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Conjugated Diene-Assisted Allylic C−H Bond Activation: Cationic Rh(I)-Catalyzed Syntheses of Polysubstituted Tetrahydropyrroles, Tetrahydrofurans, and Cyclopentanes from Ene-2-Dienes

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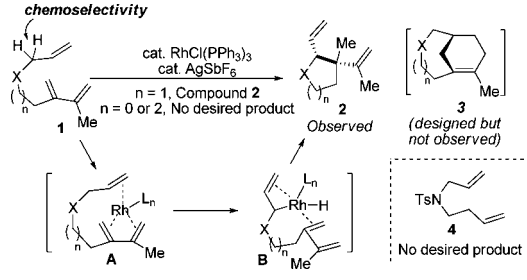
Selective C−H functionalization represents one of the most efficient and straightforward methods for accessing complex molecules from ubiquitous C−H groups.[1] Among various C−H activation/C−C bond-forming reactions, the addition of C−H bonds across multiple bonds such as alkenes and alkynes is particularly appealing in light of atom- and step-economy considerations.[2] In comparison with the addition of aromatic C−H bonds to multiple bonds, the addition of aliphatic C−H bonds to multiple bonds is more challenging because of the inertness of aliphatic C−H bonds and problems with site selectivity. Thus, many efforts have been directed to the activation of C−H bonds adjacent to heteroatoms or double bonds.[3] However, only limited examples of catalytic additions of allylic C−H bonds to alkynes and allenes have been reported.[4−6] In particular, catalytic addition of allylic C−H bonds to alkenes has not been forthcoming.

There are several reasons that may account for this lack of reactivity. First, the addition of allylic C−H bonds to alkenes requires preferential activation of an allylic C−H bond in the presence of several similar ones (the chemoselectivity challenge).[7] Second, the addition of allylic C−H bonds to alkynes and allenes forms $C(sp^2)-C(sp^3)$ bonds via easier reductive elimination, whereas the addition of allylic C−H bonds to alkenes involves a more difficult reductive elimination step to form $C(sp^3)-C(sp^3)$ bonds (the reactivity challenge).[8] Moreover, this reaction might be further challenged by issues of diastereoselectivity. Herein, we report a new strategy to meet these challenges by employing conjugated diene-assisted allylic C−H activation and the addition of the generated allyl−Rh−H complex to the alkene moiety of the conjugated diene (Scheme 1).

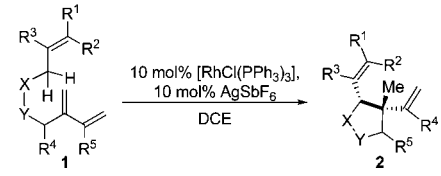
Scheme 1. Conjugated Diene-Assisted Rh(I)-Catalyzed Allylic C−H Addition to Alkenes

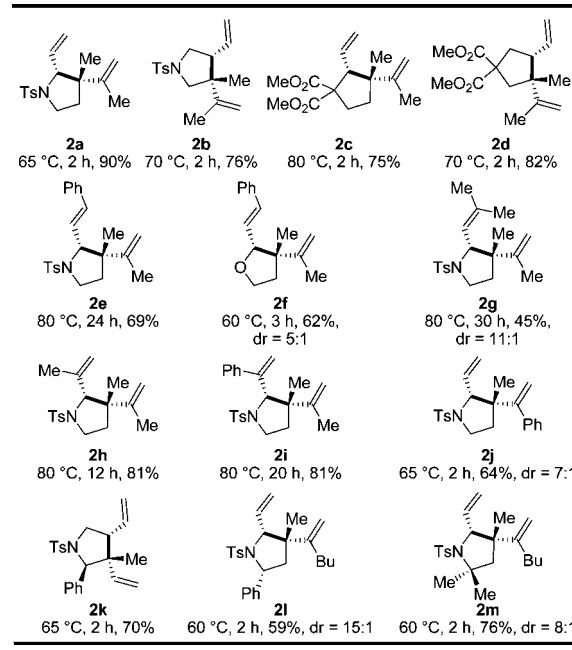


We discovered this reaction serendipitously during our attempts to develop a Rh-catalyzed intramolecular type-II Diels−Alder (D−A) reaction (Scheme 1).[9] The reaction of nitrogen-tethered ene-2-diene substrate **1a** (Table 1) in the presence of a Rh(I) catalyst (generated from $RhCl(PPh_3)_3$ and $AgSbF_6$) underwent cyclization to form substituted tetrahydropyrrole **2a**[10] rather than the [4 + 2] product **3**. We propose that intermediate **A**, a Rh complex coordinated by both diene and ene, is generated in this reaction. However, because of the ring strain associated with the alkene-insertion transition state, which would lead to the type-II [4 + 2] reaction pathway, complex **A** prefers an allylic C−H activation pathway to generate allyl−Rh−H complex **B**, which, after alkene insertion and reductive elimination, affords product **2** exclusively (Scheme 1). Highly chemoselective C−H activation was achieved in this reaction, as only the allylic C−H bond of the ene component was activated. Good diastereoselectivity was observed, as only one diastereoisomer with both vinyl groups in a cis configuration was obtained. The importance of the diene in this C−H activation/alkene insertion reaction was demonstrated by the lack of reactivity showed by ene−ene substrate **4** lacking the diene moiety (Scheme 1). We also found that substrates with different tether lengths failed to give the desired products (Scheme 1, X = NTs, $n = 0$ or 2), implying that there are likely to be geometric and conformational requirements in this diene-assisted allylic C−H bond activation/alkene insertion process.

Since the above allylic C−H activation/diene interception reaction can generate five-membered rings with two vinyl substit-

Table 1. Rh(I)-Catalyzed Cycloaddition via C−H Activation





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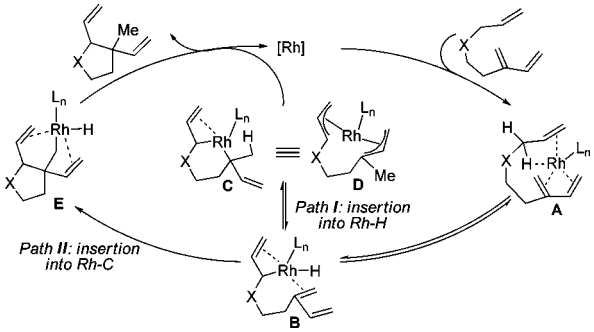
uents and a quaternary carbon center with high chemo- and diastereoselectivity, we set out to explore the substrate scope (Table 1). Importantly, the allylic C−H activation was not limited to allylic substrates with the C−H bond adjacent to a nitrogen atom. Cyclization of simple allylic substrates **1b**−**d** proceeded quite well to give **2b**−**d** as single diastereoisomers. Besides nitrogen-tethered substrates, carbon- and oxygen-tethered substrates also reacted well, generating useful cyclopentane (**2c** and **2d**) and tetrahydrofuran (**2f**) structures in good yields. C−H activation was not limited to terminal alkenes, as demonstrated by the successful reactions of the phenyl- and dimethyl-substituted alkene substrates **2e**−**g**. Substituents at the internal position of the alkene did not affect the efficiency (**2h** and **2i**). The present reaction also tolerated substituent variation at the conjugated diene moiety, as substrates with phenyl, hydrogen, and butyl at the R^4 position underwent smooth cyclization to give **2j**−**l**, respectively. Substitution at the allylic and homoallylic positions of the diene was also tolerated, affording heavily substituted tetrahydropyrrole derivatives (**2k**−**m**) in good yields and diastereoselectivities. However, substrates substituted at the allylic position of the ene part failed to undergo cyclization even at elevated temperature (for details, see the Supporting Information).

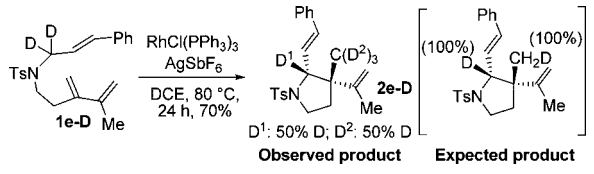
Two possible paths for the above reaction were considered (Scheme 2). The reaction is initiated by coordination of the substrate to Rh to give complex **A**, which then undergoes conjugated diene-assisted oxidative addition to the allylic C−H bond to give intermediate **B**. Subsequent alkene insertion into the Rh−H bond would give complex **C** or **D**, which would then undergo a challenging reductive elimination to form the $C(sp^3)-C(sp^3)$ bond in the final product (path **I**). Alternatively, intermediate **B** could undergo alkene insertion into the Rh−C bond to give Rh−H intermediate **E**, which would deliver the final product via reductive elimination (path **II**).[4a,c,d]

Preliminary studies to elucidate the reaction mechanism were performed. The allylic deuterium-labeled substrate **1e-D** was subjected to the reaction conditions (Scheme 3). Analysis of the product revealed that more than one deuterium was incorporated into the newly formed methyl group and that the tertiary carbon in **2e-D** was only 50% deuterated, suggesting that there is hydrogen/deuterium exchange between the forming methyl group and the deuterium-labeled methylene group in the substrate during the reaction process. This observation precludes path **II**, while path **I** is reasonable if reversible allylic C−H activation and alkene insertion are taken into consideration. This means that β-hydride elimination and reductive elimination from **C**/**D** to **B** and then to **A** can shift the original hydrogen atoms of the internal alkene to the allylic position. After equilibrium, the percentages of deuterium incorporation at both D^1 and D^2 reach 50%. This D-labeling experiment suggests that the irreversible $C(sp^3)-C(sp^3)$ reductive elimination rather than the C−H activation is the rate-determining step in the present reaction.[2c,11]

Scheme 2. Two Proposed Reaction Paths



Scheme 3. Deuteration Reaction



In conclusion, we have successfully demonstrated the first example of conjugated diene-assisted transition-metal-catalyzed activation of an allylic C−H bond and its addition to the alkene of the conjugated diene moiety in ene-2-diene substrates. This reaction generates multisubstituted tetrahydropyrroles, tetrahydrofurans, and cyclopentanes bearing quaternary carbon centers with high chemo- and diastereoselectivity. A reversible allylic C−H activation/alkene insertion prior to an irreversible C−C reductive elimination step has been proposed on the basis of the results of the D-labeling experiment. Further exploration of the mechanism and the application of this new methodology are currently underway.

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Supporting Information Available: Detailed experimental procedures, compound characterization data, and crystallographic data for **2h** (CIF). This material is available free of charge via the Internet at http://pubs.acs.org.

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