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Ni-CATALYZED THREE-COMPONENT COUPLING OF 4-METHYLENE-2-OXAZOLIDINONES, ALKYNES, AND TRIMETHYLALUMINUM

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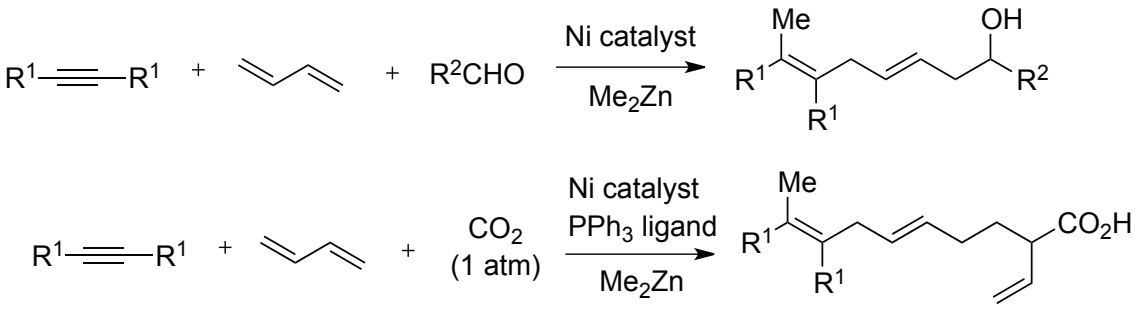
Dedicated to Prof. Dr. Masakatsu Shibasaki on the occasion of his 70th birthday

Abstract – Ni(0) catalyzes the three-component coupling reactions of 4-methylene-2-oxazolidinones, alkynes, and trimethylaluminum accompanied by extrusion of carbon dioxide to furnish 2-methyl-3-amino-2,5-heptadiene with high regio- and stereoselectivities.

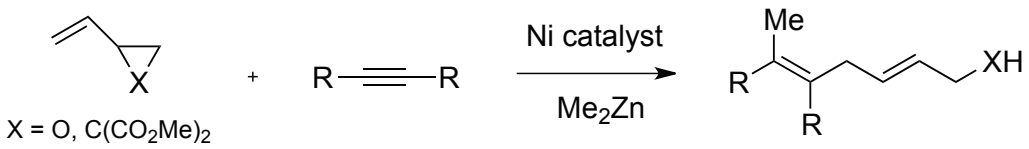
Nickelacycles are one of the most attractive and efficient active species for C-C bond transformations in modern organic synthesis.[1] Multi-component coupling reactions promoted by Ni-catalysts are straightforward and convenient methods for the construction of complicated molecules in material science and medicinal chemistry.[2] Recently, we developed a Ni-catalyzed multi-component coupling of conjugated dienes, alkynes, and aldehydes in the presence of Me_2Zn to afford 3,6-octadienyl alcohols with high regio- and stereoselectivities (Scheme 1).[3] This reaction occurs via Ni-catalyzed oxidative cyclization of conjugated dienes and carbonyls. Carbon dioxide can be used under similar conditions, as a carbonyl electrophile for the multi-component coupling reaction to afford 2-vinyl-5*E*,8*Z*-decadienoic acid.[4] In this case, phosphine ligands are essential for the oxidative cyclization of 2 equiv of 1,3-butadiene



Scheme 1. Ni-Catalyzed three-component coupling of alkynes, conjugated dienes, carbonyls, and Me_2Zn

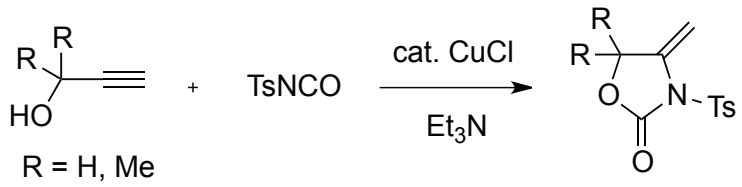
followed by dimerization to form a σ-allyl-π-allylnickel intermediate. 1,3-Butadiene can therefore provide C4 and C8 carbon units for multi-component coupling reactions involving π-allylnickel species.

Recently, we developed Ni-catalyzed three-component coupling reactions of Me_2Zn, alkynes and vinyl epoxides or vinylcyclopropanes to afford dienyl alcohols and α-heptadienyl dimethyl malonates, respectively.[5] These reactions were undertaken by exposing Me_2Zn to a reaction mixture of vinyl epoxides or vinylcyclopropanes in the presence of alkynes and a Ni-catalyst at room temperature. Allylnickel species are key active intermediates in *syn* addition to alkynes. Vinyl epoxides provided 2,5-heptadienyl alcohols as a mixture of *E*- and *Z*-isomers, whereas vinylcyclopropanes formed α-heptadienyl dimethyl malonates with excellent *E*-stereoselectivities. These stereoselectivities originate from the structure of the π-allylnickel complex; for example, vinyl epoxides readily form four- and six-membered oxanickelacycles, whereas vinylcyclopropanes provide *syn*-π-allylnickel species, which contribute to the excellent *E*-stereoselectivity.

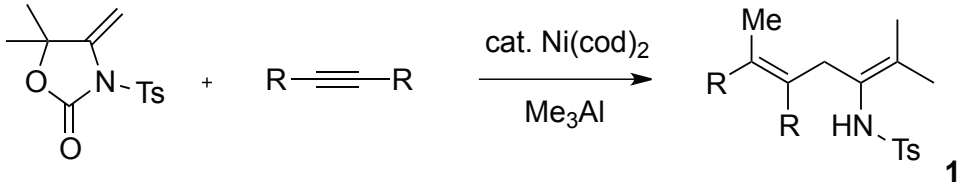


Scheme 2. Ni-Catalyzed three-component coupling with unsaturated compounds with Me_2Zn

Previously, we achieved efficient formation of 4-methylene-2-oxazolidinones from propargyl alcohols and isocyanate, followed by intramolecular addition of a nitrogen atom to the C-C triple bond, promoted by Cu and Ag catalysts (Scheme 3).[6] 4-Methylene-2-oxazolidinones are densely functionalized and useful molecules with stereochemically defined enamine and protected allylic alcohols moieties; for example, 4-methylene-2-oxazolidinones can serve as an azatrimethylenemethane intermediates, which undergo amphiphilic addition with α,β-unsaturated enones and active alkenes.[7] These versatile heterocylic compounds have potential as important synthons of physiologically active molecules and pharmaceutical products. Here, we report that *N*-*p*-toluenesulfonyl-4-methylene-2-oxazolidinone can serve as an allylazanickelacycle species, which undergoes three-component coupling reactions with alkynes and trimethylaluminum, accompanied by carbon dioxide extrusion (Scheme 4). This protocol is a useful and efficient method for synthesizing important nitrogen-containing molecules such as β-amino acids and unsaturated dienylamines.



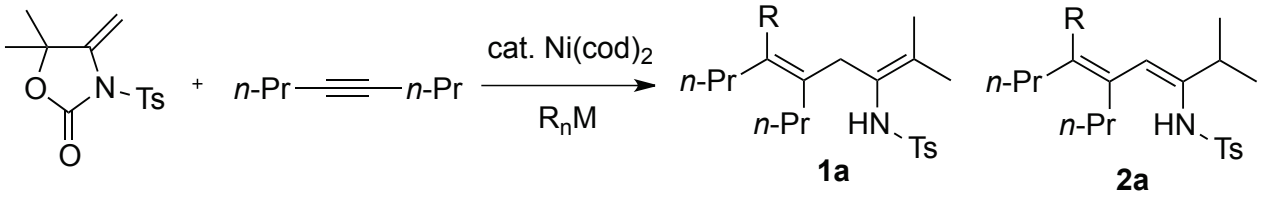
Scheme 3. Synthesis of 4-methylene-2-oxazolidinone from propargyl alcohol and isocyanate



Scheme 4. Ni-Catalyzed three-component coupling of alkynes, 4-methylene-2-oxazolidinone, and Me_3Al

The reaction was performed using 5,5-dimethyl-4-methylene-2-oxazolidinone, 4-octyne, and various organoaluminum and organozinc reagents in the presence of a $Ni(cod)_2$ catalyst at 60 ˚C under a nitrogen atmosphere. The results are summarized in Table 1. Among various types of organometallic reagents, trimethylaluminum was best for the formation of the three-component coupling product **1a** (Table 1, entry 1).[8] Monoalkoxydialkylaluminum gave the desired product **1a** in poor yield, and Me_2Zn did not participate in the expected reaction at all (Table 1, entries 2 and 3). Ethylaluminum and ethylzinc were not effective organometallic reagents (Table 1, entries 4 and 5). DIBAL-H was used as a reducing agent for the reductive coupling of the 4-methylene-2-oxazolidinone and an alkyne, but the desired reaction was not observed (Table 1, entry 6). Next, we investigated solvent effects in the multi-component coupling reaction. Screening of non-polar and aprotic polar solvents showed that toluene was the best solvent for the expected reaction (Table 1, entries 1 and 7-14). Aprotic polar solvents such as DMA, DMF, and DMSO gave the isomerized dienyl enamine **2a** as a by-product. *N*-Methylpyrrolidone (NMP) gave conjugated diene **2a** as the major product along with non-conjugated diene **1a** (Table 1, entry 12). Non-conjugated diene **1a** was not converted to conjugated diene **2a** under similar conditions, suggesting that aprotic polar solvents accelerate the formation of **2a** through a coupling process. We investigated other ligands for the coupling reactions; the results are shown in Table 1, entries 15-19. The product yield decreased irrespective of the type of phosphine ligand; no ligand gave the best yield of the desired product.

Table 1. Coupling of 4-methylene-2-oxazolidinone, 4-octyne, and organometallic reagents



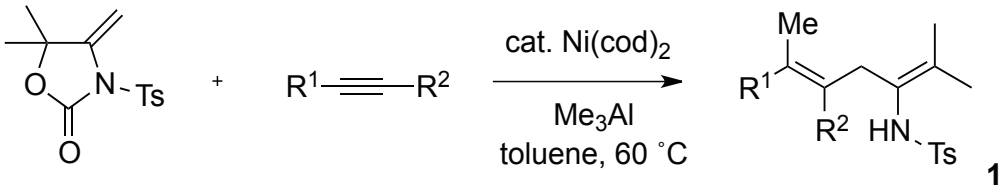
Entry	Organometallics R_nM	Solvent	Ligand	Yield (%) **1a**	**2a**
1	Me_3Al	toluene	none	64	0
2	$Me_2Al(OMe)$	toluene	none	5	0
3	Me_2Zn	toluene	none	no reaction	
4	Et_3Al	toluene	none	complex mixture	
5	Et_2Zn	toluene	none	no reaction	
6	DIBAL-H	toluene	none	complex mixture	
7	Me_3Al	*n*-hexane	none	37	0
8	Me_3Al	CPME	none	6	0
9	Me_3Al	1,4-dioxane	none	8	0
10	Me_3Al	THF	none	33	0
11	Me_3Al	DMA	none	34	36
12	Me_3Al	NMP	none	39	54
13	Me_3Al	DMF	none	30	26
14	Me_3Al	DMSO	none	22	23
15	Me_3Al	toluene	PPh_3	23	0
16	Me_3Al	toluene	$P(c\text{-Hex})_3$	33	0
17	Me_3Al	toluene	$P(OPh)_3$	23	0
18	Me_3Al	toluene	dppe	55	0
19	Me_3Al	toluene	Xantphos	29	0

[a]The reaction was undertaken in the presence of $Ni(cod)_2$ (0.05 mmol), oxazolidinone (1.0 mmol), 4-octyne (2.0 mmol), organometallic reagent (1.2 mmol) in solvent (5 mL) at 60 ˚C for 24 h under nitrogen atmosphere.

Next, we examined the coupling reaction with various alkynes in the presence of *N*-*p*-toluenesulfonyl-5,5-dimethyl-4-methylene-2-oxazolidinone and trimethylaluminum in toluene at 60 ˚C. The results are summarized in Table 2. Asymmetric alkyl-substituted internal alkynes participated in the coupling reactions and gave reasonable yields (Table 2, entries 1-4). Methyl, isopropyl-, and

trimethylsilyl-substituted unsymmetrical alkynes provided a mixture of regioisomers in ratios of 1.8:1 to 4.0:1 (Table 2, entries 5 and 6).

Table 2. Three-component coupling of 4-methylene-2-oxazolidinone, various alkynes, and Me_3Al[a]



Entry	Alkyne (R^1, R^2)		Yield of **1** (%) [ratio]
1	R^1 = *n*-Pr,	R^2 = *n*-Pr	**1a**: 64
2	R^1 = Et,	R^2 = Et	**1b**: 57
3	R^1 = Ph,	R^2 = Ph	**1c**: 37
4	R^1 = Me,	R^2 = Me	**1d**: 64
5	R^1 = Me,	R^2 = *i*-Pr	**1e**: 38 [1.8:1]
6	R^1 = Me_3Si,	R^2 = Me	**1f**: 25 [4.0:1]

[a]The reaction was undertaken in the presence of $Ni(cod)_2$ (0.05 mmol), oxazolidinone (1.0 mmol), alkyne (2.0 mmol), Me_3Al (1.2 mmol) in toluene (5 mL) at 60 ˚C for 24 h under nitrogen atmosphere.

NOE experiments showed unequivocally that **1a** was the *E*-isomer. The results are shown in Figure **1** for irradiation of the bold face protons in compound **1a**.

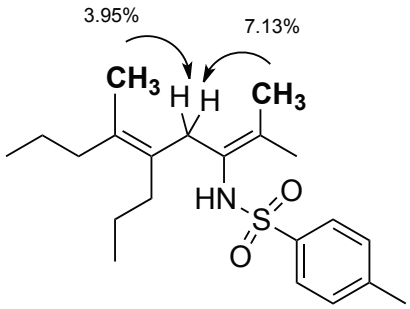
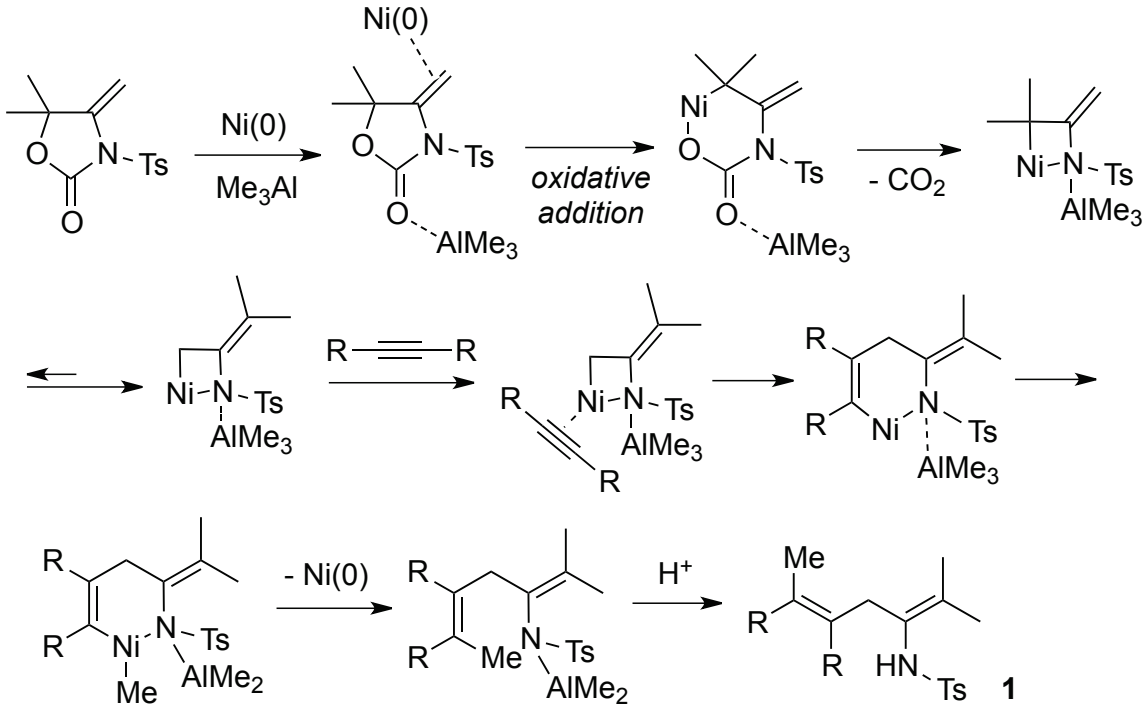


Figure 1. NOE data for irradiation of bold face protons in dienylamine **1a**

A plausible reaction mechanism for the three-component coupling reactions of 4-methylene-2-oxazolidinones in the presence of a Ni catalyst, alkyne, and trimethylaluminum is shown in Scheme 5. Oxidative addition of 4-methylene-2-oxazolidinone to a Ni(0) catalyst is accompanied by extrusion of carbon dioxide promoted by a Lewis acid. i.e., trimethylaluminum. The azatrimethylenemethanenickel intermediate can participate in the formation of azanickelacycle species,

which undergo *syn* alkyne addition to form a six-membered azanickelacycle. Transmetallation with trimethylaluminum affords a methylvinylnickel intermediate, followed by reductive elimination to afford dienylamine **1**. The general Ni(0) catalyst is the active species that promotes the multi-component coupling reaction.



Scheme 5. Plausible reaction mechanism for Ni-catalyzed coupling reaction of Me_3Al, alkyne, and 4-methylene-2-oxazolidinone

In summary, we developed Ni-catalyzed three-component coupling reactions of alkynes, 4-methylene-2-oxazolidinone, and trimethylaluminum accompanied by extrusion of carbon dioxide, to furnish 2-methyl-3-amino-2,5-heptadiene with high regio- and stereoselectivities. The formed products are useful as key enamine intermediates for the preparation of important nitrogen-containing compounds. A study is in now in progress to use this protocol in the synthesis of physiologically active molecules such as unsaturated amines and amino acids.

ACKNOWLEDGEMENTS

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8. General procedure for multi-component coupling reaction (entry 1, Table 1): A 25 mL of two-necked round-bottomed flask, equipped with a rubber septum and an air condenser at the top of which is attached a three-way stopcock fitted a nitrogen balloon. *N*-*p*-Toluenesulfonyl-5,5-dimethyl-4-methylene-2-oxazolidinone (281.3 mg, 1 mmol) and $Ni(cod)_2$ (13.8 mg, 0.05 mmol) are placed in the flask and purged with nitrogen. Freshly distilled toluene (5 mL), 4-octyne (220.4 mg, 2.0 mmol), and Me_3Al (1.2 mL of 1 M hexane solution; 1.2 mmol) are successively added while stirring the solution with a magnetic stirrer. The stirring is continued for 24 h at 60 ˚C. After the reaction completes, the reaction mixture is diluted with ethyl acetate (20 mL). The organic phase is washed with sat. aq. $NaHCO_3$ (2 x 20 mL) and brine (2 x 20 mL), and then dried over magnesium sulfate, filtered, and concentrated. The organic phase was dried ($MgSO_4$) and concentrated in vacuo to give a pale yellow oil, which was subjected to column chromatography over silica gel (hexane/EtOAc = 11/1 v/v) to give **1a** (232.5 mg, 64%).

(5*E*)-*N*-(2,6-Dimethyl-5-propyl-2,5-nonadienyl)-*p*-toluenesulfonamide (1a): IR (neat) 3277 (br),

2959 (s), 2930 (m), 2870 (m), 2343 (w), 1599 (w), 1456 (m), 1381 (m), 1325 (m), 1165 (s), 1092 (m), 665 (m) cm^{-1}; ^1H NMR (C_6D_6, 400 MHz) δ 0.85 (t, J = 7.3 Hz, 3 H), 0.87 (t, J = 7.3 Hz, 3 H), 1.26-1.41 (m, 4 H), 1.48 (s, 3 H), 1.54 (s, 3 H), 1.67 (s, 3 H), 1.87 (s, 3 H), 1.88 (t, J = 7.3 Hz, 2 H), 1.98 (t, J = 7.3, 2 H), 3.03 (s, 2 H), 5.32 (s, 1 H), 6.75 (d, J = 8.3 Hz, 2 H), 7.81 (d, J = 8.3 Hz, 2 H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ 14.2, 14.4, 18.1, 20.3, 21.0, 21.5, 21.7, 22.4, 32.9, 33.8, 36.6, 125.4, 127.4, 128.8, 129.4, 132.2, 133.4, 138.0, 143.3; High-resolution MS, calcd for $C_{21}H_{33}NO_2S$: 363.2232. Found *m/z* (relative intensity): 363.2226 (M^+, 100), 361 (2), 348 (2).