

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

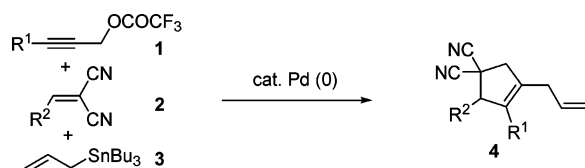
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ABSTRACT



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 cyclopentenones **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 carbocycles and heterocycles.¹ Most recently, the inter- and intramolecular cycloaddition of propargyl compounds catalyzed by π -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 π -allylpalladium complex by intramolecular proton transfer. Subsequent O-alkylation of carbonyl oxygen with π -allyl complex gives a five-membered heterocycle. It occurred to us that, by proper choice of nucleophiles (Nu) and electrophiles (E=¹Nu), the three-component coupling reaction between propargyl compounds, Nu[−], and E=¹Nu should take place in the presence of palladium catalysts (Scheme 1).

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

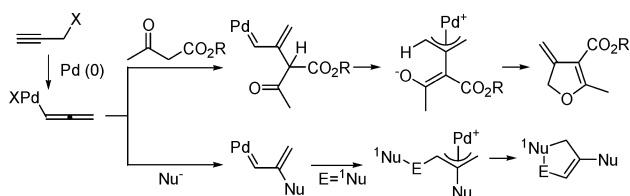
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(1) For recent reviews, see: (a) Schore, N. E. *Chem. Rev.* **1988**, 88, 1081. (b) Welker, M. E. *Chem. Rev.* **1992**, 92, 97. (c) Lautens, M.; Klute, W.; Tam, W. *Chem. Rev.* **1996**, 96, 49. (d) Nakamura, I.; Yamamoto, Y. *Chem. Rev.* **2004**, 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.

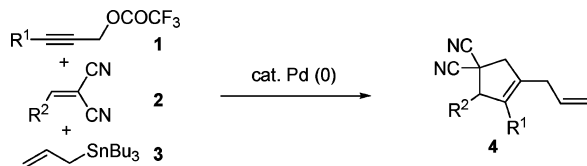
(2) For selected reviews, see: (a) Hashmi, A. S. K. *Chem. Rev.* **2007**, 107, 3180. (b) Gorin, D. J.; Sherry, B. D.; Toste, F. D. *Chem. Rev.* **2008**, 108, 3351. (c) Fürstner, A.; Davis, P. W. *Angew. Chem., Int. Ed.* **2007**, 46, 3410. For a recent example, see: (d) Zhang, G.; Zhang, L. *J. Am.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

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).

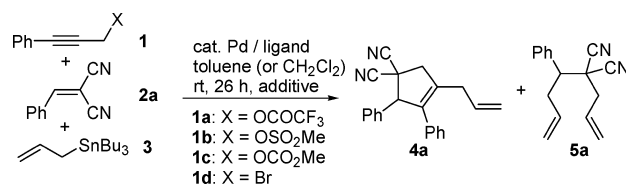
Scheme 2. Pd(0)-Catalyzed Three-Component Cycloaddition of Propargyl Trifluoroacetates, Ethylidene Malononitriles, and Allyltributylstannane



Previously, we reported that the inter- and intramolecular amphiphilic bisallylation of activated alkenes with bis- π -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 $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$ (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 $\text{Pd}(\text{PPh}_3)_4$, $\text{Pd}(\text{OAc})_2$, and $\text{Pd}(\text{acac})_2$, gave lower yields of **4a** (entries 2–4). Other transition metal catalysts, such as $\text{Pt}(\text{PPh}_3)_4$ and $\text{Ni}(\text{cod})_2$, were not effective. Triarylphosphine ligands, such as $\text{PPh}_2(o\text{-tol})$ (53%), $\text{P}(o\text{-tol})_3$ (46%), and $\text{P}(1\text{-naphthyl})_3$ (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 $\text{PPh}_2(o\text{-tol})$ (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



entry	Pd/L (20/40 mol %)	yield (%) ^b		
		1	4a	5a
1	$\text{Pd}_2(\text{dba})_3\text{CHCl}_3/\text{PPh}_3$	1a	51	27
2	$\text{Pd}(\text{PPh}_3)_4$	1a	46	28
3	$\text{Pd}(\text{OAc})_2/\text{PPh}_3$	1a	38	27
4	$\text{Pd}(\text{acac})_2/\text{PPh}_3$	1a	38	28
5	$\text{Pd}_2(\text{dba})_3\text{CHCl}_3/\text{PPh}_2(o\text{-Tol})$	1a	53	27
6	$\text{Pd}_2(\text{dba})_3\text{CHCl}_3/\text{P}(o\text{-Tol})_3$	1a	46	28
7	$\text{Pd}_2(\text{dba})_3\text{CHCl}_3/\text{P}(1\text{-Naphthyl})_3$	1a	50	32
8	$\text{Pd}_2(\text{dba})_3\text{CHCl}_3/\text{PMe}_3$	1a	0	0
9	$\text{Pd}_2(\text{dba})_3\text{CHCl}_3/\text{dppf}$	1a	0	0
10	$\text{Pd}_2(\text{dba})_3\text{CHCl}_3/\text{PPh}_2(o\text{-Tol})$	1b	42	36
11	$\text{Pd}_2(\text{dba})_3\text{CHCl}_3/\text{PPh}_2(o\text{-Tol})$	1c	0	0
12	$\text{Pd}_2(\text{dba})_3\text{CHCl}_3/\text{PPh}_2(o\text{-Tol})$	1d	0	30
13 ^c	$\text{Pd}_2(\text{dba})_3\text{CHCl}_3/\text{PPh}_2(o\text{-Tol})$	1a	66	5
14 ^{c,d}	$\text{Pd}_2(\text{dba})_3\text{CHCl}_3/\text{PPh}_2(o\text{-Tol})/\text{MS } 4 \text{ \AA}$	1a	(82)	0
15 ^{c,d,e}	$\text{Pd}_2(\text{dba})_3\text{CHCl}_3/\text{PPh}_2(o\text{-Tol})/\text{MS } 4 \text{ \AA}$	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 ¹H 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 $\text{PPh}_2(o\text{-tol})$ was used.

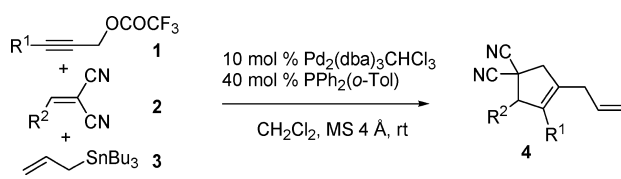
Various ethylidene malononitriles and propargyl trifluoroacetates were examined under the optimized reaction conditions:⁷ 10 mol % $\text{Pd}_2(\text{dba})_3\text{CHCl}_3$, 40 mol % $\text{PPh}_2(o\text{-tol})$, MS 4 Å, CH_2Cl_2 (0.2 M), and dropwise addition of **3**

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(6) It has been confirmed that the reaction between allyltributylstannane and $\text{PdCl}_2(\text{PPh}_3)_2$ produces bis- π -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 R², produced the desired cyclopentenones **4b–e** in high yields (entries 1–4). The electronic characteristics of an aromatic ring at R² 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 cyclopentenones **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 R² 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 cyclopentenones **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 R¹ 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)	4	yield (%) ^b
1	Ph (1a)	3-MeO-C ₆ H ₄ (2b)	43	4b	76
2	Ph (1a)	4-Cl-C ₆ H ₄ (2c)	26	4c	84
3	Ph (1a)	4-CN-C ₆ H ₄ (2d)	40	4d	74
4	Ph (1a)	4-NO ₂ -C ₆ H 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)	<i>E</i> -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 ₆ H ₄ (1e)	Ph (2a)	33	4k	74
11	2-thiophenyl (1f)	Ph (2a)	33	4l	31
12	<i>n</i> -heptyl (1g)	Ph (2a)	33	4m	71

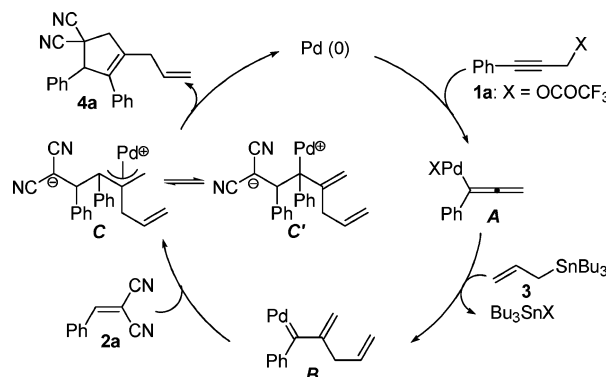
^a To a CH₂Cl₂ (1 mL, 0.2 M) solution of Pd₂(dba)₃CHCl₃ (20 mol %), PPh₂(*o*-tol) (40 mol %), propargyl trifluoroacetates **1** (0.24 mmol), ethylidene malononitriles **2** (0.2 mmol), and MS 4 Å (160 mg) was added allyltributylstannane **3** (0.24 mmol) by syringe pump at room temperature for the time 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

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

sp carbon of the 1,2-propadienyl moiety to form the palladium carbene complex **B**, which reacts with ethylidene malononitrile **2a** to give (σ-allyl)palladium complex **C'**. The σ-allyl complex **C'** is in equilibrium to (π-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 cyclopentenones 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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(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 formation 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.