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Transition-metal-catalyzed Grignard Reaction of Isoprene Bromohydrin

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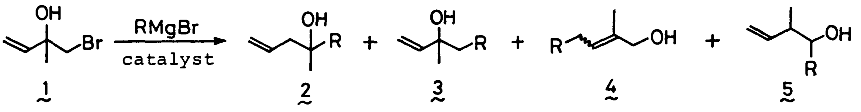
Synopsis. The coupling reaction of isoprene bromohydrin with aryl and alkyl Grignard reagents catalyzed by tetrakis(triphenylphosphine)palladium(0) selectively gave the vinyl-group-migrated products.

Isoprene bromohydrin (1-bromo-2-methyl-3-buten-2-ol) (**1**), easily obtainable from the reaction of *N*-bromosuccinimide and isoprene in tetrahydrofuran-water, is an interesting compound because of the unique behavior toward organometallic reagents. The reaction of **1** with allylic Grignard reagents in the presence of copper(I) iodide selectively gave vinyl-group-migrated products.[1] The copper(I)-catalyzed reaction of **1** with alkyllithium which has β-hydrogen yielded 2-alkyl-4-penten-2-ol, whereas with methyl-, phenyl-, or benzyllithium, 4-substituted 2-methyl-2-buten-1-ol was formed exclusively.[2] In order to examine further the transition-metal-catalyzed Grignard reaction of **1**, we tested various transition metal compounds and found that a palladium(0) complex was the most effective for the migration of the vinyl group of **1**.

Using phenylmagnesium bromide as a representative Grignard reagent, the product distribution under various catalysts was examined. The reactions were carried out in tetrahydrofuran using 5-fold excess of the Grignard reagent. In the absence of catalysts, a mixture of 2-methyl-4-phenyl-2-buten-1-ol (**4a**) and 2-methyl-1-phenyl-3-buten-1-ol (**5a**) was formed in the ratio of 37:63, together with trace amounts of 2-phenyl-4-penten-2-ol (**2a**) and 2-methyl-1-phenyl-3-buten-2-ol (**3a**). The alcohols (**4a** and **5a**) are considered to be produced *via* isoprene oxide.[2] Eight kinds of transition metal complexes, which are known as effective catalysts for the cross-coupling between Grignard reagents and organic halides,[3] were examined. Results are summarized in Table 1. Titanocene dichloride and cobalt(II) chloride did not show a significant catalytic effect. The reaction yields were poor in the cases of tris(1,3-diketonato)-iron(III) complexes and palladium(II) chloride. As reported,[1] copper(I) iodide-catalyzed reaction gave a 56:44 mixture of **2a** and **3a**. The selectivity (**2a** *vs.* **3a**) was improved by the use of bis(triphenylphosphine)-



a: R = Ph
b: p-$CH_3C_6H_4$
c: n-C_4H_9
d: n-C_6H_{13}

Table 1. Yield and product distribution of the transition-metal-catalyzed Grignard reaction of **1**

RMgBr	Catalyst	(mol%)[a]	Total Yield/%	Product Distribution			
				2	**3**	**4**(*E*/*Z*)	**5**
PhMgBr	none	—	62	tr	tr	37(3/2)	63
PhMgBr	Cp_2TiCl_2	(5)	82	tr	tr	52(4/1)	48
PhMgBr	$CoCl_2$	(5)	96	34	2	40(8/1)	24
PhMgBr	$Fe(DBM)_3$[b]	(5)	21	90	10	—	—
PhMgBr	$Fe(acac)_3$	(5)	19	89	11	—	—
PhMgBr	$PdCl_2$	(5)	7	100	tr	—	—
PhMgBr	CuI	(50)	78	56	44	—	—
PhMgBr	$Ni(PPh_3)_2Cl_2$	(5)	82	95	5	—	—
PhMgBr	$Pd(PPh_3)_4$	(0.5)	85	100	—	—	—
p-$CH_3C_6H_4MgBr$	$Pd(PPh_3)_4$	(0.5)	75	100	—	—	—
n-C_4H_9MgBr	$Pd(PPh_3)_4$	(0.5)	53	100	—	—	—
n-$C_6H_{13}MgBr$	$Pd(PPh_3)_4$	(0.5)	89	100	—	—	—

a) Of the bromohydrin used. b) Tris(dibenzoylmethanato)iron(III).

nickel(II) chloride. Of the eight catalysts which are examined, tetrakis(triphenylphosphine)palladium(0) was found to be the most effective, leading exclusive formation of the vinyl-group-migrated product (**2a**) in 85% yield. *p*-Tolylmagnesium bromide also gave the migration product (**2b**) with high selectivity in the presence of a catalytic amount (0.5 mol%) of the palladium(0) complex. This catalyst is also effective for the reaction with alkyl Grignard reagents. Coupling reactions with butyl- and hexylmagnesium bromides exclusively gave the respective homoallylic alcohols (**2c** and **2d**) in 53 and 89% yields. However, the reactions of **1** with allyl and benzylmagnesium chlorides gave complex reaction mixtures even in the presence of the palladium(0) complex.

Experimental

General. Infrared spectra were recorded on a JASCO IRA-1 spectrophotometer. ^{1}H NMR spectra were recorded on a Hitachi R-24A spectrometer (60 MHz) or on a Varian XL-200 spectrometer (200 MHz) with Me_4Si as internal standard. Mass spectra were determined using a Hitachi M-52 instrument at 20 eV. Glc analyses and preparative glc were performed on a Yanaco G1800 gas chromatograph equipped with a column packed with 20% polyethylene glycol (PEG) 20M on Celite 545 (1 m×3 mm). Elemental analyses were performed at the Elemental Analysis Center of Kyoto University. For Kugelrohr distillation, a Shibata GTO-250R glass tube oven was used.

Preparation of 1. To a suspension of *N*-bromosuccinimide (12.3 g, 69 mmol) in a mixture of tetrahydrofuran (THF)–water (3:2) (120 cm^3) was added a solution of isoprene (7.0 g, 103 mmol) in THF (50 cm^3) at 0 °C. The reaction mixture was left at 0 °C for 3 h and then overnight at room temperature. The reaction mixture was poured into a saturated aqueous sodium chloride solution and the organic layer was separated. The aqueous layer was extracted with ether and the combined organic extracts were washed with brine and dried (Na_2SO_4). The solvent was evaporated and the residue was distilled under reduced pressure to give **1** as a colorless oil (6.9 g, 61%). **1**:[4] bp 69—70 °C/46 Torr (1 Torr≈133.322 Pa); IR (neat) 3430, 2990, 1412, 1372, 1239, 1056, and 930 cm^{-1}; ^{1}H NMR (CCl_4) 5.85 (dd, J=17, 10 Hz, 1H, olefin), 5.25 (dd, J=17, 2 Hz, 1H, olefin), 5.08 (dd, J=10, 2 Hz, 1H, olefin), 3.37 (s, 2H, CH_2), 2.02 (bs, 1H, OH), 1.33 (s, 3H, CH_3).

Transition-metal-catalyzed Grignard Reaction of Isoprene Bromohydrin (1). The following example represents the general procedure. To a solution of phenylmagnesium bromide, prepared from magnesium turnings (600 mg, 25 mg-atom) and bromobenzene (2.12 cm^3, 25 mmol) in THF (20 cm^3), was added tetrakis(triphenylphosphine)-palladium (29 mg, 0.025 mmol) and the mixture was stirred at 0 °C for 10 min. A solution of **1** (825 mg, 5 mmol) in THF (5 cm^3) was then added at 0 °C and the mixture was left overnight at room temperature. The reaction was quenched by the addition of water and the product was extracted with ether. The extracts were dried (Na_2SO_4) and the solvent was evaporated. In order to remove less polar impurities such as biphenyl, the residue was adsorbed on a silica-gel column and eluted first with benzene (50 cm^3) and then with ether (100 cm^3). The ether eluate was concentrated and distilled (Kugelrohr) (bp 100 °C/3 Torr) to produce a colorless oil (689 mg, 85%). Glc analysis revealed that this oil was pure **2a**.

In other experiments, the reaction mixture was treated in a similar manner and the product distribution was analyzed by glc. Results are summarized in Table 1. Pure samples of the products were obtained by preparative glc and the structures were deduced by their spectral and analytical data.

2-Phenyl-4-penten-2-ol (2a): IR (neat) 3430, 1642, 1498, 1448, 917, 768, and 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.50—7.20 (m, 5H, Ph), 5.66 (m, 1H, olefin), 5.16 (m, 2H, olefin), 2.63 (m, 2H, CH_2), 1.60 (bs, 1H, OH), 1.58 (s, 3H, CH_3); Mass m/z 162 (M^+); Found: C, 81.19; H, 8.55%. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70%.

2-Methyl-1-phenyl-3-buten-2-ol (3a): IR (neat) 3420, 1646, 1608, 1498, 1454, 1103, 928, and 706 cm^{-1}; ^{1}H NMR (CCl_4) 7.00 (m, 5H, Ph), 5.78 (dd, J=17, 10 Hz, 1H, olefin), 4.95 (dd, J=17, 2 Hz, 1H, olefin), 4.81 (dd, J=10, 2 Hz, 1H, olefin), 2.68 (s, 2H, CH_2), 1.60 (bs, 1H, OH), 1.17 (s, 3H, CH_3); Mass m/z 162 (M^+); Found: C, 81.43; H, 8.56%. Cacld for $C_{11}H_{14}O$: C, 81.44; H, 8.70%.

2-Methyl-4-phenyl-2-buten-1-ol (4a) (a 3:2 mixture of *E*- and *Z*-isomers):[5] IR (neat) 3350, 2924, 1602, 1498, 1456, 1016, and 996 cm^{-1}; ^{1}H NMR (CCl_4) 7.03 (m, 5H, Ph), 5.43 (t, J=7 Hz, 1H, olefin), 4.03 (s, 0.8H, $Z\text{-C}\underline{\text{H}}_2\text{OH}$), 3.83 (s, 1.2H, $E\text{-C}\underline{\text{H}}_2\text{OH}$), 3.27 (d, J=7 Hz, 2H, $\text{C}\underline{\text{H}}_2\text{Ph}$), 2.03 (bs, 1H, OH), 1.72 (m, 1.2H, Z-CH_3), 1.67 (s, 1.8H, E-CH_3); Mass m/z 162 (M^+).

2-Methyl-1-phenyl-3-buten-1-ol (5a) (a 5:4 mixture of diastereomers): IR (neat) 3430, 1644, 1498, 1454, 1022, 916, 765, and 702 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.35 (m, 5H, Ph), 5.80 (m, 1H, olefin), 5.30—5.00 (m, 2H, olefin), 4.63 (d, J=5 Hz, 0.56H, $\text{C}\underline{\text{H}}\text{OH}$), 4.38 (d, J=8 Hz 0.44H, $\text{C}\underline{\text{H}}\text{OH}$), 2.56 (m, 1H, $\text{C}\underline{\text{H}}\text{CH}_3$), 1.97 (bs, 1H, OH), 1.01 (d, J=7 Hz, 1.67H, CH_3), 0.87 (d, J=7 Hz, 1.33H, CH_3); Mass m/z 162 (M^+); Found: C, 81.39; H, 8.94%. Calcd for $C_{11}H_{14}O$: C, 81.44; H, 8.70%.

2-(p-Tolyl)-4-penten-2-ol (2b): IR (neat) 3430, 1644, 1521, 1374, 920, and 822 cm^{-1}; ^{1}H NMR ($CDCl_3$) 7.21 (AA′BB′, 4H, Ph), 5.60 (m, 1H, olefin), 5.06 (m, 2H, olefin), 2.50 (m, 3H, CH_2+OH), 2.30 (s, 3H, CH_3), 1.49 (s, 3H, CH_3); Mass m/z 176 (M^+); Found: C, 81.50; H, 8.97%. Calcd for $C_{12}H_{16}O$: C, 81.77; H, 9.15%.

4-Methyl-1-octen-4-ol (2c):[2] IR (neat) 3400, 1646, 1472, 1380, 1160, and 914 cm^{-1}; ^{1}H NMR (CCl_4) 6.10—4.60 (m, 3H, olefin), 2.10 (d, J=7 Hz, 2H, allyl CH_2), 1.70 (bs, 1H, OH), 1.30 (m, 6H, $CH_2\times3$), 1.03 (s, 3H, CH_3), 0.88 (bt, 3H, CH_3); Mass m/z 124 ($M-H_2O$).

4-Methyl-1-decen-4-ol (2d):[6] IR (neat) 3400, 1645, 1472, 1382, 1159, and 916 cm^{-1}; ^{1}H NMR (CCl_4) 6.20—4.80 (m, 3H, olefin), 2.15 (d, J=7 Hz, 2H, allyl CH_2), 1.65 (bs, 1H, OH), 1.30 (m, 10H, $CH_2\times5$), 1.08 (s, 3H, CH_3), 0.89 (bt, 3H, CH_3), Mass m/z 152 ($M-H_2O$).

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