

## Remote Nucleophilic Allylation by Allylrhodium Chain Walking

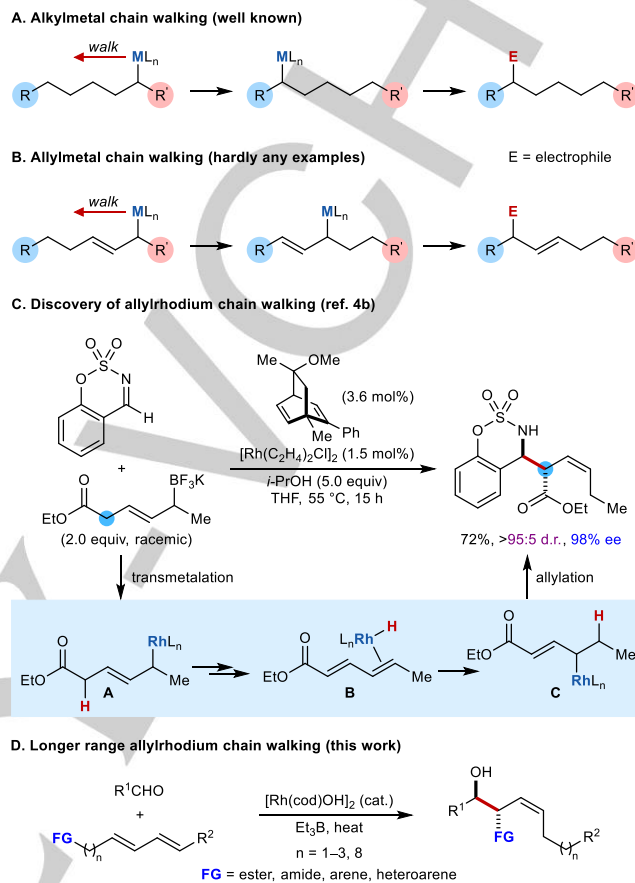
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**Abstract:** Metal migration through a carbon chain is a versatile method for achieving remote functionalization. However, almost all known examples involve the overall net migration of alkylmetal species. Here, we report that allylrhodium species obtained from hydorrhodation of 1,3-dienes undergo chain walking toward esters, amides, or (hetero)arenes over distances of up to eight methylene units. The final, more highly conjugated allylrhodium species undergo nucleophilic allylation with aldehydes and an imine to give Z-homoallylic alcohols and amines, respectively.

**Remote functionalization reactions** are those in which an initial interaction of a functional group with a reagent or catalyst leads to eventual reaction at a distal site.<sup>[1]</sup> Although achieving high efficiency and selectivity in such processes is often challenging, developments in this area can facilitate the activation of otherwise unreactive C–H and C–C bonds, thus providing powerful new tools for synthesis. Of the available methods for remote functionalization, metal migration through a carbon chain, or “chain walking”, is particularly versatile as it dispenses with the need for complex directing groups (Scheme 1A).<sup>[1g–i, 2, 3]</sup> However, most known metal chain walking reactions effectively result in the overall net migration of alkylmetal species (Scheme 1A). Chain walking of organometallics beyond simple alkylmetals, such as allylmetal species (Scheme 1B), could dramatically expand the scope of remote functionalizations, but to our knowledge, there are such few examples.<sup>[4]</sup>

During our studies of enantioselective nucleophilic allylations of imines,<sup>[4b,5]</sup> we discovered the first examples of allylrhodium chain walking (Scheme 1C).<sup>[4b]</sup> These reactions employ  $\delta$ -trifluoroboryl  $\alpha,\beta$ -unsaturated esters as precursors to allylrhodium species **A**. Chain walking of **A** towards the ester is proposed to occur *via* a 1,3-diene-ligated rhodium hydride **B** to give the more highly conjugated, and presumably thermodynamically more stable allylrhodium species **C**, which then reacts with the imine in a highly diastereo- and enantioselective nucleophilic allylation.<sup>[4b]</sup>

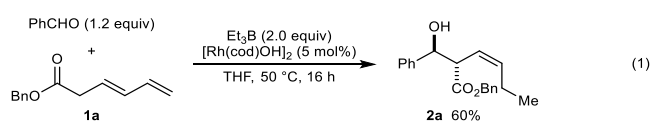
To increase the synthetic utility of allylrhodium chain walking, we wondered whether migration could be accomplished through more than just one methylene carbon. This goal was expected to be challenging because rhodium must participate in a greater number of steps before the final allylrhodium species is formed,



Scheme 1. Metal chain walking.

and in principle, any of the intermediate allylrhodium species can react with the electrophile to give complex mixtures of products. Herein, we describe remote nucleophilic allylations of aldehydes and an imine, in which allylrhodium chain walking occurs through up to eight methylene units (Scheme 1D).

For this study, the use of allylrhodium precursors that are simpler to prepare than allyltrifluoroborates was desirable. We therefore considered generating allylrhodium species by the hydorrhodation of 1,3-dienes, as described by Kimura and co-workers in related reductive nucleophilic allylations.<sup>[6]</sup> Accordingly, substrate **1a** was reacted with benzaldehyde (1.2 equiv) in the presence of  $[\text{Rh}(\text{cod})\text{OH}]_2$  (5 mol%) and  $\text{Et}_3\text{B}$  (2.0 equiv) in THF at 50 °C for 16 h.<sup>[6]</sup> Pleasingly, this reaction gave homoallylic alcohol **2a**, which was isolated as a single diastereomer in 60% yield [Eq. (1) and Table 1, entry 1].<sup>[7]</sup> The use of  $\text{Et}_3\text{SiH}$  in place of  $\text{Et}_3\text{B}$  gave no reaction.



A possible catalytic cycle is shown in Scheme 2. First, the reaction of  $[\text{Rh}(\text{cod})\text{OH}]_2$  with  $\text{Et}_3\text{B}$  generates the ethylrhodium species **3**, which undergoes  $\beta$ -hydride elimination to give

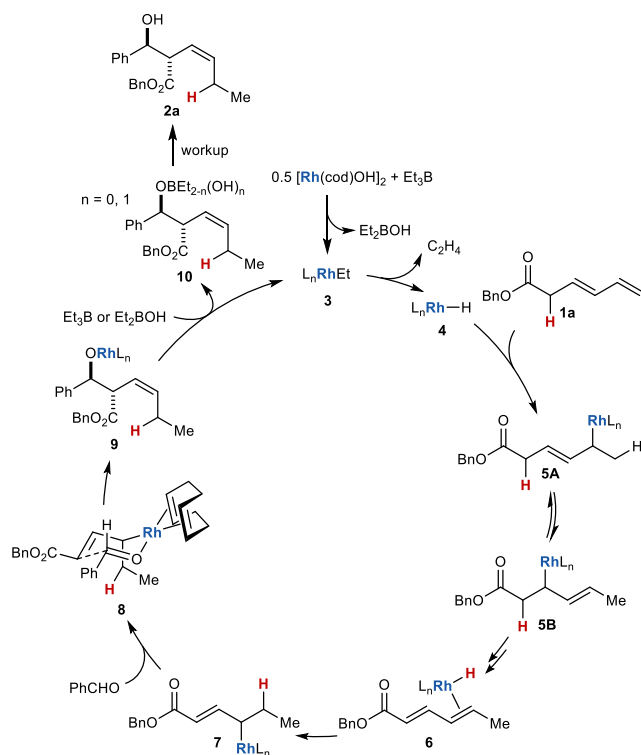
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**Scheme 2.** Proposed catalytic cycle.

rhodium hydride **4**. Hydorrhodation of 1,3-diene **1a** with **4** then provides allylrhodium species **5A**, which undergoes  $\sigma$ - $\pi$ - $\sigma$  isomerization to give **5B**.<sup>[8]</sup>  $\beta$ -Hydride elimination of **5B** gives a rhodium hydride coordinated to benzyl sorbate (as in **6**). Hydorrhodation of the alkene distal to the ester gives allylrhodium species **7**, resulting in an overall 1,4-hydrogen shift from the carbon adjacent to the carbonyl group, to the methylene carbon adjacent to the methyl group. Allylrhodium species **7** then reacts with benzaldehyde in a nucleophilic allylation through conformation **8**, in which the ethyl group occupies a pseudoaxial position to minimize unfavorable non-bonding interactions with the cyclooctadiene ligand. Reaction of the resulting rhodium alkoxide **9** with  $\text{Et}_3\text{B}$  or  $\text{Et}_2\text{BOH}$  gives **10** (which upon workup gives the product **2a**) and regenerates the ethylrhodium species **3**.

Having established proof of principle, the scope with respect to the diene was investigated (Table 1). One of two sets of conditions were employed. Method A used 2.0 equivalents of  $\text{Et}_3\text{B}$  in THF at 50 °C, whereas method B used 3.0 equivalents of  $\text{Et}_3\text{B}$  in dioxane at 80 °C. Method B was used for reactions that did not proceed in high conversion with method A. Pleasingly, a range of dienes reacted successfully with benzaldehyde to give products of chain walking–nucleophilic allylation **2** in up to 65% yield. These reactions also gave complex mixtures of other products in ca. 20% yield, which were tentatively identified as nucleophilic allylation products resulting from various intermediate allylrhodium species.<sup>[9]</sup> The complexity of the reactions prevented determination of the diastereoselectivities by  $^1\text{H}$  NMR analysis, but with a few exceptions (entries 7–9), the products **2** were isolated as single diastereomers. In addition to chain walking through one carbon (entries 1 and 2), walking through two carbons (entries 3–8) and three carbons is possible (entries 10 and 11). As well as terminal dienes ( $\text{R}^2 = \text{H}$ , entries 1, 3, and 10), the process is compatible with internal dienes with various alkyl groups at  $\text{R}^2$  (entries 2, 4, 6–8, and 11). However,

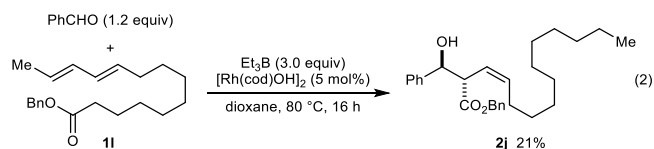
**Table 1.** Scope of the 1,3-diene.<sup>[a]</sup>

entry	diene	method	product	yield (%) <sup>[b]</sup>
<b>walking through one carbon:</b>				
1	<b>1a</b> R = H	A	<b>2a</b>	60
2	<b>1b</b> R = Me	A	<b>2b</b>	65
<b>walking through two carbons:</b>				
3	<b>1c</b> R = H	A	<b>2b</b>	41
4	<b>1d</b> R = Me	B	<b>2c</b>	51
5	<b>1e</b> R = $(\text{CH}_2)_5\text{Cl}$	B	<b>2d</b>	<5
6	<b>1f</b> R = $\text{CH}_2\text{OTBDPS}$	B	<b>2e</b>	35
7	<b>1g</b> R = OMe	B	<b>2f</b>	46 (11:1 d.r.) <sup>[c]</sup>
8	<b>1h</b> R = OPh	B	<b>2g</b>	43 (9:1 d.r.) <sup>[c]</sup>
9	<b>1i</b> R = NMe <sub>2</sub>	B	<b>2h</b>	23 (3:1 d.r.) <sup>[d,e]</sup>
<b>walking through three carbons:</b>				
10	<b>1j</b> R = OMe	B	<b>2c</b>	53
11	<b>1k</b> R = Me	B	<b>2i</b>	56

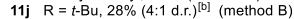
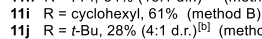
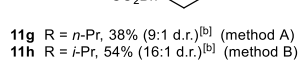
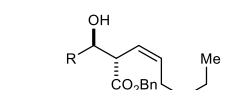
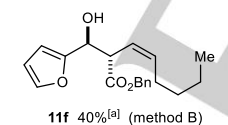
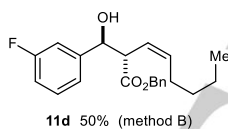
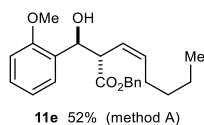
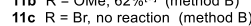
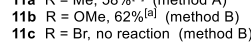
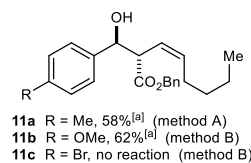
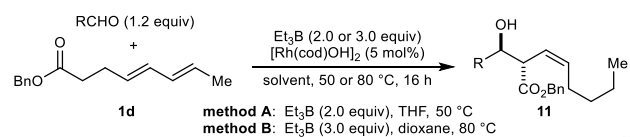
[a] Reactions were conducted with 0.30 mmol of **1**. [b] Yield of isolated product. Unless stated otherwise, the products were isolated as single diastereomers. [c] Conducted with 0.24 mmol of **1i**. [d] Isolated as a mixture of inseparable diastereomers in the ratio indicated in parentheses. [e] The reaction time was 40 h.

diene **1e**, which contains a 1-chlorobutyl group, only returned unchanged starting materials (entry 5).<sup>[10]</sup> Methyl and phenyl esters are also tolerated (entries 7 and 8). An amide also promotes chain walking, but with lower efficiency (entry 9).

Chain walking over greater distances is possible, as shown by the reaction of diene **1l**, which contains eight methylene units between the diene and the ester [Eq. (2)].

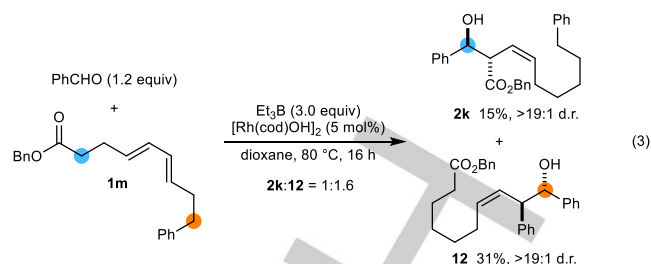


Next, variation of the aldehyde was investigated with diene **1d** (Scheme 3). Aromatic aldehydes containing various *para*-, *meta*-, or *ortho*-substituents are tolerated to give **11a**, **11b**, **11d**, and **11e** in 50–62% yield. 4-Bromobenzaldehyde returned only unchanged starting materials,<sup>[10]</sup> whereas 2-furaldehyde gave **11f** in 40% yield. Linear and branched aliphatic aldehydes are also tolerated (**11f**–**11j**). Tetrahydro-2*H*-pyran-2-ol reacted successfully to give **11k** in 58% yield.

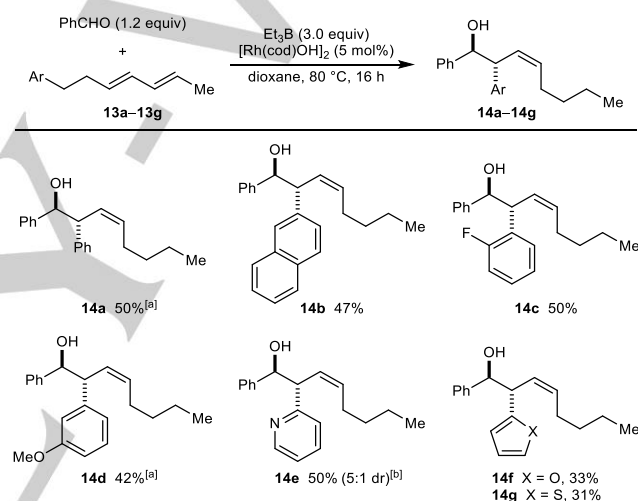


**Scheme 3.** Scope of the aldehyde. Reactions were conducted with 0.30 mmol of **1d**. Unless stated otherwise, yields are of isolated, single diastereomers. [a] The diastereoselectivity was >19:1 d.r. as determined by <sup>1</sup>H NMR analysis of the crude reaction. [b] Isolated as a mixture of inseparable diastereomers in the ratio indicated in parentheses.

Interestingly, diene **1m**, which contains an ester and a phenyl group at the termini, reacted with benzaldehyde to give a mixture of products differing in the direction of chain walking [Eq. (3)]. The product of chain walking towards the ester (**2k**) was isolated in 15% yield, while product **12**, resulting from chain walking towards the phenyl group, was obtained in 31% yield.

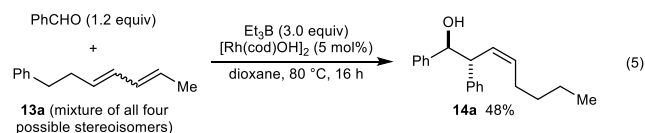
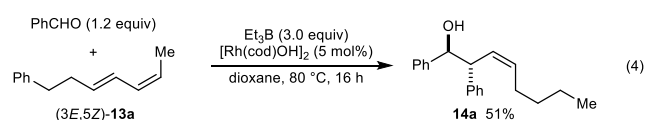


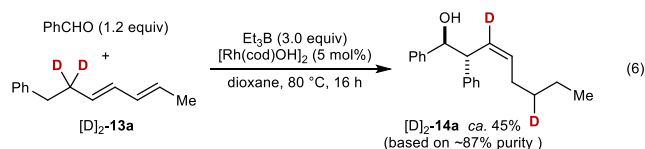
The discovery that arenes also promote allylrhodium chain walking significantly increases the possibilities of this chemistry, and this aspect was explored further in the reaction of dienes **13a**–**13g** with benzaldehyde (Scheme 4). As expected, the phenyl-terminated diene **13a** reacted successfully to give **14a** in 50% yield.<sup>[7]</sup> Other arenes that bring about chain walking include 2-naphthyl (**14b**), 2-fluorophenyl (**14c**), and 3-methoxyphenyl (**14d**). Pleasingly, heteroarenes such as 2-pyridyl (**14e**), 2-furyl (**14f**), and 2-thienyl (**14g**) groups are also effective.



**Scheme 4.** Scope of the 1,3-dienes with a (hetero)arene terminus. Reactions were conducted with 0.30 mmol of **13**. Unless stated otherwise, yields are of isolated, single diastereomers. [a] The diastereoselectivity was >19:1 d.r. as determined by <sup>1</sup>H NMR analysis of the crude reaction mixture. [b] Isolated as a mixture of inseparable diastereomers in the ratio indicated in parentheses.

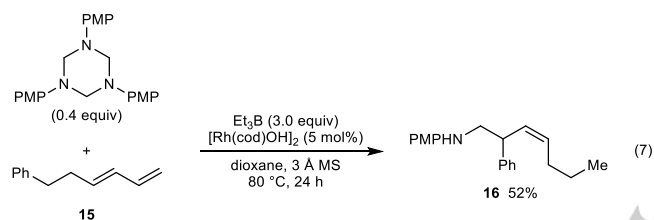
An advantageous feature of these reactions is that the stereochemistry of the starting dienes appears inconsequential, which removes the need to prepare the substrates in high stereoisomeric purity. For example, the reaction of diene (3*E*,5*Z*)-**13a** with benzaldehyde gave results that are comparable with its (*E,E*)-counterpart [Eq. (4)], compare with Scheme 4]. A mixture of all four possible stereoisomers of **13a** can also be used with similar efficiency [Eq. (5)].





The reaction of benzaldehyde with the doubly deuterium-labeled diene **[D]<sub>2</sub>-13a** gave homoallylic alcohol **[D]<sub>2</sub>-14a** in  $\leq 87\%$  purity, in which one deuterium atom was transferred to the homoallylic methylene carbon, with no evidence of deuteration at other sites [Eq. (6)]. This overall 1,4-deuterium shift is consistent with the mechanism shown in Scheme 2 (see the Supporting Information for details).

Finally, this process is not limited to aldehyde electrophiles. Although cyclic imines (Scheme 1C) and ketones are not suitable substrates, diene **15** reacted with the formalimine derived from cracking of 1,3,5-tris(4-methoxyphenyl)-1,3,5-triazinane to give homoallylic amine **16** in 52% yield [Eq. (7)]. The inclusion of 3 Å molecular sieves was beneficial in increasing the yield of this reaction.



In conclusion, we have reported the rhodium-catalyzed reductive nucleophilic allylation of aldehydes or an imine with 1,3-dienes, in which carbon–carbon bond formation occurs at a site remote from the initiation site by the overall net migration of allylrhodium species. This study illustrates the potential utility of allylmetal chain walking in remote C–H functionalization, which complements much more well-known alkylmetal chain walking processes. Compared with our previous work (Scheme 1C),<sup>[4b]</sup> we have shown that chain walking can proceed through greater distances (up to eight methylene units). Furthermore, an expanded range of functional groups was shown to promote chain walking, which includes esters, amides, and (hetero)arenes. Our future work will include the development of enantioselective variants of this process.<sup>[11]</sup>

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**Keywords:** allylation • chain walking • homogeneous catalysis • isomerization • rhodium

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[7] The relative configurations of products **2f** and **14a** were determined by converting them into cyclic derivatives, followed by <sup>1</sup>H NMR analysis of vicinal coupling constants. See the Supporting Information for details. The relative configurations of the remaining products were assigned by analogy.

[8] Under different reaction conditions, the reaction of rhodium hydrides with activated 1,3-dienes has been proposed to occur via 1,4-hydorhodation. See: R. Dada, Z. Wei, R. Gui, R. J. Lundgren, *Angew. Chem., Int. Ed.* **2018**, *57*, 3981-3984.

[9] These other products were generally not isolated, except in the case of the reaction producing **14a** (see Scheme 4). See the Supporting Information for details.

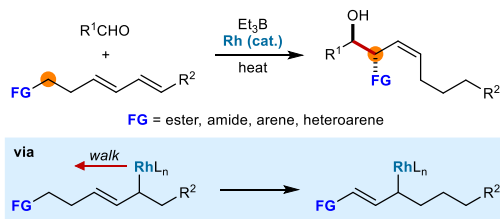
[10] The reasons for halogen-containing substrates being ineffective are not currently known, but one possibility is undesired oxidative addition of Rh(I) with the carbon–halogen bond. For selected examples of oxidation addition of Rh(I) with alkyl or aryl halides, see: a) S. Gatard, R. Çelenligil-Çetin, C. Guo, B. M. Foxman, O. V. Ozerov, *J. Am. Chem. Soc.* **2006**, *128*, 2808-2809. b) C. Tejel, M. A. Ciriano, J. A. López, S.

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[11] Using various chiral diene–rhodium complexes in these reactions led to low conversions and enantioselectivities.

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## COMMUNICATION



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Remote Nucleophilic Allylation by  
Allylrhodium Chain Walking

Allylrhodium species obtained from hydorrhodation of 1,3-dienes undergo chain walking toward esters, amides, or (hetero)arenes over distances of up to eight methylene units. The final, more highly conjugated allylrhodium species undergo nucleophilic allylation with aldehydes and an imine to give Z-homoallylic alcohols and amines, respectively.