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Nickel(0)-Catalyzed Three-Component Connection Reaction of Dimethylzinc, 1,3-Dienes, and Carbonyl Compounds**

Masanari Kimura, Shintaro Matsuo, Kazufumi Shibata, and Yoshinao Tamaru*

Since the discoveries of the thermal [4+2] cycloaddition reaction by Diels and Alder and nickel-catalyzed oligomerization by Wilke,^[1] 1,3-dienes have been recognized to be among the most useful synthetic blocks in organic synthesis. Significant expansion of their synthetic utility has been brought about by recent studies on transition metal catalyzed cyclizations^[2] and 1,2-/1,4-difunctionalization of 1,3-dienes (H, B;^[3] H, Si;^[4] H, Sn;^[5] B, B;^[6] B, Si;^[7] B, Sn;^[8] C, Si;^[9] Si, Si;^[10] Sn, Sn;^[11] etc.).^[12] In most cases, the products of the latter reactions are allylic metalloids that are capable of regio- and stereoselective allylation of carbonyl compounds.

We previously reported that, in the presence of a catalytic amount of [Ni(acac)₂] (acac = acetylacetonato) and a stoichiometric amount of triethylborane or diethylzinc, 1,3-dienes serve as a homoallyl anion equivalent and react with a wide range of carbonyl compounds to furnish bishomoallyl alcohols 1 in high yields and with high regio- and stereoselectivities^[13] (Scheme 1). A proposed mechanism involves nucleophilic addition of diene-nickel(0) complexes to carbonyl compounds coordinated by MR_n (MR_n = Et₂Zn or Et₃B) and ethyl group migration from M to Ni^{II} to yield an intermediate **I** (R = Et). This is followed by β -dehydronickelation and

[*] Prof. Dr. Y. Tamaru, Dr. M. Kimura, S. Matsuo, K. Shibata Department of Applied Chemistry Faculty of Engineering, Nagasaki University 1-14 Bunkyo-machi, Nagasaki 852-8521 (Japan) Fax: (+81)958-47-9008 E-mail: tamaru@net.nagasaki.u-ac.jp



Scheme 1. Nickel-catalyzed coupling of 1,3-dienes with alkylmetal reagents and carbonyl compounds.

reductive elimination to furnish ${\bf 1}$ and ethylene and regenerate $Ni^0.$

This sequence of reactions suggested to us that if dimethylzinc were used in place of diethylzinc, the β -dehydronickelation in the final step might be inhibited, and the intermediates **I** (R = Me) would undergo reductive elimination to provide homoallyl alcohols **2** or bis-homoallyl alcohols **7**. In fact, when dimethylzinc (4.8 mmol), 1,3-butadiene (8.0 mmol), and benzaldehyde (2.0 mmol) were exposed to [Ni(acac)₂] (0.2 mmol) in dry THF (5 mL) at room temperature for 2 h under N₂, the methyl group was transferred selectively to the distal allylic terminus, and homoallyl alcohol **2a** (R' = Ph, R'' = H in Scheme 1) was obtained in almost quantitative yield [Eq. (a), R = Ph; Table 1, entry 1]. In the product mixture, the corresponding regioisomeric product **7** (R' = Ph, R'' = H) was not detected at all.^[14]

$$Me_{2}Zn + H = \begin{pmatrix} 0 \\ R \end{pmatrix} \xrightarrow{0.1 [Ni(acac)_{2}]} (a)$$

$$OH \qquad OH$$

$$R \qquad OH$$

$$R \qquad OH$$

$$R \qquad OH$$

A number of nickel-catalyzed three-component connection reactions between organometallic compounds, alkynes (or strained alkenes), and carbonyl compounds have been reported;^[15] however, the present reaction, to the best of our knowledge, is the first example that utilizes conjugated dienes as the unsaturated hydrocarbon component.^[16] Although CrCl₂ also mediates a similar coupling reaction of alkyl iodides, 1,3-dienes, and carbonyl compounds, this reaction displays contrasting regioselectivity: The alkyl and carbonyl groups combine with 1,3-dienes at the C1 and C2 positions, respectively, to provide 2-alkylmethyl-3-buten-1-ols.^[17]

Intrigued by the synthetic possibilities and the facility with which dimethylzinc, 1,3-butadiene, and benzaldehyde combine with one another linearly in this sequence under very mild conditions with catalysis by Ni^0 in the absence of any

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Table 1. Nickel(0)-catalyzed coupling reaction of dimethylzinc, 1,3-dienes, and carbonyl compounds.^[a]

Entry	Carbonyl	1,3-Diene	$T [^{\circ}C]/t [h]$	Yield [%] ^[b, c]	
	compound			1:1:1 product ^[d]	1:2:1 product ^[e]
1	PhCHO	butadiene	25 (2)	2a : 99	3a : 0
2	РһСНО	butadiene	25 (1)	2b : 83	3b : 3
3	Сно	butadiene	25 (1)	2c : 73	3c : 17
4	tBuCHO	butadiene	25 (3)	2d : 75	3d : 20
5	∕=o	butadiene	30 (3)	2e : 0	3e : 89
6	PhCHO	isoprene	25 (5)	4a : 92 (<i>E</i> : <i>Z</i> = 2.2:1)	5a : 0
7	Рһсто	isoprene	30 (1)	4b : 40 ($E:Z=3.8:1$)	5b : 10
8	Сно	isoprene	30 (1)	4c : 62 ($E:Z=4.0:1$)	5c : 11
9	tBuCHO	isoprene	25 (3)	4d : 57 (<i>E</i> : <i>Z</i> = 2.4:1)	5d : 8
10	∕=o	isoprene	30 (3)	4e : 69 (<i>E</i> : <i>Z</i> =2.5:1)	5e : 10

[a] A mixture of [Ni(acac)₂](0.2 mmol), 1,3-butadiene or isoprene (8.0 mmol), an aldehyde or a ketone (2.0 mmol), and Me₂Zn (4.8 mmol, 1 μ in hexane) in dry THF (5 ml) was stirred at the indicated temperature under N₂ [Eqs. (a), (b)]. [b] Yields refer to the isolated materials. All products were characterized by ¹H NMR (400 MHz), ¹³C NMR (100 MHz), and IR spectroscopy, high-resolution mass spectrometry, and/or elemental analysis. [c] In addition to **2**–**5**, 1-methyl-3-phenylpropan-1-ol (15%, entry 2), 1-cyclohexylethan-1-ol (10%, entry 3), 1-methyl-3-phenylpropan-1-ol (48%, entry 7), or 1-cyclohexylethan-1-ol (20%, entry 8) was obtained. [d] The *E*:*Z* ratios are determined on the basis of ¹H and ¹³C NMR spectroscopy. [e] Compound **3** contains a small amount of an isomer (<10%),

phosphane ligands, we examined the scope of the present reaction by varying the type of carbonyl compound (Table 1, entries 1-5). Dihydrocinnamaldehyde furnished the expected **2b** in 83 % yield; however, the unexpected product **3b** (the 1:2:1 coupling product of dimethylzinc, 1,3-butadiene, and the aldehyde) was also obtained as a minor product in 3 % yield (entry 2). Interestingly, the relative amount of **3** to **2** gradually increased as the steric bulk around the carbonyl moiety increased (entries 3 and 4). Indeed, acetone gave **3e** as the sole product (entry 5).

The products **2** are regio- and stereochemically homogeneous; all possess the common structural features of (*E*)-3-hexen-1-ol (see Experimental Section). The (*E*,*E*)-3,7-decadien-1-ol structure of **3**^[18] was elucidated from spectroscopic data: In the ¹H NMR spectrum (400 MHz, CDCl₃) the olefin proton signals (multiplets) separated into signals integrating for 1 H (dt, J = 15.5, 6.0 Hz), 1 H (dt, J = 15.5, 6.0 Hz), and 2 H (m) in the presence of [Eu(fod)₃] (fod = 6,6,7,7,8,8,8-heptafluoro-2,2-dimethyl-3,5-octanedionato); the ¹³C NMR (100 MHz, CDCl₃) chemical shifts are in good agreement with the calculated values;^[19] and the IR spectrum contains a band at $\tilde{\nu} = 970$ cm⁻¹ (s).

We next examined the reaction of isoprene with carbonyl compounds under similar conditions [Eq. (b); Table 1, en-



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tries 6-10]. Isoprene selectively affords the 1:1:1 adducts 4. In contrast to 1,3-butadiene, isoprene even reacts with ketones to give 4 as the major product (entry 10). All the products 4 are regiochemically homogeneous; this indicates that isoprene selectively reacts at C1 with carbonyl compounds and at C4 with dimethylzinc. However, compounds 4 proved to be mixtures of stereoisomers ((E)- and (Z)-4 in a ratio of 2:1-4:1). As is apparent from 1H and 13C NMR spectra, 5 consists of more than three stereoisomers. However, close examination of three alcoholic fragments derived from 5 by ozonolysis and reduction of the reaction mixture with NaBH₄ revealed that 5 bears regiochemically homogeneous methyl groups at the C3 and C8 positions [Eq. (b)]; hence, isoprene molecules selectively combined with each other in a tail-to-tail manner.

The reaction mechanism remains speculative at present. One likely scenario is outlined in Scheme 2. The 1,3-butadiene – nickel(0) complex may



Scheme 2. Possible mechanism for the formation of 2/3 and 4/5.

react with carbonyl compounds by path a to give the 1:1:1 adducts $2^{[20]}$ An intermediate III (R = H) with a *syn*- π allylnickel(II) structure^[21] would undergo reductive elimination^[22] in such a way as to deliver the methyl group to the distal site, so that coordination of Ni⁰ with both Zn–O (nonbonding electron pair) and *trans*-CH=CH is better maintained.^[23] For less reactive carbonyl compounds, the potential of II to undergo oxidative cyclization might be insufficient to lead to III; hence, a small equilibrium concentration of bis-butadiene – nickel(0) complex V would then lead to VI. In this case, V is assumed to display higher reactivity than II owing to its greater polarizability (path b). Isoprene might react selectively by path a, irrespective of the type (reactivity) of carbonyl compound, since path b might be

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unfavorable owing to steric congestion in V (R = Me). A higher electron density on C1 of isoprene than on C4 might contribute to the selective nucleophilic C1 addition of isoprene to carbonyl compounds.

Organozinc compounds with no accessible β -hydrogen atoms can similarly undergo a three-component connection reaction. For example, as illustrated in Equation (c), diphenylzinc [1.2 mmol, from ZnCl₂ (1.2 mmol) and PhMgBr (2.4 mmol)] reacted with 1,3-butadiene (4.0 mmol) and benzaldehyde (1.0 mmol) to furnish (*E*)-1,5-diphenyl-3-penten-1ol (**6a**) in 61 % yield of isolated product.^[24] No 1:2:1 adducts were detected, even for the reaction with pivalaldehyde, from which **6b** was isolated as the sole product [Eq. (c)].

$$Ph_{2}Zn + H = \begin{pmatrix} 0 & 0.1 [Ni(acac)_{2}] \\ R & THF, 25 \ ^{\circ}C, 20 \ min \\ Ga: R = Ph, 61\% \\ Gb: R = fBu, 70\% \end{pmatrix}$$
 (c)

Experimental Section

(E)-1-phenyl-3-hexen-1-ol (2a): To a homogeneous solution of [Ni(acac)₂] (51.2 mg, 0.2 mmol) in dry THF (5 mL) were added 1,3-butadiene (670 µL, 8.0 mmol), benzaldehyde (212 mg, 2.0 mmol), and dimethylzinc (4.8 mL, 1_M in hexane). The mixture was stirred at room temperature for 2 h under N₂ and then quenched by adding 2M HCl (5 mL). The mixture was extracted with ethyl acetate $(2 \times 20 \text{ mL})$, and the organic extracts were combined, washed with saturated NaHCO3, dried over MgSO4, and concentrated in vacuo. The residue was purified by column chromatography on silica gel with hexane/ethyl acetate (64/1) to give 1a in 99% yield. $R_f = 0.42$ (hexane/ethyl acetate, 8/1); IR (neat): $\tilde{\nu} = 3400$ (s), 1500 (s), 1460 (s), 1050 (s), 970 (s), 760 cm⁻¹ (s); ¹H NMR (400 MHz, CDCl₃, TMS): $\delta =$ 0.98 (t, J = 7.3 Hz, 3 H), 1.86 (br s, 1 H), 2.05 (br dq, J = 6.2, 7.3 Hz, 2 H), 2.39 (m, 1 H, coalesces to br dd, J = 8.1, 13.9 Hz on irradiation at $\delta = 5.40$), 2.47 (m, 1 H, coalesces to br dd, $J\!=\!4.8,\,13.9$ Hz on irradiation at $\delta\!=\!5.40),\,4.68$ (dd, J = 4.8, 8.1 Hz, 1 H), 5.40 (ddm, J = 6.2, 15.4 Hz, 1 H), 5.63 (br dt, J = 15.4, 6.2 Hz, 1 H), 7.24 – 7.29 (m, 5 H); ¹³C NMR (100 MHz, CDCl₃, TMS): $\delta\,{=}\,13.7, 25.6, 42.7, 73.5, 124.5, 125.8, 127.3, 128.3, 136.6, 144.1;$ HR-MS calcd for C₁₂H₁₆O: 176.1201; found (%): 176.1195 (2) [M⁺], 107 (100), 77 (23), 69 (3).

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