Abstract: The replacement of a β-hydrogen on an α,β-unsaturated carbonyl system with a non-hydrogen, non-carbon atom amounts to either a net two electron oxidation or an isohypsic substitution at the β-carbon. The resulting compounds are the functional equivalents of β-dicarbonyl derivatives. Although many methods have been developed to effect this transformation, they lack generality and the process remains an underutilized one in organic synthesis.

1 Introduction

The α,β-unsaturated carbonyl group is an extremely common feature of organic compounds. As such, it serves as a very useful site for synthesis and refunctionalization. Numerous reactions have been extensively developed over the years: e.g., the Michael addition; β-cuprate addition; α-alkylation or arylation by reductive trapping or oxidative coupling; carbonyl refunctionalization by addition, oxidation, reduction, and alkylidenation; α-oxidation by halogenation-dehalogenation; and so on (Scheme 1).

Incorporation of a heteroatom at the β-position by a net two electron oxidation has also been achieved by various means but it is not a transformation that has been previ-
ously reviewed nor specifically catalogued in various standard compendia of functional group transformations. β-Hetero-α,β-unsaturated aldehydes, ketones, esters, or their analogs are often end products in themselves but they also serve as valuable synthetic intermediates where the β-substituent is used to direct or facilitate further reactions at the α-, β-, γ- or other positions.

### 1.1 Scope

Surveyed here is a wide range of methods that have been used to effect the two electron β-oxidation of α,β-unsaturated carbonyls (Scheme 2) and closely related transformations.

![Scheme 2](image)

This survey is not comprehensive for several reasons. The vast majority of such oxidations are reported on substrates that generate aromatic or other highly stabilized products such as chalcones, flavones, chromones, quinones, and aromatic products such as furans, indoles, and so on (Scheme 3). Such oxidations are usually quite facile and trivial. Only a few of these cases are mentioned.

![Scheme 3](image)

This survey concentrates on α,β-unsaturated esters, ketones, and aldehydes. The specific β-oxidation of olefins activated by other functional groups such as nitro, sulfone, or nitrile is not exhaustively covered. Some examples are included when they occur along with carbonyl activated substrates.

Replacement of hydrogen by heteroatoms less electronegative than carbon do not technically result in oxidation of the β-carbon but most will recognize the chemical similarity and utility of including silicon, phosphorus, and metals in this discussion.

Many of the methods surveyed as yet lack generality and thus have not been widely used. Finally, several cases are incidental to the major purpose of the papers cited. The majority of this review emphasizes the more restricted cases that lack aromatic or special stabilizing characteristics.

### 1.2 Organization

This survey is organized by the kind of final heteroatom-for-hydrogen replacement at the β-carbon: oxygen, nitrogen, sulfur, halogen, phosphorus, silicon, metals, carbon, and other heteroatoms. There is a brief section on heteroatom exchange.

### 1.3 General Strategies

Although not comprehensive, some general strategies of refunctionalization are presented here. These are not necessarily mechanistic patterns, but approximately so. Thus, direct oxidation (Scheme 4) implies a single one pot reaction to convert an unsaturated carbonyl system into a β-hetero containing system that may or may not involve catalytic oxidation-reduction.

![Scheme 4](image)

Addition-elimination (Scheme 5) implies oxidative or non-oxidative addition via either 1,2-addition of X–Y followed by elimination of H–Y or a 1,2- or 1,4-addition of H–XY followed by elimination of H–Y. Rearrangements of intermediates usually derived via oxidation is a variation of the oxidative addition-elimination.

The oxidation step in an addition-oxidation (Scheme 6) and the requisite, often spontaneous, elimination sequence can occur at carbon, at X, or at Y. Isohypsic reactions are those that occur with no net change in oxidation state. Isohypsic Rearrangements (Scheme 7) transfer X from an X–Y group, usually at the α-position, to the β-carbon.

Activation for metalation with an electron withdrawing group (EWG) followed by heteroatom trapping and elimination of the EWG is yet another generic strategy (Scheme 8).

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**Biographical Sketch**

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2 Oxygen

β-Hydroxy enones are the enolic tautomers of β-dicarbonyls. They occur in many natural products such as polyketides. β-Diketones (e.g., acetylacetone) and β-ketoesters (e.g., ethyl acetacetate) are extremely common functional groups. They are usually prepared by acylation rather than by β-oxidation of the corresponding unsaturated carbonyl compounds.

2.1 Direct Oxidation

A one step direct oxidation of the β-carbon of an unsaturated carbonyl should be the most desirable method to effect the stated transformation. There have been several reports of the direct β-oxidation of unsaturated esters, enones, or their acetals.

Conventional Wacker or Wacker–Tsuji oxidation with PdCl₂/CuCl/O₂ converts unactivated terminal olefins into methyl ketones. Tsuji developed new conditions using Na₂PdCl₄ and t-BuOOH for the oxidation of acyclic internal olefins activated by electron withdrawing groups (Scheme 9). Tsuji showed that the corresponding epoxides were hydrolyzed under these conditions and thus were not intermediates in the reaction.

Terminal unactivated olefins also produce internal ketals in the presence of alcohols under anhydrous Wacker type conditions. Several groups have carried out similar oxidations on activated olefins in the presence of alcohols, which form β-keto acetals in situ.

Alkyl nitrite (RONO)/PdCl₂ catalyst systems developed by Uchiumi and others are used to prepare 3,3-dimethoxypropionitrile from acrylonitrile and methyl 3,3-dimethoxy propionate from methyl acrylate on an industrial scale at UBE Industries (Scheme 10). These catalysts have turnover numbers five to six times higher than the corresponding Wacker reactions. Uchiumi attributes this to a mechanism in which Pd(II) is never fully reduced to Pd(0) but to ‘HPd(II)Cl’ which is reoxidized by nitrite back to Pd(II)Cl₂. O₂ is the stoichiometric oxidant that can be used to reoxidize NO back to the catalytic alkyl nitrite.

Hosokawa treated terminal vinyl ketones with PdCl₂/CuCl in the presence of diols, including chiral 1,3-diols, and obtained terminal acetals in decent yield (Scheme 11). Acrylate esters were similarly oxidized. In these systems, Tsuji’s Na₂PdCl₄/t-BuOOH catalyst produced mixtures. Acetal yields are greatly improved by adding HMPA to the solvent. It does not appear that
anyone has reported the use of \(N,N'\)-dimethylpropyleneurea (DMPU) or \(N,N'\)-dimethylethyleneurea (DMEU) in place of HMPA.

Toxic HMPA can be avoided by the use of supercritical \(\text{CO}_2\) (scCO\(_2\)) as solvent, in which case yields are excellent (Scheme 12).\(^\text{17}\)

Sturgess adapted Hosokawa’s conditions to oxidize hydroxy containing \(\alpha,\beta\)-unsaturated esters (Scheme 13).\(^\text{18}\)

He used an excess of a mixture of Cu(I), Cu(II), and Li(I) chlorides as co-catalyst.

The Ishii Pd(II)–NPMoV/C system also effects Wacker oxidation of non-terminal unactivated olefins, for example, in the conversion of cyclopentene to cyclopentanone.\(^\text{20}\)

\(\alpha,\beta\)-Unsaturated hydroxamic acids undergo intramolecular cyclization with Li\(_2\)PdCl\(_4\) in anhydrous MeCN (Scheme 14).\(^\text{21}\)

Using fluorinated ligands, the Wacker–Tsuji system has been extended to fluorous biphasic oxidations of olefins that also work with a cinnamate ester (Scheme 15).\(^\text{22}\)
Palladium(II) bound to silylpropylethylenediamine derivatized montmorillonite clays gives excellent yields in the Wacker–Tsuji oxidation, as well (Scheme 17).23

### 2.2 Addition-Oxidation

A variation on the direct oxidation of enones is the direct oxidation of silyl enol ethers to enones, such as has been reported by Saegusa (Scheme 18).24 Many of these enol substrates can be prepared by conjugate addition to the parent α,β-unsaturated ketones.

**Scheme 18**

A similar oxidation of TIPS enol ethers using PhIO/TMSN₃ was reported by Magnus (Scheme 19).25

**Scheme 19**

In another development, Evans used CAN to oxidize silyl enol ethers to enones, including examples with N, O, and S at the α-position (Scheme 20).26

Nicolaou has demonstrated the utility of o-iodoxybenzoic acid (IBX) for the direct oxidation of saturated ketones and aldehydes.27 With an excess of IBX, cross-conjugated dienones were obtained from higher dialkyl ketones. It is not necessary to preform an enol ether; the carbonyl compounds react directly with the reagent, presumably by a single electron transfer mechanism. Benzylic positions are also oxidized by IBX, such as cyclic β-ethers (Scheme 21).28

There are several other methods for the oxidation of enols to enones or ketones to enones. Unless there are specific examples of their use in the net addition-oxidation sequence, they are not included here.

The Saegusa, Magnus, and Evans reactions have all been extended to complex α,β-hetero silyl enol ethers. To the extent that heteroatom nucleophiles can add to enones, these methods amount to the multistep net β-oxidation of a pre- curor enone (Scheme 22).

**Scheme 20**

For example, in a series of papers on the elaboration of various sugars, Danishefsky regioselectively oxidized the enol ethers of tetrahydropyran-4-ones to dihydropyrones using Pd(OAc)₂ (Scheme 23).29,30 Some of these enols were obtained directly from hetero-Diels–Alder reactions but it was also shown that the β-alkoxy ketones could be enolized with a strong base (e.g., lithium hexamethyldisilazide) and trapped as the required silyl enol ethers in good yield (Scheme 24).31 Although palladium can be used catalytically in the Saegusa reaction, yields are much improved with stoichiometric palladium (although excess palladium is detrimental to the yields).
Scheme 23

The Magnus oxidation can introduce a labile azido group even when there is a β-heteroatom already present. In principle and by analogy to the all carbon cases, hydrolysis should reinstate the enone with expulsion of the labile azide (Scheme 25).

Scheme 24

Antus et al. used phenyliodine(III) diacetate to facilitate an intramolecular addition of a phenolic enone with subsequent oxidation to prepare the naturally occurring flavones kanzonol-D, kanzonol-E and yinyanghuo (Scheme 27).33

Scheme 25

(a) PhIO (1.2 equiv), TMSN₃ (2.4 equiv), CH₂Cl₂, –15 °C, 5 min

Scheme 26

The Evans reaction also works well on non-aromatic pyrone silyl enol ethers (Scheme 26).32

Scheme 27

A similar oxidative ring closure was accomplished using catalytic I₂ in DMSO (Scheme 28).34
Although no doubt facilitated by formation of the aromatic isoxazole, oxidation of oxime ether (isoxazoline) 1 with nickel peroxide or manganese dioxide produces the unsaturated carbonyl compound 2 (Scheme 29).35,36

\[
\text{R} = \begin{array}{c}
\text{NiO}_2 \\
\text{MnO}_2
\end{array}
\]

\[
\text{X} = \begin{array}{c}
\text{O} \\
\text{CH}_2
\end{array}
\]

\[
\text{49%} \\
\text{71%
}
\]

\[
\text{46%}
\]

Scheme 29

Lead tetraacetate (LTA) oxidizes α-enamides to β-acetoxy imidates and diacetoxyamidoesters that convert to β-acetoxy-α,β-unsaturated amidesters upon treatment with base.37 Acetate hydrolysis affords the β-keto-acylaminoester (Scheme 30).

1,4-Addition of nitrite to α,β-unsaturated carbonyl compounds produces the β-nitro carbonyl derivatives38–43 which can themselves be ketalized.40,42,43 Allylic acetals prepared from unsaturated carbonyls can be nitromercuricated;44 nitromercurio ethers can be demercurated with NaBH₄.45,46 The β-nitro carbonyls and acetals can undergo modified Nef reactions with various bases or oxidants (DBU,47 DBU/MCPBA,48 K₂CO₃/H₂O₂,49,50 borax/KMnO₄,51 NaOH/NaNO₂/AgNO₃,52 BuLi/MoOPH,53) as generally represented in Scheme 31 and generate β-dicarbonyl equivalent products. The Nef strategy has worked effectively on nitro acetals. There appears to be only one example of the Nef being performed directly on a carbonyl substrate where β-elimination of HNO₂ might otherwise compete with formation of nitronate (ref.⁴⁸, Scheme 32). In other carbonyl cases, judicious choice of base or, perhaps, inverse addition to excess base might protect against elimination prior to nitronate formation.

Similarly, β-phosphono carbonyls are formed upon 1,4-addition of phosphinic acids, their salts, or esters to unsaturated carbonyls under basic conditions,38,54–58 or free radical conditions.⁵⁹ (Scheme 33) Secondary phosphines R₂PH also form 1,4-adducts as do tertiary phosphines.⁶⁰ 1,4-Phosphoniosilylation is also induced by base or by photochemical single electron transfer.⁶¹

β-Phosphono acetals can also be prepared from enones via haloacetalization followed by Arbuzov reaction with trialkyl phosphites (Scheme 34).⁶²,⁶³

Related phosphorus containing compounds can undergo a ‘phospha-Nef’ reaction to provide the oxo derivative. In some cases, quaternary phosphonium salts simply undergo autooxidation in air.⁶⁴,⁶⁵ Alkyl phosphonates and phosphonium salts can be lithiated with n-BuLi or another strong base, quenched with O₃ and hydrolyzed to the carbonyl derivative.⁶⁶–⁶⁸ Although there are examples of this

Scheme 31

Scheme 32 (a) AcOH, MeOH, H₂O (b) 1. DBU, TMSX 2. MCPBA (c) 1. O₂ 2. Me₂S, Ref.⁴⁸

Scheme 33

Scheme 34 (a) HBr, EtOH, 70–80% (b) (EtO)₂PO, Δ, 50–85%
conversion for the preparation of 1,4-dicarbonyl and 1,2-
dicarbonyl equivalents (the isoxazolines shown in
Scheme 35) there do not appear to be any examples with
either a free or protected carbonyl β to the phosphorus.

Scheme 35  (a) 1. n-BuLi  2. O₂, 57–83%

The anions of silyl enol phosphine and phosphite adducts
have been prepared and reacted with, primarily, carbon
electrophiles followed by regeneration of the unsaturation
by phosphorus elimination. There does not appear to be a
basis for precluding O₂ or another O⁺ equivalent as a pos-
sible trap en route to the β-dicarbonyl (Scheme 36). (For
further discussion and examples, see below.)

Scheme 36

The direct oxidation of cyclic enones or maleimide to α,β-
dihydroxy enones has been accomplished with RuCl₃–
peracetic acid (Scheme 37).¹⁶

Scheme 37

Methylltartronic acid is prepared by tungstic acid catalysis
of the dihydroxylation of methacrylic acid by H₂O₂
(Scheme 38). Although isolable, the sensitive diol is fur-
ther oxidized in a one-pot procedure by basification, the

Scheme 38

addition of Pd/C, and bubbling oxygen through the solu-
tion.⁷⁰ The result is an acrylate to hydroxymalonate con-
version.

2.3  Epoxide Rearrangement

Epoxides of unsaturated carbonyl compounds are readily
available using basic hydrogen peroxide. The same sorts
of epoxy carbonyls can also be prepared by Darzens con-
densations or by several other methods. Rearrangement of
these substrates to the 1,3-dicarbonyl or the tautomeric β-
dehydroxy unsaturated carbonyl has been effected by vari-
ous means.

2.3.1  Acid Catalyzed, Base Catalyzed, Thermal
Isomerizations

There have been many studies of the rearrangements of
epoxides, including epoxyketones.⁷¹,⁷² Proton and Lewis
acid catalyzed reactions often produce 1,2- or 1,3-dicar-
bonyl compounds with concomitant migration of a non-
hydrogen (i.e. alkyl, aryl, or acyl) group. Yet, in many
cases, migration of the β-hydrogen preserves the carbon
skeleton and effects the essential transformation, which is
the subject of this survey.

Harries,⁷³ Stahler,⁷³ and Triebs⁷³ studied the autoxidation
of enones in the early 1900’s. Although there were mix-
tures and poor yields of a variety of products, it is primar-
ily when there is no α-hydrogen that alcoholic base leads
to β-hydroxy enones. The suggested mechanism is an ad-
dition-elimination process (Scheme 39).

Scheme 39

The same reaction can be carried out stepwise by epoxida-
tion of carvone and isomerization with NaOH in an over-
all yield of 25%.⁷⁴

Cromwell showed that the epoxides of some enones with-
out α-hydrogen, although inert to weaker bases, could be
rearranged with strong bases such as NaN₃ to β-hydroxy
enones (Scheme 40).⁷⁵ The mechanism using amide base
seems to involve deprotonation and formation of the enol,
similar to the mechanism proposed for the base catalyzed
Cope rearrangement of unactivated epoxides.⁷⁶ Yields
were mediocre, at best. Compounds with α-hydrogen
preferentially form α-hydroxy enones.
Rearrangement of epoxyketones can also be induced thermally in sealed tubes at 260 °C (Scheme 41). All of the examples reported by Lee-Ruff are epoxides of alkylidene cycloalkanones. β-Hydrogens migrate preferentially to β-alkyl substituents which, quite suitably for this survey, preserves the carbon skeleton and results in net β-oxidation.

Aromatic epoxy ketones also form β-diketones under photoinitiated electron transfer (PET) conditions in the presence of tertiary alkyl amines. Despite considerable study of the effect of substituents, solvents, amines, and additives (e.g., LiClO₄), the best yield of β-diketone was still only 77% at 95% conversion (contaminated with 8% β-hydroxy ketone) (not shown). A more selective but low conversion example is illustrated in Scheme 45.

2.3.3 Enzymatic Isomerization

Styrene oxide isomerase (SOI) [EC 5.3.99.7] is an enzyme that has been identified in several microorganisms. SOI from Corynbacterium sp. is highly specific for the isomerization of styrene oxide to phenylacetaldehyde (Scheme 46). trans-2,3-Epoxy-3-(4-methoxyphenyl)propanenitrile (3) was not a substrate for the wild type enzyme. It may be possible that SOI from other strains or a genetically engineered enzyme or antibody will be developed to convert epoxides of activated olefins into the β-carbonyl isomers.

2.3.4 Palladium Catalyzed (Noyori) Rearrangement

Palladium(0) isomerizes cyclic and acyclic epoxy ketones to β-hydroxy enones (Scheme 47). The yields are very

![Scheme 40](image)

Rearrangement of epoxyketones can also be induced thermally in sealed tubes at 260 °C (Scheme 41). All of the examples reported by Lee-Ruff are epoxides of alkylidene cycloalkanones. β-Hydrogens migrate preferentially to β-alkyl substituents which, quite suitably for this survey, preserves the carbon skeleton and results in net β-oxidation.

![Scheme 41](image)

2.3.2 Photolytic Isomerization

The history of photolytic isomerization of epoxy ketones spans more than 80 years. Much of what is known comes from studies of terpenes and their oxides. In some cases rearrangement occurs from the triplet state. In other cases, rearrangement occurs from the singlet state. Despite decades of extensive study of cyclic and acyclic systems, the photochemical rearrangement of epoxy ketones still affords mixtures of α- and β-dicarboxyls as well as other isomerization and fragmentation products. Typical yields of β-diketones in favorable cases are only around 40–50% (60–70% in exceptional cases). (Schemes 42–44)

![Scheme 42](image)

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low when there is α-substitution. Sometimes, greatly extended reaction times (>160 h) can improve the yields. Although a method with great promise, it is not yet general and has been noted to fail in selected cases.86–88

Scheme 47

2.3.5 Eschenmoser Fragmentation and Related Reactions

Treatment of epoxy ketones with TsNHNH₂ or similar reagents followed by base normally produces acetylenes and carbonyl compounds with concomitant carbon-carbon bond cleavage (Scheme 48).89–91

However, there were anomalous rearrangements to β-hydroxy enones in even the earliest reports (Scheme 49).89

Related rearrangements of epoxiketones to β-diketones have been reported (albeit with an alkyl shift in the example in Scheme 50).92

2.4 Oxidation of Aldols and Acetalaldols

There are many precedents for the oxidation of aldols to β-dicarbonyls. It is a transformation that can be achieved efficiently with a wide variety of reagent systems including CrO₃, Collins’ reagent, Swern, and related oxidations (DMSO, oxalyl chloride), Corey–Kim conditions (Me₂S, NCS),93 Jones oxidation, Dess–Martin periodinane, and many more (Scheme 51).94,95

Similarly, acetals and thioacetals with β-hydroxy or β-alkoxy groups can also be oxidized. Thus, a variety of

Scheme 46

Scheme 49 Anomalous Eschenmoser

Scheme 48 Normal Eschenmoser fragmentation

Scheme 50

Scheme 51 (a) Dess–Martin periodinane, 92% (Ref.94) (b) oxalyl chloride, DMSO, –78 °C, 100% (crude) (Ref.95)
multi-step sequences of reactions (additions, acetalizations, epoxidations, etc.) can be used to effect net \( \beta \)-oxidation of a precursor unsaturated carbonyl.

The aldol reaction is an extremely well developed, highly diversified and efficient route to aldols. However, a synthesis plan may sometimes preclude the aldol reaction and be better suited to enone refunctionalization. Aldols or their ethers can be prepared from enones by the addition of water or alcohols. Oxymercuration-demercuration and other means can also be used to deliver a \( \beta \)-oxygen.

Aldols can also be prepared from \( \alpha,\beta \)-epoxy ketones by regioselective reduction of the \( \alpha \)-CO bond. There are many reagents available for such transformations, among them LiAlH\(_4\), Zn/HCl, Al/Hg, NaI/NaOAc, NaSePh, NaTeH, SmI\(_2\), Pd(0), oximation, and electrochemical reduction.

Vankar has prepared both \( \alpha \)-hydroxy and \( \beta \)-hydroxy acetals by regioselective reductive cleavage of epoxy acetals (Scheme 52). Although the reactions are simple, the sequence is somewhat inefficient as it requires separate steps for the ketone to acetal to ketone protection/protection and a two electron oxidation - two electron reduction - two electron oxidation sequence to achieve a net two electron oxidation of the olefin. Functional groups in more complex substrates would have to be resistant to the broad range of reagents used in the sequence.

Yamamoto found iodobenzene diacetate [PhI(OAc)\(_2\)] with or without irradiation, to be effective for the oxidation of preformed hydroxyethers to acetals (Scheme 53). Yields with irradiation were better than the thermal reaction. LTA was also used to effect the oxidation. The method works to form dioxolanes and dioxanes as well as substituted chiral dioxanes.

Fetizon faced this refunctionalization problem in the preparation of taxol intermediates. Noyori and Tsuji conditions failed to isomerize the epoxy ketone 4 (Scheme 54). The epoxide was cleaved with aluminum amalgam to the aldol which was oxidized with CrO\(_3\)-pyridine.

Even though the Fetizon epoxide 4 is not hindered by an \( \alpha \)-substituent, it is screened from attack by palladium on the \( \text{endo} \) face. On the other hand, the axial hydroxyl is relatively unhindered from formation of a chromate ester. Nevertheless, the yield of the CrO\(_3\)-pyridine oxidation is only 31% (with no mention of side products, such as recovered enone from elimination of the chromate ester).

As part of ionomycin model studies, Weiler found that PDC (85%) was better than PCC (40%) in the oxidation of a \( \beta \)-hydroxy dithiane 5 (Scheme 55).

2.5 Addition-Elimination

A spontaneous one step addition-elimination \( \beta \)-oxygenation of an enone would require a reagent with an ‘activated’ (oxidized) oxygen nucleophile and a confluence of circumstances favoring \( \beta \)-hydrogen abstraction over epoxidation (Scheme 56). There appears to be no examples at this time but \( N \)-substituted hydroxylamines are possible progenitors of such a transformation.

2.6 Selenium Mediated Reactions

Selenium reagents have been used to effect a variety of transformations applicable to the stipulated net \( \beta \)-oxida-
tion of unsaturated carbonyls. Nucleophilic selenium reagents can cleave epoxides regioselectively to generate aldols. Electrophilic selenium reagents can seleno-functionalize olefins. Oxidation of selenide to selenoxide produces intermediates that undergo extremely facile elimination to regenerate a double bond. Although all of the chemical ingredients are present in the literature, we are unaware of a single complete work that specifically transforms enone to $\beta$-hydroxy enone via selenium mediated reactions.

In 1974, Reich showed that phenylselenenyl trifluoroacetate (CF$_3$CO$_2$SePh), prepared in situ from PhSeCl or PhSeBr and silver trifluoroacetate, oxy-selenated methyl acrylate with 65:35 regioselectivity (Scheme 57). Reich did not oxidize these compounds to prepare the $\alpha$- and $\beta$-hydroxy derivatives, but there are reasonable precedents to suggest that this should succeed (vide infra).

$$\text{Scheme 57}$$

(a) 1. PhSeO$_2$CCF$_3$, PhH, ‘instantaneous’ 2. MeOH, NaOMe

65:35 71%

<table>
<thead>
<tr>
<th>OMe</th>
<th>a</th>
<th>HO</th>
<th>PhSe</th>
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Sharpless demonstrated the utility of PhSeNa, prepared in situ from PhSeSePh and NaBH$_4$, in the opening of epoxides. Oxidation and elimination of selenoxide ‘away’ from the hydroxyl produces allylic alcohols and not enols (Scheme 58). None of his examples were with activated epoxides. Other researchers have extended the use of PhSeNa and related reagents to the regioselective opening of $\alpha,\beta$-epoxy ketones and esters.

$$\text{Scheme 58}$$

(a) PhSeNa, EtOH, r.t. (b) H$_2$O$_2$, 12 h, r.t., 50–98%

Miyashita’s primary goal, the preparation of aldols from the epoxy precursors, is achieved by using two equivalents of Na[PhSeB(OEt)$_3$] (Scheme 59). As described above, aldols can be oxidized to 1,3-dicarbonyls. However, by using only one equivalent of reagent, the intermediate $\alpha$-PhSe compounds can be isolated in good yield. The final oxidation-elimination was not described.

$$\text{Scheme 59}$$

(a) Na[PhSeB(OEt)$_3$], EtOH, 0 °C, 85% (b) Na[PhSeB(OEt)$_3$], EtOH, 0 °C, 100%

Such oxidations are not far fetched, at least on protected aldols. $\alpha$-Phenylselenenyl lactone 6 was oxidized with MCPBA and kinetic elimination was entirely selective towards the free methylene and away from the THP oxygen. Heating with rhodium trichloride isomerized the double bond to the net $\beta$-oxidation product 7 (Scheme 60).

$$\text{Scheme 60}$$

(a) MCPBA, NaHCO$_3$, 0 °C to r.t., 5 h, 56% (b) RhCl$_3$·3H$_2$O, Et$_3$N, EtOH, 90 °C, 6 h, 88%

On the route to erythronolide A, Deslongchamps took the initial 1:1 mixture of olefin regioisomers from selenoxide elimination from the spiroketal ester 8 and converted them quantitatively to the $\beta$-oxygenated unsaturated ester 9 using Pd/C (Scheme 61). Although obtained by electrophilic selenation of the enolate, Seebach oxidized the protected $\alpha$-seleno aldol to the enone in 82% yield (Scheme 62).

Kuwajima developed a procedure for the direct preparation of $\alpha$-phenylselenenyl ketones from olefins and allylic acetates (Scheme 63). Aliphatic acetates may, in turn, be derived from enones by regioselective reduction (e.g., CeCl$_3$/NaBH$_4$/MeOH). With an additional oxidation-elimination step, the net result would be the conversion of an unsaturated carbonyl system to the $\beta$-dicarbonyl derivative.

Whereas Kuwajima used excess oxidant, by using substoichiometric selenium Buynak obtained selenodiols, also with mixed regioselectivity (Scheme 64).
2.7 Isohypsic Rearrangement

Isohypsic rearrangements are those that occur without a net change in oxidation state.

Hoping to trap phenols ArOH and induce a [3,3]-sigmatropic C-functionalization of the β-carbon, Walker observed an unusual β-oxidation in an enone-α-sulfoxide (Scheme 65). The sulfur is reduced in the process and Walker suggests either an 'additive Pummerer’ rearrangement or a direct [3,3]-sigmatropic rearrangement of the sulfoxide trifluoroacetate. Overall, the sulfur is reduced by two electrons, the β-carbon is oxidized by two electrons and the whole process is redox neutral.
Related [3,3]-sigmatropic rearrangements of oxime ethers were studied by many groups, too numerous to list completely, but among them are those of Mooradian, Sheradsky, and Kaminsky. No similarly anomalous isohypsic rearrangements were reported.

House studied the related rearrangement of N-vinyl hydroxylamine esters to transfer oxygenation on nitrogen to a β-carbon. Although none of his examples bore α-carboxyls, it remains a tempting possibility. (Scheme 66)

Winterfeldt encountered two modes of rearrangement of N-oxides in maleate esters. The starting N-oxide was prepared by the addition of Et₂NOH to dimethylacetylene dicarboxylate. When suspended in diethyl ether, the thermal rearrangement of the amine oxide provided a small amount of nitronate and a 38% yield of the O-vinyl oxime ether (Scheme 67). Whereas the nitronate may arise from a 1,5-hydride shift with loss of ethylene, the symmetry of the maleate does not even allow the determination of ipso or vicinal \( N,O \)-exchange in the oxime ether product. A priori, electrostatics and Baldwin’s rules would appear to favor 3-exo-trig-formation of oxaziridine over 4-endotrig-formation of oxazetidine, hence, ipso substitution rather than an α,β-transposition.

To facilitate addition of nucleophiles to dehydro-α-amino acid esters, Ferreira, Maia, and Monteiro prepared doubly activated \( N \)-protected derivatives. The \( N \)-t-Boc-\( N \)-Ts derivatives were very susceptible to addition. With some nucleophiles, loss of \( p \)-toluenesulfinate occurred in situ followed by rearrangement of the t-Boc imine back to a β-substituted dehydroamino ester (Scheme 69).

A side product resulting from a shift of \( N \)-tosyl to \( β \)-sulfinate ester was subsequently investigated further (Scheme 70). It is included here because it represents a net two electron oxidation of the \( β \)-carbon with concomitant two electron reduction of sulfur.

Unlike the Walker sulfoxide case, this rearrangement showed a strong dependence on base and solvent and is not likely to be the result of a concerted [2,3]-sigmatropic process. In addition, the isolation of intermediates from the reaction with nucleophiles in CHCl₃ strongly supports an additive mechanism (Scheme 71).

Phenacyl sulfides prepared by the addition of phenacyl mercaptan to enones undergo photochemical Norrish
cleavage to unstable thiocarbonyl compounds that can be trapped by nitrones and hydrolyzed to the β-dicarbonyl products (Scheme 72). 132 (Acetophenone is the reduction product; the β-carbon is oxidized.) In some cases, the thiocarbonyl evades trapping and the oxo compounds are isolated directly.

A composite isohypsic strategy (Scheme 73), not yet implemented in a single example, would entail the β-addition of a heteroatom nucleophile to a conjugated dienone (for a thiol case, see ref. 133 for a germanium case, see ref. 134) followed by the known catalytic isomerization of allylic ethers and allylic amines to their enol 135 and enamine 136 forms. The β-carbon would undergo a two electron oxidation while the γ- and δ-carbons are reduced by one electron each.

2.8 Other Oxidations

In his synthesis of (+)-actinobolin, Kozikowski encountered difficulties with existing methods for the conversion of the 5,6,10-triepi model unsaturated lactone 10 to β-hy-
droxy derivative 11 (Scheme 74). Noyori rearrangement (note the α-substitution) and acid and base catalyzed rearrangements of the epoxide failed to deliver the desired product. Oxidation of the thiophenol addition product also failed (vide infra).

Eventually, a more convoluted route proved to be successful (Scheme 75). Dihydroxylation with catalytic osmium tetroxide and NMO produced diol from which the thiocarbonate was formed; tin hydride reduction cleaved the tertiary carbinol preferentially; oxygen protecting groups had to be exchanged in order to obtain decent yields from the PCC oxidation step.

Scheme 75
(a) OsO₄, NMO, water–acetone, 2:1, 24 h, 94%
(b) Im₂CS, THF, A, 5 h, 100%
(c) Bu₃SnH, PhH, A, 7 h, 85%
(d) 1. R,R = TBDMS converted to R′R′ = acetonide. 2. PCC, NaOAc, CH₂Cl₂, 1 h, 81%

Application of the sequence developed for the triepi model met with severe difficulties when applied to intermediates with the natural configuration so another variation was developed (Scheme 76).

Barton encountered several intermediates recalcitrant to more direct refuncionalization in his synthesis of β-amyrin. When enone 12 could not be epoxidized, cyanide was added. Bromination-dehydrobromination was used to introduce the double bond. The cyanide was then displaced by methoxide to provide the target of interest (13) in this survey (Scheme 77). After several more steps, β-amyrin was obtained.

The same sequence was used on alternate intermediates and a variation on the cyanide displacement was developed as well (Scheme 78). Alkaline H₂O₂ treatment of the isomeric β-cyanoenone 14 produced the epoxy amide. Reduction with chromos chloride gave the tertiary carbinol. Finally, treatment with MsCl in pyridine gave the diketone, presumably through the intermediacy of a cyanohydrin.

Scheme 76
(a) 3,5-dinitroperoxybenzoic acid, Na₃HPO₄, CH₂Cl₂, 24 h, 42%
(b) Zn dust, NaOAc, 90% AcOH, 2.5 h, 50%
(c) 1,1-di-methoxycyclohexane, PPTS, DMF, 4 h, 68%, R,R = cyclohexylidene
(d) CrO₃·pyridine, Ac₂O, CH₂Cl₂, 20 min, 51%

Scheme 77
(a) NaCN, NH₄Cl, DMF–H₂O, A, 90 h (yield not specified)
(b) 1. Br₂, AcOH, HBr, 18 h (major isomer, 34%; combined yield not specified) 2. CaCO₃, DMF, A, 1.5 h, 34%
(c) NaOMe, MeOH–PhH, A, 4 h, (yield not specified)
During the synthesis of sitophelate, Chong reported a net β-oxidation as a major (25%) side product to the Me₂CuLi opening of an α,β-epoxy ester (Scheme 79).³⁸

Another apparently exceptional case occurs during the oxidation of ferulic acid with Co(II)salen–O₂. Out of the mixture there was isolated a 30% yield of β-oxygenation product, partially accounted for by the indicated mechanism (Scheme 80).³⁹

An otherwise reliable reducing system consisting of NaI/TMSCl also produced an anomalous oxidation in a single instance (Scheme 81).⁴⁰ β-Diketone presumably arises by iodination of the double bond with in situ generated I₂ followed by α-elimination and hydrolysis of the β-iodo enone. (Note the absence of an α-hydrogen in the putative diiodo adduct.)

3 Nitrogen
β-Amino-α,β-unsaturated carbonyl compounds, sometimes referred to as the vinylogous analogs of amides, urethanes or other corresponding functional groups, are very commonly encountered species. Often obtained by oxygen-nitrogen exchange on the parent β-dicarbonyl compound, they can also be prepared from less oxidized substrates by replacement of the β-hydrogen.

3.1 Direct Amination
The palladium catalyzed δ- or β-amination of unsaturated carbonyls corresponding to the direct oxygenation reaction is also known. Several examples demonstrate intramolecular aminocyclization to pyridones.
A one-pot in situ addition-oxidation using Pd(II) has been described by Hegedus (Scheme 85). Secondary anilines gave higher yields than primary anilines, o-bromoaniline being an exception. This system is unforgiving to either α- or β-substituents on the activated olefin. Additional examples are provided by Kasahara. Hosokawa studied amides and urethanes in the β-amidation of unhindered, activated olefins (Scheme 86). Urethanes were more reactive than amides and cyclic amides were more reactive than simple acyclic acetamide. In some cases, long reaction times could be shortened by the addition of HMPA. Cenini was able to extend this system to the reaction of methyl acrylate with the slightly less reactive, acyclic urethane (ethyl carbamate). These results must be contrasted with those of Spencer who was able to ‘derail’ the oxidation and isolate good yields of simple unoxidized carbamate adducts.

3.2 Addition-Oxidation

α,β-Unsaturated carbonyl compounds readily undergo addition of nitrogen nucleophiles. In hindered cases, high pressure has been used to induce addition due to the favorable activation volumes. (The formation of β-ethers by alcohol addition is also favored by high pressure.) The resulting β-amino ketones can then be oxidized very similarly to their oxygen counterparts.

An all encompassing example is provided in Heathcock’s synthesis of the cylindricines A and B (Scheme 87). Ammonia adds to the cross conjugated ketone to form the piperidone. Enolization with LDA and trapping with TIPSOTf provides the enol ether substrate for Evans’ CAN oxidation to enone. Conjugate addition of the C6H13 side chain and aminochlorination of the pendant olefin generates the natural products. Whereas the Evans CAN oxidation appears to work on a range of carbamate protected β-amines, a t-Boc protected piperidone underwent decomposition. In this case, Sae-gusa oxidation was successful (Scheme 88). Preformed acyclic β-amino carbonyl compounds are also oxidized by Pd(II). Murahashi optimized catalyst, solvent and base for acyclic cases that were free from additional β-substitution (Scheme 89). The cyclic N-methyl-4-piperidone and N-methyl-2,3-dihydro-4(1H)-quinol-
none (not illustrated here) were both inert to these conditions suggesting amino complexation of a palladium intermediate may be necessary in this reaction.

There is an aminoselenation analog of the oxyselenation reaction. Benzeneselenamides are prepared from PhSeCl or PhSeBr and secondary amines under anhydrous conditions. They are good selenenylation agents. They also react with activated olefins in a regioselective manner to provide β-amino α-phenylselenenyl ketones.\(^\text{154}\) Oxidation to the selenoxide and elimination usually forms the allylic amine. In some cases, the product distribution includes β-amino enone (Scheme 90). Whether this arises kinetically or by isomerization under the reaction conditions is not made clear. Also as in the oxygen cases, catalytic isomerization of the double bond might be used to enhance the yields of net β-oxidation products.\(^\text{155,156}\)

Scheme 87

(a) 1. Sat. NH\(_3\)-EtOH, concd NH\(_4\)OH, 105 °C, 18.5 h, 97% 2. TEOC–OSu, K\(_2\)CO\(_3\), MeCN, 24 h, 85% (b) LDA, TIPSOTf, THF, –78 °C to r.t., 97% (c) CAN, DMF, 0 °C, 1.5 h, 91%

Scheme 88

\[ \text{Scheme 87} \]

\[ \text{Scheme 88} \]

Oxidation of unprotected amines following enone addition generates N-oxides that can undergo Polonovski rearrangement to introduce a double bond that can migrate into conjugation to reform the enone. When applied to 1-methylpiperidine-4-one the ‘direct’ two step sequence gave an overall yield of 50% (Scheme 91).\(^\text{157}\) The three step procedure via the enol silyl ether gave an 85% yield of product.\(^\text{158}\) The yields may not be directly comparable as trifluoroacetic anhydride (TFAA) is ordinarily much more reactive than acetic anhydride.

Wenkert used the Polonovski reaction to establish α,β-unsaturation in a ketoamine intermediate in the synthesis of lycopodine alkaloids (Scheme 92).\(^\text{159}\)

In a piperidine α-ketol, oxidation occurs spontaneously during the attempted deprotection of the TBDMS enol ether 15 (Scheme 93).\(^\text{160}\)
Another surprising oxidation occurred during the attempt-
ed hydrogenolysis of an aromatic quinolone enol ether (Scheme 94).161 This substrate had resisted all other at-
ttempts at oxidation, including Evans and Saegusa oxidations. It is also one the few cases where a substrate
undergoes both an oxidation and a reduction simulta-
neously in the presence of non-self-obliterating redox agents.162,163

Photochemical oxidation of aromatic \( \beta \)-amino ketones in the
presence of oxygen produces \( \beta \)-amino enones via the
cyclopropanols (14 examples, 18–75% isolated yields)
(Scheme 97).165
Lee and Kim used 1,4-phosphoniosilylation adducts as in-
termediates in the net 1,4-addition of amino and sulfur nu-
cleophiles to unsaturated ketones (Scheme 98).166
Although none of these adducts were oxidized further to
the \( \beta \)-heteroenones using CAN, Pd(0), IBX, PhIO, or oth-
er reagents, the precedents for such oxidations are well es-
tablished (vide supra).

Electrochemical oxidation of the amine adducts can also
be used to introduce unsaturation. By the sequence of
amine addition, N-acylation, oxidation and hydrolysis,
acrylates are converted into \( \beta \)-aminoacrylates (Schemes 95 and 96).164 Yields are excellent.
Oxygen nucleophiles are conspicuously absent examples. Gorlitzer developed a method for the determination of ethacrynic acid, a useful drug and pharmacological tool (e.g., as a diuretic; glutathione S-transferase inhibition; ATP Cl-dependent pump inhibition; etc.). Reaction of ethacrynic acid with an excess of NH₂OH forms a quinoline that can be detected by its blue fluorescence upon UV irradiation (Scheme 99).¹⁶⁷

Treatment of indenopyranone carboxaldehyde with hydroxylamine produces a 79% yield of amine replacement at the β-position (Scheme 100). The amino oxime was also formed as a side product in 10% yield.¹⁶⁸

Nitrosobenzene oxidizes the β-carbon of methyldiene-malonate and produces a product equivalent to that obtained from reaction of hydroxymethylene malonate with N-phenyl-hydroxylamine (Scheme 101).¹⁶⁹

The reaction of nitrosobenzene with ρ-chlorobenzylidene-malonaldehyde produced an unusual double oxidation product (Scheme 102).¹⁷⁰ The β-carbon is oxidized as is one of the aldehydes. Although the structure proof appears to be rigorous, the authors do not offer a mechanism.
3.3 Addition-Elimination

The ambident nucleophile hydroxylamine and its derivatives readily add to α,β-unsaturated carbonyls. Both N- and O-adducts can be obtained.\(^ {107,108} \)

The direction of elimination of MeOH from enone-methoxyamine adducts is dependent on the choice of base and solvent.\(^ {171} \) Thus, Seko found that \( t \)-BuOK in \( n \)-BuOH favored formation of aziridine but \( t \)-BuOK in THF favored \( β \)-aminoketone; NaOMe in DMF favored aziridine but \( t \)-BuOK in DMF favored \( β \)-aminoketone (Scheme 103).

(Right Diagram)

Although simple \( N \)-alkyl hydroxylamines can be oxidized to oximes there do not appear to be any examples of \( β \)-keto or \( β \)-carboxy hydroxylamines being oxidized to \( β \)-keto or \( β \)-carboxy oximes. However, such a compound is a likely intermediate in the reaction of excess NH\textsubscript{2}OH with cinnamic acid (Scheme 104).\(^ {172} \)

Treatment of dimethyl maleate with dimethyl hydrazine gave the simple hydrazine adduct which was N-methylated with Mel or MeBr. Elimination of Me\textsubscript{2}N left the primary amino maleate (Scheme 105).\(^ {173} \) The \( α \)-ester makes this another special case as it is likely essential to facilitate proton abstraction \( α \) to the hydrazinium.

Other oxidized amine reagents can add to enones and undergo net redox transfer to carbon via elimination. \( S,S \)-Diphenylsulfilimine (\( Ph_2 SNH \), 16) is one such reagent.\(^ {174,175} \) While it reacts with quinone, maleimide, and some other symmetrically activated olefins (Scheme 106), unsymmetrical, more polarized double bonds such as in chalcone, benzylidene acetone, methyl vinyl ketone, as well as symmetrical maleic anhydride, are inert, even under refluxing conditions. (Aziridines are the major products in some circumstances.)\(^ {176} \)

3.4 Reductive Addition

It was unexpectedly discovered that the addition of hydrazoic acid to \( γ \)-oxo-\( α,β \)-unsaturated lactones afforded the \( β \)-amino enones directly and in excellent yield (Scheme 107).\(^ {177} \) The reaction has been extended to lactams, as well.\(^ {178} \) There are some limitations. Considerable variability in \( R^1 \) and \( R^2 \) are accommodated but dissubstitution appears to be necessary in the lactone cases. The course of the reaction is sensitive to pH. Since the reaction does not appear to have been applied to simple enones, the \( γ \)-activating group is almost certainly a requirement.
Mechanistically, it is reasonable to assume the need for proton abstraction from the initial azide adduct and the flanking carbonyl provides the acidifying activation.

Another entry to the quinolone alkaloids, such as graveoline, follows from aromatic nitro precursors. Reduction with CO and catalytic Pd(II) (TMB = trimethylbenzoate) at elevated temperature generates an aniline that adds spontaneously to the enone. Oxidation to quinolone occurs during the reaction (Scheme 108). In some cases, an isolated mixture could be resubjected to the reaction conditions to further drive the reaction to the unsaturated product.

 Isoxazoles are an important class of compounds with a rich and varied chemistry. They mask a dicarbonyl system in an enol and an imine which are readily exposed by reduction of the N-O bond.

Of the many ways to prepare isoxazoles one of the simplest and useful is via addition of hydroxylamine to enones followed by an oxidation, a reaction sequence that generally proceeds in good yield. For the preparation of \( \beta \)-damascenone, Buchi examined \( \beta \)-ionone and several analogs (Scheme 109). Clearly, the isoxazole procedure is unsuited for endocyclic enones.

Enones also undergo facile nitrile oxide cycloaddition (NOC reaction) to form isoxazolines. The regiochemistry can often be controlled to place the oxygen at the \( \beta \)-carbon and form a new \( \alpha \)-C-C bond. Mild oxidation to the aromatic isoxazole followed by N-O reduction provides net \( \beta \)-oxidation with \( \alpha \)-alkylation.

The NOC and intramolecular NOC (INOC) reactions have been extensively reviewed elsewhere and are not covered here.

Isoxazoles are somewhat unique because of the facility with which they can be handled in the lab and manipulated chemically. However, many other ambident nucleophiles also add to enones and can be oxidized to their aromatic counterparts. Pyrazoles, pyrimidines, and related heterocycles can be prepared this way (Scheme 110). It is more difficult to unmask these latent \( \beta \)-heteroenones. For most practical purposes they do not surpass isoxazoles or isoxazolines for use in further synthetic elaboration.

As mentioned, hydroxylamine and \( N \)-substituted hydroxylamines readily undergo 1,4-addition to enones. Although simple alkyl hydroxylamines and their ethers can be oxidized to the corresponding oxime and oxime ethers, we are unaware of the successful oxidation of an enone adduct to \( \beta \)-keto oxime (Scheme 111).
Another isoxazole synthesis occurs upon rearrangement of an oxime O-vinyl ether. Nitrogen is transferred from oxime oxygen to carbon (Scheme 112). In this substrate, it is the acrylate α-carbon that is oxidized. Yokoyama proposes a free radical mechanism. The relative stability of acetaldehyde radical [CH$_2$C=O $\leftrightarrow$ CH$_2$C=O·] suggests that a similar rearrangement of the regioisomeric enol pyruvate might also work if it could be prepared.

Unsaturated ketones can also be directly nitrated (Scheme 114). Trifluoroacetyl nitrate (CF$_3$CONO$_2$), prepared in situ from ammonium nitrate and trifluoroacetic anhydride, has been used to nitrate the δ-carbon of dienoic esters. Anhydrous KOAc in diethylether is used to eliminate trifluoroacetate from the intermediate nitro adducts (Scheme 115).

Unactivated olefins can be nitrated in a fashion similar to the Wacker oxidation using palladium catalysis. Opposite regiochemistries are obtained from two different catalyst systems (Scheme 116). Thus, Pd(MeCN)$_2$(NO$_2$)$_2$ gives primarily internal nitration but Pd(MeCN)$_2$Cl(NO$_2$) produces the terminal nitro derivative. In principle, but

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**Scheme 111**

**Scheme 112**

**Scheme 113**

**Scheme 114**

**Scheme 115**

**Scheme 116**

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3.6 Nitration

The conversion of α,β-unsaturated carbonyl compounds to the corresponding β-nitro carbonyls can be accomplished by several means. It should be noted that β-nitro ketones and esters are useful dienophiles in the Diels–Alder reaction where it has been shown that the nitro group is able to reverse the polarity of the parent unsaturated carbonyl system.

Methyl acrylate can be nitrated with dinitrogen tetroxide–iodine on a 3.5 mole scale (Scheme 113).

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not yet in practice, the reaction might be extended to acetylodels or allylic acetylals, esters, or ethers.

Nitrosation of unactivated olefins with NOCl produces nitroso chlorides that can undergo a variety of further reactions including dimerization, oxidation of the initial nitroso adduct to the iminonitro and nitro compounds, and tautomerization of the alkyl nitroso to the oxime. In a slow and incomplete reaction, α,β-unsaturated methyl docosenoate was treated with NOCl (from isoamyl nitrite and HCl) and the resulting β-chloro, α-nitroso ester was isolated as the oxime (Scheme 117).206

Scheme 117

 Less polarized double bonds flanked by 1,4-dicarbonyls are more reactive towards NOCl.207 The product mixture contains both regioisomeric nitroso chlorides and hydroxy oximes (Scheme 118).

Scheme 118

Nitromercuration of allylic acetylals of unsaturated carbonyls occurs regioselectively.45 Treatment with base leads to elimination of mercury and formation of β-nitroacetal that is hydrolyzed to β-nitroene (Scheme 119).

Alternatively, β-nitroketones can be halogenated on the α-carbon and, after ketalization, dehalogenated with base (Scheme 120).39

Scheme 120

Alkyl and aryl nitro compounds can also be obtained from the corresponding amine precursors by oxidation with a variety of reagents.208–210 This strategy is not likely to work with β-amino unsaturated carbonyl compounds.

3.7 Azides

Upon treatment with iodoazide, unsaturated esters form β-azido, α-iodo esters of limited stability. Elimination of HI with DABCO produces the β-azido esters which are, in some cases, also unstable (Scheme 121).211,212

Scheme 121 (a) IN₃, MeCN (b) DABCO, PhH, r.t., low to 50%

3.8 Ene-Isomerization

In a study of the ene reaction of 4-phenyl-1,2,4-triazoline-3,5-dione (PTAD) with enones, Hoye established some of the determinants of α-amination vs. β-amination.213 Monosubstitution of the β-carbon favors β-amination while, disubstitution of the β-carbon favors α-amination (Scheme 122). Although it was not demonstrated with these products, it is conceivable that isomerization, possibly with cationic transition metal catalysts, would isomer-
ize the double bond back into conjugation with the amine.  

3.9 Aziridine and Azide Rearrangement

Rearrangement of \( \alpha \)-keto aziridines usually does not produce \( \beta \)-amino enones. There are, however, a few unusual examples.

When there are anion stabilizing groups on both ends of the \( N \)-silyl methyl aziridine shown in Scheme 123, fluoride induced Si–C cleavage leads to further rearrangement to amino enones.\(^{214}\) When there is only one anion stabilizing group, there is no 1,2-proton shift and the imine trimerizes. More hindered imines might resist trimerization and eventually rearrange but this was not tested. \( N \)-TMS-methyl aziridines without any activating group are resistant to cleavage with CsF.

The \( \beta \)-enamino nitrile 18 occurs as a minor product upon base catalyzed isomerization of the aziridinonitrile 17 (Scheme 124).\(^{215}\) The corresponding esters give the \( \alpha \)-amino acrylates and crotonates only.

Treatment of benzalacetophenone with \( t \)-BuNH\(_2\) and I\(_2\) produces a separable mixture of cis and trans aziridines. Irradiation of the cis aziridine produces oxazole but the trans aziridine forms a mixture, including 41\% of the \( \beta \)-\( t \)-butylamino enone (Scheme 125).\(^{216}\)

Two special cases are related by Hassner in his analysis of azide rearrangements (Scheme 126).\(^{217}\) Both examples are noteworthy in that they seem to require an electron withdrawing group to stabilize intermediates that can undergo an alkyl shift. Both examples also lack a \( \beta \)-hydrogen and require a skeletal rearrangement, something undesired in the more simplified context of this review. Whether the unsubstituted analogs containing a \( \beta \)-hydrogen will undergo a similar reaction with a hydride shift is unknown at this time.

4 Sulfur

4.1 Episulfides (Thiiranes) or Episulfoniums

There are but a few examples of the preparation \( \alpha \),\( \beta \)-carbonyl episulfides (thiiranes) from \( \alpha \),\( \beta \)-unsaturated carbonyl compounds, their rearrangement to \( \beta \)-thio or \( \beta \)-oxo

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**Scheme 122**

**Scheme 123**

**Scheme 124**

**Scheme 125**

**Scheme 126**
Enones are more rare. In fact, we are not aware of any examples to date.

Through the intermediacy of an epoxide, an unsaturated ester was converted to the α,β-thioglycidate with thiourea (Scheme 127). Note the reduction product that suggests the use of thiourea as yet another reagent for the preparation of aldols.

The combination of phosphorthioate and MCPBA produces a reagent formulated as a phosphinium polysulfide [(RO)₃PSSₙS] that reacts with N-ethyl maleimide to form a thiirane (Scheme 128). Further oxidation leads to the extrusion of SO and regeneration of the maleimide.

Thiiranes were also invoked as intermediates in the reaction of sodium polysulfide with enones en route to thiolanes and thiophenes (Scheme 129).

4.2 Addition-Oxidation

There are many methods by which to replace a β-hydrogen of an unsaturated carbonyl system with a β-sulfur. Thiols readily add to enones to provide the β-thio carbonyl compounds. Oxidation of the sulfur can lead to Pum-
merer rearrangement, elimination of the hydrogen α to sulfur or by some other path to enone. There are a number of examples of such transformations that shed light on the subtle demands for a successful reaction.

The addition-Pummerer sequence has been used on several α,β-unsaturated carbonyl systems. Following sulfide addition, various reagents have been used to obtain sulfoxide without overoxidation or elimination [MCPBA,221,222 Oxone,223 H2O2–Sc(OTf)3,224 dimethyldioxirane (DMD),225 NaIO4, CAN226]. The rearrangement of sulfoxide to β-thio-α,β-unsaturated carbonyl (cf., β-dicarbonyl) can also be carried out with various reagents, but typically trifluoroacetic anhydride is used (Scheme 130).227

The tetrahydrothiopyran-4-ones shown in Scheme 131 could not be oxidized directly with SeO2. Neither could they be oxidized completely with NCS. Sequential treatment was necessary to effect the double oxidation.228

Bakuzis was able to add thiophenol to cyclic and acyclic olefins activated by cyano, ester, and ketone functionality.229 The thioethers were then oxidized with N-chlorosuccinimide (NCS), which in most cases, decomposed to β-phenylthioenones spontaneously. Overall yields are, in general, excellent (Scheme 132).

The Bakuzis reaction has been extended to other thiols, including very hindered arylthiols.230 However, the oxidation-elimination is sensitive to stereochemistry and conformation and to the choice of solvent and oxidizing agent. The reaction sequence failed for Kozikowski in his synthesis of actinobolin, as did the use of MCPBA as oxidant (vide supra).86 It also failed in the preparation of intermediates for terpene synthesis.88 In both cases, starting enone was returned due to the facile elimination of axial thiophenol from the cyclic adducts.

Other oxidants have been used successfully in variations on the Bakuzis theme. Tanikaga used SO2Cl2.231 DDQ has been used in particularly reactive cases.232 Haynes used NCS to prepare β-thieno enones and oxidized them further to β-sulfones with MCPBA.233 de Groot introduced chloreal (trichloroisocyanuric acid) as oxidant in the transformation.234 In general, chloreal gave better results than NCS and significantly better results when the PhS group was axial (Scheme 133).235

The chloreal procedure was used in the preparation of 19, an intermediate in the synthesis of thiarednose analogs88 and 20, an intermediate in the synthesis of germacranes and oxocins (Schemes 134 and 135).88
Photochemical oxidation α to sulfur in phenacyl sulfides produces unstable thiocarbonyl compounds. In some circumstances, these compounds isomerize to the β-keto thiolates that can be derivatized, e.g., by alkylation (Scheme 136).132

### 4.3 Addition-Elimination

Carbonyl activated olefins undergo regioselective oxidative-addition to form α-halo, β-sulfur species. For example, sodium p-toluenesulfinate-iodine adds to a wide range of unsaturated carbonyl compounds to provide the α-iodo sulfones in good yields.236,237 Elimination of HI with Et3N generates β-sulfonyl enones (Scheme 137).

Scheme 137

A similar reaction occurs with arylsulfonyl bromides under irradiation conditions (Scheme 138).238

Scheme 138

The reaction, however, is sensitive to steric constraints (Scheme 139).238

Scheme 139

Another β-sulfonylation product appears as a minor component in the β-arylation of enones with arylazo aryl sulfonyl halides (Scheme 140).239
4.4 Metalation-Sulfenylation

α,β-Unsaturated carbonyls have been metalated at the β-carbon by a variety of protocols, usually for the purpose of forming new carbon-carbon bonds. The original papers cited by Chinchilla and Najera in their extensive review should be consulted for actual examples of other sorts of electrophiles used as anion traps, among them sulfur, silicon, tin, and halogens.

Evans’ studies of the 1,4-addition of silicon phosphites to enones has inspired considerable derivative work with unsaturated esters and other phosphates, phosphites and phosphines. Introduction of an anion stabilizing phosphite or quaternary phosphonium species at the β-carbon with concomitant protection of the reactive carbonyl as its silyl enol ether (or ketene acetal) allows formation of an α-phosphorus stabilized nucleophile.

To date, most of the reactions studied have involved formation of new carbon-carbon bonds (Scheme 141).

Lee and Kim, drawing on the precedents of Evans and others, extended the idea to heteroatom electrophiles, in particular, sulfur. They sulfenylated the lithiated phosphonium adduct with PhSSPh, PhSCI or MeSSMe (Scheme 142). The Lee–Kim procedure can be carried out in one pot without isolation of intermediates. It works in both cyclic and acyclic cases although it is sensitive to the choice of sulfenylating agent. The authors suggest the intermediacy of mixed dienes but have published no follow up results (such as might be obtained by diene trapping).

An illustrative suggestion draws upon Cohen’s use of phenyl thioborate [B(SPh)₃] for the preparation of 1,3-bis(phenylthio)alkenes from enones. The allylic sulfides can be lithiated with s-BuLi. These anions have been alkylated but, in principle, can be trapped with heteroatom electrophiles as well or oxidized (NCS, chloreal) and hydrolyzed (Scheme 143).

Many other possibilities may be gleaned from Chinchilla and Najera’s review.
4.5 Oxidative Addition-Elimination

There are a variety of S–X reagents that are reactive enough to add to isolated olefins but their reactions with double bonds conjugated to carbonyls are scarce. Back prepared PhSeSO\textsubscript{2}Ar reagents\textsuperscript{250} that react with cyclic and acyclic olefins in the presence of catalytic BF\textsubscript{3}·OEt\textsubscript{2} to form vicinal selenosulfones.\textsuperscript{251} Oxidation to selenoxide with MCPBA and spontaneous concerted elimination of seleninic acid produces vinyl rather than allyl sulfones (Scheme 144).

![Scheme 144](image)

Scheme 144

Toru describes the preparation of S-acyl selenosulfides\textsuperscript{252} and their free radical addition to olefins (photolytically or AIBN initiated) to form selenothiols.\textsuperscript{253,254} Toru does provide an example that demonstrates that addition to acrylates occurs regioselectively and that oxidation-elimination produces β-thiobenzoyl acrylate (Scheme 145).\textsuperscript{255}

![Scheme 145](image)

Scheme 145

4.6 Isohypsic Rearrangement

Fleming has reported the use of vinyl sulfoxide elimination for the preparation of alkynes.\textsuperscript{256} In the instance of heating ethyl 2-phenylsulphonylpropenoate, he recovered a 60% yield of ethyl 3-phenylsulfinylpropenoate, presumably via an acetylenic intermediate (Scheme 146). Addition of sodium sulfinate to activated (and unactivated) alkynes is known,\textsuperscript{257} but the addition of sulfenic acids is less common.\textsuperscript{258} This survey is not concerned with β-functionalization via acetylene addition but this novel transposition is certainly germane.

![Scheme 146](image)

Scheme 146  (a) toluene, 120 °C, 1.5 h, 60%
The best result, an 86% yield, was obtained with an activating carbonyl at the 6-position.

5.2 Addition-Oxidation

The fluoro-Pummerer rearrangement has been used to β-fluorinate Fmoc-dehydro-α-alanine via a multistep sequence (Scheme 150).221 p-MePhSH undergoes a Micheal addition onto the olefin to form the β-thio ether and oxidation with MCPBA forms the sulfoxide. Diethylaminosulfur trifluoride (DAST) and SELECTFLUOR have been used for the fluoro-Pummerer. van der Donk combined SbCl₃, which is known to catalyze the reaction, with DAST and obtained β-fluoro-β-thio ether in 70% yield. A second MCPBA oxidation and thermal elimination provided the net β-oxidation product.

5.3 Umpolung-Halogenation

Another approach to β-halogenation is via an umpolung sequence.269 Hydrazones, semicarbazides, oximes and similar groups that render the β-carbon of an enone nucleophilic rather than electrophilic can be used. The general scheme (Scheme 151) applies to both cyclic and acyclic systems.

6 Phosphorus

Phosphorus is slightly less electronegative than carbon. There is no net change in formal oxidation state at the β-carbon upon replacement of hydrogen with phosphorus. The important chemistry of phosphorus and its derivatives requires its inclusion here.

As discussed above (Section 2.2), phosphites add to enones to form β-keto phosphonates (cf., silyl enol ethers). No one appears to have reported the oxidation of a phosphite adduct to a β-keto vinylphosphonate. The successful conversion of enone to β-phosphonioenone has been achieved by 1,2-addition of phosphinate to the carbonyl (a net reduction) followed by oxidation with carbonyl transposition (Scheme 152).270 (β-Phosphonioenones are known via other routes, e.g., by heteroatom exchange with β-chloroenones.)271

The chemistry of arsenic (e.g., using AsPh₃)272 and sulfur (e.g., using Me₂S)273 adducts is being developed along similar lines.

7 Silicon

Being less electronegative than carbon, replacement of hydrogen by silicon would amount to no net change in formal oxidation state at the β-carbon. Nevertheless, silicon has also been introduced oxidatively, such as by addition followed by loss of hydride or H₂ as well as in a redox neutral manner, that is, by a proton abstraction and trapping of the anion. For all of the similarity of silicon to a proton, the functional utility of organosilicon compounds requires their consideration here.
7.1 Direct Silylation

The direct β-silylation of unsaturated carbonyls has been reported with several catalysts. Dicobalt octacarbonyl mediates β-silylation of simple acrylates; α- or β-substitution completely impedes the reaction. The reaction tolerates variation in the silane (HSiEt2Me, HSiMe3, HSiMe2Ph) and the products are exclusively trans. Excess acrylate is required as it also serves as the H2 sink co-generating methyl 3-trialkylsilyl propiolate as by product. (Scheme 153)

\[
\text{Scheme 153}
\]

Rhodium and ruthenium also catalyze the oxidative silylation of acrylates but with diminished selectivity. A platinum catalyst, PtCl2, is effective when there is substitution, such as with methacrylates; however, the β-silyl methacrylate is a minor product accounting for only 1–2% of the yield. Doyle studied several catalysts, including rhodium(II) perfluorobutyrate, Rh2(pfb)4 (Scheme 154). Addition of Et3SiH to ethyl acrylate in CH2Cl2 at room temperature led to a 74:26 ratio of vinyl silane and hydrosilylation products. At elevated temperatures (40 ºC; 65 ºC), the ratio was unchanged but yields increased. Inverse addition at room temperature shifted the product almost exclusively to hydrosilylation (98%). However, inverse addition at 65 ºC returned vinyl silane as the major product (70%). Anionic silicon reagents, e.g. (PhMe2Si)2CuLi, add 1,4 to enones and the enolates can be trapped as their TMS ethers. The silyl enol ethers can be α-sulfonylated with PhSOCl. Oxidation with MCPBA and elimination of sulfinic acid provides β-silyl enone. The example shown (Scheme 155) is a composite that demonstrates the feasibility of the sequence even though the actual synthesis occurred by an inverse (carbon) addition to the preexisting silyl enone.

\[
\text{Scheme 155}
\]

7.2 Metalation-Silylation

Chinchilla and Najera have extensively reviewed acyl vinyl anions with an emphasis on the formation of new C–C bonds. Silylation of β-lithio α,β-unsaturated esters has been reported as well. The following examples are from sources not cited in reference 240. Each of these cases contain functional groups or special features that facilitate direct lithiation. Otera implemented a straightforward sequence for the preparation of β-silyl enones by β-hydrogen replacement (Scheme 156). Although yields for each step were generally quite good (75–95%), after 5 steps the arithmetic demon takes its toll.

\[
\text{Scheme 156}
\]
In an attempt to prepare a 2-lithio derivative, Kelly instead observed deprotonation and silylation at C5 of methyl 4-thiazolecarboxylate.284 Once the 5-position was blocked, C2 was deprotonated and stannylated (Scheme 157).

Scheme 157

3-Carboxy furans and thiophenes can be deprotonated and silylated at the 2-position either via the ester monoanion or the carboxylate dianion (Scheme 158).285–287

Scheme 158

N-Protected indole-3-carboxylic acids and amides are similarly silylated (Scheme 159).288

Scheme 159

Uridine derivatives lithiate at C6 and react with tin and silyl electrophiles (Scheme 160).289 α-Methoxy acrylamides can be directly deprotonated and silylated (and sulfenylated), as well (Scheme 161).290

In symmetrical cases, β'-lithiation and silylation of unsaturated amides can, in principle, provide a skeletally equivalent net β-silylation following either catalytic isomerization of the double bond to the β' isomer or a second deprotonation followed by proton quench.291 Although the proton quench strategy was not specifically demonstrated, many other electrophiles were shown to react at the original β-position, shifting the double bond towards the first β'-trapped electrophile. (Scheme 162) When El = H, the product is the mirror equivalent of β-silylation.

In unsymmetrical cases, a three-step isomerization strategy (e.g., protonate at β' with an allylic shift; silylate the original β-position; protonate β' and shift again) should preserve the original skeletal relationships.

Scheme 160

Scheme 161

Scheme 162
8 Metals

All metals of interest are less electronegative than carbon and the metalated compounds might also be considered to be isohypsic with the β-hydrogen precursors. Their synthetic utility, especially for the possible introduction of other electronegative elements, requires their consideration here.

8.1 Direct Metalation

Chinchilla and Najera have reviewed acyl vinyl anion equivalents and their use in the formation of new carbon-carbon bonds.240 There are many methods involving halogen-metal exchange which are not applicable to the current subject as the β-position is already oxidized. We are primarily concerned with the replacement of an extant β-hydrogen with a metal either by addition-deprotonation or direct deprotonation.

Once formed, many of the β-metallo enones can be transmetalated to tin, boron, silicon, and other metals or metalloids.

Even though tin compounds can hydrostannylate double and triple bonds, there does not appear to be any direct transition metal catalyzed β-stannylation of an unsaturated ester or ketone such as is known with silicon systems (Scheme 163).

Scheme 163

The direct metalation of vinyl ethers is a well-established method of organic synthesis.292 It has been extended to highly functionalized cyclic cases, including oxygenated furans and pyrans.

Allylic ethers can be prepared from enones (and pyrones) by 1,2-reduction and protection and, as such, serve to mask the enones until a subsequent deprotection-oxidation sequence. Friesen was able to metalate the silylated glucal 22 with t-BuLi in THF and transmetalate to tin with Bu3SnCl (Scheme 164).291 It was necessary to use the TIPS or TBDPS groups due to competing deprotonation of TBDMS groups. The tin was used to facilitate formation of a new C–C bond by Stille coupling.

Dotz developed a cyclic protection scheme for other glycal configurations.294 He used the TIPS-acetonide system as shown in Scheme 165.

9 Carbon

The replacement of a carbon-hydrogen bond with a carbon-carbon bond represents a net one-electron oxidation at that carbon. It is a reaction that has been recently reviewed.240 For the latter reason, it is not a major subject of this review.

A variety of direct palladium catalyzed C–C couplings to and between sp2-centric centers are known. The Heck reaction typifies this sort of reaction.295–297 However, there have been some limitations with regard to the direct reaction of substituted α,β-unsaturated carbonyls, not unlike the situation with palladium catalyzed heteroatom replacements discussed in previous sections. The Heck reaction does work with substituted substrates such as has been shown by Chen (Scheme 166)298 and others.299,300

Further development of new Heck chemistry should proceed hand in hand with the improvements of the two electron oxidation reactions.

10 Other Elements

Although other nucleophilic and electrophilic heteroatom equivalents have been incorporated into donor reagents, there are no other major β-heteroatom replacements to report at this time.
11 Heteroatom Exchange

Throughout the discussion above, it has been explicitly shown in a few examples that once a given oxidation state has been achieved that the heteroatom attachments are subject to exchange and replacement. Such isopyspic reactions at the ipso center are not the main topic of this survey. Vinyl-X exchange reactions are much easier to search for in standard reference works.\(^2\)\(^-\)\(^3\) Heteroatom exchange is emphasized as a reminder that when searching for a particular functional derivative of an unsaturated carbonyl system, very few of them has been achieved that the heteroatom attachments are subject to exchange and replacement. Such isopyspic reactions at the ipso center are not the main topic of this survey. Vinyl-X exchange reactions are much easier to search for in standard reference works.\(^2\)\(^-\)\(^3\) Heteroatom exchange is emphasized as a reminder that when searching for a particular functional derivative of an unsaturated carbonyl system, very few of them seems to be general or widely applicable. Many of the reactions described are limited to unhindered or even unsubstituted vinyl ketones or esters. Some require aromatic substitution or other activation on the substrate. Some reagents work best on \(s\)-trans or endocyclic enones; others work best on \(s\)-cis acyclic or exocyclic substrates. Some otherwise excellent reagents are unreactive towards highly polarized double bonds but react more favorably with 1,2-disubstitution or less polarized olefins. For many of the reactions, there are many side products and yields are low.

Although there are several direct oxidation systems, mostly based on catalytic palladium, many transformations are classical multistep sequences. As such, they suffer operational and yield lowering inefficiencies.

On the positive side, many of the reagent systems are mild and would appear to accommodate a wide range of functionality elsewhere in the substrates.

The transformation of \(\alpha,\beta\)-unsaturated carbonyl compounds into their \(\beta\)-oxidized counterparts would seem to be fertile ground for the continued development of new synthetic methods.

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