Chain Walking of Allylrhodium Species towards Esters during Rhodium-Catalyzed Nucleophilic Allylations of Imines

Jose I. Martínez, Joshua J. Smith, Hamish B. Hepburn, and Hon Wai Lam*

Abstract: Allylrhodium species derived from $\delta$-trifluoroboryl $\beta,y$-unsaturated esters undergo chain walking towards the ester moiety. The resulting allylrhodium species react with imines to give products containing two new stereocenters and a $\gamma$-alkene. By using a chiral diene ligand, products can be obtained with high enantioselectivities, where a pronounced matched/mismatched effect with the chirality of the allyl trifluoroborate is evident.

The migration of metal centers along carbon chains occurs in several important reactions. Many of these migrations take place by $\beta$-hydride elimination and hydrometallation sequences, in which the direction of travel is controlled by thermodynamics, a ligand, or a nearby functional group. With few exceptions, these migrations involve simple alkylmetal species. The ability to chain walk a metal together with a second functional group has significant synthetic opportunities, but this mode of reactivity remains largely underdeveloped. Herein, we describe, to our knowledge, the first examples of allylrhodium chain walking, and its application in the preparation of enantiomerichich products.

During our studies of enantioselective Rh-catalyzed nucleophilic allylations of imines, the reaction of imine 1a with racemic allyltrifluoroborate 2a in the presence of [(Rh(cod)Cl)$_2$] (1.5 mol%) and $\text{PrOH}$ (5.0 equiv) was conducted (Scheme 1). Surprisingly, allylation at the $\alpha$- or $\gamma$-carbons relative to the boron atom of 2a was not observed. Instead, this reaction gave homoallylic sulfamates 3a (68% yield) and 4a (6% yield), each in >95:5 d.r. (Scheme 1). This result suggests the reactive intermediates are allylrhodium species 5 and 6, formed from migration of the allylrhodium species generated initially from transmetallation of 2a with rhodium.

The scope of this unexpected reaction was extended to include aldimines bearing methyl, methoxy, bromo, or diozoxy groups, which gave products with high diastereoselectivities in 65–72% yield (Table 1, entries 1–5). Ketimines containing linear alkyl groups at the imine carbon were also effective (entries 6–9). However, an isopropyl-substituted imine was recovered unchanged (entry 10). With one exception (entry 3), no products of allylation at the $\alpha$- or $\gamma$-carbons relative to the boron atom of 2a were obtained. In addition, except for the reactions producing 3a and 3d (entries 1 and 4), the alternative regioisomers were difficult to detect by $^1$H NMR spectroscopy.

Next, the potassium allyltrifluoroborate was varied (Table 2). As well as ethyl esters (Table 1) and benzyl esters (Table 2, entries 1–5, 7, and 8), a 2-naphthyl ester was accommodated (Table 2, entry 6). Regarding the substituent $\alpha$ to the boron atom, alkyl (entries 1, 2, 7, and 8) and chloroalkyl groups (entry 3) were tolerated. Product 3i was isolated along with a product of allylation without chain walking, in a 95:5 ratio (entry 2). Alkyl substituents containing phenyl or benzoyloxy groups resulted in lower conversions and yields (entries 4 and 5).

**Table 1: Investigation of imine scope.**

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3a $R = Me$</td>
<td>68[a]</td>
</tr>
<tr>
<td>2</td>
<td>3b $R = H$</td>
<td>72</td>
</tr>
<tr>
<td>3</td>
<td>3c $R = OMe$</td>
<td>65[b]</td>
</tr>
<tr>
<td>4</td>
<td>3d $R = Br$</td>
<td>65[b]</td>
</tr>
<tr>
<td>5</td>
<td>3e</td>
<td>65</td>
</tr>
<tr>
<td>6</td>
<td>3f $R = Me$</td>
<td>65</td>
</tr>
<tr>
<td>7</td>
<td>3g $R = Et$</td>
<td>53</td>
</tr>
<tr>
<td>8</td>
<td>3h $R = nBu$</td>
<td>54</td>
</tr>
<tr>
<td>9</td>
<td>3i $R = (CH$<em>3$</em>$2$)$_2$Ph</td>
<td>55</td>
</tr>
<tr>
<td>10</td>
<td>3j $R = Ph$</td>
<td>&lt;5</td>
</tr>
</tbody>
</table>

[a] Reactions were conducted using 0.30 mmol of 1. The diastereomeric ratios were confirmed by $^1$H NMR analysis of the unpurified reactions. [b] Yield of isolated products. [c] The regioisomer 4a was isolated in 6% yield (Scheme 1). [d] In the unpurified reaction, traces of a product derived from allylation without chain walking were detected. [e] Isolated as an 87:13 mixture of 3d with the regioisomeric product 4d. See Ref. [13].

Scheme 1. Discovery of allylrhodium chain walking.

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Table 2: Investigation of allyltrifluoroborate scope.[a]

<table>
<thead>
<tr>
<th>Entry</th>
<th>Product</th>
<th>Yield [%][b]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>3k R = Me</td>
<td>69</td>
</tr>
<tr>
<td>2</td>
<td>3l R = nPr</td>
<td>70[1]</td>
</tr>
<tr>
<td>3</td>
<td>3m R = (CH₂)₂Cl</td>
<td>63</td>
</tr>
<tr>
<td>4</td>
<td>3n R = (CH₂)₂Ph</td>
<td>36 (59)[6]</td>
</tr>
<tr>
<td>5</td>
<td>3o R = CH₂OBn</td>
<td>(53)[6]</td>
</tr>
<tr>
<td>6</td>
<td>3p R = Me</td>
<td>62</td>
</tr>
<tr>
<td>7</td>
<td>3q R = Me</td>
<td>67</td>
</tr>
<tr>
<td>8</td>
<td>3r R = nPr</td>
<td>58</td>
</tr>
</tbody>
</table>

[a] Reactions were conducted using 0.30 mmol of 1. The diastereomeric ratios were confirmed by 1H NMR analysis of the unpurified reactions. [b] Yield of isolated products. [c] Isolated as a 95:5 mixture of 3f and the product of allylation without allylrhodium chain walking. See Ref. [13]. [d] Using 2.5 mol% of [[Rh(cod)Cl]₂]. [e] Yields in parentheses were determined by 1H NMR spectroscopy using 1,3,5-trimethoxybenzene as an internal standard. [f] Attempts to purify 3o by column chromatography were unsuccessful. A pure sample was obtained by preparative TLC.

The reaction of 1b with allyltrifluoroborate 2h, in which boron is bonded to a primary rather than a secondary carbon, gave not only 3s, but also a significant quantity of product 7 in 80:20 d.r., derived from allylation without chain walking [Eq. (1)]. Products 3s and 7 could not be completely separated by chromatography, and their yields were determined by 1H NMR analysis using an internal standard.

Interestingly, the reaction of Z-allyltrifluoroborate 8[9] with aldimine 1b gave 3b in 70% yield (Scheme 2, top), which is the same product obtained from the corresponding E-isomer 2a (Table 1, entry 2). Furthermore, despite possessing a substitution pattern different to all allyltrifluoroborates employed until this point, allyltrifluoroborate 9 reacted in the same manner to give 3t (Scheme 2, bottom).[10] These results suggest that regardless of the geometrical or positional isomerism of the allyltrifluoroborate within the β to γ carbons, the reactions proceed through common types of allylrhodium intermediates. However, homoallylic boron reagents were unreactive.[15]

Because these reactions provide chiral products from chiral substrates, we investigated whether enantioenriched allyltrifluoroborates would give enantioenriched products. However, the reactions of (R)-2a (94% ee)[9] with aldimine 1b and ketimine 1f gave (S,S)-3b and (S,S)-3f, respectively, with low to moderate enantiomeric excesses (Scheme 3). Although chain walking of allylmetal species can proceed with high stereospecificity,[70] poor absolute stereochemical transfer is observed in the reactions described herein.

Scheme 2. Effect of geometrical and positional isomerism of the allyltrifluoroborate.

Scheme 3. Investigation of absolute stereochemical transfer with (R)-2a.

Next, chiral rhodium complexes were investigated for their ability to provide enantioenriched products from racemic allyltrifluoroborates (Scheme 4).[8] Although several chiral dienes[8] gave poor conversions[13] in the reaction of aldimine 1b with 2a, diene Li[11] gave (S,S)-3b in 72% yield and 98% ee. Several other products (S,S)-3k, (S,S)-3m, and (S,S)-3p were also prepared in the same manner. However, the yields of some of these reactions were low, and the scope is more limited than when using [[Rh(cod)Cl]₂]. For example, enantioselective additions to ketimines were unsuccessful.
Enantioselective allylations. Reactions were conducted using 0.30 mmol of 1b. The diastereomeric ratios were confirmed by $^1$H NMR analysis of the unpurified reactions. Yields are of isolated products. Enantiomeric excesses were determined by HPLC analysis on a chiral stationary phase. [a]

Interestingly, a pronounced matched/mismatched effect was observed with enantioenriched allyltrifluoroborates. The reaction of 1b with (R)\text{-}2a (94\% ee) using chiral diene L1 gave (S,S)\text{-}3b with results identical to the reaction using racemic 2a (Scheme 5, top; compare with Scheme 4). However, the corresponding reaction with (S)\text{-}2a (94\% ee) gave a complex mixture; although 3b was detected in small but unquantifiable amounts by $^1$H NMR analysis, it could not be isolated. Currently, it is unclear which steps of the proposed mechanism (vide infra) are rendered inefficient by the stereochemical mismatch of the ligand and the allyltrifluoroborate.

A proposed mechanism, using imine 1a and allyltrifluoroborate 2a as representative substrates, is shown in Scheme 6. The reaction of 2a with PrOH can reversibly generate a mixed alkoxide/fluoride boron ate complex 11, which transmetallates with rhodium complex 10 \[^{[18], [19]}\] to give interconverting allylrhodium species 12 and 13. β-Hydride elimination of 13 then gives a rhodium hydride species bound to ethyl sorbate (as in 14). \[^{[20], [21]}\] Hydrorhodation of the alkene distal to the ester then provides interconverting allylrhodium species 5 and 6. A possible driving force for this chain walking migration is the formation of a more stable, more conjugated allylrhodium species 5. Nucleophilic allylation of 1a by 5 through a chairlike conformation 15, in which the ethyl group is pseudoaxial to avoid unfavorable interactions with the cyclooctadiene ligand, \[^{[22]}\] gives 16. \[^{[23]}\] Finally, protonolysis of 16 with HX (X = Cl, F, or OPr) releases the product 3a and regenerates 10. The minor regioisomer 4a is the result of allylation of 1a with allylrhodium species 6.

Support for this mechanism was provided by the reaction of aldime 1b, allyltrifluoroborate 2c (1.5 equiv), and ethyl sorbate 17 (1.5 equiv), using [Rh(C\text{$_2$H$_4$}Cl)$_2$Cl]$_2$ as a precatalyst [Eq. (2)]. This reaction gave mostly unreacted 1b and 17, along with unidentified products resulting from decomposition of 2c. However, by HPLC-ES, small quantities of the expected product 3l derived from allyltrifluoroborate 2c (0.4\% yield), the crossover product 3a derived from ethyl sorbate (17, 3.4\% yield), and α,β,γ,δ-unsaturated benzyl ester 18 (2.7\% yield) were also detected. \[^{[13]}\]

Presumably, the initial catalytic species in this reaction is a complex of rhodium and ethyl sorbate (17), possibly the s-cis-η$^2$ complex 19, which reacts with 2c according to the mechanism.
shown in Scheme 5 to give the rhodium hydride 20 (Scheme 7). Hydrorhodation of the α,β,γ,δ-unsaturated benzyl ester would give allylrhodium species 21, which reacts with 1b to give the expected product 3i. Alternatively, a structural reorganization of 20 could give 22, which can then undergo hydrorhodation of ethyl sorbate to give allylrhodium species 5 and the crossover product 3a.

In summary, we have reported the chain walking of allylrhodium species derived from δ-trifluoroboryl β,γ-unsaturated esters during the rhodium-catalyzed nucleophilic allylation of imines, which gives products with two new stereocenters and a Z-alkene. Enantioselective catalysis is possible using a chiral diene ligand, where a strong matched/mismatched effect was observed. Further exploration of this new mode of reactivity is underway in our laboratories.

Acknowledgements

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Keywords: allyltrifluoroborates - asymmetric catalysis - imines - isomerization - rhodium


[9] The potassium allyltrifluoroborates used in this study were prepared by the copper-catalyzed 1,6-boration of α,β,γ-unsaturated esters. See the Supporting Information and: Y. Luo, I. D. Roy, A. G. E. Madec, H. W. Lam, Angew. Chem., Int. Ed. 2014, 53, 4186-4190.

[10] The relative and/or absolute configurations of the products were assigned by comparison to those of 3a (racemic), 4a (racemic), 3f (racemic), (S,S)-3l (resolved during crystallization), and (S,S)-3b, which were determined by X-ray crystallography. CCDC 1418585-1418589 contain the supplementary crystallographic data for this paper. These data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

[11] Under the same conditions, the reaction of 2a with benzaldehyde gave a complex mixture. The reaction of 2a with the N-tert-butyl imine derived from benzaldehyde returned mostly unchanged starting materials.


[13] See the Supporting Information.

[14] The relative configuration of 7 was assigned tentatively.

[15] Attempted reactions of the following homoallylic boron reagents and imine 1b under various reaction conditions led only to unchanged starting materials, suggesting that transmetalation to rhodium is difficult for these reagents.
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[20] Replacing iPrOH with tBuOH gave comparable results, thus excluding the possibility that rhodium hydride species are generated by β-hydride elimination from a rhodium isopropoxide derived from iPrOH.


[22] A novel mechanism for the formation of 3a is the 1,4-hydorhodation of ethyl sorbate to give a rhodium enolate, which then reacts with the imine in a Mannich reaction (as shown below). However, we favor the mechanism shown in Scheme 6 on the basis that an interconverting mixture of allylrhodium isomers 5 and 6 explains the formation of regioisomeric products 3a and 4a in a simpler fashion.
Migrate to create: Allylrhodium species derived from δ-trifluoroboryl β,γ-unsaturated esters undergo chain walking towards the ester moiety. The resulting allylrhodium species react with imines to give products containing two new stereocenters and a Z-alkene. By using a chiral diene ligand, products can be obtained with high enantioselectivities, where a pronounced matched/mismatched effect with the chirality of the allyltrifluoroborate is evident.