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Published on Web 10/28/2010

Dienyl Homoallyl Alcohols via Palladium Catalyzed Ene-Type Reaction of Aldehydes with 1,3-Dienes

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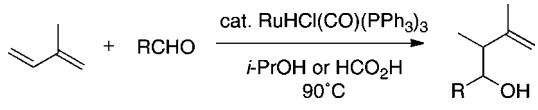
Abstract: The combination of Pd catalyst and Xantphos ligand in the presence of Et_3B nicely promotes the allylation of aldehydes with conjugated dienes to provide dienyl homoallyl alcohols in excellent yields. The reaction occurs selectively at the C−C double bond bearing higher electron density.

The carbonyl ene reaction is one of the most powerful tools in the fundamental C−C bond formation. In general, activated carbonyls, such as arylglyoxals and glyoxylates, are effectively utilized for the ene reactions.[1] Although dienyl alcohols are among the most important components in the synthesis of terpenoids, insect pheromones, physiologically active molecules, and other natural products,[2] it is extremely difficult to use conjugated dienes as the dienyl alcohol fragment for carbonyl ene reactions due to complicated side reactions, *e.g.*, Diels−Alder reaction and oligomerization.[3]

As attractive strategies for C−C bond formations involving conjugated dienes, transition-metal-catalyzed reductive coupling reactions of dienes and carbonyls have been developed.[4] For instance, under hydrogenation and hydrogen autotransfer conditions, Ru-catalyzed regioselective formation of branched homoallylic alcohols by allylation of carbonyls with diene was achieved by M. J. Krische et al. (Scheme 1).[5] Furthermore, we have previously developed the homoallylation of aldehydes with conjugated dienes in the presence of Et_3B to provide bishomoallyl alcohols via a Ni(0) catalyst (Scheme 2).[6] Under similar conditions, Rh(I) catalyzed the allylation of aldehydes with dienes to afford homoallyl alcohols with excellent regio- and stereoselectivities.[7] Et_3B serves not only as a Lewis acid but also as a reducing agent to accomplish the reductive coupling reaction of the diene and carbonyls through the allylmetal species. Thus, the linear regioselectivity observed in the Ni catalytic system is in sharp contrast to the branched regioselectivity promoted by Rh and Ru catalytic systems. Herein, we report that a system of a Pd catalyst with Et_3B nicely promotes the ene-type reaction of carbonyls with conjugated dienes to afford dienyl homoallyl alcohols as an efficient C−C bond transformation.

The coupling reaction of isoprene with PhCHO was conducted in the presence of a Pd catalyst and phosphine ligand, as shown in Table 1. In the absence of both Et_3B and a phosphine ligand, no reaction occurred. Although a monophosphine ligand was not effective (entry 2, Table 1), bidentate phosphine ligands, such as dppf, DPEphos, and BINAP, had marginal success in the formation of the coupling product **1a** (entries 3−5, Table 1). Xantphos, which has been effectively used for transition-metal-catalyzed cross-coupling reactions and aminations,[8] was the most appropriate phosphine ligand in the present reaction quantitatively giving rise to the desired alcohol **1a** (entry 6, Table 1). Other organoboranes, such as Ph_3B and *n*-Bu_3B, yielded an intractable mixture of products contrary to the result of Et_3B (entries 8 and 9, Table 1). Although Et_2Zn also served as a promoter of the reaction, **1a** was obtained in an unsatisfactory yield (entry 10, Table 1).

Scheme 1. Ru-Catalyzed C−C Coupling Reaction Employing Diene via Transfer Hydrogenation



Scheme 2. Reductive Coupling Reaction of Diene and Aldehydes by Ni and Rh Catalysts in the Presence of Et_3B

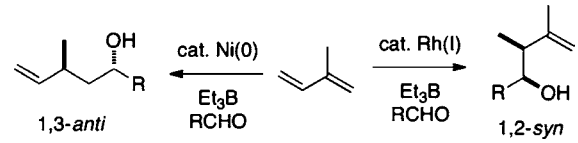
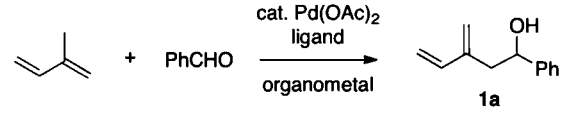


Table 1. Pd/Xantphos Promoted Allylation of PhCHO with Isoprene[a]



Entry	Ligand	Organometal	Time (h)	Yield of **1a** (%)
1	none	Et_3B	21	0
2	PPh_3	Et_3B	24	0
3	dppf	Et_3B	30	16
4	DPEphos	Et_3B	48	33
5	BINAP	Et_3B	41	64
6	Xantphos	Et_3B	24	99
7	Xantphos	none	72	complex mixture
8	Xantphos	Ph_3B	72	complex mixture
9	Xantphos	*n*-Bu_3B	72	complex mixture
10	Xantphos	Et_2Zn	48	24

[a] The reaction was undertaken in the presence of isoprene (4 mmol), benzaldehyde (1 mmol), $Pd(OAc)_2$ (10 mol %), ligand (10 mol %), and organometal (2 mmol) at room temperature under a nitrogen atmosphere.

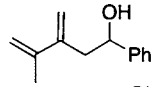
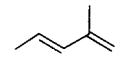
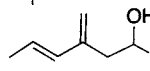
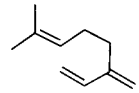
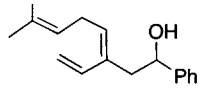
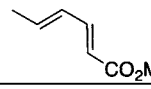
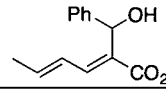
The coupling reaction of various types of conjugated dienes with PhCHO was examined under the optimized Pd/Xantphos system. The results are shown in Table 2.[9] 2,3-Dimethyl-1,3-butadiene underwent the coupling reaction to provide dienyl alcohol **1b** in high yield (entry 1, Table 2). 1,3-Dimethyl-1,3-butadiene reacted with PhCHO at the less substituted C=C double bond terminus to give dienyl alcohol **1c** exclusively (entry 2, Table 2). Myrcene reacted with the aldehyde at the C1 position to give the trienyl alcohol **1d** in a 3:1 ratio with respect to the internal olefin geometry (entry 3, Table 2). Methyl sorbate underwent the C−C bond

10.1021/ja1072417

formation at the α-position to provide (2*E*,4*E*)-hexadiene **1e** as a single isomer (entry 4, Table 2). The present reaction is more efficient and provides an alternative method for formation of stereodefined *β*-branched Baylis−Hillman adducts in comparison to the DABCO/DMSO protocol.[10] It is of profound interest that the present reaction is distinct from the homoallylation promoted by the Ni/Et_3B system but nevertheless is similarly easy to perform.[6a]

A wide structural variety of aldehydes was examined next, as summarized in Table 3. For aromatic aldehydes with an electron-donating group or a halogen, the C−C bond formation reaction proceeded smoothly to afford the dienyl alcohols in good to quantitative yields (entries 1 and 2, Table 3). Aliphatic aldehydes participated in the reaction to give the corresponding dienyl alcohols in reasonable yields (entries 3−5, Table 3). Encouraged by the compatibility of homoallylation of hemiacetals with Et_3B or in the presence of water,[6d] we conducted the reaction with five- and six-membered lactols, which resulted in the formation of the desired homoallyl alcohols (entries 6 and 7, Table 3).

Table 2. Pd/Xantphos Promoted Allylation of PhCHO with Diene[a]

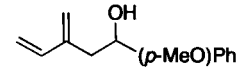
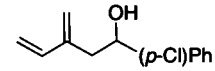
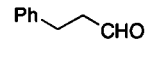
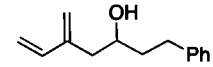
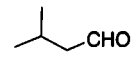
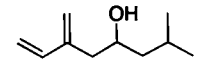
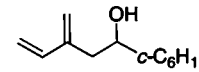
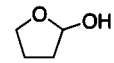
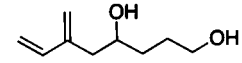
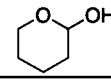
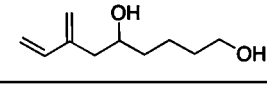
Entry	Diene	Time (h)	Product Yield (%)[ratio]
1		65	 **1b**: 85
2		72	 **1c**: 70
3		65	 **1d**: 61 [3:1]
4		68	 **1e**: 80 [single]

[a] The reaction was undertaken in the presence of diene (4 mmol), benzaldehyde (1 mmol), $Pd(OAc)_2$ (10 mol %), Xantphos (10 mol %), and triethylborane (2 mmol) at room temperature under a nitrogen atmosphere.

At this moment, although it is premature to give rationale behind these reactivities, a preliminary reaction mechanism for the coupling reaction of isoprene with benzaldehyde might be proposed, as shown in Scheme 3. The Pd/Xantphos complex activates isoprene to enhance its nucleophilicity. Reaction with the aldehyde, promoted by Et_3B as a Lewis acid, forms an oxapalladacyclopentane intermediate.[11] Next, an ethyl group is transferred from Et_3B to the allylpalladium species. Bidentate phosphine ligands with a very large bite angle tend to form *trans* complexes, which are reluctant to undergo reductive elimination.[12] Therefore, subsequent *β*-hydride elimination of allylethylpalladium to give the dienyl homoallyl alcohol predominates over the reductive elimination and is accompanied with the formation of the more stable Xantphos/Pd complex as the key catalytic species.[13]

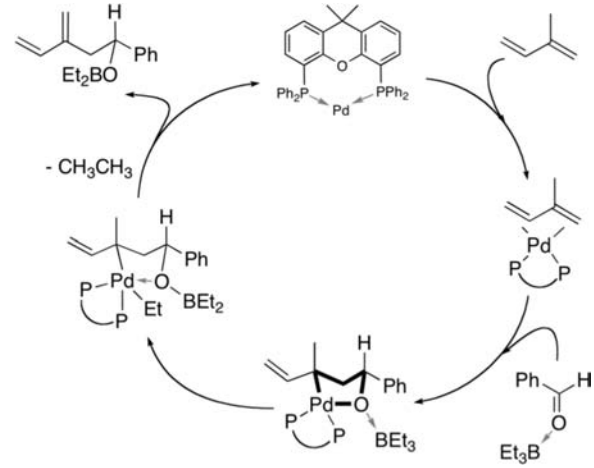
In summary, we have developed a Pd/Xantphos/Et_3B system that promotes the coupling reaction of aldehydes and conjugated dienes to afford dienyl homoallyl alcohols. The applicability and scope of this method for the efficient preparation of physiologically active molecules such as terpenoids and aymmetric ene-type reactions are currently under investigation in our laboratory.

Table 3. Pd/Xantphos Promoted Allylation of Aldehyde with Isoprene

Entry	Aldehyde	Time (h)	Product, Yield (%)
1	(*p*-MeO)PhCHO	24	 **1f**: 66
2	(*p*-Cl)PhCHO	24	 **1g**: 98
3		48	 **1h**: 64
4		69	 **1i**: 52
5	*c*-C_6H_{11}CHO	48	 **1j**: 53
6		72	 **1k**: 60
7		72	 **1l**: 50

[a] The reaction was undertaken in the presence of diene (4 mmol), benzaldehyde (1 mmol), $Pd(OAc)_2$ (10 mol %), Xantphos (10 mol %), and triethylborane (2 mmol) at room temperature under a nitrogen atmosphere.

Scheme 3. A Plausible Reaction Mechanism



Acknowledgment. Financial support from the Ministry of Education, Culture, Sports, Science, and Technology, Japanese Government (Grant-in Aid for Scientific Research (B) 21350055) is gratefully acknowledged. This work was supported by the Asahi Glass Foundation.

Supporting Information Available: Experiment procedure and NMR spectra for all products. This material is available free of charge via the Internet at http://pubs.acs.org.

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(9) 1,3-Pentadiene was not adequate for the reaction, and an intractable mixture was obtained.

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(11) When 1-hexene or α-methylstyrene was used in place of conjugated diene under similar conditions, no reaction took place at all. These results rule out the present reaction proceeds via the typical carbonyl ene reaction mechanism.

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(13) Stereoselective formation of (2*E*,4*E*)-**1e** might be executed by *endo* β-hydride elimination of *anti*-4-methoxycarbonyl-3-phenyl-2-oxapalladacyclopentane, which is prepared from a mixture of Pd/Xantphos, methyl sorbate, and benzaldehyde (entry 4 in Table 2).

JA1072417