Highly Selective Allylation Reactions Using Allylic Phosphates

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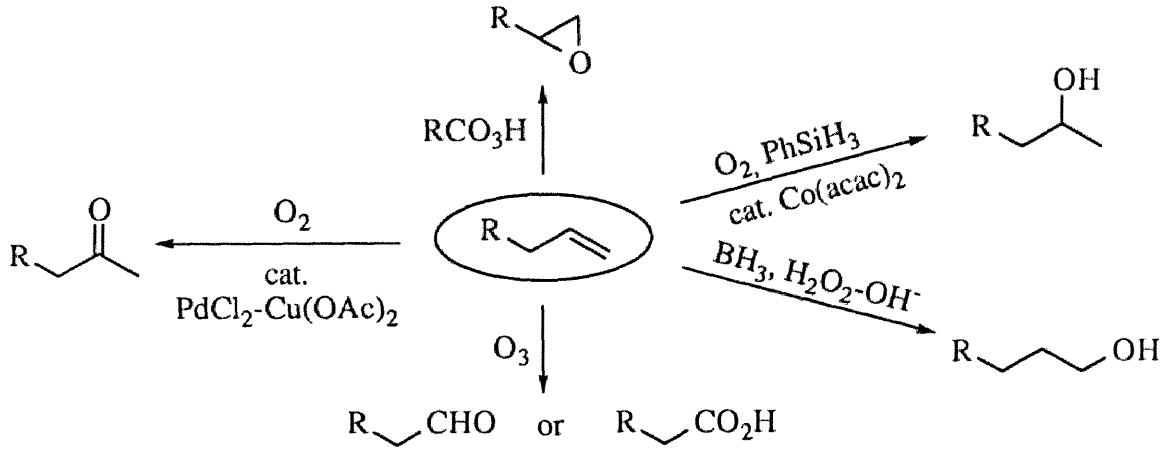
Contents

Chapter 1

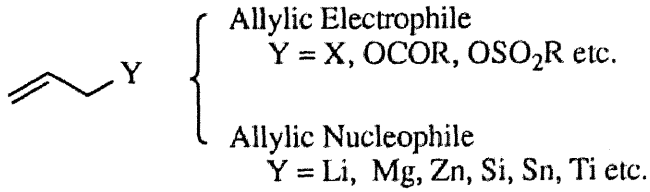
Introduction and General Summary

Highly Selective Allylation Reactions Using Allylic Phosphates

Allylic compounds have been of synthetic, mechanistic, and biological importance for more than sixty years.[1] Among the many fascinating aspects of their behavior, the stereo- and regiochemistry of their reactions have received considerable attention and allylation reaction is recognized as one of the most important processes in organic synthesis. This is why the products can be effectively converted to many kinds of functional groups at the carbon-carbon double bond (Scheme 1). There are two methods for allylation: one method uses allylic electrophiles and the other uses allylic nucleophiles (Scheme 2). Another reason for allylation of importance is that these allylation reagents have specific reactivity and regioselectivity.



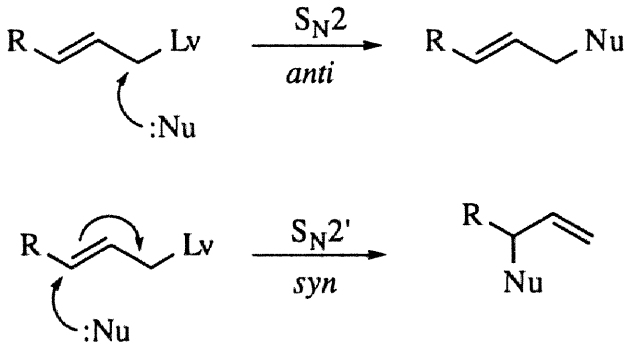
Scheme 1. Utility of Allylic System



Scheme 2. Allylic Reagents

Allylic halides, esters and sulfonates are well-known and widely used as allylic electrophiles.[1,2] Their reactivity is much higher than that of alkyl electrophiles, and nucleophilic substitution readily occurs under mild conditions. The recent development of transition metal catalyzed reactions also comes to mind.[3]

There are two types of nucleophilic substitution reactions on regioselectivity: S_N2 reaction and S_N2' reaction (Scheme 3). The regioselectivity depends on nucleophiles, leaving groups, reaction conditions and additives.



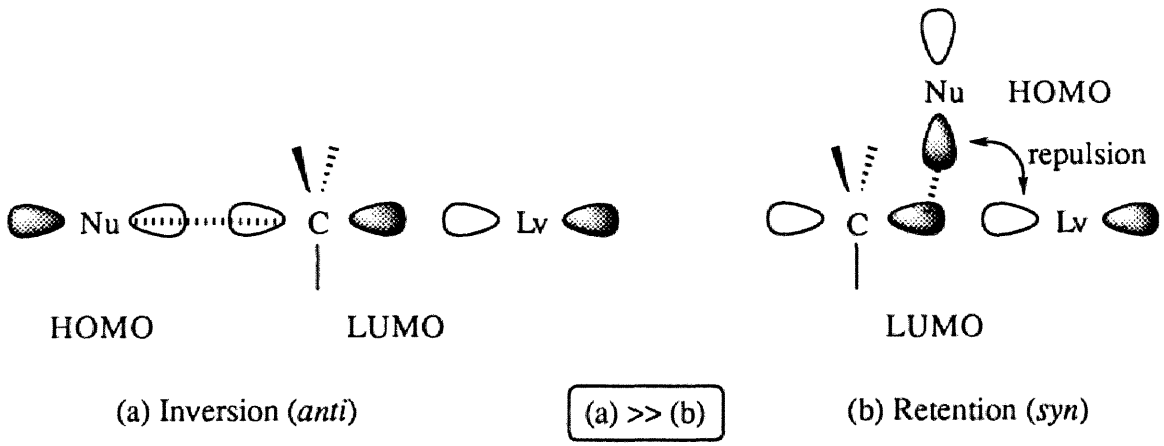
Scheme 3. Reactions of an Allylic Electrophile

Their definitions follow:[4]

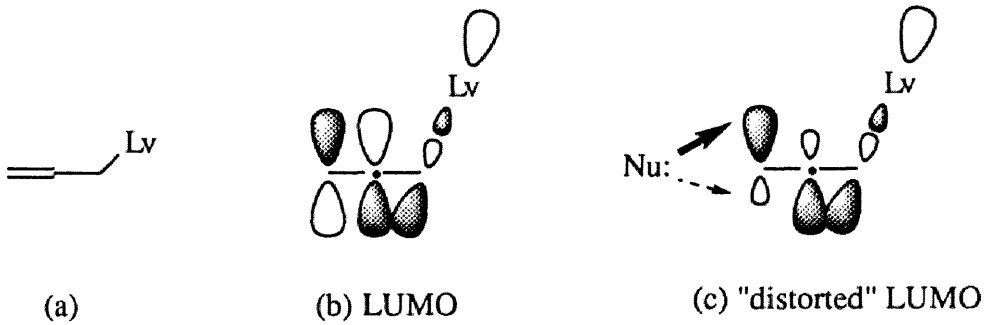
(i) S_N2 (Substitution Nucleophilic Bimolecular) The concerted displacement of one nucleophile by another. This mechanism involves stereospecific backside approach (*anti*) by the attacking nucleophile relative to the nucleofuge, causing inversion of configuration at the reaction site.

(ii) S_N2' (Substitution Nucleophilic Bimolecular with Rearrangement) A concerted nucleophilic displacement in which the site of attack is at an atom other than the original point of attachment of the nucleofuge (usually one multiple bond separated from the original point of attachment). This mechanism is kinetically indistinguishable from the S_N2 reaction, but the attack/departure stereochemistry is *cis* (*syn*).

Stereochemistry of S_N2 and S_N2' reactions is usually opposite each other ($S_N2 \Rightarrow$ *anti*, $S_N2' \Rightarrow$ *syn*). This is reasoned from frontier molecular orbital theory (Schemes 4 and 5).[5]



Scheme 4. Frontier Molecular Orbitals of S_N2 Reaction



Scheme 5. Frontier Molecular Orbitals of S_N2' Reaction

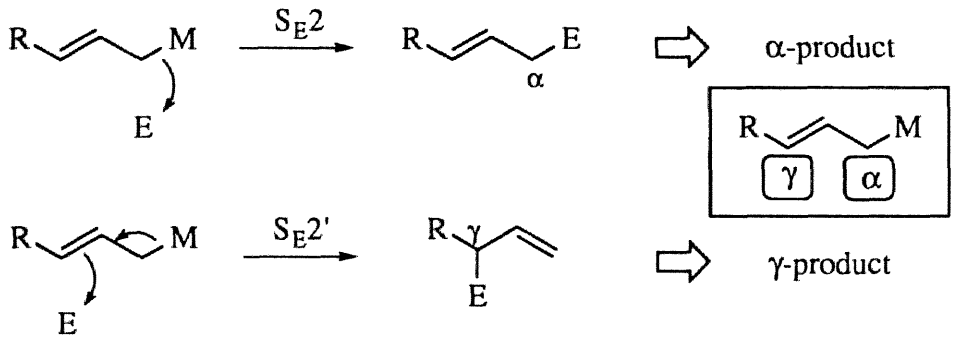
These flexible characteristics of allylic electrophiles are very useful and numerous investigations have been reported,[1,2] but there are still few general systems of highly selective coupling reactions.

Among allylic nucleophiles,[6] allylic lithium, magnesium and zinc reagents are popular because of their high reactivity, as are allylic silicon, tin and titanium reagents because of their

high chemoselectivity. There are two types of electrophilic substitution reactions on regioselectivity: S_E2 reaction and S_E2' reaction (Scheme 6).

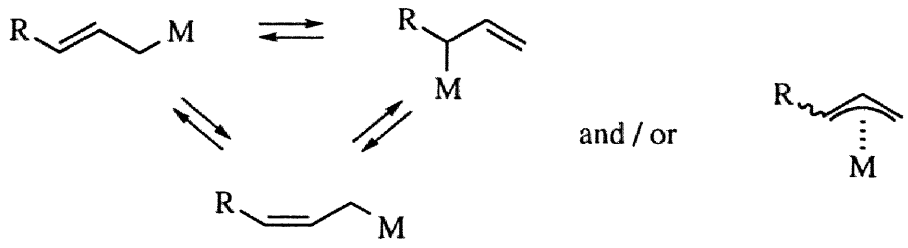
(i) S_E2 (Substitution Electrophilic Bimolecular)[4] The concerted displacement of one electrophile by another. This mechanism, which is relatively uncommon, involves stereospecific frontside approach by the attacking electrophile relative to the electrofuge, causing retention of configuration.

(ii) S_E2' (Substitution Electrophilic Bimolecular with Rearrangement)[4] A mechanism kinetically identical to the S_E2 process, but involving formation of a rearranged product.



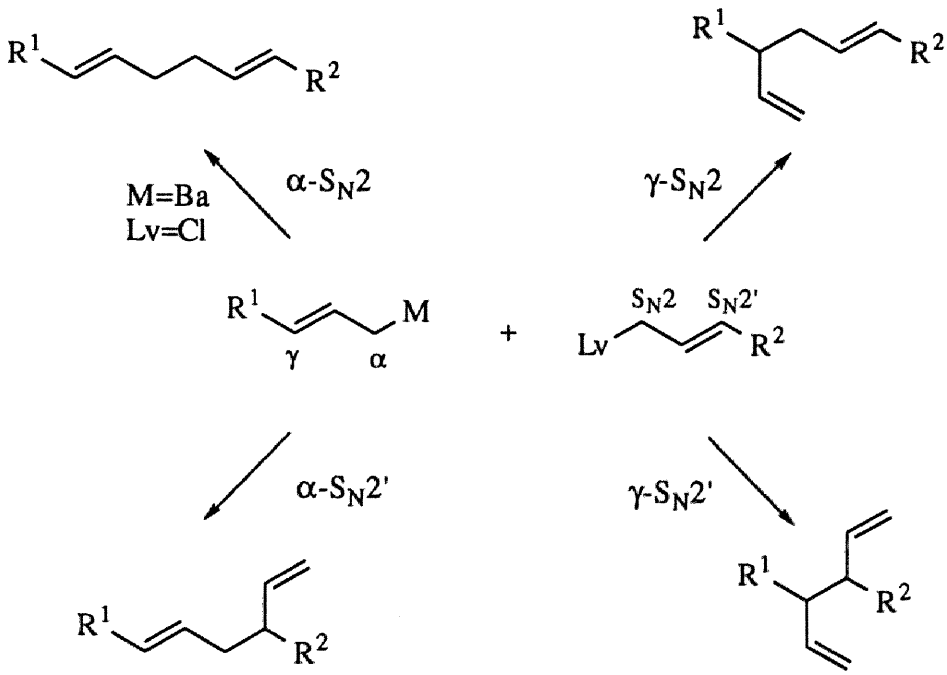
Scheme 6. Reactions of Allylic Nucleophile

Although a large number of allylic organometallics have been synthesized to develop selective allylation reactions, the utility of these methodologies is complicated by the potential for reaction through S_E2 and S_E2' pathways. In fact, most reactions give a mixture of the S_E2 and S_E2' products. In addition to regioselectivity, allylic carbanions accompany loss of *E/Z* stereoselectivity because they are generally sensitive to metallotropic rearrangements (sequential 1, 3-shifts) and exist as mixtures of rapid equilibrium among (*E*)-, (*Z*)- and/or η^3-isomers[7] (Scheme 7), and so S_E2 products are *E/Z* mixtures. In this thesis, an S_E2 product is referred to as an "α-product", and an S_E2' product as a "γ-product" for the purpose of simplification and to avoid confusion, using the reaction sites of the allylic nucleophile (Scheme 6).



Scheme 7. Equilibration of Allylic metals

In the process of allyl-allyl cross-coupling, there may be only four products by regioselectivity: α-S_N2, α-S_N2', γ-S_N2 and γ-S_N2' products (Scheme 8). Although each of them is an important 1,5-diene which is a structural unit common to terpenes, it is very difficult to synthesis them selectively,[8] and highly selective reactions have been a longstanding problem. In the author's laboratory, allylic barium reagents were demonstrated to provide an excellent solution to a highly selective α-S_N2 reaction,[9] in which the double bond geometry of barium reagents was completely retained at -78 °C.

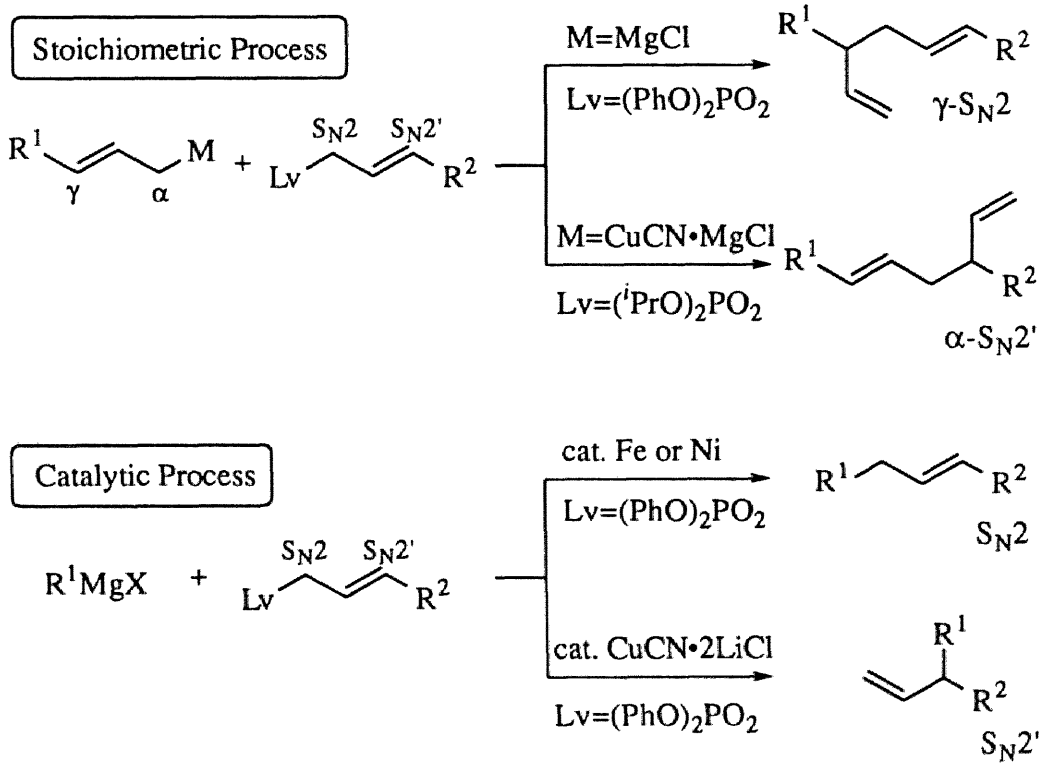


Scheme 8. Regioselective 1,5-Diene Syntheses

The author employed phosphates as leaving groups and achieved four highly selective allylation reactions, including two methods of 1,5-diene synthesis (γ-S_N2 and α-S_N2'), as follows (Scheme 9);

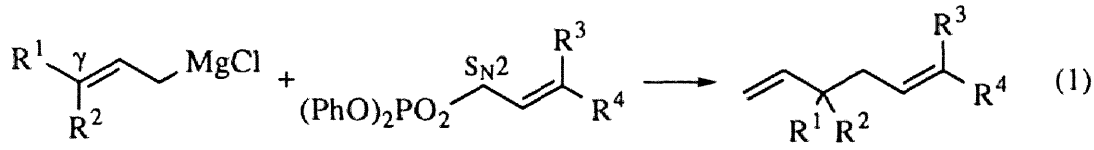
1. γ-S_N2 reaction between allylic diphenylphosphates and allylic magnesium reagents (Chapter 2-1).
2. α-S_N2' reaction between allylic diisopropylphosphates and allylic cuprates (Chapter 2-2).
3. S_N2 reaction between allylic diphenylphosphates and alkylmagnesium reagents in the presence of an iron or a nickel catalyst (Chapter 3-1).
4. S_N2' reaction between allylic diphenylphosphates and alkyl- or allylmagnesium reagents in the presence of a CuCN•2LiCl catalyst (Chapter-3-2).

In addition, a carbometallation reaction was also achieved between allylic zinc reagents and allylic ethers in the presence of a nickel catalyst (Chapter 4).



Scheme 9. Highly Selective Allylation Reactions Using Allylic Phosphates

The author first attempted to develop highly selective 1,5-diene synthesis using allylic Grignard reagents, which are very popular reagents in organic synthesis owing to their stability, high reactivity and also their ease of preparation[10] and handling. Various kinds of leaving groups were examined and only the diphenylphosphate exhibited unprecedented high γ-S_N2 selectivity. Among the variety of allyl metals, Grignard reagents were found to be the most effective (eq. 1).

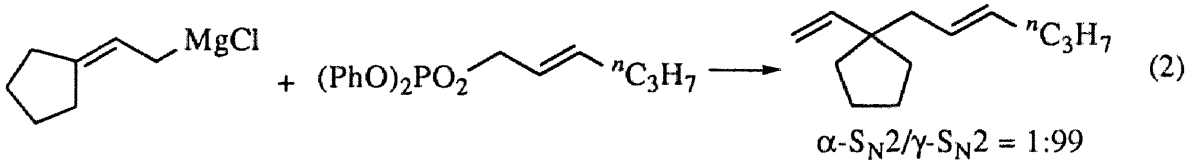


(1)

The characteristic features of the results are the following:

(1) All reactions resulted in high yields with remarkable γ-S_N2 selectivity not only with allylic diphenylphosphates but with propargylic, benzylic, and alkyldiphenylphosphates.

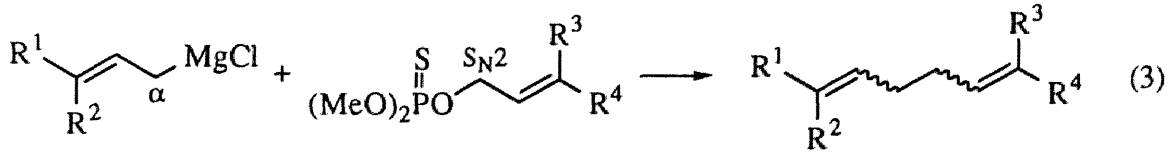
(2) This reaction is effective in generating quaternary carbon (eq. 2).



(2)

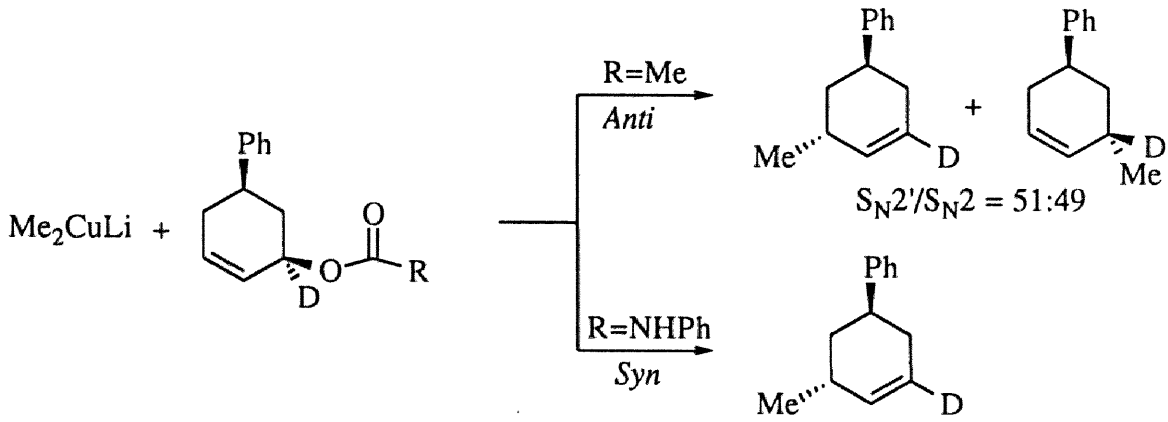
α-S_N2/γ-S_N2 = 1:99

In sharp contrast, dimethylthiophosphates showed entirely different results and afforded the α-S_N2 coupling products nearly exclusively (eq. 3).



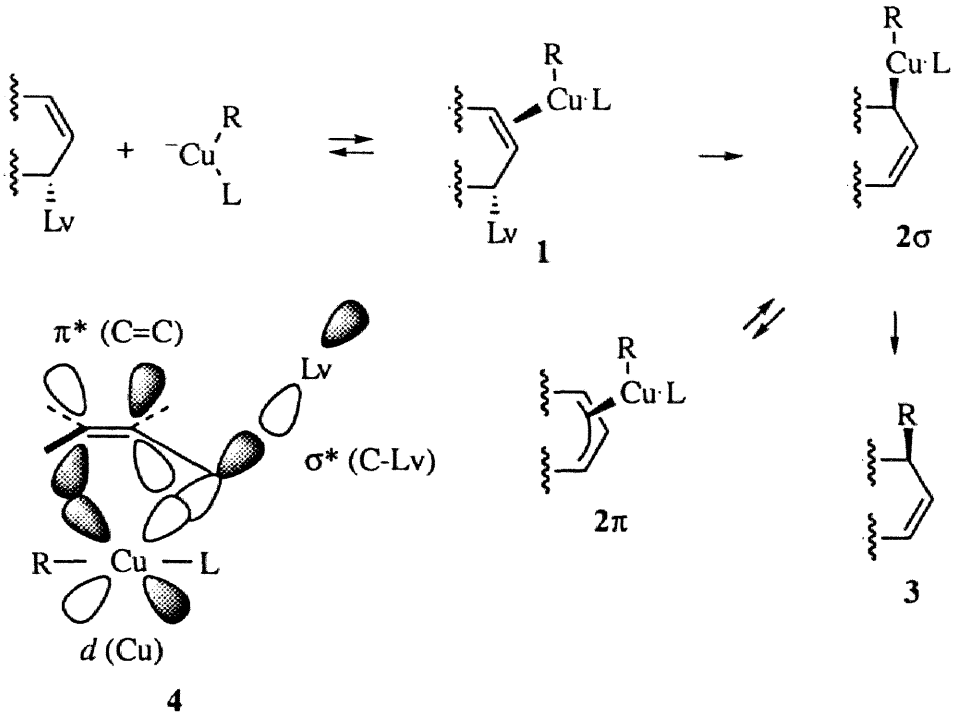
(3)

The author next developed α-S_N2' reaction. Nucleophilic substitution reaction at the allylic carbon (S_N2') is one of the most important reactions and is widely used. Especially, copper reagents are familiar to organic chemists as S_N2'-preference reagents.[11] The regio- and stereoselectivities, however, are not always applied by the same rule. For example, an allylic carboxylate was reported to react in *anti*-fashion, but an allylic carbamate to react in *syn*-fashion[12] (Scheme 10), although, in general, S_N2' reaction by copper reagents exhibits *anti*-selectivity opposite from general S_N2' reaction (*syn*, Scheme 5).



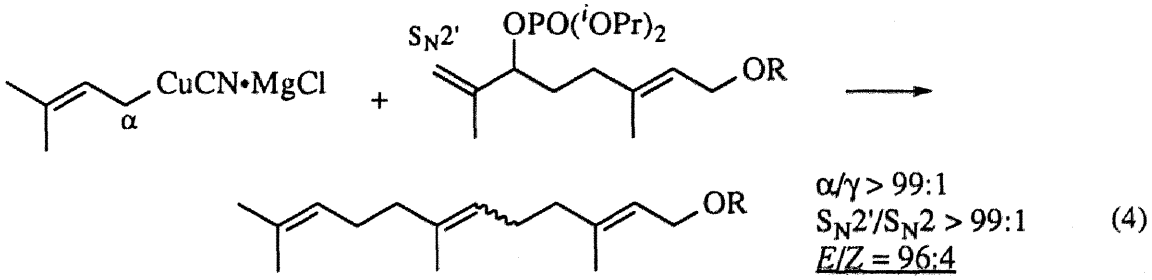
Scheme 10.

Recent studies point to a rate-determining formation of a σ-allylcopper(III) complex **2σ** (Scheme 11), originating from S_N2' attack by copper following prior cuprate complexation with the olefin as in complex **1**.[13,14] Reductive elimination from **2σ** with retention of configuration would give *anti* product **3**. An alternative view postulates overlap between a diffuse copper(I) *d* orbital and the appropriate LUMO of the allylic system, as in **4**. Simultaneous $d\pi^*$ (at the S_N2' position) and $d\sigma^*$ (at the S_N2 position) bonding accounts for the S_N2' preference with net *anti* stereochemistry.[15]

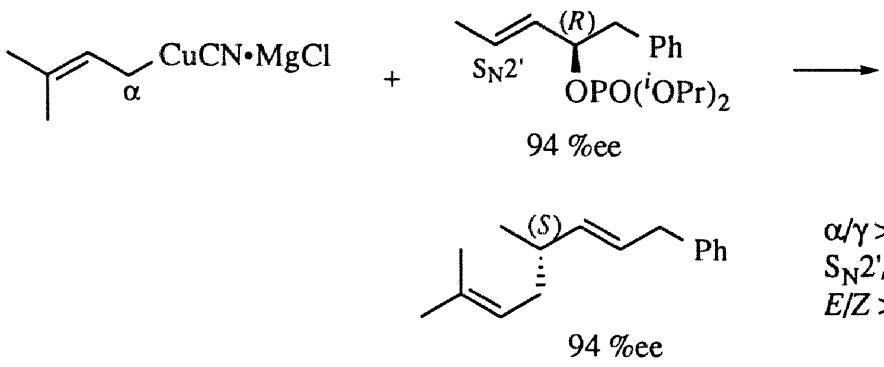


Scheme 11.

The author noted this S_N2' selectivity of copper reagents and applied it to α-S_N2' reaction. Practically, cuprate reagents, which were prepared from allylic magnesium reagents and CuCN•2LiCl, showed complete α-S_N2' selectivity toward secondary allylic electrophiles. An extensive study of effective leaving groups was done for the purpose of improving *E*, *Z*-stereoselectivity of rearranged olefins, and the phosphate leaving group solved the problem of stereochemistry (eq. 4).

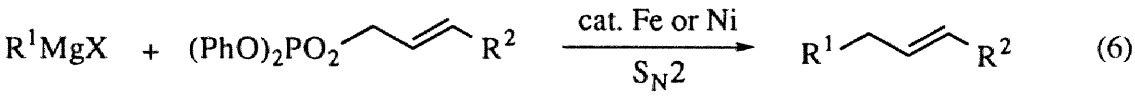


Prenylation of an optically active allylic phosphate was found to be homogeneous, and was shown to be a completely *anti*-, 1,3-chirality transfer (eq. 5).

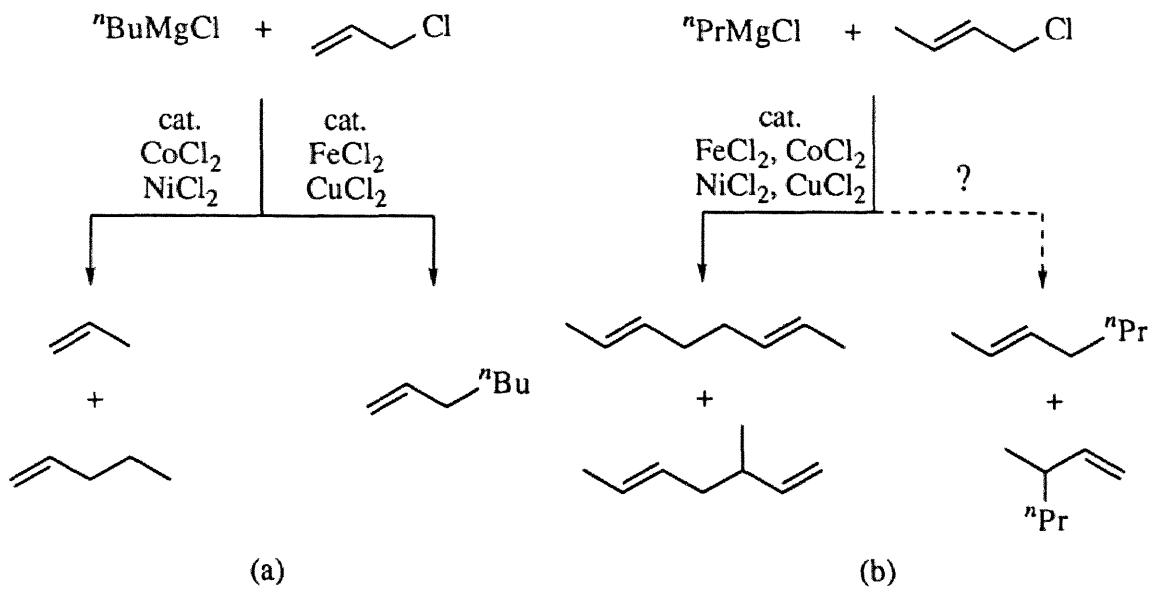


$\alpha/\gamma > 99:1$
$S_N2'/S_N2 > 99:1$
$E/Z > 99:1$ (5)

The author's next goal was the catalytic process of an α-S_N2' reaction. Transition metal catalyzed reactions between Grignard reagents and organic halides are generally described as the Kharasch reaction.[16] In allylation reactions, although butylmagnesium bromide reacted with allyl chloride to give primarily butene and propene in the presence of Co or Ni catalyst, a catalytic amount of Fe or Cu salt gave cross-coupling products[17] (Scheme 12 (a)). On the other hand, neither Fe, Co, Ni, nor Cu catalyst was effective in giving cross-coupling products of crotyl chloride, and homo-coupling reaction of the electrophile was superior to cross-coupling reaction (Scheme 12 (b)). The author examined transition metal catalyzed allylations of allylic phosphates that had been found to be allylation agents of choice in γ-S_N2 and α-S_N2' reactions. Various transition metal catalysts were examined to find one the most suitable for regioselective coupling between allylic phosphates and Grignard reagents, and iron, nickel and copper compounds showed remarkable catalytic activities. Using Fe and Ni catalysts, nearly exclusive S_N2 selectivity was obtained (eq. 6).



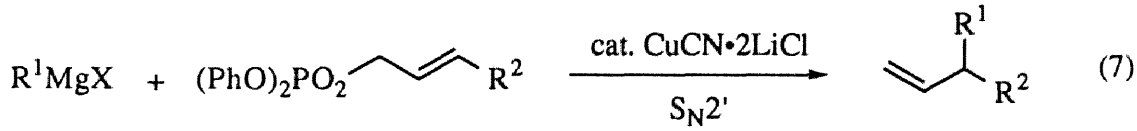
(6)



Scheme 12. Kharasch reaction

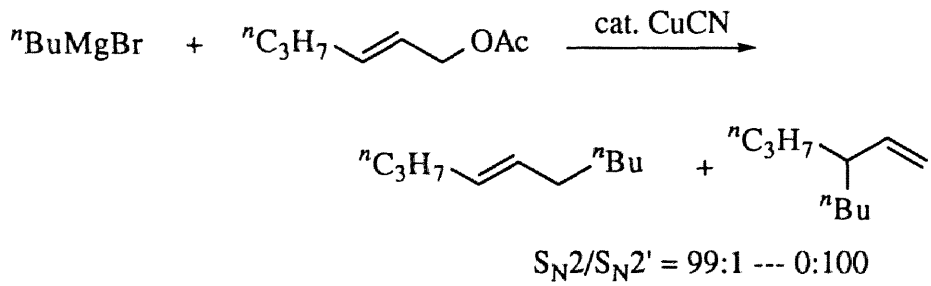
Methylation catalyzed by $Ni(acac)_2$ resulted in a low yield because of a competitive homo-coupling reaction. $Fe(acac)_3$ catalyst, however, afforded the S_N2 coupling product in high yield without contamination of homo-coupling products.

In contrast to Fe and Ni catalysts, CuCN•2LiCl catalyst smoothly afforded the S_N2' coupling products between Grignard reagents and allylic phosphates (eq. 7).



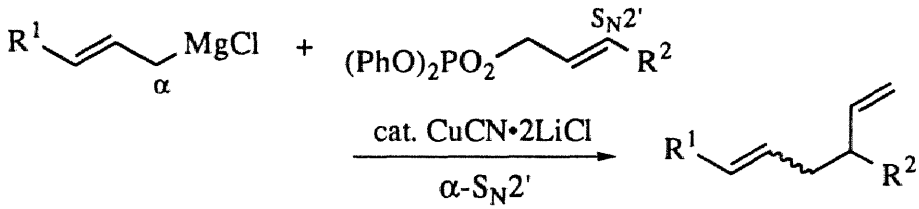
Regiocontrol in copper catalyzed Grignard reactions of allylic substrates has been studied actively but to a lesser extent,[11a,18] because regioselectivity is very sensitive to copper salts, solvents, leaving groups and reaction temperature, and is not as general as those of stoichiometric copper (or cuprate) reagents. Bäckvall reported the S_N2/S_N2' selectivity was dramatically reversed from 99:1 to 0:100 by changing the solvent and the time to add the

Grignard reagents[18b] (eq. 8). The author investigated the generality of the reaction system catalyzed by CuCN•2LiCl between Grignard reagents and allylic phosphates, and found that most reactions exhibited high S_N2' selectivity. High temperature (0 °C) and less polar solvent (toluene-ether) were requisite to obtain high regioselectivity by sp^2 carboanion Grignard reagents.



S_N2/S_N2' = 99:1 --- 0:100 (8)

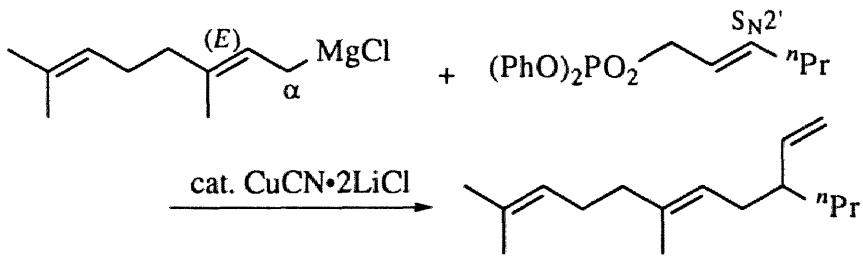
This method was further successfully applied to a regiocontrolled allyl-allyl coupling reaction that was a catalytic process of an α-S_N2' reaction (eq. 9).



(9)

In this reaction, no *E*, *Z*-stereoselectivities were observed due to the rapid isomerization of the γ-substituted allyl Grignard reagents (Scheme 7). Very recently, stereochemically homogeneous allylic metals were successfully generated at low temperature[19] in the author's laboratory, so these were applied to a stereoretentive α-S_N2' reaction. Treatment of geranylmagnesium chloride, prepared in THF below -100 °C, with (*E*)-2-hexenyl-1-diphenylphosphate in the presence of 5 mol% of CuCN•2LiCl gave the *trans*-isomer of α-S_N2'

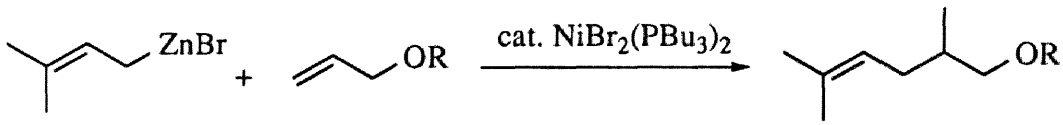
coupling product preferentially (eq. 10). This is the first example of the generation of a stereoretained allylic copper reagent.



(10)

α/γ > 99:1
S_N2/S_N2' = 6:94
E/Z = 95:5

Chapter 4 describes quite a different allylation reaction of allylmetallation of allyl ethers under a mild condition (eq. 11).



(11)

Grouping the reaction sites of allylic electrophiles, highly selective allylation or alkylation reactions were developed at three positions of allylic alcohol derivatives as shown in Table 1.

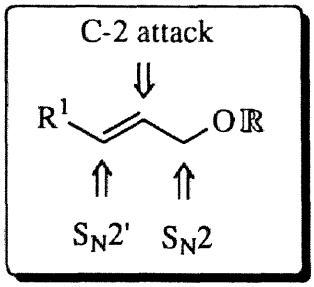
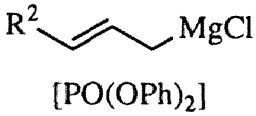
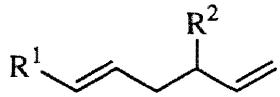
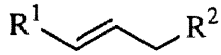
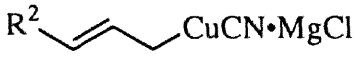
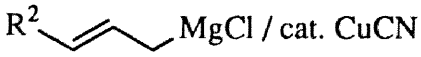
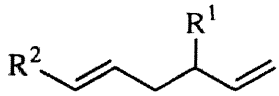
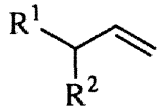
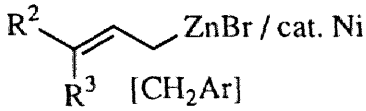
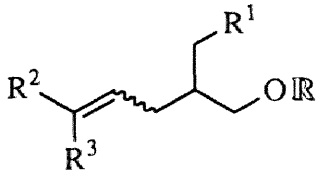


Table 1.

		Nucleophile [ℝ]	product
S_N2 reaction	Allylation	 [PO(OPh)$_2$]	
	Alkylation	R^2MgX / cat. Ni or Fe [PO(OPh)$_2$]	
S_N2' reaction	Allylation	 [PO(O^{i}Pr)$_2$] or  [PO(OPh)$_2$]	
	Alkylation	R^2CuCN•MgX [PO(O^{i}Pr)$_2$] or R^2MgX / cat. CuCN [PO(OPh)$_2$]	
C-2 attack	Allylation	 ZnBr / cat. Ni [CH_2Ar]	

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Chapter 2

Highly Selective 1,5-Diene Syntheses

Chapter 2

Highly Selective 1,5-Diene Syntheses

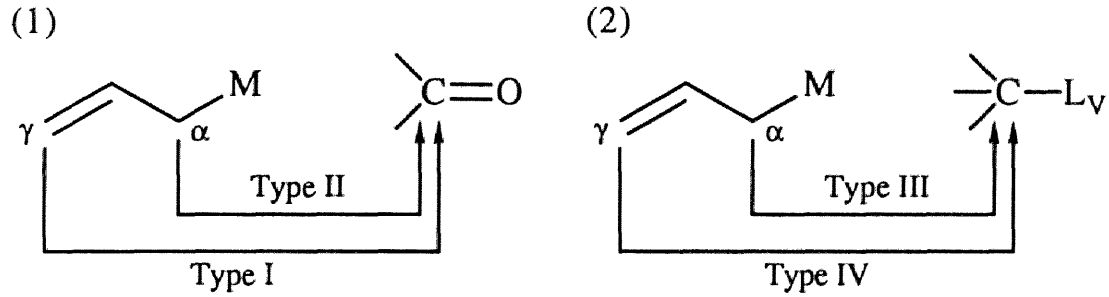
Section 1

Highly Selective γ-S_N2 Reaction of Allyl-Allyl Cross-Coupling

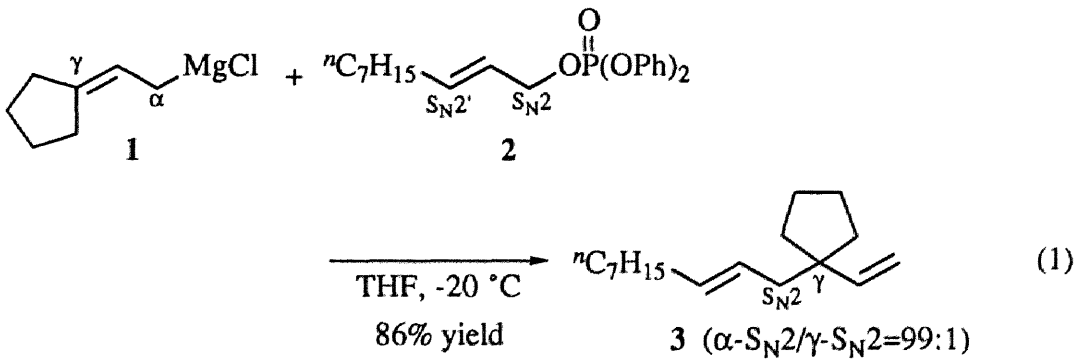
Abstract: The highly γ-S_N2 selective cross-coupling reaction of allylic Grignard reagents was achieved, using allylic diphenylphosphates as electrophiles. For example, treatment of (*E*)-2-decenyl-1-diphenylphosphate (1 equiv) with 2-cyclopentylideneethylmagnesium chloride (1.1 equiv) in THF at -20 °C afforded the γ-alkylated product in 86% yield with a γ-S_N2/α-S_N2 ratio of 99:1. All reactions resulted in high yields with remarkable γ-S_N2 selectivities not only with allylic diphenylphosphates but also with propargylic, benzylic, and alkyl-diphenyl-phosphates. On the other hand, dimethylthiophosphates afforded the α-S_N2 coupling products nearly exclusively.

Most of the allylmetal reagents combine with carbonyl compounds by the S_E2' pathway (γ) to afford homoallylic alcohols selectively (Type I, Scheme 1).[1] A method which was described previously permits the 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-S_N2 coupling of allylmetal reagent with alkyl halides which closes this methodological gap.

Scheme 1.



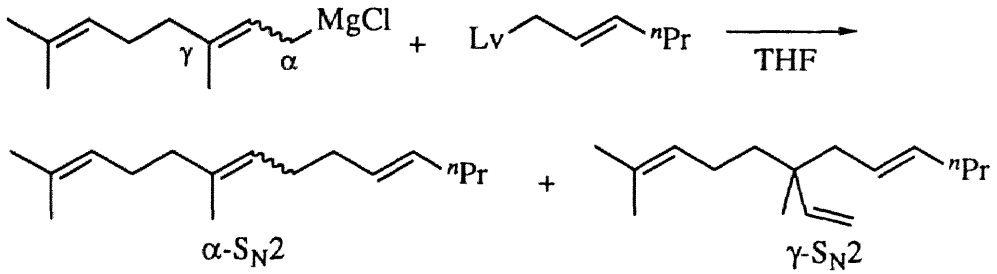
Reaction of (*E*)-2-decenyl-1-diphenylphosphate (**2**) with 1.1 equiv of 2-cyclopentylideneethylmagnesium chloride (**1**) in THF at -20 °C gave the γ-alkylated product **3** in 86% yield with a γ-S_N2/α-S_N2 ratio of 99:1 (eq. 1). Thus, the γ-carbon of the Grignard reagent **1** attacked the primary carbon (S_N2) of the phosphate **2**.



(1)

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] Using geranyl Grignard reagent as a nucleophile, which is well-known for their easiness to prepare and handle, stability and high reactivity, the various kinds of leaving groups were examined and only the diphenylphosphate ester revealed this unique regio-selectivity (entry 6). Reaction of (*E*)-2-hexenyl-1-diethylphosphate resulted in an totally unacceptable regioselectivity (entry 5).

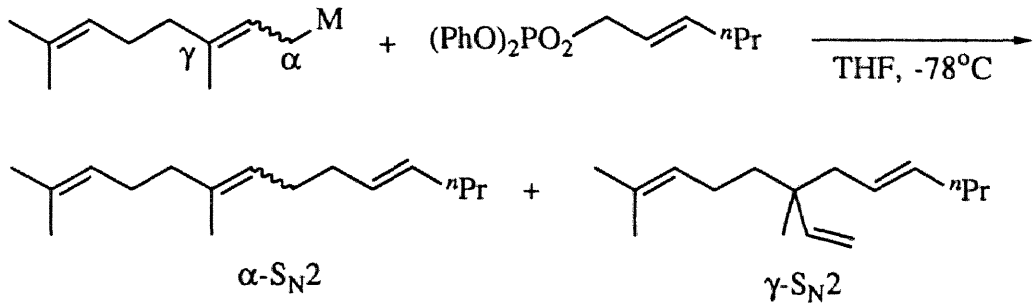
Table 1. γ-S_N2 Coupling Reaction: Effect of Leaving Groups



entry	Lv	temp,°C	yield, %	ratio (α-S_N2/γ-S_N2)
1	Cl	-40 ~ 20	75	89/11
2	Br	-78	67	16/84
3	I	-78	99	21/79
4	OMs	-78 ~ 20	16	15/85
5	$(EtO)_2PO_2$	-40 ~ 0	39	35/65
6	$(PhO)_2PO_2$	-78	67	6/94
7	$(PhO)_2P(=S)O$	-40 ~ 20	61	93/7
8	$(MeO)_2P(=S)O$	-40 ~ 20	55	98/2

Among the variety of allyl metals, Grignard reagents were found to be the most effective (Table 2). Geranylbarium reagent was reported to exhibit a highly α-S_N2 selectivity with allylic halides,[2,3] while it didn't with the allylic diphenylphosphate. Notably γ-S_N2 selectivity of this reaction originates from diphenylphosphate as a leaving group.

Table 2. Effect of Metals

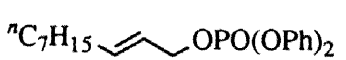
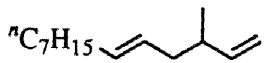
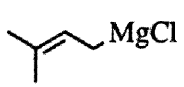
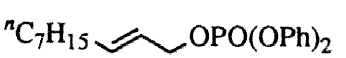
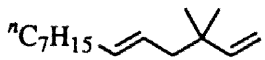
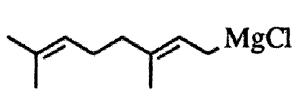
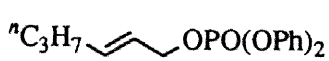
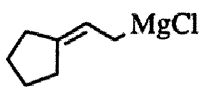
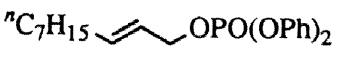
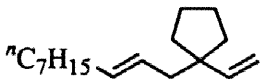
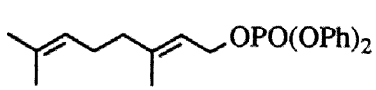
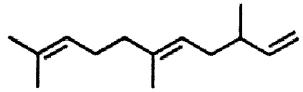
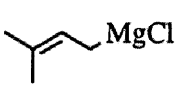
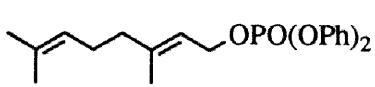
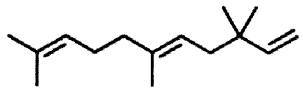
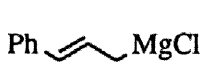
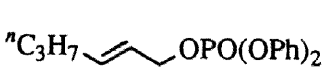
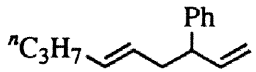
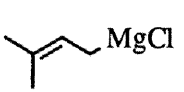
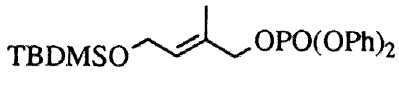
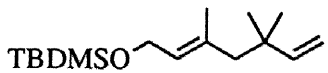


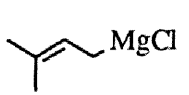
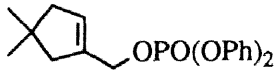
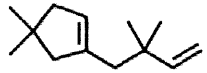
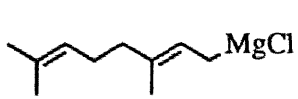
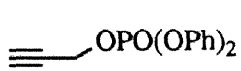
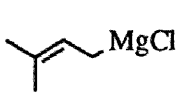
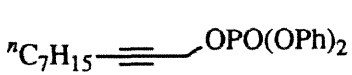
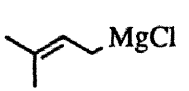
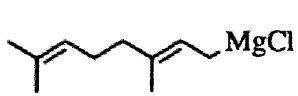
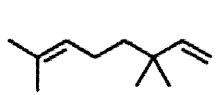
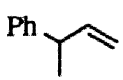
M	α-S_N2/γ-S_N2
Li[a]	12/88
K[b]	16/84
MgCl	6/94
BaCl[c]	44/56

[a] ref 6, [b] ref 8, [c] ref 2,3

Table 3 summarizes the results obtained for the reaction of various diphenylphosphates with 1.1 equiv of allylic Grignard reagents at -20 °C[9] in THF. The characteristic features of the results are as follows: (1) All reactions resulted in high yields with remarkable γ-S_N2 selectivities not only with allylic diphenylphosphates but also with propargylic (entries 10 and 11), benzylic (entry 12), and alkyl- (entries 13 and 14) diphenylphosphates. (2) The alkyl substituent at β-position of allylic diphenylphosphate had no effect on the regioselectivities (entries 8 and 9). (3) The siloxy group at C-4 position did not affect the reaction course (entry

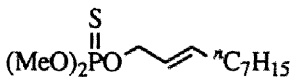
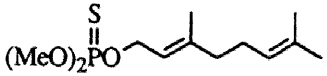
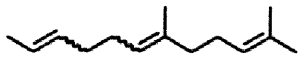
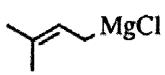
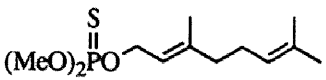
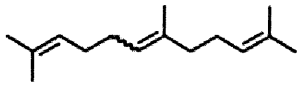
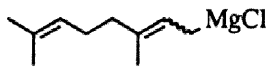
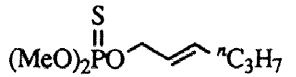
Table 3. Regioselective γ-S_N2 Reaction of Various Diphenylphosphates with Allylic Grignard Reagents[a]

Entry	Grignard reagent	Diphenylphosphate	Product	Yield, %[b]	Ratio (γ-S_N2/α-S_N2)[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] 2 equiv of the Grignard reagent were used. [f] Performed at 0~10 °C for 4.5 h.

Table 4. Regioselective α-S_N2 Reaction of Various Dimethylthiophosphates with Allylic Grignard Reagents[a]

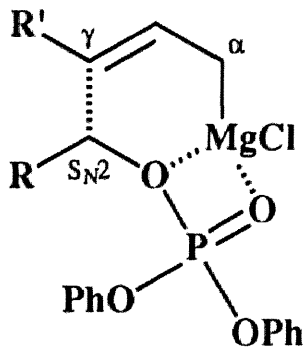
Entry	Grignard reagent	Dimethylthiophosphate	Product	Yield, %[b]	Ratio (γ-S_N2/α-S_N2)[c]
1				54	5/95
2				46	4/96
3				49	1/99
4				55	2/98

[a] The reaction was carried out using an allylic Grignard reagent (1.1 equiv) and a dimethylthiophosphate (equiv) for 1 h.
[b] Isolated yield. [c] Determined by GC analysis.

8). (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 allyl metals to an alkyl halide, an acyclic transition structure is followed 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-S_N2 alkylation product selectively via a rigid bicyclic transition structure.[10,11]

Figure 1.



In sharp contrast, the dimethylthiophosphates for which the longer P–S bond would be expected[12] showed entirely different results and afforded the α-S_N2 coupling product nearly exclusively (Table 4).

Experimental Section

General Methods. Analytical TLC was done on E. Merck precoated (0.25 mm) silica gel 60 F_{254} plates. Column chromatography was conducted by using silica gel 60 (E. Merck 9385, 230 - 400 mesh). Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrometer. ^1H NMR spectra were measured on a Varian Gemini-200 (200 MHz) spectrometer. Chemical shifts of ^1H NMR spectra were reported relative to tetramethylsilane (δ 0). Splitting patterns were designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Analytical gas-liquid phase chromatography (GLC) was performed on a Shimadzu GC-8A instrument equipped with a flame ionization detector and a capillary column of PEG-HT (0.25x25000 mm) using nitrogen as carrier gas. Microanalyses were accomplished at the Faculty of Agriculture, Nagoya University.

All experiments were carried out under an atmosphere of dry argon. Tetrahydrofuran (THF) and ether (Et_2O) were freshly distilled from sodium metal using benzophenone ketyl as indicator. Dichloromethane (CH_2Cl_2) was stored over 4-Å molecular sieves and triethylamine (Et_3N) were stored over KOH pellets. Other simple chemicals were purchased and used as such.

General Procedure for Preparation of Allylic Grignard Reagents.[13] Magnesium turnings (1.0 g, 41 mmol) were placed in a 60-mL Schlenk tube under dry argon and vigorously stirred for 3-5 days at room temperature. The resulting activated magnesium turnings were covered with dry THF (5 mL), cooled to -15 °C, and a solution of allylic chloride (10 mmol) in THF (15 mL) was added dropwise for 1-2 h at this temperature. The mixture was stirred for 2-3 h at 0 °C. The resulting clear solution (0.4-0.45 M) was ready to use. Cinnamylmagnesium chloride was prepared with dry ether as the same procedure above.

General Procedure for Preparation of Allylic Diphenylphosphates. To a solution of allylic alcohol (10 mmol) in CH_2Cl_2 (25 ml) were added 4-(dimethylamino)-pyridine (a crystal), phosphorochloridate (11 mmol) and Et_3N (15 mmol) at 0 °C. 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/EtOAc) to afford allylic diphenylphosphate almost quantitatively.

General Procedure for Cross-Coupling Reaction of Diphenylphosphates with Allylic Grignard Reagents (Table 3). To a solution of diphenylphosphate (1.0 mmol) in dry THF (6 mL) was added dropwise at -20 °C a solution of allylic magnesium chloride (0.4-0.45 M, 1.1 mmol) in THF under an 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: the γ-S_N2:α-S_N2 ratio was determined by GC analysis.

(5*E*)-3-Methyl-1,5-tridecadiene (entry 1 in Table 3): TLC R_f 0.69 (hexane); IR (neat) 3081, 2959, 2926, 2855, 1640, 1458, 1374, 994, 967, 911 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 6.5 Hz, CH_3), 0.97 (d, 3 H, J = 6.6 Hz, CH_3), 1.13-1.40 (m, 10 H, 5 CH_2), 1.88-2.05 (m, 4 H, 2 CH_2), 2.05-2.21 (m, 1 H, CH), 4.92 (dd, 1 H, J = 1.6, 10.3 Hz, vinyl), 4.96 (dd, 1 H, J = 1.6, 17.2 Hz, vinyl), 5.23-5.47 (m, 2 H, 2 vinyls), 5.76 (ddd, 1 H, J = 6.8, 10.3, 17.2 Hz, vinyl). Anal. Calcd for $C_{14}H_{26}$: C, 86.52; H, 13.48. Found: C, 86.53; H, 13.75.

(5*E*)-3,3-Dimethyl-1,5-tridecadiene (entry 2 in Table 3): TLC R_f 0.69 (hexane); IR (neat) 3085, 2959, 2926, 2855, 1640, 1468, 1379, 1362, 999, 970, 911 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 6.6 Hz, CH_3), 0.96 (s, 6 H, 2 CH_3), 1.14-1.40 (m, 10 H, 5 CH_2), 1.89-2.03 (m, 4 H, 2 CH_2), 4.89 (dd, 1 H, J = 1.5, 17.8 Hz, vinyl), 4.90 (dd, 1 H, J = 1.5, 10.3 Hz, vinyl), 5.22-5.45 (m, 2 H, 2 vinyls), 5.80 (dd, 1 H, J = 10.4, 17.8 Hz, vinyl). Anal. Calcd for $C_{15}H_{28}$: C, 86.46; H, 13.54. Found: C, 86.34; H, 13.94.

(8*E*)-2,6-Dimethyl-6-vinyl-2,8-dodecadiene (entry 3 in Table 3): TLC R_f 0.65 (hexane); IR (neat) 3083, 2965, 2926, 1638, 1456, 1375, 1001, 970, 911 cm^{-1}; ^1H NMR

(200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, *J* = 7.2 Hz, CH_3), 0.94 (s, 3 H, CH_3), 1.15-1.43 (m, 4 H, 2 CH_2), 1.58 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 1.77-2.10 (m, 6 H, 3 CH_2), 4.89 (dd, 1 H, *J* = 1.6, 17.6 Hz, vinyl), 4.98 (dd, 1 H, *J* = 1.6, 11.0 Hz, vinyl), 5.02-5.15 (m, 1 H, vinyl), 5.22-5.46 (m, 2 H, 2 vinyls), 5.73 (dd, 1 H, *J* = 11.0, 17.6 Hz, vinyl). Anal. Calcd for $C_{16}H_{28}$: C, 87.19; H, 12.80. Found: C, 87.19; H, 13.50.

1-[(*E*)-2-Decenyl]-1-vinylcyclopentane (entry 4 in Table 3): TLC R_f 0.65 (hexane); IR (neat) 3081, 2955, 2855, 1638, 1456, 1412, 1379, 999, 968, 909 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, *J* = 6.5 Hz, CH_3), 1.10-1.70 (m, 18 H, 9 CH_2), 1.80-2.08 (m, 4 H, 2 CH_2), 4.90 (dd, 1 H, *J* = 1.5, 17.3 Hz, vinyl), 4.95 (dd, 1 H, *J* = 1.5, 11.0 Hz, vinyl), 5.33-5.39 (m, 2 H, 2 vinyls), 5.81 (dd, 1 H, *J* = 11.0, 17.3 Hz, vinyl). Anal. Calcd for $C_{17}H_{30}$: C, 87.10; H,12.90. Found: C, 87.09; H, 13.07.

(5*E*)-3,6,10-Trimethyl-1,5,9-undecatriene (entry 5 in Table 3): TLC R_f 0.64 (hexane); IR (neat) 3079, 2967, 2926, 1640, 1453, 1375, 994, 911 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.98 (d, 3 H, *J* = 6.4 Hz, CH_3), 1.60 (s, 6 H, 2 CH_3), 1.68 (s, 3 H, CH_3), 1.90-2.22 (m, 7 H, 3 CH_2 and CH), 4.92 (dd, 1 H, *J* = 1.4, 10.4 Hz, vinyl), 4.96 (dd, 1 H, *J* = 1.4, 17.4 Hz, vinyl), 5.01-5.18 (m, 2 H, 2 vinyls), 5.78 (ddd, 1 H, *J* = 6.4, 10.4, 17.4 Hz, vinyl). Anal. Calcd for $C_{14}H_{24}$: C, 87.43; H, 12.58. Found: C, 87.39; H, 13.10.

(5*E*)-3,3,6,10-Tetramethyl-1,5,9-undecatriene (entry 6 in Table 3): TLC R_f 0.64 (hexane); IR (neat) 2965, 2928, 1640, 1451, 1377, 1362, 999, 911 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.97 (s, 6 H, 2 CH_3), 1.58 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3), 4.89 (dd, 1 H, *J* = 1.6, 10.4 Hz, vinyl), 4.91 (dd, 1 H, *J* = 1.6, 17.8 Hz, vinyl), 5.01-5.17 (m, 2 H, 2 vinyls), 5.82 (dd, 1 H, *J* = 10.4, 17.8 Hz, vinyl). Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.31; H, 13.23.

(5*E*)-3-Phenyl-1,5-nonadiene (entry 7 in Table 3): TLC R_f 0.51 (hexane); IR (neat) 3029, 2959, 2926, 1638, 1601, 1493, 1453, 968, 914, 756, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.82 (t, 3 H, *J* = 7.3 Hz, CH_3), 1.29 (m, 2 H, CH_2), 1.89 (dt, 2 H, *J* = 1.3, 5.0 Hz, CH_2), 2.41 (dd, 2 H, *J* = 1.7, 7.2 Hz, CH_2), 3.30 (q, 1 H, *J* = 7.2 Hz, CH), 5.01 (dd, 1

H, J = 1.6, 16.8 Hz, vinyl), 5.03 (dd, 1 H, J = 1.6, 10.8 Hz, vinyl), 5.22-5.49 (m, 2 H, 2 vinyls), 5.98 (ddd, 1 H, J = 7.4, 10.8, 16.8 Hz, vinyl), 7.12-7.37 (m, 5 H, aromatic). Anal. Calcd for $C_{15}H_{20}$: C, 89.94; H, 10.06. Found: C, 89.91; H, 10.47.

(2*E*)-1-*tert*-Butyldimethylsiloxy-3,5,5-trimethyl-2,6-heptadiene (entry 8 in Table 3): TLC R_f 0.73 (hexane/EtOAc = 10:1); IR (neat) 2959, 2930, 2859, 1639, 1472, 1381, 1362, 1256, 1105, 1067, 1005, 911, 835, 776 cm^{-1} ; ^1H NMR (200 MHz, $CDCl_3$) δ 0.07 (s, 6 H, 2 CH_3), 0.90 (s, 9 H, 3 CH_3), 0.99 (s, 6 H, 2 CH_3), 1.61 (s, 3 H, CH_3), 2.02 (s, 2 H, CH_2), 4.19 (d, 2 H, J = 6.2 Hz, CH_2), 4.87 (dd, 1 H, J = 1.5, 10.3 Hz, vinyl), 4.89 (dd, 1 H, J = 1.5, 17.8 Hz, vinyl), 5.26 (t, 1 H, J = 6.2 Hz, vinyl), 5.85 (dd, 1 H, J = 10.3, 17.8 Hz, vinyl). Anal. Calcd for $C_{16}H_{32}OSi$: C, 71.57; H, 12.01. Found: C, 71.49; H, 12.54.

1-(2,2-Dimethyl-3-butenyl)-4,4-dimethyl-1-cyclopentene (entry 9 in Table 3): TLC R_f 0.64 (hexane); IR (neat) 2955, 2867, 2840, 1640, 1466, 1379, 1362, 999, 911 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 6 H, 2 CH_3), 1.05 (s, 6 H, 2 CH_3), 2.04-2.10 (m, 6 H, 3 CH_2), 4.88 (dd, 1 H, J = 1.5, 10.7 Hz, vinyl), 4.91 (dd, 1 H, J = 1.5, 17.5 Hz, vinyl), 5.22 (br. s, 1 H, vinyl), 5.86 (dd, 1 H, J = 10.7, 17.5 Hz, vinyl). Anal. Calcd for $C_{13}H_{22}$: C, 87.56; H, 12.43. Found: C, 87.51; H, 13.00.

4,8-Dimethyl-4-vinyl-7-nonen-1-yne (entry 10 in Table 3): TLC R_f 0.39 (hexane); IR (neat) 3312, 2969, 2359, 1638, 1456, 1375, 1001, 914, 635 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.09 (s, 3 H, CH_3), 1.35-1.46 (m, 2 H, CH_2), 1.59 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3), 1.86 (q, 2 H, J = 9.0 Hz, CH_2), 1.99 (t, 1 H, J = 2.8 Hz, CH_2), 2.21 (d, 1 H, J = 2.8 Hz, CH), 4.99 (dd, 1 H, J = 1.2, 17.4 Hz, vinyl), 5.06 (dd, 1 H, J = 1.2, 10.8 Hz, vinyl), 5.10 (m, 1 H, vinyl), 5.81 (dd, 1 H, J = 10.8, 17.4 Hz, vinyl). Anal. Calcd for $C_{13}H_{20}$: C, 88.57; H, 11.43. Found: C, 88.50; H, 11.89.

3,3-Dimethyl-1-tridecen-5-yne (entry 11 in Table 3): TLC R_f 0.44 (hexane); IR (neat) 2961, 2930, 2859, 1642, 1475, 1416, 1379, 1364, 912 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 6.5 Hz, CH_3), 1.08 (s, 6 H, 2 CH_3), 1.20-1.55 (m, 10 H, 5 CH_2), 2.08-2.19 (m, 4 H, 2 CH_2), 4.94 (dd, 1 H, J = 1.3, 10.7 Hz, vinyl), 4.98 (dd, 1 H, J = 1.3, 17.5

Hz, vinyl), 5.89 (dd, 1 H, J = 10.7, 17.5 Hz, vinyl). Anal. Calcd for $C_{15}H_{26}$: C, 87.30; H, 12.70. Found: C, 87.30; H, 13.36.

3,3-Dimethyl-4-phenyl-1-butene (entry 12 in Table 3): TLC R_f 0.54 (hexane); IR (neat) 3031, 2963, 2926, 1638, 1497, 1455, 1379, 1362, 912, 766, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.00 (s, 6 H, 2 CH_3), 2.58 (s, 2 H, CH_2), 4.85 (dd, 1 H, J = 1.4, 17.4 Hz, vinyl), 4.91 (dd, 1 H, J = 1.4, 10.8 Hz, vinyl), 5.86 (dd, 1 H, J = 10.8, 17.4 Hz, vinyl), 7.10-7.35 (m, 5 H, aromatic). Anal. Calcd for $C_{12}H_{16}$: C, 89.94; H, 10.06. Found: C, 89.81; H, 10.57.

3,3,7-Trimethyl-1,6-octadiene (entry 13 in Table 3): TLC R_f 0.58 (hexane); IR (neat) 3085, 2965, 2869, 1640, 1379, 1001, 911, 831 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.99 (s, 6 H, 2 CH_3), 1.24-1.32 (m, 2 H, CH_2), 1.59 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 1.77-1.98 (m, 2 H, CH_2), 4.90 (dd, 1 H, J = 1.6, 18.1 Hz, vinyl), 4.92 (dd, 1 H, J = 1.6, 10.2 Hz, vinyl), 5.03-5.16 (m, 1 H, vinyl), 5.78 (dd, 1 H, J = 10.2, 18.1 Hz, vinyl). Anal. Calcd for $C_{11}H_{20}$: C, 86.76; H, 13.24. Found: C, 86.66; H, 13.57.

3-Phenyl-1-butene (entry 14 in Table 3): TLC R_f 0.46 (hexane); IR (neat) 3029, 2967, 2930, 1638, 1601, 1493, 1453, 1017, 912 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 1.37 (d, 3 H, J = 7.0 Hz, CH_3), 3.38-3.56 (m, 1 H, CH), 5.01-5.11 (m, 2 H, 2 vinyls), 6.02 (ddd, 1 H, J = 6.3, 10.4, 17.1 Hz, vinyl), 7.16-7.36 (m, 5 H, aromatic). Anal. Calcd for $C_{10}H_{12}$: C, 90.85; H, 9.15. Found: C, 90.61; H, 9.56.

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(9) This is the optimum temperature for obtaining the best yield and regioselectivity.

(10) Oxygen atom of phenoxide in Fig. 1 is much less basic to coordinate to magnesium. Indeed, (*E*)-2-hexenyl-1-diethylphosphate gave a 65:35 mixture of γ-S_N2 and α-S_N2

allylation products in the reaction with geranylmagnesium chloride and thus superiority of diphenylphosphate ester is obvious.

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

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Chapter 2

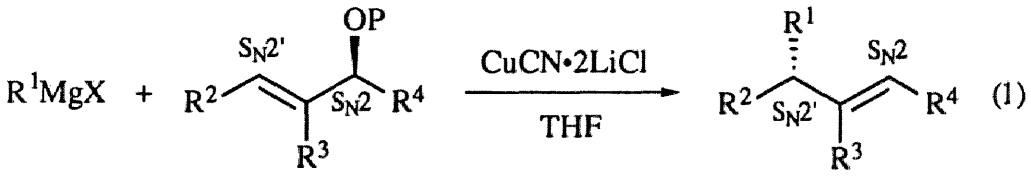
Highly Selective 1,5-Diene Syntheses

Section 2

Highly Selective α-S_N2' Reaction of Allyl-Allyl Cross-Coupling

Abstract: Treatment of secondary allylic chlorides or allylic phosphates in THF with prenyl Grignard reagent in the presence of CuCN•2LiCl gave geraniol or farnesol derivatives with high α-S_N2' selectivity. Phosphate leaving groups were highly *trans*-stereoselective for the formation of (*E*, *E*)-farnesol derivatives. Furthermore, complete *anti*-S_N2' selectivity was observed in the alkylation of optically active allylic phosphates. The present method appears to be an excellent carbon-carbon coupling reaction with high regio-, (*E*)-, and enantioselectivity. Coenzyme Q_{10} (ubiquinone 10) was efficiently synthesized using this methodology.

The substitution reaction on allylic carbon is one of the most important processes in organic synthesis. During the past decade, organocopper reagents leading to S_N2 or S_N2' coupling products have been intensively studied.[1] Organocuprates generally show anti-S_N2' selectivity in reaction with allylic carboxylates[2] and allylic sulfonates.[3,4] Recently syn-S_N2' substitution preference has been observed with allylic carbamates,[5,6] allyloxybenzothiazoles,[7] and allylic ammonium salts.[8] Although these processes are extremely useful and broadly utilized in organic synthesis,[9] there are still drawbacks and limitations to each of the known procedures. Here, we wish to report that the phosphate ester is shown to be the leaving group of choice in the remarkable S_N2'-, (*E*)-, and antiselective reaction between Grignard reagent and allylic alcohol derivatives in the presence of a copper (I) salt (eq. 1).[10] Coenzyme Q_{10} (ubiquinone 10) was efficiently synthesized with this methodology.



(1)

Scheme 1.

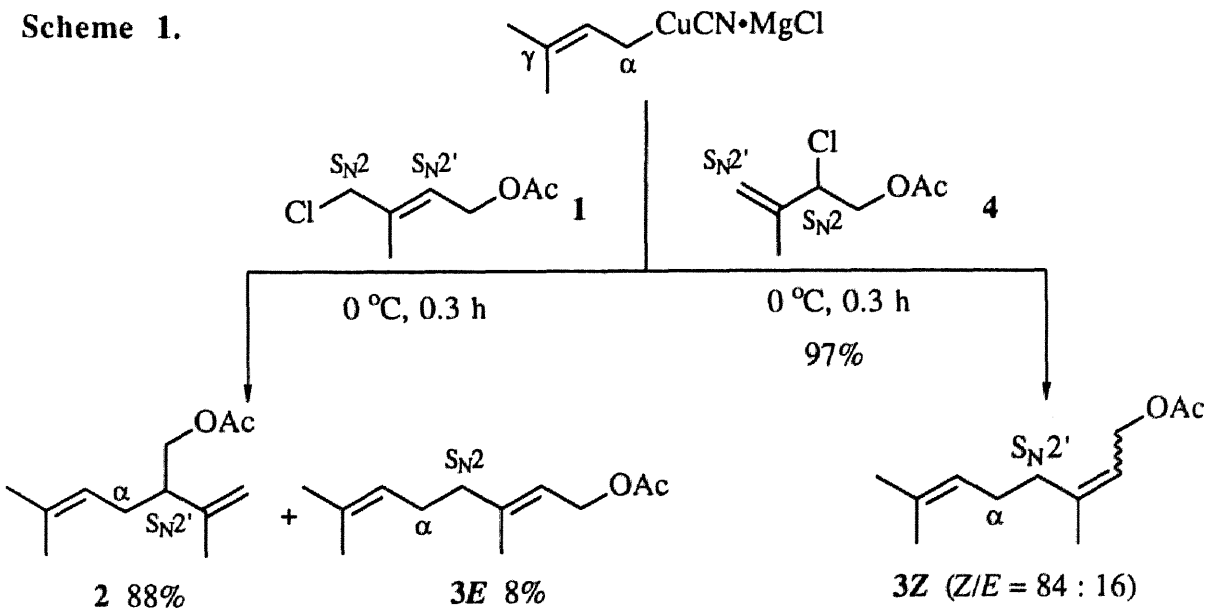
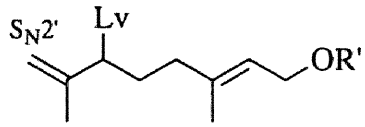


Table 1. The effect of leaving groups of secondary allylic alcohol derivatives on S_N2'/S_N2 regio- and *E/Z* stereoselectivity

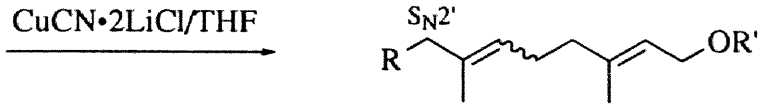
RMgX + 

5

Entry	RMgX	Substrate	Lv	R'
1	$(CH_3)_2C{=}CH\underset{\alpha}{C}H_2MgCl$	**5a**	Cl	Ac
2	$(CH_3)_2C{=}CH\underset{\alpha}{C}H_2MgCl$	**5a**	Cl	Ac
3	$(CH_3)_2C{=}CH\underset{\alpha}{C}H_2MgCl$	**5b**	$(EtO)_2PO_2$	Si(*t*-Bu)Me_2
4	$(CH_3)_2C{=}CH\underset{\alpha}{C}H_2MgCl$	**5c**	$(i\text{-}PrO)_2PO_2$	Si(*t*-Bu)Me_2
5	$(CH_3)_2C{=}CH\underset{\alpha}{C}H_2MgCl$	**5d**	$(c\text{-}C_6H_{11}O)_2PO_2$	Si(*t*-Bu)Me_2
6	$(CH_3)_2C{=}CH\underset{\alpha}{C}H_2MgCl$	**5e**	$(PhO)_2PO_2$	Si(*t*-Bu)Me_2
7	$(CH_3)_2C{=}CH\underset{\alpha}{C}H_2MgCl$	**5f**	$(Me_2N)_2PO_2$	Si(*t*-Bu)Me_2
8	$(CH_3)_2C{=}CH\underset{\alpha}{C}H_2MgCl$	**5g**	MsO	Si(*t*-Bu)Me_2
9	*n*-BuMgCl	**5g**	MsO	Si(*t*-Bu)Me_2

[a] Yield after isolation and purification.

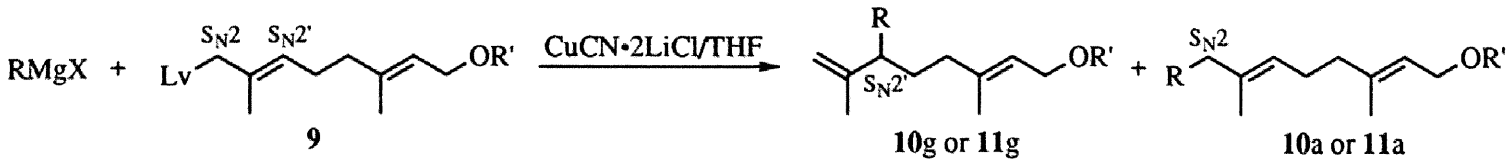
[b] Determined by GC analysis. For the entries 3–9, the ratios were determined after conversion to the corresponding alcohols.



6 – 8

Reaction Temp. (°C)	Reaction Time (h)	Product	Yield[a] (%)	S_N2'/S_N2[b] Ratio	*E*/*Z* [b] Ratio
0	1	**6**	90	> 99 : 1	46 : 54
-100	1	**6**	74	> 99 : 1	85 : 15
-78	1	**7**	94	> 99 : 1	96 : 4
-78	1	**7**	96	> 99 : 1	96 : 4
-60	1	**7**	58	> 99 : 1	96 : 4
-78	1	**7**	91	> 99 : 1	74 : 26
-20	1.5	**7**	47	> 99 : 1	59 : 41
-78	1	**7**	68	> 99 : 1	55 : 45
-78	1	**8**	87	> 99 : 1	53 : 47

Table 2. The effect of leaving groups of primary allylic phosphates on S_N2'/S_N2 regioselectivity



9 **10g or 11g** **10a or 11a**

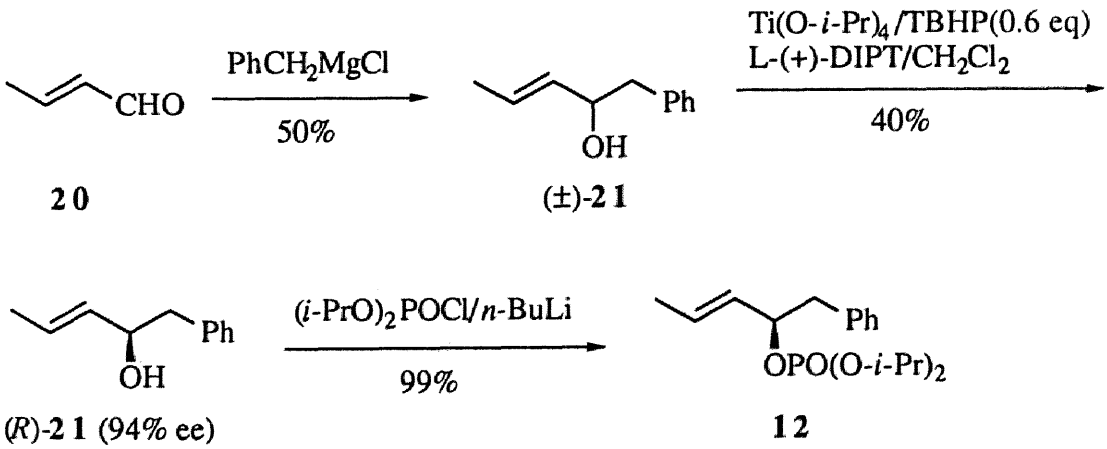
Entry	RMgX	Substrate	Lv	R'	Reaction Temp. (°C)	Reaction Time (h)	Product	Yield[a] (%)	S_N2'/S_N2[b] Ratio
1	$(CH_3)_2C{=}CH\underset{\alpha}{C}H_2MgCl$	**9a**	$(PhO)_2PO_2$	Ac	-78	1	**10**	95	88 : 12
2	$(CH_3)_2C{=}CH\underset{\alpha}{C}H_2MgCl$	**9b**	$(EtO)_2PO_2$	Ac	-50	1	**10**	95	87 : 13
3	$(CH_3)_2C{=}CH\underset{\alpha}{C}H_2MgCl$	**9c**	$(i\text{-}PrO)_2PO_2$	Ac	-40	1.5	**10**	82	88 : 12
4	*n*-BuMgCl	**9d**	$(PhO)_2PO_2$	$Si(t\text{-}Bu)Me_2$	-60	0.5	**11**	87	96 : 4

[a] Yield after isolation and purification.

[b] Determined by GC analysis.

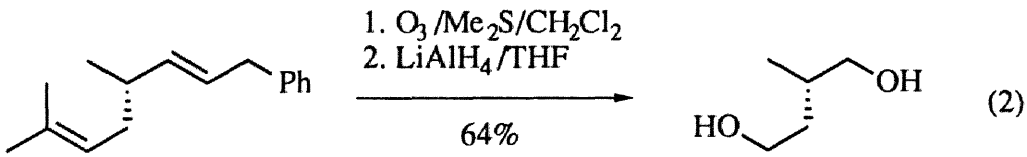
Treatment of the primary allylic chloride **1**[11] in THF with prenyl Grignard reagent in the presence of CuCN·2LiCl[12] at 0 °C for 20 min gave lavandulyl acetate (**2**) in 88% yield with a small amount of geranyl acetate (**3*E***). Similarly, reaction with the secondary allylic chloride **4**[13] afforded neryl acetate (**3*Z***) with moderate stereoselectivity in 97% yield (Scheme 1). Thus, the process exhibited an α-S_N2' coupling preference for the allylic organo-magnesium-copper complex with allylic chlorides.

In an attempt to improve *E, Z*-stereoselectivity of this process, an extensive study was made of the effect of leaving groups on stereoselectivity.[14] Some of our results of allylic derivatives **5**[13,15] are summarized in Table 1. The phosphate leaving group was much more convenient and general than a variety of other derivatives. It also solved the problem of stereoselectivity (*E*/*Z* = 96:4, $S_N2'/S_N2 \geq 99:1$, entries 3–5).[17] It should be noted that the other ester derivatives such as mesylate derivatives did not result in high stereoselectivity (entries 8 and 9) despite that reported for α, β-enoates systems.[3] With primary allylic phosphate **9**,[18] S_N2' coupling was still dominant (Table 2). No remarkable differences in S_N2'/S_N2 selectivities, however, were observed among the allylic phosphates **9a–9c** for prenylation (entries 1–3). Butylation of **9a** afforded a better regioselectivity (S_N2'/S_N2 = 96:4, entry 4).



Scheme 2.

If the displacement is stereospecific, it will result in a predictable transfer of chirality from the secondary alcohol center to a newly formed carbon atom. The stereochemical results for prenylation and butylation of (*R*)-allylic phosphate **12** with Grignard reagent and CuCN·2LiCl are shown in entries 1 and 2 of Table 3. Synthesis of the chiral substrate **12** was accomplished in three steps from (*E*)-2-butenal (**20**) as shown in Scheme 2. (*R*)-Allylic alcohol **21** (94% ee) was obtained by Sharpless kinetic resolution[20] of the corresponding racemic allylic alcohol (±)-**21**. The prenylated product **16** was found to be homogeneous by capillary GC, and was shown to be a complete 1,3-chirality transfer by 500 MHz ^{1}H NMR analysis using the shift reagents, Ag(fod) and Eu(tfc)$_3$ (entry 1, Table 3).[21] The absolute stereochemistry of the product was shown to have the *S* configuration by ozonolysis-LiAlH$_4$ reduction (eq. 2);[22] thus, in this acyclic system, the enantioselectivity of the reaction was nearly quantitative (corrected).[23] Similarly, the enantioselective butylation of **12** was accomplished with equal efficiency (entry 2, Table 3).[24]

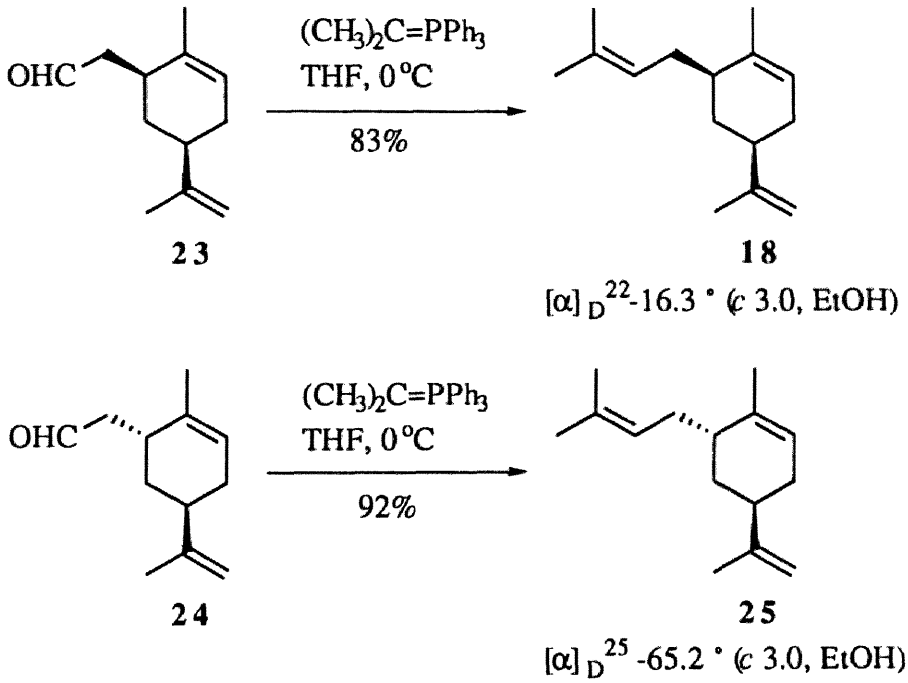


16 **22** (2)

$[\alpha]_D^{22}$ -11.1° (*c* 0.95, CH_3OH)

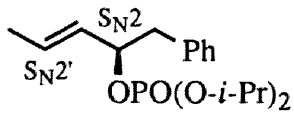
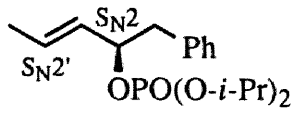
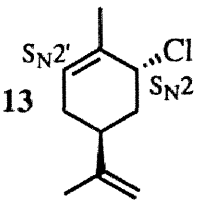
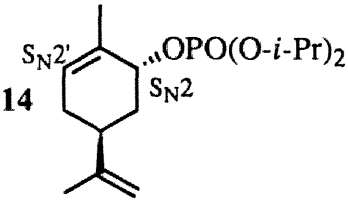
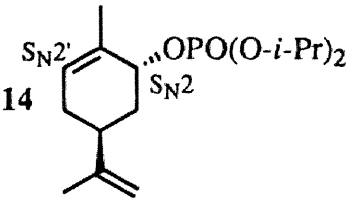
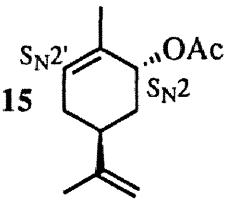
The phosphate system was similarly advantageous in a cyclic system (entries 3–5, Table 3). The result of prenylation of (+)-*trans*-carvyl chloride (**13**)[25] and the corresponding diisopropylphosphate **14**[26] with prenyl Grignard reagent/CuCN·2LiCl gave the α-S_N2' and antiselectivity (entries 3 and 4), and higher regio- and stereoselectivity were observed with a phosphate leaving group. The diastereoselectivity (cis/trans ratio) of the prenylated product was determined by GC analysis using authentic cis isomer **18** and trans isomer **25**. Optically pure **18** and **25** were prepared by Wittig reaction from chiral aldehyde **23** and **24**,[27]

respectively (Scheme 3). The α-S_N2'/α-S_N2 selectivity of **18** was calculated from the optical purity of the major cis isomer. Methylation of **14** with MeMgI was also completely regio- and stereoselective (entry 5).[26,28] With the corresponding acetate **15**, however, no methylation reaction occurred even at 20 °C (entry 6).



Scheme 3.

Table 3. S_N2'-, (*E*)-stereo-, and antiselective alkylation of chiral allylic alcohol derivatives

Entry	RMgX	Substrate	Reaction Temp. (°C)	Reaction Time (h)
1	$(CH_3)_2\underset{\gamma}{C}{=}CH\underset{\alpha}{CH_2}MgCl$	**12** 	-60	1
2	*n*-BuMgCl	**12** 	-60	1
3	$(CH_3)_2\underset{\gamma}{C}{=}CH\underset{\alpha}{CH_2}MgCl$	**13** 	-40	2.5
4	$(CH_3)_2\underset{\gamma}{C}{=}CH\underset{\alpha}{CH_2}MgCl$	**14** 	-30	1.5
5	MeMgI	**14** 	-30	1
6	MeMgI	**15** 	20	9

[a] Yield after isolation and purification.

[b] Determined by GC analysis.

[c] Determined by 500 MHz ^1H NMR spectroscopy with $Eu(tfc)_3$ and Ag(fod).

[d] Calculated from the optical purity of the major cis isomer.

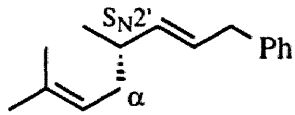
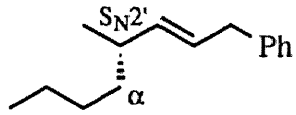
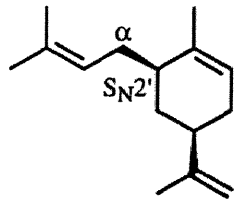
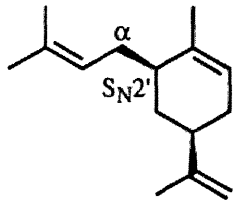
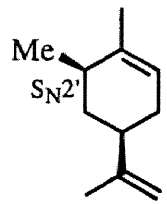
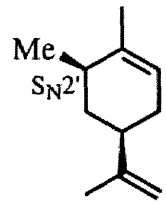
Product	Yield[a] (%)	S_N2'/S_N2 Ratio	*E*/*Z*[b] Ratio	enantio- or diastereoselectivity
16 	81	> 99 : 1[b]	> 99 : 1	97 : 3[c]
17 	89	> 99 : 1[b]	> 99 : 1	95 : 5[c]
18 	90	87 : 13[d]		96 : 4[b]
18 	63	96 : 4[d]		> 99 : 1[b]
19 	85	> 99 : 1[d]		> 99 : 1[b]
19 	< 1	—		—

Table 4. Characterization of Products **8**, **10**, **11**, and **16–19**

Product	R_f (solvent)	$[\alpha]_D^{20}$ (c, solvent)[a,b]	Molecular Formula[c]	IR (neat or CCl_4)[d] ν (cm^{-1})
8	0.76 (Hx/EtOAc, 3:1)	—	$C_{20}H_{40}OSi$ (324.6)	2980, 2950, 2880, 1470, 1260, 1120, 1080
10	0.40 (Hx/EtOAc, 10:1)	—	$C_{17}H_{28}O_2$ (264.4)	3090, 2990, 2950, 1740, 1450, 1380, 1240, 1030
11	0.76 (Hx/EtOAc, 3:1)	—	$C_{20}H_{40}OSi$ (324.6)	2950, 2880, 1470, 1390, 1260, 1110, 1080
16	0.43 (Hx)	-5.85 (1.33, $CHCl_3$)	$C_{16}H_{22}$ (214.4)	3060, 2990, 2940, 1510, 1430, 1390, 980
17	0.44 (Hx)	+15.79 (2.06, EtOH)	$C_{15}H_{22}$ (202.3)	3050, 2975, 2940, 2875, 1500, 1460, 1385
18	0.54 (Hx)	-15.05[f] (3.10, EtOH)	$C_{15}H_{24}$ (204.4)	3090, 2970, 2920, 2860, 1650, 1460, 1380
19	0.59 (Hx)	-32.61 (1.37, MeOH)	$C_{11}H_{18}$ (150.3)	3100, 2980, 2925, 2870, 1650, 1550, 1455, 1445, 1380

[a] Measured using a JASCO DIP–140 polarimeter.

[b] Hx = hexane.

[c] Satisfactory microanalysis obtained: C ± 0.44, H ± 0.35.

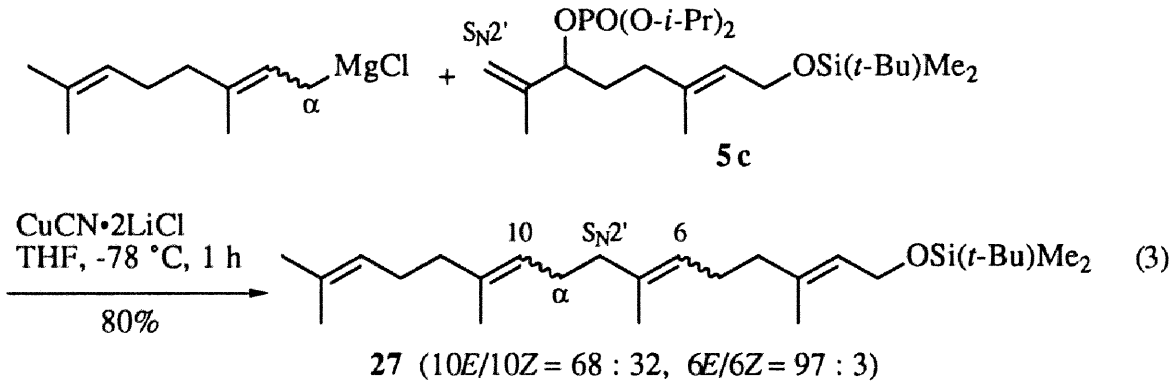
[d] Recorded on a Hitachi 260-10 Infrared spectrometer.

[e] Obtained on a Varian Gemini-200 spectrometer at 200 MHz.

[f] Value of entry 4 in Table 3.

	^{1}H-NMR ($CDCl_3$/TMS)[e] δ, *J* (Hz)
	0.07 (s, 6H), 0.86 (t, 3H), 0.90 (s, 9H), 1.1–1.5 (m, 6H), 1.58 (s, 3H), 1.65 (s, 3H), 1.9–2.2 (m, 6H), 4.19 (d, 2H, *J* = 6.2), 5.09 (t, 1H, *J* = 7.0), 5.30 (t, 1H, *J* = 6.4)
	1.3–1.8 (m, 2H), 1.60 (s, 3H), 1.61 (s, 3H), 1.68 (s, 6H), 1.8–2.2 (m, 5H), 2.06 (s, 3H), 4.58 (d, 2H, *J* = 7.2), 4.67 (s, 1H), 4.75 (s, 1H), 5.05 (m, 1H), 5.30 (t, 1H, *J* = 7.0)
	0.07 (s, 6H), 0.87 (t, 3H, *J* = 5.4), 0.90 (s, 9H), 1.1–1.5 (m, 8H), 1.58 (s, 3H), 1.60 (s, 3H), 1.8–2.1 (m, 3H), 4.19 (d, 2H, *J* = 6.4), 4.67 (s, 1H), 4.74 (s, 1H), 5.28 (t, 1H, *J* = 6.6)
	1.00 (d, 3H, *J* = 6.0), 1.70 (s, 3H), 1.80 (s, 3H), 2.00 (t, 2H, *J* = 6.0), 2.1–2.3 (m, 1H), 3.35 (d, 2H, *J* = 5.0), 5.15 (t, 1H, *J* = 7.5), 5.1–5.4 (m, 2H), 7.1–7.4 (m, 5H)
	0.89 (t, 3H, *J* = 6.6), 0.98 (d, 3H, *J* = 6.6), 1.2–1.4 (m, 6H), 2.0–2.2 (m, 1H), 3.34 (d, 1H, *J* = 6.2), 5.40 (dd, 1H, J_1 = 7.0, J_2 = 15.4), 5.53 (dt, 1H, J_1 = 6.0, J_2 = 15.2), 7.2–7.4 (m, 5H)
	1.62 (s, 3H), 1.68 (s, 3H), 1.70 (s, 3H), 1.72 (s, 3H), 1.7–2.4 (m, 8H), 4.70 (s, 2H), 5.10 (t, 1H, *J* = 7.5), 5.48 (m, 1H)
	1.04 (d, 3H, *J* = 7.0), 1.68 (s, 3H), 1.75 (s, 3H), 1.8–2.3 (m, 6H), 4.70 (s, 2H), 5.4 (m, 1H)

The potential of the present methodology for the synthesis of polyprenoids was demonstrated by the synthesis of coenzyme Q_{10} (ubiquinone 10, **26**) which is known as a biologically active compound. Although various synthetic methods[29-31] were developed, most of these encountered problems in the construction of the all-trans decaprenyl side chain. In an attempt to develop a convenient approach for the total synthesis of coenzyme Q_{10}, we investigated the stereoselectivity of the coupling reaction between geranyl Grignard reagent and secondary allylic phosphate **5c** (eq. 3). Geranylgeraniol derivative **27** was predominantly formed in this reaction and the *E*/*Z* ratio of the C_{10}–C_{11} double bond was 68:32, whereas that of the C_6–C_7 was 97:3.

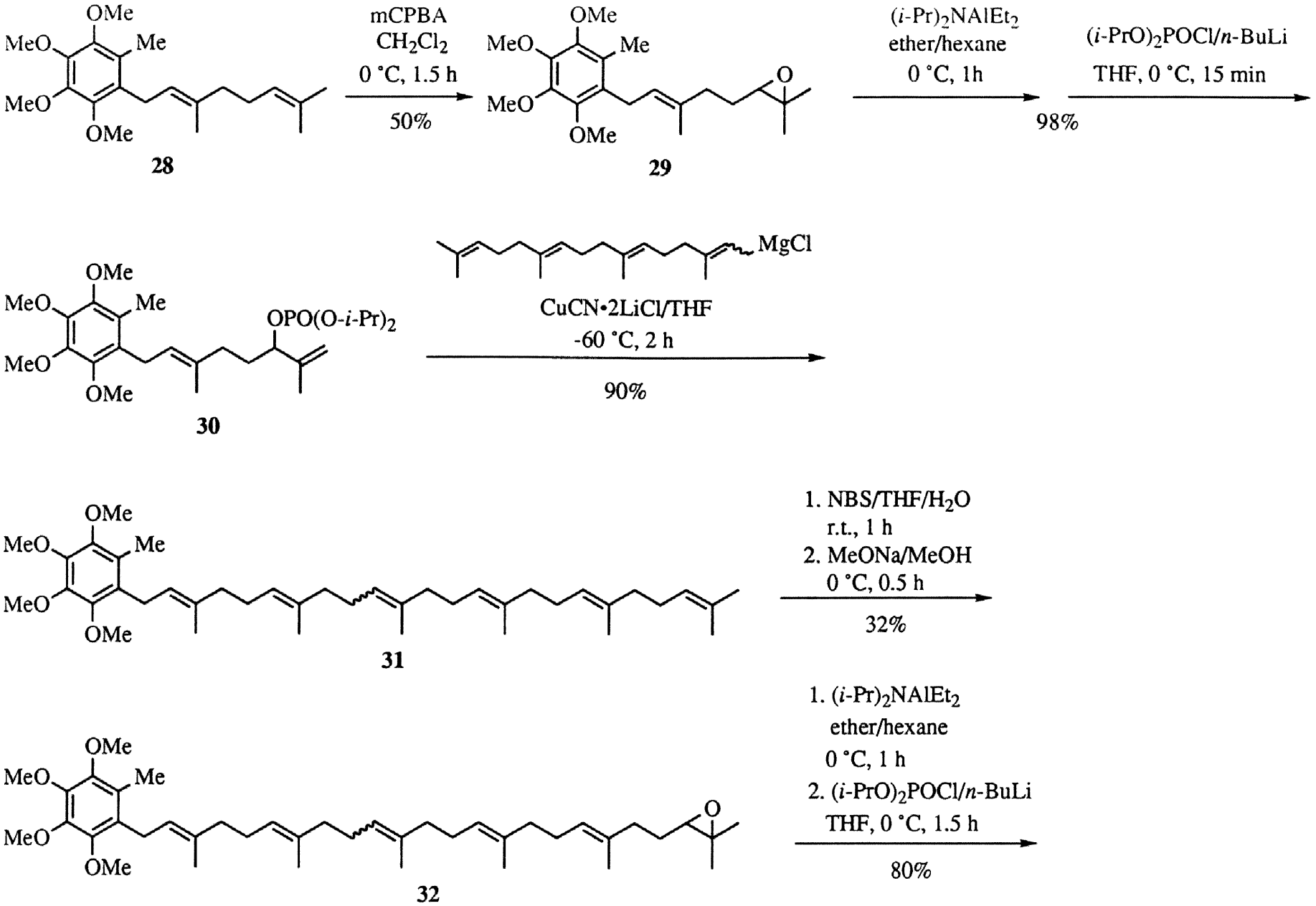


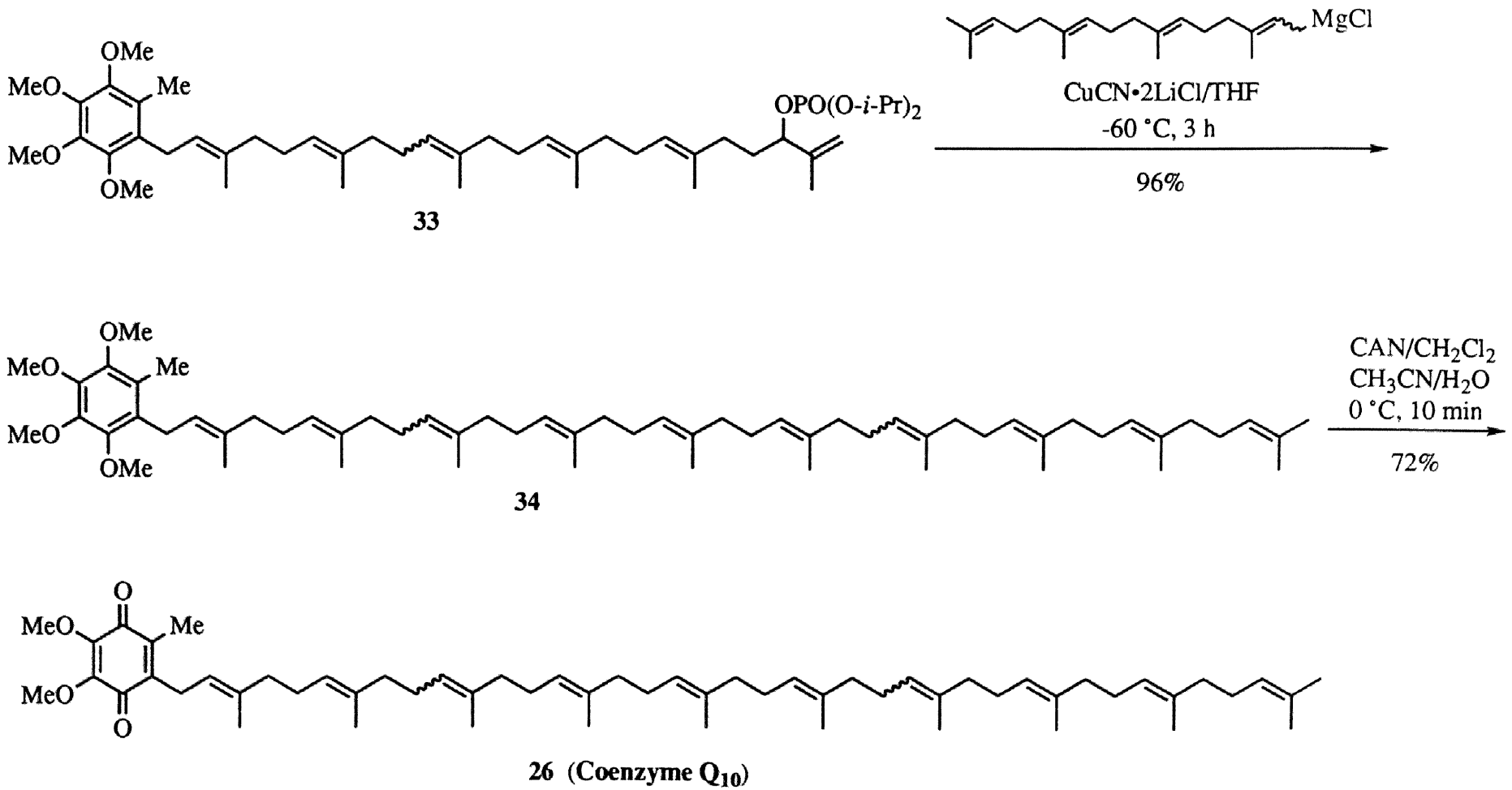
27 (10*E*/10*Z* = 68 : 32, 6*E*/6*Z* = 97 : 3)

Synthesis of coenzyme Q_{10} (**26**) could be directly carried out from reported intermediate **28**[32] by two additions of geranylgeranyl Grignard reagent (Scheme 4). This coenzyme Q_2-type compound **28** was converted to the allylic phosphate **30** by a three-step sequence: (1) epoxidation with mCPBA,[30] (2) isomerization to allylic alcohol,[16] (3) phosphorylation. Coenzyme Q_6 derivative **31** were afforded in 90% yield by treatment of **30** in THF with geranylgeranyl Grignard reagent in the presence of CuCN•2LiCl at -60 °C. **31** was converted via the terminal mono bromohydrin into the epoxide **32** in 32% yield.[33] The same sequence of synthesis of the allylic phosphate **33** from **32** followed by coupling reaction with geranylgeranyl Grignard reagent yielded a precursor of coenzyme Q_{10} **34**.[30,31] Finally,

deprotection of **34** with CAN gave coenzyme Q_{10} (**26**) in 72% yield. This product was recrystallized twice (mp 46.5–47 °C, lit.[30] mp 47 °C) and was found to be identical with the authentic specimen[34] as judged by comparison of the spectral properties (IR, ^{1}H NMR) and thin-layer chromatographic behavior.

In summary, the method described here appears to be an excellent carbon-carbon coupling reaction with high regio-, (*E*)-, and enantioselectivity.[35] Main features of the present scheme are: (1) exclusive S_N2' substitution with anti attack on both acyclic and cyclic allylic systems; (2) acyclic allylic phosphates are transformed into (*E*)-alkenes; (3) prenyl carbanion reacts at the less substituted allyl terminus (α-position); (4) optically active allylic phosphate can be simply prepared from the corresponding alcohol which, in turn, is easily obtained from readily available chiral ethynyl carbinol. Many difficulties, however, are encountered in the preparation of the corresponding chloride or mesylate.


OMe
MeO
Me
MeO
OMe
28
mCPBA
CH_2Cl_2
0 °C, 1.5 h
50%
29
$(i\text{-Pr})_2NAlEt_2$
ether/hexane
0 °C, 1h
98%
$(i\text{-PrO})_2POCl/n\text{-BuLi}$
THF, 0 °C, 15 min
OPO(O-*i*-Pr)$_2$
30
MgCl
CuCN•2LiCl/THF
-60 °C, 2 h
90%
31
1. NBS/THF/H_2O
r.t., 1 h
2. MeONa/MeOH
0 °C, 0.5 h
32%
32
1. $(i\text{-Pr})_2NAlEt_2$
ether/hexane
0 °C, 1 h
2. $(i\text{-PrO})_2POCl/n\text{-BuLi}$
THF, 0 °C, 1.5 h
80%


OMe
MeO
Me
MeO
OMe
OPO(O-i-Pr)2
MgCl
CuCN•2LiCl/THF
-60 °C, 3 h
96%
33
OMe
MeO
Me
MeO
OMe
CAN/CH2Cl2
CH3CN/H2O
0 °C, 10 min
72%
34
O
MeO
Me
MeO
O
26 (Coenzyme Q10)

Scheme 4.

Experimental Section

General Methods.

IR spectra were obtained using a Hitachi 260-10 spectrometer. ^1H NMR spectra were obtained using a Varian Gemini-200 (200 MHz) or VXR-500S (500 MHz) spectrometer. Chemical shifts of ^1H NMR spectra were reported relative to tetramethylsilane (δ 0). Splitting patterns were designated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; b, broad. Analytical gas chromatography (GC) was performed on Shimadzu Model 8A instrument with a flame-ionization detector and a capillary column of PEG-20M Bonded (25 m) using nitrogen as carrier gas. TLC was done on silica gel (Merck Silica 60 F_{254} sheets). Silica gel was purchased from Merck (silica gel 60, 230–400 mesh). Optical rotation was measured on a JASCO DIP–140 polarimeter. Microanalyses were accomplished at the Faculty of Agriculture, Nagoya University. Reactions were generally run under a positive pressure of dry argon. Tetrahydrofuran (THF) was freshly distilled before use from sodium benzophenone ketyl. Other simple chemicals were purchased and used as such.

General Procedure for Preparation of Allylic Phosphates. To a solution of allylic alcohol (1.0 mmol) in THF (3 mL) was added ^{n}BuLi (1.6 M in hexane, 0.63 mL) at -78 °C. Soon it was warmed at 0 °C, followed by phosphorochloridate (1.1 mmol). The solution was stirred for 1 h, then quenched with saturated aqueous NH_4Cl solution (5 mL). Et_2O (10 mL) was then added and the organic phase is separated, washed with brine (5 mL), and dried ($MgSO_4$). The solvent was evaporated and the crude product was purified by column chromatography on silica gel to give an allylic phosphate.

(2*E*,6*E*)-1-*tert*-Butyldimethylsiloxy-3,7,11-trimethyl-2,6,10-dodecatriene (7); Typical Procedure: To a solution of 3-methyl-2-butenylmagnesium chloride, prepared from magnesium turnings (365 mg, 15.0 mmol) and 1-chloro-3-methyl-2-butene (314 mg, 3.0 mmol) in THF (10 mL), was added a solution of CuCN (269 mg, 3.0 mmol) and LiCl (254 mg, 6.0 mmol) in THF (3 mL) at 0 °C and the resulting dark violet solution was stirred at 0 °C for 30 min. The mixture was then cooled to -78 °C and a solution of the allylic

diisopropylphosphate **5c** (449 mg, 1.0 mmol) in THF (2 mL) was added at -78 °C. The solution was stirred at this temperature for 1 h, then quenched with saturated aqueous NH_4Cl solution (15 mL). Et_2O (15 mL) was then added and the organic phase was separated, washed with brine (15 mL), and dried ($MgSO_4$). The solvent was evaporated and the crude product was purified by column chromatography on silica gel to give **7** (323 mg, 96%), the *E/Z* ratio was determined to be 96:4 by GC after converting to farnesol ($^nBu_4NF$/THF).

1-[(2*E*)-6,7-Epoxy-3,7-dimethyloct-2-enyl]-2,3,4,5-tetramethoxy-6-methylbenzene (29): To a solution of **28** (3.80 g, 10.9 mmol) in CH_2Cl_2 (30 mL) was added a solution of mCPBA (80% purity, 3.07 g, 14.2 mmol) in CH_2Cl_2 (30 mL) at 0 °C over 30 min. The reaction mixture was stirred at 0 °C for 1 h, quenched with saturated aqueous $NaHCO_3$, and then with H_2O, and dried over $MgSO_4$. The solvent was evaporated and the crude product was purified by column chromatography on silica gel using a 5:1 mixture of hexane and Et_2O as eluant to give **29** as a colorless oil; yield: 1.99 g (50%); R_f = 0.48 (hexane/ether = 1 : 1)

$C_{21}H_{32}O_5$	calc.	C	69.20	H	8.85
(364.5)	found		69.41		8.99

IR (CCl_4): ν = 3000, 2970, 2900, 1475, 1419, 1120, 1057 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.24 (s, 3H), 1.26 (s, 3H), 1.5–1.7 (m, 2H), 1.79 (s, 3H), 2.0–2.3 (m, 2H), 2.14 (s, 3H), 2.68 (t, 1H, *J* = 6.2), 3.33 (d, 2H, *J* = 6.6), 3.79 (s, 6H), 3.91 (s, 6H), 5.10 (t, 1H, *J* = 6.9).

Diisopropyl [(4*E*)-1-Isopropenyl-4-methyl-6-(2,3,4,5-tetramethoxy-6-methylphenyl)-4-hexenyl]phosphate (30): To a solution of $(i\text{-Pr})_2NAlEt_2$[16] in ether-hexane (25 mmol, 82 mL) was added a solution of oxirane **29** (1.99 g, 5.46 mmol) in hexane (17 mL) at 0 °C drop by drop over a period of 30 min. The reaction mixture was stirred at this temperature for 30 min, quenched with ice-cooled 1N HCl (100 mL). Et_2O (50 mL) was then added and the organic phase was separated, washed with brine (100 mL), and dried over $MgSO_4$. The solvent was evaporated and to a solution of the crude product in THF (20 mL)

was added a solution of ^{n}BuLi in hexane (1.61 M, 3.73 mL, 6.01 mmol) dropwise using a syringe at -78 °C. After stirring at this temperature for 10 min and then at 0 °C for 10 min, diisopropyl chlorophosphate (2.0 g, 10 mmol) was added at 0 °C and stirred at this temperature for 15 min. The reaction mixture was quenched with sat. aqueous NH_4Cl (20 mL) and the resulting organic layer was separated. The aqueous layer was extracted with ether (20 mL). The combined organic layers were dried ($MgSO_4$) and concentrated. The crude product was purified by column chromatography on silica gel using a 1:4 mixture of hexane and Et_2O as eluant to give **30** as a colorless oil; yield: 2.83 g (98%); R_f = 0.20 (hexane/ether = 1:2).

$C_{27}H_{45}O_8P$	calc.	C	61.35	H	8.58
(528.6)	found		61.29		8.83

IR (KBr): ν = 2975, 2925, 1655, 1462, 1403, 1258, 1105, 1038, 994 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.3–1.4 (m, 12H), 1.71 (s, 3H), 1.77 (s, 3H), 1.6–2.0 (m, 4H), 2.13 (s, 3H), 3.31 (d, 2H, *J* = 6.3), 3.79 (s, 6H), 3.90 (s, 3H), 3.91 (s, 3H), 4.5–4.7 (m, 3H), 4.89 (s, 1H), 4.96 (s, 1H), 5.05 (t, 1H, *J* = 6.6).

1-[(2*E*,6*E*,10*E*,14*E*,18*E*)-3,7,11,15,19,23-Hexamethyl-2,6,10,14,18,22-tetracosahexaenyl)-2,3,4,5-tetramethoxy-6-methylbenzene (31): To a solution of geranylgeranylmagnesium chloride, prepared from magnesium turnings (3.65 g, 150 mmol) and geranylgeranyl chloride (9.27 g, 30 mmol) in THF (30 mL), was added a solution of CuCN (3.28 g, 36.6 mmol) and LiCl (3.03 g, 71.5 mmol) in THF (30 mL) at -30 °C and the mixture was stirred at this temperature for 10 min and then at 0 °C for 20 min. The resulting black solution was cooled to -78 °C and a solution of **30** (1.59 g, 3.01 mmol) in THF (2 mL) was added dropwise using a syringe at -78 °C. The solution was stirred at -60 °C for 2 h, then quenched with 2N HCl solution (80 mL). The organic layer was separated and the aqueous layer was extracted with ether (50 mL). The combined organic layers were washed with 2N NaOH solution (80 mL) and brine (80 mL), and then dried ($MgSO_4$). The solvent was evaporated and the crude product was purified by column chromatography on silica gel (150 g,

hexane/ether = 20:1 ~ 10:1) to give **31** as a colorless oil; yield: 1.69 g (90%); R_f = 0.29 (hexane/ether = 10:1).

$C_{41}H_{64}O_4$ calc. C 79.30 H 10.39

(621.0) found 78.98 10.53

IR (KBr): ν = 2975, 2940, 2870, 1469, 1411, 1357, 1116, 1049 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.60 (s, 15H), 1.68 (s, 3H), 1.77 (s, 3H), 1.8–2.2 (m, 20H), 2.14 (s, 3H), 3.32 (d, 2H, *J* = 6.6), 3.79 (s, 6H), 3.91 (s, 6H), 5.0–5.5 (m, 6H).

1-[(2*E*,6*E*,10*E*,14*E*,18*E*)-22,23-Epoxy-3,7,11,15,19,23-hexamethyl-2,6,10,14,18-tetracosapentaenyl]-2,3,4,5-tetramethoxy-6-methylbenzene (32): To a solution of **31** (1.10 g, 1.77 mmol) in H_2O (0.04 mL) and THF (4 mL) was added NBS (472 mg, 2.65 mmol) portionwise. After stirring at r.t. for 1 h, H_2O (4 mL) was added. The aqueous layer was extracted with Et_2O (4 mL x 2) and the combined organic layer was dried ($MgSO_4$). Filtration and concentration provided the crude bromohydrin as an oil, which was dissolved in MeOH (4 mL). To this solution was added a solution of MeONa in MeOH (28%, 548 mg, 2.84 mmol) dropwise at 0 °C. After stirring at 0 °C for 30 min, Et_2O (10 mL) and H_2O (10 mL) were added. The organic layer was separated, dried ($MgSO_4$), and concentrated. The crude product was chromatographed on silica gel (hexane/ether = 5:1) to give **32** as an oil; yield: 361 mg (32%); R_f = 0.52 (hexane/ether = 3:2).

$C_{41}H_{64}O_5$ calc. C 77.31 H 10.13

(637.0) found 77.13 10.10

IR (CCl_4): ν = 2980, 2945, 2875, 1472, 1417, 1117, 1052 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.26 (s, 3H), 1.30 (s, 3H), 1.5–1.7 (m, 2H), 1.59 (s, 6H), 1.61 (s, 6H), 1.77 (s, 3H), 1.8–2.2 (m, 18H), 2.14 (s, 3H), 2.71 (t, 1H, *J* = 6.5), 3.32 (d, 2H, *J* = 6.6), 3.79 (s, 6H), 3.91 (s, 6H), 5.0–5.2 (m, 5H).

Diisopropyl [4*E*,8*E*,12*E*,20*E*)-1-Isopropenyl-4,8,12,16,20-pentamethyl-22-(2,3,4,5-tetramethoxy-6-methylphenyl)-4,8,12,16,20-docosapentaenyl]phosphate (33): The phosphate **33** was synthesized from **32** under the

conditions described for the formation of **30**; chromatography condition: hexane/ether = 1:2; 80% yield; R_f = 0.40 (hexane/ether = 1:4).

$C_{47}H_{77}O_8P$ calc. C 70.47 H 9.69

(801.1) found 70.40 9.81

IR (KBr): ν = 2985, 2930, 2855, 1657, 1462, 1409, 1260, 1110, 1000 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.2–1.4 (m, 12H), 1.59 (s, 12H), 1.7–1.9 (m, 2H), 1.73 (s, 3H), 1.77 (s, 3H), 1.9–2.2 (m, 18H), 2.14 (s, 3H), 3.32 (d, 2H, *J* = 6.6), 3.79 (s, 6H), 3.91 (s, 6H), 4.4–4.7 (m, 2H), 4.8–4.9 (m, 1H), 4.92 (s, 1H), 5.00 (s, 1H), 5.0–5.2 (m, 5H).

1-((2*E*,6*E*,10*E*,14*E*,18*E*,22*E*,26*E*,30*E*,34*E*)-3,7,11,15,19,23,27,31,35,39-Decamethyl-2,6,10,14,18,22,26,30,34,38-tetracontadecaenyl)-2,3,4,5-tetramethoxy-6-methylbenzene (34): The product **34**[30] was synthesized from **33** under the conditions described for the formation of **31**; chromatography condition: hexane/ether=10:1; 96% yield; R_f = 0.33 (hexane/ether = 10:1).

IR (KBr): ν = 2920, 2850, 1672, 1460, 1405, 1382, 1353, 1260, 1200, 1104 cm^{-1}.

^{1}H-NMR ($CDCl_3$): δ = 1.60 (s, 27H), 1.68 (s, 3H), 1.77 (s, 3H), 1.9–2.2 (m, 36H), 2.14 (s, 3H), 3.32 (d, 2H, *J* = 6.2), 3.79 (s, 6H), 3.90 (s, 6H), 5.0–5.2 (m, 10H).

Coenzyme Q_{10} (26): To a solution of **34** (154 mg, 0.17 mmol) in CH_3CN (0.7 mL) and CH_2Cl_2 (0.7 mL) was added a solution of CAN (290 mg, 0.53 mmol) in 50% aq. CH_3CN (1.4 mL) dropwise over a period of 5 min at 0 °C. After stirring for 5 min, H_2O (10 mL) was added and the crude product was extracted with Et_2O (10 mL), washed with 5% aq. $NaHCO_3$ (10 mL) and H_2O (10 mL), dried ($MgSO_4$), and concentrated. The resulting oil was chromatographed on silica gel (hexane/ether = 10:1) to give **26** as a yellow solid; yield: 106 mg (72%); R_f = 0.32 (hexane/ether = 4:1); mp 46.5–47.0 °C (recrystallized twice from EtOH, lit.[30] mp 47 °C).

IR ($CHCl_3$): ν = 2920, 2855, 1655, 1615, 1450, 1385, 1265, 1155 cm^{-1}.

^{1}H-NMR ($CDCl_3$, 500 MHz): δ = 1.58 (s, 3H), 1.60 (s, 24H), 1.68 (s, 3H), 1.74 (s, 3H), 1.9–2.0 (m, 18H), 2.01 (s, 3H), 2.0–2.1 (m, 18H), 3.18 (d, 2H, J = 7.3), 3.98 (s, 3H), 4.00 (s, 3H), 4.94 (t, 1H, J = 6.8), 5.06 (t, 1H, J = 6.8), 5.11 (t, 8H, J = 6.8).

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Microanalytical Data for Compounds **8**, **10**, **11**, **16–19**, and **29–33**

compound **8**:

$C_{20}H_{40}OSi$	calc.	C	74.00	H	12.42
(324.6)	found		73.60		12.77

compound **10**:

$C_{17}H_{28}O_2$	calc.	C	77.22	H	10.67
(264.4)	found		76.78		10.99

compound **11**:

$C_{20}H_{40}OSi$	calc.	C	74.00	H	12.42
(324.6)	found		73.86		12.74

compound **16**:

$C_{16}H_{22}$	calc.	C	89.66	H	10.34
(214.4)	found		89.55		10.33

compound **17**:

$C_{15}H_{22}$	calc.	C	89.04	H	10.96
(202.3)	found		89.04		11.01

compound **18**:

$C_{15}H_{24}$	calc.	C	88.16	H	11.84
(204.4)	found		88.17		11.72

compound **19**:

$C_{11}H_{18}$	calc.	C	87.93	H	12.07
(150.3)	found		88.17		11.84

compound **29**:

$C_{21}H_{32}O_5$	calc.	C	69.20	H	8.85
(364.5)	found		69.41		8.99

compound **30**:

$C_{27}H_{45}O_8P$	calc.	C	61.35	H	8.58
(528.6)	found		61.29		8.83

compound **31**:

$C_{41}H_{64}O_4$	calc.	C	79.30	H	10.39
(621.0)	found		78.98		10.53

compound **32**:

$C_{41}H_{64}O_5$	calc.	C	77.31	H	10.13
(637.0)	found		77.13		10.10

compound **33**:

$C_{47}H_{77}O_8P$	calc.	C	70.47	H	9.69
(801.1)	found		70.40		9.81

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(23) Based on the optical purity (94% ee) of **12**.

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Chapter 3

Transition Metal Catalyzed Allylation Reactions

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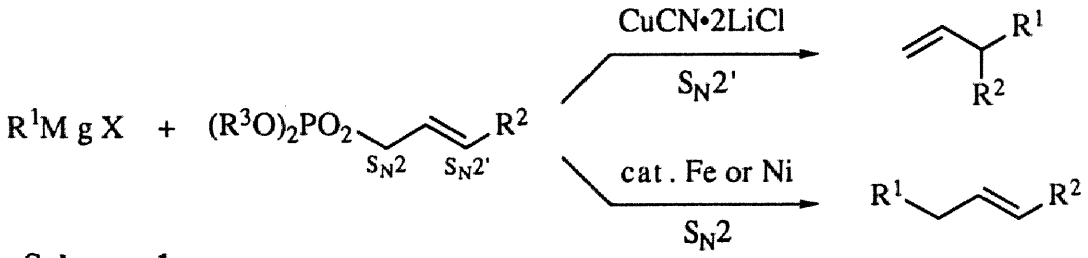
Section 1

Highly Selective S_N2 Reaction of Alkyl-Allyl Cross-Coupling

Abstract: Treatment of primary allylic phosphates in THF with Grignard reagents gave cross-coupling products with high S_N2 selectivity in the presence of an iron or a nickel catalyst. Among several phosphate leaving groups, diphenylphosphate ester showed the highest regioselectivity.

Transition metal catalyzed reaction of a variety of organic halides and Grignard reagents is generally described as the Kharasch reaction.[1] Cross-coupling reaction of allylic alcohol derivatives or allylic halides with organometallics is a recognized method for synthesis of olefinic compounds. Numerous important works on the reaction have been reported, however, control of the regio- and stereochemistry remains an unsolved problem.[2] In the iron-, cobalt-, nickel- or copper-catalyzed reaction of Grignard reagents with allylic halides, three types of reaction of allylic halide are known to occur competitively: (i) reduction, (ii) cross-coupling reaction, (iii) homo-coupling reaction. For 3-substituted allyl halides, however, homo-coupling reaction is superior to cross-coupling reaction.[3,4] In the cross-coupling reaction of allylic substrates, the regioselectivity has been actively studied with a variety of the leaving groups[2c] but to a lesser extent with phosphate leaving groups.[5] We found that phosphate esters were the most effective leaving groups for a γ-selective cross-coupling reaction of alcohol derivatives with allylic Grignard reagents (Chapter 2-1),[6] and for an S_N2'-, (*E*)-, and antiselective reaction between organocuprates and allylic alcohol derivatives (Chapter 2-2).[7] Here, we disclose a transition metal-catalyzed highly S_N2 selective substitution reaction of allylic diphenylphosphates with Grignard reagents (Scheme 1).

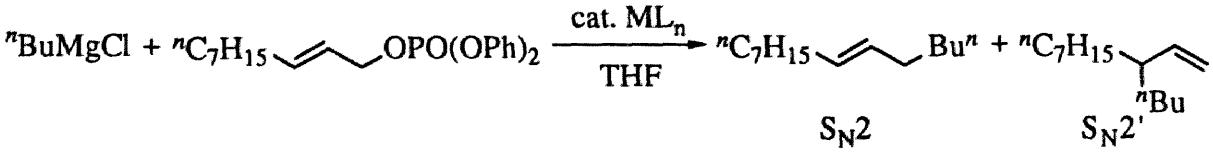


Scheme 1

We examined the transition metal catalysts most suitable for the regioselective coupling of allylic phosphates with Grignard reagents. Treatment of (*E*)-2-decenyl-1-diphenylphosphate with 2 equiv of *n*-butylmagnesium chloride in the presence of various transition metal catalysts (5–10 mol%) in THF furnished a mixture of S_N2 and S_N2' coupling products. The results are summarized in Table 1. As a consequence, iron, nickel, and copper

compounds showed remarkable catalytic activities and the coupling products were obtained in high yields at low temperature (entries 5, 6, and 9-20). In addition, nearly exclusive S_N2 selectivities were obtained using Fe[8] and Ni catalysts[9] (entries 5, 6, 9, and 10).

Table 1. Cross-Coupling Reaction of (*E*)-2-Decenyl-1-diphenylphosphate with ^{n}BuMgCl in the Presence of Various Metal Catalysts[a]

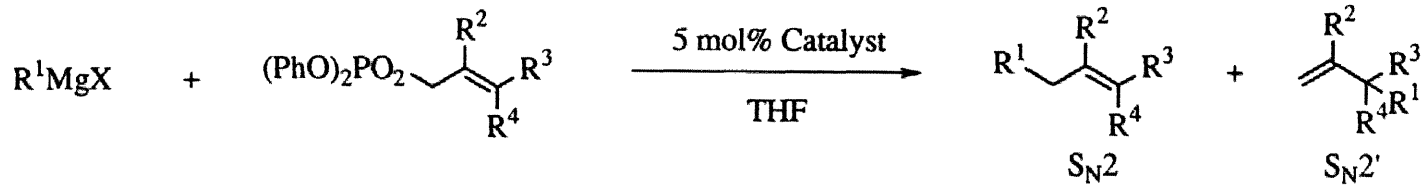


Entry	ML_n	Conditions	Yield, %[b]	S_N2:S_N2'[c]
1	——	0 °C, 6 h	32	91:9
2	$Ti(O^iPr)_4$	-23 °C, 5 h	10	89:11
3	$CrCl_2$	-23 °C, 6 h	48	81:19
4	$MnCl_2$	-30 °C, 5 h	20	93:7
5	$Fe(acac)_3$[d]	-76 °C, 1 h	94	99:1
6	$Fe(dbm)_3$[e]	-74 °C, 1 h	63	99:1
7	$CoCl_2$	-73 °C, 1 h	64	81:19
8	$(^nBuC{\equiv}C)_2Co$	-23 °C, 4 h	59	48:52
9	$NiBr_2$	-73 °C, 2 h	93	>99:1
10	$Ni(acac)_2$[d]	-73 °C, 1 h	73	>99:1
11	$Ni(CN)_2$	-23 °C, 3 h	79	52:48
12	$Ni(CN)_2$/ether	-40 °C, 7 h	94	11:89
13	CuCN•2LiCl	-76 °C, 1 h	98	1:99
14	$^nBuC{\equiv}CCu$	-75 °C, 1 h	95	14:86
15	CuI•2LiCl	-73 °C, 1 h	95	20:80
16	$CuBr_2$	-78 °C, 1 h	88	20:80
17	Li_2CuCl_4	-78 °C, 1 h	74	51:49
18	$CuBr•Me_2S$	-78 °C, 1 h	65	66:34
19	CuOTf	-75 °C, 1 h	62	81:19
20	CuSCN	-43 °C, 1 h	94	91:9
21	$AgNO_3$	-23 °C, 5 h	55	96:4
22	$CeCl_3$	-20 °C, 3 h	7	97:3

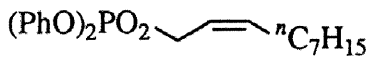
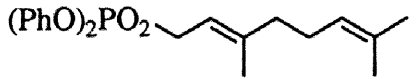
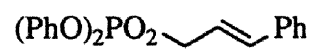
[a] The reaction was carried out using butylmagnesium chloride (2 equiv), (*E*)-2-decenyl-1-diphenylphosphate (1 equiv) and metal catalyst (0.05-0.1 equiv) in THF. [b] Isolated yield. [c] Determined by GC analysis. [d] acac = acetylacetonato. [e] dbm = dibenzoylmethanato.

We then studied the cross-coupling reaction between various Grignard reagents and primary allylic diphenylphosphates using iron and nickel (Table 2). In the reaction using $Ni(acac)_2$ catalyst, the S_N2 coupling products were selectively obtained in moderate yields (entries 2, 4-7, 12, 13, 16).[10] Use of methyl and *iso*-propyl Grignard reagents resulted in low yields because of a competitive homo-coupling reaction or reduction (entries 2 and 5). In the alkenylation and arylation reactions, the S_N2 products were still dominant (entries 7, 8). Existence of the siloxy group at C-8 position of allylic phosphate had no effect on the course of the reaction (entry 8). The diphenylphosphate leaving group was superior to the diethyl- or diisopropylphosphate leaving group[6,7] for S_N2 selective cross-coupling reaction (entries 8-10). $(^nBuC{\equiv}C)_2Ni$ was effective to obtain a higher yield in the reaction with geranyl-diphenylphosphate (entries 13 and 14). The *E/Z* ratio of the S_N2 coupling product, derived from (*Z*)-2-decenyl-1-diphenylphosphate, was 81/19 because of a rapid isomerization of the π-allylnickel intermediate (entry 12).[1c] $Fe(acac)_3$ catalyst overcame these difficulties of the homo-coupling reaction of allylic phosphates and the isomerization of cis-olefin. For example, reaction of methyl Grignard reagent selectively afforded the S_N2 coupling product in high yield without contamination of homo-coupling products (entry 1). In the butylation of (*Z*)-2-decenyl-1-diphenylphosphate, most of the double bond geometry of the product was retained (entry 11). The mechanism of iron-catalyzed reaction has not been fully elucidated yet but a plausible mechanism[11,13] is the same as a nickel catalyst. The reasons for superiorities of an iron catalyst are that the π-allyliron intermediate may have low nucleophilicity,[14] and that the cis-π-allyliron complex may be stable under the reaction condition.[14b,c,15]

Table 2. Transition Metal-Catalyzed S_N2 Cross-Coupling of Grignard Reagents and Allylic Phosphates[a]



entry	R^1MgX	allylic phosphate	Catalyst[b]	conditions °C, h	product	
					% yield[b]	ratio (S_N2/S_N2')[c]
1	MeMgI	$(PhO)_2PO_2$ ⟋⟍ $^nC_7H_{15}$	**Fe**	-75, 0.5	87	97 : 3
2			**Ni**	-75, 1.5	26[e]	94 : 6
3	^{n}BuMgCl		**Fe**	0, 2	94	99 : 1
4			**Ni**	-55, 1.5	73	> 99 : 1
5	^{i}PrMgBr		**Ni**	-75, 1.5	53[f]	> 99 : 1
6	$PhCH_2MgBr$		**Ni**	-75, 1	75	> 99 : 1
7	CH_2=CHMgBr		**Ni**	-75, 1	78	> 99 : 1
		PO ⟋⟍⟋⟍ $OSi(^tBu)Me_2$				
8	PhMgBr	**P** = $(PhO)_2PO$ (**1**)	**Fe**	-75, 0.5	93	94 : 6
9		**P** = $(EtO)_2PO$ (**2**)	**Fe**	-75, 2	80	70 : 30
10		**P** = $(^iPrO)_2PO$ (**3**)	**Fe**	-75, 2	68	73 : 27

11	^{n}BuMgCl		**Fe**	-75, 1	93[g]	98 : 2
12			**Ni**	-75, 1	81[h]	99 : 1
13			**Ni**	-20, 2	26	97 : 3
14			(^{n}BuC≡C)$_2$Ni	-45, 2	38	99 : 1
15			**Fe**	-75, 2	78	> 99 : 1
16			**Ni**	-78, 1	84	> 99 : 1

[a] Unless otherwise noted, the reaction was carried out using Grignard reagent (2 equiv), allylic diphenylphosphate (1 equiv), and Fe or Ni catalyst (0.05 equiv) in THF. [b] **Fe** = Fe(acac)$_3$; **Ni** = Ni(acac)$_2$. [c] Isolated yield. [d] Determined by GC analysis. [e] Homo-coupling products of (*E*)-2-decenyl-1-diphenylphosphate were mostly obtained (64% yield). [f] Reduction products of the allylic phosphate were formed as minor products (28% yield). [g] The *E*/*Z* ratio of the S_N2 coupling product was 6/94. [h] The *E*/*Z* ratio of the S_N2 coupling product was 81/19.

Experimental Section

General Methods.

Analytical TLC was done on E. Merck precoated (0.25 mm) silica gel 60 F_{254} plates. Column chromatography was conducted by using silica gel 60 (E. Merck 9385, 230–400 mesh). Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrometer. ^1H NMR spectra were measured on a Varian Gemini-200 (200 MHz) spectrometer. Chemical shifts of ^1H NMR spectra were reported relative to tetramethylsilane (δ 0). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded with a JEOR JMS-AX505HA mass spectrometer. Analytical gas-liquid phase chromatography (GLC) was performed on a Shimadzu GC-8A instrument equipped with a flame ionization detector and a capillary column of PEG-HT (0.25x25000 mm) using nitrogen as carrier gas. Microanalyses were accomplished at the Faculty of Agriculture, Nagoya University. All experiments were carried out under an atmosphere of dry argon. Dry tetrahydrofuran (THF) and ether (Et_2O) were used as purchased from Aldrich (anhydrous, 99.9%). Toluene was stored over sodium metal. Methylene chloride (CH_2Cl_2) was stored over 4-Å molecular sieves. Allylic diphenylphosphates were synthesized from the corresponding allylic alcohols by phosphorylation with diphenyl phosphorochloridate and triethylamine in the presence of a catalytic amount of 4-(dimethylamino)pyridine in CH_2Cl_2. Other chemicals were purchased and used as such.

General Procedure for Transition Metal-Catalyzed Cross-Coupling Reaction Between Alkyl Grignard Reagents and Primary Allylic Diphenylphosphates (Table 2). A mixture of transition metal catalyst (0.025 mmol) and allylic diphenylphosphate (0.50 mmol) was dissolved in dry THF (4 mL) under an argon atmosphere. The solution was cooled to -78 °C and a solution of alkyl Grignard reagent (1.0 mmol) in THF was added dropwise. The resulting mixture was stirred for several hours at this temperature. The reaction mixture was poured into a saturated aqueous NH_4Cl solution and 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 or hexane/EtOAc) to afford a mixture of coupling products: the S_N2/S_N2' ratio was determined by GC analysis.

(3*E*)-3-Undecene (entry 1 in Table 2): TLC R_f 0.72 (hexane); IR (neat) 2961, 2926, 2874, 2855, 1462, 1379, 965, 723 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, *J* = 6.5 Hz, CH_3), 0.96 (t, 3 H, *J* = 7.4 Hz, CH_3), 1.17–1.46 (m, 10 H, 5 CH_2), 1.87–2.08 (m, 4 H, 2 CH_2), 5.31–5.52 (m, 2 H, 2 vinyls); MS (EI, 70 ev) *m/z* (rel) 154 (100, M^+), 126 (20.94), 111 (35.53). Anal. Calcd for $C_{11}H_{22}$: C, 85.63; H, 14.37. Found: C, 85.31; H, 14.88.

(6*E*)-6-Tetradecene (entry 3 in Table 2): TLC R_f 0.72 (hexane); IR (neat) 2959, 2926, 2874, 2855, 1466, 1379, 967, 723 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 6 H, *J* = 6.3 Hz, 2 CH_3), 1.15–1.47 (m, 16 H, 8 CH_2), 1.85–2.13 (m, 4 H, 2 CH_2), 5.36–5.42 (m, 2 H, 2 vinyls). Anal. Calcd for $C_{14}H_{28}$: C, 85.63; H, 14.37. Found: C, 85.43; H, 14.59.

(4*E*)-2-Methyl-4-dodecene (entry 5 in Table 2): TLC R_f 0.67 (hexane); IR (neat) 2957, 2926, 2855, 1466, 1383, 1368, 1167, 967, 911, 723 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (d, 6 H, *J* = 6.4 Hz, 2 CH_3), 0.88 (t, 3 H, *J* = 6.5 Hz, CH_3), 1.14–1.45 (m, 10 H, 5 CH_2), 1.47–1.67 (m, 1 H, CH), 1.82–1.91 (m, 2 H, CH_2), 1.91–2.08 (m, 2 H, CH_2), 5.33–5.42 (m, 2 H, 2 vinyls). Anal. Calcd for $C_{13}H_{26}$: C, 85.63; H, 14.37. Found: C, 85.58; H, 14.50.

(3*E*)-1-Phenyl-3-undecene (entry 6 in Table 2):[16] TLC R_f 0.56 (hexane); IR (neat) 3029, 2957, 2926, 2855, 1497, 1455, 968, 745, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, *J* = 6.5 Hz, CH_3), 1.16–1.42 (m, 10 H, 5 CH_2), 1.89–2.02 (m, 2 H, CH_2), 2.23–2.36 (m, 2 H, CH_2), 2.60–2.72 (m, 2 H, CH_2), 5.33–5.54 (m, 2 H, 2 vinyls), 7.12–7.34 (m, 5 H, aromatic); MS (EI, 70 ev) *m/z* (rel) 230 (86.90, M^+), 131 (41.69), 117 (28.59), 104 (100). Anal. Calcd for $C_{17}H_{26}$: C, 88.63; H, 11.37. Found: C, 88.38; H, 11.94.

(4*E*)-1,4-dodecadiene (entry 7 in Table 2):[17] TLC R_f 0.69 (hexane); IR (neat) 3081, 2959, 2926, 2855, 1640, 1433, 1379, 992, 968, 912 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, *J* = 6.4 Hz, CH_3), 1.13–1.44 (m, 10 H, 5 CH_2), 1.90–2.12 (m, 2 H, CH_2),

2.68–2.84 (m, 2 H, CH_2), 4.94–5.09 (m, 2 H, 2 vinyls), 5.32–5.55 (m, 2 H, 2 vinyls), 5.83 (ddd, 1 H, J = 6.4, 10.0, 12.6 Hz, vinyl). Anal. Calcd for $C_{12}H_{22}$: C, 86.66; H, 13.33. Found: C, 86.39; H, 13.42.

(2*E*, 6*E*)-8-(*ter*-butyldimethylsiloxy)-2,6-dimethyl-1-phenyloctadiene (entry 8 in Table 2): TLC R_f 0.76 (hexane/EtOAc = 3/1); ^1H NMR (200 MHz, $CDCl_3$) δ 0.92 (s, 9H, 3 CH_3), 1.52 (s, 3 H, CH_3), 1.65 (s, 3 H, CH_3), 1.8-2.25 (m, 4 H, 2 CH_2), 2.99 (s, 2 H, CH_2), 4.22 (d, 2 H, J = 6.4 Hz, CH_2), 5.27 (t, 1 H, J = 7.2 Hz, CH), 5.35 (t, 1 H, J = 6.4 Hz, CH), 7.15-7.36 (m, 5 H, aromatic).

(6*Z*)-6-Tetradecene (entry 11 in Table 2): TLC R_f 0.72 (hexane); IR (neat) 3006, 2959, 2926, 2857, 1466, 1379, 967, 723 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 6 H, J = 6.0 Hz, 2 CH_3), 1.13–1.44 (m, 16 H, 8 CH_2), 1.91–2.14 (m, 4 H, 2 CH_2), 5.36 (m, 2 H, 2 vinyls); MS (EI, 70 ev) *m/z* (rel) 196 (100, M^+), 168 (36.91), 154 (17.17), 140 (21.03), 125 (43.56), 111 (99.79). Anal. Calcd for $C_{14}H_{28}$: C, 85.63; H, 14.37. Found: C, 85.40; H, 15.01.

(1*E*)-1-Phenyl-1-heptene (entry 15 in Table 2):[18] TLC R_f 0.58 (hexane); IR (neat) 3027, 2957, 2926, 2857, 1599, 1495, 963, 743, 693 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.90 (t, 3 H, J = 6.5 Hz, CH_3), 1.19–1.58 (m, 6 H, 3 CH_2), 2.20 (q, 2 H, J = 6.9 Hz, CH_2), 6.22 (dt, 1 H, J = 16.0, 6.4 Hz, vinyl), 6.38 (d, 1 H, J = 16.0 Hz, vinyl), 7.13–7.38 (m, 5 H, aromatic); MS (EI, 70 ev) *m/z* (rel) 174 (99.76, M^+), 145 (11.10), 131 (28.93), 117 (99.88), 115 (99.94), 104 (100). Anal. Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.33; H, 10.91.

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(10) The S_N2 coupling product of ^{t}BuMgCl was not effectively obtained because of the rapid reduction by the nucleophile.

(11) In the iron-catalyzed Kharasch type reaction, Fe(I) or Fe(0) species is suggested to be an active catalyst.[1d,12]

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Chapter 3

Transition Metal Catalyzed Allylation Reactions

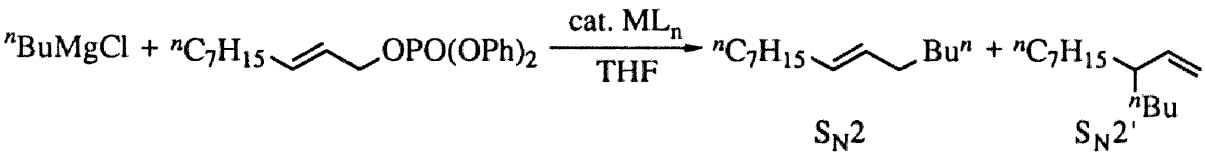
Section 2

Highly Selective S_N2' Reaction of Alkyl-Allyl and Allyl-Allyl Cross-Couplings

Abstract: The S_N2' selective Grignard coupling with primary allylic diphenylphosphates was successfully achieved in the presence of a catalytic amount of CuCN•2LiCl. γ-Substituted allyl Grignard reagents reacted with allylic phosphates selectively at the less substituted allylic terminus (α-position).

Transition metal catalyzed substitution reaction of alkyl halides with Grignard reagents (Kharasch reaction) is a beneficial method for carbon-carbon bond formation in organic synthesis.[1] In the course of our investigation on a coupling reaction between allylic phosphates and Grignard reagents (Chapter 3-1), we realized the possibility of highly selective S_N2' reaction in a catalytic process as well as highly selective S_N2 reaction in the presence of an iron or a nickel catalyst (Table 1). Among the variety of copper catalysts, CuCN•2LiCl was found to be the most effective for obtaining S_N2' selectivity (entries 7-14).

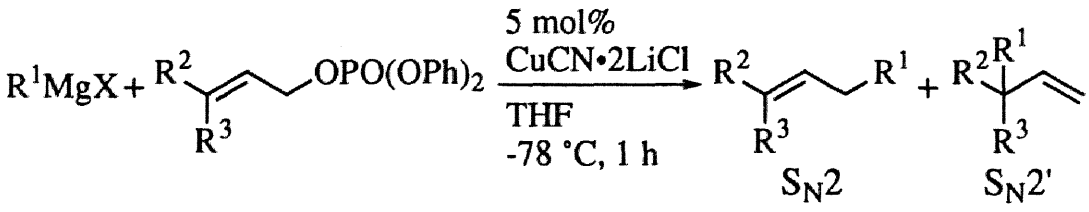
Table 1. Cross-Coupling Reaction of (*E*)-2-Decenyl-1-diphenylphosphate with ^{n}BuMgCl in the Presence of Various Metal Catalysts[a]



Entry	ML_n	Conditions	Yield, %[b]	$S_N2:S_N2'$[c]
1	$Fe(acac)_3$[d]	-76 °C, 1 h	94	99:1
2	$Fe(dbm)_3$[e]	-74 °C, 1 h	63	99:1
3	$NiBr_2$	-73 °C, 2 h	93	>99:1
4	$Ni(acac)_2$[d]	-73 °C, 1 h	83	>99:1
5	$Ni(CN)_2$	-23 °C, 3 h	79	52:48
6	$Ni(CN)_2$/ether	-40 °C, 7 h	94	11:89
7	CuCN•2LiCl	-76 °C, 1 h	98	1:99
8	^{n}BuC≡CCu	-75 °C, 1 h	95	14:86
9	CuI•2LiCl	-73 °C, 1 h	95	20:80
10	$CuBr_2$	-78 °C, 1 h	88	20:80
11	Li_2CuCl_4	-78 °C, 1 h	74	51:49
12	$CuBr•Me_2S$	-78 °C, 1 h	65	66:34
13	CuOTf	-75 °C, 1 h	62	81:19
14	CuSCN	-43 °C, 1 h	94	91:9

[a] The reaction was carried out using butylmagnesium chloride (2 equiv), (*E*)-2-decenyl-1-diphenylphosphate (1 equiv), and metal catalyst (0.05-0.1 equiv) in THF. [b] Isolated yield. [c] Determined by GC analysis. [d] acac = acetylacetonato. [e] dbm = dibenzoylmethanato.

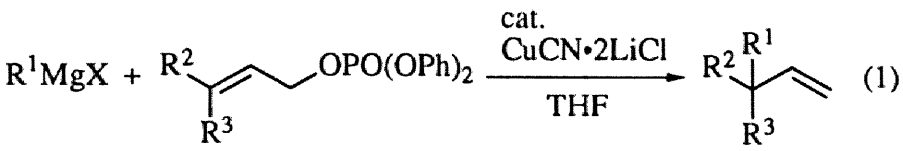
Table 2. Copper-Catalyzed S_N2' Selective Reaction Between Alkyl Grignard Reagents and Primary Allylic Diphenylphosphates[a]



Entry	R^1MgX	R^2	R^3	Yield, %[b]	$S_N2:S_N2'$[c]
1	MeMgI	$^nC_7H_{15}$	H	87	2:98
2	^{n}BuMgCl	$^nC_7H_{15}$	H	98	1:99
3	^{i}PrMgBr	$^nC_7H_{15}$	H	83	2:98
4	^{t}BuMgCl	$^nC_7H_{15}$	H	88	30:70
5				80[d,e]	2:98
6	$PhCH_2MgBr$	$^nC_7H_{15}$	H	96	18:82
7				98[e]	8:92
8	$H_2C=CHMgBr$	$^nC_7H_{15}$	H	86	95:5
9				81[e]	33:67
10	PhMgBr	$^nC_7H_{15}$	H	97	88:12
11				99[d,e]	12:88
12	^{n}BuMgCl	H	$^nC_7H_{15}$	91	<1:99
13	^{n}BuMgCl	$Me_2C=CH(CH_2)_2$	Me	97	3:97
14	^{n}BuMgCl	Ph	H	77	11:89
15				79[d,e]	6:94

[a] Unless otherwise noted, the reaction was carried out using Grignard reagent (2 equiv), allylic diphenylphosphate (1 equiv), and CuCN•2LiCl (0.05 equiv) in THF at -78 °C for 1 h. [b] Isolated yield. [c] Determined by GC analysis. [d] A 4:1 mixture of toluene and ether was used as solvent. [e] The reaction was performed at 0 °C for 1 h.

We have reported a new S_N2' selective cross-coupling reaction between Grignard reagents and allylic phosphates using a stoichiometric amount of CuCN•2LiCl (Chapter 2-2).[2] Described herein is the catalytic process of this reaction using diphenylphosphate leaving group (eq. 1).

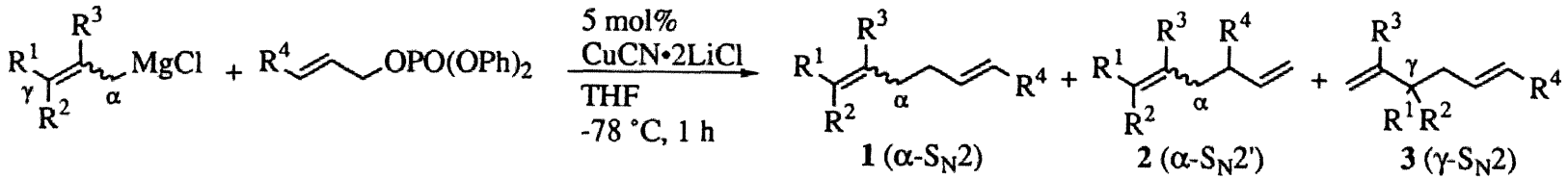


(1)

Reaction of (*E*)-2-decenyl-1-diphenylphosphate[3] with 2 equiv of *n*-butylmagnesium chloride and 5 mol% CuCN•2LiCl in THF at -78 °C for 1 h gave the butylated product in 98% yield with a S_N2/S_N2' ratio of 1:99.[4,5] The experimental results for various Grignard reagents and primary allylic diphenylphosphates are summarized in Table 2. All reactions proceeded smoothly to afford the coupling products in high yields. Nearly exclusive S_N2' selectivities were obtained in the reaction of alkyl Grignard reagents with (*E*)-2-decenyl-1-diphenylphosphate (entries 1-3). Noteworthy is the fact that even *tert*-butylmagnesium chloride showed a high S_N2' selectivity in spite of the steric hindrance (entry 5). Higher reaction temperature (0 °C) and less polar solvent (4:1 toluene-ether) were requisite to obtain high regioselectivities for *tert*-butyl, benzyl, vinyl, and phenyl Grignard reagents (entries 5, 7, 9 and 11). (*Z*)-2-decenyl-1-diphenylphosphate afforded similar results ($S_N2/S_N2' < 1:99$) to the corresponding *E*-isomer in the reaction with *n*-butyl Grignard reagent (entries 2 and 12). Existence of two alkyl substituents or a conjugated phenyl group at the C-3 position of the allylic diphenylphosphate had little effect on the reaction course (entries 13-15).

This method was further successfully applied to the regio-controlled allyl-allyl coupling which was important for selective 1,5-diene synthesis.[6] This system was aimed for a catalytic process of an α-S_N2' reaction with allylic cuprate reagents (Chapter 2-2). Some results of the reaction between (*E*)-2-decenyl- or (*E*)-2-hexenyl-1-diphenylphosphate and γ-substituted allyl Grignard reagents are listed in Table 3, and have the following characteristic features: (1) In

Table 3. Cross-Coupling of (*E*)-2-Decenyl- or (*E*)-2-Hexenyl-1-Diphenylphosphate with γ-Substituted Allyl Grignard Reagents[a]

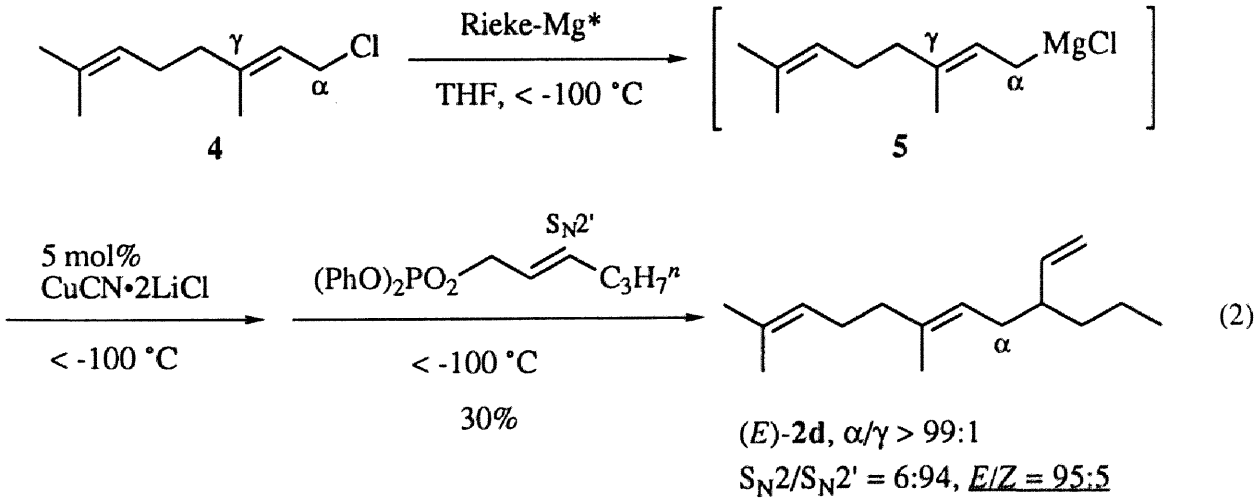


Entry	R^1	R^2	R^3	R^4	Products	Yield, %[b]	α:γ[c]	S_N2:S_N2'[c]	3:4:5[c,d]
1	Me	H	H	$^nC_7H_{15}$	**1a+2a+3a**	90[e]	79:21	27:73	6:73:21
2	$^nC_3H_7$	H	H	$^nC_7H_{15}$	**1b+2b+3b**	96[f]	76:24	29:71	5:71:24
3	Me	Me	H	$^nC_7H_{15}$	**1c+2c+3c**	95	96:4	6:94	2:94:4
4	$Me_2C=CH(CH_2)_2$	Me	H	$^nC_3H_7$	**1d+2d+3d**	90[i]	>99:1	2:98	2:98:0
5	C_2H_5	H	Me	$^nC_7H_{15}$	**1e+2e+3e**	99[j]	66:34	40:60	6:60:34
6	Ph	H	H	$^nC_7H_{15}$	**1f+2f+3f**	97[g]	30:70	76:24	6:24:70
7	Ph	H	H	$^nC_7H_{15}$	**1f+2f+3f**	89[g,h]	86:14	19:81	5:81:14

[a] Unless otherwise specified, the reaction was carried out using allylic Grignard reagent (1.2 equiv), (*E*)-2-decenyl-1-diphenylphosphate (1 equiv), and CuCN•2LiCl (0.05 equiv) in THF at -78 °C for 1 h. [b] Isolated yield. [c] Determined by GC analysis. [d] The corresponding γ-S_N2' product was not obtained in all experiments. [e] The *E*/*Z* ratio of α-S_N2' coupling product **2a** was 55/45. [f] The *E*/*Z* ratio of **2b** was 63/37. [g] The *E*/*Z* ratio of **2d** was 73/27. [h] The *E*-isomer of **2e** was produced as the major product. [i] The *E*/*Z* ratio of **2f** was >99/1. [j] The reaction was performed in a 3:2 mixture of toluene and ether at 0 °C for 1 h.

the presence of the copper catalyst, allylic magnesium reagents reacted with the allylic phosphate selectively at the less substituted allylic terminus (α-position) in all experiments.[7] (2) Use of γ-disubstituted allyl Grignard reagents resulted in higher α-S_N2' selectivities (entries 3 and 4) than γ-monosubstituted ones (entries 1 and 2). Especially geranylmagnesium chloride afforded the α-S_N2' coupling product **2** almost exclusively (entry 4). In contrast, an alkyl substituent at the β-position reduced both α/γ and S_N2/S_N2' ratios (entry 5). (3) No remarkable *E*, *Z*-stereoselectivities were observed for the α-S_N2' coupling products **2** due to a rapid isomerization of the γ-substituted allyl Grignard reagents[8] but cinnamylmagnesium chloride.

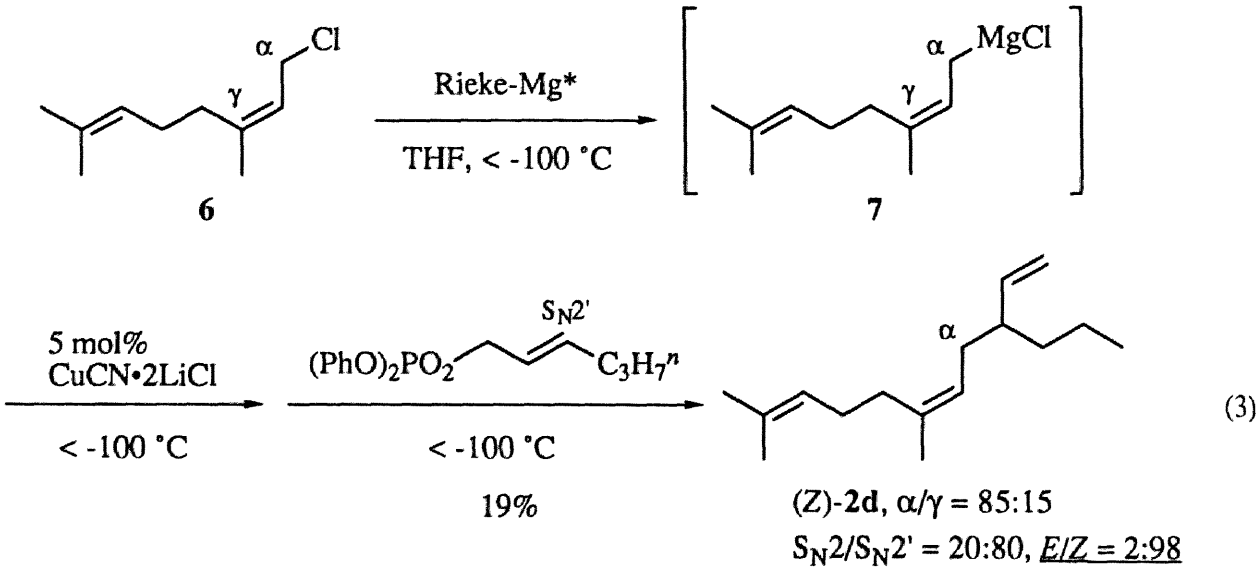
Control of the stereochemistry of carbon-carbon bond forming reaction by allylic organometallics is a challenging problem in organic synthesis.[9] Recently stereochemically homogeneous allylic metals were successfully generated from the corresponding allylic chlorides and reactive metals at low temperature.[10] Thus, we used this method to investigate the stereodivergent α-S_N2' coupling reaction.



(2)

Treatment of geranylmagnesium chloride (**5**), prepared from geranyl chloride (**4**) and Rieke magnesium[11] in THF below -100 °C, with (*E*)-2-hexenyl-1-diphenylphosphate in the presence of 5 mol% of CuCN•2LiCl gave the *trans*-isomer of the α-S_N2' coupling product

(*E*)-**6** preferentially ($\alpha/\gamma > 99:1$, $S_N2/S_N2' = 6:94$, *E*/*Z* = 95:5, 30% yield, eq. 2). Similarly, the *cis*-isomer (*Z*)-**6** was selectively obtained from neryl chloride (**7**, eq. 3). This is the first example of the generation of stereoretained allylic copper reagents.



(3)

In conclusion, the present method appears to assure an excellent carbon-carbon bond forming reaction for the following reasons: (1) various Grignard reagents and allylic phosphates can be used; (2) in the presence of copper catalyst, allylic magnesium reagents react selectively at the less substituted allylic terminus; and (3) stereoretentive α-S_N2' coupling can be achieved using stereochemically homogeneous γ-disubstituted allyl Grignard reagents and a copper catalyst at low temperature.

Experimental Section

General Methods.

Analytical TLC was done on E. Merck precoated (0.25 mm) silica gel 60 F_{254} plates. Column chromatography was conducted by using silica gel 60 (E. Merck 9385, 230–400 mesh). Infrared (IR) spectra were recorded on a Shimadzu FTIR-8100 spectrometer. ^1H NMR spectra were measured on a Varian Gemini-200 (200 MHz) spectrometer. Chemical shifts of ^1H NMR spectra were reported relative to tetramethylsilane (δ 0). Splitting patterns are indicated as s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; br, broad. Mass spectra were recorded with a JEOR JMS-AX505HA mass spectrometer. Analytical gas-liquid phase chromatography (GLC) was performed on a Shimadzu GC-8A instrument equipped with a flame ionization detector and a capillary column of PEG-HT (0.25x25000 mm) using nitrogen as carrier gas. Microanalyses were accomplished at the Faculty of Agriculture, Nagoya University. All experiments were carried out under an atmosphere of dry argon. Dry tetrahydrofuran (THF) and ether (Et_2O) were used as purchased from Aldrich (anhydrous, 99.9%). Toluene was stored over sodium metal. Allylic diphenylphosphates were synthesized from the corresponding allylic alcohols by phosphorylation with diphenyl phosphorochloridate and triethylamine in the presence of a catalytic amount of 4-(dimethylamino)pyridine in CH_2Cl_2. Allylic chlorides were prepared by treatment of the corresponding allylic alcohols with a mixture of *N*-chlorosuccinimide and dimethyl sulfide in CH_2Cl_2.[12] Other chemicals were purchased and used as such.

General Procedure for Transition Metal-Catalyzed Cross-Coupling Reaction Between Alkyl Grignard Reagents and Primary Allylic Diphenylphosphates (Table 1 and 2). A mixture of transition metal catalyst (0.025 mmol)[13] and allylic diphenylphosphate (0.50 mmol) was dissolved in dry THF (4 mL) under an argon atmosphere. The solution was cooled to -78 °C and a solution of alkyl Grignard reagent (1.0 mmol) in THF was added dropwise. The resulting mixture was stirred for 1 h at this temperature. The reaction mixture was poured into a saturated aqueous NH_4Cl solution

and extracted with ether. The combined organic extracts were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude products were purified by column chromatography on silica gel (hexane) to afford a mixture of coupling products: the S_N2/S_N2' ratio was determined by GC analysis.

3-Methyl-1-decene (entry 1, Table 2): TLC R_f 0.72 (hexane); IR (neat) 3079, 2959, 2926, 2857, 1640, 1418, 1375, 994, 911, 723, 681 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 6.4 Hz, CH_3), 0.97 (d, 3 H, J = 6.8 Hz, CH_3), 1.15–1.40 (m, 12 H, 6 CH_2), 2.10 (m, 1 H, CH), 4.86–4.99 (m, 2 H, 2 vinyls), 5.70 (ddd, 1 H, J = 7.6, 10.2, 17.5 Hz, vinyl). Anal. Calcd for $C_{11}H_{22}$: C, 85.63; H, 14.37. Found: C, 85.61; H, 14.44.

5-Vinyldodecane (entries 2 and 12, Table 2):[14] TLC R_f 0.72 (hexane); IR (neat) 3077, 2959, 2926, 2857, 1825, 1640, 1466, 1420, 1379, 995, 911, 762, 725, 683 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 6 H, J = 6.5 Hz, 2 CH_3), 1.07–1.47 (m, 18 H, 9 CH_2), 1.82–2.04 (br, 1 H, CH), 4.92 (dd, 1 H, J = 2.2, 16.4 Hz, vinyl), 4.94 (dd, 1 H, J = 2.2, 11.0 Hz, vinyl), 5.53 (ddd, 1 H, J = 8.8, 11.0, 16.4 Hz, vinyl); MS (EI, 70 ev) *m/z* (rel) 196 (58.88, M^+), 168 (39.37), 154 (55.26), 140 (100), 125 (97.31), 112 (95.56), 111 (92.52). Anal. Calcd for $C_{14}H_{28}$: C, 85.63; H, 14.37. Found: C, 85.40; H, 14.71.

3-Isopropyl-1-decene (entry 3, Table 2): TLC R_f 0.67 (hexane); IR (neat) 3077, 2959, 2924, 2857, 1638, 1466, 1420, 1385, 1368, 997, 911, 723, 681 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.82 (d, 3 H, J = 6.8 Hz, CH_3), 0.87 (d, 3 H, J = 6.6 Hz, CH_3), 0.88 (t, 3 H, J = 6.5 Hz, CH_3), 1.05–1.46 (m, 12 H, 6 CH_2), 1.48–1.66 (m, 1 H, CH), 1.66–1.82 (m, 1 H, CH), 4.91 (dd, 1 H, J = 2.2, 17.0 Hz, vinyl), 4.99 (dd, 1 H, J = 2.2, 10.4 Hz, vinyl), 5.55 (ddd, 1 H, J = 9.2, 10.4, 17.0 Hz, vinyl). Anal. Calcd for $C_{13}H_{26}$: C, 85.63; H, 14.37. Found: C, 85.40; H, 14.54.

3-*tert*-Butyl-1-decene (entry 5, Table 2): TLC R_f 0.65 (hexane); IR (neat) 3075, 2959, 2859, 1638, 1468, 1418, 1395, 1366, 999, 911, 656 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.85 (s, 9 H, 3 CH_3), 0.88 (t, 3 H, J = 6.2 Hz, CH_3), 1.12–1.40 (m, 12 H, 6 CH_2), 1.50–1.67 (m, 1 H, CH), 4.90 (dd, 1 H, J = 2.6, 17.0 Hz, vinyl), 5.01 (dd, 1 H, J =

2.6, 10.4 Hz, vinyl), 5.54 (dt, 1 H, J = 17.0, 10.4 Hz, vinyl); MS (EI, 70 ev) *m/z* (rel) 196 (9.63, M^+), 168 (10.90), 154 (7.60), 140 (100), 138 (29.78), 111 (42.21). Anal. Calcd for $C_{14}H_{28}$: C, 85.63; H, 14.37. Found: C, 85.40; H, 14.70.

3-Benzyl-1-decene (entry 7, Table 2): TLC R_f 0.49 (hexane); IR (neat) 3029, 2957, 2926, 2855, 1640, 1605, 1497, 1455, 994, 912, 745, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, 3 H, J = 6.4 Hz, CH_3), 1.10–1.50 (m, 12 H, 6 CH_2), 2.16–2.38 (m, 1 H, CH), 2.52–2.72 (m, 2 H, CH_2), 4.86 (dd, 1 H, J = 2.2, 17.0 Hz, vinyl), 4.93 (dd, 1 H, J = 2.2, 10.4 Hz, vinyl), 5.60 (ddd, 1 H, J = 8.6, 10.4, 17.0 Hz, vinyl), 7.10–7.32 (m, 5 H, aromatic). Anal. Calcd for $C_{17}H_{26}$: C, 88.63; H, 11.37. Found: C, 88.50; H, 11.67.

3-Phenyl-1-decene (entry 11, Table 2): TLC R_f 0.56 (hexane); IR (neat) 3029, 2957, 2928, 2857, 1638, 1493, 1455, 992, 912, 756, 698 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.86 (t, 3 H, J = 6.6 Hz, CH_3), 1.10–1.44 (m, 10 H, 5 CH_2), 1.69 (dt, 2 H, J = 7.0, 7.4 Hz, CH_2), 3.23 (q, 1 H, J = 7.6 Hz, CH), 4.94–5.08 (m, 2 H, 2 vinyls), 5.95 (ddd, 1 H, J = 7.6, 9.8, 17.4 Hz, vinyl), 7.13–7.36 (m, 5 H, aromatic); MS (EI, 70 ev) *m/z* (rel) 216 (71.46, M^+), 132 (37.45), 117 (100), 115 (54.51), 104 (40.24). Anal. Calcd for $C_{16}H_{24}$: C, 88.82; H, 11.18. Found: C, 88.73; H, 11.74.

2,6-Dimethyl-6-vinyl-2-decene (entry 13, Table 2):[15] TLC R_f 0.84 (hexane); IR (neat) 3083, 2963, 2930, 2861, 1638, 1414, 1377, 1003, 911, 835 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 6.7 Hz, CH_3), 0.95 (s, 3 H, CH_3), 1.10–1.37 (m, 8 H, 4 CH_2), 1.58 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3), 1.78–1.95 (m, 2 H, CH_2), 4.88 (dd, 1 H, J = 1.6, 17.6 Hz, vinyl), 4.97 (dd, 1 H, J = 1.6, 10.8 Hz, vinyl), 5.09 (tt, 1 H, J = 1.4, 7.1 Hz, vinyl), 5.70 (dd, 1 H, J = 10.8, 17.6 Hz, vinyl). Anal. Calcd for $C_{14}H_{26}$: C, 86.52; H, 13.48. Found: C, 86.37; H, 14.18.

3-Phenyl-1-heptene (entry 15, Table 2):[16] TLC R_f 0.58 (hexane); IR (neat) 3029, 2959, 2930, 2859, 1638, 1601, 1493, 1453, 994, 912, 754, 700 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.87 (t, 3 H, J = 7.0 Hz, CH_3), 1.08–1.39 (m, 4 H, 2 CH_2), 1.70 (q, 2 H, J = 7.4 Hz, CH_2), 3.23 (q, 1 H, J = 7.5 Hz, CH), 4.95–5.07 (m, 2 H, 2 vinyls), 5.95 (ddd, 1 H, J =

7.6, 9.6, 17.4 Hz, vinyl), 7.13–7.35 (m, 5 H, aromatic). Anal. Calcd for $C_{13}H_{18}$: C, 89.59; H, 10.41. Found: C, 89.51; H, 10.71.

General Procedure for Preparation of Allylic Grignard Reagent.[17] Magnesium turnings (1.0 g, 41 mmol) were placed in a 60-mL Schlenk tube under an argon atmosphere and vigorously stirred for 3-5 days at room temperature. The resulting activated Mg turnings were covered with dry THF (5 mL), cooled to -15 °C, and a solution of allylic chloride (10 mmol) in THF (15 mL) was added dropwise for 1-2 h at this temperature. The mixture was stirred for 2-3 h at 0 °C. The resulting clear solution (0.40-0.45 M) was ready to use. Cinnamylmagnesium chloride was prepared in Et_2O as the same procedure above.

General Procedure for Copper-Catalyzed Cross-Coupling Reaction of (*E*)-2-Decenyl-1-diphenylphosphate with γ-Substituted Allyl Grignard Reagents (Table 3). A mixture of CuCN (2.2 mg, 0.025 mmol) and LiCl (2.1 mg, 0.050 mmol)[13] was dissolved in dry THF (4 mL) under an argon atmosphere, and then (*E*)-2-decenyl-1-diphenylphosphate (194 mg, 0.50 mmol) was added. To the resulting solution was added dropwise a solution of allylic magnesium chloride (0.40-0.45 M, 0.60 mmol) in THF at -78 °C under argon. 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 -78 °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 products were purified by column chromatography on silica gel (hexane) to afford a mixture of coupling products: the γ/α and S_N2/S_N2' ratios were determined by GC analysis.

5-Vinyl-2-dodecene (2a): TLC R_f 0.67 (hexane); IR (neat) 3079, 2959, 2926, 2855, 1640, 1377, 994, 967, 911 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 6.4 Hz, CH_3), 1.10–1.45 (m, 12 H, 6 CH_2), 1.60 (d, 1.65 H, J = 5.8 Hz, 0.55 CH_3), 1.64 (d, 1.35 H, J = 3.6 Hz, 0.45 CH_3), 1.85–2.22 (m, 3 H, CH_2 and CH), 4.87–5.01 (m, 2 H, 2 vinyls), 5.40 (m, 2 H, 2 vinyls), 5.45–5.85 (m, 1 H, vinyl); MS (EI, 70 ev) *m/z* (rel) 194 (17.17,

M+), 179 (99.79), 165 (57.94), 151 (29.83), 138 (87.45), 123 (99.89), 109 (100), 105 (21.67). Anal. Calcd for $C_{14}H_{26}$: C, 86.52; H, 13.48. Found: C, 86.32; H, 13.97.

7-Vinyl-4-tetradecene (2b): TLC R_f 0.65 (hexane); IR (neat) 3077, 2959, 2926, 2857, 1638, 1541, 1509, 1420, 1379, 994, 967, 911 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 6 H, J = 7.2 Hz, 2 CH_3), 1.12–1.47 (m, 14 H, 7 CH_2), 1.90–2.12 (m, 5 H, 2 CH_2 and CH), 4.87–5.00 (m, 2 H, 2 vinyls), 5.33–5.43 (m, 2 H, 2 vinyls), 5.47–5.69 (m, 1 H, vinyl); MS (EI, 70 ev) *m/z* (rel) 222 (22.42, M+), 216 (43.78), 208 (15.34), 179 (40.24), 166 (9.01), 154 (13.95), 145 (13.84), 132 (36.48), 117 (100), 115 (54.18), 104 (22.32). Anal. Calcd for $C_{16}H_{30}$: C, 86.40; H, 13.60. Found: C, 86.48; H, 13.97.

2-Methyl-5-vinyl-2-dodecene (2c): TLC R_f 0.65 (hexane); IR (neat) 3077, 2959, 2926, 2855, 1640, 1456, 1377, 994, 911 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 6.5 Hz, CH_3), 1.12–1.45 (m, 12 H, 6 CH_2), 1.59 (s, 3 H, CH_3), 1.69 (s, 3 H, CH_3), 1.88–2.22 (m, 3 H, CH_2 and CH), 4.88–5.00 (m, 2 H, 2 vinyls), 5.05–5.16 (m, 1 H, vinyl), 5.50–5.69 (m, 1 H, vinyl). Anal. Calcd for $C_{15}H_{28}$: C, 86.46; H, 13.54. Found: C, 86.30; H, 13.81.

(6*E*)-2,6-Dimethyl-9-vinyl-2,6-dodecadiene ((*E*)-2d). A mixture of freshly cut lithium (32 mg, 4.61 mmol), anhydrous magnesium chloride (224 mg, 2.35 mmol), and naphthalene (641 mg, 5.00 mmol) in 7 mL of dry THF was stirred at room temperature for 14 h under argon atmosphere. To the resulting black suspension of magnesium powder in THF was slowly added a solution of geranyl chloride (**4**, 119 mg, 0.69 mmol) in THF (1.5 mL) below -100 °C. After being stirred for 20 min, a solution of CuCN (3.0 mg, 0.033 mmol) and LiCl (5.7 mg, 0.13 mmol) in THF (2 mL) was slowly added and the mixture was stirred for another 10 min at this temperature. Then, a solution of (*E*)-2-hexenyl-1-diphenylphosphate (161 mg, 0.48 mmol) in THF (2 mL) was added below -100 °C and the reaction mixture was stirred for 1 h. To the mixture was added a saturated aqueous NH_4Cl solution and 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 (*E*)-**2d** (32 mg, 30% yield, $\alpha/\gamma > 99:1$, $S_N2/S_N2' = 6:94$, $E/Z = 95:5$) as

a colorless oil: TLC R_f 0.61 (hexane); IR (neat) 3077, 2961, 2928, 2872, 1640, 1456, 1377, 1107, 994, 911, 741 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 5.9 Hz, CH_3), 1.10–1.45 (m, 4 H, 2 CH_2), 1.58 (s, 3 H, CH_3), 1.60 (s, 3 H, CH_3), 1.68 (s, 3 H, CH_3), 1.88–2.15 (m, 7 H, 3 CH_2 and CH), 4.87–5.00 (m, 2 H, 2 vinyls), 5.10 (m, 1 H, vinyl), 5.12 (m, 1 H, vinyl), 5.49–5.69 (m, 1 H, vinyl). Anal. Calcd for $C_{16}H_{28}$: C, 87.19; H, 12.80. Found: C, 87.09; H, 13.09.

The *cis*-isomer (*Z*)-**2d** (19% yield, α/γ > 85:15, S_N2/S_N2' = 20:80, *E*/*Z* = 2:98) was synthesized from neryl chloride (**6**) under the similar reaction condition.

4-Methyl-6-vinyl-3-tridecene (2e): TLC R_f 0.74 (hexane); IR (neat) 3075, 2961, 2926, 2855, 1646, 1509, 1458, 1377, 994, 967, 911, 889 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 6.4 Hz, CH_3), 0.92 (t, 3 H, J = 7.4 Hz, CH_3), 1.12–1.50 (m, 12 H, 6 CH_2), 1.65 (s, 3 H, CH_3), 1.87–2.20 (m, 5 H, 2 CH_2 and CH), 4.86–4.99 (m, 2 H, 2 vinyls), 5.16 (m, 1 H, vinyl), 5.42–5.65 (m, 1 H, vinyl); MS (EI, 70 ev) *m/z* (rel) 222 (27.68, M^+), 208 (13.63), 193 (68.13), 180 (8.58), 152 (15.24), 138 (33.80), 123 (99.79), 109 (100). Anal. Calcd for $C_{16}H_{30}$: C, 86.41; H, 13.60. Found: C, 86.30; H, 14.02.

(1*E*)-1-Phenyl-4-vinyl-1-undecene (2g): TLC R_f 0.46 (hexane); IR (neat) 3081, 3027, 2957, 2926, 2855, 1640, 1599, 1495, 1466, 1418, 1377, 994, 965, 912, 743, 693 cm^{-1}; ^1H NMR (200 MHz, $CDCl_3$) δ 0.88 (t, 3 H, J = 6.4 Hz, CH_3), 1.12–1.48 (m, 12 H, 6 CH_2), 2.02–2.30 (m, 3 H, CH_2 and CH), 4.93–5.05 (m, 2 H, 2 vinyls), 5.54–5.74 (m, 1 H, vinyl), 6.18 (dt, 1 H, J = 15.8, 6.8 Hz, vinyl), 6.38 (d, 1 H, J = 15.8 Hz, vinyl), 7.13–7.40 (m, 5 H, aromatic). Anal. Calcd for $C_{19}H_{28}$: C, 88.99; H, 11.01. Found: C, 88.89; H, 11.27.

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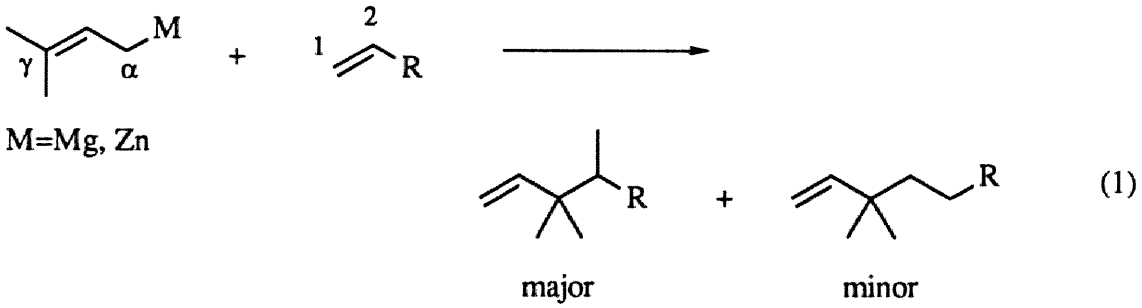
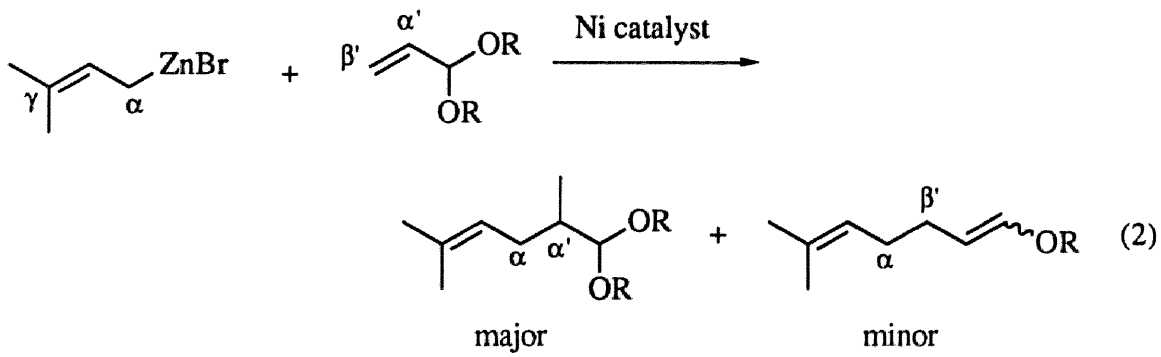
Chapter 4

Nickel Catalyzed Regioselective Allylation of Allylic Alcohol Derivatives (Allylmetallation)

Abstract: Regioselective allylmetallation of allylic alcohol derivatives was accomplished by treatment with allylzinc in the presence of a nickel catalyst. Benzylic protective group of allyl alcohol facilitated the allylmetallation.

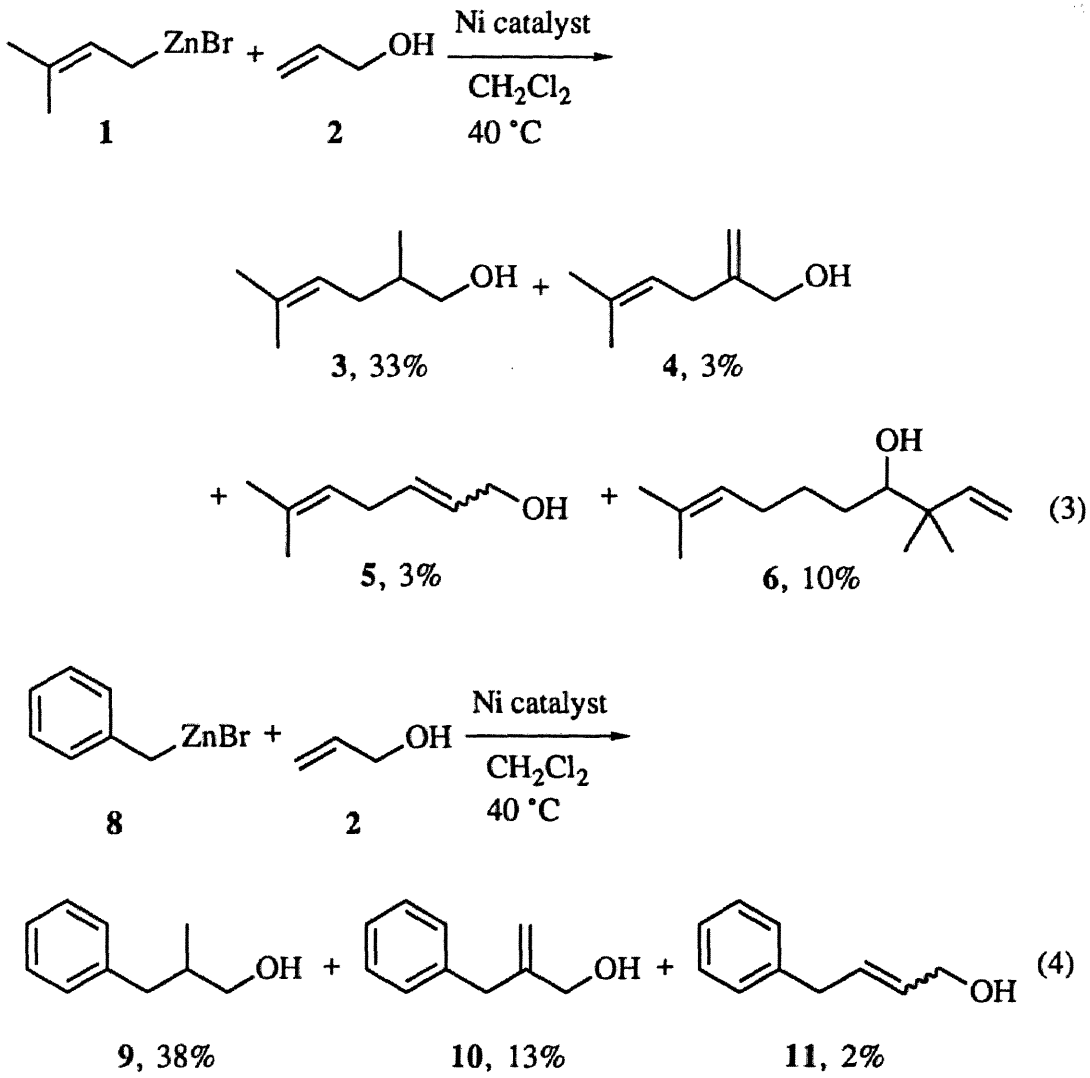
During the past two decades many investigations have been reported in the field of allylmetallation of alkenes using allylic Grignard reagents or zinc reagents.[1] For example, unsymmetrical allylic metal compounds added to 1-alkene are known to give the product (γ-C-2) in eq. 1.[1a] Recently an α,β-unsaturated acetal was shown to undergo rapid metallation upon treatment with allylzinc in the presence of nickel catalyst.[2] Thus, the allylic zinc reagent regiospecifically reacted at the α-carbon and attacked at the α'-carbon of the acetal selectively, eq. 2. Here, we wish to report further studies of this new process on allylic alcohols and their derivatives.





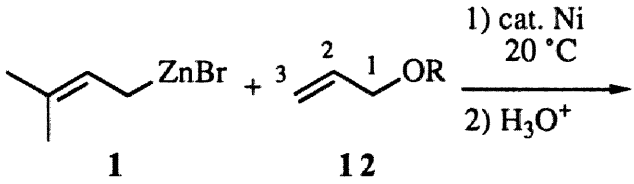
Treatment of 1 equiv of allyl alcohol (**2**) with a solution of 3-methyl-2-butenylzinc bromide (**1**) (4 eq) in CH_2Cl_2 under the influence of catalytic $NiBr_2(PBu_3)_2$ (10 mol%) at 40 °C for 35 min gave a mixture of the C-2 adduct **3** and **4** and C-3 adduct **5**[3] and **6**[4] in low combined yield, eq. 3.[5] Thus, allyl alcohol was found to be less reactive towards allylic metal reagent than α,β-unsaturated acetal, probably due to its higher basicity.

Benzylzinc reagent gave similar results: The reaction of benzylzinc bromide (**8**) with allyl alcohol (**2**) furnished the benzylated products **9**, **10**, and **11**, eq. 4.

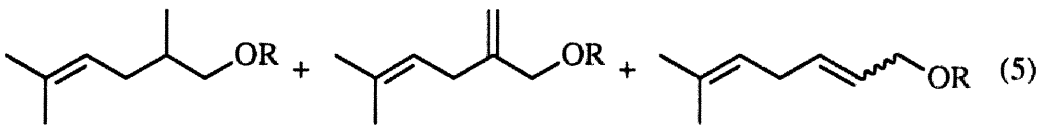


We then turned our attention to the various protective forms of allyl alcohol to facilitate the allylmetallation. Among a variety of protective groups,[6] benzyl allyl ether rapidly reacted with allylic zinc reagent. Some of our examples (eq. 5) show the following features. (1) Unsymmetrical allylic zinc reagent reacted at the primary carbon almost exclusively. (2)

Higher C-2/C-3 regioselectivity was achieved by increasing the number of phenyl groups of R. Thus, high regioselectivity of 15/1 was realized in the case of triphenylmethyl allyl ether, while the combined yield of products was lowered, probably due to the steric bulkiness of the protective group. Use of allyl 9-anthrylmethyl ether, in contrast, proved satisfactory in both regioselectivity and chemical yields (C-2/C-3 ratio = 6.9/1, 66% combined yield). Introduction of alkyl substituent at C-1 position of allyl alcohol resulted in higher regioselectivity, eq. 6, and the diastereomeric ratio of C-2 adduct **17** was 4.8:1 in 9-anthrylmethyl ether.[7] Obviously, the intermediate organozinc reagent can be trapped effectively with D_2O to afford the corresponding deuteriated products.

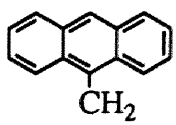


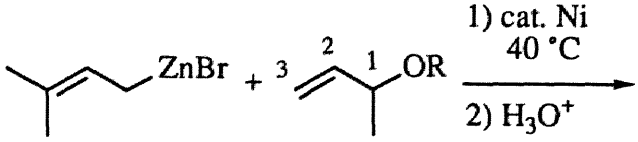
1 **12**



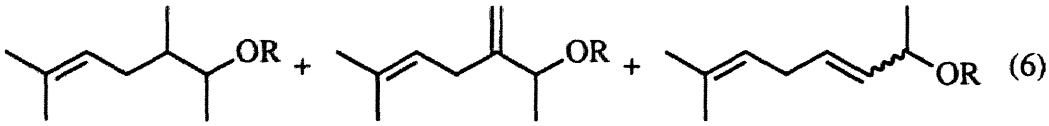
(5)

13 **14** **15**

R	**13**	**14**	**15**	ratio (C-2/C-3)
Et	14%	0%	12%	1.2/1
$PhCH_2$	48%	0%	18%	2.7/1
Ph_2CH	34%	3%	7%	5.3/1
Ph_3C	26%	4%	2%	15/1
	40%	15%	8%	6.9/1

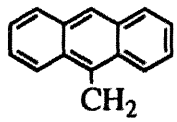


1 **16**



(6)

17 **18** **19**

R	**17**	**18**	**19**	ratio (C-2/C-3)
$PhCH_2$	52%	3%	4%	13.8/1
	60%	11%	5%	14.2/1

Experimental Section

General Methods. Reactions were generally run under a positive pressure of dry argon. Analytical TLC was done on E. Merk precoated (1.25 mm) silica gel 60 F_{254} plates. Colum chromatography was conducted by using silica gel 60 (E. Merk 9385, 230-400 mesh). Infrared (IR) spectra were recorded on a Hitachi 260-10 spectrometer. ^1H NMR spectra were obtained using a Varian Gemini-200 (200 MHz) or VXR-500S (500 MHz) spectrometer. Chemical shifts were reported in δ, downfield from tetramethylsilanee. Splitting patterns are designated as follows: s, singlet; d, doublet; t, triplet; b, broad; m, multiplet. Tetrahydrofuran (THF) was freshly distilled before use from sodium benzophenone ketyl. Methylene chloride (CH_2Cl_2) was stored over 4Å molecular sieves. Other chemicals were purchased and used as such.

General Procedure for Preparation of allyl benzylic ethers. To a suspension of sodium hydride (*ca* 50 wt% in oil, .480 mg) in THF (20 nL) was added allyl alcohol (0.69 mL, 9.9 mmol) at 0 °C. Several minutes later, benzylic bromide (1.2 mL, 9.8 mmol) and tetrabutylammonium iodide (37 mg, 0.1 mmol) were added to the mixture. The mixture is stirred for 4 h at room temperature. The reaction mixture was quenched with sat. aqueous NH_4Cl (20 mL) and the resulting organic layer was separated. The aqueous layer was extracted with ether (20 mL). The combined organic layer was dried ($MgSO_4$) and concentrated . The crude product was purified by column chromatography on silica gel (hexane-EtOAc).

General Procedure for allyation of allyl ether catalyzed by Ni Catalyst. To a solution 3-methyl-2-butenylzinc bromide (**1**) (3.0 mmol)[2] in CH_2Cl_2 (2.0 mL) was added a catalytic amount of $NiBr_2(PBu_3)_2$ (63 mg, 0.1 mmol) at 20 °C. After 10 min, allyl ether (1.0 mmol) was added at 20 °C and the resulting reddish mixture was stirred at this temperature for several hours. This mixture was poured into a saturated NH_4Cl aqueous solution and extracted with ether. The combined extracts were dried over $MgSO_4$ and concentrated. The crude products were purified by column chromatography on silica gel (hexane-EtOAc) to give

a mixture of prenylated ethers. The products ratio was determined by 500 MHz ^{1}NMR analysis.

2,5-dimethyl-4-hexen-1-ol (3): TLC R_f 0.33 (hexane/EtOAc = 15:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.88 (d, 3 H, *J* = 6.3 Hz, CH_3), 1.40 (b, 1 H, OH), 1.55-1.7 (m, 1 H, CH), 1.58 (s, 3 H, CH_3), 1.67 (s, 3 H, CH_3), 1.75 - 2.13 (m, 2 H, CH_2), 3.42 (dd, 1 H, *J* = 6.0, 10.0 Hz, CH), 3.50 (dd, 1 H, *J* = 6.0, 10.0 Hz, CH), 5.15 (t, 1 H, *J* = 6.5 Hz, vinyl). Anal. Calcd. for $C_8H_{16}O$: C, 74.94; H, 12.58. Found: C, 74.68; H, 12.32.

2-Metyl-3-phenyl-1-propanol (9): TLC R_f 0.22 (hexane/EtOAc = 3:1); ^{1}H NMR (200 MHz) δ 0.92 (d, 3 H, *J* = 7.0 Hz, CH_3), 1.97 (m, 1 H, CH), 2.42 (dd, 1 H, *J* = 7.5 Hz, Ar-CH), 3.50 (m, 2 H, CH_2), 7.15 - 7.42 (m, 5 H, Ph). Anal. Calcd. for $C_{10}H_{14}O$: C, 79.96; H, 9.39. Found: C, 80.01; H, 9.22.

3,6-Dimethyl-5-hepten-2-ol: TLC R_f 0.23 (hexane/EtOAc = 3:1); ^{1}H NMR (200 MHz, $CDCl_3$) δ 0.83 (d, 3 H, *J* = 7.0 Hz, CH_3, diastereoisomer (a)), 0.88 (d, 3 H, 7.0 Hz, diastereomer (b)), 1.21 (d, 3 H, *J* = 6.0 Hz, CH_3, (b)), 1.22 (d, 3 H, *J* = 6.0 Hz, CH_3, (a)), 1.71 (b, 1 H, OH, (a) and (b)), 1.75 - 1.90 (m, 1 H, CH, (a) and (b)), 2.35 (dd, 1 H, J = 9.0 , 14.0 Hz, Ar-CH, (a)), 2.40 (1 H, Ar-CH, (b)), 2.85 (1 H, Ar-CH, (b)), 2.90 (1 H, Ar-CH, (a)), 7.10 - 7.45 (m, 5 H, Ph, (a) and (b)). Anal. Calcd for $C_9H_{18}O$: C, 76.00; H, 12.75. Found: C, 76.21; H, 12.50.

References and Notes

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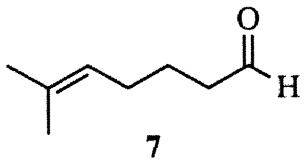
3) *trans*-Allylic alcohol was obtained as major isomer judged by 500MHz ^{1}H NMR analysis.

4) Compound **6** was supposed to be produced by reaction between the remaining 3-methyl-2-butenylzinc bromide (**1**) and aldehyde **7**, another isomer of C-3 adduct.



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5) Alkyllithium or allylic Grignard reagents are known to be readily added to allyl alcohols. The importance of intramolecular coordination was clearly demonstrated. Alkyllithiums: Crandall, J. K.; Clark, A. C. *J. Org. Chem.* **1972**, *37*, 4236; Crandall, J. K.; Rojas, A. C. *Org. Synth.* **1976**, *55*, 1. Allylic Grignard reagents: H. Felkin, H.; Kaeseberg, C. *Tetrahedron. Lett.* **1970**, 4587; Richey, H. G., Jr.; Wilkins, C. W. Jr. *J. Org. Chem.* **1980**, *45*, 5027.

6) Greene, T. W. In *Protective Groups in Organic Synthesis*; John Wiley & Sons, Inc.: New York, 1981.

7) The reaction between 1-methyl-2-propen-1-ol (**16**, R=H) and 3-methyl-2-butenylzinc bromide (**1**) in the presence of $NiBr_2(PBu_3)_2$ catalyst at 40 °C afforded **17** (R=H) in 11% yield accompanied with a trace amount of **18** (R=H) and **19** (R=H).

Publication List

Ccapter 2-1 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

J. Am. Chem. Soc. **1993**, *115*, 5879

Chapter 2-2 Superiority of Phosphate Ester as Leaving Group for Organocopper Rections. Highly S_N2'-, (*E*)-, and Antiselective Alkylation of Allylic Alcohol Derivatives

Akira Yanagisawa, Yoshiyuki Noritake, Nobuyoshi Nomura, Hisashi Yamamoto

Synlett **1991**, 251

Highly S_N2'-,(*E*)-, and Antiselective Alkylation of Allylic Phosphates. Facile Synthesis of Coenzyme Q_{10}

Akira Yanagisawa, Nobuyoshi Nomura, Yoshiyuki Noritake, Hisashi Yamamoto

Synthesis **1991**, 1130

Chapter 3 TRANSITION METAL-CATALYZED SUBSTITUTION REACTION OF ALLYLIC PHOSPHATES WITH GRIGNARD REAGENTS

Akira Yanagisawa, Nobuyoshi Nomura, Hisashi Yamamoto

Tetrahedron in press.

Chapter 3-1 Iron-Catalyzed Kharasch-Type Reaction Between Grignard Reagents and AllylicPhosphates. Highly S_N2 Selective Cross-Coupling Process

Akira Yanagisawa, Nobuyoshi Nomura, Hisashi Yamamoto

Synlett **1991**, 513

Chapter 3-2 Copper-Catalyzed S_N2'-Selective Cross Coupling Reaction Between Grignard Reagents and Allylic Phosphates

Akira Yanagisawa, Nobuyoshi Nomura, Hisashi Yamamoto

Synlett **1993**, 689

Chapter 4 NICKEL-CATALYZED REGIOSELECTIVE ALLYLATION OF ALLYLIC ALCOHOLS

Akira Yanagisawa, Nobuyoshi Nomura, Shigeki Habaue, and Hisashi Yamamoto

Tetrahedron Lett. **1989**, *46*, 6409

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