Catalytic C–H functionalizations have revolutionized chemical synthesis by providing powerful new tools for bond construction. However, a critical objective for the advancement of this field is its application to a more diverse range of transformations. Nucleophilic allylations are important reactions that could benefit from C–H functionalization principles. Most typically, these processes have employed allymetal(loid) reagents such as allytin, allyboron, or allylsilicon compounds. The generation of nucleophilic allylmetal species by the activation of allylic C–H bonds would bypass the need to prepare such reagents and potentially increase efficiency by streamlining synthetic sequences. This strategy would also be a valuable complement to nucleophilic allylations involving migratory insertions of allenes, the use of simple π-unsaturated compounds in hydrogenative or redox-triggered additions, hetero-ene reactions and Prins reactions.

Although generating electrophilic allylmetal species by allylic C–H activation is well-known, there is, to our knowledge, limited precedent for corresponding processes that provide nucleophilic allylmetals. Very recently, the groups of Schneider, Kanai and Mita and Sato described the formation and trapping of nucleophilic allylmetal species from simple hydrocarbons. In view of the nucleophilic character of allylrhodium(I) species described, we envisaged that activation of a remote C–H bond by 1,4-rhodium(I) migration could also achieve this goal. Specifically, rhodium(I)-catalyzed reaction of an arylboron reagent with the alkyne of 1,3-enyne would provide the alkynylrhodium species A (Scheme 1). This intermediate could then undergo a 1,4-rhodium(I) shift to the cis-allylic substituent to give the allylrhodium(I) species B, which could be trapped by an electrophile. This approach was expected to be challenging, given that there is only very limited precedent for rhodium(I) to migrate to C(sp3) centers. Nevertheless, the generation of electrophilic allylrhodium(III) species by a similar strategy in our rhodium(III)-catalyzed functionalizations has revolutionized chemistry by providing powerful new tools for bond construction.

Abstract: Alkenyl-to-allyl 1,4-rhodium(I) migration enables the generation of nucleophilic allylrhodium(I) species by remote C–H activation. This new mode of reactivity was employed in the diastereoselective reaction of arylboron reagents with substrates containing a 1,3-enyne tethered to a ketone, to give products containing three contiguous stereocenters. The products can be obtained in high enantioselectivities using a chiral sulfur-alkene ligand.

Scheme 1. Proposed alkenyl-to-allyl 1,4-rhodium(I) migration.

This study began with the reaction of the enynone 1a with 3,5-dimethylphenyl pinacol boronate (1.3 equiv), [[Rh(cod)Cl]2] (1.5 mol%), and K2PO4 (0.3 equiv) at 65°C for 16 hours in various solvents (Table 1). A 3-disubstituted arylboron reagent was used to minimize 1,4-rhodium(I) migration onto the aryl group as described previously as it is well-known that migration onto an aryl ring ortho to a substituent is unfavorable. Pinacol boronates were used because 3,5-disubstituted variants are easily accessed through iridium-catalyzed C–H borylation. The reaction conducted in THF/MeOH (10:1) gave diastereomeric bicycles 2aa[17] and 2ab[18] in a 13.87 ratio (entry 1). After purification, 2aa and 2ab were isolated in 11 and 46 % yield, respectively. Traces of the diketone 3a were also formed, and resulted from arylation of the alkyne of 1a with the regioselectivity opposite to that seen in the formation of 2aa/2ab, followed by a cyclization-fragmentation pathway. Notably, switching groups of Schneider, Kanai and Mita and Sato described the formation and trapping of nucleophilic allylmetal species from simple hydrocarbons. In view of the nucleophilic character of allylrhodium(I) species, we envisaged that activation of a remote C–H bond by 1,4-rhodium(I) migration could also achieve this goal. Specifically, rhodium(I)-catalyzed reaction of an arylboron reagent with the alkyne of 1,3-enyne would provide the alkynylrhodium species A (Scheme 1). This intermediate could then undergo a 1,4-rhodium(I) shift to the cis-allylic substituent to give the allylrhodium(I) species B, which could be trapped by an electrophile. This approach was expected to be challenging, given that there is only very limited precedent for rhodium(I) to migrate to C(sp3) centers. Nevertheless, the generation of electrophilic allylrhodium(III) species by a similar strategy in our rhodium(III)-catalyzed functionalizations has revolutionized chemistry by providing powerful new tools for bond construction.

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the solvent to MeCN/MeOH (10:1) reversed the sense of
diastereoselectivity and gave $2a_a$ and $2a_b$ in 66 and 5% yield,
respectively (entry 2). Using TBME/tBuCN/MeOH (10:1.2:1) gave a
further increase in diastereoselectivity (entry 3).

In the proposed catalytic cycle (Scheme 2), transmetala-
tion of the arylboronate with the rhodium methoxide
provides the arylrhodium species $5$, which undergoes migra-
tory insertion with the alkyne of $1a$ to give alkenylrhodium
species $6$. Rhodium migration gives the allylrhodium
species ($Z$)-$7$, which cyclizes onto a ketone to provide the
rhodium alkoxide $8$. Methanolation of $8$ liberates the product
$2a_a$ or $2a_b$ and regenerates $4$.

Scheme 3 presents the reactions of $1a$ with various
arylboronic acid pinacol esters. Products analogous to $3a$
were generally formed in up to 20% yield (by $^1H$ NMR analysis of the crude reaction mixtures) but were not isolated.

Next, variation of the enynone was explored, and the
substrates $1b$–$f$, containing methyl groups cis to the alkyne, all
reacted successfully with 3,5-dimethylphenyl pinacol boro-
name (Table 2). Substrates containing hydrogen, phenyl, or
alkyl groups trans to the alkyne are tolerated (entries 1–3).

With the phenyl-containing substrate $1c$, however, applica-
tion of the standard reaction conditions gave no diastereose-
lectivity (1:1 d.r.). Fortunately, switching the solvent to 2-
MeTHF/MeOH (10:1) gave the syn,syn-diastereomer $9b$ in
greater than 95:5 d.r. and 62% yield (entry 2). In contrast
to our findings using rhodium(III) catalysis, substrates contain-
ing methylene groups (as opposed to methyl groups) cis to the alkyne are unreactive. Variation of the 1,3-diketone is also possible. For example, the indane-1,3-dione $1e$ gave $9e_a$ in 74% yield and >95:5 d.r. (entry 4). Under the standard reaction conditions, the six-membered cyclic 1,3-
diketone $1f$ underwent decomposition in competition with aryldiastic.

<table>
<thead>
<tr>
<th>Entry</th>
<th>Solvent</th>
<th>d.r.</th>
<th>Yield [%]</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>THF/MeOH (10:1)</td>
<td>17:83</td>
<td>11 46 n.d.</td>
</tr>
<tr>
<td>2</td>
<td>MeCN/MeOH (10:1)</td>
<td>91:9</td>
<td>66 5 9</td>
</tr>
<tr>
<td>3</td>
<td>TBME/tBuCN/MeOH (10:1.2:1)</td>
<td>94:6</td>
<td>73 4 14</td>
</tr>
</tbody>
</table>

[a] Reactions employed 0.50 mmol of $1a$. [b] Determined by $^1H$ NMR analysis of the crude reaction mixtures. [c] Yield of the isolated product. [d] n.d. = not determined. cod = 1,5-cyclooctadiene, TBME = tert-buty$
lash$ methyl ether, THF = tetrahydrofuran.

Scheme 2. Proposed catalytic cycle.

Scheme 3. [a] Reaction of $1a$ with various arylboronates. Reactions employed 0.50 mmol of $1a$. Diastereomeric ratios were determined by $^1H$ NMR analysis of the crude reaction mixtures. Yields are of isolated, diastereomerically pure products. [b] Reaction performed with 2.5 mol% [{Rh(cod)Cl}]$_2$. [c] Reaction employed 0.45 mmol of $1a$. 

Scheme 3. [a] Reaction of $1a$ with various arylboronates. Reactions employed 0.50 mmol of $1a$. Diastereomeric ratios were determined by $^1H$ NMR analysis of the crude reaction mixtures. Yields are of isolated, diastereomerically pure products. [b] Reaction performed with 2.5 mol% [{Rh(cod)Cl}]$_2$. [c] Reaction employed 0.45 mmol of $1a$. 

Table 1: Evaluation of solvents.[a]
was formed in 67% yield (entry 5).\textsuperscript{[17]} The process is not limited to cyclic 1,3-diketones as the β-ketoester 10 reacted smoothly using 2.5 mol% of [[Rh(cod)Cl]$_2$] to give 11 in 62% yield and 95:5 d.r. [Eq. (1)].

Furthermore, the fully acyclic substrates 12a and 12b also underwent successful arylative intramolecular allylation [Eq. (2) and (3)], although the diastereoselectivities were lower compared with substrates containing cyclic ketones. For acceptable yields, it was important to use neopentyl glycol boronate, K$_2$CO$_3$, and tAmOH. Under these reaction conditions, 12a reacted with 3,5-dimethylphenyl neopentyl glycol boronate to give the diastereomeric products 13aa and 13ab in 28 and 27% yield, respectively [Eq. (2)].\textsuperscript{[21]} Improved results were obtained with 12b, which contains a geminal dimethyl group in the tether, and 13ba and 13bb were obtained in 51 and 12% yield, respectively [Eq. (3)].\textsuperscript{[21]} The same reactions conducted in 2-MeTHF instead of TBME/tBuCN gave 13ab and 13bb as the major products, but were lower yielding.

The substrate 14, which contains an E-1,3-enyne, did not undergo the reaction, and only starting materials were recovered [Eq. (4)]. This result confirms the requirement for cis-allylic hydrogen atoms to be present in the enyne to allow 1,4-rhodium(I) migration to occur (compare with Table 2, entry 1 using the Z-isomer 1b). In addition, reaction of hexadeuterated enyne $[D]_8$-1a with 3,5-dimethylphenylboronic acid pinacol ester gave $[D]_8$-2aa with greater than 95% deuterium transfer to the alkene of the cyclohexene [Eq. (5)]. This outcome is consistent with 1,4-rhodium(I) migration occurring by a C–H oxidative addition/reductive elimination through a rhodium(III) hydride intermediate as hypothesized previously for alkyl-enoyl 1,4-rhodium(I) migration.\textsuperscript{[14j]}

### Table 2: Arylative allylation of various enynones.\textsuperscript{[a]}

<table>
<thead>
<tr>
<th>Entry</th>
<th>Enynone</th>
<th>Product (Ar$_2$=3,5-Me$_2$C$_6$H$_3$)</th>
<th>d.r.$^c$</th>
<th>Yield [%]$^d$</th>
</tr>
</thead>
<tbody>
<tr>
<td>1$^b$</td>
<td>1b</td>
<td>9ba n.d.$^e$</td>
<td>50 (+ 7)$^f$</td>
<td></td>
</tr>
<tr>
<td>2$^d$</td>
<td>1c</td>
<td>9cb &gt; 95:5</td>
<td>62</td>
<td></td>
</tr>
<tr>
<td>3</td>
<td>1d</td>
<td>9da 84:16</td>
<td>52</td>
<td></td>
</tr>
<tr>
<td>4</td>
<td>1e</td>
<td>9ea &gt; 95:5</td>
<td>74</td>
<td></td>
</tr>
<tr>
<td>5$^h$</td>
<td>1f</td>
<td>9fa 84:16</td>
<td>67</td>
<td></td>
</tr>
</tbody>
</table>

[a] Reactions employed 0.50 mmol of 1b–f.\textsuperscript{[b]} Determined by $^1$H NMR analysis of the crude reaction mixtures. \textsuperscript{[c]} Yield of isolated, diastereomerically pure products. \textsuperscript{[d]} Using 2.5 mol% of [[Rh(cod)Cl]$_2$]. \textsuperscript{[e]} The d.r. value could not be determined by $^1$H NMR analysis. \textsuperscript{[f]} Yield of the isolated minor syn-syn diastereomer 9bb. \textsuperscript{[g]} Using 2-MeTHF/MeOH (10:1) in place of TBME/tBuCN/MeOH (10:1.2:1). \textsuperscript{[h]} Using 3,5-Me$_2$C$_6$H$_3$B(neo) (1.3 equiv), K$_2$CO$_3$ (1.3 equiv), and tAmOH (1.5 equiv) as the reagents in TBME/tBuCN (8.3:1). neo = neopentyl glycol.
Up until this point, all of the arylboronates evaluated possess substitution patterns that disfavor 1,4-rhodium(I) migration of intermediates such as 6 onto the aryl group. To assess whether alkenyl-to-allyl 1,4-rhodium(I) migration would still be favored when a sterically more accessible site is available, 1a was reacted with phenylboronic acid (Scheme 4). The reaction in TBME/tBuCN (8:1) in the presence of t-amyl alcohol (1.5 equiv) gave a 5:5 mixture of inseparable products, 15 and 2ja. The product 15 results from 1,4-rhodium(I) migration onto the phenyl group followed by intramolecular ketone arylation, whereas 2ja is the arylative allylation product. When the solvent was changed to 2-MeTHF, the allylation product 2jb was formed preferentially (36:64 ratio of 15/2jb) in 89:11 d.r., and was isolated as a single diastereomer in 45% yield. The reasons for this switch in chemoselectivity are not currently known.

Consistent with models proposed in prior rhodium-catalyzed nucleophilic allylations,[a,12–14] we suggest that allylation occurs through cyclic six-membered transition states (Scheme 5). In the absence of a nitrile in the reaction medium (Table 1, entry 1), we assume that (Z)-7, formed from 1,4-rhodium(I) migration of 6, cyclizes through a chairlike arrangement (TS1) to give 2aa (Scheme 5). The boatlike structure TS2 should be disfavored. However, when a coordinating nitrile is present (Table 1, entries 2 and 3), the rate of cyclization could be decreased, allowing isomerization of (Z)-7 into (E)-7.[22] Thereafter, we assume that cyclization of (E)-7 occurs through the chairlike conformation TS5 to give 2ab (Scheme 5). The alternative conformation TS3 is likely to be disfavored because of 1,3-diaxial interactions and allylic 1,3-strain. The boatlike structure TS4 is also likely to be unfavorable. However, we do not exclude the possibility that when a nitrile is present, 2aa is formed by cyclization of (E)-7 through an open transition state because of preferential coordination of rhodium to the nitrile rather than the ketone.

Similar chairlike transition states can be used to explain the outcomes of the reactions 12a and 12b [Eqs. (2) and (3)], and the diastereomeric ratios observed may be a consequence of their more flexible nature (see the Supporting Information).

Finally, preliminary efforts at developing enantioselective reactions were conducted (Table 3).[23] Only modest results were obtained with chiral diene ligands[24] (see Supporting Information), while no reaction occurred when chiral bisphosphines were used. However, the reaction of 1a with 3,5-dimethylphenylboronic acid (1.3 equiv) in the presence of \([\text{Rh}((C_5H_5)_2Cl)]_2\) (2.5 mol%), the sulfur-alkene L1[25] (5.0 mol%), and KF (1.5 equiv) in TBME/tBuCN/MeOH (40:5:1) gave (+)-2aa[27] in 61% yield and 91% ee (entry 1). The diastereomeric product (+)-2ab was obtained in 11% yield and 88% ee. Similar results were obtained with 3-chloro-5-methylphenylboronic acid (entry 2).
In summary, we have reported the rhodium-catalyzed arylative alkylation of enynes with arylboron reagents. The key step of the reaction is the alkényl-to-aryl 1,4-aryl(1) migration, a new mode of reactivity which enables the generation of nucleophilic allylrhodium(1) species without prefunctionalization of the allylic position. Cyclization of the allylhydride species onto a pendant ketone leads to bicyclic products containing three contiguous stereocenters with high diastereoselectivities. The products can be obtained in high enantioselectivities using a chiral sulfur-alkene ligand. Further applications of this promising platform for generating allylmetal species are in progress.

Acknowledgments

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Conflict of interest

The authors declare no conflict of interest.

Keywords: allylic compounds - cyclization - isomerization - reaction mechanisms - rhodium

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Table 3: Enantioselective reactions.[1]

<table>
<thead>
<tr>
<th>Entry</th>
<th>R</th>
<th>d.r.</th>
<th>Major isomer</th>
<th>Minor isomer</th>
</tr>
</thead>
<tbody>
<tr>
<td>1</td>
<td>Me</td>
<td>80:20</td>
<td>(−)-2aa 61%, 91% ee</td>
<td>(−)-2ab 11%, 88% ee</td>
</tr>
<tr>
<td>2</td>
<td>Cl</td>
<td>78:22</td>
<td>(−)-2ba 47%, 90% ee</td>
<td>(−)-2bb 10%, 90% ee</td>
</tr>
</tbody>
</table>

[a] Reactions employed 0.25 mmol of 1a. [b] Determined by 1H NMR analysis of the crude reaction mixture. [c] Yields are of isolated, diastereomerically pure products. Enantiomeric excesses were determined HPLC analysis on a chiral stationary phase.
Communications


The relative configurations of the products 2aa, 9cb, 9ea, and 9fa and the absolute configuration of (+)-2aa were determined by X-ray crystallography. CCDC 1493830 – 1493833 and 1535509 contain the supplementary crystallographic data for this paper.

These data can be obtained free of charge from The Cambridge Crystallographic Data Centre.

The relative configurations of the majority of the products described herein were determined by NOESY experiments. The relative configurations of 2ab and 2bb were assigned tentatively by analogy with 9cb, the relative configuration of which was determined by X-ray crystallography (see Ref.[17]).


This experiment gave 9ea in 22% yield (see the Supporting Information).

The relative configurations of 13aa and 13ab could not be determined unambiguously and were assigned tentatively by analogy with the reaction producing 13ba and 13bb, on the assumption that the major products in each case possess the same relative configuration. The relative configurations of 13ba and 13bb were determined by NOESY experiments. The product 13bb contained small quantities of an inseparable impurity.

Z/E Isomerization could occur through a sequence involving 1,3-rhodium transposition, bond rotation, and a second 1,3-transposition.


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