Discussion Addendum for:
Nickel-catalyzed Homoallylation of Aldehydes with 1,3-Dienes

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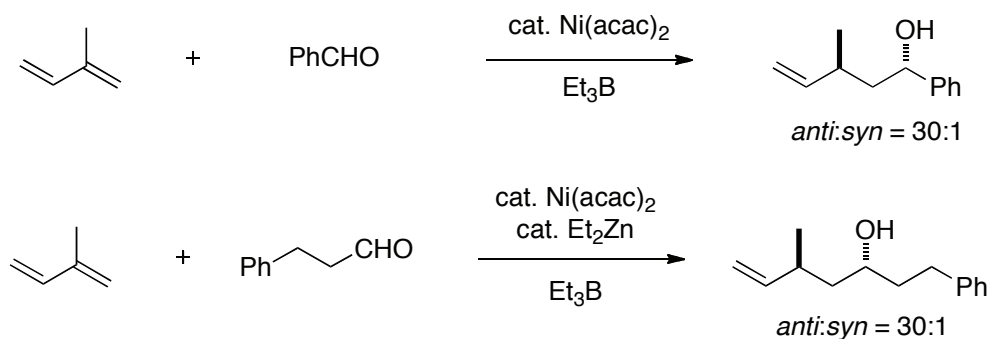
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Original article: Tamaru, Y.; Kimura, M. *Org. Synth.* **2006**, *83*, 88.

Reductive coupling reactions are among the most useful strategies for the efficient synthesis of complicated molecules and physiologically active molecules.[2] We reported for the first time that Ni-catalysts are able to promote the homoallylation of aldehydes with a wide variety of 1,3-dienes in the presence of triethylborane or diethylzinc to yield bishomoallyl alcohols with excellent regio- and stereoselectivities.[3] Based on these procedures, the scope of reductive coupling reactions have been significantly expanded in recent years. Herein, the scope of the homoallylation of aldehydes and ketones with conjugated dienes, asymmetric homoallylations of carbonyls, synthesis of natural products involving Ni-catalyzed reductive coupling, and bis-metallic homoallylations are summarized.

Scope of Homoallylation of Carbonyls with Various Conjugated Dienes

The results of the Ni-catalyzed homoallylation of benzaldehyde with conjugated dienes bearing electron-donating substituents, such as siloxy and alkoxy groups, were described (Table 1).[4] C1- and C2-siloxy-1,3-butadienes reacted with benzaldehyde highly regio- and stereoselectively and furnished homoallyation products as a single isomer in good to excellent yields. A siloxy group surpasses a methyl group in regiocontrolling effect; a substituted 1,3-butadiene possessing a siloxy group at C2 and a methyl

group at C3 reacted with benzaldehyde via the C1 carbon atom to afford 4-methyl-3-siloxy-4-penten-1-ol exclusively (entry 2, Table 1). While a C2-siloxy group enhanced the reactivity of butadiene at the C1 position, a C1-siloxy group induced reactivity at the C4 position exclusively (entries 3-5, Table 1). The present homoallylation with siloxy and methoxy-substituted butadienes is of great synthetic value as synthetic equivalents of functionalized butenyl carbanion and not as silyl enol ethers.

Table 1. Ni-Catalyzed Homoallylation of Aldehydes with Conjugated Diene

entry	diene	product (% yield) [1,3-*anti* :1,3-*syn*]	
1	OTIPS	TIPSO OH Ph	(65%) [>30:1]
2	OTIPS	TIPSO OH Ph	(84%) [>30:1]
3	Ph OTIPS	Ph TIPSO OH Ph	(81%) [>30:1]
4	TIPSO	TIPSO OH Ph	(92%)
5	TIPSO	TIPSO OH Ph	(92%) [>30:1]
6	MeO OSiMe₃	MeO Me₃SiO OH Ph	(69%) [>30:1]

Cyclohexadiene failed to react with benzaldehyde using the Ni/Et$_3$B system, whereas the Ni/Et$_2$Zn system accelerated the reaction (Figure 1). However, the major product was *syn*-1-(2-cyclohexenyl)-1-phenylmethanol, which was obtained by nucleophilic allylation of benzaldehyde with 2-cyclohexenyl benzoate through umpolung of π-allylpalladium.[5]
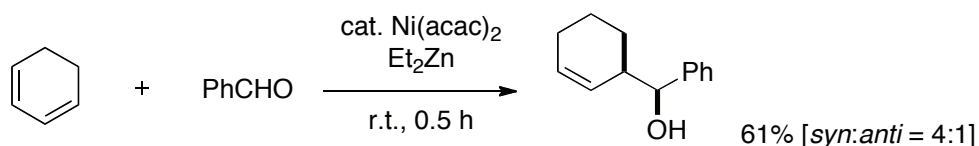

Figure 1. Ni-Catalyzed Allylation of PhCHO with 1,3-Cyclohexadiene

Asymmetric reductive coupling of dienes and aldehydes was also reported. When Ni-catalyzed homoallylation of aldehydes with 1,3-dienes was performed with bulky spirobiindane phosphoramidite ligands and diethylzinc as a reducing agent, chiral bishomoallyl alcohols were produced in high yields with excellent diastereoselectivities and enantioselectivities (Figure 2).[6]
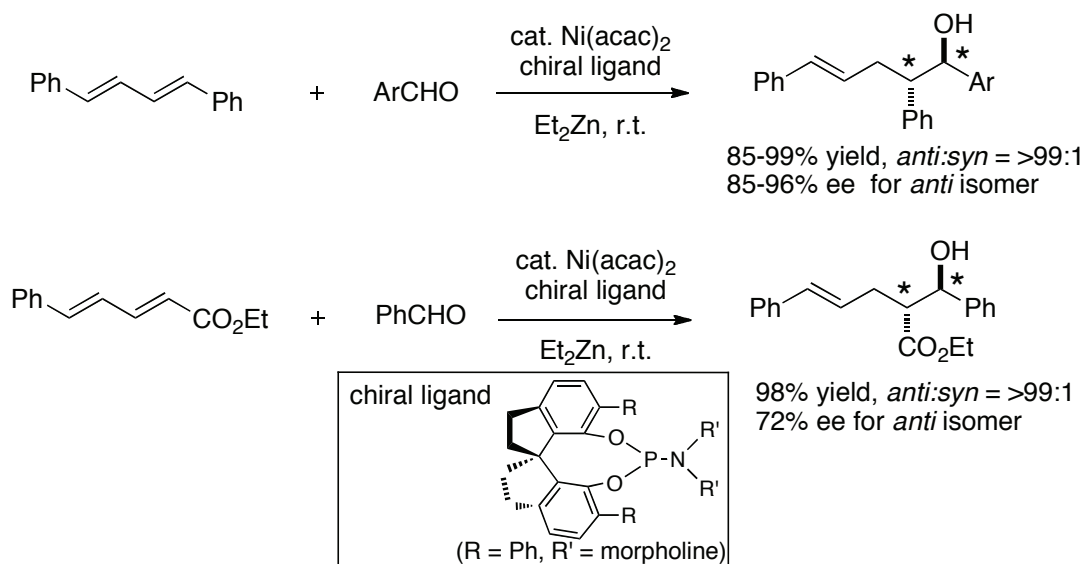

Figure 2. Asymmetric Ni-Catalyzed Homoallylation of Aldehydes
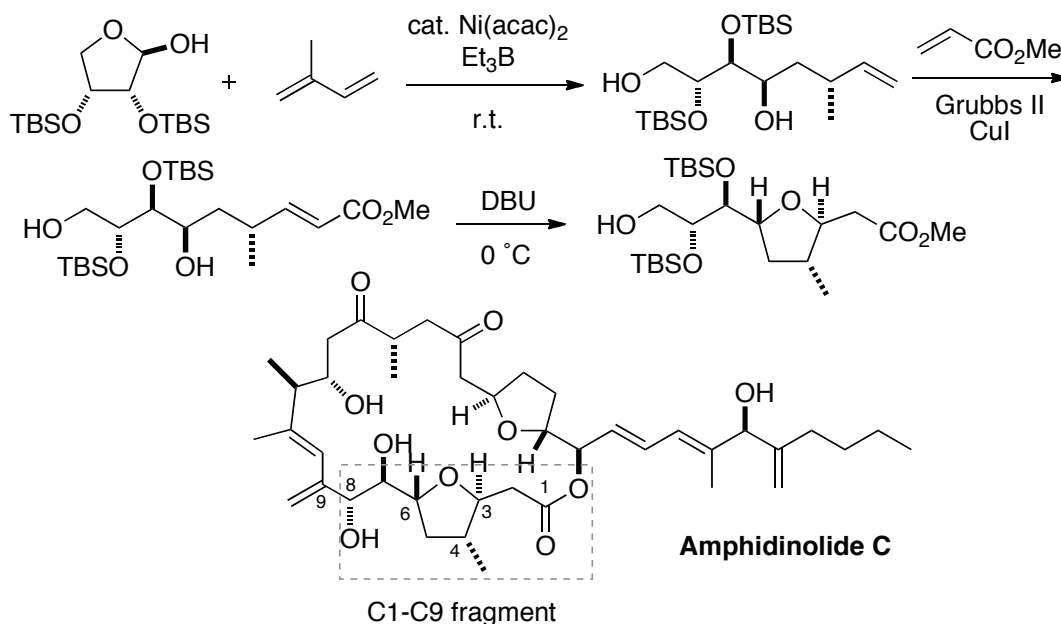

Figure 3. Formal Synthesis of C1-C9 Fragment of Amphidinolide C

Ni-catalyzed homoallylation of aldehydes with isoprene served as an important synthetic strategy for the construction of the tetrahydrofuran fragment from amphidinolide C (Figure 3).[7] Homoallylation of erythrolactol followed by cross metathesis of the hydroxyl alkene with methyl acrylate afforded ω-hydroxy α,β-unsaturated esters, which underwent cyclization upon treatment with DBU to produce tetrahydrofurans with the correct relative configuration for the C1-C9 fragment of amphidinolide C.

Bismetallative Homoallylation of Aldehydes with Dienes

Nickel-catalyzed borylative coupling reactions of diene and aldehyde were studied. In the presence of Ni catalyst, phosphine ligand, and bis(pinacolato)diboron, benzaldehyde reacted with 1,3-dienes, followed by oxidative hydrolysis with hydrogen peroxide, to provide 4-pentene-1,3-diols and 2-pentene-1,5-diols (Figure 4).[8] In this case, bis(pinacolato)diboron participated in the σ-bond metathesis providing access to allyl boronic esters. Their selectivity depends on the kind of phosphine ligands. Homoallylation products were observed exclusively using the P(SiMe₃)₃ ligand, whereas P(t-Bu)₃ provided allylation products. This borylative carbonyl-diene coupling reaction could be extended to the reaction of ketones, which afforded bis-homoallyl alcohols using Ni(cod)₂/P(t-Bu)₃ as catalyst, in contrast to the allylation product obtained with aldehydes.
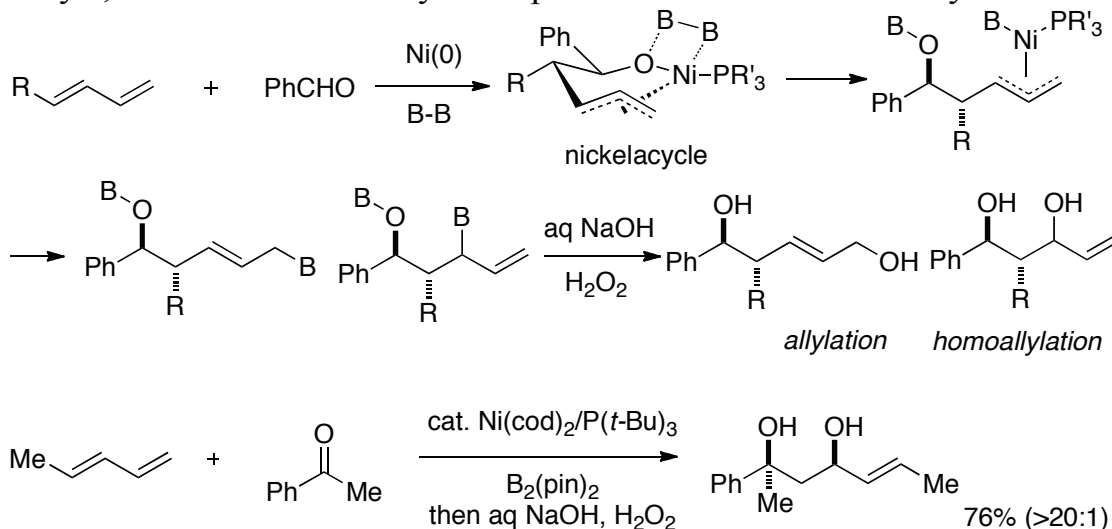

Figure 4. Borylative Coupling Reaction of Diene and Carbonyls

Ni-catalyzed silylborative coupling reactions with aldehydes and 1,3-dienes gave the corresponding bishomoallyl alcohols having an allylsilane

unit in the side chain (Figure 5).[9] This procedure was applied to the synthetic approach to optically active α-chiral allylsilane derivatives.
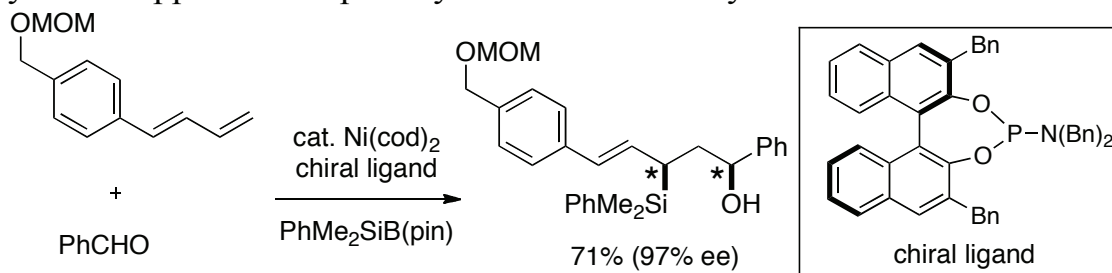

Figure 5. Borylative Coupling Reaction of Diene and Carbonyls

Transition Metal Catalyzed Coupling Reaction of Aldehydes with Dienes Promoted by Triethylborane

Transition metal catalyzed C-C bond formations involving conjugated dienes and carbonyls have been developed. When a mixture of 1,3-diene and aldehyde is used in the presence of triethylborane, the reaction changes dramatically depending on the kind of transition metal catalysts. Rh(I) catalysts promote the reductive coupling reaction of a wide variety of aldehydes with conjugated dienes in the presence of a stoichiometric amount of triethylborane to provide homoallyl alcohols in good yields (Figure 6).[10] Isoprene reacts with benzaldehyde at the C3- and C2-positions to give a regioisomeric mixture of 3-butenyl alcohols in a 6:1 ratio. Methyl sorbate reacts with aldehydes at the α-carbon position with excellent stereoselectivity producing the (Z)-3-hexen-1-ol framework as a single isomer. The similar coupling reactions of 1,3-dienes and aldehydes were observed by employment of Ru and Ir catalysts using isopropyl alcohol and formic acid as reducing agents (Figure 7).[11]
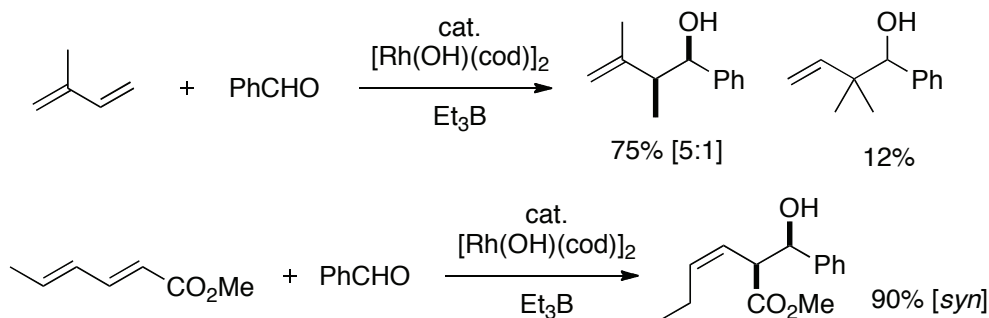

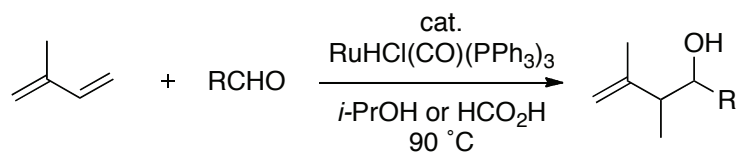**Figure 6.** Rh(I) Catalyzed Reductive Coupling of Aldehydes and Dienes

Figure 7. Ru-Catalyzed Reductive Coupling of Aldehydes and Dienes

A combination of Pd-catalyst/Xantphos and triethylborane promoted the ene-type reaction of aldehydes and conjugated dienes to afford dienyl homoallyl alcohols in excellent yields (Figure 8).[12] Methyl sorbate underwent formal Baylis-Hillman type C-C bond formation at the α-position to provide (2E,4E)-hexadien-1-ol with excellent stereoselectivity.
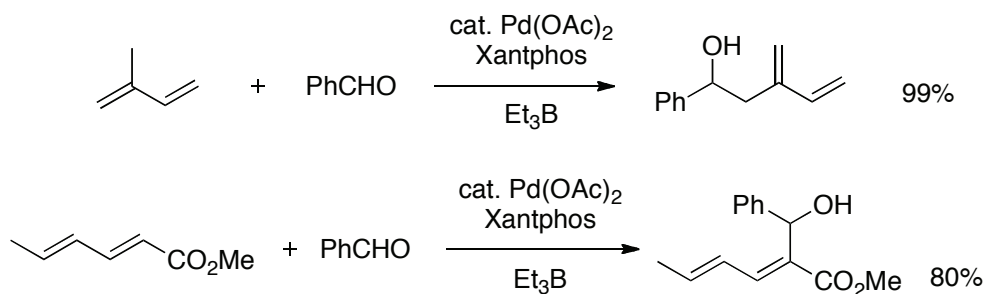

Figure 8. Pd/Xantphos Promoted Coupling Reaction of Aldehydes and Conjugated Dienes Promoted by Triethylborane

Thus, the combination of transition metal catalyst and triethylborane nicely promoted the coupling reaction of carbonyls and conjugated dienes to furnish the stereodefined bishomoallyl and homoallyl alcohols. The reductive coupling reactions offer great efficiency and a useful strategy for the synthesis of important physiologically active molecules, such as terpene alcohols and macrolides.

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Masanari Kimura was born in Nagasaki, Japan on 29 May 1967. He obtained his Ph.D. in 1995 under the direction of Professor Yoshinao Tamaru (Nagasaki University). He was Research Fellow of the Japan Society for the Promotion of Science in 1992-1995. He joined the faculty of Nagasaki University as assistant in 1995. He was a postdoctoral fellow MIT (S. L. Buchwald) in 1999-2000. He was promoted to associate professor in 2008, and to full professor in 2010. His current research interest includes the development of new reactions based on transition metals and heterocyclic chemistry.