Asymmetric Synthesis

Volume 3

STEREODIFFERENTIATING ADDITION REACTIONS

PART B

Edited by

James D. Morrison

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Dedication

Don Cram was born in Chester, Vermont on 22 April 1919. After secondary schooling in Vermont, he enrolled at Rollins College, Winter Park, Florida, on a National Honorary Scholarship, graduating with a B.S. in 1941. He obtained an M.S. in organic chemistry at the University of Nebraska in 1942 and then spent 3 war years at Merck and Company working on the isolation and structure of penicillin and other antibiotics. After the war he attended Harvard on a National Research Council Fellowship, receiving a Ph.D. in 1947. Following 4 months at MIT as a postdoctoral fellow, he moved to UCLA as an American Chemical Society Fellow, becoming assistant professor there in 1948, associate professor in 1951, and professor in 1956.

At UCLA, working with more than 160 graduate students and more than 80 postdoctoral associates, Professor Cram pioneered research in many areas, including asymmetric synthesis—particularly the stereochemistry of organometal addition to chiral ketones (Cram's Rule)—carbanion structure and stereochemistry, conformational analysis, phenonium ions and internal return, cyclophane chemistry, the stereochemistry of substitution reactions at sulfur, and, more recently, the design and synthesis of host compounds that selectively complex and orient guest compounds and catalyze their reactions (host–guest chemistry). He has authored or coauthored more than 300 research papers, several well-known textbooks, and a germinal monograph on carbanion chemistry.

Professor Cram's contributions to chemistry have been widely recognized and honored. He was elected to the National Academy of Sciences in 1961 and to the American Academy of Arts and Sciences in 1967. In 1974 he became the third recipient of the American Chemical Society's prestigious Arthur C. Cope Award for Distinguished Achievement in Organic Chemistry, and in the same year was named California scientist of the year. He has also received the ACS award for Creative Research in Organic Chemistry, two H. N. McCoy Awards for Con-

tributions to Chemistry, and the Society of Chemical Manufacturers Association Award for Creative Research in Organic Chemistry. He has been plenary lecturer at numerous international conferences and congresses and has presented seminars at academic and industrial research centers around the world. He holds honorary doctorates from Uppsala University and the University of Southern California.

It is a pleasure to dedicate this volume to Don Cram in recognition of his outstanding contributions to stereochemistry and asymmetric synthesis.

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Preface

This is the third volume of a multivolume treatise reviewing progress in asymmetric synthesis since 1971. It is the second of two volumes concerned with stereodifferentiating addition reactions. Volume 1 covered the major analytical methods used to determine enantiomer ratios.

The efficient formation of carbon–carbon bonds is, of course, crucial in all complex syntheses. The topics in this volume represent research areas of intensive investigation in leading academic and industrial laboratories; the authors are pioneers and current leaders in the search for highly stereoselective addition reactions. Their commentaries have both an authoritative sense of perspective and a forward-looking freshness.

Chapter 1 comprehensively reviews the formation of chiral metal enolates and their stereoselective alkylation reactions. Chapter 2 is a thorough discussion of chiral aldol addition reactions. Chapter 3 describes the many variations of asymmetric synthesis that may be carried out using chiral oxazolines. The alkylation of chiral hydrazones, a process that yields chiral-substituted aldehydes and ketones, is the subject of Chapter 4. Chapters 5 and 6 review a variety of cyclization processes that form carbon–carbon and carbon–heteroatom bonds, respectively. Asymmetric cycloadditions are described in Chapter 7, and sigmatropic rearrangements are covered in Chapter 8.

Because many of these subject areas have not been reviewed before, all synthetic chemists should find this volume valuable. Asymmetric synthesis has developed at a dramatic pace; the advances reported here represent some of the most significant developments.

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Stereoselective Alkylation Reactions of Chiral Metal Enolates

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ASYMMETRIC SYNTHESIS
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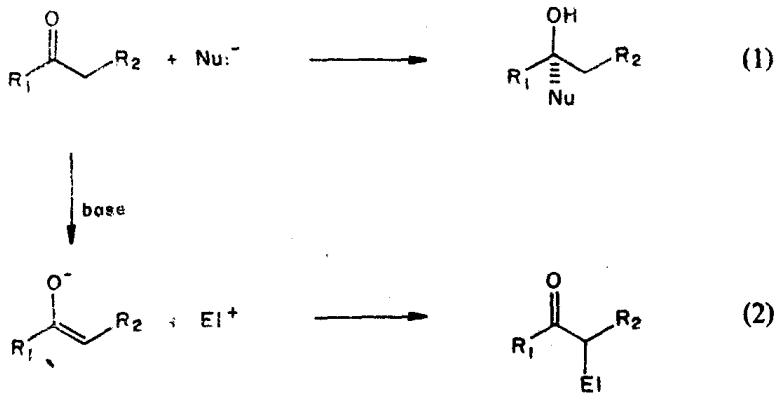
I. Prologue

Since the 1920s we have witnessed a remarkable increase in our understanding with regard to how organic molecules might be constructed. The student of biosynthesis now has a relatively firm grasp of the basic design concepts followed by nature in the construction of architecturally complex organic molecules. Similarly, the ongoing development of chemical reactions of ever increasing selectivity coupled with an evolving sophistication in the tenets of synthesis design now provide one with the basic tools to design and execute rationally the laboratory synthesis of an impressive array of organic structures. Without question, the prime activating function for the construction of carbon–carbon bonds in both laboratory and biosynthesis is the carbonyl group. This atom assemblage embodies exceptional versatility in functioning as either an electrophile [Eq. (1)] or, via its derived enolate, as a nucleophile [Eq. (2)] in a wide variety of polar bond constructions.

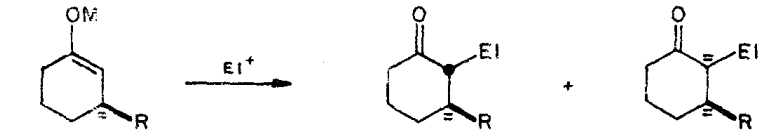


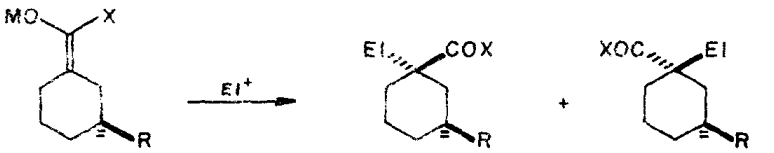
An important aspect of both carbonyl- and enolate-derived reactions is related to the issue of asymmetric induction. For example, in either of the substrates illustrated in Eqs. (1) and (2), if the substituent R_1 or R_2 contains a center of asymmetry, the resultant π-faces of either the carbonyl or enolate are rendered diastereotopic, and the potential for internal asymmetric induction, or diastereoselection, exists for both bond constructions. In the synthesis of molecules containing multiple centers of asymmetry, those control elements that are related to predictable reaction diastereoselection in both carbonyl addition and enolate alkylation are of paramount importance in synthesis design. Intensive documentation relative to the stereoselective addition of nucleophilic reagents to chiral ketones and aldehydes already exists (*1*, *2*), and empirical models such as

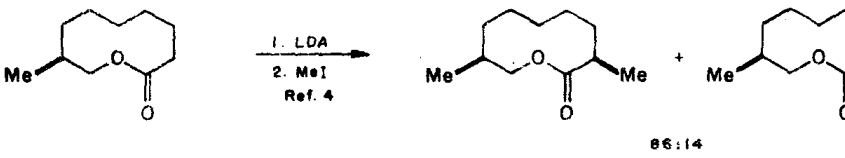
Cram's rule, as well as its descendants (*3*), provide a powerful tool for predicting the preferred reaction topology.

The objective of this chapter is to survey the literature pertinent to chiral enolate diastereoselection as expressed in reactions involving these nucleophiles and alkyl halide electrophiles. Due to the ubiquity of this class of bond constructions, a remarkably diverse set of chiral enolate systems has been systematically developed in conjunction with the evolution of the field of chemical synthesis. From this accumulated body of data a rather detailed understanding of transition-state structure has evolved, and the experienced practitioner is cognizant of those transition-state control elements (steric and stereoelectronic) that dictate enolate π-facial selectivity. In surveying chiral enolate systems as a class, it appears that three general subdivisions can be made. These three structurally distinct classes of enolates are briefly outlined here:

1. *Intraannular Chirality Transfer.* The definition of this subset of cases is best established by citing several examples [Eqs. (3)–(5)]. In these

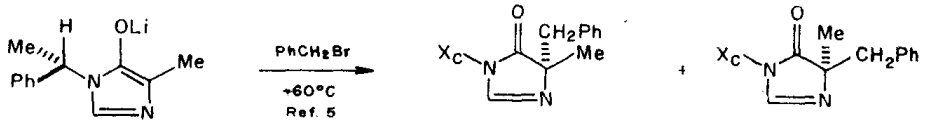






cases the resident asymmetric center is interconnected via a cyclic array of covalent bonds containing the asymmetric center to the enolate framework. In such cases the issue of enolate geometry is generally either fixed [Eq. (3)] or irrelevant to the sense of asymmetric induction [Eq. (4)]. This statement should be qualified, however, for those cases in which the size of the cycle might be such that two possible enolates could be formed, as in the case illustrated by Eq. (5) (*4*).

2. *Extraannular Chirality Transfer.* The cases illustrated here constitute typical examples of extraannular chirality transfer via the alkylation process [Eqs. (6)–(8)] (*5–7*). In each of the cited examples, the resident



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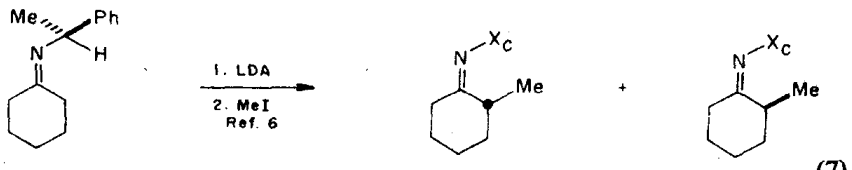

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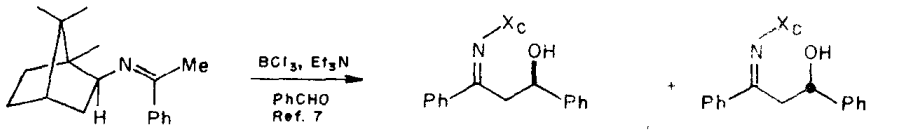
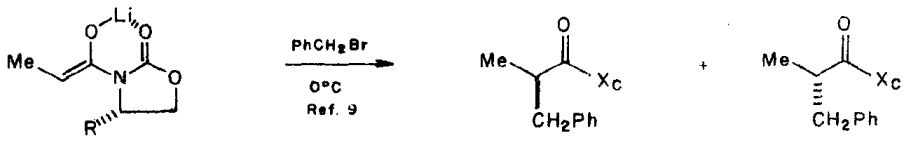


(8)

chiral moiety (X_c) is not conformationally locked at two or more contact points via covalent bonds to the trigonal center undergoing substitution. As a consequence of such conformational ambiguity, it is frequently difficult to make *de novo* predictions as to the diastereofacial bias imparted to the enolate system [Eq. (8)]. Nonetheless, with an increased understanding of acyclic conformational analysis, particularly associated with the concepts of allylic strain, a greater level of predictability associated with acyclic diastereoselection is now possible. (*8*).

3. *Chelate-Enforced Intraannular Chirality Transfer.* One productive approach to the design of chiral enolate systems in which a structurally organized diastereofacial bias is established is illustrated in Eqs. (9)–(11)



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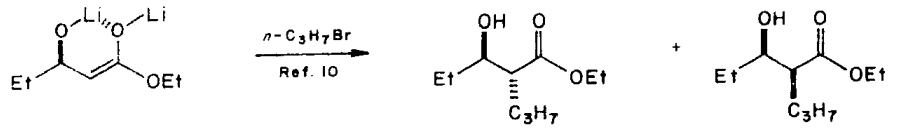

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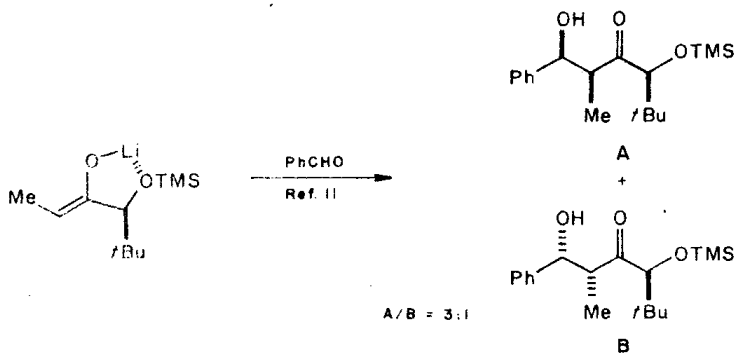
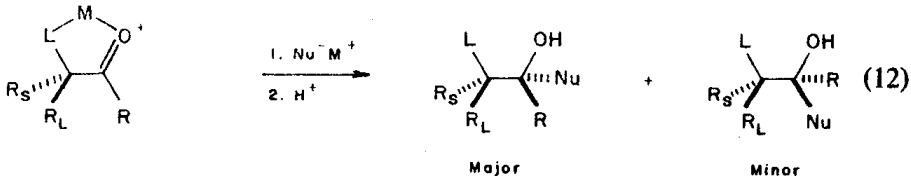


(11)

(*9–11*). In each case the presumed five- and six-membered lithium chelates provide an organizational role in fixing the orientation between the resident asymmetric center and the enolate system. Based on the preceding definitions, the postulated chelated enolates and their respective alkylation or aldol reactions constitute cases in which intraannular chirality transfer is possible.

The preceding class designations, as applied to chiral enolate asymmetric induction, may be conveniently applied to many reactions in which π-facial diastereoselection becomes an issue. For example, the Cram open-chain model for predicting π-facial selection in carbonyl addition is an example of extraannular chirality transfer (*1–3*), whereas the corresponding cyclic model [Eq. (12)] constitutes an example of chelate-enforced intraannular chirality transfer (*1, 2, 12*).



(12)

In the ensuing discussion we systematically survey stereoselective methods for enolate formation. This is followed by a comprehensive discussion that deals with the alkylation reactions of chiral enolates. The organizational format for dealing with the critical aspects of chirality transfer

presented in the preceding paragraphs is followed throughout the discussion. This chapter is not intended to be complete with respect to the treatment of all chiral enolate–electrophile reactions cited in the literature. Nonetheless, the data presented in the context of surveying this class of reactions should provide the reader with a reasonable overview of chiral enolate π-facial selectivity. A number of excellent reviews have covered the topic of the generation and synthetic utility of enolate anions (*13–19*); however, little previous emphasis has been placed on the stereochemical aspects of this topic, which is the focal point of this chapter.

II. Selective Enolate Formation

A. Introduction

Ketones, aldehydes, and carboxylic acid derivatives constitute a class of carbon acids the acidities of which fall in the pK_a range (DMSO) of 25 to 35. Largely through the efforts of F. A. Bordwell and co-workers, an extensive compilation of hydrocarbon acidity data now exists on a range of functionally diverse organic molecules. (*20*). Representative values for a selection of carbonyl substrates are summarized in Table 1. Also included in this table are selected pK_a data for compounds commonly employed as bases in the enolization process (*21, 20f*). Since the early 1960s tremendous advances have been made in the methodology of specific enolate generation, and an excellent review adequately surveys this topic in detail (*18*). Without question, the application of strong base technology to the selective deprotonation process has been of paramount importance in promoting the utilization of enolate nucleophiles in organic synthesis. In retrospect, it is not surprising that metal amide bases have enjoyed such popularity because they are sufficiently basic (R_2NH, $pK_a \approx 41$–44) to deprotonate quantitatively virtually all carbonyl-activated carbon acids (Table I). The introduction of sterically hindered amide bases **1–4** has been a particularly important innovation in this field, and these reagents are now universally accepted for carbonyl deprotonation. In contrast to the alkali metal amides derived from ammonia, the illustrated dialkylamides are all quite soluble in ethereal solvent systems. It is remarkable that the bis(silyl)amides **4a–4c** have been found to exhibit good solubility in hydrocarbon aromatic solvents (*23a*). Both lithium diisopropylamide (LDA, **1**) (*24*) and lithium isopropylcyclohexylamide (LICA, **2**) (*25*) ex-

TABLE 1
pK_a Data for Representative Carbonyl Compounds and Related Substrates in DMSO[a]

Substrate	pK_a (DMSO)	Substrate	pK_a (DMSO)
H_3CCCH_3 (O)	26.5	$N{\equiv}CCH_3$	31.3
$PhCCH_3$ (O)	24.6[b]	$EtOCCH_3$ (O)	30–31[c]
$PhCCH_2CH_3$ (O)	24.4	$EtOCCH_2Ph$ (O)	22.7
$PhCCH_2OMe$ (O)	22.9	$EtOCCH_2SPh$ (O)	21.4
$PhCCH_2Ph$ (O)	17.7	Me_2NCCH_3 (O)	34–35[c]
$PhCCH_2SPh$ (O)	17.1	CH_3SCH_3 (O)	35.1
Representative group VI acids (*21*)			
HOH	27.5	NH_3	41[d]
CH_3OH	27.9	$HN(CH_2)_4$	44[d]
$(CH_3)_2CHOH$	29.3		
$(CH_3)_3COH$	29.4		

[a] From (*21*, *22*).
[b] The corresponding pK_a estimates in water have also been determined independently by two groups: pK_a(PhCOCH$_3$) = 15.8, 17.0.
[c] Extrapolated values (*20g*).
[d] Extrapolated values (*20f*).

hibit similarly high levels of kinetic deprotonation selectivity, and, although rigorous data are not available, lithium hexamethyldisilylamide (LHDS) (**4a**) is probably comparable. In addition to the previously mentioned alkylamide bases, the silylamides **4d** and **4e** have also enjoyed widespread acceptance as sterically hindered amides that are effective in enolate generation (*23*, *26*). Finally, lithium tetramethylpiperidide (LTMP, **3**) is probably the most sterically hindered amide base in existence (*27*).

The superior regioselection observed for both LDA (**1**) and KHDS (**4c**) in the deprotonation of 2-methylcyclohexanone [Eq. (13)] serves to highlight kinetic selectivity noted for these bases (Table 2). From the tabulated