Monoterpenoid Synthesis by Transition Metal Catalyzed Coupling of Enediylmagnesium with C_5-Organic Halides

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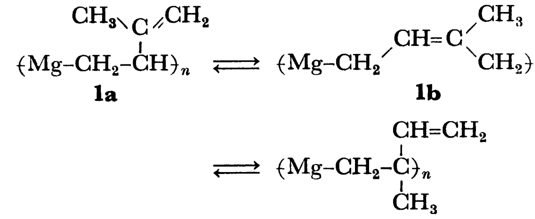
Synopsis. A series of isoprene coupling dimers bonded at 1-2, 1-3, 1-4, 2-4, 3-4, or 4-4 position was prepared by regiocontrolled catalysis of trasition metals or without catalysts in the reaction of 2-methyl-2-butene-1,4-diylmagnesium or 3-methyl-2-butenylmagnesium chloride with C_5-alkenyl halides.

Organolithium-[1] or organomagnesium-[2] assisted terpenoid synthesis by insertion of isoprene to metal-carbon bond have recently been extensively studied and transition metal catalysts have been found to be effective for selective 1,4-addition of isoprene to these organometals. We have investigated the monoterpene synthesis using unique bifunctional 2-methyl-2-butene-1,4-diylmagnesium **1**, which is now readily obtainable by direct reaction of magnesium with isoprene.[3] The compound **1** is more reactive than the usual alkyl- or allylmagnesium compounds due to the higher ionicity of metal-carbon bond[3] and has four reactive sites, C_1, C_2, C_3, and C_4, arisen from the following rapid equilibrium, though the most part of it assumes the structure **1b** in tetrahydrofuran. This paper describes the selective synthesis of 1-4 (head to tail), 3-4, and 2-4 bonded isoprene dimers consisting of the same carbon skeleton as naturally occurring monoterpenoids by regiocontrolled catalysis in the reaction of **1** or 3-methyl-2-butenylmagnesium chloride.



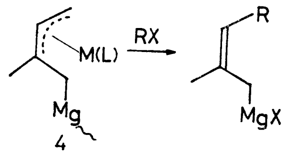
$$\underset{\textbf{1a}}{\left(\text{Mg-CH}_2\text{-}\overset{\overset{\text{CH}_3\diagdown\text{C}\diagup\!\!\!\!=\text{CH}_2}{|}}{\text{CH}}\right)_n} \rightleftarrows \underset{\textbf{1b}}{\left(\text{Mg-CH}_2\diagup\text{CH=C}\overset{\diagup\text{CH}_3}{\diagdown}\text{CH}_2\right)_n} \rightleftarrows \underset{\textbf{1c}}{\left(\text{Mg-CH}_2\text{-}\overset{\overset{\text{CH=CH}_2}{|}}{\underset{\underset{\text{CH}_3}{|}}{\text{C}}}\right)_n} \qquad (1)$$

The 1:1 reaction of **1** with 1-chloro-3-methyl-2-butene in THF at 30 °C for 1 h followed by hydrolysis gave a 4-3 bonded isoprene dimer, 2,3,6-trimethyl-1,5-heptadiene **2** (78%), and a 4-4 bonded dimer, 2,7-dimethyl-1,6-octadiene **3** (22%) in 99% combined yield. Thus, C_3-carbon atom of **1** reacts predominantly. To realize the regioselective control of the various reaction sites in equilibrium, catalysis of Ni(II), Pd(II), and Ti(IV) complexes was examined since these are known as effective catalysts for regio- or stereoselective coupling of allyl halides with organomagnesium compounds.[2,4] The reaction required lower temperatures (0—5 °C) for the effective catalysis because **1** is reactive at 30 °C towards alkenyl halides without catalysts. As shown in Table 1, the addition of Ni(II) or Pd(II) complexes was effective for selective 4-4 coupling of the isoprene units and hydrolysis of the product with dilute aqueous (2 mol dm^{-3}) HCl gave **3** exclusively. This result may be explained by considering **4** as the intermediate. $TiCl_2(\eta^5\text{-}C_5H_5)_2$ and $ZrCl_2(\eta^5\text{-}C_5H_5)_2$ were not so effective for this system presumably due to the formation of catalytically inactive Cp_2M(isoprene) complexes.[5]

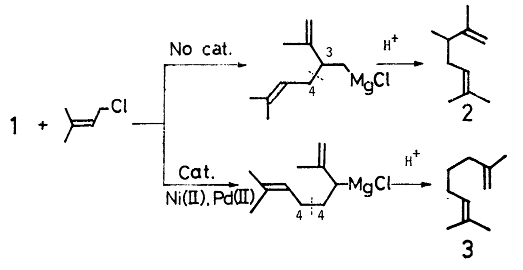
Table 1. Regioselection in reaction of **1** with 1-chloro-3-methyl-2-butene in THF[a)]

Catalyst	% Ratio of regioisomer		Yield/%
	2	**3**	
None[b)]	78	22	99
$NiCl_2(PPh_3)_2$	12	88	72
$NiCl_2$	29	71	65
$PdCl_2(PPh_3)_2$	6	94	75
$PdI_2(PPh_3)_2$	17	83	83

a) Reaction was carried out at 0 °C for 10 h in the presence of catalst (2 mol%) and the reaction mixture was hydrolyzed. b) Reacted at 30 °C for 5 h.



The successful control of the regioselectivity prompted us to prepare myrcene by reaction of **1** with 2-chloromethyl-1,3-butadiene using the Ni(II) catalysts. The reaction proceeds in good yield (75—78%) and myrcene **6** was obtained in 93—95% selectivity by hydrolysis (Table 2). The ratio of α-(**6a**) to β-myrcene **6b** was 8:2 but the ratio changed to 3:7 by protonation with piperidine or pyrrolidine depending on the basicity of protonolysis agents. Similar interconversion have been observed in the protonolysis of enediylmagnesium.[3] In the absence of catalyst, C_3-atom of **1** predom-



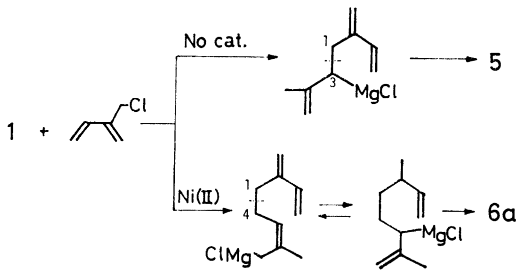
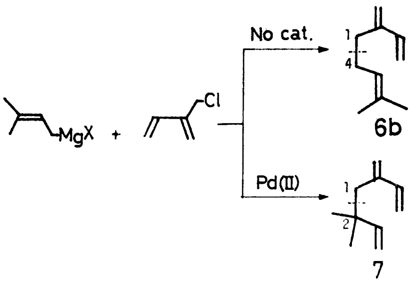


Table 2. Products of transition-metal catalyzed reaction of **1** with 2-chloromethyl-1,3-butadiene in THF[a)]

Catalyst	% Products ratio **5**	% Products ratio **6**	Yield/%
None[b)]	92	8	99
$NiCl_2$(dppe)[c)]	5	95	75
$NiCl_2(PPh_3)_2$	7	93	78
$PdCl_2(PPh_3)_2$	41	59	89
$(\eta^5\text{-}C_5H_5)_2TiCl_2$	73	27	62

a) The reaction mixture was hydrolyzed, after carrying out the reaction at 0 °C for 10 h in the presence of catalyst (2 mol%). b) Reaction was done at 30 °C for 1 h. c) 1,2-Bis(diphenylphosphino)ethane complex.

inantly was alkylated with 2-chloromethyl-1,3-butadiene to give a 1-3 bonded dimer, 2,3-dimethyl-5-vinyl-1,5-hexadiene **5**, consistent with the reaction shown in Eq. 1. The reaction of 3-methyl-2-butenylmagnesium chloride with 2-chloromethyl-1,3-butadiene also produced pure β-myrcene in 92% yield without catalyst. The addition of 2.0 mol% of $PdCl_2(PPh_3)_2$ catalyst caused the production of 2-1 bonded isoprene dimer **7** in 80% regioselectivity (68% yield). If this Pd(II) catalyzed reaction is applicable also to the reaction of 3-methyl-2-butenylmagnesium chloride with 1-chloro-3-methyl-2-butene, the 2-4 bonded isoprene dimer whose carbon skeleton is identical with yomogi alcohol or artemisia alcohol should be formed. Actually the 2-4 bonded dimer formed but the selectivity was poor (25%) presumably due to the rapid reaction in the absence of catalyst to give a 4-4 bonded dimer even at 0 °C. The dimer **3** was obtained in 75% selectivity (70% yield) in this case.



One of the most important characteristics of the reaction shown in Eqs. 1 and 2 is that the products still retain the reactivity towards a further attack of dienes or electrophiles for preparation of various derivatives of sesqui- or diterpenes. The regioselectivity observed in the present Ni(II) or Pd(II)-catalyzed reaction is considered to be due to the combined steric and electronic effects of the $-CH_2MgCl$ substituent on the η^3-allyl moiety.

Experimental

2-Methyl-2-buten-1,4-diylmagnesium **1** was prepared as previously noted.[3)] 1-Chloro-3-methyl-2-butene prepared according to the method of Tanaka[6)] and 2-chloromethyl-1,3-butadiene by Alieva's method[7)] were purified by distillation after drying over calcium hydride. All the reaction products were characterized by ^1H NMR, IR, and MS in essentially the same way as described previously.[3)]

Reaction of 1 with 1-Chloro-3-methyl-2-butene. To the THF (40 ml) solution of **1** (1.0 g, 11 mmol) was added 1-chloro-3-methyl-2-butene (1.1 ml, 10 mmol) at −70 °C and then transition metal catalysts (2.0 mol% of **1**). The mixture was allowed to react at 0 °C for 10 h under magnetic stirring and was hydrolyzed with 2 mol dm^{-3} HCl after the addition of pentane (50 ml). The pentane fraction was distilled and the products were finally separated by gas chromatography. Resulting 2,3,6-trimethyl-1,5-heptadiene **2** and 2,7-dimethyl-1,6-octadiene **3** were identified with authentic samples obtained from **1** and isoprene.[3)]

Reaction of 1 with 2-Chloromethyl-1,3-butadiene. The reaction of **1** (1.0 g, 11 mmol) with 2-chloromethyl-1,3-butadiene (1.0 ml, 10 mmol) was carried out under the same reaction conditions as above mentioned reaction. Piperidine (2.0 ml, 20 mmol) or pyrrolidine (1.7 ml, 20 mmol) was added and the mixture was heated to 50 °C for 30 min for the complete protonation. Resulting α- and β-myrcene were identified with authentic samples purchased from Takasago Perfumary Co. with NMR and IR. Characterization of the 1-3 bonded isoprene dimer was made from the following data.

2,3-Dimethyl-5-vinyl-1,5-hexadiene: IR (neat) 1644, 1595, 992, 891 cm^{-1}; NMR($CDCl_3$) $\delta=6.38$ (d of d, 1, $J=10.3$ and 16.9, CH), 5.23 and 5.00 (two d, 4, CH_2), 4.69 (d, 2, $J_{gem}=1.9$, CH_2), 2.26 (d, 2, $J=7.8$, CH_2), 2.02 (m, 1, CH), 1.69 (s, 3, CH_3), 0.99 (d, 3, CH_3); M^+ 136. Calcd for $C_{10}H_{16}$; M, 136.

Reaction of 3-Methyl-2-butenylmagnesiumchloride with Alkenyl Halides. To the 3-methyl-2-butenylmagnesiumchloride (1.4 g, 11 mmol) in THF (40 ml) was added THF solution (5 ml) of 2-chloromethyl-1,3-butadiene (1.0 ml, 10 mmol) or 1-chloro-3-methyl-2-butene (1.1 ml, 10 mmol) at −70 °C. Reaction was carried out at 0 °C for 10 h. The reaction products were distilled, isolated with preparative GC and identified with authentic samples[3)] except the followings.

3,3-Dimethyl-5-vinyl-1,5-heptadiene 7. IR (neat) 1640, 1593, 1415, 1382, 1366, 990, 895 cm^{-1}; NMR ($CDCl_3$) $\delta=6.36$ (d of d, 1, CH), 5.87 (d of d, 1, CH), 5.25 and 5.00 (two d, 2, CH_2), 5.03 and 4.85 (two d, 2, CH_2), 4.96 (bs, 2, CH_2), 2.21 (s, 2, CH_2), 1.01 (s, 6, CH_3); M^+, 136. Calcd for $C_{10}H_{16}$; M, 136.

3,3,6-Trimethyl-1,5-heptadiene(2-4 Bonded Dimer). IR (neat) 1674, 1643, 995, 908, 884, 830 cm^{-1}; NMR ($CDCl_3$) $\delta=5.80$ (d of d, 1, CH), 5.51 (t, 1, CH), 4.68 and 4.91 (two d, 2, CH_2), 2.25 (d, 2, CH_2), 1.98 (bs, 12, CH_3); M^+, 138. Calcd for $C_{10}H_{18}$; M, 138.

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