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Synthetic Applications of the O–H Insertion Reactions of Carbenes and Carbenoids derived from Diazocarbonyl and Related Diazo Compounds

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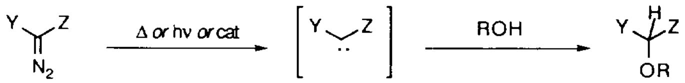
Contents

I. Introduction

A. Scope

The decomposition of diazo compounds in the presence of hydroxylic compounds (water, alcohols, phenols or carboxylic acids) results in the formation of a new C–O bond by a formal insertion of the carbene (or carbenoid) into the O–H bond (Scheme 1). Certain examples of the reaction are very common, for example the esterification of carboxylic acids using diazomethane, but in other cases, for example the formation of ethers from diazocarbonyl compounds and alcohols, the reactions are less widely used, despite the fact that they often proceed in high yield. The purpose of the present review is to highlight the synthetic applications of such ether forming reactions, and in particular those involving diazocarbonyl compounds, or related diazo compounds such as diazophosphonates, covering the literature to the end of 1994. Some facets of the chemistry have been covered in earlier reviews (see also Section I.C),[1] most notably the recent article by Kirmse which deals with mechanistic aspects of the reaction.[2]



Scheme 1

B. The O–H Insertion Reaction

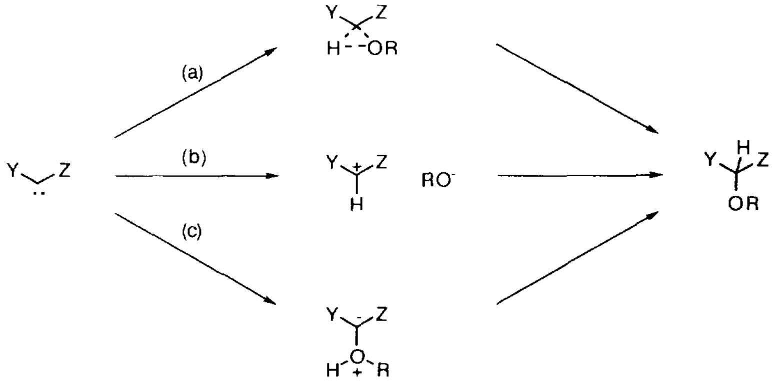
Along with cyclopropanation of alkenes, the insertion into single bonds is the most characteristic reaction of carbenes. Whereas the insertion into C–H bonds has been widely used in organic synthesis, the insertion into polar X–H bonds (X = N, O, S *etc.*) has found less use until relatively recently, although one example that has found synthetic application is the intramolecular insertion of rhodium carbenoids, derived by rhodium(II) carboxylate mediated decomposition of diazocarbonyl compounds, into the N–H bond of β-lactams. This reaction now forms the basis of Merck's commercial synthesis of the antibiotic thienamycin.[3,4]

In contrast to the concerted insertion of singlet carbenes into C–H bonds, "insertion" into polar X–H bonds is almost certainly stepwise. In the case of O–H bonds, 3 mechanisms are generally discussed (Scheme 2):

(a) a concerted O–H insertion,

(b) protonation of the carbene to give a carbocation (or protonation of the diazo compound to give a diazonium ion which subsequently loses nitrogen),

(c) nucleophilic attack on the electrophilic carbene to give an ylide, followed by hydrogen transfer.



Scheme 2

Although the concerted pathway (a) cannot be completely excluded, there is no direct experimental evidence to support it, and it is likely that most, if not all, O–H insertion reactions of carbenes proceed by one of the stepwise processes (b) or (c). Since the present purpose is to concentrate on the synthetic applications of O–H insertion reactions, for a comprehensive discussion of the mechanistic aspects of the reaction, which have also recently been the subject of theoretical calculations,[5] the reader is referred to Kirmse's excellent review.[2]

C. Diazocarbonyl Compounds

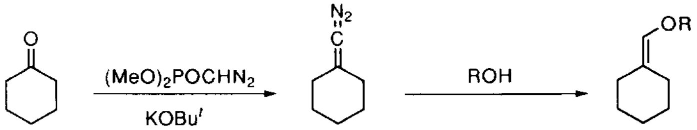
The ready availability, relative stability and facile decomposition, under thermal, photochemical, and acid or transition-metal catalysed conditions of diazocarbonyl compounds makes them useful intermediates for synthesis. They are easily prepared from a variety of simple precursors,[6] and participate in a wide range of useful transformations. Several important reviews which deal with the chemistry of α-diazocarbonyl compounds have appeared over the last 15 years.[7-16]

D. O-H Insertion Reactions involving other Diazo Compounds or Carbene Precursors

Although the present review concentrates on the preparation of ethers by the O–H insertion reactions of carbenes (or carbenoids) derived from diazocarbonyl compounds, it would be wrong to give the impression that these are the only synthetically useful carbene-based etherification methods. Indeed many other useful O–H insertion reactions are known, some of which are briefly summarised in this Section.

(i) Vinylidene carbenes

Reaction of dimethyl diazomethylphosphonate with ketones in the presence of potassium *tert*-butoxide gives transient diazoalkenes which, in the presence of alcohols, decompose to give enol ethers in a synthetically useful reaction (Scheme 3).[17,18] In the case of allyl alcohol, there is <5% competing cyclopropanation.

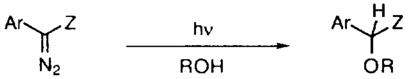


R = Me, 50-60%
R = Bu^t, 56%
R = allyl, 60%

Scheme 3

(ii) Arylcarbenes

The photochemical decomposition of aryl- and diaryl-diazomethanes in the presence of alcohols to give ethers (Scheme 4) has been extensively investigated from the mechanistic point of view. Many sophisticated kinetic and spectroscopic studies, especially using laser flash photolysis and matrix isolation techniques have been performed, and have provided detailed information about the nature of the intermediates, absolute rates of reaction of the carbenes with alcohols, and competition with other processes such as C–H insertion.[2,19-26] With the emphasis on mechanistic studies, it is difficult to gain an impression of the synthetic utility of the photochemical O–H insertion reactions of arylcarbenes, although where "preparative" yields are reported, they are usually good.[27,28]



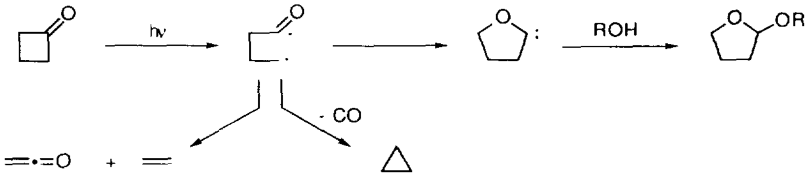
Z = H, alkyl, aryl

Scheme 4

The reaction can also be carried out thermally,[29-32] or in the presence of acid (p-TsOH, $HClO_4$, picric acid); [33-37] both types of reaction have been subject to a detailed kinetic study.

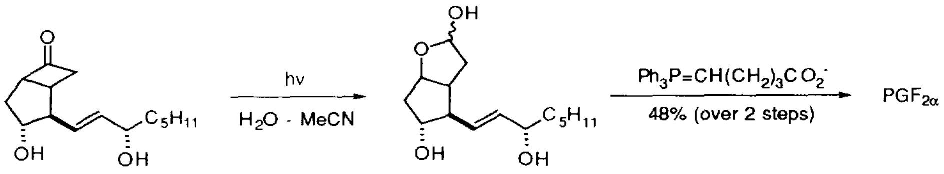
(iii) Oxacarbenes

Cyclic oxacarbenes can be generated by irradiation of cyclic ketones, and the resulting carbenes are intercepted by alcohols to give acetals.[38,39] The reaction, which was developed in the 1960s,[40-42] works particularly well for cyclobutanones, which undergo efficient α-cleavage to give 1,4-acyl alkyl diradicals. The formation of the oxacarbene, and its subsequent reaction with alcohols (Scheme 5), in competition with decarbonylation or cycloelimination has been studied in detail.[43-45]



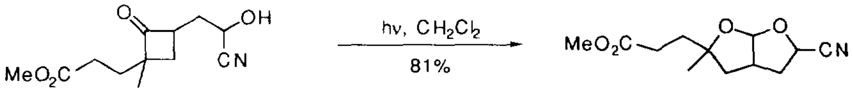
Scheme 5

The overall conversion of a cyclobutanone into a 2-alkoxytetrahydrofuran (a protected lactol) is a useful transformation, and a number of applications in synthesis have been reported, most notably from the groups of Roberts and Pirrung. For example, Roberts has shown that irradiation of bicyclo[3.2.0]heptanones in the presence of alcohols or water gives ring expanded products which are useful intermediates in the synthesis of prostaglandins (Scheme 6).[46-48]



Scheme 6

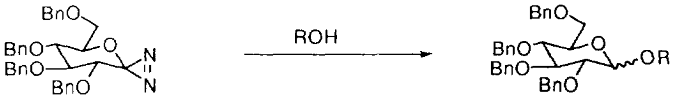
Pirrung has used intramolecular trapping of photochemically generated oxacarbenes as a route to bicyclic acetals, for example as illustrated in Scheme 7.[49,50]



Scheme 7

(iv) Glycosylidene carbenes

Oxacarbenes generated at the anomeric centre of carbohydrates are known as glycosylidenes, and have proved extremely useful in the synthesis of a wide range of sugar derivatives. All the major contributions have been made by Vasella, who has reviewed his work in this area.[51,52] The carbene is generated from the corresponding diazirine or tosylhydrazone, and the basic reaction is illustrated in Scheme 8. For some recent examples, the reader should consult references 53-62.

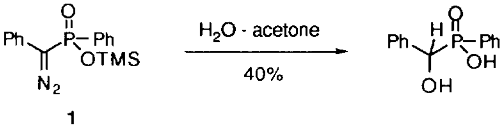


R = alkyl, aryl, carbohydrate

Scheme 8

II. Thermal Reactions

The simple thermal decomposition of diazocarbonyl compounds in the presence of alcohols to give ethers is extremely rare. In what is probably the earliest example of an O–H insertion reaction, heating benzoylphenyldiazomethane at 50°C in methanol gives rise to PhCOCH(OMe)Ph in 30% yield; the major product, Ph_2CHCO_2Me, arises by competing Wolff rearrangement.[63] Treatment of the diazophosphinate **1** with aqueous acetone results in hydrolysis of the silyl ester and formation of the hydroxy compound by O–H insertion into water (Scheme 9).[64]



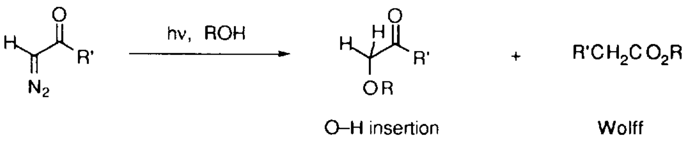
Scheme 9

III. Photochemical Reactions

The reactions in this and subsequent Sections are subdivided according to the type of diazo compound involved: diazoketones, diazoesters, diazoamides, diazophosphonates and related phosphoryl diazo compounds, diazosulfones. If a compound contains more than one functional group attached to the diazo carbon it is included in the later sub-section in the sequence; *e.g.* diazoketophosphonates are covered under diazophosphonates.

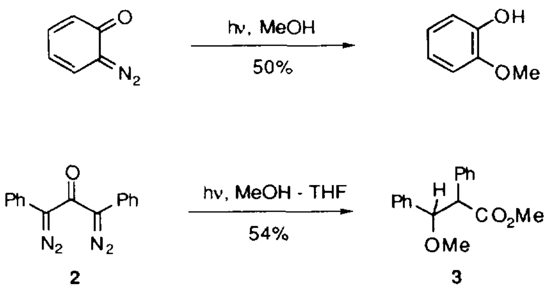
A. Diazoketones

The formation of α-alkoxyketones by irradiation of diazoketones in the presence of alcohols is not a synthetically useful process. In most cases, photochemical Wolff rearrangement supervenes, and esters are the major or exclusive products (Scheme 10).[65-69] In the presence of good hydrogen-donating alcohols, such as isopropanol, and a radical initiator, reduction of the diazo group to the corresponding CH_2 group occurs.[70]



Scheme 10

In the rather special case of 2-diazophenol (6-diazo-2,4-cyclohexadien-1-one), irradiation in methanol gives 2-methoxyphenol in 50% yield (Scheme 11).[71] The photochemical decomposition of the bis-diazoketone **2** in methanol-THF results in one O–H insertion reaction and one Wolff rearrangement to give the methoxyester 3 (Scheme 11).[72]

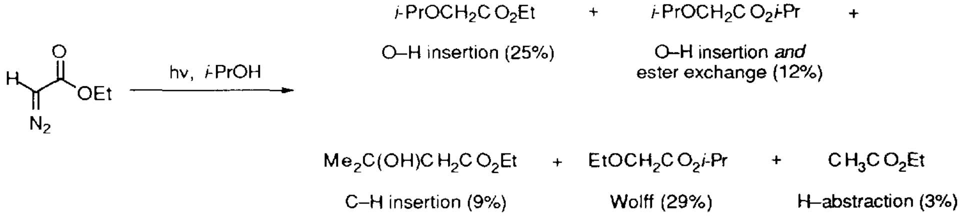


Scheme 11

B. Diazoesters

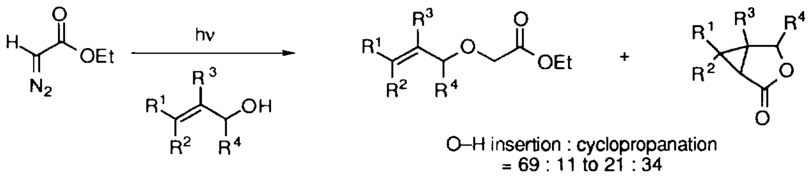
The photochemical decomposition of diazoesters in the presence of alcohols also suffers from competing Wolff rearrangement, and often little of the desired ether formed by O–H insertion is isolated; fortunately from a synthetic point of view, ethers can be formed in high yield using transition-metal catalysis (see Section V).

The photochemical reactions of ethyl diazoacetate (EDA) have been widely studied,[68,73-77] and as an example of the complications that ensue from competing pathways, the results of irradiation in isopropanol are shown in Scheme 12.[73] In addition to O–H insertion (total 37%), the major products arise from competing Wolff rearrangement, C–H insertion and H-abstraction; the observed ester exchange is a photochemical process since it does not occur in the starting material or product in the dark.[75] Therefore, using the *same* alkyl diazoacetate, RO_2CCHN_2, as the alcohol, ROH, trap for the carbene, results in increased yields (65-80%) of the O–H insertion product, RO_2CCH_2OR. O–H Insertion is suppressed in the presence of triplet sensitisers,[68,76], and recent laser flash photolysis studies have provided detailed information on the nature of the intermediate ethoxycarbonylcarbene,[77] indicating that the O–H insertion products are formed from the singlet carbene.



Scheme 12

When EDA is irradiated in methanol and oxetane (as an alternative carbene trap) complex mixtures of products arising from competing O–H insertion and reaction with the cyclic ether (by C–H insertion, oxonium ylide formation *etc.*) are formed.[78] Irradiation of EDA in allylic alcohols leads to O–H insertion in competition with cyclopropanation; the initially formed cyclopropanecarboxylates undergo lactonisation to give oxabicyclo-[3.1.0]hexanones (Scheme 13).[79] In general, O–H insertion is the major pathway, although it is suppressed in the presence of benzophenone, again indicating that the ethers derive from the singlet carbene.

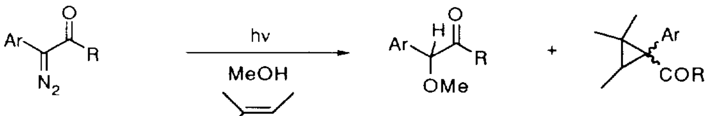


O–H insertion : cyclopropanation = 69 : 11 to 21 : 34

Scheme 13

In contrast to EDA itself, irradiation of methyl (methylmercury)diazoacetate, $MeHgCN_2CO_2Me$, in methanol results in the formation of the O–H insertion product in 98% yield.[80] The photochemistry of diethyl-(mercury)bisdiazoacetate, $Hg(CN_2CO_2Et)_2$, on the other hand is much more complex and gives mixtures of products.[81] Irradiation of dimethyl diazomalonate in alcohols parallels that of EDA in that O–H insertion occurs in competition with ester exchange, Wolff rearrangement and H-abstraction.[82,83] The yield of alkoxymalonate is highest in the case of methanol (78%) or *tert*-butanol and lowest for isopropanol (21%) where H-abstraction, presumably by the triplet carbene, to give dimethyl malonate (41%) is a major pathway. The relative ease of O–H insertion reactions with methanol compared to ethanol, isopropanol, and *tert*-butanol (in order of decreasing reactivity) has also been noted in the reactions of both diazomethane and diphenyldiazomethane.[84,85]

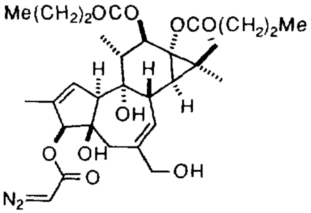
The photochemical reactions of aryldiazoacetates, $ArCN_2CO_2R$, have also been studied in detail.[86-89] Some interesting neighbouring group effects have been observed; for example, irradiation of methyl aryldiazoacetates in a mixture of methanol and 2-methyl-2-butene leads to the O–H insertion product in only 7% yield, with the major product being the cyclopropane (71%). Similar results were obtained with the diazocarboxylic acid, although the corresponding sodium salt gave >90% O–H insertion with little if any cyclopropanation (Scheme 14).[86,88] The authors ascribe the effect to reduced electrophilicity of the carbene by some association of the negatively charged carboxylate anion with the vacant carbene *p*-orbital. Whatever the explanation, the simple change from diazoester to diazocarboxylate enhances the value of the O–H insertion process.



7%	R = OMe	71%
10%	R = OH	71%
>90%	R = ONa	<1%

Scheme 14

A detailed laser flash photolysis study on the reaction of (methoxycarbonyl)phenylcarbene, generated from methyl phenyldiazoacetate, with water to give methyl mandelate by O–H insertion has suggested that the process is most accurately described as a conjugate addition of water across the entire acylcarbene function.[89] Irradiation of the corresponding diazo(thio)ester, $PhCN_2COSMe$, on the other hand, results in complete Wolff rearrangement with no O–H insertion products being formed.[90] Diazoesters have been incorporated into chymotrypsin and their photochemical decomposition studied,[91-93] and recently the diazoacetyl phorbol derivative **4** has been prepared as a potential photoaffinity label for protein kinase C.[94] In model experiments, irradiation of **4** in methanol resulted in the desired O–H insertion product.



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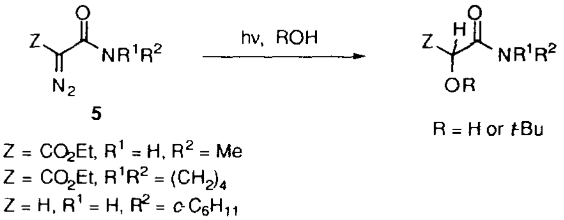
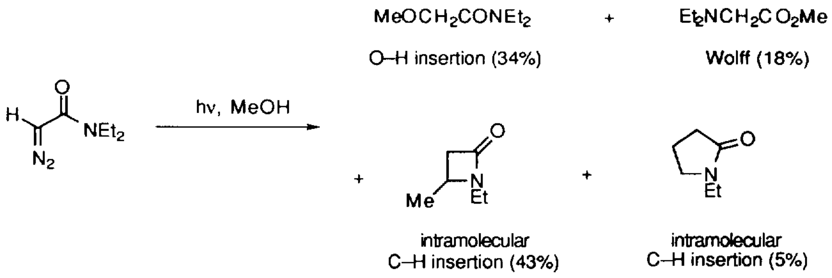
C. Diazoamides

Irradiation of 3-diazo-1-methyloxindole in ethanol gives the O–H insertion product, 3-ethoxy-1-methyloxindole in only 24% yield.[95] Likewise irradiation of the diazoamides **5** in water or *tert*-butanol gives the corresponding O–H insertion products (Scheme 15).[96]



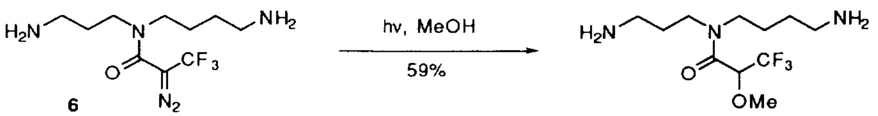
Scheme 15

However, with *N*,*N*-diethyldiazoacetamide as substrate, intramolecular C–H insertion to give both β- and γ-lactams by insertion into the *N*-ethyl CH_2- or CH_3- groups respectively, competes very effectively with intermolecular O–H insertion into methanol (Scheme 16).[97-99] In the absence of methanol, the yields of β- and γ-lactams are 57 and 43% respectively; solvent effects are clearly important in determining the product ratio, and the conformation of the starting diazoamide is also believed to be a key factor.



Scheme 16

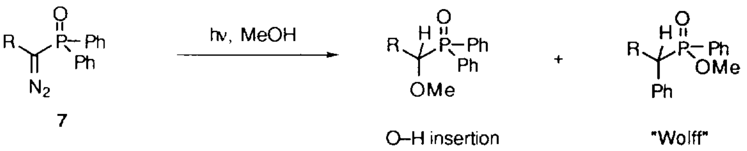
Photoaffinity labels based on diazoamides **6** derived from spermidine have been prepared, and shown to participate in photochemical O–H insertion reactions (Scheme 17).[100]



Scheme 17

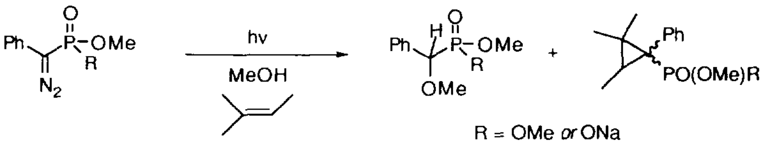
D. Diazophosphonates and Related Compounds

The photochemical decomposition of phosphoryl diazo compounds in the presence of alcohols also suffers from competing processes such as Wolff-type 1,2-shifts, and in most cases synthetically useful amounts of O–H insertion products are not formed. Much of the original work is due to Regitz, who studied the competition between O–H insertion and rearrangement in a series of diazophosphine oxides **7** (Scheme 18).[101-104] In general, yields of O–H insertion product are high for **7** (R = Ph), but in the case of R = H, COPh or CO_2Et, rearrangement by 1,2-shift dominates.



Scheme 18

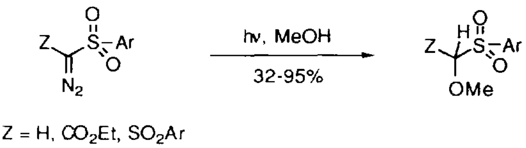
The photochemistry of diazobenzylphosphonates, $ArCN_2PO(OR)_2$, has been studied in detail by Tomioka.[105-107] In the case of dimethyl diazobenzylphosphonate, the yield of the α-alkoxyphosphonate, $PhCH(OR)PO(OMe)_2$, is very much dependent on the alcohol used (methanol gives higher yields than ethanol or isopropanol) and the temperature of the reaction (at very low temperatures C–H insertion processes supervene). Neighbouring group effects (*cf.* Scheme 14) have also been observed in diazophosphonates, with O–H insertion being favoured over cyclopropanation on moving from the diazophosphonate ester to the mono-sodium salt of the diazoacid (Scheme 19). The extent of neighbouring group participation is very much dependent on the nature of the carbene substituents.



Scheme 19

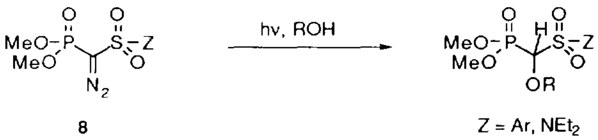
E. Diazosulfones

The formation of α-alkoxysulfones by photolysis of diazosulfones in alcohols usually proceeds in good yield (Scheme 20), although in some cases Wolff-type rearrangement to give intermediate sulfenes (subsequently trapped by the alcohol present) and H-abstraction processes compete.[108-111] Under radical type conditions, H-abstraction dominates.[70]



Scheme 20

A range of diazo compounds **8** incorporating both phosphonate and sulfone substituents have been prepared as potential photoaffinity labels, and shown to undergo O–H insertion reactions (Scheme 21), in competition with other processes.[112-114]



Scheme 21

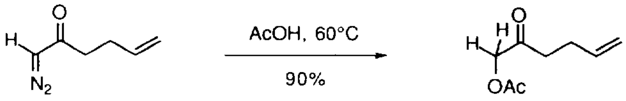
IV. Acid Catalysed Reactions

A. Protic Acids

The formation of carboxylate esters by the reaction of carboxylic acids with diazo compounds, most commonly diazomethane itself, is one of the best known reactions of diazo compounds. The reaction proceeds by initial protonation of the diazo carbon to give a diazonium cation which can react directly with a nucleophile or lose nitrogen to give a carbocation (*cf.* path b, Scheme 2). Most of the studies on the acid catalysed reactions of diazocarbonyl compounds with alcohols (or water) concentrate on the mechanistic aspects, although the reaction does proceed in synthetically useful yields in many cases.

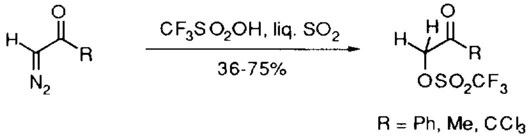
(i) Diazoketones

Diazoketones only became readily available in 1928 when both Robinson and Bradley, and Arndt and Eistert independently discovered that the reaction of acid chlorides with *excess* diazomethane gave the diazoketone rather than the α-chloroketone. Interestingly Robinson and Bradley's first paper on the subject includes the reaction of benzoyldiazomethane with acetic acid to give α-acetoxyacetophenone in quantitative yield.[115] Similar reactions were reported in a subsequent paper,[116] and more recently the reaction has been used as a key step in the preparation of an acetoxyketone precursor to the β-lactam 1-carbacephalothin (Scheme 22).[117]



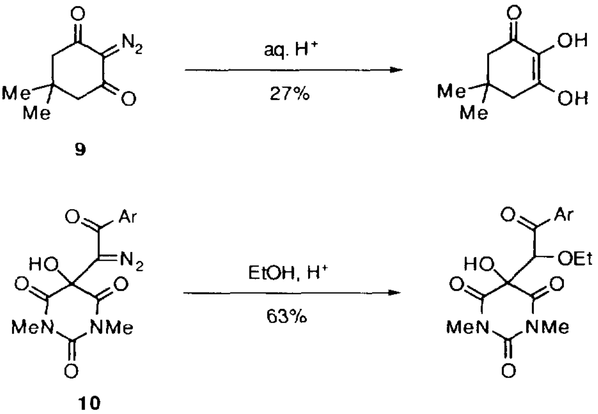
Scheme 22

Diazoketones also react with sulfonic acids to give α-sulfonyloxyketones; an example is shown in Scheme 23.[118] The formation of α-tosyloxyketones by the corresponding reaction with tosic acid has also been described, although no yields were reported.[119]



Scheme 23

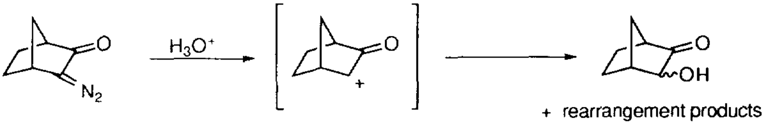
Acid catalysed O–H insertion reactions involving water and alcohols are well known. For example, acid catalysed decomposition (aq. $HClO_4$-dioxan) of benzoylphenyldiazomethane gives benzoin in 88% yield;[120] the corresponding methyl ether is formed in 66% yield when the reaction is carried out in methanol.[121] A more detailed study of the reaction has shown that it proceeds by way of Ph(MeO)C=CPh(OH), a remarkably stable enol.[122,123] Two further examples of acid catalysed O–H insertion reactions are shown in Scheme 24. Diazodimedone **9** gives the corresponding hydroxyketone in 27% yield when treated with dilute sulfuric acid,[124] and the diazoketone **10** derived from alloxan is converted into the α-ethoxyketone by reaction with ethanolic sulfuric acid.[125]



Scheme 24

Many detailed kinetic and mechanistic studies have been carried out on the reactions of diazoketones, under acidic conditions, which often lead to the formation of α-hydroxyketones. Thus simple diazoalkanones, $RCOCHN_2$[126-130] benzoyldiazomethanes, $ArCOCHN_2$[131-136] disubstituted diazoketones, $R^1COCN_2R^2$,[137-142] and benzoylaryldiazomethanes, $Ar^1COCN_2Ar^2$,[143-146] have all been studied in detail.

In the case of diazo bicyclic ketones such as diazocamphor and related compounds, the acid catalysed decomposition is complicated by rearrangements, and the simple O–H insertion product (Scheme 25) is usually accompanied by one or more products resulting from rearrangement of the intermediate carbocation.[147-152]

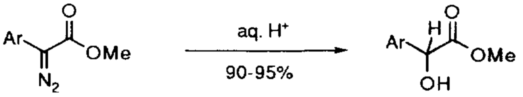


Scheme 25

(ii) Diazoesters

The acid catalysed decomposition of ethyl diazoacetate (EDA) to give ethyl glycolate is one of the most studied of all reactions involving a diazoester. The initial work was done by Brønsted and Bell, who showed that in the presence of ethanol or phenol the corresponding ethoxy- or phenoxy-acetate was formed.[153] Since then, many kinetic and mechanistic studies have been reported.[154-161] Ethyl glycolate is also formed during the acid catalysed decomposition of the monoethyl ester of diazomalonic acid,[162-164] or of ethyl (trimethylsilyl)diazoacetate.[165]

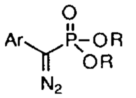
Acid catalysed decomposition of diazoarylacetates gives the corresponding mandelates in excellent yield (Scheme 26).[166,167] The reaction also works for the corresponding diazoamides,[166] although the reaction of the thioester, methyl phenyldiazo(thio)acetate, proceeds differently due to competing 1,2-migration of the methylthio group.[167] The acid catalysed reactions of ethyl diazofurylacetate are complicated by a range of competing reactions including fragmentation of the furan ring.[168,169]



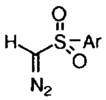
Scheme 26

(iii) Diazophosphonates and Diazosulfones

The acid catalysed reactions of diazophosphonates **11** and diazosulfones **12** have been investigated in some detail, although little synthetic use has been made of the reactions.[170-175]



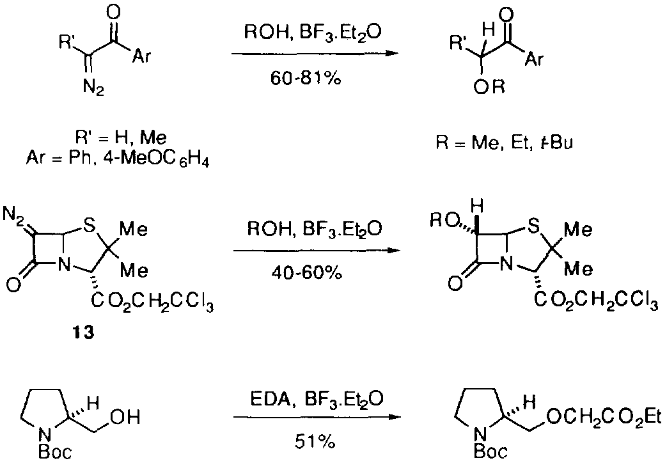
11



12

B. Lewis Acids

Lewis acids, in particular boron trifluoride etherate, are extremely effective catalysts for the conversion of diazocarbonyl compounds into α-alkoxycarbonyl compounds by O–H insertion into alcohols. The first examples of the reaction were published over 40 years ago by Newman; some examples are shown in Scheme 27.[176] Aluminium chloride and tin(IV) chloride are also reported to be effective, and in no case were products arising from Wolff rearrangement observed. Despite the good yields, the BF_3-catalysed O–H insertion reactions have been little used in synthesis to date. The second two examples shown in Scheme 27 illustrate the potential;[177,178] the diazopenicillin **13** gives the corresponding alkoxy β-lactams in moderate yield, but in the case of the prolinol derivative, the reaction failed with a closely related secondary alcohol and a bulkier diazoester, ethyl diazoisovalerate.



Scheme 27

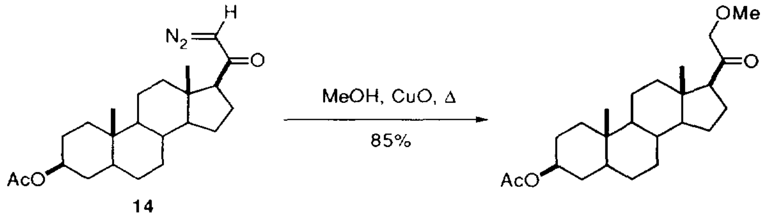
It should be noted that boron trifluoride and aluminium chloride are also effective catalysts for the alkylation of alcohols by diazoalkanes.[179-181]

V. Transition Metal Catalysed Reactions

The transition metal catalysed decomposition of diazocarbonyl compounds, first discovered by Silberrad and Roy almost 90 years ago,[182] has attracted much attention in the last 10 years.[8-10,12,15] It is often the method of choice since it takes place under relatively mild conditions, and consequently uses of diazocarbonyl compounds in synthesis have increased dramatically in recent years particularly as a result of the development of new catalysts. The following discussion of metal catalysed O–H insertion reactions is sub-divided according to the metal.

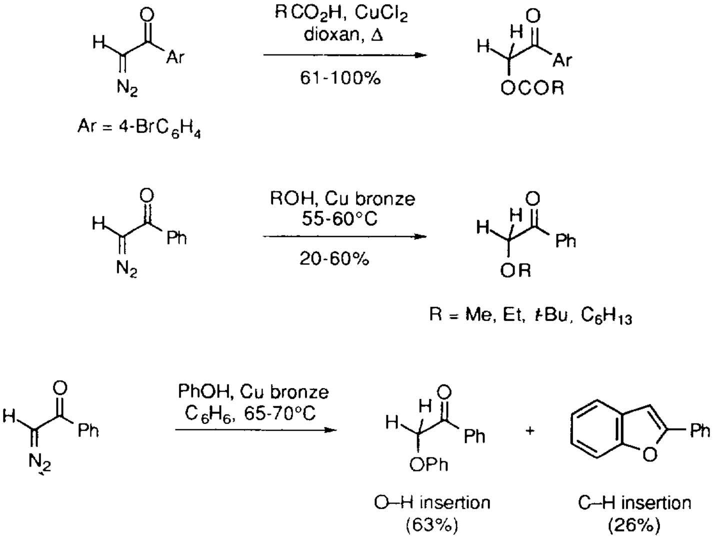
A. Copper

An early use of copper catalysed O–H insertion reaction is the synthesis of α-methoxyketones from diazoketones.[183] Treatment of the steroidal diazoketone **14** with copper(II) oxide in methanol gave the corresponding methoxyketone in 85% yield (Scheme 28). Use of silver(I) oxide as catalyst gave only products derived from Wolff rearrangement.



Scheme 28

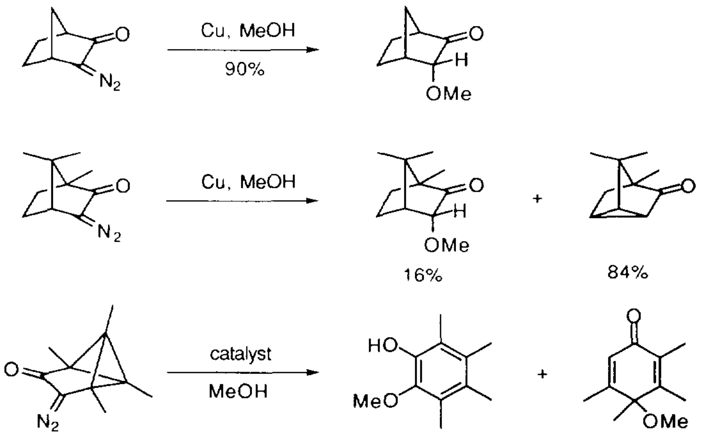
Application of the above conditions (MeOH, CuO) to benzoyldiazomethane resulted only in the formation of methyl phenylacetate by Wolff rearrangement.[183] However use of copper(II) chloride, metallic copper or copper(II) acetylacetonate (acac) with aroyldiazomethanes does lead to O–H insertion products. Thus the copper(II) chloride catalysed reaction of 4-bromobenzoyldiazomethane with carboxylic acids gives the corresponding acyloxyketones (Scheme 29); the reaction was originally proposed as a method of identifying organic acids.[184] The first detailed investigation of the O–H insertion reaction with alcohols was carried out by Yates in 1952.[185] Benzoyldiazomethane was decomposed in various alcohols in the presence of copper bronze and gave the α-alkoxyacetophenone in reasonable yield (Scheme 29). Phenol gave α-phenoxyacetophenone by O–H insertion (63%) together with 2-phenylbenzofuran (26%), presumably forced by cyclodehydration of α-(*ortho*-hydroxyphenyl)acetophenone, the formal product of aromatic C–H insertion (Scheme 29). When benzoylcliazomethane was decomposed by copper bronze in ethanolic solutions of thiophenol or aniline, the observed products were solely the result of S–H and N–H insertion respectively.



Scheme 29

The copper powder catalysed decomposition of aroyldiazomethanes has also been studied in aqueous solution, and gives the expected α-hydroxyacetophenones.[186] Cu(acac)$_2$ is also an effective catalyst; reaction of benzoyldiazomethane with various alcohols (MeOH, EtOH, *i*-PrOH, *t*-BuOH) giving the corresponding alkoxyketones in 36-65% yield. In all cases except that of *tert*-butanol, reaction in aqueous alcohol only gives the product of O–H insertion into the alcohol, *i.e.* the alkoxyketone rather than the hydroxyketone.[187] Cyclic diazoketones also react under copper catalysed conditions, and both the reactions in Scheme 24 have been carried out in this manner.[124,125]

Copper powder catalysed decomposition of 3-diazo-2-norbornanone in methanol gave the *endo*-methoxyketone in good yield (Scheme 30). Decomposition of diazocamphor under similar conditions, however, gives mainly cyclocamphanone, the product of intramolecular C–H insertion (Scheme 30).[188] Metal catalysed decomposition of the more complex tricyclic diazoketone shown in Scheme 30 gives a mixture of 2-methoxy-3,4,5,6-tetramethylphenol and 4-methoxy-3,4,5,6-tetramethylcyclohexa-2,5-dienone, the ratio of products depending on the catalyst used. Cu(acac)$_2$ gives only the phenol (45%) whereas both rhodium(II) acetate and silver(I) perchlorate give mixtures. The mechanisms of product formation are discussed by the authors.[189]

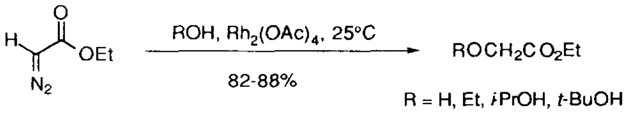


Scheme 30

The copper catalysed reactions of diazoesters have also been investigated. Copper(II) chloride catalysed reactions of EDA with butanol, benzyl alcohol or allyl alcohol give the corresponding O–H insertion products, although in poor yield.[190] In the last case, competing cyclopropanation is observed (see Section V.B for a more detailed discussion of the competition between O–H insertion and cyclopropanation). The metallocarbenoid derived from diazomalonate under metallic copper catalysis undergoes smooth O–H insertion into alcohols, in contrast to the photochemical reaction which gives a range of products arising from Wolff rearrangement, H-abstraction *etc.* (*cf.* Section III.B).[82] The copper(I) iodide-trimethyl phosphite complex is also an effective catalyst for the formation of alkoxymalonates from diazomalonate.[191,192] A range of copper catalysts was investigated in the diastereoselective O–H insertion reactions of carbenoids derived from menthyl phenyldiazoacetate, although with the exception of copper(II) triflate, none were as effective as rhodium(II) acetate (see Scheme 35).[193]

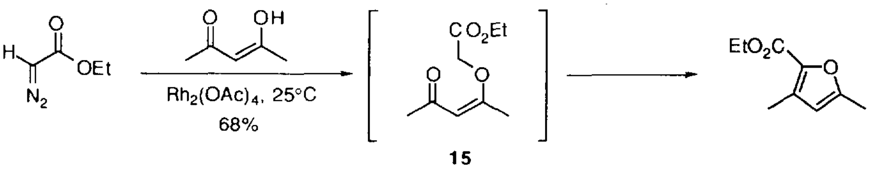
B. Rhodium

In 1973 the Belgian research group of Teyssié and Hubert and co-workers reported that rhodium(II) acetate was an extremely effective catalyst for the decomposition of EDA, and that the resulting carbenoid readily underwent O–H insertion reactions with a range of alcohols and water to give the corresponding alkoxyacetates in excellent yield (Scheme 31).[194] The fact that the reaction showed first-order dependence on the concentration of the rhodium catalyst was taken as strong evidence that the metal was involved in the rate-determining step.



Scheme 31

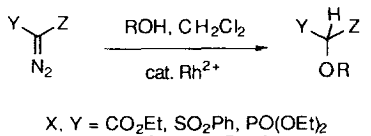
The same group showed that rhodium(II) acetate also catalysed the O–H insertion reaction with phenol to give MeO_2CCH_2OPh (90%), as well as the S–H and N–H insertion reactions with thiophenol and aniline, both in excellent yield.[195] With highly enolised β-diketones, such as pentane-2,4-dione, the reaction took a different course, in that the initial O–H insertion product **15** underwent cyclisation to give ethyl 3,5-dimethylfuran-2-carboxylate (Scheme 32).



Scheme 32

In subsequent papers, Teyssié *et al.* examined the competition between the O–H insertion reactions of rhodium carbenoids and other reactions such as cyclopropenation of alkynes[196] and cyclopropanation of alkenes.[197] In the rhodium(II) catalysed reaction of methyl diazoacetate with simple acetylenic alcohols such as propargyl alcohol or 1-butyn-4-ol, there is a general preference for O–H insertion over addition to the triple bond. Use of rhodium(II) trifluoroacetate in place of rhodium(II) acetate further increases the preference for O–H insertion. However, the O–H insertion reaction is apparently more sensitive to steric effects, and with more hindered alcohols such as 5-methyl-1-butyn-4-ol, cyclopropenation dominates.[196] Likewise with allylic alcohols, there is always a preference for O–H insertion rather than cyclopropanation in the rhodium(II) catalysed reactions of diazoacetates. A wide range of rhodium catalysts were investigated, and the proportion of cyclopropanation increased as the metal ligands were made more lipophilic.[197] Intermolecular O–H insertion reactions of diazoesters also compete effectively with intramolecular attack on an aromatic ring by the rhodium carbenoid.[198]

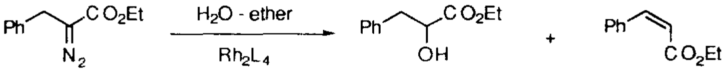
In a comparative study, it was shown in our own laboratories that diazophosphonates are less readily decomposed by rhodium(II) acetate than are the corresponding diazoesters. However, rhodium(II) trifluoroacetamide is a superior catalyst and even relatively stable diazo(bis)phosphonates undergo O–H insertion reactions using this catalyst. Thus the reaction is a general route to alkoxy-esters, -sulfones and -phosphonates, (Scheme 33) although in some cases H-abstraction competes.[199,200] The reaction also works well for phenols.[201]



X, Y = CO_2Et, SO_2Ph, $PO(OEt)_2$
R = Me, *i*-Pr, *t*-Bu, Ar

Scheme 33

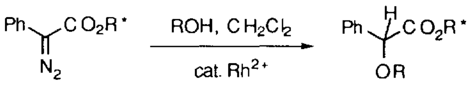
Diazoesters containing a CH_2 group α to the diazo function normally undergo 'elimination' to give α,β-unsaturated esters.[202] However, O–H insertion competes effectively with this elimination process, especially when using rhodium catalysts containing bulky carboxylate ligands (Scheme 34).[203] The elimination reaction, which usually gives predominantly the *cis*-enoate, is favoured by the use of rhodium(II) trifluoroacetate or perfluorobutyrate.



Ratio of O–H insertion : 'elimination'
= 16.5 : 1 to 1 : 5.1 depending on L

Scheme 34

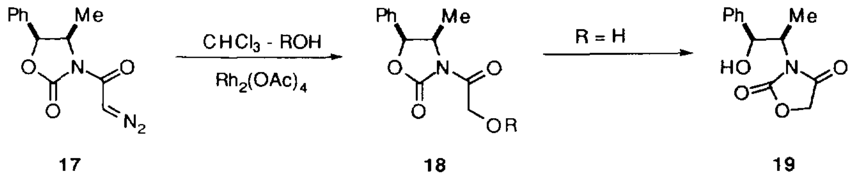
Modest diastereoselectivity is observed in the O–H insertion reactions of rhodium carbenoids derived from diazoesters of chiral alcohols. Thus the phenyldiazoacetates **16** of menthol, 8-phenylmenthol, and 2-phenylcyclohexanol undergo rhodium(II) catalysed O–H insertion reactions with water or alcohols in good yield (40-95%) and varying diastereoselectivity (up to 53%) (Scheme 35).[193,204] A closely related reaction using a vinyldiazoacetate of pantolactone also resulted in modest diastereoselectivity in the O–H reaction with water.[205]



16

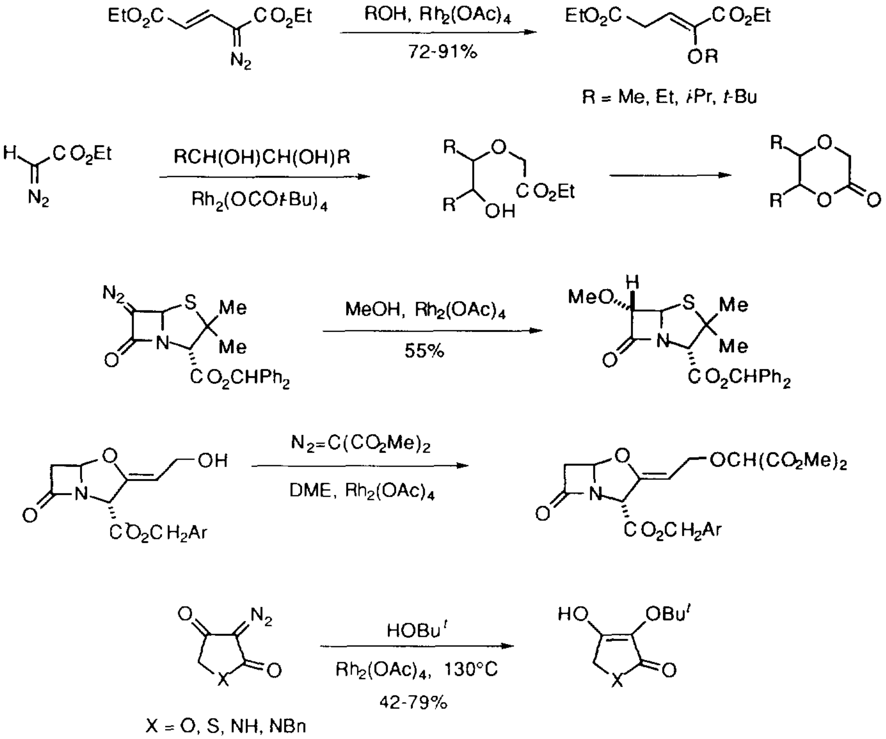
Scheme 35

The O–H insertion reaction of rhodium carbenoids is so facile that there are reports of reaction with adventitious water. For example, rhodium(II) acetate catalysed decomposition of the diazoacetyl oxazolidone **17** in chloroform gave the oxazolidinedione **19** in poor yield; when the reaction was repeated in the presence of water, **19** was formed in high yield. The reaction presumably involves initial O–H insertion to give **18** (R = H), followed by trans-lactamisation (Scheme 36). When **17** was treated with rhodium(II) acetate in ethanol, the O–H insertion product **18** (R = Et) was formed in 97% yield.[206] Other reports of O–H insertion into adventitious water have appeared.[207,208]



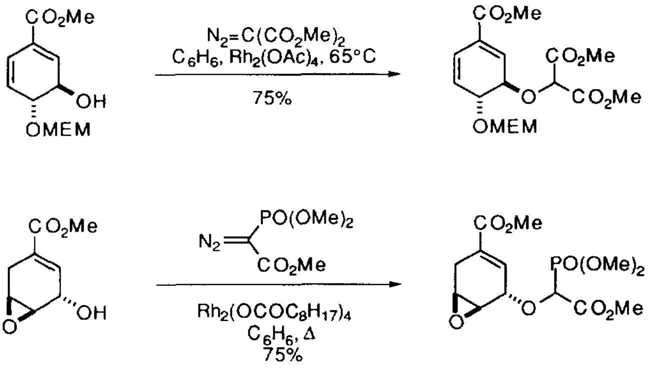
Scheme 36

The pioneering work of Teyssié *et al.* has resulted in rhodium(II) carboxylates being the current catalysts of choice for many carbenoid transformations. This is certainly the case for carbenoid O–H insertion reactions, and most of the recent synthetic applications employ rhodium(II) catalysts. Some examples are shown in Scheme 37.[209-213] In the penicillin example (*cf.* Scheme 27), the reaction is also catalysed by $Cu(acac)_2$ and $BF_3.Et_2O$.[211]



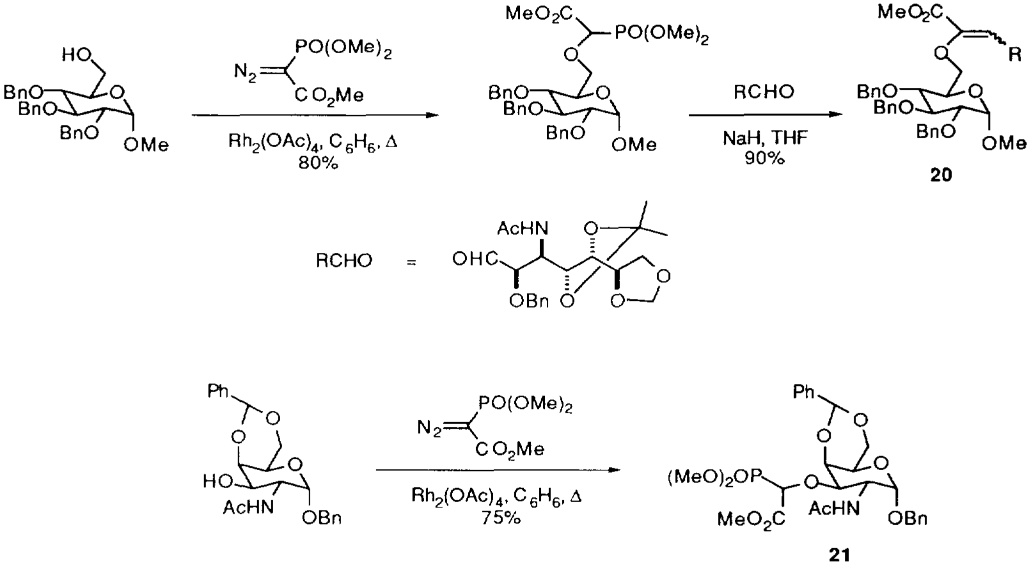
Scheme 37

One of the areas where the rhodium catalysed O–H insertion reaction has found wide application is in the synthesis of shikimate and chorismate derivatives.[214] Thus there are many examples of rhodium(II) mediated reactions of diazomalonates and diazophosphonates with highly functionalised cyclohexanols; two examples are shown in Scheme 38, and since the next step is usually the introduction of the enol side chain, the use of diazophosphonates is preferred since it allows subsequent olefination by a Wadsworth-Emmons reaction.[215-222]



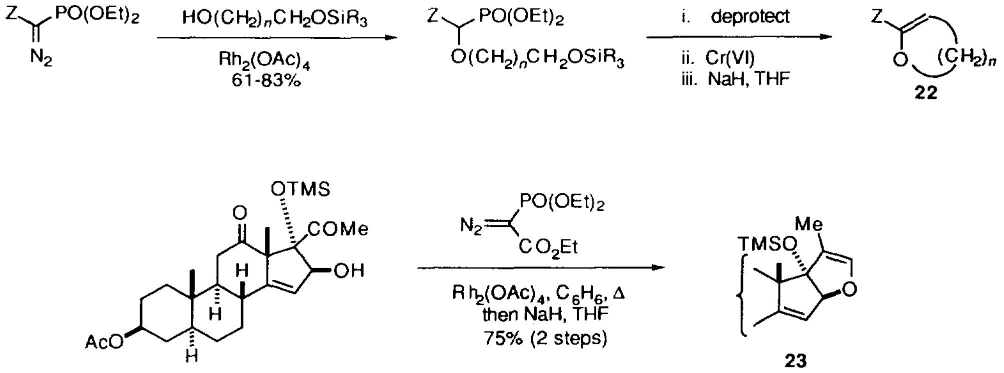
Scheme 38

The O–H insertion reaction of a rhodium carbenoid derived from a diazophosphonate, followed by Wadsworth-Emmons olefination of the resulting alkoxyphosphonate has proved a useful tactic in synthesis. It has been used in the preparation of 2-aryloxy-3-phenylpropenoates,[201] and in the synthesis of the disaccharide **20** (mixture of geometric isomers) and the galactopyranoside **21** (Scheme 39).[223,224] In the second example, there is no competing N–H insertion.



Scheme 39

The O–H insertion reaction has also been used in conjunction with the intramolecular Wadsworth-Emmons reaction in the synthesis of cyclic ethers **22** (Z = Ac, CO_2Et, n = 2,3,4),[225,226] and of a key intermediate **23** for cephalostatin 7 (Scheme 40).[227]



Scheme 40

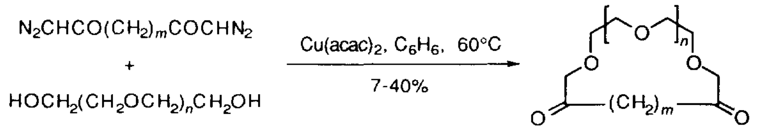
C. Other Metals

Apart from copper and rhodium, very few other metals or their salts have found successful use in the formation of O–H insertion products from diazocarbonyl compounds. The conversion of benzoyldiazomethane into α-ethoxyacetophenone (Scheme 29) is catalysed by Ni(acac)$_2$ (80% yield), Pb(acac)$_2$ (60%) and the 2Ti(acac)$_3$TiCl$_6$ complex (62%) in addition to Cu(acac)$_2$.[187] Likewise the O–H insertion reactions of phenyldiazoacetates **16** of chiral alcohols (Scheme 35) are mediated by Ni(acac)$_2$ as well as copper and rhodium catalysts.[193] Finally, AgBF$_4$, Pd(OAc)$_2$ and Mo$_2$(OAc)$_4$ have all been used for the intramolecular O–H insertion reaction to give the oxepanes shown in Scheme 44, although in each case the yield was much worse than that obtained using rhodium(II) acetate.[228]

VI. Intramolecular Reactions: Synthesis of Cyclic Ethers

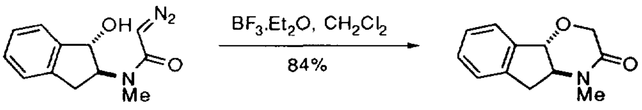
The intramolecular O–H insertion reactions of carbenes and carbenoids constitutes a useful route to cyclic ethers. Medium ring ethers, in particular, are difficult to prepare,[229,230] and the rhodium carbenoid route, developed in our own laboratories, provides an effective solution to the problem.

The earliest use of the intramolecular O–H insertion reaction was in the synthesis of macrocyclic ethers.[231] Cu(acac)$_2$ catalysed decomposition of bis-diazoketones in the presence of 1,n-diols gave the macrocycles **24**, albeit in modest yield (Scheme 41). Cyclisation of the (diazoacetyl)aminoindanol **25** gives the corresponding oxazinone (Scheme 42); the reaction can be effected using rhodium(II) acetate, but boron trifluoride etherate gives a better yield.[232]



24

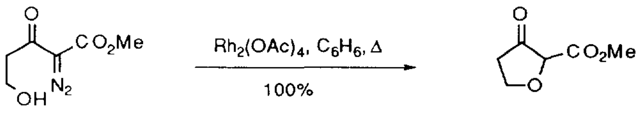
Scheme 41



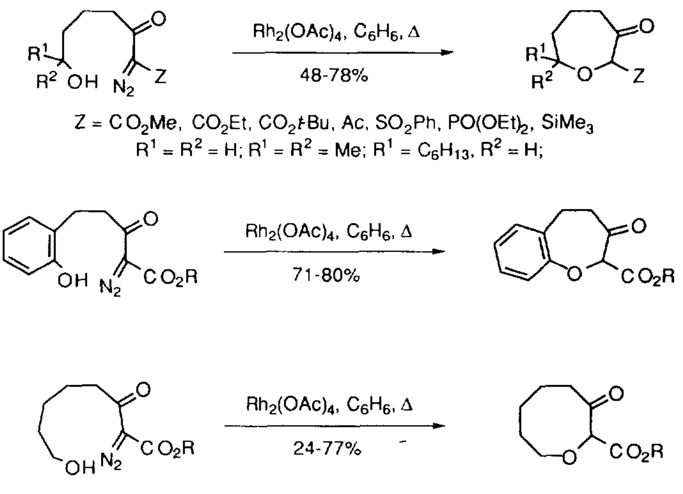
25

Scheme 42

The use of the rhodium carbenoid intramolecular O–H insertion reactions in the synthesis of simple cyclic ethers was developed simultaneously in Rapoport's and in our own laboratories. Whereas Rapoport reported a single example involving the formation of a tetrahydrofuranone (Scheme 43),[233] we concentrated on the preparation of 7- and 8-membered cyclic ethers (Scheme 44).[234-237] Thus a range of diazo alcohols were cyclised by treatment with rhodium(II) acetate to give oxepanes and oxocanes in synthetically useful yields (Scheme 44). The initial poor yield (25-30%) of the oxocane was subsequently improved (77%) by Meier and coworkers by increasing the addition time of the diazo compound to the catalyst.[238] The oxepane forming reactions have been extended to include diazoketosulfones, diazodiketones, diazoketophosphonates and diazoketosilanes as well as diazoketoesters.[239,240] It is noteworthy that in most cases there is no competing intramolecular C–H insertion of the rhodium carbenoids, although in attempts to make a 9-membered cyclic ether, C–H insertion to give a cyclopentanone derivative did supervene.[237]

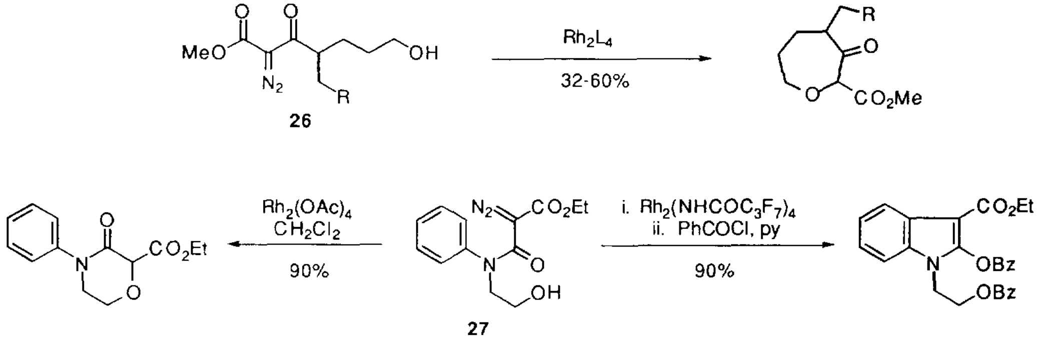


Scheme 43



Scheme 44

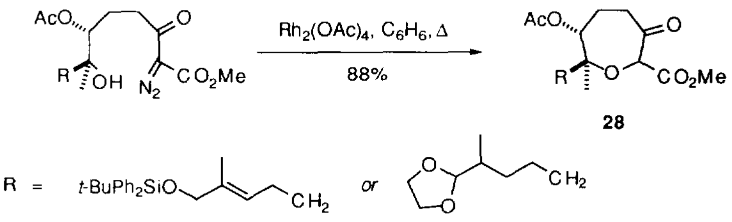
The general lack of products arising from competing reactions of the rhodium carbenoids again illustrates the great ease of the O–H insertion reaction. Further evidence for the chemoselectivity of rhodium carbenoids was obtained in the decomposition of the diazoketoesters **26** (R = Ph, $CH=CH_2$, $C\equiv CH$) in which the oxepanes were always the major product indicating the preference for O–H insertion over attack on the π-bond (Scheme 45).[241] However, the chemoselectivity can be influenced by choice of ligands on rhodium;[15] for example, decomposition of the diazoamide **27** results in clean O–H insertion when rhodium(II) acetate is used as catalyst. With rhodium(II) perfluorobutyramide, however, exclusive attack on the aromatic ring is observed (Scheme 45).[208]



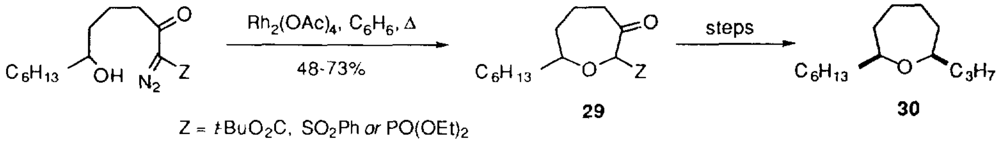
Scheme 45

As a result of this chemoselectivity, the intramolecular O–H insertion reaction can be used in quite complex substrates in the knowledge that cyclic ethers are likely to be the major products. Thus various highly substituted oxepanes **28** related to the diterpene zoapatanol have been prepared using the rhodium carbenoid method (Scheme 46).[242] Likewise the method has been used to prepare the *cis*-2,7-disubstituted oxepane skeleton **30** of the marine natural product isolaurepinnacin by simple elaboration of the initial rhodium carbenoid cyclisation product

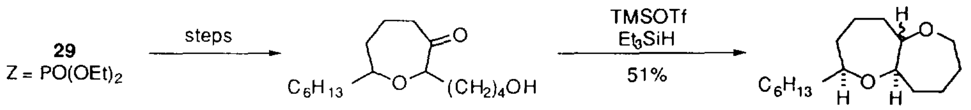
29 (Scheme 47),[243,244] and a range of pyrano-oxepane and oxepano-oxepane subunits of marine polyether toxins (Scheme 48).[245]



Scheme 46

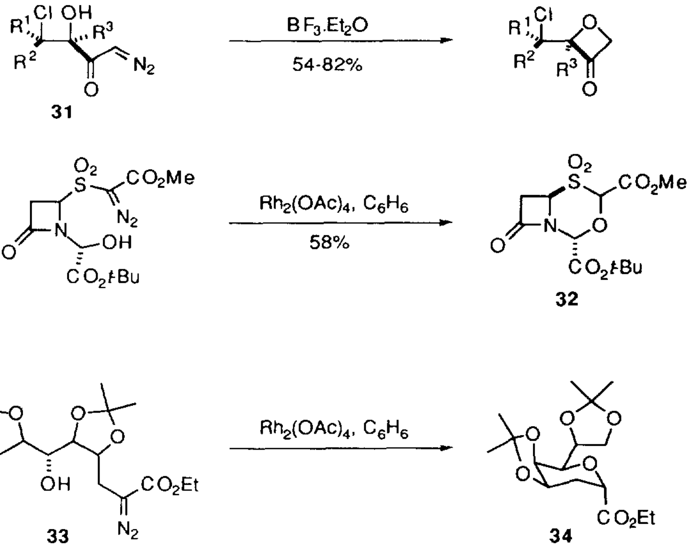


Scheme 47



Scheme 48

Finally it should be noted that the intramolecular O–H insertion of rhodium carbenoids is not limited to the preparation of 5-, 7- and 8-membered rings. Some reactions involving the formation of 4- and 6-membered rings are shown in Scheme 49. The first example involves the boron trifluoride mediated cyclisation of diazoketones **31** to give oxetanones in good yield.[246] The oxetanones can also be prepared directly from the epoxy diazoketone precursors to the chlorohydrin diazoketones **31** by treatment with tin(IV) chloride. The oxacepham β-lactam **32** has been prepared by intramolecular O–H insertion of the rhodium carbenoid derived from the diazosulfone (Scheme 49); the same product is formed from the THP-protected alcohol, presumably via the oxonium ylide followed by elimination of dihydropyran.[247] Intramolecular O–H insertion reactions have also been used in the modification of carbohydrates. Thus rhodium carbenoid cyclisation of the diazoester **33** gives the protected 2-deoxy KDO derivative **34** (Scheme 49).[248]



Scheme 49

VII. Conclusion

Whatever the exact mechanism the O–H insertion reaction of carbenes and carbenoids is a useful tool for the formation of C–O bonds. Although it has found use in simple etherification reactions, it is the intramolecular variant that would appear to offer the greatest promise in synthesis. It is hoped that this review has succeeded in highlighting the synthetic potential of carbene, and in particular transition metal carbenoid, O–H insertion reactions, and will stimulate further research in the area.

VIII. Acknowledgements

We thank former members of our research group, Julie Heslin, Roger Taylor, Martin Davies, Eric-Robert Sie, Enrique Aller, and, in particular, Geoff Cox, for their contributions in the area of O–H insertion reactions of rhodium carbenoids, and Glaxo, Fisons, Merck Sharp & Dohme, the SERC/EPSRC and the EU for funding our work.

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