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Allenylcyclobutanol, a Versatile Initiator for the Palladium-Catalyzed Cascade Reaction: A Novel Route to Bicyclo[5.3.0] and -[6.3.0] Frameworks

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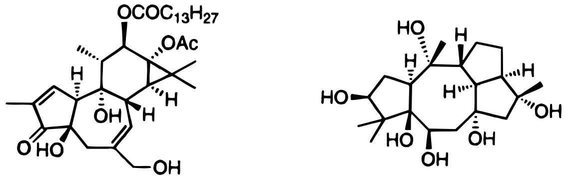
Carbopalladation[1] has emerged as one of the most important methods for the preparation of a wide range of molecular frames. Of these, the carbopalladation of allenes[2] is particularly attractive from both a theoretical and practical standpoint, thereby prompting the recent activity in this field. However, its intramolecular version[2f−h] has received relatively little attention. Here, we report a novel unprecedented type of intramolecular carbopalladation of allenes, in which the ring transformation of the π-allylpalladium **B**[3] *in situ* generated by the intramolecular carbopalladation of **A** is accompanied by the strain release of the cyclobutane ring to directly give the fused bicyclo[*n* + 3.3.0] ring system **C** (Scheme 1).

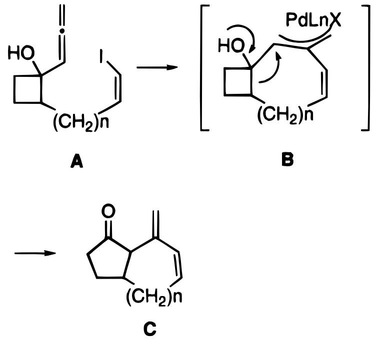
This sequential process provides a unique entry into the biologically important natural products having 5,7-[4] and 5,8-fused ring frameworks,[5] such as phorbol (**1**)[6] and kalmanol (**2**)[7] (Figure 1).



1 **2**

Figure 1.

Scheme 1



A goal of this novel cascade reaction was initiated by its intermolecular version to examine the feasibility of the carbopalladation accompanied by ring expansion of allenylcyclobutanols giving rise to the direct formation of substituted cyclopentanones, and also to determine its optimum reaction conditions. The experimental results are summarized in Table 1[8] and revealed the following features.

Namely, in all cases, this cascade reaction took place to afford conjugated **5** and **6** and unconjugated cyclopentenones **7** having a β-substituent in various ratios depending on the substrates used and resulting in a better yield in the case of the R′ group bearing electron donor substituents (entries **8**−**11**) rather than electron-withdrawing substituents (entries **6** and **7**). The relative stereochemistry of substrates **3a** and **3b** did not significantly affect the yield of this reaction.

The use of THF as a solvent resulted in a better yield than that of DMF (entries 1 and 2 in Table 1). Thus, we could confirm the cascade carbopalladation−ring expansion reaction of allenylcyclobutanols to afford β-substituted cyclopentenones. This cascade reaction was also characteristic for the substrates having an allenylcyclobutanol framework.[10]

We are now ready for developing the intramolecular version of this cascade reaction. The results for substrates **13a**,**b** and **17a**,**b**, where the allene and vinyl

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(1) For recent reviews, see: (a) Negishi, E. *Pure Appl. Chem.* **1992**, *64*, 323−334. (b) de Meijere, A.; Meyer, F. E. *Angew. Chem., Int. Ed. Engl.* **1994**, *33*, 2379−2411. (c) Negishi, E.; Copéret, C.; Ma, S.; Liou, S.-Y.; Liu, F. *Chem. Rev.* **1996**, *96*, 365−393. (d) Tietze, L. F. *Chem. Rev.* **1996**, *96*, 115−136. (e) Malacria, M. *Chem. Rev.* **1996**, *96*, 289−306.

(2) For the recent studies of the intermolecular carbopalladation of allenes, see: (a) Yamamoto, Y.; Al-Masum, M.; Asao, N. *J. Am. Chem. Soc.* **1994**, *116*, 6019−6020. (b) Larock, R. C.; Zenner, J. M. *J. Org. Chem.* **1995**, *60*, 482−483. (c) Trost, B. M.; Gerusz, V. J. *J. Am. Chem. Soc.* **1995**, *117*, 5156−5157. (d) Desarbre, E.; Mérour, J.-Y. *Tetrahedron Lett.* **1996**, *37*, 43−46. (e) Yamamoto, Y.; Al-Masum, M.; Fujiwara, N. *J. Chem. Soc., Chem. Commun.* **1996**, 381−382. For the recent studies of the intramolecular version, see: (f) Ma, S.; Negishi, E. *J. Org. Chem.* **1994**, *59*, 4730−4732. (g) Ma, S.; Negishi, E. *J. Am. Chem. Soc.* **1995**, *117*, 6345−6357. (h) Doi, T.; Yanagisawa, A.; Nakanishi, S.; Yamamoto, K.; Takahashi, T. *J. Org. Chem.* **1996**, *61*, 2602−2603.

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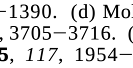

d

(4) For review and some recent examples of synthetic studies, see: (a) Booker-Milburn, K. I. *Synlett* **1992**, 809−810. (b) Marcos, I. S.; Oliva, I. M.; Díez, D.; Basabe, P.; Lithgow, A. M.; Moro, R. F.; Garrido, N. M.; Urones, J. G. *Tetrahedron* **1995**, *51*, 12403−12416. (c) Winkler, J. D.; Hong, B.-C.; Bahador, A.; Kazanietz, M. G.; Blumberg, P. M. *J. Org. Chem.* **1995**, *60*, 1381−1390. (d) Molander, G. A.; Harris, C. R. *J. Am. Chem. Soc.* **1995**, *117*, 3705−3716. (e) Lautens, M.; Kumanovic, S. *J. Am. Chem. Soc.* **1995**, *117*, 1954−1964 and references cited therein.

(5) For some recent synthetic studies, see: (a) Booker-Milburn, K. I.; Thompson, D. F. *Synlett* **1993**, 592−594. (b) Molander, G. A.; Eastwood, P. R. *J. Org. Chem.* **1995**, *60*, 4559−4565. (c) Miller, S. J.; Kim, S.-H.; Chen, Z.-R.; Grubbs, R. H. *J. Am. Chem. Soc.* **1995**, *117*, 2108−2109. (d) Myers, A. G.; Condroski, K. R. *J. Am. Chem. Soc.* **1995**, *117*, 3057−3083 and references cited therein.

(6) For recent synthetic studies, see: (a) Wender, P. A.; Lee, H. Y.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8954−8957. (b) Wender, P. A.; Kogen, H.; Lee, H. Y.; Munger, J. D.; Wilhelm, R. S.; Williams, P. D. *J. Am. Chem. Soc.* **1989**, *111*, 8957−8958. (c) Wender, P.; McDonald, F. *J. Am. Chem. Soc.* **1990**, *112*, 4956−4958. (d) Wender, P. A.; Irie, K.; Miller, B. L. *J. Org. Chem.* **1993**, *58*, 4179−4181. (e) Sugita, K.; Shigeno, K.; Neville, C. F.; Sasai, H.; Shibasaki, M. *Synlett* **1994**, 325−329 and references cited therein.

(7) For recent synthetic studies, see: (a) Paquette, L. A.; Borrelly, S. *J. Org. Chem.* **1995**, *60*, 6912−6921. (b) Borrelly, S.; Paquette, L. A. *J. Am. Chem. Soc.* **1996**, *118*, 727−740 and references cited therein.

(8) The substrates **3a** and **3b** were prepared from 2-heptylcyclobutanone (**8**)[9] (for experimental details, see Supporting Information).

(9) Nemoto, H.; Shiraki, M.; Fukumoto, K. *J. Org. Chem.* **1996**, *61*, 1347−1353.

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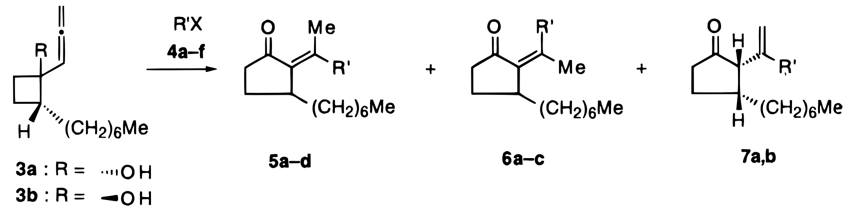
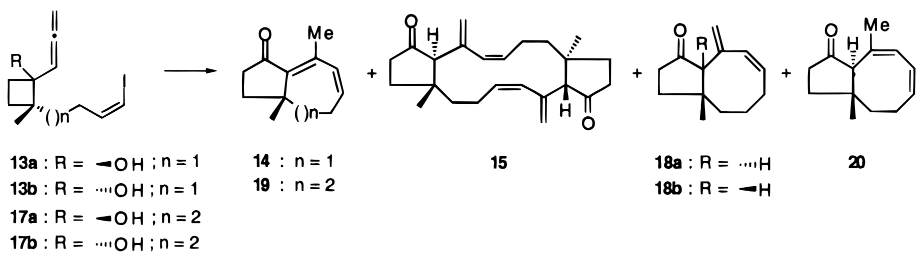
Table 1. Intermolecular Cascade Carbopalladation–Ring Expansion Reaction between 3a,b and 4a–e[a]



				product			
				ratio[b]			
entry	4	substrate	time (h)	**5** (**a**–**d**)	**6** (**a**–**d**)	**7** (**a**,**b**)	yield (%)[c]
1	**4a**: R′ = Ph; X = I	**3a**	12	76 (**a**)	24 (**a**)	0	33
2[d]		**3a**	20	52 (**a**)	0	48 (**a**)	76
3		**3b**	12	82 (**a**)	18 (**a**)	0	34
4	**4b**: R′ = Ph; X = OTf	**3a**	6	62 (**a**)	38 (**a**)	0	27
5		**3b**	6	69 (**a**)	31 (**a**)	0	23
6	**4c**: R′ = *p*-NO_2Ph; X = I	**3a**	6	67 (**b**)	33 (**b**)	0	20
7		**3b**	6	66 (**b**)	34 (**b**)	0	21
8	**4d**: R′ = *p*-MePh; X = I	**3a**	6	71 (**c**)	0	29 (**b**)	79
9		**3b**	6	100 (**c**)	0	0	67
10	**4e**: 1-iodonaphthalene	**3a**	10	78 (**d**)	22 (**c**)	0	75
11		**3b**	10	73 (**d**)	27 (**c**)	0	52

[a] Conditions: 10 mol % $Pd(PPh_3)_4$, K_2CO_3 (5 equiv), **4** (5 equiv), 80 °C, DMF. [b] Ratio was calculated from the isolated yields of each products. [c] Isolated total yield. [d] THF was used as solvent.

Table 2. Intramolecular Carbopalladation–Ring Expansion Reaction of 13a,b and 17a,b[a]



				product					
				ratio[b]					
entry	substrate	time (h)	temp.	**14**	**15**	**18** (**a or b**)	**19**	**20**	yield (%)[c]
1	**13a**	16	rt	0	100	–	–	–	80
2	**13a**	16	80 °C	100	0	–	–	–	63
3	**13b**	16	80 °C	100	0	–	–	–	67
4	**17a**	12	reflux	–	–	0	62	38	53
5	**17a**	12	80 °C	–	–	63 (**a**) 8 (**b**)	25	4	60
6	**17a**	12	80 °C	–	–	22 (**a**) 23 (**b**)	48	7	81
7	**17b**	12	80 °C	–	–	100 (**b**)	0	0	24
8	**17b**	12	reflux	–	–	0	100	0	34

[a] Conditions: 10 mol % $Pd(PPh_3)_4$, Ag_2CO_3 (2 equiv), toluene for entries 1–4, 7, and 8; 10 mol % $Pd(PPh_3)_4$, Ag_2CO_3 (2 equiv), 4 Å molecular sieves, toluene for entry 5; 10 mol % $Pd(OAc)_2$, 20 mol % dppe, 4 Å molecular sieves, toluene for entry 6. [b] Ratio was calculated from the isolated yields of each products for entries 1–3 and ^{1}H-NMR integration of methyl signals for entries 5–8. [c] Isolated total yield.

iodide units were tethered by four- and five-carbon chains, respectively, are summarized in Table 2.[11]

The cascade reaction of **17a**,**b** proceeded in the same way as that of **13a**,**b** to give the bicyclo[6.3.0] system with a comparable yield to that of the bicyclo[5.3.0] system. The definite effects of molecular sieves[12] on the yield of this cascade reaction was noteworthy, thus making this methodology also efficient for the synthesis of the [6.3.0] system.[13]

Supporting Information Available: Experimental Procedures for all substrates and characterization data for all products (15 pages).

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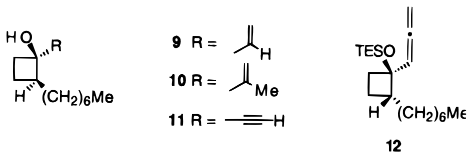
(10) We have examined this cascade reaction of **9**–**12** under the conditions of entry 2 in Table 1 and failed to detect any products resulting from this cascade reaction.



(11) The substrates **13a**,**b** and **17a**,**b** were prepared from 2-(3-(*tert*-butyldiphenylsiloxy)propyl)-2-methylcyclobutanone (**16**)[9] (for experimental details, see Supporting Information).

(12) For recent examples of the effect of molecular sieves on the palladium-catalyzed reaction, see: (a) Lauten, M.; Ren, Y. *J. Am. Chem. Soc.* **1996**, *118*, 9597–9605. (b) Trost, B. M.; Higuchi, R. I. *J. Am. Chem. Soc.* **1996**, *118*, 10094–10105.

(13) For general procedure for intermolecular cascade carbopalladation–ring expansion reaction, see Supporting Information.