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C—C Bond Formation by Addition to C=O, C=N and Reactions Involving Olefinic Double Bonds

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Volume E 21 b

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METHODS OF
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METHODS OF ORGANIC CHEMISTRY

(HOUBEN-WEYL)

ADDITIONAL AND SUPPLEMENTARY VOLUMES OF THE 4TH EDITION

GEORG THIEME VERLAG STUTTGART · NEW YORK

VOLUME E 21 b

STEREOSELECTIVE SYNTHESIS

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Preface

There was a time when stereoselectivity of a reaction was mostly of mechanistic interest and reactions that could result in the formation of stereoisomers were considered a nuisance and had to be avoided at best. However, this situation has changed over the past two decades, during which stereoselective synthesis has grown into a reliable methodology. This development began with the remodelling of readily available chiral compounds from nature. More recently, these "ex-chiral-pool" synthetic strategies have been complemented and, in many cases, surpassed by the powerful techniques of asymmetric synthesis.

Originally, only a few laboratories were concerned with the design of routes to enantiomerically pure compounds. Since the demand for nonracemic chiral drugs and pesticides has enormously increased, methods of asymmetric synthesis are now bound to be applied by almost every practising chemist. However, newcomers to the field soon find themselves confronted with a confusing vocabulary, with no guidance as to the appropriate method to solve their problem, and with lack of well-documented procedures. This situation frequently leads to frustration or at least to unnecessary work.

This called for the present volume set of the HOUBEN-WEYL series *Methods of Organic Chemistry*. Since the 1950s HOUBEN-WEYL has served the synthetic community by giving comprehensive critical reviews of the existing synthetic methods in a consistent style and with high reliability. The editors, authors and publisher of HOUBEN-WEYL "Stereoselective Synthesis" have worked together to confer this philosophy to the field of asymmetric synthesis. Thus, we hope to supply a treatise which should become the standard reference in the field.

"Stereoselective Synthesis" gives a comprehensive treatment of chemical transformations in which a new stereocenter is created, i.e., all enantio- and those diastereodifferentiating reactions which allow the absolute and relative configuration of a new stereogenic unit to be controlled. Consequently, mechanism-controlled reactions (e.g. S_N2 displacements), "ex-chiral-pool" syntheses which do not lead to new stereogenic units, and *E*/*Z* selective formation of alkenes are not covered.

Following the general introductory chapters covering principles, nomenclature, separation and analysis, the chapters on individual synthetic methods are organized by the type of bond that is broken or formed. Only starting material and products are considered as a basis for the classification, not the reaction mechanism. In the typical HOUBEN-WEYL style, the scope of the most important methods is illustrated with tables of selected examples. Insight into the practical application of the methods can be obtained from the experimental procedures provided.

The wealth of material forced us to break up the work into five volumes (E21a through e). Access to and properties of the common chiral auxiliaries, solvents, reagents and catalysts which are used in various different reactions is covered comprehensively in Volume E 21e avoiding duplication of information in the individual chapters.

The transition of HOUBEN-WEYL from German to English brought about changes in the layout and in the style of presentation without, however, sacrificing the high standard of quality and reliability that is the hallmark of HOUBEN-WEYL.

Special thanks go to our 101 authors who have spent a great deal of time and effort to achieve the goals we have set. We are also indebted to the editorial staff in Stuttgart, who had to cope with the special challenges of editing and publishing a gigantic amount of complex material.

May 1995

Günter Helmchen
Reinhard W. Hoffmann
Johann Mulzer
Ernst Schaumann

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Volume E 21b

1.3. Formation of C–C Bonds by Addition to Carbonyl Groups

1.3.1. Addition of σ-Type Organometallic Compounds

R. M. DEVANT and H.-E. RADUNZ

1.3.1.1. Theoretical Models

Among C–C bond forming reactions, the nucleophilic addition of σ-type carbanions to aldehydes and ketones is one of the most widely used and extensively studied reactions in organic chemistry. Its synthetic utility is, in particular, derived from the possibility of controlling the stereochemistry of the formed product. Since a stereogenic center is created during the addition of an organometallic reagent to a prostereogenic carbonyl compound, stereoselection is possible if another stereogenic center is already present in the reaction system. In this type of reaction there are three different general routes to stereoselective product formation.

(1) Addition of an achiral organometallic reagent to a chiral carbonyl compound.

(2) Addition of a chiral organometallic reagent to an achiral carbonyl compound.

(3) Addition of an achiral organometallic reagent to an achiral carbonyl compound in the presence of a chiral catalyst, additive or solvent.

Reactions of type 1 and 2 lead to mixtures of diastereomers that are either racemic or enantiomerically pure, depending on whether the substrates are racemates or pure enantiomers. This kind of stereoselection is termed diastereofacial selection[1]. If both substrates, the organometallic reagent and the carbonyl compound, contain a stereogenic center the stereochemical outcome of the addition reaction is governed by double stereodifferentiation[1].

Reactions of type 3 are examples of enantiofacial stereoselection, since the products are mixtures of enantiomers which contain only the stereogenic center formed during the addition reaction. The stereoselectivity inducing chirality is brought into the system via a catalyst, additive or solvent.

The ratio of stereoisomers in a kinetically controlled, irreversible addition reaction is dependent on the relative rate constants leading to the respective diastereomeric transition states. Since the rate constant is a function of the free energy of activation ($\Delta G^{\neq}$), the difference in the energy of the two diastereomeric transition states ($\Delta\Delta G^{\neq}$) is responsible for the ratio of the isomers.

Prediction of the stereochemical outcome of a nucleophilic addition reaction is a delicate problem as the energy difference between the diastereomeric transition states is relatively small. A difference of 1.8 kcal mol^{-1} gives isomers in a ratio of 96.4:3.6 at 25 °C; a difference of 2.8 kcal mol^{-1} leads to a preference of 99:1[2].

Despite difficulties in estimating correct transition state geometries, several models have been proposed which allow prediction of the stereochemical course of nucleophilic addition reactions to acyclic and cyclic carbonyl compounds.

One of the first empirical rules for the addition of an organometallic reagent to chiral aldehydes bearing the stereogenic center adjacent to the carbonyl group was suggested by Cram[3–7] (see Section A.2.3.5.2.). In Cram's "open-chain" model for acyclic carbonyl compounds, bearing no substituents capable of complexing with the organometallic reagent, the conformation of the carbonyl compound is assumed to have the large substituent (L) of the stereogenic center antiperiplanar to the carbonyl group. In an addition reaction, the predominantly formed diastereomer results from sterically controlled, perpendicular attack from the least hindered side of the double bond (Figure 1).

for references see p 1156

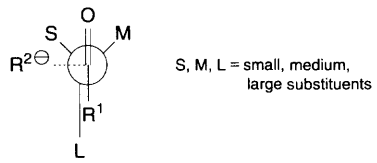

Figure 1. Cram's open-chain model.

Even if this simple, formal picture does not reflect the mechanistic course of the reaction, it allows the major diastereomer formed in a multitude of addition reactions, where the stereochemistry is determined only by steric interactions to be predicted.

A similar steric model, proposed by Prelog, predicts the major diastereomer in the addition of Grignard reagents to chiral esters of α-oxo acids[8, 9]. An antiperiplanar arrangement of the dicarbonyl moiety with the ester carbonyl group flanked by the two least bulky substituents of the stereogenic center is assumed. Again the major diastereomer results from attack of the nucleophile from the sterically least hindered side (Figure 2).

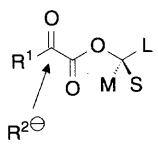

Figure 2. Prelog's model for α-oxo acids.

A different situation exists for α-chiral carbonyl compounds bearing an oxygen or amino substituent at the stereogenic center. This type of compound is capable of forming a chelate complex with the organometallic reagent. Cram's "cyclic model" explains the stereochemistry of addition reactions to α-heteroatom-substituted carbonyl compounds on the basis of a five-membered chelate which favorably fixes the conformation of the reactants. The incoming nucleophile approaches the carbonyl group from the face opposite to the large substituent L (Figure 3)[10, 11].

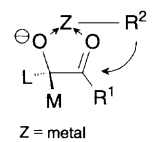

Figure 3. Cyclic model.

In cases where the heteroatom substituent is the medium (M) group, the cyclic and the open-chain model predict the same stereochemistry. In cases where the heteroatom substituent is small (S), the two models predict opposite stereochemical results. This leads to an order of stereospecificity, with the stereospecificity highest when both models predict the correct stereochemistry, with substantially lower specificity when the cyclic model only applies, and with the lowest degree of stereospecificity when only the open-chain model predicts the correct stereochemical result.

The stereoselectivity of an addition reaction is considerably lower when the reactions are conducted in polar solvents, complexing additives such as *N,N,N′,N′*-tetramethylethylenediamine are used, or when the stereogenic center carries a methoxy group instead of a hydroxy group. This behavior is explained as competition between the cyclic model and a dipolar model, proposed for carbonyl compounds bearing a polar substituent such as chlorine with a highly

polarizable bond at the stereogenic α-carbon[12]. The Cornforth "dipolar model" suggests an antiperiplanar arrangement of the carbonyl group and the polarized C–Cl bond, with the nucleophile approaching from the less hindered side (Figure 4).

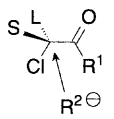

Figure 4. Dipolar model.

In every case the dipolar and the cyclic model predict the opposite stereochemistry. Reaction conditions which allow both models to compete lower the predicted stereoselectivity from that model.

In contrast to the open-chain and dipolar models, which are based on conformations of the carbonyl compound not representing energy minima, Karabatsos proposed a different model assuming an early, "reactant-like" transition state in which the most stable conformation of the free carbonyl compound is preserved[13, 14]. Thus, the C–M bond eclipses the carbonyl double bond and, in order to minimize the energy of the transition state, the nucleophile approaches close to the small substituent on the stereogenic center (Figure 5).

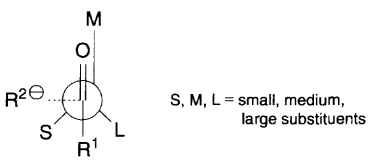

Figure 5. The Karabatsos model.

Therefore, the ratio of diastereomers is dependent on the M ↔ O versus L ↔ O and not on the R^2 ↔ S versus R^2 ↔ M interactions as is the case in Cram's open-chain model.

A further improvement of the theory of 1,2-asymmetric induction was introduced by Felkin[15]. Neither Cram's open-chain model nor the Karabatsos model is able to explain why the stereoselectivity increases when either the incoming nucleophile $R^{2\ominus}$ or the substituent at the carbonyl group (R^1) increases in bulk. To explain these experimental observations the following assumptions are made for the Felkin model:

(1) The transition state for the nucleophilic addition reaction to a carbonyl compound is essentially "reactant-like", rather than "product-like".

(2) In the transition state, the torsional strain involving the partially formed bond between the nucleophile and the carbonyl group represents a substantial fraction of the total strain, even when the degree of bonding is low. Thus, in the case of acyclic carbonyl compounds, a staggered conformation is preferred in the transition state (Figure 6).

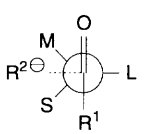

Figure 6. Preferred Felkin transition state.

for references see p 1156

(3) The major steric interactions in the transition state involve the nucleophile ($R^{2\ominus}$) and the carbonyl substituent (R^1). This implies that any conformation is destabilized with respect to that shown in Figure 6 if $R^{2\ominus}$ or R^1 increase in bulk and as a result, the stereoselectivity increases.

(4) A polar substituent, such as chlorine, stabilizes the transition states in which the incoming nucleophile and the polar group are remote (Figure 6, L = Cl).

A direct comparison of Cram's, Cornforth's, Karabatsos's and Felkin's model was possible by ab initio calculations. Several different conformations of a "supermolecule", consisting of a chiral substrate (2-chloropropanal or 2-methylbutanal) and a nucleophile (simulated by $H^{\ominus}$), were calculated[16,17]. The resulting curves, which represent the energy of the different transition states, show that the Felkin transition state lies close to the minima, whereas all other transition state models have significantly higher energies[18,19]. Assuming a Boltzmann distribution for the transition states, the Felkin model accounts for more than 99% of the total yield. In order to predict the 1,2-asymmetric induction, it is therefore justified to take into account only the preferred Felkin transition state and to avoid more complex treatments involving various different transition state geometries[20,21].

In all of the models for 1,2-asymmetric induction described above, a perpendicular attack of the nucleophile ($R^{2\ominus}$) is assumed. However, quantum mechanical calculations and crystallographic data show that the nucleophile approaches the carbonyl group at an angle (ϕ) of between 100° and 110°[2,16,22] (Figure 7).

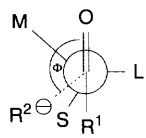

Figure 7. 'Realistic' nucleophile approach Felkin model.

Nonperpendicular attack of the nucleophile explains Felkin's hypothesis for the predominance of interactions involving R^1 and R^2 over interactions involving the carbonyl oxygen. Additionally, as R^1 increases in bulk, the nucleophile is pushed towards the stereogenic center and can better "feel" the difference between the substituents, resulting in an increase in stereoselectivity.

Complexation of the carbonyl oxygen with the counterion of the nucleophile reduces the optimal angle of attack, leading to a decrease in stereoselectivity. Since "hard" nucleophiles[23] are generally associated with highly active cations which are capable of strong "electrophilic assistance", this observation explains the empirical rule that "soft" nucleophiles give higher stereoselectivities than "hard" nucleophiles[24].

In the case of substituted cyclic ketones, particularly cyclohexanones, the stereochemical outcome of an addition reaction is determined by the predominance of either equatorial or axial attack of the nucleophile, leading to axial or equatorial alcohols, respectively[25–27] (Figure 8).

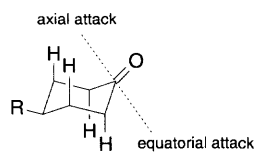

Figure 8. Nucleophilic attack on substituted cyclohexanones.

An empirically derived rule states that axial attack is favored with unhindered cyclic ketones where steric hindrance is negligible[28]. This leads to the concept of "product development

control", implying an essentially product-like transition state with the ratio of isomers reflecting the thermodynamic stabilities of the products[29]. However, it is proposed that "steric approach control" operates with hindered cyclic ketones, implying an early reactant-like transition state with the nucleophile approaching from the least hindered side of the carbonyl group[29]. Since axial attack encounters steric hindrance from the 3,5 axial substituents, equatorial attack is predominant regardless of the size of the incoming nucleophile. Objections to the concept of product development control have arisen as nucleophilic addition reactions are usually run under irreversible reaction conditions and the observed ratio of stereoisomers differs significantly from the ratio in thermodynamic equilibrium[30, 31].

Felkin's model for 3-substituted cyclohexanones is based on the assumption that the premises valid for acyclic carbonyl compounds are also applicable to cyclic substrates[32–34]. Thus, a reactant-like transition state is proposed for both types of nucleophilic addition reaction. While steric strain and torsional strain can be minimized simultaneously in a staggered transition state for acyclic carbonyl compounds, this is not possible in the case of cyclohexanones. Equatorial attack, leading to an axial alcohol ($A^{\neq}$; Figure 9), leads to torsional strain resulting from partial bond eclipsing; axial attack implying an essentially staggered transition state ($E^{\neq}$; Figure 9), results in steric interactions between the incoming nucleophile and the substituent in the 3-position. Therefore, the ratio of stereoisomers is determined by the relative magnitudes of torsional and steric strain. For unhindered cyclic ketones the steric strain is small and axial attack of the nucleophile predominates. For hindered cyclic ketones, or when a bulky nucleophile approaches the carbonyl group, steric strain is overriding the torsional strain and equatorial attack is preferred.

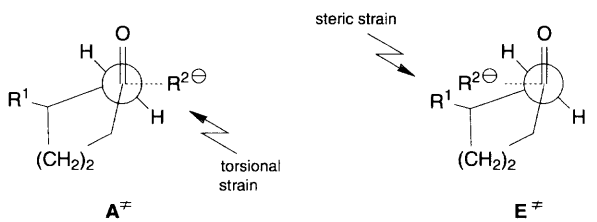

Figure 9. Equatorial ($A^{\neq}$) and axial ($E^{\neq}$) attack on 3-substituted cyclohexanones.

Model calculations generally support Felkin's hypothesis[35–38]. However, an additional controlling factor is the stabilization of the transition state by the approach of the nucleophile antiperiplanar to a vicinal bond[35]. In the transition state for axial attack (Figure 8), the incipient bond is approximately antiperiplanar to two axial C–H bonds. Flattening of the ring improves this antiperiplanarity and, therefore, the more flattened the cyclic ketone, the more axial attack is preferred.

Since equatorial attack is roughly antiperiplanar to two C–C bonds of the cyclic ketone, an extended hypothesis of antiperiplanar attack was proposed[39]. Since the incipient bond is intrinsically electron deficient, the attack of a nucleophile occurs *anti* to the best electron-donor bond, with the electron-donor order: C–S > C–H > C–C > C–N > C–O. The transition state-stabilizing donor–acceptor interactions are assumed to be more important for the stereochemical outcome of nucleophilic addition reactions than the torsional and steric effects suggested by Felkin.

for references see p 1156

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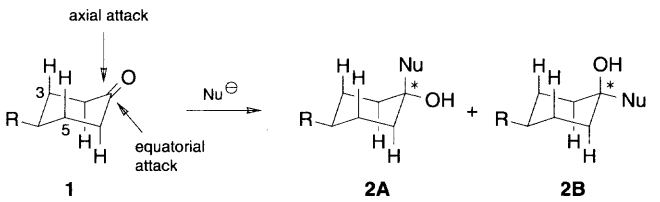
1.3.1.2. Formation of C–C Bonds by Addition to Cyclic Ketones

The stereochemical outcome of nucleophilic addition reactions to cyclic ketones is the subject of numerous experimental and theoretical studies, with substituted cyclohexanones and cyclopentanones having been intensively studied. In addition reactions to substituted cyclohexanones **1** the problem of simple diastereoselectivity is manifested in the predominance of either axial attack of a nucleophile, leading to the equatorial alcohol **2A**, or equatorial attack of the nucleophile which leads to the axial alcohol **2B**.



At least two different, competing interactions are involved in the determination of the stereochemical course of such addition reactions. The ratio of the stereoisomeric products thus reflects the relative magnitudes of these competing interactions. It is generally accepted that the nucleophilic addition to a cyclic ketone involves an early, reactant-like transition state. Consequently, the steric strain between an incoming nucleophile and the axial hydrogens at C-3 and C-5 destabilizes the axial transition state, thus directing the nucleophile into the equatorial position. A rule of thumb is that with bulky nucleophiles equatorial attack predominates. The nature of the interaction which leads to predominant axial attack is still under debate. Several hypotheses have been developed in order to explain experimental results which show a distinct preference for axial attack (see also Section 1.3.1.1.). Among these, the rationalizations discussing transition-state stabilization and destabilization via stereoelectronic factors have received the widest acceptance.

One hypothesis proposes a destabilizing, repulsive interaction between two occupied orbitals. The equatorial transition state is destabilized compared to the axial transition state by torsional strain which is introduced by bond eclipsing of the incipient bond with the axial C-2 and C-6 carbon–hydrogen bonds. This Felkin model[33–37] relies on the assumption that an incipient bond, even if it is only partially formed, suffers from severe repulsion in the case of eclipsing vicinal σ-bonds.

Anh's model[38, 39] proposes a transition state stabilizing charge-transfer interaction between an occupied σ_1-orbital and a vacant σ_2^*-orbital. The axial transition state is stabilized due to delocalization of the σ-orbital of the incipient bond into the σ*-orbitals of the antiperiplanar C-2 and C-6 carbon–hydrogen bonds. During equatorial attack a similar, but weaker, antiperiplanar interaction occurs between the incipient bond and the vicinal carbon–carbon bonds of the cyclohexanone ring. Therefore, in the absence of a strong steric interaction, axial attack is preferred. Flattening of the cyclohexanone ring improves the antiperiplanar alignment of the axial incipient bond and the vicinal axial C-2 and C-6 carbon–hydrogen bonds, thus leading to an improvement of the predominant axial attack.

Cieplak's model suggests an alternative, transition state stabilizing interaction[40, 41]. During axial attack of a nucleophile, the vacant σ*-orbital of the intrinsically electron-deficient incipient bond interacts with the occupied σ-orbitals of the axial C-2 and C-6 carbon–hydrogen bonds. During equatorial attack, the σ*-orbital interacts with the occupied orbitals of the C-2–C-3 and C-5–C-6 ring bonds. The effect of hyperconjugative σ-assistance favors axial attack because C–H bonds are better electron donors than C–C bonds. In contrast to the other hypotheses, Cieplak's model is able to explain the decrease in axial selectivity upon electroneg-

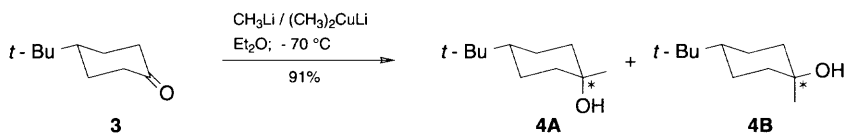
for references see p 1170

ative substitution at the cyclohexanone system or the nucleophile, since introduction of an electronegative substituent decreases the electron donation of vicinal bonds into the vacant σ^*-orbital of the incipient bond. Although very successful, Cieplak's model has been criticized as being based on a paradox assumption[42] because electron donation into the vacant σ^*-orbital of the incipient bond is a forbidden interaction according to the Frontier Molecular Orbital (FMO) Theory[43,44]. Since the FMO theory is one of the most successful theories for describing the course of organic reactions, it is unlikely that nucleophilic addition reactions to cyclic ketones obey an anti-FMO mechanism. According to the FMO theory the addition of a nucleophile to a carbonyl group is controlled by an interaction of the HOMO of the nucleophile with the ($\pi^*_{C=O}$)-LUMO of the cyclohexanone. Since the LUMO orbital is actually more extended on the axial face of the trigonal center compared to the equatorial face[42–46], nucleophilic reagents would prefer the axial approach. However, when the nucleophile is very bulky, steric strain overrides the stereoelectronic preference for axial attack.

Although the true nature of the interaction leading to predominant axial attack remains a point of discussion and awaits final clarification, there is nevertheless a vast body of experimental results indicating the possibilities and limitations of diastereoselective addition to cyclic ketones.

Nucleophilic Addition to Cyclohexanones

Cyclohexanones exist in the chair conformation with substituents occupying an equatorial position whenever possible. Although there is always a small equilibrium concentration of other conformational isomers, the influence of these conformers on the stereochemical course of nucleophilic additions is thought to be insignificant[7]. Nevertheless, 4-*tert*-butylcyclohexanone is often chosen as the substrate in nucleophilic addition reactions since, due to the large size of the substituent, the system is virtually locked in a single chair conformation. Addition reactions of various organometallic reagents to several substituted cyclohexanones are summarized in Tables 1 and 2. Lithium, magnesium, zinc and cadmium alkyl and aryl reagents generally exhibit low to moderate equatorial selectivity in additions to 4-substituted cyclohexanones (Table 1). Apparently, even with nucleophiles as small as methyl, the steric interaction with the axial hydrogens at C-3 and C-5 of the cyclohexanone ring is sufficiently strong to overcome the axial selectivity which is observed in hydride reductions. The equatorial selectivity increases with decreasing reaction temperature[1,2,32] and with increasing steric demand of the nucleophile[1,9,16]. Thus, addition of *tert*-butylmagnesium bromide to 4-*tert*-butylcyclohexanone leads exclusively to the axial alcohol[16]. Compared to the organometallic reagents already discussed, zirconium and titanium reagents lead to a higher preference for equatorial attack[11–15,31]. However, titanium reagents are only suitable for the transfer of *n*-alkyl nucleophiles. With branched alkyl nucleophiles, such as isopropyl, reduction of the carbonyl group, rather than the addition product, is observed[12,22]. With respect to alkylation with methylorganometallic reagents, the higher-order cuprate prepared in situ from copper(I) iodide and methyllithium shows a remarkably high equatorial selectivity upon addition to 4-*tert*-butylcyclohexanone[2].



3 **4A** **4B**

***cis*-4-*tert*-Butyl-1-methylcyclohexanol (4A); Typical Procedure[2]:**

5.70 g (30 mmol) of copper(I) iodide are suspended under a nitrogen atmosphere in 100 mL of anhyd Et_2O at 0 °C. 40 mL of 2 M CH_3Li (80 mmol) in Et_2O are added and the light tan solution is stirred for 10 min. After cooling to −70 °C, 1.54 g (10 mmol) of 4-*tert*-butylcyclohexanone (**3**) in 25 mL of anhyd Et_2O are added over a 5-min period. Stirring at −70 °C is continued for a further 30 min. The reaction mixture is

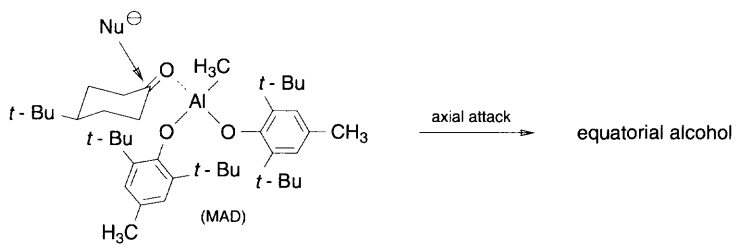
then poured into sat. aq NH_4Cl. The aqueous layer is separated and extracted with Et_2O. The combined organic phase is dried over $MgSO_4$ and the solvent is evaporated under reduced pressure to give a crystalline product (1.80 g) which is purified by sublimation (60 °C/1 Torr); yield: 1.55 g (91 %); d.r. (*cis*/*trans*) 94:6 [determined by VPC (carbowax 20 M column) and NMR in the presence of $Eu(fod)_3$]; mp 62–65 °C.

The equatorial selectivity observed with organolithium reagents is enhanced in diethyl ether as the reaction solvent by the addition of lithium perchlorate (Table 1)[32]. ^{13}C-NMR studies[47] indicate that the formation of a complex between lithium perchlorate and the carbonyl group, which also leads to a dramatic enhancement of the rate of the addition reaction, accounts for the increased diastereoselectivity.

With respect to organomagnesium compounds, the influence of the nontransferable ligand on the diastereoselectivity of nucleophilic addition reactions has been investigated[22]. Thus, organolithium reagents were transmetalated with several magnesium carboxylates and sulfonates and the diastereoselectivity of subsequent addition reactions was determined. Although additions of phenylorganometallic reagents to 4-substituted cyclohexanones usually show a rather low diastereoselectivity[6, 7, 16, 18, 32], reaction of the magnesium reagent obtained by transmetalation of phenyllithium with the sterically demanding magnesium bis(2,4,6-trimethylphenylsulfonate) proceeds with considerable diastereoselectivity[22] (Table 1).

In line with other alkylorganometallic reagents, trialkylaluminum reagents also exhibit a slight preference for equatorial attack if an equimolar amount of the reagent is used. However, the diastereoselectivity is reversed when an excess of the trialkylaluminum reagent is employed[6, 7, 10]. This unusual axial selectivity is explained by the so-called "compression effect"[6, 7], where the effective size of the carbonyl group is increased by complexation with one equivalent of the trialkylaluminum to such an extent that, in the transition state of equatorial attack, severe interactions with the equatorial hydrogens at the adjacent carbon atoms may occur. Thus, the transition state of equatorial attack is destabilized and axial attack is predominant.

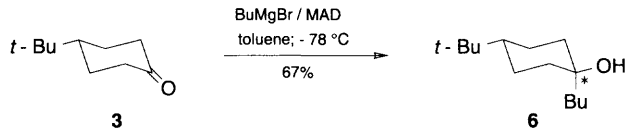
Complexation of cyclic ketones with aluminum reagents is a general method for achieving high axial selectivity, even in addition reactions with organolithium and Grignard reagents. One of the most effective complexing agents is the sterically demanding methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide) (MAD). Thus, pre-complexation of 4-*tert*-butylcyclohexanone with MAD, prior to the addition of an organolithium or Grignard reagent, lead to the almost exclusive formation of the equatorial alcohol via predominant axial attack (Table 1)[3, 4]. This extraordinarily high diastereoselectivity is explained by the formation of a sterically favorable complex **5** between the cyclic ketone and MAD, followed by the addition of the nucleophile from the least hindered (axial) face of the ketone.



5

The initial formation of an "ate" complex by attack of the nucleophile on the aluminum reagent, followed by reaction with the ketone, is unlikely since treatment of the ketone with a mixture of MAD and the organometallic reagent gave results comparable to those obtained with the organometallic reagent in the absence of MAD.

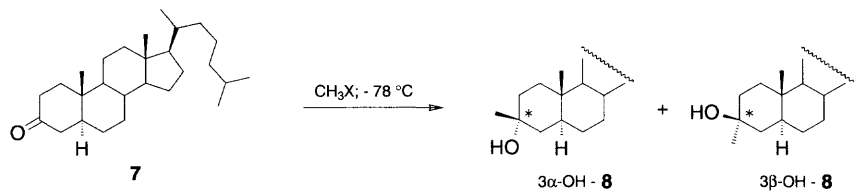
for references see p 1170



3 6

***trans*-1-Butyl-4-*tert*-butylcyclohexanol (6); Typical Procedure[3,4]:**
To a solution of 1.44 g (3 mmol) of MAD in 10 mL of toluene are added 154 mg (1 mmol) of 4-*tert*-butylcyclohexanone (**3**) at −78 °C. Butylmagnesium bromide (3 mmol) in Et_2O is added and the reaction mixture is stirred at −78 °C for 2 h. After quenching with 1 N HCl and extraction with Et_2O, the combined extract is dried and concentrated. The crude product is purified by column chromatography on silica gel (Et_2O/hexane); yield: 142 mg (67%); d.r. 100:0 [determined by capillary GC (column: PEG-HT, 0.25 mm × 25 m; temp.: 130 °C) by comparison with authentic samples].

The methodology of precomplexing a cyclic ketone with MAD, followed by addition of a nucleophile, has also been successfully used for the methylation of 5α-cholestan-3-one (**7**). Thus, addition of methyllithium[4] or methylmagnesium iodide[57] to the steroidal ketone affords predominantly 3β-methyl-5α-cholestan-3α-ol, whereas alkylation with methyllithium/MAD almost exclusively affords 3α-methyl-5α-cholestan-3β-ol via predominant axial attack of the nucleophile[4].

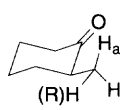


7 3α-OH - **8** 3β-OH - **8**

8: *3-methyl-5α-cholestan-3-ol*

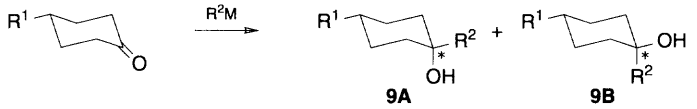
CH_3X	d.r. (3α-OH/3β-OH)	Yield (%)	Ref
CH_3Li	73:27	90	4
CH_3Li/MAD	2:98	96	4

With regard to the stereochemistry of nucleophilic addition reactions, the above noted trends for 4-substituted cyclohexanones are comparable to those observed with 2- and 3-substituted cyclohexanones (Table 2). However, the predominance of equatorial attack, observed with organometallic reagents, other than aluminum reagents, increases in the order 4-substitution < 3-substitution < 2-substitution[2–4,12–14,23,31,32]. This clearly indicates that the steric influence of the substituent increases the closer the substituent is to the reaction site. Thus, 2-methylcyclohexanone is attacked from the equatorial side to a much larger extent than 4-*tert*-butylcyclohexanone. It has been suggested that the high equatorial selectivity observed with 2-methylcyclohexanone is due to the methyl substituent introducing a pseudoaxial hydrogen (H_a), thus increasing steric strain in the case of axial attack[48].



Although it might be expected that a larger substituent at the 2-position of cyclohexanone would hinder axial attack to a greater extent, addition reactions to 2-methyl-, 2-ethyl- and

Table 1. Alkylation of 4-Substituted Cyclohexanones



R^1	R^2M; equiv	Solvent; Temp. (°C)[a]	d.r. (**9A**/**9B**)	Yield[a] (%)	Ref
t-Bu	CH_3Li; 2.0	Et_2O; 5	65:35	94	1
	CH_3Li	Et_2O; −78	79:21	81	2, 32
	CH_3Li; 2/$LiClO_4$; 1	Et_2O; −78	92:8	96	32
	CH_3Li; 2.0/$(CH_3)_2CuLi$; 3.0	Et_2O; −70	94:6	91	2
	CH_3Li; 3.0/MAD; 3.0[b]	toluene; −78	1:99	84	3, 4
	CH_3MgBr; 2.0	Et_2O; 0	60:40	95	1, 5
	$(CH_3)_3Al$; 1.0	benzene; n.r.	76:24	n.r.	6, 7
	$(CH_3)_3Al$; 3.0	benzene; n.r.	12:88	n.r.	6, 7
	$(CH_3)_2Cd$; 2.0[e]	Et_2O; 0	53:47	[d]	8, 9
	$(CH_3)_2Zn$; 2.0[e]	Et_2O; 0	47:53	[f]	8, 9
	$(CH_3)_2TiCl_2$; 1.0	CH_2Cl_2; −78	82:18	92	11, 12, 31
	$(CH_3)_4Ti$; LiCl	Et_2O; −50	38:62	n.r.	12
	$CH_3Ti(O\text{-}i\text{-}Pr)_3$	Et_2O; 25	86:14	99	12–14, 31
	$CH_3Ti(O\text{-}i\text{-}Pr)_3$	hexane; −15 → 22	94:6	n.r.	12, 31
	$CH_3Zr(OBu)_3$; 1.5	Et_2O; 20	80:20	95	15
t-Bu	EtMgBr;	toluene; −78	48:52	95	3, 4
	EtMgBr; 3.0/MAD; 3.0	toluene; −78	0:100	91	3, 4
	Et_3Al; 1.0	benzene; n.r.	88:12	n.r.	6, 7, 10
	Et_3Al; 4.0	benzene; n.r.	14:86	n.r.	6, 7, 10
t-Bu	PrMgBr; 4.0	Et_2O; 0	67:33	66	9
	i-PrMgBr; 2.2	Et_2O; 0	82:18	47	16
t-Bu	BuMgBr	toluene; −78	56:44	58	3, 4
	$BuZr(O\text{-}i\text{-}Pr)_3$; 1.5	Et_2O; −80 → 20	86:14	78	15
	BuMgBr; 3.0/MAD; 3.0	toluene; −78	0:100	67	3, 4
t-Bu	*t*-BuMgBr; 2.2	Et_2O; 0	100:0	22	16
t-Bu	C_6H_5MgBr; 2.2	Et_2O; 0	49:51	89	16
	C_6H_5Li; 2.0	Et_2O; −78	58:42	n.r.	32
	C_6H_5Li; 2/$LiClO_4$; 1	Et_2O; −78	69:31	n.r.	32
	$2,4,6\text{-}(CH_3)_3C_6H_2SO_2OMgC_6H_5$	THF; 78 → 0	90:10	82	22
	$(C_6H_5)_3Al$; 1.0	benzene; n.r.	51:49	n.r.	6, 7
	$(C_6H_5)_3Al$; 4.0	benzene; n.r.	8:92	n.r.	6, 7
t-Bu	H−≡−Na; 1.75	Et_2O/NH_3; n.r.	12:88	68	17
CH_3	CH_3MgI;	Et_2O; 22	52:48	n.r.	7, 12
	$CH_3Ti(O\text{-}i\text{-}Pr)_3$	Et_2O; −15 → 22	88:12	n.r.	12, 31
CH_3	C_6H_5Li; 1.2	Et_2O; 25	47:53	74	18
	C_6H_5MgBr; 1.2	Et_2O; 25	54:46	53	18

[a] n.r. = not reported.
[b] MAD = methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide).
[c] Prepared in situ by treatment of methylmagnesium bromide (4 equiv) with cadmium iodide (2 equiv).
[d] 5% unreacted ketone recovered.
[e] Prepared in situ by treatment of methylmagnesium iodide (4 equiv) with zinc bromide (2 equiv).
[f] 20% unreacted ketone recovered.

for references see p 1170