Addition of Allylic Grignard Reagents to Homoallylic Alcohols: Structural Effects on Addition and Cyclization

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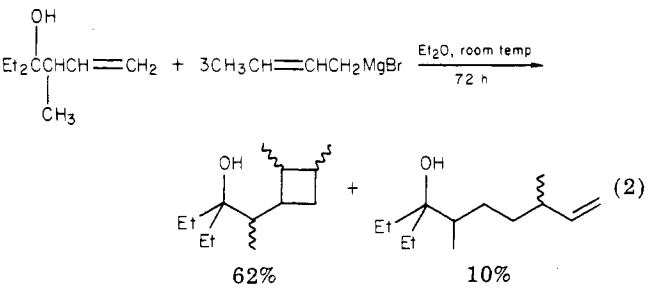
Addition of allylic Grignard reagents to homoallylic alcohols under normal reaction conditions (ether, 23 °C) yields acyclic addition products and cyclobutanes. The latter result from the addition of the more substituted end of the allylic system in the Grignard reagent to the olefinic carbons of the homoallylic alcohols followed by cyclization. The proportion of each product is markedly dependent upon the structures of the Grignard reagents and also the structures of the homoallylic alcohols. The kinetics and mechanisms of each step are discussed. In addition, the consistent stereochemistry of the cyclobutane products, which was confirmed by high-field NMR analyses and independent syntheses of possible isomeric compounds, showed the addition and cyclization steps to be highly stereospecific along with retention of configuration of the carbon–magnesium bond.

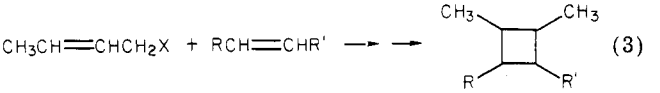
Carbomagnesiation reactions in which carbon–magnesium bonds add to unactivated carbon–carbon multiple bonds are new but relatively well documented. These include the Normant reaction initiated by Cu(I) species[2] and additions to fulvenes,[3] alkenols,[4] alkenylamines,[5] alkenyl ethers,[6] allenic alcohols, ethers,[7] and alkynols.[8] These systems, except for the Normant reaction,[2] have some common structural features in which an achimerically assisting functionality is present. The credit for the initial discovery of such systems is due to Eisch and Husk, who in 1965 reported the addition of allylmagnesium bromide to allylidiphenylcarbionol (eq 1).[8] Very recently, Eisch[8] and Richey[9] reported detailed accounts of the reaction using similar substrates. Only homoallylic alcohols were shown to undergo appreciable addition to form *acyclic* adducts, while other alcohols gave much less addition.

$$Ph_2C(OH)CH_2CH{=}CH_2 + 2CH_2{=}CHCH_2MgBr \xrightarrow[36\ h]{Et_2O,\ room\ temp} Ph_2C(OH)(CH_2)_4CH{=}CH_2 \quad (1)$$
70%

However, Broxterman[10] in 1969 claimed that under similar sets of conditions cyclobutanes were formed besides the addition products predictable from Eisch's results (eq 2). Even though there are some reports on the intermolecular addition of Grignard reagents to nonfunctionalized olefins under rather strenous conditions accompanied by some cyclobutane formation,[11-13] this is, to our knowledge, the first finding where cyclobutane, a relatively high-energy species, is formed intermolecularly under *normal* reaction conditions.



In an overall sense, a metal-induced 2 + 2 cycloaddition was realized (eq 3).



Consequently, as a model substrate, allyldimethylcarbinol was treated with an excess of allylmagnesium bromide in ether (see Experimental Section) to give only modest yields of products, among which a terminal adduct, resulting from addition of an allyl group to the terminal carbon of the double bond in the homoallylic alcohol, was a major product (eq 4). Various attempts to increase the yields of the products met with little success, and no appreciable catalytic effect could be observed with $CuIMe_2S$,

$$Me_2C(OH)CH_2CH{=}CH_2 \xrightarrow{2.5\ equiv\ of\ CH_2{=}CHCH_2MgBr} Me_2C(OH)(CH_2)_4CH{=}CH_2 + Me_2C(OH)CH_2CH(CH_3)CH_2CH{=}CH_2 \quad (4)$$
19% 1%

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Table I. Reactions of Allylmagnesium Bromide with Homoallylic Alcohols[a]

$$CHR^1{=}CR^2CH_2C(R)_2OH \xrightarrow[Et_2O]{CH_2{=}CHCH_2MgBr} 13a + 14a$$

	starting alcohol[b]			product yield,[c] %	
	R^1	R^2	R	13a	14a
1	H	H	H (44)	8	38
2	H	H	Me (70)	19	1
3	H	H	Et (45)	39	0
4	H	H	*i*-Pr (21)	85	0
5	H	H	*t*-Bu (0)	96	0

[a] The alcohol (0.1 M) and the Grignard reagent (0.25 M initially) in diethyl ether were stirred at 23 °C for 72 h. [b] The values in parentheses represent the percent of recovered alcohol. [c] See eq 6 for identity of products.

$PdCl_2$, Li_2PdCl_4, $(C_3H_6)_2Pt_2Cl_4$, $MgBr_2$, or $Ni(acac)_2$. Furthermore, the reaction of 3-buten-1-ol with the Grignard reagent afforded mostly an internal adduct under the same conditions (eq 5).

$$HOCH_2CH_2CH{=}CH_2 \xrightarrow{CH_2{=}CHCH_2MgBr} HOCH_2CH_2CH(CH_3)CH_2CH{=}CH_2 + HOCH_2(CH_2)_4CH{=}CH_2 \quad (5)$$

38% 8%

Thus, a slight variation in the structures of the alcohols caused quite different product compositions. Furthermore, *no trace of cyclobutane was observed in either case.* Consequently, it was decided to examine the effects of the structures of homoallylic alcohols and Grignard reagents in the hope of elucidating the nature of the reaction.[14]

Results

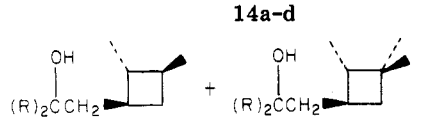
When allylmagnesium bromide was treated with a series of homoallylic alcohols differing mainly in the size of their α-substituents (R), a product trend was observed. The bulkier the α-substituents (R) became, the more rapid was the reaction leading to **13**, the terminal adduct (eq 6). The results are given in Table I.

$$CHR^1{=}CR^2CH_2C(R)_2OH + R^3R^4C{=}CR^5CH_2MgX \longrightarrow$$

9a-d

$$(R)_2C(OH)(CH_2)_3CR^3R^4C{=}CH_2 + (R)_2C(OH)CH_2CH(CH_3)CR^3R^4C{=}CH_2 +$$

13a-d **14a-d**



15 **16** (6)

a, $R^3 = R^4 = R^5 = H$; b, $R^3 = R^4 = H$, $R^5 = Me$; c, $R^3 = Me$, $R^4 = R^5 = H$; d, $R^3 = R^4 = Me$, $R^5 = H$; $R^1 = R^2 = H$; R, see Tables I-IV

Anomalously, 3-buten-1-ol (entry 1, Table I) was consumed more rapidly to form mainly an internal adduct, **14a** (eq 6), than even its next higher homologue allyldimethylcarbinol (entry 2, Table I), suggesting that the mechanism for internal addition might be different from that of terminal additions.

The same trend was observed in the reactions of (2-methylallyl)magnesium chloride (Table II). Justification for the use of the chloride instead of the bromide was based on its ready availability and the report that chlorides show almost the same reactivity as the bromides[10] (vide infra).

Table II. Reaction of (2-Methylallyl)magnesium Chloride with Homoallylic Alcohols[a]

$$CHR^1{=}CR^2CH_2C(R)_2OH \xrightarrow[Et_2O]{CH_2{=}C(CH_3)CH_2MgCl} 13b + 14b$$

	starting alcohol[b]			product yield,[c] %	
	R^1	R^2	R	13b	14b
1	H	H	H (40)	26	29
2	H	H	Me (23)	67	3
3	H	H	Et (29)	66	tr
4	H	H	*i*-Pr (tr)[d]	91	tr
5	H	H	*t*-Bu (9)	78	tr
6	H	H	Ph (tr)	82	tr

[a-c] See corresponding footnotes in Table I. [d] tr = trace.

Table III. Reactions of Crotylmagnesium Bromide with Homoallylic Alcohols[a]

$$CHR^1{=}CR^2CH_2C(R)_2OH \xrightarrow[Et_2O]{CH_3CH{=}CHCH_2MgBr} 13c + 14c + 15$$

	starting alcohol[b]			product yield,[c] %		
	R^1	R^2	R	13c	14c	15
1	H	H	H (31)	5	57 (t/e = 2)[d]	3
2	H	H	Me (70)	5	tr	14
3	H	H	Et (59)	10	tr	21
4	H	H	*i*-Pr (31)	16	tr	31
5	H	H	*t*-Bu (tr)	87	0	0
6	H	H	Ph (2)	76	0	15

[a-c] See the corresponding footnotes in Table I. [d] threo/erythro.

Product distributions changed dramatically when substituents were added to the allyl Grignard reagent. At the same time the usual accelerating effect by the α-substituents in the homoallylic alcohols was easily recognizable. In the same series of reactions with crotylmagnesium bromide (Table III), cyclobutanes (**15**, eq 6) were formed by uniform stereochemical integrity which was confirmed by 360-MHz ^1H NMR spectra and independent syntheses of four possible isomers (vide infra). This stereospecificity is remarkable since the cyclobutane products with three asymmetric carbon atoms could, in principle, give four products excluding enantiomeric pairs. Besides the main products depicted in Table III, a few minor products in yields less than 2% were detected. Of special significance was the fact that bulky α-substituents in the homoallylic alcohols not only accelerated the addition as usual but also exerted a marked retarding effect on cyclization, eventually leading to none in the case of the bulky allyldi-*tert*-butylcarbinol (entry 5, Table III). A possible cause of this phenomenon will be discussed later.

Reactions of (3,3-dimethylallyl)magnesium chloride gave clean results, affording the open-chain terminal adducts only in minor quantities. The major products were the cyclobutanes (**16**, eq 6), and significantly all of these had the same stereochemistry. The methyl group on the methine carbon in the cyclobutanes was exclusively trans to the β-hydroxyethyl side chain, indicating that the ring closure processes had been stereoselective.

It was of interest that (3,3-dimethylallyl)magnesium chloride did not add to disubstituted homoallylic alcohols (alcohols where R^1 or R^2 was *not* H) like *cis*- or *trans*-crotyldi-*tert*-butylcarbinol or 3-methyl-3-buten-1-ol.

Identification of Products. The identities of all products (isolated by chromatography) were confirmed by

(14) More details are described in a part of a Ph.D. Thesis. Kang, J. Ph. D. Dissertation, Purdue University, West Lafayette, IN, 1980.

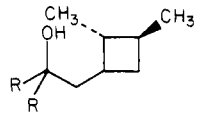
Table IV. Reactions of (3,3-Dimethylallyl)magnesium Chloride with Homoallylic Alcohols[a]

$$CHR^1{=}CR^2CH_2C(R)_2OH \xrightarrow[Et_2O]{(CH_3)_2C{=}CHCH_2MgCl} \text{13d + 14d + 16}$$

	starting alcohol[b]			product yield,[c] %		
	R^1	R^2	R	13d	14d	16
1	H	H	H (64)	tr	22	3
2	H	H	Me (69)	tr	0	14
3	H	H	Et (31)	tr	0	43
4	H	H	*i*-Pr (22)	tr	0	77
5	H	H	*t*-Bu (tr)	55	0	42
6	H	H	Ph (tr)	ca. 10	0	ca. 87

[a-c] See the corresponding footnotes in Table I.

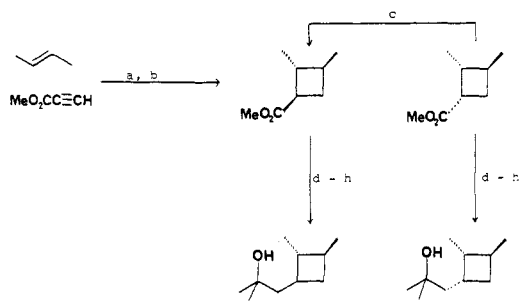
Table V. ^{1}H NMR (360-MHz) Spectra of Cyclobutanes[a,b]



R	chemical shifts, δ
Me	2.21 (dt, *J* = 10.5 and 7.5 Hz, 1 H), 1.6-1.8 (m, 3 H), 1.45 (dd, *J* = 10.5 and 14.2 Hz, 1 H), 1.30-1.42 (m, 1 H), 1.25 (br s 1 H), 1.17 (s, 3 H), 1.16 (s, 3 H), 1.09 (q, *J* = 9.8 Hz, 1 H), 0.99 (d, *J* = 6.0 Hz, 3 H), 0.97 (d, *J* = 6.2 Hz, 3 H)
Et	2.19 (dt, *J* = 10.0 and 7.5 Hz, 1 H), 1.55-1.75 (m, 3 H), 1.42 (q, *J* = 7.5 Hz, 2 H), 1.41 (q, *J* = 7.5 Hz, 2 H), 1.30-1.45 (m, 2 H), 1.05-1.20 (m, 1 H), 0.98 (d, *J* = 6.4 Hz, 3 H), 0.97 (d, *J* = 6.9 Hz, 3 H), 0.84 (t, *J* = 7.5 Hz, 3 H), 0.83 (t, *J* = 7.5 Hz, 3 H)
i-Pr	2.15 (dt, *J* = 10.0 and 7.3 Hz, 1 H), 1.85 (heptet, *J* = 6.7 Hz, 1 H), 1.82 (heptet, *J* = 6.7 Hz, 1 H), 1.55-1.75 (m, 4 H), 1.48 (dd, *J* = 9.5 and 14.5 Hz, 1 H), 1.25-1.40 (m, 1 H), 1.09 (q, *J* = 9.8 Hz, 1 H), 1.00 (d, *J* = 6.6 Hz, 3 H), 0.97 (d, *J* = 6.6 Hz, 3 H), 0.91 (d, *J* = 6.7 Hz, 12 H)
t-Bu	7.1-7.6 (m, 10 H), 2.42 (dd, *J* = 4.0 and 14.1 Hz, 1 H), 2.20 (dd, *J* = 8.8 and 14.1 Hz, 1 H), 1.95 (s, 1 H), 1.76 (dt, *J* = 9.9 and 7.7 Hz, 1 H), 1.53-1.65 (m, 1 H), 1.40-1.53 (m, 1 H), 1.3-1.4 (m, 1 H), 0.85-0.95 (m, 1 H), 0.84 (d, *J* = 6.8 Hz, 3 H), 0.82 (d, *J* = 6.4 Hz, 3 H)

[a] In $CDCl_3$. [b] Compounds **15** in eq 6.

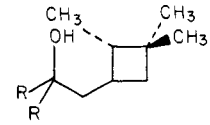
Scheme I



(a) $AlCl_3$, C_6H_6; (b) H_2, PtO_2; (c) Et_3N, Δ; (d) $LiAlH_4$, Et_2O; (e) $MeSO_2Cl$, Et_3N, pentane; (f) NaCN, Me_2SO; (g) NaOH, H_2O; (h) MeLi, Et_2O

elemental analyses, proton (90 and 360 MHz) and carbon-13 NMR spectra, and high- and low-resolution mass spectral analyses (Tables V–VIII and Experimental Section).

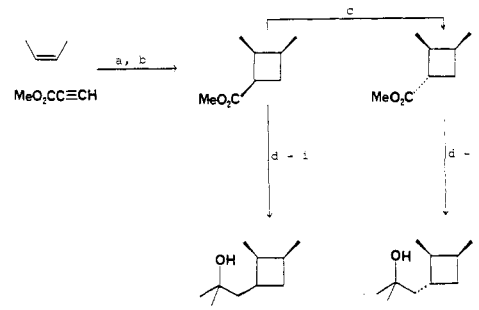
Table VI. ^{1}H NMR (360-MHz) Spectra of Cyclobutanes[a,b]



R	chemical shifts, δ
H	3.06 (t, *J* = 6.8 Hz, 2 H), 1.4-1.9 (complex, a 20-line pattern, 5 H), 1.21 (t, *J* = 8.1 Hz, 1 H), 0.92 (s, 3 H), 0.88 (s, 3 H), 0.81 (d, *J* = 6.9 Hz, 3 H)
Me	1.8-1.9 (m, 2 H), 1.69 (dd, *J* = 3.1 and 13.9 Hz, 1 H), 1.58 (quintet, *J* = 6.9 Hz, 1 H), 1.46 (dd, *J* = 9.3 and 13.9 Hz, 1 H), 1.3-1.4 (m, 1 H), 1.17 (s, 3 H), 1.16 (s, 3 H), 0.98 (s, 3 H), 0.97 (s, 3 H), 0.87 (d, *J* = 6.9 Hz, 3 H)
Et	1.75-1.85 (m, 2 H), 1.50-1.75 (m, 3 H), 1.42 (q, *J* = 7.4 Hz, 4 H), 1.15-1.25 (m, 1 H), 0.98 (s, 3 H), 0.96 (s, 3 H), 0.87 (d, *J* = 6.6 Hz, 3 H), 0.843 (t, *J* = 7.4 Hz, 3 H), 0.836 (t, *J* = 7.3 Hz, 3 H)
i-Pr	1.75-1.95 (m, 4 H), 1.63-1.70 (m, 1 H), 1.45-1.60 (m, 2 H), 1.30-1.40 (m, 1 H), 0.98 (s, 3 H), 0.95 (s, 3 H), 0.92 (d, *J* = 6.6 Hz, 6 H), 0.90 (d, *J* = 6.2 Hz, 6 H), 0.88 (d, *J* = 6.7 Hz, 3 H)
t-Bu	1.95-2.05 (m, 1 H), 1.75-1.85 (m, 2 H), 1.6-1.7 (m, 1 H), 1.5-1.6 (m, 1 H), 1.1-1.4 (m, 1 H), 1.03 (s, 9 H), 1.01 (s, 9 H), 0.97 (s, 3 H), 0.95 (s, 3 H), 0.88 (d, *J* = 6.5 Hz, 3 H)
$CH{=}CPh_2$[c] (17)	7.1-7.3 (m, 10 H), 6.05 (d, *J* = 9.6 Hz, 1 H), 2.54 (dddd, *J* = 9.6, 8.2, 8.2 and 10.2 Hz, 1 H), 1.89 (dq, *J* = 8.2 and 6.0 Hz, 1 H), 1.80 (dd, *J* = 8.2 and 10.2 Hz, 1 H), 1.57 (dd, *J* = 10.2 Hz, 1 H), 1.01 (s, 3 H), 0.86 (s, 3 H), 0.84 (d, *J* = 6.6 Hz, 3 H)

[a] In $CDCl_3$. [b] Compounds **16** in eq 6. [c] An attempted purification when R was Ph resulted in dehydration to form **17** (insert the $CH{=}CPh_2$ group for the $CH_2C(R_2)OH$).

Scheme II

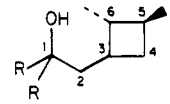


(a) $AlCl_3$, C_6H_6; (b) H_2, PtO_2; (c) $LiN(i\text{-}Pr)_2$, THF, −78 °C/MeOH; (d) $LiAlH_4$, Et_2O; (e) $MeSO_2Cl$, Et_3N, pentane; (f) NaCN, Me_2SO; (g) NaOH, H_2O; (h) MeMgI, Et_2O; (i) MeLi, Et_2O

Also, the stereochemistry of the cyclobutane products was deduced by independent syntheses of all four stereoisomers of cyclobutane, **15** (R = Me) (Schemes I and II).[14,15] In addition, the stereoisomeric distribution of the acyclic adduct **14c** (R = H) was estimated following a series of syntheses of authentic samples (Scheme III).[14] The latter served as important indicators in proposing a transition-

(15) Synthetic aspects of this study and related synthesis will be submitted for publication in due course.

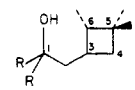
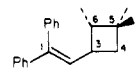
Table VII. Carbon-13 Chemical Shifts of Cyclobutanes[a] (ppm)



R	1	3	2	4	5 and 6	Me	Me	R
Me	71.37	45.69	50.31	36.81	36.30	20.41	18.70	30.03 (q) 29.33 (q)
Et	75.02	45.76	44.58	36.14	36.14	20.32	18.71	31.54 (t) 31.02 (t) 7.82 (q)
	(72.45)[b]	(46.08)[b]	(44.09)[b]	(36.50)[b]	(36.45)[b] (36.38)[b]	(20.52)[b]	(18.92)[b]	(32.01 (t))[b] (31.37 (t))[b] (8.05(q))[b]
i-Pr	77.55	46.17	39.55	35.93	36.53	20.18	18.64	34.66 (d) 34.29 (d) 17.54 (q)
Ph	77.03	45.87	48.28	35.86	36.36 36.06	20.30	18.45	147.44 (s) 128.24 (d) 127.98 (d) 126.78 (d) 126.59 (d) 126.09 (d) 125.98 (d)

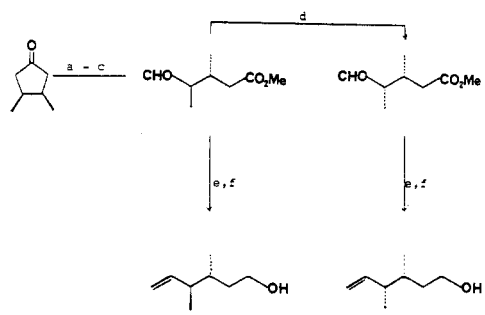
[a] 20-MHz spectra in $CDCl_3$ unless otherwise noted. [b] 37.5-MHz spectra in C_6D_6.

Table VIII. Carbon-13 Chemical Shifts of Cyclobutanes[a] (ppm)

R	1	3	4	2	5	6	Me	Me	Me	R
										
H	61.62	45.85	40.92	39.60	34.55	34.55	30.47	22.48	14.05	
Me	71.29	46.04	42.39	50.25	35.21	33.97	30.38	22.41	13.43	30.04 (q) 29.21 (q)
Et	75.05	46.11	42.22	44.66	35.17	33.17	30.37	22.33	13.31	31.55 (t) 30.97 (t) 7.83 (q)
i-Pr	77.52	46.54	42.59	39.51	34.83	33.64	30.34	22.29	13.39	34.63 (d) 34.23 (d) 17.54 (q) 17.39 (q)
t-Bu	80.23	46.56	42.23	39.70	34.86	35.16	30.38	22.26	13.40	42.14 (s) 41.90 (s) 28.73 (q)
										
17	142.86	46.74	41.21	?	34.63	37.69	30.23	22.22	13.43	140.53 (s) 140.34 (s) 134.91 (d) 130.13 (d) 128.60 (d) 128.00 (d) 127.28 (d) 126.80 (d) 126.74 (d)

[a] 20-MHz spectra in $CDCl_3$.

Scheme III



(a) mCPBA, CH_2Cl_2; (b) H_2SO_4, MeOH; (c) PCC, CH_2Cl_2; (d) base; (e) $Ph_3P{=}CH_2$, Et_2O; (e) $LiAlH_4$, Et_2O

state geometry for the formation of **14c** (R = H) (vide infra).

Kinetic Study. In order to follow the course of these reactions more closely, a kinetic study was undertaken involving the reaction of crotylmagnesium bromide with allyldiethylcarbinol (see entry 3, Table III). The choice was made because (1) the reaction between the two was moderately fast, (2) a reasonable ratio of the uncyclized adduct to the cyclobutane product was obtained, and (3) it was desirable to see whether the other three possible cyclobutane products, which were formed in neglibible amounts in the exploratory study (Table III), would be formed in significant amounts as intermediates.

A 0.1 M solution of allyldiethylcarbinol in diethyl ether

Table IX. Reactions of Crotylmagnesium Bromide with Allyldiethylcarbinol,[a] Time Study

time, h	yields after reaction, % SM[b]	M[c]	N[c]	13c[d]	15[e]	material balance	ratio 15/13c
1	100					100	
3	98.7	0.7	0.4	0.2	tr	100	
6	96.4	0.5	0.4	1.0	0.2	98.5	0.2
18	94.0	0.8	0.1	4.1	1.0	100.0	0.3
24	89.4	0.8	0.3	4.6	2.9	98.0	0.6
42	78.2	0.7	0.3	8.0	9.0	96.2	1.1
48	75.3	0.5	0.6	8.3	11.1	95.8	1.3
72	61.6	0.5	0.2	9.0	22.7	95.0	2.5
96	50.6	0.7	0.2	9.5	27.0	88.2	2.8
120	41.0	0.7	0.2	10.4	28.8	81.1	2.8
144	28.3	0.7	0.2	9.8	28.1	67.1	2.9

[a] The alcohol (0.1 M) and the Grignard reagent (0.25 M, initially) were stirred in ether at 23 °C. [b] Starting material (allyldiethylcarbinol). [c] Identity of this compound is unknown. [d] 1,1-Diethyl-5-methyl-6-hepten-1-ol. [e] *trans,trans*-1-(2-Hydroxy-2-ethylbutyl)-2,3-dimethylcyclobutane.

was stirred with 0.25 M ethereal solution of crotylmagnesium bromide at 23 °C in the presence of an internal standard (see Table IX). At the time intervals shown, an aliquot of the mixture was withdrawn by a syringe, worked up, and analyzed by GC. The results are summarized in Table IX.

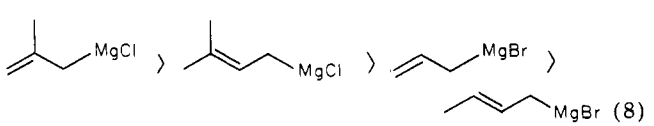
The results showed that the intervention of the other species did not occur at any point, thereby indicating that **13c** and **15** were formed without the intermediacy of other species. The material balance, however, progressively deteriorated after 72 h of reaction possibly due to dehydration of products catalyzed by the increasing amounts of magnesium bromide.[8] After 144 h, the material loss was so appreciable that a precise description of the system became impossible after this time.

A plot of the averages of the concentration of the starting alcohol and that calculated from the amounts of products vs. reaction time implied a first-order reaction in the starting alcohol as might be expected (Figure 1). From the slope, the rate constant k_1 for the consumption of the starting alcohol can be estimated to be 2×10^{-6} s^{-1} with a half-life of approximately 100 h. This means that the standard conditions for the exploratory studies (Tables I–IV) were not long enough to complete the reaction in some cases, expecially those with α-alkyl groups (in homoallylic alcohols) smaller than isopropyl. Since other substrates might also be expected to follow the same kinetics with different reaction rates, a comparison of the compositions of reaction mixtures at the same time interval (72 h) should have equivalent significance. One can compare the reactivities of the various alcohols as is demonstrated in eq 7. For terminal additions of the crotyl group

$$k_1^{R} = \frac{[\ln A/A_0]_R}{[\ln A/A_0]_{Et}} k_1^{Et} \qquad (7)$$

to the alcohols, which include both the open-chain and cyclobutane adducts (vide infra) in Table III, the relative reactivites of various alcohols are 3-buten-1-ol (**1**) < allyldimethylcarbinol (**2**) < allyldiethylcarbinol (**3**) < allyldiisopropylcarbinol (**4**) < allyldiphenylcarbinol (**6**) < allyldi-*tert*-butylcarbino (**5**).

With the same reasoning, one can roughly compare the reactivities of the individual Grignard reagents. Only a small difference exists with decreasing order:



(8)

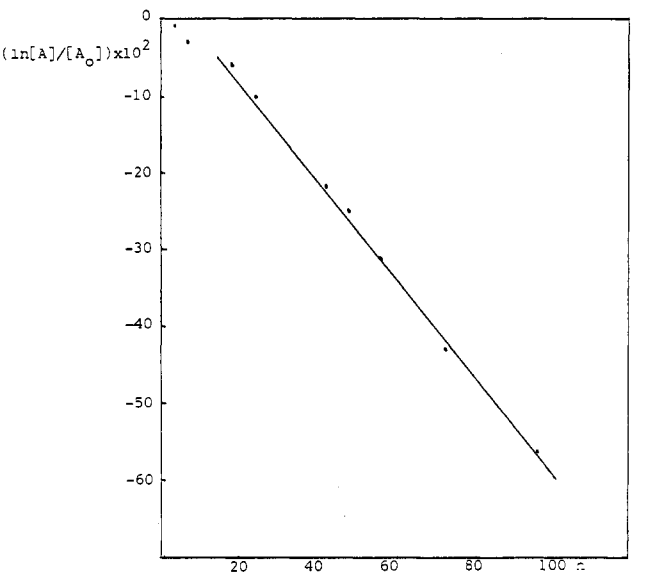


Figure 1. A time plot of unused allyldiethylcarbinol in the reaction with crotylmagnesium bromide at 23 °C in diethyl ether.

Discussion

From the foregoing results and other reports,[4-10] one can conclude the following: (1) The reaction requires an anchoring functionality. (2) Only *allylic* Grignard reagents add significantly to *homoallylic* alcohols under normal reaction conditions.[9,10] (3) Steric *hindrance* in the homoallylic alcohols *increases* the rate of terminal addition. (4) Only substituted allylic Grignard reagents give cyclobutane products, the ratio of the latter to uncyclized adduct decreasing with increasing size of the α-substituents of the homoallylic alcohols. (5) The 3,3-dimethylallyl Grignard reagent gives higher ratios of cyclization products than the crotyl Grignard reagent.

It is clear from the above observation that one can rule out the possibility of an initial bimolecular-type addition mechanism since such a mechanism is inconsistent with the steric acceleration effects ((3) above). Therefore, one can conclude that the additions occur *intramolecularly* via anchimeric assistance by the metal–oxygen moiety.

When a limited amount of an alcohol, ROH, is treated with an excess of a Grignard reagent, R'MgX, which has already attained the Schlenk equilibrium (eq 9), at least

$$2R'MgX \rightarrow R'_2Mg + MgX_2 \qquad (9)$$

$$R'MgX,\ R'_2Mg,\ MgX_2 \xrightarrow{ROH} R'MgOR + ROMgX + Mg(OR)_2 \qquad (10)$$

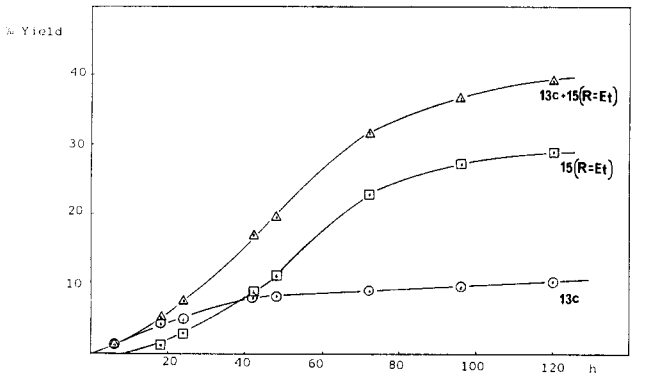
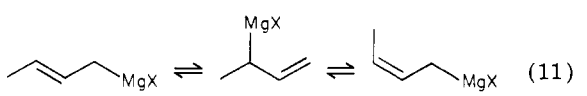


Figure 2. Kinetics of product formation in the reaction of crotylmagnesium bromide with allyldiethylcarbinol at 23 °C in diethyl ether.

six species are conceptually possible (eq 10). The presence of these six species and their self-association and association with each other would be very complicated. However, under the reaction condition (23 °C), the exchange rates are so enormously fast on NMR time scales that virtually no distinction could be made by NMR.[16] Consequently, relative reaction rates would be governed mainly by the rate-determining intramolecular step, namely, delivery of the allylic moieties to the olefinic portion of the homoallylic alcohols. Mechanistic considerations, therefore, can be based, to a good approximation, on the monomeric (unassociated) alkylmagnesium alkoxide R'MgOR.

Rates of Individual Reactions. It is instructive to plot the time-dependent concentrations data of the two main products from Table IX (see Figure 2). From the data, the following may be conceived: The magnesio derivative of the open-chain alcohol **13c** builds up significantly during 0–35 h period, before it cyclizes to the corresponding magnesiocyclobutane product. The rate of this cyclization is apparently greater than consumption of the starting alcohol, and an equilibrium is established between the open-chain product and the cyclized product, after a long period of time. On this basis, a tentative mechanism (including transition-state geometries) can be proposed within the framework of the existing data.

Initial Addition. The results in Tables I–IV show that the initial addition reaction occurs entirely at the more substituted carbon of the allylic system in the Grignard reagents *regardless of steric environment of the homoallylic alcohols.* This is reminiscent of Grignard addition reactions to unhindered carbonyl compounds even though allylic Grignard reagents are known to exist almost exclusively with magnesium bonded to the primary carbon atoms.[17,18]



(11)

primary trans secondary cis primary

[primary cis] > [primary trans] >> [secondary]

Thus, it is proposed that the addition reaction proceeds via a six-membered transition state like that which has been proposed for the carbonyl additions,[19] which resembles closely the thermally allowed intramolecular ene reaction.[20]

Scheme IV

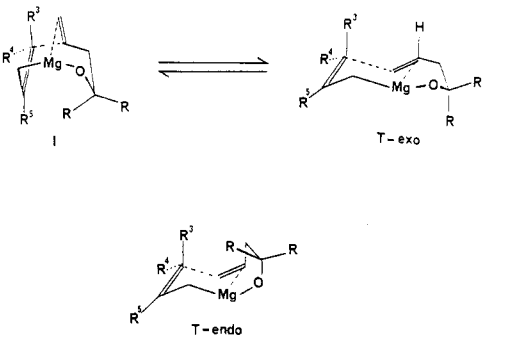
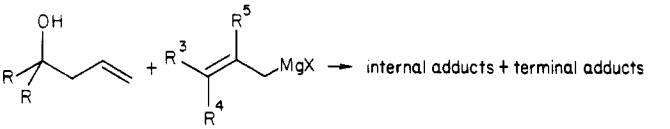
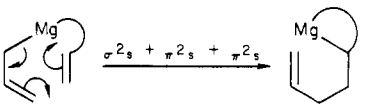


Table X. Internal vs. Terminal Addition as a Function of the α-Substituents of Homoallylic Alcohols



entry	R	R^3	R^4	R^5	internal/terminal
1	H	H	H	H	5
2	H	Me	H	H	7
3	H	Me	Me	H	7
4	H	H	H	Me	1
5	Me	H	H	H	5×10^{-2}
6	Me	H	H	Me	4×10^{-2}
7	Et or higher				0



(12)

This would also provide a reason why saturated Grignard reagents add to alkenols to a negligible extent if at all.[10] Also, the failure of the addition to the electron-rich disubstituted homoallylic alcohols (*ci-* and *tran*-crotylidi-*tert*-butylcarbinol and 3-methyl-3-buten-1-ol) under the standard conditions could be attributed to their poor enophilic nature,[20] although other explanations such as steric hindrance could be offered. Apparently, the intramolecularity of this ene-type reaction not only lowers the activation energy sufficiently to be observable under ordinary conditions but also influences the reaction so that high regio- and stereospecificities were observed (see Tables I–IV).

Thus, chair-like six-membered transition states can be envisioned for both internal and terminal additions (Scheme IV).[20c] The transition state T-endo can be disregarded on the grounds of the increased 1,3-diaxial-type interactions in both the five-membered and six-membered rings. Comparing the other two transition states, I and T-exo, any operation that would increase the steric interaction between R and R^5 groups in the transition state I would discouraged formation of the internal adducts, thereby increasing the yields of the terminal adducts via the transition state T-exo. Table X illustrates this substituent-directing effect. Thus, introduction of even one

(16) (a) Ashyby, E. C.; Laemmle, J.; Neumann, H. M. *Acc. Chem. Res.* **1974**, *7*, 272. (b) Ashby, E. C.; Nackashi, J.; Parris, G. E. *J. Am. Chem. Soc.* **1975**, *97*, 3362.

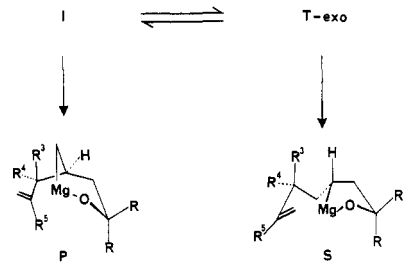
(17) (a) Roberts, J. D.; Young, W. G. *J. Am. Chem. Soc.* **1945**, *67*, 148. (b) Young, W. G.; Roberts, J. D. *Ibid.* **1945**, *67*, 319.

(18) Nordlander, J. E.; Young, W. G.; Roberts, J. D. *J. Am. Chem. Soc.* **1961**, *83*, 4914.

(19) Benkeser, R. A.; Broxterman, W. E. *J. Am. Chem. Soc.* **1969**, *91*, 5162.

(20) (a) Hoffmann, H. M. R. *Angew. Chem., Int. Ed. Engl.* **1969**, *8*, 556. (b) Killinger, T. A. *J. Org. Chem.* **1978**, *43*, 2161. (c) After completion of this study, an elegant use of this intramolecular metallo-ene reaction for construction of five- and six-membered rings has been made. See: Oppolzer, W.; Pitteloud, R.; Strauss, H. F. *J. Am. Chem. Soc.* **1982**, *104*, 6476; Oppolzer, W.; Pitteloud, R. *Ibid.* **1982**, *104*, 6478.

Scheme V



methyl group (entries 5 and 6) almost eliminates the internal addition due to the increased interaction in the transition state I (Scheme IV), while a small decrease in internal additions was observed with R^5 = Me (entry 4). This is understandable since the R^5 group resided on an sp^2 carbon, slightly pointing away from the R groups larger than methyl. This directing effects by the substituents is explained rather nicely by the proposed transition states (See also the discussion on Cyclization.).

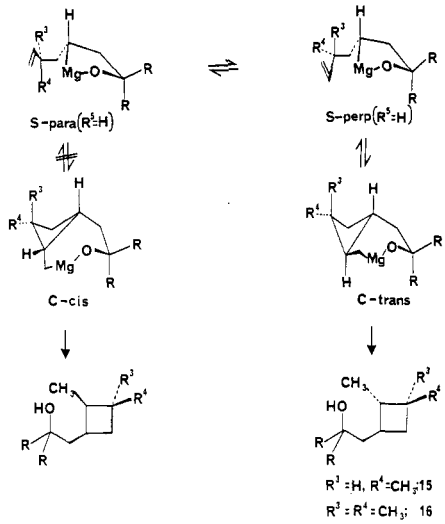
Moreover, as discussed previously, the R groups have other fundamental roles—one of them being their accelerating effects. Thus, a more than 100-fold increase in the rate of terminal addition was observed by replacement of α-hydrogens in 3-buten-1-ol by *tert*-butyl groups for R.[14] Most probably, the bulky R groups in T-exo push both the vinyl and the allylmagnesio moieties away from the R groups, eventually forcing them close to each other—a harnessing effect by steric repulsion.

Cyclization. Following the initial transition states I and T-exo, two new species, P and S, would be formed as a result of carbomagnesiation (Scheme V). Although ligand exchanges in P and S are possible to form the corresponding acyclic forms, it is more likely that the original cyclic alkylmagnesium alkoxides P and S be retained since a tremendous influence on cyclization by the R groups was observed (vide infra).

In no case was cyclization from the primary alkylmagnesium alkoxide P observed. This was likely due to the energy difference between primary and secondary carbanions (vide infra). From the secondary alkylmagnesium alkoxide S, no cyclized product was observed when $R^3 = R^4$ = H (Tables I and II), while only a modest yield of cyclobutane product was obtained if one of the R^3 and R^4 groups was methyl. But virtually all intermediate S underwent cyclization if $R^3 = R^4$ = Me *and* the R groups were not prohibitively large. Thus, the so-called "gem-dimethyl" effect[21] was observed.

It is also illuminating to examine the ratio of the cyclized products to the uncyclized terminal adducts in the reactions of the crotyl Grignard reagent with homoallylic alcohols where both products are produced in reasonable ratios (Table III). Convincingly, the bulkiness of the α-substituents on the alcohols display a rather remarkable "retarding" effect on cyclization (cyclized/uncyclized ratios in Table III: Me, 2.8; Et, 2.1; *i*-Pr, 1.9; Ph, 0.2; *t*-Bu, 0). Thus, it is likely that the cyclic secondary alkylmagnesium alkoxide S does not undergo ring cleavage processes by ligand exchange, and therefore, the sterically demanding R groups in S push the 3-butenyl side chain away from the carbon–magnesium bond by a 1,3-diaxial-type interaction, thereby inhibiting the cyclization. On must bear in mind that these reaction systems are thermodynamically controlled. Consequently, "the retarding effect" has to be understood in terms of kinetic as well as thermodynamic phenomena. The same "retarding effect" to cyclization can be observed, to a lesser extent, in the reactions of (3,3-dimethylallyl)magnesium chloride (Table IV). Most probably, the aforementioned "entropy effect" overrides this pushing effect to some degree.

Scheme VI



It is to be noted that by adding the crotyl moiety to a homoallylic alcohol a pair of asymmetric centers are created in P and S in Scheme V. With the assumption that an equatorial methyl group was favored in I (Scheme IV), it would be predicted that, on protonolysis of P (R = R^3 = R^5 = H and R^4 = Me), the adduct would be a compound with the threo configuration as the major isomer, if not the exclusive one. This was indeed observed in the crotyl adduct of 3-buten-1-ol, **14c** (Table III, entry 1, threo/erythro = 2). Also, two of the three asymmetric centers in the cyclobutane products are determined at this stage. An underlying assumption here is that the configuration of the carbon–magnesium bond is maintained throughout. This is reasonable since in related cases where intramolecular coordination sites are provided for metals (Li, Mg, etc.) such as this, retention of configuration of the carbon–metal bond is observed.[8b,22,23] The fact that the cyclobutane products obtained possessed uniformly a trans,trans configuration lends some credence to this assumption.

The transition state of terminal addition of the crotyl group, T-exo, would also favor an equatorial methyl group, i.e., T-exo ($R^3 = R^5$ = H and R^4 = Me). This event coupled with the retention of the configuration of the magnesium–carbon bond leads to S ($R^3 = R^5$ = H and R^4 = Me) that, upon cyclization, would guarantee a cis relationship between the β-hydroxyethyl group and its transannular methyl group in the resulting cyclobutane products. This was clearly observed (Table III). Conversely, if configurational scrambling occurred in homogeneously defined S (R^3 = H, R^4 = Me, and R^5 = H) to form a diastereomeric pair, the stereochemical homogeneity in the cyclobutane

(21) (a) Allinger, N. L.; Zalkow, V. *J. Am. Chem. Soc.* **1960**, *25*, 701 and references therein. (b) For "gem-dimethyl effect" in Grignard cyclization, see: ref 13c and Hill, E. A.; Link, D. C.; Donndelinger, P. *J. Org. Chem.* **1981**, *46*, 1177.

(22) (Retention of configuration) (a) Walborsky, H. M.; Young, A. E. *J. Am. Chem. Soc.* **1961**, *85*, 2595. (b) For a related case, see: Still, W. C.; Streekumar, C. *Ibid.* **1980**, *102*, 1201. (c) McGarvey, G. J.; Kimura, M. *J. Org. Chem.* **1982**, *47*, 5420.

(23) More examples of configurational scramblings are found in the literature: (a) Whitesides, G. M.; Kaplan, F.; Roberts, J. D. *Ibid.* **1963**, *85*, 2167. (b) Whitesides, G. M.; Witanowski, M.; Roberts, J. D. *Ibid.* **1965**, *87*, 2854. (c) Witanowski, M.; Roberts, J. D. *Ibid.* **1966**, *88*, 737. (d) Frankel, G.; Dix, D. T. *Ibid.* **1966**, *88*, 979. (e) Frankel, G.; Cotterel, C. E.; Dix, D. T. *Ibid.* **1971**, *93*, 1704. (f) Penchhold, E.; Adams, D. G.; Frankel, G. *J. Org. Chem.* **1971**, *36*, 1308.

Table XI. Analytical Data for Products

compd (R)	elemental anal.	C	H	NMR ($CDCl_3$)[a]	IR (neat)[b]	MS, *m/e*
14a (H) ($C_7H_{14}O$)	calcd	73.63	12.36	5.5–6.1 (m, 1 H), 4.8–5.2 (m, 2 H), 3.68 (t, J = 7 Hz, 2 H),	3120–3450, 1060, 920	96.904 (M – H_2O),
	found	73.55	12.52	1.1–1.3 (m, 6 H), 0.92 (d, J = 7 Hz, 3 H)		81, 71, 67
13a (H) ($C_7H_{14}O$)	calcd	73.63	12.36	5.5–6.1 (m, 1 H), 4.8–5.2 (m, 2 H), 3.65 (t, J = 7 Hz, 2 H),	3390, 3125, 1060, 910	
	found	73.46	12.57	2.06 (m, 2 H), 1.1–1.8 (m, 7 H)		
13a (Me) ($C_9H_{18}O$)	calcd	76.00	12.75	5.5–6.1 (m, 1 H), 4.8–5.2 (m, 2 H), 2.06 (m, 2 H), 1.2–1.6	3330, 3080, 1150, 910	126, 907 (M – CH_3),
	found	76.24	12.99	(m, 7 H), 1.19 (s, 6 H)		109, 96
13a (Et) ($C_{11}H_{22}O$)	calcd	77.58	13.02	5.5–6.1 (m, 1 H), 4.8–5.2 (m, 2 H), 2.06 (m, 2 H), 1.2–1.7	3450, 3120, 1150, 915	152, 157 (M – H_2O),
	found	77.48	13.12	(m, 1 H), 0.84 (t, J = 7 Hz, 6 H)		141, 124
13a (*i*-Pr) ($C_{13}H_{22}O$)	calcd	78.73	13.21	5.5–6.1 (m, 1 H), 4.8–5.2 (m, 2 H), 1.2–2.2 (m, 11 H),	3450, 3080, 1140, 910	180, 188 (M – H_2O),
	found	78.73	13.44	0.92 (d, J = 7 Hz, 6 H), 0.91 (d, J = 7 Hz, 6 H)		
13a (*t*-Bu) ($C_{15}H_{30}O$)	calcd	79.54	13.39	5.5–6.1 (M, 1 H), 4.8–5.2 (m, 2 H), 2.08 (m, 2 H), 1.2–1.8	3700, 3080, 1410,	208, 221 (M – H_2O),
	found	79.43	13.55	(m, 7 H), 1.03 (s, 18 H)	1390, 1000, 910	169, 152, 143
14b (H) ($C_8H_{16}O$)	calcd	74.94	12.58	4.70 (br d, 2 H), 3.69 (t, J = 7 Hz, 2 H), 1.2–2.2 (m, 6 H),	3330, 3120, 1460,	128, 108 (M), 95,
	found	74.75	12.85	1.70 (s, 3 H), 0.88 (d, J = 7 Hz, 3 H)	1060, 890	83, 71
13b (H) ($C_8H_{16}O$)	calcd	74.94	12.58	4.68 (br s, 2 H), 3.65 (t, J = 7 Hz, 2 H), 2.03 (br t, 2 H),	3330, 3080, 1460,	128, 120 (M), 120,
	found	74.72	12.72	1.2–1.7 (s, 3 H)	1060, 890	95
14b (Me)				4.7 (br d, 2 H), 1.70 (s, 3 H), 1.22 (d, 6 H), 1.1–2.5		
				(m, 6 H), 0.95 (d, J = 7 Hz, 3 H)		
13b (Me) ($C_{10}H_{20}O$)	calcd	76.86	12.90	4.68 (s, 2 H), 2.02 (br t, 2 H), 1.70 (s, 3 H), 1.3–1.65	3450, 3150, 1470,	138.195 (M – H_2O),
	found	76.67	12.92	(m, 7 H), 1.18 (s, 6 H)	1160, 890	141, 131, 123
13b (Et) ($C_{12}H_{24}O$)	calcd	78.19	13.12	4.68 (s, 2 H), 2.03 (br t, 2 H), 1.71 (s, 3 H), 1.15–1.65	3330, 3030, 1440,	166.174 (M – H_2O),
	found	78.32	13.33	(m, 10 H), 1.09 (s, 1 H), 0.85 (t, 6 H)	1360, 1160, 880	138, 111
13b (*i*-Pr) ($C_{14}H_{28}O$)	calcd	79.18	13.29	4.73 (s, 2 H), 1.73 (s, 3 H), 1.2–2.2 (m, 11 H), 0.96	3570, 3080, 1380,	194.201 (M – H_2O),
	found	79.45	13.27	(d, J = 7 Hz, 6 H), 0.94 (d, J = 7 Hz, 6 H)	1160, 890	169, 151
13b (*t*-Bu) ($C_{16}H_{32}O$)	calcd	79.93	13.41	4.7 (s, 3 H), 2.7 (br t, 2 H), 1.75 (s, 3 H), 1.2–1.7 (m, 7 H),	3640, 3080, 1610,	183.175 (M – C_4H_9),
	found	80.12	13.24	1.04 (s, 18 H)	1590, 1200, 890	166, 143, 123
13b (Ph) ($C_{20}H_{24}O$)	calcd	85.67	8.62	7.04–7.5 (m, 10 H), 4.62 (s, 2 H), 2.0–2.4 (m, 2 H), 1.94	3450, 3080, 1600,	280.182 (M), 262,
	found	85.45	8.91	(br t, 2 H), 1.04 (s, 3 H), 1.0–1.6 (m, 5 H)	1160, 810, 700	206, 194
14c (H)[c] ($C_8H_{16}O$)	calcd	75.00	12.59	5.6–5.8 (m, 1 H), 4.8–5.1 (m, 2 H), 3.4–3.6 (m, 2 H), 2.05–	3330, 3080, 1060, 990,	110.116 (M – H_2O),
	found	74.87	12.70	2.2 (m, 1 H),[d] 1.5–1.8 (m, 2 H),[d] 1.25–1.40 (m, 2 H),[d]	915	95, 84, 82
				1.05–1.20 (m, 1 H),[d] [1.00 (d, J = 6.9 Hz, 67%[c]), 0.96		
				(d, J = 6.9 Hz, 33%[c]), 3 H],[d] 0.86 (d, J = 6.4 Hz, 3 H)[d]		
13c (Me) ($C_{10}H_{20}O$)	calcd	76.86	12.90	5.5–5.9 (m, 1 H), 4.8–5.1 (m, 2 H), 1.2–2.2 (m, 8 H), 1.29	3390, 3080, 1150, 910	138.141 (M – H_2O),
	found	76.63	13.12	(s, 6 H), 0.97 (d, J = 7 Hz, 3 H)		123, 109, 95
14c (Me)				5.5–5.9 (m, 1 H), 4.8–5.1 (m, 2 H), 1.2–2.3 (m, 5 H), 1.13		
				(s, 6 H), 0.98 (d, J = 7 Hz, 3 H), 0.88 (d, J = 7 Hz, 3 H)		
15 (Me) ($C_{10}H_{20}O$)	calcd	76.86	12.40	2.05–2.35 (m, 1 H), 1.01–0.95 (m, 7 H), 1.16 (s, 6 H),	3390	141.129 (M – CH_3),
	found	76.61	13.08	0.98 (br d, J = 6 Hz, 6 H)		138, 123, 112, 96
13c (Et) ($C_{12}H_{24}O$)	calcd	78.20	13.12	5.4–5.6 (m, 1 H), 4.8–5.1 (m, 2 H), 1.9–2.3 (m, 1 H),	3390, 3080, 1450, 920	166.172 (M – H_2O),
	found	78.11	13.30	1.1–1.8 (m, 11 H), 0.98 (d, J = 7 Hz, 3 H), 0.84 (t, J =		155, 109
				7 Hz, 6 H)		
15 (Et), ($C_{12}H_{24}O$)	calcd	78.20	13.12	2.0–2.4 (m, 1 H), 1.05–1.9 (m, 11 H), 0.96 (br d, 6 H),	3390	166.172 (M – H_2O),
	found	78.03	13.41	0.83 (br t, 6 H)		155, 137, 110
13c (*i*-Pr) ($C_{14}H_{28}O$)	calcd	79.18	13.39	5.4–5.9 (m, 1 H), 4.7–5.1 (m, 2 H), 1.05–2.3 (m, 10 H),	3390, 3080, 1200	212.214 (M), 195,
	found	79.02	13.35	0.97 (d, J = 7 Hz, 6 H), 0.93 (d, J = 7 Hz, 3 H), 0.91		169
				(d, J = 7 Hz, 6 H)		
15 (*i*-Pr) ($C_{14}H_{28}O$)	calcd	79.18	13.39	2.05–2.45 (m, 1 H), 1.05–2.05 (m, 9 H), 0.97 (d, J = 6 Hz,	3390	169.159 (M – C_3H_7),
	found	79.21	13.49	6 H), 0.95 (d, J = 7 Hz, 3 H), 0.88 (d, J = 7 Hz, 6 H),		151, 138, 115
				0.85 (d, J = 7 Hz, 3 H)		
13c (*t*-Bu) ($C_{16}H_{32}O$)	calcd	79.93	13.41	5.4–6.1 (m, 1 H), 4.8–5.1 (m, 2 H), 1.1–2.3 (m, 8 H), 1.03	3570, 3050, 1390,	183.175 (M – C_4H_9),
	found	80.12	13.34	(s, 18 H), 0.98 (d, J = 7 Hz, 3 H)	1200, 995, 910	165, 143

13c (Ph) ($C_{20}H_{24}O$)	calcd	85.67	8.63	7.1–7.6 (m, 10 H), 5.4–5.9 (m, 1 H), 4.8–5.1 (m, 2 H), 1.04–2.4 (m, 8 H), 0.89 (d, J = 7 Hz, 3 H)	3570, 3450, 1480, 910	262.272 (M – H_2O), 220, 206
	found	85.32	8.72			
15 (Ph) ($C_{20}H_{24}O$)	calcd	85.67	8.63	7.1–7.4 (m, 10 H), 1.0–2.6 (m, 8 H), 0.87 (d, J = 7 Hz, 3 H), 0.83 (d, J = 7 Hz, 3 H)	3570	262.172 (M – H_2O), 220, 206, 191
	found	85.54	8.61			
14d (H) ($C_9H_{18}O$)	calcd	76.00	12.75	5.6–6.0 (m, 1 H), 4.7–5.1 (m, 2 H), 3.4–3.8 (m, 2 H), 1.0–1.9 (m, 4 H), 0.95 (s, 6 H), 0.84 (d, J = 7 Hz, 3 H)	3330, 3080, 1050, 1005, 910	142.306 (M), 124, 109, 98
	found	75.93	12.97			
13d (H)				5.6–6.0 (m, 1 H), 4.7–5.0 (m, 2 H), 3.5 (t, J = 7 Hz, 2 H), 1.0–1.9 (m, 7 H), 0.97 (s, 6 H)		
16 (H) ($C_9H_{18}O$)	calcd	76.00	12.75	3.52 (t, 2 H), 1.05–2.0 (m, 7 H), 0.99 (s, 3 H), 0.96 (s, 3 H), 0.88 (d, J = 7 Hz, 3 H)	3390	142.134 (M), 113, 109, 82, 72
	found	75.87	12.80			
13d (Me)				5.78 (m, 1 H), 4.7–5.0 (m, 2 H), 1.0–1.9 (m, 6 H), 1.19 (s, 6 H), 0.99 (s, 6 H)		
16 (Me) ($C_{11}H_{22}O$)	calcd	77.58	13.02	1.25–2.0 (m, 7 H), 1.15 (s, 6 H), 0.97 (s, 6 H), 0.86 (d, J = 7 Hz, 3 H)	3450	155.144 (M – CH_3), 152, 137, 126, 96
	found	77.53	13.21			
16 (Et) ($C_{13}H_{26}O$)	calcd	78.72	13.21	1.05–2.10 (m, 11 H), 0.97 (s, 6 H), 0.94 (d, J = 7 Hz, 3 H), 0.83 (t, J = 7 Hz, 6 H)	3450	180.187 (M – H_2O), 169, 151, 124, 110
	found	78.56	13.40			
16 (*i*-Pr) ($C_{15}H_{30}O$)	calcd	79.58	13.36	1.05–2.15 (m, 9 H), 0.95 (s, 6 H), 0.80–1.05 (m, 15 H)	3530	208.219 (M – H_2O), 183, 152, 138
	found	79.47	13.54			
13d (*t*-Bu) ($C_{17}H_{34}O$)	calcd	80.24	13.47	5.79 (dd, 1 H), 4.7–5.0 (m, 2 H), 1.05–1.80 (m, 7 H), 1.01 (s, 18 H), 0.95 (s, 6 H)	3770, 3050, 1390, 1370, 1000, 910	197.192 (M – C_4H_8), 143, 123
	found	80.29	13.53			
16 (*t*-Bu) ($C_{17}H_{34}O$)	calcd	80.24	13.47	1.1–2.1 (m, 7 H), 0.85–2.05 (m, 27 H)	3700	180.205 (M – H_2O – C_4H_8), 197, 166
	found	80.00	13.61			
17[f]				7.0–7.5 (m, 10 H), 6.05 (d, J = 10 Hz, 1 H), 2.3–2.8 (m, 1 H), 1.3–2.1 (m, 3 H), 1.00 (s, 3 H), 0.87 (s, 3 H), (d, J = 7 Hz, 3 H)	1670, 1602, 1500, 1370, 780, 770, 705	276.188 (M), 250, 233, 220, 206

[a] 90 MHz unless otherwise noted; in δ. [b] In cm^{-1}. [c] A 1:2 mixture of erythro and threo configuration. [d] 360 MHz. [e] By integration. [f] bp 153–155 °C (0.35 mm).

products would have not been observed as in a similar system studied by Hill.[13b]

A consideration of molecular models of the secondary alkylmagnesium alkoxide S points out the fact that two transition-state geometries are possible for cyclization, one in which the carbon–magnesium bond is parallel to the carbon–carbon double bond, S-para and another where the carbon–magnesium bond is perpendicular to the double bond, S-perp (Scheme VI).[13d] Each geometry would effect different stereochemical results. By the fact that the cycloproducts maintained consistently a trans geometry of the methyl group to the neighboring β-hydroxyethyl side chain, only the perpendicular transition geometry, S-perp, can be operative as was found in related cases.[13d]

Energetics of Addition and Cyclization. The most important driving force for the addition of an alkyl group to a carbon–carbon double bond is the change in enthalpy due to the formal conversion of the double bond to two single bonds (eq 13). This is estimated to be about −22

$$RCH_2MgX + R'CH{=}CH_2 \xrightarrow{\Delta H = -22\ \text{kcal/mol}} R'CH(RCH_2)CH_2MgX \quad (13)$$

kcal/mol.[13d] This value is large enough to overcome opposing forces such as entropy loss upon addition and free energy increase upon change of the nature of carbanions (vide infra).

The initial additions, internal (I → P) or terminal (T → S), involve an energetically unfavorable conversion of an allylic carbanion to either a primary or a secondary carbanion. To the extent that the data of Dessy[24] suggests the relative stabilities of allylic, primary, and secondary "carbanions", one might have predicted that the internal additions would be favored intrinsically over the terminal additions. But as the α-substituents (R) become progressively larger, the steric interaction between the R and R^5 group comes into play, eventually dominating over the stability differences (see Scheme IV and Table X).

Cyclization (S-perp → C-trans in Scheme VI) is aided also by the favorable enthalpy changes upon saturation of the double bond as well as upon conversion of a secondary carbanion to a primary one (about −3 kcal/mol).[24] But these are overwhelmed by an enormous amount of ring strain in the resulting cyclobutane (26 kcal/mol),[25] and, to a lesser extent, an entropy decrease on cyclization (~10 eu,[13d] hence ~3 kcal/mol at 23 °C).

Thus, in order for a cyclization to be observable, other positive effects would have to countercontribute to the deficit (4 kcal/mol), which is manifested by the "entropy effect" exerted by the R^3 and R^4 groups (Scheme VI). In the absence of this reinforcement, i.e., $R^3 = R^4 = H$, the equilibrium S ⇌ C-trans is so unfavorable that no cyclized product is observed in the reactions of allyl and 2-methylallyl Grignard reagents. On the basis of the above rough estimate the "deficit" (4 kcal/mol), it appears that ca. 4.6 kcal/mol of the entropy effect by a methyl group (cyclized/uncyclized = ~3) and ca. 6.7 kcal/mol of the entropy effect by gem-dimethyl groups (cyclized/uncyclized = ~100) are achieved in C-trans (R = Et).

Experimental Section

Methods. Infrared spectra were taken as thin films on sodium chloride plates using a Perkin-Elmer 127 spectrophotometer. Proton magnetic resonance spectra (^1H NMR) were obtained on a Varian A-60 (60 MHz), a Perkin-Elmer R-32 (90 MHz), and a

(24) Dessy, R. E.; Kitching, W.; Psarras, T.; Salinger, R.; Chen, A.; Chievers, T. *J. Am. Chem. Soc.* **1966**, *88*, 460.

(25) Kaarsemaker, S.; Coops, J. *Recl. Trav. Chem. Pays-Bas* **1952**, *71*, 261.

Nicolet NTC-360 (360 MHz) spectrometers. Carbon-13 magnetic resonance spectra (^{13}C NMR) were obtained on a Varian CFT-20 (20 MHz) and a Nicolet NTC-150 (37.5 MHz) spectrometers. Typically, pulse with (7–9 μs) and pulse delay (1–3 s) were employed for 8K spectra. Chemical shifts were recorded on the δ scale in parts per million with respect to Me_4Si, and apparent coupling constants were recorded in hertz. ^{13}C NMR and 360-MHz ^1H NMR spectra data were placed in appropriate tables in the Results unless otherwise noted. Gas chromatographic analyses and separations were accomplished on the following: (A) a 10% carbowax 20M on Chromosorb A column, 20 ft. × $^1/_4$ in., (B) a 10% Carbowax 20M on Chromosorb G column, 15 ft × $^1/_4$ in., (C) a 15% poly-*m*-phenyl ether (6 ring) on Chromosorb W column, 6 ft × $^1/_4$ in., or (D) a 10% Carbowax 1500 on Chromosorb W column. The amount of a component was determined from triangulation of its GC peaks relative to the peak area due to an added internal standard to the GC sample of the solvent-stripped product mixture by assuming that all alcoholic materials had the same weight factors. Mass spectra were obtained on a Consolidated Electrodynamics spectrometer Type 21-110B, with typical parameters of ionization voltage (70 V), filament current (3A), total emission current (100 mA), and sample temperature (150 °C). Elemental analyses were performed by Dr. C. S. Yeh and her staff in the microanalytical laboratory at Purdue University.

All reactions involving organometallic reagents were carried out under dry argon or nitrogen atmosphere. Hypodermic syringes and double-ended needles were used as means of transferring the reagent solutions. The allylic Grignard reagents were prepared as usual in such a manner that a 0.5–0.7 M concentration of the reagents could be obtained in more than 90% yield from the reaction of the allylic halides with a fivefold excess of magnesium (Mallinckrodt, AR, maximum impurity: heavy metals, 0.01%; Fe, 0.03%; Mn, 0.15%) for more than 15 h at subambient temperature, and the supernatants were transferred with a Flex needle to dry reagent bottles and stored in a refrigerator. In cases of the insoluble allylic magnesium chlorides in ether, the suspended fine particles could also be transferred and manipulated in the same manner as soluble Grignard reagents. The latter were standardized prior to use by established methods.[26]

General Procedure. To an ether solution of a homoallylic alcohol (10–20 mmol) in a dry 250-mL, side-arm, round-bottom flask equipped with a magnetic stirrer and a condenser connected to a mercury bubbler were added at 0 °C under nitrogen ether and 2.5 equiv of the Grignard reagent (0.5–0.7 M in ether) through the rubber-septumed side arm by syringes, so that the initial concentrations would be 0.1 M in the alcohol and 0.25 M in the Grignard reagent (before formation of alkoxides). The solution was stirred at room temperature for 72 h, and hydrolysis was carried out by slow addition of a saturated ammonium chloride solution. The aqueous layer was extracted with 2 × 25 mL of ether, and the combined extracts were washed with brine and dried over anhydrous potassium carbonate. Solvents were stripped off by a rotary evaporator, and the residue was analyzed and separated by gas chromatography or column chromatography. The yields reported in the respective tables are based on the allylic alcohol *used initially*. The material balance less than 100% probably represents some loss of volatile starting materials during the workup, formation of some byproducts, and analytical errors. The analytical data for isolated pure products are summarized in Tables V–VIII and XI.

Kinetic Study of the Reaction of Crotylmagnesium Bromide with Allyldiethylcarbinol (3). To a flame-dried 1-L, three-necked, round-bottom flask equipped with a magnetic stirrer, a conderser connected to a mercury bubbler, and a rubber-septum inlet to permit withdrawal of aliquots by syringes were added 7.69 g (60 mmol) of allyldiethylcarbinol and 5.129 g of *n*-heptadecane as an internal standard in 317 mL of ether, followed by the addition of 283 mL of 0.53 M (150 mmol) of crotylmagnesium bromide at 0 °C with a double-ended needle. The reaction mixture was stirred at room temperature under nitrogen, and at various time intervals indicated in Table IX, a 30-mL aliquot was taken by a syringe and hydrolyzed with about 30 mL of saturated NH_4Cl. The aqueous layer was extracted with 20 mL of ether, and the combined extracts were dried over hydrous K_2CO_3, concentrated, and analyzed by GC (column B at 175 °C).

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Registry No. **1**, 627-27-0; **2**, 624-97-5; **3**, 1907-46-6; **4**, 36971-15-0; **5**, 754-56-3; **6**, 4165-79-1; **13a** (R = H), 4117-10-6; **13a** (R = Me), 88295-55-0; **13a** (R = Et), 88295-56-1; **13a** (R = *i*-Pr), 88295-57-2; **13a** (R = *t*-Bu), 88295-58-3; **13b** (R = H), 1892-00-8; **13b** (R = Me), 73331-76-7; **13b** (R = Et), 88295-61-8; **13b** (R = *i*-Pr), 88295-62-9; **13b** (R = *t*-Bu), 88295-63-0; **13b** (R = Ph), 88295-64-1; **13c** (R = Me), 18479-58-8; **13c** (R = Et), 88295-67-4; **13c** (R = *i*-Pr), 88295-68-5; **13c** (R = *t*-Bu), 88295-69-6; **13c** (R = Ph), 88295-70-9; **13d** (R = H), 26799-27-9; **13d** (R = Me), 88295-72-1; **13d** (R = *t*-Bu), 88295-73-2; **14a** (R = H), 25913-87-5; **14b** (R = H), 88295-59-4; **14b** (R = Me), 88295-60-7; *erythro*-**14c** (R = H), 88295-65-2; *threo*-**14c** (R = H), 88295-74-3; **14c** (R = Me), 88295-66-3; **14d** (R = H), 88295-71-0; **15** (R = Me), 88295-45-8; **15** (R = Et), 88295-46-9; **15** (R = *i*-Pr), 88295-47-0; **15** (R = *t*-Bu), 88295-48-1; **15** (R = Ph), 88295-54-9; **16** (R = H), 88295-49-2; **16** (R = Me), 88295-50-5; **16** (R = Et), 88302-68-5; **16** (R = *i*-Pr), 88295-51-6; **16** (R = *t*-Bu), 88295-52-7; **17**, 88295-53-8; CH_2=$CHCH_2MgBr$, 1730-25-2; CH_2=$C(CH_3)CH_2MgCl$, 5674-01-1; CH_3CH=$CHCH_2MgBr$, 6088-87-5.

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