Studies in Stereochemistry. XXXVII. Open-Chain Models for 1,3-Asymmetric Induction in Stereospecific Addition Polymerization[1]

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Abstract: An experimental model for 1,3-asymmetric induction in stereospecific addition polymerization has been developed. Addition of phenylmetallics to 4-phenyl-2-pentanone (I) gave a diastereomeric mixture of 2,4-diphenyl-2-pentanols (III) in which the α dominated over the β isomer by factors that ranged from 5 to 1.3, depending on the temperature, the metal, and the solvent (in decreasing order of importance). Addition of methylmetallics to 1,3-diphenyl-1-butanone (II) gave a diastereomeric mixture of 2,4-diphenyl-2-pentanols (III) in which the β dominated over the α isomer by factors that ranged from 1.43 to 1, depending on the metal and the temperature (in decreasing order of importance). Addition of 2-phenyl-1-propylmetallics to acetophenone gave a diastereomeric mixture of 2,4-diphenyl-2-pentanols (III) in which the α to β isomer ratio varied from extremes of 3.2 to 0.82; the extremes were obtained by variation in solvent and by adding titanium tetrachloride. The absolute configurations of the optically active 2,4-diphenyl-2-pentanols (III) were determined by their respective reductions to *meso*- and optically active 2,4-diphenylpentane (IV) by reactions of known stereochemical course. Reduction of the (+)-α-III with 5% palladium on charcoal gave 96% *meso*- and 4% (+)-IV, whereas (+)-β-III gave 30% *meso*- and 70% (+)-IV (reaction occurs with predominant inversion). Reduction of (+)-α-III with Raney nickel gave 8% *meso*- and 91% (+)-IV, whereas (+)-β-III gave 87% *meso*- and 12% (+)-IV. Open-chain models that correlate the stereochemical direction of the addition reactions with the steric interactions in the product-determining transition state for the reaction are suggested. By selection of experimental conditions and the order in which the groups attached to the last formed asymmetric center were introduced into alcohol III, the balance of diastereomers could be changed by factors as high as 7. This degree of stereospecificity is associated solely with 1,3-asymmetric induction and provides evidence that many stereospecific addition polymerizations can be satisfactorily explained on the basis of similar effects.

Three general explanations have been advanced to account for formation of isotactic or syndiotactic polymers in addition polymerization. In the first, the stereochemical memory is seated in the solid organometallic catalyst located at the growing end of the polymer chain, and the incoming olefin sterically adapts to the asymmetric surface of the solid catalyst.[2] In the second explanation, the stereochemical memory is seated in the asymmetric center of the polymer chain closest to the growing end of the chain. Thus, the stereospecificity would reflect 1,3-asymmetric induction at the growing end of the chain.[3] In the third explanation, the stereochemical memory involves sites further down the chain, as well as the asymmetric site closest to the growing end of the chain.[3a,b,4]

Although 1,2-asymmetric induction in addition reactions of acyclic systems has been subjected to systematic study[3a,5] and 1,4-asymmetric induction in addition reactions of α-keto esters[6] has been extensively investigated, little has appeared on 1,3-asymmetric induction in addition reactions in open-chain systems.

The present work was undertaken to determine the plausibility of a 1,3-asymmetric induction explanation for stereospecific addition polymerization. In this

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(2) (a) G. Natta, P. Pino, and G. Mazzanti, *Gazz. Chim. Ital.*, **87**, 528 (1957); (b) C. M. Fontana and R. J. Osborne, *Polymer Sci.*, **47**, 522 (1960); (c) P. Cossee, *Tetrahedron Letters*, **17**, 12, 17 (1960).

(3) (a) D. J. Cram and K. R. Kopecky, *J. Am. Chem. Soc.*, **81**, 2748 (1959); (b) D. J. Cram, *J. Chem. Educ.*, **37**, 317 (1960); (c) D. J. Cram and D. R. Wilson, *J. Am. Chem. Soc.*, **85**, 1245 (1963); (d) J. Furakawa and T. T. Tsuruta, *J. Polymer Sci.*, **46**, 275 (1959); (e) G. I. Fray and R. Robinson, *Tetrahedron*, **18**, 261 (1962); (f) M. Roha, *Advan. Polymer Sci.*, **4**, 353 (1966).

(4) W. E. Goode, F. H. Owens, and W. L. Meyers, *J. Polymer Sci.*, **47**, 75 (1960).

(5) (a) D. J. Cram and F. A. Abd Elhafez, *J. Am. Chem. Soc.*, **74**, 5828 (1952); (b) D. J. Cram and J. D. Knight, *ibid.*, **74**, 5835 (1952); (c) F. A. Abd Elhafez and D. J. Cram, *ibid.*, **74**, 5846 (1952); (d) D. J. Cram, F. A. Abd Elhafez, and H. Weingarten, *ibid.*, **75**, 2293 (1953); (e) D. J. Cram and F. D. Greene, *ibid.*, **75**, 6005 (1953); (f) D, J. Cram, F. A. Abd Elhafez, and H. L. Nyquist, *ibid.*, **76**, 22 (1954); (g) D. J. Cram and J. Allinger. *ibid.*, **76**, 4516 (1954); (h) D. J. Cram and J. E. McCarty, *ibid.*, **76**, 5740 (1954); (i) D. J. Cram and D. R. Wilson, *ibid.*, **85**, 1245 (1963); (j) J. W. Cornforth, R. H. Cornforth, and K. K. Mathews, *J. Chem. Soc.*, 112 (1959); (k) J. H. Stocker, D. Sidisunthorn, B. M. Benjamin, and C. J. Collins, *J. Am. Chem. Soc.*, **82**, 3913 (1960); (l) Y. Gault and H. Felkin, *Bull. Soc. Chim. France*, 1342 (1960); (m) H. Felkin, *ibid.*, 1050 (1956); (n) I. Elphimoff-Felkin and H. Felkin, *ibid.*, 450 (1957); (o) J. Sicher, M. Svoboda, M. Hrda, J. Rudinger, and F. Sorm, *Collection Czech. Chem. Commun.*, **18**, 487 (1953); (p) J. Sicher, *ibid.*, **20**, 1389 (1955); (q) T. Matsumato, T. Nishida, and H. Shirahoma, *J. Org. Chem.*, **27**, 79 (1962); (r) T. Matsumoto and K. Hata, *J. Am. Chem. Soc.*, **79**, 5506 (1957); (s) D. Flĕs and A. Markovac-Prpić, *Croat. Chem. Acta*, **29**, 183 (1957); (t) D. Flĕs and B. Bolenović, *J. Am. Chem. Soc.*, **78**, 3072 (1956); (u) D. Flĕs and B. Bolenović, *Croat Chem. Acta*, **27**, 149 (1955); (v) M. Flĕs, *ibid.*, **35**, 257 (1963); (w) G. J. Karabatsos, *J. Am. Chem. Soc.*, **89**, 1367 (1967); (x) M. Cherest, H. Selkin, and N. Pruddent, *Tetrahedron Letters*, **18**, 2199 (1968); (y) J. Nathieu and J. Raynal, *Bull. Soc. Chim. France*, 1211 (1968).

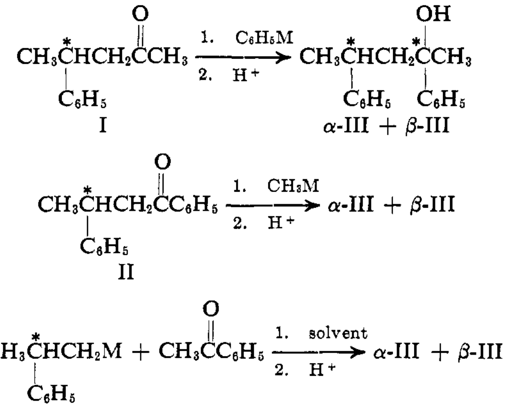
(6) (a) V. Prelog, *Helv. Chim. Acta*, **36**, 308 (1953); (b) V. Prelog and G. Tsatsas, *ibid.*, **36**, 1178 (1953); (c) J. A. Berson and M. A. Greenbaum, *J. Am. Chem. Soc.*, **80**, 445 (1958); (d) I. Ugi, *Z. Naturforsch.*, **20b** (5), 405 (1965).

Table I. Results of Catalytic Hydrogenations of Diastereomers of 2,4-Diphenyl-2-pentanols ((+)-*α*-III and (+)-*β*-III) to (+)- and *meso*-2,4-Diphenylpentane ((+)- and *meso*-IV)

Run	Alcohol: Nature	Alcohol: $[\alpha]^{25}_{546}$,[a] deg	Catalyst	Time, hr	Yield of IV,[b] %	% *meso*-IV[c]	(+)-IV: %[c]	(+)-IV: $[\alpha]^{25}_{546}$,[a] deg
1[d]	(+)-*α*-III	+56.9[e]	Raney Ni	24	8	8	90	+117
2[d]	(+)-*α*-III	+48.8[f]	Raney Ni	1.5	90	8	91	+108
3	(+)-*α*-III	+48.8[f]	Pd–C	24	89	96[g]	4	. . .
4[d]	(+)-*β*-III	+30.3[f]	Raney Ni	1.5	60	87	12	. . .
5	(+)-*β*-III	+34.2[e]	Pd–C	96	94	27	73	+116
6[h]	(+)-*β*-III	+30.3[f]	Pd–C	24	41	30	70	. . .

[a] Carbon tetrachloride, *c* 1–3. [b] Based on weight of product. [c] These per cent compositions were based on vpc analyses (see Experimental Section). Rotations were taken on isomer samples separated by vpc. [d] 1–2 % of an unidentified compound of long retention time on vpc was formed. [e] Alcohols of maximum rotation. [f] Optically impure samples. [g] $[\alpha]^{25}_{546}$ +0.3° (*c* 1.3, carbon tetrachloride). [h] An nmr analysis of the hydrocarbon product gave 28% *meso*-IV and 72% (+)-IV.

and the next paper,[7] three systems based on the addition of organometallic reagents to ketones have been devised and studied. In this paper the steric direction and stereospecificity of addition of phenylmetallics to 4-phenyl-2-pentanone (I), of methylmetallics to 1,3-diphenyl-1-butanone (II), and of 2-phenyl-1-propylmetallics to acetophenone to give diastereomers of 2,4-diphenyl-2-pentanol (III) were examined.



$$\underset{\textstyle\text{I}}{\mathrm{CH_3\overset{*}{C}H(C_6H_5)CH_2C(=O)CH_3}} \xrightarrow[2.\ \mathrm{H^+}]{1.\ \mathrm{C_6H_5M}} \underset{\textstyle\alpha\text{-III} + \beta\text{-III}}{\mathrm{CH_3\overset{*}{C}H(C_6H_5)CH_2\overset{*}{C}(OH)(C_6H_5)CH_3}}$$

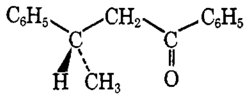
$$\underset{\textstyle\text{II}}{\mathrm{CH_3\overset{*}{C}H(C_6H_5)CH_2C(=O)C_6H_5}} \xrightarrow[2.\ \mathrm{H^+}]{1.\ \mathrm{CH_3M}} \alpha\text{-III} + \beta\text{-III}$$

$$\mathrm{CH_3\overset{*}{C}H(C_6H_5)CH_2M} + \mathrm{CH_3C(=O)C_6H_5} \xrightarrow[2.\ \mathrm{H^+}]{1.\ \text{solvent}} \alpha\text{-III} + \beta\text{-III}$$

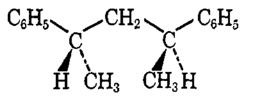
Results

Starting Materials and Products. Racemic ketone II was prepared as before,[8] and racemic ketone I was obtained by an analogous synthesis from 3-phenylbutanoic acid[8] (see Experimental Section). Optically active (+)-II and (−)-II were each brought to maximum rotation by fractional crystallization of the ketones prepared respectively from (+)- and (−)-3-phenylbutanoic acids of about 93% optical purity[9a] and known configurations.[9] Treatment of (+)-II with methylmagnesium iodide gave a mixture of (+)-*α*-III and (+)-*β*-III which were separated from one another by chromatography. The symbols *α* and *β* are experimental designations, the *α* isomer moving faster on thin layer chromatography than the *β* isomer.

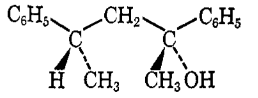
The relative configurations of the *α* and *β* diastereomers of III were established by catalytic reduction of the alcohols by reactions of known stereochemical course to the (+)- and *meso*-2,4-diphenylpentanes (IV), distinguishable by the difference in their optical and nmr spectral properties as well as their vapor-phase chromatographic behavior. Reductions of tertiary benzyl alcohols with Raney nickel catalyst have been demonstrated to proceed with higher retention of configuration,[10] whereas employment of 5% palladium on charcoal as a catalyst led to product of predominantly inverted configuration.[10c,11] The results of the reductions of (+)-*α*-III and of (+)-*β*-III with each catalyst are recorded in Table I. With Raney nickel catalyst, (+)-*α*-III gave 91% (+)-IV and 8% *meso*-IV, and with palladium on charcoal, 4% (+)-IV and 96% *meso*-IV. With Raney nickel catalyst, (+)-*β*-III gave 12% (+)-IV and 87% *meso*-IV, whereas with palladium on charcoal, 73% (+)-IV and 27% *meso*-IV. These data coupled with the known absolute configuration of (+)-II allow configurations to be assigned to (+)-*α*-III, (+)-*β*-III, and (+)-IV. In runs 1 and 5, alcohols of maximum rotation were used, and the samples of (+)-IV obtained had the same rotations. This rotation is probably close to maximum, although the possibility exists that a small amount of epimerization might have occurred at C-4 during the reduction[9c] of 2,4-diphenyl-2-pentanol (III). If so, the two catalysts must have produced the same amount of epimerization which would be fortuitous.[9c]



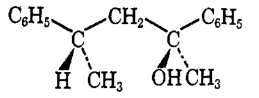
(*S*)-(+)-II



2-(*S*)-4-(*S*)-(+)-IV



2-(*R*)-4-(*S*)-(+)-III
(+)-*α*-III



2-(*S*)-4-(*S*)-(+)-III
(+)-*β*-III

The nmr spectra of *meso*- and (+)-IV were consistent with those previously reported for *meso*- and (±)-IV.[12]

The 2-phenyl-1-propylmetallics which were added to acetophenone to form the isomers of III were prepared from 1-bromo-2-phenylpropane.[13]

Addition of Organometallics to Ketones. The addition reactions of ketones I and II to organometallic reagents to give mixtures of diastereomers of III were always carried out in the presence of excess organo-

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[7] T. J. Leitereg and D. J. Cram, *J. Am. Chem. Soc.*, **90**, 4019 (1968).

[8] S. W. Ela and D. J. Cram, *ibid.*, **88**, 5777 (1966).

[9] D. J. Cram, *ibid.*, **74**, 2137 (1952); (b) D. J. Cram, *ibid.*, **74**, 2149 (1952); (c) D. J. Cram, *ibid.*, **74**, 5518 (1952); (d) V. Prelog and H. Scherrer, *Helv. Chim. Acta*, **42**, 2227 (1959).

[10] (a) D. J. Cram, *J. Am. Chem. Soc.*, **76**, 4516 (1954); (b) W. A. Bonner, *ibid.*, **81**, 3336 (1959); (c) S. Mitsui, Y. Senda, and K. Konno, *Chem. Ind.* (London), **32**, 1354 (1963).

[11] A. M. Khan, F. J. McQuillin, and S. Jardine, *Tetrahedron Letters*, 2649 (1966).

[12] (a) F. A. Bovey, F. P. Hood, III, E. W. Anderson, and L. C. Snyder, *J. Chem. Phys.*, **42**, 3900 (1965); (b) D. Doskocilova and B. Schneider, *J. Polymer Sci.*, **B3**, 213 (1965); (c) see also A. D. Williams, J. I. Brauman, N. J. Nelson, and P. J. Flory, *J. Am. Chem. Soc.*, **89**, 4807 (1967).

[13] R. Adams and J. D. Garber, *ibid.*, **71**, 525 (1949).

Table II. Results of Reactions of Organometallic Reagents with 4-Phenyl-2-pentanone (I) and 1,3-Diphenyl-1-butanone (II) to Give Mixtures of Diastereomers of 2,4-Diphenyl-2-pentanol (α- and β-III)

Run	Starting material Ketone	 Organometallic	Solvent	Temp, deg	Time, hr	Yield of III, %	% comp III α	 β	α-III/β-III
1	I	C_6H_5Li	Ether	35	0.7	100	57	43	1.3
2	I	C_6H_5Li	Ether	0	1.3	97	56	44	1.3
3	I	C_6H_5Li	Ether	−78	10	100	63	37	1.7
4	I	C_6H_5MgBr	Ether	35	0.7	98	69	31	2.2
5	I	C_6H_5MgBr	Ether	0	1.2	98	67	33	2.0
6	I	C_6H_5MgBr	Ether	−78	7	100	76	24	3.2
7	I	C_6H_5MgBr	Ether	−110	6	36	83	17	5.0
8	I	C_6H_5MgBr	Heptane	0	1.2	27^a	72	28	2.6
9	I	C_6H_5MgBr	Heptane	−78	8	0^b	. .	. .	. . .
10	I	$C_6H_5MgBr + TiCl_4{}^c$	Heptane	0	2.5	2	67^d	33^d	2.0
11	I	$TiCl_4$, $C_6H_5MgBr^e$	Heptane	0	1.2	4	70^d	30^d	2.3
12	II	CH_3Li	Ether	0	1.2	96	50	50	1.0
13	II	CH_3MgCl	Ether	0	1.2	12	44	56	0.78
14	II	CH_3MgBr	Ether	0	1.2	98	42	58	0.72
15	II	CH_3MgI	Ether	0	1.2	100	42	58	0.72
16	II	CH_3MgBr	Ether	35	0.7	100	42	58	0.72
17	II	CH_3MgBr	Ether	0	1.2	96	43	57	0.75
18	II	CH_3MgBr	Ether	−78	9	21	41	59	0.70

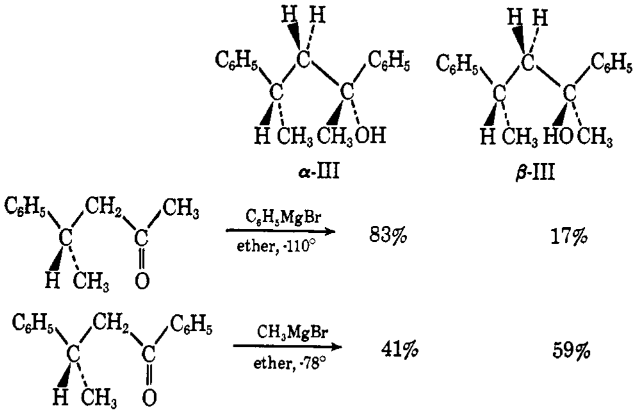
[a] This low yield probably reflects decomposition of the Grignard regent during displacement of ether by heptane. [b] Ketone I was virtually insoluble in heptane at −78°, and this may be responsible for lack of reaction. [c] To a mixture of Grignard and salt, ketone was added. [d] Because of the low yield of III, these values are good to only ±3% instead of the usual ±1%. [e] A mixture of salt and ketone was added to the Grignard reagent.

metallic reagent. In all runs the ketone was added to the organometallic reagent. The yield of III was determined gravimetrically after chromatographic separation of the mixture of α- and β-III from by-products of the reaction. The relative amounts of α- and β-III were determined by nmr spectral analysis of the mixture of isomers obtained from the chromatographic purification. Analysis by this method of known synthetic mixtures of α- and β-III showed that experimental and calculated ratios agreed to within ±1%. With phenyl ketone II as substrate, the effects on the diastereomer ratio (α-III/β-III) of changing the methylmetallic and the temperature were determined. When methyl ketone I was used, the changes of the ratio with changes in the phenylmetallic, the solvent, and temperature were examined. Table II records the results.

In the addition reactions of 2-phenyl-1-propylmetallics to acetophenone, besides the desired alcohols III, 1-phenylethanol (V) was also produced by a competing reduction reaction. The mixtures of diastereomeric alcohols III were separated chromatographically from V, and the yields were determined gravimetrically. The relative amounts of α- and β-III in the chromatographed diastereomeric mixture were determined to ±1% by the nmr spectral method. A large excess of organometallic reagent over acetophenone was always employed, and the ketone was added to the organometallic. The effects on the yields of III and V and on the diastereomer ratio (α-III/β-III) of changes of the organometallic, of solvent, of temperature, and of the presence of transition metal catalysts were examined. Table III records the results.

Discussion

Open-Chain Model for Steric Control of 1,3-Asymmetric Induction. In the products of the reaction of methyl ketone I with phenylmetallic reagents, α-III dominated over β-III by factors of 1.3 to 5. In contrast, in the products from phenyl ketone II and methylmetallic reagents, β-III dominated over α-III by factors of 1.0 to 1.4 (Table II). As in the cases of 1,2- and 1,4-asymmetric induction,[5,6] the configuration of the predominant diastereomer can be altered by inverting the order in which the two groups are introduced to compose the second asymmetric center of the system. The stereochemical direction of the asymmetric induction is formulated for runs 7 and 18, which provide the extremes in product ratios. For sake of simplicity, only one enantiomer of the starting materials and products is shown although racemates were employed.



An open-chain model for steric control of 1,3-asymmetric induction which resembles that employed for 1,2-asymmetric induction is formulated (*vide infra*).[5a] In this model, L (large), M (medium), and S (small) denote the groups attached to the asymmetric center of the starting material in terms of their effective size. The conformation selected for transition state of the product-controlling step is that which places the reacting carbonyl between the two least bulky groups on the adjacent carbon atom. The group that adds to the carbonyl then comes in over the smallest group (S) attached to the asymmetric center of the starting material. The ground-state conformations of the ketone are of no concern, since equilibration is undoubtedly much faster than the addition reaction. Other models can be written that also correlate the data, but this one is suggested because it most resembles that formulated for

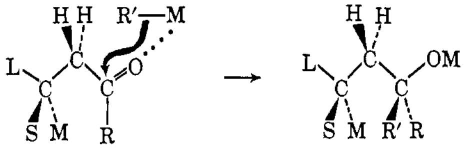
Table III. Results of Reactions of 2-Phenyl-1-propylmetallics (RM) with Acetophenone to Give 1-Phenylethanol (V) and Mixtures of Diastereomers of 2,4-Diphenyl-2-pentanol (α- and β-III)

Run	RM	Catalyst	Solvent	Temp, deg	Time, hr	Yield, % V	Yield, % III	% comp of III α	% comp of III β	α-III/ β-III
19[a]	RLi	None	THF	0	1.2	36	16	50	50	1.0
20	RLi	None	Ether–THF,[b] 1:1	0	1.5	33	18	50	50	1.0
21	RLi	None	Ether–THF,[c] 3:1	0	1.7	42	40	49	51	0.96
22	RLi	None	Ether–THF,[c] 3:1	−78	16	27	32	45	55	0.82
23[a]	RLi	None	Heptane	0	1.2	8	20	52	48	1.1
24	RLi	$TiCl_4$[d]	Heptane	0	1.2	52	5	76[e]	24[e]	3.2
25	RMgBr	None	THF	0	1.2	50	47	50	50	1.0
26	RMgBr	None	Ether–THF,[c] 3:1	−78	18	50	7	60[e]	40[e]	1.5
27	RMgBr	None	Ether	+35	0.7	31	69	54	46	1.3
28	RMgBr	None	Ether	0	1.2	26	57	56	44	1.3
29	RMgBr	None	Ether	−78	12	18	52	62	38	1.6
30[f]	RMgBr	None	Ether	−78	8	14	42	63	37	1.7
31	RMgBr	None	Heptane	+88	0.7	24	76	51	49	1.0
32	RMgBr	None	Heptane	0	1.2	10	90	51	49	1.0
33	RMgBr	None	Heptane	−78	8	2	16	55	45	1.2
34	RMgBr	$TiCl_4$[g]	Heptane	0	1.2	54	7	63[e]	37[e]	1.7
35	RMgBr	$TiCl_4$[g]	Heptane	−78	9	20	0	. .	. .	. . .
36	RMgBr	$TiCl_4$[h]	Heptane	0	3	49	4	72[e]	28[e]	2.6
37	RMgBr	$AlCl_3 + TiCl_4$[g]	Heptane	0	5	38	1	70[e]	30[e]	2.5
38	RMgBr[i]	$AlCl_3 + TiCl_4$[g]	Heptane	0	4	50	35	57	43	1.3
39	RMgBr	$TiCl_3$[g]	Heptane	0	1.3	16	82	52	48	1.1
40	RMgBr	$R_2AlBr + RAlBr_2 + TiCl_4$	Heptane	0	1.3	27	2	62[e]	38[e]	1.6
41	RMgBr	VCl_4[g]	Heptane	0	1.3	25	20	52	48	1.1

[a] Unidentified material was produced, 2% in run 19 and 8% in run 23. [b] Initial solvent composition was 1:1, the final was 3:1 ether–tetrahydrofuran. [c] Initial solvent composition was 3:1, the final was 6:1 ether–tetrahydrofuran. [d] Titanium tetrachloride was added to the organolithium reagent. [e] Because of the low yield of III, the error in the analyses of diastereomers was ±3% instead of the usual ±1%. [f] Reaction mixture was quenched with 15 ml of water. [g] Titanium tetrachloride was mixed with ketone and then added to the Grignard. [h] Grignard was mixed with titanium tetrachloride and ketone was added. [i] Eight equivalents of Grignard reagent was used.

1,2-asymmetric induction. Other experimental tests of the validity of this model are desirable.

Model for steric control of 1,3-asymmetric induction



Dependence of Stereospecificity on Experimental Conditions and Metal of the Organometallic Reagent. In the reactions of ketones I and II to give III (Table II), the stereospecificity of the addition could be varied by as much as a factor of about 4 by changes in the experimental conditions or character of the organometallic. For example, in run 1 ketone I was added to phenyllithium in ether at 35° and gave α-III/β-III = 1.3, whereas in run 7 where phenylmagnesium bromide was employed in ether at −110°, the ratio increased to 5. In the reactions of ketone I, the following generalizations emerge from the data of Table II. (1) Phenyllithium gives lower stereospecificity than phenylmagnesium bromide (compare runs 1 and 4, 2 and 5, 3 and 6). (2) The lower the temperature, the higher the stereospecificity. The best example is found in the reactions of phenylmagnesium bromide in which α-III/β-III values gradually change from 2.2 to 5.0 as the temperature is lowered from +35 to −110° (runs 4–7). (3) The scanty data suggest that heptane may provide slightly more stereospecificity than ether (compare runs 5 and 8). (4) Addition of titanium tetrachloride to the reaction mixture produced negligible effects (compare runs 8 and 11).

In addition of methylmetallics to phenyl ketone II (Table II), α-III/β-III values are much less subject to variation. Visible in the data are the following generalizations. (1) Methyllithium shows no stereospecificity, and the three methylmagnesium halides (chloride, bromide, and iodide) show about the same specificity (compare runs 12–15). (2) With methylmagnesium bromide changes in temperature from +35 to −78° have little effect on the stereospecificity (runs 16–18). This result is in direct contrast to the relatively large effect of temperature observed with phenylmagnesium bromide and methyl ketone I. The source of this difference in behavior is obscure.

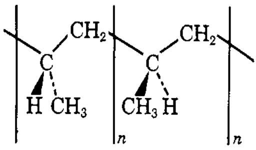
In the reactions of 2-phenyl-1-propylmetallics with acetophenone to give the diastereomers of III (Table III), the ratio of α-III/β-III varied from extremes of 0.82 (run 22) to 3.2 (run 24). The data provide the following generalizations. (1) In the absence of added transition metal salt, the alkyllithium reagent gave ratios of 0.82 to 1.1 which changed little with solvent or temperature (runs 19–23). (2) With alkylmagnesium bromide in the absence of transition metal salts, substantial changes in solvent and temperature produced changes in α-III/β-III of only 1.0 to 1.7 (runs 25–38). (3) Addition of titanium tetrachloride to the organometallic in heptane increased the ratio by factors up to 3. Thus, in the absence of salt the alkyllithium gave a value of 1.1 (run 23), whereas with the salt added to the organometallic the ratio increased to 3.2 (run 24). In the absence of salt the alkylmagnesium bromide gave a value of 1 (run 32), which increased to 2.6 when titanium tetrachloride was added to the reagent (run 36). When the salt was added to the ketone first, the change in ratio was much less pronounced. (4) In general, the higher the value of α-III/β-III, the higher the ratio of *reduction* to *addition* product (V *vs.* III).

Models for Stereospecific Addition Polymerization. The observations of 1,3-asymmetric induction in these addition reactions have an important bearing on the character of the stereochemical component of the mechanism for stereoregular addition polymerization. Five questions will be treated.

(1) Are the factors which measure the stereospecificity in our addition reactions of the same order of magnitude as those observed in addition polymerization leading to stereoregular polymers? Considerable evidence indicates that stereoregular polymers contain heterotactic units. Both isotactic and syndiotactic methyl methacrylate polymers contain up to 20% heterotactic impurities.[14] Flory, *et al.*, have concluded that 5–10% of stereoirregular units contaminate typical isotactic polypropylene.[15] This degree of irregularity brought theoretical calculations and experimental values of certain physical properties into agreement. On the basis of nmr analysis Stehling placed 5% as the upper limit for the presence of syndiotactic units in isotactic polypropylene.[16] Natta, *et al.*, on the basis of the absence of a peak corresponding to a syndiotactic impurity in the 100-Mc nmr spectrum of selectively deuterated isotactic polypropylene, suggested that such impurities could not exceed 0.5%.[17] Although the earlier work[17a] was questioned by Flory and Baldeschwieler,[18] the later results[17b] appear unequivocal.

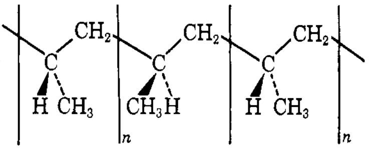
Thus with the exception of the formation of isotactic polypropylene, the balance of evidence points to a stereospecificity in addition polymerization of the same order of magnitude as we have observed in our addition reactions. This fact constitutes permissive evidence that the stereochemical memory in most polymerizations is in the asymmetric unit closest to the end of the growing chain, and supports the 1,3-asymmetric induction hypothesis for stereospecific polymerization.

(2) What is the character of the stereochemical imperfections in stereoregular polymers such as isotactic polypropylene? Formulas VI and VII summarize the two simplest possibilities. In VI, a *stereoblock* polymer is drawn in which an imperfection results in a change of configuration for a sizable portion of the chain. This type of polymer is predicted if the stereochemical memory resides in the asymmetric center closest to the end of the growing chain. Formula VII depicts a polymer in which the configurational imperfections are corrected as the chain grows so that the bulk of the asymmetric centers of the chain have the same configurations. This type of polymer is predicted if the stereochemical memory resides in the metal surface at the very end of the growing chain and if only a single metal site is used in the development of each chain. Flory, *et al.*,[15] have concluded that isotactic polypropylene possesses a stereoblock character. This conclusion supports the 1,3-asymmetric induction hypothesis for sterospecific polymerization. However, this conclusion rested on the assumption of a higher degree of configurational imperfections than appears valid[17b] for the most stereoregular samples of polypropylene.



VI

stereoblock isotactic polypropylene

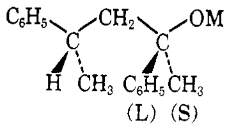


VII

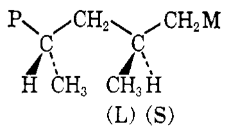
self-correcting imperfect isotactic polypropylene

(3) Are the kinds of experimental variables that effect the stereospecificity in polymerization related to those that effect stereospecificity in our addition reactions? In the addition reactions of ketones I and II, the character of the metal, the temperature, and the solvent were the important experimental parameters. These same changes in reaction conditions were found to be important in controlling the stereochemical course of anionic addition polymerizations.[19] The addition of 2-phenyl-1-propylmetallics to acetophenone resembles in a formal sense the anionic polymerization of propylene. The increase in stereospecificity was striking when titanium tetrachloride was added as a catalyst for the addition to the ketone. This same catalyst provides isotactic polypropylene.[20]

(4) How does the stereochemical direction of asymmetric induction in our addition reactions correlate with the direction observed in similar stereoregular 1,3-addition polymerizations? A possible comparison is that of the addition of 2-phenyl-1-propyllithium to acetophenone with the polymerization of propylene. In titanium tetrachloride catalyzed polymerizations of propylene at low temperatures in a heterogeneous reaction, isotactic polymer is formed.[20] Syndiotactic polymer predominates when higher temperatures and titanium tetrachloride are employed or when the reaction is conducted homogeneously with a vanadium tetrachloride catalyst.[21] When 2-phenyl-1-propyllithium is added to acetophenone in the presence of titanium tetrachloride, the α configuration predominated by the largest factor (3.2) observed (run 24). From a stereoelectronic point of view, this configuration of our predominant organometallic addition product resembles the configuration of a growing syndiotactic polypropylene chain. Formulas VIII and IX indicate the character of the configurational relationships. When 2-phenyl-1-propyllithium was added to acetophenone in 3:1 ether–tetrahydrofuran, the β isomer predominated by a small factor (1.2) in run 22. This isomer most resembles isotactic polymer from a stereoelectronic



VIII, α configuration



IX, syndiotactic configuration

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(14) F. A. Bovey and G. C. D. Tiers, *J. Polymer Sci.*, **44**, 173 (1960).

(15) P. J. Flory, J. E. Mark, and A. Abe, *J. Am. Chem. Soc.*, **88**, 639 (1966).

(16) F. C. Stehling, *J. Polymer Sci.*, **A2**, 1815 (1964).

(17) (a) G. Natta, E. Lombardi, A. L. Segre, A. Zembelli, and A. Marinangeli, *Chim. Ind.* (Milan), **47**, 378 (1965); (b) A. L. Segre, *Macromolecules*, **1**, 93 (1968).

(18) P. J. Flory and J. D. Baldeschwieler, *J. Am. Chem. Soc.*, **88**, 2873 (1966).

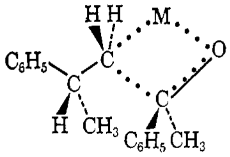
(19) (a) A. Zembelli, G. Natta, and I. Pasquon, *J. Polymer Sci.*, **C4**, 411 (1963); (b) T. G. Fox, B. S. Garrett, W. E. Goode, S. Gratch, J. F. Kincaid, A. Apell, and J. D. Stroupe, *J. Am. Chem. Soc.*, **80**, 1769 (1958); (c) J. D. Stroupe and R. E. Hughes, *ibid.*, **80**, 2341 (1958).

(20) (a) G. Natta, *Atti Accad. Nazl. Lincei, Mem. Classe Sci. Fis. Mat. Nat., Sez. II*, **4**, 61 (1955); *J. Polymer Sci.*, **16**, 143 (1955); (b) G. Natta, P. Pino, P. Corradini, F. Danusso, E. Mantica, G. Mazzanti, and G. Moraglio, *J. Am. Chem. Soc.*, **77**, 1708 (1955).

(21) G. Natta, A. Zambelli, G. Langi, I. Pasquon, E. R. Mognaschi, A. L. Segre, and P. Centola, *Makromol. Chem.*, **81**, 161 (1965).

point of view. The fact that either type of configuration can be made to predominate in both our additions and in the addition polymerizations supports the view that the same factor controls the steric course, namely, 1,3-asymmetric induction. The greater stereospecificity observed in polymerization leading to isotactic polymer (over that of our additions) might reflect a potentiation of steric effects by compression due to the steric requirements of the coiled polymer chain and the solid catalyst surface.

A model for the formation of the α isomer in our addition reactions to acetophenone is formulated (X). The formula applies to the predominant conformation of the transition state and again places the oxygen, the metal, and its ligands in the least hindered conformation.



X

Experimental Section

General. Nuclear magnetic resonance (nmr) spectra were recorded with a Varian-A-60 instrument. Hexadeuterated (97–98%) dimethyl sulfoxide (DMSO) was used as a solvent for all analytical spectra. For other nmr spectra spectral grade carbon tetrachloride with 2–5% added tetramethylsilane was used. All melting points are corrected. All boiling points are uncorrected. Rotations were taken on a Perkin-Elmer Model 141 polarimeter at a temperature of 25° and a wavelength of 546 mμ. Spectral grade carbon tetrachloride was used as a solvent. Thin-layer chromatograms (tlc) were taken on silica gel G plates and developed with 10% phosphomolybdic acid in ethanol unless otherwise indicated.

Starting Materials. All of the racemic ketones had been prepared previously. Racemic 4-phenyl-2-pentanone (I) was prepared by adding methyllithium to 3-phenylbutanoic acid[9a] in ether and was purified by chromatography on silica gel in about 90% yield. This material exhibited one spot on tlc with 1:4 ether–pentane on silica gel plates and gave after distillation $n^{25}\mathrm{D}$ 1.5050 (lit.[22] $n^{25}\mathrm{D}$ 1.5048).

Preparation of racemic 1,3-diphenyl-1-butanone (II) has been described previously in detail.[8] Material of mp 72.5–73.5° was employed. Optically active (+)-II, mp 46.9–48.7°, $[\alpha]$ +17.4° (c 7.5, carbon tetrachloride), was prepared from (+)-3-phenylbutanoic acid of about 93% optical purity by the same procedure. The product was brought to maximum rotation by fractional crystallization from hexane. One recrystallization gave mp 49.2–50.1°, $[\alpha]^{25}{}_{546}$ +18.8° (c 1.0, carbon tetrachloride). Two more recrystallizations from hexane gave mp 49.3–49.9°, $[\alpha]^{25}{}_{546}$ +18.9°, $[\alpha]^{25}\mathrm{D}$ +14.4° (c 2.6, carbon tetrachloride). The melting point on an admixture of II of maximum optical rotation with that of racemic material was mmp 47.3–67.0°. Optically active (−)-II, mp 46.7–49.0°, $[\alpha]$ +17.4° (c 2.2, carbon tetrachloride), was also prepared by the same method[8] from (−)-3-phenylbutanoic[9a] acid of about 93% optical purity. One recrystallization from hexane gave mp 49.0–49.5°, $[\alpha]$ −19.0° (c 1.7, carbon tetrachloride). Two more recrystallizations gave mp 49.3–49.7°, $[\alpha]^{25}{}_{546}$ −18.9°, $[\alpha]^{25}\mathrm{D}$ −14.6° (c 1.8, carbon tetrachloride). Kline and Brewster[23] report (−)-II, mp 45–55°, $[\alpha]^{22}\mathrm{D}$ −12.2° (carbon tetrachloride), and (+)-II, mp 48–70°, $[\alpha]^{25}\mathrm{D}$ +10.6° (carbon tetrachloride).

By the procedure of Adams and Garber,[13] 1-bromo-2-phenylpropane was prepared in 52% yield, bp 57–58° (0.28 mm), $n^{25}\mathrm{D}$ 1.5469 (lit.[13] $n^{25}\mathrm{D}$ 1.5462). *Anal.* Calcd for $C_9H_{11}Br$: C, 54.29; H, 5.57. Found: C, 54.47; H, 5.49.

2,4-Diphenyl-2-pentanols (α-III and β-III). A solution of Grignard reagent was prepared under nitrogen from 2.72 g (0.112 g-atom) of magnesium and 15.9 g (0.112 mol) of methyl iodide in 150 ml of ether. To this solution was added a solution of 1,3-diphenyl-1-butanone, 5.00 g (0.0223 mol), in 100 ml of ether at room temperature over the space of 30 min. The reaction mixture was then heated to reflux for about 40 min, cooled, and hydrolyzed with a concentrated aqueous solution of ammonium chloride. The mixture was transferred to a separatory funnel and shaken, and the phases separated. The aqueous phase was washed with two 150-ml portions of ether. The combined organic phases were washed with 200 ml of water and two 200-ml portions of saturated sodium chloride and then were dried. The ether was evaporated on the steam bath, and the residues were transferred to a tared flask. The crude yield was 5.68 g (contaminated with solvent).

This material gave infrared and nmr spectra in accord with a mixture of alcohol diastereomers (see below). By tlc no trace of starting ketone was visible; tlc did show, in a number of solvent systems (4:1 pentane–ether, 9:1 chloroform–pentane, 85:15 pentane–ethyl acetate), two spots of roughly equal intensity (iodine chamber) which were both slower moving than starting ketone. In 4:1 pentane–ether the retardation factors of the two spots were 0.36 and 0.28 (ratio equal to 1.3). A portion of this material was submitted to flash distillation. By tlc and nmr the distilled material did not appear to differ from undistilled material. When the diastereomeric alcohols were subjected to vpc conditions, decomposition resulted.

A part of the mixture of diastereomeric alcohols was subjected to elution chromatography on 600 g of 80–200 mesh silica gel. The column was prepared in pure pentane and measured 70 cm in height and 4.2 cm in diameter. The crude mixture of alcohols (4 g) was dissolved in about 25 ml of pentane and placed on the column. Fractions were collected as the solvent was varied from 0, 1, 2, 5, and 10% ether in pentane. In this way 1.40 g of pure isomer α-III and 1.54 g of pure isomer β-III were collected.

A portion of each isomer was flash distilled; by tlc and nmr distilled material was identical with undistilled material. Superposition of the nmr spectra of the two isomers produced a spectrum that was identical with that of the original mixture. *Anal.* Calcd for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found for α-III: C, 85.03; H, 8.38. Found for β-III: C, 85.12; H, 8.18.

Optically Active 2,4-Diphenyl-2-pentanols ((+)-α-III and (+)-β-III). By the above procedure, (+)-II, optically impure ($[\alpha]^{25}{}_{546}$ +16.6° (c 3.2, carbon tetrachloride), was converted to a mixture of (+)-α-III and (+)-β-III, which were separated (see above) to give optically impure (+)-α-III, $[\alpha]^{25}{}_{546}$ +49.0° (c 1.4, carbon tetrachloride), and (+)-β-III, $[\alpha]^{25}{}_{546}$ +30.3° (c 1.6, carbon tetrachloride). Likewise, (+)-II, $[\alpha]^{25}{}_{546}$ +18.9° (c 1, carbon tetrachloride), was converted to (+)-α-III, $[\alpha]^{25}\mathrm{D}$ +56.9° (c 1.1, carbon tetrachloride). All samples were oils. *Anal.* Calcd for $C_{17}H_{20}O$: C, 84.95; H, 8.39. Found for (+)-α-III: C, 85.10; H, 8.29. Found for (+)-β-III: C, 85.00; H, 8.31.

Reduction of (+)-α-2,4-Diphenyl-2-pentanol ((+)-α-III) with Hydrogen on 5% Palladium on Charcoal (Run 3). A mixture of 0.157 g (0.000655 mol) of (+)-α-III, $[\alpha]^{25}{}_{546}$ +48.8° (c 1.5, carbon tetrachloride), 25 ml of absolute ethanol, and 0.100 g of 5% palladium on charcoal was magnetically stirred at 25° under a hydrogen atmosphere for 24 hr. The mixture was filtered through a pad of Celite, and the filtrate was evaporated on a rotatory evaporator. The residue on tlc (5% ether–pentane) exhibited only two spots, the slower moving of which was starting material. The hydrocarbon and alcohol were separated by chromatography on 20 g of silica gel, and the hydrocarbon was eluted with pentane, 0.130 g (89%). The per cent composition of this material was determined by vpc on a 6 ft × 0.5 in. column of 15–20% Carbowax 20M on 60–80 Firebrick at 165° and a helium pressure of 15 psi in a Perkin-Elmer Model 154 machine with a thermal conductivity detector. The retention times for *meso*- and (+)-IV were 57 and 70 min, respectively. Integration of the peak areas gave 4% (+)-IV and 96% *meso*-IV.

The *meso* isomer was $[\alpha]^{25}{}_{546}$ +0.3° (c 1.3, carbon tetrachloride). The nmr spectrum of the substance was identical with that reported for the compound.[12c] *Anal.* Calcd for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 90.87; H, 8.97.

Reduction of (+)-β-2,4-Diphenyl-2-pentanol ((+)-β-III) with Hydrogen on 5% Palladium–Charcoal (Run 5). From 0.325 g (0.00136 mol) of (+)-β-III, $[\alpha]^{25}{}_{546}$ +34.2° (c 1.5), there was obtained by the above procedure (4 days) 0.282 g (94%) of a hydrocarbon mixture, $[\alpha]^{25}{}_{546}$ +85.7° (c 1.1). Analysis (vpc) indicated the presence of 73% (+)-IV and 27% *meso*-IV. The two isomers were separated by preparative vpc to give (+)-IV, $[\alpha]^{25}{}_{546}$ +116° (c 0.8). *Anal.* Calcd for $C_{17}H_{20}$: C, 91.01; H, 8.99. Found: C, 90.95; H, 9.05. Run 6 was conducted in a similar fashion.

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[22] C. L. Arcus and T. J. Howard, *J. Chem. Soc.*, 673 (1961).

[23] J. H. Brewster and M. W. Kline, *J. Am. Chem. Soc.*, **74**, 5179 (1952).

Reduction of (+)-α-2,4-Diphenyl-2-pentanol ((+)-α-III) with W-1 Raney Nickel (Run 1). In an inert atmosphere, 0.312 g (0.00130 mol) of (+)-α-III, $[\alpha]^{25}_{546}$ +56.9° (*c* 1.2), was stirred for 24 hr at reflux with 40 ml of absolute ethanol and 1 g of W-1 Raney nickel. Analysis by vpc of the hydrocarbon mixture obtained after chromatography (0.022 g or 8%) gave 90% (+)-IV, 8% *meso*-IV, and 2% of unidentified material. The (+)-IV obtained by preparative vpc gave $[\alpha]^{25}_{546}$ +117° (*c* 0.5). Run 2 was similarly conducted with fresher W-1 Raney nickel[24] to give a 90% yield of hydrocarbon (see Table I).

Reduction of (+)-β-2,4-Diphenyl-2-pentanol ((+)-β-III) with W-1 Raney Nickel (Run 4). Application of the above procedure to (+)-β-III, $[\alpha]^{25}_{546}$ +30.3° (*c* 1.5), produced hydrocarbon in 60% yield after chromatography. Analysis (vpc) of the material gave 87% *meso*-IV, 12% (+)-IV, and 1% unknown material.

Analysis of the Diastereomeric Mixtures of 2,4-Diphenyl-2-pentanols (III). The reaction products (III) from the ketones and organometallics were chromatographed with 150 parts of silica gel to 1 part of crude III. The column was developed with mixtures of ether–pentane ranging in composition from 0:100 to 10:90. The diastereomeric alcohols were eluted as a single fraction well separated from by-products and were analyzed by nmr spectroscopy. Solvent was removed from all fractions on a rotary evaporator. An approximately 30 mol % solution of the mixture of α- and β-III was dissolved in hexadeuterated dimethyl sulfoxide. The solvent was used as an internal standard and exhibited a peak at τ 7.48. The hydroxyl group singlets and the methine methyl doublets for the diastereomers had sufficiently different chemical shifts to allow integrations of the absorptions and calculation of the amounts of α- and β-III. The nmr spectrum (in τ values) of α-III gave an aromatic multiplet at 2.24–2.89 rising to a singlet at 2.71 (ten hydrogens), a singlet at 5.10 (one hydrogen) assigned to the hydroxyl hydrogen, a quartet at 6.64–7.06 (one hydrogen) assigned to the methine hydrogen, a multiplet at 7.67–7.92 (two hydrogens) assigned to the methylene hydrogens, a singlet at 8.49 (three hydrogens) assigned to the methyl group adjacent to the hydroxyl group, and a doublet at 8.79–9.06 (three hydrogens) assigned to the methyl group adjacent to hydrogen. The nmr spectrum (in τ values) of β-III was as follows: an aromatic multiplet at 2.26–3.06 (ten hydrogens), a singlet at 5.02 (one hydrogen), a quartet at 7.02–7.47 (one hydrogen), a multiplet at 7.67–7.89 (two hydrogens), a singlet at 8.42 (three hydrogens), and a doublet at 8.52–8.79 (three hydrogens). When known amounts of the two diastereomers were mixed together in different proportions and analyzed, the experimental and calculated ratios agreed to within ±1%.

In those runs in which acetophenone was added to 2-phenyl-1-propylmetallics, the product III was isolated and analyzed as in the other runs. The 1-phenylethanol (V) produced was washed from the column with 1:1 ether–pentane, the solvent was evaporated, and the alcohol was weighed.

Reaction of Phenyllithium with 4-Phenyl-2-pentanone (I) (Run 2). A 100-ml, three-necked, round-bottomed flask was fitted with a reflux condenser, a pressure-equalizing dropping funnel, and a magnetic stirrer. A stream of dry nitrogen was passed through the system which was dried with a hot-air gun. A serum cap was placed over the third neck. About 10 ml of dry ether was placed in the dropping funnel, and 0.450 g (0.00278 mol) of 4-phenyl-2-pentanone was added. Finally, an additional 15 ml of ether was added by means of a syringe. To the flask was added 20 ml of ether and 7.5 ml (0.00750 mol) of a 1.0 *M* solution of phenyllithium in ether (Columbia Organic Chemical Co.). The flask was cooled to 0° by means of an ice bath, and the substrate solution was added dropwise over a 10-min period to the stirring organometallic solution. An extra 2 ml of ether was used to complete the addition. Then, the contents of the flask were stirred at 0° under a positive pressure of dry nitrogen for a total of 70 min. Water (20 ml) was placed in the funnel and added dropwise to the flask. The aqueous layer was separated and extracted with 50 ml of ether. The ether layers were combined, dried, and evaporated under reduced pressure. The sample was prepared for analysis as described above.

Run 3 was conducted similarly except that both ketone and organometallic were cooled to −78° before mixing. The reaction was quenched with 10 ml of reagent methanol.

Run 1 was similarly made except the addition of reactants was carried out at 35°, and the reaction was quenched with 10 ml of water.

Run 12 employed 6.5 ml (0.0111 mol) of 1.7 *M* methyllithium in ether (Foote Mineral Co.) and 0.480 g (0.00214 mol) of 1,3-diphenyl-1-butanone and was conducted as in run 2.

Reaction of Phenylmagnesium Bromide with 4-Phenyl-2-pentanone (I) in Ether (Run 5). Under nitrogen in a dry flask was placed 0.250 g (0.0103 g-atom) of magnesium. By means of a syringe and serum cap was added 15 ml of anhydrous ether, and through a dropping funnel was added in 10 ml of dry ether 1.62 g (0.0103 mol) of bromobenzene. After reaction the mixture was cooled to 0°, and 0.400 g (0.00247 mol) of I in 10 ml of dry ether was added dropwise with stirring in a nitrogen atmosphere. The residual ketone was washed into the flask with 5 ml of ether, and after 70 min at 0° the reaction was quenched with 20 ml of water. The product III was chromatographed and analyzed as described above.

Runs, 4, 6, and 7 were modeled after run 5 except for the temperature and time differences. In the low-temperature runs, the ether solution of ketone was cooled before addition. The low-temperature runs were quenched with reagent methanol, and the high-temperature runs with water.

Reaction of Phenylmagnesium Bromide with 4-Phenyl-2-pentanone (I) in Heptane (Run 8). The Grignard reagent was prepared from 0.810 g (0.00515 mol) of bromobenzene and 0.125 g (0.00515 g-atom) of magnesium in 15 ml of ether. After reaction, 20 ml of heptane was added, and the mixture was heated to 90° for 1 hr under a flow of dry nitrogen which carried solvent from the flask. Heptane was added to give a volume of 15 ml and the flask was cooled to 0°. Ketone I, 0.200 g (0.00124 mol) in 15 ml of heptane, was added dropwise to the stirring Grignard solution. After 70 min the reaction was quenched with 15 ml of water.

Run 9 was similarly conducted except for the temperature, time, and the quenching of the mixture with methyl alcohol.

Reaction of the Complex of 4-Phenyl-2-pentanone (I) and Titanium Tetrachloride with Phenylmagnesium Bromide in Heptane (Run 11). The Grignard reagent was prepared as in run 8 in heptane. A solution of 0.16 ml (0.0014 mol) of titanium tetrachloride in 7 ml of heptane was added to 0.200 g (0.00124 mol) of ketone I in 8 ml of heptane. A dark yellow oil separated from the heptane solution. The heterogeneous solution was added at 0° to the Grignard reagent with stirring. After 70 min the mixture was quenched with 15 ml of water.

Reaction of 4-Phenyl-2-pentanone with a Mixture of Phenylmagnesium Bromide and Titanium Tetrachloride in Heptane (Run 11). The Grignard reagent was prepared as in run 8 from 0.250 g (0.0103 g-atom) of magnesium and 1.62 g (0.0103 mol) of bromobenzene. The solution was concentrated to a volume of 10 ml of heptane. Titanium tetrachloride (0.16 ml or 0.0014 mol) in 10 ml of heptane was added to the stirred reagent at 0°. A solution of 0.200 g (0.00124 mol) of ketone in 15 ml of ether was added dropwise at 0° and stirring was continued for 2.5 hr. The mixture was quenched with 15 ml of water.

Reaction of Methylmagnesium Bromide with 1,3-Diphenyl-1-butanone (II) (Run 14). To a dried flask under pure dry nitrogen was added 0.270 g (0.0111 g-atom) of magnesium turnings and 15 ml of dry ether. Methyl bromide gas was bubbled through this mixture until all of the magnesium had reacted. The system was kept under a positive pressure of dry nitrogen at all times. A solution of 0.500 g (0.00223 mol) of ketone II in 20 ml of dry ether was added dropwise with stirring; the temperature was kept at 0°. An additional 3 ml of ether was used to rinse the residual ketone into the flask. After 70 min the reaction was quenched with 20 ml of water.

Runs 16, 17, and 18 were similarly conducted except for the temperature and time differences. With the low-temperature reactions, the mixtures were quenched with methanol.

Run 13 involved methylmagnesium chloride and was carried out as was run 14 except that methyl chloride was employed, and its reaction with magnesium was initiated by addition of a small amount of 1,2-dibromoethane.

Run 15 was carried out as was run 14 except that methyl iodide was substituted for methyl bromide.

Procedure for Drying Tetrahydrofuran. The solvent was refluxed over lithium aluminum hydride and under dry nitrogen for 24 hr, and approximately 60 ml was placed in a 100-ml, one-necked flask containing small particles of potassium. After the flask was attached to a vacuum line, the contents were frozen by means of a liquid nitrogen bath and degassed. The solvent was then warmed to room temperature, stirred for 24 hr, frozen, and degassed again. This material was distilled into a flask containing small particles of potassium and a small amount of naphthalene. The distillation was performed by cooling the second flask with a liquid nitrogen bath and allowing the ether vapors from the original flask to con-

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[24] L. W. Covert, *J. Am. Chem. Soc.*, **54**, 4116 (1932).

dense. On warming to room temperature a deep green color developed, indicating the radical anion of naphthalene. Finally, the solvent was distilled by the above method into a vessel containing molecular sieves. This vessel was flushed with dry nitrogen after the distillation and was removed from the vacuum line, and a serum cap was quickly placed over the open neck. Portions of solvent were removed from this vessel by means of a syringe.

Reaction of Acetophenone with 2-Phenyl-1-propyllithium in Tetrahydrofuran (Run 19). A 100-ml, three-necked, round-bottomed flask was fitted with a pressure-equalizing dropping funnel, a condenser, and a magnetic stirring device. The system was flushed with nitrogen and dried. After cooling 10 ml of dry tetrahydrofuran and 0.053 g (0.0074 g-atom) of lithium wire were placed in the flask. A positive pressure of nitrogen was maintained throughout the entire reaction. With vigorous stirring 1.48 g of 2-phenyl-1-bromopropane in 10 ml of tetrahydrofuran was added, and the flask was warmed slightly to initiate the reaction. When all the lithium had reacted, the flask was cooled to 0° and 0.200 g of acetophenone in 20 ml of tetrahydrofuran was added dropwise. After 70 min, 15 ml of water was used to quench the reaction. The aqueous phase was extracted twice with 30-ml portions of methylene chloride. The organic layers were combined, washed with 30 ml of water, dried, and evaporated. The crude material was purified and analyzed in the usual way.

Runs 30, 21, and 22 were similarly conducted except that, after the lithium reagent was prepared in tetrahydrofuran, sufficient ether was added to provide the desired composition. The temperatures and times are recorded in Table III.

Reaction of Acetophenone with 2-Phenyl-1-propyllithium in Heptane (Run 23). A 100-ml, three-necked, round-bottomed flask was fitted with a pressure-equalizing dropping funnel, a reflux condenser, and a magnetic stirring device. The system was flushed with dry nitrogen and dried. A positive pressure of nitrogen was kept throughout the experiment. After cooling, 1.48 g (0.0074 mol) of 2-phenyl-1-bromopropane in 15 ml of ether was placed in the flask and warmed to approximately 50°. Then, 3 ml (0.006 mol) of a freshly prepared 2 *N* *t*-butyllithium in hexane solution and 5 ml of heptane was added dropwise to the warm, stirring bromide solution. After 45 min the flask was allowed to cool and was immersed in an ice bath. A solution of 0.200 g (0.0017 mol) of acetophenone in 15 ml of heptane was added dropwise. The reaction was quenched after 70 min with 15 ml of water.

Reaction of Acetophenone with 2-Phenyl-1-propyllithium in Heptane at 0° in the Presence of Titanium Tetrachloride (Run 24). The lithium reagent was prepared from 1.48 g of bromide and 3.6 ml of 2 *N* *t*-butyllithium in hexane in 20 ml of heptane. The organometallic solution was cooled to 0° and 0.21 ml (0.0017 mol) of titanium tetrachloride in 5 ml of heptane was added. After this heterogeneous mixture was stirred for 15 min, 0.200 g of acetophenone in 15 ml of heptane was added dropwise. After 70 min quenching was effected with 15 ml of water.

Reaction of Acetophenone with 2-Phenyl-1-propylmagnesium Bromide in Ether (Run 28). To 0.180 g (0.0074 g-atom) of magnesium in a dry flask in an atmosphere of dry nitrogen was added first 10 ml of dry ether followed by 1.48 g (0.0074 mol) of 1-bromo-2-phenylpropane in 5 ml of dry ether. Another 5 ml of ether was used to rinse the remaining bromide into the flask. After reaction was complete, a solution of 0.200 g (0.0017 mol) of acetophenone in 15 ml of ether was added dropwise to a stirred solution of the Grignard reagent at 0°. The residual ketone was washed into the flask with 5 ml of additional dry ether. After the prescribed time (Table III) the reaction mixture was submitted to the usual isolation procedures.

Runs 27–30 were similarly conducted except that the temperature and reaction times were adjusted (Table III).

Run 25 was similarly carried out except that tetrahydrofuran was employed as solvent, and the temperatures and time were adjusted (Table III).

Run 26 was made similarly except that the Grignard reagent was prepared in an ether–tetrahydrofuran mixture, and the ketone was added in an ether solution. Table III records the temperature and time of reaction.

Reaction of Acetophenone with 2-Phenyl-1-propylmagnesium Bromide in Heptane (Run 32). The Grignard reagent was prepared in ether. Heptane (15 ml) was added, and the flask was heated to approximately 90° for 1 hr while a stream of dry nitrogen carried the ether vapors from the reaction vessel. The volume of heptane was again brought to 15 ml. The flask was immersed in an ice bath, and a solution of 0.200 g of acetophenone in 15 ml of heptane was added dropwise by means of the funnel. After 70 min 15 ml of water was added and the product isolated and analyzed as before.

Runs 31 and 33 were similarly conducted except for time and temperature differences (Table III).

Reaction of Acetophenone with 2-Phenyl-1-propylmagnesium Bromide in Heptane in the Presence of Titanium Tetrachloride (Run 34). After preparation of the organometallic in 15 ml of heptane, 0.200 g of acetophenone in 10 ml of heptane was placed in the funnel. Another pressure-equalizing dropping funnel was attached to the first, which was fitted with a magnetic stirring device. In the second funnel were placed 5 ml of heptane and 0.21 ml (0.0017 mol) of titanium tetrachloride by means of a syringe. This solution was added to the stirring substrate solution, and a yellow, viscous liquid separated. After the organometallic solution had been cooled to 0°, the agitated yellow oil in heptane was added dropwise. After 70 min 15 ml of water was used to quench the reaction. The purification and analysis procedures were described earlier.

Run 35 was similarly conducted except for temperatures and times (Table III).

In run 36, a solution of 0.21 ml of titanium tetrachloride in 5 ml of heptane was added to the Grignard reagent which had been prepared in heptane as before and cooled to 0°. A dense, brown, heterogeneous mixture separated. Acetophenone (0.200 g) in 15 ml of heptane was added dropwise, and the reaction was quenched after 3 hr of stirring at 0° with 15 ml of water.

Run 37 was similarly conducted except that 0.226 g (0.0017 mol) of dry aluminum chloride was added to the organometallic solution before addition of the titanium chloride solution. Table III records the times and temperatures.

Run 38 was conducted as was run 37 except that 8 equiv of Grignard reagent/equiv of ketone was used instead of 4.

Reaction of Acetophenone with 2-Phenyl-1-propylmagnesium Bromide in Heptane in the Presence of Titanium Trichloride (Run 39). After the organometallic reagent was prepared in heptane, 0.26 g (0.0017 mol) of titanium trichloride was added to the reaction flask, which was cooled to 0°. Then, 0.200 g of acetophenone in 15 ml of heptane was added dropwise to the stirring, brown, heterogeneous mixture. After 70 min had elapsed, 15 ml of water was introduced.

Reaction of Acetophenone with 2-Phenyl-1-propylmagnesium Bromide in Heptane in the Presence of Titanium Tetrachloride and 2-Phenyl-1-propylaluminum Sesquebromides (Run 40).[25] A 100-ml, three-necked, round-bottomed flask was fitted with a pressure-equalizing dropping funnel, a condenser, and a magnetic stirring apparatus. The system was dried under a flow of dry nitrogen and 0.045 g (0.0017 g-atom) of reagent grade aluminum foil was added. The flask was again dried, and a positive pressure of nitrogen was maintained throughout the reaction. After cooling, 0.996 g (0.0051 mol) of the bromide in 15 ml of heptane was added dropwise by means of the funnel. After refluxing for 20 hr no apparent reaction had taken place. Three drops of 1,2-dibromoethane were added and refluxing was continued. Gradually, a greenish black precipitate formed. After 14 hr this mixture was transferred to a vessel containing the Grignard reagent prepared in the usual way from 1.48 g of bromide and 0.180 g of magnesium in 10 ml of heptane.

The flask was cooled to 0° and 0.21 ml of titanium tetrachloride in 5 ml of heptane was added. The material became so viscous that the flask was shaken manually to ensure proper stirring. Then, 0.200 g of acetophenone in 10 ml of heptane was added, and the reaction was allowed to proceed for 70 min. At that time 15 ml of water was added. Purification and analysis of the products were carried out as described earlier.

Reaction of Acetophenone with 2-Phenyl-1-propylmagnesium Bromide in Heptane in the Presence of Vanadium Tetrachloride (Run 41). The organometallic reagent was prepared and cooled to 0°; then, 0.18 ml (0.0017 mol) of vanadium tetrachloride in 5 ml of heptane was added followed by 0.200 g of acetophenone in 15 ml of heptane. The contents were stirred for 70 min, and the reaction was quenched with 15 ml of water.

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[25] A. Von Grosse and J. M. Mavity, *J. Org. Chem.*, **5**, 106 (1940).