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Synthesis of Alkylidenecyclopropanes by Palladium-Catalyzed Reaction of Propargyl-Substituted Malonate Esters with Aryl Halides by Anti-carbopalladation Pathway

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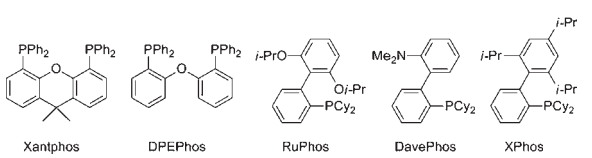
Supporting Information

ABSTRACT: Palladium-catalyzed arylative cyclization of propargyl-substituted malonate esters with aryl halides offers a stereoselective approach to alkylidenecyclopropanes. The reaction proceeds by an anti-carbopalladation pathway, which guarantees the exclusive stereocontrol of the resulting double bond. The highly strained as well as densely substituted skeletons of the products facilitate further versatile transformations, which underscores the importance of the products as synthetic intermediates.

Alkylidenecyclopropanes (ACPs) are useful building blocks[1] and are found in many bioactive compounds.[2] Preparations of ACPs have hence been investigated over the past few decades.[3,4] However, the conventional syntheses of multisubstituted ACPs are usually achieved by multistep preparations, which require preformation of cyclopropane derivatives or allenes (Scheme 1).[5] These methods often encounter difficulty in controlling the stereochemistry of the carbon−carbon double bond of ACPs.[6]

Palladium-catalyzed intramolecular arylative cyclization of unsaturated compounds having a nucleophilic moiety with aryl halides represents an attractive method to construct cyclic compounds.[7] Although the method has provided a number of five-membered cyclic compounds so far, preparation of strained three-membered rings has remained a considerable challenge.[8] Recently, we reported palladium-catalyzed cyclization reactions of allylic alcohols and allylic amines with aryl halides, which yielded arylated epoxides and aziridines, respectively.[8j,k] During the course of our study, we envisioned that propargyl-substituted malonate esters would undergo palladium-catalyzed intramolecular cyclization to afford multisubstituted ACPs.[9] The reaction should represent facile and stereoselective synthesis of multisubstituted ACPs from readily available starting materials.



Treatment of propargyl malonate ester **1a** with bromobenzene in the presence of cesium carbonate under palladium/Xantphos catalysis afforded phenyl-substituted ACP **2a** in 51% yield (Table 1, entry 1). Several ligands were screened, and Xantphos proved to be most effective for the cyclization. Biaryl-based bulky phosphines (RuPhos and DavePhos) also gave the product (entries 3 and 4). DPEPhos, which is structurally similar to Xantphos yet lacks the bridging dimethylmethylene backbone, resulted in lower yield

Scheme 1. Conventional Synthesis of ACPs

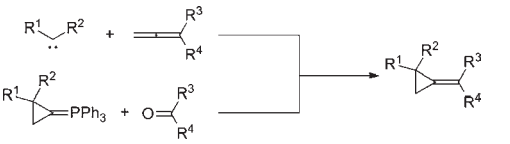
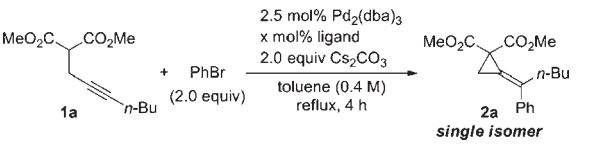


Table 1. Effect of Ligand on Palladium-Catalyzed Cyclopropanative Arylation[a]



entry	ligand	*x* (mol %)	yield (%) 1a	yield (%) 2a
1	Xantphos	10	23	51
2	Xantphos	5	23	27
3	RuPhos	10	0	30
4	DavePhos	10	13	45
5	DPEPhos	10	0	12
6[b]	Xantphos	10	0	78

[a] A mixture of $Pd_2(dba)_3$ (0.0075 mmol), ligand (0.030 mmol), Cs_2CO_3 (0.6 mmol), **1a** (0.3 mmol), and PhBr (0.6 mmol) was boiled in toluene (0.75 mL) for 4 h. Yields are determined by ^1H NMR using tetrabromoethane as an internal standard. [b] $Pd_2(dba)_3$ (0.0025 mmol) and Xantphos (0.010 mmol) were added three times at t = 0, 3, and 6 h.

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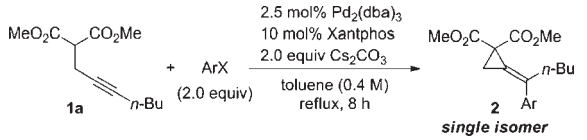
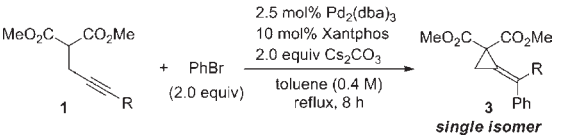
Table 2. Scope of Aryl Halides[a]



entry	ArX	2	yield[b] (%)
1[c]	PhOTf	**2a**	77
2	2-MeC_6H_4Br	**2b**	85
3	1-naphthyl-Br	**2c**	91
4	4-ClC_6H_4Br	**2d**	76
5	4-$CF_3C_6H_4Br$	**2e**	90
6	4-EtOC(=O)C_6H_4Br	**2f**	71
7	4-NCC_6H_4Br	**2g**	72
8	2-$MeOC_6H_4Br$	**2h**	60
9[d]	4-$MeOC_6H_4OTf$	**2i**	61
10	3-pyridinyl-Br	**2j**	74

[a] A mixture of Cs_2CO_3 (1.0 mmol), **1a** (0.5 mmol), and ArX (1.0 mmol) was boiled in toluene (1.25 mL) for 8 h. $Pd_2(dba)_3$ (0.0042 mmol) and Xantphos (0.017 mmol) were added three times at t = 0, 3, and 6 h. [b] Isolated yields. [c] $Pd_2(dba)_3$ (0.0125 mmol) and Xantphos (0.05 mmol) were present from the beginning, not added separately. [d] 5 mol % RuPhos was used as a ligand instead of Xantphos.

Table 3. Scope of Propargyl Malonate Esters[a]



entry	**1**, R	3	yield[b] (%)
1	**1b**, Me	**3b**	73
2	**1c**, c-C_3H_5	**3c**	83
3	**1d**, t-Bu	**3d**	0
4	**1e**, Ph	**3e**	70
5	**1f**, 4-$CF_3C_6H_4$	**3f**	53

[a] The reaction conditions are the same as those in Table 2. [b] Isolated yields.

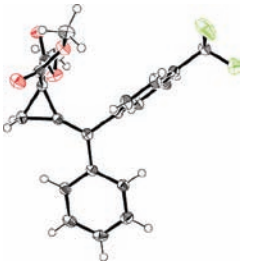
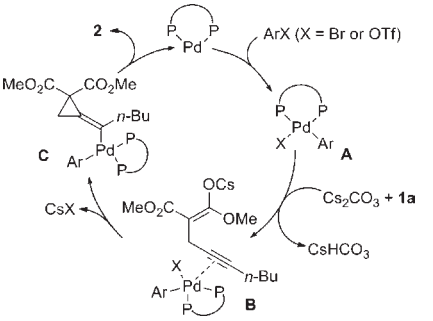


Figure 1. ORTEP drawing of compound **3f**.

Scheme 2. Reaction Mechanism



(entry 5). Other ligands such as triphenylphosphine, tricyclohexylphosphine, and XPhos failed to afford the product. After further examination of the reaction conditions, we found that adding the catalyst and ligands in three portions gave **2a** in 78% yield (entry 6).[10−12] It is worth noting that a cyclopropane ring and an arylated carbon−carbon double bond were formed in a single operation. Additionally, the products were obtained without notable decomposition, although ACPs were reactive under palladium catalysis.[1,13]

The scope of aryl halides is summarized in Table 2. The reaction of phenyl triflate provided the product in good yield without separately adding the catalyst and ligand in three portions (Table 2, entry 1).[14] Sterically demanding aryl bromides also participated in the cyclization reaction (entries 2 and 3). Electron-deficient aryl bromides were smoothly converted to the corresponding products (entries 4 and 5). Ethoxycarbonyl and cyano groups were well-tolerated under the reaction conditions (entries 6 and 7). The reaction of **1a** with electron-rich aryl halides resulted in modest yields of ACPs (entries 8 and 9). Notably, heteroaryl bromide was also applicable to this reaction (entry 10).

The scope of the substituents at the alkyne terminal was investigated (Table 3). Propargyl malonate esters bearing a methyl or cyclopropyl terminal underwent the cyclization smoothly to yield the corresponding products (Table 3, entries 1 and 2). However, a *tert*-butyl group was too bulky for the cyclization reaction (entry 3). The reactions of malonates having an aryl moiety also furnished the corresponding products (entries 4 and 5).[15]

We determined the configuration of the carbon−carbon double bond in the product on the basis of the X-ray diffraction analysis of **3f** (Figure 1).[16] The introduced phenyl group is located at the trans position of the quaternary carbon bearing two carbonyl groups. It should be noted that these ACPs would be difficult to synthesize with high stereoselectivity by the known methods.[3,4]

A plausible mechanism is illustrated in Scheme 2, based on the stereochemistry of the products and Gore's report.[17] Initial oxidative addition of aryl halide to zerovalent palladium occurs to afford arylpalladium bromide or triflate **A**. Intermediate **A** would then activate the alkyne moiety of **1a** through π-coordination. Deprotonation of the acidic methyne proton by cesium carbonate would induce intramolecular cyclization onto the activated alkyne to form vinylpalladium **C** by anti-carbopalladation. The subsequent reductive elimination from **C** yields **2** and regenerates the initial palladium complex. In comparison with aryl bromides as an arylating agent, the cyclopropanative cyclization step would be more favorable in the reaction of aryl triflates because the palladium center of **B** is more cationic to activate the alkyne more efficiently. The modest efficiency in the reactions of electron-rich aryl bromides (Table 2, entries 8 and 9) and the higher reactivity of aryl triflates (entry 1) experimentally justify the importance of the cationic character of the palladium center.

The ACPs thus synthesized are expected to be useful intermediates in organic synthesis, and transformations of ACPs were hence explored. The $Yb(OTf)_3$-catalyzed ring-opening intramolecular Friedel−Crafts reaction of dimethyl benzylidenecyclopropane-1,1-dicarboxylate reported by Wang[18] was applicable also to **2a**, having a tetrasubstituted alkene unit, to yield dimethyl

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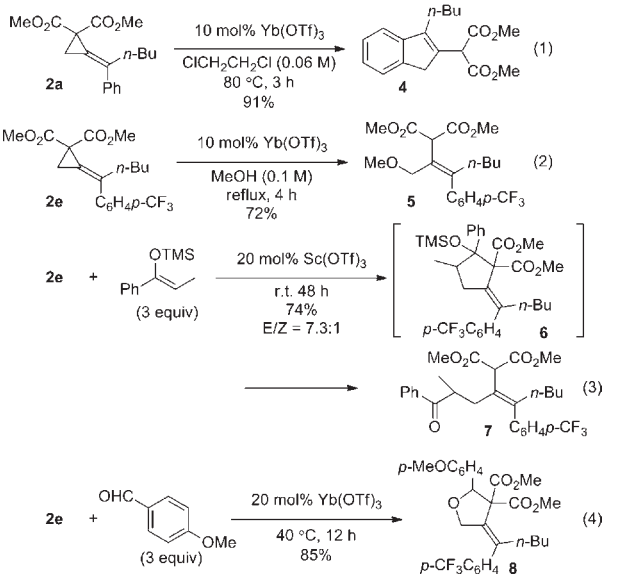
2-(3-butyl-1*H*-inden-2-yl)malonate (**4**) (eq 1). ACP **2e** was converted to allylic methyl ether **5** under $Yb(OTf)_3$ catalysis[19] in methanol (eq 2). Notably, the ring-opening etherification proceeded with perfect retention of the configuration of the double bond, making it useful as a new stereo- and regioselective approach to tetrasubstituted alkenes. Lanthanide triflate-catalyzed insertion of silyl enolate and aldehyde into **2e** took place (eqs 3 and 4), representing the first examples of ring-expanding insertion of silyl enolate and aldehyde to 2-alkylidenecyclopropane-1,1-dicarboxylate.[20−22] Carbocyclic intermediate **6** was unstable for purification and was converted to linear alkenone **7**. In these insertion reactions, the geometry of the tetrasubstituted double bond was again satisfactorily or perfectly retained.



In conclusion, we have developed a new method for stereoselective synthesis of ACPs by palladium-catalyzed reactions of propargyl-substituted malonate esters with aryl halides. The products bear a stereodefined double bond, electron-withdrawing functional groups, and a strained ring, which facilitate further transformations. The syntheses of other strained hetero- and carbocycles by this methodology are currently under investigation in our laboratory.

■ ASSOCIATED CONTENT

Supporting Information. Spectroscopic data, general procedure, and $^1H/^{13}C$ 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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■ REFERENCES

(1) (a) Nakamura, I.; Yamamoto, Y. *Adv. Synth. Catal.* **2002**, *344*, 111–129. (b) Brandi, A.; Cicchi, S.; Cordero, F. M.; Goti, A. *Chem. Rev.* **2003**, *103*, 1213–1270. (c) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117–3179. (d) Goti, A.; Cordero, F. M.; Brandi, A. *Top. Curr. Chem.* **1996**, *178*, 1–97. (e) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49–92. (f) de Meijere, A.; Kozhushkov, S. I.; Khlebnikov, A. F. *Top. Curr. Chem.* **2000**, *207*, 89–147. (g) Binger, P.; Schuchardt, U. *Chem. Ber.* **1981**, *114*, 3313–3324. (h) Masarwa, A.; Marek, I. *Chem.—Eur. J.* **2010**, *16*, 9712–9721. (i) Pellissier, H. *Tetrahedron* **2010**, *66*, 8341–8375. (j) Murakami, M.; Matsuda, T. *Chem. Commun.* **2011**, *47*, 1100–1105.

(2) (a) Evans, J. R.; Napier, E. J.; Fletton, R. A. *J. Antibiot.* **1978**, *31*, 952–958. (b) Nemoto, T.; Yoshino, G.; Ojika, M.; Sakagami, Y. *Tetrahedron* **1997**, *53*, 16699–16710.(c) Zemlicka, J. In *Recent Advances in Nucleosides: Chemistry and Chemotherapy*; Chu, C. K., Ed.; Elsevier Science: Amsterdam, 2002; pp 327−357. (d) Zemlicka, J. In *Advances in Antiviral Drug Design*; de Clercq, E., Ed.; Elsevier: Amsterdam, 2007; pp 113−167.

(3) (a) Binger, P.; Büch, H. M. *Top. Curr. Chem.* **1987**, *135*, 77–151. (b) Ohta, T.; Takaya, H. *Comprehensive Organic Synthesis*; Pergamon: Oxford, 1991; Vol. 5, pp 1185. (c) Krief, A. *Top. Curr. Chem.* **1987**, *135*, 1–75.(d) *Carbocyclic Three-Membered Ring Compounds*; Houben-Weyl Methoden der Organischen Chemie E17; Thieme: Stuttgart, 1996.

(4) Recent reviews of the preparation of ACPs:(a) Brandi, A.; Goti, A. *Chem. Rev.* **1998**, *98*, 589–635. (b) Audran, G.; Pellissier, H. *Adv. Synth. Catal.* **2010**, *352*, 575–608. (c) Marek, I.; Simaan, S.; Masarwa, A. *Angew. Chem., Int. Ed.* **2007**, *46*, 7364–7376.

(5) Recent representative examples of synthesis of ACPs from cyclopropane derivatives:(a) Yang, Z.; Xie, X.; Fox, J. M. *Angew. Chem., Int. Ed.* **2006**, *118*, 4064–4066. (b) Simaan, S.; Masarwa, A.; Zohar, A.; Stanger, A.; Bertus, P.; Marek, I. *Chem.—Eur. J.* **2009**, *15*, 8449–8464. (c) Xie, X.; Yang, Z.; Fox, J. M. *J. Org. Chem.* **2010**, *75*, 3847–3850. From allenes by addition of carbene:(d) Gregg, T. M.; Farrugia, K. M.; Frost, J. R. *Org. Lett.* **2009**, *11*, 4434–4436. (e) Xu, L.; Huang, X.; Zhong, F. *Org. Lett.* **2006**, *8*, 5061–5064. (f) Gregg, T. M.; Algera, R. F.; Frost, J. R.; Hassan, F.; Stewart, R. J. *Tetrahedron Lett.* **2010**, *51*, 6429–6432.

(6) To the best of our knowledge, there is only one example of synthesis of ACPs with controlling the geometry of the double bond: Huval, C. C.; Singleton, D. A. *J. Org. Chem.* **1994**, *59*, 2020–2024.

(7) For selected recent reviews of palladium-catalyzed arylative cyclization reaction of unsaturated compounds bearing a nucleophilic moiety with aryl halides, see:(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) Dénès, F.; Pérez-Luna, A.; Chemla, F. *Chem. Rev.* **2010**, *110*, 2366–2447. (d) Wolfe, J. P. *Synlett* **2008**, 2913–2937.

(8) For representative examples of syntheses of small rings by palladium-catalyzed cyclization, see:(a) Baudoin, O.; Herrbach, A.; Guéritte, F. *Angew. Chem., Int. Ed.* **2003**, *42*, 5736–5740. (b) Welbes, L. L.; Lyons, T. W.; Cychosz, K. A.; Sanford, M. S. *J. Am. Chem. Soc.* **2007**, *129*, 5836–5837. (c) Chaumontet, M.; Piccardi, R.; Audic, N.; Hitce, J.; Peglion, J.-L.; Clot, E.; Baudoin, O. *J. Am. Chem. Soc.* **2008**, *130*, 15157–15166. (d) Hulot, C.; Blond, G.; Suffert, J. *J. Am. Chem. Soc.* **2008**, *130*, 5046–5047. (e) Ma, S.; Jiao, N.; Yang, Q.; Zheng, Z. *J. Org. Chem.* **2004**, *69*, 6463–6466. (f) Innitzer, A.; Brecker, A.; Mulzer, J. *Org. Lett.* **2007**, *9*, 4431–4434. (g) Shu, W.; Jia, G.; Ma, S. *Org. Lett.* **2009**, *11*, 117–120. (h) Paugam, R.; Gaucher, A.; Dorizon, P.; Ollivier, J.; Salaün, J. *Tetrahedron Lett.* **2000**, *56*, 8495–8503. (i) Grigg, R.; Dorrity, M. J.; Malone, J. F. *Tetrahedron Lett.* **1990**, *31*, 1343–1346. (j) Hayashi, S.; Yorimitsu, H.; Oshima, K. *J. Am. Chem. Soc.* **2009**, *131*, 2052–2053. (k) Hayashi, S.; Yorimitsu, H.; Oshima, K. *Angew. Chem., Int. Ed.* **2009**, *48*, 7224–7226.

(9) Syntheses of ACPs by cyclization reaction from alkyne bearing leaving group at homopropargyl position with no stereoselectivity and low functional group tolerance:(a) Harada, T.; Imaoka, D.; Kitano, C.; Kusukawa, T. *Chem.—Eur. J.* **2010**, *16*, 9164–9174. (b) Okuda, Y.;

Morizawa, Y.; Oshima, K.; Nozaki, H. *Tetrahedron Lett.* **1984**, *25*, 2483–2486. (c) Harada, T.; Wada, H.; Oku, A. *J. Org. Chem.* **1995**, *60*, 5370–5371. (d) Harada, T.; Iwazaki, K.; Otani, T.; Oku, A. *J. Org. Chem.* **1998**, *63*, 9007–9012.

(10) Thermal instability of a Pd/Xantphos catalyst was recently mentioned:Martinelli, J. R.; Watson, D. A.; Freckmann, D. M. M.; Barder, T. E.; Buchwald, S. L. *J. Org. Chem.* **2008**, *73*, 7102–7107.

(11) Addition of silver triflate did not improve the yield of the product; it gave a complex mixture.

(12) The reaction on a 5 mmol (10× larger) scale afforded an 84% yield of (*E*)-**2a**, which demonstrates the scalability.

(13) We assume that the substituents around the tetrasubstituted double bond of the products are sterically hindered enough to kinetically inhibit the interaction between palladium species and the double bond.

(14) Aryl iodides were not suitable in this reaction, being converted to the products in much lower yields. The stronger coordination of iodide to palladium would lead to inhibition of a reactive (cationic) palladium species. For the inhibitory effect of iodide, see:Fors, B. P.; Davis, N. R.; Buchwald, S. L. *J. Am. Chem. Soc.* **2009**, *131*, 5766–5768.

(15) We tried using homopropargyl-substituted malonate ester, instead of propargyl malonate, which resulted in the formation of a cyclopentene derivative, not cyclobutane, by a 5-*endo* cyclization. Details of the 5-*endo* cyclization will be reported in due course.

(16) Crystal data for compound **3f**: $C_{21}H_{17}O_4F_3$, M_w = 390.35, monoclinic, space group $P2_1/c$, final R indices $[I > 2\sigma(I)]$, R_1 = 0.0410, wR_2 = 0.1095, R indices (all data) R_1 = 0.0492, wR_2 = 0.1150, a = 7.919(2) Å, b = 12.674(5) Å, c = 18.528(7) Å, β = 100.482(15)°, V = 1828.3(11) Å^3, T = 123 K, Z = 4, reflections collected/unique 4185/3513; GOF = 1.069 $[I > 2\sigma(I)]$. CCDC No. 818379.

(17) (a) Bouyssi, D.; Balme, G.; Fournet, G.; Monterio, N.; Gore, J. *Tetrahedron Lett.* **1991**, *32*, 1641–1644. (b) Fournet, G.; Balme, G.; van Hemelryck, B.; Gore, J. *Tetrahedron Lett.* **1990**, *31*, 5147–5150.

(18) Hu, B.; Xing, S.; Wang, Z. *Org. Lett.* **2008**, *10*, 5481–5484.

(19) Hu, B.; Ren, J.; Wang, Z. *Tetrahedron* **2011**, *67*, 763–768. In this report, isomerization of the double bond was observed. This was indeed the case for our attempted methanolysis of **2e** under the same conditions. We thus modified the reaction conditions to find the present protocol that retains the stereochemistry.

(20) Several Lewis acid are known to catalyze similar insertion into 2-arylcyclopropane-1,1-dicarboxylate esters:(a) Qu, J.-P.; Deng, C.; Zhou, Z.; Sun, X.-L.; Tang, Y. *J. Org. Chem.* **2009**, *74*, 7684–7689. (b) Fang, J.; Ren, J.; Wang, Z. *Tetrahedron Lett.* **2008**, *49*, 6659–6662.

(21) Syntheses of tetrahydrofuran derivatives from MCPs and ACPs by different mechanisms were reported. Thermal reaction:(a) Yamago, S.; Nakamura, E. *J. Org. Chem.* **1990**, *55*, 5553–5555. Lewis-acid-catalyzed reaction of MCPs that have no substituents on the double bond:(b) Lautens, M.; Han, W. *J. Am. Chem. Soc.* **2002**, *124*, 6312–6316. Reaction induced by activation of aldehydes:(c) Shi, M.; Xu, B.; Huang, J.-W. *Org. Lett.* **2004**, *6*, 1175–1178. Palladium-catalyzed reaction:(d) Nakamura, I.; Oh, B. H.; Saito, S.; Yamamoto, Y. *Angew. Chem., Int. Ed.* **2001**, *40*, 1298–1300.

(22) Synthesis of tetrahydro-1,2-oxazine by Lewis-acid-catalyzed reaction of ACPs with diaryl nitrones by a similar mechanism:Hu, B.; Zhu, J.; Xing, S.; Fang, J.; Du, D.; Wang, Z. *Chem.—Eur. J.* **2009**, *15*, 324–327.