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 hydrorhodation 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. 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 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.

For this study, the use of allylrhodium precursors that are simpler to prepare than allyl trifluoroborates was desirable. We therefore considered generating allylrhodium species by the hydrorhodation of 1,3-dienes, as described by Kimura and co-workers in related reductive nucleophilic allylations. Accordingly, substrate 1a was reacted with benzaldehyde (1.2 equiv) in the presence of [Rh(cod)OH]2 (5 mol%) and Et3B (2.0 equiv) in THF at 50 °C for 16 h. Pleasingly, this reaction gave homoallylic alcohol 2a, which was isolated as a single diastereomer in 60% yield (Eq. (1) and Table 1, entry 1). The use of Et3SiH in place of Et3B gave no reaction.

A possible catalytic cycle is shown in Scheme 2. First, the reaction of [Rh(cod)OH]2 with Et3B generates the allylrhodium species 3, which undergoes β-hydride elimination to give

A. Allymetal chain walking (well known)

B. Allymetal chain walking (hardly any examples)

C. Discovery of allylumium chain walking (ref. 4b)

D. Longer range allylumium chain walking (this work)

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Scheme 2. Proposed catalytic cycle.

Rhodium hydride 4. Hydorhodation of 1,3-diene 1a with 4 then provides allylrhodium species 5A, which undergoes σ-π-σ isomerization to give 5B. β-Hydride elimination of 5B gives a rhodium hydride coordinated to benzyl sorbate (as in 6). Hydorhodation 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 nonbonding interactions with the cyclooctadiene ligand. Reaction of the resulting rhodium alkoxide 9 with Et₃B or Et₂B(OH) 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 Et₃B in THF at 50 °C, whereas method B used 3.0 equivalents of Et₂B 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.

Table 1: Scope of the 1,3-diene.

| Entry | Diene | Method | Product | Yield (%) |
|-------|-------|--------|---------|-----------|
| 1     | 1a    | A      | 2a      | 60        |
| 2     | 1b    | A      | 2b      | 65        |
| 3     | 1c    | A      | 2b      | 41        |
| 4     | 1d    | B      | 2c      | 51        |
| 5     | 1e    | B      | 2d      | <5        |
| 6     | 1f    | B      | 2e      | 35        |
| 7     | 1g    | B      | 2f      | 46 (11:1 d.r.) |
| 8     | 1h    | B      | 2g      | 43 (9:1 d.r.) |
| 9     | 1i    | B      | 2h      | 23 (3:1 d.r.) |
| 10    | 1j    | B      | 2c      | 53        |
| 11    | 1k    | B      | 2i      | 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). 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, whereas 2-furaldehyde gave 11f in 40% yield. Linear and branched aliphatic aldehydes are also tolerated (11f–11j). Tetrahydro-2H-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 1H NMR analysis of the crude reaction mixture. [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. Other arenes that bring about chain walking include 2-naphthyl (14b), 2-fluorophenyl (14c), and 3-methoxyphenyl groups (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 1H 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 (3E,5Z)-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)].
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The reaction of benzaldehyde with the doubly deuterium-labeled diene [D]-13a gave homoallylic alcohol [D]-14a in ≤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 formaldehyde derived from cracking of 1,3,5-tris(4-methoxyphenyl)-1,3,5-triazinanone 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 amine 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 allylmetal chain walking processes. Compared with our previous work (Scheme 1C), 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)aranes. Our future work will include the development of enantioselective variants of this process.[11]

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[1] For selected reviews: a) R. Breslow, Acc. Chem. Res. 1980, 13, 170-177. b) H. Schwarz, Acc. Chem. Res. 1989, 22, 282-287. c) H. Jiang, L. Albrecht, K. A. Jorgensen, Chem. Sci. 2013, 4, 2287-2300. d) I. Franco, C. Mazet, Org. Biomol. Chem. 2014, 12, 233-241. e) M. Vílchez-Herrera, L. Domke, A. Börner, ACS Catal. 2014, 4, 1706-1724. f) G. Gliu, J. Wu, Org. Chem. Front. 2015, 2, 169-178. g) A. Vasquez, J. Bruffaerts, I. Marek, Nature Chem. 2016, 8, 209-219. h) J. Bruffaerts, D. Pietro, I. Marek, Org. Biomol. Chem. 2016, 14, 10325-10330. i) H. Sommer, F. Julià-Hernández, R. Martin, I. Marek, ACS Cent. Sci. 2018, 4, 153-165. For selected, recent examples of chain walking alkylmetal species, see: a) G. C. Tsui, M. Lautens, Angew. Chem., Int. Ed. 2010, 49, 8938-8941. b) A. Renaudat, L. Jean-Gerard, R. Jazbar, C. E. Kelafidis, E. Clot, O. Baudoin, Angew. Chem., Int. Ed. 2010, 49, 7261-7265. c) E. W. Werner, T.-S. Mei, A. J. Bückle, M. S. Sigman, Science 2012, 338, 1455-1458. d) W.-C. Lee, C.-H. Wang, Y.-H. Lin, W.-C. Shih, T.-G. Ong, Org. Lett. 2013, 15, 5358-5361. e) A. Millot, P. Larini, E. Clot, O. Baudoin, Chem. Soc. Rev. 2013, 42, 2241-2247. f) T.-S. Mei, H. Patel, M. S. Sigman, Nature 2014, 508, 340-344. g) T. Yamakawa, N. Yoshikai, Chem. Asian J. 2014, 9, 1242-1246. h) J. S. Bair, Y. Schramm, A. G. Sergeev, E. Clot, O. Eisenstein, J. F. Hartwig, J. Am. Chem. Soc. 2014, 136, 13098-13101. i) E. Larianov, L. Lin, L. Guénée, C. Mazet, J. Am. Chem. Soc. 2014, 136, 16882-16894. j) C. M. Filiboux, T. Rovis, J. Am. Chem. Soc. 2015, 137, 508-517. k) L. Lin, C. Romano, C. Mazet, J. Am. Chem. Soc. 2016, 138, 10344-10350. l) H. H. Patel, M. S. Sigman, J. Am. Chem. Soc. 2016, 138, 14226-14242. m) D. Poty, K.-F. Zhang, A.-S. Goulierre, O. Baudoin, Angew. Chem., Int. Ed. 2016, 55, 14793-14797. n) Y. He, Y. Cai, S. Zhu, J. Am. Chem. Soc. 2017, 139, 1061-1064. o) F. Julià-Hernández, T. Moragas, J. Cornella, R. Martin, Nature 2017, 545, 88-92. p) Y. Ebe, M. Onoda, T. Nishimura, H. Yorimitsu, Angew. Chem., Int. Ed. 2017, 56, 5067-5071. q) M. Gaydou, T. Moragas, F. Julià-Hernández, R. Martin, J. Am. Chem. Soc. 2017, 139, 12161-12164. r) F. Zhou, J. Zhu, Y. Zhang, S. Zhu, Angew. Chem., Int. Ed. 2018, 57, 4058-4062. s) C. Romano, C. Mazet, J. Am. Chem. Soc. 2018, 140, 1474-4750.

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