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Chain-Walking Strategy for Organic Synthesis: Catalytic Cycloisomerization of 1,*n*-Dienes

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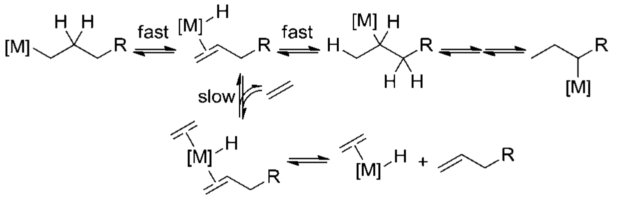
Supporting Information

ABSTRACT: The catalytic construction of carbon−carbon bonds in small organic molecules via chain walking is described. Catalytic cycloisomerization of 1,*n*-dienes via chain walking was achieved using a palladium−1,10-phenanthroline catalyst to form five-membered-ring products. By means of a cycloisomerization/hydrogenation protocol, 1,7- to 1,14-dienes were selectively converted to bicyclo[4.3.0]nonane derivatives. The use of chain walking provides a new method in organic synthesis to functionalize unreactive carbon−hydrogen bonds by letting the catalyst look for preferable bond-forming sites by moving around on the substrate.

Chain walking is a mechanism in which an alkylmetal species undergoes rapid *β*-hydride elimination and reinsertion to change the position of the metal on the alkyl chain without dissociation of the olefin during the process (Scheme 1).[1] Ever since the development of palladium−*α*-diimine catalysts by Brookhart and co-workers, olefin polymerization via chain walking has provided various unique polymers[2] such as highly branched polyethylenes[2a] and their copolymers with polar monomers.[2b] The palladium−*α*-diimine catalysts can also polymerize olefins other than ethylene.[2c−f] For example, polymerization of 1-hexene provides products with much less branching than normal poly(1-hexene).[2a] Osakada and co-workers also reported on chain-walking polymerization of 1,6-dienes possessing only one terminal vinyl group.[2d] In these examples, many bond formations occurred at both terminal carbons of the substrate including unactivated methyl carbons. These results essentially indicate that chain walking may be used to functionalize unactivated carbon−hydrogen bonds by letting the catalyst move around on parts of the substrate carbon chain distant from the olefin moiety.[3]

Scheme 1. Mechanism of Chain Walking



Although the chain-walking mechanism has been incorporated into many olefin polymerization processes, its use for carbon−carbon bond formation in small organic molecules has rarely been investigated.[4] Long-distance olefin isomerization, which involves olefin dissociation processes, has been used for many carbon−carbon bond formations.[5] However, the reactions are often not regioselective or form new bonds only on carbons where carbon−carbon double bonds or metal−carbon bonds are relatively stabilized (i.e., bonds stabilized by functional groups or the least hindered carbon−metal bonds). Under the situation where chain walking occurs, bond-forming sites can be controlled by the catalyst, which looks for preferable sites to form bonds by walking around on the substrate. In addition, if two or more isomerizable carbon−carbon double bonds are present, olefin isomerization may occur at each olefin part, and selective bond formation is even more difficult to achieve.

To examine the use of chain walking for organic synthesis, cycloisomerization of 1,*n*-dienes was chosen as our target reaction.[6] Cycloisomerization of 1,5- or 1,6-dienes has been extensively studied by many researchers using a variety of transition-metal catalysts to form five-membered-ring products. If we could incorporate the chain-walking mechanism into the cycloisomerization reaction, dienes other than 1,5- or 1,6-dienes would also be transformed to five-membered-ring products. There have been only a limited number of reports on cycloisomerization of 1,*n*-dienes to form five-membered rings when *n* is larger than 6 (e.g., 1,7- and 1,8-dienes).[7] For these examples, the reactions are considered to proceed via stepwise olefin isomerization pathways where both olefin isomerization and exchange rapidly occur.

Here we report the use of the chain-walking process for the palladium-catalyzed synthesis of small organic molecules containing carbocycles. Cycloisomerization of several dienes other than 1,6-dienes proceeded in the presence of a palladium−1,10-phenanthroline catalyst to form five-membered-ring products.

For our initial investigation, 1,8-diene **1a** was reacted with catalysts previously used for cycloisomerization of 1,6-dienes. When palladium−1,10-phenanthroline complex **2a**[8] was employed as a catalyst in the presence of $NaBAr^f_4$ [Ar^f = 3,5-$(CF_3)_2C_6H_3$], cycloisomerization proceeded to give five-membered-ring products, including **3a** as the major product along with **4a** (Table 1, entry 1). Reactions of several other palladium and ruthenium catalysts were also conducted for the reaction but resulted in poor yields or no detection of cyclized

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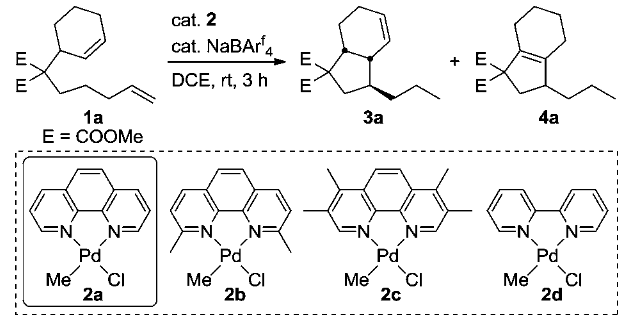
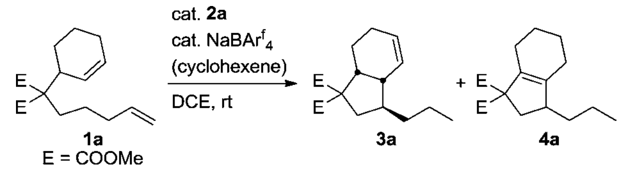
Table 1. Optimization of the Pd-Catalyzed Cycloisomerization of 1,8-Diene 1a via Chain Walking[a]



entry	2	amount of 2 (mol %)	DCE (mL)	conv. (%)[b]	yield (%)[c]	
					3a	4a
1	**2a**	10	2	98	69	18
2	**2b**	10	2	>99	4	nd[d]
3	**2c**	10	2	>99	15	82
4	**2d**	10	2	99	28	58
5	**2a**	2.5	2	99	82	7
6	**2a**	2.5	5	>99	84	10

[a] Reaction conditions: **1a** (0.1 mmol), **2**, NaBAr$^f_4$ (1.2 equiv to **2**), DCE, rt, 3 h. [b] Determined by GC analysis. [c] Determined by GC analysis using **5a** for calibration. [d] Not determined.

Table 2. Time Dependence of Pd-Catalyzed Cycloisomerization of 1a via Chain Walking[a]



entry	cyclohexene (equiv)	time (h)	conv. (%)[b]	yield (%)[c]	
				3a	4a
1	–	2	96	83	6
2[b]	–	3	>99	84	10
3	–	4	>99	76	13
4	–	8	>99	70	22
5	–	24	>99	63	33
6	10	2	99	76	3
7	10	3	99	78	4
8	10	4	>99	77	5
9	10	8	>99	76	5
10	10	24	>99	75	6

[a] Reaction conditions: **1a** (0.1 mmol), **2** (0.0025 mmol), NaBAr$^f_4$ (0.003 mmol), DCE (5 mL), rt. [b] Determined by GC analysis. [c] Determined by GC analysis using **5a** for calibration.

products even at high conversion.[9] Modification of the ligand of the palladium catalyst was then examined. Installation of methyl groups at the 2- and 9-positions of 1,10-phenanthroline to increase the steric bulk seriously lowered the product yield, and considerable olefin isomerization without cyclization was observed (entry 2). On the other hand, when ligands such as 3,4,7,8-tetramethyl-1,10-phenanthroline and 2,2′-bipyridine were used, tetrasubstituted olefin product **4a** became the major product (entries 3 and 4). After optimization of the reaction conditions using 1,10-phenanthroline as a ligand, the reaction with 2.5 mol % **2a** in 5 mL of dichloroethane (DCE) was found to give the highest yield of **3a** (entry 6).

Next, the cycloisomerization reaction was monitored by GC analysis (Table 2, entries 1−5). The reaction was fast in the beginning, and the amount of the product gradually increased until the reaction time reached 3 h. After this point, however, the yield of **3a** was suddenly reduced. In contrast, the amount of **4a** kept increasing for up to 24 h. These results indicate that some amount of **3a** was converted to **4a** during the reaction.

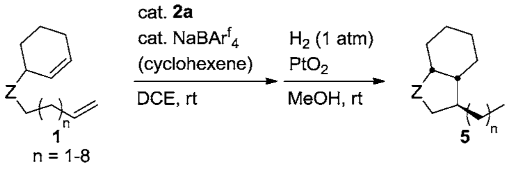
The time dependence of the yield of **3a** led us to investigate additives that would suppress the isomerization of **3a** to **4a**. For this purpose, we chose cyclohexene as an additive, reasoning that additives such as this, whose coordinating ability is stronger than that of **4a** but weaker than that of **3a**, may be effective for inhibiting the recoordination of **3a** by competitive coordination. Indeed, addition of 10 equiv of cyclohexene suppressed the formation of **4a** (Table 2, entries 6−10). The product yield was slightly lowered, probably because of somewhat accelerated olefin exchange before cyclization. However, the use of an additive would allow us to run the cycloisomerization without closely monitoring the reaction by GC analysis for each substrate.

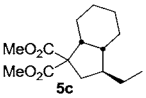
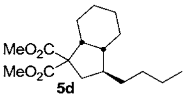
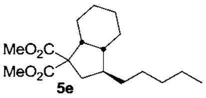
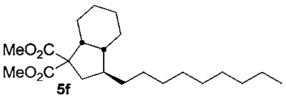
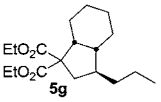
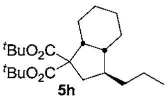
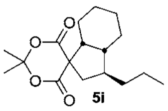
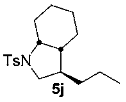
Although **3a** was found to be the major product in the reaction of **1a**, small amounts of several isomers of **3a** were also formed. To determine the efficiency of the cyclization, the products were hydrogenated using platinum oxide as a catalyst (Table 3, entry 1). Although tetrasubstituted olefin **4a** in the product was not reduced, the rest of the products were successfully hydrogenated to give bicyclo[4.3.0]nonane derivative **5a** along with its minor diasteromer in high yields with high diastereoselectivity, whether cyclohexene was used for cycloisomerization or not.

The reactions of several other 1,*n*-dienes were then examined, and the product yields were determined using the cycloisomerization/hydrogenation protocol. 1,7-Diene **1c** was similarly converted to bicyclo[4.3.0]nonane **5c** in high yield with or without using cyclohexene (entry 2). The reaction was also applicable to substrates with two olefin parts connected by longer carbon linkages. While the reaction of 1,9-diene **1d** provided the corresponding five-membered-ring products in good yields with high diastereoselectivity in either case (entry 3), the cyclization product from 1,10-diene **1e** was obtained in as high as 80% yield only when the reaction was performed without cyclohexene (entry 4). The cycloisomerization also proceeded efficiently in the absence of cyclohexene with 1,14-diene **1f**, which gave the product in 75% yield (entry 5). 1,8-Dienes with ethyl (**1g**) and *tert*-butyl (**1h**) malonate moieties were also converted to the corresponding bicyclo[4.3.0]nonane derivatives **5g** and **5h** in good yields (entries 6 and 7). Substrates other than malonate derivatives were also applicable to this reaction. Meldrum's acid derivative **1i** was converted to tricyclic compound **5i** (entry 8). X-ray diffraction analysis of **5i** unambiguously showed the formation of the bicyclo[4.3.0]-nonane backbone, and the stereochemistry of **5i** was also confirmed. The reaction also proceeded with nitrogen-tethered substrate **1j**, and the corresponding pyrrolidine derivative **5j** was obtained in 57% yield when cyclohexene was used as an additive (entry 9).

The proposed mechanism is shown in Figure 1a. First, the terminal olefin reacts with the catalyst because of its small size relative to the disubstituted olefin, and an alkylpalladium species is formed. Then chain walking starts to get to a position where the other olefin coordinates to the metal and inserts into the palladium−carbon bond the most easily. Syn *β*-hydride

Table 3. Chain-Walking Cycloisomerization/Hydrogenation of Various 1,*n*-Dienes[a]



entry	1	product	yield (%)[b,c]	d.r.[c]
1	**1a**	**5a**	88 (86)	95:5 (94:6)
2	**1c**	 **5c**	87 (84)	95:5 (94:6)
3	**1d**	 **5d**	76 (77)	95:5 (94:6)
4	**1e**	 **5e**	80 (60)	92:8 (95:5)
5	**1f**	 **5f**	75 (44)	94:6 (95:5)
6	**1g**	 **5g**	87 (83)	95:5 (95:5)
7[d]	**1h**	 **5h**	72[e] (80[e])	nd[f] (nd[f])
8	**1i**	 **5i**	65 (59)	90:10 (92:8)
9[d,g]	**1j**	 **5j**	44 (57)	>99:1 (>99:1)

[a] Reaction conditions: **1a** (0.5 mmol), **2** (0.0125 mmol), NaBAr$^f_4$ (0.015 mmol), DCE (25 mL), rt. [b] Combined yields of diastereomers, as determined by GC analysis. [c] Numbers in parentheses are those obtained for the reaction in the presence of 10 equiv of cyclohexene. [d] Performed with 0.025 mmol of **2** and 0.03 mmol of NaBAr$^f_4$. [e] The yield of the major diastereomer is given because the peak of the minor diastereomer overlapped with that of a trace amount of a non-hydrogenated product. [f] Not determined. [g] Performed for 24 h.

elimination occurs, forming the initial product **3a**. While there is enough substrate that can react with the palladium, recoordination of **3a** is suppressed because the terminal olefin reacts much more readily than **3a**, which contains only a disubstituted olefin surrounded by a bulky group. However, after the reaction system runs out of the substrate, recoordination of **3a** occurs from the face opposite to the one originally bound to the palladium before dissociation (Figure 1b). Olefin insertion into the palladium–hydrogen bond followed by chain walking gives the more stable tetrasubstituted olefin product, **4a**.

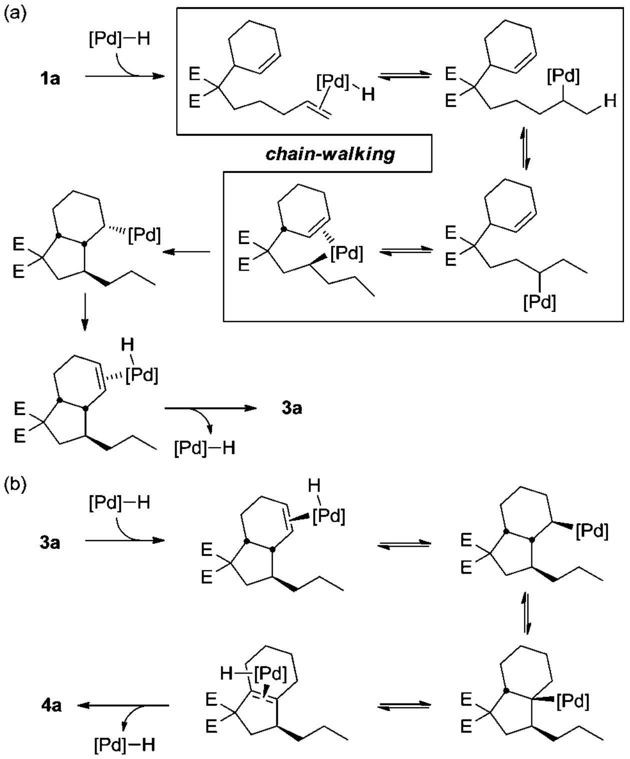
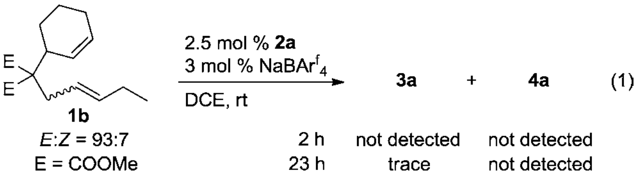


Figure 1. Mechanism of (a) catalytic cycloisomerization of 1,8-diene **1a** to **3a** via chain walking and (b) further isomerization of **3a** to **4a**.

To obtain highly branched polymers by olefin polymerization via chain walking, the relative order of the rates should be chain walking > intermolecular carbon–carbon bond formation > olefin exchange. For the palladium–α-diimine catalysts, olefin exchange is suppressed considerably by the large substituents on both sides of the square-planar palladium faces. In contrast, the use of the chain-walking process for organic synthesis may be achieved when intermolecular carbon–carbon bond formation is slower and chain walking is still faster than olefin exchange. Widenhoefer and co-workers reported that complex **2a** isomerized a 1,6-diene into a five-membered-ring product containing a trisubstituted olefin, indicating that the chain-walking process and other intramolecular processes with catalyst **2a** are much faster than olefin exchange.[8]

To gain further understanding of the mechanism, we performed the reaction with 1,6-diene **1b** (trans:cis = 93:7), an isomer of **1a**, but only a trace amounts (or less) of products **3a** and **4a** were observed (eq 1). When a 1:1 mixture of **1a** and **1b** was used for the reaction, **1b** was mostly recovered after 3 h, while most of **1a** was converted to **3a** or **4a** (eq 2). If the reaction of **1b** occurred via a stepwise olefin isomerization pathway, internal olefins such as **1b** should have a reactivity



E:*Z* = 93:7
E = COOMe

	3a	4a
2 h	not detected	not detected
23 h	trace	not detected

$$\mathbf{1a} + \mathbf{1b} \xrightarrow[\text{DCE, rt, 3 h}]{\text{2.5 mol \% }\mathbf{2a}\text{, 3 mol \% NaBAr}^f_4} \mathbf{3a} + \mathbf{4a} + \mathbf{1b} \qquad (2)$$

1b: *E*:*Z* = 92:8; 1:1 mixture

3a 41%; **4a** 1%; **1b** 48%, *E*:*Z* = 92:8

high enough to be at least comparable to that of **1a**. In fact, in a previously reported example of cycloisomerization of a 1,7-diene to form a five-membered ring, isomerized 1,6-diene intermediates were shown to have higher reactivities than the original 1,7-diene.[7c,e] This strongly suggests that the reaction proceeds via a chain-walking mechanism.

In summary, we have demonstrated the remarkable potential of the chain-walking strategy in organic synthesis by enabling the selective formation of five-membered-ring products from various 1,*n*-dienes. We believe that the use of the chain-walking strategy will offer diverse novel methods in organic synthesis to construct carbon−carbon bonds that are otherwise difficult to form. Transition-metal-catalyzed direct functionalization of unreactive carbon−hydrogen bonds has become a powerful tool for carbon−carbon bond formation,[3] but there are still limitations in scope, particularly in terms of functionalization of sp^3-hybridized carbon−hydrogen bonds. In addition, the site selectivity of the functionalization generally relies upon that of carbon−hydrogen bond cleavage controlled by electronics, sterics, and/or directing groups. Therefore, the use of chain walking should provide an alternative approach for the functionalization of unreactive sp^3-hybridized carbon−hydrogen bonds. Further investigation of the chain-walking strategy to develop new types of carbon−carbon bond-forming reactions is underway.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Full experimental details, characterization data, and crystallographic data (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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Notes

The authors declare no competing financial interest.

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(1) In general, the term "chain walking" may also be used for a mechanism where both *β*-hydride elimination/reinsertion and olefin exchange occur rapidly, but in this paper, we refer to chain walking only as a mechanism in which olefin exchange is much slower than *β*-hydride elimination/reinsertion, considering the mechanism of the chain-walking polymerization and what the term really represents.

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(9) See Table S1 in the Supporting Information for details.