Unprecedented γ-Selective Nucleophilic Substitution Reaction of Allylmetal Reagents: A New Cross-Coupling of Diphenylphosphates with Allylic Grignard Reagents

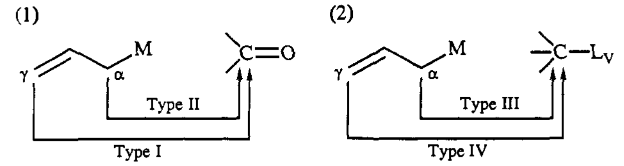
Akira Yanagisawa, Hiroaki Hibino, Nobuyoshi Nomura, and Hisashi Yamamoto*

School of Engineering, Nagoya University
Chikusa, Nagoya 464-01, Japan

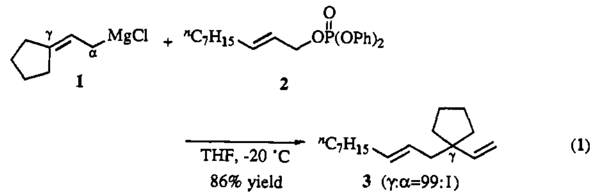
Received March 8, 1993

Most allylmetal reagents combine with carbonyl compounds by the S_E2' pathway to afford homoallylic alcohols selectively (Type I, Scheme I).[1] A method described previously permits selective coupling with carbonyl compounds at the α-position (Type II) using allylbarium reagent.[2] The same reagent reacts with alkyl halides to give α-alkylation product almost exclusively (Type III).[3] We shall first describe a new selective coupling of Type IV, the selective γ-coupling of an allylmetal reagent with alkyl halides which closes this methodological gap.

Scheme I



Reaction of (*E*)-2-decenyl 1-diphenylphosphate (**2**) with 1.1 equiv of 2-cyclopentylideneethylmagnesium chloride (**1**) in THF at -20 °C gave the γ-alkylated product **3** in 86% yield with a γ/α ratio of 99/1 (eq 1). Thus, the γ-carbon of the Grignard reagent **1** attacked the primary carbon of the phosphate **2**.



The unprecedented feature of this coupling reaction is appealing in organic synthesis, and thus, using the allylic diphenylphosphate as substrate,[4] we carefully studied the selectivity of this process.[5] Among the variety of allyl metals, Grignard reagent was found to be the most effective. γ/α ratios of the products obtained by the reaction of (*E*)-2-hexenyl 1-diphenylphosphate with other geranyl metal reagents in THF at -78 °C were, for M = Li,[6] γ/α = 88/12; for M = K,[8] γ/α = 84/16; for M = Mg, γ/α = 94/6; and for M = Ba,[2,3] γ/α = 56/44. Using geranyl Grignard reagent as a nucleophile, we examined the various kinds of leaving groups,and only the diphenylphosphate ester revealed this unique regioselectivity. For example, reaction of (*E*)-2-hexenyl bromide with geranylmagnesium chloride at -78 °C resulted in much lower γ-selectivity (γ/α = 84/16) with moderate yield (67%). Use of the corresponding mesylate at 20 °C afforded a similar result (γ/α = 85/15) in low yield (16%). Reaction of (*E*)-2-hexenyl 1-diethylphosphate at 0 °C resulted in a totally unacceptable regioselectivity (γ/α = 65/35, 39%).

Table I summarizes the results obtained for the reaction of various diphenylphosphates with 1.1 equiv of allylic Grignard reagents at -20 °C[9] in THF.[10] The characteristic features of the results are as follows: (1) all reactions resulted in high yields with remarkable γ-selectivities not only with allylic diphenylphosphates but also with alkyl (entries 13 and 14), benzylic (entry 12), and propargylic diphenylphosphates (entries 10 and 11); (2) the alkyl substituent at the β-position of allylic diphenylphosphate had no effect on the regioselectivities (entries 8 and 9); (3) the siloxy group at the C-4 position did not affect the reaction course (entry 8); and (4) no allenylated product was obtained in the reaction using propargyl diphenylphosphate (entry 11).

The reason for these striking features in regioselectivity have not yet been fully elucidated. It may be due to the fact that, in the normal alkylation of an allyl metal to an alkyl halide, an acyclic transition structure is formed that brings a mixture of α- and γ-alkylation products. With diphenylphosphates, on the other hand, bidentate leaving groups coordinate with magnesium metal, as shown in Figure 1, to produce a γ-alkylation product selectively via a rigid bicyclic transition structure.[11,12]

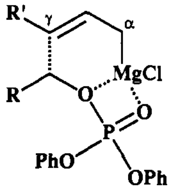


Figure 1. Rigid bicyclic transition structure formed in the reaction of diphenylphosphates when bidentate leaving groups coordinate with Mg to produce a γ-alkylation product.

In sharp contrast, the dimethylthiophosphates, for which the longer P–S bond would be expected,[13] showed entirely different

---

[1] A review: Courtois, G.; Miginiac, L. *J. Organomet. Chem.* **1974**, *69*, 1.

[2] Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 8955.

[3] (a) Yanagisawa, A.; Hibino, H.; Habaue, S.; Hisada, Y.; Yamamoto, H. *J. Org. Chem.* **1992**, *57*, 6386. (b) Corey, E. J.; Shieh, W.-C. *Tetrahedron Lett.* **1992**, *33*, 6435.

[4] Phosphate leaving groups were effective for S_N2'-, (*E*)-, and antiselective reactions between organocuprates and allylic alcohol derivatives: Yanagisawa, A.; Nomura, N.; Noritake, Y.; Yamamoto, H. *Synthesis* **1991**, 1130.

[5] Recent approaches to γ-selective cross-coupling reactions of allylic halides: (a) Yamamoto, Y.; Maruyama, K. *J. Am. Chem. Soc.* **1978**, *100*, 6282. (b) Yamamoto, Y.; Yatagai, H.; Maruyama, K. *J. Am. Chem. Soc.* **1981**, *103*, 1969. (c) Trost, B. M.; Keinan, E. *Tetrahedron Lett.* **1980**, *21*, 2595. (d) Godschalx, J.; Stille, J. K. *Tetrahedron Lett.* **1980**, *21*, 2599. (e) Yamamoto, Y.; Maruyama, K.; Matsumoto, K. *J. Chem. Soc., Chem. Commun.* **1984**, 548. (f) Calò, V.; Lopez, L.; Pesce, G. *J. Chem. Soc., Chem. Commun.* **1985**, 1357. (g) Calò, V.; Lopez, L.; Pesce, G. *J. Chem. Soc., Perkin Trans. 1* **1988**, 1301. (h) Araki, S.; Shimizu, T.; Jin, S.; Butsugan, Y. *J. Chem. Soc., Chem. Commun.* **1991**, 824. See also: (i) Hatanaka, Y.; Ebina, Y.; Hiyama, T. *J. Am. Chem. Soc.* **1991**, *113*, 7075.

[6] Prepared from geranyl chloride and lithium biphenylide:[7] Yanagisawa, A.; Habaue, S.; Yamamoto, H. *J. Am. Chem. Soc.* **1991**, *113*, 5893.

[7] (a) Holy, N. L. *Chem. Rev.* **1974**, *74*, 243. (b) Cohen, T.; Bhupathy, M. *Acc. Chem. Res.* **1989**, *22*, 152.

[8] Prepared by transmetalation of geranyltrimethyltin with Me_3SiCH_2K in THF at -78 °C: Ståhle, M.; Hartmann, J.; Schlosser, M. *Helv. Chim. Acta* **1977**, *60*, 1730.

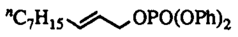
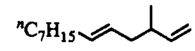
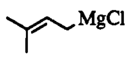
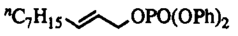
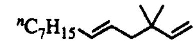
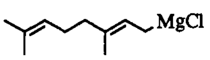
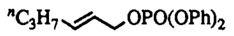
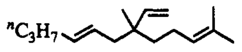
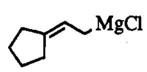
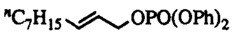
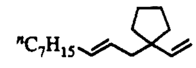
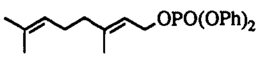
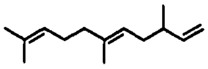
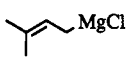
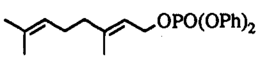
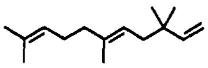
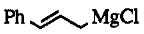
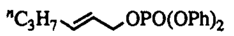
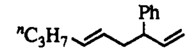
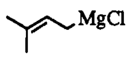
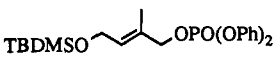
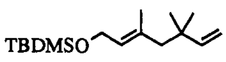
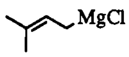
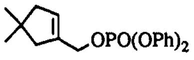
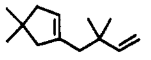
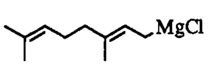
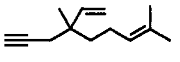
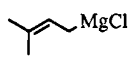
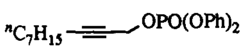
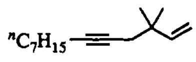
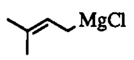
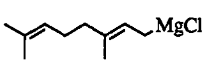
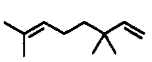
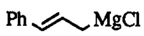
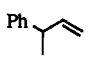
[9] This is the optimum temperature for obtaining the best yield and regioselectivity.

[10] A representative experimental procedure is given by the reaction of (*E*)-2-decenyl 1-diphenylphosphate with 2-cyclopentylideneethylmagnesium chloride (entry 4 in Table I): To a solution of (*E*)-2-decenyl diphenylphosphate (386 mg, 1.0 mmol) in dry THF (6 mL) was added dropwise at -20 °C a solution of 2-cyclopentylideneethylmagnesium chloride (0.44 M, 2.5 mL, 1.1 mmol) in THF under argon atmosphere. The reaction mixture was stirred for 1 h at this temperature. A saturated NH_4Cl aqueous solution (10 mL) was added to the mixture at -20 °C, and the aqueous layer was extracted with ether. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude product was purified by column chromatography on silica gel (hexane) to afford a mixture of coupling products (199 mg, 86% combined yield): the γ/α ratio was determined to be 99/1 by GC analysis.

[11] The oxygen atom of phenoxide in Figure 1 is much too little basic to coordinate to magnesium. Indeed, (*E*)-2-hexenyl 1-diethylphosphate gave a 65:35 mixture of γ- and α-allylation product in the reaction with geranylmagnesium chloride, and thus superiority of diphenylphosphate ester is obvious.

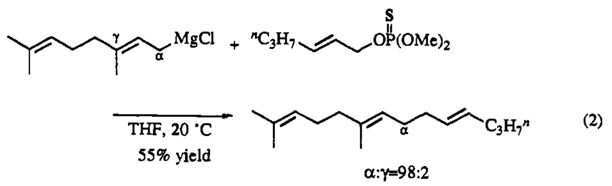
0002-7863/93/1515-5879$04.00/0

Table I. Regioselective Cross-Coupling Reaction of Various Diphenylphosphates with Allylic Grignard Reagents[a]

Entry	Grignard reagent	Diphenylphosphate	Product	Yield, %[b]	Ratio (γ/α)[c]
1				78	94:6
2				81	92:8
3				88	92:8 (94:6)[d]
4				86	99:1
5				84	96:4
6				82	93:7
7				99[d]	94:6
8				80	93:7
9				70[e]	92:8
10				79[e]	99:1
11				74	99:1
12				95[e]	99:1
13		$CH_3OPO(OPh)_2$		60[f]	93:7
14		$CH_3OPO(OPh)_2$		76	95:5

[a] Unless otherwise specified, the reaction was carried out using an allylic Grignard reagent (1.1 equiv) and a diphenylphosphate (1 equiv) at −20 °C for 1 h. [b] Isolated yield. [c] Determined by GC analysis. [d] Performed at −78 °C. [e] Grignard reagent (2 equiv) was used. [f] Performed at 0∼10 °C for 4.5 h.

results and afforded the α-coupling product nearly exclusively (20 °C), (RMgCl, R′OP(═S)(OMe)$_2$, α/γ ratio, yield): R = geranyl, R′ = (*E*)-2-hexenyl, 98/2, 55% (eq 2); R = prenyl, R′ = geranyl, 99/1, 49%; R = crotyl, R′ = geranyl, 96/4, 46%; R = crotyl, R′ = (*E*)-2-decenyl, 95/5, 54%.



(2)

Acknowledgment. Financial support of this research by the Ministry of Education, Science and Culture of the Japanese Government is greatly appreciated.

Supplementary Material Available: Experimental procedures and characterization data for the products shown in Table I (5 pages). Ordering information is given on any current masthead page.

---

(12) Detailed mechanism of the γ-alkylation is under active investigation.

(13) P-S bond length of 1.86 Å was reported: *CRC Handbook of Chemistry and Physics*, 67th ed.; Weast, R. C., Ed.; CRC Press: Boca Raton, FL, 1986; F-160.