Catalytic 1,4-Rhodium(III) Migration Enables 1,3-Enynes to Function as One-Carbon Oxidative Annulation Partners in C–H Functionalizations**

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Abstract: 1,3-Enynes containing allylic hydrogens cis to the alkyne are shown to act as one-carbon partners, rather than two-carbon partners, in various rhodium-catalyzed oxidative annihilations. The mechanism of these unexpected transformations is proposed to occur through double C–H activation, involving a hitherto rare example of the 1,4-migration of a RhIII species. This phenomenon is general across a variety of substrates, and provides a diverse range of heterocyclic products.

The metal-catalyzed, directing-group-promoted oxidative C–H functionalization[1] of aromatic Csp2/C0H bonds with alkynes[2, 3] has been widely exploited to prepare a rich variety of heterocyclic[4] and carbocyclic products.[5] In the reactions of unsymmetrical alkynes, high regioselectivity is usually observed when the two substituents on the alkyne are electronically well-differentiated. For example, with alkynes containing one alkyl and one aryl substituent, the initial C–C bond formation usually occurs with high regioselectivity at the alkyne carbon bearing the sp3-hybridized group. This regioselectivity is maintained in the oxidative annulation of 1,3-enynes, as demonstrated by the groups of Fagnou (Scheme 1a)[6a] and Ackermann,[6b] for example. Herein, we describe a new mode of oxidative annulation, in which 1,3-enynes are able to function as one-carbon,[7] rather than two-carbon reaction partners (Scheme 1b). We propose this reactivity arises from a hitherto rare example of 1,4-RhIII migration, which opens up new possibilities in C–H functionalization reactions. [8] This phenomenon is general for substrates containing directing groups such as enols, phenols, carboxylic acids, or imides, resulting in a range of heterocyclic products.

During our investigations into ruthenium-, rhodium-, and palladium-catalyzed oxidative annihilations of 2-aryl cyclic 1,3-dicarbonyl compounds with alkynes,[5f,g] the reaction of substrate 1a with 1,3-enyne 2a in the presence of [{Cp*RhCl2}2] (2.5 mol%) and Cu(OAc)2 (2.1 equiv) in dioxane at 120 °C was conducted [Eq. (1)]. Surprisingly, in addition to providing the expected spiroindene 3a in 21% yield, this reaction also gave benzopyran 4a in 25% yield.[9]

A possible mechanism for the formation of 4a is shown in Scheme 2. Generation of the rhodium diacetate complex 5 from [{Cp*RhCl2}2] and Cu(OAc)2 is followed by cyclorhodation of substrate 1a to provide the rhodacycle 6. Coordination and migratory insertion of the 1,3-enyne 2a with the regioselectivity observed previously[6] can then provide a new rhodacycle 7. Reductive elimination of 7 would then give the expected spiroindene 3a as described with alkynes.[5e] However, an alternative pathway is the reversible protonolysis of 7 with AcOH to provide the alkenylrhodium species 9A.[10] Notably, this process enables the activation of a Csp2/C1H bond. The 1,4-migration of rhodium(I)
is well-known,[11–13] but the corresponding 1,4-migrations of rhodium(III) are rare, with the only reports to date being stoichiometric studies of alkynyl to aryl migrations described by Ishii and co-workers.[8] Presumably, the activation barrier of this one-carbon annulation to occur, the reaction of 1,3-enyne 2a with unprotected 2-hydroxyethyl groups were tolerated (Table 2, entry 1). 1,3-Enynes containing protected or free hydroxy groups underwent oxidative annulation with 1,3-enyne 2a in 61% yield with 11h, which contains a methyl group at the alkenyl carbon proximal to the alkyne, as shown by the successful annulations of 1,3-enynes 2f and 2g (Table 2, entries 5 and 6). Notably, a silyl-protected hydroxy-methyl substituent at the trans-position of the 1,3-enyne 2h led to 11h in 61% yield with >95:5 E:Z selectivity at the enol silane (Table 2, entry 7).[17] Finally, 1,3-enyne 2h, which contains a methyl group at the alkenyl carbon proximal to the alkyne was also effective, providing 11i with >95:5 E:Z selectivity (Table 2, entry 8).[17] This unusual oxidative annulation was found to be a general phenomenon, and not merely limited to 2-aryl-3-hydroxy-2-cyclohexenones. Several other aromatic substrates containing enol, phenol, carboxylic acid, or imide directing groups underwent oxidative annulation with 1,3-enyne 2a to give a diverse range of five- or six-membered oxygen and nitrogen heterocycles 13a–e (Scheme 3).[18] }
temperature to 90°C gave the spiroindene 15 in 53% yield and only 7% of benzopyran 11e [Eq. (2)]. This experiment contrasts with that shown in Table 2, entry 4, in which the corresponding (Z)-1,3-enyne 2e gave benzopyran 11e only. These results suggest that 1,4-Rh III migration (8 to 9 in Scheme 2) occurs by a direct pathway that is contingent upon the close proximity of Rh with the cis-allylic hydrogens. We postulate that the formation of benzopyran 11e in 7% yield in Equation (2) results from some type of E/Z isomerization occurring at the higher temperature of 90°C.

To gain further insight into this process, the reaction of 1g with the hexadeuterated 1,3-enyne [D]6-2a was conducted [Eq. (3)]. Three compounds were isolated from this experiment: recovered [D]6-2a in 20% yield with no deuterium depletion detected, spiroindene [D]6-3g in 19% yield with no

Table 2: Oxidative annulation reactions of 1g with various 1,3-enynes.^[a]

| Entry | 1,3-Enyne | Product | Yield [%][b] |
|-------|-----------|---------|-------------|
| 1     | 2b        | 11b R = OTBS | 84          |
| 2     | 2c        | 11c R = OH  | 62          |
| 3     | 2d        | 11d R = Ph  | 73          |
| 4     | 2e        | 11e R = H  | 64          |
| 5     | 2f        | 11f n = 1  | 93          |
| 6     | 2g        | 11g n = 2  | 89          |
| 7     | 2h        | 11h       | 61          |
| 8     | 2i        | 11i       | 61          |

[a] Reactions were conducted with 0.50 mmol of 1g. [b] Yield of isolated products. [c] Reaction conducted at 90°C. [d] Reaction conducted using 0.37 mmol of 1g.

Scheme 3. Oxidative annulation reactions of various substrates with 1,3-enyne 2a. Yields are of isolated products. [a] Reaction conducted in the presence of K2CO3 (3.0 equiv), and a second portion of [[Cp*RhCl2]2] (2.5 mol%) was added after 1 h. [b] Using 5 mol% of [[Cp*RhCl2]2].
deuterium depletion detected, and benzopyran [D],4g in 65 % yield, with incomplete deuteration (77 % D) at the alkynyl carbon adjacent to the quaternary center. Several conclusions can be drawn from these results.

First, the formation of spiroindene [D],3g suggests that C–H functionalization at the methyl group cis to the alkynyl in the 1,3-ene is involved in the product-determining step, since the reaction of 1g with the non-deuterated 1,3-ene 2a led to none of the spiroindene 3g being detected (Table 1, entry 7). Second, the deuteration pattern in [D],4g is consistent with the 1,4-RhIII migration mechanism shown in Scheme 2. However, the incomplete deuteration (77 % D) at the internal alkene suggests that 1,4-RhIII migration may occur by an acetate-assisted, concerted metalation–deprotonation of 16 to form rhodacyle 17, followed by deuterolysis with AcOD (Scheme 4).[19] Incomplete deuteration would arise as a result of competitive protonolysis of 17 with the AcOH that is also present in the reaction, or by adventitious water.

In conclusion, we have reported an unexpected mode of oxidative annulation in RhIII-catalyzed C–H functionalizations when 1,3-enynes containing allylic hydrogens cis to the alkynyl are present. The mechanism of these reactions is proposed to occur through double C–H activation, including that of a Csp2–H bond, involving a hitherto rare example of the 1,4-migration of a RhIII species. Of broader significance, the generation of an allyl–metal species from sequential C–H functionalization–1,4-metal migration opens up new opportunities in synthesis, and exploitation of this pathway in other transformations is underway in our laboratories.

Keywords: catalysis · C–H functionalization · enyne · oxidation · rhodium

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The best results were obtained using non-anhydrous dioxane. Other solvents such as toluene, tAmOH, EtOH, and DMF were inferior to dioxane. Bases such as K 2CO3, K 3PO4, or Et 3N, or additives such as Ag2SHF2 or Ag2CO3 had a detrimental effect.

The E/Z stereochemistries of products 11h and 11i were determined on the basis of nOe experiments. See the Supporting Information for details.

The structure of 13e was confirmed by X-ray crystallography. CCDC 1006281 contains 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.

The proposed concerted metalation–deprotonation mechanism for 1,4-RhIII migration contrasts with 1,4-RhI migration, which is generally considered to proceed by an oxidative addition–reductive elimination sequence. For example, see Refs. [11a] and [130].

The experiment in Equation (4) also demonstrates that C–H functionalization of the 4-nitrophenyl ring of 1g is irreversible in the presence of 2a. Exposure of 1g to the conditions shown in Equation (4) but in the absence of 2a led to partial deuterium incorporation (28% D) at theortho-positions of the 4-nitrophenyl ring, showing that C–H functionalization of 1g is reversible when the 1,3-enyne is not present. See the Supporting Information for details.