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Ni-Catalyzed Three-component Coupling Reaction of Conjugated Enyne, Carbonyls, and Dimethylzinc to Construct Allenyl Alcohols

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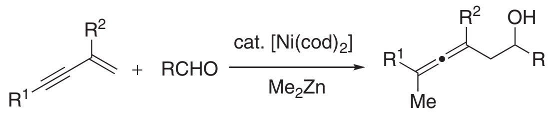
Nickel catalyzes the three-component coupling reaction of dimethylzinc, enyne, and carbonyls to provide tetrasubstituted allenyl alcohols. Diethylzinc and diphenylzinc can participate in similar coupling reactions to provide the corresponding allenyl alcohols in reasonable yields.

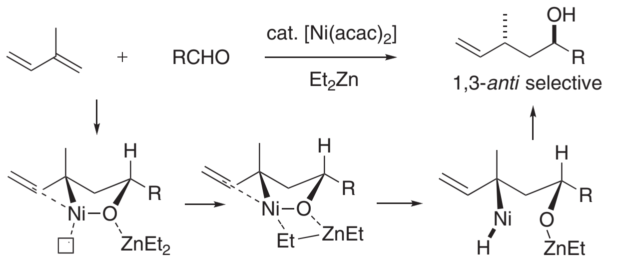
Multicomponent coupling reactions can be utilized as efficient synthetic strategies for versatile C–C bond transformations in a single manipulation.[1] However, in general, it is very difficult to control the regio- and stereoselectivities in multistep reactions. We have developed the highly regio- and stereoselective Ni-catalyzed reductive coupling reactions of carbonyls and dienes involving triethylborane and diethylzinc through an oxanickelacycle intermediate to afford bishomoallyl(4-pentenyl) alcohols (Scheme 1).[2] In this case, triethylborane and diethylzinc could serve as reducing agents as well as Lewis acids for the stereocontrolled homoallylation reactions. When isoprene was used as the diene, the reductive coupling proceeded with high regio- and stereoselectivities and the bishomoallyl alcohols were produced as the sole product with exclusive 1,3-*anti* stereoselectivity.

When dimethylzinc was employed in place of diethylzinc, the reaction features changed. Ni catalyst accelerated the three-component coupling reaction of aldehydes, conjugated dienes, and dimethylzinc in a 1:1:1 ratio to provide homoallylic alcohols (Scheme 2).[3] In this case, oxidative cyclization of the conjugated diene and aldehyde proceeded smoothly to form an oxanickelacycle intermediate followed by σ-bond metathesis with dimethylzinc to form the allylmethylnickel species. Methyl group transfer from the Ni metal center to the allylic termini led to the homoallyl alcohols via 1,4-addition.

Herein, we would like to disclose that Ni(0) catalyzes the three-component coupling reaction of dimethylzinc, conjugated enynes, and aldehydes to provide tetrasubstituted allenyl alcohols in good to reasonable yields with high regio- and stereoselectivities (eq 1).



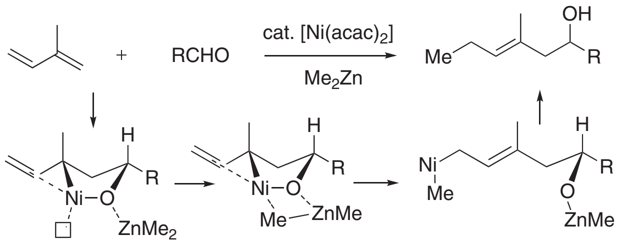
(1)



Scheme 1. Ni-Catalyzed homoallylation of aldehyde with conjugated diene promoted by diethylzinc.

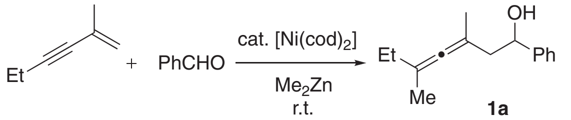
The reaction was conducted by exposing dimethylzinc to a THF solution of a mixture of a conjugated enyne and aldehyde in the presence of [Ni(cod)$_2$] catalyst under nitrogen atmosphere. The results using 2-methyl-1-hexen-3-yne and PhCHO are summarized in Table 1.[4]

After investigating various amounts of enyne and dimethylzinc, 2.4 equivalents of enyne and dimethylzinc based on PhCHO provided the best result (Entry 3, Table 1). Aprotic



Scheme 2. Ni-Catalyzed three-component coupling reaction of aldehyde, diene, and dimethylzinc.

Table 1. Ni-Catalyzed multicomponent coupling reaction of enyne, PhCHO, and Me$_2$Zn[a]

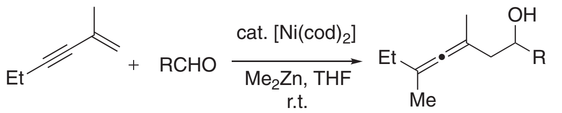


1a

Entry	Enyne /mmol	Me$_2$Zn /mmol	Solvent	Yield of **1a** /% [ratio]
1	0.6	1.2	THF	34 [5:1]
2	1.2	0.6	THF	53 [5:1]
3	1.2	1.2	THF	66 [5:1]
4	1.2	1.2	toluene	62 [2:1]
5	1.2	1.2	hexane	56 [2:1]
6	1.2	1.2	DMA	57 [6:1]

[a]The reaction was undertaken in the presence of [Ni(cod)$_2$] (0.05 mmol), enyne (indicated amount; mmol), PhCHO (0.5 mmol), Me$_2$Zn (indicated amount, 1 M hexane solution) in solvent (1.5 mL) at room temperature for 24 h under N$_2$.

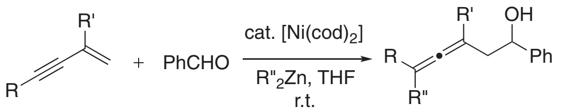
Table 2. Ni-Catalyzed multicomponent coupling reaction of enyne, PhCHO, and Me$_2$Zn[a]



Entry	RCHO	Time/h	Yield/% [ratio]
1	PhCHO	24	**1a**: 66 [5:1]
2	*p*-(OMe)PhCHO	48	**1b**: 63 [3:1]
3	*p*-ClPhCHO	48	**1c**: 54 [5:1]
4	MesCHO	72	**1d**: 58 [>25:1]
5	*n*-C_5H_{11}CHO	72	**1e**: 32 [5:1]
6	*c*-C_6H_{11}CHO	72	**1f**: 54 [7:1]
7	*t*-BuCHO	72	**1g**: 61 [10:1]

[a]The reaction was undertaken in the presence of [Ni(cod)$_2$] (0.05 mmol), enyne (1.2 mmol), aldehyde (0.5 mmol), Me$_2$Zn (1.2 mmol; 1 M hexane solution) in THF (1.5 mL) at room temperature under N$_2$.

Table 3. Ni-Catalyzed multicomponent coupling reaction of enyne, PhCHO, and Me$_2$Zn[a]



Entry	Enyne		Zinc	Time	Yield/%
	R	R′	R″	/h	[ratio]
1	*n*-Bu	Me	Me	24	**1h**: 61 [5:1]
2	Ph	Me	Me	72	**1i**: 56 [2:1]
3	Me$_3$Si	Me	Me	72	**1j**: 40 [1:1]
4	Et	Me	Et	24	**1k**: 50
5[b]	Et	Me	Ph	48	**1l**: 34 [1:1]
6[b]	Et	Me	Bn	72	**1m**: 0

[a]The reaction was undertaken in the presence of [Ni(cod)$_2$] (0.05 mmol), enyne (1.2 mmol), PhCHO (0.5 mmol), organozinc agent (2.4 mmol; 1 M hexane solution) in THF (1.5 mL) at reflux (Entry 2), 50 °C (Entry 3), room temperature (Entries 1 and 4–6), under N$_2$. [b]Ph$_2$Zn and Bn$_2$Zn were prepared from ZnCl$_2$ with 2 equivalents of phenylmagnesium bromide and benzylmagnesium chloride, respectively.

polar solvents, such as THF and DMA, gave higher stereoselectivities.

As for the aromatic aldehydes, PhCHO and *p*-anisaldehyde underwent the three-component coupling reactions smoothly to provide the tetrasubstituted allenyl alcohols **1** as a mixture of diastereoisomers in 5:1 and 3:1 ratios, respectively (Entries 1 and 2, Table 2). *p*-Chlorobenzaldehyde showed marginal success in the formation of the allenyl alcohol with moderate yield (Entry 3, Table 2). Mesityl aldehyde provided the expected alcohol **1d** with excellent diastereoselectivity (Entry 4, Table 2). Primary, secondary, and tertiary aliphatic aldehydes, such as hexanal, cyclohexanecarbaldehyde, and pivalaldehyde gave the desired allenyl alcohols in modest to reasonable yields with higher stereoselectivities, although the reaction required a longer period to complete (Entries 5–7, Table 2). In these cases, it is notable that cyclobutene ring formation via [2 + 2] cycloaddition of the alkene and alkyne moieties of the enyne was not detected at all.[5]

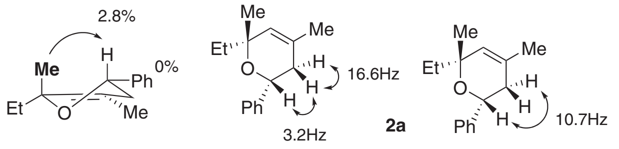
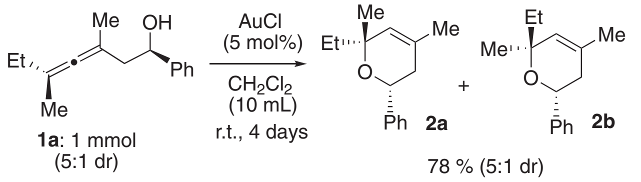


Figure 1. NOE experimental data and ^{1}H NMR spectral data of the cyclized major product **2a**.

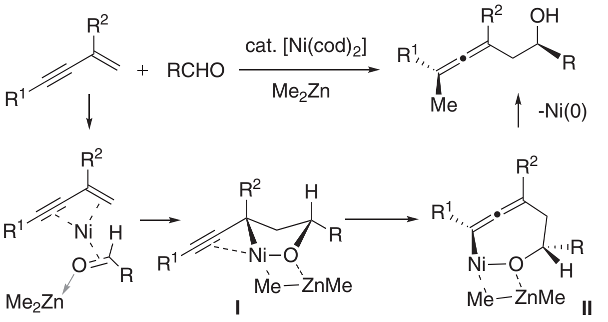
Next, we developed a similar coupling reaction with a wide variety of enynes and organozinc reagents in the presence of Ni-catalyst and PhCHO under the optimized conditions of Table 1. The results are summarized in Table 3. 4-*n*-Butyl- and 4-phenyl-substituted enynes could take part in the coupling reactions to give the desired allenyl alcohols **1h** and **1i** in reasonable yields (Entries 1 and 2, Table 3). 4-Trimethylsilyl-substituted enyne gave the expected coupling product **1j** in moderate yield (Entry 3, Table 3). In place of dimethylzinc, diethylzinc could serve as ethylating agent for similar coupling reaction giving rise to the tetrasubstituted allenyl alcohols **1k** (Entry 4, Table 3). Diphenylzinc which is prepared from ZnCl$_2$ and phenylmagnesium bromide participated in the desired reaction, hence the tolerance for a variety of organozinc reagents has high potential synthetic utility. Dibenzylzinc provided no expected coupling product **1m**; instead, homopropargyl(3-butynyl) alcohol was obtained in modest yield by the 1,2-addition reaction of benzylzinc and aldehyde at the alkene moiety.

The structure of the allenyl alcohol **1a** was determined on the basis of transformation to the 5,6-dihydropyran via the 6-*endo* cycloisomerization of the β-hydroxyallene promoted by Au(I)-catalyst (eq 2). Au-Catalyzed cycloisomerization takes place following the intramolecular oxycyclization of the β-hydroxyallene via the σ-gold complex developed by Krause et al.[6] Cyclized products, dihydropyrans **2a** and **2b**, were unequivocally characterized by NOE experimental analysis and the coupling constant in the ^{1}H NMR spectral data (Figure 1).



(2)

A plausible reaction mechanism for the three-component coupling reaction of enyne, aldehyde, and dimethylzinc in the presence of Ni(0) catalyst is illustrated in Scheme 3. Oxidative cyclization of the enyne and aldehyde involving a Ni(0) species proceeds to form oxanickelacycle intermediate **I** via addition of the carbonyl group of the aldehyde to the terminal olefinic carbon atom of the enyne moiety with excellent regioselectivity. The nickel atom undergoes a 1,3-shift to the γ-position of the propargylnickel moiety with retention of configuration to afford the stereodefined 7-membered allenylnickel species **II**. Methyl group transfer from dimethylzinc to the nickelacycle provides an allenyl methyl nickel species, followed by formation of the



Scheme 3. Plausible mechanism for three-component coupling reaction of Me_2Zn, aldehyde, and enyne.

tetrasubstituted allenyl alcohols through reductive elimination, liberating the Ni(0) active species.

On the contrary to our results, in the presence of phosphine ligand, Ni-catalyzed selective formations of dienyl alcohols from 1,3-enynes and aldehydes via alkene-coordinated nickelacycloalkenes have been reported.[7,8] These complementary selectivities might originate in the stabilities of the oxanickelacycle intermediates.

In summary, we have developed a Ni-catalyzed three-component coupling reaction of dimethylzinc, enyne, and carbonyls to provide tetrasubstituted allenyl alcohols with high regio- and stereoselectivities. Diethylzinc and diphenylzinc could participate in the coupling reaction to provide the corresponding β-hydroxyallenes in reasonable yields.

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This paper is dedicated to Professor Teruaki Mukaiyama in celebration of the 40th anniversary of the Mukaiyama aldol reaction.

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4 The reaction was undertaken as follows (Table 1, Entry 3): Into a nitrogen-purged flask with [Ni(cod)$_2$] (13.8 mg, 0.05 mmol) was introduced successively THF (1.5 mL), benzaldehyde (53 mg, 0.5 mmol), 1,3-enyne (113 mg, 1.2 mmol), and dimethylzinc (1.2 mL, 1 M in hexanes) via syringe. The homogeneous mixture was stirred at room temperature for 24 h, during which the reaction was monitored by TLC. After dilution with ethyl acetate (30 mL), the mixture was washed successively with 2 M HCl, sat. $NaHCO_3$, and brine, and then dried ($MgSO_4$) and concentrated in vacuo. The residual oil was subjected to column chromatography over silica gel (hexane/ethyl acetate = 20/1, v/v) to give **1a** (71.4 mg, 66%) in a 5:1 ratio. Spectral data (Supporting Information) are available electronically on the CSJ-Journal Web site, http://www.csj.jp/journals/chem-lett/index.html.

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