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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].

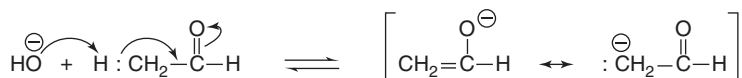
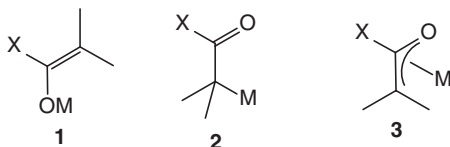
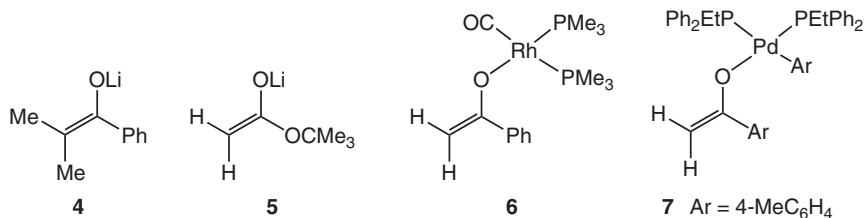


Figure 1.1 Formation of the enolate anion by removal of an α -hydrogen by base is the first step in the aldol addition [2].



Scheme 1.1 General enolate structures.

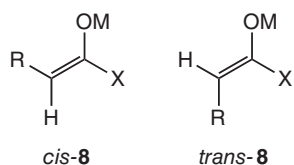
The metal–oxygen interaction may be considered a highly polar covalent bond or a tight ion pair in the case of alkali and earth alkali metals. The O–metal bond and the resulting carbon–carbon double-bond character were early recognized in enolate chemistry by means of NMR spectroscopy that revealed a 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 ^1H 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**.

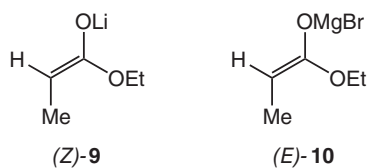
The structural feature of the O–metal bond has a substantial consequence that holds for carbonyl compounds with nonidentical substituents in the α -position: the configurational isomerism with respect to the carbon–carbon double bond giving rise to *cis*- or *trans*-enolates **8** (Scheme 1.3). This 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** ($X = \text{Me}$, $M = \text{Li}$, $R = n\text{Bu}$) 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.



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

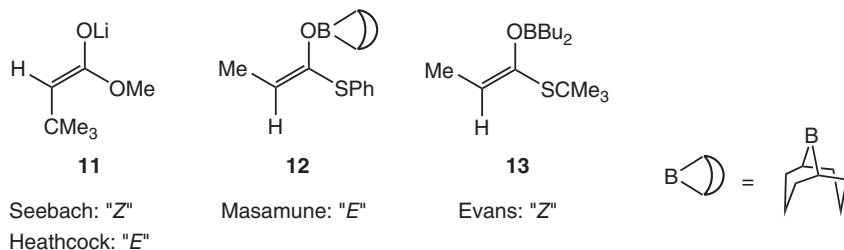
At a glance, the descriptors *Z* and *E* might seem to be appropriate for O–metal-bound enolates like **6**. Indeed, *E/Z* nomenclature causes no problems when the configuration of preformed enolates derived from aldehydes, ketones, and amides has to be assigned, because the O–metal residue at the enolate 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).



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

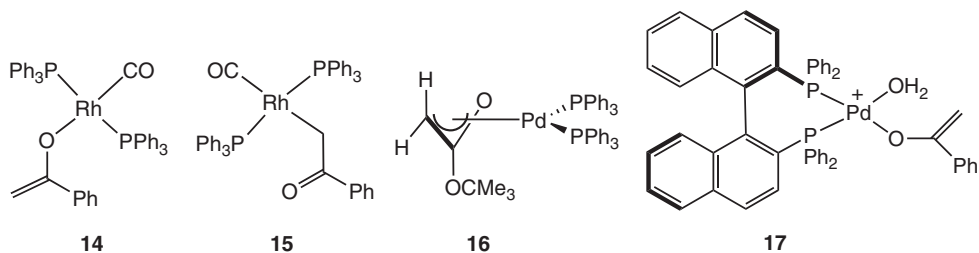
CIP-based nomenclature [17], as demonstrated by the related boron enolates **12** and **13**.



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].

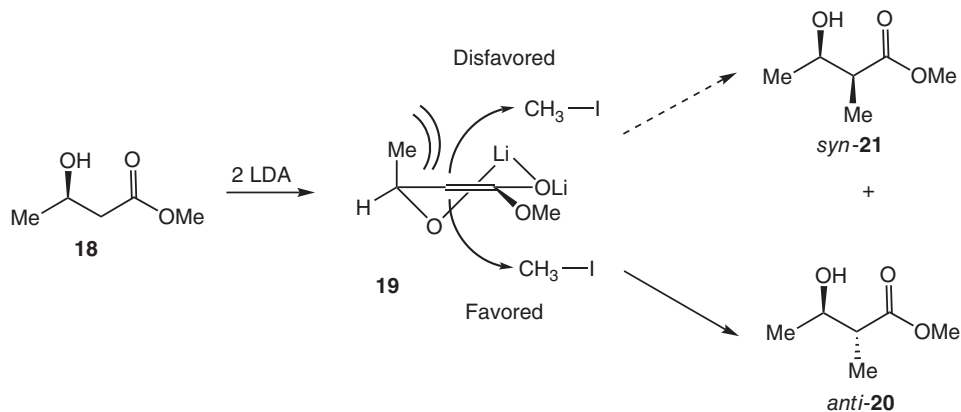
The third species in Scheme 1.1, the oxallyl enolate **3**, featuring an η^3 -metal bond is also typical for transition metals and may coexist with the O- and C-bound species in equilibria. Enolates with oxallyl structure **3** were obtained by directed preparation and characterized [24] and also postulated 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 $\pi(\text{CC})\text{-Li}$ 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 ($X = \text{H, alkyl, aryl, OR, SR, NR}_2, \text{ML}_n$) 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 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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