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Chain Walking as a Strategy for Carbon–Carbon Bond Formation at Unreactive Sites in Organic Synthesis: Catalytic Cycloisomerization of Various 1,*n*-Dienes

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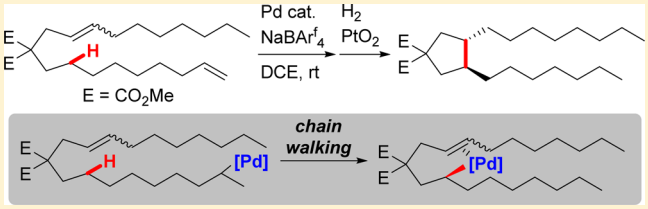
Supporting Information

ABSTRACT: Carbon–carbon bond formation at unreactive sp^3-carbons in small organic molecules via chain walking was achieved for the palladium-catalyzed cycloisomerization of 1,*n*-dienes. Various 1,*n*-dienes (n = 7–14) such as those containing cyclic alkenes, acyclic internal alkenes, and a trisubstituted alkene can be used for the chain-walking cycloisomerization/hydrogenation process, and five-membered ring compounds including simple cyclopentane and pyrrolidine derivatives can easily be prepared. Chain walking over a tertiary carbon was also found to be possible in the cycloisomerization. It is not necessary for the linker portion of the diene to contain a quaternary center, and diene substrates with two alkene moieties linked by a tertiary carbon or a nitrogen atom can also be used as substrates. Column chromatography using silica gel containing silver nitrate was found to be effective for isolating some of the cycloisomerization products without hydrogenation. Deuterium-labeling experiments provided direct evidence to show that the reaction proceeds via a chain-walking mechanism.



1. INTRODUCTION

Carbon–carbon bond formation constitutes the most crucial and fundamental processes in organic synthesis. In general, these bonds are formed utilizing reactive functional groups that have been preinstalled at bond-forming sites of substrates (Figure 1a). In search of more efficient processes, transition-metal-catalyzed direct functionalization of unreactive carbon–hydrogen bonds, which are ubiquitous in organic molecules, has attracted considerable attention and is now used as a powerful tool for carbon–carbon bond formation (Figure 1b). However, there are still limitations in scope, particularly in terms of functionalization of sp^3-hybridized carbon–hydrogen bonds.[1]

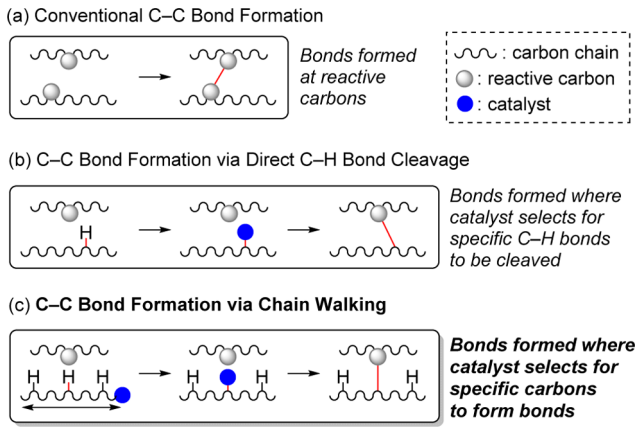
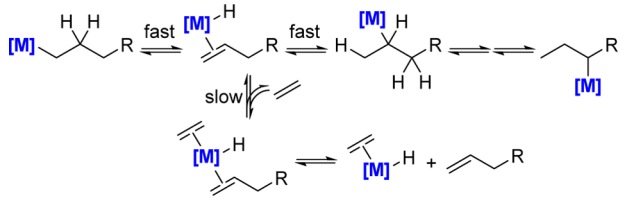


Figure 1. Strategies for carbon–carbon bond formation.

In addition, site selectivity generally relies upon that of carbon–hydrogen bond cleavage controlled by electronics, sterics, and/or directing groups.[2]

We envisioned that the use of chain walking may provide an alternative approach for functionalizing unreactive sp^3-hybridized carbon–hydrogen bonds (Figure 1c). Chain walking, a frequently used term in olefin polymerization, is a mechanism in which an alkylmetal species undergoes a rapid β-hydride elimination and reinsertion to change the position of the metal on the alkyl chain without dissociation of the alkene during the process (Scheme 1). The term, chain walking, has also been used for a mechanism where both β-hydride elimination/reinsertion and alkene exchange rapidly occur, but we only refer to the term as a mechanism in which alkene exchange is much slower than β-hydride elimination/reinsertion, considering the mechanism for chain-walking polymerization and what the term really represents.

Scheme 1. Mechanism of Chain Walking



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Ever since the development of α-diimine palladium catalysts by Brookhart and co-workers, olefin polymerization via chain walking has permitted a wide variety of unique polymers to be produced.[3] In order to obtain these polymers, chain walking must occur rapidly, and at the same time, alkene exchange must be much slower than polymer formation. For the case of α-diimine palladium catalysts, alkene exchange is suppressed to a considerable extent by the presence of large substituents on both sides of the square planar palladium faces. Therefore, we speculated that the use of the chain-walking process for organic synthesis would be possible, if removal of the large substituents would accelerate alkene exchange, thus making it faster than that of polymer formation. In many examples of chain-walking polymerization, bond formation occurs between carbons at the alkene moieties and unactivated terminal sp^3-carbons of the substrates.[3a,d−i] These results essentially indicate that chain walking may be used to functionalize unactivated carbon−hydrogen bonds by allowing catalysts to move around on the carbon chains from distant alkene moieties of substrates.

Although the chain-walking mechanism has been incorporated into many olefin polymerization processes, its use in organic synthesis has remained limited, and investigations of carbon−carbon bond formation in small organic molecules are particularly rare.[4] Long-distance alkene isomerization,[5] which involves rapid alkene dissociation processes, has been reported by several researchers such as Grotjahn[5b] and Mazet.[5d] Alkene isomerization after carbon−carbon bond formation has also been used in some catalytic reactions.[6,7] Ozawa, Kubo, and Hayashi reported an asymmetric Mizoroki−Heck type reaction of 2,3-dihydrofuran, which proceeds via enantioselective carbon−carbon bond formation, followed by selective alkene isomerization.[6] The combination of carbon−carbon bond formation/alkene isomerization has recently become a powerful tool in asymmetric synthesis, largely based on the efforts of Sigman and co-workers, and the isomerization processes are considered to proceed via chain-walking mechanisms, in which only slow alkene exchange occurs.[7]

The use of the long-distance alkene isomerization to form carbon−carbon bonds at unreactive sites has been studied as well, but these reactions are often not regioselective or only form new bonds on carbons where carbon−carbon double bonds or metal−carbon bonds are relatively stabilized (i.e., those bonds that are stabilized by functional groups or the least hindered carbon−metal bonds).[8] For example, alkylzirconocenes are known to isomerize and eventually form zirconocenes bearing primary alkyl groups, which can be used for further bond formation, and mechanistic studies by Labinger, Bercaw, and co-workers suggested that alkene exchange reaction occurs rapidly during the isomerization process.[8a] Excellent regioselectivity to functionalize terminal sp^3-carbons has also been achieved for catalytic carbonylations such as hydroformylation[8c] and hydroesterification[8d] via alkene isomerization. Ryu and co-workers developed enone isomerization/addition reactions, in which carbon−carbon bond formation occurred selectively at the α-position of the carbonyl groups.[8b] Baudoin and co-workers recently reported on the arylation of methyl groups at the γ- and δ-positions of α-amino esters.[4d] Although the product yields were moderate, the palladium center had effectively migrated from the α-position to the γ- or δ-position.

Under the conditions where efficient chain walking occurs, bond-forming sites can be controlled by catalysts, which are selective for preferable sites to form bonds by moving around on substrates (Figure 1c), and this type of reaction may be difficult in the absence of the chain-walking mechanism. Therefore, we examined catalytic carbon−carbon bond formation taking advantages of this feature of the chain-walking mechanism.

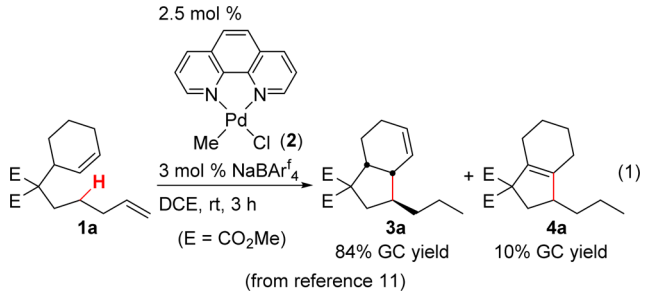
In order to examine the use of chain walking in organic synthesis, the cycloisomerization of 1,*n*-dienes was chosen as our target reaction,[9] because dienes contain two alkene moieties and selective bond formation would be very difficult if rapid alkene exchange were to isomerize both alkene moieties. The cycloisomerization of 1,5- or 1,6-dienes has been extensively studied using various transition-metal catalysts to form five-membered rings.[9a−e,g] If it were possible to incorporate the chain-walking mechanism into the reaction, dienes other than 1,5- or 1,6-dienes might also be transformed into five-membered ring products. There have been only a few reports on the cycloisomerization of 1,*n*-dienes to form five-membered rings where *n* is larger than 6, such as 1,7- and 1,8-dienes,[10] but carbon−carbon bonds were formed via stepwise alkene isomerization pathways where both alkene isomerization and exchange occur rapidly in these examples.

We reported on the palladium-catalyzed chain-walking cycloisomerization of 1,*n*-dienes in a communication as a demonstration of the use of the chain-walking process for the synthesis of small organic molecules.[11] In this communication, substrates were limited to those bearing cyclohexene moieties, and isolating the cycloisomerization products was difficult at this point. In addition, no direct evidence to support the chain-walking mechanism was provided.

Here we provide a the full account of the chain-walking cycloisomerization of 1,*n*-dienes including (i) a vastly expanded substrate scope, (ii) an efficient isolation technique for the cycloisomerization products without the need for hydrogenation, and (iii) the results of deuterium-labeling experiments which strongly suggest the presence of the chain-walking process for this reaction.

2. RESULTS AND DISCUSSION

2.1. Chain-Walking Cycloisomerization/Hydrogenation of Various 1,*n*-Dienes. We previously reported on the chain-walking cycloisomerization of 1,*n*-dienes using a 1,10-phenanthroline palladium catalyst **2**[12] as a communication in 2012.[11] The reaction of 1,8-diene **1a** gave **3a** as the major product in high yield along with **4a** and small amounts of other byproducts (eq 1). The substrate scope was then examined



using a hydrogenation/cyclization protocol in order to estimate the efficiency of the cyclization and to simplify the product analysis (eq 2).

In the previous communication, only a limited class of substrates, namely, 1,*n*-dienes bearing a cyclohexene and a linear terminal alkene moiety was used for the reaction. In this

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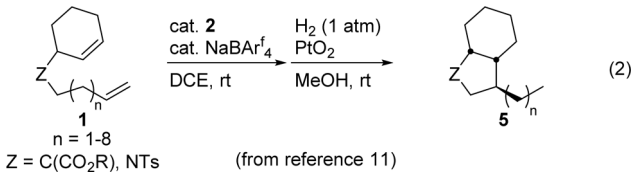
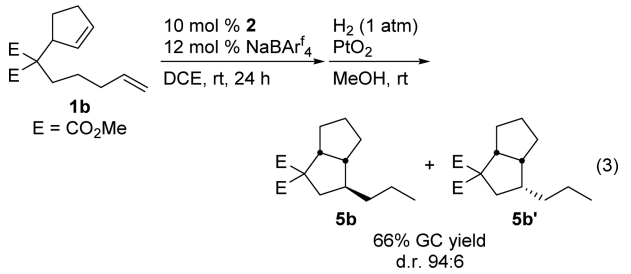


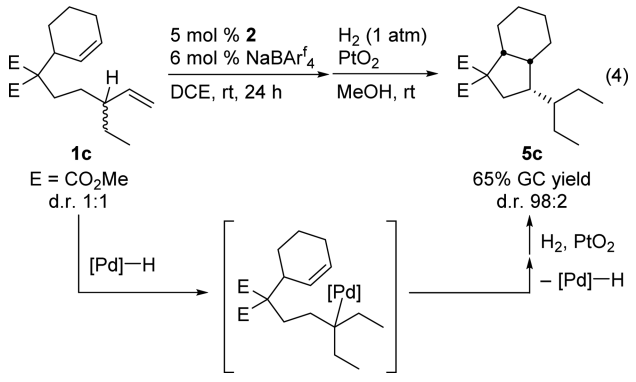
section, we describe a significantly expanded substrate scope including more simple substrates than the previous ones.

2.1.1. Chain-Walking Cycloisomerization/Hydrogenation of 1,n-Dienes Containing a Cyclopentene and a Linear Terminal Alkene Moiety. The reaction of 1,8-diene **1b**, which contains a cyclopentene ring, was first investigated. When the cycloisomerization was performed for 24 h using 10 mol % of **2**, five-membered ring formation via chain walking proceeded to give bicyclo[3.3.0]octane derivatives **5b** and **5b′** in 66% total yield with 96:4 diastereoselectivity (eq 3). The structures of the



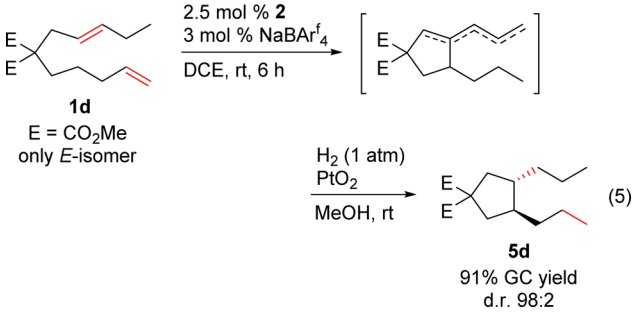
major product **5b** and the minor product **5b′** were similar to those obtained by Curran's radical cyclization of dimethyl (3-cyclopentenyl)iodomalonate with 1-hexene,[13] except that Curran's products contained *n*-butyl groups instead of *n*-propyl groups. A comparison of the ^{1}H NMR data suggested that our major product **5b** and minor product **5b′** have the same stereochemistry as Curran's minor and major products, respectively.

2.1.2. Chain-Walking Cycloisomerization/Hydrogenation of a 1,8-Diene Containing a Cyclic Alkene and a Branched Terminal Alkene Moiety. The reaction was examined with 1,8-diene **1c**, containing a branch close to the terminal alkene moiety. The cycloisomerization of **1c** is not as efficient as that of **1a**, but when the reaction was conducted for 24 h using 5 mol % of **2**, the corresponding five-membered ring product **5c** was obtained in 65% yield with a 98:2 diastereoselectivity (eq 4). The structure and the stereochemistry of product **5c** were



determined by NMR analysis including a NOESY experiment. The results showed that the chain-walking process in this cycloisomerization can proceed over a tertiary carbon.

2.1.3. Chain-Walking Cycloisomerization/Hydrogenation of 1,n-Dienes Containing an Acyclic Internal Alkene Moiety. The cycloisomerization was also investigated with 1,8-diene **1d**, which has an acyclic internal alkene and a terminal alkene moiety. The reaction of **1d** for 6 h gave a complex mixture of compounds in which the yield of none of the products appeared to exceed 50% by GC analysis. It turned out, however, that the hydrogenation of the crude mixture in the presence of a catalytic amount of platinum oxide gave cyclopentane derivative **5d** in 91% GC yield with 98:2 diastereoselectivity (eq 5). This result indicated that the chain-walking cyclo-



isomerization forming a five-membered ring proceeds efficiently in the case of a diene substrate bearing an acyclic internal alkene moiety, but without a cycloalkene moiety in the substrate, significant alkene isomerization occurs after cyclization resulting in the formation of an alkene moiety with cis and trans geometries in many positions of the product. The ^{13}C NMR spectrum of **5d** showed that there is only one signal corresponding to a carbonyl carbon, which strongly suggests that **5d** has a C_2-symmetric structure. A comparison of the ^{1}H NMR data of **5d** with those of similar cyclopentane derivatives which contain two methyl groups instead of *n*-propyl groups[14] also showed that the signals on the cyclopentane ring of product **5d** appeared much closer to those of the C_2-symmetric analog[14a] than those of the C_s-symmetric compound.[14b]

The cycloisomerization/hydrogenation was found to be applicable to various 1,*n*-dienes containing a crotyl group, and the corresponding cyclopentane derivative was obtained with a degree of high diastereoselectivity (Table 1). The cycloisomerization was slower, and the reaction time was extended to 24 h for this class of substrates, probably because some of the cyclization products contain a terminal alkene moiety, which may competitively coordinate to the metal center. The reaction of 1,7-diene **1e** gave product **5e** in 77% yield (entry 1), and a higher yield of 91% was obtained for the reaction of 1,8-diene **1f** (entry 2). On the other hand, a slight elongation of the linker between the alkene moieties had no effect on the product yield, and the reactions of 1,9-diene **1g** and 1,10-diene **1h** gave cyclopentane derivatives **5g** and **5h**, respectively, in 89% yield (entries 3 and 4). Further extension of the linker to 1,14-diene **1i**, which requires chain walking over eight carbons, still did not reduce the yield significantly, and product **5i** was obtained in 80% yield (entry 5). Diethyl malonate derivative **1j** provided product **5s** in 83% yield (entry 6), and di-*tert*-butyl malonate derivative **1k** was converted to cyclopentane derivative **5k** in 68% yield when 5 mol % of the palladium catalyst was used (entry 7). The reaction of nitrogen-tethered substrate **1l** under the standard reaction conditions only gave a 6% yield of pyrrolidine derivative **5l** (entry 8). The use of cyclohexene as an additive[11] was found to be effective for acyclic substrate **1l**. The reaction in the presence of 20 equiv of

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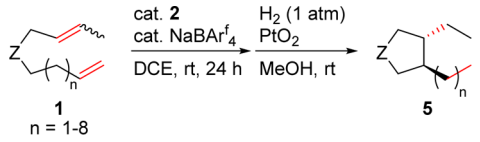
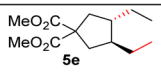
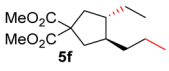
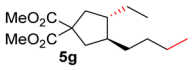
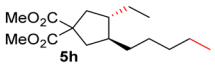
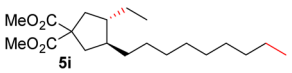
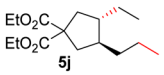
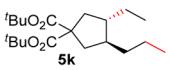
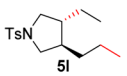
Table 1. Chain-Walking Cycloisomerization/Hydrogenation of Various 1,*n*-Dienes Containing an Acyclic Internal Alkene Moiety[a]

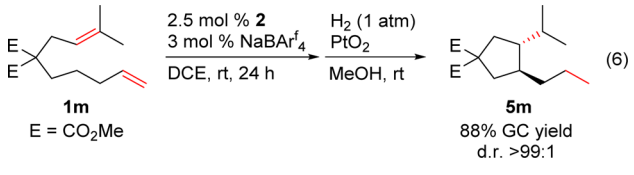


entry	1 (*E*:*Z*)	Product 5	yield (%)[b]	d.r.
1	**1e** (82:18)	 **5e**	77	92:8
2	**1f** (82:18)	 **5f**	91	97:3
3	**1g** (84:16)	 **5g**	89	96:4
4	**1h** (80:20)	 **5h**	89	96:4
5	**1i** (82:18)	 **5i**	80	93:7
6	**1j** (80:20)	 **5j**	83	95:5
7[c]	**1k** (81:19)	 **5k**	68	96:4
8	**1l** (84:16)		6	97:3
9[d]	**1l** (84:16)	 **5l**	26	97:3
10[d,e]	**1l** (84:16)		62	97:3

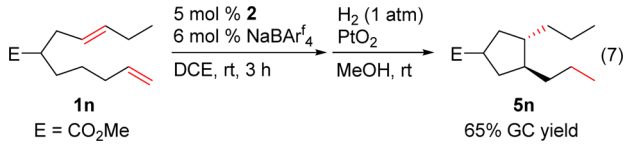
[a]Reaction conditions: **1** (0.5 mmol), **2** (0.0125 mmol, 2.5 mol %), NaBAr$^f_4$ (0.015 mmol, 3 mol %), DCE (25 mL), rt, 24 h. [b]Combined yields of diastereomers, determined by GC analysis. [c]Performed with 0.025 mmol (5 mol %) of **2** and 0.03 mmol (6 mol %) of NaBAr$^f_4$. [d]Performed in the presence of 20 equiv of cyclohexene. [e]Performed with 0.05 mmol (10 mol %) of **2** and 0.06 mmol (12 mol %) of NaBAr$^f_4$.

cyclohexene improved the yield to 26% (entry 9), and when 10 mol % of palladium catalyst **2** was used, pyrrolidine derivative **5l** was obtained in 62% yield (entry 10).

2.1.4. Chain-Walking Cycloisomerization/Hydrogenation of a 1,n-Diene Containing a Trisubstituted Alkene Moiety. The applicability of 1,*n*-dienes containing a 1,2-disubstited alkene moiety prompted us to investigate a substrate involving a trisubstituted alkene moiety. The reaction of 1,8-diene **1m**, which contains a prenyl group, for 24 h under the standard reaction conditions proceeded efficiently and gave five-membered ring product **5m** in 88% yield with excellent diastereoselectivity (eq 6). A notable feature of this reaction is that a facile placement of an isopropyl group on the cyclopentane ring was achieved by the simple use of a prenyl group.

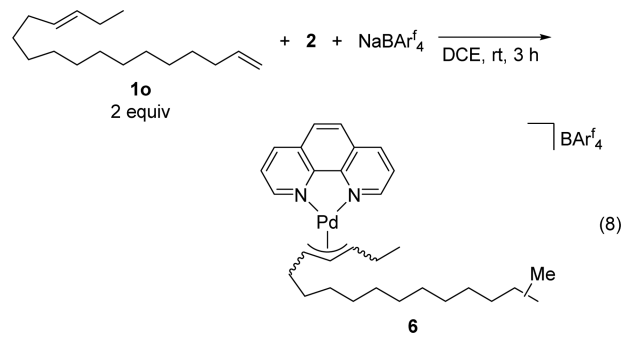


2.1.5. Chain-Walking Cycloisomerization/Hydrogenation of a 1,n-Diene without a Quaternary Carbon. The substrates used so far contained a quaternary carbon or a trisubstituted nitrogen atom at the linker portion of the two alkene moieties, which inhibits the metal center from walking from one alkene moiety to the other. In order to test the possible applicability of substrates without a quaternary carbon, the reaction of 1,8-diene **1n**, which has only one methoxycarbonyl group on the linker portion, was examined. The cycloisomerization of **1n** was less efficient than **1d**, and 5 mol % of **2** was needed, but after hydrogenation, cyclization product **5n** was obtained in 65% yield (eq 7). It is unclear whether the lower efficiency was



caused by the chain walking of the metal center beyond the tertiary carbon or the lack of a quaternary center which may facilitate the cyclization by the Thorpe−Ingold effect, but these findings at least show that the cycloisomerization does not require the presence of a linker atom with no hydrogen atom.

The reactivity of a substrate with two alkene moieties connected by a methylene chain without any substituent was also examined. The reaction of 1,14-diene **1o** under the standard cycloisomerization conditions did not give any observable amounts of cyclization products, and most of substrate **1o** was recovered. The stoichiometric reaction of **1o** with the palladium catalyst was then investigated. The reaction of palladium complex **2** and NaBAr$^f_4$ with 2 equiv of **1o** for 3 h at rt, followed by washing with hexane, provided π-allylpalladium complex **6**, whose structural assignments were supported by ESI-MS and NMR analyses (eq 8).[15] A similar



reaction of **1o** with **2** and NaBAr$^f_4$ in $CDCl_3$ also showed the signals corresponding to complex **6**. These results indicate that in the absence of any substituents on the linker portion, the palladium center rapidly migrates over to the other alkene moiety and forms a π-allyl complex without closing a five-membered ring.

2.2. Isolation of the Chain-Walking Cycloisomerization Products. As described above, the reaction of **1a** not only provided the major product **3a** in high yield but also produced small amounts of other isomerization products such as **4a**, alkene isomerization products, diastereomers of **3a**, and other cyclization products (eq 9). When we published our initial communication, it was difficult to separate **3a** from the mixture in high yield by simple silica gel column or size exclusion chromatography. In this section, we describe an efficient

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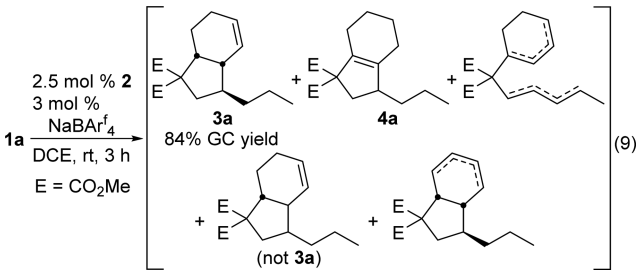
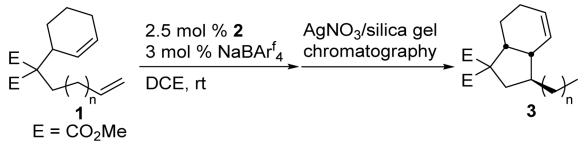
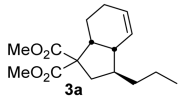
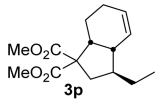
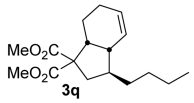
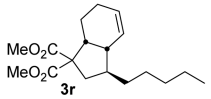
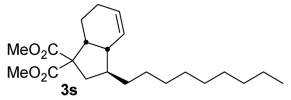


isolation technique for the isolation of the cycloisomerization products.

After an examination of available purification methods, column chromatography using silica gel containing 25% silver nitrate[16] was found to be effective for the isolation of cyclization product **3** (Table 2). When 1,8-diene **1a** was used as a substrate, the corresponding five-membered ring product **3a** was obtained in 78% yield as a 96:4 diastereomeric mixture (entry 1). The reaction of 1,7-diene **1p** also gave the corresponding product **3p**, but the isolated yield was lower than that of **3a** (entry 2). The reactions of 1,9-diene **3q**, 1,10-diene **3r**, and 1,14-diene **3s** also provided cycloisomerization products having the same bicycle[4.3.0]non-2-ene core structure as the major products, but as the length of the linker between the two alkene moieties became longer, the isolated yield gradually decreased, partly because the separation of **3** from other isomers became more difficult (entries 3−5).

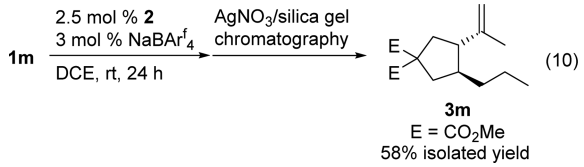
Table 2. Isolation of Chain-Walking Cycloisomerization Products 3[a]



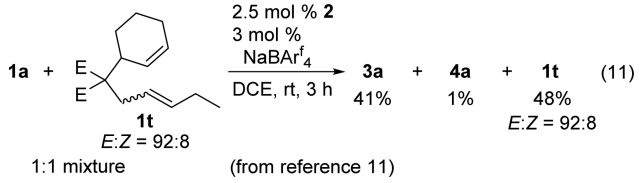
entry	1	Product 3	isolated yield (%)[b]	d.r.
1	**1a** (n = 2)	 **3a**	78	96:4
2	**1p** (n = 1)	 **3p**	56	97:3
3	**1q** (n = 3)	 **3q**	63	97:3
4	**1r** (n = 4)	 **3r**	56	97:3
5	**1s** (n = 8)	 **3s**	50	97:3

[a]Reaction conditions: **1** (0.5 mmol), **2** (0.0125 mmol, 2.5 mol %), NaBAr$^f_4$ (0.015 mmol, 3 mol %), DCE (25 mL), rt. [b]Combined yields of diastereomers.

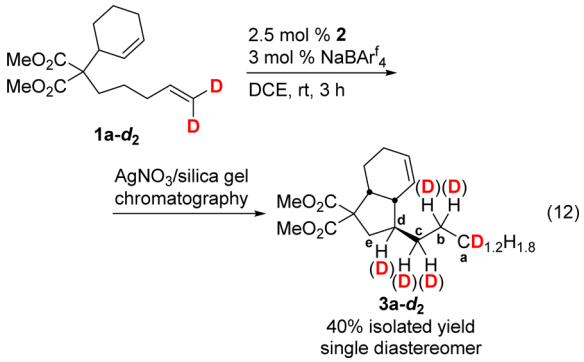
The isolation of cycloisomerization products in high yields was generally difficult in cases of the reactions of substrates without a cycloalkane moiety. However, in the case of the reaction of **1m**, the alkene moiety of the product had a high tendency to be formed at the terminus, and cyclopentane derivative **3m**, which contains an isopropenyl group on the ring, was produced in 58% yield (eq 10).



2.3. Mechanistic Considerations of the Chain-Walking Cycloisomerization. In the previous communication on the cycloisomerization of 1,*n*-dienes, we postulated that the reaction proceeds via chain walking. However, little mechanistic information was obtained at that time. Monitoring of the reaction of **1a** indicated that **3a** was the primary product and **4a** was formed later via the isomerization of **3a** (Table S3, entries 1−6 in the Supporting Information). The effect of the addition of cyclohexene to suppress the formation of **4a** can also be explained by the proposed mechanism (Table S3, entries 7−11). The reaction in the presence of 1,6-diene **1t** also indicated a strong possibility that the reaction proceeded via a chain-walking mechanism (eq 11).[11] However, no direct evidence in favor of chain-walking mechanism in this cycloisomerization was provided. In this section, we describe the results obtained from a deuterium-labeling experiment and mechanistic considerations based on the experimental results.



2.3.1. Experiments Using Deuterium-Containing Substrate ***1a-d$_2$.*** The reaction was examined using 1,8-diene **1a-*d*$_2$**, which contains two deuterium atoms at the terminal carbon of the vinyl group. The cycloisomerization of **1a-*d*$_2$** proceeded similar to that of **1a** under the standard conditions, and after silver nitrate/silica gel column chromatography, the major diastereomer of **3a-*d*$_2$** was isolated in 40% yield in pure form (eq 12).



The areas of the peaks in the ESI-MS spectrum of the isolated product **3a-*d*$_2$** were similar to those of substrate **1a-*d*$_2$**, suggesting that no significant intermolecular H/D exchange had occurred during the reaction, and most of the product molecules retained two deuterium atoms located at the terminal

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vinyl carbon (Figure 2 and Table 3). However, the NMR spectra of **3a-d_2** indicated that some of the deuterium atoms

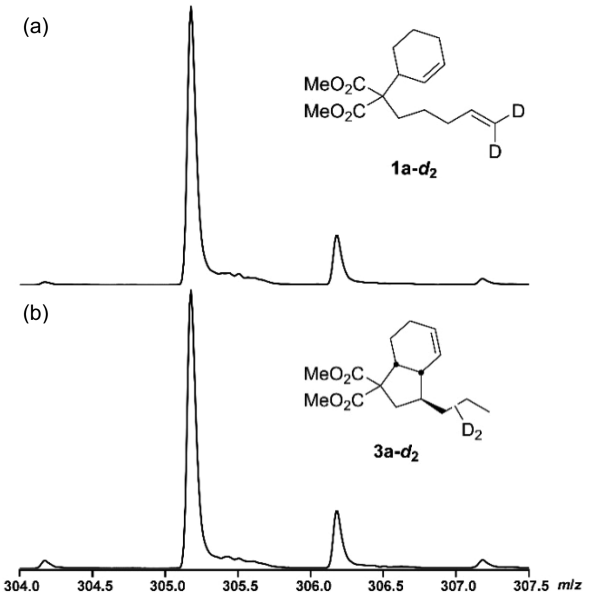


Figure 2. ESI-MS spectra of (a) **1a-d_2** and (b) **3a-d_2**.

Table 3. ESI-MS Area Ratios of 1a-d_2 and 3a-d_2

		ESI-MS area ratios (m/z =)			
entry	compound	304.2	305.2	306.2	307.2
1	**1a-d_2**	1%	82%	15%	2%
2	**3a-d_2**	2%	77%	16%	4%

had migrated to other positions in the product molecule. The ^{1}H NMR spectrum of **3a-d_2** showed that the terminal methyl group contained only 1.8 protons meaning about 40% of the deuterium atoms at the terminal carbon had been exchanged with hydrogens. The ^{2}H NMR spectrum also suggested that there were observable amounts of deuterium atoms on the three carbons (labeled **b**, **c**, and **d** in Figure 3) next to the terminal methyl groups. The presence of deuterium atoms on carbons at **a**−**c** was also confirmed by the ^{13}C NMR spectrum combined with the DEPT90 spectrum, which showed 1:1:1

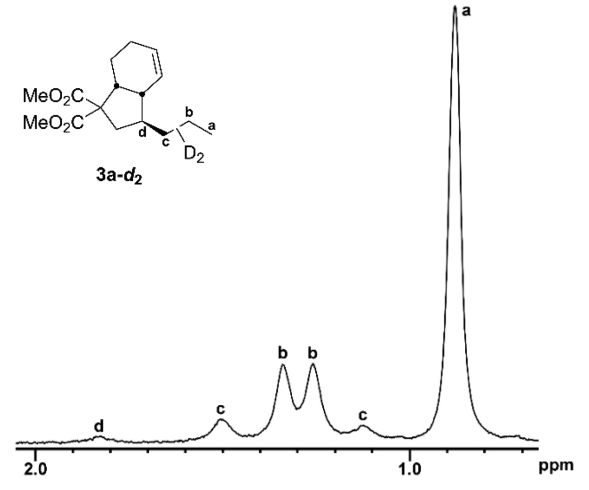


Figure 3. ^{2}H{^{1}H} NMR spectrum of **3a-d_2**.

triplet ($CHDR_2$) signals corresponding to the carbons at positions **b** and **c** (Figure 4).

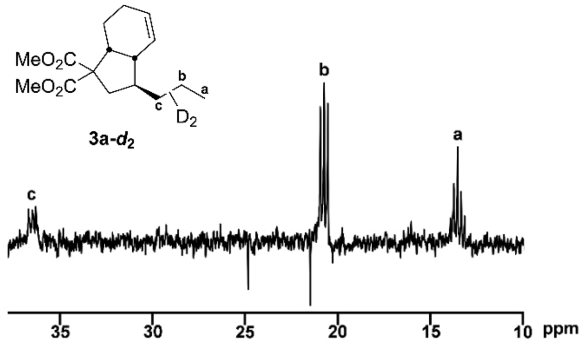
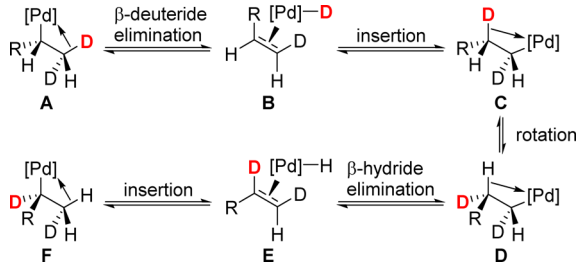


Figure 4. DEPT90 spectrum of **3a-d_2**.

The results of these deuterium-labeling experiments provided important insights into the mechanism of the cycloisomerization. Deuterium atoms at the terminal carbon can migrate to other positions via chain walking, but the mechanism is somewhat complicated depending on the position to which deuterium atoms migrate. Moving the deuterium from position **a** to **b** is relatively facile as depicted in Scheme 2. Agostic

Scheme 2. Possible Mechanisms of H/D Exchange between Positions a and b via Chain Walking



intermediate **A** has a palladium center at position **b**, and *β*-deuteride elimination gives deuterido alkene complex **B**. Insertion of the alkene into the Pd−D bond provides either the original alkyl complex **A** or primary alkyl complex **C**, in which a deuterium atom has migrated from position **a** to **b**. In order to move the palladium back from position **a** to **b** with keeping the deuterium at position **b**, bond rotation to form another agostic intermediate **D** is necessary, and *β*-hydride elimination from **D**, followed by reinsertion, gave secondary alkyl palladium complex **F**, which has the same structure as **A** except that a deuterium atom at position **a** and the hydrogen atom at position **b** are exchanged with each other.

Deuterium incorporation at position **c** can be achieved by a similar process to that shown in Scheme 3, but the situation becomes slightly more complicated. Intermediate **F** is first converted to either ***anti***- or ***syn***-**G** by exchanging the hydrogen interacting with the metal from the one at position **a** to one of the two hydrogens at position **c**. *β*-Hydride elimination from ***anti***-**G** forms intermediate ***trans***-**H** which contains a trans alkene which should be more stable than a cis alkene, and reinsertion of the trans alkene in the opposite direction may provide ***anti***-**I** to place the metal at position **c**. In order to move the deuterium atom from position **b** to position **c**, bond rotation to form agostic intermediate ***syn***-**J** is necessary. Intermediate ***syn***-**J** can be transformed into ***syn***-**L** by *β*-hydride

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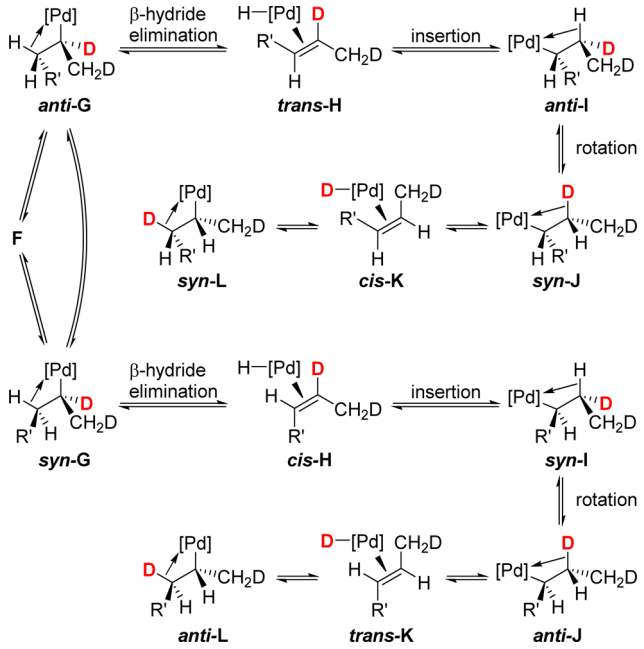
Scheme 3. Possible Mechanisms of H/D Exchange between Positions b and c from Intermediate F via Chain Walking (R = CH_2R')



elimination and reinsertion, but the reaction must proceed through ***cis*-K**, which has a relatively unstable cis alkene structure. Therefore, the H/D exchange process from ***anti*-G** to ***syn*-L** needs to proceed through both trans and cis alkene intermediates. The other agostic intermediate ***syn*-G** can also be converted to ***anti*-L** via a similar process, but this reaction also involves both ***cis*-H** and ***trans*-K**, which means that the formation of both trans and cis alkene intermediates must occur. Therefore, the deuterium incorporation at position **c** essentially shows that the chain-walking process in this reaction proceeds through both trans and cis alkene intermediates.

The results of the deuterium-labeling experiment also revealed that the H/D exchange only occurred at positions **a**–**d**, and the deuterium atoms did not spread out to the cyclohexene ring, which is consistent with the proposition that the reaction proceeds via a chain-walking mechanism and not via a stepwise isomerization process. The fact that the levels of deuterium incorporation diminished with distance from the original position **a** indicates that chain walking does not occur at the level where the H/D exchange reaches an equilibrium, but only to some extent, and the desired alkene insertion can compete with the chain-walking process.

*2.3.2. A Proposed Mechanism for the Chain-Walking Cycloisomerization of **1a**.* The proposed mechanism for the formation of **3a** is shown in Figure 5. The catalyst first reacts with the terminal alkene moiety of diene **1a** because it is smaller than the other alkene moiety, and hydrometalation results in the formation of an alkylpalladium species. Chain walking of the alkylpalladium intermediate along the alkyl chain eventually makes it possible for the other alkene moiety to coordinate to the metal and easily be inserted into the palladium–carbon bond. In this reaction, five-membered ring formation to place the hydrogens around the newly formed carbon–carbon bond in the anti orientation may be sufficiently favorable to permit the reaction to proceed. After the ring formation, *syn*-*β*-hydride elimination occurs to form the primary product **3a**. While there

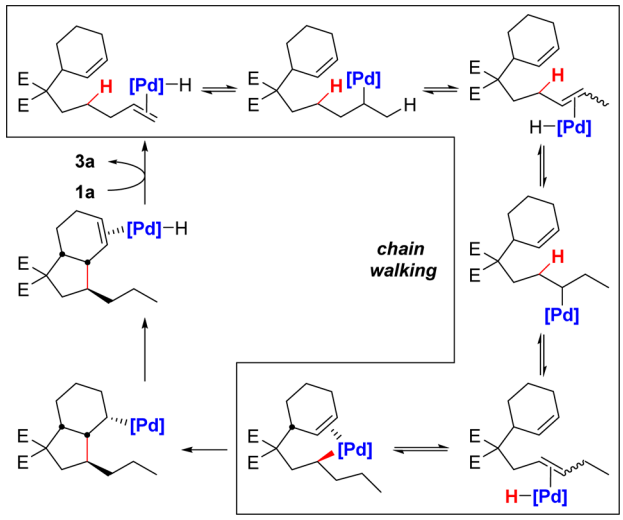


Figure 5. A proposed mechanism for the chain-walking cycloisomerization of 1,8-diene **1a**.

is a sufficient amount of **1a**, the small terminal alkene moiety of **1a** most frequently coordinates to the catalyst to drive **3a** out of the catalyst via an associative exchange mechanism.[12b]

Chain-walking isomerization of alkylpalladium species may not seem to be a facile process, but Brookhart and co-workers conducted detailed experimental mechanistic studies on the chain-walking isomerization of a butylpalladium species bearing an *α*-diimine ligand, and the results showed that <10 kcal/mol is required for the reaction to proceed.[17a] Theoretical studies were also conducted for the isomerization of the alkylpalladium species via *β*-hydride elimination and reinsertion. For example, Morokuma and co-workers theoretically studied the isomerization of an isopropylpalladium complex possessing an unsubstituted diimine ligand to an *n*-propyl complex and reported that the energy barrier for this process was 6.9 kcal/mol.[17b]

2.4. Synthesis of Prostane. One of the advantages of the chain-walking cycloisomerization of 1,*n*-dienes is that two different alkyl groups other than methyl groups can be placed stereoselectively at two adjacent carbons in the cyclopentane ring. In principle, the formation of similar structures by the standard cycloisomerization of 1,6-dienes may be achieved by the use of substrates possessing two internal alkene moieties, but few methods have been reported for the corresponding transformation in which only a limited number of substrates are used.[18]

Therefore, the cycloisomerization/hydrogenation protocol was applied to the first synthesis of prostane, which is the basic framework of prostaglandins (Scheme 4). The cycloisomerization of 1,12-diene **7** proceeded efficiently, and after hydrogenation using platinum oxide, cyclopentane derivative **8** was isolated in 57% yield in 2 steps. Treatment of **8** with sodium hydroxide in ethanol/water hydrolyzed the ester moieties to give dicarboxylic acid **9** in 95% yield. Decarboxylation of **9** to form a monocarboxylic acid, followed by Barton decarboxylation, provided prostane **10** in 61% yield.

3. CONCLUSIONS

We achieved the synthesis of small organic molecules via catalytic carbon–carbon bond formation reactions that involve a chain walking mechanism. Palladium-catalyzed cycloisomerization was found to be applicable to various 1,*n*-dienes from

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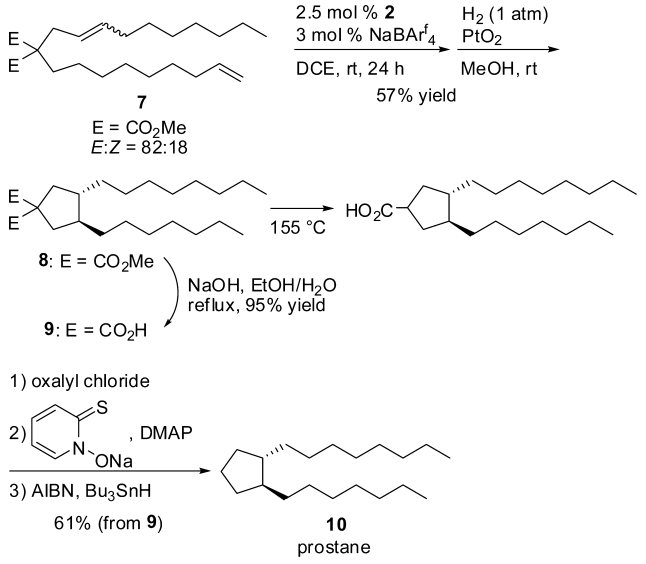
Scheme 4. Synthesis of Prostane



1,7- to 1,14-dienes using the chain-walking mechanism to move the palladium center to the position where the carbopalladation of the other alkene forms a five-membered ring. The applicable substrates were not limited to those having a cyclohexene ring, but a wide variety of 1,*n*-dienes such as those containing (i) a cyclopentene ring, (ii) an acyclic 1,2-disubsituted alkene, and (iii) a trisubstituted alkenes. Chain walking over a tertiary carbon was found to be possible in the cycloisomerization reaction. A diene substrate with two alkene moieties linked by a tertiary carbon can also be used as a substrate. The results of a deuterium-labeling experiment provided direct evidence that the reaction proceeds via a chain-walking mechanism.

We believe the chain-walking strategy provides a new route to the construction of carbon−carbon bonds as described in Figure 1, and further extensions of this strategy including more innovative cycloisomerization and combinations of the chain-walking cyclization with other types of reactions are currently under way.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/jacs.5b10804.

Full experimental details and characterization data (PDF)

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Notes

The authors declare no competing financial interest.

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