Organic Synthesis Highlights

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Preface

Organic synthesis is as highly developed, versatile, and interdisciplinary branch of natural science. It allows the preparation of complex molecules and new materials with unexpected properties. Based on the accomplishments of modern analytical techniques (spectroscopy, X-ray analysis, chromatography) and on the knowledge of quantum chemistry, the mechanistic understanding of organic reactions has been immensely enlarged and may now be used in the planning of more efficient synthetic routes. Novel, highly selective reagents appear every month. New reactions or modifications of old reactions have been devised to meet the ever-increasing demands of selectivity in modern synthesis.

"Organic Synthesis Highlights" provides an overview of the rapid progress, the trends, and the accomplishments of synthetic organic chemistry over the past five years. It was written by five young authors, who are all active researchers in different fields of organic chemistry. "Organic Synthesis Highlights" in not another textbook on organic chemistry. It addresses university teachers, research chemists in industry, and advanced students. Instead of attempting to cover the entire subject in full-blown detail, its essay-like approach gives the reader an impression of the competitive atmosphere, the creativity, and resourcefulness which is so characteristic of organic synthesis today.

The book contains 49 articles on almost every aspect of modern organic synthesis. In the first part, methodology, reagents, and reactions are described, especially with respect to their chemo-, regio-, and stereoselectivity potential. Particular emphasis has been laid on the rapidly developing organometallic and biooriented procedures. Wherever necessary, mechanisms are discussed for a better understanding of the reaction. In the second part, this knowledge is applied to the synthesis of target compounds, mostly natural products with remarkable physiological properties such as pheromones, alkaloids, prostaglandins, and steroids. Frequent use is made of retrosynthetic analysis to show how a multi-step synthesis may be planned to avoid inefficient bond connections and isomeric mixtures. The syntheses are discussed with the aid of concise flowcharts aiming at the principal understanding of the sequence and leaving the details to the more than 1 000 references which consider even the most recent literature.

It is the hope of the authors that this volume might be helpful in many respects: for getting a quick introduction to a new research area, for preparing seminars, lectures, or examinations, for getting a hint of how to solve a specific problem in synthesis, or just for having fun with good new chemistry.

Berlin, September 1990 J. Mulzer

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Abbreviations

9-BBN	9-Bora-bicyclo[3.3.1]nonane
Bn = Bzl	Benzyl
Bz	Benzoyl
DEAD	Diethyl-azo-dicarboxylate
DIBAH = DIBAL	Diisobutyl-aluminium-hydride
DHP	Dihydropyrane
DME	Dimethoxy-ethane
DMF	Dimethylformamide
DMAP	4-*N*,*N*-Dimethylaminopyridine
DMSO	Dimethylsulfoxide
DBN	1,5-Diaza-bicyclo[4.3.0]nonene-5
DBU	1,5-Diaza-bicyclo[5.4.0]undecylene-5
BOC	tert-Butyloxy-carbonyl
BuLi	n-Butyllithium
LAH	Lithiumaluminiumhydride
LDA	Lithiumdiisopropylamide
MEM	2-Methoxyethoxymethyl
MOM	Methoxy-methyl
MsCl	Methanesulfonylchloride
MCPBA = mCPBA	m-Chloroperbenzoic acid
HMPA = HMPT	Hexamethylphosphoric acid triamide
NBS	*N*-Bromosuccinimide
PCC	Pyridiniumchlorochromate
PDC	Pyridinium-dichromate
Phth	Phthaloyl
PPA	Polyphosphoric acid
PPTS	Pyridinium-p-tosylate
TBDMS	ter-Butyldimethylsilyl
TBDPS	tert-Butyldiphenylsilyl
TMEDA	Tetramethyl-ethylene-diamine
TMM	Trimethylene methane
TMS	Trimethylsilyl
Ts	Tosyl
THP	Tetrahydropyranyl

Contents

Part I. Methods, Reagents and Mechanisms

A. Various Aspects of Stereodifferentiating Addition Reactions

Cram's Rule: Theme and Variations 3
J. Mulzer

Stereoselective Reactions of Cyclic Enolates 9
K. Krohn

Chiral Sulfoxides in the Synthesis of Enantiomerically Pure Compounds 14
K. Krohn

Chiral Cyclic Acetals in Synthesis 19
H.-J. Altenbach

Syntheses with Aliphatic Nitro Compounds 25
M. Braun

Boron: Reagents for Stereoselective Syntheses 33
M. Braun

α-Hydroxylation of Carbonyl Compounds 40
H.-U. Reissig

Electrophilic Aminations 45
K. Krohn

Asymmetric Induction in Diels-Alder Reactions 54
K. Krohn

Chiral Lewis Acids 66
H.-J. Altenbach

C–C Bond-Forming Reactions in Aqueous Medium 71
H.-U. Reissig

Natural Product Synthesis via 1,3-Dipolar Cycloadditions 77
J. Mulzer

[4 + 1] and [3 + 2] Cycloadditions in the Synthesis of Cyclopentanoids 96
K. Krohn

Recent Applications of the Paterno-Büchi Reaction 105
M. Braun

Diastereoselective Claisen Rearrangements 111
H.-J. Altenbach

Ester Enolate Claisen Rearrangements 116
H.-J. Altenbach

B. Cyclization Reactions

The Weiss Reaction 121
H.-U. Reissig

Radical Reactions for Carbon-Carbon Bond Formation 126
M. Braun

Cyclization of Allyl- and Vinylsilanes 131
K. Krohn

Nazarov and Pauson-Khand Reactions 137
K. Krohn

Polyepoxide Cyclizations 145
H.-J. Altenbach

Syntheses of Macrocyclic Ethers 151
H.-J. Altenbach

Halolactonization: The Career of a Reaction 158
J. Mulzer

C. Organotransition Metals in Synthesis

New Aromatic Substitution Methods 167
M. Braun

Palladium-Catalyzed Arylation and Vinylation of Olefins 174
H.-U. Reissig

Regio- and Stereoselective Aryl Coupling 181
H.-J. Altenbach

Benzannulation Reactions Employing Fischer Carbene Complexes 186
H.-U. Reissig

Methylenations with Tebbe-Grubbs Reagents 192
H.-U. Reissig

D. Electrochemistry in Selective Synthesis

Anodic Oxidation and Amidoalkylation 199
H.-U. Reissig

E. Bio-oriented Methodology

Enzymes in Organic Synthesis, I 207
J. Mulzer

Enzymes in Organic Synthesis, II 216
J. Mulzer

Enzyme Chemistry – Valuable New Applications 224
H.-J. Altenbach

Biomimetic Natural Product Syntheses 232
M. Braun

F. Synthesis with Ex-Chiral-Pool Starting Materials

(*R*)- and (*S*)-2,3-Isopropylidene Glyceraldehyde – "Unbiased" Chiral Starting Materials 243
J. Mulzer

Chiral Building Blocks from Carbohydrates 251
K. Krohn

Part II. Applications in Total Synthesis

A. Synthesis of Classes of Natural Products

Some Recent Highlights From Alkaloid Synthesis 263
K. Krohn

Synthesis of *O*-Glycosides 277
K. Krohn

Cembranoid Syntheses 286
H.-J. Altenbach

Optically Active Glycerol Derivatives 292
H.-J. Altenbach

Asymmetric Syntheses of α-Amino Acids 300
H.-J. Altenbach

B. Synthesis of Individual Natural Products

Compactin and Mevinolin 309
M. Braun

The Coriolin Story, or The Thirteen-Fold Way 323
J. Mulzer

Frontalin 335
M. Braun

Milbemycin β_3 344
H.-U. Reissig

Daunosamine 351
M. Braun

Two Strategies, One Target: Swainsonine 359
H.-U. Reissig

Syntheses of Statine 365
H.-J. Altenbach

C. Syntheses of Non-Natural Target Compounds

Fenestranes – A Look at "Structural Pathologies" 371
K. Krohn

"Starburst Dendrimers" and "Arborols" 378
K. Krohn

Author Index 385

Subject Index 391

I. Methods, Reagents and Mechanisms

A. Various Aspects of Stereodifferentiating Addition Reactions

This chapter deals with various aspects of addition to sp^2-carbons. Addition reactions permit C,C- and C-heteroatom bonds to be formed in such a way as to create new stereocenters, and hence enantiomers or diastereomers. The process is called "stereodifferentiation" and it must be performed with as much selectivity as possible; a stereoisomer ratio of 9:1- or better is desirable. Cycloadditions like the Diels-Alder reaction produce two bonds in one step with the potential for up to of 16 stereoisomers! It is one of the great achievements of modern synthetic methodology that such additions may be controlled to yield only one isomer by use of appropriate auxiliaries and conditions. Sigmatropic rearrangements like the Claisen rearrangement proceed with self-immolative stereochemistry, which means that a new stereocenter is generated at the cost of a previous one. In the Claisen case, a C–O bond is transformed into a C–C bond with a quantitative chirality transfer.

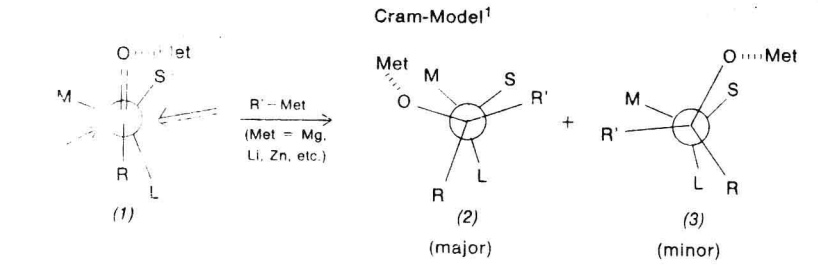
Literature: Asymmetric Synthesis (*J. D. Morrison*, Editor), Academic Press, 1983/84, Vol. 2 + 3.
Natural Products Synthesis Through Pericyclic Reactions, *G. Desimoni, G. Tacconi, A. Barco, G. P. Pollini*, ACS Monograph 180, American Chemical Society, Washington, D. C., 1983.
Stereodifferentiating Reactions, *Y. Izumi, A. Tai*, Kodansha, 1977.

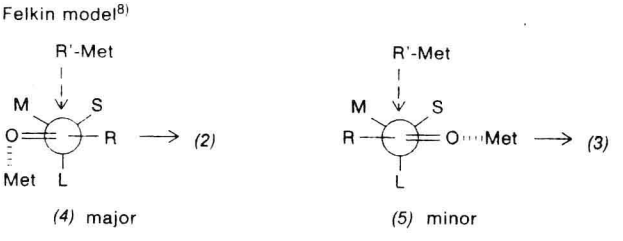
Cram's Rule: Theme and Variations

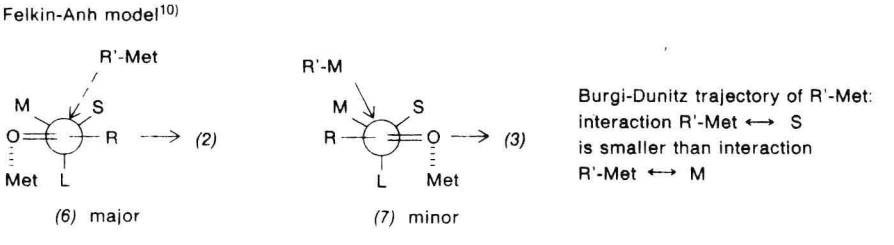
Cram's rule was formulated in the early fifties and has been an evergreen in organic stereochemistry ever since. In their original paper [1] Cram and Abd Elhafez studied the addition of various organometals and complex hydrides to prochiral carbonyl functions, summarizing their findings in the following postulate: "In non-catalytic reactions of this type that diastereomer will predominante which could be formed by the approach of the entering group from the least hindered side of the double bond when the rotational conformation of the C–C-bond is such that the double bond is flanked by the two least bulky groups attached to the adjacent center".

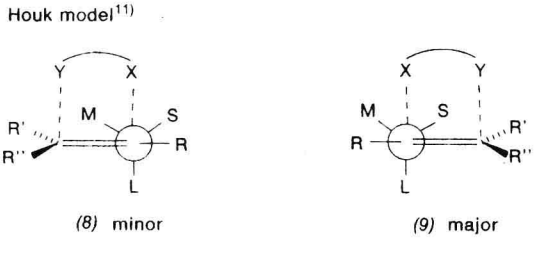
Despite its verbose formulation this so-called "Cram's rule" soon became an indispensable ingredient of organic textbooks; the simple substituent classification according to effective size (L = large, M = medium, S = small) and the seductively clear influence of steric shielding on the direction of nucleophilic attack were responsible for this popularity. In today's view, Cram's rule – similar to Prelog's rule [2] – attempts a heuristic treatment of the problem of diastereoface selectivity. Owing to the vicinal chiral center, both faces of the carbonyl group are diastereotopic, which means that *re*- and *si*-attack differ in energy [3] and unequal amounts of the adducts (*2*) and (*3*) are produced. Recently, general descriptions of these phenomena have been developed, resulting in the Seebach-Prelog topicity concept [4]. In principle, Cram's rule has been applied to both 1,2- and 1,3-inductions; this article, however, will be restricted to the 1,2-case, following Cram's original definition [1].

Ironically, concepts based on questionable premises frequently turn out particularly fruitful. In fact, Cram's rule appears highly oversimplified in several respects: (a) No distinction is made between ground state and reactive conformation. The postulate that (*1*) is the ground state conformation of the metal carbonyl complex, is incorrect, as shown by Cornforth [5] and Karabatsos [6]. True, however, is that complexation is indispensable for the activation of the carbonyl group. An uncomplexed carbonyl group is unreactive towards organometallic attack. (b) In view of the low rotational barriers around C(O)–C-bond axes more than one reactive conformation may be involved, according to the Curtin-Hammett principle [7]. Among these, (*1*) is highly unfavorable, as it leads to the fully eclipsed arrangements (*2*) and (*3*) in the course of nucleophilic addition! (c) The substituents are classified as S, M, and L only with respect to their bulk. Any dipolar interactions with the nucleophile are neglected. This deficiency was partly remedied by Cornforth [5]; he suggested a "dipolar model" for electronegative α-substituents (Cl, etc.), which he assumed would adopt the L-position in (*1*). A more general improvement was made by Felkin [8] who realized the importance of the transition state. To avoid eclipsing interactions









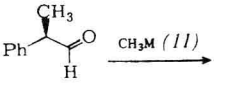
Felkin preferred the semi-staggered geometries (*4*)/(*5*) and postulated nucleophilic attack from an antiperiplanar position with respect to substituent L. Thus, instead of considering *one* conformation and *two* modes of attack, as Cram and Cornforth had done, Felkin suggested *two* reactive conformations (*4*)/(*5*) and only *one* mode of attack. L is generally the substituent with the highest repulsive effect, which may be of steric or dipolar (e.g. OR, NR_2) origin. For electronegative substituents like OR or NR_2 the transition states (*4*)/(*5*) gain an extra stabiliza-

tion by electron transfer from the nucleophile into the low-lying σ*-orbital of the C–L bond ("antiperiplanar effect" [9].

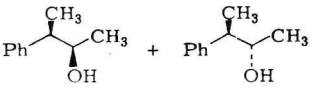
However, Felkin's interpretation failed to explain why (*4*) is favored over (*5*). The answer to this problem was given by Bürgi/Dunitz and Anh [10] who developed the concept of "non-perpendicular attack". Due to repulsion from the carbonyl-oxygen, the nucleophile approaches the carbonyl-carbon at an angle of ca. 100° with respect to the carbonyl axis. Thus, (*4*) changes to (*6*) and (*5*) to (*7*), with (*6*) (R′M interacts with S) clearly better than (*7*) (R′M interacts with M). This co-called Felkin-Anh model has been reconsidered by Heathcock in a series of papers [10a]. He found that steric and electronic effects are sometimes comparable for two substituents (e.g. OMe and Ph), so that altogether four reactive conformations have to be considered: two for OMe and two for Ph in the role of L. Such considerations have also been the subject of ab-initio calculations by Houk [10b].

Some time ago, Houk extended the Felkin-Anh concept to the stereochemistry of C=C-additions ("Houk's model" [11]). In this case, the reactive conformations are (*8*) (= (*6*)) and (*9*) (= (*7*)). In contrast to the carbonyl addition, no repulsive interactions need here be considered. Hence, orthogonal quasicyclic transition states are postulated, and the reactive conformation must be so chosen that a minimum of steric interactions arises *inside* the cyclic framework. This means that (*9*) is a better geometry than (*8*).

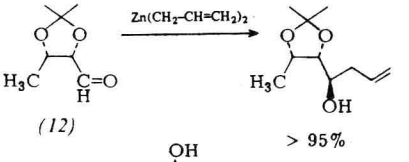
Despite this fascinating theoretical evolution, reported cases of high Cram-Felkin-Anh selectivity have been rare for some years. Only quite recently have new solutions to this problem emerged. One possibility is replacement of the traditional Grignard or organolithium compound by novel organometallics. For example, the trialkoxy titanates (*11b*)/(*11c*) show a far superior Felkin-Anh selectivity in many cases [12,13]. High selectivity is also found for the



(*10*)

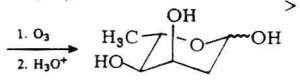


(*11*)	M =	Cram : anti-Cram	
(*a*)	MgI	2	1[1)]
(*b*)	$Ti(O_iPr)_3$	88	12[12)]
(*c*)	$Ti(OPh)_3$	93	7[12)]

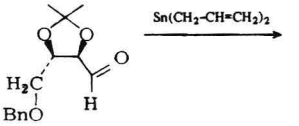


(*12*)

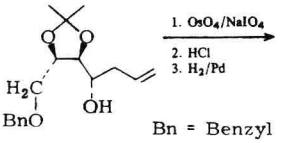
> 95%



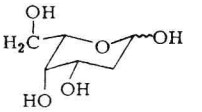
L-Digitoxose[14)]



(*13*)



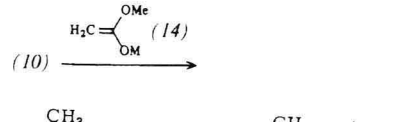
Bn = Benzyl



2-Desoxy-L-lyxo-hexose[15)]

addition of tin(II) or zinc diallyl to alkoxy aldehydes like (*12*) and (*13*).

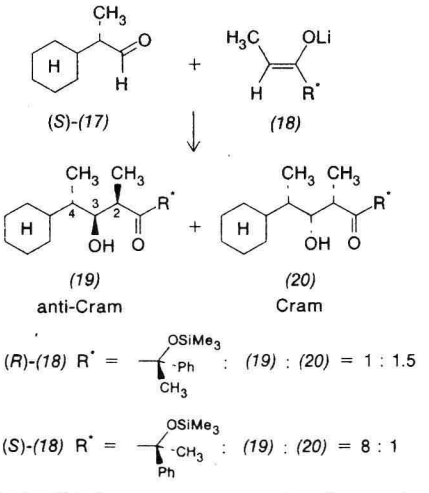
Fuganti [14] and Mukaiyama [15] utilized this observation in certain monosaccharide syntheses. High Felkin-Anh selection was also found for 2-metallated furane [15a], thiazole [15b] and chromium(II) allyl reagents [15c]. Similarly, the Cram-Felkin-Anh selectivity of ester enolates may be dramatically enhanced by using the *O*-silyl-derivatives (*14b*) under BF_3-catalysis instead of the lithium compounds (*14a*) [16].



(*14a*) M = Li: (*15*) : (*16*) = 3 : 1

(*14b*) M = $SiMe_2tBu$: (*15*) : (*16*) = 15 : 1 [16]

A conceptually different approach makes use of "double stereodifferentiation". This means that the effect of the chiral center in the carbonyl compound is superimposed upon a second stereodirecting effect from the nucleophile. If both effects operate in the same direction, "matched" stereocontrol is achieved, and the individual effects are mutually reinforcing. In the "mismatched" case the individual effects are counteracting and stereocontrol is drastically reduced [17]. For example, in the addition of the chiral enolate (*18*) to the α-chiral aldehyde (*S*)-(*17*) the Cram product is hydroxy ketone (*20*). It can be seen that the influence of the enolate overrides the effect of (*17*): weak Cram selection is observed for (*R*)-(*18*), whereas (*S*)-(*18*) strongly induces formation of the anti-Cram adduct (*19*). With (*R*)-(*17*) these selectivites are reversed, so that (*R*)-(*18*)leads to weak anti-Cram and (*S*)-(*18*) to strong Cram selection [17a]. This principle of "double stereodifferentiation" is by no means restricted to carbonyl additions. It can be extended to any kind of addition between prochiral sp^2-centers.

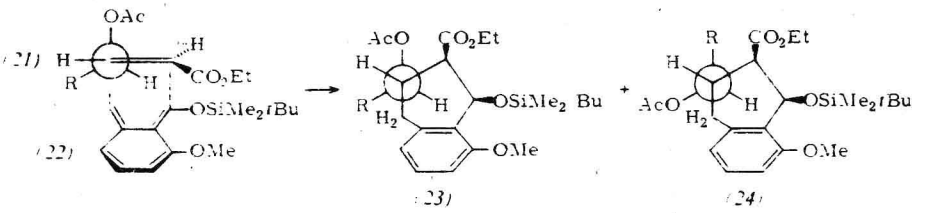


C=C-Additions Following "Houk's Model"

Houk's model has been applied to hydroborations [19], osmylations [20], and cycloadditions [21]. Significant stereoselection may be achieved by utilizing the "antiperiplanar effect" [9] of an OR-substituent, which adopts the position of substituent L. Thus, in the Diels-Alder addition of the in-situ diene (*21*) to acrylic ester (*22*) a 4:1-ratio is observed in favor of the "Houk product" (*23*). In a similar fashion, Houk's model describes cuprate additions to enone systems like (*25*). The selectivity in favor of (*26*) may be explained via the transition state (*27*).

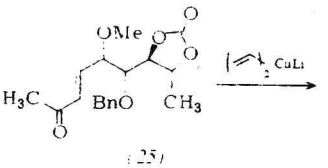
Chelate Cram Model

In his original publication [1] Cram discussed a "cyclic model" in addition to the acyclic one. The cyclic model, now better known as the "*chelate Cram model*", should be operative in

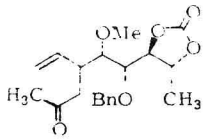


(21) (22) (23) (24)

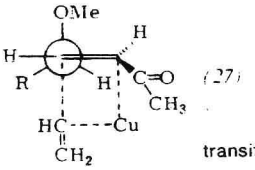
4 : 1



(25)



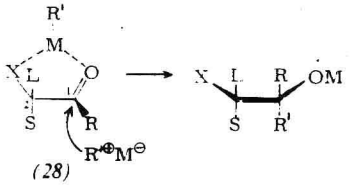
> 97% (26)



(27) transition state

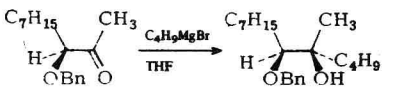
the case of α-alkoxy, α-hydroxy-, and α-amino-carbonyl compounds. Prior to organometallic addition the cation M forms a chelate (*28*) which is attack from the least hindered face, i.e. from the side of S. The corresponding induction

Chelate Cram Model



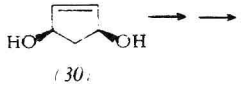
(28)

X = NH_2, NR_2, OR, OH

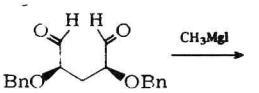


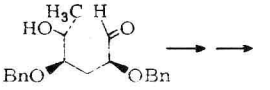
(29) > 100 : 1

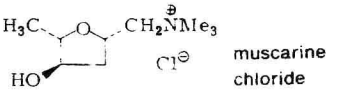
is thus opposite to the Felkin-Anh model. It turns out that the chelate model is far more reliable and efficient than the non-chelate model. In particular, ketones like (*29*) exhibit an extraordinary degree of stereoselection [23]. Applications in synthesis are manifold, one example being the conversion of diol (*30*) into racemic muscarine [24]. However, no reliable

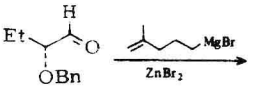


(30)

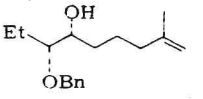








(31)



39 : 1 anti-Cram selectivity[25]