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Cobalt-Catalyzed Intermolecular [2+2] Cycloaddition between Alkynes and Allenes**

Wei Ding and Naohiko Yoshikai*

Abstract: An intermolecular [2+2] cycloaddition reaction between an alkyne and an allene is reported. In the presence of a cobalt(I)–diphosphine catalyst, a near equimolar mixture of the alkyne and the allene is converted to 3-alkylidenecyclobutene derivative in good yield with high regioselectivity. The reaction tolerates a variety of internal alkynes and mono- or disubstituted allenes bearing various functional groups. The reaction is proposed to involve regioselective oxidative cyclization of the alkyne and the allene to form 4-alkylidenecobaltacyclopentene intermediate, followed by C–C reductive elimination.

Cyclobutane and cyclobutene derivatives are important structural elements in natural products and biologically active compounds,^[1] and have also served as versatile synthetic intermediates owing to their strain-driven chemical reactivities.^[2] The [2+2] cycloadditions represent the most straightforward and atom-economical approaches toward such four-membered carbocycles,^[3] where the use of allene as one of unsaturated reactants has received considerable attention.^[4] With alkyne as the other unsaturated reactant, [2+2] cycloaddition leading to a 3-alkylidenecyclobutene skeleton has been extensively explored in intramolecular settings under thermal^[5] or transition metal-catalyzed^[6] conditions (Scheme 1a). By contrast, examples of intermolecular alkyne–allene [2+2] cycloaddition are sporadic,^[7] and limited to those involving activated alkynes such as dimethyl acetylenedicarboxylate or activated allenes such as 4-vinylideneoxazoline-2-one under thermal conditions. For example, the latter case reported by Tamaru and coworkers required the use of large excess of a terminal alkyne as the reaction partner (Scheme 1b).^[7c,d] To our knowledge, selective intermolecular [2+2] cycloaddition between electronically unbiased alkynes and allenes under transition metal catalysis remains elusive, while different types of allene/alkyne cycloaddition and dimerization have been reported using rhodium and nickel catalysts.^[8] Herein, we report that a cobalt–diphosphine catalyst promotes intermolecular [2+2] cycloaddition between an alkyne and an allene in a near equimolar ratio (Scheme 1c). The reaction tolerates a broad range of internal alkynes and mono- or disubstituted allenes, affording 3-alkylidenecyclobutenes with high regioselectivity.

a) Intramolecular [2+2]: Many examples

b) Intermolecular [2+2]: Rare and limited to activated alkyne or allene

c) This work: Intermolecular [2+2] between unactivated alkyne and allene

Scheme 1. Alkyne–allene [2+2] cycloaddition.

Previous studies by Cheng and Hilt demonstrated the ability of low-valent cobalt catalysts to promote intermolecular [2+2] cycloaddition between internal alkynes and strained alkenes.^[9] Ogoshi reported cobalt-catalyzed [2+2] cycloaddition between 1,3-enynes and vinylarenes to give 1-alkenylcyclobutenes.^[10] More recently, Rajanbabu achieved cobalt-catalyzed 1,3-enyne/ethylene [2+2] cycloaddition and (asymmetric) hydrovinylation in a tandem fashion.^[11] Inspired by these precedents,^[12,13,14] the present study began with exploration of the reaction between 4-octyne (**1a**) and cyclohexylallene (**2a**) (Table 1; see Tables S1–S3 for more detail). With a catalytic system comprised of CoBr₂ (5 mol%), dppf (5 mol%), and In (20 mol%), a 1:1 mixture of **1a** and **2a** underwent clean conversion in DCE at 60 °C, affording the desired [2+2] cycloadduct **3aa** as a single regio- and stereoisomer in 89% yield (entry 1). The reaction was found to be highly sensitive to the ligand. Among typical diphosphine ligands other than dppf, only dppb promoted the reaction to a significant extent (entries 2–4), while PPh₃ was only moderately effective (entry 5). A comparable reaction efficiency was observed using CoCl₂ instead of CoBr₂ (entry 6), whereas the use of CoI₂ led to a significant drop in the yield of **3aa** (entry 7). Regarding the reductant, Zn was much less effective than In (entry 8). While CH₂Cl₂ could be used as alternative solvent (entry 9), other solvents such as MeCN were rather detrimental (entry 10). **Virtually no [2+2] cycloadduct was observed using InBr₃ (10 mol%) alone as the catalyst^[15] or using InBr₃ (10 mol%) in place of In (entries 11 and 12), suggesting that a low-valent cobalt species is catalytically active. Note also**

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that the present [2+2] cycloaddition did not proceed at all under thermal conditions, at a temperature up to 100 °C.

Table 1. Effect of reaction conditions.^[a]

Entry	Deviation from standard conditions	Yield [%] ^[c]
1	None	89
2	dppe instead of dppf	0
3	dppp instead of dppf	2
4	dppb instead of dppf	67
5	PPh ₃ (10 mol%) instead of dppf	45
6	CoCl ₂ instead of CoBr ₂	87
7	CoI ₂ instead of CoBr ₂	47
8	Zn instead of In	26
9	CH ₂ Cl ₂ instead of DCE	80
10	MeCN instead of DCE	32
11	InBr ₃ (10 mol%) as the catalyst	0
12	InBr ₃ (10 mol%) instead of In	1

[a] The reaction was performed using 0.2 mmol each of **1a** and **2a** for 24 h. [b] Abbreviation: dppf = 1,1'-bis(diphenylphosphino)ferrocene; dppe = 1,2-bis(diphenylphosphino)ethane; dppp = 1,3-bis(diphenylphosphino)propane; dppb = 1,4-bis(diphenylphosphino)butane; [c] Determined by GC using *n*-tridecane as an internal standard.

With the optimized Co–dppf catalytic system in hand, we explored the scope of the present [2+2] cycloaddition with respect to alkynes (Table 2). A variety of dialkyl- and diarylalkynes participated in the cycloaddition with **2a** to afford the desired products **3aa–3ja** in good to excellent yields. The *E*-stereochemistry of **3fa** was unambiguously established by the X-ray crystallographic analysis.^[16] Phenyl(alkyl)alkynes also underwent cycloaddition with **2a**, with preferential C–C bond formation between the allenic terminus and the acetylenic carbon proximal to the phenyl group, affording the products **3ka–3sa** with good to excellent regioselectivities (ca. 5:1 to > 20:1). Hydroxy, methoxy, allyloxy, and ester substituents were well tolerated (see **3pa–3sa**). In contrast to these cases, the reaction of 1-(1-naphthyl)-1-propyne resulted in the product **3ta** with rather low regioselectivity of 1.6:1, while excellent regioselectivity was observed for the reaction of 1-(2-thienyl)-1-hexyne (see **3ua**). Enynes were also amenable to the [2+2] cycloaddition, affording the products **3va–3xa** with varying level of regioselectivity. An alkynyl ester also took part in the reaction to afford the product **3ya** with moderate regioselectivity. A twofold cycloaddition of 1,4-bis(alkynyl)benzene was achieved to afford the product **3za**. Unfortunately, the reaction using a

terminal alkyne such as phenylacetylene or 1-octyne led to an intractable mixture of products.

Table 2. [2 + 2] Cycloaddition of various alkynes with allene **2a**.^[a]

1a	2a (1.0–1.5 equiv)	3aa–3za
3aa (R = <i>n</i> -Pr), 90% 3ba (R = Et), 89% 3ca (R = <i>n</i> -Bu), 92% 3da (R = <i>n</i> -Pent), 94% 3ea (R = CH ₂ OBn), 77%	3fa (Ar = Ph), 83% 3ga (Ar = 4-MeOC ₆ H ₄), 81% 3ha (Ar = 4-MeC ₆ H ₄), 80% 3ia (Ar = 4-FC ₆ H ₄), 74% 3ja (Ar = 2-thienyl), 80%	3fa (X-ray)
3ka , 73% (r.r. > 20:1)	3la , 80% (r.r. = 10:1)	3ma , 79% (r.r. = 4.5:1)	3na , 71% (r.r. = 7:1)
3oa , 84% (r.r. = 5.2:1)	3pa , 62% (r.r. > 20:1)	3qa , 72% (r.r. = 15:1)	3ra , 65% (r.r. > 20:1)
3sa , 72% (r.r. = 13:1)	3ta , 83% (r.r. = 1.6:1)	3ua , 79% (r.r. > 20:1)
3va , 61% (r.r. = 7:1)	3wa , 71% (r.r. = 1:1)	3xa , 80% (r.r. = 5:1)	3ya , 84% (r.r. = 2.2:1)

[a] The reaction was performed on a 0.4 mmol scale (r.r. refers to regioisomer ratio).

We next examined the reaction using various allenes (Table 3). A variety of monoalkyl-substituted allenes participated in the reaction with **1a** or **1f** to afford the desired products in moderate to good yields. The reaction tolerated functional groups such as hydroxy (**3ae**), siloxy (**3af**), allyloxy (**3ag**), ester (**3ah**), phthalimide (**3ai**), and chloro (**3aj**) groups on the allene substrate. Phenylallene also underwent the desired cycloaddition at 80 °C (see **3ak**). Furthermore, 1,1-disubstituted allenes such as 5-vinylidenenonane and vinylidencyclohexane underwent regioselective cycloaddition on the terminal C=C bond to afford **3fl** and **3am**, respectively, in good yields. A twofold cycloaddition using **1f** and bisallene **2n** was also achieved in moderate yield.

Table 3. [2 + 2] Cycloaddition of various allenes.^[a]

[a] The reaction was performed on a 0.4 mmol scale. [b] The reaction was performed at 80 °C.

We also probed the reactivity of 1,3-disubstituted allenes. The reaction between the alkyne **1e** and 1,3-dihexylallene (**2o**) under the standard conditions afforded the desired cycloadduct **3eo** in 68% yield, which was accompanied by an Alder-ene-type product,^[5g] that is, a [3]dendralene derivative **4a** in 22% yield (Scheme 2a). Likewise, cyclonona-1,2-diene (**2p**) also participated in the reaction with **1e** to afford a mixture of the cycloadduct **3ep** and the dendralene **4b** in 72% and 19% yields, respectively (Scheme 2b). The formation of the Alder-ene products in these cases and the absence of such products in the reactions of terminal allenes can be rationalized by a mechanism involving regioselective oxidative cyclization of alkyne and allene (vide infra).

Scheme 2. Reactions of 1,3-disubstituted allenes.

Monitoring of the [2+2] cycloaddition between **1a** and **2a** indicated the presence of a significant induction period (Figure S3). Thus, only a trace amount of **3aa** was formed during the initial 2 hours, followed by gradual increase in the reaction rate toward the completion of the reaction in 9 hours. This behavior may be attributed to relatively slow reduction of the Co^{II} precatalyst to an active low-valent cobalt species. A control reaction using a combination of preformed cobalt(I) complex CoCl(PPh₃)₃ (5 mol%) and dppe (5 mol%) did not afford **3aa** at all after 24 h at 60 °C, while the addition of a catalytic amount of InBr₃ (10 mol%) to this system dramatically promoted the cycloaddition, affording **3aa** in 91% yield within 10 min at room temperature (Scheme 3a). These observations would suggest that the present catalytic system involves a cationic Co^I species, which is generated through reduction of Co^{II} to Co^I and abstraction of the remaining halide on cobalt by in situ-generated InBr₃.^[17]

Scheme 3b shows proposed reaction pathways. Regioselective oxidative cyclization between alkyne **1** and the less substituted C=C bond of allene **2** would form a 4-alkylidenecobaltacyclopentene intermediate **A**, followed by reductive elimination to afford the [2+2] cycloadduct **3**. For the case of 1,3-dialkyl allene, **A** could also undergo β-hydride elimination–reductive elimination sequence via an alkenyl(hydrido)cobalt intermediate **B**, which would account for the formation of the triene **4**.^[8a] The regioselectivity observed for phenyl(alkyl)alkynes (see **3ka–3sa**) is in line with the typically observed regioselectivity of cobalt-catalyzed reductive couplings involving such alkynes.^[12] The low regioselectivity of the reaction of 1-(1-naphthyl)-1-propyne (see **3ta**) could be attributed to the steric repulsion between the cobalt center and the 1-naphthyl group (R¹) during the oxidative cyclization process.

Scheme 3. Control experiments and proposed reaction pathways.

The present cycloadducts are amenable to further synthetic transformations. Pd/C-catalyzed hydrogenation of **3fa** took place exclusively on the exo C=C bond to afford the cyclobutene **5** in 76% yield, while hydroboration-oxidation of the same substrate regioselectively afforded the alcohol **6** in 61% yield (Scheme 4a). Diels–Alder reactions of **3va** and **3xa** with maleic anhydride afforded the tricyclic product **7** and the tetracyclic product **8**, respectively, in moderate yields.^[16]

Scheme 4. Product transformations.

In summary, we have developed an intermolecular [2+2] cycloaddition reaction between alkynes and allenes promoted by a cobalt–diphosphine catalyst. The reaction tolerates various internal alkynes as well as mono- and disubstituted allenes, and

displays high regioselectivity with respect to both the alkynes and allenes, thus affording a variety of 3-alkylenecyclobutenes that are otherwise difficult to access. Further studies on the reactivity of these cyclobutene derivatives as well as the cobalt catalysis involving unsaturated substrates are ongoing in our laboratory.

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Keywords: cycloaddition • alkyne • allene • homogeneous catalysis • cobalt

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A cobalt–diphosphine catalyst promotes a selective [2+2] cycloaddition reaction between an alkyne and an allene, affording a 3-alkylidenecyclobutene with high regioselectivity. The reaction tolerates various internal alkynes and mono- and disubstituted allenes with different functional groups, and can be achieved using a near equimolar mixture of the unsaturated reactants.