Arylative Intramolecular Allylation of Ketones with 1,3-Enynes Enabled by Catalytic Alkenyl-to-Allyl 1,4-Rhodium(I) Migration

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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. This method can be obtained in high enantioselectivities using a chiral sulfur-alkene ligand.

Catalytic C–H functionalizations have revolutionized chemical synthesis by providing powerful new tools for bond construction.[3] However, a critical objective for the advancement of this field is its application to a more diverse range of transformations. Nucleophilic allylations[2] are important reactions that could benefit from C–H functionalization principles. Most typically, these processes have employed allylmetal(l oid) reagents such as allyltin, allylboron, or allylsilicon compounds.[2] 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,[1,4] the use of simple π-unsaturated compounds in hydrogenative or redox-triggered additions,[5,6] hetero-ene reactions,[7] and Prins reactions.[8]

Although generating electrophilic allylmetal species by allylic C–H activation is well-known,[9,10] there is, to our knowledge, limited precedent for corresponding processes that provide nucleophilic allylmetalts.[11] Very recently, the groups of Schneider,[11a] Kanai,[11b] and Mita and Sato[11c] described the formation and trapping of nucleophilic allylmetal species from simple hydrocarbons. In view of the nucleophilic character of allylrhodium(I) species,[12,13,14] we envisaged that activation of a remote C–H bond by 1,4-rhodium(I) migration[12c,13,14] could also achieve this goal. Specifically, rhodium(I)-catalyzed reaction of an arylboron reagent with the alkyne of a 1,3-enyne would provide the allylrhodium 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.[12c,14c,m] Nevertheless, the generation of electrophilic allylrhodium(III) species by a similar strategy in our rhodium(III)-catalyzed oxidative annulations of 1,3-enynes provided some encouragement.[10] Herein, we describe the implementation of this strategy in arylative intramolecular allylations of ketones to give stereochemically complex fused bicycles with high diastereoselectivities. Preliminary results of enantioselective reactions are also provided.

This study began with the reaction of the enyne 1a with 3,5-dimethylphenyl pinacol boronate (1.3 equiv), [[Rh-(cod)Cl]]¹ (1.5 mol%), and K₂PO₄ (0.3 equiv) at 65 °C for 16 hours in various solvents (Table 1). A 3,5-disubstituted aryloboron reagent was used to minimize 1,4-rhodium(I) migration onto the aryl group as described previously.[15d] As it is well-known that migration onto an aryl ring ortho to a substituent is unfavorable,[15e,15f] pinacol boronates were used because 3,5-disubstituted variants are easily accessed through iridium-catalyzed C–H borylation.[16] The reaction conducted in THF/MeOH (10:1) gave diastereomeric bicyclic 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 arylrhodation of the alkyne of 1a with the regioselectivity opposite to that seen in the formation of 2aa/2ab, followed by a cyclization-fragmentation pathway.[14a,19] Notably, switching...
the solvent to MeCN/MeOH (10:1) reversed the sense of diastereoselectivity and gave 2aa and 2ab 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), transmetalation of the arylboronate with the rhodium methoxide 4 provides the arylrhodium species 5, which undergoes migratory insertion with the alkyne of 1a to give alkenylrhodium species 6. 1,4-Rhodium migration gives the allylrhodium species (Z)-7, which cyclizes onto a ketone to provide the rhodium alkoxide 8. Methanolysis of 8 liberates the product 2aa or 2ab 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. The reaction is tolerant of halide (2ba, 2ea, and 2ha), methoxy (2ca and 2fa), trifluoromethyl (2da), and carboxylate groups (2ea). In addition, 3,5-disubstituted (2aa–2ea), 3,4,5-trisubstituted (2fa), and 2,5-disubstituted arylboronates (2ga and 2ha) are tolerated. 2,5-Disubstituted arylboronates gave lower yields (2ga and 2ha), which is presumably a consequence of the steric hindrance of the ortho-substituent. Finally, a heteroarylboronate is also tolerated (2ia).

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 boronate (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, application of the standard reaction conditions gave no diastereoselectivity (1:1 d.r.). Fortunately, switching the solvent to 2-MeTHF/MeOH (10:1) gave the syn,syn-diastereomer 9cb in greater than 95:5 d.r. and 62% yield (entry 2). In contrast to our findings using rhodium(III) catalysis,10 substrates containing 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 9ea 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 arylative allylation. However, by changing the arylboronate to the more reactive neopentyl glycol ester, and using K2CO3 and tAmOH in place of K3PO4 and MeOH, respectively, 9fa...
Table 2: Arylative alkylation of various enynones.[a]

| Entry | Enynone | Product (Ar = 3,5-Me₂C₆H₃) | d.r.[N] | Yield [%][b] |
|-------|---------|-----------------------------|--------|--------------|
| 1[a]  | 1b      | 9ba n.d.[c]                  | 50 (+ 7)[d] |              |
| 2[b]  | 1c      | 9cb > 95:5                   | 62     |              |
| 3     | 1d      | 9da 84:16                    | 52     |              |
| 4     | 1e      | 9ea > 95:5                   | 74     |              |
| 5[c]  | 1f      | 9fa 84:16                    | 67     |              |

[a] Reactions employed 0.50 mmol of 1b–f. [b] Determined by 1H NMR analysis of the crude reaction mixtures. [c] Yield of isolated, diastereomerically pure products. [d] Using 2.5 mol% of [[Rh(cod)Cl]₂] in place of TBME/tBuCN/MEOH (10:1:1). [e] Using 2-MeTHF/MEOH (10:1:1); [f] Using 3,5-Me₂C₆H₅B(neo) (1.3 equiv), K₂CO₃ (1.3 equiv), and tAmOH (1.5 equiv) as the reagents in TBME/tBuCN (8:3:1). neo = neopentyl glycol.

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(III) migration to occur (compare with Table 2, entry 1 using the Z-isomer 1b). In addition, reaction of hexadeuterated enyne [D]₁a with 3,5-dimethylphenylboronic acid pinacol ester gave [D]₂-2aa with greater than 95% deuterium transfer to the alkene of the cyclohexene [Eq. (5)]. This outcome is consistent with 1,4-rhodium(III) hydride intermediate as hypothesized previously for alkynyl-to-aryl 1,4-rhodium(III) migration.[14f]

was formed in 67% yield (entry 5).[17] The process is not limited to cyclic 1,3-diketones as the 3,5-dimethylphenylboronic acid pinacol ester gave [D]₂-2aa with greater than 95% deuterium transfer to the alkene of the cyclohexene [Eq. (5)]. This outcome is consistent with 1,4-rhodium(III) hydride intermediate as hypothesized previously for alkynyl-to-aryl 1,4-rhodium(III) migration.[14f]
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 sterically more accessible site is available, 1a was reacted with phenylboronic acid (Scheme 4). The reaction in TBME/BuCN (8:1) in the presence of 1.5 equiv of (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.

Consistent with models proposed in prior rhodium-catalyzed nucleophilic allylations,[4a,12b–e] 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 [Rh(C5H5)2Cl]2 (2.5 mol%), the sulfur-alkene L1[25] (5.0 mol%), and KF (1.5 equiv) in TBME/ButCN/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 allylative allylation of enynes with arylboron reagents. The key step of the reaction is the alkényl-to-allyl 1,4-rhodium(I) migration, a new mode of reactivity which enables the generation of nucleophilic allyrhodadium(I) species without prefunctionalization of the allylic position. Cyclization of the allyrhodium 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 allymetal species are in progress.

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Conflict of interest

The authors declare no conflict of interest.

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The relative configurations of the majority of the products described herein were determined by NOESY experiments. The relative configurations of 2ab and 2jb 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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