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Synthesis of 1,2-Disubstituted Cyclopentenes by Palladium-Catalyzed Reaction of Homopropargyl-Substituted Dicarbonyl Compounds with Organic Halides via 5-*Endo-Dig* Cyclization

Daishi Fujino, Hideki Yorimitsu,* and Atsuhiro Osuka

Department of Chemistry, Graduate School of Science, Kyoto University, Kitashirakawa, Sakyo-ku, Kyoto 606-8502, Japan

yori@kuchem.kyoto-u.ac.jp

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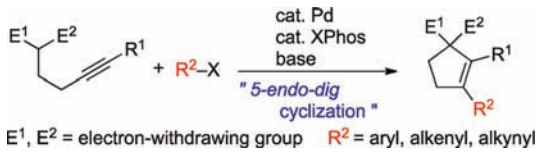
ABSTRACT



Palladium catalysts with bulky biaryl phosphine ligands allow homopropargyl-substituted dicarbonyl compounds to undergo intramolecular addition via a rare 5-*endo-dig* pathway. C–C bond forming reductive elimination follows the addition to introduce alkenyl and alkynyl as well as aryl groups by using the corresponding organic halides. The cyclization is versatile enough to be applicable to the synthesis of highly substituted dihydropyrrole and a fused tricyclic compound.

The intramolecular addition of enolates to alkynes is a powerful tool to construct five-membered cyclic compounds bearing an olefinic moiety.[1] A number of metal-catalyzed reactions have been developed to improve reaction conditions and expand the scope of substrates.[2] The cyclizations usually proceed in a 5-*exo-dig* mode to provide methylenecyclopentanes starting from ε,ζ-alkynyl carbonyl compounds. However, synthesis of cyclopentene derivatives via 5-*endo-dig* cyclization of δ,ε-alkynyl carbonyl compounds has been relatively unexplored despite their synthetic utility.[3] Indeed, detailed theoretical investigations[4] recently revealed an unfavorable stereoelectronic effect operating in 5-*endo-dig* cyclization while the original Baldwin rules assigned 5-*endo-dig* as a favorable process.[5]

Molybdenum and tungsten catalysts first achieved the challenging 5-*endo-dig* cyclizations of enolates yet formally via metal vinylidene intermediates, thus inherently limiting the reaction scope to substrates having a terminal alkyne moiety.[6] Subsequently, gold catalysts have been allowed to employ enolates bearing an internal alkyne owing to their high affinity to alkynes, expanding the scope of substrates.[7–11] While these reactions overcome the hindrances of the *5-endo-dig* cyclization of enolates, they

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(5) Baldwin, J. E. *J. Chem. Soc., Chem. Commun.* **1976**, 734–736.
(6) (a) McDonald, F. E.; Olson, T. C. *Tetrahedron Lett.* **1997**, *38*, 7691–7692. (b) Maeyama, K.; Iwasawa, N. *J. Am. Chem. Soc.* **1998**, *120*, 1928–1929. (c) Iwasawa, N.; Miura, T.; Kiyota, K.; Kusama, H.; Lee, K.; Lee, P. H. *Org. Lett.* **2002**, *4*, 4463–4466. (d) Iwasawa, N.; Maeyama, K.; Kusama, H. *Org. Lett.* **2001**, *3*, 3871–3873. (e) Miura, T.; Iwasawa, N. *J. Am. Chem. Soc.* **2001**, *124*, 518–519. (f) Kusama, H.; Yamabe, H.; Iwasawa, N. *Org. Lett.* **2002**, *4*, 2569–2571.
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(8) During the preparation of this manuscript, Shibata's group reported enantioselective *5-endo-dig* cyclization using a Zn- and Yb-cocatalyst system: Suzuki, S.; Tokunaga, E.; Reddy, D. S.; Matsumoto, T.; Shiro, M.; Shibata, N. *Angew. Chem., Int. Ed.* **2012**, *51*, 4131–4135.

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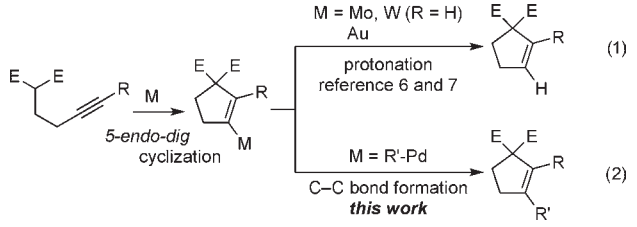
resulted in the formation of only one C−C bond, finalized by in situ protonation of vinylmetal intermediates (Scheme 1, eq 1). Therefore, we envisioned that utilization of the vinylmetal intermediates for further bond forming events should enhance the synthetic potential of the 5-*endo-dig* cyclization for preparing densely substituted complex cyclopentenes. To this end, the most promising design can be the use of π-acidic organopalladium species for alkyne activation, which should terminate the cyclization by C−C bond forming reductive elimination (Scheme 1, eq 2).[12] Although palladium-catalyzed arylative cyclization of enolates was extensively investigated so far,[12a,b] the cyclization mode was again severely restricted to *exo* with the exception of highly activated substrates.[9g,13]

Scheme 1. Fate of Vinylmetal Intermediate Generated by *5-Endo-Dig* Cyclization

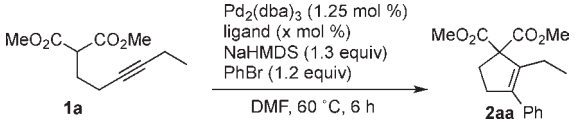


Recently, our group reported palladium-catalyzed arylative cyclization reactions of allylic alcohols, allylic amines, and propargyl-substituted malonate esters to yield highly strained cyclic compounds.[14] To achieve these unprecedented cyclizations, the careful choice of ligands was crucial. Along this line, we disclose herein that the appropriate choice of ligand realized palladium-catalyzed 5-*endo-dig* cyclization of homopropargyl-substituted dicarbonyl compounds with concomitant formation of two C−C bonds in a single operation. The reaction is versatile and offers an efficient route to various cyclopentene derivatives containing a fully substituted *endo*-alkene unit, which are otherwise difficult to synthesize.

We initially investigated the effect of a ligand on the phenylative cyclization reaction of **1a** (Table 1, Figure 1). The use of Xantphos, which is effective in our previous work,[14c] gave the desired product in only 6% yield (entry 1). Other ligands such as dppb, tri-*tert*-butylphosphine, and triphenylphosphine were also ineffective for this reaction (entries 2, 3, and 4). Only biaryl-based bulky phosphines served as suitable ligands for this cyclization, and the best yield was obtained with XPhos (entry 7).[15] Interestingly, the employment of the bulky electron-rich biaryl ligand did not retard the 5-*endo-dig* cyclization, which usually required highly electrophilic Lewis acids in the previous works.[6,7] It is noteworthy that the catalytic amount could be reduced to 0.50 mol % on a large scale, which demonstrates the high efficiency of the catalytic system (entry 8). In addition, we could employ readily available and economical LDA as an alternative base.

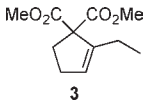
The scope of aryl halides proved to be broad (Table 2). Chlorobenzene instead of bromobenzene could be used for the arylative cyclization at an elevated temperature (entry 1). Electron-deficient and -rich aryl halides gave the corresponding products in good to excellent yields without any decomposition of their functional groups (entries 2−6). Notably, sterically demanding aryl as well as heteroaryl bromides were also converted smoothly (entries 7 and 8).

Table 1. Effect of Ligand on Palladium-Catalyzed 5-*Endo-Dig* Arylative Cyclization[a]



entry	ligand	*x* (mol %)	**1a** yield (%)	**2aa** yield (%)
1	Xantphos	2.5	88	6
2	dppb	2.5	99	0
3[c]	P*t*-Bu$_3$•HBF$_4$	5.0	74	8
4	PPh$_3$	10	85	0
5	SPhos	2.5	14	84
6	RuPhos	2.5	0	85
7	XPhos	2.5	0	95[b]
8[d]	XPhos	0.50	0	77[b]

[a] A mixture of $Pd_2(dba)_3$ (1.25 mol %, 0.0038 mmol), ligand (*x* mol %, 0.0075 mmol), NaHMDS (1.3 equiv, 0.39 mmol), **1a** (0.30 mmol), and PhBr (0.36 mmol) was stirred at 60 °C in DMF (0.75 mL) for 6 h. Yields were determined by ^{1}H NMR using tetrabromoethane as an internal standard. [b] Isolated yield. [c] 13% of protonated product **3** was obtained. [d] A mixture of $Pd_2(dba)_3$ (0.25 mol %, 0.0075 mmol), XPhos (0.50 mol %, 0.015 mmol), LDA (1.1 equiv, 3.3 mmol), **1a** (3.0 mmol), and PhBr (1.05 equiv, 3.15 mmol) was stirred at 60 °C in DMF (3.0 mL) for 12 h.



(9) For examples of metal-catalyzed *endo-dig* cyclization of enolates having an alkyne moiety that are electronically activated and/or structurally constrained, see: (a) Ito, H.; Makida, Y.; Ochida, A.; Ohmiya, H.; Sawamura, M. *Org. Lett.* **2008**, *10*, 5051–5054. (b) Barabé, F.; Levesque, P.; Korobkov, I.; Barriault, L. *Org. Lett.* **2011**, *13*, 5580–5583. (c) Kozak, J. A.; Patrick, B. O.; Dake, G. R. *J. Org. Chem.* **2010**, *75*, 8585–8590. (d) Hessa, W.; Burton, J. W. *Adv. Synth. Catal.* **2011**, *353*, 2966–2970. (e) Fei, N.; Yin, H.; Wang, S.; Wang, H.; Yao, Z.-J. *Org. Lett.* **2011**, *13*, 4208–4211. (f) Deng, C.-L.; Zou, T.; Wang, Z.-Q.; Song, R.-J.; Li, J.-H. *J. Org. Chem.* **2009**, *74*, 412–414. With a stoichiometric base: (g) Hu, J.; Wu, L.-Y.; Wang, X.-C.; Hu, Y.-Y.; Niu, Y.-N.; Liu, X.-Y.; Yang, S.; Liang, Y.-M. *Adv. Synth. Catal.* **2010**, *352*, 351–356. (h) Lavallée, J. F.; Berthiaume, G.; Deslongchamps, P. *Tetrahedron Lett.* **1986**, *27*, 5455–5458.

(10) For selected examples of metal-catalyzed 5-*endo-dig* cyclization accompanying an attack by carbon nucleophiles other than enolates such as allylic silane, see: (a) Buzas, A. K.; Istrate, F. M.; Gagosz, F. *Angew. Chem., Int. Ed.* **2007**, *46*, 1141–1144. (b) Gorin, D. J.; Watson, I. D. G.; Toste, F. D. *J. Am. Chem. Soc.* **2008**, *130*, 3736–3737. (c) Zhang, L.; Kozmin, S. A. *J. Am. Chem. Soc.* **2005**, *127*, 6962–6963. (d) Ajamian, A.; Gleason, J. L. *Org. Lett.* **2003**, *5*, 2409–2411. (e) Imamura, K.; Yoshikawa, E.; Gevorgyan, V.; Yamamoto, Y. *J. Am. Chem. Soc.* **1998**, *120*, 5339–5340.

(11) For an example of metal-catalyzed 4-*exo-dig* cyclization of enolate: Deng, C.-L.; Song, R.-J.; Liu, Y.-L.; Li, J.-H. *Adv. Synth. Catal.* **2009**, *351*, 3096–3100. See also ref 9d. It should be noted that simple ring strain does not lead to the formation of endocyclic products: (a) Bailey, W. F.; Ovaska, T. V. *Tetrahedron Lett.* **1990**, *31*, 627–630. (b) Bailey, W. F.; Ovaska, T. V. *J. Am. Chem. Soc.* **1993**, *115*, 3080–3090.

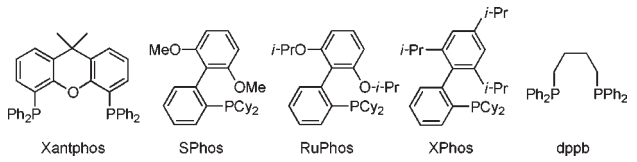
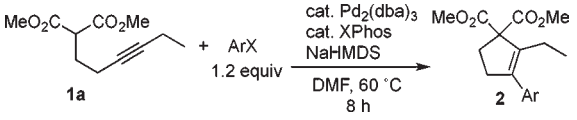


Figure 1. Phosphine ligands examined. Cy = cyclohexyl.

Table 2. Scope of Aryl Halides[a]



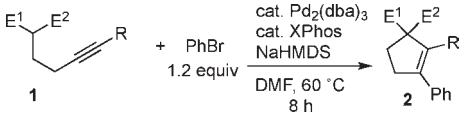
entry	ArX	2	yield (%)
1[b]	C_6H_5Cl	**2aa**	81
2	4-$CF_3C_6H_4Br$	**2ab**	98
3	4-MeOC(=O)C_6H_4Br	**2ac**	82
4	4-PhC(=O)C_6H_4Br	**2ad**	77
5	4-$MeOC_6H_4Br$	**2ae**	85
6	4-$Me_2NC_6H_4Br$	**2af**	76
7	2-MeC_6H_4Br	**2ag**	87
8	3-pyridinyl-Br	**2ah**	72

[a] A mixture of $Pd_2(dba)_3$ (1.25 mol %, 0.0038 mmol), XPhos (2.5 mol %, 0.0075 mmol), NaHMDS (1.3 equiv, 0.39 mmol), **1a** (0.30 mmol), and ArX (0.36 mmol) was stirred at 60 °C in DMF (0.75 mL) for 8 h. Yields are isolated yields. [b] Reaction was carried out at 100 °C.

A wide range of homopropargyl-substituted dicarbonyl compounds underwent the arylative 5-*endo*-*dig* cyclization (Table 3).[16] Bulky *tert*-butyl malonate ester derivative **1a** participated in the cyclization reaction (entry 1). Aside from diesters, a β-diketone and ketoester were also viable nucleophiles (entries 2 and 3). 1,2-Diarylcyclopentene **2ea** was synthesized in high yield (entry 4). It is worth noting that substrate **1f** bearing an alkene moiety neither suffered from direct Mizoroki–Heck reaction of the double bond nor underwent tandem 5-*endo*-*dig* cyclization/intramolecular 5-*exo*-*trig* cyclization to form a bicyclic skeleton (entry 5).

The optimized conditions are so robust and versatile that we could introduce alkenyl and alkynyl halides, besides aryl halides (Scheme 2). The resulting conjugated diene and enyne motifs can be platforms for further functionalizations to construct complex cyclic frameworks.

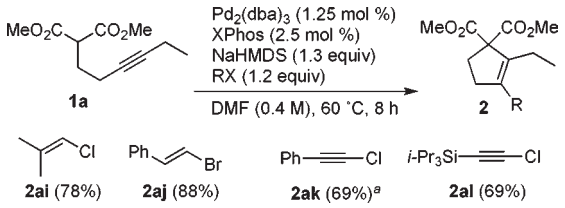
Table 3. Scope of Homopropargyl-Substituted Dicarbonyl Compounds[a]



entry	E^1	E^2	R	2	yield (%)
1[b]	CO_2t-Bu	CO_2t-Bu	Et	**2ba**	90
2	COPh	COPh	Et	**2ca**	68
3	COMe	CO_2Et	Et	**2da**	70
4	CO_2Me	CO_2Me	Ph	**2ea**	94
5	CO_2Me	CO_2Me		**2fa**	90

[a] Reaction conditions are identical to those in Table 2. Yields are isolated yields. [b] Reaction was carried out at 100 °C.

Scheme 2. Alkenylative and Alkynylative Cyclization

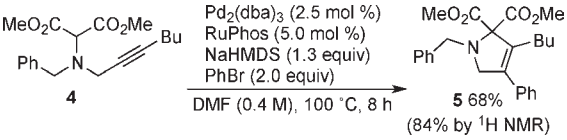


[a] Reaction was carried out at 100 °C.

The cyclization strategy is also applicable to the synthesis of 3-pyrroline **5** from aminomalonate **4** despite the high Lewis basicity of a tertiary amine (Scheme 3). Azacycle **5** has an unsaturated proline skeleton, which will find application in organic synthesis.[9d,17] In this case, RuPhos was the better ligand and the Pd-XPhos system gave a low yield of **5** due to the competitive protonation of the vinylpalladium intermediate.[18]

Starting from **6**, intramolecular arylative cyclization afforded tricyclic compound **7** in good yield (Scheme 4). This achievement highlights the robustness of our 5-*endo*-*dig* cyclization since the intramolecular coordination of the alkyne moiety to the palladium center (vide infra) might be unfavorable due to the resulting strain on the tethering chain.

Scheme 3. Synthesis of 3-Pyrroline

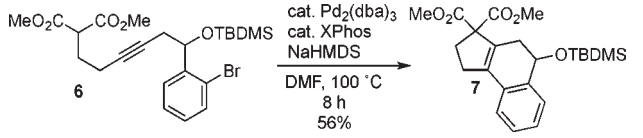


(12) (a) Balme, G.; Bouyssi, D.; Lomberget, T.; Monterio, N. *Synthesis* **2003**, 2115–2134. (b) Guo, L.-N.; Duan, X.-H.; Liang, Y.-M. *Acc. Chem. Res.* **2011**, *44*, 111–122. (c) Wolfe, J. P. *Synlett* **2008**, 2913–2937. (d) Schultz, D. M.; Wolfe, J. P. *Synthesis* **2012**, *44*, 351–361. Pd-catalyzed Conia-ene reaction: (e) Corkey, B. K.; Toste, F. D. *J. Am. Chem. Soc.* **2005**, *127*, 17168–2053.

(13) 5-*Endo*-*dig* arylative cyclizations of structurally limited substrates, which were activated by the conjugation of the aromatic ring and structural rigidity: (a) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2006**, *71*, 3325–3327. (b) Zhang, D.; Liu, Z.; Yum, E. K.; Larock, R. C. *J. Org. Chem.* **2007**, *72*, 251–262. (c) Duan, X.-H.; Guo, L.-N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2006**, *8*, 3053–3056.

(14) (a) Hayashi, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2009**, *131*, 2052–2053. (b) Hayashi, S.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7224–7226. (c) Fujino, D.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2011**, *133*, 9682–9685.

Scheme 4. Intramolecular Arylative Cyclization[a]



[a] A mixture of $Pd_2(dba)_3$ (2.5 mol %, 0.0075 mmol), XPhos (5.0 mol %, 0.015 mmol), NaHMDS (1.3 equiv, 0.39 mmol), and **6** (0.30 mmol) was stirred at 100 °C in DMF (0.75 mL) for 8 h.

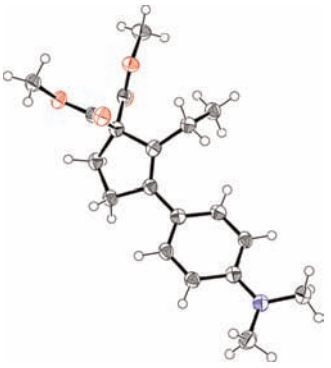
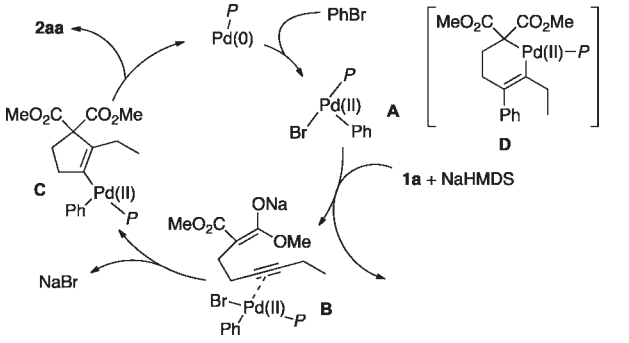


Figure 2. ORTEP drawing of compound **2af**.

A plausible mechanism is shown in Scheme 5, based on the unambiguously determined structure of one of the products (Figure 2)[19] and Toste's and our reports.[7,14c] After oxidative addition, arylpalladium intermediate **A** would activate the alkyne moiety of **2a** through π-coordination. Deprotonation of the acidic methine proton by NaHMDS would induce 5-*endo*-*dig* cyclization to form vinylpalladium **C**. The following reductive elimination yields phenyl-substituted cyclopentene **2aa** and regenerates the initial palladium complex. One would conceive another mechanism that involves sequential syn-arylpalladation/isomerization,[13a,20] or less likely a direct anti-arylpalladation, to afford palladacycle **D**. However, the formations of byproduct **3** (Table 1, entry 3) and **8** (Scheme 3)[18] indicate the intermediacy of **C** in our system.[21] The successful intramolecular cyclization (Scheme 4) also eliminates the possibility of the intermediacy of **D**.

Scheme 5. Plausible Mechanism



In conclusion, we have demonstrated that palladium catalysts with bulky biaryl phosphine ligands allow homopropargyl-substituted dicarbonyl compounds to undergo intramolecular addition via a rare 5-*endo*-*dig* pathway. The addition is followed by C−C bond forming reductive elimination, resulting in the efficient synthesis of 1,2-disubstituted cyclopentenes of synthetic difficulty. Syntheses of other heterocycles by this methodology are currently under investigation in our laboratory.

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Supporting Information Available. General procedure, spectroscopic data, and the $^1H/^{13}C$ NMR spectra of all the products. This material is available free of charge via the Internet at http://pubs.acs.org.

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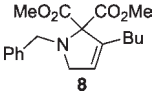
(16) We examined the reaction of bishomopropargyl-substituted malonate ester, instead of homopropargyl malonate, which resulted in the formation of a cyclopentane derivative via a 5-*exo* cyclization. See ref 12a.

(17) (a) Takahashi, K.; Midori, M.; Kawano, K.; Ishihara, J.; Hatakeyama, S. *Angew. Chem., Int. Ed.* **2011**, *50*, 2342–2345. (b) Hess, W.; Burton, J. W. *Chem.—Eur. J.* **2010**, *16*, 12303–12306.

(18) The reaction led to the concomitant formation of a protonated byproduct **8**.

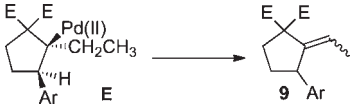


8

(19) Crystal data for compound **2af**: $C_{19}H_{25}NO_4$, M_w = 331.40, monoclinic, space group *Cc*, final R indices [$I > 2\sigma(I)$], R_1 = 0.0462, wR_2 = 0.1068, R indices (all data) R_1 = 0.0563, wR_2 = 0.1154, a = 7.9128(2) Å, b = 13.2027(3) Å, c = 17.3219(4) Å, β = 105.2565(15)°, V = 1745.85(7) Å^3, T = 123 K, Z = 4, reflections collected/unique: 2807/2373. GOF = 1.055 [$I > 2\sigma(I)$]. CCDC No.: 868309.

(20) Chernyak, N.; Gorelsky, S. I.; Gevorgyan, V. *Angew. Chem., Int. Ed.* **2011**, *50*, 2342–2345 and references therein.

(21) It was unlikely that a Heck reaction of **3** that might be first generated in situ led to product **2** via intermediate **E** because none of double bond isomers **9** were observed. The formation of **2ea** also supports our mechanism since the plausible cyclopentylpalladium intermediate that can be formed by the arylpalladation of **3** cannot undergo *syn*-β-hydride elimination due to the anti H/Pd stereochemistry.



The authors declare no competing financial interest.