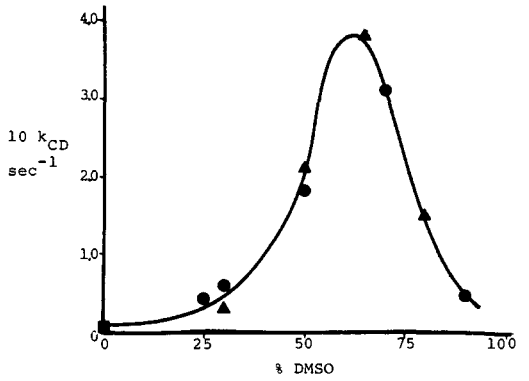

Figure 1. The rate constant at 25.0° for deacylation of *m-tert*-butylphenyl acetate at kinetic saturation with β-cyclodextrin as a function of the volume percent dimethyl sulfoxide in H_2O. Buffers were used, at 10 m*M*, which had an aqueous pH of 9.5: ●, Na_2CO_3–$NaHCO_3$ buffer; ▲, $Na_2B_2O_7$ buffer; ■, both buffers.

due to an altered pK_a of the buffer in this medium (k_{un} also changes, from 3×10^{-5} sec^{-1} in H_2O through 7.5×10^{-4} sec^{-1} in 60% DMSO to a maximum 1.3×10^{-3} sec^{-1} in 80% DMSO before decreasing at higher DMSO concentrations). Thus β-cyclodextrin in 60% DMSO accelerates substrate cleavage 13000-fold compared with the rate using a simple aqueous solution of the same buffer.

The second approach simplifies the system by eliminating buffers, and stoichiometrically generating the anion of β-cyclodextrin (pK_a = 11.8)[8] with NaOH. At kinetic saturation with β-cyclodextrin, the pseudo-first-order rate constant for substrate deacylation was proportional to the fraction of cyclodextrin ionized. Thus a rate constant k_{CD}' for reaction within the substrate-cyclodextrin monoanion complex could be determined. In H_2O k_{CD}' was 1.1 sec^{-1}, in 65% DMSO it rose to 5.0 sec^{-1}, while in 99% DMSO k_{CD}' was 2.3 sec^{-1}.

Obviously the solvent dependences of this particular reaction are complex, and other reactions will show different detailed behavior. However, significant rate increases in nonaqueous and mixed solvents can also be anticipated for many other cyclodextrin-promoted processes. Thus a new area of investigation is opened by our observation that cyclodextrin-substrate complexing can occur in nonaqueous polar solvents. It might also be noted that some other types of binding forces between molecules, such as hydrogen bonding or ion pairing, are likely to be disrupted by highly polar solvents. Thus cyclodextrins, which can utilize lyophobic binding of substrates, are particularly attractive for studies in such media.

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(1) For a review, cf. D. W. Griffiths and M. L. Bender, *Adv. Catal.*, **23**, 209 (1973).
(2) Small amounts of organic cosolvents are sometimes added, but the only systematic exploration to high concentrations of organic solvent seems to be that of T. S. Straub and M. L. Bender, *J. Am. Chem. Soc.*, **94**, 8875 (1972), who used isopropyl alcohol and found that at modest concentrations it completely suppressed the cyclodextrin effect. This kind of observation has led to the general impression (ref 1) "that inclusion complexes are apparently formed only in aqueous solution".
(3) For a good discussion relative to cyclodextrin, cf. W. P. Jencks, "Catalysis in Chemistry and Enzymology", McGraw-Hill, New York, N.Y., 1969, Chapter 8.
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(9) P. Campbell, Ph.D. Thesis, Columbia University, 1970.
(10) This excludes buffer catalysis. The decrease in rate is a salt effect, which is also seen with LiCl.

Brock Siegel, Ronald Breslow*
Department of Chemistry, Columbia University
New York, New York 10027
Received August 4, 1975

Metal-Assisted Terpenoid Synthesis. I. Regioselective Isoprene Insertion into an Allyl-Magnesium Bond and the Applications to Synthesis of Natural Terpenoids

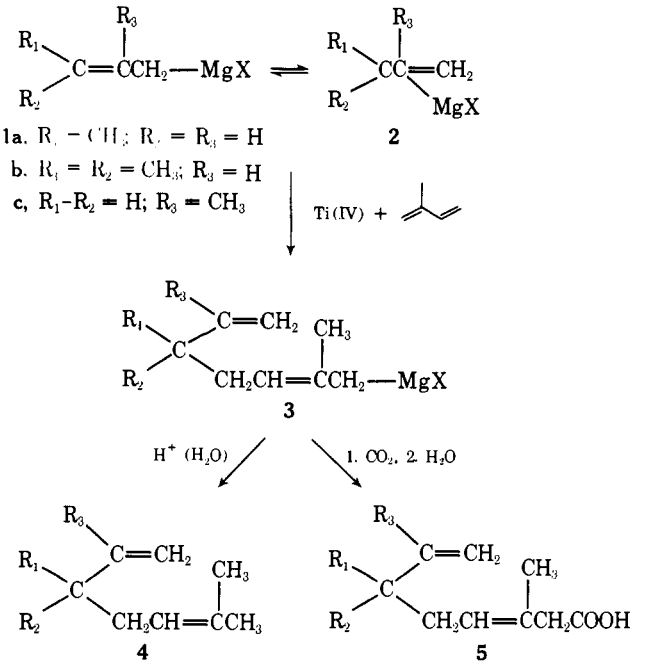
Sir:

Olefin or diene insertion into Grignard reagents assisted by transition metal compounds has long been known.[1] Uncatalyzed reactions of allylic Grignard reagents with 1,3-butadiene and isoprene to yield cyclohexane derivatives have been reported.[2] To the best of our knowledge, however, regioselective insertion of isoprene has not yet been reported. We wish to report here highly regioselective isoprene insertion into an allyl-magnesium bond effected by a catalytic amount of Cp_2TiCl_2 (Cp = η^5-C_5H_5) or $TiCl_2(OEt)_2$ and the synthetic application for natural terpenoids.

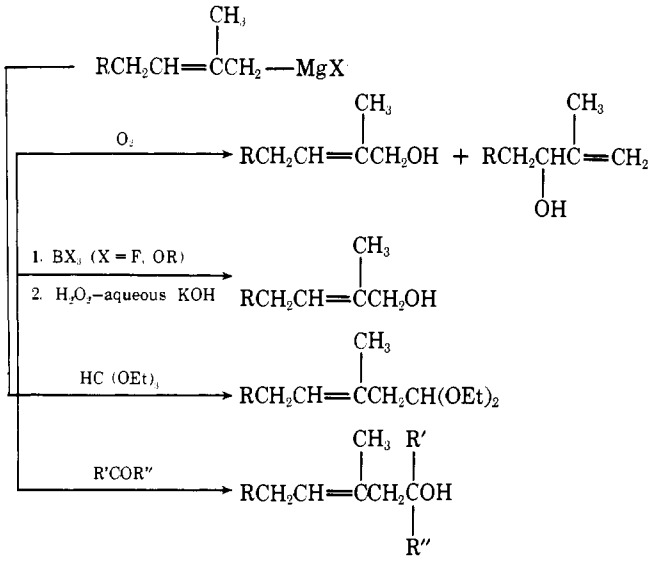
Upon treating a THF solution of crotylmagnesium chloride (**1a**, 1 mol) with isoprene (1.5 mol) containing Cp_2TiCl_2 (0.01 mol) at 50–60° a 90% yield (based on the Grignard reagent) of 3,6-dimethyl-1,5-heptadiene (**4a**) was obtained after hydrolysis, no isomeric products being detected in the GLC (Apiezon 45 m, Golay column). Similarly prenylmagnesium chloride (**1b**) gave a nearly quantitative yield of 3,3,6-trimethyl-1,5-heptadiene (**4b**). The absence of coupling products is remarkable in view of the reported transition metal-catalyzed coupling reactions of Grignard reagents.[1,3]

When the reaction mixture, after the isoprene insertion into **1b** (step 1), was treated with carbon dioxide, the corresponding carboxylic acid (**5b**) was obtained in 80% yield. These results imply that a substituted allyl Grignard compound (**3a–c**)[4] is formed by regioselective isoprene inser-

Scheme I

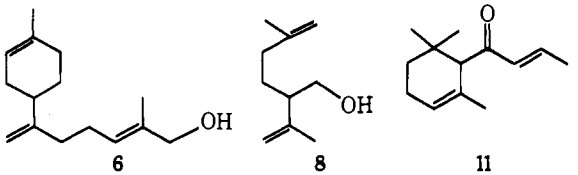


Scheme II



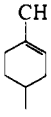
tion. The selectivity requires a particular orientation of an isoprene unit with respect to the Mg-η^1-allyl bond in the transition state and a kinetically controlled attack of the isoprene tail carbon into isomeric form **2** rather than **1**.[4] Apparently attendance of the titanium ion achieves these conditions. The reaction without the titanium compound does not take place under comparable conditions and under forced conditions the allyl Grignards give Wurtz-type reaction products.

The newly formed substituted allyl magnesium compound undergoes usual Grignard reactions (step 2): a few examples are shown in Scheme II. The apparent two-step reaction can be carried out virtually as a one batch process, and the pure products (>90%) were obtained by simple distillation. Concerning the stereochemistry of the double bonds in the products, the trans isomers are predominant in each case (>80%). The utility is demonstrated for synthesis of natural terpenes such as lanceol (**6**), lavandurol (**8**), and damascone (**11**), as well as double bond isomers of geraniol (3,7-dimethyl-3,7-octadien-1-ol) (**7**), geranic acid (3,7-dimethyl-3,7-octadienoic acid) (**9**), citral (3,7-dimethyl-3,7-octadienal) (**10**), and geranylacetone (6,10-dimethyl-6,10-undecadien-2-one) (**12**) (see Table I). Lanceol,[5] for example, was synthesized as follows. A THF solution of 2-(4-methyl-3-cyclohexenyl)allylmagnesium chloride (50 mmol), prepared from 10-chloro-1,8-*p*-methadiene, was treated with isoprene (100 mmol) in the presence of Cp_2TiCl_2 (0.5 mmol) at 60–70°. The reaction mixture was then treated with BF_3OEt_2 (60 mmol) at 5° for 0.5 hr, and subsequently oxidized at 10° with an alkaline hydrogen peroxide solution (50 ml of 3% aqueous NaOH plus 8 ml 30% H_2O_2). After usual work-up, *cis*- and *trans*-lanceol (1:4) were obtained as a yellow oil. The stereoisomers were separated by preparative GLC and identified by spectral analysis including mass spectrometry.[5]



6 8 11

Table I. Terpenoid Synthesis Using the Isoprene Insertion[a]

$CH_2=CCH_2MgX$ (R_3 in R_3)	Reagent for step 2	Product (% yield)[b]
	1. BF_3OEt_2	6 (52)[c]
	2. H_2O_2–aqueous NaOH	7 (60), 8 (10)
CH_3–	CH_2O	7 (60), 8 (10)
CH_3–	CO_2	9 (80)
CH_3–	$HC(OEt)_3$	10 (55)
CH_3–	1. $CH_3CH=CHCHO$ 2. CrO_3–acetone 3. H_2SO_4–AcOH	11 (40)
CH_3–	$CH_2=CHCOCH_3$[d]	12 (30)

[a] The isoprene reaction was generally carried out using a mole ratio of the allyl Grignard reagent (the entry at the extreme left)/isoprene/Cp_2TiCl_2 = 100/150/1 at 60° for 10 hr. [b] The isolated yield based on the allyl Grignard reagent. [c] The organoboron compound being the intermediate, secondary alcohol was not formed. [d] Two mole percent of CuCl was used.

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(4) The structure of allylMgX in solution is best described as "dynamic η^1-allyl" coordination. See, for example, G. Wilke, B. Bogdanovcc, P. Hardt, P. Heimbach, W. Keim, M. Krondr, W. Oberkirch, K. Tanaka, E. Steinrücke, D. Walter, and H. Zimmermann, *Angew. Chem.*, **78**, 157 (1966).
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Susumu Akutagawa

Central Research Laboratory, Takasago Perfumery Co. Ltd. 31-36 5-Chome, Kamata, Ohta-ku, Tokyo, 114

Sei Otsuka*

Department of Chemistry, Faculty of Engineering Science Osaka University Toyonaka, Osaka, Japan 560

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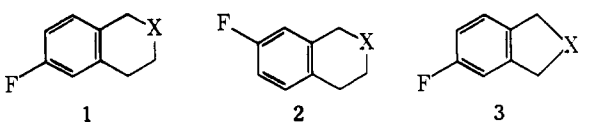
Polar Field Effects on ^{19}F Chemical Shifts. An Important Effect

Sir:

Although our recent ^{19}F NMR studies[1] of model systems **1, 2,** and **3** appeared to resolve the debate regarding the importance of polar field effects on ^{19}F chemical shifts,[2] Fukunaga and Taft[3a,b] have concluded on the basis of more recent work that the field phenomenon is relatively unimportant, a viewpoint diametrically opposed to ours. Thus, we are prompted to report in a preliminary form new data from systems **1** and **2** (X = CF_2) and **3** (X = NH, $^+NH_2$, O, CO and CF_2) which, together with the previously published results, not only strongly support our previous conclusions but, in addition, bring unambiguously to light an often neglected feature of the electric field model.



1 2 3

The relative ^{19}F chemical shifts in DMF and benzene are listed in Table I together with the previously published data.[4] An important conclusion follows from these results. Apart from the obvious fact that charged and strongly dipolar substituents (X = O, CO, CF_2, and SO_2) exert significant deshielding effects on ^{19}F chemical shifts in these