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Stereoselective Coupling Reaction of Dimethylzinc and Alkyne toward Nickelacycles

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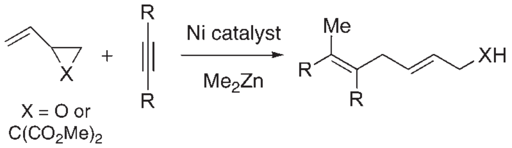
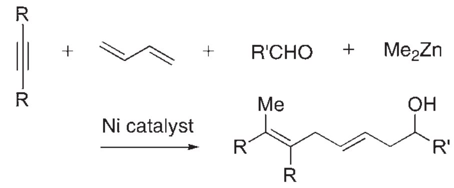
ABSTRACT



Ni catalyst promotes the three-component coupling reaction of vinyloxacyclopropane, alkyne, and dimethylzinc to provide 2,5-heptadienyl alcohol in high yields. Vinylcyclopropane also participates in a similar three-component coupling reaction to afford dimethyl (α-heptadienyl)malonate with excellent *E*-stereoselectivity.

Metallacycles are attractive and convenient key intermediates for C–C bond formation and C–C bond cleavage reactions.[1] Within this decade, examples of Ni-catalyzed ring-expansion[2] and C–C bond-cleavage reactions[3] have been extensively developed as efficient functional transformations. We previously reported the Ni(0) catalyst accelerated oxidative cyclization of aldehydes and conjugated dienes in the presence of Et$_3$B[4] and Et$_2$Zn,[5] with subsequent reductive coupling, to provide bis-homoallyl alcohols with excellent regio- and stereoselectivities through key oxanickelacycle intermediates. Furthermore, we demonstrated that similar catalytic systems promoted the multicomponent coupling reaction of Me$_2$Zn, alkyne, conjugated diene, and aldehyde, in this order, to provide 3,6-octadienyl alcohols with excellent regio- and stereoselectivities (Scheme 1).[6]

Scheme 1. Ni-Catalyzed Multicomponent Coupling Reaction with Alkyne, Diene, Aldehyde, and Me$_2$Zn



Ikeda et al. revealed the Ni-catalyzed coupling reaction of allyl chloride, an alkyne, and Me$_2$Zn in the presence of Ni catalyst via the *syn* stereoselective addition of a

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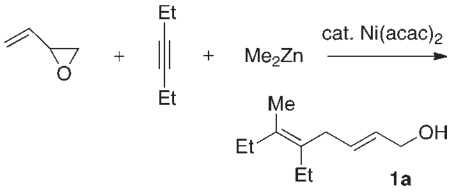
π-allylnickel species followed by methyl group transfer to the alkyne to produce 1,4-pentadiene.[7] Furthermore, the Ni(0) metal-catalyzed coupling reaction of alkyne-tethered vinylcyclopropanes with allyl chloride has been reported.[8] In this case, the addition of the π-allylnickel species to the alkyne moiety proceeds with β-*syn* elimination of the cyclopropyl C−C bond giving the (*E*)-1, 3-diene with excellent regio- and stereoselectivities. Encouraged by these multicomponent coupling reactions involving π-allylnickel species by Ikeda's protocols and our previous strategies utilizing oxanickelacycles with alkynes and organozinc reagents, we were prompted to develop stereodefined functionalizations using allylating agents and alkynes based on the structural variety of oxanickelacycles.

Herein, we would like to report the regio- and stereocontrolled three-component coupling reaction of alkynes, Me_2Zn, and vinyloxacyclopropane and vinylcyclopropane through nickelacycle intermediates to provide dienyl homoallylalcohols and α-dienyl malonates.

The reaction was readily conducted by exposing Me_2Zn to a mixture of vinyloxacyclopropane and alkynes at room temperature under nitrogen atmosphere. The results using various kinds of ligands and solvents are shown in Table 1.[9] It was clear that THF was the most effective solvent (entries 1−6, Table 1). In all cases, the alkynes tended to attack on the terminal carbon atom of the vinylic group to afford heptadienyl alcohol **1a** via methyl group transfer from Me_2Zn in a 3:1 ratio of *E* and *Z* isomers with respect to the C-2 olefin geometry. Although various kinds of ligands such as monodentate, bidentate phosphine, and NHC ligands were employed in the reaction (entries 7−10, Table 1), it was the absence of ligand at room temperature that provided the best result in the formation of **1a** (entry 1, Table 1).

Table 1. Ni-Catalyzed Three-Component Connection Reaction of Alkyne, Vinyloxacyclopropane and Me_2Zn[a]

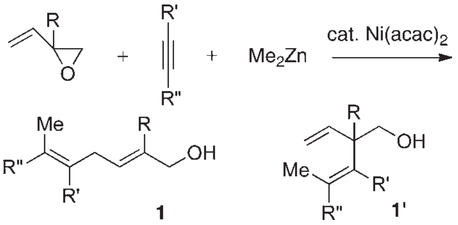


entry	ligand	solvent	conditions	yield of **1a** (%) [*E*/*Z*]
1	none	THF	rt, 24 h	92 [3:1]
2	none	THF	50 °C, 24 h	89 [3:1]
3	none	ether	rt, 24 h	84 [3:1]
4	none	toluene	rt, 24 h	81 [3:1]
5	none	CH_2Cl_2	rt, 24 h	59 [3:1]
6	none	dioxane	rt, 24 h	20 [3:1]
7	Ph_3P	THF	rt, 48 h	71 [3:1]
8	*n*-Bu_3P	THF	rt, 48 h	no reaction
9[b]	dppf	THF	rt, 48 h	no reaction
10[c]	NHC	THF	rt, 24 h	81 [1:1]

[a] The reaction was undertaken in the presence of vinyloxacyclopropane (1 mmol), $Ni(acac)_2$ (0.1 mmol), ligand (0.2 mmol), and dimethylzinc (1.2 mmol; 1 M hexane solution) in solvent (3 mL) under nitrogen atmosphere. [b] dppf: diphenylphosphinoferrocene (0.1 mmol) was used. [c] NHC ligand was prepared from 1,3-bis(2,6-diisopropylphenyl)-imidazolium chloride with 0.2 mmol of *t*-BuOK.

Next, we conducted the multicomponent coupling reaction of substituted vinyloxacyclopropane, various alkynes, and Me_2Zn under the optimized conditions of Table 1. Although diphenylacetylene participated in the coupling reaction in good yield to afford a mixture of *E* and *Z* isomers (entry 1, Table 2), bis(trimethylsilyl)acetylene and an electron-deficient alkyne did not provide the desired results (entries 2 and 3, Table 2). An unsymmetrical alkyne took part in the reaction in high yield to give regio- and stereoisomers as an inseparable mixture (entry 4, Table 2). Terminal alkynes also provided the expected products **1e** and **1f** in moderate to good yields, along with the branched regioisomers **1e′** and **1f′** (entries 5 and 6, Table 2). 2-Methyl-2-vinyloxacyclopropane underwent a similar

Table 2. Ni-Catalyzed Coupling Reaction of Various Alkyne, Substituted Vinyloxacyclopropane, and Me_2Zn[a]



entry	epoxide R	alkyne R′	R″	time (h)	yield (%) [*E*:*Z* ratio]
1	H	Ph	Ph	24	**1b**: 84 [2:1]
2	H	TMS	TMS	24	**1c**: 35 [2:1]
3	H	CO_2Me	CO_2Me	24	no reaction
4	H	Et	Ph	24	**1d**: 93 [8:5:2:1]
5	H	H	Ph	24	**1e**: 81 [2:1], **1′e**: 15
6	H	H	TMS	24	**1f**: 64 [2:1], **1′f**: 33
7	Me	Et	Et	24	**1g**: 100 [1:2]
8	Me	Ph	Ph	24	**1h**: 75 [1:3]
9	Me	TMS	TMS	24	**1i**: 61 [1:1]

[a] The reaction was undertaken in the presence of vinyloxacyclopropane (1 mmol), $Ni(acac)_2$ (0.1 mmol), and dimethylzinc (1.2 mmol; 1 M hexane solution) in THF (3 mL) at room temperature under nitrogen atmosphere.

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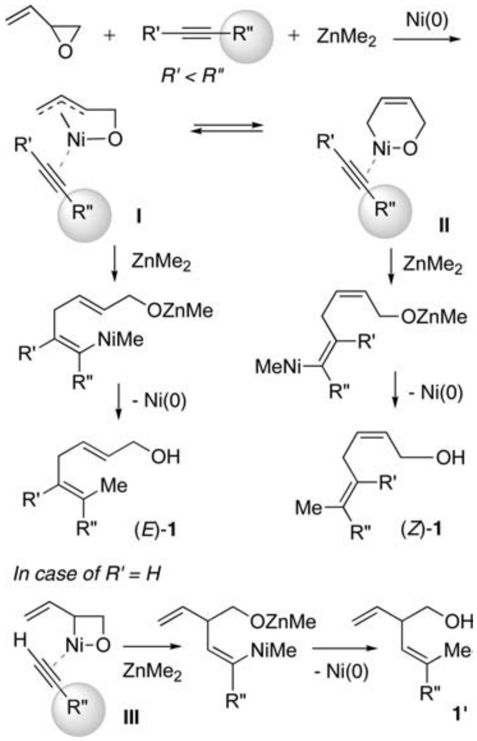
(9) See the Supporting Information.

coupling reaction with good to excellent yields, and employment of 3-hexyne led to the formation of the desired product **1g** in quantitative yield in a 1:2 ratio of *E* and *Z* isomers (entry 7, Table 2). Diphenylacetylene and bis(trimethylsilyl)acetylene also showed similar reactivities and selectivities in moderate to good yields (entries 8 and 9, Table 2).

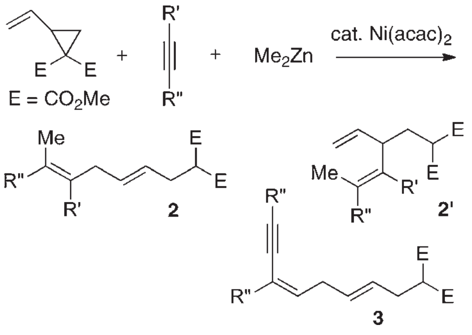
A plausible reaction mechanism for the multicomponent coupling reaction of vinyloxacyclopropane, alkyne, and dimethylzinc is displayed in Scheme 2. Low stereoselectivities for the coupling reactions using vinyloxacyclopropane might originate from the formation of the π-allyloxanickelacycle intermediate **I** in equilibrium with the 6-membered oxanickelacycle **II**. It is known that vinyloxacyclopropane readily undergoes oxidative addition toward Ni(0) metal species coordinated by alkynes to form four- or six-membered oxanickelacycles. This is followed by methyl group transfer from the Zn atom to the Ni metal center, leading to C–C bond formation and a mixture of *E* and *Z* isomers. Terminal carbons of phenylacetylene and trimethylsilylacetylene attack on the allylic position of vinyloxacyclopropane to afford the branched regiosomers **1′** owing to less steric repulsion between the H atom of the terminal alkyne and the allylic moiety of intermediate **III** (Scheme 2).

Scheme 2. Reaction Mechanism for Coupling Reaction of Vinyloxacyclopropane, Alkyne, and Me_2Zn



Next, we investigated the coupling reaction of alkynes, Me_2Zn, and vinylcyclopropane derived from dimethyl malonate and 1,4-dichloro-2-butene under similar catalytic conditions (Table 3). In most cases, the reaction proceeded smoothly at room temperature within several hours and the coupling products were obtained with excellent *E*-stereoselectivities (entries 1 and 2, Table 3). The trimethylsilyl group also took part in efficient coupling to give the corresponding desired product **2c** in moderate yield with *E*-stereoselectivity (entry 3, Table 3). Unsymmetrical internal alkynes participated in the coupling reaction giving rise to a mixture of regioisomers with exclusive *E*-stereoselectivities (entries 4 and 5, Table 3). In all cases, the stereochemistry with respect to the Me group and the olefinic main chain is the *Z*-form, as in the reaction of vinylcyclopropane. The reaction using terminal alkynes such as trimethylsilylacetylene and phenylacetylene was changed dramatically, and the desired products **2** were not obtained at all. Instead, the dienynes **3f** and **3g**, involving dimerization of the terminal alkynes, were produced as major products (entries 6 and 7, Table 3).

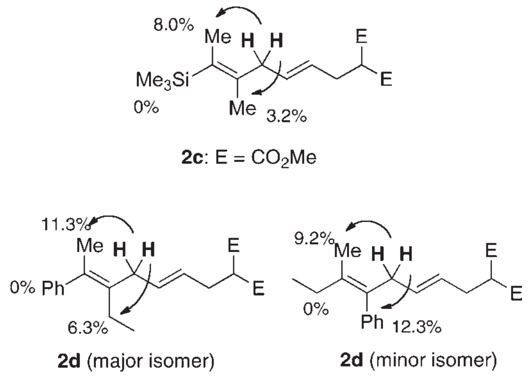
Table 3. Ni-Catalyzed Three-component Connection Reaction of Various Alkyne, Vinylcyclopropane, and Me_2Zn[a]



entry	R′	R″	time (h)	yield (%) [*E*:*Z*]
1	Et	Et	1	**2a**: 84 [8:1]
2	Ph	Ph	3	**2b**: 73 [*E* only]
3	TMS	TMS	3	**2c**: 63 [*E* only]
4	Et	Ph	6	**2d**: 92 [*E* only][b]
5	Me	TMS	1	**2e**:83 [*E* only]
6	H	Ph	24	**3f**: 71 [*E* only]
7	H	TMS	6	**3g**: 56 [*E* only], **2′g**: 24

[a] The reaction was undertaken in the presence of vinylcyclopropane (1 mmol), $Ni(acac)_2$ (0.1 mmol), alkyne (1 mmol), and diethylzinc (1.2 mmol; 1 M hexane solution) in THF (3 mL) at room temperature under nitrogen atmosphere. [b] Product **2d** was obtained as a mixture of regioisomer in a 3:1 ratio.

The stereochemistry of the products was unequivocally determined on the basis of NOE experiments. The results of irradiation at the bold protons are illustrated in Figure 1. According to the NOE results, irrespective of the kinds of regioisomers derived from the symmetrical and unsymmetrical alkynes, it was apparent that methyl group transfer from Me_2Zn to the acetylenic triple bond proceeded in a *syn* manner to deliver *Z*-stereochemistry with respect to the C5 olefinic geometry and *E*-stereochemistry with respect to the C2 position by the ring expanding reaction processes of the vinyl cyclopropyl groups.



2c: E = CO_2Me

2d (major isomer)

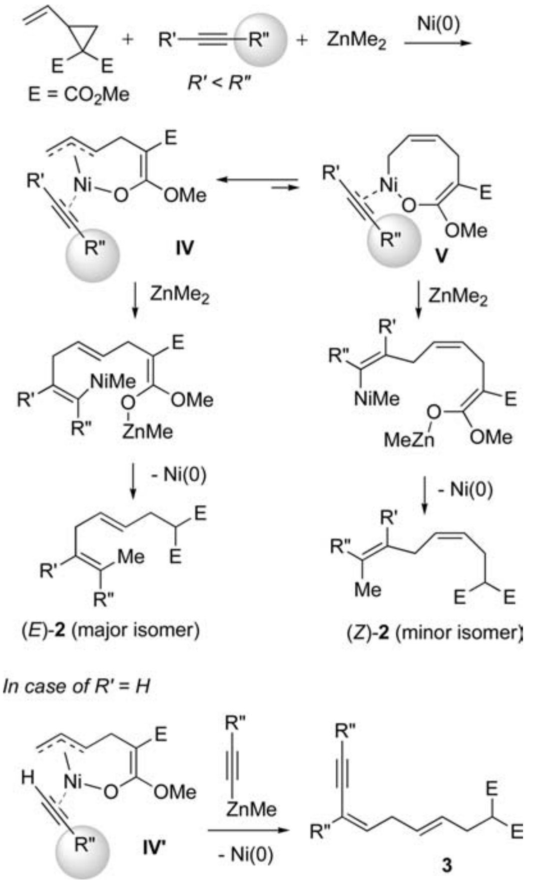
2d (minor isomer)

Figure 1. NOE data for the irradiation at the bold methylene protons.

A reaction mechanism for the coupling reaction of alkyne, vinylcyclopropane, and Me_2Zn is displayed in Scheme 3. The exclusive *E*-stereochemistry might stem from the stability of the produced nickelacycles. Formation of allylnickel species **IV** would predominate over that of 8-membered ring species **V** owing to the entropy effect for the ring-closing reaction. This is followed by insertion of the alkyne to the allylic terminus of the allylnickel species to provide (*E*)-**2** isomer exclusively. As in the case of using terminal alkyne, zinc acetylide derived from dimethylzinc and terminal alkyne might preferentially participate in the coupling reaction via transmetalation with allylnickel species **IV**′ to give rise to diene–yne **3** as the major products.[10]

In summary, we have developed a Ni-catalyzed three-component coupling reaction of Me_2Zn, alkynes, and vinyloxacyclopropanes and vinylcyclopropanes to afford dienyl alcohols and α-heptadieneyl dimethyl malonates in excellent yields with high stereoselectivities. The application and scope of this method for the synthesis of complicated molecules, such as terpenes and physiologically active molecules, are currently under investigation.

Scheme 3. Reaction Mechanism for Coupling Reaction of Vinylcyclopropane, Alkyne, and Me_2Zn



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Supporting Information Available. Experimental procedures 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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(10) Since Ni(0) catalysts tend to promote a head-to-tail dimerization of terminal alkynes in the presence of organozinc reagents to give the enyne framework, the aleternative coupling reaction involving dimerization of terminal alkyne followed by carbonickelation toward vinylcyclopropane to provide diene–yne **3** might be probable. (a) Giacomelli, G.; Marcacci, F.; Caporusso, A. M.; Lardicci, L. *Tetrahedron Lett.* **1979**, *20*, 3217. (b) Ogoshi, S.; Ueta, M.; Oka, M.; Kurosawa, H. *Chem. Commun.* **2004**, 2732. (c) Nakao, Y.; Shirakawa, E.; Tsuchimoto, T.; Hiyama, T. *J. Organomet. Chem.* **2004**, *689*, 3701. (d) Takahashi, G.; Shirakawa, E.; Tsuchimoto, T.; Kawakami, Y. *Adv. Synth. Catal.* **2006**, *348*, 837.