HETEROCYCLES, Vol. 95, No. 2, 2017, pp. 722-729. © 2017 The Japan Institute of Heterocyclic Chemistry
Received, 31st August, 2016, Accepted, 14th October, 2016, Published online, 19th December, 2016
DOI: 10.3987/COM-16-S(S)59

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

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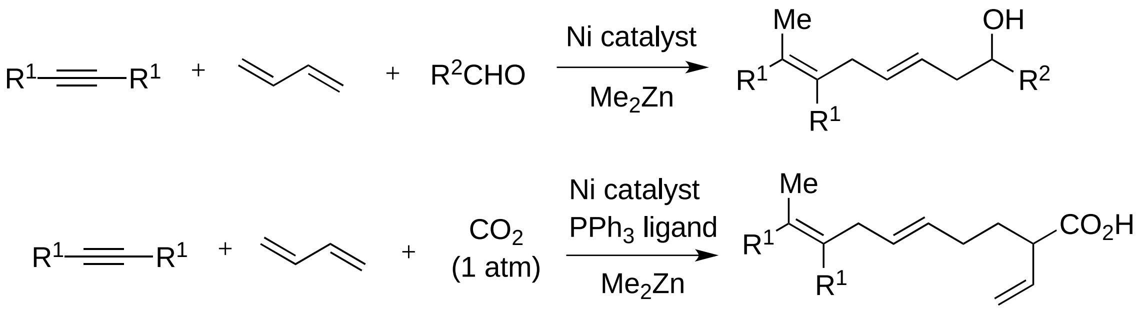
Dedicated to Prof. Dr. Masakatsu Shibasaki on the occasion of his 70th birthday

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.

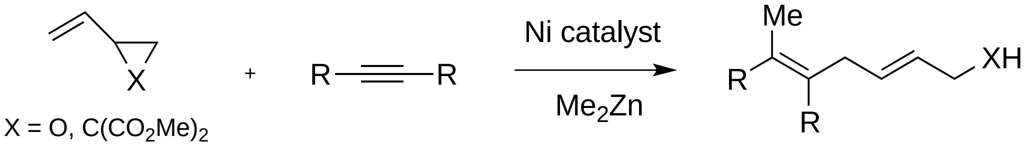
Nickelacycles are one of the most attractive and efficient active species for C-C bond transformations in modern organic synthesis.[1] Multi-component coupling reactions promoted by Ni-catalysts are straightforward and convenient methods for the construction of complicated molecules in material science 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

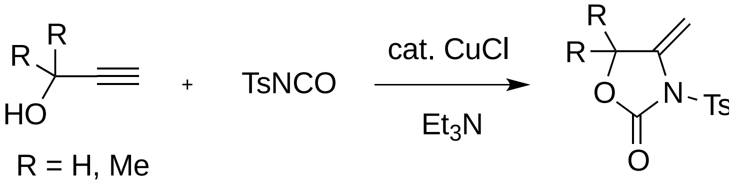
followed by dimerization to form a σ-allyl-π-allylnickel intermediate. 1,3-Butadiene can therefore provide C4 and C8 carbon units for multi-component coupling reactions involving π-allylnickel species.

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.

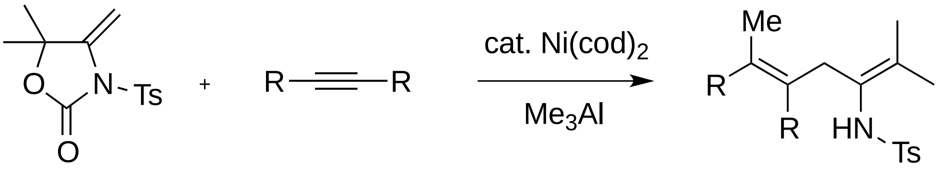


Scheme 2. Ni-Catalyzed three-component coupling with unsaturated compounds with Me_2Zn

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



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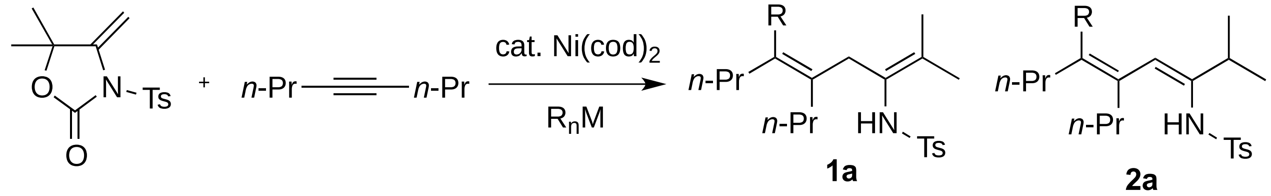
Scheme 4. Ni-Catalyzed three-component coupling of alkynes, 4-methylene-2-oxazolidinone, and Me_3Al

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

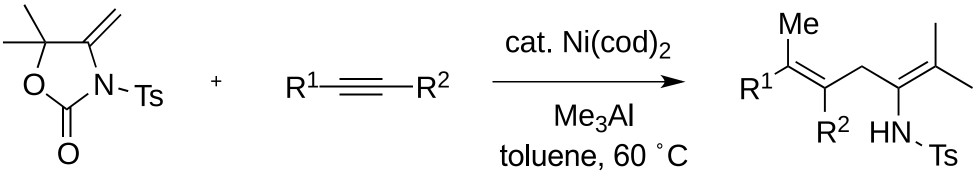


Entry	Organometallics R_nM	Solvent	Ligand	Yield (%) 1a	2a
1	Me_3Al	toluene	none	64	0
2	$Me_2Al(OMe)$	toluene	none	5	0
3	Me_2Zn	toluene	none	no reaction	
4	Et_3Al	toluene	none	complex mixture	
5	Et_2Zn	toluene	none	no reaction	
6	DIBAL-H	toluene	none	complex mixture	
7	Me_3Al	*n*-hexane	none	37	0
8	Me_3Al	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*-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**.

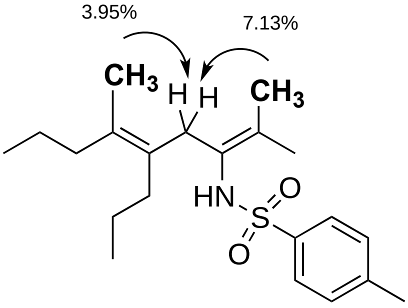
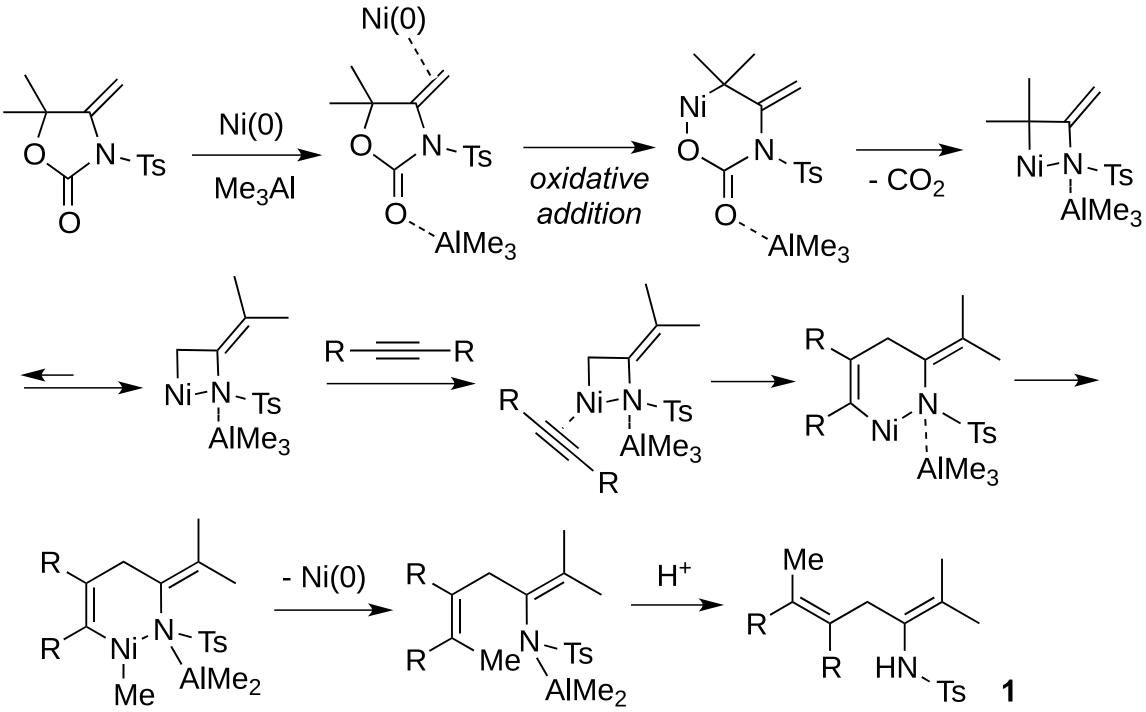


Figure 1. NOE data for irradiation of bold face protons in dienylamine **1a**

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

Financial support from the Ministry of Education, Culture, Sports, Science, and Technology, Japanese Government (Grant-in-Aid for Scientific Research (B) 26288052), is gratefully acknowledged.

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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$_3$Al (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}; ^{1}H 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).