1
Organic Synthesis: General Remarks

1.1
Introduction

Organic reactions almost never yield exclusively the desired product. Students learn this when they perform their first synthesis in the laboratory, for example the synthesis of anisole from phenol. Although the starting materials, the intermediates, and the product are all colorless, the reaction mixture will turn uncannily dark. This darkening shows that in reality much more is going on in addition to the expected process, and that obviously quite complex chemistry must be occurring, giving rise to extended conjugated polyenes from simple starting materials. Fortunately these dyes are usually formed in minute amounts only and the student will hopefully also learn not to be scared by color effects, and that even from pitch-black reaction mixtures colorless crystals may be isolated in high yield.

Because most reactions yield by-products and because isolation and purification of the desired product are usually the most difficult parts of a preparation, the work-up of each reaction and the separation of the product from by-products and reagents must be carefully considered while planning a synthesis. If product isolation seems to be an issue, the work-up of closely related examples from the literature (ideally two or three from different authors) should be studied. Many small, hydrophilic organic compounds which should be easy to prepare are still unknown, not because nobody has attempted to make them, but because isolation and purification of such compounds can be very difficult. Therefore the solubility of the target compound in water and in organic solvents, and its boiling or melting point, should be looked up or estimated, because these will aid choice of the right work-up procedure.

The chemical stability of the target compound must also be taken into account while planning its isolation. Before starting a synthesis one should also have a clear idea about which analytical tools will be most appropriate for following the progress of the reaction and ascertaining the identity and purity of the final product. Last, but not least, the toxicity and mutagenicity of all reagents, catalysts, solvents, products, and potential by-products should be looked up or estimated, and appropriate precautionary measures should be taken.

Side Reactions in Organic Synthesis. Florencio Zaragoza Dörwald

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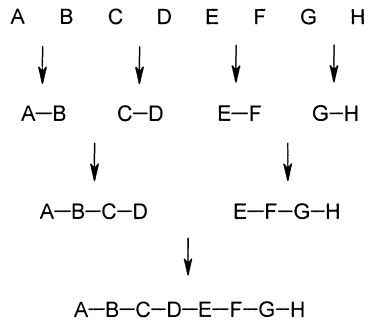
1.2 Synthesis Design

The synthesis of a structurally complex compound requires careful retrosynthetic analysis to identify the shortest synthetic strategies which are most likely to give rapid access to the target compound, ideally in high yield and purity. It is critical to keep the synthesis as short as possible, because, as discussed throughout this book, each reaction can cause unexpected problems, especially when working with structurally complex intermediates. Also for synthesis of "simple-looking" structures several different approaches should be considered, because even structurally simple compounds often turn out not to be so easy to make as initially thought.

1.2.1 Convergent vs Linear Syntheses

If a target compound can be assembled from a given number of smaller fragments, the highest overall yields will usually be obtained if a convergent rather than linear strategy is chosen (Scheme 1.1). In a convergent assembly strategy the total number of reactions and purifications for all atoms or fragments of the target are kept to a

convergent strategy:



7 reactions, total yield with respect to monomer A: 51%
(for 80% yield per coupling step)

linear strategy:

A → A–B → A–B–C → A–B–C–D → A–B–C–D–E →

A–B–C–D–E–F → A–B–C–D–E–F–G → A–B–C–D–E–F–G–H

7 reactions, total yield with respect to monomer A: 21%
(for 80% yield per coupling step)

Scheme 1.1. Convergent and linear assembly strategies.

minimum. If a linear strategy is chosen the first fragment (A in Scheme 1.1) will be subjected to a large number of reactions and purifications, and the total yield with regard to this first fragment will be rather low. Syntheses should be organized in such a way that expensive and/or structurally complex fragments are subjected to the fewest possible number of transformations.

1.2.2 Retrosynthetic Analysis

1.2.2.1 Introduction

When planning a synthesis, the most suitable starting materials should be chosen. These should be structurally and/or stereochemically as closely related to the target as possible, to keep the synthesis brief. The first steps of a good synthesis may even be low-yielding (if the products are easy to purify), because at these early stages little work and reagents have been invested and the intermediates are still cheap. Poor yields at later stages of a multistep synthesis, however, strongly reduce its usefulness, because most steps of the synthesis will have to be run on a large scale, using large amounts of solvents and reagents, to obtain a small amount only of the final product, which will, accordingly, be rather expensive.

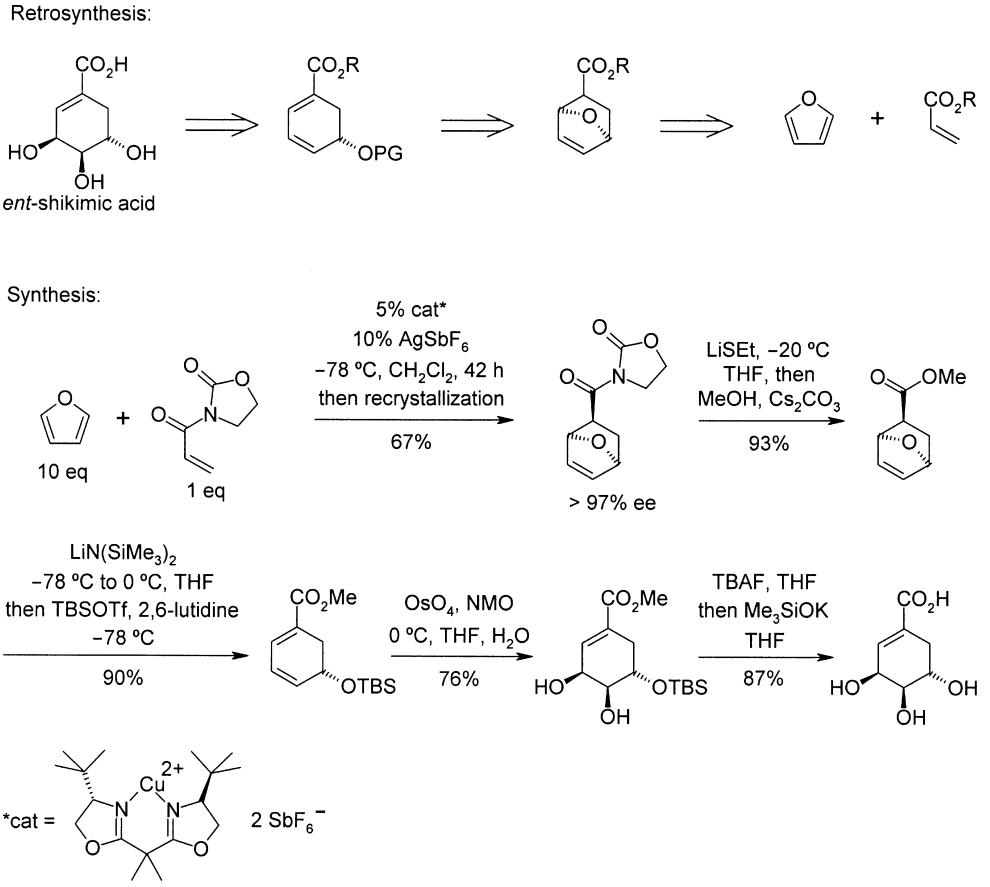
In a retrosynthesis the easiest bonds to make are often cleaved first (i.e. these bonds will be made at the end of the synthesis), yielding several fragments which can be joined together at late stages of the synthesis, using straightforward and high-yielding chemistry. Such reactions would usually be condensations, for example acetal, amide, or ester formation, or the formation of carbon–heteroatom bonds, but might also be high-yielding C–C bond-forming reactions if the required reaction conditions are compatible with all the structural elements of the final product.

If the target contains synthetically readily accessible substructures (e.g. cyclic elements accessible by well established cycloaddition or cyclization reactions), these might be chosen as starting point of a disconnection [1]. If such substructures are not present, their generation by introduction of removable functional groups (e.g. by converting single bonds into double bonds or by formal oxidation of methylene groups to carbonyl groups, Scheme 1.5) should be attempted. If this approach fails to reveal readily accessible substructures, the functional groups present in the target structure which might assist the stepwise construction of the carbon framework must be identified, and the bonds on the shortest bond paths between these groups should be considered as potential sites of disconnection (Scheme 1.3). Retro-aldol or Mannich reactions, optionally combined with the "Umpolung" of functional groups, have been the most common and successful tools for disconnection of intricate carbon frameworks, but any other, high-yielding C–C bond-forming reaction can also be considered. As illustrated by the examples discussed below, a good retrosynthesis requires much synthetic experience, a broad knowledge of chemical reactivity, and the ability to rapidly recognize synthetically accessible substructures.

1.2.2.2 Shikimic Acid

In Scheme 1.2 one possible retrosynthetic analysis of the unnatural enantiomer of shikimic acid, a major biosynthetic precursor of aromatic α-amino acids, is sketched. Because *cis* dihydroxylations can be performed with high diastereoselectivity and yield, this step might be placed at the end of a synthesis, what leads to a cyclohexadienoic acid derivative as an intermediate. Chemoselective dihydroxylation of this compound should be possible, because the double bond to be oxidized is less strongly deactivated than the double bond directly bound to the (electron-withdrawing) carboxyl group.

Despite being forbidden by the Baldwin rules (5-*endo*-trig ring opening; see Section 9.2), cyclohexadienoic acid derivatives such as that required for this synthesis can be prepared by base-induced ring scission of 7-oxanorbornene derivatives, presumably because of the high strain-energy of norbornenes. The required 7-oxanorbornene, in turn, should be readily accessible from furan and an acrylate via the

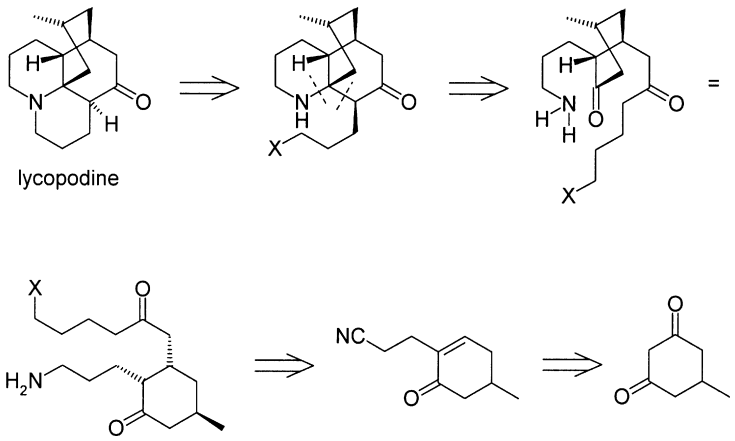


Scheme 1.2. Retrosynthetic analysis and synthesis of *ent*-shikimic acid [2].

Diels–Alder reaction. With the aid of an enantiomerically pure Lewis acid this Diels–Alder reaction yields a highly enantiomerically enriched 7-oxanorbornene, so that the remaining steps of this elegant synthesis only need to proceed diastereoselectively and without racemization.

1.2.2.3 **Lycopodine**

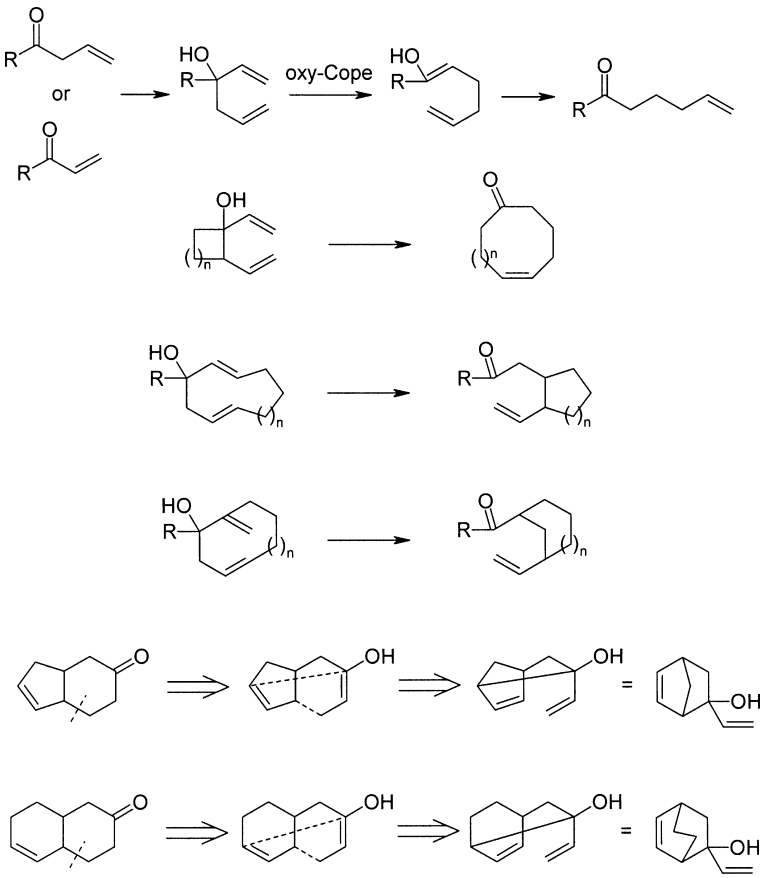
A further target which contains a readily accessible and easily recognizable substructure is the alkaloid lycopodine. Being a β-amino ketone, a possible retrosynthesis could be based on an intramolecular Mannich reaction, as outlined in Scheme 1.3. In this case two of the targets four rings would be generated in one step by a Mannich condensation; this significantly reduces the total number of steps required. A robust, intramolecular *N*-alkylation was chosen as last step. Realization of this synthetic plan led to a synthesis of racemic lycopodine in only eight steps with a total yield of 13 % [3]. Fortunately the Mannich reaction yielded an intermediate with the correct relative configuration.



Scheme 1.3. Retrosynthesis of lycopodine based on an intramolecular Mannich reaction [3].

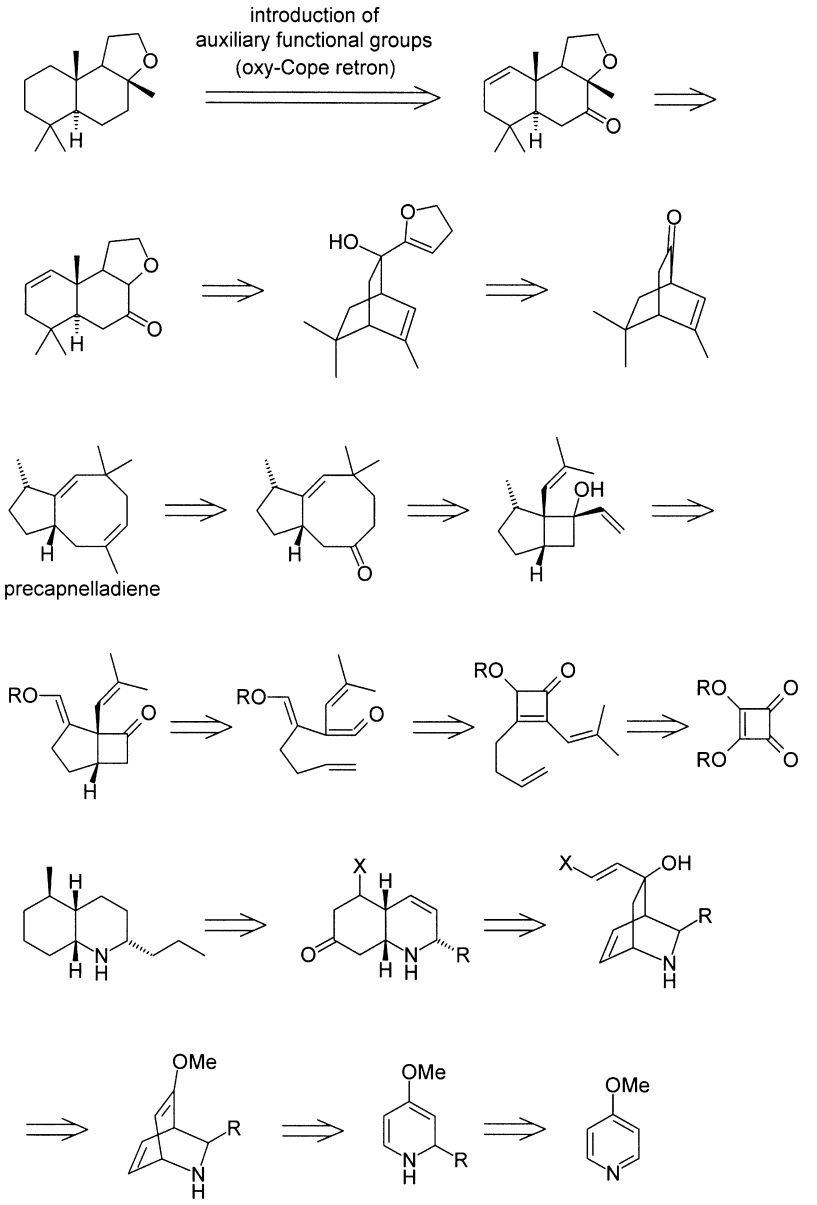
1.2.2.4 **The Oxy-Cope Rearrangement**

Less obvious than the retrosyntheses discussed above are those based on intramolecular rearrangements, because these often involve a major change of connectivity between atoms. For instance, exploitation of oxy-Cope rearrangements as synthetic tools requires some practice and the ability to recognize the substructures accessible via this reaction from readily available starting materials. Oxy-Cope rearrangements yield 4-penten-1-yl ketones by formal allylation of a vinyl ketone at the β position or γ-vinylation of an allyl ketone (Scheme 1.4). This rearrangement can be used to prepare decalins [4] or perhydroindenes [5, 6] from bicyclo[2.2.2]octenones or norbornenones, respectively, which can be prepared by using the Diels–Alder reaction. Moreover, oxy-Cope rearrangements may be used for ring expansions or contractions.



Scheme 1.4. The oxy-Cope rearrangement.

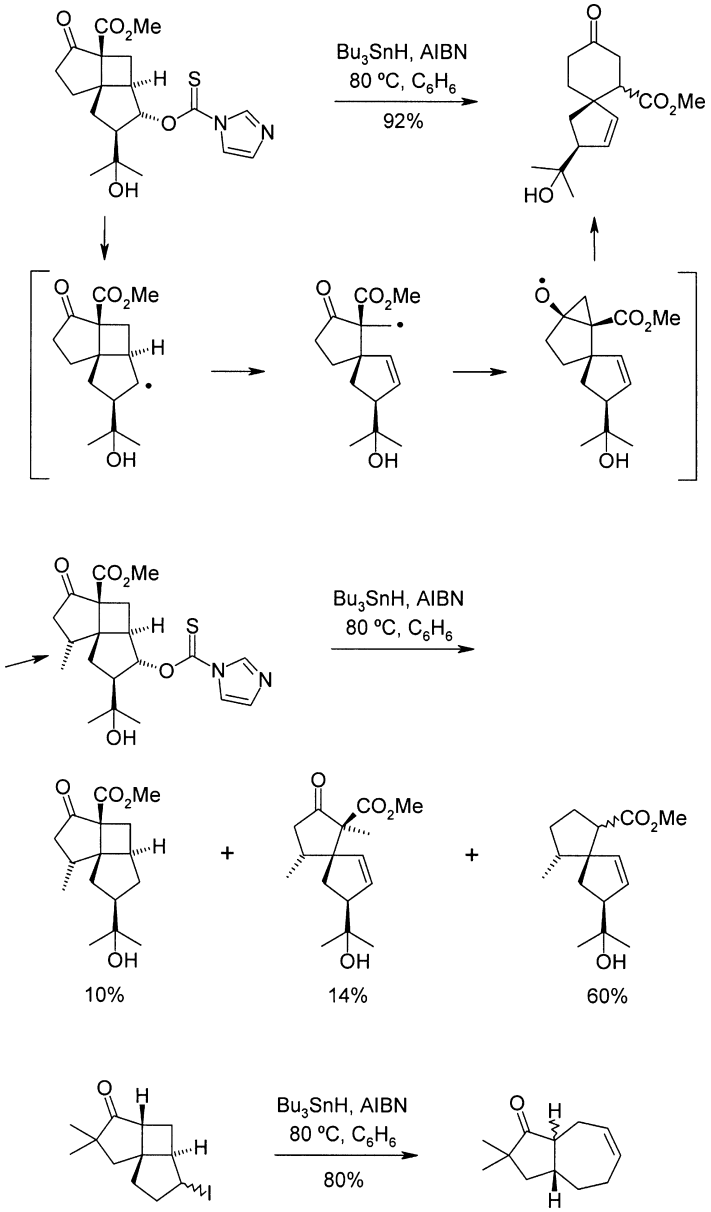
Numerous natural products have been prepared using the oxy-Cope rearrangement as the key step [5], in particular, and with high virtuosity, by the group of L.A. Paquette [4, 6, 7]. Three examples of retrosynthetic analyses of natural products or analogs thereof based on the oxy-Cope rearrangement are shown in Scheme 1.5. Because all the products are devoid of a keto group, the required 4-penten-1-yl ketone substructure (i.e. the oxy-Cope retron [1]) must be introduced during the retrosynthesis in such a way that accessible starting materials result.



Scheme 1.5. Retrosynthesis of an ambergris-type ether, of precapnelladiene, and of an alkaloid based on the oxy-Cope rearrangement [8–10].

1.2.2.5 Conclusion

As will be shown throughout this book, the outcome of organic reactions is highly dependent on all structural features of a given starting material, and unexpected products may readily be formed. Therefore, while planning a multistep synthesis, it is important to keep the total number of steps as low as possible.



Scheme 1.6. Rearrangement of polycyclic cyclobutylmethyl radicals [11, 12].

Even the most experienced chemist will not be able to foresee all potential pitfalls of a synthesis, specially so if multifunctional, structurally complex intermediates must be prepared. The close proximity or conformational fixation of functional groups in a large molecule can alter their reactivity to such an extent that even simple chemical transformations can no longer be performed [11]. Small structural variations of polyfunctional substrates might, therefore, bring about an unforeseeable change in reactivity.

Examples of closely related starting materials which upon treatment with the same reagents yield completely different products are sketched in Scheme 1.6. The additional methyl group present in the second starting material slows addition to the carbonyl group of the radical formed by ring scission of the cyclobutane ring, and thus prevents ring expansion to the cyclohexanone. Removal of the methoxycarbonyl group leads to cleavage of a different bond of the cyclobutane ring and thereby again to a different type of product [12].

The understanding and prediction of such effects and the development of milder and more selective synthetic transformations, applicable to the synthesis of highly complex structures or to the selective chemical modification of proteins, DNA, or even living cells will continue to be the challenge for current and future generations of chemists.

1.3 Hard and Soft Acids and Bases

One of the most useful tools for predicting the outcome of chemical reactions is the principle of hard and soft acids and bases (HSAB), formulated by Pearson in 1963 [13–15]. This principle states that hard acids will react preferentially with hard bases, and soft acids with soft bases, "hard" and "soft" referring to sparsely or highly polarizable reactants. A selection of hard and soft Lewis acids and bases is given in Table 1.1.

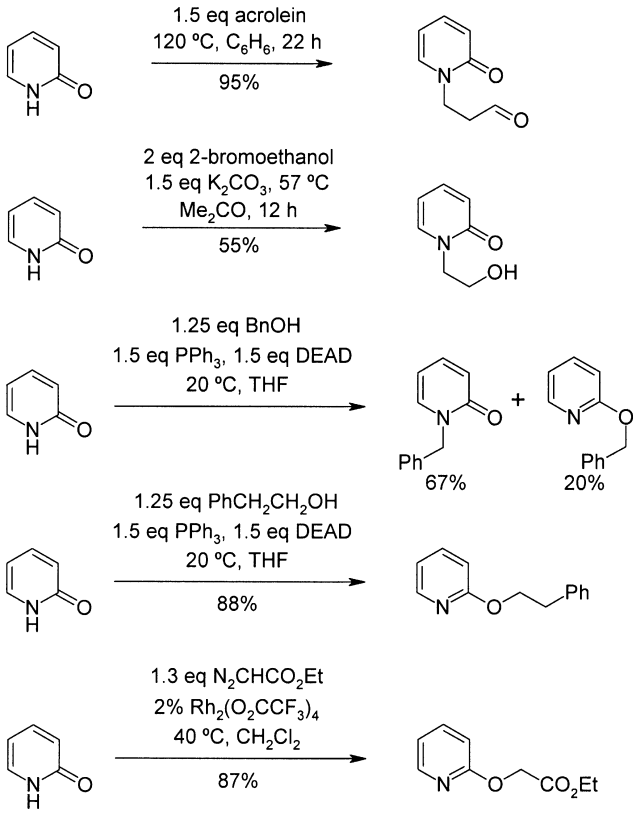
Several chemical observations can be readily explained with the aid of the HSAB principle. For instance, the fact that the early transition metals in high oxidation states, for example titanium(IV), do not usually form complexes with alkenes, carbon monoxide, or phosphines, but form stable oxides instead can be attributed to their hardness. The late transition metals, on the other hand, being highly polarizable, because of their almost completely filled *d* orbitals, readily form complexes with soft bases such as alkenes, carbanions, and phosphines, and these complexes are often unreactive towards water or oxygen. For the same reason, in alkali or early transition metal enolates the metal is usually bound to oxygen, whereas enolates of late transition metals usually contain M–C bonds [17, 18]. While alkali metal alkyls or Grignard reagents react with enones presumably by initial coordination of the metal to oxygen followed by transfer of the alkyl group to the carbonyl carbon atom [16, 19], organocuprates or organopalladium compounds preferentially coordinate and transfer their organic residue to soft C–C double bonds.

Table 1.1. Hard and soft Lewis acids and bases [13, 15, 16] (Z = electron-withdrawing group, M = metal). The acidic or basic centers in molecules are in italics.

Hard acids (non-metals)	**Borderline acids (non-metals)**	**Soft acids (non-metals)**
H^+, *B*$(OR)_3$, *B*F_3, *B*Cl_3, R*C*O^+, *C*O_2, N*C*$^+$, R_3*Si*$^+$, *Si*$^{4+}$, R*P*O_2^+, RO*P*O_2^+, As^{3+}, R*S*O_2^+, RO*S*O_2^+, *S*O_3, Se^{3+}, Cl^{7+}, I^{7+}, I^{5+}	*B*R_3, R^+ (softer $CH_3^+ > RCH_2^+ > R_2CH^+ > R_3C^+ >$ vinyl$^+ \approx C_6H_5^+ \approx$ RC≡*C*$^+$ harder), R*C*HO, R_2*C*O, R_2*C*=NR, *N*O^+, *S*O_2	*B*H_3, Ar–Z, *C*=C–Z, quinones, carbenes, H*O*$^+$, R*O*$^+$, R*S*$^+$, R*Se*$^+$, R*Te*$^+$, Br_2, Br^+, I_2, I^+
Hard acids (metals)	**Borderline acids (metals)**	**Soft acids (metals)**
Li^+, Na^+, K^+, *Be*Me_2, Be^{2+}, R*Mg*X, Mg^{2+}, Ca^{2+}, Sr^{2+}, *Al*Cl_3, *Al*Me_3, *Al*H_3, *Al*$(OR)_3$, Al^{3+}, *Ga*Me_3, Ga^{3+}, *In*Me_3, In^{3+}, *Sn*R_3^+, *Sn*Me_2^{2+}, Sn^{2+}, Sc^{3+}, La^{3+}, *Ti*$(OR)_4$, Ti^{4+}, Zr^{4+}, *V*O_2^+, Cr^{3+}, Fe^{3+}, Co^{3+}, Ir^{3+}, Th^{4+}, *U*O_2^{2+}, Pu^{4+}, Yb^{3+}	*Ga*H_3, *Sn*$(OR)_4$, *Sn*Cl_4, Pb^{2+}, Sb^{3+}, Bi^{3+}, *Sc*$(OTf)_3$, *Sc*Cl_3, Fe^{2+}, Co^{2+}, Ni^{2+}, Cu^{2+}, R*Zn*$^+$, Zn^{2+}, *Yb*$(OTf)_3$, *Yb*Cl_3	Cs^+, *Tl*Me_3, Tl^+, Tl^{3+}, *Pd*$(PAr_3)_2$, *Pd*$(PAr_3)_2^{2+}$, Pd^{2+}, Pt^{2+}, Cu^+, Ag^+, Au^+, *Cd*R^+, Cd^{2+}, *Hg*R^+, Hg^+, Hg^{2+}, M^0
Hard bases	**Borderline bases**	**Soft bases**
NH_3, R*N*H_2, R_2*N*$^-$, *N*$_2H_4$, *H*$_2O$, *OH*$^-$, R*O*H, R*O*$^-$, R_2*O*, R*C*O_2^-, *C*O_3^{2-}, *N*O_3^-, *P*O_4^{3-}, *S*O_4^{2-}, *Cl*O_4^-, F^-, Cl^-	Al*H*$_4^-$, N_2, *N*$_3^-$, Ph*N*H_2, R_3*N*, C_5H_5*N*, R_2C=*N*R, *N*O_2^-, *S*O_3^{2-}, Br^-	H^-, B*H*$_4^-$, R^- (softer RC≡*C*$^-$ > vinyl$^-$ > R_3*C*$^-$ harder), *C*$_6H_6$, R_2*C*=CR_2, RC≡*C*R, *C*N$^-$, RN*C*, *C*O, *P*R_3, *P*$(OR)_3$, *As*R_3, R*S*$^-$, *S*CN$^-$, R*S*H, R_2*S*, *S*$_2O_3^{2-}$, R*Se*$^-$, I^-

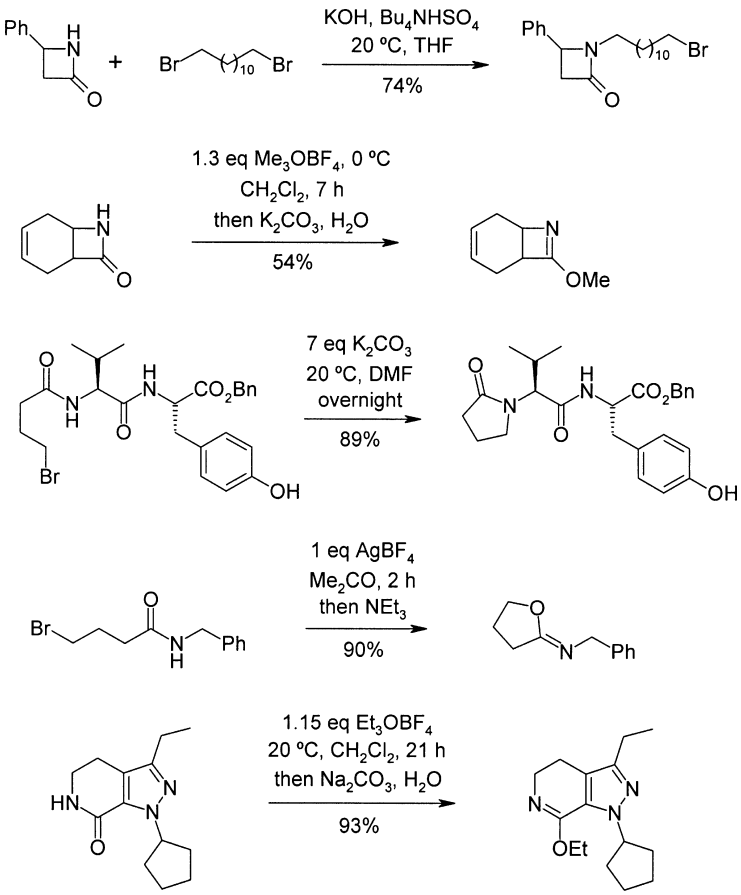
HSAB is particularly useful for assessing the reactivity of ambident nucleophiles or electrophiles, and numerous examples of chemoselective reactions given throughout this book can be explained with the HSAB principle. Hard electrophiles, for example alkyl triflates, alkyl sulfates, trialkyloxonium salts, electron-poor carbenes, or the intermediate alkoxyphosphonium salts formed from alcohols during the Mitsunobu reaction, tend to alkylate ambident nucleophiles at the hardest atom. Amides, enolates, or phenolates, for example, will often be alkylated at oxygen by hard electrophiles whereas softer electrophiles, such as alkyl iodides or electron-poor alkenes, will preferentially attack amides at nitrogen and enolates at carbon.

2-Pyridone is *O*-alkylated more readily than normal amides, because the resulting products are aromatic. With soft electrophiles, however, clean *N*-alkylations can be performed (Scheme 1.7). The Mitsunobu reaction, on the other hand, leads either to mixtures of *N*- and *O*-alkylated products or to *O*-alkylation exclusively, probably because of the hard, carbocation-like character of the intermediate alkoxyphosphonium cations. Electrophilic rhodium carbene complexes also preferentially alkylate the oxygen atom of 2-pyridone or other lactams [20] (Scheme 1.7).



Scheme 1.7. Regioselective alkylation of 2-pyridone [20–22].

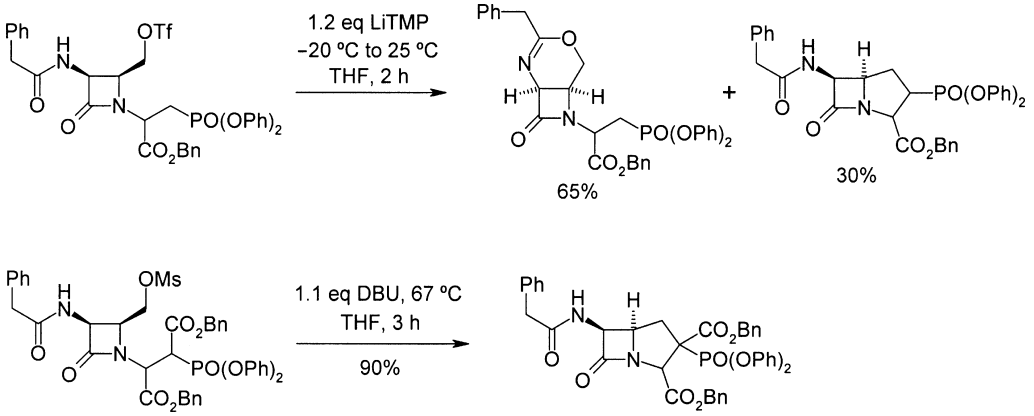
Lactams and some non-cyclic, secondary amides (RCONHR) can be alkylated with high regioselectivity either at nitrogen (Section 6.6) or at oxygen. *N*-Alkylations are generally conducted under basic reaction conditions whereas *O*-alkylations are often performed with trialkyloxonium salts, dialkyl sulfates, or alkyl halides/silver salts without addition of bases. Protonated imino ethers are formed; these are usually not isolated but are converted into the free imino ethers with aqueous base during the work-up. Scheme 1.8 shows examples of the selective alkylation of lactams and of the formation of 2-pyrrolidinones or 2-iminotetrahydrofurans by cyclization of 4-bromobutyramides.



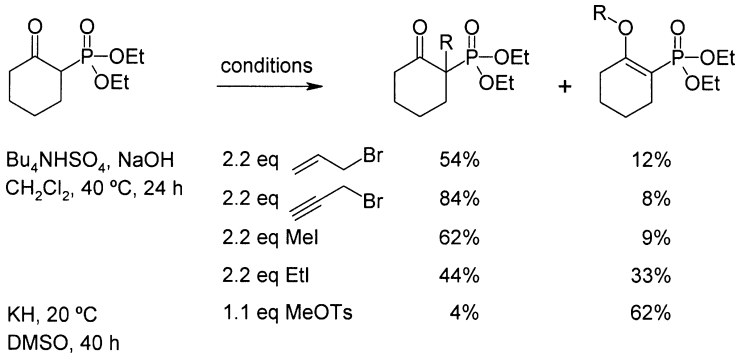
Scheme 1.8. Regioselective alkylation of amides [23–27].

The triflate sketched in Scheme 1.9 mainly alkylates the amide at oxygen, instead of alkylating the softer, lithiated phosphonate. Selective *C*-alkylation can be achieved in this instance by choosing a less reactive mesylate as electrophile and by enhancing the acidity of the phosphonate.

The regioselectivity of the alkylation of enolates can also be controlled by the hardness of the alkylating agent [29]. As illustrated by the examples in Scheme 1.10, allyl, propargyl, or alkyl bromides or iodides mainly yield *C*-alkylated products, whereas the harder sulfonates preferentially alkylate at oxygen.



Scheme 1.9. Intramolecular alkylation of amides and phosphonates [28].

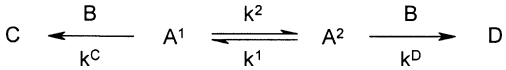


Scheme 1.10. Regioselective alkylation of enolates [30, 31].

1.4 The Curtin–Hammett Principle

In the 1940s the idea was prevalent among chemists that the conformation of a reactant could be determined from the structure of a reaction product, i.e. the major conformer would yield the major product. This assumption was shown to be incorrect by Curtin and Hammett in the 1950s [32].

For a reaction in which a starting material A is an equilibrium mixture of two conformers (or diastereomers, tautomers, rotamers, etc.) A^1 and A^2 (Eq. 1.1), two extreme situations can be considered – one in which equilibration of A^1 and A^2 is slow if compared with their reaction with B ($k^1, k^2 \ll k^C, k^D$), and one in which equilibration of A^1 and A^2 is much faster than their reaction with B ($k^1, k^2 \gg k^C, k^D$).



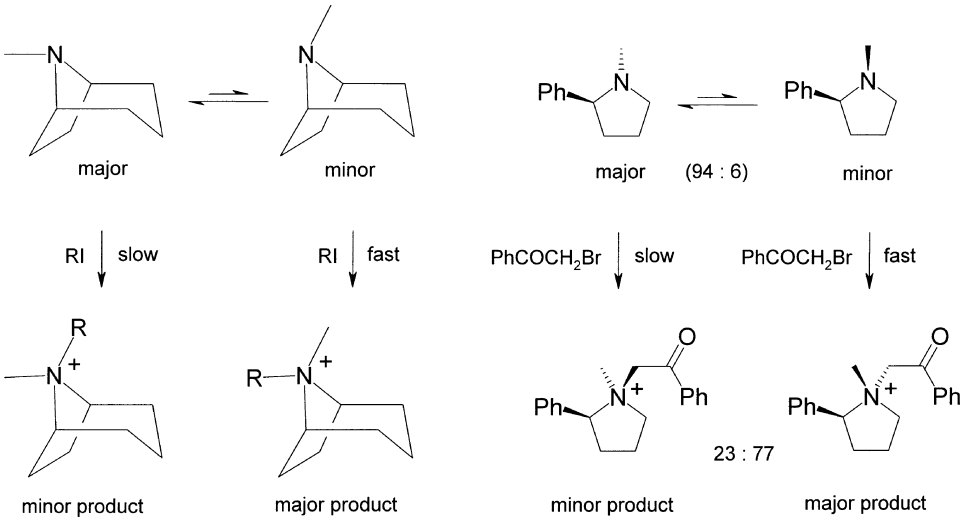
(Eq. 1.1)

If equilibration of A^1 and A^2 is slow, the product ratio [C]/[D] will be equal to the ratio of conformers of the starting material A ($[A^1]/[A^2]$) and independent of the ratio k^C/k^D. If equilibration is rapid, however, the amount of C and D formed will depend both on the ratio of starting materials ($[A^1]/[A^2]$) and on the ratio of the two reaction rate constants k^C and k^D: $[D]/[C] = [A^2]/[A^1] \times k^D/k^C$ [32].

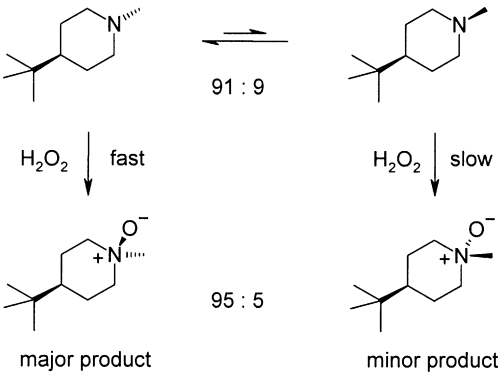
The main implication of these derivations is that if equilibration is rapid, the product ratio cannot always be intuitively predicted if the reaction rates k^C and k^D are unknown. Because energy-rich conformers, present in low concentrations only, are often more reactive than more stable conformers, it is not unusual for the main product of a reaction to result from a minor conformer which cannot even be observed.

Two examples of such situations are sketched in Scheme 1.11. Quaternization of tropane occurs mainly from the less hindered "pyrrolidine side" (equatorial attack at the piperidine ring), even though the main conformer of tropane has an equatorial methyl group. Similarly, 1-methyl-2-phenylpyrrolidine yields mainly an *anti* alkylated product via alkylation of the minor *cis* conformer when treated with phenacyl bromide [33]. In both instances the less stable conformer is more reactive to such an extent that the major product of the reaction results from this minor conformer. A further notable example of a reaction in which the main product results from a minor but more reactive intermediate is the enantioselective hydrogenation of α-acetamidocinnamates with a chiral rhodium-based catalyst [34].

This does, however, not need to be so. Oxidation of 1-methyl-4-*tert*-butylpiperidine, for example, yields mainly the amine *N*-oxide derived from the most stable conformer (Scheme 1.12). In this example the more energy-rich (less stable) conformer reacts more slowly than the major conformer.



Scheme 1.11. Diastereoselective quaternization of tertiary amines [32, 33, 35].



Scheme 1.12. Diastereoselective oxidation of 4-*tert*-butyl-1-methylpiperidine [32, 36, 37].

To conclude, the Curtin–Hammett principle states that the relative amounts of products formed from two interconverting conformers depend on the reactivity of these two conformers if the interconversion of these conformers is rapid, and cannot always be intuitively predicted.

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