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# Palladium-Catalyzed Three-Component [3 + 2] Cycloaddition of Propargyl Trifluoroacetates, Ethylidene Malononitriles, and Allyltributylstannane†

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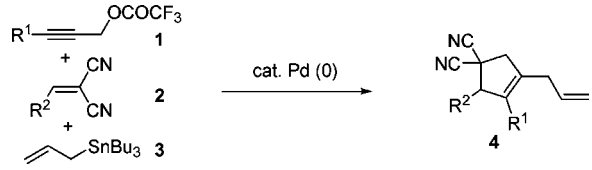
## ABSTRACT




**A novel Pd(0)-catalyzed three-component [3 + 2] cycloaddition of propargyl trifluoroacetates 1, ethylidene malononitriles 2, and allyltributylstannane 3 afforded a variety of multisubstituted cyclopentenes 4 in good to high yields under mild reaction conditions.**

Transition-metal-catalyzed [3 + 2] cycloaddition is regarded as one of powerful strategies for the construction of the useful five-membered carbocyles and heterocyles.[1] Most recently, the inter- and intramolecular cycloaddition of propargyl compounds catalyzed by $\pi$-electrophilic transition metals, such as gold and platinum, has been developed as an attractive synthetic method.[2] While propargylic derivatives are useful substrates in the gold- and platinum-catalyzed reactions, very few studies have been carried out on the palladium-catalyzed cycloaddition reactions. The reaction of hard nucleophiles such as alkyl magnesium or zinc reagents with propargyl compounds in the presence of palladium catalysts gives allenes.[3] Tsuji explored an interesting palladium-catalyzed cycloaddition reaction of propargyl carbonates with soft nucleophiles to give *exo*-methylenefurans (Scheme 1).[4a] The reaction proceeds through the formation of a palladium carbene complex that was isomerized to a $\pi$-allylpalladium complex by intramolecular proton transfer. Subsequent O-alkylation of carbonyl oxygen with $\pi$-allyl complex gives a five-membered heterocycle. It occurred to us that, by proper choice of nucleophiles (Nu) and electrophiles (E═[1]Nu), the three-component coupling reaction between propargyl compounds, $Nu^-$, and E═[1]Nu should take place in the presence of palladium catalysts (Scheme 1).

† This paper is dedicated to Professor Saverio Florio at the University of Bari on the occasion of his 70th birthday.

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(1) For recent reviews, see: (a) Schore, N. E. *Chem. Rev.* **1988**, *88*, 1081. (b) Welker, M. E. *Chem. Rev.* **1992**, *92*, 97. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, *96*, 49. (d) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, *104*, 2127. (e) Barluenga, J.; Santamaría, J.; Tomás, M. *Chem. Rev.* **2004**, *104*, 2259. (f) Rubin, M.; Rubina, M.; Gevorgyan, V. *Chem. Rev.* **2007**, *107*, 3117.

(2) For selected reviews, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, *107*, 3180. (b) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, *108*, 3351. (c) Fürstner, A.; Davis, P. W. *Angew. Chem., Int. Ed.* **2007**, *46*, 3410. For a recent example, see: (d) Zhang, G.; Zhang, L. *J. Am. Chem. Soc.* **2008**, *130*, 12598.

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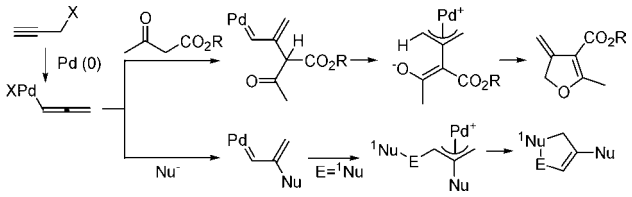
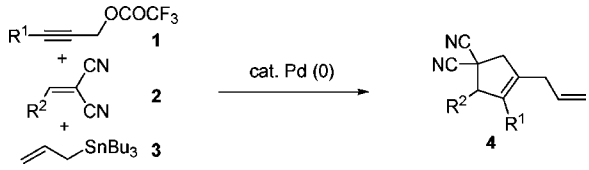
**Scheme 1.** Cycloaddition Reaction via Propargyl Compounds Initiated Palladium Carbene Intermediate



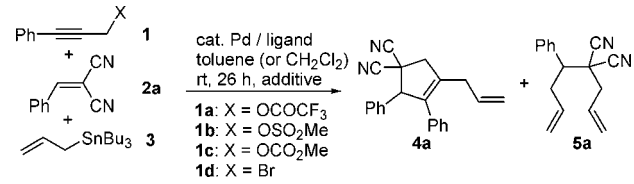
Herein, we report a novel palladium(0)-catalyzed three-component [3 + 2] cycloaddition of propargyl trifluoroacetates **1**, ethylidene malononitriles **2**, and allyltributyltin **3**, affording the highly substituted cyclopentenes **4** in good to high yields under mild reaction conditions (Scheme 2).

**Scheme 2.** Pd(0)-Catalyzed Three-Component Cycloaddition of Propargyl Trifluoroacetates, Ethylidene Malononitriles, and Allyltributylstannane



Previously, we reported that the inter- and intramolecular amphiphilic bisallylation of activated alkenes with bis-$\pi$-allylpalladium, derived from allyltributylstannane-allylchloride-palladium catalyst, gave the corresponding 1,2-bisallylated alkanes and carbocycles efficiently.[5] We further investigated the Pd-catalyzed reaction with activated alkenes, allyltributylstannane, and propargyl compounds instead of allyl chlorides. The reaction of phenyl propargyl trifluoroacetate **1a** (1 equiv), phenylethylidene malononitrile **2a** (1.2 equiv), and allyltributylstannane **3** (1.2 equiv) in toluene was carried out in the presence of $Pd_2(dba)_3CHCl_3$ (10 mol %) and $PPh_3$ (40 mol %) under Ar atmosphere at room temperature for 26 h. 1,2-Bisallylated alkanes **5a** were obtained in 27% yield as expected from the previous result,[5,6] but the major product was 4-allyl-2,3-diphenyl-cyclopent-3-ene-1,1-dicarbonitrile **4a** (51% yield) (Table 1, entry 1). Other palladium catalysts, such as $Pd(PPh_3)_4$, $Pd(OAc)_2$, and $Pd(acac)_2$, gave lower yields of **4a** (entries 2−4). Other transition metal catalysts, such as $Pt(PPh_3)_4$ and $Ni(cod)_2$, were not effective. Triarylphosphine ligands, such as $PPh_2$(*o*-tol) (53%), P(*o*-tol)$_3$ (46%), and P(1-naphthyl)$_3$ (50%), showed higher reactivity compared to that of the trialkylphosphine ligand ($PMe_3$) and bidentate phosphine ligand (dppf) (entries 5−9). Propargyl mesylate (**1b**) was also effective, whereas methyl propargyl carbonate (**1c**) and propargyl bromide (**1d**) did not produce the corresponding product **4a** (entries 10−12). When allyltributylstannane **3** was added dropwise by syringe pump for 26 h, the yield of **4a** increased up to 66% along with small amounts (∼5%) of **5a** (entry 13). We thought that the lower yield of **4a** might be due to the decomposition of **1a** in the presence of a trace amount of water. Thus, the reaction was carried out in the presence of molecular sieves 4 Å, affording the corresponding product **4a** in 82% yield without formation of **5a** (entry 14). The use of a lesser amount of $PPh_2$(*o*-tol) (20 mol %) gave 74% yield of **4a** and 18% of **5a** (entry 15). It is noteworthy that the use of other nucleophiles, such as allyltriphenylstannane, allyltrimethylsilane, and tetrabutylstannane did not produce the corresponding cyclopentene products, and **1a** was always decomposed.

**Table 1.** Screening of Reaction Conditions for the Formation of Cyclopentenes **4a**[a]



| | | | yield (%)[b] | |
|---|---|---|---|---|
| entry | Pd/L (20/40 mol %) | 1 | 4a | 5a |
| 1 | $Pd_2(dba)_3CHCl_3/PPh_3$ | **1a** | 51 | 27 |
| 2 | $Pd(PPh_3)_4$ | **1a** | 46 | 28 |
| 3 | $Pd(OAc)_2/PPh_3$ | **1a** | 38 | 27 |
| 4 | $Pd(acac)_2/PPh_3$ | **1a** | 38 | 28 |
| 5 | $Pd_2(dba)_3CHCl_3/PPh_2$(*o*-Tol) | **1a** | 53 | 27 |
| 6 | $Pd_2(dba)_3CHCl_3/P$(*o*-Tol)$_3$ | **1a** | 46 | 28 |
| 7 | $Pd_2(dba)_3CHCl_3/P$(1-Naphthyl)$_3$ | **1a** | 50 | 32 |
| 8 | $Pd_2(dba)_3CHCl_3/PMe_3$ | **1a** | 0 | 0 |
| 9 | $Pd_2(dba)_3CHCl_3$/dppf | **1a** | 0 | 0 |
| 10 | $Pd_2(dba)_3CHCl_3/PPh_2$(*o*-Tol) | **1b** | 42 | 36 |
| 11 | $Pd_2(dba)_3CHCl_3/PPh_2$(*o*-Tol) | **1c** | 0 | 0 |
| 12 | $Pd_2(dba)_3CHCl_3/PPh_2$(*o*-Tol) | **1d** | 0 | 30 |
| 13[c] | $Pd_2(dba)_3CHCl_3/PPh_2$(*o*-Tol) | **1a** | 66 | 5 |
| 14[c,d] | $Pd_2(dba)_3CHCl_3/PPh_2$(*o*-Tol)/MS 4 Å | **1a** | (82) | 0 |
| 15[c,d,e] | $Pd_2(dba)_3CHCl_3/PPh_2$(*o*-Tol)/MS 4 Å | **1a** | 74 | 18 |

[a] To a mixture of Pd catalysts (20 mol %) and phosphine ligands (40 mol %) in toluene (0.5 mL, 0.4 M) were added propargyl acetate **1a** (0.24 mmol), phenylethylidene malononitrile **2a** (0.2 mmol), and allyltributyltin **3** (0.24 mmol), and the mixture was stirred at room temperature for 26 h. [b] $^1$H NMR yield determined by using dichloroethane as an internal standard. Isolated yield is shown in parentheses. [c] Allyltributyltin **3** was added by syringe pump for 26 h. $CH_2Cl_2$ (1 mL, 0.2 M) was used as a solvent. [d] MS 4 Å (160 mg) was used. [e] 20 mol % of $PPh_2$(*o*-tol) was used.

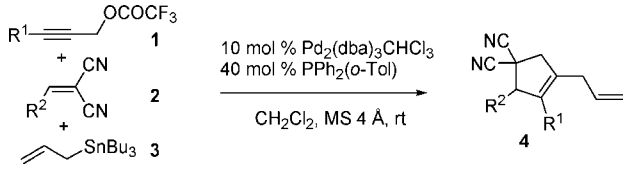
Various ethylidene malononitriles and propargyl trifluoroacetates were examined under the optimized reaction conditions:[7] 10 mol % $Pd_2(dba)_3CHCl_3$, 40 mol % $PPh_2$(*o*-tol), MS 4 Å, $CH_2Cl_2$ (0.2 M), and dropwise addition of **3**

(5) (a) Nakamura, H.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **1997**, *119*, 8113. (b) Nakamura, H.; Aoyagi, K.; Shim, J.-G.; Yamamoto, Y. *J. Am. Chem. Soc.* **2001**, *123*, 372.

(6) It has been confirmed that the reaction between allyltributylstannane and $PdCl_2(PPh_3)_2$ produces bis-$\pi$-allylpalladium complex; see: Nakamura, H.; Iwama, H.; Yamamoto, Y. *J. Am. Chem. Soc.* **1996**, *118*, 6641. However, **5a** is not formed in the present reaction conditions without propargyl compounds.

with syringe pump (Table 2). The reaction of phenyl propargyl trifluoroacetate **1a** and **2b**−**e**, substituted with an electron-donating and an electron-withdrawing aromatic group at $R^2$, produced the desired cyclopentenes **4b**−**e** in high yields (entries 1−4). The electronic characteristics of an aromatic ring at $R^2$ did not exert a significant influence on the yield of **4**. Not only the naphthyl-substituted alkene **2f** but also a heteroaromatic ring such as 2-thiophenyl-substituted alkene **2g** afforded the corresponding cyclopentenes **4f** and **4g** in good to high yields (entries 5 and 6). The reaction of **1a** with 2-(3-phenyl-allylidene)-malononitrile **2h** gave the desired product **4h** in 41% yield (entry 7). The reaction of **1a** with **2i** and **2j** bearing a cyclopropyl and bulky cyclohexyl group at $R^2$ gave the corresponding products **4i** and **4j** in moderate yields (entries 8 and 9). The reaction of **2a** with **1e** or **1f** bearing a 4-fluorophenyl or 2-thiophenyl group at the alkynyl terminus gave the desired cyclopentenes **4k** and **4l** in 74% and 31% yields, respectively (entries 10 and 11). The reaction of **2a** with **1g** having an *n*-heptyl substituent at $R^1$ produced the corresponding cyclopentene **4m** in good yield (entry 12).

**Table 2.** Pd(0)-Catalyzed Three-Component Cycloaddition with Various Propargyl Trifluoroacetates, Ethylidene Malononitriles, and Allyltributylstannane[a]

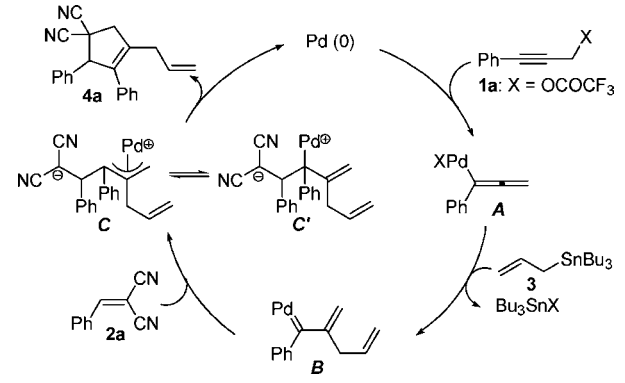



| entry | $R^1$ | $R^2$ | time (h) | | yield (%)[b] |
|---|---|---|---|---|---|
| 1 | Ph (**1a**) | 3-MeO-$C_6H_4$ (**2b**) | 43 | **4b** | 76 |
| 2 | Ph (**1a**) | 4-Cl-$C_6H_4$ (**2c**) | 26 | **4c** | 84 |
| 3 | Ph (**1a**) | 4-CN-$C_6H_4$ (**2d**) | 40 | **4d** | 74 |
| 4 | Ph (**1a**) | 4-$NO_2$-$C_6H_4$ (**2e**) | 40 | **4e** | 71 |
| 5 | Ph (**1a**) | 2-naphthyl (**2f**) | 26 | **4f** | 87 |
| 6 | Ph (**1a**) | 2-thiophenyl (**2g**) | 22 | **4g** | 62 |
| 7 | Ph (**1a**) | *E*-CH=CHPh (**2h**) | 43 | **4h** | 41 |
| 8 | Ph (**1a**) | cyclopropyl (**2i**) | 43 | **4i** | 48 |
| 9 | Ph (**1a**) | cyclohexyl (**2j**) | 43 | **4j** | 64 |
| 10 | 4-F-$C_6H_4$ (**1e**) | Ph (**2a**) | 33 | **4k** | 74 |
| 11 | 2-thiophenyl(**1f**) | Ph (**2a**) | 33 | **4l** | 31 |
| 12 | *n*-heptyl (**1g**) | Ph (**2a**) | 33 | **4m** | 71 |

[a] To a $CH_2Cl_2$ (1 mL, 0.2 M) solution of $Pd_2(dba)_3CHCl_3$ (20 mol %), $PPh_2$(*o*-tol) (40 mol %), propargyl trifluoroacetates **1** (0.24 mmol), ethylidene malononitriles **2** (0.2 mmol), and MS 4 Å (160 mg) was added allyltributylstannane **3** (0.24 mmol) by syringe pump at room temperature for the time shown in the table. [b] Isolated yields.

A plausible reaction mechanism is shown in Scheme 3.[8] Initially, the reaction of propargyl compound **1a** with the palladium catalyst forms 1,2-propadienylpalladium intermediate **A**. The nucleophile, allyltributylstannane **3**, attacks the sp carbon of the 1,2-propadienyl moiety to form the palladium carbene complex **B**, which reacts with ethylidene malononitrile **2a** to give ($\sigma$-allyl)palladium complex **C′**. The $\sigma$-allyl complex **C′** is in equilibrium to ($\pi$-allyl)palladium complex **C**, which undergoes intramolecular C-alkylation with the stable carboanion to give the cyclopentene **4a**.

**Scheme 3.** Plausible Reaction Mechanism




In conclusion, we have developed a novel palladium-catalyzed three-component [3 + 2] cycloaddition of propargyl compounds, ethylidene malononitriles, and allyltributylstannane to give highly substituted cyclopenetenes under mild reaction conditions. The reaction most probably proceeds through the intermolecular [3 + 2] cycloaddition reaction between in situ generated palladium carbene complex and activated alkene. Although various synthetic methods for the formation of cyclopentene rings have been reported,[9] the present procedure provided an efficient and new three-component cycloaddition method to access a highly substituted cyclopentene ring. Further extension of this method to the intramolecular version and application to the synthesis of the biologically important multisubstituted carbocycles and heterocycles are in progress.

**Acknowledgment.** We thank the faculty members of the Instrumental Analysis Center at Tohoku University for the measurement of NMR and mass spectra.

**Supporting Information Available:** Experimental procedures and characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

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(7) The reaction of other activated alkenes, such as 2-cyano-3-phenylacrylic acid methyl ester or 3-cycanochromone, gave the corresponding cyclopentene products in 20−30% yields under standard conditions.

(8) An alternative reaction mechanism is a [4 + 2] cycloaddition between Pd-carbene and alkene to form a six-membered cyclic palladium species. Subsequent reductive elimination gives the [3 + 2] cycloaddition product. However, this pathway is less reasonable for the regioselective fromation of the corresponding cyclopentene product.

(9) For selected examples for the formation of multisubstituted cyclopentene, see: (a) Trost, B. M.; Rudd, M. T. *J. Am. Chem. Soc.* **2005**, *127*, 4763–4776. (b) Trost, B. M.; Nanninga, T. N.; Satoh, T. *J. Am. Chem. Soc.* **1985**, *107*, 721–723. (c) Feng, J.; Lu, X.; Kong, A.; Han, X. *Tetrahedron* **2007**, *63*, 6035–6041. (d) Rhee, J. U.; Krische, M. J. *Org. Lett.* **2005**, *7*, 2493–2495. (e) Barluenga, J.; Palomas, D.; Rubio, E.; González, J. M. *Org. Lett.* **2007**, *9*, 2823–2826. (f) Jin, T.; Yang, F.; Liu, C.; Yamamoto, Y. *Chem Commun.* **2009**, 3533–3535.