Rhodium-Catalyzed Activation of C(sp^3)−X (X = Cl, Br) Bond: An Intermolecular Halogen Exchange Case
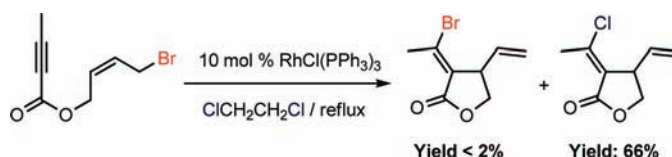
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ABSTRACT

A RhCl(PPh$_3$)$_3$-catalyzed halogen-exchange reaction between allyl and alkyl halides with β-H atoms was observed. The possible mechanism of the reaction involves oxidative addition and reductive elimination of the C(sp^3)−X bonds, which is not common in organometallic chemistry.

Oxidative addition and reductive elimination are fundamental organometallic reaction steps in a catalytic process.[1] Most transition-metal-catalyzed cross-coupling reactions involve oxidative addition of aryl or vinyl halides. However, oxidative addition of alkyl halides is challenging in coupling reactions due to the relatively low activity of alkyl halides and the facile β-hydride elimination of metal−alkyl intermediates.[2] Recently, Fu et al. have achieved a C(sp^3)−C(sp^3) coupling reaction by applying the sterically hindered and electron-rich trialkylphosphanes as ligands to inhibit the β-hydrogen elimination of metal−alkyl intermediates, and impressive results have been achieved.[3] Besides that, only a few examples of some specific reductive eliminations which were considered unfavorable in organometallic chemistry have been reported. For instance, reductive elimination of the alkyl−metal−alkyl bond from the high-valent transition metal complexes [Pt(PEt$_3$)$_2$(Ph)$_2$I$_2$][4] and [Rh(CO)(PPh$_3$)$_3$MeCl$_2$][5] was observed. A direct iodomethane

reductive elimination from a Rh(III) species was reported.[6] Hartwig and Vigalok reported the observation of reductive elimination of the aryl−metal−halide bond to form aryl halide compounds from an arylpalladium halide complex[7] and an arylplatinum halide complex,[8] respectively.

In this paper, we report several foundational processes in the transition-metal-catalyzed reaction: (1) oxidative addition of alkyl halides occurs through a possible radical chain

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reaction; (2) reductive elimination of an alkyl−Rh−halide and an allylic−Rh−halide bond.

Recently, we reported the cycloisomerization of 1,6-enynes catalyzed by Wilkinson's catalyst, in which an intramelocular halogen shift was observed.[9] During the course of further investigation of this reaction, we found that when we conducted the reaction with brominated 1,6-enyne substrate **1a** and RhCl(PPh₃)₃[10] in 1,2-dichloroethane, only a trace of desired product **2a** was isolated; instead, an intermolecular halogen exchange compound **2b** was isolated in reasonable yield (Scheme 1). Apparently, the chloro atom on **2b** comes from

Scheme 1. Cyclization of Brominated 1,6-Enyne Substrate
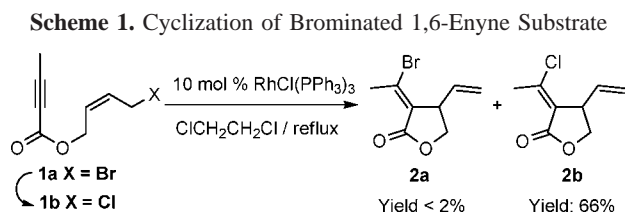
the solvent DCE. To explore whether the halogen exchange occurred prior to or after the cyclization reaction, we monitored the reaction with gas chromatography. The GC results showed that the substrate **1a** has been transformed to (Z)/(E)-**1b** before the cyclization step.[11] This implied that halogen exchange

occurred between allyl bromide and the solvent DCE prior to the cyclization. Further investigation showed that these types of halogen exchange between allyl and alkyl halides are quite common in the presence of Wilkinson's catalyst (Table 1).

Under these catalytic conditions, an allyl ester functional group could be tolerated (Table 1, entries 1 and 3). Halogen exchange of a *cis*-allylic halide occurred with partial isomerization to form *trans*-allylic product; however, no secondary halide was detected (Scheme 2).

Scheme 2. Halogen Exchange of *cis*-Allylic Halide
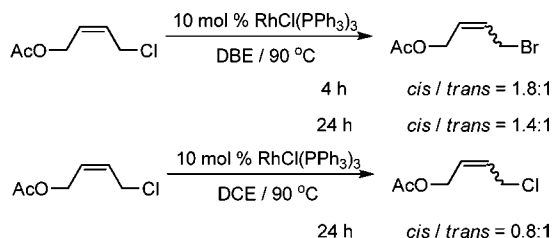
As far as Wilkinson's catalyst is concerned, the reaction can be rationalized by the mechanism illustrated in Scheme 3. First, oxidative addition of an alkyl bromide (the solvent)

Scheme 3. Possible Mechanism
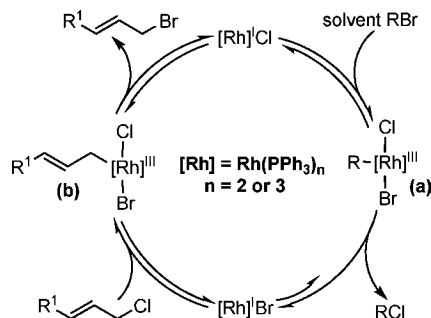
to RhCl(PPh₃)ₙ (n = 2 or 3) generates the intermediate **a**. Reductive elimination of **a** produces the key catalytic species RhBr(PPh₃)ₙ and the compound RCl. Oxidative addition of an allylic chloride to RhBr(PPh₃)ₙ affords intermediate **b**. Finally, reductive elimination of intermediate **b** results in an allylic bromide.

Table 1. Halogen Exchange between Allyl and Alkyl Halides[a]

entry	substrate	solvent[b]	product	yield (%)[c]
1		DCE		78
2	Ph	DCE	Ph	87
3	AcO	DCE	AcO	84
4	C₇H₁₅	DCE	C₇H₁₅	82
5		DCE		37[d]
6	C₇H₁₅	DBE	C₇H₁₅	78
7	Ph	DBE	Ph	72
8	Ph	*n*-BuBr	Ph	39

[a] All of the reactions were carried out with substrate (0.2 mmol) and RhCl(PPh₃)₃ (18.5 mg, 0.02 mmol) in 3 mL of a specified solvent within 6 h. [b] DBE: BrCH₂CH₂Br. DCE: ClCH₂CH₂Cl. [c] Isolated yield. [d] Conversion determined by GC−MS.

(7) (a) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2001**, *123*, 1232–1233. (b) Roy, A. H.; Hartwig, J. F. *J. Am. Chem. Soc.* **2003**, *125*, 13944–13945. (c) Roy, A. H.; Hartwig, J. F. *Organometallics* **2004**, *23*, 1533–1541.
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(10) The Wilkinson's catalyst was freshly prepared by the standard procedure; see the Supporting Information.
(11) For details, see the Supporting Information.

Although the activity of oxidative addition of a transition metal toward alkyl halides is usually lower than that toward allyl halides, the much larger concentration of alkyl halide makes the oxidative addition of alkyl halides favorable. In this proposed mechanism, reductive elimination of intermediate **a** is an irreversible process because of the much lower concentration of RCl compared to that of the solvent RBr. Therefore, the chloro atom was accumulated in the form of RCl. To confirm this hypothesis, we designed the following control experiments (Scheme 4). The reaction was carried
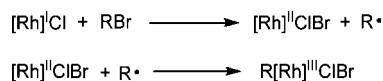
Scheme 4. Control Experiment[a]
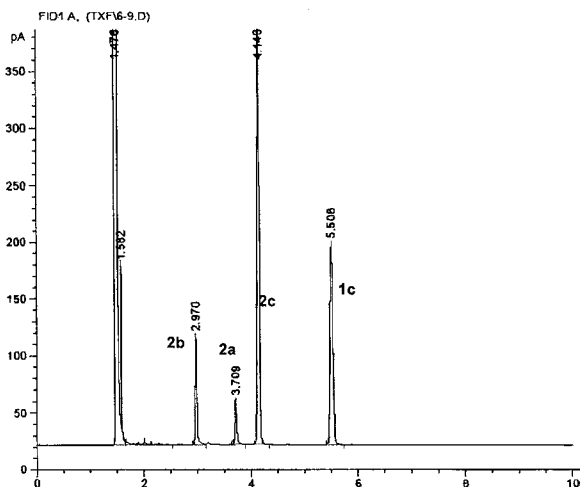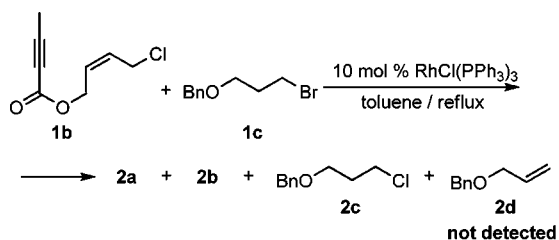
[a] The reaction was carried out with **1b** (0.2 mmol), **1c** (0.2 mmol), and RhCl(PPh$_3$)$_3$ (0.02 mmol) in toluene (3 mL).

out in toluene with **1b** and **1c** in the presence of Wilkinson's catalyst. When the molar ratio of **1b** and **1c** was 1:1, **2a** and **2b** were isolated in comparable yields with **2c** as the coproduct and partial unreacted **1c** (the GC result is shown in Scheme 4). Meanwhile, we have not detected **2d** in the reaction, which indicated that β-hydride elimination was suppressed with the catalyst system. Moreover, when the ratio of **1b** and **1c** was increased to 1:20, **2a** was the only product, and no **2b** was detected by GC.

In regard to the process of oxidative addition of alkyl halide in this mechanism, we proposed the mechanism of a radical chain reaction (Scheme 5).[12] The complex [Rh]^{I}Cl

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Scheme 5. Proposed Mechanism of Radical-Chain Reaction

can facilitate an electron transfer to an alkyl halide to form a radical pair ([Rh]^{II}ClBr + R$^•$). This pair can be collapsed to the oxidative adduct R[Rh]^{III}ClBr. Based on this proposed mechanism involving a radical-chain reaction, we envision that the cyclopropane of substrate **3** would progress C–C cleavage through radical cleavage induced by RhBr(PPh$_3$)$_3$ (Scheme 6). It is obvious that the radical

Scheme 6. Proposed Radical-Chain Reaction
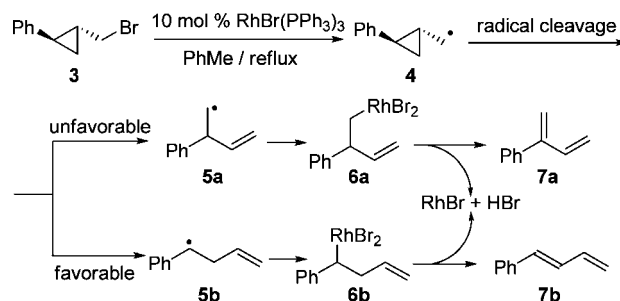
cleavage preferably forms the intermediate **5b**. Then, the oxidative adduct intermediate **6b** undergoes β-hydride elimination to give the diene product **7b**. The trivalent Rh complex RhHBr$_2$L$_n$ eliminates HBr to regenerate the catalyst RhBrL$_n$ (n = 2 or 3).[13] If oxidative addition does not involve radical chain reaction, oxidative addition of substrate **3** to RhBr(PPh$_3$)$_n$ and then β-carbon elimination would generate the intermediates **6a** and **6b** (Scheme 7).[14]

**Scheme 7.** Proposed Mechanism Involving Direct Oxidative Addition
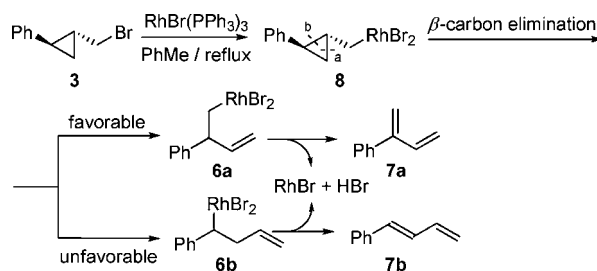
The cleavage of bond b in **8** is more unfavorable because of the steric repulsion between the phenyl on the cyclo-

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propane ring and the ligands of the catalyst.[15] Therefore, in this case, **7a** would be the main product.[16] It is noted that we only isolated **7b** in 22% yield and have not detected the diene **7a** during the course of reaction. The compound **3** can be recovered without RhBr(PPh$_3$)$_3$ under reflux in toluene. In addition, we have observed a substantial decrease of conversion in the transformation of **9a** to **9b** when we added the radical scanvenger 4-hydroxy-TEMPO to the reaction system (Scheme 8, eq

Scheme 8. Experiments with 4-Hydroxy-TEMPO and ^{i}PrOH as Additives
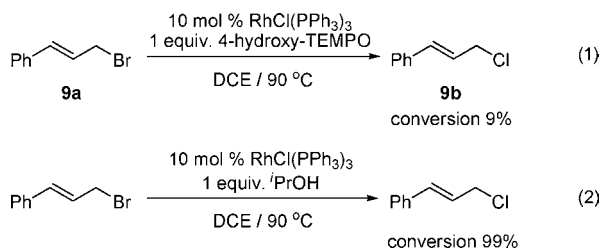
1).[17] To explore whether the coordinating ability of the hydroxyl group on 4-hydroxy-TEMPO may influence the

catalyst efficiency, we have also performed a control experiment (Scheme 8, eq 2). The result showed that the employment of ^{i}PrOH as additive could achieve high yield under the same reaction conditions. On the basis of this consideration and the experimental results above, we prefer the proposed mechanism involving a radical chain reaction.

In conclusion, we have found a RhCl(PPh$_3$)$_3$-catalyzed halogen-exchange reaction between allyl and alkyl halide with β-H atoms. Further studies on the scope and applications of the reaction are ongoing in our laboratory and will be reported in due course.

Supporting Information Available: Experimental procedures along with copies of spectra. This material is available free of charge via the Internet at http://pubs.acs.org.

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(16) Since intermediate **6b** is more stable because the Rh center is at the more stabilized benzylic position, we envisioned both **7a** and **7b** could be detected in the mechanism without radical chain reaction.

(17) We presumed the chloro atom on **9b** may come from the catalyst.