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Palladium-Catalyzed Synthesis of Endocyclic Allenes and Their Application in Stereoselective [2 + 2]Cycloaddition with Ketenes

Masamichi Ogasawara,* Atsushi Okada, Kiyohiko Nakajima, and Tamotsu Takahashi*

Catalysis Research Center and Graduate School of Life Science, Hokkaido University, and SORST, Japan Science and Technology Agency (JST), Kita-ku, Sapporo 001-0021, Japan, and Department of Chemistry, Aichi University of Education, Igaya, Kariya, Aichi, 448-8542, Japan

ogasawar@cat.hokudai.ac.jp; tamotsu@cat.hokudai.ac.jp

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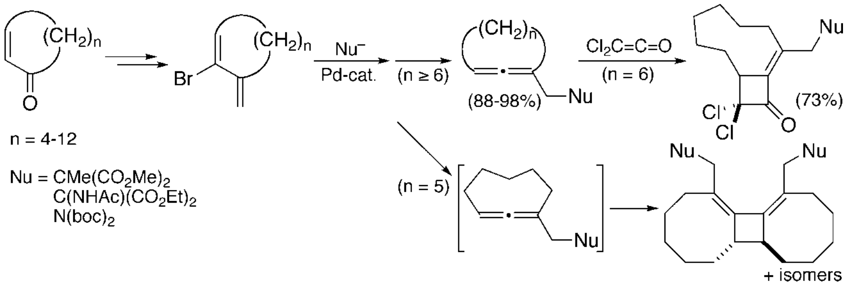
ABSTRACT



Palladium-catalyzed reactions of various 2-bromo-3-*exo*-methylenecycloalkenes with a stabilized nucleophile were examined. When the carbocycles were nine-membered or larger, the corresponding endocyclic allenes were isolated in excellent yields. In a reaction of the eight-membered cyclic substrate, initial formation of a cycloocta-1,2-diene derivative was detected; however, it dimerized slowly. The seven-membered carbocycle was inert to the reaction. Using a chiral Pd-catalyst, an axially chiral endocyclic allene was obtained in 65% ee. The cyclic allenes were applied to [2 + 2]cycloaddition with ketenes, and the stereoselectivity was studied.

Allenes are unique compounds with characteristic reactivity and steric properties, which originate in the cumulated propadienyl structures.[1] Although allenes have gained much attention as synthetic intermediates recently,[2] their applications in organic synthesis are still relatively unexplored compared to those of alkenes and alkynes.[2d] These situations can be attributed to their limited availability[1,3] as well as complicated stereoselective issues to be controlled in the organic transformations of allenes. Three strategies success-

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(1) (a) Taylor, D. R. *Chem. Rev.* **1967**, *67*, 317. (b) Pasto, D. J. *Tetrahedron* **1984**, *40*, 2805. (c) Rutledge, T. F. *Acetylenes and Allenes*; Reinhold: New York, 1969. (d) Patai, S., Ed. *The Chemistry of Ketenes, Allenes, and Related Compounds*; Wiley: Chichester, 1980. (e) Landor, S. R., Ed. *The Chemistry of the Allenes*; Academic Press: London, 1982. (f) Coppola, G. M.; Schuster, H. F. *Allenes in Organic Synthesis*; Wiley: New York, 1984. (g) Krause, N.; Hashmi, A. S. K., Eds. *Modern Allene Chemistry*; Wiley-VCH: Weinheim, 2004.

(2) (a) Marshall, J. A. *Chem. Rev.* **1996**, *96*, 31. (b) Wang, K. K. *Chem. Rev.* **1996**, *96*, 207. (c) Yamamoto, Y.; Radhakrishnan, U. *Chem. Soc. Rev.* **1999**, *28*, 199. (d) Hashmi, A. S. K. *Angew. Chem., Int. Ed.* **2000**, *39*, 3590. (e) Zimmer, R.; Dinesh, C. U.; Nandanan, E.; Khan, F. A. *Chem. Rev.* **2000**, *100*, 3067. (f) Lu, X.; Zhang, C.; Xu, Z. *Acc. Chem. Res.* **2001**, *34*, 535. (g) Ma, S.; Li, L. *Synlett* **2001**, 1206. (h) Tius, M. A. *Acc. Chem. Res.* **2003**, *36*, 284. (i) Ma, S. *Acc. Chem. Res.* **2003**, *36*, 701. (j) Ma, S. *Eur. J. Org. Chem.* **2004**, 1175. (k) Brandsma, L.; Nedolya, N. A. *Synthesis* **2004**, 735.

(3) (a) Krause, N., Ed. *Science of Synthesis: Houben-Weyl Methods of Molecular Transformations*; Georg Thieme Verlag: Stuttgart, 2008; Volume 44 (Cumulenes and Allenes). (b) Brummond, K. M.; DeForrest, J. E. *Synthesis* **2007**, 795.

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fully used so far for controlling the selectivity issues are: (1) incorporation of an allenic moiety and a reactant into a single molecule rendering its transformation intramolecular, (2) steric discrimination of the two cumulated C═C double bonds in terminal allenes, and (3) electronic differentiation of the two C═C bonds by introduction of functional substituents which serve as directing groups.

Among internal allenes, endocyclic allenes[4,5] possess a characteristic topological property: the carbon chains connecting the two allenic termini could effectively shield one side of the allenic skeletons. This might direct allenic reactions with incoming molecules onto the unencumbered faces, and thus the endocyclic allenes have potential for being unique synthons in stereoselective transformations (Figure 1). Although various endocyclic allenes have been prepared so far, only a few methods, namely, ring enlargement of cycloalkenes by the Doering−Moore−Skattebøl reaction and dehydrohalogenation of 1-halocycloalkenes, are applicable to systematic preparation of endocyclic allenes of various ring sizes.[4]

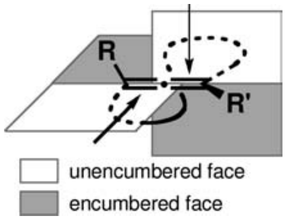
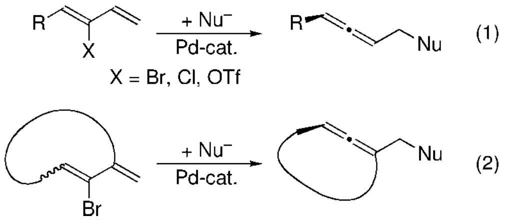


Figure 1. Steric properties of endocyclic allenes.

Recently, we developed a palladium-catalyzed reaction of preparing functionalized allenes starting with either 2-halo-1,3-dienes[6a−d] or 1,3-dien-2-yl triflates[6e] and a stabilized nucleophile (eq 1 in Scheme 1). The reaction was extended into an asymmetric counterpart using a chiral Pd catalyst, and enantiomerically enriched axially chiral allenes were obtained in up to 93% ee.[6d−i] In this report, we would like to describe a method of preparing various endocyclic allenes utilizing the Pd-catalyzed reaction as a key step (eq 2 in Scheme 1). The method enables us to convert readily available cycloalkenones into the corresponding endocyclic allenes in high yields with excellent selectivity. This is a rare method which is applicable to the preparation of endocyclic allenes of a wide range of ring sizes.

Scheme 1



The key compounds in our endocyclic allene synthesis are yet unknown 2-bromo-3-*exo*-methylenecycloalkenes (**3a**−**f**), and their preparation is depicted in Scheme 2. Readily available 2-cycloalken-1-ones **1**[7] were converted into the corresponding 2-bromo-2-cycloalken-1-ones **2** in good yields by a successive Br_2 and NEt_3 treatment. Conversion of **2** into the bromodiene **3** was achieved by Peterson's protocol; i.e., a reaction of **2** with Me_3SiCH_2MgCl followed by an acidic treatment of the generated alcohols at 60 °C afforded the bromodienes **3a**−**f** in pure forms after vacuum distillation. The seven- to nine-membered carbocycles **3d**−**f** were formed as (*E*)-isomers exclusively for geometric reasons. The ten-membered cyclic compound **3c** was isolated as a mixture of two isomers with the (*E*)-isomer being predominant (*E*/*Z* = 96/4).[8] In contrast, the larger-ring homologues **3a**,**b** were preferentially obtained in their thermodynamically favored (*Z*)-isomers (>99%).

Scheme 2

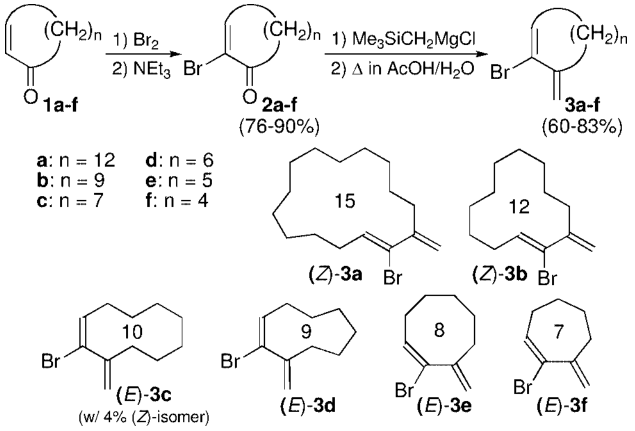


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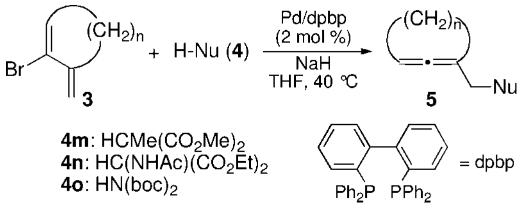
Table 1. Palladium-Catalyzed Preparation of Endocyclic Allenes[a]



entry	substrate 3	H-Nu 4	time (h)	product	yield (%)[b]
1	**3a** ($n = 12$)	**4m**	12	**5am**	92
2	**3a** ($n = 12$)	**4n**	48	**5an**	93
3	**3b** ($n = 9$)	**4m**	12	**5bm**	95
4	**3b** ($n = 9$)	**4n**	24	**5bn**	98
5	**3b** ($n = 9$)	**4o**	48	**5bo**	97
6	**3c** ($n = 7$)	**4m**	12	**5cm**	94
7	**3d** ($n = 6$)	**4m**	14	**5dm**	98
8	**3d** ($n = 6$)	**4n**	48	**5dn**	88
9	**3d** ($n = 6$)	**4o**	72	**5do**	89

[a] The reaction was carried out at 40 °C in THF in the presence of the palladium catalyst (2 mol %) generated from [PdCl(η^3-C_3H_5)]$_2$ and dpbp. [b] Isolated yields.

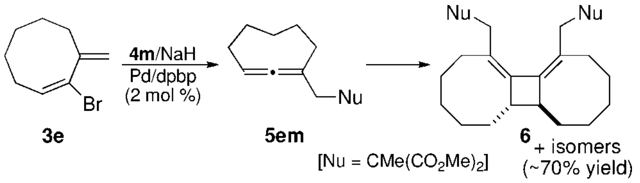
The 2-bromo-3-*exo*-methylenecycloalkenes **3a**−**f** obtained here were applied in the Pd-catalyzed reaction with a soft nucleophile. It was found that a series of endocyclic allenes **5** could be prepared and isolated in excellent yields (88−98%) as persistent species when the size of the carbocycles was nine or larger. The results of the Pd-catalyzed reaction for **3a**−**d** are summarized in Table 1. The cyclic bromide **3a** was reacted with CHMe(CO$_2$Me)$_2$ (**4m**) and NaH in THF in the presence of a Pd catalyst (2 mol %) generated in situ from [PdCl(η^3-C_3H_5)]$_2$ and dpbp[9] to give the corresponding endocyclic allene **5am** in 92% yield (Table 1, entry 1). A variety of nucleophiles, such as stabilized carbanions (**4m** and **4n**) and an N-nucleophile (**4o**), could be used for the present reactions.

The (*E*)/(*Z*)-geometry in **3** is not critical for the Pd-catalyzed reaction.[10] A Pd-catalyzed reaction between **3c** ($E/Z = 96/4$) and **4m** was terminated prior to its completion (ca. 80% conversion), and unreacted **3c** was recovered from the reaction mixture. An ^{1}H NMR analysis revealed that the recovered **3c** was also a mixture of the two isomers with $E/Z = 93/7$. Indeed, both the substrates with (*Z*)-configuration (**3a** and **3b**; entries 1−5) and those with (*E*)-configuration (**3c** and **3d**; entries 6−9) reacted with **4** smoothly under palladium catalysis to give **5** in equally good yields. In all cases, the reactions proceeded cleanly, and no appreciable byproducts were detected in the reaction mixtures.

While the compounds **3a**−**d** are excellent precursors to the endocyclic allenes in the Pd-catalyzed reaction, the smaller carbocycles **3e** and **3f** show different reactivity.

A reaction of **3e** with **4m** under the same conditions as in Table 1 was somewhat slower and needed a longer reaction time (36 h) until total consumption of **3e**. Although initial formation of the eight-membered cyclic allene **5em** could be confirmed by various NMR measurements (a characteristic long-range coupling between the vinyl *H* and -C*H*$_2$Nu with $^5J_{HH}$ = 1.7 Hz in the ^{1}H NMR spectrum; a ^{13}C NMR resonance of the allenic central sp-C in the low field at δ 204.2), it was not stable and was slowly converted to an isomeric mixture of homodimers in a few hours (ca. 70% yield, Scheme 3).[11,12] The structure of the major isomer **6** was unambiguously determined as shown in Scheme 3 by an X-ray analysis (see Supporting Information).

Scheme 3



On the other hand, the seven-membered cyclic substrate **3f** was inert to the Pd-catalyzed reaction with **4m** under the identical conditions and remained unchanged.

As shown in Figure 1, unique stereoselectivity was expected in reactions of the endocyclic allenes **5** by the shielding effect of the polymethylene chains connecting the two allenic termini. To examine this possibility, the 12-, 10-, and 9-membered endocyclic allenes (**5bm**, **5 cm**, and **5dm**) were applied to [2 + 2]cycloaddition reactions with ketenes.[13,14] Reactions of an acyclic allene **7** were also examined for comparison. The results are summarized in Table 2.

A reaction of the acyclic allene **7** with dichloroketene (**8x**) proceeded at 23 °C to give **9x** in 57% yield as a mixture of four isomers in a 61:12:24:3 ratio (Table 2, entry 1). Similarly, a reaction between **5bm** and **8x** afforded a mixture of four isomeric products (entry 2). Apparently, the 12-membered carbocycle in **5bm** is too large to display the expected stereochemical control. The smaller-membered cyclic allenes, however, exhibited the stereoselectivity in the [2 + 2]cycloaddition. A product from **5cm** and **8x** consisted

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[9] dpbp = 2,2′-bis(diphenylphosphino)-1,1′-biphenyl. See: Ogasawara, M.; Yoshida, K.; Hayashi, T. *Organometallics* **2000**, *19*, 1567.

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[11] Jacobs, T. L.; McClenon, J. R.; Muscio, O. J., Jr. *J. Am. Chem. Soc.* **1969**, *91*, 6038.

[12] A kinetically stabilized eight-membered endocyclic allene was reported, see: Price, J. D.; Johnson, R. P. *Tetrahedron Lett.* **1986**, *27*, 4679.

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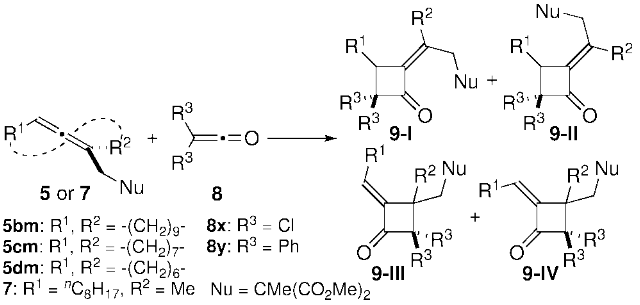
Table 2. [2 + 2]Cycloaddition Reactions of Allenes with Ketenes



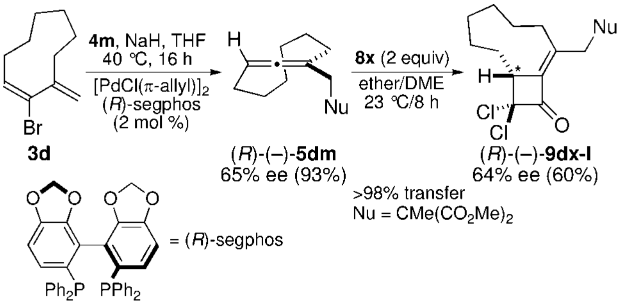
entry	allene	ketene	conditions	yield (%)^a	ratio^b I:II:III:IV
1	**7**	**8x**^{c}	23 °C, 36 h	57 (**9x**)	61:12:24:3
2	**5bm**	**8x**^{c}	23 °C, 80 h	61 (**9bx**)	43:9:40:8
3	**5cm**	**8x**^{c}	23 °C, 24 h	80 (**9cx**)	70:--:30:--
4	**5dm**	**8x**^{c}	23 °C, 8 h	73 (**9dx**)	>99:--:--:--
5	**7**	**8y**^{d}	80 °C, 8 h	63 (**9y**)	62:14:20:4
6	**5dm**	**8y**^{d}	80 °C, 40 h	65 (**9dy**)	>99:--:--:--

^{a} Isolated yields. ^{b} Determined by ^{1}H of the crude products. ^{c} Dichloroketene (2 equiv to **5**/**7**) was generated in situ by dropwise addition of trichloroacetyl chloride to Zn−Cu couple in ether/DME. ^{d} With isolated diphenylketene (2 equiv to **5**/**7**) in benzene.

of only two isomers (**9cx-I** and **9cx-III**), both of which were produced by the addition of **8x** at the unencumbered faces in **5cm** (entry 3). More remarkably, a reaction between nine-membered **5dm** and **8x** gave a product **9dx-I** as a single isomer in 73% yield (entry 4). Reactions with less reactive diphenylketene **8y** needed higher temperature but showed analogous stereoselectivity (entries 5 and 6). These results clearly indicate that the cyclic structures in the smaller endocyclic allenes direct a reacting ketene from the unencumbered faces as expected (see Figure 1).

In the reactions in Table 2, the starting allenes are axially chiral and the cycloaddition products possess a newly generated stereogenic center in them. Thus, axial-to-central chirality transfer might be possible.[15] For this purpose, asymmetric synthesis of the scalemic endocyclic allene **5dm** was examined according to our previous studies.[6d−i] Under the optimized conditions shown in Scheme 4, (*R*)-(−)-**5dm**[16] was obtained in moderate enantioselectivity of 65% ee (93% yield) using a chiral bisphosphine ligand (*R*)-segphos.[17] As expected, the [2 + 2]cycloaddition of the enantiomerically enriched (*R*)-**5dm** with **8x** afforded (*R*)-(−)-**9dx-I** of 64% ee in 60% yield. The chirality transfer of the reaction was estimated to be >98% (Scheme 4).

Scheme 4



In conclusion, we have developed a novel protocol for converting readily available cycloalkenones into the corresponding endocyclic allenes. Various endocyclic allenes of nine-membered or larger carbocycles were obtained in excellent yields by a Pd-catalyzed reaction with soft nucleophiles. The reaction of the nine-membered cyclic allene **5dm** with an appropriate ketene gave a single-isomeric product. This stereoselectivity is unique to the smaller endocyclic allenes. Larger cyclic allenes and acyclic allenes of analogous structures afforded the [2 + 2]cycloaddition products as a mixture of stereoisomers.

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Supporting Information Available: Detailed experimental procedures, compound characterization data, and crystallographic data for **6**. This material is available free of charge via the Internet at http://pubs.acs.org.

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