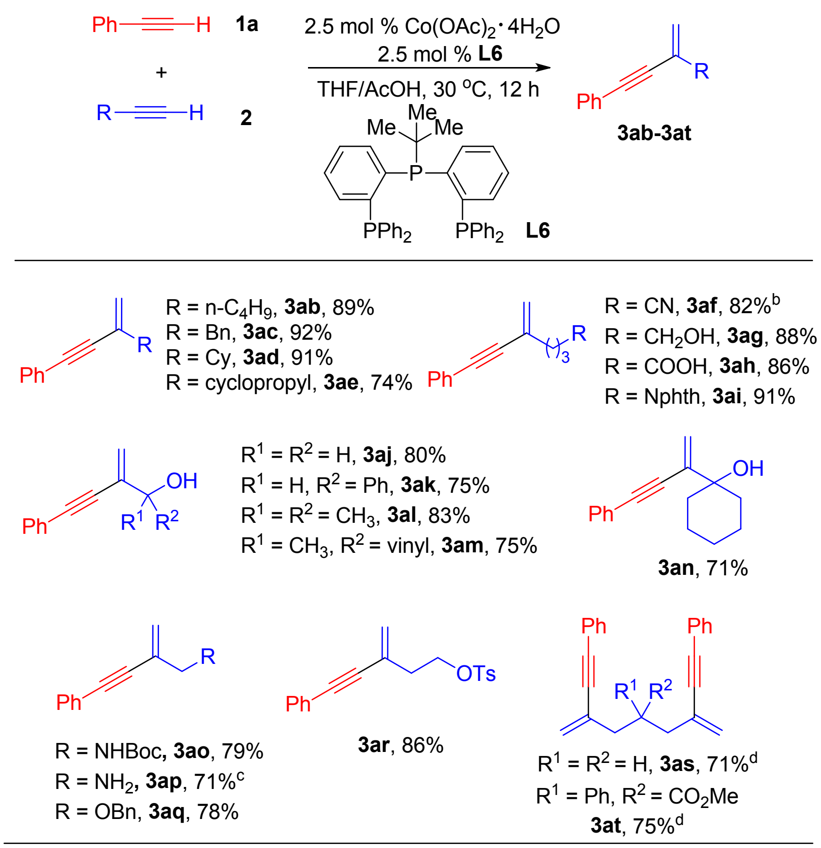
The scope of acceptor aliphatic alkynes was further checked as shown in Scheme 3. Different from the previous reports that only propargyl alcohols and amines can be used as acceptor alkynes,[8] phenylacetylene **1a** react with simple n-butyl and benzyl substituted alkynes to give the 1,3-enynes **3ab** and **3ac** in high yields. Branched cyclohexyl and cyclopropyl groups have no negative effect to the yields of **3ad** and **3ae**. Various functional groups, cyano, hydroxyl, carboxylic acid and phthalimide, can all be tolerated in **3af** to **3ai**. Primary, secondary and tertiary propargyl alcohols could be converted to enynes smoothly (**3aj** to **3an**). Free and Boc-protected propargyl amines as well as propargyl ether participate in this cross-dimerization reaction as the acceptor alkynes (**3ao** to **3aq**). **3ar** with a tosylate function is prepared in high yield, which can be used in further alkylation transformation. Finally, diynes **2s** and **2t** could be transformed to the bis-enynes **3as** and **3at** respectively when 2.5 equivalent phenylacetylene **1a** was used.

Scheme 2. The Scope of Donor-alkynes[a]



[a]Conditions: **2a** (0.5 mmol, 1.0 equiv), **1** (0.65 mmol, 1.3 equiv), THF/AcOH (1:1, 1.0 mL). [b]at 60 °C.

Scheme 3. The Scope of Acceptor-alkynes[a]

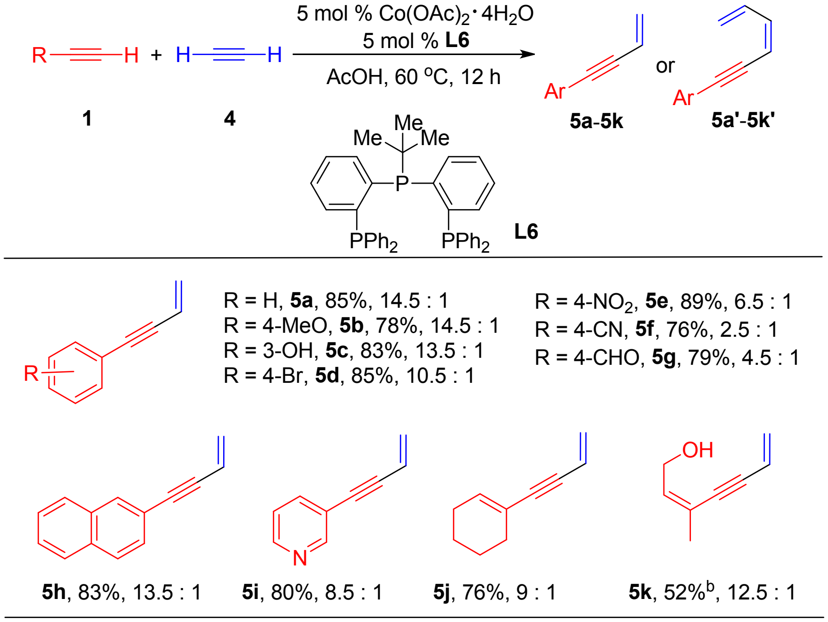


[a]Conditions: **2a** (0.5 mmol, 1.0 equiv), **1** (0.65 mmol, 1.3 equiv), THF/AcOH (1:1, 1.0 mL).

[b]at 60 °C. [c]CH_3CN (1.0 ml) as solvent, 60 °C. [d]2.5 equivalent of **1a** (1.25 mmol) was used.

Inspired by the possible acidity difference directed cross-selectivity, we further examined the reaction of gas acetylene as a donor or acceptor alkyne. To the best of our knowledge, there is no cross-dimerization of simple acetylene gas with other alkynes before. Considering the acidity sequence (aryl alkyne > acetylene > alkyl alkyne), simple acetylene could be used as an acceptor to react with aryl alkynes or a donor with aliphatic alkynes. Higher reaction temperature and catalyst loading are required to convert phenylacetylene **1a** to enyne **5** probably because of the easier coordination of small gas acetylene with cobalt complex. The scope of aryl alkyne is summarized in Scheme 4. Various functional groups at different positions on the phenyl ring could be tolerated and compounds **5a** to **5g** were isolated in high yields. Small amount of **5'** with two acetylene coupled could be observed and the ratio of **5'** increases for electron-deficient aryl alkynes (**5e** to **5g**). A vinyl group was also installed on the 1-naphthyl, 3-pyridyl and alkenyl alkynes smoothly (**5h** to **5k**). 25% acetate of **5k** was isolated under the standard condition, which comes from the further esterification with solvent acetic acid. The reactions between acetylene (donor alkyne) and alkyl alkynes produces only trace amount of desired 1,3-enynes, probably because acetylene itself is easier to react with the possible cobalt-acetylide intermediate than alkyl alkynes.

Scheme 4. The scope of gas acetylene as acceptor-alkyne[a]

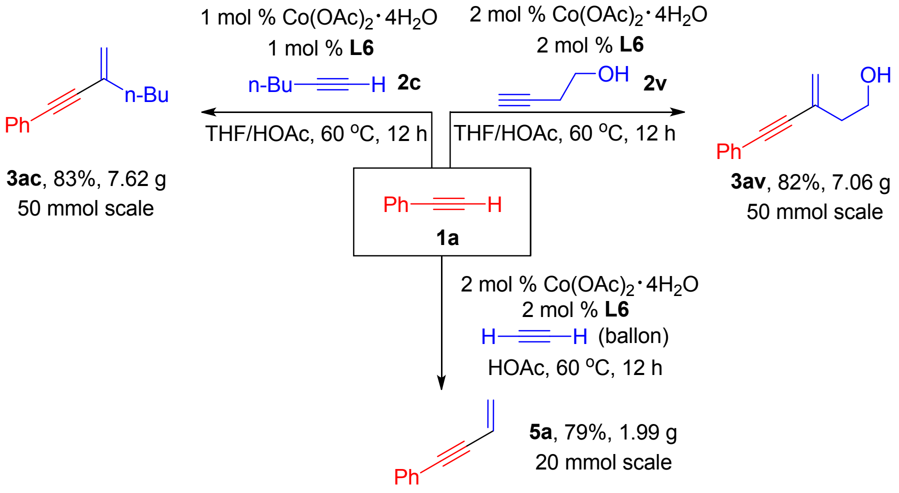


[a]Conditions: **1** (1 mmol, 1.0 equiv), balloon pressure acetylene, AcOH (2.0 mL). [b]25% of acetate of **5k** was isolated.

Large Scale Synthesis

To prove the practicality of this cobalt-catalyzed cross-dimerization reaction, gram-scale synthesis of different 1,3-enynes was conducted (scheme 5). 50 mmol of 1-hexyne **2c** was converted to 7.62 g of **3ac** (83%) with 60 mmol of phenyl acetylene **1a**. The catalyst loading could be decreased to 1 mol % when the reaction was run at 60 ^{o}C. Similarly, **3av** could be prepared in 7 gram scale and the existence of free hydroxyl group requires 2 mol% cobalt catalyst. Finally, enyne **5a** was synthesized in 2 gram scale with balloon pressure acetylene and 2 mol% catalyst.

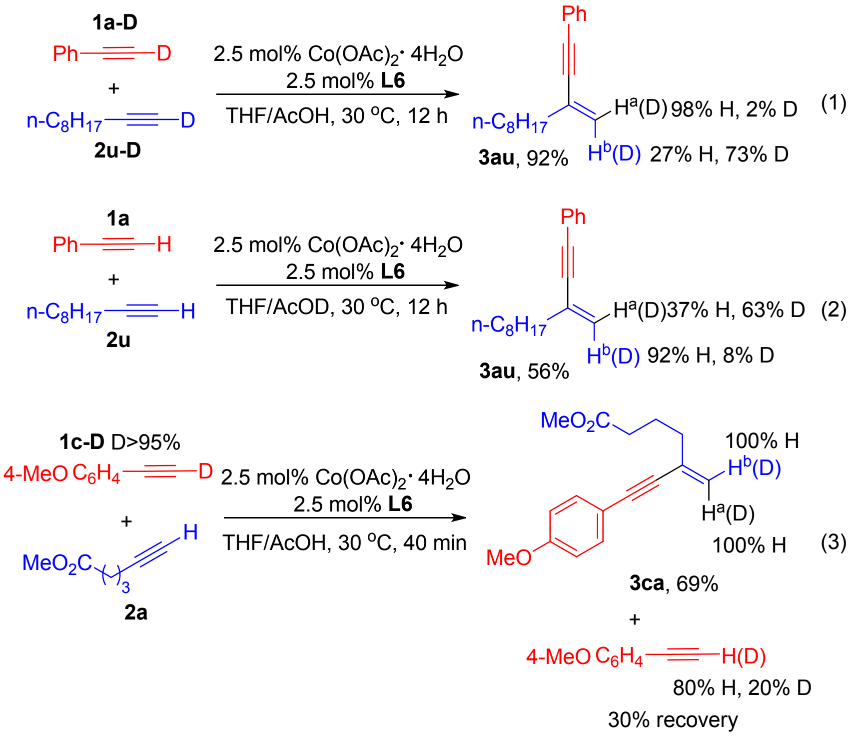
Scheme 5. Gram-scale synthesis.



Mechanism Studies

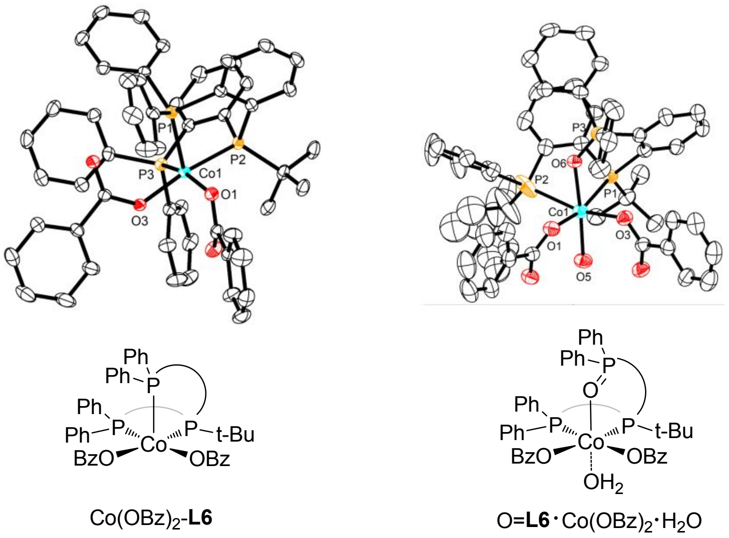
D-Labeling experiments were conducted to explore the reaction mechanism (scheme 6). When both D-labeled **1a-D** and **2u-D** were subjected to the standard condition in acetic acid and THF, **3au** was isolated with 92% yield, in which the hydrogen (H^{a}) cis to alkyne is 98% proton (eq 1). A protonation of the cobalt-carbon bond by the solvent acetic acid may occur. Meanwhile, the hydrogen (H^{b}) cis to alkyl group is assigned to be 27% proton and a slow exchange with acetic acid for the aliphatic terminal alkyne is proposed. On the contrast, when the reaction of **1a** and **2u** was carried out in AcOD, only 56% of **3au** was obtained after the same reaction time (12 hours) (eq 2). The relatively slow reaction in AcOD may suggest that the protonation with acetic acid is involved in the rate-determine step. The 8% of D incorporation of H^{b} could be explained by the slower exchange of aliphatic alkyne with solvent acetic acid. 37% H incorporation at H^a may come from the small amount of water and **1a**, although much more D^+ is in the solvent AcOD. To exclude the possibility that aromatic alkynes have the fast H/D exchange with solvent and then protonate the alkenyl-cobalt intermediate, reaction of **1c-D** and **2a** was conducted in acetic acid (eq 3). After 40 minutes, **3ca** could be isolated in 69% yield and 30% of **1c** was recovered with 80% D/H exchange. No any D-incorporation in **3ca** further supports the protonation with solvent acetic acid.

Scheme 6. D-Labeling Experiments



To get more insight into the reaction mechanism, the single crystal X-ray analysis of the catalyst was conducted. $Co(OBz)_2$-**L6** was selected for its better solubility in organic solvents than $Co(OAc)_2$-**L6**. A crystal of $Co(OBz)_2$-**L6** was obtained from THF and hexane. In the crystal structure of $Co(OBz)_2$-**L6** as shown in Scheme 7 (left), the cobalt complex adopts a 5-coordinate square pyramidal geometry, with two acetate groups, one of the side phosphorus atom and the middle phosphorus atom of **L6** in one plane.[11] The axial position was occupied by the other side phosphorus atom in **L6**. The carboxylates are bound to cobalt in a κ^1 mode. Another complex was isolated when Co(OBz)$_2$ and **L6** were mixed in the presence of air. The crystal structure of the complex reveals that one of the side phosphorus atom was oxidized. In the solid state, the complex O=**L6**·Co(OBz)$_2$·H$_2$O adopts a distorted octahedral geometry, with the phosphine oxide oxygen and the water oxygen at the axial direction (scheme 7, right). O=**L6**·Co(OBz)$_2$·H$_2$O is not active in the cross-dimerization reaction, which could explain why the reaction cannot be carried out in the air.

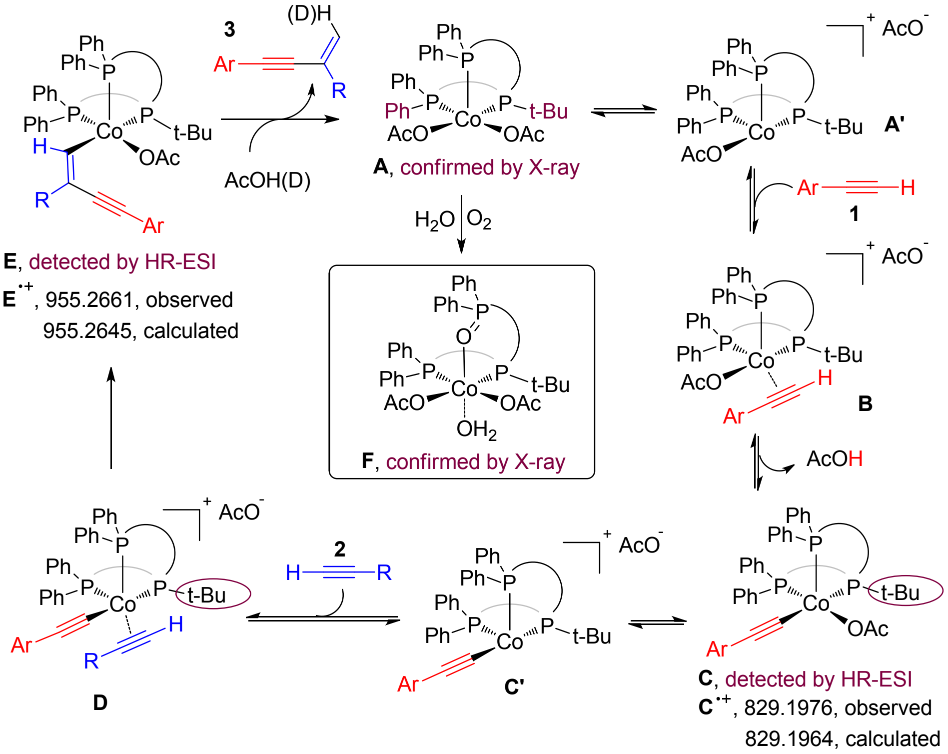
Scheme 7. The crystal structures of Co(OBz)$_2$-L6 and O=L6.Co(OBz)$_2$.H$_2$O with thermal ellipsoids at 30% probability. All hydrogens and solvent were omitted for clarity.



Mechanistic Proposal

Based on the experiments above and literature reports, one catalytic cycle was proposed in scheme 8. One of the acetate in the 17-electron complex **A** dissociates to form a cationic complex **A'**. Aryl alkyne **1** and aliphatic alkyne **2** compete to coordinate with complex **A'** to form cationic intermediate **B**. Deprotonation of terminal alkyne assisted by inter- or intramolecular acetate generates the Co(II)-acetylide **C** and release acetic acid.[12] More acidic aryl or alkenyl alkyne **1** is easier to participate in this step, which accounts for the facts that **1** reacts as the donor alkyne and only trace amount of homo-dimerization products of aliphatic alkynes **2** can be detected. An equilibrium between **C** and cationic **C'** exists. Another alkyne further coordinates with intermediate **C'** to form **D**. At this time, less hindered aliphatic alkyne **2** is preferred because of the steric hindrance in **L6**. The bulky substituents on the triphos ligands, especially the t-Bu group at the middle P, make the Ar and R groups in **1** and **2** locate at the less hindered direction, which is crucial for the gem-selectivity. The regioselectivity may decrease when R is relatively bigger and t-Bu group in **L6** was replaced by smaller group. Alkenyl-cobalt intermediate **E** was formed by migrative insertion of Co-acetylide bond to alkyne **2** and the coordination of acetate anion. From **E**, further migrative insertion into alkyne **2** could generates trimer or oligomers.[13] The applying of acetic acid as solvent is the key for the selective dimerization. Protonation of **E** with acetic acid releases the products **3** and regenerates the catalyst **A**. The attempts to isolate intermediates **C** and **E** were not successful. However, high resolution ESI-MS was applied to provide supports for these possible reaction intermediates (see SI). When phenylacetylene **1a** was added into the mixture of $Co(OAc)_2$ and **L6**, a peak at 829.1976 could be observed, which matches with the radical cation peak of intermediate **C** (829.1964, calculated). A low peak at 955.2661 could be found after the addition of acceptor alkyne **2a**, which indicates the formation of intermediate **E** (955.2645, calculated). Complex **A** could be oxidized in air to form inactive complex **F**, which was characterized by single crystal X-ray diffraction analysis.

Scheme 8. Mechanistic Proposal



In conclusion, we have developed a $Co(OAc)_2$/triphos catalyst system for the selective cross-dimerization between aryl or alkenyl alkynes and aliphatic alkynes. Conjugated 1,3-enynes with a variety of useful functional groups can be prepared in high yields under mild condition. Gas acetylene is also applied to this atom-economic cross-dimerization reaction for the first time. The use of cobalt acetate and easily available bulky tridentate phosphine ligands is crucial to distinguish alkynes at different reaction steps and control the regioselectivity. The structure of the catalyst was elucidated by single crystal X-ray diffraction analysis. D-Labeling experiments and high-resolution ESI-MS were applied to support the proposed mechanism. Extension of acceptors and a chiral version of the triphos ligand are under investigation in our group.

ASSOCIATED CONTENT

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Notes

The authors declare no competing financial interests.

Supporting Information. Detailed experimental procedures, characterization data, copies of ^{1}H, ^{13}C NMR spectra, and X-ray crystal structure. This material is available free of charge via the Internet at http://pubs.acs.org. CCDC 1897113 and 1897114 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif. brief

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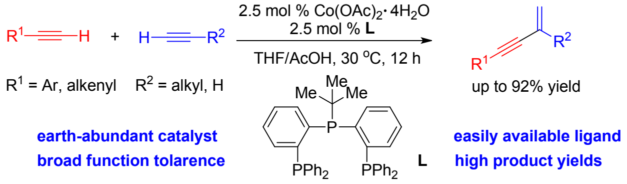
R1—≡—H + H—≡—R2
2.5 mol % Co(OAc)2·4H2O
2.5 mol % L
THF/AcOH, 30 °C, 12 h
R1 = Ar, alkenyl
R2 = alkyl, H
R1
R2
up to 92% yield
Me
Me
Me
P
PPh2
PPh2
L
earth-abundant catalyst
broad function tolarence
easily available ligand
high product yields