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From Preparation to Applications in Asymmetric Synthesis

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From Preparation to Applications in Asymmetric Synthesis

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Preface

Undoubtedly, natural product synthesis over the past 50 years has been the flagship of organic chemistry. Has it, in the early days, required a lonely genius such as R. B. Woodward to master structural complexity, there is now a whole bunch of researchers well in a position to handle even much more complicated targets. This remarkable advance in scope and capability is due to several factors, in part to the advent of powerful instrumentation such as crystal diffraction, NMR spectroscopy, high-pressure liquid chromatography, and so on, but equally to the development of new chemical methodology mainly based on mechanistic insights. This has resulted in numerous spectacular innovations, in particular in the control of stereo- and regiochemistry and catalytic transformations, thus avoiding waste and enhancing efficiency.

There can be no doubt that enolate chemistry has been a cornerstone in these developments from early on up to the present day. I remember very well how macrolides such as erythromycins have been elusive targets in the early 1970s, and it was these very target molecules that stimulated the interest in aldol chemistry as the obvious biomimetic access. In this way enolates, which had, so far, been generated as transitory intermediates in protic media, were pinned down structurally and exploited with respect to their full synthetic potential.

Many people have noted that these developments have now come to a head and so, a broad and comprehensive overview of the subject has been overdue, although multifaceted aspects of enolate chemistry have been highlighted in numerous reviews. Fortunately, one of the main players in this field has now stepped in, presenting an ambitious textbook, which in a highly systematic way gives an answer to almost any question that may arise when applying enolate chemistry. Enol ethers are included as well, which is inevitable in view of Mukaiyama aldol chemistry and catalytic alkylation.

The text starts with a brief historic overview and then describes in great detail the various ways of enolate generation and the structural properties of metallated enolates (Chapters 1 – 3). This sets the stage for asymmetric enolate reactions. In Chapter 4, diastereoselective auxiliary-controlled enolate alkylations and aldol additions are presented with main focus on Evans' type auxiliaries, without, however, neglecting alternative auxiliaries. The largest chapter (Chapter 5) is devoted

to enantioselective catalysis in enolate alkylations (i.e., mostly Trost–Tsuji allylation), aldol additions, Reformatsky reactions, and others.

In summary, as far as I can judge, all important aspects of the field have been covered. Mechanistic aspects have been widely discussed, and the practical relevance of the individual methodology has been illustrated by many synthetic applications taken from both academia and industry. I am sure that this book will find its way into the library of all those actively involved in any area of asymmetric synthesis.

August 2015

Johann Mulzer
Universität Wien

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Introductory Remarks

The "central role in synthetic organic chemistry played by the carbonyl group" [1] is well recognized, and enolate chemistry is definitely a major part of carbonyl chemistry; the number of conversions involving enolates became legion. In textbooks of organic chemistry dating back to the 1950s or earlier, the question of the structure of enolates – the reactive species in widely applied carbon–carbon bond forming reactions like the aldol addition, the Claisen condensation, and the Mannich and Michael reactions – was simply answered by the concept of the enolate anion, described as a resonance hybrid of the carbanionic and the oxyanionic resonance formulas. The metal cation was usually ignored completely or little attention was paid to it. The mechanism given in the 1965 edition of Roberts and Caserio for the aldol addition (Figure 1.1) may serve for a representation of the enolate concept in teaching.

This point of view was acceptable as long the corresponding reactions were run in highly polar protic, frequently aqueous solvents that allowed for a at least partial dissociation into an enolate anion and a metal cation. At the times however when, initiated by Wittig's seminal contributions, the concept of the "directed aldol reaction" [3] came up, the protic milieu had to be given up, and the generation and conversion of preformed enolate were moved into moderately polar solvents like cyclic and acyclic ethers, chlorinated hydrocarbons, or even alkanes and arenes, frequently with tertiary amines as cosolvents, the idea of charge separation or even dissociation into a "free" enolate anion and a metal cation became doubtful. As a consequence, the question arose whether the metal is linked to the carbonyl oxygen (O-bound enolates **1**) or to the α-carbon atom (C-bound enolates **2**). Is it the oxygen or the carbon atom that balances on the ball? In addition, a third structure is possible, wherein the metal forms an η^3 bond to the enolate (oxallyl enolate **3**) (Scheme 1.1).

After almost half century of intensive, fundamental, and fruitful investigations of enolate structures, there is now clear evidence indicating that enolates of groups 1, 2, and 13 metals – lithium and boron being the most relevant ones – exist as the O-bound tautomers **1**; the same holds in general for silicon, tin, titanium, and zirconium enolates [4]. Numerous crystal structure analyses and spectroscopic data confirmed type metalla tautomer **1** to be the rule for enolates of the alkali metals, magnesium, boron, and silicon [5].

Modern Enolate Chemistry: From Preparation to Applications in Asymmetric Synthesis, First Edition.
Manfred Braun.

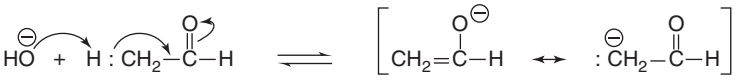
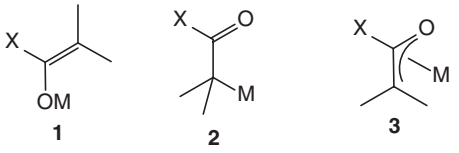
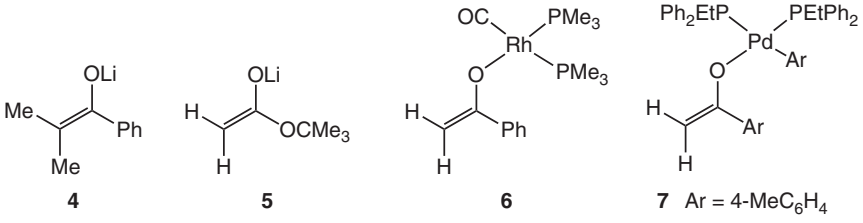


Figure 1.1 Formation of the enolate anion by removal of an α-hydrogen by base is the first step in the aldol addition [2].



Scheme 1.1 General enolate structures.

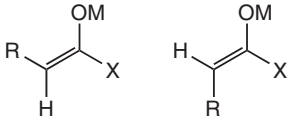
The metal–oxygen interaction may be considered a highly polar covalent bond or a tight ion pair in the case of alkali and earth alkali metals. The O–metal bond and the resulting carbon–carbon double-bond character were early recognized in enolate chemistry by means of NMR spectroscopy that revealed a rotation barrier of at least 27 kcal mol^{-1} for the enolate **4**, as determined in triglyme [6]. Not only the methyl groups in **4** are nonequivalent but also the α-protons (3.14 and 3.44 ppm in benzene) in "Rathke's enolate" **5** derived from *t*-butyl acetate [7] – to give just two illustrative examples of lithium enolates. The double-bond character holds of course also all O-bound enolates, including those of transition metals – rhodium enolate **6** [8] and palladium enolate **7** [9] may serve as illustrative examples: in their ^{1}H NMR spectra, the nonisochronous olefinic protons displaying two singlets at 4.40 ppm/4.62 ppm and 4.90 ppm/4.99 ppm, respectively (Scheme 1.2).



Scheme 1.2 Examples of nonequivalency of α-substituents in lithium enolates **4** and **5**, rhodium enolate **6**, and palladium enolate **7**.

The structural feature of the O–metal bond has a substantial consequence that holds for carbonyl compounds with nonidentical substituents in the α-position: the configurational isomerism with respect to the carbon–carbon double bond giving rise to *cis*- or *trans*-enolates **8** (Scheme 1.3). This diastereomerism was recognized in the early stage of enolate research by NMR spectroscopy [10, 11] and later impressively confirmed by crystal structure analyses [12]. Chemists learned to generate *cis*- or *trans*-enolates selectively and to handle them under conditions that prohibited them from *cis*–*trans* isomerization. In an early, fundamental work

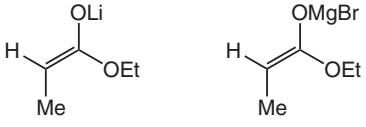
in enolate chemistry, House and Trost disclosed that *cis*- and *trans*-**8** (X = Me, M = Li, R = *n*Bu) do not interconvert even at elevated temperature [13]. Seminal contributions in the groups of Dubois and Fellmann [14] and Ireland *et al.* [15] revealed the distinct influence of enolate configurations to the stereochemical outcome of the aldol reaction and the Claisen–Ireland rearrangement, so that, in turn, these reactions served as a probe for deducing the configuration of enolates.



cis-**8** *trans*-**8**

Scheme 1.3 General structures of diastereomeric *cis*- and *trans*-O-bound enolates.

At a glance, the descriptors *Z* and *E* might seem to be appropriate for O–metal-bound enolates like **6**. Indeed, *E*/*Z* nomenclature causes no problems when the configuration of preformed enolates derived from aldehydes, ketones, and amides has to be assigned, because the O–metal residue at the enolate double bond has the higher priority. However, application of the *E*/*Z* descriptors to ester enolates leads to the dilemma that enolates with different metals but otherwise identical structures will be classified by opposite descriptors, as illustrated by lithium and magnesium enolates **9** and **10**, respectively: the former would have to be termed *Z*, and the latter *E* (Scheme 1.4).

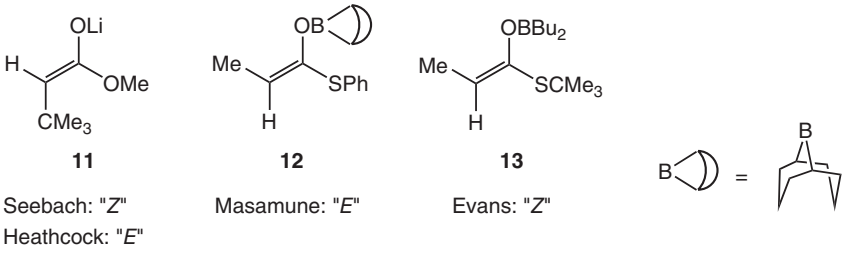


(Z)-**9** *(E)*-**10**

Scheme 1.4 Opposite assignment of configurations (*Z* and *E*) in an ester enolate depending on the O-bound metal.

In order to circumvent this complication, a pragmatic solution has been proposed by Evans: irrespective of the formal Cahn–Ingold–Prelog criteria, the oxygen atom bearing the metal (the OM residue) is given a higher priority, and the *ipso*-substituent X (in enolates **8**) the lower one [4b]. Although this convention has been accepted by other authors, there are both practical and principal objectives against it. The following examples (Scheme 1.5) may illustrate the confusing situation that occurs: the identical diastereomer of enolate **11** has been termed *E* by Heathcock [4d], and *Z* by Seebach [12b], the latter using the correct Cahn–Ingold–Prelog assignment. Another nightmare in this respect is thioester enolates, as again opposite descriptors are spread out in the literature by using either Evans' convention [4b, 16] or

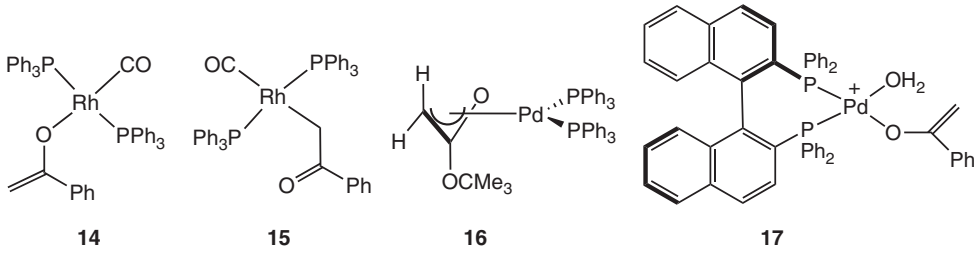
CIP-based nomenclature [17], as demonstrated by the related boron enolates **12** and **13**.



Scheme 1.5 Examples of contradictory assignment of configurations in enolates.

Aside this confusion, there is a principal argument, not to use Evans' convention, because the hard descriptors *E* and *Z* must not be redefined. The soft descriptors *cis* and *trans*, however, can be used without violation of the strict definitions of the unequivocal *E* and *Z*. Therefore, in this book, the recommendation of Eliel *et al.* [18] is followed using the soft descriptors *cis* and *trans*, if a series or a class of enolates are addressed [19]. Thereby, "*cis*" means that the OM substituent is on the same side as the higher-priority group at the α-carbon atom, and "*trans*" means that the OM substituent is on the opposite side. Only in those cases, where an individual enolate is concerned, *E*/*Z* nomenclature is used according to its strict definition.

The C-bound metalla tautomers **2** are typical for the less electropositive metals [4e]. They have been postulated occasionally for zinc [20] and copper [21] but are a rule for mercury [10a]. Carbon-bound enolates of molybdenum, tungsten, manganese, rhenium, iron, rhodium, nickel, iridium, and palladium have been detected and characterized [22], but one has to be aware of the phenomenon that they exist in equilibrium with the O-bound metalla tautomers. The interconversion of the palladium enolates **14** and **15** (Scheme 1.6), whose activation barrier has been determined to amount to approximately 10 kcal mol^{-1}, may serve



Scheme 1.6 Rhodium and palladium enolates. Equilibrating O- and C-bound tautomers **14** and **15**; rhodium complex **16**, characterized by its crystal structure, as an example of an η^3-oxallyl enolate; cationic palladium complex **17**, proven as intermediate in Shibasaki's enantioselective aldol addition.

as a typical example [8]. The dynamic of O- and C-bound tautomers **1** and **2** (Scheme 1.1) with transition metals is obviously a delicate balance depending on the individual enolate, the metal, and the ligands [9, 23].

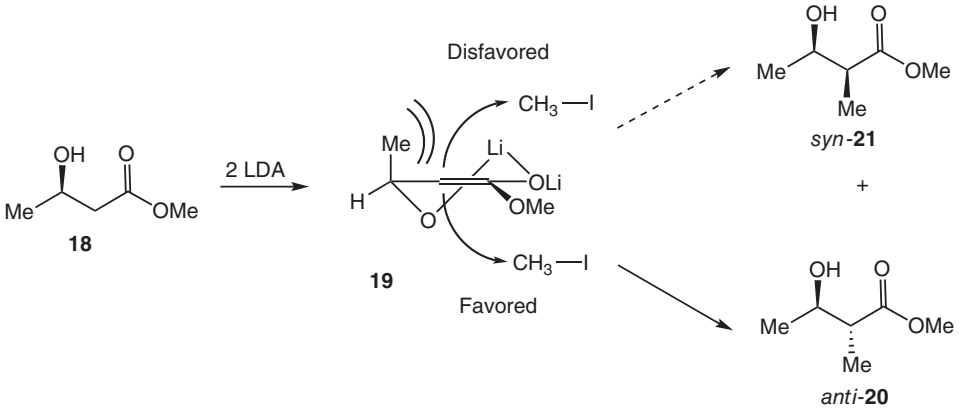
The third species in Scheme 1.1, the oxallyl enolate **3**, featuring an η^3-metal bond is also typical for transition metals and may coexist with the O- and C-bound species in equilibria. Enolates with oxallyl structure **3** were obtained by directed preparation and characterized [24] and also postulated as reactive intermediates [25]. The unambiguously characterized rhodium complex **16** (Scheme 1.6) may serve as an illustrative example. According to several theoretical calculations, lithium enolates may form an η^3 bond, resulting from a π(CC)–Li bond in addition to the OLi bond [26].

At the time the chemistry of main group enolates flourished already for a while, that of late transition metals had a shadowy existence in synthetic organic chemistry. Their stoichiometric preparation and the sluggish reactivity – tungsten enolates, for example, required irradiation to undergo an aldol addition [24a] – did not seem to predestine them to become versatile tools in asymmetric syntheses [27]. The breakthrough however came when palladium and rhodium enolates were discovered as key intermediates in enantioselective catalyses. After aldol reactions of silyl enol ethers or silyl ketene acetals under rhodium catalysis were shown to occur via enolates of the transition metal [8] and after the first steps toward enantioselective variants were attempted [28], palladium catalysis enabled indeed aldol additions with substantial enantioselectivity [29], where O-bound palladium enolate **17** was identified as intermediate cationic palladium complex in the catalytic cycle [29b]. In α-carbonyl arylation reactions [30] and in several decarboxylative allylic alkylations [31], palladium enolates of different structure types play a key role as reactive, selectivity-determining intermediates also.

Very soon after protocols for the generation of "preformed" O-bound enolates **1** [32] derived from aldehydes, ketones, esters, thioesters, amides, carboxylates, and acyl transition-metal complexes (X = H, alkyl, aryl, OR, SR, NR_2, ML_n) had developed, they became workhorses in asymmetric synthesis. Retrospectively, one realizes that stereoselective enolate chemistry reached a first summit during the heyday of chiral auxiliaries in asymmetric synthesis during the last two decades of the past century. Until today, the most versatile of those enolates with chiral auxiliaries – the topic of Chapter 4 – are widely used in drug and natural product syntheses. The feature common to all these protocols is the quantitative generation of the "preformed enolate" prior to the conversion by treatment with a suitable reactant. The more recent "boom" in enolate chemistry – the topic of Chapter 5 – is mainly based on enantioselective catalyses involving either main group or transition-metal enolates as reactive intermediates. Accordingly, they are not "preformed" but generated in the course of the catalytic cycle.

Diastereoselective reactions of enolates that are derived from *a carbonyl compound with a chiral carbon skeleton* constitute the earliest concept that provided stereochemical control in enolate chemistry in the classical transformations like alkylation, aldol reaction, and Micheal additions. Beginning with stereocontrol

exhibited by cyclic enolates, protocols were developed later for open-chained ketone, ester, and amide enolates and reached a high level of sophistication and versatility. The diastereoselective alkylation of 3-hydroxybutanoate **18** that was elaborated independently by Seebach [33] and Frater [34] may serve as an illustrative example of this concept: after a double deprotonation by lithium diisopropylamide (LDA), the *cis*-enolate with an assumed chelated structure **19** is generated and subsequently alkylated from the sterically less hindered face to give anticonfigured α-methylated butanoate **20**, the diastereomeric ratio of *anti*-**20** to *syn*-**21** amounting to 95 : 5 (Scheme 1.7).



Scheme 1.7 Diastereoselective methylation of 3-hydroxybutanoate **18** – an example of a diastereoselective conversion of a lithium enolate with a chiral skeleton.

However, diastereoselective transformations like this are *not to be discussed* within this monograph, as they do not fulfill the criteria of "asymmetric synthesis," according to Marckwald's definition (in today's language): "this would mean […] those reactions, or sequences of reactions, which produce chiral nonracemic substances from achiral compounds with the intermediate use of chiral nonracemic materials, but excluding a separation operation" [35]. Thus, diastereoselective conversions not included for that reason in this book are, for example, aldol additions, Mannich reactions, and Michael additions of enolates to ketones, imines, and α,β-unsaturated carbonyl compounds, respectively, *with any chiral skeleton.* For such stereoselective enolate reactions that are not asymmetric syntheses, the reader is referred to the literature, which treated this topic in a comprehensive manner [36].

This monograph restricts itself to enolates that are *not stabilized* by electron-withdrawing groups, meaning that stabilized anions derived from β-diketones, β-keto esters, β-imino esters, and so on will not be treated. Furthermore, the *restriction to O-enolates* is kept through this book, meaning that aza-enolates are not discussed. Concerning the metals at the enolate, the so-called half metals boron and silicon are included – not only for systematic reasons (as being more electropositive elements than carbon) but first and foremost for their eminent

importance in synthesis. For the "silicon enolates," the common terms "silyl enol ethers" or "silyl ketene acetals" are used as synonyms.

A final restriction concerns the question of the "ionic character" of the highly polar enolates of alkali metals and alkaline earth metals, in particular those of lithium. After a half century's spectroscopic investigation and computational studies that were accompanied by considerable debates, a general of answer to the question of the iconicity of organolithium compounds in general and enolates in particular seems not to be possible. As a tendency that results from theoretical calculations, the oxygen–lithium bond is assumed to be more polar than the carbon–lithium bond; however, a quantification of the iconicity varies considerably [26]. It seems that for understanding and rationalizing stereoselective conversions of the polar enolates, the question of their "ionic character" is by far less important than the knowledge of their molecular structures in the crystalline state and in solution – the topic of Chapter 3.

In Chapters 2, 4, and 5, several experimental procedures have been included that are typical for the method on hand. From the numerous protocols found in the literature, such procedures were chosen that describe the preparation, isolation, and characterization of an individual compound. Procedures that yield products in gram scale or larger are generally preferred.

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31. Streuff, J., White, D.E., Virgil, S.C., and Stoltz, B.M. (2010) *Nat. Chem.*, **2**, 192–196, and references therein.
32. For an informative discourse upon the historical development of the term "enolate", see Ref. [4d], p. 3–4
33. (a) Seebach, D. and Hungerbühler, E. (1980) in *Modern Synthetic Methods 1980* (ed R. Scheffold), Salle und Sauerländer, Frankfurt am Main, Aarau, pp. 131–140; (b) Seebach, D., Imwinkelried, R., and Weber, T. (1986) in *Modern Synthetic Methods 1986* (ed R. Scheffold), Springer-Verlag, Berlin, pp. 125–259.
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36. (a) See the relevant chapters on stereoselective carbon-carbon bond formations Helmchen, G., Hoffmann, R.W., Mulzer, J., and Schaumann, E. (eds) (1995) *Houben Weyl, Stereoselective Synthesis*, vol. E21b and 21c, Thieme, Stuttgart; (b) For a more recent review, see: Braun, M. (2012) *Comprehensive Chirality*, (eds E.M. Carreira, H. Yamamoto), Elsevier, **2**, pp. 346–369.

2
General Methods for the Preparation of Enolates

In the large multitude of their applications in synthesis, the highly reactive, moisture-, air-, and temperature-sensitive metal enolates are not "prepared" in the word's classical meaning, involving isolation, purification, and characterization. Instead, they are usually generated without isolation, subsequently treated with a suitable reagent or reactant in a "one-pot" or "consecutive reaction," or occur as reactive intermediates in a catalytic cycle. This situation implies on the one hand that, very frequently, enolates are used without knowledge of their exact structure. On the other hand, one has to be aware that all reagents, solvents, and additives required for and present during the preparation of the enolate still persist in the consecutive reaction, so that one should not be too surprised to realize that "the same enolate" when generated in various ways may exhibit completely different chemical behavior. This holds, to give just two remarkable examples, for lithium salts and amines, whose presence can seriously change the reactivity of an enolate [1]. Clearly, the individual metal determines the structure of the enolate and strongly influences its reactivity and selectivity; however, the role of solvents, cosolvents, additives, and salts must not be neglected. Thus, the proper choice of the conditions used for enolate formation might be the first step to successful application. Therefore, an overview on the different ways for the preparation of enolates is given, emphasizing their regioselective and stereoselective formation.

2.1
Enolate Formation by Deprotonation

The deprotonation in α-position of a carbonyl group induced by treatment with strong, nonnucleophilic bases is the most important, most convenient, and most frequently applied procedure for the preparation of preformed enolates of alkali metals and magnesium (Equation 2.1) [2]. A sufficient thermodynamic acidity, prerequisite to an efficient quantitative formation of an enolate **3**, requires the difference between the pK_a value of the conjugate acid **4** of the base **2** and the corresponding carbonyl compound **1** (at least) to reach or to surpass the value of 2 [$pK_{a\,(4)} - pK_{a\,(1)} \geq 2$] [3]. Even if this thermodynamic condition is met, an efficient

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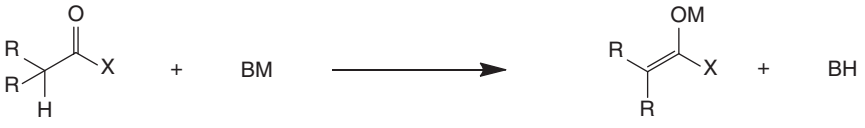
Manfred Braun.

preparation of a preformed enolate requires in addition a sufficiently high deprotonation rate, the so-called kinetic acidity.



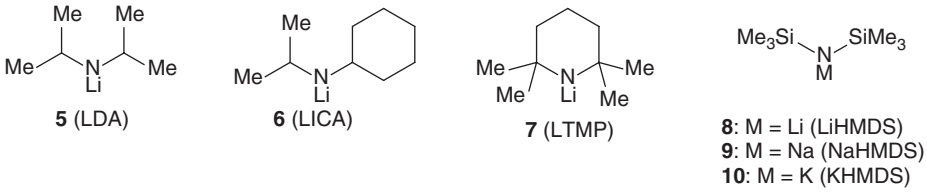
1 **2** **3** **4**

R = H, alkyl, aryl
X = H, alkyl, aryl, OR, NR_2, OM
M = Li, Na, K, MgX

(2.1)

For the quantitative conversion of aldehydes, ketones, carboxylic esters, thioesters and amides, and even carboxylates (1: X = H, R, OR, NR_2, OM) into the corresponding preformed enolates, these requirements are best fulfilled by amid bases of – first and foremost – lithium but also sodium, potassium, and, to a minor extent, magnesium [4]. Indeed, the enormously fruitful role of preformed enolates in organic synthesis developed only after lithium dialkylamides (Scheme 2.1) had settled in the laboratories of synthetic chemists and the lithium diisopropylamide "(LDA) era" [1] had begun. LDA (**5**), reported for the first time in 1950 [5] shortly after diisopropylaminomagnesium bromide [6], was accepted reluctantly and became popular only when it had proven its utility in Wittig's "directed aldol reaction" that is based on azallyl lithium reagents generated by deprotonation of aldimines [7]. Aside from LDA that undoubtedly became the standard base for enolate formation, various related lithium dialkylamides were introduced later on, among which the sterically more demanding lithium isopropylcyclohexylamide [8] (LICA, **6**) and lithium tetramethylpiperidide [9] (LTMP, **7**) were also frequently applied. These lithium dialkylamides combine a high basicity with a nonnucleophilic character, necessary to avoid addition to the carbonyl compound instead of deprotonation, and a high solubility in etheric solvents due to the lipophilicity of the alkyl residues. In view of the weak acidity of dialkylamines (with pK_a values around 36 for the conjugate acids) [10], it is obvious that, for almost all of the carbonyl compounds **1**, dialkylamides of alkali metals fulfill the condition of sufficiently high basicity for a quantitative and irreversible deprotonation. If, however, bis(trimethylsilyl)amide base of lithium (LiHMDS, **8**), bis(trimethylsilyl)amide base of sodium (NaHMDS, **9**), and bis(trimethylsilyl)amide base of potassium (KHMDS **10**) [11] are used for the generation of the corresponding lithium, sodium, and potassium enolates, respectively, one has to take into account the distinctly lower basicity, as indicated by the difference in acidity between diisopropylamine (pK_a 36) and hexamethyldisilazane (pK_a 26).

In modern syntheses, the alkali amide bases **5**–**10** (Scheme 2.1) have proven themselves the most frequently applied ones due to their reliability and versatility. They have, more or less completely, replaced traditionally used bases [2a] like

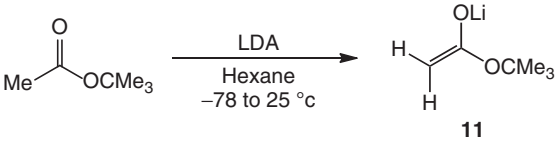


Scheme 2.1 Standard bases for the formation of alkali metal enolates.

potassium *t*-butoxide, which is in general not suitable for quantitative generation of nonstabilized enolates, as well as sodium and potassium hydrides. This also holds for triphenylmethyl lithium, sodium, and potassium, despite the fact that these carbanions are sufficiently basic and played an important role in the pioneer times of enolate chemistry. Their disadvantage is clearly the tedious separation of triphenylmethane that requires chromatography – in contrast to the easy removal of the previously mentioned amines during the acidic work-up, but on the other hand, they permit to obtain amine-free alkali metal enolates – a substantial advantage in some cases: it avoids complications that originate from the "R_2NH effect" [1]. To give an example, diisopropylamine that originates from the deprotonation by means of LDA is not a spectator, but a player: when the enolate is quenched by a deuteron source (like MeOD), the carbonyl compound formed has not incorporated a deuterium, but a hydrogen atom. A hydrogen-bonded aggregate between the enolate and diisopropylamine seems to be responsible for this effect [12]. The unsubstituted amides of alkali metals are hardly used any more for enolate formation due to the complicated handling of liquid ammonia that functions as the solvent. Extremely hindered bases like lithium di-*t*-alkylamide [13a] or lithium-*t*-butyl-*t*-octylamide [13b] also failed to find wide application, probably due to the sluggishness of their reactions. LDA, LICA, LTMP, and LiHMDS are recommended to be prepared freshly by treatment of the corresponding amine with *n*-butyllithium and used in a one-pot reaction. In a molar scale, LDA is accessible by reaction of lithium metal with diisopropylamine and styrene in diethyl ether [14]. NaHMDS and KHMDS are generated from bis(trimethylsilyl)amine and sodium or potassium amide, respectively. Alternatively, the commercially available solutions and/or suspensions of the bases **5**–**10** can be used.

Among alkali metal enolates, those derived from ketones are the most robust one; they are stable in etheric solutions at 0 °C. The formation of aldehyde enolates by deprotonation is difficult because of the very fast occurring aldol addition. Whereas LDA has been reported to be definitely unsuitable for the generation preformed aldehyde enolates [15], potassium amide in liquid ammonia, potassium hydride in THF, and "super active" lithium hydride seem to be appropriate bases for the metallation of aldehydes [16]. In general, preformed alkali metal enolates of aldehydes did not find wide application in stereoselective synthesis. Ester enolates are very frequently used, although they are more capricious than ketone enolates. They have to be formed fast and quantitatively, because otherwise a Claisen condensation readily occurs between enolate and ester. A complication with ester enolates originates from their inherent tendency to form ketene under elimination

of the corresponding alkoxide [17]. Therefore, ester enolates are usually prepared and handled in solutions at −78 °C. However, the enolates of α-aryl-substituted esters are less fragile but also acetate enolates. Thus, the lithium enolate of *t*-butyl acetate ("Rathke enolate") **11**, prepared in hexane with LDA, is remarkably stable up to 110 °C and can be isolated as a pure solid material (Scheme 2.2) [18]. When heated to 130 °C in vacuo, lithium *t*-butoxide sublimes off, and the lithium enolate of *t*-butyl acetoacetate forms [19].



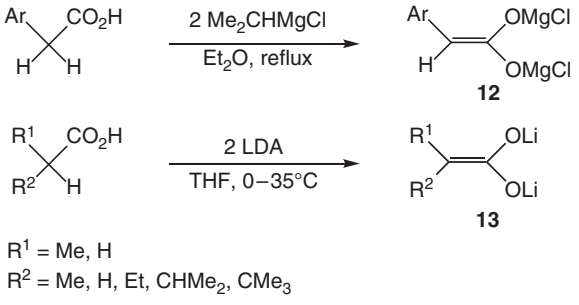
11

Scheme 2.2 Preparation of Rathke's enolate **11**.

Lithium Enolate 11 [19]

A 50-ml two-necked flask was equipped with a magnetic stirrer and a connection to the combined nitrogen/vacuum line and closed with a septum. The air in the flask was replaced by nitrogen. A 1.6 M solution of *n*-butyllithium in hexane (6.25 ml, 10.0 mmol) was injected by syringe. After dilution by addition of an 8.75-ml portion of dry hexane, the solution was cooled to 0 °C. After dropwise addition of diisopropylamine (1.40 ml, 1.16 g, 10.0 mmol) within 2 min, the mixture was cooled to −78 °C. *t*-Butyl acetate (1.35 ml, 1.16 g, 10.0 mmol) was added slowly through syringe and stirring was continued for 30 min. Upon warming to room temperature, a colorless precipitate formed. The supernatant solution was removed by syringe, and the residue was washed several times by addition and subsequent removal of dry hexane through syringes. Finally, the residue was died in oil-pump vacuum to give solid enolate **11**. Yield: 0.57–0.69 g (45–55%). ^{1}H NMR ([D_6]-benzene): $\delta = 1.56$ (s, 9H), 3.14 (s, 1H), 3.43 (s, 1H).

Compared to an alkoxy anion RO^-, the dialkyl amide anion R_2N^- is a poor leaving group. Therefore, amide and lactam enolates are much more stable than ester enolates and can be handled under similar conditions as ketone enolates. An elegant solution to overcome ketene formation in deprotonated carboxylic derivatives has been opened by doubly deprotonated carboxylic acids, which have been first substantiated under the form of the dimagnesium compounds, the so-called Ivanov reagent **12**, generated by deprotonation of α-arylcarboxylic acids with isopropylmagnesium chloride [20]. A more general route to doubly deprotonated carboxylic acids was opened by Creger, who introduced dilithiated reagents **13** that do not require an anion-stabilizing effect by α-aryl substituents. It turned out that, here again, LDA is the metallation agent of choice, sufficiently basic to doubly deprotonate not only acetic acid, but also various alkanoic acids. Even isobutyric carboxylate – a weak carbon acid – could be converted into the lithium enolate **13** ($R^1 = R^2 = Me$) (Scheme 2.3) [21, 22].

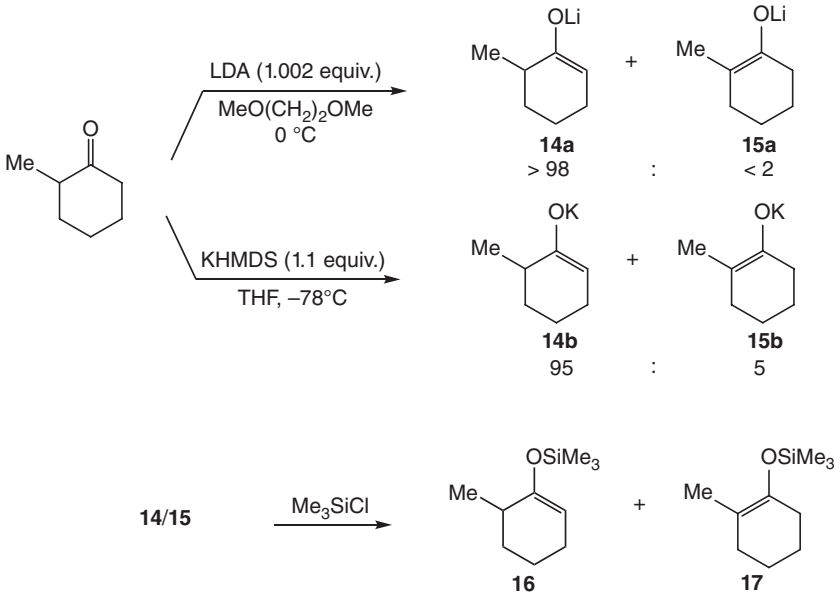


Scheme 2.3 Preparation of Ivanov's reagent **12** and dilithiated carboxylic acids **13**.

Doubly Lithiated Carboxylic Acids 13 [22a]

Under nitrogen, a solution of LDA was prepared from diisopropylamine (28.0 ml, 20.2 g, 200 mmol) in 150 ml of absolute THF and 160 ml of a 1.25 M solution of *n*-butyllithium in hexane (200 mmol). To this mixture was added under stirring at −30 °C a solution of the carboxylic acid (100 mmol) in 100 ml of THF. In most cases, a colorless voluminous precipitate formed during the addition. In order to complete the deprotonation, the mixture was stirred at 50 °C for 1 h. Then, all volatile material was removed by evacuation and collected in a cooling trap. The enolates **13** formed white solid materials or had a glassy consistence. They were dissolved in THF and used immediately for subsequent reactions.

The problem of regioisomerism arises when enolates are generated from unsymmetrical ketones with acidic protons in both the α- and α′-positions. Fundamental studies of House and coworkers [23] revealed that suitable conditions for a controlled kinetic or thermodynamic enolate formation provide a solution to the problem, particularly for ketones with different degrees of substitution adjacent to the carbonyl position. Thus, 2-methylcyclohexanone turned out to give the less substituted lithium enolate **14a** when added to LDA in 1,2-dimethoxyethane – a result that is attributed to a kinetically controlled deprotonation by the attack of the sterically demanding base to the more readily accessible proton. The ratio of the regioisomeric lithium enolates **14a** and **15a** was determined to exceed 98 : 2 by conversion into the silyl enol ethers **16** and **17**. Without loss in regioselectivity, the solvent can be replaced by THF in a simpler protocol [24]. An essential detail of the protocols is the use of a slight excess of LDA over the ketone (Scheme 2.4): for kinetic deprotonation, an excess of the ketone over LDA has to be strictly avoided, because the excess of the ketone serving as proton source causes enolate equilibration. Procedures that are representative for deprotonation of ketones with LDA are given in the following text. In order to obtain enolate **14a** regioselectively, LiHMDS in THF can be used instead of LDA. A very remarkable observation was made in the course of mechanistic studies by Zhao and Collum [25]: the rate of the deprotonation of 2-methylcyclohexanone by LiHMDS in toluene was enhanced by a factor of



Scheme 2.4 Regioselective preparation of less substituted enolates derived from 2-methylcyclohexanone.

3000 upon addition of triethylamine (and the ratio of regioisomers **14a:15a** was found to surpass 95 : 5). The observation of triethylamine participation in the deprotonation step had serious implications on the rationale of enolate formation by means of lithium amide bases (vide infra). Under kinetic control, the potassium enolate **14b** of 2-methylcyclohexanone is accessible in a regioselective manner by using KHMDS. Here again, the ketone is added to an excess of the base. The regioisomer ratio **14b:15b** amounts to 95 : 5, as determined after quenching as silyl enol ethers **16**/**17** [26].

Lithium Enolate 14a by Deprotonation of 2-Methylcyclohexanone in 1,2-Dimethoxyethane and Quenching as Silyl Enol Ether 16 [23]

A solution of methyllithium (100 mmol) in diethyl ether was concentrated under reduced pressure. The residual solid methyllithium was dissolved under a nitrogen atmosphere in 1,2-dimethoxyethane (100 ml) containing a few milligrams of triphenylmethane that served as indicator. After cooling to 0 °C, diisopropylamine (10.10 g, 100 mmol) was added under stirring. To the LDA solution thus formed, 2-methylcyclohexanone (11.18 g, 99.8 mmol) was added dropwise under stirring within a period of 10 min, until the red color of the triphenylmethyl anion had almost disappeared to give a solution of enolate **14a**.

For quenching, a solution of triethylamine (5.0 ml, 4.4 g, 44 mmol) and freshly distilled chlorotrimethylsilane (20 ml, 18.4 g, 169 mmol) was centrifuged in order to remove the

insoluble triethylamine hydrochloride. The supernatant solution was added through a cannula under stirring to the solution of the lithium enolate **14a** at 0 °C. A precipitate of lithium chloride formed, and the mixture was stirred for 15 min at room temperature. Pentane and cold aqueous $NaHCO_3$ were added. The organic layer was separated and dried. After removing the solvent, the residual oil (49.5 g) was submitted to fractional distillation through a short Vigreux column. A forerun (bp 30–59 °C/9.3 mbar) was discarded, and the fraction boiling at 59–61 °C (9.3 mbar) was collected. It contained the silyl enol ether **16** that contained less than 2% of the regioisomer **17**; n_D^{22} 1.44401.

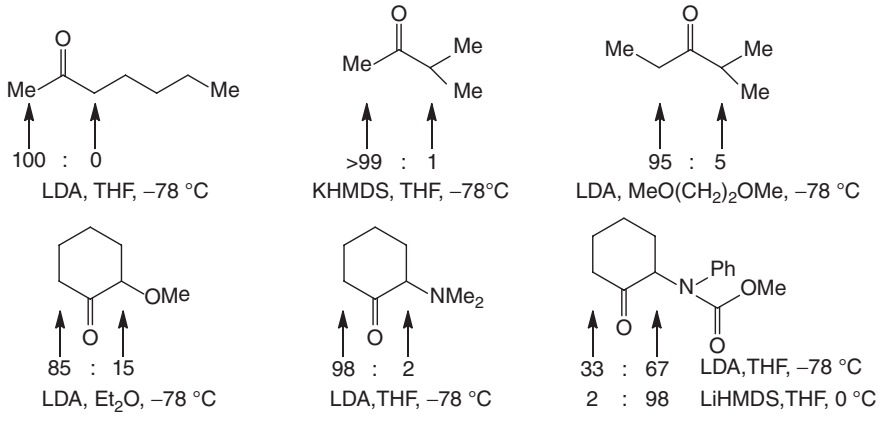
Lithium Enolate 14a by Deprotonation of 2-Methylcyclohexanone in THF and Quenching as Silyl Enol Ether 16[24c]

A mixture of diisopropylamine (0.11 mol, 11.1 g) and 70 ml of THF was cooled to below −50 °C. A solution of *n*-butyllithium (0.11 mol) in 73 ml of hexane was added by syringe. After the resulting LDA solution had been cooled to −75 °C, a mixture of 2-methylcyclohexanone (11.2 g, 0.1 mol) and 20 ml of THF was added dropwise over 10 min. During this addition, the reaction mixture was kept between −70 and −60 °C. Then, the cooling bath was removed and the mixture was allowed to reach −50 °C.

For quenching, freshly distilled chlorotrimethylsilane (14.1 g, 0.13 mol) was added in one portion, while allowing the temperature to rise to ∼15 °C. Diethylamine (3 g) was subsequently added to the white suspension, and stirring at 10–20 °C was continued for 5 min. The reaction mixture is then poured into 200 ml of ice water. After vigorous shaking and separation of the layers, the aqueous layer was extracted twice with small portions of pentane. The combined organic layers were washed once with a concentrated aqueous solution of ammonium chloride and dried over $MgSO_4$. The solution was concentrated under reduced pressure, and the remaining liquid carefully distilled to give the pure silyl enol ether **16**; bp 70 °C/16 mbar, n_D^{20} 1.4453, in greater than 80% yield.

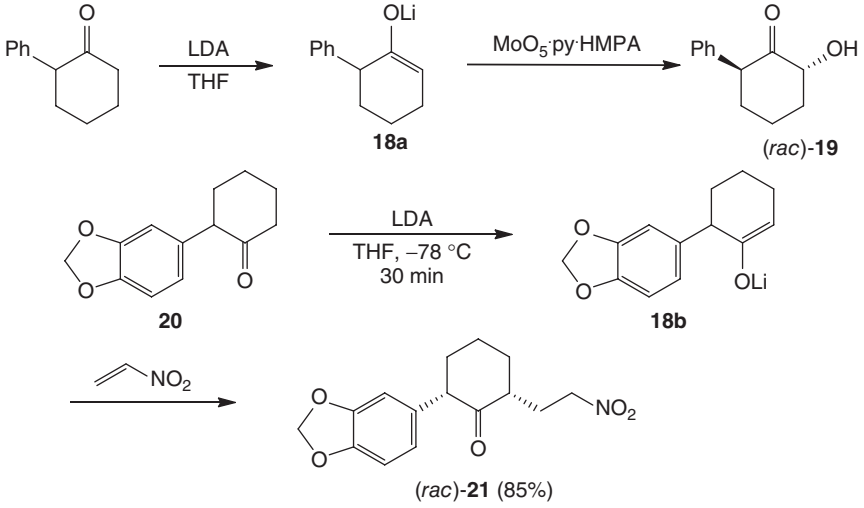
Kinetically controlled deprotonation also leads to the lower substituted alkali enolates of acyclic ketones, as illustrated by selected examples in Scheme 2.5: 2-heptanone [27], 3-methyl-2-butanone [26a], and 2-methyl-3-pentanone [23]. Under the conditions of kinetic deprotonation with LDA, α-alkoxy-substituted ketones behave similar to their alkyl-substituted counterparts giving predominantly the less substituted enolate, as illustrated for 2-methoxycyclohexanone [28] in Scheme 2.5. α-Dialkylamino ketones also follow this tendency. In α-carbamato-substituted ketones, however, regioselectivity is reversed, and enolization predominantly occurs toward the nitrogen atom – a result that might be caused by the electron-withdrawing nature of the urethane moiety; this effect becomes even more dominant when the enolate is formed under thermodynamic control (LiHMDS, equilibrating conditions) [29].

Due to its steric demand, LDA even leads to the less substituted enolate **18a** from 2-phenylcyclohexanone, and the formation of the thermodynamically favored conjugated regioisomer is widely suppressed, as proven by oxidation with Vedejs' reagent MoO_5·pyridine·hexamethylphosphoric triamide (HMPA) leading diastereoselectively to hydroxyketone **19** [30]. To give a more recent example, the



Scheme 2.5 Kinetically controlled, regioselective deprotonation of selected ketones.

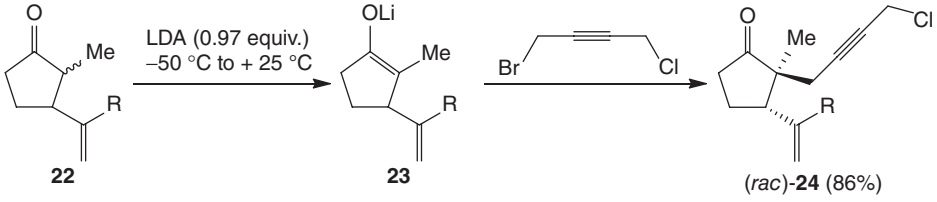
related, analogously generated contrathermodynamic enolate **18b** generated in a regioselective manner from 2-aryl-substituted cyclohexanone **20** served for the regio- and diastereoselective preparation of nitro compound **21**, an intermediate in a synthesis of the alkaloid γ-lycorane [31] (Scheme 2.6).



Scheme 2.6 Contrathermodynamic formation of lithium enolates **18a** and **18b** derived from 2-arylcyclohexanones.

It has been shown by House *et al.* [23] that when in related enolization experiments an excess of the ketone was added to LDA, the formation of the higher-substituted enolate results under thermodynamic control through

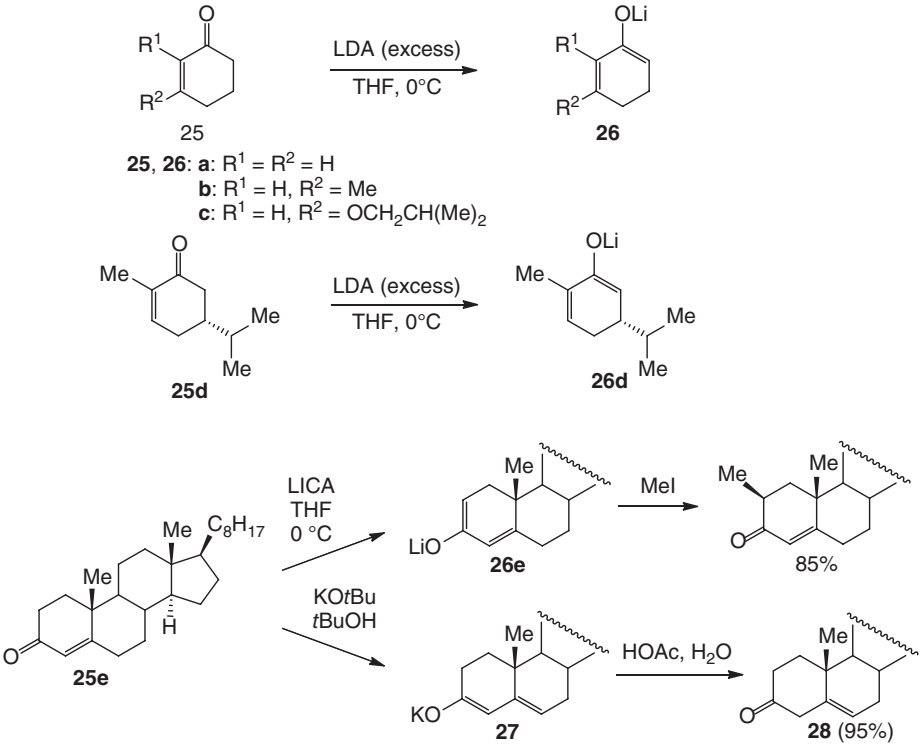
equilibration between the regioisomeric enolates and the ketone. If the generation of a thermodynamically controlled enolate is aimed, one can take advantage of this procedure, as demonstrated by a more recent example [32] of the alkylation of ketone **22** (a mixture of diastereomers) through the higher-substituted enolate **23** that forms exclusively and leads to the product **24** under diastereoselective generation of a quaternary center. The excess of the starting ketone **22** over the base LDA and exposure to the reaction mixture to room temperature are essential in order to provide thermodynamic control in enolate formation (Scheme 2.7).



Scheme 2.7 Example for formation of the higher-substituted enolate by deprotonation under thermodynamic control; R = $CH_2CH_2OSitBuMe_2$.

In α,β-unsaturated ketones, the abstraction of a proton in γ-position occurs under thermodynamic control, whereas the α′-proton is considered to be the kinetically more acidic one. Thus, in cyclohex-2-enone **25a**, 3-methylcyclohex-2-enone **25b**, the alkoxy enone **25c**, or the related terpene carvone **25d**, a deprotonation by addition of the ketone to a THF solution of LDA leads under kinetic control to the cross-conjugated enolates **26** whereas the linearly conjugated regioisomers do not form [33]. When applied to steroidal enone **25e**, a related protocol using LICA as a base again leads to the kinetic enolate **26e**, as proven by alkylation with iodomethane [34]. On the contrary, application of the weaker base potassium *t*-butoxide in the protic solvent *t*-butanol to the same substrate **25e** may serve as an illustrative example for thermodynamically controlled enolate formation [35]. Linearly conjugated dienolates like **27** have been used as valuable intermediates for the deconjugation of α-enones, as protonation in α-position is usually much faster than in γ-position [36]. Thus, regioselective protonation of enolate **27** leads to the contrathermodynamic enone **28** (Scheme 2.8).

The deprotonation of carbonyl compounds **1** (Equation 2.1) leads to diastereomeric *cis*- and/or *trans*-enolates unless precursors with two identical residues R have been chosen. As the configuration at the enolate double bond has a crucial effect on the stereochemical outcome of almost all the consecutive reactions, the controlled preparation of *cis*- and *trans*-enolates is prerequisite to any successful application in asymmetric synthesis. It is therefore not surprising that enormous effort was put into the elaboration of protocols for selective formation of the diastereomers of preformed, O–metal bound enolates. This search led to the insight that stereoselective enolate formation depends on a multitude



Scheme 2.8 Regioselective deprotonation reactions of α,β unsaturated ketones. Compound **25e**: cholest-4-en-3-one.

of parameters that vary from the kind of carbonyl compound (ketone, ester, amide, etc.), the individual substrate with its particular substitution pattern, the metal, the base, the solvent, the cosolvent, salts used as additives, temperature, concentration, and even the progressive of conversion. A meticulously detailed – comprehensive at that time – overview has been given by Heathcock; it includes valuable experimental procedures for the preparation of individual enolates [2c]. From the viewpoint of a certain interval, it seems that the following correlations meet a high degree of reliability, as will be demonstrated in Chapters 4 and 5 by their application in asymmetric syntheses. A selection of illustrative and typical examples is given in Table 2.1.

Under *thermodynamic control*, the formation of *cis*-enolates is generally favored, except for the 4- to 10-membered rings of cyclic ketones, lactones, and lactams that necessarily form *trans*-enolates for geometrical reasons. It is obvious that a twofold deprotonation of carboxylic acids does not give rise to diastereomeric enolates.

The amides of carboxylic acids and related carbonyl compounds like *N*-acyl oxazolidinones lead to *cis*-enolates under the conditions of kinetic control by