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Diastereoselective Construction of 7-Methylenebicyclo[3.2.1]oct-3-en-2-one Derivatives by Palladium-Catalyzed Cyclization of Propargylic Acetates with 2-Oxocyclohex-3-enecarboxylates

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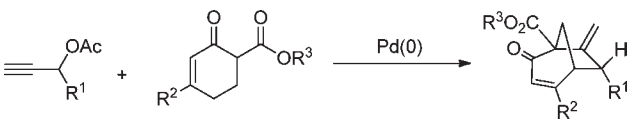
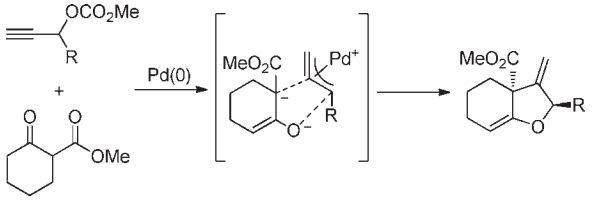
ABSTRACT



The reaction of propargylic acetates with 2-oxocyclohex-3-enecarboxylates in the presence of a palladium catalyst is described. Substituted 7-methylenebicyclo[3.2.1]oct-3-en-2-ones were synthesized in a highly diastereoselective manner.

Palladium-catalyzed reactions of propargylic compounds with nucleophiles have received considerable attention and have been extensively studied due to their versatile and specific reactivity.[1] The reaction of propargylic compounds with bis-nucleophiles is one example of the more successful chemical processes developed to date.[2] In this reaction, a substrate having two nucleophilic moieties within the molecule reacted sequentially with the π-propargylpalladium complex, resulting from propargylic compounds and palladium catalysts, to afford the cyclized product. For example, we have recently reported the reaction of propargylic carbonates with β-keto esters,[2i] in which substituted tetrahydrobenzofuranones having a quaternary carbon stereocenter were synthesized in a highly diastereoselective manner (Scheme 1).

Scheme 1. Palladium-Catalyzed Reaction of Propargylic Carbonates with β-Keto Esters



Although various heterocyclic molecules can be synthesized by this type of cyclization, no examples have been reported on the construction of carbocyclic molecules, presumably because of the difficulty in designing the bis-nucleophiles.[3] In planning our investigation of this reaction, we focused on the nucleophilic activity of 2-oxocyclohex-3-enecarboxylates. By introducing a conjugated enone system within the substrate, it was thought that both the α-carbon of the keto ester moiety and the

(1) (a) Tsuji, J. *Palladium Reagents and Catalysts: Innovations in Organic Synthesis*; Wiley: New York, 1995; pp 453. (b) Tsuji, J. *Palladium Reagents and Catalysts: New Perspectives for the 21st Century*; Wiley: England, 2004; pp 543. (c) Tsuji, J.; Mandai, T. *Angew. Chem., Int. Ed. Engl.* **1995**, *34*, 2589. (d) Guo, L.-N.; Duan, X.-H.; Liang, Y.-M. *Acc. Chem. Res.* **2011**, *44*, 111 and references therein.

(2) (a) Tsuji, J.; Watanabe, I.; Minami, I.; Shimizu, I. *J. Am. Chem. Soc.* **1985**, *107*, 2196. (b) Geng, L.-F.; Lu, X.-Y. *Chin. J. Chem.* **1993**, *11*, 91. (c) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **1999**, *40*, 9025. (d) Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Org. Lett.* **2000**, *2*, 527. (e) Damez, C.; Labrosse, J.-R.; Lhoste, P.; Sinou, D. *Tetrahedron Lett.* **2003**, *44*, 557. (f) Duan, X.-H.; Liu, X.-Y.; Guo, L.-N.; Liao, M.-C.; Liu, W.-M.; Liang, Y.-M. *J. Org. Chem.* **2005**, *70*, 6980. (g) Yoshida, M.; Higuchi, M.; Shishido, K. *Tetrahedron Lett.* **2008**, *49*, 1678. (h) Yoshida, M.; Higuchi, M.; Shishido, K. *Org. Lett.* **2009**, *11*, 4752. (i) Yoshida, M.; Higuchi, M.; Shishido, K. *Tetrahedron* **2010**, *66*, 2675.

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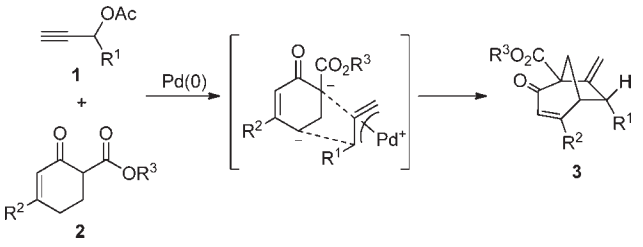
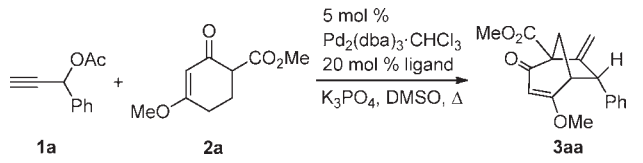
γ-carbon of the enone moiety could act as the nucleophiles, which might enable the formation of a carbocyclic ring. Herein, we describe the palladium-catalyzed reaction of propargylic acetates **1** with 2-oxocyclohex-3-enecarboxylates **2**, in which functionalized bicyclo[3.2.1]octenones **3** have been constructed in a highly stereoselective manner (Scheme 2).

Scheme 2. Palladium-Catalyzed Reaction of Propargylic Acetates **1** with 2-Oxocyclohex-3-Enecarboxylates **2**



The initial reactions were attempted using 1-phenyl-2-propynyl acetate (**1a**) and methyl 4-methoxy-2-oxocyclohex-3-enecarboxylate (**2a**) (Table 1). When **1a** and **2a** were reacted with 5 mol % of $Pd_2(dba)_3 \cdot CHCl_3$, 20 mol % DPPE and K_3PO_4 in DMSO at 120 °C, the cyclization gave the bicyclo[3.2.1]octenone **3aa** in 36% yield as a single stereoisomer (Table 1, entry 1). After experimenting with various ligands and reaction temperatures (entries 2−7), we found that the yield of **3aa** could be improved to 81% when DPPF was used as the ligand (entry 5).

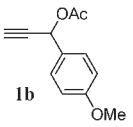
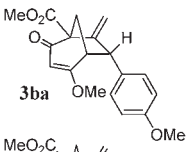
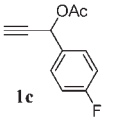
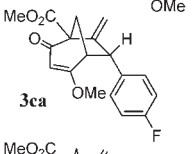
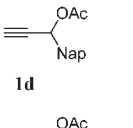
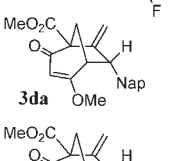
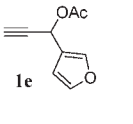
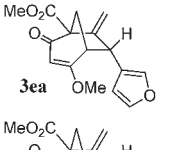
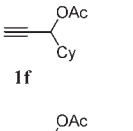
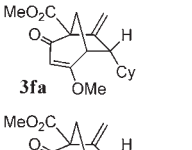
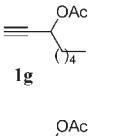
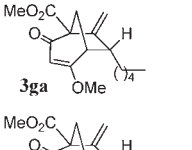
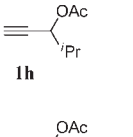
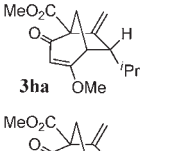
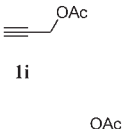
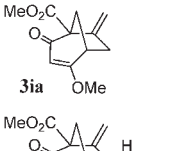
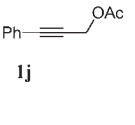
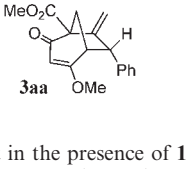
Table 1. Effect of Ligand and Temperature in the Reaction of **1a** with **2a**



entry	ligand	temp (°C)	time (min)	yield of **3aa** (%)
1	DPPE	120	5	36
2	DPPP	120	5	59
3	DPPB	120	5	53
4	DPPPent	120	5	67
5	DPPF	120	5	81
6	DPPF	80	7	68
7	DPPF	50	15	19

Having identified a useful set of reaction conditions, we next conducted the reactions of various substituted propargylic acetates, **1b**−**1j**, with **2a** (Table 2). The propargylic acetates **1b** and **1c** having a *p*-methoxyphenyl and a *p*-fluorophenyl group successfully reacted with **2a** in the presence of the palladium catalyst to

Table 2. Reactions using Propargylic Acetate **1b**−**j** with **2a**[a]

entry	propargylic aetate	product	yield (%)
1			69
2			80
3[b]			82
4			80
5[c]			78[d]
6			54
7			52
8			40
9			80

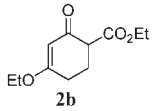
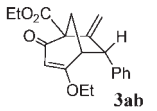
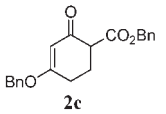
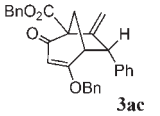
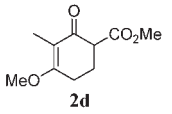
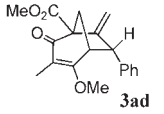
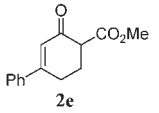
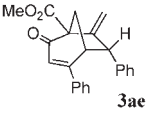
[a] Reactions were carried out in the presence of **1** and **2a**, **5** mol % $Pd_2(dba)_3$- $CHCl_3$, 20 mol % DPPF and 2 equiv K_3PO_4 in DMSO at 120 °C for 5 min. [b] Nap = 2-naphthyl. [c] Cy = cyclohexyl. [d] BINAP was used as the ligand.

produce the bicyclo[3.2.1]octenones **3ba** and **3ca** in 69 and 80% yield, respectively (entries 1 and 2). When the reactions of the substrates **1d** and **1e** containing a 2-naphthyl and a 3-furanyl group were carried out, the corresponding products **3da** and **3ea** were obtained in good yields (entries 3 and 4). The reactions of the substrates **1f**, **1g** and **1h**, which have a cyclohexyl, a pentyl and an isopropyl group, respectively, also afforded the bicyclo[3.2.1]octenones **3fa**, **3ga** and **3ha** in

(3) Some examples about the palladium-catalyzed carboannulations using propargylic compounds with mononucleophiles have been reported: (a) Duan, X.-H.; Guo, L.-N.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *Org. Lett.* **2006**, *8*, 5777. (b) Guo, L.-N.; Duan, X.-H.; Bi, H.-P.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2007**, *72*, 1538. (c) Bi, H.-P.; Guo, L.-N.; Gou, F.-R.; Duan, X.-H.; Liu, X.-Y.; Liang, Y.-M. *J. Org. Chem.* **2008**, *73*, 4713 and see also ref 1d.

moderate yields (entries 5−7). The corresponding product **3ia** was produced from the reaction of the nonsubstituted propargylic acetate **1i** in 40% yield (entry 8).[4] When the substrate **1j** containing a phenyl group on the alkynyl moiety was subjected to the reaction, the bicyclo[3.2.1]octenone **3aa**, which was the same product from the reaction of **1a**, was obtained in 80% yield (entry 9).

Table 3. Reactions using 2-Oxocyclohex-3-enecarboxylates **2b**−**2e** with **1a**[a]

entry	β-keto ester	product	yield (%)
1	 **2b**	 **3ab**	76
2	 **2c**	 **3ac**	82
3	 **2d**	 **3ad**	64[b]
4	 **2e**	 **3ae**	75

[a] Reactions were carried out in the presence of **1a** and **2**, 5 mol % $Pd_2(dba)_3$-$CHCl_3$, 20 mol % DPPF and 2 equiv K_3PO_4 in DMSO at 120 °C for 5 min. [b] Reaction was carried out in the presence of 20 mol % BINAP at 80 °C.

Table 3 shows our attempts using various 2-oxocyclohex-3-enecarboxylates, **2b**−**2e**, with **1a**. The reactions of the substrates **2b** and **2c** containing an ethyl and a benzyl ester moiety successfully proceeded to give the bicyclo[3.2.1]octenones **3ab** and **3ac** in 76 and 82% yield, respectively (entries 1 and 2). When the reaction of **2d** having a methyl group on the α-position of the enone system was carried out, the corresponding product **3ad** was obtained in 64% yield (entry 3). The substrate **2e**, which has a phenyl group at the β-position, was also converted to the bicyclo[3.2.1]octenone **3ae** in 75% yield (entry 4). The structure of **3ab**, including the stereochemistry, was confirmed by X-ray crystallographic analysis (Figure 1). Since in all cases the resulting products **3aa**−**3ia** and **3ab**−**3ae** had been obtained as a single stereoisomer, it was determined that the reaction had proceeded in a highly stereoselective manner.

A plausible mechanism for the production of the bicyclo[3.2.1]octenones **3** is shown in Scheme 3. By

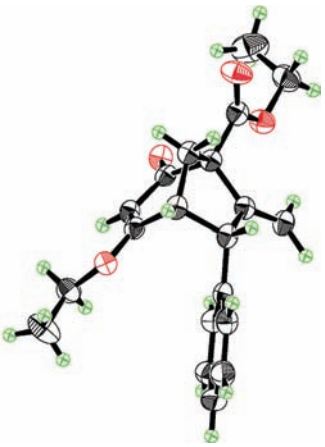
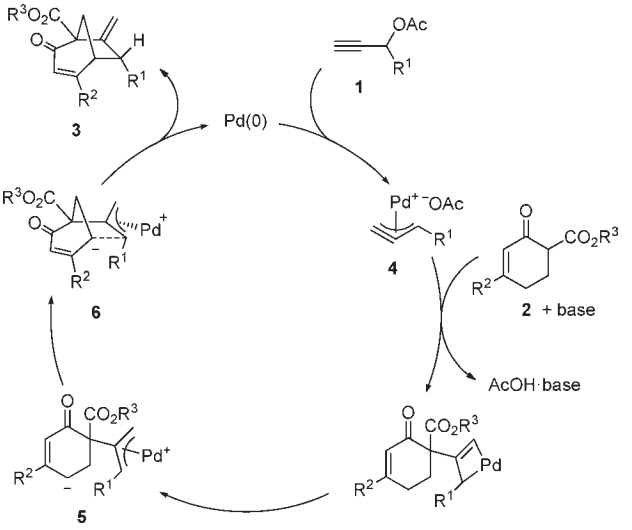


Figure 1. ORTEP representation of **3ab**.

reacting with the palladium catalyst, the propargylic acetate **1** is transformed to the π-propargylpalladium complex **4**,[5] which reacts with the 2-oxocyclohex-3-enecarboxylate **2** and base to lead to the π-allylpalladium intermediate **5**. The intermediate **5** is further subjected to intramolecular attack of the γ-carbon of the enone moiety via the favorable transition state **6** to produce the bicyclo[3.2.1]octenone **3** with high regio- and diastereoselectivity. The results from the reactions of the propargylic acetates **1a** and **1j** to produce the same product **3aa** (Table 1 and entry 9 in Table 2) support our hypothesis that the reaction proceeds via the formation of a common π-allylpalladium intermediate **5**.

Scheme 3. Proposed Reaction Mechanisms



In conclusion, the effort described above has led to the development of a palladium-catalyzed reaction of propargylic acetates with 2-oxocyclohex-3-enecarboxylates.

(4) As the reason for the low yield of **3ia**, it is expected that the part of propargyl acetate (**1i**) is vaporized in the reaction because of the volatility.

(5) (a) Tsutsumi, K.; Ogoshi, S.; Nishiguchi, S.; Kurosawa, H. *J. Am. Chem. Soc.* **1998**, *120*, 1938. (b) Tsutsumi, K.; Kawase, T.; Kakiuchi, K.; Ogoshi, S.; Okada, Y.; Kurosawa, H. *Bull. Chem. Soc. Jpn.* **1999**, *72*, 2687.

The process produces substituted bicyclo[3.2.1]octenones in a highly stereoselective manner. Since various natural products having a bicyclo[3.2.1]octane structure have been reported,[6,7] our methodology would provide a new protocol for the synthesis of these compounds with high efficiency.

Acknowledgment. This study was supported in part by a Grant-in-Aid for the Encouragement of Young Scientists (B) from the Japan Society for the Promotion of Science (JSPS), the Takeda Science Foundation, the Uehara Memorial Foundation and the Program for the Promotion of Basic and Applied Research for Innovations in the Bio-oriented Industry (BRAIN).

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

(6) Examples showing biologically active natural products having a bicyclo[3.2.1]octenone core include: (a) Huang, Y.-L.; Tsai, W.-J.; Shen, C.-C.; Chen, C.-C. *J. Nat. Prod.* **2005**, *68*, 217. (b) Huang, S.-X.; Zhao, Q.-S.; Xu, G.; Xiao, W.-L.; Li, R.-T.; Hou, A.-J.; Peng, S.-L.; Ding, L.-S.; Sun, H.-D. *J. Nat. Prod.* **2005**, *68*, 1758. (c) Konopleva, M. M.; Matlawska, I.; Wojcinska, M.; Ahmed, A. A.; Rybczynska, M.; Paszel, A.; Ohta, S.; Hirata, T.; Bylka, W.; Mabry, T. J.; Cannon, J. F. *J. Nat. Prod.* **2006**, *69*, 394. (d) Sun, H.-D.; Huang, S.-X.; Han, Q.-B. *Nat. Prod. Rep* **2006**, *23*, 673. (e) Chang, S.-F.; Yang, L.-M.; Lo, C.-H.; Liaw, J.-H.; Wang, L.-H.; Lin, S.-J. *J. Nat. Prod.* **2008**, *71*, 87. (f) Tiefenbacher, K.; Mulzer, J. *Angew. Chem., Int. Ed.* **2008**, *47*, 2548. (g) Coy, E. D.; Cuca, L. E.; Sefkow, M. *J. Nat. Prod.* **2009**, *72*, 1245.

(7) Recent examples for the construction of bicyclo[3.2.1]octenones include: (a) Mao, Z.; Li, Y.; Chen, J.; Wang, Y.; Zhang, H. *Bioorg. Med. Chem. Lett.* **2010**, *20*, 4116. (b) Goodell, J. R.; McMullen, J. P.; Zaborenko, N.; Maloney, J. R.; Ho, C.-X.; Jensen, K. F.; Porco, J. A., Jr.; Beeler, A. B. *J. Org. Chem.* **2009**, *74*, 6169. (c) Rueping, M.; Kuenkel, A.; Tato, F.; Bats, J. W. *Angew. Chem., Int. Ed.* **2009**, *48*, 3699. (d) Orac, C. M.; Bergmeier, S. C. *Tetrahedron Lett.* **2009**, *50*, 1261. (e) Bhunia, S.; Liu, R.-S. *J. Am. Chem. Soc.* **2008**, *130*, 16488. (f) Katayama, S.; Yamauchi, M. *Chem. Pharm. Bull.* **2005**, *53*, 666. (g) Toyota, M.; Ihara, M. *Synlett* **2002**, 1211.