Investigations towards the reactivity of rhodium-bound carbenes

Investigations Towards The Reactivity of Rhodium Bound Carbenes

by

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In loving memory of my grandparents
Violet and Ernest King

To all my teachers, past and present,
without whose enthusiasm and dedication
none of this would have been possible.

For giving me the impetus to carry on
when the will was lacking and for
having faith in my ability to succeed
when I had none.

For all of this and more, I thank you.

Contents

Abstract

A short series of diazo compounds containing a primary alcohol and one or more other carbene traps were synthesised. The result in each case, from rhodium (II) acetate mediated decomposition where products could be isolated was that O-H insertion is observed at the expense of all other intramolecular processes. A few other catalysts were tried and a similar result was observed. Even catalysts such as copper (II) acetate, commonly used for cyclopropanations did not lead to any cyclopropanes, O-H insertion being the only observed product.

The variation of the rate of decomposition of a small selection of diazo compounds with a range of rhodium (II) catalysts is described. The catalysts chosen represent a wide range of ligand pKa, (0.17 → 12.40, trifluorobutyrate and acetamide respectively). The results show that the rate of decomposition of the diazo substrates is at a maximum when the pKa of the ligand is ≈10. The relative rates of decomposition of the diazo compounds are unaffected by the catalyst used.

The synthesis of α-alkoxyesters by rhodium mediated decomposition of α-diazoesters was considered. Use of ethyl 2-diazo-3-phenylpropanoates leads to the formation of O-H insertion products and ethyl cinnamates. The ratio of insertion product to cinnamate was found to vary with the ligand on rhodium. The use of chiral α-diazophenylacetates was unsuccessful in inducing any chirality to the newly formed chiral centre. The use of chiral rhodium catalysts was also tried but again found to be unsuccessful. The possible reasons for this have been discussed.

Acknowledgements

The culmination of a PhD means that the years of frustration and banging your head against a wall are finally at a close, and I must heartily thank my supervisor Prof. Christopher Moody for not giving up hope earlier and wondering quite what he'd let himself in for. His enthusiasm over the past three years has been both endless and welcome, and his supervision exemplary.

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Finally (and in no way last) my thanks and best wishes must go to the guys who have helped me forget all about this chemistry lark and help keep my sanity. In particular Alex for being an all round good egg, and Haygez for being the one friend to lean on and rely upon over these last seven years and without whom all this would have been made all the more difficult.

Abbreviations

p-ABSA	p-Acetamidobenzylsulphonylazide
acac	Acetylacetonoate
ca.	Cira
DCM	Dichloromethane
DHP	Dihydropyran
GC	Gas chromatography
MEK	Methylethylketone
PCC	Pyridinium chlorochromate
PDC	Pyridinium dichromate
PPTS	Pyridinium p-toluenesulphonate
RT	Room temperature
TBDMS	Tetrabutyldimethylsilyl
TIPS	Triisopropylsilyl
Tf	Triflate
TLC	Thin layer chrmatography
THF	Tetrahydrofuran

Chapter One

Carbenes In Ether Synthesis

A Review of the O-H Insertion Process

Introduction

Diazo compounds were first synthesised in 1883[1] by Curtius, and ever since they have held a fascination for organic chemists. The linear structure of the diazo group was strongly supported in 1935[2] by electron diffraction and subsequently proved beyond doubt by experiment in 1957.[3]

The fascination of these compounds arises from both the wide variety of reactions they undergo and the lack of general rules to describe their behaviour. Subtle differences in the substitution pattern of the diazo compound may have a profound effect on the outcome of a reaction.

The last century has seen a lot of work devoted to every aspect of the chemistry of diazo compounds; from their synthesis and decomposition, to an attempt to throw light on the mechanisms by which the resulting carbenes may react. The synthesis of diazo compounds has been extensively covered in both books and reviews[4] and it is not the intention to discuss the synthesis of diazo compounds in this review.

The decomposition of diazo compounds by either irradiation, heat or metals, results in the generation of a substituted carbene. These carbenes will undergo all the reactions of 'typical' carbenes, including, cyclopropanation, C-H insertion, X-H insertion, Wolff rearrangements[5] and dimerisation. The reactions of diazo derived carbenes with olefins and alkynes (cyclopropanation and cyclopropenation) has been extensively investigated and again reviews on this subject are available.[6] The next most studied reaction of diazo derived carbenes is that of C-H insertion. More recently, this process has received extensive attention since the introduction of chiral metal salts, and the ability to form optically active cyclopentanones by intramolecular C-H insertion.[7]

Of the three decomposition methods available, irradiation of diazo compounds to form carbenes has been studied most widely, even though the metal catalysed decomposition of ethyl diazoacetate was first reported in 1906.[8] Copper

mediated diazo decomposition was not taken up until 1952 when Yates[9] studied this process extensively. More recently a renewed interest has surfaced since the introduction of chiral copper ligands by Pfaltz,[10] Masamune,[11] and Evans[12] which give high (>90%) enantioselectivities for cyclopropanations.

Since the discovery of rhodium (II) acetate in 1973[13] as an effective catalyst for diazo compound decomposition, there has been a lot more activity in both the synthetic uses of diazo compounds,[14] and the reactions diazo compounds undergo. Indeed, there are now a few reviews which cover the use of metals for diazo compound decompositions.[15,6]

However, in all this time, the least studied of all the carbene reactions has been X-H insertion. Our interest in diazo chemistry is centred around the O-H insertion processes that diazo derived carbenes undergo. The aim of this review is to present a complete picture of the work which has been done on the O-H insertion process. The review is divided into two sections; *Photochemical and Thermal Decomposition* and *Metal Catalysed Decomposition.*

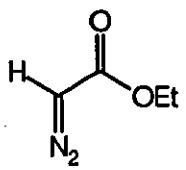
Photochemical and Thermal Decomposition

The simplest carbene is methylene, *i.e.*: CH_2:, readily available from the photolysis of diazomethane. The first recorded reaction of methylene with alcohols was in 1942.[16] Little was done on the subject until 1967, when Kerr published the results of competitive studies of methylene for different alcohols (Table 1).[17]

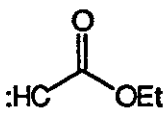
Table 1

Alcohol	Rel. Rate
Methanol	2.01
Ethanol	1.95
iso-Propanol	1.37
tert-Butanol	1.00

The increase in rate was considered to be due to the decrease in steric demand of the alcohol going from methanol to *tert*-butanol. These results would also seem to correlate well with the increase in alcohol acidity (*tert*-butanol to methanol), and with subsequent studies on the relative reaction rates observed with carboethoxycarbene (**2**) generated by either photolysis or metal catalysed decomposition of ethyl diazoacetate (**1**).

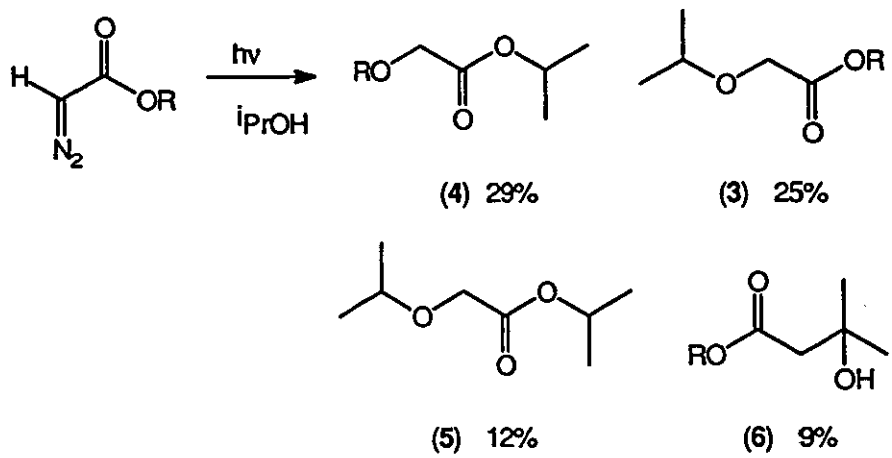


(**1**)



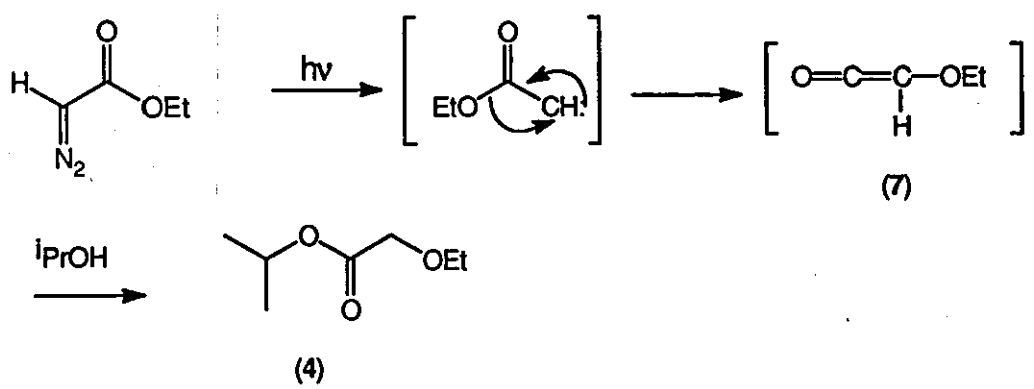
(**2**)

One of the most commonly used diazo compounds for carbene investigations is ethyl diazoacetate (EDA) (**1**). This is a dark yellow oil, which decomposes to carbethoxycarbene (**2**) on irradiation with light or by heating (ca. 85°C). In 1968[18] Strausz *et al.* described the first observed O-H insertion product from EDA and *iso*-propanol (**3**, Scheme 1, R=Et). The major product however, was the 'pseudo' Wolff rearrangement product (**4**). The two other minor products from the reaction are C-H insertion in the secondary C-H of *iso*-propanol leading to (**6**) and ester exchange on the already formed O-H insertion product, leading to (**5**); although these authors later suggested an alternative mechanism for the production of (**5**), (see later).[19]



Scheme 1

Carbenes maybe involved in the Wolff rearrangement and it seems reasonable that the production of (4) is a Wolff like rearrangement involving migration of the ethoxy group (Scheme 2).



Scheme 2

That the migration to give (4) proceeds *via* a ketene (7) and not a carbocation is given precedence by the acid catalysed decomposition of EDA in *iso*-propanol (Table 2). No rearranged product (4) is observed, suggesting that any cationic species which is produced by protonation of the diazo carbon is rapidly trapped by nucleophiles present.

Table 2

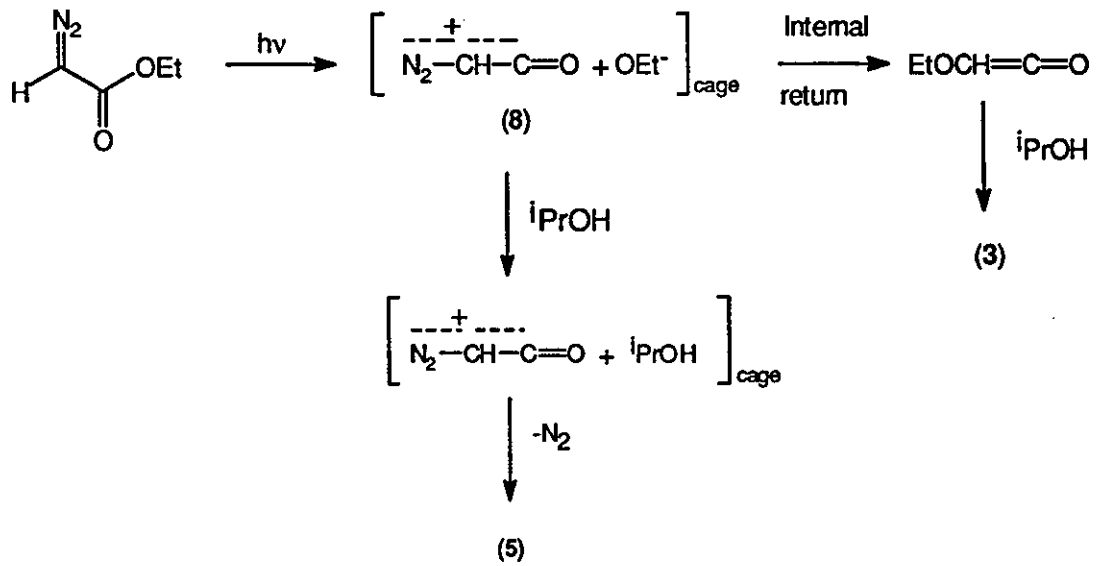
	Products (%)	
Acid	**3**	Other
HBr	12	Ethyl bromoacetate
HCl	24	Ethyl Chloroacetate
TsOH	98	None

Furthermore, addition of lithium bromide to the photolysis reaction mixture leads to no bromoacetate, indeed the original product distribution was unaffected.

The appearance of products from 'Wolff' type rearrangement is commonly noted in the photolysis of diazo compounds, indeed it is nominally the major reaction product in a lot of cases.

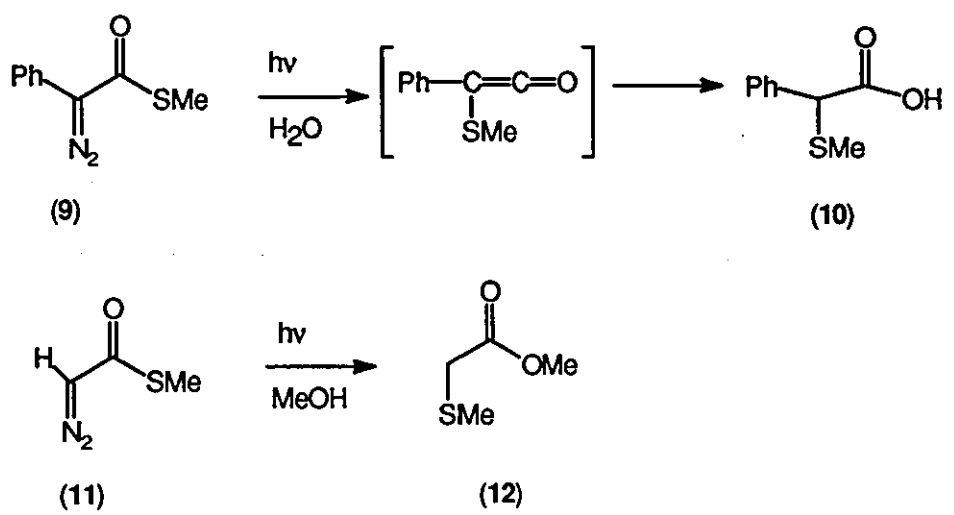
The formation of (**5**, Scheme 1) appears to be a photoinduced process. The irradiation of a variety of diazo acetates in *iso*-propanol leads, in all cases, to a small amount of (**5**) 13-20%. However, control experiments in the absence of light give no (**5**) at all; thermal decomposition of EDA (180°C, sealed tube), gives (**3**) 75% and (**5**) 19%, but no 'Wolff' rearrangement (**4**) or C-H insertion (**6**). This observation led DoMinh *et al.* to suggest an alternative mechanism, which competes with carbene formation, for the production of (**5**) (Scheme 3).

The suggested carbocation (**8**) would be unstable and rapid reaction within the solvent cage, would add to the yield of apparently rearranged product. If, a small number of ethoxide ions did manage to migrate from the solvent cage then this would explain the formation of the small amount of (**5**).



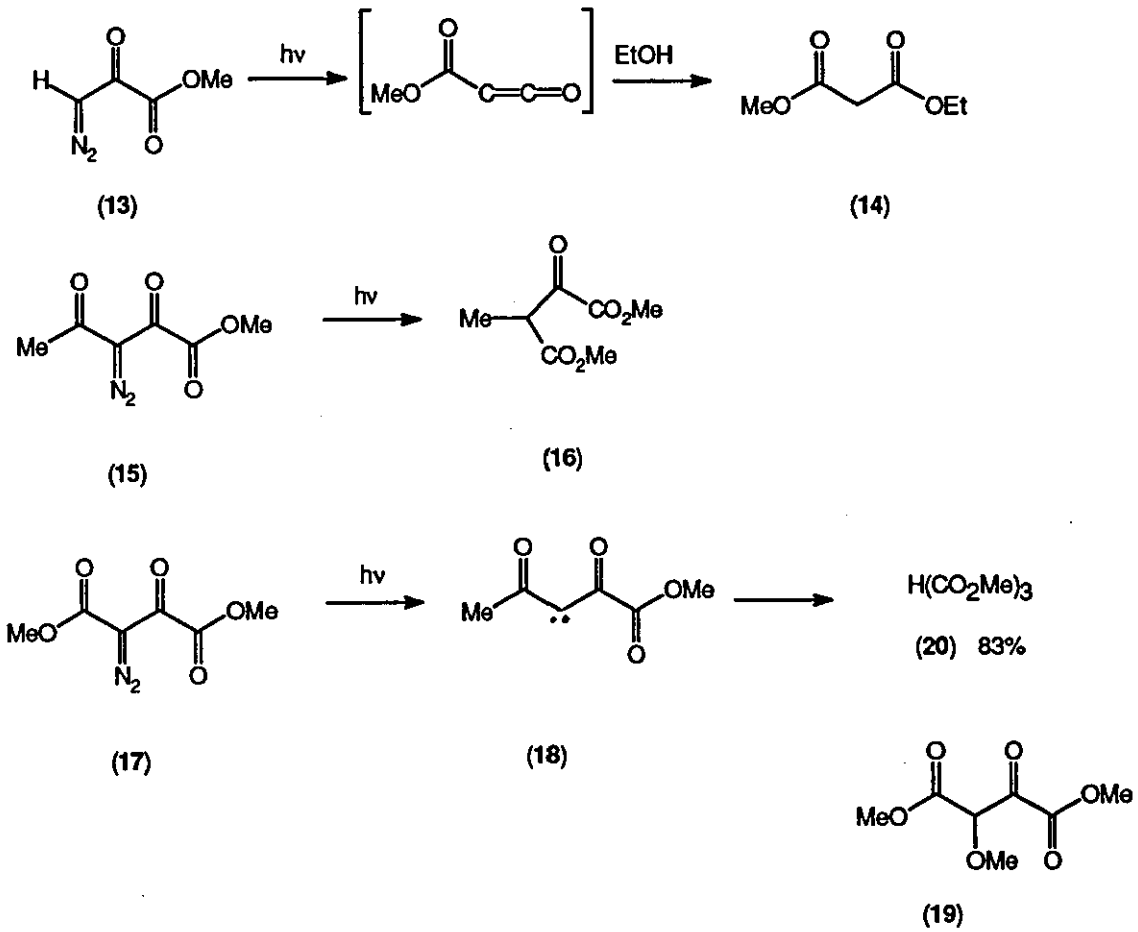
Scheme 3

If the Wolff rearranged product arose from the ketene (Scheme 2), then thioacetates would be expected to give more rearranged product than O-H insertion, due to the larger migratory aptitude of the thioalkyl group over alkoxides. In fact, this is shown to be the case; methyl α-diazophenylthioacetate (**9**) was found to give exclusively α-(methylthio)phenylacetic acid (**10**) on irradiation in aqueous solution,[20] and S-methyl diazothioacetate (**11**) gave only methyl methylthioacetate (**12**) on irradiation in methanol (Scheme 4).[21]



Scheme 4

Methyl diazoglyoxylate (**13**) led to a poor yield (37%) of ethyl methyl malonate (**14**) and no O-H insertion product.[22] The formation of (**14**) arises from the migration of the ester group to form an intermediate ketene (Scheme 5).



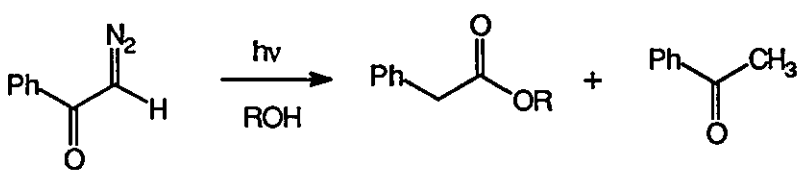
(13) (14) (15) (16) (17) (18) (19)

Scheme 5

However, this result is unexpected, as the ester moiety is not renowned for its migratory aptitude. If the same reaction conditions are applied to methyl 3-diazo-2,4-dioxopentanoate (**15**), then the observed product (**16**) is derived from methyl, not carbomethoxy migration, a more obvious result. O-H Insertion is only observed if the electronics of the system are changed further, to methyl

3-diazo-2,4-dioxo-4-methoxybutanoate (**17**). A small amount of O-H insertion (**19**) (9%) is now seen, against carbomethoxy migration (83%) (**20**). However, in this case, (**19**) may also formed by the ketene derived from methoxy migration to the carbene, as well as direct O-H insertion.

The photolysis of diazoacetophenone (**21**) is good example of the unpredictability of diazo compounds. Both Ziffer[23] and Padwa[24] have reported that the photolysis of diazoacetophenone in alcohols proceeds to give Wolff rearrangement (**22**), not O-H insertion into the alcohol (Scheme 6).



(21) (22) (23)

Scheme 6

The remainder of the reaction product isolated was acetophenone (the so called 'reduced' product) (**23**). On going from methanol to *tert*-butanol the amount of this 'reduced' product increases. Padwa explains this by the suggestion that the initially formed singlet diazoacetophenone is hydrogen bonded by the solvent. Decomposition to a singlet carbene (stabilised by H-bonding) which then rearranges may take place. As the strength of H-bonding decreases (methanol - *tert*-butanol) and effective stabilisation goes down, more intersystem crossing to the triplet can occur with a subsequent rise in 'reduced' product formation.

Other groups have noticed varying amounts of 'reduced' product from photolysis of diazo compounds. Ando[25] photolysed methyl diazomalonate and noted the reduced product varied from 0% (*tert*-butanol) to 41% (*iso*-propanol) according to the alcohol being used. The explanation suggested, was that the amount of dimethyl malonate produced was dependent on the hydrogen donating ability of

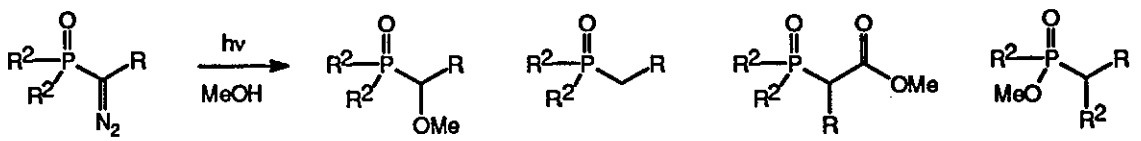
the alcohol, rather than any stabilising effect by H-bonding to the excited states (and hence carbene) of the dimethyl diazomalonate.

It is considered that the 'reduced' products isolated from diazo compound decompositions arises from the triplet carbene. The majority of the evidence for this comes from the observation that photolytic decomposition using a triplet sensitiser, leads to a significant increase in 'reduced' products, at the expense of Wolff rearrangement or O-H insertion.

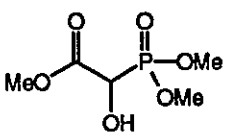
The question of whether a photochemically generated carbene will undergo appreciable amounts of Wolff rearrangement or O-H insertion, is a complex one. The difficulty in trying to predict which diazo compounds will give rearranged products has already been hinted at. In the case of phosphorus substituted carbenes, the situation is even more complex and confusing.

A range of 16 different phosphonodiazomethanes were taken and irradiated in methanol solution,[26] and the results are summarised in Table 3.

Table 3



(28) (24) (25) (26) (27)



(29)

			Yields (%)			
	R^1	R^2	(24)	(25)	(26)	(27)
a	OMe	COPh	--	≈50	≈50	--
b		COMe	--	≈50	≈50	--
c		CO_2Me	>99	--	--	--
d	OMe/ONa	CO_2Me	--	--	--	(29)
e	OMe/Ph	H	48.7	--	--	35
f	OMe	Ph	>99	--	--	--
g	Ph	$CONH_2$	81	--	--	--
h		CO_2Et	22	--	--	61
i		H	--	--	--	61
j		COPh	--	--	--	77
k		COPh	13	5	12	44
l		Me	32	7	--	15
m		Ph	100	--	--	--
n		4-Br-C_6H_4	18	5	9	42
o		4-MeO-C_6H_4	18	5	10	31
p		4-Me_2N-C_6H_4	20	--	23	14
q		4-NO_2-C_6H_4	11	--	10	28

The first point to note is the probability of insertion (**24**) occurring is independent of the substitution at phosphorus (a,b,c,j,k). The insertion reaction - when it does go - is equally unpredictable. Regitz reports two conflicting results for the same reaction (j,k) in 1970 and 1971.[25] However, in both cases, the major product (77% (**26**) and 56% (**27**) respectively) is that derived from 'Wolff' rearrangement. Although no explicit experimental is given, these results are nevertheless intriguing.

Substitution at the diazo carbon also has a startling effect (a,b,c,f). Acetyl and benzoyl (a,b) give no O-H insertion, (**24**) only products derived from 'Wolff' rearrangement or 'reduction'(**25**). Conversely, carbo*methoxy* or phenyl (c,f) gives rise exclusively, to O-H insertion.

Substitution at the phenyl group on the diazo carbon, has by comparison significantly little effect (n,o,p,q). In all these cases the major product was 'Wolff' rearrangement (**26**, **27**; 37-51%). Substitution of the phenyl ring had most influence on whether it was the substituted phenyl moiety which migrated to give (**26**), or one of the two phenyl groups on phosphorus, to give (**27**). Even then, no obvious pattern is apparent. Bromo, dimethylamino and methoxy (n,o,p) all have a +M effect on the phenyl ring, but it is only in the dimethylamine case where migration is significantly increased.

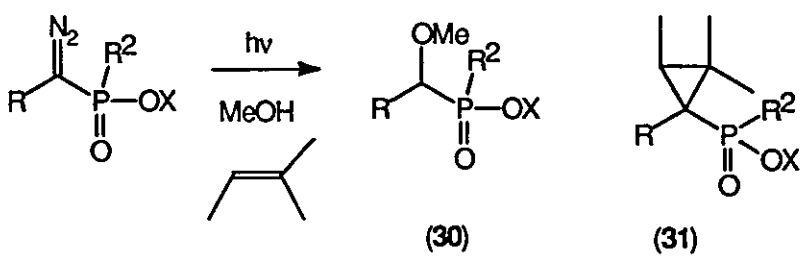
Where the diazo compound is a phosphonoacetate derivative (e,i), O-H insertion is only observed when substitution at phosphorus is not by two alkyl groups (e); even then, 'Wolff' rearrangement is still significant (35%).

The photochemistry of phosphonic acids has also been looked at (c,d). These too, show interesting behaviour. The product distribution goes from O-H insertion (d, both groups on phosphorus the same), to α-hydroxyphosphonic acid (**29**, e) when one of the groups on phosphorus is changed to its sodium salt.

Tomioka[27] reports an inversion of reaction product distribution on employing

α-diazo phosphonic acids and α-diazophenylacetic acids rather than their alkylated equivalents. The results are shown in Tables 4 and 5. Two traps were employed for the photolysis; methanol and 2-methylbut-2-ene, and resulting yields measured.

Table 4

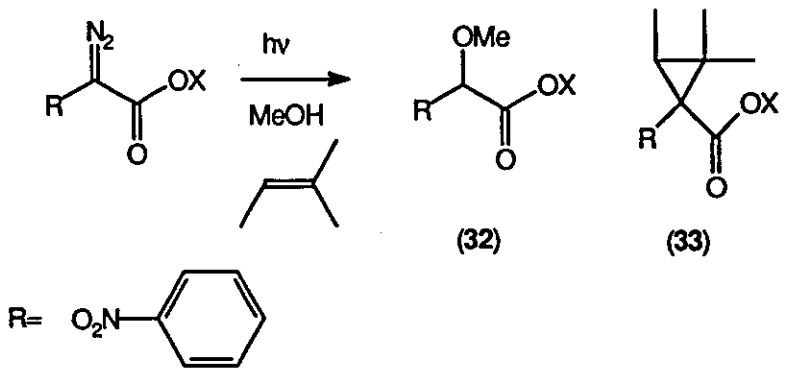


(30) (31)

	R	R^2	X	(30)	(31)
i	Ph	OMe	Me	17.8	81.1
ii			Na	72.5	16.4
iii	4-Cl-C_6H_5	OMe	Me	17.4	80.3
iv			Na	62.8	27.6
v	Ph	Ph	Me	38.3	57.4
vi			Na	73.9	13.5

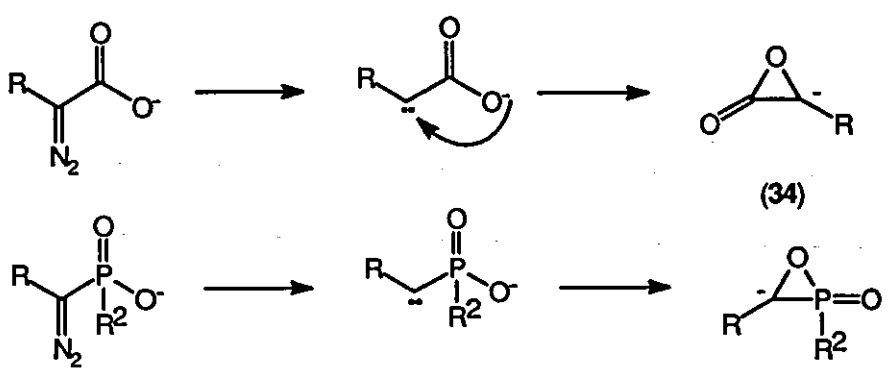
The explanation for this startling reversal in product distribution is that the negative charge on oxygen can interact with the free p-orbital on the formed singlet carbene, which can go on to afford either an oxiranone or an oxaphosphirane (Scheme 7, **34**). The formation of (**34**) will generate a charge reversal at the carbene centre, the resulting carbanion being rapidly protonated by the alcohol. Subsequent attack of methanol at carbon, will give the observed insertion product (**30** and **32**). Interestingly, in these cases no 'Wolff' rearrangement product is noted.

Table 5



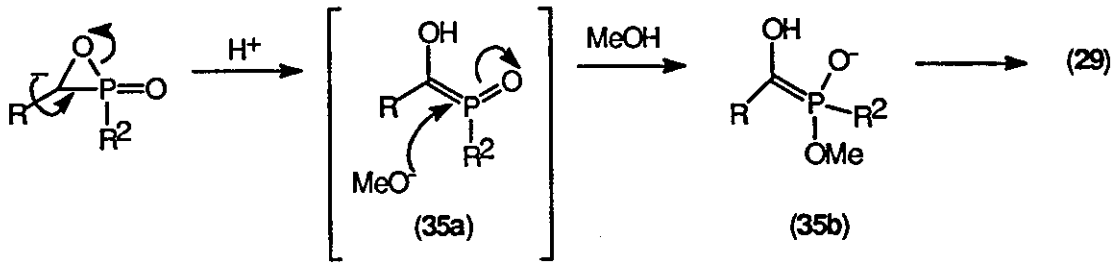
	X	(32)	(33)
vii	Me	9.2	90.8
viii	H	12.3	87.7
ix	H/Et_3N*	96.4	3.6
x	Na	>99.9	<0.1

* 5 mol excess of triethylamine



Scheme 7

This argument can also be invoked to explain the apparent anomaly in Table 3 (d), giving the production of (**29**). Oxaphosphirane (**34**, R=MeO_2C, R^2=OMe) could ring open to give phosphorus ketene equivalent (**35a**). Subsequent attack of methanol on phosphorus, would lead to (**29**) via the enolate eqivalent (**35b**, Scheme 8).

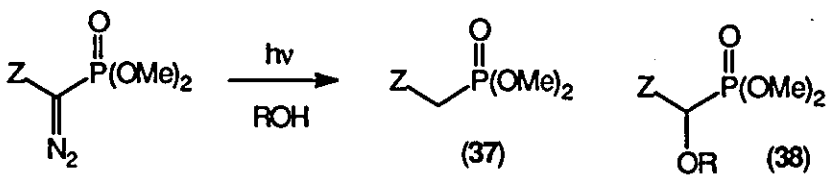


Scheme 8

In the cases where the formation of an oxaphosphirine (**34**) is suggested (iv, vi Table 4, ix, x Table 5), the yield of cyclopropanation products (**31, 33**) would be expected fall, as 2-methyl-but-2-ene is a reagent useful for the trapping of electrophilic carbenes. Indeed, this is found to be the case experimentally as attack of the oxygen at the carbene centre will drastically reduce the population of electrophilic carbenes accordingly. Bartlett[28] has observed similar results with α-diazophosphonic acid monoesters, and indeed originally suggested oxaphosphiranes as the reason for the observed behaviour.

In some instances, the reactions of diazo compounds with homologous alcohols can be radically different (Table 6).[29]

Table 6



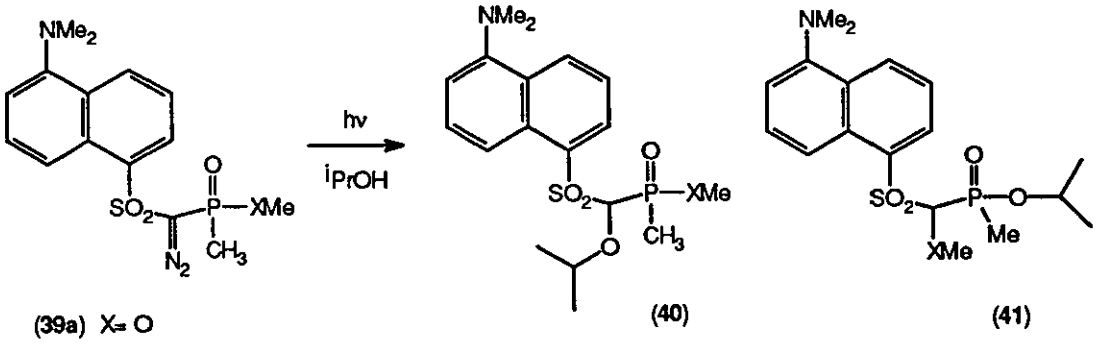
		Z	R	(37)	(38)
a	(36a)	Et_2NSO_2	Me	17	31
b			Et	24	33
c	(36b)	$(^iPrO)_2P(O)$	Me	41	44
d			Et	>95	--

The photolysis of α-diazo-β-diethylsulphonamidetrimethylphosphonate (**36a**, a,b) in both methanol and ethanol gives a mixture of 'reduced' product (**37**) and O-H insertion (**38**). However, the bis-phosphonatediazo (**36b**, c,d) only gives insertion product when photolysed in methanol. When photolysed in ethanol, only 'reduced' product is observed in the crude reaction mixture. In either case, no 'Wolff' rearrangement was noted. There is no obvious explanation for this result. Both alcohols have similar physical and chemical properties (methanol, ethanol: ε=32.6, 24.3 and pKa=15.5, 15.9 respectively).

In contrast, sulphonephosphonate diazo (**39a** & **39b**) gave a negligible amount of 'reduced' product on photolysis in *iso*-propanol (Scheme 9).[30]

When X=O (**39a**), insertion (**40a**) is the only major product, with no 'Wolff' rearrangement (**41a**) being observed. Insertion is still seen when X=S (**40b**), but 'Wolff' rearrangement is now the preferred process (**41b**), rearranged product (**41b**) being formed in 2.5 times greater amount than insertion (**40b**). This result contrasts nicely with the attempted insertion of methanol into methyl diazothioacetate, (**11**) and of water into methyl α-diazophenylthioacetate (**9**, Scheme 2) which showed only 'Wolff' rearrangement. This observation is an indication of

the difficulty of forming a phosphorus ketene equivalent (**42**), and that the migration of groups from phosphorus to carbon is slow.

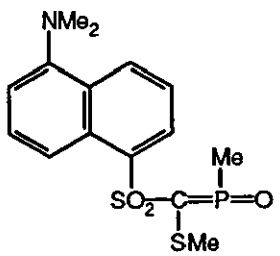


(39a) X= O

(39b) X= S

(40)

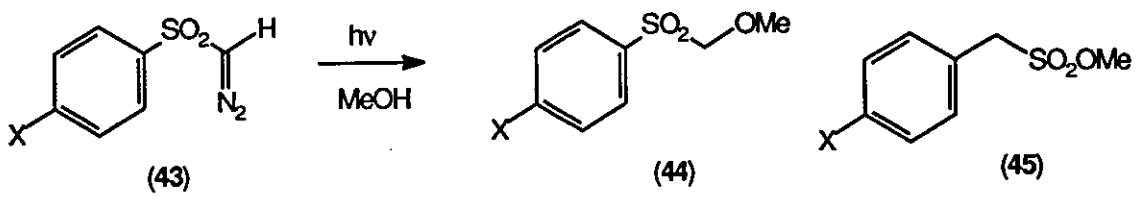
(41)



(42)

Scheme 9

A similarly small amount of 'Wolff' rearrangement is observed with sulphone diazoacetates (**43**, Scheme 10). Insertion (**44**) is the major product in all the cases looked at, the 'Wolff' rearranged product (**45**) not exceeding 12%.

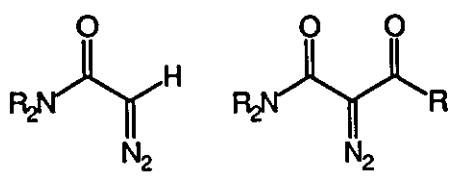


(43) (44) (45)

X	(44)	(45)
MeO	78	12
CH_3	76	10
H	79	8
NO_2	32	7

Scheme 10

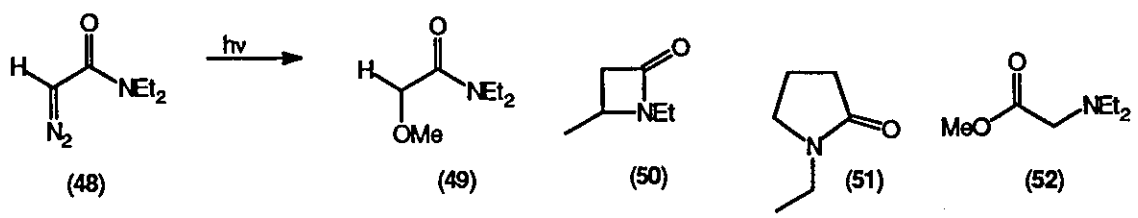
Another group of diazo compounds which show quite different and interesting results from photolytic O-H insertion are diazoamides **(46, 47)**.



(46) (47)

In the case of N,N-diethyldiazoacetamide **(48)**, four products are detected on photolysis in methanol (Table 7).[31]

Table 7

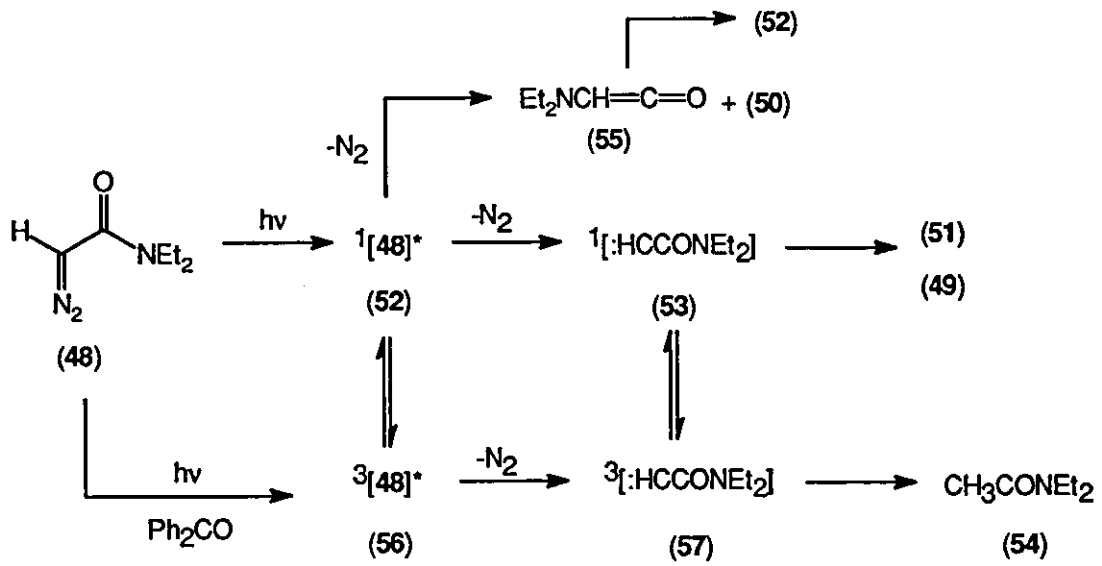


(48) (49) (50) (51) (52)

	% MeOH added	(49)	(50)	(51)	(52)
a	0	--	36.5	45.8	4.4
b	1	6.0	38.2	41.7	9.5
c	2	10.1	37.6	35.3	11.9
d	100	33.0	36.6	16.4	11.4
e	100*	26.8	2.0	8.3	<1
f	100	34	43	5	18[31]

* 5 fold excess of sensitiser (Ph_2O) was used

The first thing to note is that N,N-diethyldiazoacetamide (**48**) shows a high propensity for β-lactam formation by intramolecular C-H insertion, (**50**) even in neat methanol (d). 'Wolff' rearrangement (**52**) is the minor product in all cases, although it approaches γ-lactam (**51**) formation in neat methanol. The most interesting result is that the sensitized photodecomposition (e) still leads to a large proportion of O-H insertion (**49**). Assuming that the sensitized decomposition leads to a triplet carbene, this results implies that (in this case at least), triplet and singlet carbenes are in rapid equilibrium and intersystem crossing to the singlet is of comparable speed to reaction. However, 'Wolff' rearrangement, (**52**) which would also be expected to derive from the singlet carbene species is curiously absent (e). Likewise, radical cyclisation to the lactams (**50,51**) (a triplet process) is also not as favoured as O-H insertion (**49**). The reaction scheme which best describes these observations, is depicted in Scheme 11.



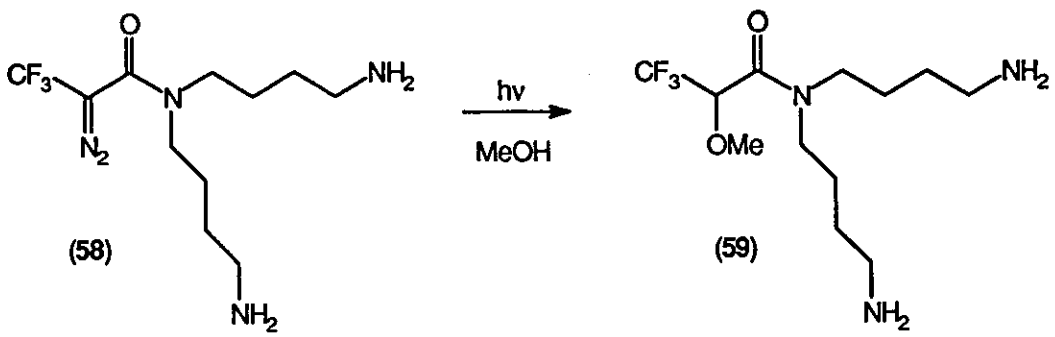
Scheme 11

Diazoacetamide (**48**) forms an excited singlet state (**52**) on irradiation. This excited singlet can either a) react by loss of nitrogen to give β-lactam (**50**) or aminoketene (**55**). The aminoketene going on to give the 'Wolff' rearranged product (**52**); or b) intersystem crossing to give the excited triplet diazoacetamide (**56**). Both the formed excited states can subsequently lose nitrogen to form the carbene, the singlet carbene (**53**) may go on to give either the O-H insertion product (**49**) or γ-lactam (**51**). The triplet carbene (**57**) may undergo intersystem crossing to the singlet, which can go on as described, or presumably may itself react to give the 'reduced' product.

These equilibria must exist, to fit the observed facts. Sensitized decomposition gives O-H insertion, but no 'Wolff' rearrangement (e); (**48**)→(**56**)→(**57**)→(**53**). The small amount of (**50**) present is probably from the decay of (**56**)→(**52**). The rate formation of γ-lactam (**50**) must be significantly faster than rearrangement to aminoketene (**55**), as no amount of (**52**) is noted.

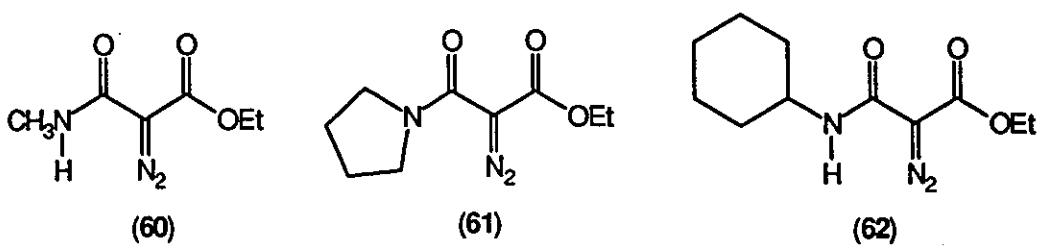
Rando has found a similar result to Tomioka for the photolysis of (**48**), (f).[31] The rate of C-H insertion of diazoamides, maybe significantly curtailed by the introduction of strongly electron withdrawing substituents. Thus, the photolysis of

(58) in methanol,[33] produced exclusively the O-H insertion product (59), with no 'Wolff' rearrangement or C-H insertion products being detected (Scheme 12).



Scheme 12

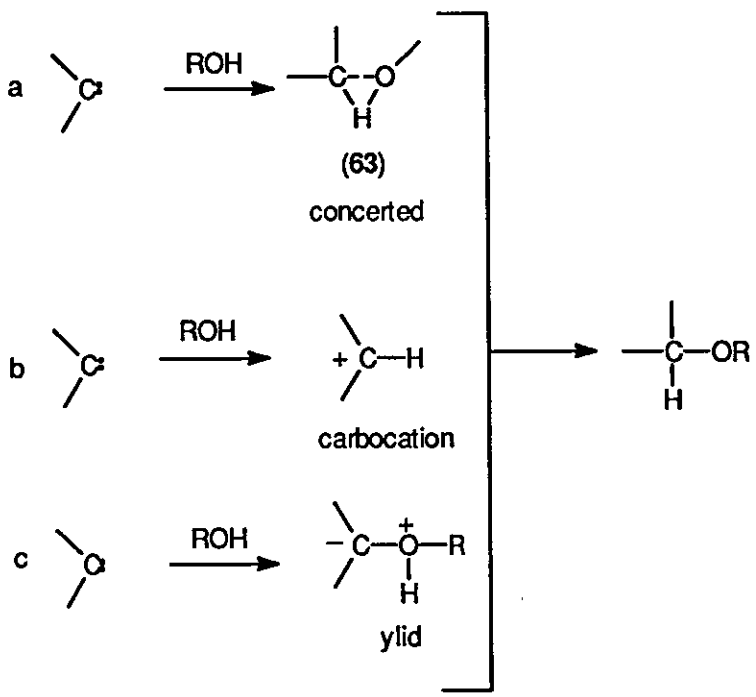
Thornton[34] has studied the photolysis of a small selection of α-diazo-β-amidoesters (**60** - **62**), in order to assess the rate of *inter*molecular O-H insertion with respect to C-H insertion.



Photolysis in binary mixtures of *tert*-butanol and 2,3-dimethylbutane, leads in all cases, to good yields of the O-H insertion product. It was subsequently found, that the relative selectivity of O-H versus C-H insertion was in the order of 10^3-10^4 to 1. This result is in stark contrast from what one might expect, given the nominal yields quoted (Tables 3-7) for the O-H insertion process. This result lends further evidence to the unpredictability of the O-H insertion process.

Mechanism of O-H Insertion Process

The mechanism for the O-H insertion of carbenes can be considered to proceed in three different ways (Scheme 13).



Scheme 13

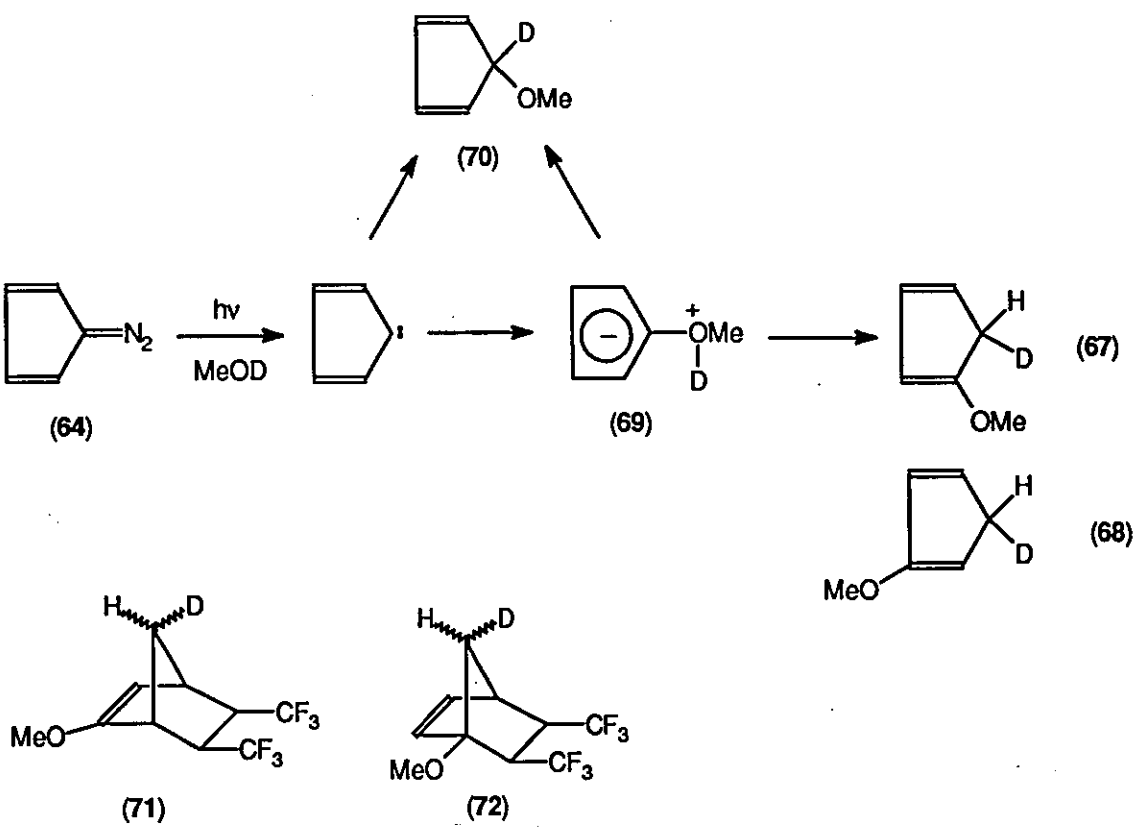
The first equation (a) shows the concerted process, where C-O and C-H bond formation is simultaneous with O-H bond breaking. No discrete intermediates are involved, the structure (**63**) representing the transition state for the process.

Equation (b) considers the protonation of the carbene by the alcohol, to give a carbocation. This mechanism maybe invoked if the carbocation so generated is particularly stable. Likewise, with equation (c), which proposes a ylid intermediate.

Most of the mechanistic studies which have been done, suggest the intermediacy of an ylid (c). Some specific examples are known which are

explained by the intervention of carbocations, (b), but none have been reported which argue the case for direct insertion (a). However, the concerted mechanism cannot be ruled out entirely, and it is possible, as with other process, that prudent choice of solvents and conditions would enable a concerted mechanism to be the most plausible explanation of events.

Kirmse[35] has reported the O-H insertion into diazocyclopentadiene (**64**, Scheme 14), and diazocycloheptatriene (**66**, Scheme 15), - most easily generated from the photolysis of tropone tosylhydrazone sodium salt (**65**).



Scheme 14

If the O-H insertion of diazocyclopentadiene was to go *via* an ylid (eq. (c), Scheme 13), the ylid formed, should be stable, due to the aromatic character of the cyclopentadiene anion. The resultant ylid (**69**), may undergo deuterium

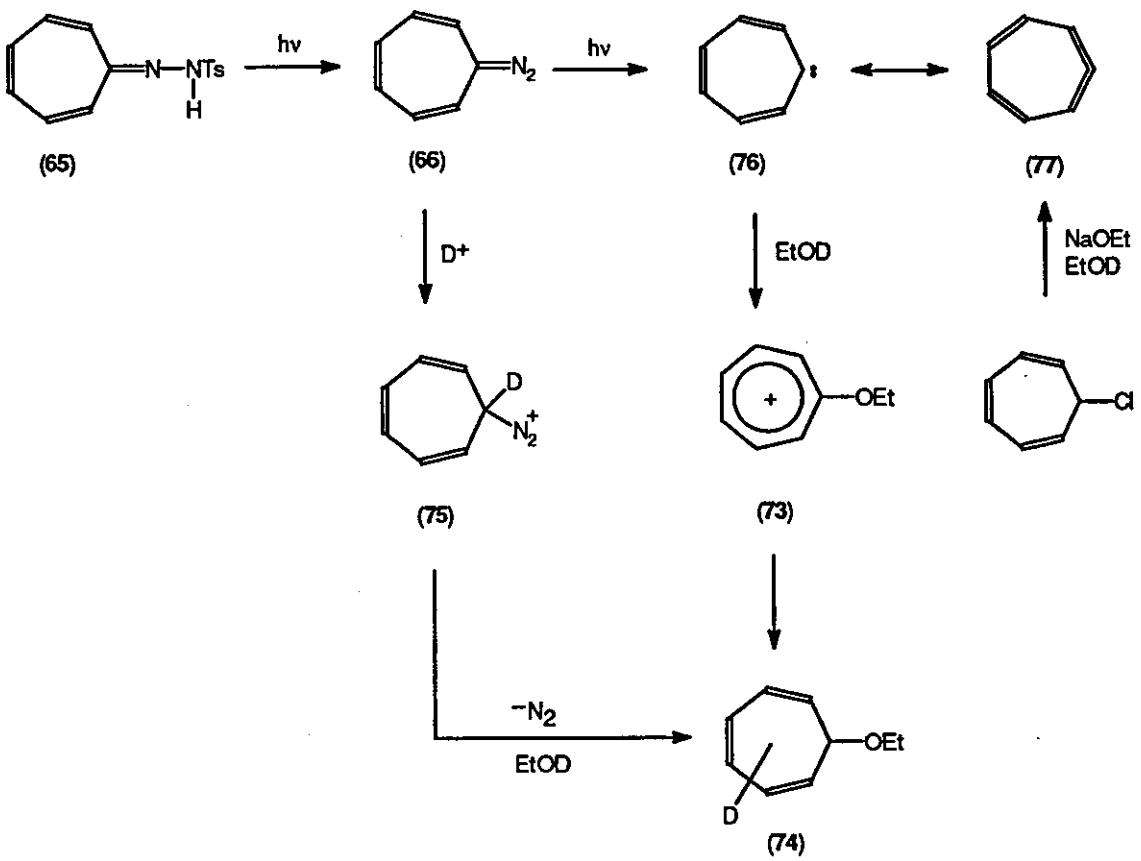
transfer to C-1 (**70**) or C-2 (**67**) of the cyclopentadiene residue. A subsequent 1,3 shift may produce (**68**). However, 1,5-shifts cannot produce (**70**) exclusively. On the other hand, if the insertion were to be concerted, then the only observable product should be (**70**), with the carbene carbon containing both the alkoxide group and deuterium.

In fact, no product corresponding to (**70**) was detected. To show that this was not merely a result of room temperature equilibrium, the photolysis was performed at -78°C and the resultant insertion products trapped as their Diels-Alder adducts, with hexafluorobut-2-yne (**71**, **72**, ratio 4:1). Proton and deuterium NMR spectroscopy showed that the adducts carried deuterium only at C-7. The conclusion therefore, must be that insertion, in this case proceeds via an ylid (**69**).

Photolysis of diazocycloheptatriene (**66**, Scheme 15) in methanol-d_1, gave an insertion product (**74**) where deuterium was randomly substituted in the ring. The obvious inference is that the tropylium ion (**73**) is the intermediate involved.

However, a carbene, need not be involved. Deuteration of the diazocycloheptatriene (**66**) would lead to a diazonium ion (**75**). Loss of nitrogen from this diazonium ion, and subsequent capture of alkoxide would lead to the same observed result (**74**).

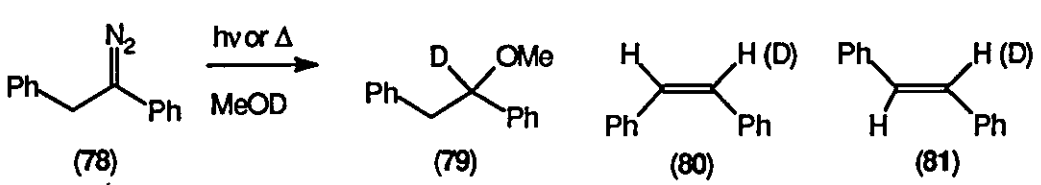
Formation of the carbene (**76**) from an alternative route would give evidence for carbene involvement. Treatment of chlorocycloheptatriene, with sodium ethoxide in ethanol-d_1 generates an allene (**77**) which is in equilibrium with the carbene (**76**). Work-up of this reaction mixture gives a similar result, with deuterium randomly distributed throughout the ring (**74**).



Scheme 15

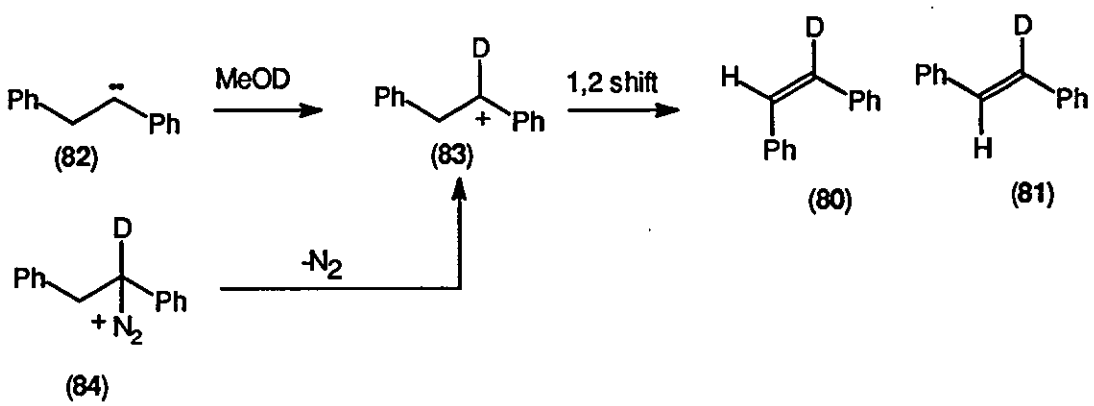
In the case of diazocyclopentadiene, O-H insertion must go via an ylid intermediate (Scheme 15), as distinct from diazocycloheptatriene, which reacts via a carbocation (Scheme 14).

Other cases have been observed which support the intermediacy of a carbocation. Tomioka[36] has looked at the decomposition of 1,2-diphenyldiazoethane (**78**) in methanol-d_1 (Scheme 16).



Scheme 16

The major product of this reaction was the ether (**79**) from O-H insertion. However, appreciable amounts of stilbenes were formed (**80**, **81**, 18.3 and 25.6% respectively). Significant deuterium incorporation (10.6%) in these stilbenes was noted. If the alkene was derived from rearrangement of the carbene, no deuterium would be expected to be incorporated. The obvious route to formation of this deuterio alkene is from protonation of the carbene (**82**) to give a carbocation (**83**) (Scheme 17). Subsequent loss of a proton would give the observed stilbenes (**80**, **81**).



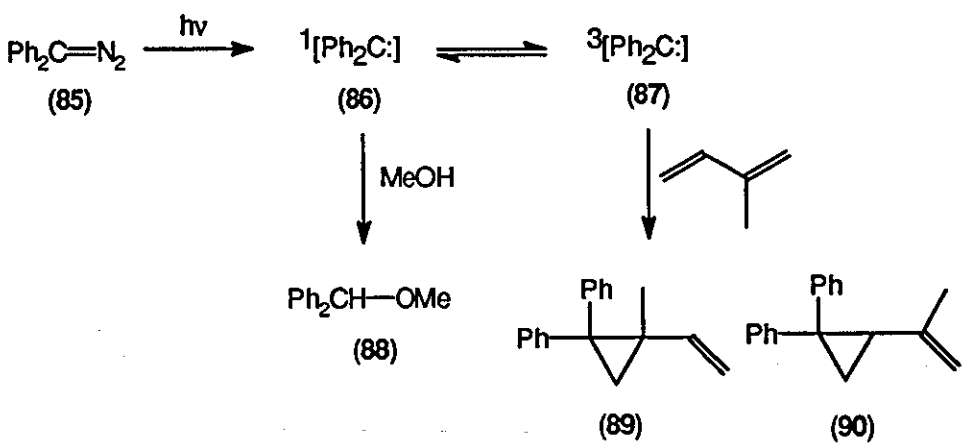
Scheme 17

If it is the carbene which is protonated, to give the carbocation (**83**), then decomposition of the starting diazo (**78**) by boron trifluoride etherate, would be expected to give a high percentage of deuterium incorporation. This is indeed the case, with ca.85% deuterium incorporation in the stilbenes being observed.

To show that protonation of the starting diazo-1,2-diphenylethane to a diazonium ion (**84**) with subsequent loss of nitrogen to give the carbocation, (**83**) was not responsible for the observed deuterium distribution, decomposition by thermolysis was carried out. In this thermolytic case, negligible amounts of deuterium incorporation were noted.

Both these results suggest that the deuteriated stilbenes must be derived from an intermediate carbocation (**83**), formed by protonation of the carbene (**82**). Obviously, this is not the sole mechanism operating - as deuterium incorporation is <100%, - but it cannot be ruled out in discussions of the photolytic O-H insertion process.

It was commented on earlier, that for N,N-diethylacetamidocarbene (**53**, Scheme 11) there must be rapid equilibrium between the singlet and triplet states of the carbene. Studies by Eisenthal[37] have showed that this singlet (**86**) - triplet (**87**) equilibrium must also be true for diphenylcarbene (**86**, Scheme 18). The ratio of cyclopropanes (**89**, **90**) to O-H insertion (**88**) was found to be independent of excitation method and concentration of the trap, i.e. the same result was obtained if either methanol or isoprene was in excess. This observation coupled with picosecond flash photolysis kinetics experiments, forced the group to conclude that the triplet and singlet states of the generated carbene (**86**) were in rapid equilibrium. Other groups have reached the same conclusion, from slightly different starting points.[38]



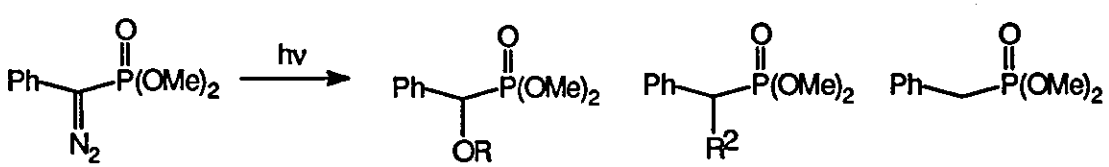
Scheme 18

Studies by Turro[39] and Tomioka[40] have shown that the temperature of reaction has a significant effect on the product distribution observed, in either competition reactions or reaction with alcohols alone.

In the competition reaction of diphenylcarbene with methanol and isoprene, it was found, in the majority of cases, that cyclopropanation is favoured at the extremes of the temperature range covered,[38] (-87°C → -23°C and ca.50°C → 60°C). However, this result is further complicated by the observation that product distribution is also solvent dependent. Thus, acetonitrile as co-solvent gives predominately O-H insertion at all temperatures and dioxane the reverse, giving predominately cyclopropanation throughout the temperature range covered.

Tomioka[39] was concerned however, with how the reaction of dimethyl - phosphonophenyldiazomethane (**91**) with alcohols varied with temperature. The results of this study are presented in Table 8.

Table 8



(91) (92) (93) (94)

	Alcohol	T/°C	(92)	(93)*	(94)
a	MeOH	27	98.4	Tr**	1.6
b		3	95.2	Tr	4.8
c		-72	95.8	Tr	3.8
d		-196	17.8	76.5	5.6
e	$(CH_3)_2CHOH$	27	60.8	26.1	12.1
f		3	48.4	20.4	31.2
g		-72	7.3	20.5	72.2
h		-196	8.4	64.4	27.2

* Total yield of all C-H insertion products, ** signifies only a trace amount of material was detected.

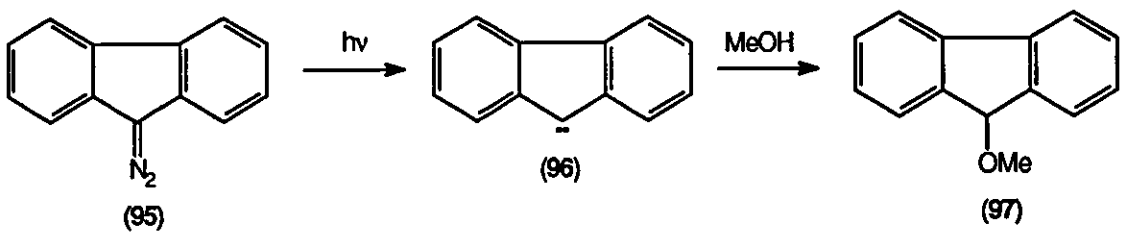
As the temperature decreases, the yield of insertion product (**92**) drops accordingly. In the case of methanol - which is a poor hydrogen donor - no appreciable yield of 'reduced' product (**94**) is noted, regardless of temperature (a-d). With *iso*-propanol however, 'reduced' product formation is a maximum at the lowest temperature attainable without freezing the reaction mixture (g). Once frozen, the major product now becomes C-H insertion (**93**) (h).

Hirayama[41] has suggested that the hydrogen bonding ability of alcohols is decreased with decreases in temperature. If this is so, then it is not unreasonable to suggest that the activation energy of ether formation would rise with decrease in temperature. The resulting ylid would not be as effectively stabilised at these lower hydrogen bonding efficiencies. Hydrogen bonding of singlet carbenes has already been alluded to in the case of diazoacetophenone (Scheme 6).

Once the reaction mixture is frozen, then mobility of the radicals determines the reaction course. As the radicals are largely immobile, recombination will occur and so C-H insertion (**93**) is the principal pathway. In solution however, the radicals have the chance to diffuse apart before reacting, so 'reduced' (**92**) product formation is now predominant.

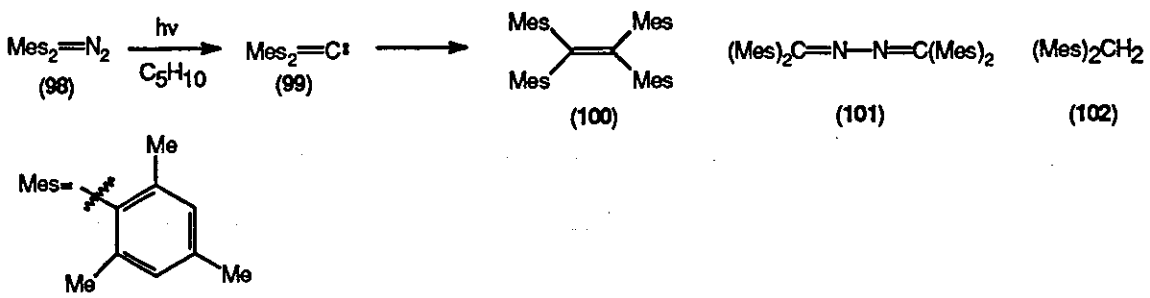
Tomioka also found that the carbene derived from (**91**) existed in rapid equilibrium between singlet and triplet forms. Direct irradiation or sensitised decomposition of the starting diazo compound (**91**) led to the same reaction product distribution. This observation is similar to that made for diphenylcarbene (**86, 87** Scheme 18).

Similar evidence for singlet - triplet carbene equilibrium has been put forward by Zupancic[42] for fluorenylidene (**96**, Scheme 19). Irradiation of (**95**) either directly or in the presence of sensitiser leads to a good yield of methyl ether (**97**). This implies that conversion to the singlet carbene is faster than any bimolecular reactions the triplet carbene undergoes.



Scheme 19

However, not all the carbenes studied have shown rapid singlet - triplet equilibration. Indeed, studies on dimesitylcarbene[43] (**99**, Scheme 20) suggest that once present as the triplet carbene intersystem crossing to singlet carbene does not occur. Photolysis of dimesityldiazomethane (**98**) in pentane gave the dimer (**100**) in good yield (80%), along with some 'reduced' product (**102**, ca.30%), both the result of reaction of triplet carbene. However, no azine (**101**) was present in the reaction mixture, a common product from reactions of singlet aryl carbenes. The azine is derived from reaction of singlet carbene (**99**) with the starting diazo compound (**98**). Also, addition of methanol[44] to the reaction mixture, did not cause a quenching of the EPR signal assigned to the triplet carbene, however the quantum yields of the triplet reactions measured did decrease.



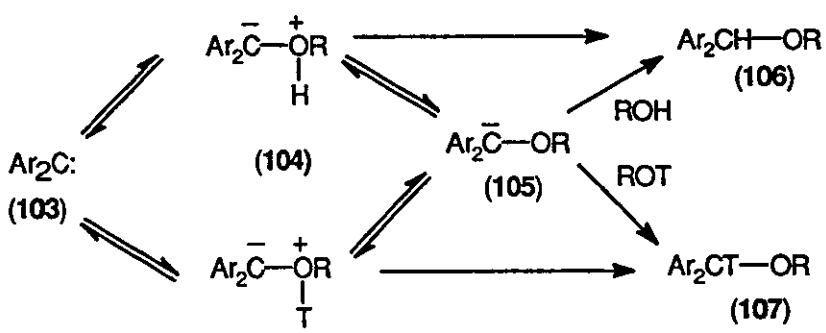
Scheme 20

The implication is that an initially formed singlet undergoes rapid intersystem crossing to the triplet state - as proposed for other aryl carbenes - but the

reverse process to the singlet carbene cannot occur, so appreciable amounts of triplet carbene can build up. Only oxygen was found to be a rapid quencher for triplet mesitylcarbene (**99**), suggesting that steric crowding was responsible for the carbenes apparent long lifetime (ca. 200 μs vs. ca. 1.7 μs for diphenylcarbene (**86**, Scheme 18).

Bethell has investigated the thermal decomposition of diazodiphenylmethanes with alcohols[45] and water[46] in a bid to deduce the mechanism of ether formation. Thermal decomposition in tritiated alcohols reveals a secondary isotope effect, which varies according to the acidity of the reacting alcohol. The most interesting result comes from the decomposition of diphenyldiazomethane in tritiated *tert*-butanol in the presence of methanol. This experiment reveals that the observed isotope effect is reduced in the presence of the added methanol.

The mechanism which best explains these observations is that of an intermediate ylid (**104**, Scheme 21).



Scheme 21

The formed arylcarbene (**103**) maybe trapped by either 'normal' or tritiated alcohol to give the ylid (**104**). *Intra*molecular proton transfer, will lead to the two product ethers (**106**, **107** respectively). However, proton transfer between oxygen is likely to be faster than transfer from oxygen to carbon, and it is probable that deprotonation will occur to give the intermediate carbanion (**105**). Reprotonation to give the products (**106**, **107**) is now a competitive process, and

will be most likely from the more acidic alcohol. Thus, decomposition in a mixture of tritiated *tert*-butanol and methanol lowers the observed isotope effect with respect to *tert*-butanol on its own.

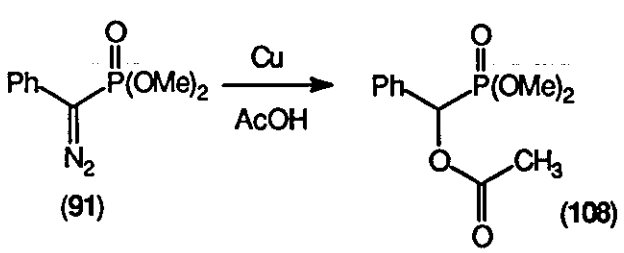
It would seem therefore, from all the examples discussed, that the general opinion in the case of photolytic or thermal decomposition is that ether formation occurs via an oxygen ylid which rearranges either by a 1,2-hydrogen shift or by proton exchange with the solvent.

Metal Catalysed Decomposition

Even though diazo compound decomposition can be accomplished by a variety of metals, only copper salts and rhodium (II) salts have gained any significant use in organic synthesis. Often, insertions which do not go by thermolysis or photolysis may well work in the presence of metals.

The decomposition of *para*-bromo-α-diazoacetophenone and *para*-phenyl-α-diazoacetophenone with copper (I) chloride, in the presence of organic acids was reported in 1951[47] as a qualitative test. Good yields of O-H insertion into the carboxylate group were realised.

Just over a decade later Seyferth[48] reported the use of copper powder for the O-H insertion of acetic acid with dimethyl phosphonophenyldiazomethane (**91**, Scheme 22).

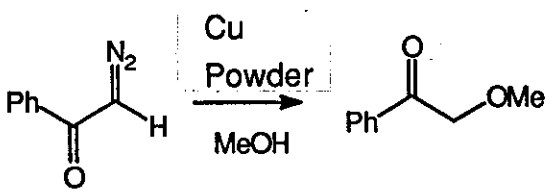


(91) (108)

Scheme 22

No yield for the production of acetate (**108**) was reported however.

In 1952 Yates[9] reported the first extensive study into the copper catalysed decompositions of a selection of diazo compounds. Copper powder was used as the catalyst. Action of copper powder on diazoacetophenone (**21**, Scheme 23) gave the O-H insertion product (**109**) in 55% yield, no 'Wolff' rearranged product (**22**) was detected.



(21) (109) 55%

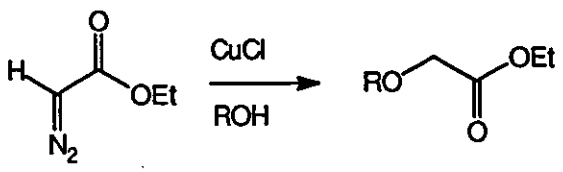
Scheme 23

This result is in complete contrast to the photochemical decomposition of diazoacetophenone[25] which gave only 'Wolff' rearrangement (**22**) and 'reduced' acetophenone (**23**). However, in 1950 Casanova[49] reported that the copper (I) oxide catalysed decomposition of diazoacetophenone gave only 'Wolff' rearranged α-methoxyacetophenone (**22**). Steroidal ketones though, gave good yields of insertion products with methanol and copper (I) oxide.

Yates showed that copper was an efficient catalyst for insertion into thiols and aniline as well as alcohols. Importantly, in none of the cases investigated was the 'Wolff' rearranged product observed. Indeed, this is a major feature of metal catalysed diazo decompositions.

Copper (I) chloride was subsequently shown to catalyse the decomposition of ethyl diazoacetate[50] (**1**) in the presence of thiols and alcohols to give the appropriate X-H insertion products. Reaction yields were generally poor for the O-H insertion process (Table 9).

Table 9

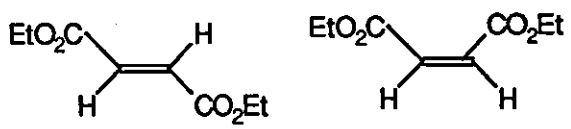


(1) (110)

R= Allyl, Benzyl, *n*-Butyl

	R	(110)
a	Allyl	17
b	Benzyl	49
c	*n*-Butanol	15

In the case of allyl alcohol (a), cyclopropanation only accounted for 13% of the products obtained. In all cases (a, b, c) the major by-product was the result of carbene dimerisation to give **(111)** and **(112)**.



(111) **(112)**

The major alternative to copper powder for diazo decompositions is copper (II) acetylacetonates (acac). In 1967 Takebayashi[51] published the results of a survey of fourteen different acac complexes.

The decomposition of diazoacetophenone was looked at in the presence of ethanol and a catalytic amount of metal acac complex. The most efficient catalysts are listed in Table 10.

Table 10

$M(acac)_n$	Reaction Temp./°C	Reaction Time/min	Yield(%)
None	80	1800	0*
$Cu(acac)_2$	50	30	60
$Ni(acac)_2$	70	180	80
$Pb(acac)_2$	80	1200	60
$2Ti(acac)_2TiCl_6$	80	1800	62

* No reaction took place

Nickel appears to be the best metal complex for this transformation. Copper is by far the fastest metal complex, without affording too large a drop in yield, (80 → 60%). Although both lead and titanium complexes give good yields of insertion product, they would not warrant use synthetically as copper and nickel both give, as good yields, in a significantly shorter time.

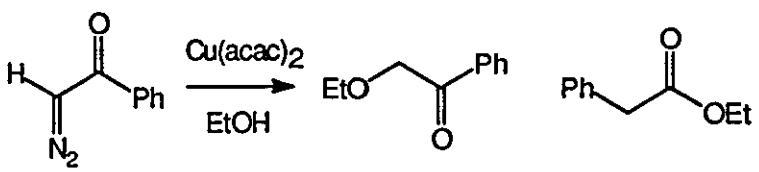
The other metal complexes which were tried (and presumably gave little or no yield) are as follows:
a) +2 oxidation state; Ba, Be, Ca, Cd, Co, Mg, Mn.
b) +3 oxidation state; Al, Co, Fe, Mn.

Competition experiments between water and alcohol as traps for the intermediate metal-carbene complex, gave the interesting result that only insertion into the alcohol was observed, except when using *tert*-butanol, when insertion into water was the sole isolable product.

This corroborates Thornton's[35] observation that photolytically insertion into water was 1.9 times faster than O-H insertion into *tert*-butanol.

Addition of amines to the reaction mixture (especially pyridine) caused a significant reduction in the amount of insertion product observed and the appearance of the hitherto unobtained 'Wolff' rearrangement product (Table 11).

Table 11



(21) **(113)** **(114)**

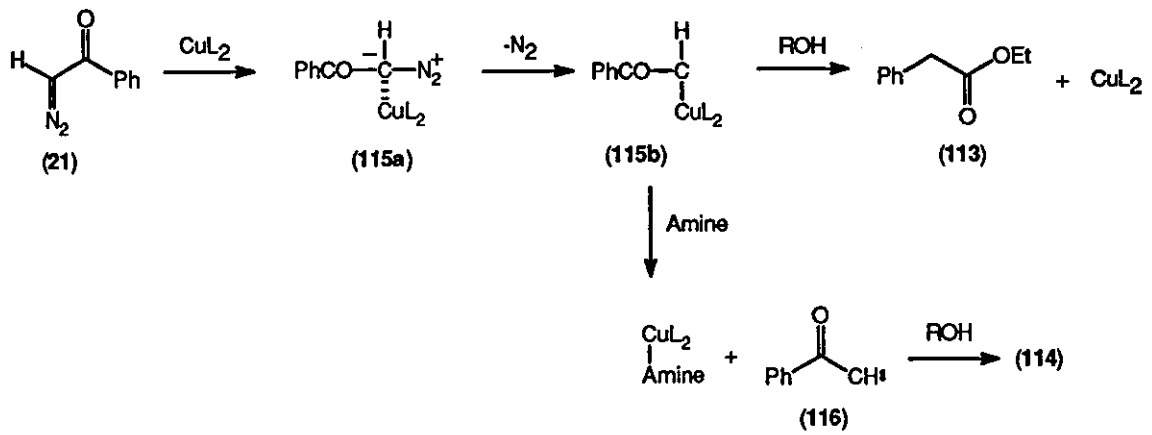
Amine	% amine	**(113)**	**(114)**
py*	0	60	0
	1.3	35	8
	6.7	12	26
	13.3	6	41
	20	5	59
$(Et)_3N$	1.3	60	Tr**
	13.3	54	14
	20	37	12

* Pyridine, ** Only a trace of 'Wolff' rearranged product was obtained

Addition of more than ca. 13% of pyridine has no further effect in reducing the yield of O-H insertion product. A similar, but less striking effect is also achieved with triethylamine. The smaller influence of triethylamine is presumably due to its larger steric requirement.

The explanation of this effect is given in Scheme 24. The starting diazoacetophenone (**21**) forms an encounter complex (**115a**) with the copper catalyst. This initial complex can then lose nitrogen to give the metal bound carbene (**115b**). With no amine present, this metal carbene can react as

expected, to give the insertion product (**113**) and free the catalyst to re-enter the cycle.

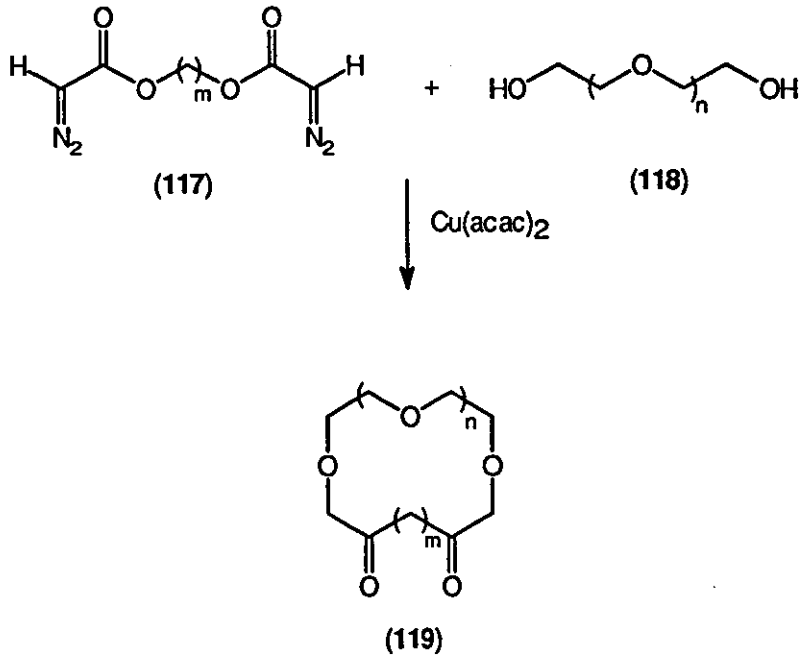


Scheme 24

In the presence of amine however, the intermediate complex (**115b**) maybe be attacked by the amine, resulting in displacement of the carbene. This 'free' carbene (**116**) is now able to rearrange, to give the 'Wolff' rearranged product, (**114**). This would be analogous to direct irradiation to give the free carbene, in which complete rearrangement and no O-H insertion is observed.

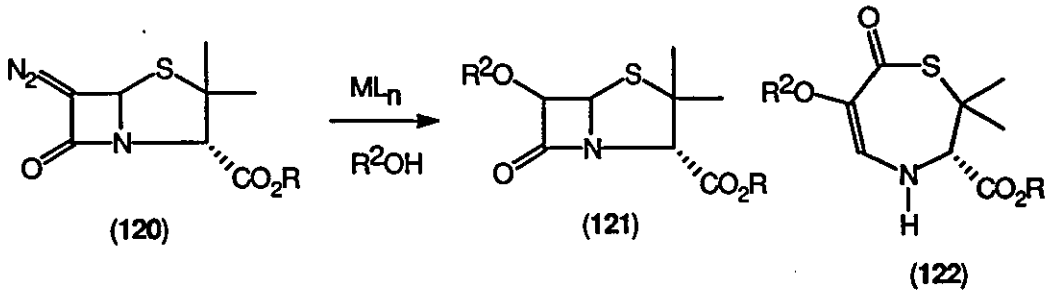
More recently, Kulkowitt and McKervey[52] has used copper acac to form macrocyclic crown ethers (**119**), by the double O-H insertion of α-ω-bisdiazo-esters (**117**) with α,ω-dihydroxypolyethers (**118**, Scheme 25).

Copper acac has also been found to be superior to rhodium (II) acetate in O-H insertion to benzhydryl 6-diazopenicillanate (**120**).[53] Metal catalysed insertion gave a mixture of the wanted O-H insertion product (**121**) and alkoxy thiazepines (**122**). Several alcohols were tried, and the results are summarised in Table 12.



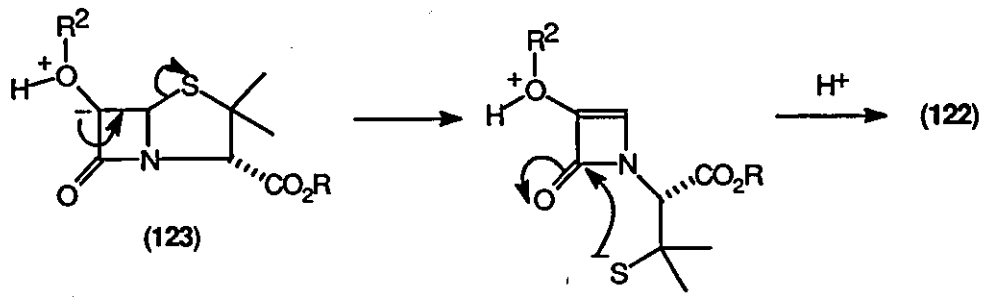
Scheme 25

Table 12



	$Cu(acac)_2$		$Rh_2(OAc)_4$	
Alcohol	**(121)**	(122)	**(121)**	**(122)**
MeOH	56	23	55	19
EtOH	12	76	20	29
Allyl alcohol	9	56	<5	70
tert-BuOH	--	--	6	72
$PhCH_2OH$	--	--	<5	67

In all cases, the yield of thiazepine (**122**) was significant, only when the trap was methanol was good yield of O-H insertion obtained. The thiazepine is envisaged to arise from rearrangement of the intermediate ylid (**123**, Scheme 26).



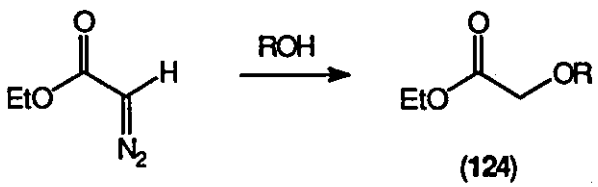
Scheme 26

This rearrangement, would appear to support the intermediacy of an ylid in the metal catalysed O-H insertion process, similar to the photochemical and thermolytic cases.

A few other copper catalysts have been reported as giving high yields of O-H insertion into methyl and ethyl α-diazomalonates.[54] Boron trifluoride etherate has also been reported as an efficient catalyst for the synthesis of α-alkoxy ketones, from α-diazoketones as long ago as 1950.[55] The use of boron trifluoride has been mentioned earlier.

Rhodium (II) acetate was found to be an effective catalyst for the decomposition of diazo compounds in 1973, by Paulissen et al.[14] In his original paper on O-H insertion, ethyl diazoacetate is decomposed in the presence of a variety of hydroxylic components (Table 13).

Table 13



(124)

Catalyst	R	Yield (%), **(124)**
$Rh_2(OAc)_4$	Et	88
	Me_2CH	83
	tert-BuOH	82
	H	80
	CH_3CO	93
$RhCl_3.3H_2O$	Et	64
	tert-BuOH	58
$RhCl(PPh)_3$	Et	49

The Table amply demonstrates the generality and high yields that rhodium mediated decompositions provide. Yields are significantly better than for the copper powder (55%) and copper (I) chloride (Table 9) cases.

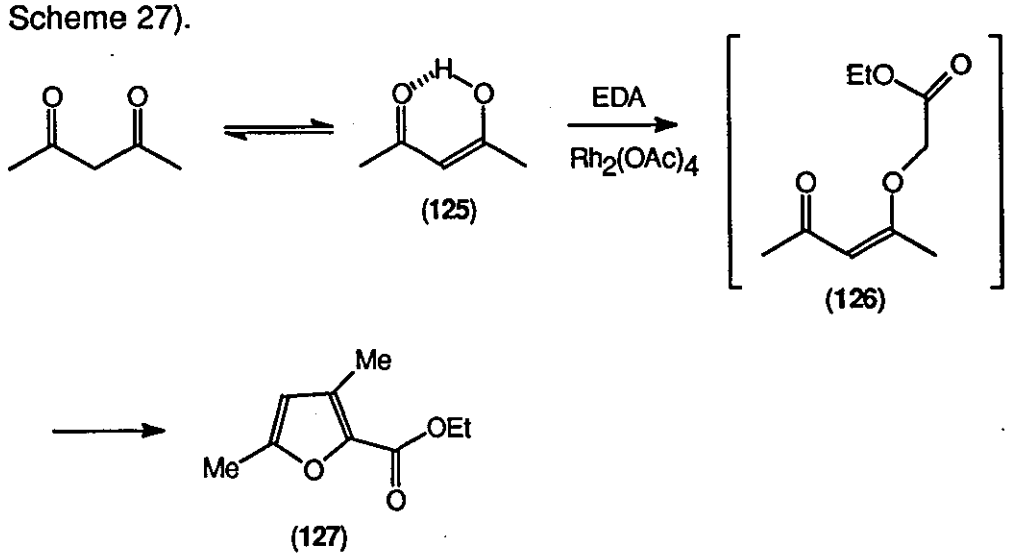
Competition experiments were also run, to compare the reactivities of the three alcohols used for the rhodium bound carbene (Table 14).

Table 14

Alcohol	Rel. Reactivity
EtOH	2.12
iso-PrOH	1.20
tert-BuOH	1.00

These measured reactivities correlate well with those deduced by Kerr for photolytically generated methylene (Table 1). One important point to note however is that alternative products resulting from either 'Wolff' rearrangement, C-H insertion or dimerisation are completely absent.

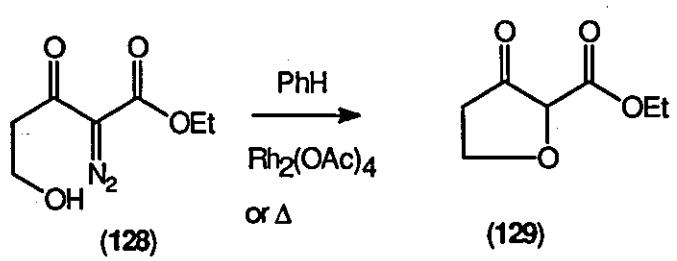
Rhodium (II) acetate has also been reported to be able to effect the insertion of ethyl diazoacetate into the enolate of penta-2,4-dione (**125**).[56] The intermediate vinyl ether (**126**) is not isolated, undergoing rapid, facile cyclisation to the furan (**127**, Scheme 27).



(125) (126) (127)

Scheme 27

The first rhodium (II) mediated *intra*molecular O-H insertion was reported by Moyer et al[57] in 1985, (Scheme 28).

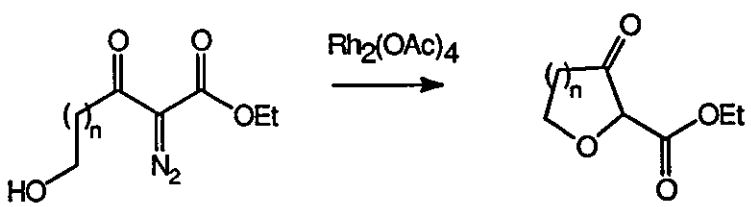


(128) (129)

Scheme 28

The cyclisation of ethyl α-oxo-β-diazo-ω-hydroxypentanoate (**128**) to ethyl dihydro-2-oxofuran (**129**), was affected in excellent yield (quantitative) in refluxing benzene with 1.5 mol% of rhodium (II) acetate.

Attempts to make larger than 6-membered rings by N-H insertion, were hampered by competing C-H insertion to the substituted cyclopentanones. Moody[58] also reports competing C-H insertion, when trying to cyclise α-diazo-ω-hydroxy compounds (**130**) to rings greater than 8-membered (**131**, n>4) (Scheme 29).



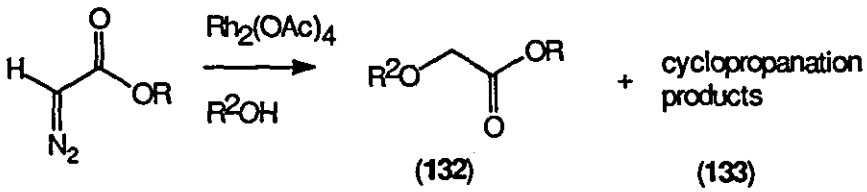
(130) (131)

Scheme 29

For medium size rings, 5-, 6-, 7-, yields tend to be moderate to good (57-80%), however yields of 8- membered rings were poor (12-32%). Attempts to form a 10- membered ring by O-H insertion were unsuccessful[59] resulting in complex product mixtures. Although it is noted that there was some evidence for C-H insertion, to the cyclopentanone. More recently, it has been reported that 8- membered cyclic ethers can be made by O-H insertion, by changing the experimental conditions.[60] Thus, addition of the diazo compound to a dilute solution of rhodium (II) acetate in toluene over 14 hours, leads to a good yield (55%) of the 8- membered cyclic ether.

Noels[61] and workers have studied the decomposition of ethyl, *tert*-butyl and *n*-butyl diazoacetates in a wide selection of unsaturated alcohols, both alkenes and alkynes (Table 15).

Table 15



(132) (133)

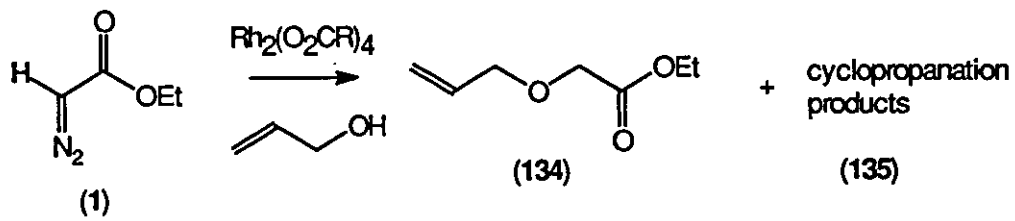
R	R^2	(132)	(133)
a Et	CH_2=CH-CH_2OH	66	15
b	CH_2=CH-CH(Me)-OH	62	13
c ^nBu		68	20
d ^tBu		64	23
e Et	CH_2=CH-$C(Me)_2$-OH	56	14
f ^nBu		64	18
g ^tBu		64	23
h Et	HC≡C-CH_2-OH	77	6
i Me	HC≡C-$(CH_2)_2$-OH	50	19
j Et	HC≡C-CH(Et)-OH	56	20
k Et	HC≡C-$C(Me)_2$-OH	38	58

It was found that the O-H insertion process (**132**) with alkene alcohols, is largely unaffected by steric demand of the alcohol, (a-g). However, with alkynes, when the α-carbon is sterically hindered (k) then cyclopropanation becomes the main reaction pathway. It should be noted that yields from cyclopropanation (**133**) are relatively poor. The only reasonably good yield for cyclopropenation occurs when O-H insertion is dis-favoured (k). Significantly better yields for cyclopropanation and cyclopropenation are observed when the unsaturation is not in competition with O-H insertion[62]

In this study, Noels used several different rhodium carboxylates, all of which give good yields of O-H insertion. Table 16 lists the results of changing the rhodium

(II) carboxylate used on the yield of insertion of allyl alcohol into ethyl diazo-acetate (1).

Table 16



(1) (134) (135)

R	(134)	(135)
CH_3	66	15
tert-Bu	46	19
n-C_6H_{13}	63	14
CH_2-O-CH_3	46	11
CF_3	64	6
C_7F_{15}	63	13
C_6F_5	62	19
Ferrocenyl	66	34
1-Adamantyl	53	17

It is self-evident from the Table that rhodium (II) carboxylates are efficient catalysts for the O-H insertion process.

In conclusion, it can be seen that rhodium (II) carboxylates offer significant advantages over the photolytic decomposition of diazo compounds to produce ethers in good yields. 'Wolff' rearrangement products, which plague the majority of photolysis decompositions, are welcomely absent. In fact, O-H insertion reactions appear to be cleaner, with only ether formation predominating, even when *inter*molecular cyclopropanation may compete as a carbene trapping process.

Chapter Two

Carbenes in Heterocyclic Synthesis

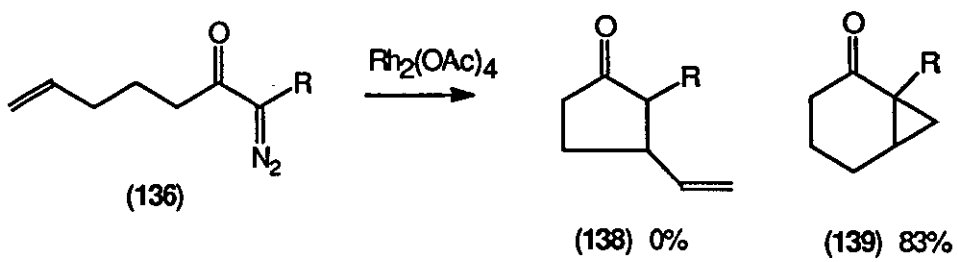
A Look at the Reactivity Towards Different Functional Groups

Introduction

Even though a considerable amount of work has been done on the reactions of metal bound carbenes, relatively little work is available on the chemoselectivity of metal carbenoid mediated reactions. As the studies which have been done are recent, the metal used is invariably rhodium.

Some competition studies on photolytically generated carbenes have already been alluded to and discussed. However nearly all of these are examples of *inter*molecular competitions. Our interest was in the behaviour of rhodium bound carbenes with respect to two or more possible *intra*molecular reactions. The inter- and intra- molecular processes may well be very different.

Ceccherelli[63] has found that attempts to make vinyl cyclopentanones (**138**, R=H, Scheme 30) from intramolecular C-H insertion reactions of α-diazoketones (**136**, R=H) fail. The only product isolated from the reaction mixture being cyclopropane (**139**) in 83% yield.

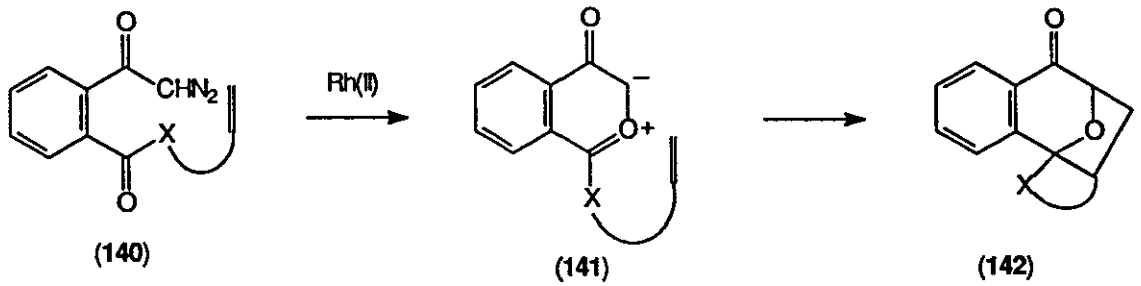


(136) (138) 0% (139) 83%

Scheme 30

Conversely, it was found that when the reacting carbene was derived from a β-ketoester, cyclopentanones, of the general structure (**138**, R=CO_2Et) were isolated in good yield. This observation was borne out by Taber.[64]

Padwa[65] has reported many examples where intramolecular carbonyl ylid formation (**141**) has competed effectively over intramolecular cyclopropanation. The general reaction is given below (Scheme 31).

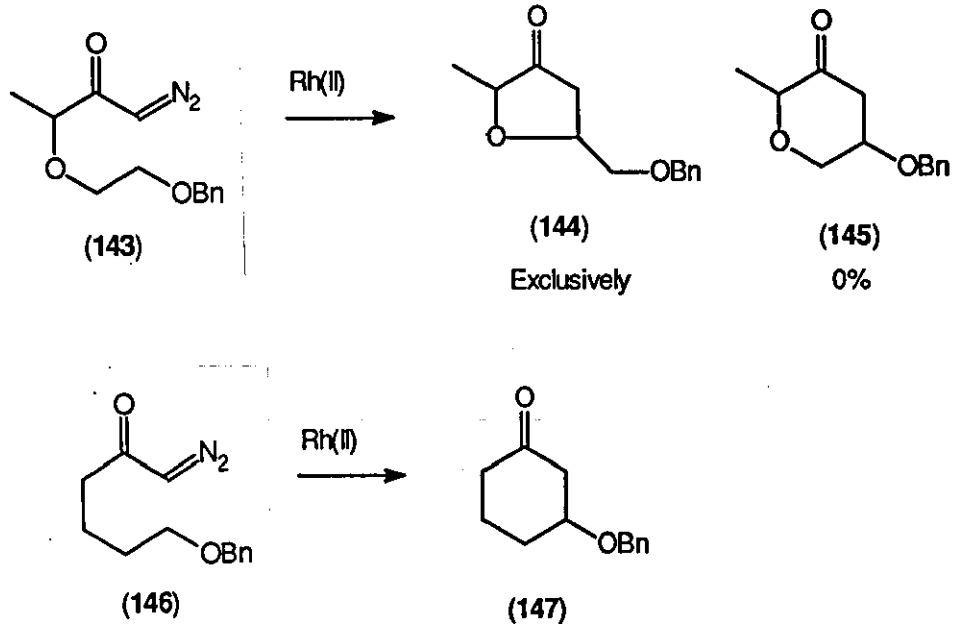


(140) (141) (142)

Scheme 31

Indeed, the only products observed from the reaction of these unsaturated esters (**140**), have been the tricycles (**142**). Formation of tricycle (**142**) arises from attack of the ester carbonyl on the rhodium bound carbene, to give an intermediate ylid (**141**). Subsequent intramolecular 1,3 dipolar addition to the tethered double bond, gives rise to the observed tricycle (**142**).

Adams[66] has shown that C-H insertion is preferred α to oxygen, (Scheme 32). When two or more oxygens are available, the ring formed will be five membered.



(143) (144) Exclusively (145) 0%

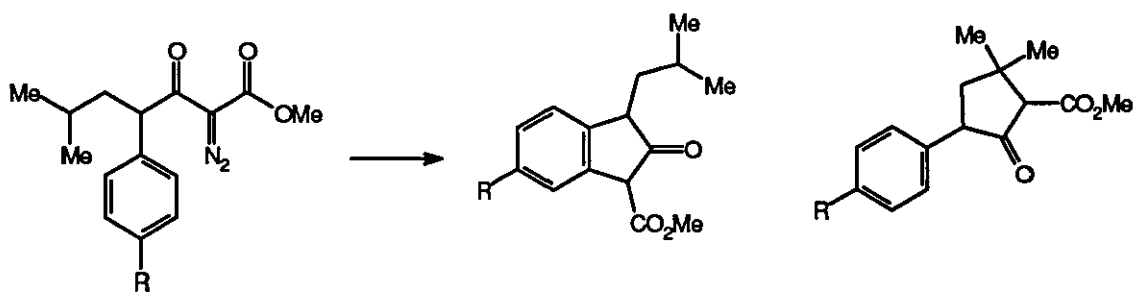
(146) (147)

Scheme 32

The decomposition of diazo compound (**143**), leads exclusively to the five membered cyclic ether (**144**) in preference to the six membered ether, (**145**). If the carbon analogue (**146**) is considered, then the six membered carbocycle (**147**) is the only product formed. Insertion α to oxygen has superseded the usually observed five membered ring formation.[64]

Hashimoto[67] has looked at the effect of phenyl substitution on the competition between aromatic C-H insertion and aliphatic C-H insertion (Table 17).

Table 17



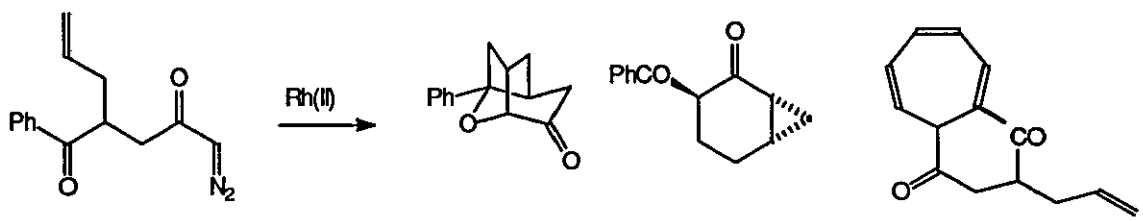
(148) (149) (150)

R	Catalyst	(149)	(150)
Me	$Rh_2(O_2CCPh_3)_4$	>99	1
OMe		>99	1
F		>99	1
F	$Rh_2(OAc)_4$	1	>99

In the cases that were looked at, it would appear that changing the substituent (and hence electronics) has little effect on the outcome of the reaction. However, the catalyst being used - rhodium (II) triphenylacetate - is exceptionally large, and the result observed may well be an artefact of the steric requirement of the catalyst, rather than the electronics of the system. Indeed, it had been reported earlier in 1992,[68] by these workers, that this catalyst exhibited an exceptionally high selectivity for primary C-H insertion versus tertiary C-H insertion, the opposite result to that noted previously.[64]

Rhodium (II) acetate, on the other hand, shows the reverse selectivity, preferring C-H insertion to the cyclopentanone (**150**).

Padwa has also shown that prudent choice of catalyst, may significantly alter the outcome of a reaction (Scheme 33).[69]



(151) (152) (153) (154)

Catalyst	(152)	(153)	(154)
$Rh_2(OAc)_4$	38	38	0
$Rh_2(cap)_4$[a]	43	32	0
$Rh_2(tfa)_4$[b]	0	0	80

[a] rhodium (II) caprolactam; [b] rhodium (II) trifluoroacetate

Scheme 33

The decomposition of diazo ketone (**151**) gives the possibility of three products. Compound (**152**) arises from carbonyl ylid formation and capture of the 1,3 dipole by the double bond. Cyclopropanation of the double bond leads to (**153**). Another potential reaction is cyclopropanation of the solvent benzene, subsequent rearrangement would give cycloheptatriene (**154**).

Decomposition with either rhodium (II) acetate or caprolactam (cap) leads to a mixture of (**152**) and (**153**). No cycloheptatriene (**154**) is observed. However, if the more electron deficient rhodium catalyst is used, rhodium (II) trifluoroacetate (tfa), then only cycloheptatriene is observed, quite a surprising result.

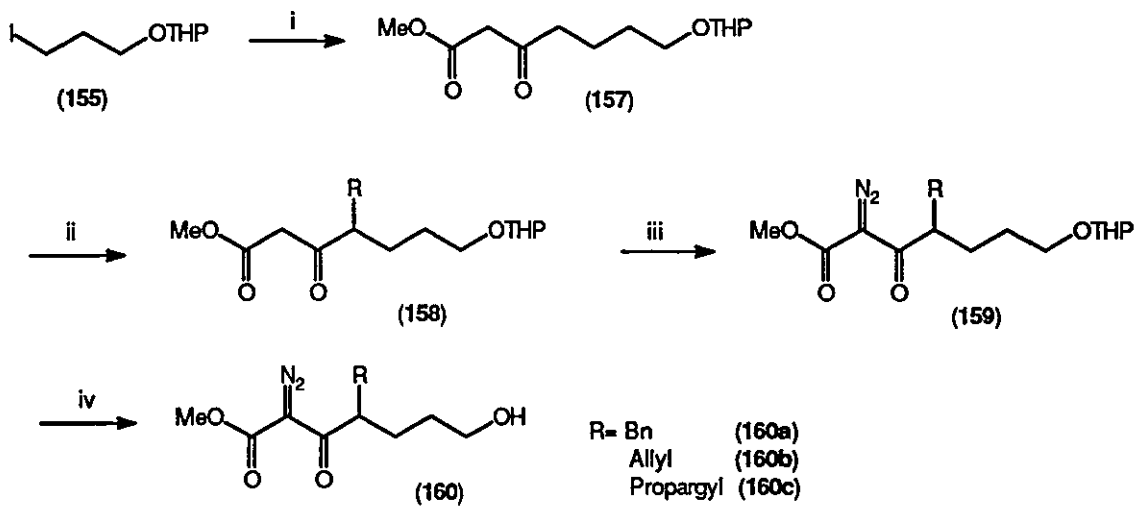
Moody[58,59] has already shown that attempts to make oxygen heterocyclic rings larger than 8- membered, by intramolecular O-H insertion, leads to the production of cyclopentanones. We wished to compare directly the reactivity of rhodium bound carbenes between O-H insertion and other carbene processes.

The synthesis of a selection of bifunctional α-diazo-β-diketones and α-diazo-β-ketoesters would allow the direct comparison of the ability of different functional groups to trap the rhodium bound carbene. Also, we wished to see if changes in catalyst would have the same effect as Padwa has observed, when applied to the O-H insertion process.

The synthesis and decomposition of a range of bifunctional diazo compounds was undertaken, both β-ketoesters and β-diketones and the results of this study are presented here.

Synthesis of α-Diazo-β-ketoesters

A general scheme for the synthesis of bifunctional β-ketoesters was wanted, which would allow the synthesis of several bifunctional diazo compounds from a common intermediate. The route chosen is given below (Scheme 34).



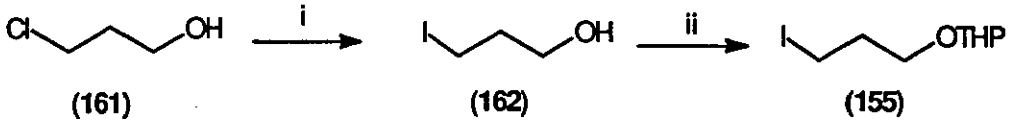
Reagents
i) NaH, BuLi, -78°C, THF, methylacetoacetate (156); ii) NaH, BuLi, 0°C, R-X, THF; iii) Et_3N, TsN_3, MeCN; iv) THF, Acetic acid, H_2O (3:3:2)

Scheme 34

The dianion of methyl acetoacetate (**156**) was treated with tetrahydropyran ether of 3-iodopropanol (**155**), to give the alkylated β-ketoester, methyl 3-oxo-7-hydropyranyloxyheptanoate (**157**), in around 50% yield. This reaction was quite reliable and amenable to scale-up. Subsequent reactions performed on scales up to five grams were successful.

1-Tetrahydropyranyl-3-iodopropanol (**155**) was readily prepared from 3-chloropropanol (**161**) in two steps (Scheme 35). Finkelstein exchange of chloride for iodide was accomplished with sodium iodide in refluxing methyl ethyl ketone overnight. This gave 3-iodopropanol (**162**) in good yield. Protection of the hydroxy group as its tetrahydropyranyl ether (**155**) was effected in good yield (>70%), with dihydropyran in dichloromethane, using pyridinium

para-toluenesulphonate as acid catalyst.



(161) (162) (155)

Reagents
i) NaI, MEK, Δ; ii) DCM, DHP, PPTS

Scheme 35

Original attempts to perform a Finkelstein halide exchange on tetrahydropyranyl protected 3-chloropropanol were characterised by poor yields and loss of material.

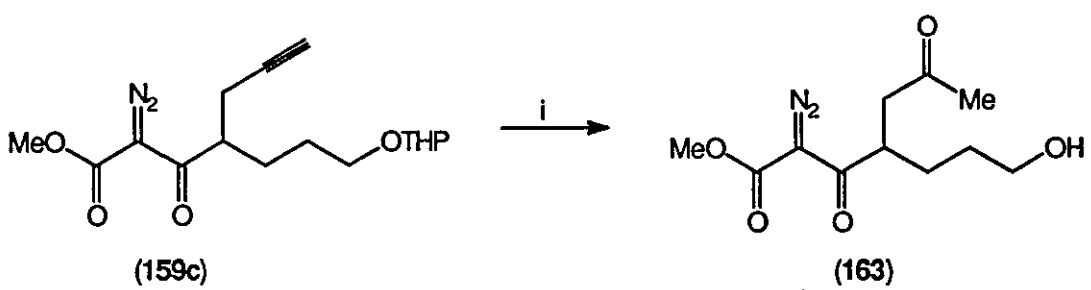
The tetrahydropyranyl ether was chosen as a protecting group as this would allow the synthesis of starting material, methyl 3-oxo-7-tetrahydropyranyloxy-heptanoate (**157**) on a large scale. However, tetrahydropyranyl ethers are chiral and subsequent NMR spectra of products are unduly complicated due to the diastereotopicity of all protons.

The synthesised methyl 3-oxo-7-tetrahydropyranyloxyheptanoate (**157**) is now a common starting material for the production of all the desired bifunctional α-diazo-β-ketoesters.

Alkylation of (**157**) can be achieved in varying yield by treatment with sodium hydride and *n*-butyl lithium at 0°C, followed by a suitable alkyl halide quench. The resulting alkylated products (**158 a-c**), proved very difficult to purify, a lot of material being lost in the process. The problem of purification was thought to be due to the presence of the readily enolisable β-keto functionality. The crude alkylation product (**158 a-c**) was partially purified, by removal of baseline material, by passage through a short silica column, and this 'crude' material subjected to diazo transfer reaction under standard conditions[70]. Once converted to the diazo compound (**159 a-c**) products were easily purified by column chromatography. This observation lends credibility to the idea that it is the enolisable methylene protons which caused purification problems.

Deprotection of the tetrahydropyranyl ethers (**159a-c**) was readily accomplished using acidic aqueous tetrahydrofuran. Thus, heating a mixture of (**159a-c**) in a mixture of acetic acid, THF, water at 70°C for 30 min, gave the deprotected hydroxy compound (**160 a-c**) in 61-94% yield.

Synthesis of methyl 2-diazo-3-oxo-4-(2-oxopropyl)-7-hydroxyheptanoate (**163**) was readily achieved in moderate (48%) yield, by hydroxylation of methyl 2-diazo-3-oxo-4-propargyl-7-tetrahydropyranyloxyheptanoate (**159c**), with mercury (II) sulphate (13 mol%) in aqueous THF at 70°C (Scheme 36).



(159c) (163)

Reagents
i) $HgSO_4$, THF, H_2O, Δ

Scheme 36

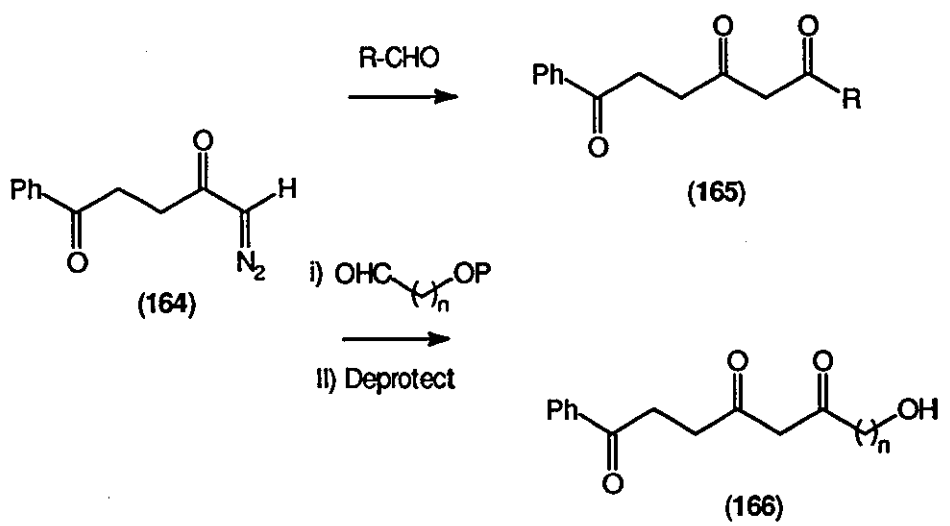
Thus, it can be seen that a selection of bifunctional diazo compounds are readily available by a short (6 steps), reasonably efficient synthesis (15-25% overall yield).

This selection of groups was chosen (**160 a-c, 163**) to allow the direct comparison of the O-H insertion process for other intramolecular processes; aromatic C-H insertion and aromatic cyclopropanation (**160a**), cyclopropanation to an unsubstituted double bond (**160b**) and cyclopropenation to an unsubstituted triple bond (**160c**).

Synthesis of (**163**) would give a direct comparison of Padwa's work, to see if carbonyl ylid formation may compete effectively with O-H insertion, in the same way it has been reported for cyclopropanation.

Synthesis of 2-Diazo-1,3-diketones

A similar, common intermediate approach which was used for the synthesis of β-ketoesters, was sought after for the synthesis of bifunctional β-diketones. Recently, Holmquist et al[71] has published a series of papers on the synthesis of β-diketones using a tin (II) chloride coupling reaction (Scheme 37).



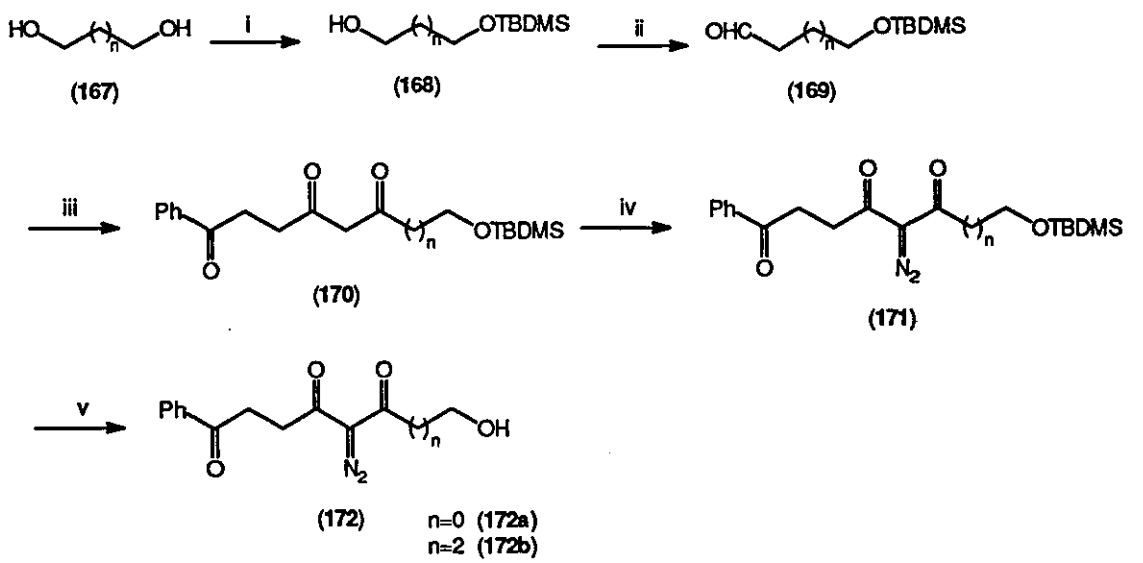
Scheme 37

1-Diazo-5-phenyl-2,5-pentadione (**164**) reacts with an aldehyde in the presence of anhydrous tin (II) chloride to yield a β-diketone of general structure (**165**). Use of this coupling reaction should give an easy route to 1-benzoyl-n-hydroxy-4,6-diketones (**166**).

The final route chosen to two di-functional diazo compounds (**172a, 172b**) is given in (Scheme 38).

α,ω-diols (**167** n=0, n=2) can be successfully protected as their *tert*-butyldimethylsilyl (TBDMS) ethers, (**168**) by treatment with *tert*-butyldimethylsilyl chloride in dichloromethane with triethylamine as base. Yields of protected diol can be maximised by keeping the diol in significant excess (20-30 equivalents). Excess diol may be easily removed by replacement

of the dichloromethane with ether. The diols are sufficiently polar that two layers are formed and the excess diol can be separated off.



Reagents
i) DCM, PPTS, TBDMS-Cl; ii) DCM, PCC; iii) (164), Et_2O, $SnCl_2$; iv) Et_3N, TsN_3, MeCN; v) HF-py, Et_2O, 0°C

Scheme 38

Oxidation of the mono-protected diol (**168**) to the aldehyde (**169**) was most efficiently achieved with a mixture PCC and Celite. However, this simple functional group interconversion proved to be more difficult than anticipated. Yields were unable to be improved above 75% or so. Several oxidizing agents were tried, these are listed in Table 18.

Table 18

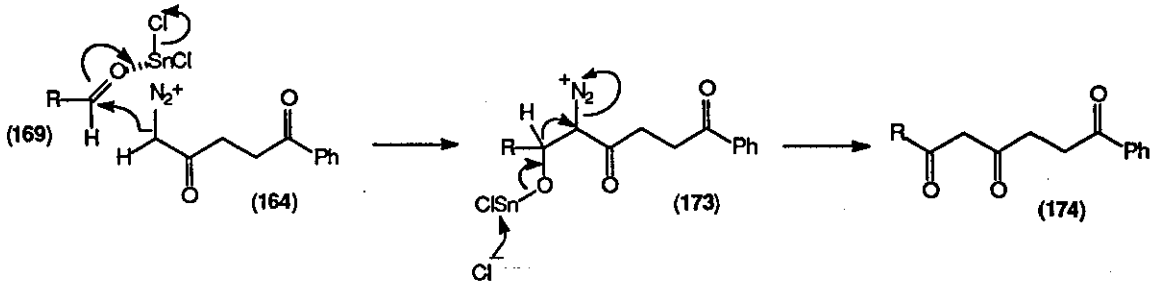
Oxidizing Agent	Yield of Aldehyde (%)
PCC	35-40
PCC/Celite	50-75
$(COCl)_2$/DMSO	56
PDC	starting material recovered
Collin's Reagent*	complex product mixture

* Chromium (VI) oxide/pyridine

The increased yield seen with PCC on the addition of Celite to the reaction mixture, is almost certainly due to increased stirring efficiency. Without the addition of Celite to the reaction mixture, stirring stops after a short while, due to fouling of the stirrer bar by the polymeric chromium complex formed as the oxidation proceeds. Recovery of all the produced aldehyde from this polymeric tar is extremely difficult, so slightly lower yields for the alcohol oxidation are realised.

The low yield obtained from the Swern oxidation is surprising, but several attempts were unable to improve the yield beyond 56%. The use of PCC/Celite, is however somewhat experimentally easier and in this respect preferable.

Reaction of the obtained aldehyde (**169**) with 1-diazo-5-phenyl-2,5-pentane-dione[72] (**164**) in the presence of anhydrous tin (II) chloride affords the β-diketone (**170**). Yields for this reaction are also a little down on those reported in the literature. This maybe due to the additional oxygen present in the aldehydes (**169**) which although protected, may also be able to co-ordinate to the tin (II) chloride. This additional co-ordination will increase the steric demand of the tin, and hence may well lower the efficiency of nucleophilic attack of the diazo (**164**) on this tin complex (Scheme 39).



Scheme 39

Subsequent 1,2 hydride shift and loss of nitrogen from intermediate (**173**), leads to the desired β-diketones (**174**).

Evidence that additional oxygens in the substrate may cause problems in this coupling reaction, comes from the observation that first attempts at this coupling, using tetrahydropyranyl protected aldehydes were unsuccessful. No coupled material (**174**) was isolated in these cases, complete destruction of starting materials being observed.

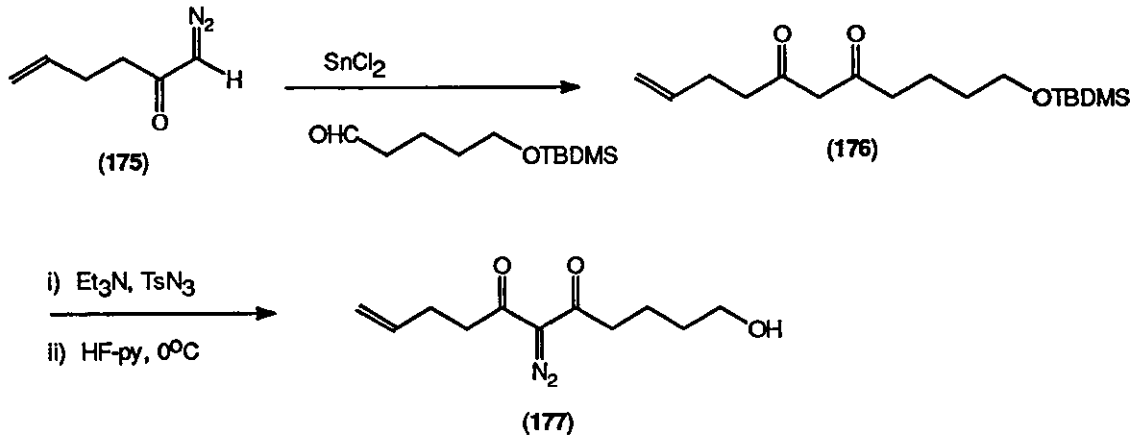
Attempts to perform the tin coupling reaction with *tert*-butyldimethylsilylbutanol (**168**, n=2), however, were all unsuccessful, for no apparent reason. Attempts to make this analogue were aborted after being unable to obtain the required β-diketone (**170**, n=2).

Once again, purification of the β-diketones (**170**) proved to be difficult, due to the readily enolisable central methylene. However, direct diazo transfer under standard conditions on impure material isolated from the tin coupling reaction proved the best option available.

Deprotection of the α-diazo-β-keto protected alcohols (**171**) was unable to be effected by the aqueous acetic acid method used previously (**159** → **160**, Scheme 34). From earlier experiences in this laboratory[73] it was known that tetrabutylammonium fluoride was unsuitable for the deprotection of silyl ethers in the presence of diazo groups. It was considered that this incompatibility was due to the high basicity of the TBAF reagent, not fluoride directly. A 'milder' source of fluoride was required.

Pyridine-hydrogen fluoride was tried and found to be useful for the removal of the silyl protecting group in the presence of the diazo group. However, this deprotection was only able to be carried out in 41-65% yield.

In order to be able to compare the effect of β-diketones with β-ketoesters, the tin coupling reaction was repeated using 1-diazo-2-oxohex-4-ene (**175**, Scheme 40).



Scheme 40

The resulting β-diketone (**176**) was subjected to diazo transfer and deprotection as described before, to yield 6-diazo-1-hydroxy-10-ene-5,7-undecadione (**177**).

The original idea was to attempt to make three substrates (**172**), where the cyclised ring size would be 5,6 or 7 membered (n=0,1 or 2). It was intended that this would allow us to see at what ring sizes, if any, carbonyl ylid formation could compete effectively with O-H insertion. However the difficulty of making the case when n=1 (from 1,4-butanediol) has already been mentioned.

Rhodium Catalysed Decomposition of Substrates

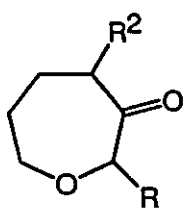
The decomposition of the di-functional α-diazo-β-ketoesters and α-diazo-β-diketones was carried out in refluxing benzene under nitrogen, in the presence of 2 mol% of rhodium (II) catalyst.

In the cases where a reasonable amount of substrate was available (**160a**, **160b**), a small selection of rhodium (II) carboxylate catalysts were tried, to see if any effect on product distribution was observed, similar to that noted by Padwa.

The procedure adopted for the decompositions, was to add the metal catalyst to a refluxing solution of the diazo compound in benzene - 100 mg of diazo compound to 5 ml of benzene. The reaction was followed by thin layer chromatography, and once the starting diazo compound had disappeared, the reaction was stopped.

The benzene was subsequently removed and the crude product analysed by NMR. Distillation (by Kugelrohr) or column chromatography gave the observed isolated products.

In all cases, the major and only observed isolated product was the oxepanone, of general structure (**178**) from O-H insertion.



(178)

The yields for oxepanone formation for the various catalysts tried from these intramolecular competitive decompositions are given in Table 19.

Table 19

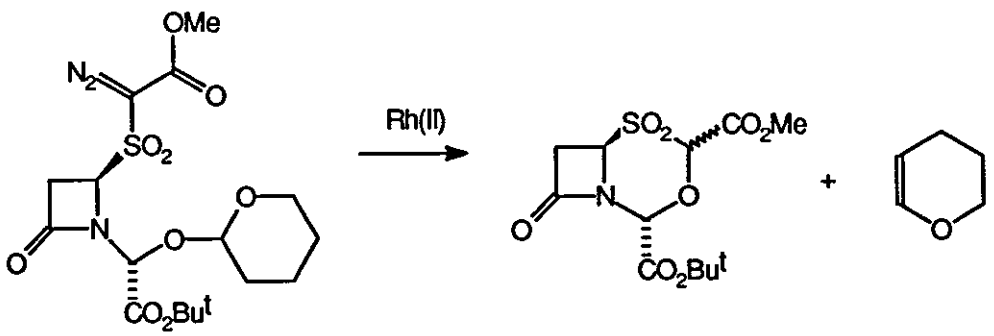
	Catalyst			
Substrate	OAc	$HNCOCH_3$	pfb	$Cu(acac)_2$
160a	53	48	32	--
160b	35	--	60	13
160c	37	--	--	--
172b	23			
177	13*			

* after conversion to TIPS protected enolate; pfb = perfluorobutyrate

The most interesting result from the Table, is that decomposition of (**160b**) in the presence of $Cu(acac)_2$, gave no indication of cyclopropanation onto the alkene present in the molecule. This result seems strange, given the well documented observation of copper being an efficient cyclopropanation catalyst.

Attempts with palladium (II) acetate - well known for its ability to co-ordinate to double bonds - to give cyclopropanation products were equally unsuccessful, no isolable material being salvaged from the reaction mixture. However in this case O-H insertion, to give the oxepanone was not observed either.

Attempt with rhodium (II) acetate to form the cyclopropane with the oxygen still protected as its tetrahydropyranyl ether (**159b**, Scheme 34) were equally fruitless, with no products being isolated from the reaction mixture. Stoodley, however has recently reported[74] O-H insertion into a THP protected alcohol (**180**, Scheme 41), which gave a six membered heterocycle (**181**). Dihydropyran was acting as a leaving group.



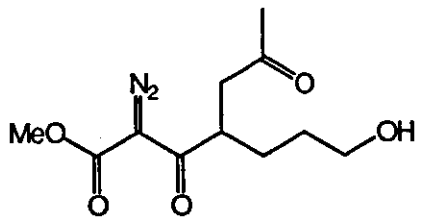
(180) (181)

Scheme 41

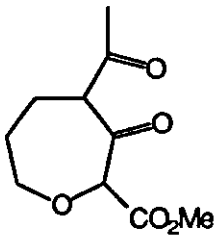
Changing the ligand on rhodium, will have a significant effect on the electron density of the metal centre. Although Padwa reports remarkably high chemoselectivities on changing the ligand at rhodium,[75] this situation is obviously absent in this case. The only apparent effect from changing the electron density at rhodium is to lower the yield of isolated oxepanone (**178**).

If the mechanism of ether formation, is viewed as nucleophilic attack of oxygen on the metal-carbene complex, rather than electrophilic attack of the carbene on the oxygen - hydrogen bond, then perhaps the lack of cyclopropanation derived products is not too surprising. By complexing the carbene to a metal centre, the reactivity is lowered - as the carbene is stabilised, by d_{π}-p_{π} backbonding from the metal centre. The carbene is no longer sufficiently electrophilic to react with an unsubstituted double or triple bond. This may help to explain the case when the complexing metal is rhodium, but it does not explain why no cyclopropanation was observed with copper acac.

In the case of (**163**), no isolable product was obtained. However, NMR on the crude reaction mixture implied that, in this case some other process as well as oxepanone formation had occurred. Attempted Kugelrohr distillation gave a colourless, impure oil, whose structure could not be elucidated, but which had no signal arising from an acetyl group. The residue from the distillation, was assigned as the expected oxepanone, (**179**) although attempts to purify this material better, to allow complete characterisation were unsuccessful.

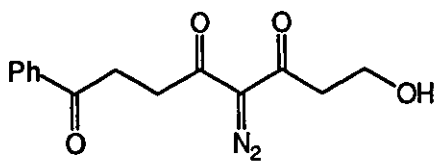


(163)

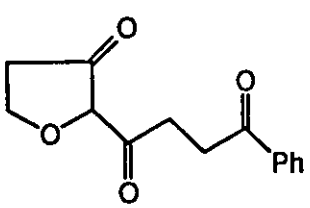


(179)

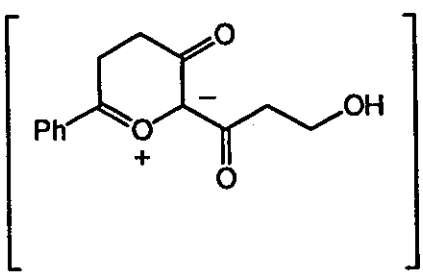
Substrate (**172b**) shows that oxepanone formation proceeds exclusively when the competing process is carbonyl ylid formation. When the product of ether formation is an oxotetrahydrofuran derivative however (Scheme 42), no cyclised product (**182**) was formed.



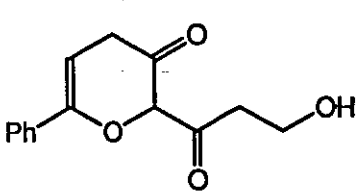
(172a)



(182)



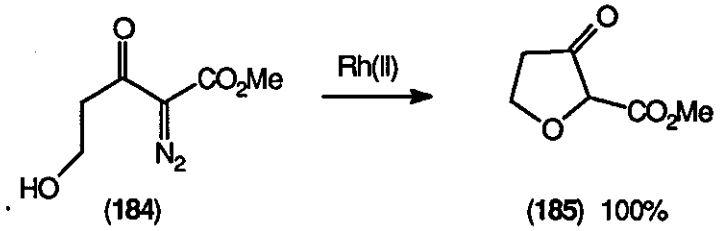
Hydrogen Transfer



(183)

Scheme 42

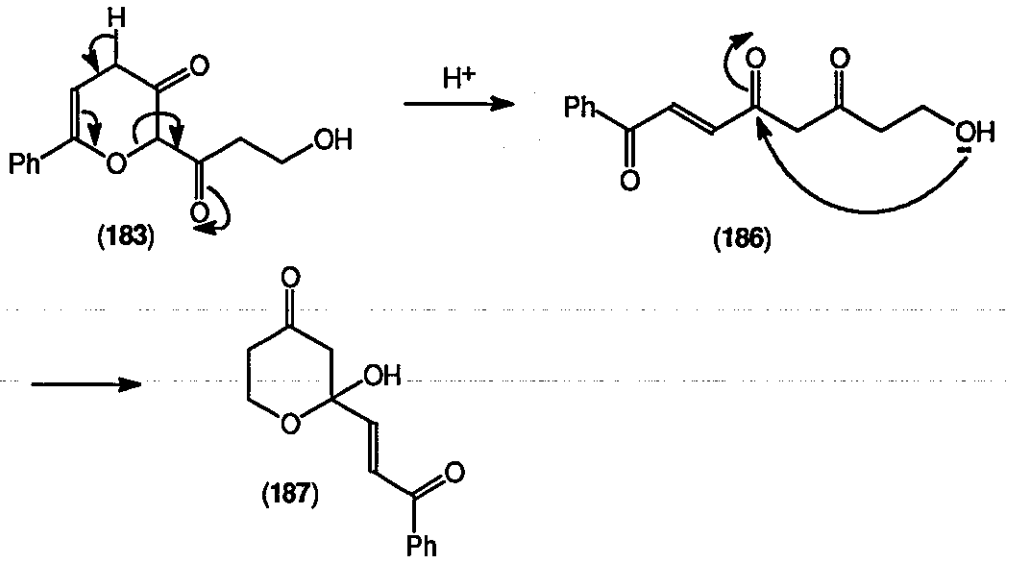
Rapoport has reported the synthesis of oxotetrahydrofurans (Scheme 43) by O-H insertion methodology,[57] so this result does seem a little strange. Thus, refluxing methyl 1-hydroxy-2-diazo-3-oxopentanoate (**184**) in benzene in the presence of 1.5 mol% of rhodium (II) acetate gave cyclisation to (**185**) in quantitative yield.



(184) (185) 100%

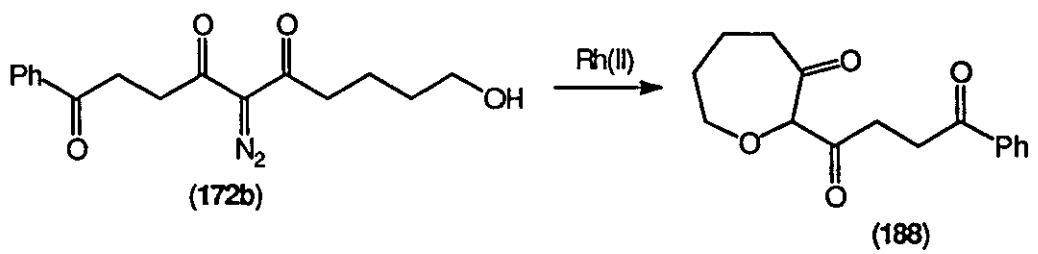
Scheme 43

If carbonyl yield formation had occurred with (**172a**, Scheme 42) then hydrogen transfer[76] in the intermediate carbonyl ylid would lead to cyclic enol ether (**183**). This cyclic enol ether, would be well set up for acid catalysed ring opening to (**186**), as the resultant anion will be very stable and the so formed double bond in conjugation, (Scheme 44).



(183) (186) (187)

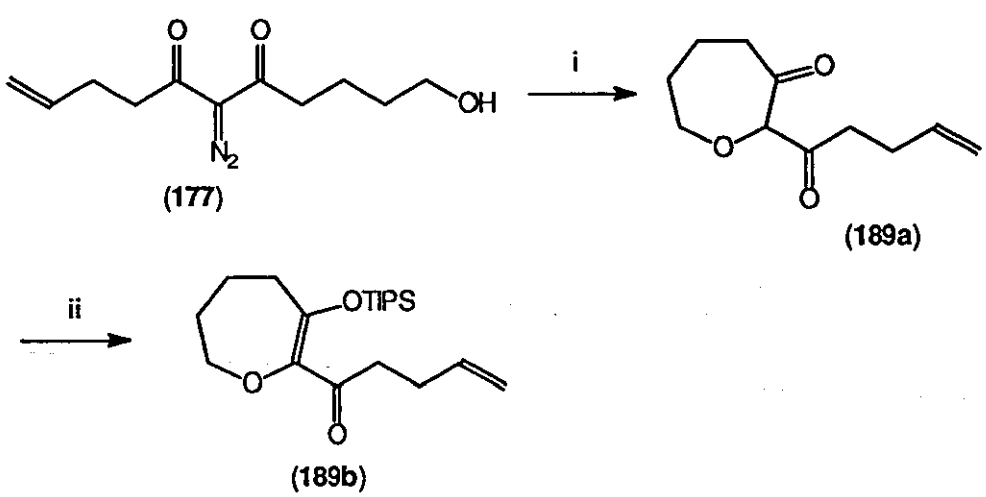
Once protonated, this alcohol (**186**), may recyclise to an oxotetrahydropyran (**187**). Even now, this may react further, with the last carbonyl group leading to a 6,5 spirocycle. Observation of the carbonyl ylid derived enol ether (**183**), was in retrospect somewhat unlikely. Enol ether formation and subsequent decomposition may also be responsible for the low isolated yield of oxepanone (**188**) derived from (**172b**, Scheme 45).



(172b) (188)

Scheme 45

Decomposition of substrate (**177**) with rhodium (II) acetate in refluxing benzene (Scheme 46), leads to the expected oxepanone (**189a**). Evidence for the formation of (**189a**) comes from NMR of the crude reaction mixture. However, attempts to purify this oxepanone were hampered by product decomposition.



(177) (189a) (189b)

Reagents
i) $Rh_2(OAc)_4$, PhH, Δ; ii) Et_3N, Et_2O, TIPS-Tf

Scheme 46

In this case, it was possible to trap the oxepanone as its triisopropylsilyl ether (**189b**), using triisopropylsilyl triflate in dichloromethane, with triethylamine as base. The overall yield for both these steps was poor, only 13%. However, the silylated enol ether (**189b**) was now able to be purified and fully characterised. This proves that the expected oxepanone (**189a**) was indeed formed, but the yield of formation is unknown.

Conclusion

The preference for rhodium bound carbenes to under go O-H insertion seems to be overwhelming. Competing processes may lower the yield of O-H insertion product, but do not usually negate its formation. Even catalysts renowned for cyclopropanation, cannot be enticed to form cyclopropanes when *intra*molecular O-H insertion is an option, *intra*molecular O-H insertion being a very rapid and facile process.

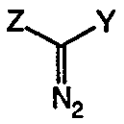
Chapter Three

A Qualitative Look at Rates

Introduction

Even though diazo compounds have been the subject of research for more than a century, few studies have looked at either the net stability of diazo compounds towards decomposition (metal catalysed or otherwise), or the rate of decomposition of diazo compounds and hence their rate of reaction for a given process.

One of the few papers which has looked at the relative stabilising ability of different functional groups α- to the diazo moiety was published by Regitz[77] in 1970. A selection of diazo compounds, of general structure (**190**) were synthesised and their rate of thermal decomposition in mesitylene measured. In this case only the rate of disappearance of starting diazo compound was of importance, the reaction of the subsequently formed carbene has not been considered and indeed, the authors were not concerned with the fate of the carbene formed. Although the *actual* rate of decomposition of the diazo compounds may be effected by the reacting substrate (in this thermal decomposition, the absence of any carbene trap may have a detrimental effect on the actual rate measured) the relative rates of decomposition of a group of diazo compounds may well be the same.



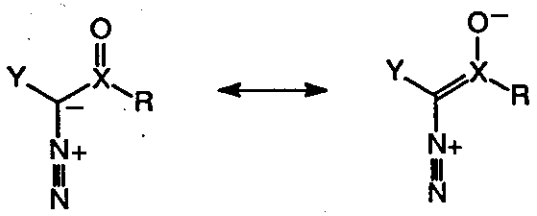
(190)

After suitable kinetic treatment, an order of stabilising ability, for Z was deduced.

$$H > (EtO)_2PO > EtOCO > (Ph)_2PO > Aryl\text{-}SO_2 > MeCO > PhCO > Ph$$

most stable — least stable

The explanation forwarded for the observed stability was related to the electron withdrawing ability of the stabilising group Z. Diazo compounds exist as two main canonical forms, (**191, 192**).



(191) (192)

This structure has little charge delocalisation (only that due to the other stabilising group Y), so is more stable due to beneficial charge interactions. When Z= H, the argument is similar, limited charge delocalisation can occur (via the other stabilising group Y). When X=C, i.e. a diazoketone, charge separation is somewhat more easily achieved. The diazo group is now effectively isolated, and thus appears as more reactive. By this argument alone, diazomethane would be expected to be stable (no charge delocalisation can occur at all), which of course it is not. So, although this explanation predicts the trend of relative stabilities observed by Regitz, it does not fully explain the observed rates *per se*.

Our interest in diazo stabilities was concerned with the rhodium (II) carboxylate catalysed decomposition, and we wished to see if the same pattern of stability would be observed.

The effect on product distribution by changing the ligand on rhodium has already been alluded to. We proposed that changes in the electron density at rhodium (and hence the generated carbene) should have a pronounced effect on the rate of O-H insertion. A few different catalysts have already been described (in Chapter Two) in the competition experiments on bifunctional diazo compounds. In these cases, ligand changes at rhodium had no effect on the outcome of the reaction, but the rate of reaction was not measured. Changes in the ligand at

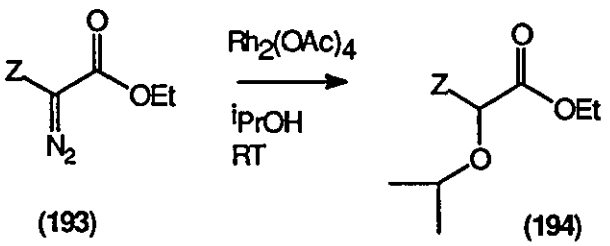
rhodium may well increase the rate of the O-H insertion process and allow us to find a more efficient catalyst than rhodium (II) acetate.

The results from our investigations of the stability of diazo compounds to rhodium mediated decomposition and of the rate of reaction with different rhodium (II) catalysts are presented here. Part of this work was undertaken by Drs. Eric Sie and David Miller[78] and is included here with their permission.

Effect of Substituent Groups

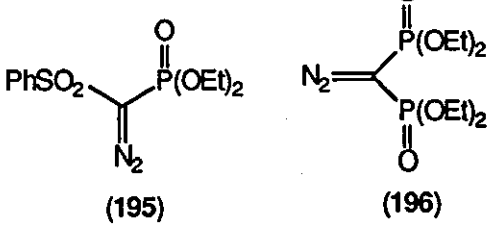
To investigate the effect of the stabilising groups α- to the diazo moiety, a range of diazo compounds (**193**) (largely di-substituted) were synthesised. This work is that of Dr. E. Sie and the synthesis of all these diazo compounds has previously been described.[79] The results of this work are summarised in Table 20.

Table 20



(193) (194)

	Z	Time/h	O-H Insertion Yield (**194**) (%)
a	H	0.5	64
b	MeCO	2.0	Mixture of Products
c	N≡C	3.0	86
d	$PhSO_2$	18.0	64
e	EtO_2C	125	66
f	$(EtO)_2PO$	10 (reflux)	83



(195) (196)

It can readily be seen that the nature of the stabilising group Z has a profound effect on the overall stability of the resultant diazo compound towards rhodium (II) acetate mediated decomposition. The decomposition of ethyl diazoacetate

(a) being moderately fast, with triethyl phosphonodiazoacetate (f) being quite stable; decomposition only occurs after 10 hours heating under reflux in *iso*-propanol.

It is interesting to note that the diazoketone (b), did not give rise to an appreciable amount of O-H insertion product. Indeed, the O-H insertion product was unable to be separated from the other products of decomposition that were present.

Compounds (**195** and **196**) are remarkably stable. Decomposition of (**195**) to afford the O-H insertion product only occurring after 72 hours at reflux in toluene. The same reaction conditions applied to (**196**) gave no O-H insertion product at all, only recovered starting material.

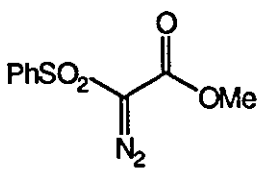
The Table would seem to be largely in reasonable agreement with the results obtained by Regitz. There are however, two notable exceptions, (a) and (c). In the case of (a), no delocalisation of charge, to give the mesomer (**192**) can occur, and as such should be expected to be stable. Likewise for (c). Delocalisation of charge onto the nitrile moiety would be expected to be limited and thus impart reasonable stability to the diazo compound.

There is no obvious reason why these two examples should be radically different. However, this selection of diazo compounds shows, in a similar fashion to the study by Regitz, that simple electron withdrawing arguments alone cannot explain the relative stabilities (either thermal or transition metal) observed for simple diazo compounds.

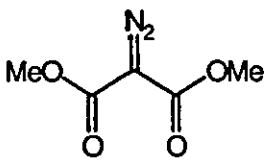
One fundamental assumption, in all of this, is that loss of nitrogen to form the rhodium bound carbene is rate determining. Perhaps, in these later cases, some other factors (albeit, unknown) are involved and the rate determining step in the reaction is no longer formation of the carbene, but some other intermediate. The net result, would be rapid consumption of the starting diazo by rhodium (II) acetate, with the possibility of a shorter perceived reaction time, measured as a function of disappearance of starting diazo compound.

Effect of Rhodium Ligands

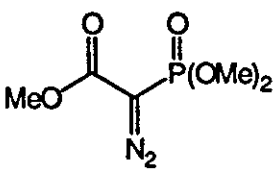
To investigate the effect different rhodium catalysts would have on the rate of O-H insertion, three diazo compounds were chosen which had a broad range of decomposition times with rhodium (II) acetate. Methyl rather than ethyl esters were used, to simplify NMR analysis of the crude reaction mixtures. The diazo compounds chosen for this study are shown below; methyl phenylsulphonyldiazoacetate (**197**), dimethyl diazomalonate (**198**) and trimethyl phosphonodiazoacetate (**199**).



(197)

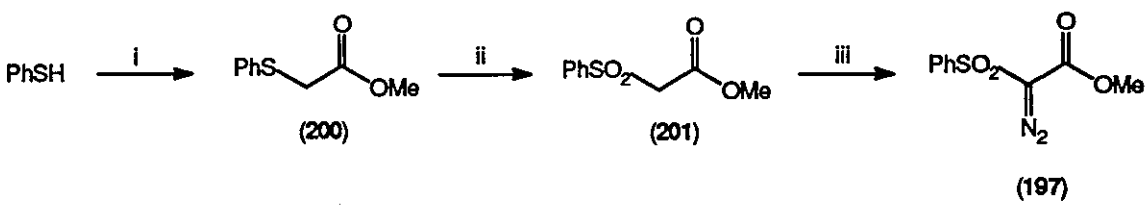


(198)



(199)

Methyl phenylsulphonyldiazoacetate (**197**) was synthesised in a short, three step procedure from thiophenol (Scheme 47).



(200) (201) (197)

Reagents
i) NaH, Et_2O, Methyl bromoacetate; ii) Oxone, MeOH, H_2O; iii) TsN_3, Et_3N, MeCN

Scheme 47

Thiophenol was deprotonated with sodium hydride in ether and the resultant anion quenched with methyl bromoacetate, to give the sulphide (**200**). Oxidation of this sulphide to the sulphone (**201**), proved to be marginally more difficult than expected. Attempts to oxidise the sulphide to the sulphoxide, using aqueous sodium periodate were unsuccessful, leading to re-isolation of starting material. *meta*-Chloroperbenzoic acid was found to be an efficient oxidant for conversion

of the sulphide to the sulphone, but this did not seem to practical on a large scale. Finally, Oxone[a] was tried and although yields were slightly lower than those from *meta*-chloroperbenzoic acid, use of this reagent allowed the oxidation to be performed on reasonable scales.

The sulphone (**201**) was subjected to diazo transfer, using standard conditions and this led to the desired methyl phenylsulphonyldiazoacetate (**197**) in good yield. Recrystallisation of this material led to fine yellow needles. Dimethyl diazomalonate (**198**) was prepared by standard diazo transfer on dimethyl malonate. Trimethyl phosphonodiazoacetate (**199**) was prepared by diazo transfer on trimethyl phosphonoacetate, using sodium hydride as base.[80]

A small selection of five rhodium catalysts were chosen (Table 21). All these compounds had already been described in the literature, either as crystal structures or as suggested catalysts for cyclopropanation.[81] However, the use of any of these catalysts for O-H insertion reactions had not been considered.

Table 21

A	$Rh_2(O_2CCH_3)_4$
B	$Rh_2(O_2CCF_3)_4$
C	$Rh_2(O_2CC_3F_7)_4$
D	$Rh_2(NHCOCH_3)_4$
E	$Rh_2(NHCOCF_3)_4$

Rhodium (II) acetate (A) is commercially available. The others were made by ligand exchange using literature procedures. Thus rhodium (II) trifluoroacetate (B) was prepared by the procedure of Johnson,[82] rhodium (II) perfluorobutyrate (C) by the procedure of Doyle,[83] rhodium (II) acetamide (D) by the procedure of Ahsan,[84] and rhodium (II) trifluoroacetamide (E) by the procedure of Dennis.[85]

The reaction studied was the O-H insertion into *iso*-propanol (Scheme 48).

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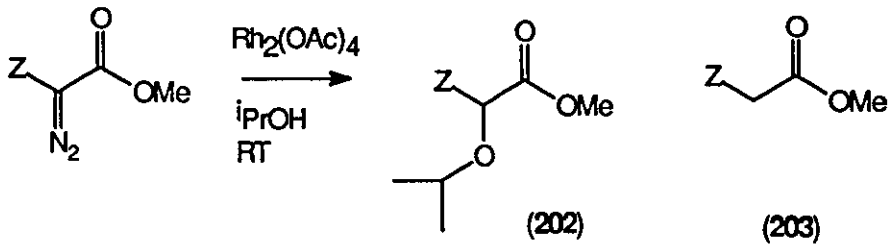
[a] Oxone is potassium peroxymonosulphate



Scheme 48

Thus, the relevant diazo compound (**197-199**) was dissolved in 5 ml of *iso*-propanol and the rhodium (II) catalyst added (2 mol%). The reaction was monitored by thin layer chromatography and timing stopped when no starting diazo compound appeared to be left. The relative amounts of insertion (**202**) and 'reduced' product (**203**) were estimated by ^{1}H NMR on the crude reaction mixtures. Identification of the insertion product was facilitated by the heptet of the *iso*-propyl group, which comes at around δ3.5. Also, the methine α- to oxygen will appear as a singlet (or doublet when coupled to phosphorus) at around δ4.0-5.0. Identification of the 'reduced' product is readily achieved by comparison of NMR data with the diazo compound precursors. The results of this study are presented in Table 22.

It can readily be seen that changes in the ligand on rhodium have a considerable effect on the rate of O-H insertion. Rhodium (II) trifluoroacetate (B) was found to be the slowest of the catalysts tried, while rhodium (II) trifluoroacetamide (E) was the most efficient catalyst. The highest yields of insertion product tended to be with either rhodium (II) acetate (A) or rhodium (II) trifluoroacetamide (E).

Table 22

Catalyst	Diazo	Time/h	Yields(%) (202)	(203)
$Rh_2(O_2CCH_3)_4$	(197)	26.0	77	--
	(198)	96.0	78	--
	(199)	3.5*	20	50
$Rh_2(O_2CCF_3)_4$	(197)	3.0*	--	80
	(198)	8.5*	90	--
	(199)	16.0*	Tr**	75
$Rh_2(O_2CC_3F_7)_4$	(197)	4.0*	--	100
	(198)	4.5*	71	--
	(199)	11.0	34	36
$Rh_2(NHCOCH_3)_4$	(197)	0.5*	61	32
	(198)	1.0*	84	--
	(199)	7.0*	28	--
$Rh_2(NHCOCF_3)_4$	(197)	0.25	89	--
	(198)	2.0	72	--
	(199)	72.0	53	--

* reaction mixture heated to reflux, ** trace amount detected by NMR

Some trends are evident from the Table. For a given series of diazo compounds, the order of relative rates of decomposition is independent of catalyst. I.e. methyl phenylsulphonyldiazoacetate was always the fastest to decompose and trimethyl phosphonodiazoacetate the slowest.

'Reduced' product is generally only observed when the reaction mixture has to be refluxed to bring about decomposition. Some blank experiments were carried out to deduce the origin of this 'reduced' product. In the case of methyl phenylsulphonyldiazoacetate (**197**) and dimethyl diazomalonate (**198**) thermal decomposition in refluxing *iso*-propanol produced *only* the 'reduced' product, with no O-H insertion detected by NMR. However, the time required for this thermal decomposition was long, one and three days respectively.

Consequently, thermal decomposition alone cannot be responsible for the quantity of 'reduced' product observed in a lot of the decompositions where heating to reflux was necessary. This does suggest that the rhodium catalyst plays a part in the production of this 'reduced' product. Perhaps, rhodium mediated decomposition of the substrate does occur, but the higher temperatures involved allow the carbene to free itself from the metal. Once freed in this way, decay to a triplet species and hydrogen abstraction would be a rapid and facile process, although the complete absence of O-H insertion in the blank experiments remains intriguing.

In the case of rhodium carboxylates, as the electrophilicity of the rhodium centre is increased, i.e. the ligand becomes more electron withdrawing, a drop off in reaction rate is observed. Thus changing the ligand from acetate (A) to trifluoroacetate (B) to perfluorobutyrate (C) sees an increase in decomposition times.

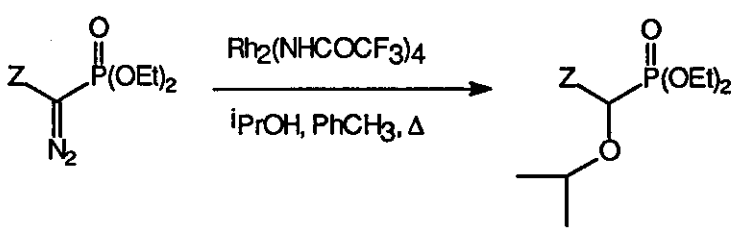
This increase in reaction time is due to the alcohol being able to co-ordinate more effectively onto the now, electron deficient rhodium metal. If this complexation to rhodium is too strong, (catalyst B and C) then the diazo substrate is unable to dislodge the alcohol and co-ordinate to the rhodium. On refluxing the reaction mixture, the alcohol complexation is now readily reversible and diazo substrate co-ordination and subsequent decomposition can now occur.

In the case of rhodium (II) acetamide (D), the electron density at rhodium is increased relative to rhodium (II) acetate (A). Acetamide has an +I effect relative to acetate's -I effect. The consequence of which is that the complexation of the diazo substrate to the rhodium centre is less favorable than would be the case with acetate as the rhodium ligand. This manifests as a decrease in reaction rate. Changing the ligand to trifluoroacetamide (E) is accompanied by the expected increase in rate. However, the increase in rate observed is rather spectacular, being significantly faster than rhodium (II) acetate.

Presumably, a fine balance exists between the ability of the rhodium (II) complexes to co-ordinate the diazo substrate and the alcohol. Rhodium (II)

trifluoroacetamide provides a rhodium centre which is not so electrophilic that alcohol co-ordination is irreversible or slow, but electrophilic enough that co-ordination and decomposition of the diazo substrate is very rapid.

Having found that rhodium (II) trifluoroacetamide was an excellent catalyst for O-H insertion,[86] the decomposition of substrates (**195** and **196**) which were stable to rhodium (II) acetate were tried. It was found that O-H insertion into *iso*-propanol could now be achieved, in good yield, by refluxing the substrate in toluene for two hours (Scheme 49).



Z = $PhSO_2$ (**195**) 79%
$(EtO)_2PO$ (**196**) 81%

Scheme 49

There obviously exists an optimum value for the pKa of the complexing ligand, to achieve facile O-H insertion (Table 23). At high values (>12, acetamide = 12.40) the rate is very slow. Reaction rate begins to slow down again as pKa falls (<5, acetic acid = 4.76). The O-H insertion rate appears to be at an optimum when pKa of the ligand on rhodium is about ten (trifluoroacetamide = 10.36). The use of other ligands with suitable pKa values (for example rubeanic acid, pKa = 10.89) may also prove to be valuable as rhodium (II) catalysts and it may well be possible to exceed rhodium (II) trifluoroacetamide as an efficient catalyst for diazo compound decomposition. Indeed, trifluoro*thio*acetamide may well be an interesting ligand to try.

Table 23

Ligand	Time/h*	pKa of Ligand
CH_3CO_2	26.0	4.76
CF_3CO_2	3.0**	0.25
$C_3F_7CO_2$	4.0**	0.17
CH_3CONH_2	0.5**	12.40
CF_3CONH_2	0.25	10.36

* Time given in Table 22 for decomposition of (197); ** Reaction mixture heated to reflux

In a recent communication Pirrung[87] suggested that the rhodium - rhodium metal bond length may have some effect on the catalytic properties of rhodium (II) complexes. A short list of the rhodium - rhodium bond lengths of some rhodium (II) complexes are given below (Table 24).[88]

Table 24

	Bridging Ligand	Axial Ligand	r(Rh-Rh)/Å
a	CH_3CO_2H	H_2O	2.385
b		pyridine	2.3963
c	CH_3CONH_2	H_2O	2.415
d	CF_3CO_2H	H_2O	2.409
e		ethanol	2.396
f	CF_3CONH_2	pyridine	2.472

From the Table it can be seen that the rhodium - rhodium metal distance varies according to the axial ligand bound on the free co-ordination site of rhodium. No comparison of rhodium (II) trifluoroacetamide with axially bound water ligands is available and it can be seen that pyridine as an axial ligand lengthens the inter rhodium distance (entries a,b). However, rhodium (II) trifluoroacetate (entry d) has a longer inter rhodium distance than rhodium (II) acetate (entry a) but is significantly slower at causing the decomposition of diazo substrates (Table 22).

This result alone supports the idea that the pKa of the complexing ligand has more effect on the observed rate of diazo compound decomposition than the rhodium - rhodium bond distance in the catalytic rhodium (II) complex. The inter rhodium distance will change during the reaction course, complexation of the alcohol to rhodium will have a different effect on the metal bond distance than complexation of the diazo substrate. Although rhodium (II) trifluoroacetamide appears to posses the longest rhodium metal bond, this does not explain the high activity of this catalyst *per se.*

In conclusion, rhodium (II) trifluoroacetamide has been shown to be a highly effective catalyst for the O-H insertion of alcohols into diazo compounds. Fine tuning of the rate of insertion by prudent choice of bridging ligand may well be possible and a more rapid catalyst found. The rate of O-H insertion has been shown to be more closely related to the pKa of the complexing ligand, than the rhodium - rhodium bond distance present in the catalyst.

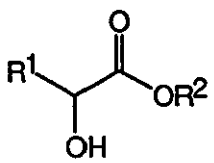
Other processes (such as aromatic C-H insertion)[89] have also been shown by other members of this laboratory to be more rapid with the use of rhodium (II) trifluoroacetamide than rhodium (II) acetate.

Chapter Four

a-Alkoxy and a-Hydroxy Esters
and
cis-Cinnamates from Diazoesters

Introduction

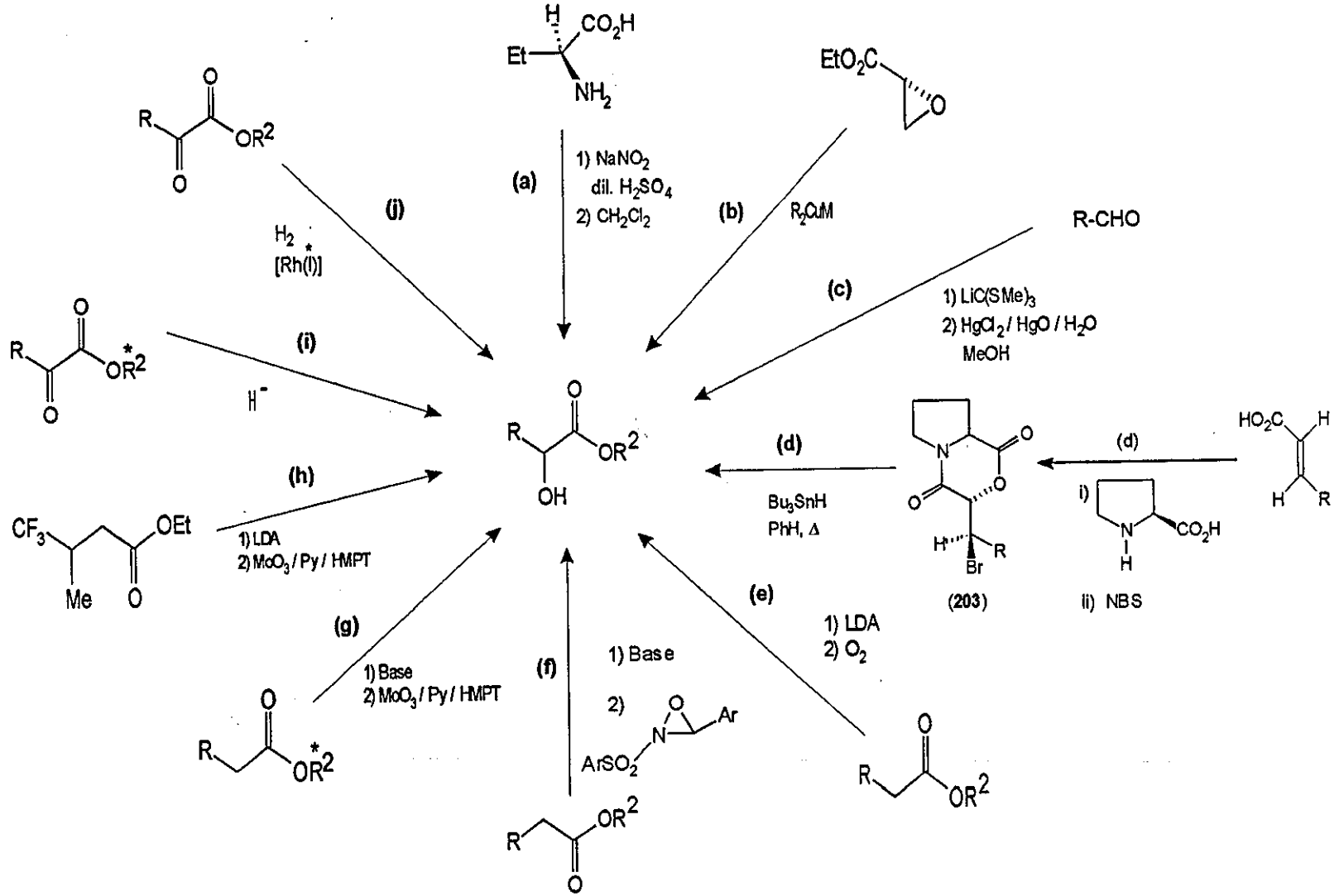
The synthesis of α-hydroxy and α-alkoxy carbonyl compounds, for example α-alkoxy esters (**202**), is of considerable importance. These compounds are useful synthetic intermediates and this structural array is present in many biologically active molecules. In recent years, attention has turned towards constructing this moiety in optically pure form, from achiral starting materials.



(**202**)

Good enantiomeric excesses have been achieved for the production of α-hydroxy ketones, but less work has considered the synthesis of α-hydroxy esters.

This overview of α-hydroxyesters is not intended to be in any way exhaustive, but to give an idea of some of the methods used to synthesise these compounds. The methods used may be broken down into two main groups; reaction at either an sp^2 or sp^3 carbon. More recently, synthetic methods have been described which allow α-hydroxyesters to be made in optically active form. For a more detailed account of specific reactions, the reader is advised to refer to the reference quoted. All the methods considered are summarised below (Scheme 50).


(a)
1) NaNO2
dil. H2SO4
2) CH2Cl2
(b)
R2CuM
(c)
1) LiC(SMe)3
2) HgCl2 / HgO / H2O
MeOH
R-CHO
(d)
Bu3SnH
PhH, Δ
(203)
(d)
i)
ii) NBS
(e)
1) LDA
2) O2
(f)
1) Base
2)
(g)
1) Base
2) MoO3 / Py / HMPT
(h)
1) LDA
2) MoO3 / Py / HMPT
(i)
H-
(j)
H2
[Rh(I)]

Scheme 50

Reaction at an sp^3 Centre

Probably the most obvious and easiest way to synthesise α-hydroxy esters (and acids) is by deamination of the corresponding α-aminoacid (a).[90] Treatment of an aminoacid with sodium nitrite gave the diazonium salt, which rapidly lost nitrogen in the acidic medium to leave the α-hydroxy acid, with retention of configuration at C-2. Esterification was carried out by diazomethane, to give the methyl ester. Treatment of an α-diazoketone[91] with sulphuric acid will also give an α-hydroxy ester. The diazotization of the amino acid therefore, need not necessarily go via the diazonium species. This route lacks generality, as starting materials are limited, although the α-hydroxyester produced will be optically active.

A more general route to α-hydroxyesters is by the ring opening of epoxides by suitable anions, commonly organocuprates (b).[92] This method may be made enantioselective by using an optically pure epoxide, as the chiral centre is defined in the epoxide, not by the subsequent ring opening by the organocuprate.

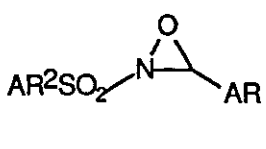
Reaction at an sp^2 Centre

Reaction of an aldehyde with the lithium salt of tris(methylthio)methane, gave a masked α-hydroxyester (c).[93] Desulphurisation with mercury (II) chloride and mercury (II) oxide in aqueous methanol gave the desired α-hydroxyester. Although this method has extensive generality, there is little scope for enantioselectivity. Indirect hydroxylation of α,β-unsaturated acids by asymmetric halolactonisation leads to optically active α-hydroxy acids (d).[94] Treatment of α,β-unsaturated acids with (s)-proline and N-bromosuccinimide gave bromolactone (**203**). Recrystallisation of the crude mixture, gave (**203**) as one diastereoisomer. Debromination with tri-*n*-butyl tin hydride, followed by reflux in 36% hydrochloric acid gave the α-hydroxyacid in 90% optical purity.

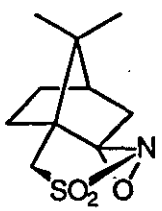
Direct hydroxylation of enolates would seem to be an obvious route to α-hydroxyesters. Indeed, the reaction of the enolates of amides and esters with molecular oxygen was reported in 1975 (e).[95] However, this procedure suffers

from two main drawbacks, firstly all the esters employed contained a tertiary carbon at the α-position. Attempts at direct hydroxylation with systems containing a secondary α-carbon resulted in complex oxidations with accompanying α-carbon cleavage. Secondly, as the incoming electrophile is small, (O_2) the prospect of enantioselective hydroxylation is also small.

Alternative sources of 'electrophilic' oxygen have also been used. Most recently oxaziridines of general structure (**204**) have been used to form α-hydroxy carbonyl compounds from enolates (f).[96]



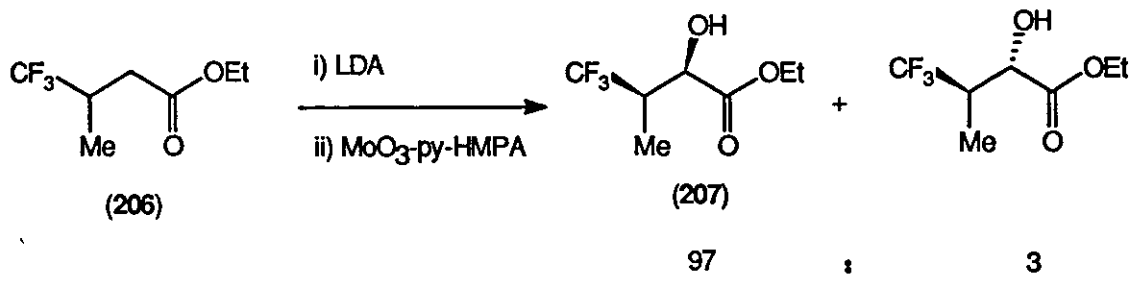
(204)



(205)

Formation of ketone or ester enolates with a suitable base, followed by addition of oxaziridine gave α-hydroxyketones and esters. The use of enantiomerically pure, chiral oxaziridines such as (**205**) has allowed the direct hydroxylation of enolates to be made enantioselective. The actual enantioselectivities observed with esters are however, modest (40-60% ee). Lactones are found to yield higher enantioselectivities (up to 77% ee) than straight chain esters.

Similar results are obtained if molybdenum (VI) oxide is used as the source of 'electrophilic' oxygen (g).[97] In these cases, the chiral induction arises from the use of a chiral ester as substrate. The exception to this is the hydroxylation of ethyl 3-methyl-4,4,4-trifluorobutanoate (**206**, Scheme 51) (h).[98] Treatment with lithium diisopropylamide followed by MoO_3-Py-HMPA complex led to ethyl 2-hydroxy-3-methyl-4,4,4-trifluorobutanoate in 58% yield and 97:3 diastereomeric excess in favour of the 'trans' isomer (**207**). No obvious reason for this high selectivity is apparent, though the authors suggest that the trifluoromethyl group may help to chelate the lithium metal.



Scheme 51

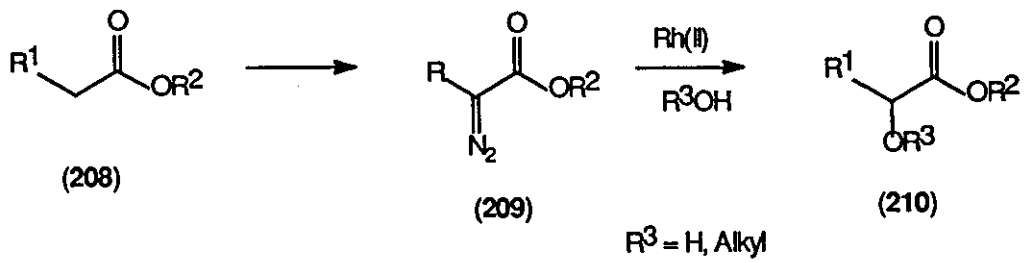
The use of molybdenum (VI) oxide however, requires the presence of co-solvents such as hexamethylphosphoramide (HMPA) or hexamethylphosphorus triamide (HMPT), both of which are irritants and highly toxic. The enantioselectivity observed with both oxaziridines and molybdenum (VI) oxide reactions, tends to be very sensitive to the base used for deprotonation and other reaction conditions, and as such the predictability of these methods is limited.

In terms of optical purity, the most successful method for the synthesis of α-hydroxyesters is the metal hydride reduction of chiral glyoxylates. 8-Phenylmenthol and α-(arylsulphonamido)borneols are among the chiral auxiliaries which have been used for this metal hydride reduction (j).[99] The diastereoselectivities obtained are usually in excess of 10:1, but selectivities as high as 99:1 have been observed. The main limitation of this method is that a chiral auxiliary is required and the appropriate glyoxylate must be able to be synthesised.

The problem of a chiral auxiliary may be overcome by the use of a chiral hydrogenation catalyst and molecular hydrogen. Although a glyoxylate precursor is still required, no chiral auxiliary is needed which may save some considerable synthetic effort. The use of chiral rhodium (I) complexes (k)[100] allows simple esters (such as methyl and *n*-propyl) to be effectively hydrogenated with optical yields as high as 76% and chemical yields of >95%.

Given the limitations of the methods described, we wished to develop a method to both α-hydroxyesters and α-alkoxyesters which was mild, used non-toxic

reagents and was of general applicability. The route chosen is outlined below (Scheme 52).

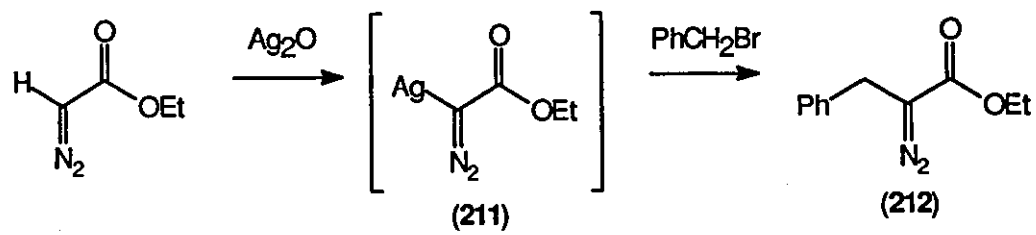


Scheme 52

Thus, rhodium (II) mediated decomposition of a suitable α-diazoester (**209**) in the presence of R^3OH would lead to the desired α-hydroxy or α-alkoxyester (**210**). It was envisaged that α-diazoesters of the general structure (**209**) would be able to be synthesised from the corresponding saturated ester (**208**).

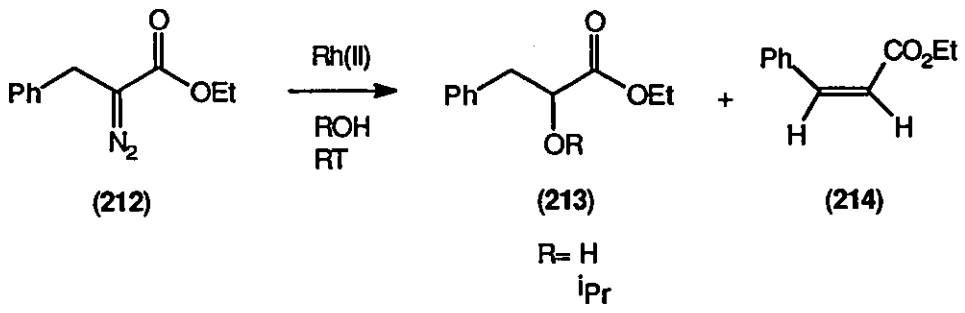
Initial Studies - Cinnamate Formation

Initial studies were conducted using ethyl 2-diazo-3-phenylpropanoate (**212**) which was readily available from reaction of the silver salt of ethyl diazoacetate (**211**) with benzyl bromide (Scheme 53).[101]



Scheme 53

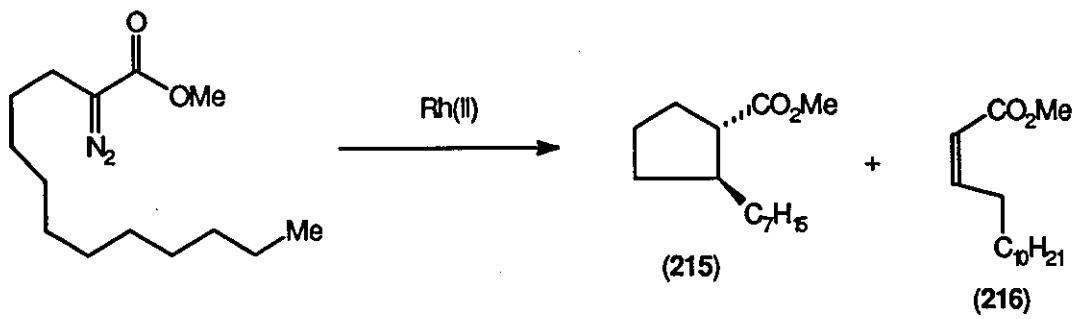
However, subsequent attempts to form the α-alkoxyester (**213**) by rhodium (II) acetate mediated decomposition of (**212**) varied from poor yielding (R=^{i}Pr, 10%) to good (R=H, 65%). The major by-product in all cases was *cis*-ethyl cinnamate (**214**, Scheme 54).



Scheme 54

The formation of α,β-unsaturated ketones and esters from rhodium (II) carboxylate mediated decomposition of diazo compounds has recently been noted by Taber as a by-product of C-H insertion reactions.[102] Taber looked briefly at the relative ratio of desired cyclopentanone (**215**) *versus* unwanted α,β-unsaturated ester (**216**) and how this varied with a small selection of rhodium (II) carboxylates (Table 25).

Table 25

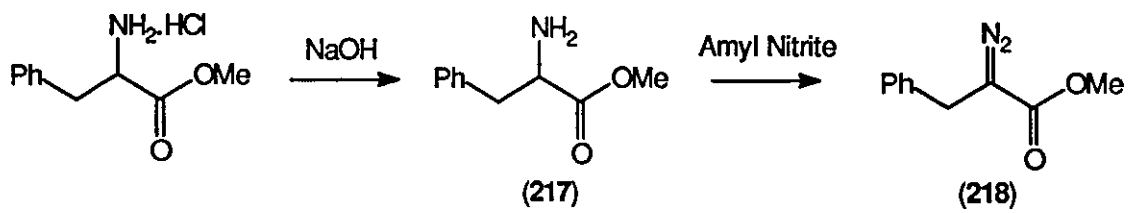


Rh(II) Ligand	Yield*	(215)	(216)
$(CH_3)_3CCO_2$	97	85	15
n-$C_8H_{17}CO_2$	90	78	22
$C_6H_5CO_2$	88	78	22
CH_3CO_2	92	66	34
CF_3CO_2	93	52	48

*Total yield of (**215**) and (**216**)

Taber notes that by NMR analysis the double bond produced was exclusively Z (see later). We undertook to perform a further study, to determine if O-H insertion may compete effectively with cinnamate formation. A series of rhodium (II) catalysts were synthesised by ligand exchange in the usual way, all catalysts used (except rhodium (II) naphthalene-1-carboxylate) have been previously described in the literature.[103]

The synthesis of methyl 2-diazo-3-phenylpropanoate (**218**) was attempted so as to simplify the subsequent NMR analysis on the crude reaction mixture (Scheme 55). Insertion of methanol into this methyl 2-diazo-3-phenylpropanoate (**218**) would give a series of methyl resonances which should be separated and allow a more accurate measurement of product ratios.



Scheme 55

Thus, methyl 2-diazo-3-phenylpropanoate (**218**) was synthesised by diazotisation of phenyl alanine (**217**) with amyl nitrite and acetic acid in chloroform.[104] Phenyl alanine is commercially available as its hydrochloride salt, neutralisation with sodium hydroxide gives the free base which can then be treated with amyl nitrite. However, this short synthesis turned out to be rather troublesome. Purification of the desired diazo compound (**218**) was found to be difficult, and a major contaminant which possessed an amyl functionality (by NMR) could not be separated from the desired material. The insertion of methanol and water into (**218**) gave the expected insertion products in low yield, but attempts to repeat the synthesis of starting material (**218**) were fraught with the problems outlined above. It was decided therefore to use the originally synthesised ethyl 2-diazo-3-phenylpropanoate (**212**) for this study of catalyst ligand effects.

Reaction of ethyl 2-diazo-3-phenylpropanoate (**212**) with diethyl ether presaturated with water in the presence of rhodium (II) carboxylates led to a mixture of α-hydroxyester (**213**, R=H, Scheme 54) and ethyl cinnamate (**214**). The ratio of both products was easily estimated from NMR analysis of the crude reaction mixture. The results of this study are summarised below (Table 26).

Table 26

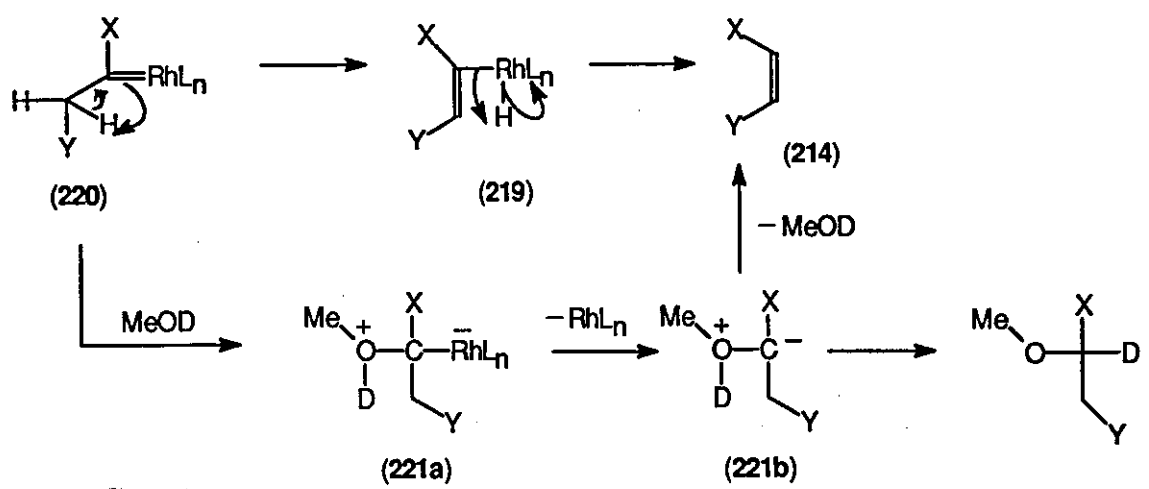
	Rh (II) Ligand	(**213**)	(**214**)	pKa of ligand
1	2-Ph-$C_6H_4CO_2$	16.5	1.0	3.46
2	2,4,6-Me_3-$C_6H_2CO_2$	10.3	1.0	3.44
3	1-$C_{10}H_7CO_2$	8.0	1.0	4.16
4	9-$C_{14}H_9CO_2$	7.6	1.0	3.65
5	CH_3CO_2	4.6	1.0	4.76
6	2-HO-$C_6H_4CO_2$	1.8	1.0	3.00
7	CF_3CONH	1.7	1.0	10.36
8	CF_3CO_2	1.0	2.1	0.25
9	$C_3F_7CO_2$	1.0	5.1	0.17

The ratio of insertion (**213**) to cinnamate formation (**214**) is highly dependent on the rhodium (II) catalyst used. There appears to be no direct correlation between the amount of cinnamate observed and the electron withdrawing ability of the complexing ligand. However, once the pKa of the ligand drops below one (entries 8,9) cinnamate formation is now the preferred process. The results would suggest that sterically demanding ligands (entries 1,2) promote O-H insertion. Where the steric demand of the ligands are similar (entries 5,8) then electronic factors will determine the amount of O-H insertion product observed. However, anthracene which is sterically larger than naphthalene (entries 3,4) leads to a lower proportion of O-H insertion.

Similar results were also obtained when insertion into *iso*-propanol was investigated, although it was not possible to obtain any accurate product ratios from the crude NMR.

Interestingly, analysis of the crude reaction mixture NMR revealed that in all cases a small amount of *trans*-cinnamate (by comparison with authentic material) was formed. However, the amount of *trans*-cinnamate observed was independent of the catalyst used, and always the minor isomer. The origin of this *trans*-cinnamate is unknown, if it was derived by elimination from the first formed O-H insertion product, then as the amount of insertion product observed increased, the amount of *trans*-cinnamate observed would also be expected to rise. Even in the cases where O-H insertion was highest however (entries 1,2), the amount of *trans*-cinnamate observed was still negligible. Even so, the assumption is that the *trans*-cinnamate observed does arise from elimination from either the formed insertion product or intermediate ylid.

The origin of the *cis*-cinnamate is assumed to arise by β-elimination from the intermediate rhodium bound carbene (**220**, Scheme 56). A *cis* geometry maybe reasonably expected as hydride transfer to rhodium may proceed such that substituents X and Y are as far from rhodium and the complexing ligands as possible.



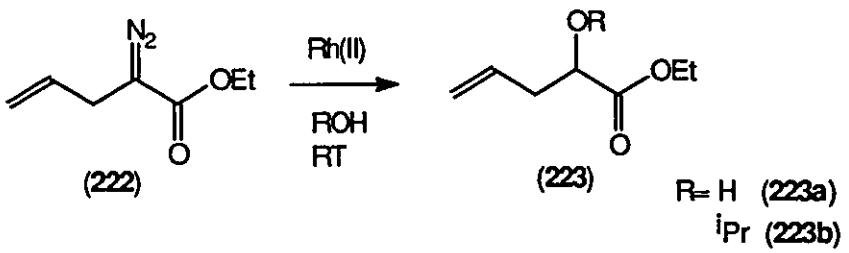
Scheme 56

Subsequent β-elimination of intermediate rhodium hydride (**219**) would lead to the observed *cis*-cinnamate (**214**). To help support the intermediacy of this rhodium hydride species (**219**), O-H insertion into methanol-d_1 should lead to no deuterium incorporation in the observed cinnamate. If the observed isolated

cinnamate contained deuterium, then the cinnamate must have arisen by elimination from the first formed O-D insertion product. Although, if elimination from the insertion product to give cinnamate did occur, one would expect it to proceed to give the more thermodynamically stable *trans* geometry. Insertion into methanol-d_1 did seem to lead to cinnamates which contained no deuterium, however the corresponding O-D insertion product was unable to be isolated in a pure enough state for proper charaterisation. The indication by proton NMR was that an insertion product containing deuterium had been formed but this was not supported by carbon NMR (no triplet carbon was observed). This experiment obviously requires repeating, ideally with freshly prepared ethyl 2-diazo-3-phenylpropanoate (**212**) so the introduction of water from refrigerated storage of the diazo substrate is minimised. Drying of the reagent methanol-d_1 would also be prudent.

The use of methanol-d_1 does not prove the existence of a rhodium hydride species, but does lend credibility to it. Cinnamates may also arise, if the intermediate carbene is attacked by the reacting alcohol to form an ylid (**221a**) (similar to O-D insertion proper). Loss of this ylid from rhodium would give an intermediate (**221b**) which has two major reaction pathways. Firstly, either deuterium shift or, deprotonation at oxygen and then reprotonation at carbon will give the expected insertion product. Secondly, loss of methanol-d_1 from the ylid (**221b**) by deprotonation will now give the cinnamate by-product. Again, though a *trans*-geometry is more likely to be expected than *cis* for this elimination. The implication from the available NMR evidence and use of methanol-d_1, is therefore, that a rhodium hydride and β-elimination are more than likely responsible for the formation of the observed *cis*-cinnamate.

Similar results were obtained on attempting O-H insertion with ethyl 2-diazopent-4-enoate (**222**, Scheme 57). Thus, treatment of (**222**) with rhodium (II) acetate in the presence of either water or *iso*-propanol gave by crude NMR the expected insertion product (**223**). Surprisingly, no elimination to give ethyl pent-2,4-diene was noted. Purification of the crude insertion product was as troublesome as for insertion products (**213**). The product from *iso*-propanol insertion (**223a**) was isolated in 28%, but products from water insertion (**223b**) were unable to be isolated in a pure state.



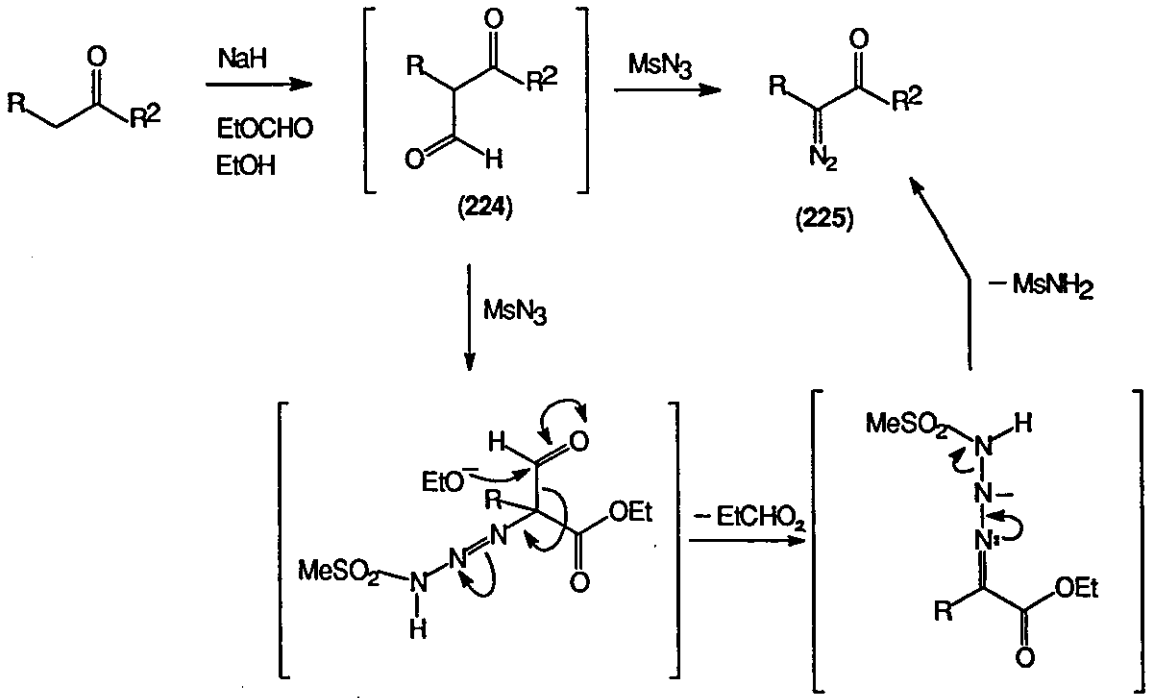
Scheme 57

Synthesis and Decomposition of 2-Diazo-4-phenylbutanoates

To test the propensity of α-diazoesters for β-elimination it was decided to extend the carbon chain by one, and synthesise α-diazoesters derived from 4-phenylbutyric acid. If these α-diazoesters did undergo β-elimination, the resultant double bond would only be in conjugation with the ester moiety, a not too dissimilar case to the α-diazoketone discussed previously. (β-Elimination may be prevented altogether by reducing the carbon chain length by one, giving diazophenylacetates. This approach was also adopted and the results obtained are discussed in Chapter Five.)

The synthesis of α-diazoketones has been described by Taber.[105] Aliphatic ketones may be converted to α-diazoketones in a convenient two step, one pot synthesis (Scheme 58).

The treatment of ketones with sodium hydride and ethyl formate in dry ether (with a catalytic amount of ethanol) under Claisen conditions leads to the condensation product (**224**). This is not isolated, but immediately treated with mesyl azide, which leads to the desired α-diazoketone (**225**). The formyl group is eliminated during formation of the diazo moiety. Introduction of a formyl group leads to a β-diketone which is now sufficiently acidic to undergo diazo transfer with mesyl azide.



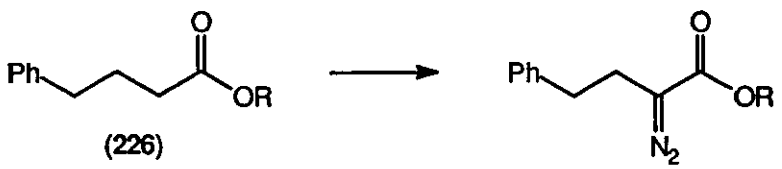
Scheme 58

An improvement to Taber's original method has quite recently been reported by Danheiser.[106] The use of 2,2,2-trifluoroethyl trifluoroacetate as the acylating agent in the first step, was reported to give much higher yields of α-diazoketones than the use of ethyl formate. Danheiser also uses lithium hexamethylsilazide as base rather than the weaker sodium hydride.

Although the pKa of esters is markedly higher than ketones, it was envisaged that use of a strong base for the initial formylation step (such as lithium diisopropylamide for example) would overcome this problem, and this 'deformylative diazo transfer' methodology could be applied to the synthesis of α-diazoesters.

Esterification of 4-phenylbutanoic acid with either ethanol or menthol gave (**226**) in high yield. However, conversion to the α-diazoester (**227**) proved to be rather inefficient (Table 27).

Table 27

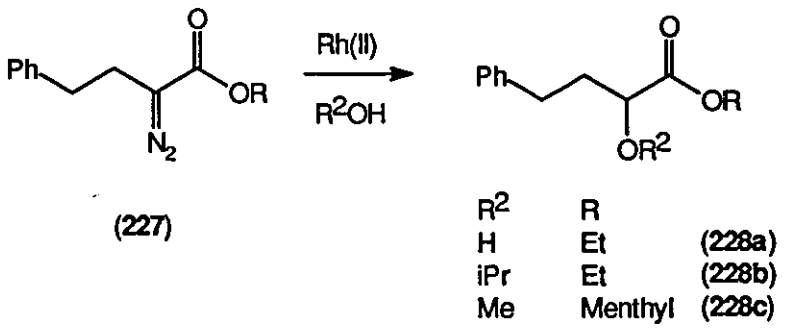


R= Et (**227a**)
Menthyl (**227b**)

R	Base	'Formylating' Agent	Yield (**227**) (%)
Et	LDA[a]	EtOCHO	≈20
Menthyl	LDA	EtOCHO	10
	LiHMS[b]	$CF_3CH_2CO_2CF_3$	19[c]

[a] lithium diisopropylamide, [b] lithium hexamethylsilazide, [c] reaction at room temperature, not -78°C

Synthesis of ethyl 2-diazo-4-phenylbutanoate (**227a**) with lithium diisopropylamide as base, led to an inseparable mixture of desired diazo compound and starting ester (**226**) in around 20% yield. Insertion with either *iso*-propanol or water proceeded in good yield and these insertion products were readily separable from the starting ester (**226**). When the starting ester was menthyl, the yield from the deformylative diazo transfer procedure was reduced further to around 10%. Use of Danheiser's modified procedure with lithium hexamethylsilazide as base, gave a slightly improved yield of 19%, when performed at room temperature. The original conditions employed for ketones, form the trifluoromethyl-β-diketone at -78°C. Attempted reaction of menthyl 4-phenylbutanoate under these conditions resulted in complete recovery of starting material, with no α-diazoester (**227b**) being formed.



(227)

R^2	R	
H	Et	(228a)
iPr	Et	(228b)
Me	Menthyl	(228c)

Scheme 59

Decomposition of these α-diazoesters (**227a**, **227b**) gave the expected insertion products (**228a-c**, Scheme 59) in varying yield. In all three cases no elimination to the α,β-unsaturated ester was observed. The yield obtained for the ethyl derivatives (**227a** and **227b**) was in both cases higher (70 and 62% respectively) than the yield of O-H insertion product obtained for the menthyl ester (**227c**, 27%).

From all these results it would seem that α-diazoesters do not tend to undergo β-elimination to α,β-unsaturated esters preferentially, unless the double bond so produced is extensively conjugated, or the catalyst used for decomposition is strongly electrophilic.

Chapter Five

Diazophenylacetates and a Discussion of Mechanism

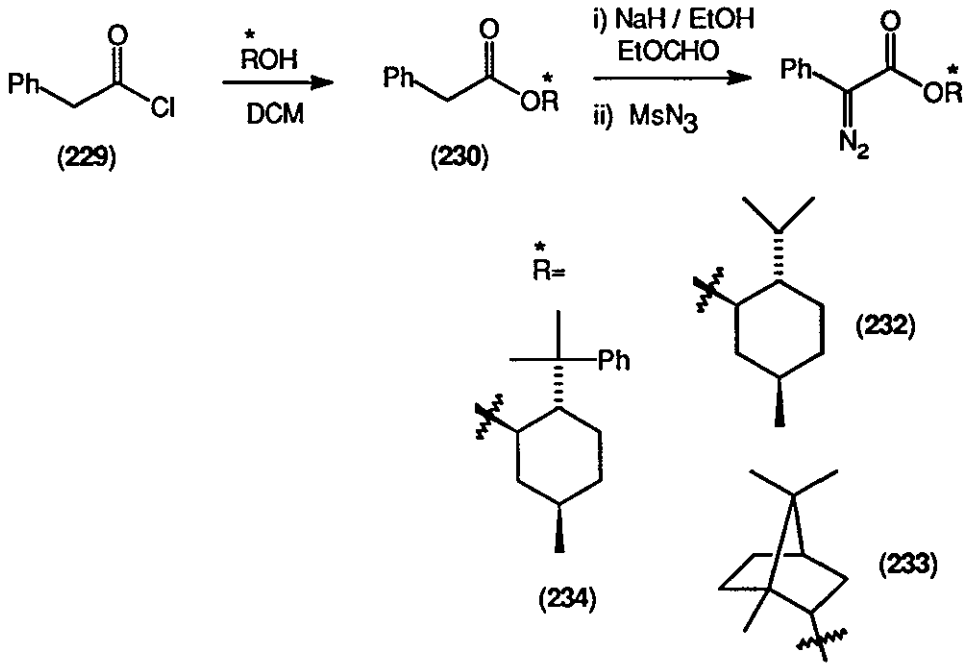
Introduction

It has already been suggested in Chapter Four, that the use of diazophenyl-acetates as substrates for O-H insertion reactions would prevent the major side reaction of β-elimination interfering and lowering the yield of O-H insertion product observed. This Chapter deals with the synthesis and decomposition of a range of diazophenylacetate derivatives. The use of chiral phenylacetates gives the opportunity of chiral induction at the chiral centre formed during the O-H insertion process. Indeed, a lot of work has been done by Taber and others on the relative merits of chiral induction during C-H insertions or cyclopropanations, but the question of chiral induction from O-H insertion has not been addressed. The use of a chiral catalyst and achiral substrates could also be envisaged to give some chiral induction, and indeed this would the preferred method. This Chapter is divided into two main sections, the first deals with the synthesis and decomposition of chiral diazophenylacetates and their insertions into water, methanol and *iso*-propanol. The second section looks at the results from the use of chiral rhodium (II) catalysts. A discussion of the lack of diastereoselectivity and enantioselectivity observed in these catalytic decompositions will be entered into.

Diazophenylacetates

Synthesis

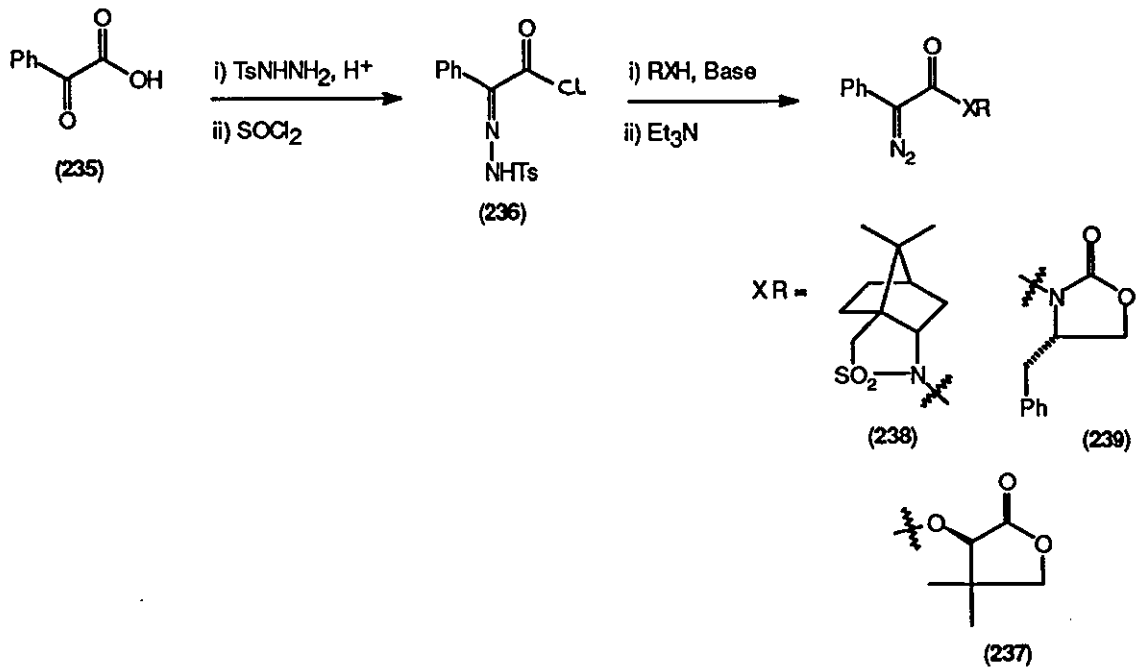
The synthesis of the diazophenylacetates used is given below (Scheme 60). Thus, phenylacetyl chloride (**229**) was treated with the required alcohol and triethylamine in dichloromethane at 0°C. The crude ester (**230**) was purified by either distillation under vacuum (R= Et) or by column chromatography (all other cases).



Scheme 60

Treatment of the purified phenylacetates (**230**) with sodium hydride and a catalytic amount of ethanol, then ethyl formate in dry ether followed by mesyl azide gave the desired diazophenylacetates (**231-233**) in moderate to poor yield (7-41%). The fact that this 'deformylative diazo transfer' methodology works in these cases is due to the increased acidity of the α-methylene group by comparison with the homologues (**226**). However, the cases when the ester group was larger than ethyl, i.e. menthyl (**232**), borneol (**233**) and 8-phenyl-menthyl (**234**) the yield of diazophenylacetate obtained by this route was very poor (12, 7 and 16% respectively). In the case of 8-phenylmenthol (**234**) the reaction mixture had to be refluxed to get the formylation to proceed and achieve any significant conversion (16%) of the phenylacetate to its diazo derivative (**234**).

Three other chiral diazophenylacetates were synthesised. The auxiliaries used for these were, pantalactone, Oppolzer's camphor sultam and Evans' chiral oxazolidinone. The synthesis of these other chiral diazophenylacetates is given below (Scheme 61).



Scheme 61

Phenylglyoxylic acid (**235**) was treated with a solution of tosyl hydrazide in dilute hydrochloric acid, which gave phenylgloxylate hydrazone. Recrystilisation of this crude material gave pure hydrazone which was reacted with thionyl chloride in benzene. After dissolution of the hydrazone had occurred, removal of the benzene gave the desired phenylglyoxylyl chloride tosylhydrazone (**236**). This procedure is identical to that given for glyoxylyl chloride tosylhydrazone.[107] Once acid chloride (**236**) had been made, subsequent reaction with the required chiral auxiliary in the presence of a suitable base led to the desired chiral diazophenylacetates (**237-239**).

Acid chloride (**236**) was reacted with pantalactone in dichloromethane and an excess of triethylamine, this gave diazophenylacetate (**237**). Treatment of camphor sultam or 4-benzyl-2-oxazolidinone with *n*-butyl lithium in dry THF under nitrogen gave the corresponding nitrogen anion. Addition of acid chloride (**236**) quenched this anion and the crude reaction mixture was treated with an excess of triethylamine to generate the diazo group. Work-up and

chromatography led to the required diazophenylacetates (**238** and **239**) respectively. Diazophenylacetate (**238**) was isolated as a crystalline pale yellow solid and a crystal suitable for single crystal X-ray analysis was able to be grown. The crystal structure is shown in Figure 1 and a complete table of atom co-ordinates, bond lengths and angles is listed in the appendix.

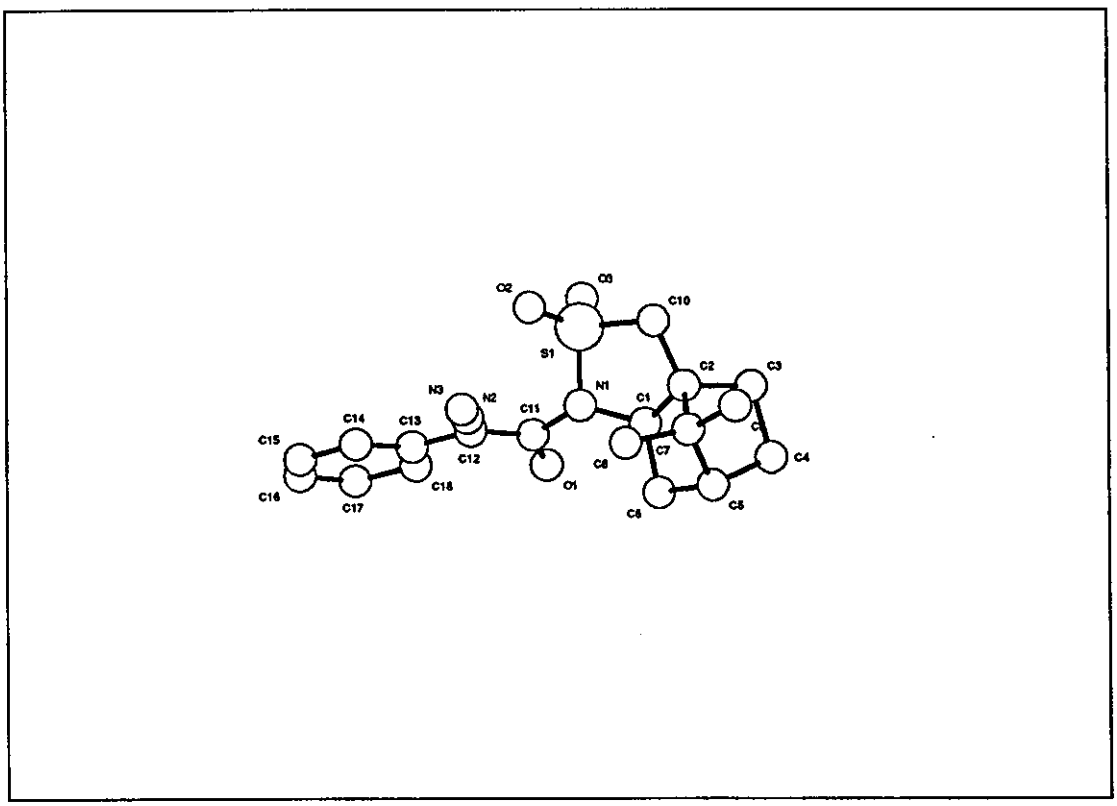


Figure 1

The crystal structure shows that the diazo moiety in this case at least is situated some reasonable distance from the auxiliary and that in this case the prospect of chiral induction seems low.

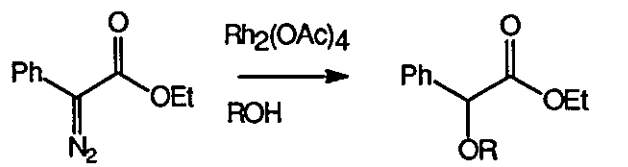
Yields from these acid chloride reactions were generally low and could not be improved beyond 20% or so. The synthesis of these chiral diazophenylacetates (**237-239**) is utilising the Bamford-Stevens reaction[108] to introduce the diazo moiety by alkaline cleavage of the tosyl hydrazone.

It can be readily seen that the synthesis of diazoesters is a non-trivial matter and significant work would be required before these compounds could be considered as viable synthetic intermediates. No general, high yielding method is available - at present - for their construction.

Decomposition

All these auxiliaries were chosen as they have all been shown to exhibit good diastereoselectivity in various reactions.[109] The use of 8-phenylmenthol as a chiral auxiliary in the synthesis of chiral mandelates has already been mentioned in Chapter Four.

The initial feasibility study, prior to the synthesis of these chiral diazo-phenylacetates (**232-234** and **237-239**) looked at the decomposition of ethyl diazophenylacetate (**231**, Scheme 62). Reaction with water and *iso*-propanol in the presence of a catalytic amount of rhodium (II) acetate led to good yields of the expected ethers (**240**).



(231)

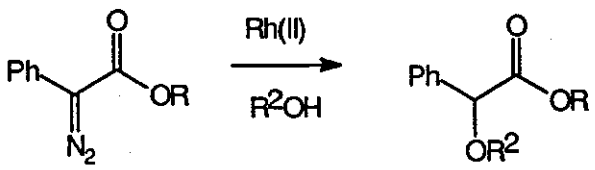
R= H (240a) 96%
iPr (240b) 77%

Scheme 62

These reactions showed that if the possibility of β-elimination was removed then the observed yield of O-H insertion product would rise accordingly. Although the β-elimination product was not always observed or isolated (Scheme 59), the yield of O-H insertion in these long chain cases is generally lower than for the analogous diazophenylacetates. Reactions appeared to yield fewer side products, and isolation and purification of the product ethers was straightforward causing no problems.

Decomposition of all the chiral diazophenylacetates, by rhodium (II) acetate in the presence of water, methanol or *iso*-propanol proceeded in moderate to excellent yield (Table 28).

Table 28



(241)

	R	R^2	Yield (**241**)%
a	menthyl (**232**)	H	88
b		Me	79
c		^{i}Pr	74
d	borneol (**233**)	H	50
e	8-phenylmenthyl (**234**)	H	87
f		Me	67
g		^{i}Pr	79
h	pantalactone (**237**)	H	32
i		^{i}Pr	42
j	camphor sultam (**238**)	Me	15*

* isolated yield of one diastereomer, the other was unable to be obtained in a pure state for analysis

For chiral auxiliaries which contain only carbocyclic rings (a-g) the yield of O-H insertion product is high (>67%). In the cases where the auxiliary contains some heteroatoms (h-j) the yield obtained is significantly reduced, if observed at all. For diazophenylacetate (**238**), only the O-H insertion product from methanol was obtainable. In all other cases (water, *iso*-propanol) no insertion product was detected in the crude reaction mixture or could be isolated. Attempts to obtain any O-H insertion product from diazophenylacetate (**239**) were also unsuccessful. Decomposition by rhodium (II) acetate in the presence of either

water or methanol resulted in complete decomposition of the diazo compound, but no formation of the desired ether. There is no obvious reason why these heteroatom containing auxiliaries are less efficient in the O-H insertion process. Although the heteroatoms present may compete for available binding sites on rhodium, any complexation must be reversible and subsequently displaced by the diazo moiety which needs to bind to rhodium in order to react. The possibility of the heteroatoms present reacting with the rhodium bound carbene cannot be overlooked. All these auxiliaries contain oxygen as either a carbonyl or sulphone grouping. Rhodium (II) acetate has been used successfully for carbonyl ylid formation and rhodium is generally regarded as an oxyphilic metal. Intramolecular (geometry permitting) trapping of the carbene by these substrate oxygens would lower the amount of O-H insertion product detected.

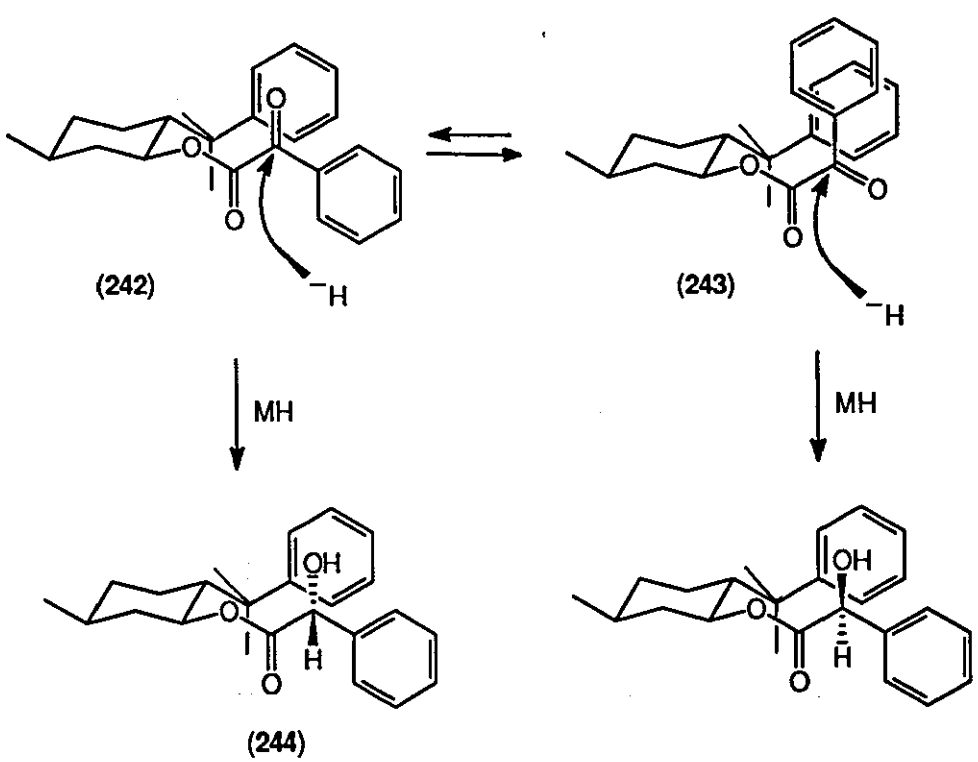
Intermolecular trapping of the rhodium bound carbene by substrate rather than alcohol is less likely due to the vast excess of alcohol which existed in the reaction mixture. However, if reaction with the substrate alcohol is particularly slow then other reaction pathways may become viable processes. For example, attempts to repeat the decomposition of (**234**) in the presence of *iso*-propanol led to isolation of the water insertion product (**241e**), even after drying of the *iso*-propanol with calcium hydride overnight. A similar problem was encountered on attempting the insertion of *tert*-butanol into diazophenylacetate (**234**). Only the product from water insertion could be isolated. Again, dry *tert*-butanol led to the same result. These results show that in this case at least, the reaction with water is significantly faster than either *iso*-propanol or *tert*-butanol and insertion into these alcohols cannot compete effectively with water. In this case, the problem with water was put down to water actually absorbed by the substrate diazo compound (**234**) itself (from refrigerated storage) rather than water introduced from reagents or the atmosphere.

The presence of any diastereomeric excess from chiral induction should be immediately apparent from inspection of the proton NMR spectra of the crude reaction mixture. The only cases where any chiral induction was noted were when insertion into *iso*-propanol was achieved (c, g, i). The diastereomeric excess noted, was however, very small (1.12 - 1.19 :1) and was largely independent of the chiral auxiliary used. A similarly small diastereomeric excess

was also noted with diazophenylacetate (**238**, j). When the auxiliary is 8-phenylmenthol (**234**) this result is in stark contrast to diastereomeric excesses reported for the metal hydride reduction of the analogous glyoxylate (Scheme 50).

A Discussion of Mechanism

The reacting centre in both the metal hydride reduction of the glyoxylate and the rhodium catalysed decomposition of the diazo substrate (**234**) is an sp^2 carbon. It was envisaged that these two systems might well show similar behaviour. In the metal hydride case, the model generally put forward to explain the high diastereomeric excess observed is given below (Scheme 63).

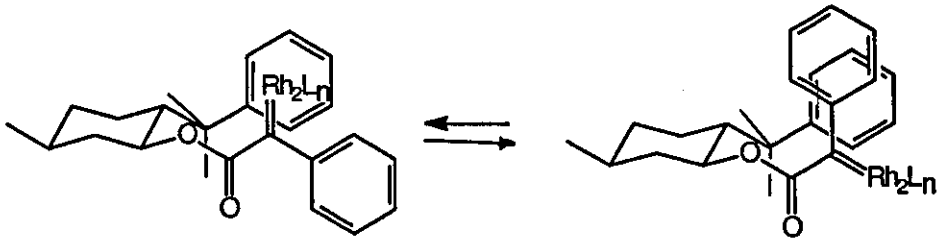


Scheme 63

The ground state conformation of the phenylglyoxylate is generally regarded as being (**242**) with the two phenyl rings co-planar. Rotation about the central carbon-carbon bond leads to the conformer (**243**) with the keto carbonyl planar

with the phenyl ring at C-8. If one of these two confomers is preferred over the other then reduction with a suitably hindered metal hydride will lead to an observed diastereoselectivity.

Attack of the metal hydride on (**242**) leads to (**244**). An increase in steric bulk of the incoming metal hydride would be expected to result in a larger observed diastereomeric excess, if the conversion of (**242**) ⇌ (**243**) is slow at the temperature of the reaction. Indeed this is the case, changing the metal hydride from diisobutylaluminium hydride to potassium tributylborohydride increases the selectivity from 6.7:1 to 32:1 in favour of attack from the front face (**242**) as predicted by the model. The hybridisation of the rhodium bound carbene is proposed to be sp^2, and thus it was envisaged that the intermediate carbene may show a similar preference for one of the two possible analogous conformers (**245** and **246**). In this case, the conformer (**245**), was expected to be the dominant one for the ground state of the rhodium bound carbene, due to the larger steric bulk of the bound rhodium (II) acetate over the phenyl moiety.

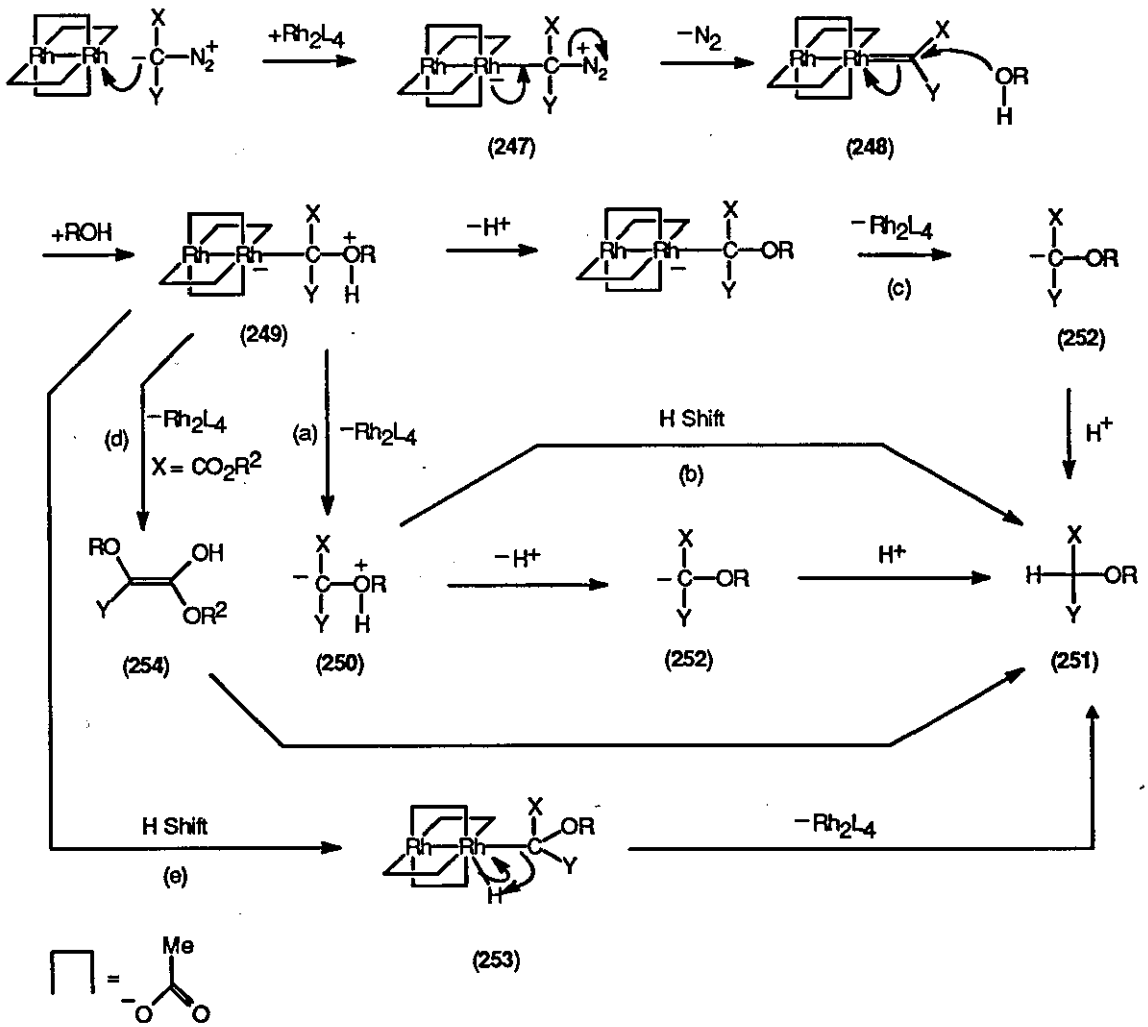


(246) (245)

The rhodium bound carbene however, is already at a relatively high energy (with respect to the starting diazo compound), and as such the two confomers (**245** and **246**) may now appear close in energy, so that attack on either is now equally likely. Also, the incoming nucleophile in the O-H insertion process is small and may only meet limited steric buffeting by the phenyl group on C-8, probably insufficient to prevent backside attack on either conformer if it was indeed predominant. The net result in either case would be no observable diastereoselectivity. However, in some cases (noted above) a small amount of selectivity is observed. An explanation for this may be put forward from a more detailed look at a possible mechanism for the O-H insertion process.

A brief and rather simplistic view of bonding will be discussed, only in an attempt to clarify the position with regards to the subsequent mechanistic discussion. Much theoretical work has been done on this subject and it is well beyond the scope of this discussion.[110] Rhodium (II) acetate has the commonly called lantern structure, and as such has a free co-ordination site available to appropriate Lewis bases. Each rhodium is both co-ordinately and electronically unsaturated having a total of 15 electrons: 9 of its own and 6 from four bridging acetate ligands. These are shared accordingly, 8 electrons fill the 4 sp^3d^2 hybrids which make-up the rhodium - ligand bonds and 1 electron occupies a 5^{th} sp^3d^2 hybrid orbital which makes the rhodium - rhodium metal bond. The remaining 6 electrons occupy the three remaining d orbitals and can be considered for our purpose as non-bonding. Thus each rhodium atom within the complex has 16 electrons, the last electron coming from the shared metal sigma bond.

Although no extensive mechanistic studies have been done on these rhodium (II) acetate catalysed reactions, a plausible mechanism which helps to explain the results above can be considered (Scheme 64).



Scheme 64

The initial step in the process must be the co-ordination of the diazo carbon to the vacant sp^3d^2 hybrid orbital on rhodium. The diazo compound acting as a Lewis base. This co-ordination must be in competition with complexation by free alcohols and thus will have some effect on the rate of reaction; strongly bound alcohols will not allow the diazo compound to bind to the rhodium at normal temperatures and reaction is only seen as the temperature of reaction is increased (see Chapter Three). Initial complexation gives the complex (**247**) which will carry an overall negative charge. Loss of nitrogen from this complex will be facilitated by electron donation from rhodium, i.e. d_π-p_π backbonding from filled d orbitals to the empty p orbital on carbon. This gives the neutral, stabilised carbene

complex (**248**). The effectiveness of this backbonding will determine how stable the resultant carbenoid is and how fast nitrogen will be lost. The substituents on carbon, will influence the energy of the empty p orbital and its availability for receiving electrons. Likewise, the energy of the filled d orbitals on rhodium will be influenced by the complexing ligands, and this will determine the net availability of these d electrons to be donated for pi bonding. As the energy difference between these two participating orbitals increases, the amount of backbonding present (and hence stabilising effect) will decrease and the resultant carbenoid will be more reactive.

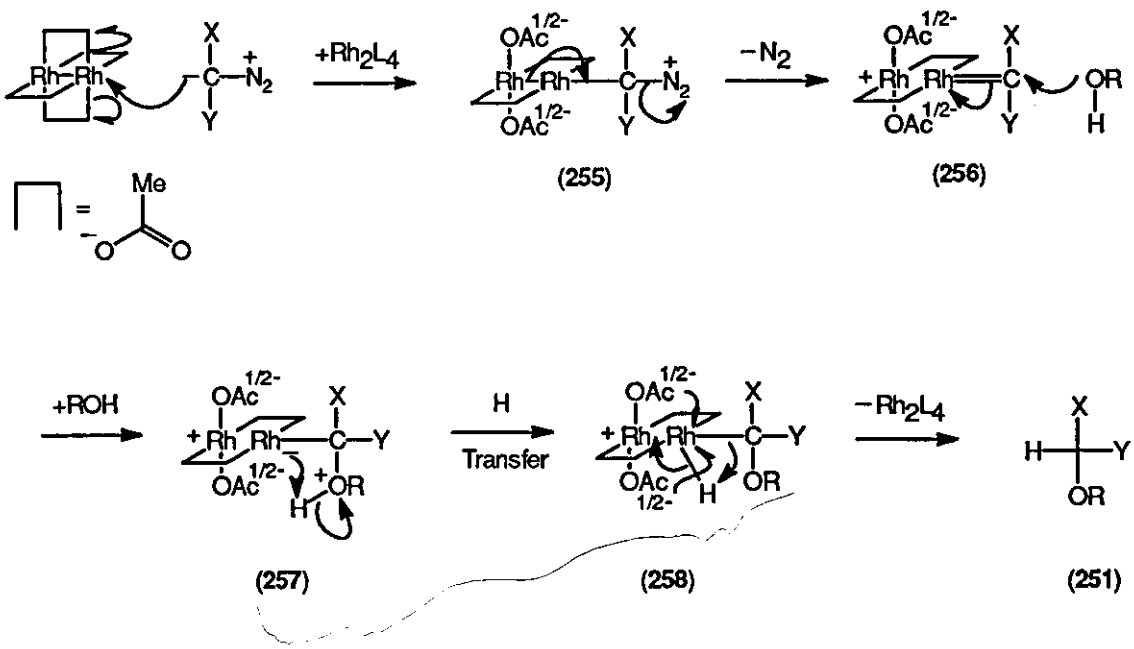
Attack of a nucleophile (in this case an alcohol) at the carbon of this stabilised carbene leads to the production of an ylid (**249**). This ylid has several fates. Firstly, it may leave rhodium (a) as a free ylid (**250**), giving back the rhodium (II) acetate catalyst as a 16 electron complex. Rapid facile rearrangement by a 1,2 hydrogen shift (b) would give the desired O-H insertion product (**251**). Oxonium ylids are not particularly stable and as such, decomplexation to give a free ylid, in the case of oxygen at least seems unlikely. However, the negative charge which resides on carbon is partially stabilised by the two withdrawing groups X and Y. Deprotonation by the bulk solvent at oxygen would expected to be a reasonably facile process and would lead to a stabilised carbanion (**252**). Subsequent reprotonation (again from the bulk solvent) would now give the desired O-H insertion product (**251**). This carbanion (**252**) may also arise from deprotonation of the intermediate ylid (**249**), whilst it is still bound to rhodium. The formed ether may now leave rhodium to give the carbanion (**252**) (c). The intermediate ylid (**249**) may also be lost by rearrangement to the enolate (**254**) (d). Subsequent reprotonation will again lead to the desired O-H insertion product.

The other alternative is hydrogen transfer from oxygen to rhodium (e) (with appropriate re-hybridisation). This would lead to a seven co-ordinate rhodium (**253**), having a capped octahedral structure, not totally unreasonable for a second row late transition metal complex. However, a metal hydride can easily be invoked if the bridging acetate ligands are disturbed (Scheme 65). Carbon migration from rhodium to hydrogen with the electrons in the rhodium - hydrogen bond being returned to the metal leads to the desired O-H insertion product and

regeneration of the catalyst. Migration of carbon to other atoms is known in some cases to occur with retention of stereochemistry (for example, hydroboration rearrangement to oxygen).

Throughout these mechanisms, the lantern structure of the rhodium (II) acetate remains intact and unbroken. The rhodium complex existing as either a 16 or 18 electron species. Doyle et al[111] have suggested transition states for the C-H insertion process which also retain the integrity of the rhodium lantern.

An alterative mechanism involving disruption of the lantern structure is given below (Scheme 65).

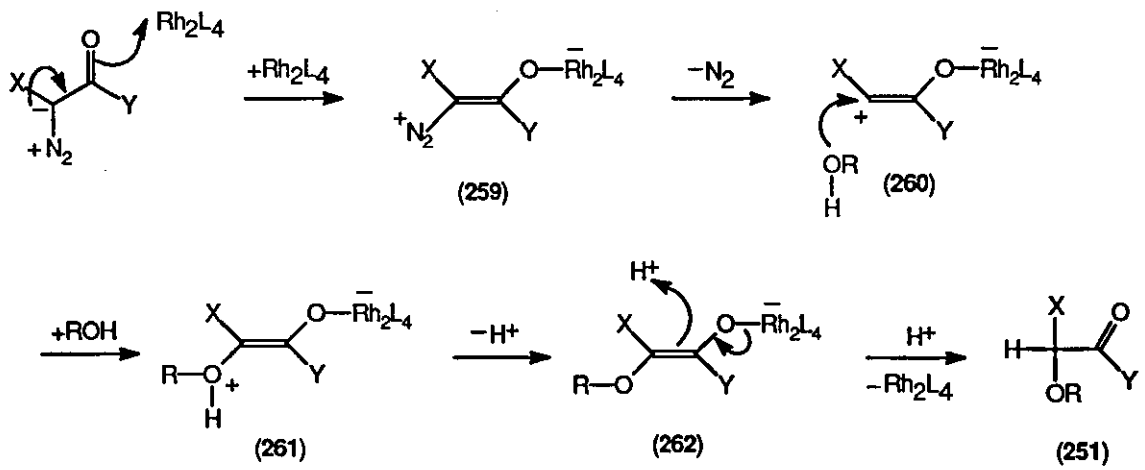


Scheme 65

Initial complexation of the diazo carbon to rhodium will now be accompanied by displacement of two acetate groups, to give complex (**255**). Loss of nitrogen is now facilitated by breaking of the central rhodium - rhodium metal bond, to form the metal carbenoid species (**256**). One of the two rhodium atoms has now been formally oxidised. Attack of a nucleophile on this carbenoid now gives an ylid (**257**) (an equivalent species to (**249**, Scheme 64). This intermediate ylid (**257**) can also undergo the same range of reactions as described for the

previous case (**249**, Scheme 64). Proton transfer to rhodium to give a rhodium hydride species (**258**) now has rhodium as four co-ordinate. A concerted rearrangement may now take place, by attack of the free acetate ligands on to rhodium coupled with carbon transfer to hydrogen and reformation of the central rhodium - rhodium bond. This leads to the desired O-H insertion product (**251**) and re-generates the catalyst to re-enter the cycle. One major consequence of this mechanism is that the hydrogen atom which ends up on the starting diazo carbon, must come from the reacting alcohol not the bulk solvent.

A third mechanism may also be considered (Scheme 66) which does not go via a metal bound carbene at all, rather a vinyl cation.

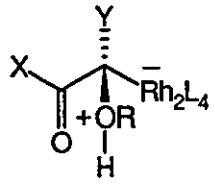


Scheme 66

Complexation of the diazo compound to rhodium may also be achieved by formation of the enolate (**259**), bonding to rhodium is now via oxygen, not carbon. Loss of nitrogen from this enolate will lead to a vinyl cation species (**260**), which may be subsequently trapped by a suitable nucleophile. Reaction of an alcohol with this vinyl cation will lead to an oxonium ion (**261**). Deprotonation will give an enol ether (**262**), which may then decomplex from rhodium to re-generate the catalyst and desired O-H insertion product (**251**). However, there is no obvious route to the β-elimination product from this vinyl cation route. Also α-phosphonodiazo compounds would not be expected to be able to form the phosphorus equivalent of enolate (**259**) and thus a different

mechanism for their decomposition would be needed. This argument also applies to the elimination of rhodium acetate from the intermediate ylid (**249**, Scheme 64 (d)); the phosphorus equivalent of (**254**) is doubtful and as such this possible route may be considered unlikely.

The same arguments may be applied to any of the chiral diazophenylacetates used, but for the purpose of discussion we shall look at 8-phenylmenthyl diazophenylacetate. The ground state conformations of a rhodium bound carbenoid have already been discussed. If one assumes that the initial attack on the carbenoid species (**249** or **257**) was stereospecific, this would lead to a chiral ylid of general structure (**263**). The question now arises, what are the consequences of the above mechanisms on the stereochemical integrity of intermediate ylid (**263**)?

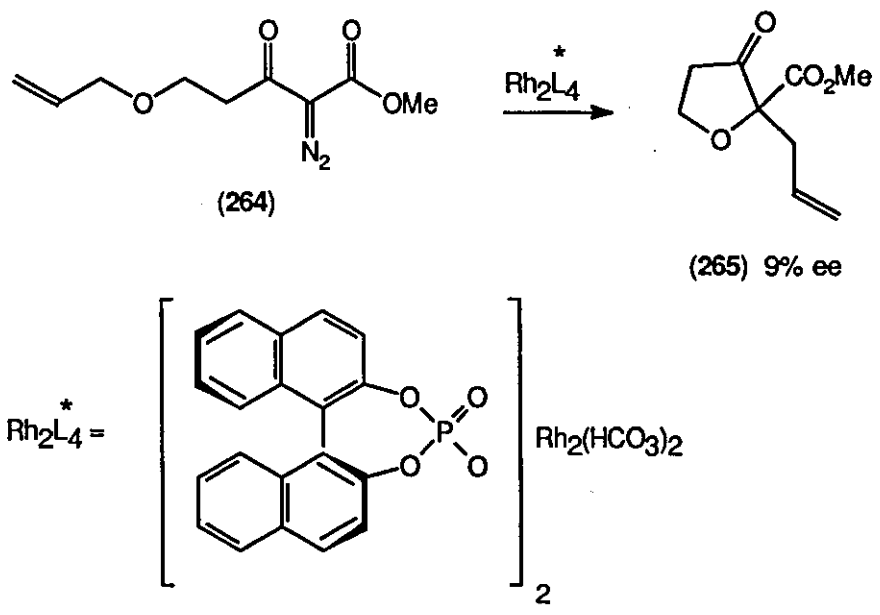


(263)

If the intermediate species (**249**) deprotonates to the bulk solvent ((c), Scheme 64) and is lost from rhodium as a carbanion (**252**), this will be planar and the newly formed stereocentre destroyed. Any observed stereoselectivity must then arise from stereoselective reprotonation. This is also the case if an ylid eliminates from the rhodium catalyst (**250**, (a), Scheme 64) or elimination of rhodium leads to an enolate (**254**, (d), Scheme 64). If the rhodium is bound to oxygen (Scheme 64), an enolate also exits in this case and the same argument applies. In all these cases it can be imagined that any observed stereoselectivity may well be small. Although elimination of an ylid (**250**) leads to a planar species, intramolecular hydrogen shift may occur stereoselectivly if the substrate posses additional chirality. Thus, if the reaction mechanism goes via any of these processes, then stereoselective O-H insertion will only be possible from a chiral auxiliary approach. Use of a chiral catalyst with an achiral substrate will be pointless as any induced enantioselectivity will subsequently be lost.

However, if the mechanism goes via some metal hydride species ((e), Scheme 64 and Scheme 65), then the formation of this hydride intermediate (**253**, Scheme 64 and **258**, Scheme 65) will not effect the already formed chiral centre. Subsequent loss of the rhodium catalyst by hydride transfer is likely to be stereoselective. In these cases, both the chiral auxiliary and chiral catalyst approaches should be able to induce some stereoselectivity into the O-H insertion process.

Evidence for a rhodium hydride type species can be derived from the observation of McKervey et al[112] that decomposition of allyl diazo ether (**264**, Scheme 67) with a chiral rhodium binapthylphosphonate complex (**266**) produces the cyclic ether (**265**) with a 9% ee.



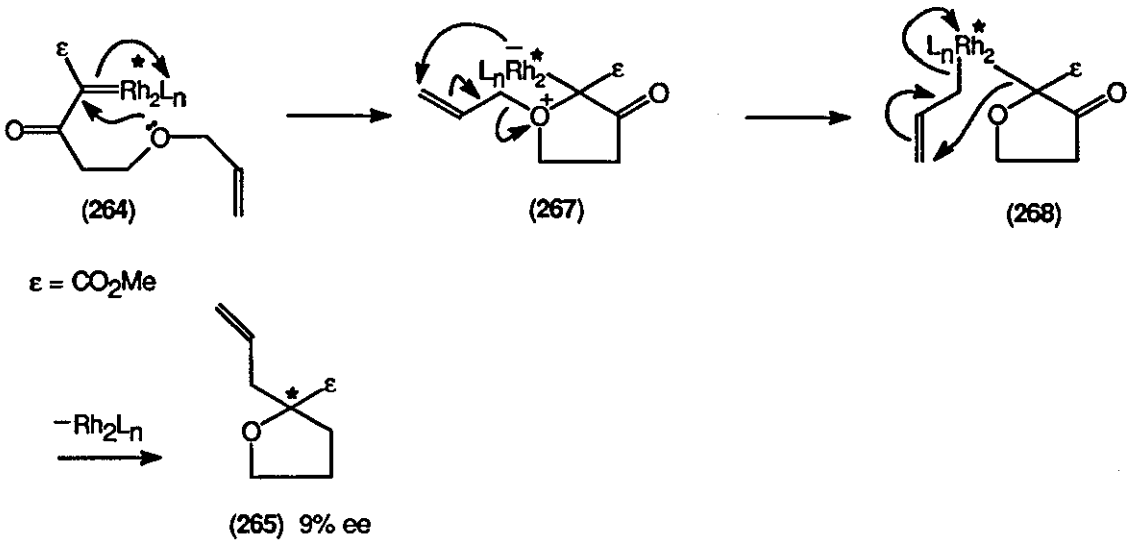
(264)

(265) 9% ee

(266)

Scheme 67

A proposed mechanism based on the discussions above is presented below (Scheme 68).



Scheme 68

Attack of the ether oxygen on the carbenoid carbon must give an intermediate oxonium ylid (**267**). Rearrangement of this ylid to an allyl rhodium species (**268**), with subsequent allyl migration and loss of rhodium leads to the observed cyclic ether (**265**). If the formed ylid intermediate (**267**) oses rhodium at this point (as discussed above) then subsequent formation of the cyclic ether by 2,3-sigmatropic rearrangement would not be expected to be enantioselective. The fact that cyclic ether (**267**) is formed in a modest enantiomeric excess, suggests the involvement of the chiral rhodium catalyst (in this case at least) until after or during the allyl group migration. The use of a substituted (and thus more sterically demanding) allyl ether might result in a higher observed enantiomeric excess, as it will be attack of the ether oxygen at the carbenoid centre to form intermediate ylid (**267**) which defines the enantiomeric excess observed.

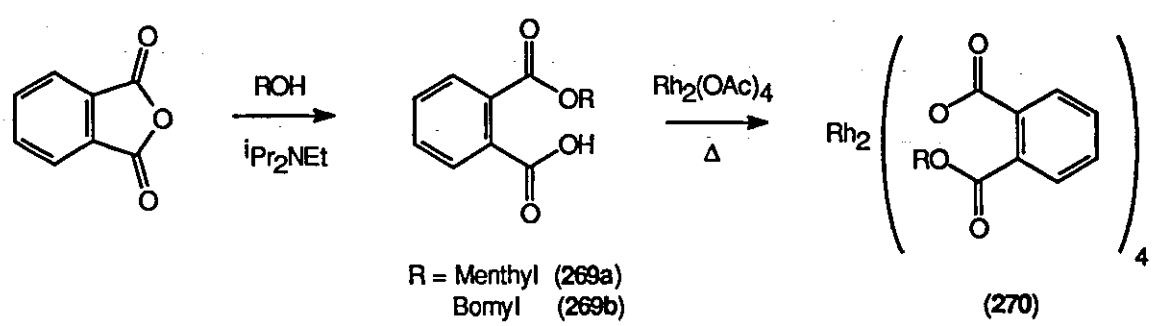
However, all of this aside, the lack of diastereoselectivity with chiral diazophenylacetates has still to be explained. Which of the mechanisms and ylid decomposition routes outlined above is most likely for the O-H insertion process into alcohols and water?

For the O-H insertion process the attacking nucleophile is usually small (methanol, *iso*-propanol etc.) and thus not very sterically demanding. The likelihood is that production of the intermediate ylid (**263**) will not be particularly stereoselective. The use of 'masked' hydroxy groups (for example, tetrahydropyranyl ethers described in Chapter Two) or larger alcohols may improve the prospect of stereoselectivity. Initially, the intermediacy of a vinyl cation (Scheme 66) seems unlikely. However, if the diazo compound is particularly large and hence the diazo carbon hindered, then bonding through oxygen may be the only available route for decomposition. Indeed, more sterically demanding diazo compounds decompose significantly slower than their simple counterparts.

The possible effect of rhodium - rhodium bond lengths on reaction rates has already been mentioned (Chapter Three), applying these ideas it would imply that the scenario which invokes disruption of the acetate lantern structure would fit this better. Also, seven co-ordinate rhodium complexes do not seem to have be reported, so if we wish to consider the metal hydride route Scheme 65 would seem the most likely mechanistic choice.

Chiral Catalysts

The synthesis of some novel rhodium (II) carboxylates, derived from phthalic anhydride was undertaken, to see if any chiral induction from the catalyst may be invoked as the chiral auxiliary approach had been largely unsuccessful. The synthesis of these new catalysts is outlined below (Scheme 69).



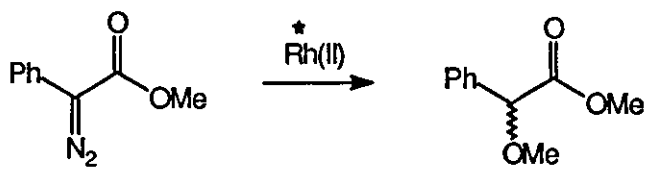
R = Menthyl (269a)
Bornyl (269b)

(270)

Scheme 69

Thus, phthalic anhydride was stirred overnight with either menthol or borneol in the presence of diisopropylethylamine. Extraction by aqueous base and re-acidification gave the crude phthalic half esters (**269**). Excess menthol was removed by sublimation and the residue purified by column chromatography. The bornyl half ester was purified by column chromatography. Ligand exchange with rhodium (II) acetate as a melt at 120°C gave the crude rhodium catalysts (**270**). Column chromatography gave the pure catalysts, proton and carbon NMR spectroscopy showed no presence of uncomplexed ligand. FAB Mass spectrometry showed the presence of the correct molecular ion (an accurate mass measurement was not possible due to the high molecular mass of the catalysts, and analytically pure samples for microanalysis were unable to be prepared).

The model reaction chosen for O-H insertion with these chiral catalysts was the insertion of methanol into methyl diazophenylacetate (**271**, Scheme 70).

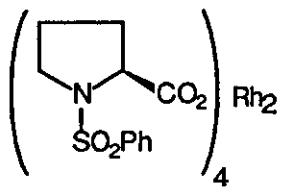


(**271**) (**272**)

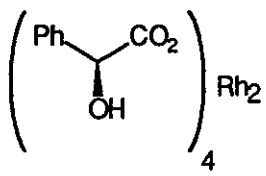
Scheme 70

The decomposition of diazo compound (**271**) in methanol solution with rhodium (II) catalysts proceeded smoothly to give a good yield (>70%) of insertion product (**272**). Removal of methanol and chromatography on the crude residue gave pure insertion product (>97% by GC). Analysis of this purified material by chiral gas chromatography allowed the near complete separation of enantiomers, and estimates of any enantiomeric excess. Attempts to distinguish the two enantiomers by chiral shift NMR spectroscopy were totally unsuccessful, a minimum amount chiral shift reagent caused rapid and complete broadening of all the resonance peaks. An authentic racemic sample (**272**) was synthesised by the decomposition of diazo compound (**271**) with rhodium (II) acetate.

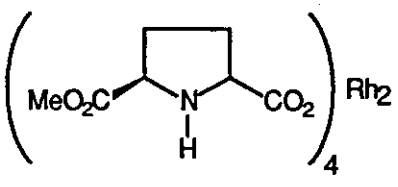
For comparison this decomposition was also performed with chiral catalysts known to induce chirality into other process (C-H insertion or cyclopropanation). The other catalysts used for this study are shown below (**273 - 276**).[113]



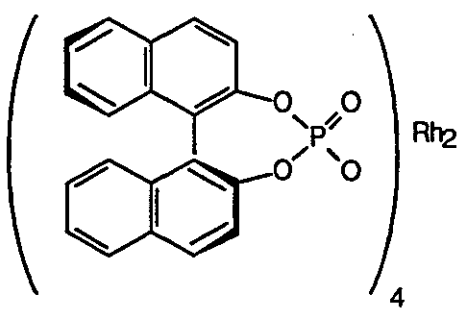
(273)



(274)



(275)



(276)

The ligands used in each case are N-benzenesulphonyl-(L)-proline (**273**), (S)-mandelic acid (**274**),[114] methyl 2-pyrrolidinone-5-(R)-carboxylate (MEPY) (**275**)[115] and tetrakisbinaptholphosphate dirhodium (II) (**276**).[116]

All the catalysts used (**270, 273-276**) gave moderate to good yields of the insertion product (**272**) at room temperature decomposition (Table 29). Analysis by chiral GC however, showed that in no case had any significant chiral induction been realised. Additionally no improvement in enantioselectivity was noted when the decomposition was performed at -78°C with degassed methanol,[b] in the presence of N-benzenesulphonyl-L-proline dirhodium (II).

[b] The methanol was degassed by ultrasound under a blanket of argon.

Table 29

Catalyst	Isolated Yield(%)
(270a)	77
(270b)	54
(273)	60
(273)	2.2*
(274)	>95
(275)	14
(276)	65

* decomposition at -78°C with degassed methanol under argon.

An example of a chiral GC trace is given in Figure 2. The genuine racemate is included (top). Two examples of chiral catalyst decomposition are shown, menthyl 2-carboxybenzoate (**270a**) and Pirrung's phosphate catalyst (**276**). Two main points need to be noted about the analysis procedure, firstly there is considerable overlap of the two enantiomers. Secondly, the peak shape of both enantiomers is substantially different. The S-enantiomer (t_R= ≈68 min; by comparison with an independently synthesised authentic sample) has a significantly broader peak shape. Estimation of peak areas by extrapolation of the peak sides giving two triangles which maybe measured, leads, in all cases to a ratio which is predominately in favour of (S) (Table 30).

Table 30

Catalyst		Peak Ratio*
$Rh_2(OAc)_4$, (racemate)		1.07 (R)
(270a)		1.37 (S)
(270b)		1.20 (S)
(273)		1.12 (S)
(273)	-78°C	1.20 (R)
(277)		1.24 (S)
(277)	-78°C	1.01 (S)
(274)		1.15 (S)
(275)		1.30 (S)
(276)		1.30 (S)

* indicates which enantiomer is apparently predominant

The Table suggests that the detection of a small enantiomeric excess is beyond the analysis procedure. Initially, decomposition with N-benzenesulphonyl-L-proline dirhodium (II) (**273**) appeared to occur with some enantioselectivity. However, synthesis of the enantiomeric catalyst (**277**) failed to invoke enantioselectivity in the opposite direction and the original observation was considered to be an artefact of the analysis procedure because of incomplete separation of the two enantiomers.

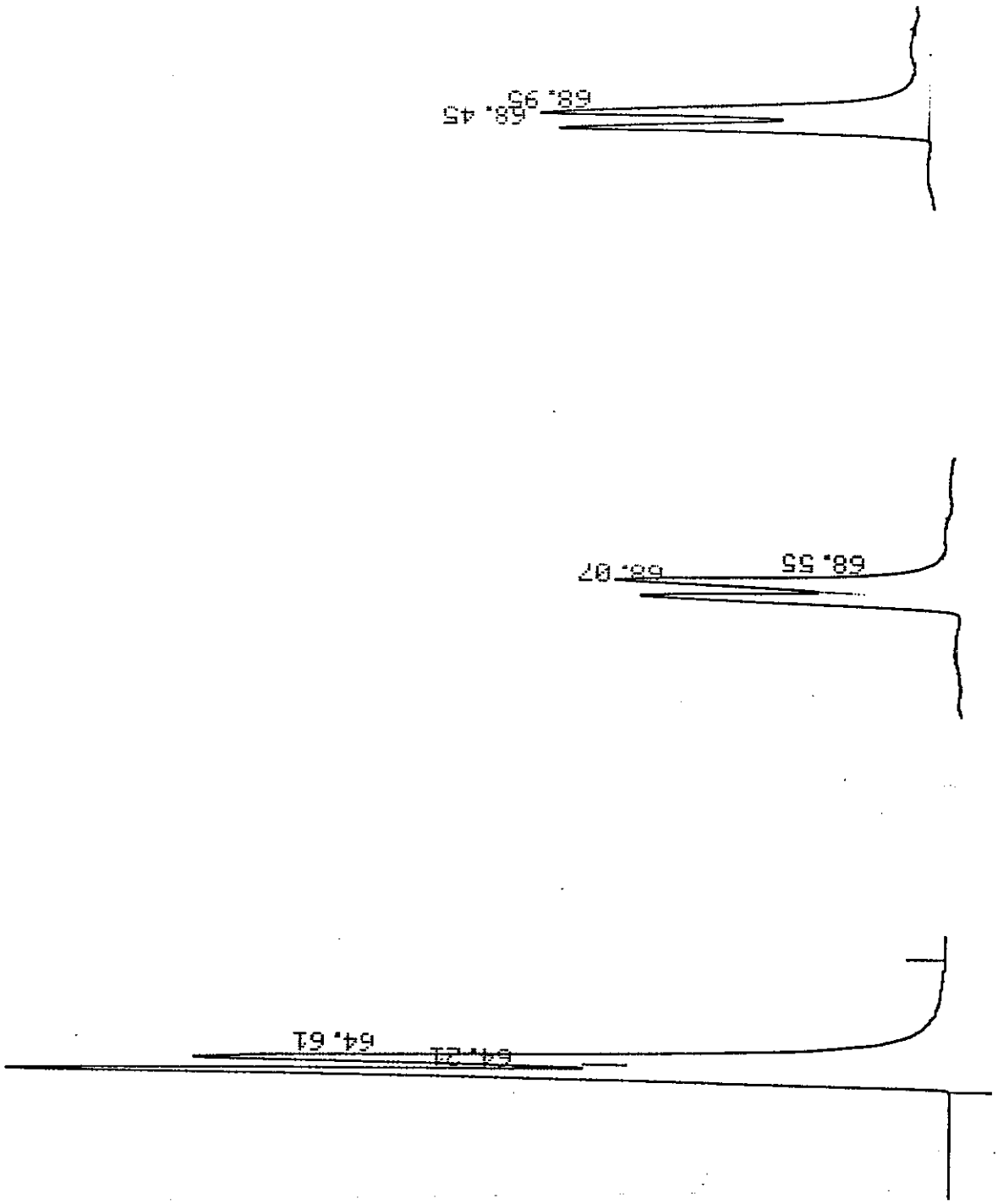


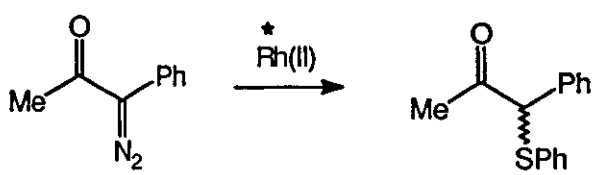
Figure 2

Top, Genuine racemate from $Rh_2(OAc)_4$ decomposition; Middle, catalyst (**270a**); Bottom, catalyst (**276**).

Also decomposition with catalyst (**273**) at room temperature and -78°C leads to apparent induction in opposite directions. Cooling the reaction mixture seems an unlikely way to reverse the sense of chiral induction, and this observation was again put down to the limitations of the analysis used.

The use of catalysts (**275**), (**276**) and (**270a**) does however seem promising. The enantiomeric catalyst in each case needs to be synthesised and tried, any induction in the direction of (S) would show that this result is also due to the analysis procedure not any real induction on the part of the catalyst. Ideally, another analysis protocol, perhaps chiral HPLC or a different chiral GC column would allow complete separation of the two enantiomers and a more accurate and reliable indication of chiral induction.

Recently, Brunner has reported that S-H insertion of thiophenol into diazophenylmethylketone (**278**) with a variety of chiral rhodium (II) carboxylates and carboxamides and solvents gave the product thioether (**279**) in good yield and optical yields of up to 12% ee (Scheme 71).[117]



(**278**) (**279**)

Scheme 71

This result is in stark contrast to the lack of selectivity noted for O-H insertion. However, the enantioselectivity seen is small and as such not synthetically useful. The enantiomeric excess was measured by chiral HPLC and as such should be able to be viewed as a reliable result. The origin of this selectivity does remain however, something of a mystery and no obvious explanation is apparent.

Conclusions

The use of rhodium (II) carboxylates have been shown to be efficient catalysts for the O-H insertion process. The use of different ligands on rhodium has been shown to have a significant effect on the rate of diazo compound decomposition, but not the outcome of a reaction when other processes compete with O-H insertion for the intermediate rhodium carbenoid.

The use of mono substituted diazoesters at present has been shown not to be viable as part of a synthetic strategy, more efficient and general routes to their synthesis are required. However, once produced, the conversion to α-hydroxy or α-alkoxyester can be achieved readily, and in general high yields of O-H insertion product are obtained.

The use of chiral diazo compounds and chiral rhodium catalysts has led to the conclusion (from present available data) that the O-H insertion process probably proceeds via a rhodium hydride species (**257**) and that disruption of the lantern structure of the rhodium dimers also occurs. It should be possible to achieve better enantioselectivity in other processes (for example, 2,3 sigmatropic rearrangements), but the outlook for enantioselective O-H insertion is bleak.

Experimental Section

Commercially available reagents were used throughout without further purification, except for those detailed below which were purified as described. Solvents were distilled from calcium chloride through a 36 cm Vigreux column.

'Light petroleum' refers to the fraction boiling in the range 40-60°C; ether refers to diethyl ether. Dichloromethane was distilled from phosphorus pentoxide prior to use. THF was distilled from sodium benzophenone ketyl under nitrogen, prior to use. Triethylamine was distilled from and stored over potassium hydroxide pellets. Sodium iodide was dried over phosphorus pentoxide in a vacuum oven at 70°C overnight. Chloropropanol was dried by distillation from potassium carbonate under vacuum. 8-Phenylmenthol was synthesised by the literature procedure of Ort.[118] *tert*-Butanol and *iso*-propanol were dried by distillation from calcium hydride. Kugelrohr distillations were performed on a Buchi GKR-51 Kugelrohr apparatus and distillation pressures are quoted were applicable.

Analytical thin layer chromatography was carried out using aluminium backed plates coated with Merck Kieselgel 60 GF_{254}. Plates were visualised under UV light (at 254 nm) or by staining with ammonium molybdate reagent, followed by heating. Flash chromatography was carried out using Merck Kieselgel 60 H silica or Sorbsil C 60 silica gel. Pressure was applied at the column head with hand bellows. Samples were applied as a saturated solution in an appropriate solvent.

All carbenoid insertion reactions had their NMR recorded before isolation and purification of the insertion product.

Elemental analyses were recorded either by Medac Ltd, Brunel University, Uxbridge, or on a Perkin-Elmer 2400 Elemental Analyser at Loughborough University.

Optical Rotations were recorded on an Optical Activity polarimeter at 298 K and are reported as specific rotations, where c= g/100 ml.

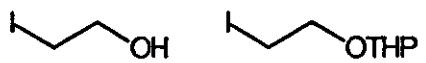
Infrared spectra were recorded in the range 4000-600 cm^{-1} using either a Perkin-Elmer 257 spectrophotometer or a Nicolet FT-205 spectrometer with internal calibration. Spectra were recorded as thin films.

NMR spectra were recorded on a Bruker AC-250 MHz spectrometer at 298 K or a Bruker WH-400 (SERC NMR Spectroscopy Centre, Warwick), with tetramethylsilane as internal reference. All coupling constants (*J*) are reported in Hz, multiplicities are as follows; s (singlet), bs (broad singlet), d (doublet), dd (doublet of doublets), t (triplet), dt (doublet of triplets), q (quartet), dq (doublet of quartets), p (quintet), hp (heptet).

Mass spectra were recorded on a Kratos MS80 spectrometer (Electron Impact), Chemical Ionization spectra were recorded on VG Analytical ZAB-E instument (SERC Mass Spectrometry Service Centre, University Collage of Swansea, Swansea). Compounds characterised by high resolution mass spectrometry were chromatographically homogeneous.

Not all diazo compounds synthesised gave expected mass spectra, so some compounds have no associated accurate mass measurements. However, subsequent decomposition experiments and full characterisation of products proves the integrity of the starting diazo compound.

Experimental for Chapter Two



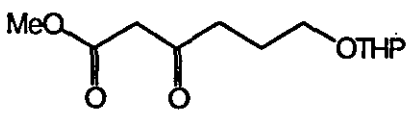
(162) (155)

1-Iodopropanol (162)

Dried 1-chloropropanol (5 g, 53 mmol) and sodium iodide (12 g, 80 mmol) were dissolved in MEK (150 ml) under nitrogen. The reaction mixture was refluxed for 20 h. After this time the precipitated sodium chloride was filtered off and the MEK removed. The residue was taken up in ether (200 ml) and washed with sodium metabisulphite (2x100 ml) and brine (2x100 ml). The organic layer was dried ($MgSO_4$) and then removed *in vacuo*. The residue obtained was distilled (Kugelrohr) to give the *title compound* as a colourless oil (9 g, 91%), b.p. 70°C, 0.8 mmHg; δ_H (250 MHz; $CDCl_3$) 3.70 (2 H, t, *J*= 5.9, HO-$\underline{CH_2}$-), 3.30 (2 H, t, *J*= 6.7, -$\underline{CH_2}$-I), 2.68 (1 H, bs, $\underline{OH}$), 2.04 (2 H, p, *J*= 6.4, -CH_2-$\underline{CH_2}$-CH_2-); δ_C (62.9 MHz; $CDCl_3$) 62.1, 35.6, 3.11; *m/z* (EI), 186 (M^+, 58%), 59 (100), 31 (100), 127 (28).

1-Tetrahydropyranyloxy-3-iodopropane (155)

To a stirred solution of pyridinium p-toluenesulphonate (27 mg, 10 mol%) and 1-iodopropane (2 g, 11 mmol) in DCM (200 ml) was added dihydropyran (0.9 g, 11 mmol) over 10 min. The reaction mixture was stirred at room temperature for 16 h. The DCM was removed *in vacuo* and the resulting residue taken up in ether. The ether layer was washed with water (2x200 ml) and brine (100 ml), dried ($MgSO_4$) and removed *in vacuo*. The residue obtained was chromatographed (ether/light petroleum eluent). Distillation (Kugelrohr) gave the *title compound* as a colourless oil (2.2 g, 74%), b.p. 110°C, 0.5 mmHg; found: C, 35.7; H, 5.6 $C_8H_{15}IO_2$ requires C, 35.7; H, 5.6%; ν_{max}(film)/cm^{-1}, 2936, 2864, 1464, 1452, 1076 and 1032. δ_H (250 MHz; $CDCl_3$) 4.56 (1 H, bt, O-$\underline{CH}$-O), 3.87-3.76 and 3.54-3.39 (4 H, m, O-$\underline{CH_2}$-), 3.30 (2 H, t, *J*= 6.8, I-$\underline{CH_2}$-), 2.14 (2 H, q, *J*= 8.3, -CH_2-$\underline{CH_2}$-CH_2-), 1.83-1.48 (6 H, m, ($\underline{CH_2}$)$_3$); δ_C (62.9 MHz; $CDCl_3$) 98.8, 66.8, 62.2, 33.5, 30.6, 25.4, 19.4, 3.4.



(157)

Methyl 3-Oxo-7-tetrahydropyranyloxyheptanoate (157)

A suspension of sodium hydride (80% disp. 1.7 g, 57 mmol) in dry THF (250 ml) under nitrogen at 0°C was treated with methyl acetoacetate (6.6 g, 57 mmol). After hydrogen evolution had ceased the reaction was cooled to -78°C and butyl lithium (1.6M, 36 ml) was added. The reaction mixture was stirred for 15 min, after which time 1-tetrahydropyranyloxy-3-iodopropane was added and the reaction mixture stirred for a further 4 h. The cold bath was removed and water (20 ml) slowly added. Once warmed to room temperature, the reaction mixture was diluted with water (250 ml) and extracted with ether (2x200 ml). The organic layer was dried ($MgSO_4$) and removed *in vacuo*. Column chromatography on the resulting oil (ether/light petroleum eluent) gave a pale yellow oil which was distilled (Kugelrohr) to give the *title compound* as a colourless oil (6 g, 50%), b.p. 190°C, 0.5 mmHg; ν_{max}(film)/cm^{-1}, 2945, 2871, 1748, 1717, 1629, 1648, 1438, and 1076; δ_H (250 MHz; $CDCl_3$) 4.57 (1 H, bt, O-CH-O) 4.20-3.71 and 3.51-3.37 (4 H, m, O-CH_2-), 3.72 (3 H, s, OMe), 3.40 (2 H, s, CO-CH_2-CO), 2.60 (2 H, t, *J*= 6.8, CO-CH_2-), 1.74-1.53 (10 H, m, $(CH_2)_5$); δ_C (62.9 MHz; $CDCl_3$) 202.3, 167.4, 98.7, 66.6, 62.1, 52.1, 48.8, 42.5, 30.5, 28.9, 25.3, 20.2, 19.4.

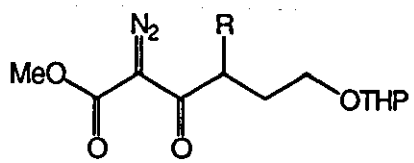
General Procedure for Alkylation of Methyl 3-Oxo-7-tetrahydropyranyloxyheptanoate

A suspension of sodium hydride (80% disp. 279 mg, 9.3 mmol) in dry THF (25 ml) under nitrogen at 0°C was treated with methyl 3-Oxo-7-tetrahydropyranyloxyheptanoate (2 g, 7.8 mmol). After hydrogen evolution had ceased *n*-butyl lithium (1.6 M, 5.8 ml) was added. The reaction mixture was stirred for 15 min, after which time the appropriate alkyl bromide was added and the reaction mixture left to stir for an additional 0.5-1.5 h. The reaction mixture was then quenched with satd. ammonium chloride solution and the aqueous layer extracted with ether

(2x100 ml). The ether was dried ($MgSO_4$) and removed *in vacuo*. Chromatography (ether/light petroleum eluent) on the resultant oil gave the desired alkylated product of limited purity, which was used directly for the next step without further purification or characterisation.

General Procedure for Diazo Transfer

The roughly purified product from above (1-2 g) was dissolved in acetonitrile (10 ml) and p-ABSA (1.2 eq) added. Triethylamine (1 eq) was added dropwise and the reaction mixture was stirred at room temperature for 5-6 h. The acetonitrile was removed *in vacuo* and the residue taken up in ether (50 ml). The formed precipitate was filtered off and the organic layer was washed with brine (100 ml). The organic layer was dried ($MgSO_4$) and removed *in vacuo*. Chromatography (ether/light petroleum eluent) on the resulting oils gave the *title compounds*, as yellow oils.



(159)

Methyl 4-Benzyl-2-diazo-3-oxo-7-tetrahydropyranyloxyheptanoate (159a)

(1.9 g; 70% over two steps); found: MH^+, 375.1920. $C_{20}H_{27}N_2O_5$ requires 375.1920; ν_{max}(film)/cm^{-1} 2943, 2869, 2139, 1723, 1654, 751 and 701; δ_H (250 MHz; $CDCl_3$) 7.16-7.32 (5 H, m, Ar), 4.53 (1 H, bt, O-CH-O), 4.05-3.92, 3.82-3.64 and 3.36-3.29 (4 H, m, O-CH_2-), 3.78 (3 H, s, OMe), 2.97-3.05 and 2.61-2.69 (2 H, q, -CH_2-Ph), 1.81-1.46 (11 H, m, $(CH_2)_5$ and -CH-(Bz)-CH_2-); δ_C (62.9 MHz; $CDCl_3$) 195.4, 161.4, 139.4, 129.2, 128.3, 126.2, 98.7, 67.2, 65.9, 62.2, 52.1, 48.5, 38.1, 30.7, 27.9, 25.5, 19.5; *m/z* (CI) M^+ 375 (0.5%), 291 (55), 102 (100), 85 (100).

Methyl 2-Diazo-3-oxo-4-(3-tetrahydropyranyloxypropyl)-hept-6-yne (159c)

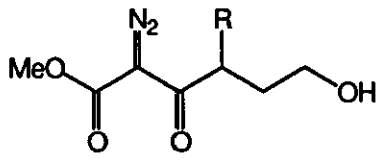
(842 mg, 34% over two steps); found: MH^+, 323.1610. $C_{16}H_{23}N_2O_5$ requires 323.1607; ν_{max}(film)/cm^{-1} 3287, 2946, 2870, 2142, 1721 and 1654; δ_H (250 MHz; $CDCl_3$) 4.57 (1 H, bt, O-CH-O), 3.82 (3 H, s, OMe), 3.80-3.69 (3 H, m, O-CH_2- & CO-CH-), 3.61-3.36 (2 H, m, O-CH_2-), 2.60-2.25 (2 H, m, -CH_2-C≡CH), 1.97 (1 H, t, *J*= 2.6, H-C≡), 1.84-1.38 (10 H, m, $(CH_2)_5$); δ_C (62.9 MHz; $CDCl_3$) 193.2, 161.4, 988, 81.6, 69.7, 67.2, 62.3, 52.3, 45.8, 30.7, 27.9, 26.9, 25.5, 20.4, 19.6; *m/z* (CI) MH^+ 323 (5%), 211 (45), 195 (82), 85 (100).

Methyl 2-Diazo-3-oxo-4-(3-tetrahydropyranyloxypropyl)-hept-6-ene (159b)

(1.4 g, 52% over two steps); found: C, 59.7; H, 7.7; N, 8.3 $C_{16}H_{24}N_2O_5$ requires C, 59.2; H, 7.5; N, 8.6%; ν_{max}(film)/cm^{-1} 2940, 2868, 2136, 1722 and 1652; δ_H (250 MHz; $CDCl_3$) 5.76-5.38 (1 H, m, CH_2=CH-), 5.07-4.97 (2 H, m, CH_2=), 4.57-4.54 (1 H, bt, O-CH-O), 3.84 (3 H, s, OMe), 3.83-3.68 (3 H, m, O-CH_2- and CO-CH-), 3.56-3.25 (2 H, m, O-CH_2-), 2.45-2.35 and 2.25-2.17 (2 H, m, -CH_2-CH=CH_2), 1.80-1.48 (10 H, m, $(CH_2)_5$); δ_C (62.9 MHz; $CDCl_3$) 195.4, 161.5, 135.5, 116.7, 98.7, 62.3, 67.3, 57.1, 46.3, 36.0, 30.7, 28.0, 27.3, 25.5, 19.6.

General Procedure for Deprotection of THP Protected Alcohols

The THP protected diazo compounds were taken up in THF:water:acetic acid (3:3:2). This solution was heated to 60°C for 1-3 h. Once complete by TLC, the reaction mixture was cooled and diluted with ether (100 ml). The organic layer was washed with 10% sodium bicarbonate until carbon dioxide evolution ceased. The ether solution was then washed with brine (2x50 ml) and dried ($MgSO_4$). The ether was removed and the resulting residue purified by column chromatography (ether/light petroleum eluent) to give the *title compounds* as pale yellow oils.



(160)

Methyl 4-Benzyl-2-diazo-7-hydroxy-3-oxo-heptanoate (160a)

(1 g, 94%); found: C, 62.1; H, 6.3; N, 9.6 $C_{15}H_{18}N_2O_4$ requires C, 62.1; H, 6.3; N, 9.4%; found: MH^+, 291.134(5). $C_{15}H_{19}N_2O_4$ requires 291.1345; ν_{max}(film)/cm^{-1} 3450, 2978, 2140, 1722, 1652, 751 and 701; δ_H (250 MHz; $CDCl_3$) 7.15-7.30 (5 H, m, Ar), 3.61 (3 H, s, OMe), 3.60 (2 H, t, *J*= 6.1, O-CH_2-), 3.03-2.98 and 2.69-2.61 (2 H, m, -CH_2-Ph), 1.98 (1 H, bs, OH), 1.86-1.75 (1 H, m, CO-CH-), 1.54-1.44 (4 H, m, $(CH_2)_2$); δ_C (62.9 MHz; $CDCl_3$) 195.5, 162.3, 139.4, 129.1, 128.3, 126.2, 65.8, 62.2, 52.2, 48.4, 37.8, 30.1, 27.3, 15.2; *m/z* (CI) MH^+ 291 (100%), 263 (30), 231 (15).

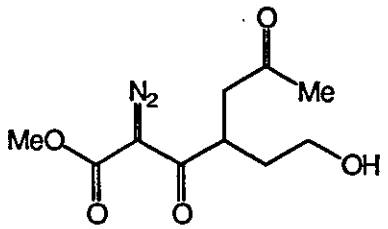
Methyl 2-Diazo-7-hydroxy-3-oxo-4-propargyl-heptanoate (160c)

(429 mg, 73%); found: C, 55.4; H, 5.9; N, 11.7 $C_{11}H_{14}N_2O_4$ requires C, 55.5; H, 6.0; N, 11.5%; found: MH^+, 239.103(2). $C_{11}H_{15}N_2O_4$ requires 239.1032; ν_{max}(film)/cm^{-1} 3421, 3405, 2954, 2871, 2144, 1721 and 1652; δ_H (250 MHz; $CDCl_3$) 3.89 (3 H, s, OMe), 3.69 (1 H, q, *J*= 6.3, CO-CH-), 3.58 (2 H, t, *J*= 5.82, O-CH_2-), 2.59-2.36 (2 H, m, -CH_2-C≡CH), 1.98 (1 H, t, *J*= 2.7, HC≡C-), 1.94 (1 H, bs, OH), 1.88-1.37 (4 H, m, $(CH_2)_2$); δ_C (62.9 MHz; $CDCl_3$) 194.2, 161.6, 81.6, 69.7, 65.8, 52.3, 45.5, 29.6, 27.2, 20.2; *m/z* (CI) MH^+ 239 (35%), 221 (85), 211 (100).

Methyl 4-Allyl-2-diazo-7-hydroxy-3-oxo-heptanoate (160b)

(200 mg, 43 %); found: C, 55.0; H, 6.9; N, 10.9 $C_{11}H_{16}N_2O_4$ requires C, 55.0; H, 6.7; N, 11.7%; found: MH^+, 241.1190. $C_{11}H_{17}N_2O_4$ requires 241.1188; ν_{max}(film)/cm^{-1} 3440, 2992, 2944, 2140, 1720 and 1640; δ_H (250 MHz; $CDCl_3$) 5.80-5.67 (1 H, m, CH_2-CH=CH_2), 5.07-4.97 (2 H, m, CH=CH_2), 3.71 (3 H, s,

OMe), 3.70-3.59 (3 H, m, O-CH_2- and CO-CH-), 2.43-2.40 and 2.24-2.16 (2 H, m, -CH_2-CH=CH_2), 2.15 (1 H, bs, OH), 1.60-1.50 (4 H, m, $(CH_2)_2$); δ_C (62.9 MHz; $CDCl_3$) 195.1, 161.3, 135.3, 116.7, 62.1, 46.0, 35.6, 29.9, 27.0; *m/z* (CI) MH^+ 241 (60%), 223 (70), 213 (100), 195 (65), 181 (62).



(163)

Methyl 2-Diazo-7-hydroxy-3-oxo-4-(2-oxopropyl)heptanoate (163)

Methyl 2-diazo-3-oxo-4-(3-tetrahydropyranyloxypropyl)-hept-6-yne (1 g, 3.1 mmol) was dissolved in a mixture of THF and water (30 ml: 20 ml). Mercuric sulphate was added (120 mg, 13 mol%) and the reaction mixture heated at 70°C for 1 h until adjudged complete by TLC. The reaction mixture was extracted with ether (2x50 ml). The organic layers were combined, dried ($MgSO_4$) and removed *in vacuo*. The remaining residue was purified by column chromatography (ether/light petroleum eluent) to give the *title compound* as a pale yellow oil (503 mg, 48%); found: MH^+, 257.113(7). $C_{11}H_{16}N_2O_5$ requires 257.1109; ν_{max}(film)/cm^{-1} 3426, 2954, 2869, 2143, 1727, 1722, 1715 and 1651; δ_H (250 MHz; $CDCl_3$) 3.97-3.88 (1 H, m, CO-CH-), 3.85 (3 H, s, MeO-), 3.67-3.62 (2 H, dt, *J*= 4.3 & 1.25, -CH_2-OH), 3.13-3.01 (1 H, m, CH_2=CH-CH_2-), 2.61-2.52 (1 H, m, CH_2=CH-CH_2-), 2.15 (4 H, s and bs, CH_3-CO & OH), 1.78-1.38 (4 H, m, $(CH_2)_2$); δ_C (62.9 MHz; $CDCl_3$) 207.1, 195.0, 163.4, 61.6, 52.3, 44.5, 41.3, 29.7, 29.5, 27.3; *m/z* (CI) MH^+ 257 (25%), 239 (100), 229 (30), 211 (40).

General Procedure for Protection of Diols

To a stirred DCM solution of diol (5 eq) and triethylamine (1.4 eq) under nitrogen, was added dropwise a solution of tributyldimethylsilyl chloride (1 eq). The reaction mixture was stirred for ca. 6h, after which time the DCM was

removed *in vacuo*. The residue was suspended in ether (100 ml) and washed with water (5x50 ml). The organic layer was dried ($MgSO_4$) and evaporated to leave a pale yellow oil. Chromatography on this oil (ether/light petroleum eluent) gave the desired mono protected diols.

(168a) (168b)

1-t-Butyldimethylsiloxypropan-1-ol (168a)

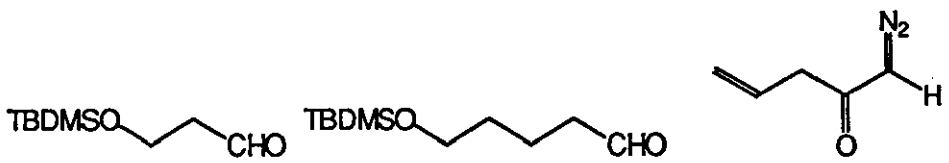
ν_{max}(film)/cm^{-1} 3406, 2956, 2911, 2858, 1098 and 837; δ_H (250 MHz; $CDCl_3$) 3.77-3.68 (4 H, m, O-$\underline{CH_2}$), 2.84 (1 H, bs, $\underline{OH}$), 1.70 (2 H, q, J= 5.24 & 5.73, CH_2-$\underline{CH^2}$-CH_2), 0.82 (9 H, s, ^tBu-Si), 0.08 (6 H, s, Me_2Si).

1-t-Butyldimethylsiloxypentan-1-ol (168b)

ν_{max}(film)/cm^{-1} 3357, 2953, 2931, 1472 and 1468; δ_H (250 MHz; $CDCl_3$) 3.67-3.58 (4 H, m, O-$\underline{CH_2}$), 1.62-1.37 (6 H, m, -($\underline{CH_2}$)$_3$-), 0.90 (9 H, s, ^tBu-Si), 0.09 (6 H, s, Me_2Si).

General procedure for Oxidation to Aldehyde

The silyl protected diol was dissolved in 200 ml DCM. Celite was added (equivalent mass to PCC). PCC (2 eq) was added to this suspension. The reaction mixture was stirred for 2.5 h at room temperature. The PCC/Celite was filtered off and the DCM removed *in vacuo*. Work-up varied according to diol used and is given below.



(169a) (169b) (175)

1-t-Butyldimethylsiloxypropanal (169b)

The residue from oxidation was distilled (Kugelrohr) directly to yield the *title compound* as an impure, pale yellow oil (1.3 g, 41%); b.p. 115°C, 8 mmHg; ν_{max}(film)/cm^{-1} 2957, 2930, 2886, 2858, 2826, 1728, 1472 and 1442; δH (250 MHz; $CDCl_3$) 9.81 (1 H, t, *J*= 2.08, CHO), 3.99 (2 H, t, *J*= 5.75, O-CH_2-), 2.62-2.55 (2 H, m, OHC-CH_2-), 0.91 (9 H, s, ^{t}Bu-Si), 0.056 (6 H, s, Me_2Si).

1-t-Butyldimethylsiloxypentanal (169a)

The residue from oxidation was taken up in ether and washed with water until no more colour entered the aqueous layer. The organic layer was dried ($MgSO_4$) and removed *in vacuo* to leave a dark coloured oil. Purification by column chromatography (ether/light petroleum eluent) gave the *title compound.* Purity was determined by NMR and the aldehyde was used without further purification (2.78 g, 76%); ν_{max}(film)/cm^{-1} 2955, 2930, 2887, 2822, 1729, 1472 and 1463; δ_H (250 MHz; $CDCl_3$) 9.82 (1 H, t, *J*= 1.75, CHO), 3.63 (2 H, t, *J*= 6.0, 0-CH_2-), 2.46 (2 H, dt, *J*= 1.75 & 7.0, OHC-CH_2-), 1.74-1.52 (4 H, m, -(CH_2)$_2$-), 0.91 (9 H, s, ^{t}Bu-Si), 0.05 (6 H, s, Me_2Si).

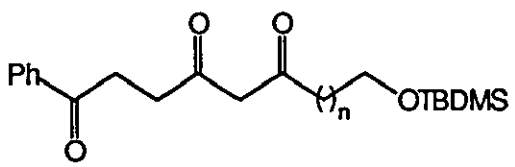
1-Diazo-2-oxohex-4-ene (175)

To a mechanically stirred solution of 4-pentenoic acid (5 g, 50 mmol, 51 ml) and methyl chloroformate (5.67 g, 60 mmol, 4.6 ml) in ether (300 ml) under nitrogen, was added triethylamine (6 g, 60 mmol, 8 ml) dropwise over 5 min. The reaction mixture was left to stir at room temperature for ca. 3 h. After this time, precip-

itated triethylamine hydrochloride was filtered off and the filtrate cooled to 0°C. Diazomethane (100 mmol in ether) at 0°C was added with stirring and the reaction mixture left to warm to room temperature overnight. The ether was removed and the resulting oil purified by column chromatography (ether/light petroleum eluent) to give the *title compound* as a volatile yellow oil (2.8 g, 50%); ν_{max}(film)/cm^{-1} 3049, 2920, 2105, 1639, 1374 and 1328; δ_H (250 MHz; $CDCl_3$) 5.90-574 (1 H, m, CH_2=C<u>H</u>-), 5.29 (1 H, bs, <u>H</u>-CH_2-), 5.12-4.98 (2 H, m, <u>CH_2</u>=), 2.40-2.34 (4 H, m, (<u>CH_2</u>)2).

Representative Procedure for Tin Coupling Reactions

Purification of the tin coupling products was only rough, cleaner products being obtained from the diazo transfer reactions of the following step. Identification was undertaken by the ^{1}H NMR, which showed sizable peaks due to impurities.



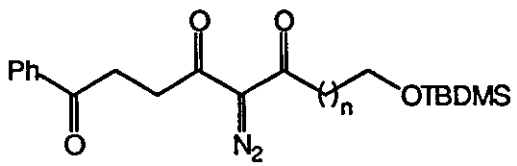
(170)

1-t-Butyldimethylsiloxy-10-phenyl-5,7,10-decanetrione (170)

To a solution of 1-t-butyldimethylsiloxypentanal (1.2 g, 5.3 mmol) and 1-diazo-5-phenyl-2,5-pentanedione (1 g, 5.3 mmol) in dry DCM (5 ml) under nitrogen, at 0°C, was added anhydrous tin (II) chloride (200 mg, 20 mol%). The reaction mixture was stirred for ca. 4 h until complete by TLC. The reaction mixture was filtered through a short silica plug, using DCM as eluent (50 ml). The filtrate was collected and solvent removed to leave a brown residue. Chromatography on the resultant oil (ether/light petroleum eluent) gave the desired coupled product of limited purity, which was used directly for diazo transfer without further purification or characterisation.

General Procedure for Diazo Transfer Reactions

To a stirred solution of the β-diketone (1.5 mmol) and mesyl azide (2 mmol) in acetonitrile was added triethylamine (2 mmol). The reaction mixture was stirred until complete by TLC (normally 2-4 h). Once complete the reaction mixture was diluted with water (50 ml) and extracted with ether (2x50 ml). The ether layers were combined and washed successively with 10% sodium hydroxide (50 ml) and brine (50 ml). The ether layer was dried ($MgSO_4$) and removed *in vacuo*. Chromatography on the resulting oils (ether/light petroleum eluent) gave the *title compounds*.



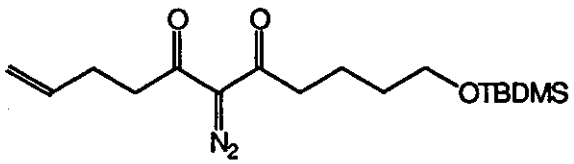
(171)

1-t-Butyldimethylsiloxy-6-diazo-10-phenyl-5,7,10-decanetrione (171a)

(316 mg, 58%); ν_{max}(film)/cm^{-1} 2929, 2896, 2857, 2120, 1668 and 1605; δ_H (250 MHz; $CDCl_3$) 8.03-7.87 (2 H, m, o-Ph), 7.45-7.23 (3 H, m, Ph), 3.59 (2 H, t, *J*= 6.21, O-$\underline{CH_2}$-), 3.32 (2 H, t, *J*= 5.56, PhCO-$\underline{CH_2}$-), 3.12 (2 H, t, *J*= 4.62, -$\underline{CH_2}$-$COCH_2$), 2.73 (2 H, t, *J*= 7.04, -CH_2CO-$\underline{CH_2}$-), 1.74-1.49 (4 H, m, -$(\underline{CH_2})_2$-), 0.84 (9 H, s, ^{t}Bu-Si), 0.046 (6 H, s, Me_2Si); δ_C (62.9 MHz; $CDCl_3$) 197.3, 192.5, 189.1, 137.8, 133.1, 128.5, 127.9, 78.6, 62.6, 40.4, 34.3, 32.4, 32.0, 25.7, 20.4, 18.2, -3.7.

1-t-Butyldimethylsiloxy-4-diazo-8-phenyl-3,5,8-octanetrione (171b)

(478 mg, 65%); ν_{max}(film)/cm^{-1} 2955, 2992, 2857, 2126, 1687 and 1662; δ_H (250 MHz; $CDCl_3$) 7.96-7.92 (2 H, m, Ph), 7.52-7.38 (3 H, m, Ph), 3.91 (2 H, t, *J*= 6.1, SiO-$\underline{CH_2}$), 3.35-3.29 & 3.19-3.14 (2 H, m, $(\underline{CH_2})_2$), 2.84 (2 H, t, *J*= 6.07, CO-$\underline{CH_2}$), 0.81 (9 H, s, ^{t}Bu-Si), 0.92 (6 H, s, Si-$\underline{Me_2}$); δ_C (62.9 MHz; $CDCl_3$) 198.1, 191.2, 189.6, 136.6, 133.2, 128.6, 128.1, 59.5, 42.7, 34.9, 32.5, 25.8, 18.3, -5.5.



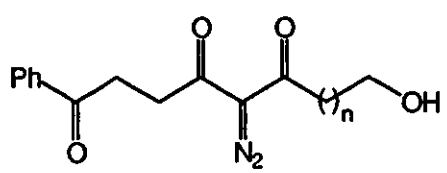
(176)

1-t-Butyldimethylsiloxy-5,7-dioxo-6-diazo-undecan-10-ene (176)

(550 mg, 86%); ν_{max}(film)/cm^{-1} 2954, 2930, 2857, 2115, 1669 and 1655; δ_H (250 MHz; $CDCl_3$) 5.89-5.78 (1 H, m, CH_2=C<u>H</u>-), 5.11-4.98 (2 H, m, <u>CH_2</u>=), 3.63 (2 H, t, J= 6.16, SiO-<u>CH_2</u>-), 2.85 (2 H, t, J= 7.16, -<u>CH_2</u>-CO), 2.75 (2 H, t, J= 7.03, CO-<u>CH_2</u>) 2.45-2.39 (2 H, m, =CH-<u>CH_2</u>-), 1.76-1.53 (4 H, m, $(CH_2)_2$), 0.90 (9 H, s, ^{t}Bu-Si), 0.044 (6 H, s, Si-Me_2); δ_C (62.9 MHz; $CDCl_3$) 204.3, 192.2, 136.6, 115.7, 62.7, 40.5, 40.0, 32.1, 28.0, 25.9, 20.7, 18.2.

General Procedure for Deprotection of Silyl Protected Alcohols

To a stirred solution of the diazo (0.75-1.5 mmol) in THF (5 ml) at 0°C, under nitrogen, was added dropwise, 0.9 ml (1.14 ml per mmol of substrate) of hydrogen fluoride pyridine complex. The reaction mixture was stirred for 3-4 h at 0°C. If not complete after this time, more HF-py complex was added (0.1 ml), and the reaction mixture stirred for 30 mim. Once complete by TLC, the reaction mixture was diluted with ether (50 ml) and excess hydrogen fluoride destroyed with sodium hydrogencarbonate. The ether layer was then washed with water (2x50 ml), brine (2x50 ml) and dried ($MgSO_4$). Removal of the solvent *in vacuo* left a dark coloured oil, which was purified by column chromatography (neat ether/ethyl acetate eluent) to give the *title compounds.*



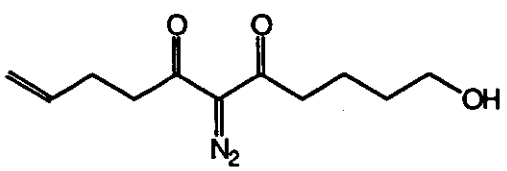
(172)

6-Diazo-1-hydroxy-10-phenyl-5,7,10-decanetrione (172a)

(111 mg, 47%); ν_{max}(film)/cm^{-1} 3486, 2939, 2125, 1733, 1666, 1662 and 1597; δ_H (250 MHz; $CDCl_3$) 7.99-7.85 (2 H, m, Ph), 7.57-7.14 (3 H, m Ph), 3.60 (2 H, t, *J*= 6.1, HO-$\underline{CH_2}$-), 3.38 (2 H, t, *J*= 6.2, PhCO-$\underline{CH_2}$-), 3.13 (2 H, t, *J*= 5.54, -$\underline{CH_2}$-CO), 2.78 (2 H, t, *J*= 7.3, CO-$\underline{CH_2}$-), 2.48 (1 H, bs, $\underline{OH}$), 1.79-1.53 (4 H, m, ($\underline{CH_2}$)2); δ_C (62.9 MHz; $CDCl_3$) 198.2, 191.2, 189.5, 136.4, 133.3, 128.6, 128.1, 84.2, 62.0, 40.3, 34.3, 32.5, 31.9, 20.2.

4-Diazo-1-hydroxy-8-phenyl-3,5,8-octanetrione (172b)

(127 mg, 41%); found: MH$^+$, 275.1030. $C_{14}H_{15}N_2O_4$ requires 275.1032; ν_{max}(film)/cm^{-1} 3548, 2864, 2947, 2938, 2128, 1665, 1610 and 1595; δ_H (250 MHz; $CDCl_3$) 7.99-7.5 (2 H, m, Ph), 7.57-7.14 (3 H, m, Ph), 3.93 (2 H, t, *J*= 5.41, HO-$\underline{CH_2}$), 3.39 (2 H, t, *J*= 5.66, PhCO-$\underline{CH_2}$), 3.14 (2 H, t, *J*= 4.82, -$\underline{CH_2}$-CO), 2.99 (2 H, t, *J*= 5.45, CO-$\underline{CH_2}$), 2.85 (1 H, bs, $\underline{OH}$); δ_C (62.9 MHz; $CDCl_3$) 198.3, 191.2, 189.8, 137.5, 133.4, 128.7, 128.1, 84.7, 58.0, 43.0, 34.3, 32.5; *m/z* (CI) MH$^+$ 275 (25%), 247 (100).



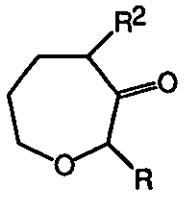
(177)

5,7-Dioxo-1-hydroxy-6-diazo-undecan-10-ene (177)

(297 mg, 85%); found: MH$^+$, 225.1240. $C_{11}H_{17}N_2O_3$ requires 225.1239; ν_{max}(film)/cm^{-1} 3424, 3079, 2940 2124, 1663 and 1436; δ_H (250 MHz; $CDCl_3$) 5.89-5.75 (1 H, m, CH_2=$\underline{CH}$-), 5.11-4.98 (2 H, m, $\underline{CH_2}$=), 3.64 (2 H, t, *J*= 6.23, HO-$\underline{CH_2}$), 2.87-2.61 (4 H, m, 2x CO-$\underline{CH_2}$), 2.44-2.36 (2 H, q, *J*= 6.96, =CH-$\underline{CH_2}$-), 1.91-1.55 (5 H, m, ($\underline{CH_2}$)2 & $\underline{OH}$); δ_C (62.9 MHz; $CDCl_3$) 192.3, 190.1, 136.5, 115.8, 83.7, 62.0, 40.2, 39.8, 31.9, 27.9, 20.3; *m/z* (CI) MH$^+$ 225 (10%), 207 (20), 197 (100), 179 (97).

General Procedure for Decomposition/Competition Experiments

The relevant di-functional diazo compound (100 mg) was taken up in dry benzene (5 ml) under nitrogen. Once the reaction mixture was refluxing, the catalyst was added and the reaction course followed by TLC. Once complete, the benzene was removed *in vacuo* and the resulting residue was subjected to a short silica plug (100 ml, 50% ether/light petroleum eluent). The solvent was removed and the resulting residue was purified by chromatography (ether/light petroleum eluent).



(178)

Methyl 4-Allyl-3-oxooxepane-2-carboxylate

(31 mg, 35%); found: MH^+, 213.1130. $C_{11}H_{17}O_4$ requires 213.1127; ν_{max}(film)/cm^{-1} 2952, 2937, 2863, 1754, 1720, 1642 and 1436; δ_H (250 MHz; $CDCl_3$) 5.78-5.61 (1 H, m, CH_2=C<u>H</u>-), 5.07-4.99 (2 H, m, <u>CH_2</u>=), 4.49 (1 H, s, O-<u>C</u>H-(CO_2Me)-CO), 4.35-4.28 (1 H, m, O-<u>CH_2</u>-), 3.78 (3 H, s, <u>OMe</u>), 3.39-3.30 (1 H, dt, *J*= 4.3 & 1.8, O-<u>CH_2</u>-), 3.16-3.07 (1 H, m, CO-<u>C</u>H-(CH_2)$_3$-), 2.55-2.45 (1 H, m, =CH_2-<u>CH_2</u>), 2.13-1.74 (5 H, m, =CH_2-<u>CH_2</u>- & (<u>CH_2</u>)$_2$); δ_C (62.9 MHz; $CDCl_3$) 208.5 (keto), 166.2 (keto), 168.4 (enol), 135.4 (enol), 135.3 (keto), 116.9 (keto), 116.7 (enol), 86.6 (keto), 84.5 (enol), 73.1 (enol), 72.3 (keto), 70.7 (enol), 52.7 (keto), 52.2 (enol), 48.6 (keto), 43.2 (enol), 34.7 (keto), 34.4 (enol), 30.1 (keto), 29.8 (enol), 28.8 (keto), 29.6 (enol); *m/z* (CI) MH^+ 213 (100%).

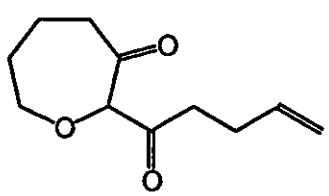
Methyl 4-Benzyl-3-oxooxepane-2-carboxylate

(49 mg, 53%); found: MH^+, 263.1280. $C_{15}H_{19}O_4$ requires 263.1283; ν_{max}(film)/cm^{-1} 3042, 2940, 2855, 1754, 1720, 1603 and 1496; δ_H (250 MHz; $CDCl_3$) 7.28-7.12 (5 H, m, Ph), 4.45 (1 H, s, O-<u>C</u>H-CO(CO_2Me)-), 4.31-4.25 (1

H, m, O-$\underline{CH_2}$), 3.48 (3 H, s, $\underline{OMe}$), 3.46-3.37 (1 H, m, -CO-$\underline{CH}$(Bz)-CH_2-), 3.32-3.36 (1 H, dt, *J*= 10 & 1.7, -$\underline{CH_2}$-O-), 3.13-3.05 (1 H, m, -$\underline{CH_2}$-Ph), 2.65-2.57 (1 H, m, -$\underline{CH_2}$-Ph), 1.95-1.40 (4 H, m, ($\underline{CH_2}$)2); δ_C (62.9 MHz; $CDCl_3$) 208 (enol), 168.2 (enol), 166.1 (keto), 139.5 (keto), 139.3 (enol), 129.2 (keto), 129.0 (enol), 128.4 (enol), 128.3 (keto), 126.3 (enol), 126.1 (keto), 86.7 (keto), 84.5 (enol), 71.7 (keto), 70.7 (enol), 53.0 (keto), 52.7 (enol), 50.9 (enol), 49.7 (enol), 36.9 (keto), 36.4 (enol), 30.7 (keto), 29.9 (enol), 29.6 (keto), 29.1 (enol); *m/z* (Cl) MH^+ 263 (85%), 245 (25), 91 (45).

Methyl 3-Oxo-4-propargyloxepane-2-carboxylate

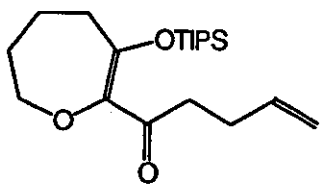
(32 mg, 37%); found: MH^+, 211.0970. $C_{11}H_{15}O_4$ requires 211.0970; ν_{max}(film)/cm^{-1} 3286, 2954, 2933, 1753, 1720 and 1449; δ_H (250 MHz; $CDCL_3$) 4.5 (1 H, s, O-$\underline{CH}$-CO(CO_2Me)-), 4.38-4.33 (1 H, m, O-$\underline{CH_2}$), 4.06-3.87 (1 H, m, HC≡C-CH_2-$\underline{CH}$-), 3.81 (enol) & 3.78 (keto) (3 H, s, $\underline{OMe}$), 3.40-3.30 (1 H, dt, *J*= 11.4 & 1.65, -$\underline{CH_2}$-O-), 2.57-2.47 (2 H, m, HC≡C-$\underline{CH_2}$-), 1.99 (1 H, t, *J*= 2.16, $\underline{HC}$≡C-), 1.38-1.26 (4 H, m, ($\underline{CH_2}$)2); δ_C (62.9 MHz; $CDCl_3$) 207.7 (keto), 165.4 (keto), 163.5 (enol), 86.7 (keto), 84.2 (enol), 73.1 (enol), 72.7 (keto), 70.6 (keto), 69.9 (enol), 69.5 (keto), 53.0 (keto), 52.4 (keto), 52.1 (enol), 50.6 (enol), 48.7 (keto), 29.8 (keto), 29.2 (keto), 28.7 (enol), 26.9 (enol), 20.3 (keto), 19.3 (enol); *m/z* (Cl) MH^+ 211 (55%), 157 (100), 139 (80), 58 (82).



(189a)

2-(1-Oxopent-4-ene)-3-oxo-4,5,6,7-tetrahydrooxepin (189a)

δ_H (250 MHz; $CDCL_3$) 13.91 (1 H, bs, $\underline{OH}$), 8.02-7.97 (2 H, m, Ar), 7.60-7.26 (3 H, m, Ar), 3.93 (2 H, t, *J*= 5.03, O-$\underline{CH_2}$-), 3.37 (2 H, t, *J*= 7.02, CO-$\underline{CH_2}$-), 2.99 (2 H, t, *J*= 6.78, -$\underline{CH_2}$-CO-), 2.61 (2 H, m, HO-C-$\underline{CH_2}$-), 1.96-1.68 (4 H, m, ($\underline{CH_2}$)2); δ_C (62.9 MHz; $CDCL_3$) 198.6, 190.2, 136.8, 133.0, 128.5, 127.9, 74.3, 36.7, 32.7, 31.9, 30.2, 28.1, 25.5, 22.7.

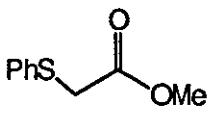


(189b)

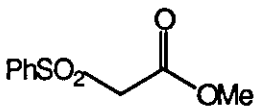
2-(1-Oxopent-4-ene)-3-triisopropylsiloxy-4,5,6,7-tetrahydrooxepin (189b)

To a stirred solution of 2-(1,4-Dioxo-4-phenylbutyl)-3-hydroxy-4,5,6,7-tetrahydrooxepin (79 mg, 0.40 mmol) and triethylamine (41 mg, 0.40 mmol) in DCM (2 ml) at 0°C under nitrogen was added triisopropylsilyltriflate (122 mg, 0.40 mmol) dropwise. The reaction mixture was stirred overnight and allowed to come to room temperature. The reaction mixture was diluted with water (5 ml) and ether (5 ml). The organic layer was washed sequentially with water (5 ml) and brine (5 ml). The ether was dried ($MgSO_4$) and removed *in vacuo* to leave a pale yellow oil. Chromatography on the residue (ether/light petroleum eluent) gave the *title compound* as a colourless oil (18 mg, 13%); found: MH^+, 353.2512. $C_{20}H_{37}O_3Si$ requires 353.2512; δ_H (250 MHz; $CDCL_3$) 5.89-5.77 (1 H, m, CH_2=C<u>H</u>-), 5.08-4.93 (2 H, m, <u>CH_2</u>=), 3.83 (2 H, t, *J*= 6.56, O-<u>CH_2</u>-), 2.71-2.63 (4 H, m, CH_2=CH-<u>CH_2</u>- & O-C=C-<u>CH_2</u>-), 2.34-2.28 (2 H, m, CO-<u>CH_2</u>-), 1.86-170 (4 H, m, (<u>CH_2</u>)2), 1.07 (21 H, s, $^iPr_3$); δ_C (62.9 MHz; $CDCl_3$) 201.6, 137.8, 114.9, 75.0, 44.2, 33.7, 32.0, 31.2, 23.7, 18.0, 13.4; *m/z* (CI) MH^+ 253 (25%), 197 (25), 58 (100), 44 (95).

Experimental for Chapter Three



(200)



(201)

Methyl phenylthioacetate (200)

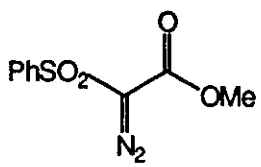
To a fresh solution of sodium methoxide (2 g, 86 mmol) in methanol (100 ml) was added thiophenol (8 g, 72 mmol). The reaction mixture was stirred at room temperature for ca. 0.5 h. Methyl bromoacetate (13.5 g, 88 mmol) was added dropwise and the reaction mixture stirred for a further 18 h. The methanol was reduced *in vacuo* and the resulting residue diluted with water. The water layer was extracted with ether (2x100 ml). The ether was dried ($MgSO_4$) and removed *in vacuo* to leave a pale yellow oil. Kugelrohr distillation gave the *title compound* as a colourless oil (9.8 g, 63%), b.p. 110°C, 0.3 mmHg; found: M^+, 182.0402. $C_9H_{10}O_2S$ requires 184.0402; ν_{max}(film)/cm^{-1} 2980, 2953, 1736, and 1582; δ_H (250 MHz; $CDCl_3$) 7.41-7.17 (5 H, m, Ph), 3.69 (3 H, s, OMe), 3.64 (2 H, s, PhS-CH_2-); δ_C (62.9 MHz; $CDCl_3$) 170.0, 134.6, 129.8, 129.0, 126.9, 52.4, 36.3; *m/z* (EI) M^+ 182 (90%), 123 (100), 45 (72).

Methyl phenylsulphonylacetate (201)

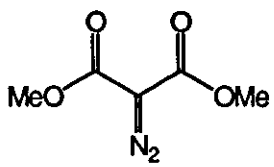
To a cooled methanolic solution of methyl phenylthioacetate (1 g, 15 mmol) at 0°C was added a slurry of Oxone (27 g, 45 mmol) in water (100 ml), over 10 min. Once added the reaction mixture was stirred at room temperature for 2 h. Excess Oxone was filtered off and the filtrate diluted with water (100 ml) before extraction into ether (2x100 ml). The organic layer was dried ($MgSO_4$) and removed *in vacuo* to leave a colourless oil. Kugelrohr distillation gave the *title compound* as a colourless oil (1.7 g, 54%); b.p. 182°C, 0.8 mmHg; found: MNH_4^+, 232.0644. $C_9H_{14}NO_4S$ requires 232.0638; ν_{max}(film)/cm^{-1} 2952, 1744 and 1584; δ_H (250 MHz; $CDCl_3$) 7.97-7.94 & 7.70-7.56 (5 H, m, Ph), 4.15 (2 H, s, CH_2), 3.70 (3 H, s, OMe); δ_C (62.9 MHz; $CDCl_3$) 162.9, 138.7, 134.4, 129.3, 128.5, 60.8, 53.1, *m/z* (CI) MNH_4^+ 232 (100%).

General Procedure for Diazo Transfer Reactions

To a solution of an active methylene compound in acetonitrile was added tosyl azide (1 eq) and triethylamine (1.2 eq). The solution was stirred at room temperature for ca. 20 h. Afterwards, water (100 ml) and 10% sodium hydroxide solution (30 ml) were added. The aqueous layer was extracted with ether (2x150 ml). The ether layer was dried ($MgSO_4$) and removed *in vacuo*, to leave a pale yellow oil. Purification by column chromatography (ether/light petroleum eluent) gave the *title compounds.*



(197)



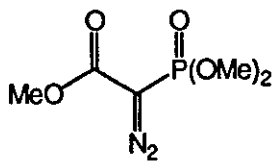
(198)

Methyl Phenylsulphonyldiazoacetate (197)

Diazo transfer was carried out as above on methyl phenylsulphonylacetate; removal of the solvent gave a yellow solid, which was recrystallized from ether to give the *title compound* as pale yellow needles (3.1 g, 65%); found: MNH_4^+, 258.0549. $C_9H_{12}N_3O_4S$ requires 258.0549; ν_{max}(film)/cm^{-1} 2124, 1718 and 1582; δ_H (250 MHz; $CDCl_3$) 8.09-8.01 & 7.82-7.39 (5 H, m, Ph), 3.77 (3 H, s, O<u>Me</u>); δ_C (62.9 MHz; $CDCl_3$) 160.0, 141.6, 134.1, 129.2, 127.8, 52.9; *m/z* (CI) MNH_4^+ 258 (100%), 241 (50), 125 (45), 102 (42).

Dimethyl diazomalonate (198)

Standard diazo transfer conditions on dimethylmalonate (6 g, 30 mmol) gave the *title compound* as a yellow oil (5 g, 55%); ν_{max}(film)/cm^{-1} 3620, 2132, 1762. δ_H (250 MHz; $CDCl_3$) 3.8 (6 H, s, (O<u>Me</u>)2), δ_C (62.9 MHz; $CDCl_3$) 160.7, 51.5.



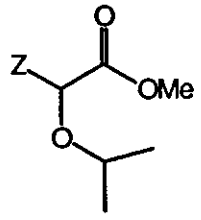
(199)

Trimethyl diazophosphonoacetate (199)

Trimethyl phosphonoacetate (5 g, 27 mmol) was added to a freshly made refluxing suspension of potassium butoxide in benzene (20 ml) (potassium 1.2 g, 30 mmol in *tert*-BuOH 2.2 g 30 mmol) under nitrogen. The reaction mixture was refluxed for 10 min and then allowed to cool to room temperature. Once cold, tosyl azide (5.3 g, 27 mmol) in benzene (50 ml) was added over 10 min. The reaction mixture was stirred for an additional 4 h at room temperature. The benzene was washed with 10% sodium hydroxide (2x100 ml) and water (2x100 ml). The organic layer was dried ($MgSO_4$) and removed *in vacuo* to leave a dark yellow oil. Purification by column chromatography (ether eluent) gave the *title compound* as a pale yellow oil (2.2 g 40%); found: C, 28.79; H, 4.35; N, 13.08 $C_5H_9N_2O_5P$ requires C,28.84; H, 4.32; N, 13.46; found M^+, 208.0249. $C_5H_9N_2O_5P$ requires 208.0249; ν_{max}(film)/cm^{-1} 2956, 2128, 1710; δ_H (250 MHz; $CDCl_3$) 3.82 (6 H, s, P-(O<u>Me</u>)$_2$), 3.87 (3 H, s, CO-O<u>Me</u>); δ_C (62.9 MHz; $CDCl_3$) 163.4, 54.0, 53.9, 52.7; *m/z* (EI, 70 eV) M^+ 208 (25%), 189 (100), 93 (100), 79 (70), 63 (90), 47 (85).

General Procedure for Isopropanol Insertion Reactions

The diazo compound (100 mg) was dissolved in *iso*-propanol (2 ml). To this solution was added the rhodium catalyst (2 mol%). The reaction mixture was stirred at room temperature until adjudged complete by TLC. Once the reaction was complete the *iso*-propanol was removed *in vacuo* and the residue purified by column chromatography (ether/light petroleum eluent) to give the *title compound*. If no insertion had occurred at room temperature after 2 days, the reaction mixture was refluxed until completion and work-up was completed as above.



(202)

Methyl 2-isopropyloxyphenylsulphonylacetate (202)

(99 mg, 89%); found: MNH_4^+, 290.1062. $C_{12}H_{20}NO_5S$ requires 290.1062; ν_{max}(film)/cm^{-1} 2979, 2935, 1754, 1448, 761 and 688; δ_H (250 MHz; $CDCl_3$) 7.57-7.48 & 7.30-7.19 (5 H, m, Ph), 4.98 (1 H, s, ^iPrO-CH-), 4.06-3.91 (1 H, hp, *J*= 6.14, $(Me)_2$-CH-), 3.77 (3 H, s, CO-OMe), 0.90-0.89 (3 H, d, *J*= 1.66, Me-CH(Me)-), 0.88-0.87 (3 H, d, *J*= 1.48, Me-CH(Me)-); δ_C (62.9 MHz; $CDCl_3$) 164.8, 135.7, 134.5, 129.9, 128.9, 92.4, 76.7, 53.3, 22.0, 21.4; *m/z* (CI) MNH_4^+ 290 (100%), 273 (25), 185 (75).

Dimethyl 2-isopropyloxymalonate (202)

(98 mg, 89%); found: MNH_4^+, 208.1185. $C_8H_{18}NO_5$ requires 208.1185; ν_{max}(film)/cm^{-1} 2977, 2939, 1790, 1438, 1385 and 1022; δ_H (250 MHz; $CDCl_3$)4.61 (1 H, s, ^iPrO-CH), 3.81 (6 H, s, $(CO\text{-}OMe)_2$), 3.81-3.72 (1 H, hp, *J*= 6.13, (Me_2)CH-), 1.23-1.19 (6 H, d, *J*= 9.42, $(Me)_2$CH); δ_C (62.9 MHz; $CDCl_3$) 167.6, 76.6, 73.5, 52.8, 21.8; *m/z* (CI) MNH_4^+ 208 (100%).

Trimethyl 2-isopropyloxyphosphonoacetate (202)

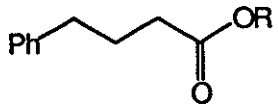
(22 mg, 20%); found: MH^+, 241.0841. $C_8H_{18}O_6P$ requires 241.0841; ν_{max}(film)/cm^{-1} 2962, 1754, 1139 and 1034; δ_H (250 MHz; $CDCl_3$) 4.48-4.40 (1 H, d, *J*= 20.0, ^iPrO-CH-), 3.88-3.84 (9 H, m, (MeO)P(O) & CO-OMe), 3.87-3.70 (1 H, hp, *J*= 6.13, $(Me)_2$CH-), 1.25-1.21 (6 H, m, $(Me)_2$CH-); δ_C (62.9 MHz; $CDCl_3$) 168.9, 76.4, 75.3, 74.8, 72.7, 54.1-52.7, d, *J* = 89.4, 22.0, 21.1; *m/z* (CI) MH^+ 241 (100%), 199 (75).

General Procedure for Synthesis of Rhodium (II) Carboxylates

Rhodium (II) acetate (100 mg, 0.226 mmol) was placed in a dry 25 ml round bottom flask under argon. The appropriate ligand (12-14 eq.) was placed in the flask and this mixture heated to 120°C until the reaction mixture was a melt. The reaction mixture was stirred as a melt for 12 h, then cooled to room temperature. Once cool the solid was dissolved in DCM (30 ml) and washed with 5% sodium hydroxide solution (30 ml). The organic layer was dried ($MgSO_4$) and removed *in vacuo*. The residue was purified by column chromatography (ethyl acetate/light petroleum eluent) to give the required catalyst. Identification was checked by FAB mass spectrometry (all the catalysts used have previously been described - see Chapter Three).

Experimental for Chapter Four

α-Diazoesters



(226)

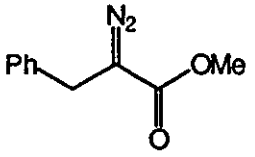
Ethyl 4-Phenylbutanoate (226)

To a solution of 4-phenylbutanoic acid (10 g, 61 mmol) in ethanol (150 ml) was added 6 drops of conc. hydrochloric acid. The reaction mixture was refluxed overnight. After this time, the ethanol was removed *in vacuo* to leave a pale yellow oil. Distillation of this residue gave the *title compound*, (9.95 g, 85%) b.p. 218-220°C, 30 mmHg; δ_H (250 MHz; $CDCl_3$) 7.32-7.06 (5 H, m, Ar), 4.16-4.07 (2H, q, J= 7.14, $\underline{OCH_2}$), 2.65 (2 H, t, J= 7.31, Ph-$\underline{CH_2}$), 2.16 (2 H, t, J= 7.83, CO-$\underline{CH_2}$), 1.93 (2H, p, J= 7.36, -CH_2-$\underline{CH_2}$-CH_2), 1.28 (3 H, t, J= 10.94, OCH_2-$\underline{CH_3}$).

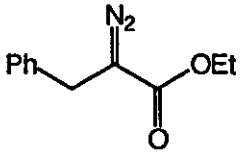
Menthyl 4-Phenylbutanoate (226)

4-Phenylbutanoic acid (5 g, 30 mmol) was dissolved in DCM (100 ml) under nitrogen. A catalytic amount of DMF was added, followed by oxalyl chloride (3.2 ml, 37 mmol). The reaction mixture was stirred at room temperature until hydrogen chloride evolution ceased. The resulting solution was concentrated *in vacuo*. This crude acid chloride was then added dropwise to a stirred solution of menthol (5.8 g, 37 mmol) and triethylamine (3.7 g, 37 mmol) in DCM (100 ml) at room temperature protected by a drying tube. Once the addition was complete, the reaction mixture was left to stir overnight. The resulting suspension was washed with water (2x100 ml), dried ($MgSO_4$) and removed *in vacuo*, to leave a dark coloured oil. Column chromatography on this oil (ether/light petroleum eluent), gave the *title compound* as a colourless oil, (5 g, 55%); found: M^+, 302.2250. $C_{20}H_{30}O_2$ requires 302.2246; $[\alpha]_D^{23}$= +55.47° (c= 0.505 in $CHCl_3$); ν_{max}(film)/cm^{-1} 3027, 2955, 2928, 1728, 1454, 742 and 699; δ_H (250 MHz; $CDCl_3$) 7.30-7.07 (5 H, m, Ar), 4.76-4.65 (1 H, dt, J= 10.80 & 4.34, O-$\underline{CH}$), 2.64 (2 H, t, J= 7.32, -$\underline{CH_2}$-CO), 2.30 (2 H, t, J= 7.50, Ph-$\underline{CH_2}$), 2.01-1.84 (4 H, m, CH_2-$\underline{CH_2}$-$\underline{CH_2}$ & $(\underline{CH})_2$), 1.71-1.32 (4 H, m, $(\underline{CH_2})_2$), 1.12-0.83 (9 H, m, $\underline{CH}$ & $\underline{CH_2}$ & $(Me)_2$), 0.78 (3 H, d, J= 6.91, Me); δ_C (62.9 MHz; $CDCl_3$) 172.9, 141.5,

128.5, 128.4, 125.9, 74.0, 47.1, 41.0, 35.2, 34.3, 34.1, 31.4, 26.8, 26.3, 23.4, 22.0, 20.7, 16.3; *m/z* (EI, 70 eV), M^+ 302 (0.4%), 138 (55), 91 (50), 83 (100).



(218)



(212)

Methyl 2-Diazo-3-phenylpropanoate (218)

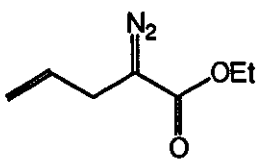
Phenylalanine methyl ester hydrochloride (1000 mg, 4.6 mmol) was dissolved in water (10 ml). To this solution, sodium hydroxide (186 mg, 4.6 mmol) was added and the reaction mixture stirred at room temperature for ca. 15 min. After this time the aqueous reaction mixture was extracted with ethyl acetate (2x20 ml). The organic layer was dried ($MgSO_4$) and removed *in vacuo* to leave a colourless oil. This crude free ester was dissolved in chloroform (25 ml). To this solution was added isoamyl nitrite (645 mg, 5.52 mmol) and glacial acetic acid (90 mg, 1.5 mmol). The reaction mixture was refluxed for ca. 20 min. Once completed the reaction mixture was cooled and washed sequentially with 1 N sulphuric acid (20 ml), water (2x20 ml) and satd. sodium bicarbonate solution (20 ml). The chloroform layer was dried ($MgSO_4$) and removed *in vacuo* to leave a dark yellow oil. Column chromatography (ether/light petroleum eluent) on this residue furnished the *title compound* as a yellow oil, (584 mg, 67%); ν_{max}(film)/cm^{-1} 2084, 1739, 1457, 1351, 737 and 701; δ_H (250 MHz; $CDCl_3$) 7.36-7.20 (5 H, m, Ar), 3.78 (3 H, s, OMe), 3.30 (2 H, s, CH_2); δ_C (62.9 MHz; $CDCl_3$) 137.2, 128.8, 128.5, 128.3, 127.1, 64.9, 52.0, 29.3. Subsequent attempts to repeat this preparation led to material of lower purity and attempts to clean the material up have failed.

Ethyl 2-Diazo-3-phenylpropanoate (212)

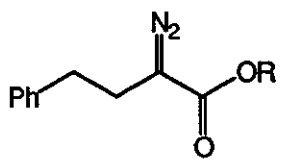
The *title compound* was prepared by the literature procedure of Schollkopf with the following modifications:

1) After addition of the silver (I) oxide was complete, the reaction mixture was stirred for 5 h at 0°C,
2) After addition of benzyl bromide the reaction mixture was allowed to warm to room temperature and was stirred at room temperature for 5 days,
3) After work-up, the residue was purified by column chromatography (ether/light petroleum eluent).

Yellow oil, (2.5 g, 52%); ν_{max}(film)/cm^{-1} 2982, 2084, 1686, 1455, 1267, 1107, 738 and 700; δ_H (250 MHz; $CDCl_3$) 7.33-7.21 (5 H, m, Ar), 4.35-4.15 (2 H, q, J= 7.13, $\underline{OCH_2}$), 3.55 (2 H, s, Ph-$\underline{CH_2}$), 1.27 (3 H, t, J= 7.08, CH_2-$\underline{CH_3}$); δ_C (62.9 MHz; $CDCl_3$) 137.2, 129.4, 128.1, 127.0, 60.8, 53.3, 29.2, 14.4.



(222)



(227)

Ethyl 2-Diazopent-4-enoate (222)

The *title compound* was prepared by the same method as ethyl 2-diazo-3-phenylpropanoate (**212**) using allyl bromide in place of benzyl bromide, except after the addition of allyl bromide the reaction mixture was stirred for 8 days. (540 mg, 13%) ν_{max}(film)/cm^{-1} 2084, 1692, 1630, 1371 and 1334; δ_H (250 MHz; $CDCl_3$) 5.90-5.74 (1 H, m, -$\underline{CH}$=CH_2), 5.20-5.01 (2 H, m, CH=$\underline{CH_2}$), 4.27-4.06 (2 H, q, J= 7.00, $\underline{OCH_2}$), 3.07-3.03 (2 H, m, =CH-$\underline{CH_2}$), 1.31-1.24 (3 H, t, J= 6.99, $OCH_2\underline{CH_3}$); δ_C (62.9 MHz; $CDCl_3$) 132.6, 117.6, 60.88, 53.2, 27.3, 14.5.

Ethyl 2-Diazo-4-phenylbutanoate (227a)

To a solution of ethyl formate (518 mg, 7 mmol) and ethyl 4-phenylbutanoate (1000 mg, 5.2 mmol) in THF (20 ml) at 0°C under nitrogen, was added freshly prepared LDA (7 mmol) (prepared from diisopropylamine (709 mg, 7 mmol) and *n*-butyl lithium (4.5 ml, 1.6 M) over ca. 5 min. Once the addition was complete

the reaction mixture was stirred for ca. 20 min at 0°C. After this time, mesyl azide (847 mg, 7 mmol) was added, and the reaction mixture left to warm up to room temperature over 2 h. The reaction mixture was diluted with water (20 ml) and extracted into ether (30 ml). The ether layer was washed with 5% sodium hydroxide (30 ml) and water (2x30 ml). The organic layer was then dried ($MgSO_4$) and removed *in vacuo*, to leave a dark yellow oil. Column chromatography on this residue gave the *title compound*, contaminated with some starting ethyl 4-phenyl butanoate (ca. 40% starting material); (total mass 500 mg, 44%); ν_{max}(film)/cm^{-1} 2083, 1734 (sm), 1690; δ_H (250 MHz; $CDCl_3$) 7.33-7.16 (7.5 H, m, Ar), 4.25-4.17 (2 H, q, *J*= 7.09, $\underline{OCH_2}$ (prod.)), 4.16-4.07 (0.4 H, q, *J*= 7.14, $\underline{OCH_2}$ (sm)), 2.83 (2 H, t, *J*= 7.70, -$\underline{CH_2}C{=}N_2$ (prod.)), 2.65-2.56 (2.9 H, m, Ph-$\underline{CH_2}$ (sm & prod.), 2.32 (0.83 H, t, *J*= 7.33, CO-$\underline{CH_2}$ (sm)), 2.01-1.89 (0.78 H, p, *J*= 7.10, CH_2-$\underline{CH_2}$-CH_2 (sm)), 1.28-1.21 (3.5 H, m, OCH_2-$\underline{CH_3}$ (sm & prod.)); δ_C (62.9 MHz; $CDCl_3$) 173.2 (sm), 142.4 (sm), 140.3 (prod.), 128.6 (prod.), 128.5 (prod.), 128.4 (sm), 126.4 (prod.), 126.0 (sm), 60.8 (prod.), 60.3 (sm), 35.2 (prod.), 34.0 (sm), 33.7 (prod.), 26.6 (sm), 25.4 (prod.), 14.5 (prod.), 14.3 (sm).

Menthyl 2-Diazo-4-phenylbutanoate (227b)

To a solution of hexamethylsilazane (398 mg, 2.5 mmol) in dry THF (10 ml) under nitrogen at room temperature was added *n*-butyl lithium (1.6 M, 1.6 ml). The reaction mixture was stirred for 20 min. and then menthyl 4-phenylbutyrate (500 mg, 1.65 mmol) was added. The reaction was stirred for 1 h. After this time 2,2,2-trifluoroethyl trifluoroacetate (490 mg, 2.5 mmol) was added and the reaction mixture stirred for a further 1 h. The reaction was then quenched with 5% hydrochloric acid (10 ml) and ether (20 ml) added. The ether layer was washed with brine (2x30 ml) and dried ($MgSO_4$). Removal of the solvent *in vacuo* left an orange oil which was subjected to column chromatography (ether/light petroleum eluent), to furnish the *title compound* as a yellow oil (105 mg, 19%); ν_{max}(film)/cm^{-1} 2956, 2927, 2870, 2082, 1682, 1169, 749 and 699; δ_H (250 MHz; $CDCl_3$) 7.32-7.16 (5 H, m, Ph), 4.79-4.69 (1 H, dt, *J*= 10.80 & 4.35, O-$\underline{CH}$), 2.79 (2 H, t, *J*= 7.30, Ph-$\underline{CH_2}$), 2.56 (2 H, t, J= 6.62, -$\underline{CH_2}$-C(N_2)-), 2.04-0.91 (8 H, m, $(\underline{CH_2})_3$ & $(\underline{CH})_2$), 0.91-0.89 (6 H, m, $(Me)_2$), 0.79-0.76 (3 H,

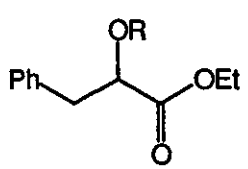
d, J= 6.92, Me); δ_C (62.9 MHz; $CDCl_3$) 140.2, 128.6, 128.5, 128.4, 126.4, 74.7, 47.2, 41.3, 34.2, 31.4, 26.5, 25.5, 23.7, 22.0, 20.7, 16.6.

General Procedure For Insertion Into Water

The appropriate α-diazoester (100 mg) was dissolved in ether (3 ml) saturated with water. To this solution was added rhodium acetate (2 mol%). The reaction mixture was stirred at room temperature until adjudged complete by TLC. Once complete, the ether was dried ($MgSO_4$) and removed *in vacuo*, to leave a dark oil. Purification by column chromatography (ether/light petroleum eluent) gave the *title compounds* as either colourless oils or white solids.

Methyl 2-Hydroxy-3-phenylpropanoate

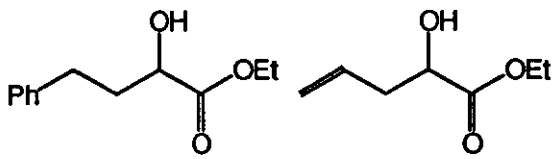
(99 mg, 65%); found: MNH_4^+, 198.1130. $C_{10}H_{16}NO_3$ requires 198.1130; δ_H (250 MHz; $CDCl_3$)7.32-7.18 (5 H, m, Ar), 4.46-4.42 (1 H, dd, J= 4.43 & 4.46, -CH-OH), 3.75 (3 H, s, OMe), 3.15-2.90 (2 H, m, Ph-CH_2-), 2.83 (1 H, bs, OH); δ_C (62.9 MHz; $CDCl_3$) 174.6, 136.3, 130.4, 128.4, 126.9, 71.2, 52.5, 40.5; *m/z* (CI), MNH_4^+ 198 (100%), 181 (20), 162 (20), 108 (20), 91 (35).



(213)

Ethyl 2-Hydroxy-3-phenylpropanoate (213)

(48 mg, 10%); found: MNH_4^+, 212.1287. $C_{11}H_{18}NO_3$ requires 212.1287; ν_{max}(film)/cm^{-1} 3504, 2982, 2934, 1735, and 1497; δ_H (250 MHz; $CDCl_3$) 7.35-7.20 (5 H, m, Ar), 4.46-4.39 (1 H, m, HO-CH-), 4.19 (2 H, q, J= 7.16, O-CH_2-), 3.25-2.91 (2 H, m, Ph-CH_2-), 2.84 (1 H, d, J =6.18 -OH), 1.25 (3 H, t, J= 7.22, OCH_2-CH_3); δ_C (62.9 MHz; $CDCl_3$) 173.4, 136.4, 129.5, 128.4, 128.1, 126.9, 71.2, 61.7, 40.6, 14.2; *m/z* (CI), MNH_4^+ 212 (70%), 195 (80), 176 (75), 91 (100).



(228a) (223b)

Ethyl 2-Hydroxy-4-phenylbutanoate (228a)

(67 mg, 70%); found: C, 68.15; H, 7.59; $C_{12}H_{16}O_3$ requires C, 69.23; H, 7.69; ν_{max}(film)/cm^{-1} 3503, 3028, 2982, 1731, 700 and 647; δ_H (250 MHz; $CDCl_3$) 7.32-7.19 (5 H, m, Ar), 4.25-4.14 (3 H, m, HO-CH- & O-CH_2-), 2.88 (1 H, d, J= 5.37, HO-), 2.80-2.73 (2 H, m, Ph-CH_2-), 2.17-1.90 (2 H, m, -CH-CH_2-), 1.28 (3 H, t, J= 7.17, OCH_2-CH_3); δ_C (62.9 MHz; $CDCl_3$) 175.3, 141.2, 128.6, 128.4, 126.0, 69.7, 61.7, 36.0, 31.1, 14.2.

Ethyl 2-Hydroxypent-4-enoate (223b)

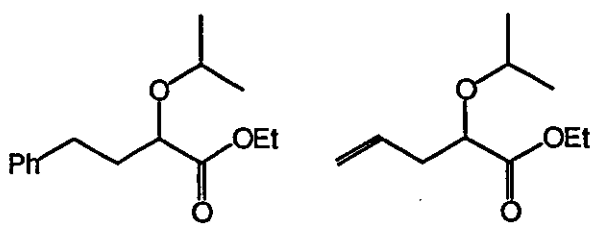
No isolated yield, only crude NMR available, δ_H (250 MHz; $CDCl_3$) 5.89-5.76 (1 H, m, -CH=CH_2), 5.19-5.12 (2 H, m, CH=CH_2), 4.30-4.20 (3 H, m, OCH_2 & -CH-OH), 3.05 (1 H, bs, OH), 3.59-2.44 (2 H, m, =CH-CH_2-), 1.33-1.30 (3 H, t, J= 7.06, OCH_2CH_3).

General Procedure For Insertion Into Isopropanol

The appropriate α-diazo ester (100 mg) was dissolved in DCM (3 ml). *iso*-Propanol (2 eq) was added followed by rhodium acetate (2 mol%). The reaction mixture was stirred at room temperature until judged complete by TLC. The DCM and excess *iso*-propanol were removed *in vacuo*, to leave a dark yellow oil. This resultant oil was subjected to column chromatography (ether/light petroleum eluent) to furnish the *title compounds* as colourless or pale yellow oils.

Ethyl 2-Isopropyloxy-3-phenylpropanoate (213)

(16 mg, 9.2%); found: MH^+, 237.1490. $C_{14}H_{21}O_3$ requires 237.1491; ν_{max}(film)/cm^{-1} 2976, 2934, 1748, 734 and 699; δ_H (250 MHz; $CDCl_3$) 7.35-7.21 (5 H, m, Ar), 4.22-4.13 (2 H, dq, *J*= 7.18 & 1.38, O-$\underline{CH_2}$), 4.08-4.02 (1 H, dd, *J*= 8.42 & 5.22, ^iPrO-$\underline{CH}$-), 3.49 (1 H, hp, J= 6.16, $Me_2\underline{CH}$-), 3.01-2.91 (2 H, m, Ph-$\underline{CH_2}$-), 1.23 (3 H, t, *J*= 7.18, $OCH_2\underline{CH_3}$), 1.16-1.14 (3 H, d *J*= 6.12, Me), 0.96-0.93 (3 H, d, *J*= 6.06, Me); δ_C (62.9 MHz; $CDCl_3$) 173.0, 137.3, 128.4, 128.0, 126.4, 78.2, 72.3, 60.7, 39.6, 22.5, 21.2, 14.1; *m/z* (CI) MH^+ 237 (50%), 195 (90), 163 (85), 91 (100).



(228b) (223a)

Ethyl 2-Isopropyloxy-4-phenylbutanoate (228b)

(70 mg, 62%); found: MNH_4^+, 268.1913. $C_{15}H_{26}NO_3$ requires 268.1913; ν_{max}(film)/cm^{-1}2974, 2933, 2905, 1749, 734 and 700; δ_H (250 MHz; $CDCl_3$) 7.30-7.18 (5 H, m, Ar), 4.23-4.14 (2 H, m, O-$\underline{CH_2}$), 3.90 (1 H, m, ^iPrO-$\underline{CH}$-), 3.60 (1 H, hp, *J*= 6.10, Me_2-$\underline{CH}$-), 2.85-2.65 (2 H, m, $PhCH_2$-$\underline{CH_2}$-), 2.06-1.97 (2 H, m, Ph-$\underline{CH_2}$), 1.28 (3 H, t, *J*= 7.10, OCH_2-$\underline{CH_3}$), 1.22-1.21 (3 H, d, *J*= 6.15, Me), 1.17-1.14 (3 H, d, *J*= 6.05, Me); δ_C (62.9 MHz; $CDCl_3$) 173.7, 141.3, 128.5, 128.4, 125.9, 77.6, 72.0, 60.7, 35.2, 31.6, 22.8, 21.6, 14.3; *m/z* (CI) MNH_4^+ 268 (100), 251 (85), 177 (20), 146 (17).

Ethyl 2-Isopropyloxypent-4-enoate (223a)

Ethyl 2-diazopent-4-enoate (100 mg, 0.65 mmol) was dissolved in *iso*-propanol (3 ml). Rhodium acetate (2 mol%) was added and the reaction mixture stirred at room temperature until adjudged complete by TLC. Once complete, the excess *iso*-propanol was removed *in vacuo* to leave a green coloured oil. Kugelrohr

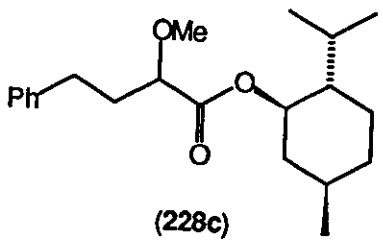
distillation of the crude reaction mixture gave the *title compound* (34 mg, 28%); b.p. 110°C, 6 mmHg; ν_{max}(film)/cm^{-1} 2978, 2934, 1750, 1610, 1270 and 734; δ_H (250 MHz; $CDCl_3$) 5.87-5.77 (1 H, m, CH_2=C<u>H</u>-), 5.16-5.05 (2 H, m, <u>CH_2</u>=), 4.27-4.13 (2 H, m, O<u>CH_2</u>), 3.79-3.92 (1 H, dd, J= 6.01 & 6.03, ^{i}PrO-<u>CH</u>), 3.67-3.60 (1 H, hp, *J*= 6.15, $(CH_3)_2$<u>CH</u>), 2.46-2.42 (2 H, m, =CH-<u>CH_2</u>), 1.28 (3 H, t, *J*= 7.18, OCH_2-<u>CH_3</u>), 1.21-1.87 (3 H, d, *J*= 6.15, <u>Me</u>), 1.16-1.13 (3 H, d, *J*= 6.03, <u>Me</u>); δ_C (62.9 MHz; $CDCl_3$) 173.4, 133.3, 118.6, 76.4, 71.9, 60.6, 37.6, 22.6, 21.4, 14.1.

General Procedure For Insertion Into Methanol

The appropriate α-diazoester (100 mg) was dissolved in methanol (2 ml). Rhodium acetate (2 mol%) was added and the reaction followed by TLC. Once adjudged complete, the methanol was removed *in vacuo* and the resulting residue purified by column chromatography (ether/light petroleum eluent) to afford the *title compounds* as colourless or pale yellow oils.

Methyl 2-Methoxy-3-phenylpropanoate

(22 mg, 21%); found: MH^+, 195.1021. $C_{11}H_{15}O_3$ requires 195.1021; ν_{max}(film)/cm^{-1} 3030, 2952, 1737, 701 and 657; δ_H (250 MHz; $CDCl_3$) 7.31-7.20 (5 H, m, Ar), 4.00-3.95 (1 H, dd, *J*= 5.45 & 5.45, MeO-<u>CH</u>), 3.71 (3 H, s, -CH<u>OMe</u>), 3.35 (3 H, s, CO<u>OMe</u>), 3.03-2.99 (2 H, m, Ph-<u>CH_2</u>); δ_C (62.9 MHz; $CDCl_3$) 172.6, 136.9, 129.3, 126.4, 126.7, 81.7, 58.4, 51.9, 39.2; *m/z* (CI) MNH_4^+ 212 (100%), 195 (100), 180 (15), 162 (40), 135 (60).



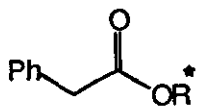
(228c)

Menthyl 2-Methoxy-4-phenylbutanoate (228c)

1:1 Mixture of diastereoisomers (28 mg, 27%); found: MNH_4^+, 350.2695. $C_{21}H_{36}NO_3$ requires 350.2695; δH (250 MHz; $CDCl_3$) 7.32-7.17 (5 H, m, Ph), 4.86-4.72 (1 H, m, O-CH_2), 3.73-3.67 (1 H, m, MeO-CH), 3.40 & 3.38 (3 H, s, MeO-), 2.77-2.70 (1 H, m, -CH-), 2.06-1.66 (10 H, m, $(CH_2)_4$ & $(CH)_2$), 0.92-0.88 (6 H, m, $(Me)_2$), 0.79-0.75 (3 H, m, Me); δC (62.9 MHz; $CDCl_3$) 172.32, 141.5, 128.53, 128.46, 126.03, 79.99, 75.04, 74.77, 58.08, 57.88, 46.88, 46.85, 40.91, 40.85, 34.64, 34.57, 34.20, 31.42, 31.38, 31.23, 26.31, 26.08, 23.33, 23.01, 22.01, 20.86, 20.74, 16.17, 15.82; *m/z* (CI) MNH_4^+ 350 (60%), 333 (30), 212 (100).

Experimental for Chapter Five

α-Diazophenylacetates



(230)

General Procedure For Phenylacetate Esters (230)

Phenylacetyl chloride (5 g, 32 mmol) was added dropwise to a stirred solution of the alcohol (32 mmol) and pyridine (2.1 g, 32 mmol) in DCM (50 ml) at room temperature. The reaction mixture was left to stir overnight. After this time, water (100 ml) was added and the DCM layer washed sequentially with water (100 ml), satd. copper sulphate (100 ml) and water (100 ml). The organic layer was dried ($MgSO_4$) and removed *in vacuo* to leave a dark coloured residue. Column chromatography of this oil (ether/light petroleum eluent) gave the *title compounds* as colourless or pale yellow oils.

Menthyl Phenylacetate

(5.2 g, 60%); found: M^+, 274.1948. $C_{18}H_{26}O_2$ requires 274.1933; ν_{max}(film)/cm^{-1} 2956, 2928, 2870, 1731 and 1200; δ_H (250 MHz; $CDCl_3$) 7.34-7.11 (5 H, m, Ar), 4.77-4.62 (1 H, dt, *J*= 10.85 & 4.37, O-CH-), 3.59 (2 H, s, Ph-CH_2-), 1.99-0.97 (9 H, m, $(CH)_3$ & $(CH_2)_3$), 0.89 (3 H, d, *J*= 6.51, Me), 0.84 (3 H, d, *J*= 7.01, Me), 0.69 (3 H, d, *J*= 6.96, Me); δ_C (62.9 MHz; $CDCl_3$) 171.2, 134.4, 129.2, 128.4, 126.9, 74.6, 47.0, 41.8, 40.7, 34.2, 31.4, 26.1, 23.3, 22.0, 20.7, 16.2; *m/z* (EI, 70 eV), M^+ 274 (0.2%), 138 (70), 118 (55), 91 (66), 83 (100).

Bornyl phenylacetate

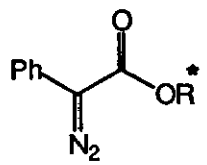
(2.2 g, 42%); found: M^+, 272.1788. $C_{18}H_{24}O_2$ requires 272.1777; $[\alpha]_D^{23}$= -30.69° (c= 1.499 in $CHCl_3$) ν_{max}(film)/cm^{-1} 2955, 2880, 1732, 1455, 1303, 703 and 695; δ_H (250 MHz; $CDCl_3$) 7.40-7.12 (5 H, m, Ar), 4.91-4.85 (1 H, m, O-CH-), 3.58 (2 H, s, Ph-CH_2), 2.37-2.18 (1 H, m, -CH-), 1.29-1.11 (6 H, m, $(CH_2)_3$), 0.87 (3 H, s, Me), 0.84 (3 H, s, Me), 0.77 (3 H, s, Me); δ_C (62.9 MHz; $CDCl_3$) 171.8, 134.4, 129.2, 128.4, 126.9, 80.2, 48.7, 47.8, 44.8, 41.8, 36.7, 27.9, 27.0, 19.6, 18.8, 13.4; *m/z* (EI, 70 eV), M^+ 272 (24%), 136 (35), 91 (100).

8-Phenylmenthyl Phenylacetate

(1.04 g, 68%); found: C, 78.28; H, 8.24, $C_{24}H_{30}O_2.H_2O$ requires C, 78.26; H, 8.69; found: M^+, 350.2230. $C_{24}H_{30}O_2$ requires 350.2246; $[\alpha]_D^{23}$= +24.4° (c= 0.45, in DCM); δ_H (250 MHz; $CDCl_3$) 7.31-7.07 (10 H, m, Ar), 4.89-4.75 (1 H, dt, *J*= 13.05 & 8.61, O-CH), 2.97 (2 H, s, Ph-CH_2), 2.07-1.98 (1 H, m, OCH-CH), 1.77-1.30 (4 H, m, $(CH_2)_2$), 1.28 (3 H, s, Me), 1.19 (3 H, s, Me), 1.13-0.86 (2 H, m, -CH_2-), 0.84 (3 H, d, *J*= 6.52, Me); δ_C (62.9 MHz; $CDCl_3$) 171.3, 151.2, 134.3, 128.2, 128.3, 127.9, 126.7, 125.4, 125.0, 74.5, 50.2, 41.4, 41.1, 39.6, 34.5, 31.2, 28.3, 26.4, 24.3, 21.7; *m/z* (EI, 70 eV) M^+ 350 (0.2%), 214 (45), 118 (80), 91 (100).

Typical Procedure for Synthesis of α-Diazoesters

A solution of ethyl phenylacetate (1000 mg, 6 mmol) and ethyl formate (520 mg, 7 mmol) in dry ether (10 ml), was added to a stirred suspension of sodium hydride (365 mg, 80% disp.) in ether (20 ml) at 0°C under an atmosphere of nitrogen. The reaction mixture was stirred overnight allowing the mixture to warm to room temperature. After this time a solution of mesyl azide (847 mg, 7 mmol) in ether (10 ml) was added and the reaction mixture left to stir at room temperature for 24 h. The reaction mixture was diluted with water (10 ml) and the ether layer separated. The organic layer was washed with 15% sodium hydroxide (2x30 ml) and brine (2x30 ml). The ether layer was dried ($MgSO_4$) and removed to leave a dark orange oil. Column chromatography (ether/light petroleum eluent) gave the *title compound.*



(231 - 234)

Ethyl Diazophenylacetate (231)

Bright orange, low melting solid, (467 mg, 41%); found: M^+, 190.0742. $C_{10}H_{10}N_2O_2$ requires 190.0742; ν_{max}(film)/cm^{-1} 2982, 2085, 1702, 1598, 755 and 690; δ_H (250 MHz; $CDCl_3$) 7.50-7.06 (5 H, m, Ar), 4.31-4.21 (2 H, q, *J*= 7.07, O-$\underline{CH_2}$), 1.33 (3 H, t, *J*= 7.12, OCH_2-$\underline{CH_3}$); δ_C (62.9 MHz; $CDCl_3$) 165.3, 128.8, 125.7, 125.6, 123.9, 60.9, 53.4, 14.4; *m/z* (EI, 70 eV), M^+ 190 (55%), 162 (60), 118 (85), 105 (100).

Menthyl Diazophenylacetate (232)

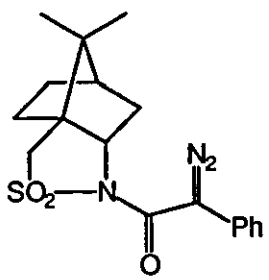
Yellow oil, (264 mg, 12%); found: MH^+, 301.1916. $C_{18}H_{25}N_2O_2$ requires 301.1933; $[\alpha]_D^{23}$= +63.81° (c= 0.642 in $CHCl_3$); 7.52-7.06 (5 H, m, Ar), 4.93-4.83 (1 H, dt, *J*= 10.86 & 4.41, O-$\underline{CH}$), 2.26-0.95 (9 H, m, ($\underline{CH}$)3 & ($\underline{CH_2}$)3), 0.93-0.90 (6 H, 2d, *J*= 2.78 & 3.31, $(Me)_2$), 0.82 (3 H, d, *J*= 6.96, Me); δ_C (62.9 MHz; $CDCl_3$) 169.2, 128.9, 125.8, 125.6, 123.9, 75.0, 47.1, 41.3, 34.2, 31.4, 26.5, 23.6, 22.0, 20.7, 16.5; *m/z* (CI) MH^+ 310 (3%), 273 (35), 152 (100).

Bornyl Diazophenylacetate (233)

Orange oil, (78 mg, 7%); found: MH^+, 299.1760. $C_{18}H_{23}N_2O_2$ requires 299.1760; $[\alpha]_D^{23}$= -21.9° (c= 0.502 in DCM); ν_{max}(film)/cm^{-1} 2956, 2931, 2085, 1704, 1499, 755 and 736; δ_H (250 MHz; $CDCl_3$) 7.51-7.14 (5 H, m, Ar), 5.11-5.05 (1 H, m, O-$\underline{CH}$), 2.49-2.39 (1 H, m, -CH_2-$\underline{CH}$), 1.88-1.07 (6 H, m, ($\underline{CH_2}$)3), 0,994 (3 H, s, Me), 0.89 (6 H, s, $(Me)_2$); δ_C (62.9 MHz; $CDCl_3$) 165.4, 128.9, 125.7, 123.9, 80.8, 49.0, 47.9, 37.0, 28.1, 27.1, 19.7, 18.9 13.6; *m/z* (CI) MH^+ 299 (7%), 271 (21), 227 (35), 152 (55), 137 (100).

8-Phenylmenthyl Diazophenylacetate (234)

The procedure above was followed with the following modifications:
1) Formation of the α-formylphenylacetate was accomplished by refluxing the reaction mixture overnight,
2) Addition of mesyl azide was made to the refluxing reaction mixture and the reaction mixture refluxed for an additional 5 h. Work-up was as described above.
Orange oil, (300 mg, 16%); $[\alpha]_D^{23}$= -72.9° (c= 4.58 in DCM); ν_{max}(film)/cm^{-1} 2957, 2924, 2087, 1693, 1498, 756, 739, 750 and 691; δ_H (250 MHz; $CDCl_3$) 7.39 (5 H, m, Ar), 5.12-5.02 (1 H, dt, *J*= 10.7 & 4.5, O-CH-), 2.05-0.92 (8 H m, $(CH_2)_3$ & $(CH)_2$), 1.35 & 1.14 (3 H, s, Me), 0.89 (3 H, d, *J*= 6.46 Me); δ_C (62.9 MHz; $CDCl_3$) 163.9, 151.3, 129.6, 128.7, 127.8, 125.9, 125.4, 125.3, 125.2, 123.7, 74.3, 50.9, 42.3, 39.6, 34.5, 31.4, 28.4, 26.6, 24.4, 21.7.



(238)

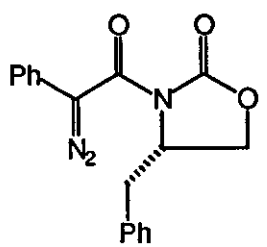
N-(phenyldiazoacetyl)camphorsultam (238)

Camphorsultam (300 mg, 1.39 mmol) was dissolved in dry THF (5 ml) under nitrogen and cooled to 0°C. This solution was treated with *n*-butyl lithium (1.6 M, 1.8 ml) and stirred for 20 min. Phenylglyoxylyl choride tosylhydrazone (469 mg, 1.39 mmol) was added and the reaction mixture stirred for ca. 16 h, allowing it to warm to room temperature. After this time, water was added (10 ml) and the reaction mixture extracted with ether (2x20 ml). The ether was dried ($MgSO_4$) and removed to leave a dark yellow solid. Chromatography on this solid (ether/light petroleum eluent) gave the *title compound* as a honey yellow crystalline solid (26 mg, 8%), m.p. 122.2-124.0 (dec.); ν_{max}(film)/cm^{-1} 3055, 2897, 2965, 2096, 1662, 1199, 691 and 670; δ_H (250 MHz; $CDCl_3$) 7.46-7.19 (5

H, m, Ph), 4.16-4.07 (1 H, m, N-CH), 3.41 (2 H, s, -CH_2-SO_2), 1.97-1.91 (7 H, m, (CH_2)3 7 CH), 1.16 & 0.98 (6 H, s, (Me)2; δ_C (62.9 MHz; $CDCl_3$) 163.1, 129.0, 126.7, 125.1, 124.6, 64.3, 52.3, 48.5, 48.0, 44.7, 36.9, 32.5, 26.8, 20.4, 19.9.

Single-Crystal X-ray Analysis of N-(phenyldiazoacetyl)camphorsultam

Crystal data: $C_{18}H_{21}N_3O_3S$ M_r= 359.445; monoclinic, space group $P2_1$; a= 11.672(7) Å, b= 7.00(1) Å, c= 12.869(8) Å; β=122.22(5)° (from 16 reflections in hol zone); V= 889.53 $Å^3$; Z= 2; ρ_{calc}= 1.342 gcm^{-3}; μ(MoKα radiation, λ= 0.71069 A)=1.61 cm-1; crystal dimensions 0.6 x 0.4 x 1.0 mm. Intensity data: max sinΘ/λ= 0.6 A; h -15→11; k 0→6; l 0→12; 1651 reflections of which 1207 classed as observed (F/σ(F)>6). Data was collected on Stöe Stadi-2 Weissenberg diffractometer. The structure was solved by direct methods (SHELXS) and refined by full matrix least squares refinement (unit weights). Non-H atoms treated anisotropically, phenyl H atoms are in calculated positions with isotropic thermal refinement, remainding H atoms found from difference map and only isotropic thermal parameters were refined. Final values: R= 0.0482; R_w= 0.0482 for 1207 observations and 246 refined parameters. A full list of atom co-ordinates is given in the appendix.

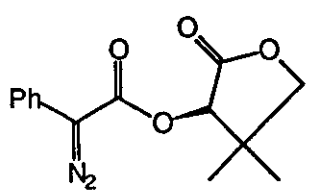


(239)

N-(phenyldiazoacetyl)-4-(S)-benzyl-2-oxazolidinone (239)

4-Benzyl-2-oxazolidinone (300 mg, 1.69 mmol) was dissolved in dry THF (5 ml) under nitrogen and cooled to 0°C. This solution was treated with *n*-butyl lithium (1.6 M, 2.2 ml) and stirred for 20 min. Phenylglyoxylyl choride tosylhydrazone (570 mg, 1.69 mmol) was added and the reaction mixture stirred for ca. 16 h,

allowing it to warm to room temperature. After this time, water was added (10 ml) and the reaction mixture extracted with ether (2x20 ml). The ether was dried ($MgSO_4$) and removed to leave a dark yellow oil. Chromatography on this oil (ether/light petroleum eluent) gave the *title compound* (53 mg, 10%); ν_{max}(film)/cm^{-1} 2095, 1777, 1657, 940, and 890; δ_H (250 MHz; $CDCl_3$) 7.51-7.07 (5 H, m, Ph), 4.97-4.86 (1 H, m, N-CH-), 4.36-4.29 & 4.19-4.12 (2 H, m, O-CH_2), 3.36-3.29 & 2.92-2.83 (2 H, m, Ph-CH_2-); δ_C (62.9 MHz; $CDCl_3$) 163.4, 157.3, 134.8, 129.3, 129.0, 128.9, 127.5, 126.8, 125.3, 124.8, 67.0, 55.6, 37.7.



(237)

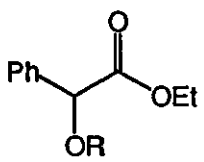
(R)-Dihydro-4,4-dimethyl-2-oxofuranyl Diazophenylacetate (237)

Phenylglyoxylyl chloride tosylhydrazone (518 mg, 1.54 mmol) was dissolved in DCM (10 ml). To this solution was added (R)-pantalactone (200 mg, 1.54 mmol). Triethylamine (470 mg, 4.62 mmol) was dripped in over ca. 5 min and the reaction mixture left to stir at room temperature overnight. Water (10 ml) was added and the DCM layer washed. The DCM layer was dried ($MgSO_4$) and removed to leave a dark orange oil. Chromatography on the residue (ether/light petroleum eluent) gave the *title compound* (53 mg, 13%) as an orange oil; ν_{max}(film)/cm^{-1} 2913, 2090, 1806, 1789, 1713, 693,647; δ_H (250 MHz; $CDCl_3$) 7.50-7.09 (5 H, m, Ph), 5.54 (1 H, s, O-CH), 4.07 (2 H, s, -CH_2-), 1.26 (3 H, s, Me), 1.37 (3 H, s, Me); δ_C (62.9 MHz; $CDCl_3$) 172.2, 164.5, 130.8, 129.5, 126.3, 124.1, 76.1, 75.2, 62.9, 40.2, 23.0, 19.6.

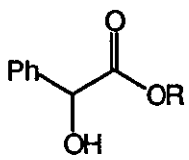
All diastereomeric excess were determined by 250 MHz ^{1}H NMR.

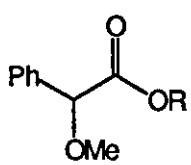
Insertion into Water

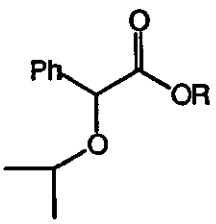
Reactions were carried out on 100 mg of diazo compound and experimental details are identical to those given previously.



(231a - 231b)







(241 a - i)

Ethyl 2-Hydroxyphenylacetate (240a)

(92 mg, 96%); found: C, 66.53; H, 6.80; $C_{10}H_{12}O_3$ requires C, 66.67; H, 6.67; ν_{max}(film)/cm^{-1} 3461, 2983, 1735, 1454, 733 and 698; δ_H (250 MHz; $CDCl_3$) 7.43-7.10 (5 H, m, Ar), 5.15 (1 H, s, HO-CH-), 4.31-4.09 (2 H, m, O-CH_2), 3.60 (1 H, bs, HO-), 1.20 (2 H, t J= 7.19, OCH_2-CH_3); δ_C (62.9 MHz; $CDCl_3$) 173.2, 138.4, 128.5, 128.4, 126.5, 72.7, 62.2, 14.0.

Menthyl 2-Hydroxyphenylacetate (241a)

1:1 Mixture of diastereoisomers (80 mg, 88%); found: C, 74.35; H, 9.19; $C_{18}H_{26}O_3$ requires C, 74.48; H, 8.97; found: MH^+, 291.1960. $C_{18}H_{27}O_3$ requires 291.1960; ν_{max}(film)/cm^{-1} 3453, 3414, 2956, 2947, 2872, 1732, 1722, 692 and 628; δ_H (250 MHz; $CDCl_3$) 7.43-7.25 (5 H, m, Ar), 5.15-5.12 & 5.11-5.08 (1 H, d, J= 5.96, HO-CH-), 4.82-4.72 & 4.71-4.60 (1 H, dt, J= 10.78 & 4.25, COO-CH-), 3.58-3.55 & 3.48-3.46 (1 H, d, J= 5.67, HO-), 2.16-0.91 (9 H, m, $(CH_2)_3$ & $(CH)_3$), 0.90-0.74 (6 H, m, Me_2), 0.59-0.56 & 0.40-0.38 (3 H, d, J= 6.99, Me); δ_C (62.9 MHz; $CDCl_3$) 173.49, 173.34, 138.71, 138.58, 128.47, 128.36, 128.27, 126.65, 126.45, 76.64, 76.54, 73.12, 72.81, 47.05, 46.83, 40.71,

40.05, 34.08, 34.04, 31.40, 31.30, 26.35, 25.35, 23.42, 22.96, 21.96, 21.87, 20.68, 20.46, 16.36, 15.58; *m/z* (CI) MH^+ 291 (65%), 308 (100), 170 (50), 156 (75).

Bornyl 2-Hydroxyphenylacetate (241d)

1:1 Mixture of diastereoisomers (25 mg, 50%); found: MNH_4^+, 306.2069. $C_{18}H_{28}NO_3$ requires 306.2069; ν_{max}(film)/cm^{-1} 3480, 2955, 2879, 1737, 709 and 699; δ_H (250 MHz; $CDCl_3$) 7.46-7.27 (5 H, m, Ar), 5.20-5.16 (1 H, m, HO-CH-), 4.98-4.88 (1 H, m, COO-CH-), 3.55-3.51 (1 H, m, HO-), 2.41-2.17 (2 H, m, O-CH-CH_2-), 1.71-1.58 (3 H, m, CH-CH_2), 1.26-1.02 & 0.62-0.51 (2 H, m, CH_2), 0.87-0.84 & 0.52 (9 H, m, Me_3); δ_C (62.9 MHz; $CDCl_3$) 167.34, 167.32, 138.8, 138.7, 128.47, 128.33, 128.30, 126.48, 126.34, 82.28, 81.99, 73.00, 72.81, 48.82, 47.84, 44.86, 44.60, 36.44, 36.33, 27.92, 27.70, 27.00, 26.69, 19.61, 19.59, 18.81, 18.78, 13.48, 13.09; *m/z* (CI) MNH_4^+ 306 (40%), 289 (5), 137 (100).

8-Phenylmenthyl 2-Hydroxyphenylacetate (241e)

1:1 Mixture of diastereoisomers (86 mg, 87%); found: MNH_4^+, 384.2539. $C_{24}H_{34}NO_3$ requires 384.2539; ν_{max}(film)/cm^{-1} 3504, 2956, 2925, 2871, 1723, 1455, 764, 737 and 700; δ_H (250 MHz; $CDCl_3$) 7.36-7.19 (10 H, m, Ar), 4.88-4.78 (3 H, m, O-CH_2 & HO-CH-), 4.04 (1 H, bs, HO-CH-), 3.23 & 2.16 (1 H, bs, OH), 2.06-1.83 (12 H, m, $(CH_2)_3$), 1.63-1.02 (6 H, m, $(CH)_3$), 1.33 & 1.20 (6 H, s, Me), 1.06 & 0.93 (6 H, s, Me), 0.86-0.84 & 0.78-0.76 (6 H, d, J = 6.43 & 6.44, Me); δ_C (62.9 MHz; $CDCl_3$) 172.94, 171.81, 152.1, 151.88, 138.27, 136.12, 128.38, 128.10, 128.02, 127.93, 127.86, 126.93, 126.26, 125.47, 125.37, 125.27, 125.23, 76.89, 76.05, 73.77, 72.04, 50.16, 41.37, 40.58, 39.64, 39.31, 34.30, 31.26, 31.09, 29.73, 26.75, 26.41, 26.09, 22.62, 21.63, 21.56; *m/z* (CI) MNH_4^+ 384 (15%), 367 (10), 215 (100), 119 (95).

(R)-Dihydro-4,4-dimethyl-2-oxofuranyl 2-Hydroxyphenylacetate (241h)

1:1 Mixture of diastereoisomers (12 mg, 32%); found: MNH_4^+, 282.1341. $C_{14}H_{20}NO_5$ requires 282.1342; δ_H (250 MHz; $CDCl_3$) 7.39-7.31 (5 H, m, Ph),

5.37 & 5.35 (1 H, s, HO-CH), 4.02 & 4.016 (2 H, s, O-CH_2), 3.43 & 3.37 (1 H, bs, -OH), 1.21 & 1.07 (3 H, s, Me), 0.95 & 0.67 (3 H, s, Me); δ_C (62.9 MHz; $CDCl_3$) 172.97, 172.40, 171.56, 171.08, 137.88, 137.22, 128.63, 128.75, 128.67, 126.79, 126.50. 76.26, 76.09, 76.05, 76.01, 73.01, 72.82, 40.34, 40.11, 22.96, 22.62, 19.71, 19.09; *m/z* (CI) MNH_4^+ 282 (100), 247 (25).

Insertion into Isopropanol

Reactions were carried out on 100 mg of diazo compound and experimental details have been given previously

Ethyl 2-Isopropyloxyphenylacetate (240b)

(99 mg, 77%); found: MH^+, 223.1334. $C_{13}H_{19}O_3$ requires 223.1334; ν_{max}(film)/cm^{-1} 2976, 1751, 1203, 690 and 715; δ_H (250 MHz; $CDCl_3$) 7.49-7.26 (5 H, m, Ar), 4.97 (1 H, s, ^iPrO-CH-), 4.23-4.10 (2 H, m, O-CH_2), 3.68 (1 H, hp, *J*= 6.14, Me_2-CH-), 1.21 (3 H, t, *J*= 5.89, OCH_2-CH_3); δ_C (62.9 MHz; $CDCl_3$) 171.5, 137.3, 128.4, 128.3, 127.0, 78.5, 70.6, 61.0, 22.0, 14.0; *m/z* (CI) MH^+ 223 (100), 240 (85), 198 (20), 180 (65), 149 (30).

Menthyl 2-Isopropyloxyphenylacetate (241c)

1:1.12 Mixture of diastereoisomers (77 mg, 74%); found: MH^+, 333.2430. $C_{21}H_{33}O_3$ requires 333.2430; δ_H (250 MHz; $CDCl_3$) 7.47-7.26 (5 H, m, Ar), 7.48-7.26 (5 H, m, Ar), 4.96 & 4.93 (1 H, s, -CH-OH), 4.72-4.59 (1 H, m, O-CH), 3.74-3.64 (1 H, hp, *J*= 6.10, $(Me)_2$CH), 1.97-0.89 (8 H, m, $(CH_2)_3$ & $(CH)_2$), 1.28-1.18 (6 H, m, ^iPr), 0.89-0.82 (6 H, m, $(Me)_2$), 0.69-0.63 & 0.45-0.42 (3 H, m, Me); δ_C (62.9 MHz; $CDCl_3$) 171.14, 137.56, 137.50, 128.89, 128.34, 128.24, 128.19, 127.26, 126.86, 78.76, 78.64, 75.00, 74.93, 71.12, 70.72, 47.13, 46.94, 40.79, 40.27, 34.18, 34.38, 31.31, 26.09, 25.45, 23.30, 22.96, 22.29, 22.01, 21.94, 20.69, 20.61, 16.12, 15.59; *m/z* (CI) MNH_4^+ 350 (55%), 333 (55), 212 (95), 149 (100).

(R)-Dihydro-4,4-dimethyl-2-oxofuranyl 2-Isopropyloxyphenylacetate (241i)

1:1.19 Mixture of diastereoisomers (16 mg, 42%); found: MNH_4^+, 324.1811. $C_{17}H_{26}NO_5$ requires 324.1811; δ_H (400 MHz; $CDCl_3$) 7.70-7.45 & 7.38-7.31 (5 H, m, Ph), 5.37 & 5.31 (1 H, s, ^iPrO-CH), 5.13 & 5.127 (1 H, s, O-CH-CO), 3.93 (2 H, s, O-CH_2), 3.90-3.77 & 3.77-3.69 (1 H, hp, Me_2-CH-O), 1.28-1.26 & 1.23-1.18 (6 H, 4d, J= 3.83, 3.8, 3.8 & 3.83, Me_2-CHO-), 1.04 & 0.93 (3 H, s, Me), 0.93 & 0.65 (3 H, s, Me); δ_C (100.61 MHz; $CDCl_3$) 171.95, 171.48, 170.80, 170.45, 136.99, 136.40, 129.33, 128.67, 128.53, 128.38, 127.24, 126.73, 78.26, 77.68, 76.00, 75.89, 75.22, 74.95, 71.40, 70.92, 40.31, 40.10, 22.86, 22.56, 22.17, 21.94, 21.86, 21.52, 19.61, 19.05; *m/z* (CI) MNH_4^+ 324 (100%).

8-Phenylmenthyl 2-Isopropyloxyphenylacetate (241g)

1:1.2 Mixture of diastereoisomers (86 mg, 79%); found: MH^+, 409.2743. $C_{27}H_{37}O_3$ requires 409.2743; ν_{max}(film)/cm^{-1} 2968, 2926, 1725, 1175, 1145, 737 and 700; δ_H (250 MHz; $CDCl_3$) 7.43-7.11 (5 H, m, Ph), 4.79-4.69 (3 H, m, CO-O-CH & ^iPrO-CH), 4.04 (1 H, s, ^iPrO-CH), 3.67-3.57 & 352-3.47 (1 H, hp, J= 6.12 & 6.11, $(CH_3)_2$-CH), 1.99-0.87 (14 H, m, $(CH_3)_2$, $(CH_2)_3$ & $(CH)_2$), 0.84-0.81 & 0.74-0.71 (3 H, d, J= 6.37 & 6.47, $(Me)_2$); δ_C (62.9 MHz; $CDCl_3$) 170.44, 170.35, 152.17, 150.19, 137.39, 136.88, 128.41, 128.16, 128.00, 127.96, 127.90, 127.80, 127.14, 125.77, 125.59, 125.43, 125.29, 125.24, 78.95, 77.73, 76.26, 74.93, 70.58, 70.32, 50.51, 50.07, 41.60, 40.46, 40.14, 39.52, 34.47, 31.29, 31.07, 29.70, 28.84, 27.26, 23.90, 23.81, 22.26, 22.09, 21.95, 21.74, 21.66; *m/z* (CI) MH^+ 409 (32%), 426 (25), 212 (95), 149 (100).

Insertion into Methanol

Reactions were carried out on 100 mg of diazo compound and experimental details have been given previously.

Menthyl 2-Methoxyphenylacetate (241b)

1:1 Mixture of diastereoisomers (81 mg, 79%); found: MH^+, 381.2430. $C_{25}H_{33}O_3$ requires 381.2430; ν_{max}(film)/cm^{-1} 2955, 2929, 2871, 1745, 1730,

734 and 697; δ_H (250 MHz; $CDCl_3$) 7.46-7.27 (5 H, m, Ph), 4.80-4.60 (4 H, m, O-$\underline{CH_2}$ & MeO-$\underline{CH}$), 3.42 & 3.32 (3 H, s, $\underline{Me}O$), 2.02-0.97 (9 H, m, ($\underline{CH_2}$)$_3$ & ($\underline{CH}$)$_3$), 0.92-0.81 (9 H, m, (Me)$_3$), 0.71-0.68 (3 H, d, *J*= 6.94, $\underline{Me}$), 0.64-0.61 (3 H, d, *J*= 7.44, $\underline{Me}$), 0.44-0.41 (3 H, d, *J*= 7.50, $\underline{Me}$); δ_C (62.9 MHz; $CDCl_3$) 170.33, 170.31, 136.55, 136.51, 128.64, 128.53, 128.45, 127.33, 126.98, 82.78, 82.75, 75.22, 75.11, 57.27, 57.23, 47.07, 46.88, 40.80, 40.22, 34.17, 34.14, 31.38, 31.30, 26.16, 25.47, 23.28, 22.96, 21.99, 21.92, 20.70, 20.57, 16.12, 15.59; *m/z* (CI) MH^+ 305 (60%), 322 (30), 184 (100), 121 (100).

8-Phenylmenthyl 2-Methoxyphenylacetate (241f)

1:1 mixture of diastereoisomers (73 mg, 67%), found: MH^+, 381.2430. $C_{25}H_{33}O_3$ requires 381.2430; δ_H (250 MHz; $CDCl_3$) one diastereoisomer: 7.42-7.10 (5 H, m, Ph), 4.84-4.74 (1 H, dt, *J*= 6.06 & 4.41, O-$\underline{CH}$), 4.53 (1 H, s, MeO-$\underline{CH}$), 3.33 (3 H, s, $\underline{Me}O$), 2.01-0.82 (8 H, m, ($\underline{CH_2}$)$_3$ & ($\underline{CH}$)$_2$), 1.09 (3 H, s, $\underline{Me}$), 0.91 (3 H, s, $\underline{Me}$), 0.85-0.82 (3 H, d, *J*= 6.36, $\underline{Me}$); δ_C (62.9 MHz; $CDCl_3$) 169.68, 150.07, 135.65, 128.78, 128.47, 127.95, 127.81, 125.65, 125.19, 83.06, 76.40, 57.10, 50.34, 41.64, 40.02, 34.34, 31.23, 29.33, 27.19, 23.79, 21.66; other diastereoisomer δ_H (250 MHz; $CDCl_3$) 7.40-7.10 (5 H, m, Ph), 4.85-4.75 (1 H, dt, *J*= 10.71 & 4.28, O-$\underline{CH}$), 3.67 (1 H, s, MeO-$\underline{CH}$), 3.27 (3 H, s, $\underline{Me}O$), 2.02-1.07 (8 H, m, ($\underline{CH_2}$)$_3$ & ($\underline{CH}$)$_2$), 1.32 (3 H, s, $\underline{Me}$), 1.19 (3 H, s, $\underline{Me}$), 0.59-0.54 93 H, d, *J*= 11.13, $\underline{Me}$); δ_C (62.9 MHz; $CDCl_3$) 169.56, 153.2, 136.4, 128.28, 128.05, 127.10, 125.48, 124.97, 81.53, 74.72, 56.99, 50.11, 40.57, 39.48, 31.08, 29.27, 26.24, 23.33, 21.65; *m/z* (CI) MH^+ 381 (9%), 398 (12), 215 (100), 184 (82), 121 (100).

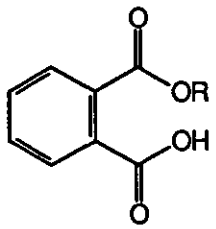
N-(α-methoxyphenylacetyl)camphorsultam (241j)

1:1.1 Mixture of diastereoisomers (5 mg, 15%) found: MH^+, 364.1583. $C_{19}H_{26}O_4NS$ requires 364.1577; δ_H (400 MHz; $CDCl_3$) 7.66-7.51 & 7.34-7.26 (5 H, m, Ph), 5.43 (1 H, s, MeO-$\underline{CH}$), 3.97-3.94 (1 H, m, N-$\underline{CH}$), 3.45 (2 H, s, -$\underline{CH_2}$-SO_2), 3.44 (3 H, s, -$\underline{OMe}$), 1.99-1.86 (2 H, m, -$\underline{CH_2}$-), 1.74-1.71 (2 H, m, -$\underline{CH_2}$-), 1.42-1.25 (2 H, m, -$\underline{CH_2}$-), 0.88 (3 H, s, $\underline{Me}$), 0.74 (3 H, s, $\underline{Me}$); δ_C (100.6 MHz; $CDCl_3$) 170.59, 135.36, 128.64, 128.35, 127.64, 82.07, 64.69,

57.46, 53.12, 48.47, 47.55, 44.25, 37.39, 32.49, 29.58, 26.32, 19.80, 19.69; *m/z* (CI) MH^+ 364 (100%), 349 (35), 332 (40), 300 (65), 121 (50).

Experimental for Chapter Five

Novel Rhodium Catalysts



(269)

Menthyl (2-Carboxy)benzoate (269a)

Phthalic anhydride (5 g, 33 mmol) was suspended in DCM (20 ml). Menthol (5.2 g, 33 mmol) was added and to this stirred mixture was added diisopropylethylamine (6.8 ml, 40 mmol) dropwise. the reaction mixture was stirred at room temperature overnight. After this time water (30 ml) was added and the DCM layer washed. The organic layer was then washed with dil. hydrochloric acid (2x30 ml) and then dried ($MgSO_4$). Removal of the DCM *in vacuo* left a white solid. Excess menthol was removed by Kugelrohr sublimation to leave the *title compound* as a white solid (1.6 g, 16%); m.p. 106.0-108.2 °C; $[\alpha]_D^{23}$= -86.61°; found: C, 71.03; H, 7.89; $C_{18}H_{24}O_4$ requires C, 71.05; H, 7.89; found: MH^+ 305.1753 $C_{18}H_{25}O_4$ requires 305.1753; δ_H (250 MHz; $CDCl_3$) 7.92-7.89 & 7.65-7.54 (5 H, m, Ph), 5.03-4.93 (1 H, dt, *J*= 10.89 & 4.37, O-CH), 2.26-2.01 (1 H, m, OCH-CH-), 2.01-1.96 (1 H, m, Me-CH), 1.74-1.67 (2 H, m, -CH_2-), 1.68-1.44 (4 H, m, $(CH_2)_2$), 0.95-0.92 (3 H, d, *J*= 6.49, Me), 0.91-0.90) (3 H, d, *J*= 3.47, Me), 0.85-0.82 (3 H, d, *J*= 6.94, Me); δ_C (62.9 MHz; $CDCl_3$) 172.5, 167.7, 134.2, 132.2, 130.5, 129.8, 129.7, 128.6, 77.5, 47.0, 40.3, 34.2, 31.4, 29.1, 23.3, 22.2, 21.0, 16.1; *m/z* (CI) MH^+ 305 (90%), 104 (100).

Bornyl (2-Carboxy)benzoate (269b)

Phthalic anhydride (15 mg, 33 mmol) and borneol (5 g, 33 mmol) was dissolved in DCM (100 ml). Diisopropylethylamine (4.3 g, 33 mmol) was dripped in over 5 min. and the reaction mixture stirred at room temperature overnight. After this time, water (70 ml) was added and the organic layer washed. The DCM layer was dried ($MgSO_4$) and removed *in vacuo*. The residue was purified by column chromatography (ether/light petroleum eluent) to leave the *title compound* as a

white solid (10 g, 33%); found: MH^+ 303.1596 $C_{18}H_{23}O_4$ requires 303.1596; δ_H (250 MHz; $CDCl_3$) 7.91-7.87 & 7.70-7.56 (5 H, m, Ph), 5.16-5.10 (1 H, m, O-CH), 2.50-2.42 (1 H, $OCHCH_2$-CH), 2.00-1.90 (1 H, m, -CH_2-), 1.77-1.70 (2 H, m, -CH_2-), 1.36-1.18 (3 H, m, $(CH_2)_2$), 0.96 (3 H, s, Me), 0.91 (3 H, s, Me), 0.89 (3 H, s, Me); δ_C (62.9 MHz; $CDCl_3$) 172.8, 168.4, 133.8, 132.1, 130.7, 130.1, 129.8, 128.9, 82.1, 49.0, 47.9, 44.9, 36.2, 28.0, 27.2, 20.1, 19.7, 18.9, 13.6; *m/z* (CI) MH^+ 303 (0.1%), 136 (30), 110 (55), 95 (100).

General Procedure for Synthesis of Rhodium Catalysts

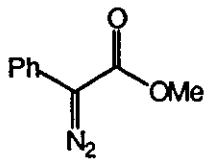
Rhodium (II) acetate (100 mg, 0.23 mmol) and the appropriate ligand (12 eq.) was heated as a melt at 120°C under argon for 24 h. After this time the reaction mixture was cooled then dissolved in DCM (30 ml). The DCM layer was washed with 5% sodium hydroxide (30 ml) and water (40 ml) then dried ($MgSO_4$). Removal of the DCM *in vacuo* left a dark green solid which was subjected to column chromatography (ether/light petroleum eluent) to give the *title compounds.*

Tetrakis-μ-menthyl-(2-carboxy)benzoate dirhodium (II) (270a)

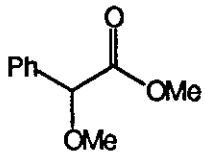
(105 mg, 33%); $[\alpha]_D^{23}$= -68.18°; δ_H (250 MHz; $CDCl_3$) 7.90-7.86 (1 H, m, o-Ph), 7.56-7.52 (1 H, m, o-Ph), 7.52-7.34 (3 H, m, Ph), 4.60-4.50 (1 H, m, -O-CH_2), 2.07-1.87 (2 H, m, -CH_2-), 1.61-1.32 (2 H, m, -CH_2-), 1.29-0.92 (2 H, m, -CH_2-), 0.88-0.84 (6 H, m, $(Me)_2$), 0.76-0.73 (3 H, d, *J*= 6.87, Me); δ_C (62.9 MHz; $CDCl_3$) 183.5, 166.3, 135.3, 131.1, 130.2, 129.4, 129.2, 127.7, 75.2, 48.9, 40.3, 34.2, 31.4, 26.2, 23.4, 22.0, 20.8, 16.3; *m/z* (FAB) MNa^+ 1441 (25%), 1419 (55), 849 (100).

Tetrakis-μ-bornyl-(2-carboxy)benzoate dirhodium (II) (270b)

(100 mg, 31%); δ_C (62.9 MHz; $CDCl_3$) 183.2, 166.9, 135.2, 131.1, 130.0, 129.2, 128.9, 127.5, 80.6, 48.8, 47.7, 36.3, 27.7, 27.2, 19.6, 18.9, 13.5; *m/z* (FAB) MNa^+ 1434 (15%), 1411 (80), 849 (100).



(271)



(272)

Methyl Diazophenylacetate (271)

The *title compound* was synthesised in exactly the same manner as ethyl diazophenylacetate described earlier (2.13 g, 37%); ν_{max}(film)/cm^{-1} 2088, 1706, 1249, 755 and 691; δ_H (250 MHz; $CDCl_3$) 7.49-7.13 (5 H, m, Ar), 3.84 (3 H, s, O<u>CH</u>$_3$); δ_C (62.9 MHz; $CDCl_3$) 165.5, 128.9, 125.4, 125.3, 123.8, 51.9.

Methyl 2-Methoxyphenylacetate (272)

Methyl diazophenylacetate (100 mg, 0.57 mmol) was dissolved in HPLC grade methanol (3 ml). The appropriate rhodium catalyst was added (2 mol%) and the reaction mixture stirred until adjudged cpmplete by TLC. Once complete the methanol was removed *in vacuo* to leave a dark green residue. Column chromatography (ether/light petroleum eluent) gave methyl 2-methoxyphenyl-acetate as a colourless oil, (62 mg, 60%); found: MNH_4^+, 198.1130. $C_{10}H_{16}NO_3$ requires 198.1130; ν_{max}(film)/cm^{-1} 2953, 1752, 1455, 1436, 1109, 732 and 699; δ_H (250 MHz; $CDCl_3$) 7.46-7.27 (5 H, m, Ph), 4.78 (1 H, s, MeO-<u>CH</u>-), 3.71 (3 H, s, -CO-O<u>Me</u>), 3.41 (3 H, s, <u>Me</u>O-); δ_C (62.9 MHz; $CDCl_3$) 171.2, 136.2, 128.9, 128.7, 127.3, 82.6, 57.3, 52.3 *m/z* (CI) MNH_4^+ 198 (100%), 181 (35), 166 (35).

Gas Chromatography Analysis

A small sample of methyl 2-methoxyphenylacetate (1-2 mg) was dissolved in DCM (2 ml). Of this solution 1 µl was injected onto the GC column. Conditions: Detector Temperature 250°C; Injector Temperature 200°C; Initial Column Temperature 80°C. The column was held at 80°C for 30 min. then ramped at a rate of 1°C/min until 110°C, then held at 110°C for 30 min.. Column: SGE CYDEXB (0.25 mm (i.d.)) 30 m chiral capillary column. Gas chromatographs

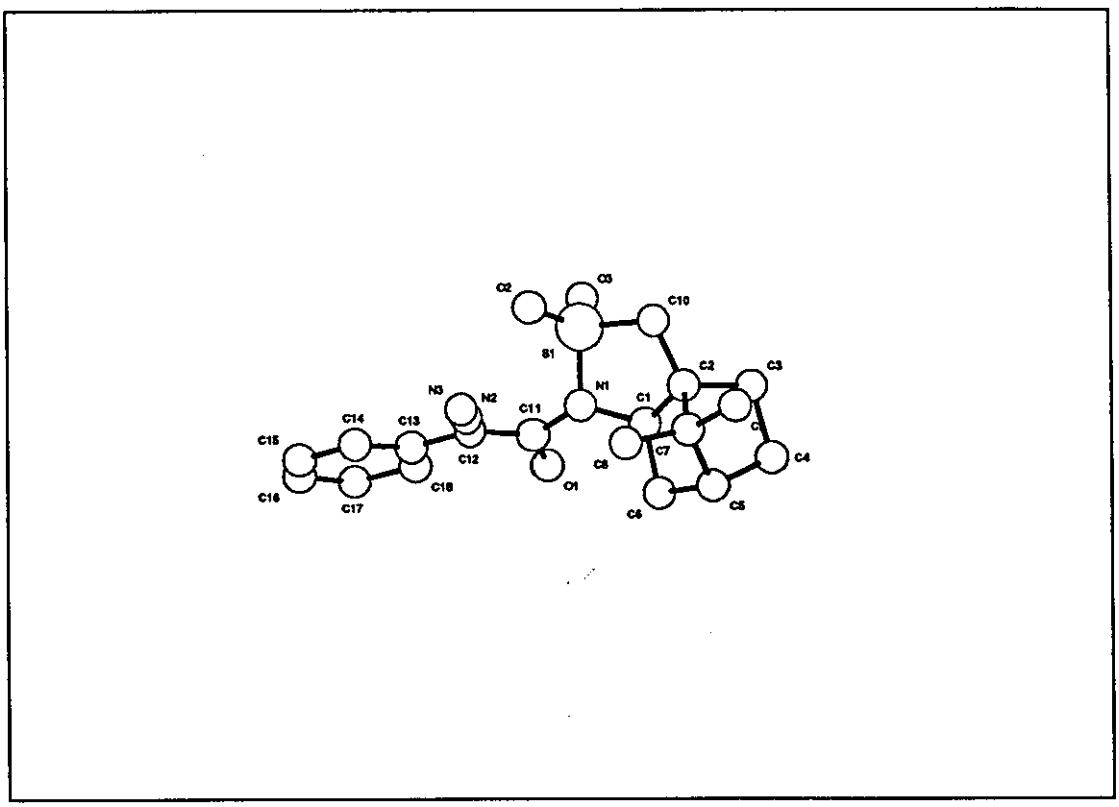
were recorded using a Pye-Unicam Series 204 Gas Chromatograph with a flame ionisation detector and a Spectra Physics SP4270 integrator.

Authentic (S)-Methyl 2-Methoxyphenylacetate

(S)-Methyl 2-methoxyphenylacetic acid (100 mg, 0.60 mmol) was dissolved in methanol (2 ml). To this stirred solution was added thionyl chloride (6 µl, 0.080 mmol). The reaction mixture was stirred at room temperature overnight. After this time the methanol was removed *in vacuo*, and the residue purified by column chromatography (ether/light petroleum eluent) to give the *title compound* (48 mg, 44%). Spectral data was identical to that reported earlier for racemic methyl 2-methoxyphenyacetate.

Appendix

Single X-Ray Crystal Structure of N-(Phenyldiazoacetyl)camphorsultam (238)



Atom Co-ordinates

Hydrogen Atoms

ATOM	X	Y	Z	U ISO
H( )	.1121	.1378	.5381	.1212
	.0007	.0016	.0007	.0331
H( )	.0806	1.1124	.7072	.1966
	.0008	.0020	.0008	.0519
H( )	.2313	.5449	.5809	.0967
	.0007	.0016	.0006	.0266

H( )	.1017	.8071	.8039	.1192
	.0009	.0024	.0007	.0279
H( )	.1887	.5281	.7545	.1802
	.0008	.0020	.0008	.0477
H( )	.0804	.7094	-.0117	.1234
	.0000	.0000	.0000	.0304
H( )	.4001	1.0241	.3310	.1477
	.0000	.0000	.0000	.0357
H( )	.3181	.4788	.2767	.0722
	.0000	.0000	.0000	.0195
H( )	.5190	.7766	.4373	.1086
	.0000	.0000	.0000	.0243
H( )	.1048	.8824	-.0034	.0868
	.0000	.0000	.0000	.0226
H( )	.5339	.5421	.3842	.0834
	.0000	.0000	.0000	.0219
H( )	.4643	1.1594	.2608	.0966
	.0000	.0000	.0000	.0254
H( )	.2826	1.0625	.1792	.1128
	.0000	.0000	.0000	.0265
H( )	.6389	.7649	.3264	.1085
	.0000	.0000	.0000	.0224
H( )	.3211	.6079	-.0023	.0946
	.0000	.0000	.0000	.0232
H( )	.5641	.6087	.1210	.0692
	.0000	.0000	.0000	.0178
H( )	.5737	.4613	.2259	.1035
	.0000	.0000	.0000	.0270
H( )	.34291	.0537	.0081	.0995
	.0000	.0000	.0000	.0256
H( )	.4356	.8602	.0225	.0953
	.0000	.0000	.0000	.0272
H( )	.49511	.0757	.1065	.1249
	.0000	.0000	.0000	.0302
H( )	.3047	.4179	.0803	.1620

	.0000	.0000	.0000	.0408

Non-Hydrogen Atoms

ATOM	X	Y	Z	UEQ
S(1)	910 (1)	7646 (0)	1605 (1)	67 (2)
N(1)	2452 (4)	7546 (11)	2914 (3)	50 (6)
C(1)	3305 (5)	6369 (10)	2632 (5)	50 (8)
C(12)	2015 (6)	8604 (12)	4477 (5)	57 (9)
C(11)	2542 (6)	7116 (11)	4047 (5)	56 (10)
C(13)	1766 (6)	8436 (14)	5476 (5)	67 (11)
O(2)	218 (5)	9346 (12)	1577 (5)	99 (10)
C(6)	4852 (6)	6699 (12)	3525 (5)	64 (9)
O(3)	204 (6)	10305 (12)	4001 (6)	69 (10)
C(14)	1353 (7)	10028 (16)	5837 (7)	87 (14)
C(7)	4101 (7)	8794 (11)	1780 (6)	61 (10)
C(8)	3959 (7)	10504 (13)	2442 (6)	73 (12)
C(4)	5106 (7)	5738 (13)	1783 (6)	77 (12)
C(10)	1531 (5)	7685 (14)	616 (4)	59 (8)
C(9)	4178 (9)	9541 (14)	714 (7)	87 (16)
C(2)	3020 (5)	7192 (12)	1391 (5)	55 (9)
C(3)	3531 (7)	5597 (13)	893 (6)	67 (11)
C(15)	1110 (8)	9883 (20)	6779 (8)	103 (17)
C(18)	1972 (7)	6684 (16)	6074 (6)	82 (13)
C(16)	1274 (9)	8173 (24)	7349 (7)	108 (18)
C(17)	1716 (8)	6588 (20)	7036 (8)	99 (16)
N(3)	1844 (8)	11815 (13)	3672 (7)	105 (15)

Bond Lengths

N(1) - S(1)	1.688 (4)	C(7) - C(5)	1.564 (10)
O(2) - S(1)	1.428 (7)	C(4) - C(5)	1.537 (11)
O(3) - S(1)	1.438 (7)	N(3) - N(2)	1.128 (10)

C(10) - S(1)	1.769 (5)	C(15) - C(14)	1.387 (12)
C(1) - N(1)	1.478 (7)	C(8) - C(7)	1.528 (10)
C(11) - N(1)	1.437 (7)	C(9) - C(7)	1.516 (9)
C(6) - C(1)	1.556 (8)	C(2) - C(7)	1.557 (9)
C(2) - C(1)	1.558 (7)	C(3) - C(4)	1.567 (9)
C(13) - C(12)	1.467 (9)	C(2) - C(10)	1.512 (7)
N(2) - C(12)	1.312 (10)	C(3) - C(2)	1.556 (10)
0(1) - C(11)	1.203 (8)	C(16) - C(15)	1.363 (16)
C(14) - C(13)	1.389 (11)	C(17) - C(18)	1.422 (11)
C(18) - C(13)	1.398 (11)	C(17) - C(16)	1.371 (14)
C(5) - C(6)	1.551 (9)		

Bond Angles

O(2) - S(1) - N(1)	110.3 (3)	C(4) - C(5) - C(6)	108.5 (7)
O(3) - S(1) - N(1)	109.8 (4)	C(4) - C(5) - C(7)	103.7 (5)
O(3) - S(1) - O(2)	116.4 (3)	N(3) - N(2) - C(12)	175.3 (8)
C(10) - S(1) - N(1)	95.2 (2)	C(15) - C(14) - C(13)	120.2 (10)
C(10)- S(1) - O(2)	114.4 (4)	C(8) - C(7) - C(5)	114.4 (5)
C(10) - S(1)- O(3)	108.7 (4)	C(9) - C(7) - C(5)	113.5 (6)
C(1) - N(1) - S(1)	106.1 (3)	C(9) - C(7) - C(8)	108.1 (7)
C(11) - N(1) - S(1)	118.9 (4)	C(2) - C(7) - C(5)	92.0 (5)
C(11) - N(1) - C(1)	116.0 (5)	C(2) - C(7) - C(8)	115.7 (5)
C(6) - C(1) - N(1)	113.8 (5)	C(2) - C(7) - C(9)	112.7 (6)
C(2) - C(1) - N(1)	104.0 (5)	C(3) - C(4) - C(5)	103.1 (5)
C(2) - C(1) - C(6)	103.4 (5)	C(2) - C(10) - S(1)	106.8 (3)
C(13) - C(12) - C(11)	126.5 (7)	C(7) - C(2) - C(1)	104.0 (5)
N(2) - C(12) - C(11)	115.6 (6)	C(10) - C(2) - C(1)	107.6 (4)
N(2) - C(12) - C(13)	117.5 (7)	C(10) - C(2) - C(7)	119.8 (6)
0(1) - C(11) - N(1)	120.5 (6)	C(3) - C(2) - C(1)	103.8 (6)
C(12) - C(11) - N(1)	114.7 (6)	C(3) - C(2) - C(7)	103.1 (5)
C(12) - C(11) - 0(1)	124.4 (6)	C(3) - C(2) - C(10)	116.8 (5)
C(14) - C(13) - C(12)	119.7 (8)	C(2) - C(3) - C(4)	102.2 (5)
C(18) - C(13) - C(12)	119.8 (7)	C(16) - C(15) - C(14)	119.9 (11)
C(18) - C(13) - C(14)	120.5 (7)	C(17) - C(18) - C(13)	117.8 (10)

C(5) - C(6) - C(1)	101.9 (4)	C(17) - C(16) - C(15)	121.3 (8)
C(7) - C(5) - C(6)	102.0 (5)	C(16) - C(17) - C(18)	120.3 (10)

References

1. Curtius, T.; *Ber. Dtsch. Chem. Ges.*, 27, 2230, 1883.

2. Boersch, H.; *Monasch. Chem.*, **65**, 311, 1935.

2. Clusius, K; Luthi, U; *Helv. Chim. Acta*, **40**, 445, 1957.

4. Regitz, M; Maas, G; *Diazo Compounds, Properties and Synthesis*, Academic press, 1986.

Patai, S; *The Chemistry of Diazonium and Diazo Groups*, vols. 1 & 2, J. Wiley & Sons, 1978.

Kruglaya, O.A.; Vyazankin, N.S.; *Russ. Chem. Rev.*, **49**, 357, 1980.

Regitz, M.; *Synthesis*, 351, 1972.

5. Meier, H.; Zeller, K-P.; *Angew. Chem. Int. Ed.*, **14**, 32, 1975.

6. Mass, G.; *Topics Curr. Chem.*, 137, Springer-Verlag, 1987.

7. Leading reference: Doyle, M.P.; *J. Am. Chem. Soc.*, **113**, 1423, 1991.

8. Silberrad, O.; Roy, C.; *J. Chem. Soc.*, 179, 1906.

9. Yates, P.; *J. Chem. Soc.*, **74**, 5376, 1952.

10. Muller, D.; Umbricht, B.W.; Pfaltz, A.; *Helv. Chim. Acta.*, **74**, 232, 1991.

11. Lowenthal, R.E.; Abiko, A.; Masamune, S.; *Tetrahedron Lett.*, 6005, 1990.

12. Evans, D.A.; Woerpel, K.A.; Hinman, M.M.; Faul, M.M.; *J. Am. Chem. Soc.*, **113**, 726, 1991.

13. Paulissen, R.; Reimlinger, H.; Hayez, E.; Hubert, A.; Teyssie, Ph.; *Tetrahedron Lett.*, 2233, 1973.

14. For examples of the use of $Rh_2(OAc)_4$ in ether synthesis within a synthetic strategy, see Campbell, M.M.; Sainsbury, M.; Searle, P.A.; *Synthesis*, 179, 1993 and references therein.

15. Doyle, M.P.; *Chem. Ber.*, **86**, 919, 1986.

Adams, J.; Spero, D.M.; *Tetrahedron*, **47**, 1765, 1991.

16. Meerwein, H.; Rathjen, H.; Werner, H; *Ber.*, **75**B, 1610, 1942.

17. Kerr, J.A.; O'Grady, V.; Trotman-Dickenson, A.F.; *J. Chem. Soc. (A)*, 897, 1967.

18. Strausz, O.P.; DoMinh, T.; Gunning, H.E.; *J. Am. Chem. Soc.*, **90**, 1660, 1968.

19. Dominh, T.; Strausz, O.P.; Gunning, H.E.; *J. Am. Chem. Soc.*, **91**, 1261, 1969.

20. Jones, J.; Kresge, A.J.; *J. Org. Chem.*, **57**, 6467, 1992.

21. Hixson, S.S.; Hixson, S.H.; *J. Org. Chem.*, **37**, 1279,1972.

22. Gallucci, R.R.; Jones, M.; *J. Am. Chem. Soc.*, **107**, 4404, 1985.

23. Ziffer, H.; Sharpless, N.E.; *J. Org. Chem.*, **27**, 1944, 1962.

24. Padwa, A.; Layton, R.; *Tetrahedron Lett.*, 2167, 1965.

25. Ando, W.; Hagiwara, T.; Migita, T.; *Bull. Chem. Soc. Japan*, 1951, 1975.

26. Regitz, M.; Scherer, H.; Anschutz, W.; *Tetrahedron Lett.*, 753, 1970.

Reigitz, M.; Liedhegener, A.; Anschutz, W.; Eckes, H.; *Chem. Ber.*, **104**, 2177, 1971.

Tomioka, H.; Hirai, K.; *J. Chem. Soc. Chem. Commun.*, 1611, 1990.

27. Tomioka, H.; Hirai, K.; *J. Chem.Soc. Chem. Commun.*, 362, 1989.

Tomioka, H; Hirai, K; Tabayashi, K; Murata, S.; Izawa, Y; Inagki, S; Okajima, T.; *J Am. Chem. Soc.*, **112**, 7692, 1990.

28. Bartlett, P.A.; Carruthers, N.I.; *J. Chem. Soc. Chem. Commun.*, 536, 1982.

29. Bartlett, P.A.; Carruthers, N.I.; Winter, B.A.; Long, K.P.; *J. Org. Chem.*, **47**, 1284, 1982.

30. Stackhouse, J.; Westheimer, F.H.; *J. Org. Chem.*, **46**, 1891, 1981.

31. Tomioka, H.; Kitagawa, H.; Izawa, Y.; *J. Org. Chem.*, **44**, 3072, 1979.

32. Rando, R.R.; *J. Am. Chem. Soc.*, **94**, 1629, 1972.

33. Nagarajan, S.; Ganem, B.; *J. Org. Chem.*, **50**, 5735, 1985.

34. Wydila, J.; Thornton, R.; *Tetrahedron Lett.*, 233, 1983.

35. Kirmse, W.; Loosen, K.; Sluma, H.-D.; *J. Am. Chem. Soc.*, **103**, 5935, 1981.

36. Tomioka, H.; Hayashi, N.; Sugiura, T.; Izawa, Y; *J. Chem. Soc. Chem. Commun.*, 1364, 1986.

37. Eisenthal, K.B.; Turro, N.J.; Aikawa, M.; Buthcher, J.A.; Dupoy, C.; Hefferon, G.; Hetherington, W.; Korenowski, G.M.; McAuliffe, M.J.; *J. Am. Chem. Soc.*, **102**, 6565, 1980.

38. Bethell, D.; Stevens, G.; Tickle, P.; *J. Chem. Soc. Chem. Commun.*, 792, 1970.

39. Turro, N.J; Cha, Y.; Gould, I.R.; *Tetrahedron Lett.*, 5951, 1985.

40. Tomioka, H.; Inagaki, T.; Nakamura, S.; Izawa, Y.; *J. Chem. Soc. Perkin Trans. 1*, 130, 1979.

41. Hirayama, S.; *Bull. Chem. Soc. Japan*, **48**, 2653, 1975.

42. Zupancic, J.J.; Grasse, P.B.; Lapin, S.C.; Schuster, G.B.; *Tetrahedron*, **41**, 1471, 1985.

43. Nazran, A.S.; Griller, D.; *J. Chem. Soc. Chem. Commun.*, 850, 1983.

44. Nazran, A.S.; Griller, D.; *J. Am. Chem. Soc.*, **106**, 543, 1984.

45. Bethell, D.; Newall, A.R.; Whittaker, D.; *J. Chem. Soc. (B)*, 23, 1971.

46. Bethell, D.; Howard, R.D.; *J. Chem. Soc. (B)*, 430, 1968.

47. Erickson, J.L.E.; Dechary, J.M.; Kesling, M.R.; *J. Chem. Soc.*, 5301, 1951.

48. Seyferth, D.; Hilbert, P.; Marmor, R.S.; *J. Am. Chem. Soc.*, **89**, 4811, 1967.

49. Casanova, R.; Reichstein, T.; *Helv. Chim. Acta.*, **33**, 417, 1950.

50. Saegusa, T.; Ito, Y.; Kobayashi, S.; Hirota, K.; Shimitzu, T.; *J. Org. Chem.*, **33**, 544, 1968.

51. Takebayashi, M.; Ibata, T.; Kohara, H.; Hong Kim, B.; *Bull. Chem. Soc. Japan*, **40**, 2392, 1967.

52. Kulkowitt, S.; McKervey, M.A.; *J. Chem. Soc. Chem. Commun.*, 616, 1981.

53. Matlin, S.A.; Chan, L.; *J. Chem. Soc. Chem. Commun.*, 798, 1980.

54. Pellicciari, R.; Cogolli, P.; *J. Chem. Soc. Perkin Trans. 1*, 2483, 1976.

55. Newman, M.S.; Beal, P.F.; *J. Chem. Soc.*, 5161, 1950.

56. Paulissen, R.; Hubert, A.J.; Teyssie, P.; *Tetrahedron Lett.*, 607, 1974.

57. Moyer, M.P.; Feldman, P.L.; Rapoport, H.; *J. Org. Chem.*, **50**, 5223, 1985.

58. Moody, C.J.; Taylor, R.J.; *J. Chem. Soc. Perkin Trans. 1*, 721, 1989.

59. Heslin, J..C.; Moody, C.J.; *J. Chem. Soc. Perkin Trans. 1*, 1417, 1988.

60. Meier, H.; Stavridou, E.; Roth, S.; Mayer, W.; *Chem. Ber.*, **123**, 1411, 1990.

61. Noels, A.f.; Petiniot, A.D.; Hubert, A.J.; Teyssie, Ph.; *Tetrahedron*, **38**, 2733, 1982.

62. Petiniot, N.; Anciaux, A.J.; Noels, A.F.; Hubert, A.J.; Teyssie, Ph.; *Tetrahedron Lett.*, 1239, 1978.

Anciaux, A.J.; Hubert, A.J.; Noels, A.F.; Petiniot, N.; Teyssie, Ph., *J. Org. Chem.*, **45**, 695, 1980.

63. Ceccherelli, P.; Curini, M.; Marcotullio, M.C.; Rosati, O.; *Tetrahedron*, **44**, 9767, 1992.

64. Taber, D.F.; Ruckle, R.E.; *J. Am. Chem. Soc.*, **108**, 7686, 1986.

65. Padwa, A.; Fryxell, G.E.; Zhi, L.; *J. Org. Chem.*, **53**, 2875, 1988.
Padwa, A.; Carter, S.P.; Nimmesgern, H.; Stull, P.D.; *J. Am. Chem. Soc.*, **110**, 2894, 1988.

Padwa, A.; Chinn, R.L.; Hornbuckle, S.F.; Zhang, Z.J.; *J. Org. Chem.*, **56**, 3271, 1991.

66. Adams, J.; Poupart, M.-A.; Grenier, L.; Schaller, C.; Ouimet, N.; Frenette, R.; *Tetrahedron Lett.*, 1749, 1989.

67. Hashimoto, S.; Watanabe, N.; Ikegami, S.; *J. Chem. Soc. Chem. Commun.*, 1508, 1992.

68. Hasimoto, S.; Watanabe, N.; Ikegami, S.; *Tetrahedron*, **33**, 2709, 1992.

69. Padwa, A.; Austin, D.J.; Hornbuckle, S.F.; Semones, M.A.; *J. Am. Chem. Soc.*, **114**, 1874, 1992.

Padwa, A.; Austin, D.J.; Hornbuckle, S.F.; Price, A.T.; *Tetrahedron Lett.*, 6427, 1992.

70. Regitz, M.; Hocker, J.; Liedhegener, A.; *Org. Syn. Coll. Vol. V*, Wiley, 179, 1979.

71. Holmquist, C.R.; Roskamp, E.J.; *J. Org. Chem.*, **54**, 3258, 1989.

See also Padwa, A.; Hornbuckle, S.F.; Zhang, Z.; Zhi, L.; *J. Org. Chem.*, **55**, 5297, 1990.

72. Padwa, A., Fryxell G. E., Zhi L.; *J. Am. Chem. Soc.*, **112**, 3100, 1990,

73. Sie, E.-R.H.B.; *Loughborough University*, personal communication.

74. Crackett, P.H.; Sayer, P.; Stoodley, R.J.; Greengrass, C.W.; *J. Chem. Soc. Perkin Trans. 1*, 1235, 1991.

75. Padwa, A.; Carter, S.P.; Hornbuckle, S.F.; Semones, A.; Doyle, M.P.; Protopopova, M.N.; *J. Am. Chem. Soc.*, **114**, 1874, 1992.

76. As reported for carbonyl ylids, see Padwa, A.; Hornbuckle, S.F.; *Chem. Rew.*, **91**, 263, 1991.

77. Regitz, M.; Bartz, W.; *Chem. Ber.*, **103**, 1477, 1970.

78. Sie, E.-R.H.B.; Miller, D.J.; *Loughborough University*, personal communication.

79. Sie, E.-R.H.B.; PhD. Thesis, *Loughborough University*, 1992.

80. This procedure for the synthesis of phosphonodiazoacetates was developed by Dr. Eric Sie, *Loughborough University*.

81. Doyle, M.P.; Bagheri, V.; Wandless, T.J.; Harn, N.K.; Brinker, D.A.; Eagle, C.T.; Loh, K.-L.; *J. Am. Chem. Soc.*, **112**, 1906, 1990.

82. Johnson, S.A.; Hunt, H.R.; Neumann, H.M.; *Inorg. Chem.*, **2**, 960, 1963.

83. Doyle, M.P.; Mahapatro, S.N.; Caughey, A.C.; Chinn, M.S.; Colsman, M.R.; Ham, N.K., Redwine, A.E.; *Inorg. Chem.*, **26**, 3070, 1987.

84. Ahsan, M.Q.; Bernal, I.; Bear, J.L.; *Inorg. Chem.*, **25**, 260, 1986.

85. Dennis, A.M.; Howard, R.A.; Lancon, D.; Kadish, K.M.; Bear, J.L.; *J. Chem. Soc. Chem. Comm.*, 399, 1982.

86. Cox, G.G.; Kulagowski, J.J.; Moody, C.J.; Sie, E.-R.H.B.; *Synlett*, 975, 1992.

87. Pirrung, M.C.; Zhang, J.; *Tetrahedron Lett.*, 5987, 1992.

88. From 'Multiple Bonds Between Metal Atoms', Cotton, F.A.; Walton, R.A.; Oxford University Press, 1993.

89. Elliot, M.; Doyle, K.J.; Personal Communication.

90. For an example see Mori, K.; Sasaki, M.; Tamada, S.; Suguro, T.; Masuda, S.; *Tetrahedron*, **35**, 1601, 1979.

91. Haddow, J.; Suckling, C.J.; Wood, H.C.S.; *J. Chem. Soc. Perkin Trans. 1*, 1297, 1989.

92. Chong, J.M.; Sharpless, K.B.; *Tetrahedron*, **26**, 4683, 1985.

Larcheveque, M.; Petit, Y.; *Tetrahedron*, **28**, 1993, 1987.

Roush, W.R.; Essenfeld, A.P.; Warmus, J.S.; Brown, B.B.; *Tetrahedron Lett.*, 7305, 1989.

93. Fuji, K.; Ueda, M.; Sumi, K.; Fujita, E.; *Synthetic Commun.*, 209, 1981.

Beautement, K.; Clough, J.M.; *Tetrahedron Lett.*, 475, 1987.

94. Terashima, S.; Jew, S.-S.; *Tetrahedron Lett.*, 1005, 1977.

95. Wasserman, H.H.; Lipshutz, B.H.; *Tetrahedron Lett.*, 1731, 1975.

96. For a review of oxaziridines in asymmetric synthesis see Davis, F.A.; Chen, B.-C.; *Chem. Rev.*, **92**, 919, 1992.

Leading references see Davis, F.A.; Vishwakarma, L.C.; Billmers, J.M.; *J. Org. Chem.*, **49**, 3241, 1984.

Naraska, K.; Ukaji, Y.; Watanabe, K.; *Bull. Chem. Soc. Jpn.*, **60**, 1457, 1987.

Davis, F.A.; Weismiller, M.C.; Lal, G.S.; Chen, B.-C.; Pizeslawski, R.M.; *Tetrahedron Lett.*, 1613, 1989.

Chen, B.-C.; Weismiller, M.C.; Davis, F.A.; *Tetrahedron*, **47**, 173, 1991.

97. For leading references see Gamboni, R.; Mohr, P.; Waespe-Sarcevic, N.; Tamm, C.; *Tetrahedron Lett.*, 203, 1985.

Gamboni, R.; Tamm, C.; *Helv. Chim. Acta.*, **69**, 615, 1986.

98. Morizawa, Y.; Yasuda, A.; Uchida, K.; *Tetrahedron Lett.*, 1833, 1986.

99. Solladie-Cavallo, A.; Bencheqroun, M.; *Tetrahedron Assymetry*, **2**, 1165, 1991.

Akiyama, T.; Nishimoto, H.; Ozaki, S.; *Tetrahedron Lett.*, 1335, 1991.

Xiang, Y.B,; Snow, K.; Belley, M.; *J. Org. Chem.*, **58**, 993, 1993.

100. Ojima, I.; Kogure, T.; *J. Chem. Soc. Chem. Commun.*, 428, 1977.

101. Schollkopf, U.; Rieber, N.; *Chem. Ber.*, **102**, 488, 1969.

102. Taber, D.F.; Hennessy, M.J.; Louey, J.P.; *J. Org. Chem.*, **57**, 436, 1992.

Taber, D.F.; Hoerrner, R.S.; *ibid.*, **57**, 441, 1992.

103. Tetra-2,4,6-Trimethylbenzoate dirhodium (II) and Tetra-9-Anthracenyl dirhodium (II):
Callot, H.J.; Metz, F.; *Tetrahedron*, **41**, 4495, 1985.

Tetra-2-Phenylbenzoate dirhodium (II):
Cotton, F.A.; Thompson, J.L.; *Inorg. Chim. Acta*, **81**, 193, 1984.

Tetrasalicylate dirhodium (II):
Bancroft, D.P.; Cotton, F.A.; Han, S.; *Inorg. Chem.*, **23**, 2408, 1984.

104. Takamura, N.; Mizoguchi, T.; *Tetrahedron Lett.*, 4495, 1971.

105. Taber, D.F.; Ruckle, R.E.; Hennessay, M.J.; *J. Org. Chem.*, **51**, 4077, 1986.

106. Danheiser, R.K.; Miller, R.F.; Brisbois, R.G.; Park, S.Z.; *J. Org. Chem.*, **55**, 1959, 1990.

107. Blankley, C.J.; Sauter, F.J.; House, H.O.; *Org. Syn. Coll. Vol. V*, Wiley, 258, 1979.

108. Bamford, W.R.; Stevens, T.S.; *J. Chem. Soc.*, 4735, 1952.

109. A review of Oppolzer's Camphor Sultam as a chiral auxiliary in asymmetric thermal reactions: Kim, B.H.; Curran, D.P.; *Tetrahedron*, **49**, 293, 1993.

Leading references for pantalactone and other α-hydroxyesters as chiral auxiliaries: Durst, T.; Koh, K.; *Tetrahedron Lett.*, 6799, 1992.

Davies, H.M.L.; Cantrell, W.R.; *Tetrahedron Lett.*, 6509, 1991.

Leading references for Evans' chiral oxazolidinones in asymmetric synthesis: Evans, D.A.; Ng, H.P.; Clark, J.S.; Rieger, D.L.; *Tetrahedron*, **48**, 2127, 1992.

Evans, D.A.; Britton, T.C.; Ellman, J.A.; Dorow, R.L.; *J. Am. Chem. Soc.*,**112**, 4011, 1990.

Evans, D.A.; Britton, T.C.; Dorow, R.L.; Dellaria, F.; *Tetrahedron*, **44**, 5525, 1988.

110. Interested readers are referred to the discussion in: 'Multiple Bonds Between Metal Atoms', Cotton, F.A.; Walton, R.A.; Oxford University Press, 1993, and references therein.

111. Doyle, M.P.; Westrum, L.J.; Wolthuis, W.N.E.; See, M.M.; Boone, W.P.; Bagheri, V.; Pearson, M.M.; *J. Am. Chem. Soc.*, **115**, 958, 1993.

112. McCarthy, N.; McKervey, M.A.; Ye, T.; McCann, M.; Murphy, E.; Doyle, M.P.; *Tetrahedron Lett.*, 5983, 1992.

113. These catalysts have previously been described in the literature and were prepared by ligand exchange from rhodium (II) acetate in the usual way.

Roos, G.H.P.; McKervey, M.A.; *Synthetic Commun.*, 1751, 1992.

114. Agaskar, P.A.; Cotton, F.A.; Falvello, L.R.; Han, S.; *J. Am. Chem. Soc.*, **108**, 1214, 1986.

115. A sample of this catalyst was generously provided by Dr. M.P. Doyle, Trinity University, San Antonio, Texas, 78212.

116. A sample of this catalyst was generously provided by Dr. M.C. Pirrung, Duke University, P.M.Gross Chemical Laboratory, Durham, North Carolina, 27706, U.S.A..

117. Brunner, H.; Wutz, K.; Doyle, M.P.; *Monatshefte Chem.*, **121**, 755, 1990.

118. Ort, O.; *Org. Syn. Coll. Vol. V*, Wiley, 203, 1979.