COMPREHENSIVE ORGANIC SYNTHESIS

Selectivity, Strategy & Efficiency in Modern Organic Chemistry

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Preface

The emergence of organic chemistry as a scientific discipline heralded a new era in human development. Applications of organic chemistry contributed significantly to satisfying the basic needs for food, clothing and shelter. While expanding our ability to cope with our basic needs remained an important goal, we could, for the first time, worry about the quality of life. Indeed, there appears to be an excellent correlation between investment in research and applications of organic chemistry and the standard of living. Such advances arise from the creation of compounds and materials. Continuation of these contributions requires a vigorous effort in research and development, for which information such as that provided by the *Comprehensive* series of Pergamon Press is a valuable resource.

Since the publication in 1979 of *Comprehensive Organic Chemistry*, it has become an important first source of information. However, considering the pace of advancements and the ever-shrinking timeframe in which initial discoveries are rapidly assimilated into the basic fabric of the science, it is clear that a new treatment is needed. It was tempting simply to update a series that had been so successful. However, this new series took a totally different approach. In deciding to embark upon *Comprehensive Organic Synthesis*, the Editors and Publisher recognized that synthesis stands at the heart of organic chemistry.

The construction of molecules and molecular systems transcends many fields of science. Needs in electronics, agriculture, medicine and textiles, to name but a few, provide a powerful driving force for more effective ways to make known materials and for routes to new materials. Physical and theoretical studies, extrapolations from current knowledge, and serendipity all help to identify the direction in which research should be moving. All of these forces help the synthetic chemist in translating vague notions to specific structures, in executing complex multistep sequences, and in seeking new knowledge to develop new reactions and reagents. The increasing degree of sophistication of the types of problems that need to be addressed require increasingly complex molecular architecture to target better the function of the resulting substances. The ability to make such substances available depends upon the sharpening of our sculptors' tools: the reactions and reagents of synthesis.

The Volume Editors have spent great time and effort in considering the format of the work. The intention is to focus on transformations in the way that synthetic chemists think about their problems. In terms of organic molecules, the work divides into the formation of carbon–carbon bonds, the introduction of heteroatoms, and heteroatom interconversions. Thus, Volumes 1–5 focus mainly on carbon–carbon bond formation, but also include many aspects of the introduction of heteroatoms. Volumes 6–8 focus on interconversion of heteroatoms, but also deal with exchange of carbon–carbon bonds for carbon–heteroatom bonds.

The Editors recognize that the assignment of subjects to any particular volume may be arbitrary in part. For example, reactions of enolates can be considered to be additions to C—C π-bonds. However, the vastness of the field leads it to be subdivided into components based upon the nature of the bond-forming process. Some subjects will undoubtedly appear in more than one place.

In attacking a synthetic target, the critical question about the suitability of any method involves selectivity: chemo-, regio-, diastereo- and enantio-selectivity. Both from an educational point-of-view for the reader who wants to learn about a new field, and an experimental viewpoint for the practitioner who seeks a reference source for practical information, an organization of the chapters along the theme of selectivity becomes most informative.

The Editors believe this organization will help emphasize the common threads that underlie many seemingly disparate areas of organic chemistry. The relationships among various transformations becomes clearer and the applicability of transformations across a large number of compound classes becomes apparent. Thus, it is intended that an integration of many specialized areas such as terpenoid, heterocyclic, carbohydrate, nucleic acid chemistry, *etc.* within the more general transformation class will provide an impetus to the consideration of methods to solve problems outside the traditional ones for any specialist.

In general, presentation of topics concentrates on work of the last decade. Reference to earlier work, as necessary and relevant, is made by citing key reviews. All topics in organic synthesis cannot be treated with equal depth within the constraints of any single series. Decisions as to which aspects of a

topic require greater depth are guided by the topics covered in other recent *Comprehensive* series. This new treatise focuses on being comprehensive in the context of synthetically useful concepts.

The Editors and Publisher believe that *Comprehensive Organic Synthesis* will serve all those who must face the problem of preparing organic compounds. We intend it to be an essential reference work for the experienced practitioner who seeks information to solve a particular problem. At the same time, we must also serve the chemist whose major interest lies outside organic synthesis and therefore is only an occasional practitioner. In addition, the series has an educational role. We hope to instruct experienced investigators who want to learn the essential facts and concepts of an area new to them. We also hope to teach the novice student by providing an authoritative account of an area and by conveying the excitement of the field.

The need for this series was evident from the enthusiastic response from the scientific community in the most meaningful way — their willingness to devote their time to the task. I am deeply indebted to an exceptional board of editors, beginning with my deputy editor-in-chief Ian Fleming, and extending to the entire board — Clayton H. Heathcock, Ryoji Noyori, Steven V. Ley, Leo A. Paquette, Gerald Pattenden, Martin F. Semmelhack, Stuart L. Schreiber and Ekkehard Winterfeldt.

The substance of the work was created by over 250 authors from 15 countries, illustrating the truly international nature of the effort. I thank each and every one for the magnificent effort put forth. Finally, such a work is impossible without a publisher. The continuing commitment of Pergamon Press to serve the scientific community by providing this *Comprehensive* series is commendable. Specific credit goes to Colin Drayton for the critical role he played in allowing us to realize this work and also to Helen McPherson for guiding it through the publishing maze.

A work of this kind, which obviously summarizes accomplishments, may engender in some the feeling that there is little more to achieve. Quite the opposite is the case. In looking back and seeing how far we have come, it becomes only more obvious how very much more we have yet to achieve. The vastness of the problems and opportunities ensures that research in organic synthesis will be vibrant for a very long time to come.

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Abbreviations

The following abbreviations have been used where relevant. All other abbreviations have been defined the first time they occur in a chapter.

Techniques

CD	circular dichroism
CIDNP	chemically induced dynamic nuclear polarization
CNDO	complete neglect of differential overlap
CT	charge transfer
GLC	gas–liquid chromatography
HOMO	highest occupied molecular orbital
HPLC	high-performance liquid chromatography
ICR	ion cyclotron resonance
INDO	incomplete neglect of differential overlap
IR	infrared
LCAO	linear combination of atomic orbitals
LUMO	lowest unoccupied molecular orbital
MS	mass spectrometry
NMR	nuclear magnetic resonance
ORD	optical rotatory dispersion
PE	photoelectron
SCF	self-consistent field
TLC	thin layer chromatography
UV	ultraviolet

***Reagents, solvents,* etc.**

Ac	acetyl
acac	acetylacetonate
AIBN	2,2′-azobisisobutyronitrile
Ar	aryl
ATP	adenosine triphosphate
9-BBN	9-borabicyclo[3.3.1]nonyl
9-BBN-H	9-borabicyclo[3.3.1]nonane
BHT	2,6-di-*t*-butyl-4-methylphenol (butylated hydroxytoluene)
bipy	2,2′-bipyridyl
Bn	benzyl
t-BOC	*t*-butoxycarbonyl
BSA	*N*,*O*-bis(trimethylsilyl)acetamide
BSTFA	*N*,*O*-bis(trimethylsilyl)trifluoroacetamide
BTAF	benzyltrimethylammonium fluoride
Bz	benzoyl
CAN	ceric ammonium nitrate
COD	1,5-cyclooctadiene
COT	cyclooctatetraene
Cp	cyclopentadienyl
Cp*	pentamethylcyclopentadienyl
18-crown-6	1,4,7,10,13,16-hexaoxacyclooctadecane
CSA	camphorsulfonic acid
CSI	chlorosulfonyl isocyanate
DABCO	1,4-diazabicyclo[2.2.2]octane
DBA	dibenzylideneacetone
DBN	1,5-diazabicyclo[4.3.0]non-5-ene
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene

DCC	dicyclohexylcarbodiimide
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEAC	diethylaluminum chloride
DEAD	diethyl azodicarboxylate
DET	diethyl tartrate (+ or –)
DHP	dihydropyran
DIBAL-H	diisobutylaluminum hydride
diglyme	diethylene glycol dimethyl ether
dimsyl Na	sodium methylsulfinylmethide
DIOP	2,3-*O*-isopropylidene-2,3-dihydroxy-1,4-bis(diphenylphosphino)butane
DIPT	diisopropyl tartrate (+ or –)
DMA	dimethylacetamide
DMAC	dimethylaluminum chloride
DMAD	dimethyl acetylenedicarboxylate
DMAP	4-dimethylaminopyridine
DME	dimethoxyethane
DMF	dimethylformamide
DMI	*N*,*N*′-dimethylimidazolone
DMSO	dimethyl sulfoxide
DMTSF	dimethyl(methylthio)sulfonium fluoroborate
DPPB	1,4-bis(diphenylphosphino)butane
DPPE	1,2-bis(diphenylphosphino)ethane
DPPF	1,1′-bis(diphenylphosphino)ferrocene
DPPP	1,3-bis(diphenylphosphino)propane
E^+	electrophile
EADC	ethylaluminum dichloride
EDG	electron-donating group
EDTA	ethylenediaminetetraacetic acid
EEDQ	*N*-ethoxycarbonyl-2-ethoxy-1,2-dihydroquinoline
EWG	electron-withdrawing group
HMPA	hexamethylphosphoric triamide
HOBT	hydroxybenzotriazole
$IpcBH_2$	isopinocampheylborane
Ipc_2BH	diisopinocampheylborane
KAPA	potassium 3-aminopropylamide
K-selectride	potassium tri-*s*-butylborohydride
LAH	lithium aluminum hydride
LDA	lithium diisopropylamide
LICA	lithium isopropylcyclohexylamide
LITMP	lithium tetramethylpiperidide
L-selectride	lithium tri-*s*-butylborohydride
LTA	lead tetraacetate
MCPBA	*m*-chloroperbenzoic acid
MEM	methoxyethoxymethyl
MEM-Cl	β-methoxyethoxymethyl chloride
MMA	methyl methacrylate
MMC	methylmagnesium carbonate
MOM	methoxymethyl
Ms	methanesulfonyl
MSA	methanesulfonic acid
MsCl	methanesulfonyl chloride
MVK	methyl vinyl ketone
NBS	*N*-bromosuccinimide
NCS	*N*-chlorosuccinimide

NMO	*N*-methylmorpholine *N*-oxide
NMP	*N*-methyl-2-pyrrolidone
Nu^-	nucleophile
PPA	polyphosphoric acid
PCC	pyridinium chlorochromate
PDC	pyridinium dichromate
phen	1,10-phenanthroline
Phth	phthaloyl
PPE	polyphosphate ester
PPTS	pyridinium *p*-toluenesulfonate
Red-Al	sodium bis(methoxyethoxy)aluminum dihydride
SEM	β-trimethylsilylethoxymethyl
Sia_2BH	disiamylborane
TAS	tris(diethylamino)sulfonium
TBAF	tetra-*n*-butylammonium fluoride
TBDMS	*t*-butyldimethylsilyl
TBDMS-Cl	*t*-butyldimethylsilyl chloride
TBHP	*t*-butyl hydroperoxide
TCE	2,2,2-trichloroethanol
TCNE	tetracyanoethylene
TES	triethylsilyl
Tf	triflyl (trifluoromethanesulfonyl)
TFA	trifluoroacetic acid
TFAA	trifluoroacetic anhydride
THF	tetrahydrofuran
THP	tetrahydropyranyl
TIPBS-Cl	2,4,6-triisopropylbenzenesulfonyl chloride
TIPS-Cl	1,3-dichloro-1,1,3,3-tetraisopropyldisiloxane
TMEDA	tetramethylethylenediamine [1,2-bis(dimethylamino)ethane]
TMS	trimethylsilyl
TMS-Cl	trimethylsilyl chloride
TMS-CN	trimethylsilyl cyanide
Tol	tolyl
TosMIC	tosylmethyl isocyanide
TPP	*meso*-tetraphenylporphyrin
Tr	trityl (triphenylmethyl)
Ts	tosyl (*p*-toluenesulfonyl)
TTFA	thallium trifluoroacetate
TTN	thallium(III) nitrate

1.1
Reduction of C=O to CHOH by Metal Hydrides

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1.1.1 INTRODUCTION

The reduction of the carbonyl group of aldehydes and ketones to the corresponding alcohol is ubiquitous in organic synthesis. Since the first report of reduction by diborane more than half a century ago,[1] metal hydride reagents have achieved preeminence as the reagents of choice for performing this synthetic transformation. The opportunities for variation in the metal, ligands, counterion and reaction conditions have enabled most problems of stereo-, regio- or chemo-selectivity in synthesis to be overcome satisfactorily. The majority of the complex metal hydrides described in this chapter that exhibit useful reducing properties are readily available from commercial sources, which has contributed enormously to their widespread acceptance and application.

The state of the art of reductions with metal hydrides a decade ago was the subject of comprehensive reviews. A detailed survey of reductions of carbonyl compounds with alkali and alkaline earth metal hydrides, borane and derivatives, alane and derivatives, metal borohydrides, metal aluminohydrides, silanes, stannanes and transition metal hydrides was compiled.[2] The properties, preparation and applications of each reagent were discussed together with methods for their determination, handling techniques

and mechanistic aspects. The functional group selectivity of selected reagents was assessed,[3] and Brown described a 40-year odyssey in the development of a range of complex nucleophilic alumino- and boro-hydrides from their electrophilic counterparts, borane and alane.[4] Reductions by metal alkoxyaluminum hydrides were the subject of an exhaustive *Organic Reactions* review which emphasized the mechanism, scope, limitations and synthetic utility of the reagents.[5]

It is not the intention of this chapter to reiterate the conclusions of these compilations, but rather to concentrate on important synthetic developments that have appeared subsequently.

1.1.1.1 Kinetics and Mechanism

In spite of four decades of investigation, the full details of the mechanism of reduction of ketones by sodium borohydride and lithium aluminum hydride remain to be established.[6] Sodium borohydride reacts with first-order kinetics involving a rate-determining hydride attack on the carbonyl carbon, but the nature of the interaction of the metal cation or boron atom with the carbonyl oxygen is unknown. An *ab initio* theoretical study of borohydride addition to formaldehyde concluded that the traditional [2 + 2] four-center transition state, with simultaneous CH and BO bond formation and BH bond breaking, was not the optimum representation. The preferred alternative was a single-step mechanism with a nonsynchronous four-center transition state with a product-like geometry involving transfer of BH_3 from the hydride, already bonded to carbon, to the carbonyl oxygen atom.[7] The energy of this pathway was further reduced by the incorporation of a water molecule, an OH substituent on boron or a metal counterion. The importance of a metal counterion was demonstrated experimentally in a series of ketone reductions with lithium and sodium alumino- and boro-hydrides. In ethereal solvents reduction proceeded uneventfully, but, when macrocyclic cryptands, specific to either metal ion, were added, no reduction was observed.[8] The details of the effect of the metal counterion and reaction medium on the reduction of carbonyl compounds with alkali metal alumino- or boro-hydrides has been reviewed recently.[9]

The reduction of a series of chiral acyclic ketones, lacking polar functional groups, with a range of lithium, sodium and potassium alumino- and boro-hydrides was investigated in various solvents under different reaction conditions. The changes in steric bulk of the reagents and reaction medium enabled a semiempirical scale for the effective size of the reagent to be applied to the stereochemical analysis of the observed diastereoselectivity.[10]

The reduction kinetics of mesityl phenyl ketone, selected for its convenient rate, with lithium and sodium aluminum hydrides in THF were studied in detail.[11] In the presence of excess hydride, the reaction was first-order in hydride and ketone. A lithium counterion was worth a 10-fold increase in rate over sodium, indicating the influence of the cation on the mechanism. The observed deuterium kinetic isotope effect ($k_H/k_D = 1.27$) was consistent with a rate-determining transfer of hydride to the carbonyl carbon. Further evidence for the association of the counterion with the carbonyl oxygen during reduction was obtained from comparison of entropies of activation of both reactions. The results were rationalized by considering the metal hydrides as solvent-separated ion pairs and/or free ions, prior to coordination of the metal cation to the carbonyl oxygen and hydride delivery *via* a cyclic transition state. Analogous experiments on the reduction of camphor led to the same kinetic conclusions. Significantly, lithium *t*-butoxy- and methoxy-aluminohydrides were observed to follow kinetics consistent with disproportionation of the alkoxide species to give LAH which was the predominant reducing agent.[12]

The kinetics of reduction of 15 cyclohexanones by $Li(Bu^tO)_3AlH$ were investigated and found to follow a simple second-order process.[13] The rate constants were determined at various temperatures and were found to exceed the corresponding values for sodium borohydride. Activation parameters were derived for the reduction, which was nearly isoenthalpic, and rate differences were attributed to the entropic contribution. The results were consistent with a simple four-centred transition state, but additional work is required for a definitive conclusion.

First-order kinetic behavior was observed in the reduction of aldehydes and reactive ketones with 9-BBN-H dimer, but with hindered ketones intermediate or three-halves order kinetics were observed.[14] Monomeric 9-BBN-H was the active intermediate, as in the case of the hydroboration of alkenes and alkynes by this reagent. 9-BBN-H was less sensitive to steric effects than sodium borohydride; hindrance on one side of the ketone caused a moderate rate decrease, while a significant drop was observed with bulky groups on either side of the carbonyl group. The rate was also sensitive to electronic factors; electron-releasing substituents increased the rate of reduction, and electron-withdrawing groups retarded it. These data strongly suggested that the boron atom was coordinated to the carbonyl oxygen during reduction, but it was not established if this was in advance of hydride transfer or simply in the transition state.

Although a polar mechanism is generally accepted for hydride reduction, evidence for an electron transfer mechanism in the reduction of hindered aromatic ketones by main group hydrides has been presented.[15] Dimesityl ketone formed deeply colored, electron paramagnetic resonance active solutions with neutral hydrides of aluminum, boron and magnesium in THF. The kinetic analysis for alane reduction, which produced a long-lived paramagnetic intermediate, suggested a radical cation–radical anion pair as a relatively stable intermediate. The contribution of this pathway in the reduction of dialkyl ketones remains to be established.

1.1.2 THEORY OF STEREOSELECTIVITY

1.1.2.1 Acyclic Carbonyl Compounds

The origin and magnitude of the stereoselectivity observed in the reduction of chiral carbonyl compounds has long been an area of intense theoretical and practical study. Efforts have concentrated largely on the 1,2-asymmetric induction that occurs in the hydride addition to a carbonyl group flanked by an asymmetric center (Scheme 1). Cram's rule was formulated to rationalize the results of nucleophilic addition to aldehydes and ketones containing nonpolar groups.[16] The most stable conformation (**1**) was assumed to arise by minimization of the interaction between the largest group (R^l) and the carbonyl group, which was coordinated to the incoming reagent. Addition then occurred preferentially on the side of the smallest substituent (R^s) rather than the larger medium sized group (R^m). The outcome of Cram reduction of ketone (**2**) to alcohol (**3**) is illustrated. This rule enabled a large body of experimental results to be correlated, but its theoretical basis was subsequently shown to be flawed.

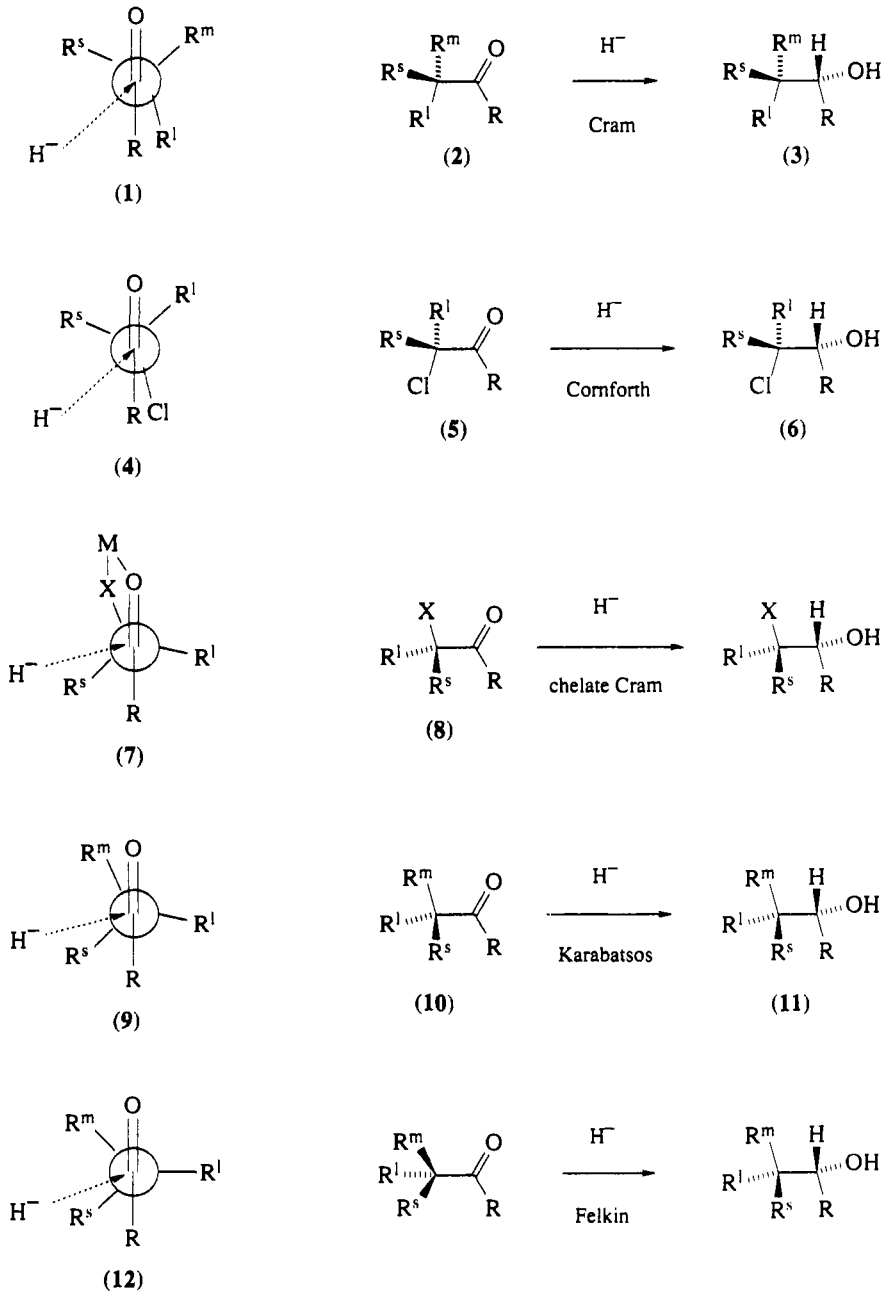
The results for reduction of α-halo aldehydes and ketones were anomalous and led to Cornforth's dipolar model (**4**), in which the dipoles due to the carbonyl group and the carbon–halogen bond were in an antiperiplanar arrangement. Reduction then proceeded from the less-hindered side of ketone (**5**), leading to alcohol (**6**).[17] The possibility of chelation when the α-substituent was an alcohol, alkoxy or amino group (X) was covered by Cram's cyclic or chelate model (**7**).[18] The chelating group (X) and the carbonyl group were eclipsed, coordinating to the metal (M), and reduction occurred from the less-hindered side. This model has been widely used to rationalize diastereoselectivity in reduction of ketones (**8**) when chelation is important, depending on the nature of the substituent (X) and the metal ion.

Information about the ground state conformations of carbonyl compounds that demonstrated that conformations with one bond eclipsing the carbonyl group were energetically favored led Karabatsos to propose an alternative model.[19] Calculations suggested that the most favored conformation (**9**) would have the medium-sized group (R^m) of ketone (**10**) eclipsing the carbonyl group, and addition of hydride would occur from the side of the less bulky substituent (R^s) to give alcohol (**11**). Comparison of the calculated energies of the other possible transition states with this conformation allowed the magnitude of diastereoselectivity to be correlated with experimental results.

The most influential contribution to the interpretation of 1,2-asymmetric induction in carbonyl group reduction was that of Felkin.[20] Attention was directed for the first time to the structure of the transition state, which was assumed to be very similar to that of the substrate. Torsional strain caused by interactions between the partially formed hydride–carbonyl bond and the full bonds at the adjacent center was of paramount importance. The nucleophile was assumed to attack perpendicular to the carbonyl group plane and staggered to the largest or most electronegative group (R^l). This angle of approach was later revised to the Bürgi–Dunitz trajectory,[21] derived from crystallographic studies, which placed the incoming hydride much closer to the substituent (R^s). This interaction was the decisive influence on the selection of the transition state illustrated (**12**) over the alternative which would have the positions of the small (R^s) and medium (R^m) groups exchanged. This model was successfully applied to acyclic and cyclic ketones and allowed crude quantitative rationalization of experimental diastereoisomeric ratios.[22]

Support for the Felkin model was provided by *ab initio* calculations of a range of transition state geometries for reductions of carbonyl compounds with and without an adjacent polar substituent.[23] The transition state energies were found to be minimized in the Felkin conformation as a consequence of the *anti* disposition of the bond forming to the incoming hydride and the bond between the adjacent carbon and the largest or most electronegative group (R^l). Other models that correctly predicted the stereochemical outcome required transition states of significantly higher energy.

Further refinement of the model by calculated trajectory analysis enabled the steric influence of the group (R) attached directly to the carbonyl to be assessed. Increasing the size of R was known to enhance the reduction diastereoselectivity.[22] This may be understood by the perturbation of the trajectory of the



Scheme 1

nucleophile from perpendicular to the carbonyl plane away from the bulky group; the interactions of the nucleophile with the α-center would thus become more decisive. Quantitative support for such deviations from normal approach was provided by calculations on hydride addition to pivaldehyde.[24]

Ab initio calculations of transition state geometries for additions of lithium and sodium hydrides to formaldehyde, acetaldehyde, propionaldehyde and acetone indicated that nucleophilic attack *anti* to a methyl group was disfavored over attack *anti* to a hydrogen by 1–2 kcal mol^{-1} (1 kcal = 4.18 kJ). The combination of the torsional effects identified by Felkin, steric influences and the tendency to avoid attack *anti* to an alkyl group controlled the observed stereoselectivities. Importantly, in agreement with the Felkin model, when two alkyl substituents were present, the most stable conformation had the larger group perpendicular to the carbonyl group and the remaining alkyl group away from the incoming nucleophile. The alternative conformation with an *anti* carbon–hydrogen bond was disfavored because the alkyl groups were unable to attain their preferred dihedral angles. The incorporation of these effects into

an MM2 force field enabled good qualitative rationalization of $LiAlH_4$ reductions of a wide range of alkyl ketones.[25]

The computational support for Felkin's torsional strain model and its success in interpretation of experimental diastereoselectivities has led to its widespread adoption. It appears to be the preeminent open transition state involved in reductions when chelation is not important. Complementary selectivity observed in reductions that do involve chelation may be understood in terms of Cram's cyclic model.

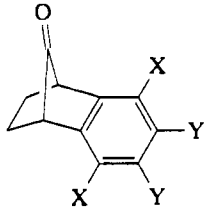
1.1.2.2 Cyclic Carbonyl Compounds

The stereochemistry and mechanism of reduction of cyclic ketones by metal hydride reagents provided a unique opportunity for comparison of experimental results with theoretical expectation. The models proposed by Cram, Cornforth and Karabatsos described above were inadequate to explain the stereochemical outcome, and so a wide range of models was developed to explain the dichotomy between cyclic and acyclic results.[26] The theoretical basis, applications and limitations of these models have been critically reviewed.[6] The effect of steric influences, torsional and electronic factors, and the nature of the cation on the rate of reduction, stereochemical outcome and position of the transition state have also been surveyed.[27]

The stereochemical characteristics of lithium trimethoxyaluminohydride and lithium aluminum hydride in the reduction of cyclic ketones were analyzed by a linear combination of steric strain and product stability control. Qualitative and quantitative explanation of the experimental observations was possible using this approach.[28]

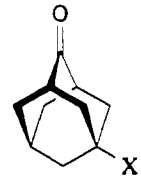
Consideration of the stabilizing interaction between the low-lying σ^*-orbital associated with the bond forming between the incoming hydride and the carbonyl carbon, and remote electron-donor σ-orbitals led Cieplak to an explanation for many kinetic and stereochemical effects in cyclohexanones that were previously unexplained.[29] The normal preference for axial attack in simple cyclohexanones was attributed to the improved electron-donor ability of carbon–hydrogen bonds over carbon–carbon bonds that would be antiperiplanar to the incoming nucleophile in the transition state.

The electronic contribution to reduction stereoselectivity was assessed with a series of substituted 9-benzonorbornenones (**13**) with a range of reducing agents.[30] The observed selectivity, increasing *anti* attack with electron-rich benzene rings, paralleled the homoconjugation sequence. Analogous results were observed in the reduction of a series of 5-substituted adamantanones (**14**) with electronically varied substituents (X), providing strong support for the importance of σ-participation in diastereoselectivity.[31] The unexpected preference for axial reduction of 2-methoxy-4-pyranones (equation 1) with an equatorial methoxy group, even with L-selectride, was explained by the electronic effects of the two conformationally defined carbon–oxygen bonds.[32]



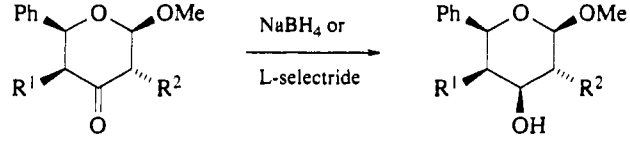
X = F, Cl, H, OMe
Y = F, Cl, H, OMe

(13)



X = Ar, Bu^t, F, Cl, OH, CF_3

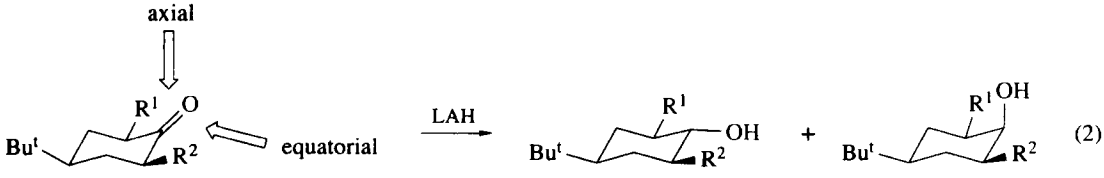
(14)



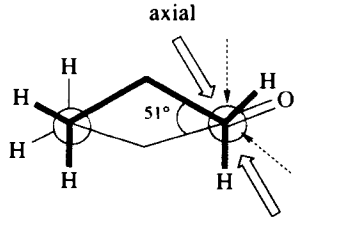
(1)

Felkin identified torsional effects in cyclohexanone reductions that accounted for the observed stereoselectivity. Minimization of these torsional effects, in the absence of steric hindrance, led to the predominance of axial attack (equation 2).[33] Recently, a computational approach has provided quantitative support for this model.[25] The eclipsing interactions between the incoming nucleophile and the bonds α to

the carbonyl group are more serious, for any given trajectory, from the equatorial direction. The differences are clearly illustrated in the Newman projection of cyclohexanone (**15**). Differences in bond lengths and thus torsional bond energies were used to explain observed stereoselectivity in heterosubstituted cyclohexanones.

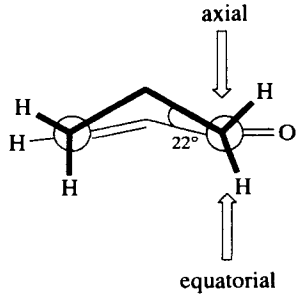


$R^1 = R^2 = H$	92	:	8
$R^1 = Me, R^2 = H$	83	:	17
$R^1 = R^2 = Me$	53	:	47



(15)

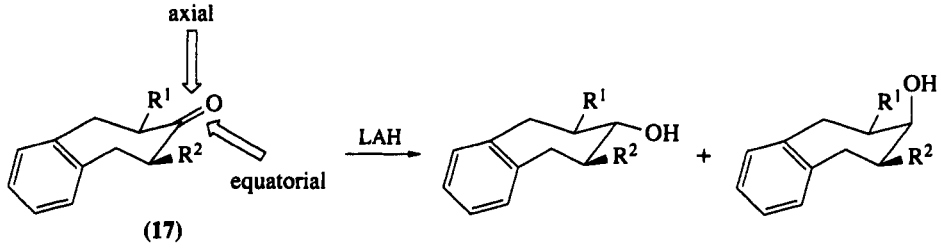
The dramatically enhanced axial selectivity demonstrated in the addition of sterically undemanding nucleophiles, such as lithium aluminum hydride, to conjugated cyclohexenones was explained by the application of the modified MM2 model.[34] The important difference between cyclohexanones and their unsaturated counterparts was the flattening of the ring. The internal dihedral angle was reduced from 51° in cyclohexanone to 22° in cyclohexenone. This in turn produced a dramatic change in the torsional interactions corresponding to axial and equatorial attack, illustrated on the Newman projection (**16**). Calculated energies of transition states for axial and equatorial addition were used to calculate diastereoisomeric ratios that showed good agreement with experimental results.



(16)

The accuracy and applicability of the model was tested further on the lithium aluminum hydride reduction of a series of benzocycloheptenones (**17**; equation 3). Dynamic NMR studies and MM2 calculations demonstrated that the chair conformation shown was the most stable. Since the substrates were sterically unhindered most models predicted that axial attack would be favored. Conversely, MM2 calculations indicated that the transition state for equatorial approach was of lower energy than its axial counterpart. In fact equatorial reduction to give the axial alcohol predominated (60:40) with a single methyl substituent (**17**; R^1 = Me), and was the exclusive outcome in the more hindered case with two methyl groups (**17**; R^1

= R^2 = Me).[35] Felkin's torsional strain approach was considered to be the only model consistent with these results, but an alternative interpretation based on participation of the aromatic ring, consistent with Cieplak's model, has recently been advanced.[36] The significance of torsional interactions was related to the degree of puckering in the cyclic ketone according to the 'flattening rule'.[37]



(17) (3)

R^1 = Me, R^2 = H	40	:	60
R^1 = R^2 = Me	0	:	100

The success of this method for calculating quantitative stereoselectivities of reductions of substituted five-, six- and seven-membered ring and bicyclic ketones was impressive, but additional examples are required to demonstrate its generality.

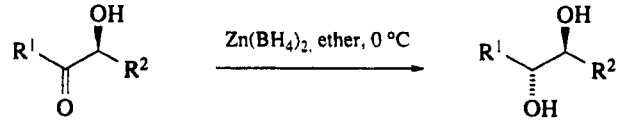
1.1.3 DIASTEREOSELECTIVITY

1.1.3.1 Acyclic Carbonyl Compounds

The development of reliable methods for the diastereoselective reduction of carbonyl compounds in a wide range of acyclic systems has been an area of explosive growth in recent years.[38] This was prompted by the requirements of modern total synthesis in which redundant diastereoisomers are avoided,[39] together with enhanced theoretical understanding of stereoselectivity which allows rationalization of the results.

An exhaustive compilation of examples of reduction of acyclic ketones with an adjacent chiral center appeared recently and is not reproduced here.[40] Those methods that give excellent levels of asymmetric induction likely to be useful in synthesis are highlighted here. The results are collected according to the substrate being reduced rather than the reducing agent. Most of the examples can be rationalized by consideration of the Felkin transition state or, where appropriate, the chelated transition state (Section 1.1.2.1).

α-Hydroxy ketones (**18**) were reduced to the corresponding *anti*-diols (**19**) by zinc borohydride with good selectivity (77:23–99:1) *via* a chelated transition state (equation 4). Silylation with the bulky TBDMS group gave the protected derivatives (**20**) which were reduced by Red-Al at –78 °C preferentially to the *syn* products (**21**) according to a Felkin transition state with the silyl ether in the perpendicular position (equation 5).[41] Selectivity was good (76:24–98:2), except when R^1 was a branched or long chain alkyl group, presumably due to an unfavorable interaction with the silyl ether. These complementary methods were used to synthesize various diastereoisomers of a possible fragment of polyoxygenated antibiotics.[42] Analogous results were observed when a range of reducing agents were screened for reduction of α-benzyloxy alkynic ketone (**22**; Scheme 2).[43] The *anti* isomer (**23**) was produced by zinc borohydride (95:5) *via* chelation control, and K-selectride gave the *syn* Felkin product (**24**; 90:10). The generality of these results was demonstrated on five additional substrates. Significantly, Red-Al was *anti* selective, due to coordination to the benzyloxy group, which was not as effective as TBDMS at suppressing chelation. The dramatic difference between these two protecting groups was again manifested in the



(18) (19) (4)