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Cobalt-Catalyzed Intramolecular Reaction between Vinylcyclopropane and Alkyne: Switchable [5 + 2] Cycloaddition and Homo-Ene Pathways**

Chunlin Wu and Naohiko Yoshikai*

Abstract: Cobalt–diphosphine catalysts have been found to promote intramolecular reactions between vinylcyclopropane and alkyne, which selectively afford either [5 + 2] cycloaddition product or homo-ene reaction product under solvent control. The former product is exclusively formed in noncoordinating 1,2-dichloroethane, while the latter is dominant in coordinating solvents such as acetonitrile and dimethylacetamide. Furthermore, a highly enantioselective variant of the homo-ene reaction has been achieved, affording chiral tetrahydrofuran, pyrrolidine, and cyclopentane derivatives bearing 1,3-diene and alkylidene substituents.

Vinylcyclopropane (VCP) has proven to serve as a versatile C5 unit in transition metal-catalyzed cycloaddition reactions involving 2π units such as alkyne, alkene, and allene.^[1] Since Wender's first report on the rhodium(I)-catalyzed intramolecular [5 + 2] cycloaddition between tethered VCP and alkyne to form cycloheptadiene,^[2] the scope of rhodium-catalyzed VCP cycloaddition has significantly expanded to enable various [5 + 2], [5 + 2 + 1], and other cycloadditions in intra- and intermolecular settings.^[3–6] Meanwhile, the intramolecular VCP/alkyne cycloaddition has also been achieved using other transition metals such as ruthenium,^[7] nickel,^[8] iron,^[9] and iridium.^[10] Depending on the transition metal, the VCP/alkyne cycloaddition is proposed to involve either alkyne/alkene oxidative cyclization to form a metallacyclopentene **A** (for Ru,^[11] Ni,^[12] and Fe^[9]) or cyclopropane cleavage to form a metallacyclohexene **B** (for Rh^[13] and Ir^[10]) as the initial step (Scheme 1). The intermediates **A** and **B** would converge to a metallacyclooctadiene **C** via β -carbon elimination and migratory insertion, respectively, and C–C reductive elimination of this common intermediate would lead to the cycloheptadiene product. In this connection, Louie reported on a diversion of the reaction pathway of **C** under nickel–N-heterocyclic carbene (NHC) catalysis.^[8] Thus, using *ItBu* (1,3-di-*tert*-butylimidazolidene), β -hydride elimination outcompetes reductive elimination to selectively afford a "homo-ene" product, while otherwise the two pathways compete with each other depending on the alkyne substituent.^[12]

The [5 + 2] cycloaddition/homo-ene selectivity is an illustrative case of the competition between reductive elimination

and β -hydride elimination, which represents a persistent problem in transition metal-catalyzed C–C bond forming reactions.^[14] Herein, we report that cobalt–diphosphine catalysis allows for facile switch between [5 + 2] and homo-ene pathways, with the solvent being a major selectivity-controlling factor. Thus, the [5 + 2] cycloaddition is exclusively promoted in noncoordinating 1,2-dichloroethane (DCE), while the homo-ene pathway operates dominantly in coordinating solvents such as acetonitrile and dimethylacetamide (DMA). This chemoselectivity control proved effective for a broad range of tethered VCP/alkyne substrates. Moreover, the homo-ene reaction was achieved in a highly enantioselective fashion using a chiral diphosphine ligand.

Scheme 1. Transition metal-catalyzed intramolecular reaction between vinylcyclopropane and alkyne.

Driven by our interest in exploring "noble" and unique catalytic activity of earth-abundant cobalt,^[15–17] we initiated the present study with the reaction of an ether-tethered VCP/alkyne substrate **1a**, testing catalytic systems comprising CoBr₂ (10 mol%), ligand (12 mol%), and Zn dust as a reductant in different solvents (Table 1; see Table S1–S9 for more detail). The screening using DCE as the solvent identified dppp as an effective ligand for the [5 + 2] cycloaddition, affording the cycloheptadiene derivative **2a** in 80% yield (entry 1). Other common diphosphine ligands did not promote the reaction, except that dppe afforded **2a** in a low yield (entries 2–4; see also Table S1). Interestingly, replacement of DCE with MeCN dramatically changed the outcome of the Co–dppp-catalyzed reaction, affording the homo-ene product **3a** as the dominant product (entry 5). With subsequent ligand screening, Xantphos proved to afford **3a** in a higher yield (entry 8). Xantphos also

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exhibited exclusive selectivity toward **3a** in other coordinating solvents such as DMA, dimethylformamide (DMF), and N-methylpyrrolidinone (NMP) (entries 9–11; see also Table S7). Note that various other diphosphines also promoted the formation of **3a** in coordinating solvents (Table S3–S6), indicating that the selectivity toward **3a** is not uniquely attributable to the nature of Xantphos. Upon further screening, the use of CoI_2 precatalyst and ZnI_2 additive was found to accelerate the [5 + 2] cycloaddition in DCE, allowing efficient formation of **2a** with a lower catalyst loading (5 mol%) at a lower temperature (60 °C; entry 12).^[17b,c] Furthermore, the same catalytic system exclusively promoted the homo-ene reaction in NMP (entry 13), illustrating the decisive effect of the solvent on chemoselectivity (see also Table S8 and S9). The catalyst loading for the homo-ene reaction using Xantphos could also be reduced to 5 mol% (entry 14).

Table 1. Effect of ligands and solvents on intramolecular VCP/alkyne reaction.^[a]

Entry	Ligand ^[b]	Solvent	2a [%] ^[b]	3a [%] ^[b]
1	dppp	DCE	80	0
2	dppe	DCE	20	0
3	dppf	DCE	0	0
4	Xantphos	DCE	0	0
5	dppp	MeCN	5	45
6	dppe	MeCN	0	0
7	dppf	MeCN	0	0
8	Xantphos	MeCN	0	70
9	Xantphos	DMA	0	65
10	Xantphos	DMF	0	55
11	Xantphos	NMP	0	70
12 ^[d]	dppp	DCE	85 ^[e]	0
13 ^[d]	dppp	NMP	0	86
14 ^[f]	Xantphos	MeCN	0	87 ^[e]

[a] The reaction was performed on a 0.05 mmol scale at a concentration of 0.2 M. [b] dppp = 1,3-bis(diphenylphosphino)propane; dppe = 1,2-bis(diphenylphosphino)ethane; dppf = 1,1'-bis(diphenylphosphino)ferrocene; Xantphos = 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene. [c] Determined by GC using *n*-tridecane as an internal standard. [d] CoI_2 (5 mol%) and dppp (6 mol%) were used, and ZnI_2 (10 mol%) was added. The reaction was performed at 60 °C. [e] Isolated yield. [f] CoBr_2 (5 mol%) and Xantphos (6 mol%) were used.

With the above conditions in hand, we explored the scope of the [5 + 2] cycloaddition and the homo-ene reaction. The [5 + 2] cycloaddition reactions of various VCP/alkyne substrates under

the Co–dppp catalytic system are summarized in Table 2. The oxygen-tethered VCP/alkyne substrates bearing aryl and heteroaryl substituents on the alkyne moiety underwent [5 + 2] cycloaddition to afford the corresponding cycloheptadienes **2a–2l** in moderate to good yields. The reaction tolerated functional groups such as bromide (**2c**), trifluoromethyl (**2d**), ester (**2e**), and ketone (**2f**) groups as well as heteroaryl substituents such as 2-thienyl (**2j**), 2-benzothienyl (**2k**), and 2-benzofuranyl (**2l**) groups. Methyl and *n*-hexyl groups could also be tolerated on the alkyne terminus (**2m** and **2n**), while the substrate bearing a cyclohexyl group did not give the desired product. Note that a substrate bearing a terminal alkyne moiety failed to participate in this [5 + 2] cycloaddition as well as in the homo-ene reaction under the Co–Xantphos catalysis. The substrate bearing a methyl substituent at the allylic position afforded the product **2o** as a major diastereomer. Besides the oxygen-tethered substrates, nitrogen- or carbon-tethered VCP/alkynes also smoothly participated in the [5 + 2] cycloaddition, affording the desired products **2p** and **2q** in good yields.

Table 2. Cobalt-catalyzed intramolecular [5 + 2] cycloaddition between VCP and alkyne.^[a]

2a , 85%	2b (R = F), 77%	2c (R = Br), 63%	2d (R = CF_3), 70%	2e (R = CO_2Et), 76%	2f (R = COMe), 63%	2g (R = OMe), 53% ^[b]	2h , 70%
2i , 71%	2j , 62%	2k (X = S), 62%	2l (X = O), 30%	2m (R = Me), 60%	2n (R = <i>n</i> -Hex), 76%	2o , 70% ^[c]	2p , 94%
						2q , 85%	

[a] The reaction was performed on a 0.5 mmol scale at 0.33 M. [b] 10 mol% of CoI_2 and 12 mol% of dppp were used. [c] Isolated as a pure diastereomer. The diastereomer ratio in the crude product was 9.5:1 as determined by GC analysis.

The homo-ene reaction under the Co–Xantphos catalytic system^[18] was also achieved using a variety of VCP/alkynes (Table 3). As was the case with the [5 + 2] cycloaddition, a variety of aryl and heteroaryl-substituted substrates participated in the reaction to afford the desired triene products **3a–3k** in

good yields. Furthermore, alkyl groups including a cyclohexyl group could be tolerated as the alkyne substituent (see **3l–3n**). The reaction of the substrate with allylic branching again took place diastereoselectively (**3o**). The nitrogen- and carbon-bridged substrates were also amenable to the homo-ene reaction (**3p** and **3q**). Note that the stereochemistry of the 1,3-diene and alkylidene moieties was unambiguously confirmed by X-ray crystallographic analysis of **3j** (see the box in Table 3).^[18]

Table 3. Cobalt-catalyzed intramolecular homo-ene reaction between VCP and alkyne.^[a]

[a] The reaction was performed on a 0.5 mmol scale at 0.33 M. [b] 10 mol% of CoBr₂ and 12 mol% of Xantphos were used.

Having demonstrated the generality of the [5 + 2] cycloaddition and the homo-ene reactions, we became interested in the feasibility of their enantioselective variants using chiral cobalt–diphosphine catalysts. Our attempts on the enantioselective [5 + 2] cycloaddition, which was previously achieved by Shintani and Hayashi using a chiral rhodium catalyst,^[31] have met with limited success (Table S10). On the other hand, we were able to achieve highly enantioselective homo-ene reaction (Table 4; see Table S11 for optimization results). Thus, the reaction of the model substrate **1a** proceeded under a catalytic system comprising CoBr₂ (10 mol%), (*R,R*)-QuinoxP* (12 mol%), and Zn (50 mol%) in DMA at 40 °C, affording the desired product **3a** in 79% yield with 98% ee. High enantioselectivities (90–99% ee) were also achieved for selected oxygen, nitrogen, or carbon-tethered substrates bearing different aryl, heteroaryl, or alkyl substituents at the

alkyne terminus (Table 4). The absolute configuration of **3p** was determined to be *R* by X-ray crystallographic analysis.^[19]

Table 4. Enantioselective homo-ene reaction between VCP and alkyne.^[a]

[a] The reaction was performed on a 0.5 mmol scale at 0.33 M. The enantiomeric excess was determined by chiral HPLC.

To gain insight into the mechanism of the [5 + 2] cycloaddition and homo-ene reaction and the possible origin of their divergence, density functional theory (DFT) calculations were performed on the reaction pathway of a model complex (**CP1**) between a VCP/alkyne substrate and a cationic cobalt(I)–diphosphine species (Figure 1a).^[20–22] **CP1** undergoes oxidative cyclization (**TS1**) with moderate activation energy (12.1 kcal mol^{−1}) to afford cobaltacyclopentene **CP2**, which is followed by facile β-carbon elimination (**TS2**) leading to cobaltacyclooctadiene **CP3**. An alternative pathway leading to **CP3**, which involves cyclopropane cleavage (**TS1'**) and alkyne insertion (**TS2'**), was found to require much higher activation energies. The preference for the oxidative cyclization pathway appears in accordance with numerous examples of alkyne/alkene couplings under low-valent cobalt catalysis.^[17b,c,23] **CP3** can then undergo C–C reductive elimination (**TS3**) to afford [5 + 2] adduct–cobalt complex (**PD1**), or β-hydride elimination (**TS4**) and C–H reductive elimination (**TS5**) to furnish homo-ene product–cobalt complex (**PD2**). The former pathway required a lower activation energy by 3.3 kcal mol^{−1}, in consistent with the experimentally observed selectivity in noncoordinating DCE. It is worthwhile to note that the *cis*-olefin moiety of cobaltacyclooctadiene acts as a π-acceptor to facilitate C–C reductive elimination,^[24] as judged from much shorter Co–olefin bonding in **TS3** than in **CP3**.

Interestingly, the energetics of these chemoselectivity-determining steps was greatly affected by taking a MeCN molecule into the computational model (Figure 1b). MeCN strongly coordinates to cobaltacyclocloctadiene (Co–N = 2.00 Å), thus forming an octahedral geometry (CP3S). The strong coordination of MeCN is retained in the transition states of β -hydride elimination (TS4S; Co–N = 1.99 Å) and C–H reductive elimination (TS5S; Co–N = 1.97 Å). By contrast, the octahedral

geometry collapses in the transition state of C–C reductive elimination (TS3S), which no longer enjoys coordination of MeCN (Co–N = 4.55 Å). Reflecting these structural features, the β -hydride elimination/C–H reductive elimination pathway becomes energetically favored over the C–C reductive elimination, which would qualitatively account for the observed chemoselectivity switch in coordinating solvents.

Figure 1. (a) Free energy diagram ($S = 0$) for [5 + 2] cycloaddition and homo-ene reaction mediated by a model cobalt(I)–diphosphine species (PCM(DCE)-M06L/SDD(Co)-6-311+G(2d,p)//M06L/SDD(Co)-6-31G(d)). (b) Optimized structures of key intermediates and transition states incorporating MeCN as a coordinating solvent (PCM(MeCN)-M06L/SDD(Co)-6-311+G(2d,p)//M06L/SDD(Co)-6-31G(d)).

In summary, we have demonstrated the capability of cobalt in promoting intramolecular reaction between VCP and alkyne, enabling either [5 + 2] cycloaddition or homo-ene reaction by appropriate choice of the solvent and other reaction conditions. The chemodivergence has been achieved for a broad range of substrates. A highly enantioselective homo-ene reaction has also been achieved for the first time using a cobalt–chiral diphosphine catalyst. DFT calculations provided qualitative insight into the reaction mechanism and the influence of coordinating solvents on the chemoselectivity, while the effect of individual (chiral) diphosphine ligands on the energy profile, chemoselectivity, and enantioselectivity deserves further investigation. We envision that cobalt catalysis holds promise not only for emulating the rich synthetic chemistry of VCPs under transition metal catalysis, but also for enabling their

unique transformations with high chemo-, regio-, and stereoselectivities.

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Keywords: cobalt • cycloaddition • C–C bond cleavage • cyclopropane • asymmetric catalysis

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and Alkyne: Switchable [5 + 2]
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Cobalt–diphosphine catalysts have been found to promote intramolecular reactions between vinylcyclopropane and alkyne to selectively afford [5 + 2] cycloaddition or homo-ene reaction product. The former product is exclusively formed in noncoordinating dichloroethane, while the latter pathway is dominant in coordinating solvents such as acetonitrile and dimethylacetamide. Furthermore, a highly enantioselective variant of the homo-ene reaction has been achieved.