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APPLICATIONS OF ORGANOMETALLIC REAGENTS IN β-LACTAM CHEMISTRY

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INTRODUCTION

Since the β-lactams are a group of antibiotics of unparalleled importance in chemotherapy, considerable effort has been expended in the development of novel, more active compounds. Extensive investigations of microbial secondary metabolites have led, for example, to the discovery of the penicillins, cephalosporins, the nocardicins, the carbapenem antibiotics and the monobactams. The search for improved antibiotics has engendered the design of new methodology both for the total synthesis and semi-synthesis of β-lactam derivatives. Any synthetic approach to β-lactam antibiotics must address the issue of molecular instability. The penicillins and cephalosporins, etc., are active since they are potent electrophiles. They acylate, and thereby inhibit, the enzyme that catalyses peptidoglycan chain crosslinking in bacterial cell wall biosynthesis. In general β-lactam antibiotics contain a plethora of functionality closely assembled in a low molecular weight molecule. As a result the chemistry of these systems is remarkably rich.[1]

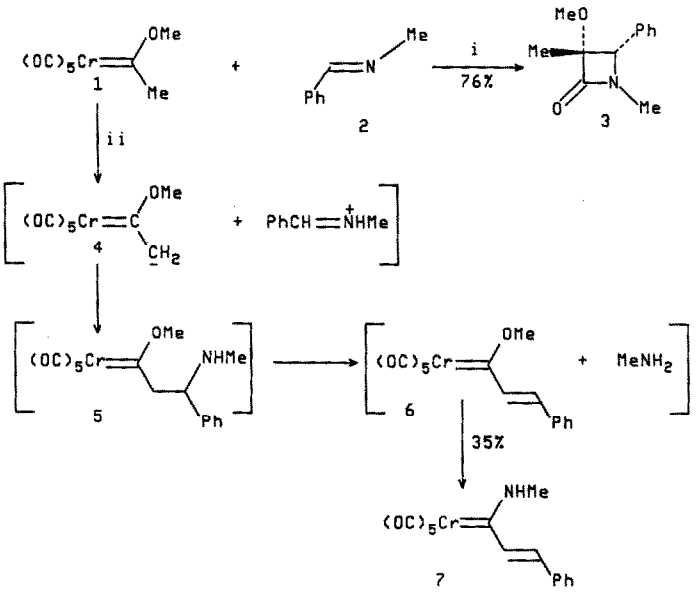
This review summarizes the applications of transition metal complexes in β-lactam chemistry. In many cases the unique reactivities of such complexes are ideally suited for the preparation and derivatization of β-lactam systems under mild and specific conditions. This review is focussed exclusively on reactions that involve the construction or ring system rearrangement of β-lactam systems. Additionally, all the reagents discussed involve the chemistry of metal carbon bonds. The use of transition metal reagents solely as Lewis acids, as redox reagents or for a protection deprotection sequence are explicitly excluded. Reactions that involve transition metal reagents not directly linked to carbon, for example titanium enolates, are beyond the scope of this review.

1. The Preparation of β-Lactams from Pentacarbonyl Chromium Carbenes

In 1982 McGuire and Hegedus reported that, on photolysis in the brilliant Colorado sunshine, the Fischer carbene 1 reacted with the imine 2 to produce the monocyclic β-lactam 3 (76%).[2] However, the thermal reaction between 1 and 2 gave the amino carbene 7. Hegedus suggested that the formation of 7 took place via the carbene anion 4, an aldol type condensation to produce 5, β-elimination of methylamine and aminolysis of the resultant unsaturated carbene complex 6. Such a reasonable mechanism is fully consistent with known chemistry of Fischer carbenes.[3]

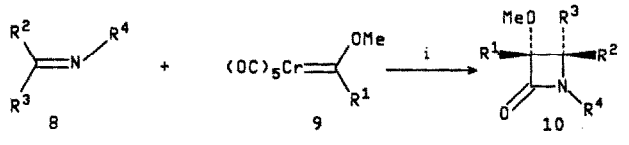
A variety of imines 8 were converted into the corresponding β-lactams 10 by photolytic reaction with the corresponding carbene complex 9.[4,5] Yields were modest to excellent (20-90%). Of particular note is the reaction to produce the N-anisyl-2-azetidinone derivative 11 (66%) since ceric ammonium nitrate oxidation of this substance readily gave 12 (90%). Such β-lactams lacking an N-substituent could not be made directly from 8 (R^4=H) due to carbene iminolysis rather than cyclization.

SCHEME 1

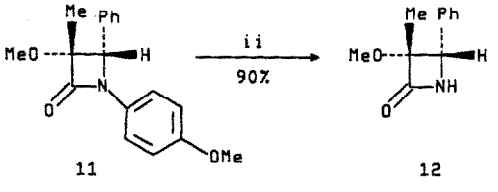


Reagents: (i) hν, Et_2O; (ii) 50°C

SCHEME 2

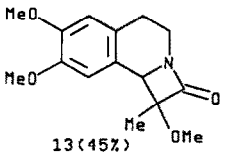


R^1=Me, Ph; R^2=H, Ph, COPh, C(=NPh)Ph; R^3=Ph, Me, PhCH=CH;
R^4=Me, Ph, $CH_2P(O)(OEt)_2$, $CH(CO_2Me)P(O)(OEt)_2$, $CH=CH_2$

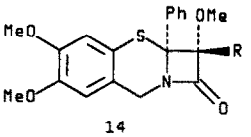


Reagents: (i) hν, Et_2O; (ii) $(NH_4)_2[Ce(NO_3)_6]$, MeCN, H_2O

The Hegedus carbene chemistry is particularly elegant in its application to the conversion of cyclic imines, Δ^1-thiazolines, 4H- and 2H- 1,3-benzothiazines and related heterocyclic substances into the corresponding bicyclic β-lactams. The versatility of the process is exemplified by the preparations of 13 to 18 from the corresponding methoxy carbenes.[1,2,4,5]

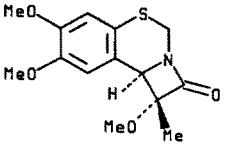


13(45%)

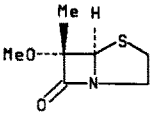


14

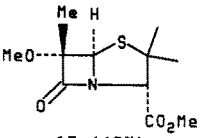
(R=Me, 61%; R=Ph, 25%)



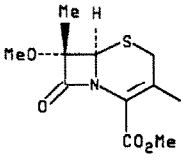
15 (37%)



16 (81%)



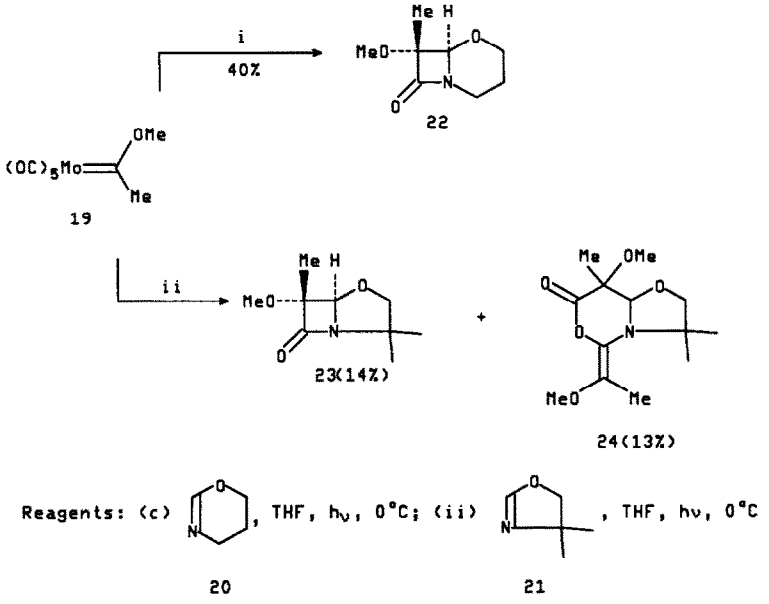
17 (42%)



18 (52%)

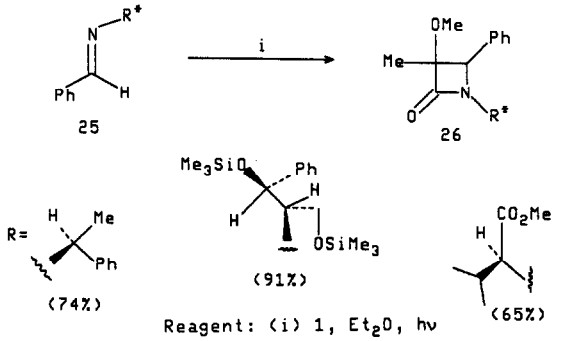
In contrast to these heterocyclic systems, chromium carbenes failed to produce bicyclic β-lactams on photolysis in the presence of oxazines or oxazolines. However, the corresponding molybdenum carbene 19 reacted, on photolysis, with 20 and 21 to produce 22 (40%) and 23 (14%) accompanied by 24 (13%).

SCHEME 3



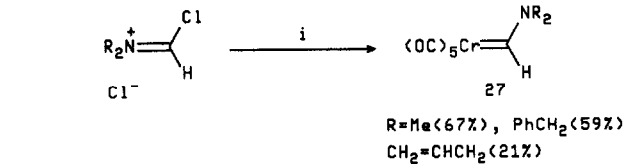
In an attempt to generate optically pure monocyclic β-lactams, Hegedus studied the photocyclization of 1 with the imines 25 bearing a chiral N-substituent. Poor to modest diastereoisomeric excesses (15-60%) were observed in the product β-lactams 26. The absolute stereochemistries of the major diastereoisomers (at C-3 and C-4) were not determined. It is possible that chiral ligands on chromium or in the carbene ester substituent[3] should provide superior absolute stereochemical control in the Hegedus chemistry.

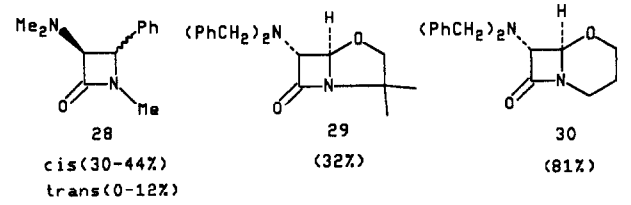
SCHEME 4

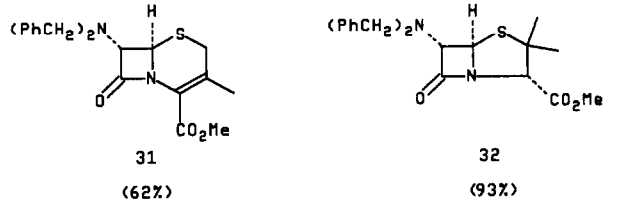


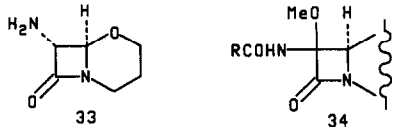
Most recently Hegedus and coworkers have reported a simple synthesis of chromium carbenes 27 bearing the C(H)-NR_2 substituent.[6] Subsequent photolytic reaction in the polar solvent acetonitrile, but not in diethyl ether, was used to prepare a series of mono and bicyclic β-lactams including 28 to 32. The preparation of 32 in >99% ee from the chiral thiazoline is especially noteworthy.

SCHEME 5



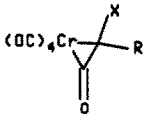




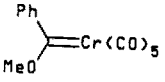


Although the oxacepham 30 could be debenzylated via hydrogenolysis over palladium on carbon to produce 33 (94%), neither 31 nor 32 could be converted into the corresponding primary amines. It is clear, however, that the amino carbene 27 (R=$PhCH_2$) is of very considerable potential in the elaboration of β-lactams bearing the crucial acylamino substituent. It may be possible by some variant of this chemistry to elaborate 3-methoxy-3-acylamino-2-azetidinone derivatives 34.

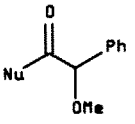
Hegedus has studied the mechanism of these useful photochemical reactions.[6] He has demonstrated that the process involves CTML excitation and subsequent formation of the chromium ketene complex. Subsequent reaction with the imine gave the β-lactam product. The stereochemistry of these imine and chromium ketene reactions exactly parallel results with free ketenes. However, yields in the chromium carbene reactions are much higher. The intermediacy of chromium ketene complexes 35 was unequivocally established by photolysis of 36 in the presence of methanol or dibenzylamine to produce 37. Additionally, chromium ketene complexes derived from aminocarbenes 27 were also trapped by methanol or amine nucleophiles.



35



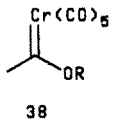
36



37

Nu = OMe (69%), $N(CH_2Ph)_2$ (28%)

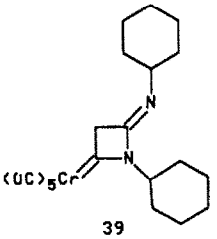
In 1974 Fischer and coworkers observed that the hydroxy carbene 38a reacted with dicyclohexyl carbodiimide to produce 39 (47%).[7] The authors speculated that this reaction proceeded via the unsubstituted chromium vinylidene 40[8] and formal [2+2] cycloaddition. We reexamined this reaction in an attempt to prepare β-lactam systems. Thus the carbene 38b was reacted with toluene-4-sulfonyl chloride and the imine 2 in dichloromethane. The resultant product, the azetidinylidene complex 41a (25%), was authenticated by an X-ray crystallographic study.[9] In the same way the complexes 41b (9%) and 41c (6%) were prepared from the corresponding imines. Oxidation of these substances using iodosobenzene or pyridine-N-oxide gave the benzylidene-β-lactams 42 (87-100%). It is possible that 41a-c were produced from the cycloaddition of 40 with the imines. Alternatively 41a-c may have arisen from an aldol-type stepwise mechanism. Consistent with this mechanism the formation of 41a was shown to be solvent dependent. Thus reaction of 38b with 2 and toluene-4-sulfonyl chloride in dry t-butanol gave 41a (22%). In contrast, reaction in methanol gave 41a (9%) and 43 (9%). Although these reactions demonstrate that azetidinylidene chromium carbene complexes can be prepared and converted into β-lactams, the overall efficiency of the process was disappointing. Additionally the reaction could not be extended to more heavily functionalized imine systems.



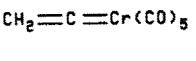
38

a R=H

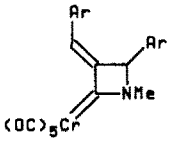
b $R=O^{-}\overset{+}{N}Me_4$



39



40



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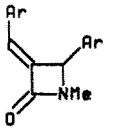
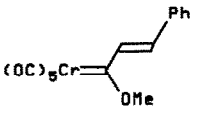


42

a Ar=Ph

b Ar=3-MeC_6H_4

c Ar=4-MeC_6H_4

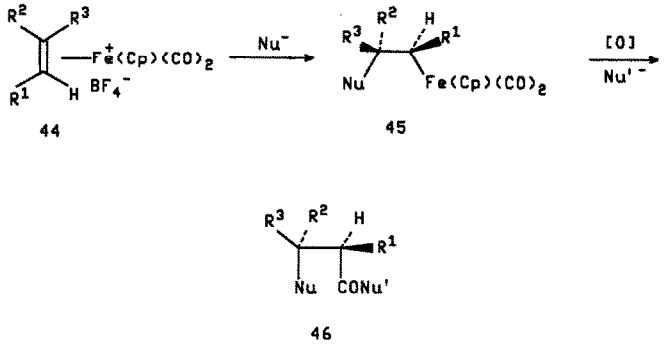


43

2. Dicarbonyl-η^5-cyclopentadienyl(alkene)iron Cations in β-Lactams Synthesis

Rosenblum has extensively studied the addition of nucleophiles to dicarbonyl-η^5-cyclopentadienyl (Fp) (alkene) iron salts 44 to produce the corresponding alkyl iron adducts 45.[10] Furthermore, it was demonstrated that oxidation of 45 gave 46 in which the alkyl residue migrated to the CO with retention of configuration. Subsequently this chemistry was extended to the synthesis of β-lactams.[11]

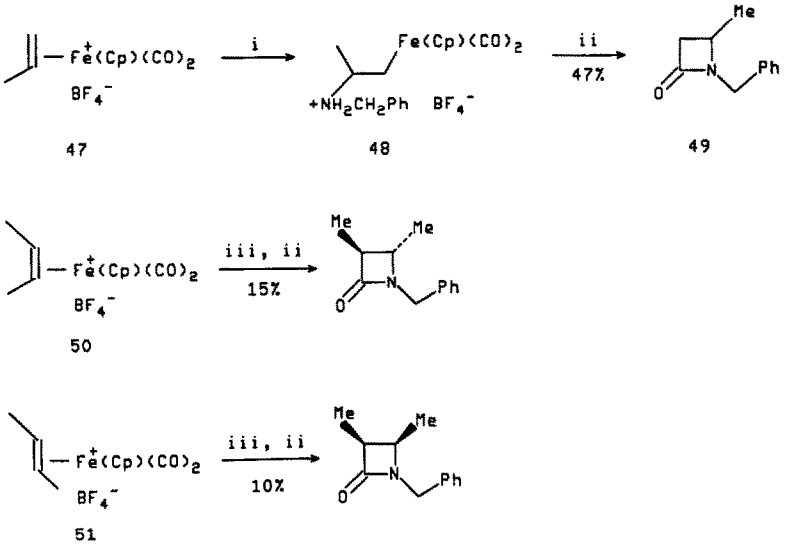
SCHEME 6



44 45 46

Thus reaction of the propylene complex 47 with benzylamine gave 48. Subsequent oxidation using chlorine gave the β-lactam 49 (45%). The stereochemistry of the reaction is illustrated by the conversion of the complexes 50 and 51 into the corresponding β-lactams. These results are in accord with a trans addition of benzylamine followed by carboxamidation with retention of configuration. Since the cyclization to produce the β-lactam proceeded via the β-amino acid chloride, the yields obtained were only modest. As an alternative 48 was cyclized to give 49

SCHEME 7



47 48 49

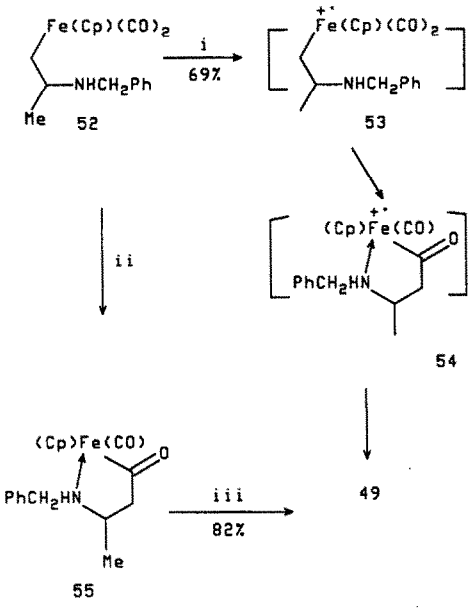
50

51

Reagents: (i) $PhCH_2NH_2$, CH_2Cl_2, -25°C; (ii) Cl_2, CH_2Cl_2, -78°C; Et_3N; (iii) $PhCH_2NH_2$, $CHCl_3$, $MeNO_2$, -24°C

(69%) by reaction with sodium hydroxide to produce the free amine 52 followed by lead dioxide or silver oxide oxidation. Presumably this process involved sequential one electron oxidation at iron and the intermediacy of 53 and 54. On heating 52 was converted into 55 and this material in turn was smoothly oxidized to produce 49 in superior yield (82%). Since the oxidation of 55 was slower than the direct oxidation of 52 it was clearly not an intermediate in the conversion of 52 into 49 (Scheme 8)

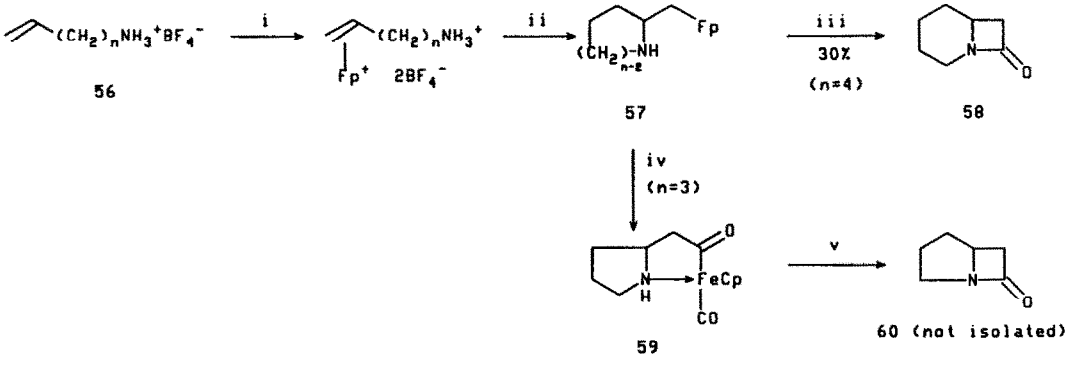
SCHEME 8



Reagents: (i) Ag_2O or PbO_2, THF, 25°C; (ii) MeCN, Bu_3P, 70°C; (iii) Ag_2O, 70°C

Rosenblum has extended this chemistry to the production of the bicyclic β-lactams 58[11], 60[11], 65[12], 69[13] and 70[13]. Scheme 9 outlines the preparation of the carbacepham and carbapenam frameworks via alkene-cation exchange, cyclization of the amine alkene complexes and oxidative cyclization. Whilst the bicyclic β-lactam 58 could be prepared via the direct oxidation of 57 (n=4), attempts to prepare 60 from 57 (n=3) gave only polymer. However, thermolysis of 57 (n=3) gave 59 and this, on oxidation, gave 60 in solution.

SCHEME 9

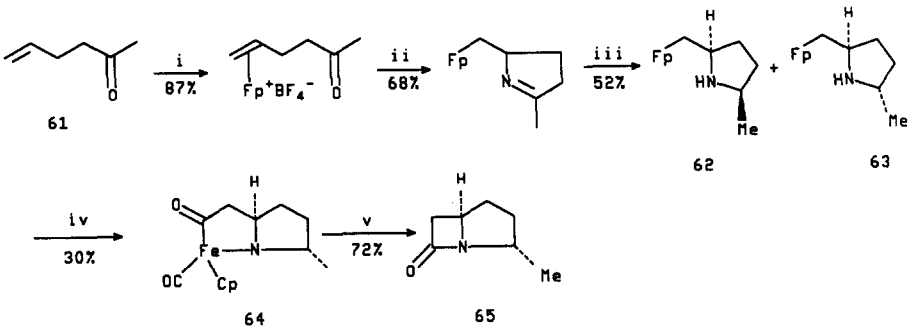


Reagents: (i) $Me_2C{=}CH_2.Fp^+BF_4^-$; (ii) Bu_3N; KO^tBu; (iii) Ag_2O, THF, 65°C; (iv) Ph_3P, THF, Δ; (v) Ag_2O, THF, 25°C

Fp=$Fe(CO)_2Cp$

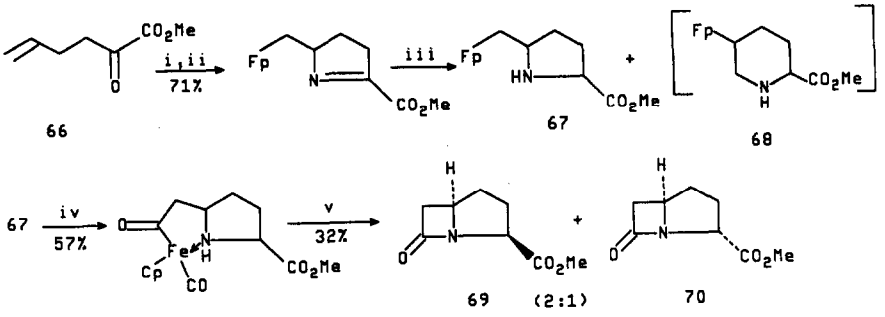
Schemes 10 and 11 outline the adaption of this chemistry to the elaboration of the functionalized carbapenams 65, 69 and 70. These procedures underscore the versatility of Fp-iron chemistry, in that the required iron alkyl intermediates were easily generated via reductive amination. It is important to mention a caveat at this point. Work up conditions for the generation of 67 (Scheme 11) were critical. Acid work up gave both 67 and 68 clearly indicating that isomerization was taking place via reversible C-N cleavage and Fp-alkene cation formation.

SCHEME 10



Reagents: (i) $Me_2C{=}CH_2.Fp^+BF_4^-$, CH_2Cl_2, Δ; (ii) NH_3, CH_2Cl_2; (iii) $NaBH_4$, EtOH; (iv) Bu_3P, MeCN, Δ; (v) Ag_2O, THF

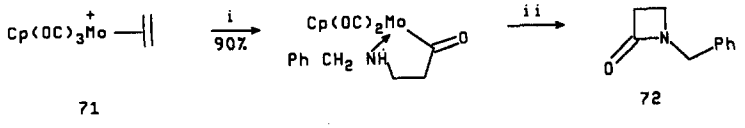
SCHEME 11



Reagents: (i) $Me_2C{=}CH_2.Fp^+PF_6^-$, CH_2Cl_2, 40°C; (ii) NH_3, CH_2Cl_2; (iii) $NaBH_4$, MeOH; (iv) MeCN, Δ; (v) Ag_2O, THF

Rosenblum has additionally demonstrated that his β-lactam methodology is not unique to iron. Thus the molybdenum complex 71 was transformed into the corresponding β-lactam 72 (9%) (Scheme 12).[11]

SCHEME 12

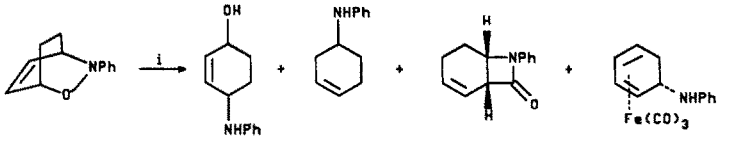


Reagents: (i) $PhCH_2NH_2$; (ii) Ag_2O

3. Ferrilactam Intermediates in β-Lactam Construction

The reaction of 3,6-dihydro-1,2-oxazine derivatives with di-iron nonacarbonyl 74 has been extensively studied by Shvo and coworkers.[14-16] They observed that on warming in benzene, 73 and 74 gave four products including the bicyclic β-lactam 75[14] (Scheme 13). Examination of the reaction between 74 and 76 provided important mechanistic insights on the formation of the β-lactam system.[16] The major product formed in this reaction (Scheme 14) was the ferrilactam complex 77 (L=CO). An X-ray crystallographic study of the derived trimethyl phosphite complex 77 (L=$(MeO)_3P$) established the structure of this product. In addition the crystal structure

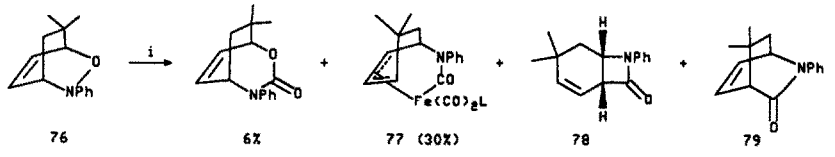
SCHEME 13



73 8% 6% 75 (8%) 25%

Reagent: (i) $Fe_2(CO)_9$ (74), PhH

SCHEME 14

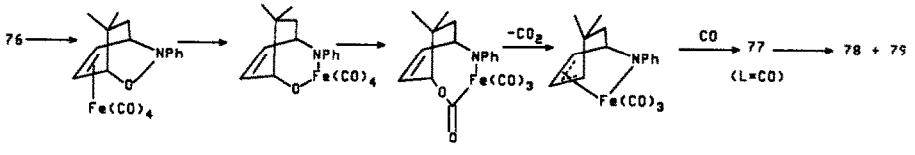


76 6% 77 (30%) 78 79

Reagent: (i) $Fe_2(CO)_9$ (74), PhH

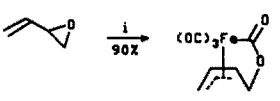
showed that the distances between the two terminii of the π-allyl system and the carbamoyl carbon were extraordinarily short for non-bonding distances (2.727Å and 3.183Å). On thermolysis in benzene 77 (L=CO) was converted cleanly into 78 and 79 (yields unspecified). On the basis of these observations the authors speculated that the β-lactam 78 was formed as shown in Scheme 15.

SCHEME 15



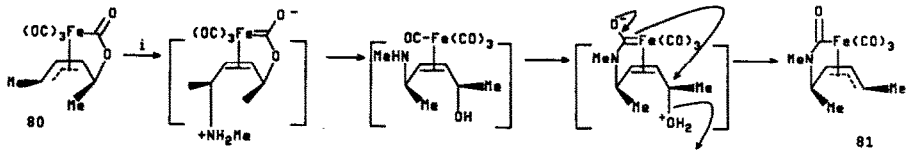
Both Aumann[17] and Ley[18] have demonstrated that ferrilactone complexes structurally related to 77 may easily be synthesized from the reaction of vinyl oxiranes with iron pentacarbonyl or di-iron nonacarbonyl (Scheme 16). Additionally, reaction of these complexes with amines gave the corresponding ferrilactam systems (Scheme 17). Aumann first rigorously established the stereochemistry of reaction and showed that the ferrilactone to ferrilactam reaction proceeded with inversion at C-2 and C-5 and allyl migration (see 80 and 81).

SCHEME 16



Reagent: (i) $Fe(CO)_5$, PhH, hν, 20°C

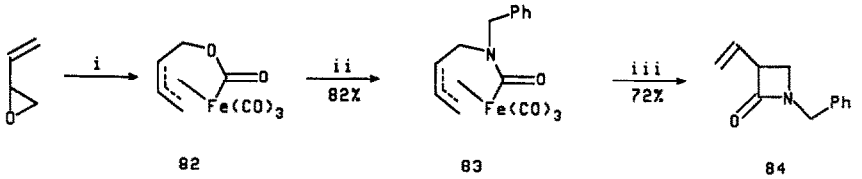
SCHEME 17



Reagent: (i) $MeNH_2$, Et_2O

In an extension of work on alkenyl β-lactones,[18] Ley and coworkers have established that the ferrilactone to ferrilactam transformation was preparatively useful in the synthesis of β-lactam systems.[19] Thus the ferrilactone **82**, derived from 1,3-butadiene monoepoxide, was converted into **83** and subsequently the β-lactam **84** (Scheme 18). Crucial in this approach was the oxidative conversion of **83** into **84** using ceric ammonium nitrate. This methodology has been

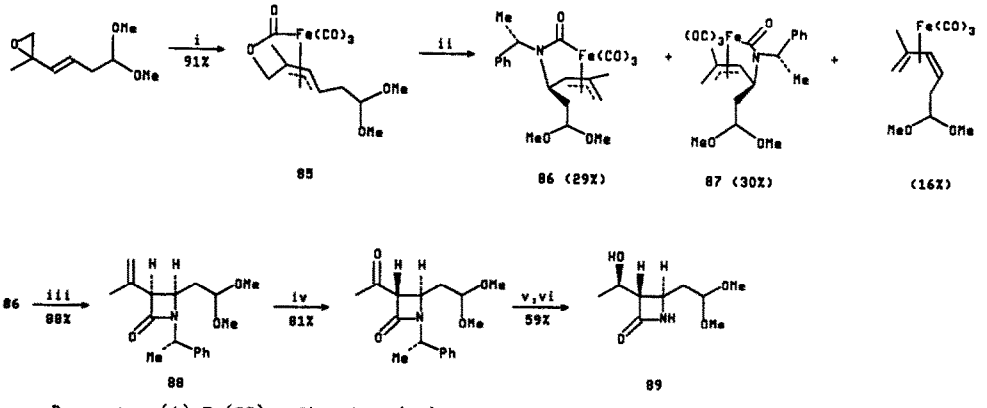
SCHEME 18



Reagents: (i) $Fe(CO)_5$, PhH, h ; (ii) $PhCH_2NH_2$, $ZnCl_2$, THF, Et_2O; (iii) $(NH_4)_2[Ce(NO_3)_6]$, EtOH, -30°C

used to prepare the monocyclic β-lactam **89** (Scheme 19)[20] which is an intermediate in the Kametani synthesis of thienamycin.[21] The crucial step in this synthesis was the conversion of **85** into the diastereoisomeric ferrilactam complexes **86** and **87**, chromatographic separation and oxidation of **86** to produce the azetidinone **88**.

SCHEME 19

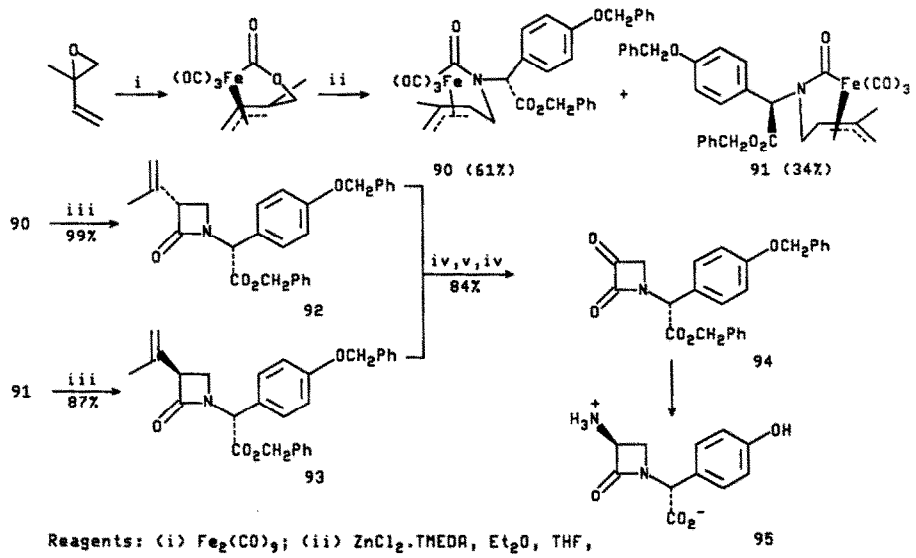


Reagents: (i) $Fe(CO)_5$, PhH, hν; (ii) $ZnCl_2$.TMEDA, Et_2O, THF, (S)-PhCH(Me)NH_2; (iii) MeOH, $(NH_4)_2[Ce(NO_3)_6]$, -30°C; (iv) O_3, CH_2Cl_2, -78°C; Me_2S; (v) KH, $KBHEt_3$, Et_2O, THF, 0°C; (vi) Na, EtOH, NH_3, -78°C.

Ley has also used his methodology to convert isoprene epoxide into the optically pure β-lactam **94** (Scheme 20).[22] This 2,3-azetidinedione derivative had been previously converted into 3-amino-nocardicinic acid **95** by Ban and coworkers.[23] Again the key process was the condensation

reaction of the racemic ferrilactone with a chiral amine to produce the ferrilactams 90 and 91. Although these substances could be separated by chromatography, the mixture was easily converted into 94 via the diastereoisomeric mixture of β-lactams 92 and 93. Although several steps were needed to convert the isopropenyl group into a β-amino functionality, the preparation of 94 is noted both for its brevity and overall efficiency (79%).

SCHEME 20

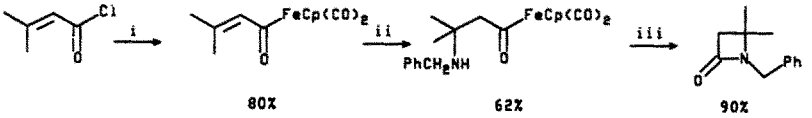


Reagents: (i) $Fe_2(CO)_9$; (ii) $ZnCl_2$.TMEDA, Et_2O, THF, (R)-$NH_2CH(CO_2CH_2Ph)C_6H_4$-4-OCH_2Ph; (iii) $(NH_4)_2[Ce(NO_3)_6]$, MeOH, -30°C; (iv) O_3, CH_2Cl_2, -78°C; Me_2S; (v) $^tBuMe_2SiO_3SCF_3$, Et_3N, 0°C

4. Iron Acyl Complexes in β-Lactam Synthesis

The use of iron acyl complexes in the synthesis of β-lactams has been approached by a number of authors. Ojima has shown that addition of nitrogen nucleophiles to α,β-unsaturated iron acyl complexes proceeded in a conjugated sense to generate the β-aminoacyl complexes in good yield.[24] These species were subjected to oxidative cleavage of the iron-acyl bond and subsequent lactamization (Scheme 21) in a manner analogous to that used by Rosenblum (Section 2). It should be noted that this sequence does not involve metallacyclic intermediates and indeed cyclization is only a subsequent reaction of the liberated ligand. To this extent this sequence only parallels a procedure available from traditional organic synthesis, whereby the Fp-acyl group acts as a masking residue for the carboxylate functionality.

SCHEME 21

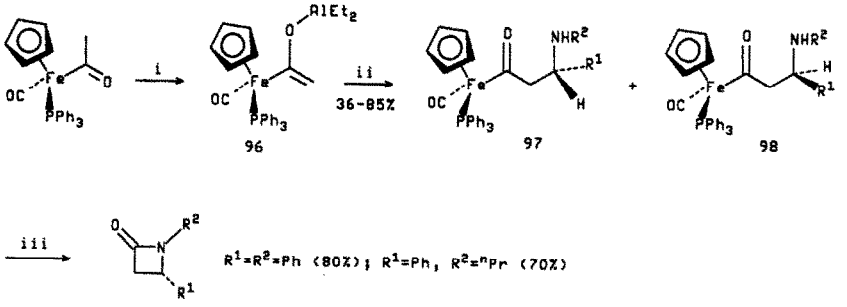


Reagents: (i) $NaFeCp(CO)_2$, THF, -78°C to -25°C; (ii) $PhCH_2NH_2$, 25°C; (iii) Br_2, Et_3N, -78°C.

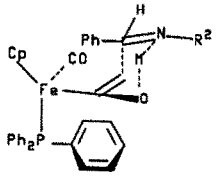
A more significant contribution to the synthesis of β-lactams via iron acyl complexes has been developed independently by Liebeskind[25] and Davies.[26] Both authors recognized that β-amino iron acyls should be available from the reaction of ferraenolates and imines. More importantly, they both demonstrated that the ferraenolate 96, which contains an asymmetric tetrahedral iron, reacted with imines to produce the corresponding complexes 97 with excellent

diastereoselectivities (97:98 = 1.3:1 - >20:1,[25] >49:1[26])(Scheme 22). Liebeskind unequivocally identified the structure of the major diastereoisomers 97 by an X-ray crystallographic study and ^{1}H NMR spectral comparisons. Davies has argued that the diastereoselectivity of reaction of

SCHEME 22

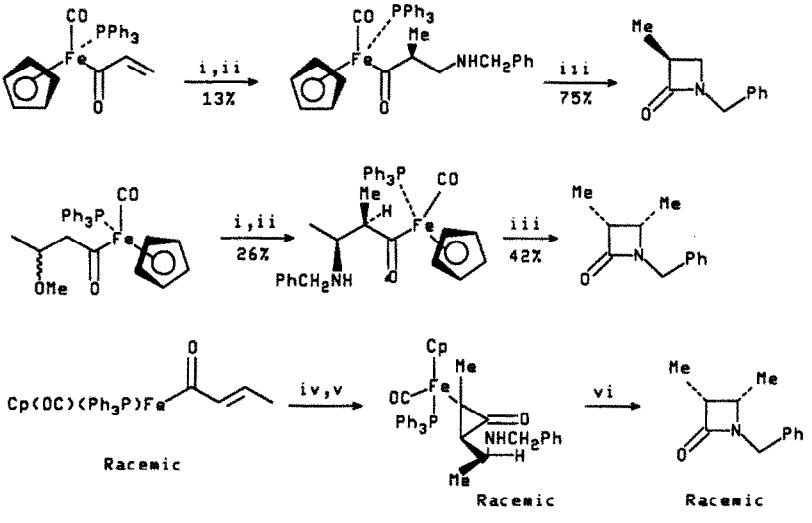


Reagents: (i) $LiN^{iso}Pr_2$, THF, -42°C; Et_2AlCl; (ii) $R^1CH{=}NR^2$, -42°C; (iii) I_2, Et_3N, CH_2Cl_2, -42° to 0°C



99

SCHEME 23*



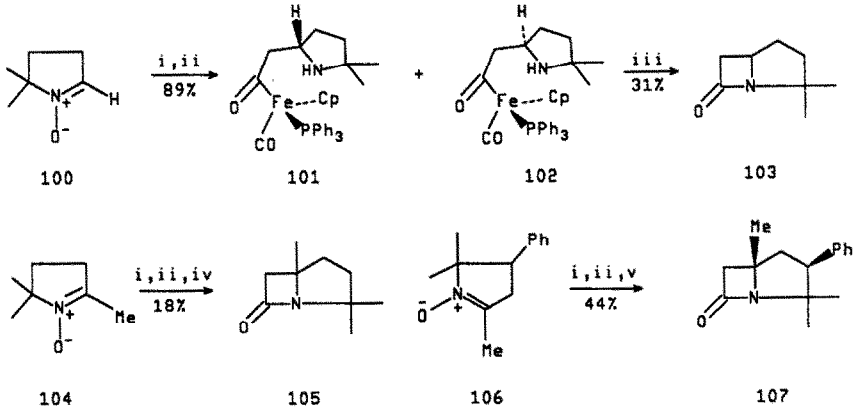
Reagents: (i) $PhCH_2NHLi$, THF, -78°C; (ii) MeI, -78°C; (iii) Br_2, CH_2Cl_2, -78°C; (iv) $PhCH_2NHLi$, THF, -78°C; (v) MeI; (vi) Br_2, CS_2, -78°C

* Compounds are optically pure unless otherwise noted.

ferraenolates with imines and aldehydes can be explained in terms of preferential formation of the transition state 99. However, in a full paper Liebeskind has discussed in detail the problems with this model, especially in explaining the variation in diastereoselectivity on changing the imine or counter cation.[27] The directing effect of the triphenylphosphine ligand has also been used by Liebeskind[27,28] and Davies[29,30] to influence the outcome of nucleophilic attack on α,β-unsaturated acyl complexes. Thus in an analogous manner to Ojima, the β-aminoacyl unit was constructed by the conjugate addition of nitrogen nucleophiles. However, unlike Ojima's system, the addition is stereoselective. Thus the metal center is acting as a chiral auxiliary as well as an elaborate protecting group. Representative examples from both laboratories are summarized (Scheme 23).

Liebeskind has additionally studied the reaction of the ferraenolate 96 with cyclic imines and related species.[27] Although neither thiazoline nor oxazoline derivatives reacted with 96, three cyclic nitrones 100, 104 and 106 were converted into the corresponding bicyclic β-lactams 103, 105 and 107 by reaction with 96 (Scheme 24). Whilst these studies establish that the carbapenam framework may be elaborated using this methodology, the ferraenolate chemistry has not yet been demonstrated to be useful for the elaboration of bicyclic β-lactams bearing additional ring heteroatoms. It is possible that a dianion equivalent for 96 may prove more versatile in synthesis.

SCHEME 24*



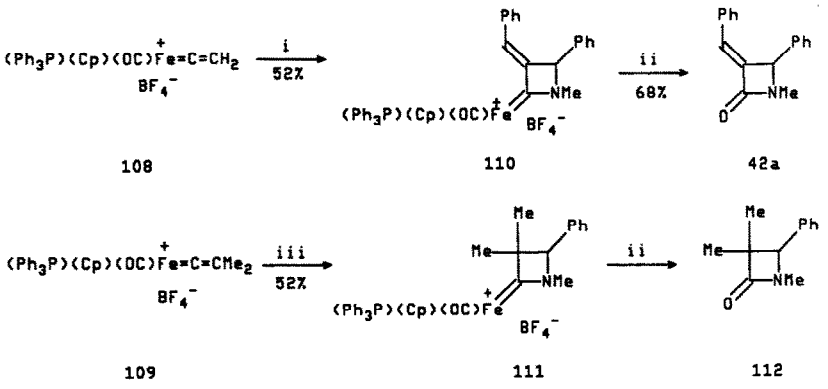
Reagents: (i) $(Ph_3P)(Cp)(OC)FeC(=CH_2)OAlEt_2$ (96), THF, -78°C; (ii) $TiCl_3$, THF, H_2O; (iii) Br_2, CH_2Cl_2, -78°C; (iv) Br_2, CS_2, -45°C; (v) I_2, CH_2Cl_2, Et_3N

* All structures are racemic.

5. Cationic Iron(II) Vinylidenes in β-Lactam Synthesis

Metal vinylidenes are potent electrophilic reagents that contain the formal metal-carbon-carbon cumulene bond system.[8] We considered that such compounds should act as ketene surrogates and undergo formal [2+2] cycloaddition reactions with imines and related species. The phosphine substituted vinylidenes 108 and 109[31] reacted with the imine 2 to produce the 2-azetidinylidine complexes 110 and 111[32] (Scheme 25). The reaction of 108 with 2 to provide 110 closely parallels earlier chromium chemistry (see section 1) and probably involved the intermediacy of 113 and 114 and subsequent aldol reaction with a second equivalent of the imine 2. Clearly the dimethyl substituted vinylidene 108 can only react once with the imine 2 to produce 111. The product was obtained as a mixture of diastereoisomers (8:5, Fe, CHPh). Although these results established that imines and the vinylidenes 108 and 109 did indeed undergo [2+2] cycloaddition reactions, the methodology was limited on several counts. Firstly the reaction was not successful for cyclic imines and related species. Secondly the yields of β-lactams 42a and 112 produced on the oxidation of 110 and 111 were only modest (the overall yield of 112 was

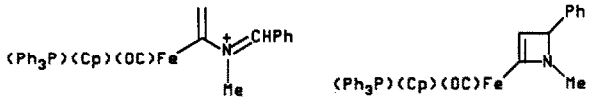
SCHEME 25



108 110 42a

109 111 112

Reagents: (i) PhCH=NMe (2); (ii) PhIO, CH_2Cl_2; (iii) PhCH=NMe (2), CH_2Cl_2, -78° to 25°C

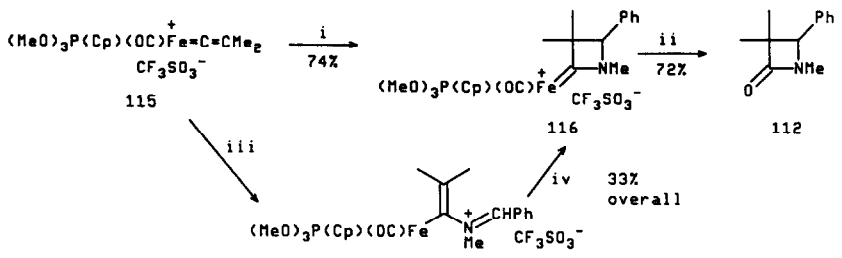


113 114

only 19%). In contrast with 108 and 109, the corresponding trimethyl phosphite substituted vinylidenes proved to be very versatile in synthesis. No doubt both the enhanced π-acidity and smaller cone angle of the trimethyl phosphite ligand increased the electrophilicity of the vinylidene 115.[8] Thus the vinylidene 115 reacted smoothly with simple imines including 2 and with 2-thiazoline derivatives to produce the corresponding [2+2] cycloadducts (Schemes 26 and 27).[33] The reaction between 115 and 2 was particularly informative in that the process was unequivocally demonstrated to proceed via a stepwise mechanism. The vinyl iron intermediate 117 could be isolated by chromatography and this material, on standing, slowly cyclized to produce the target carbene complex 116. Optimally, 116 was prepared by mixing 115 and 2 at low temperatures followed by brief heating. Again the [2+2] adduct 116 was obtained as a mixture of diastereoisomers (1.5:1). Low stereochemical control was the result of facile E,Z-isomerization at the intermediate vinyl iron 117 stage. Consistent with this analysis the 2-thiazoline (118) reacted with 115 to produce 119 as a 15:1 mixture of diastereoisomers (Scheme 27).[33,34] Clearly E,Z-isomerization at the intermediate vinyl iron stage is impossible with the 2-thiazoline (118). The more heavily substituted heterocyclic systems 121 and 124 were also converted in the same way into the bicyclic carbenes 122 (8:1) and 125 (>10:1). In both these substances the azetidinylidene ligands both had the exo (CO_2Et or CO_2Me) stereochemistry and the diastereoselectivities refer to the Fe and C-5 centers. The product complexes 116, 119, 122 and 125 were easily oxidized to produce the corresponding β-lactams 112, 120, 123 and 126 using ether iodosobenzene or tetrabutylammonium nitrite at high pressure.[34]

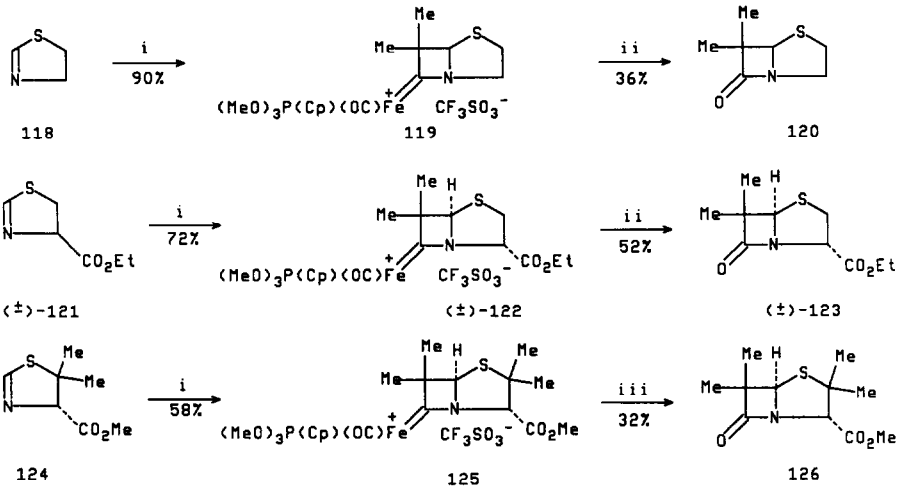
It is clear from these results that the vinylidene 115 readily reacts with sterically hindered thiazoline derivatives. As such it offers advantages over classical ketene approaches.[35] However it will be necessary to prepare vinylidene reagents bearing heteroatom functionality before this approach can be applied to the construction of useful antibiotics.

SCHEME 26



Reagents: (i) PhCH=NMe (2), $ClCH_2CH_2Cl$, Amberlyst A21, -78° to 84°C; (ii) $Bu_4N^+NO_2^-$, CH_2Cl_2, 7000 atm.; (iii) PhCH=NMe (2), CH_2Cl_2, -78° to 25°C; (iv) 25°C, 8 days

SCHEME 27

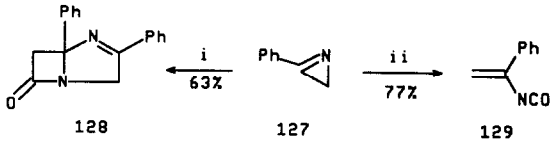


Reagents: (i) 115, $ClCH_2CH_2Cl$, Amberlyst A21, -78° to 84°C; (ii) PhIO, EtOH; (iii) $Bu_4N^+NO_2^-$, CH_2Cl_2, 7000 atm.

6. Ring Expansion Carbonylation Reactions

Alper has studied the preparation of β-lactam systems using the ring expansion carbonylation of azirines and aziridines as the key step. Thus, for example, the 1-azirine 127 was carbonylated under catalysis by tetrakis-triphenylphosphine palladium(0) (10 mol%) to produce the azapenem system 128.[36,37] In contrast carbonylation of 127 in the presence of bis-dibenzylideneacetone palladium(0) gave the vinyl isocyanate 129[37] (Scheme 28).

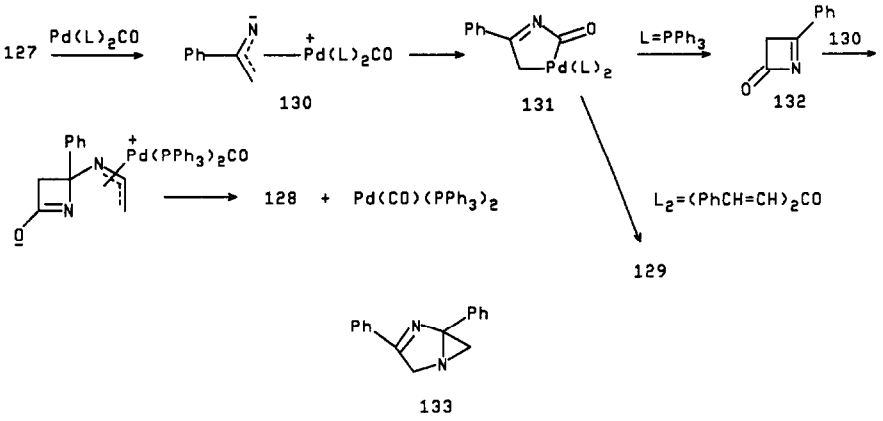
SCHEME 28



Reagents: (i) CO, 1 atm., PhH, $Pd(PPh_3)_4$, 40°C; (iii) CO, 1 atm., $Pd(PhCH=CHCOCH=CHPh)_2$, PhH, 40°C

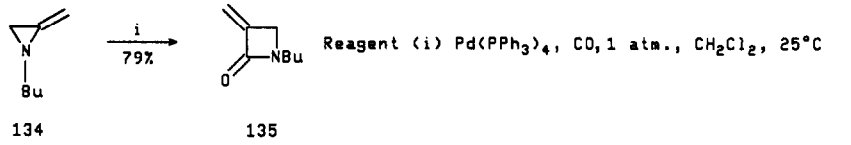
Alper suggested Scheme 29 to explain the catalytic cycle. This is most reasonable on two counts. Firstly he ruled out the intermediacy of 133 since related aziridines were not carbonylated under the reaction conditions. Additionally, 3-azirin-2-one derivatives such as 132 are potent electrophiles rapidly intercepted by nucleophilic attack at C-4.[38] Using bis-dibenzylideneacetone palladium(0) as catalyst, the intermediate 131 was proposed to undergo reductive elimination to produce the vinyl isocyanate 129. Possibly in this case the η^3-palladium species 130 was of insufficient nucleophilicity and thus 132 underwent competitive electrocyclic ring opening to give 129.

SCHEME 29



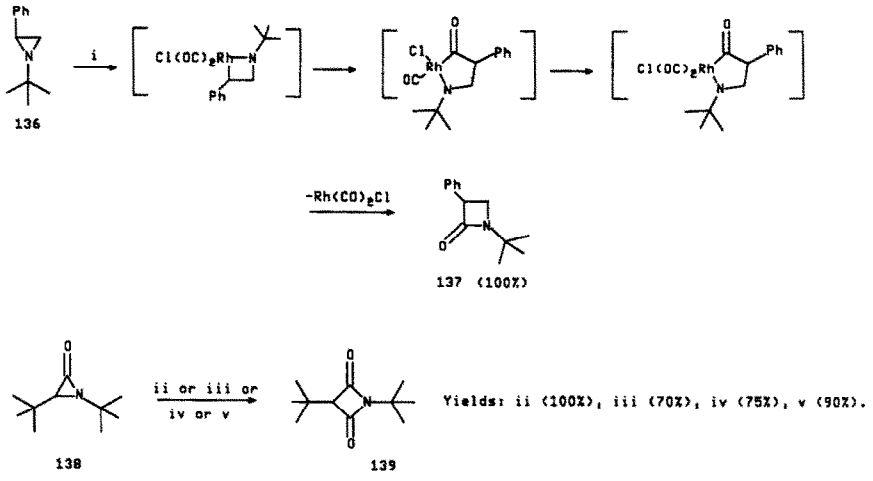
In an extension of this chemistry a series of methylene aziridine derivatives underwent ring expansion carbonylation to produce the corresponding α-methylene-β-lactams, as demonstrated by the transformation of 134 to 135[39] (Scheme 30).

SCHEME 30



Although aziridine derivatives did not undergo ring expansion carbonylation using palladium catalysis, Alper has achieved such transformations using rhodium catalysis. Thus simple aziridines, for example 136, were converted regiospecifically into the corresponding 3-substituted β-lactams 137. The authors suggested the reasonable catalytic cycle outlined in Scheme 31.[40] Additionally, a series of α-lactams such as 138 underwent rhodium or cobalt catalyzed carbonylation to produce 2,4-azetidinediones including 139.[41]

SCHEME 31

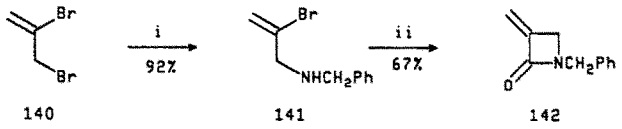


Reagents: (i) $[Rh(CO)_2Cl]_2$, PhH, CO, 20 atm., 90°C; (ii) $[Rh(CO)_2Cl]_2$, PhH, CO, 30 atm., 40°C; (iii) $[Rh(CH_2{=}CHCH_2)_2Cl]_2$ as ii; (iv) $[Rh(1,5\text{-}COD)Cl]_2$ as ii; (v) $Co_2(CO)_8$, PhH, N_2, 65°C

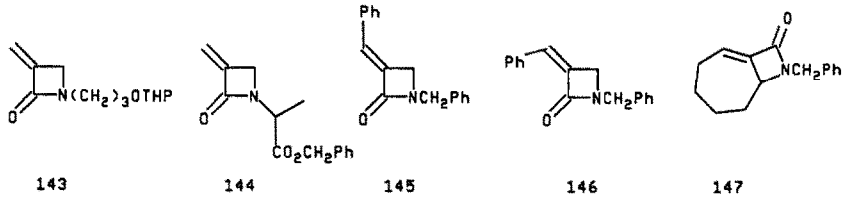
7. The Synthesis of β-Lactams via Palladium Catalyzed Carbonylation of Vinyl Halides

Ban has developed a useful method for the conversion of 2-bromopropenyl bromides into α-methylene-β-lactams. Thus 140 was reacted with benzylamine and the resultant bromo amine 141 carbonylated to produce the β-lactam 142 in excellent overall yield (Scheme 32). The method was extended to eleven additional α-alkylidene-β-lactams including 143 to 147 (15-90%).[42,43] The

SCHEME 32

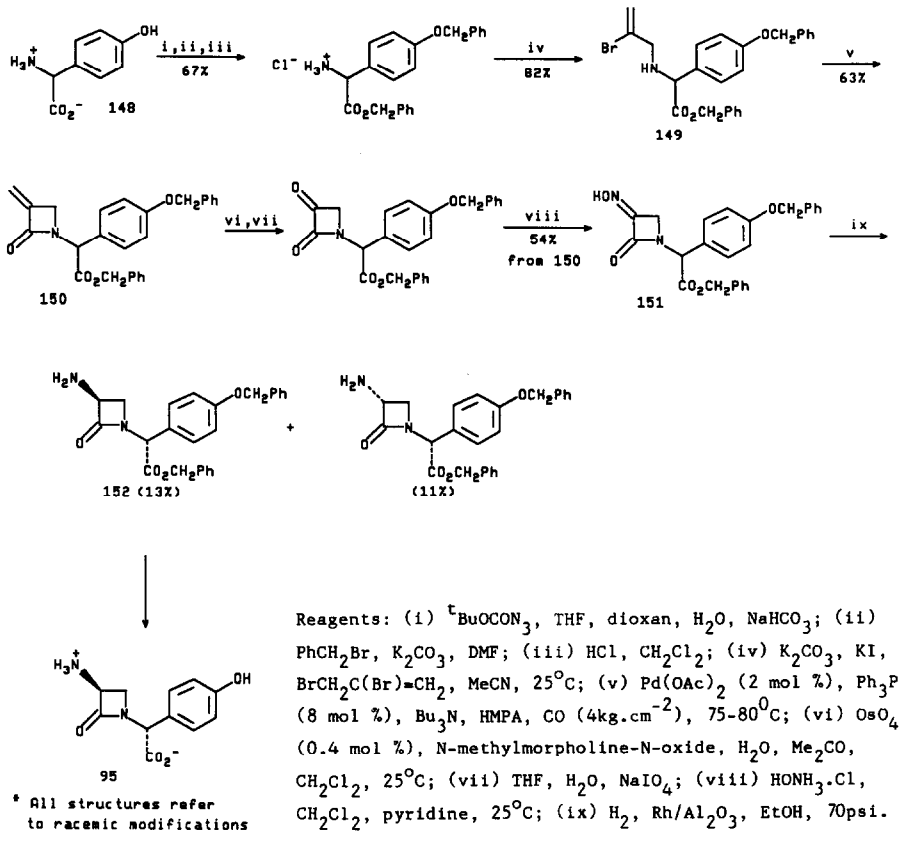


Reagents: (i) $PhCH_2NH_2$, K_2CO_3, DMF; (ii) $Pd(OAc)_2$ (2 mol %), Ph_3P (8 mol %), Bu_3N, HMPA, CO, 1 atm., 100°C



validity of the method for antibiotic synthesis was underscored by a successful synthesis of racemic 3-ANA (95) which is the amino acid precursor for the nocardicin group of antibacterials (Scheme 33).[23,44] Racemic 4-hydroxy-phenylglycine (148) was converted into the vinyl bromide 149 and subsequently into the racemic α-methylene β-lactam 150. All these steps proceeded efficiently. However, the conversion of the α-methylene substituent in 150 into the β-amino group required a low yield multistep process in which the relative stereochemistry at the two asymmetric centers was not controlled. As a result hydrogenation of the oxime 151 gave both the racemic ANA derivative 152 and its epimer. Cooper had previously converted the toluene-4-sulfonate salt of 152 into 3-ANA (95).[45]

SCHEME 33*



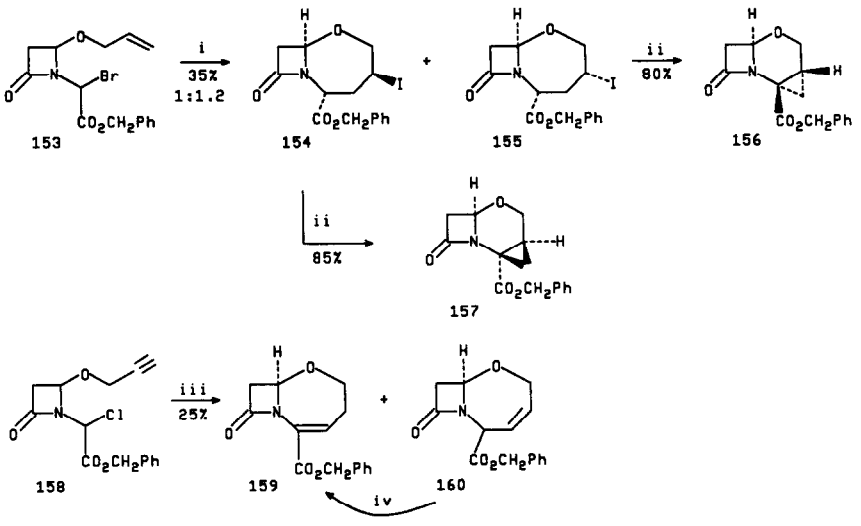
Reagents: (i) $^{t}BuOCON_3$, THF, dioxan, H_2O, $NaHCO_3$; (ii) $PhCH_2Br$, K_2CO_3, DMF; (iii) HCl, CH_2Cl_2; (iv) K_2CO_3, KI, $BrCH_2C(Br)=CH_2$, MeCN, 25°C; (v) $Pd(OAc)_2$ (2 mol %), Ph_3P (8 mol %), Bu_3N, HMPA, CO (4kg.cm^{-2}), 75-80°C; (vi) OsO_4 (0.4 mol %), N-methylmorpholine-N-oxide, H_2O, Me_2CO, CH_2Cl_2, 25°C; (vii) THF, H_2O, $NaIO_4$; (viii) $HONH_3.Cl$, CH_2Cl_2, pyridine, 25°C; (ix) H_2, Rh/Al_2O_3, EtOH, 70psi.

The crucial palladium mediated cyclization reactions of 141 to 142 or 149 to 150 clearly proceed via oxidative insertion of a palladium(0) species into the vinyl carbon-bromine bond, carbonylation and cyclization via reductive elimination, thereby regenerating the catalyst.

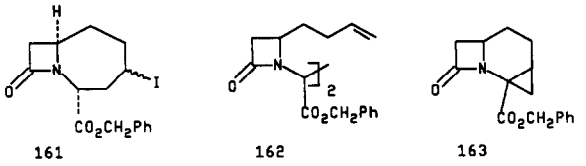
8. Bicyclic β-Lactam Synthesis via Alkene Palladium Complexes

In 1986 Mori and coworkers reported a simple method for the palladium(0) catalyzed cyclization of monocyclic β-lactams bearing an alkene and an alkyl halide residue.[46] The method provides a simple and very convenient entry into the homo-oxacepham framework and to cyclopropane analogs of the oxacephem and related molecules (Scheme 34). For example, the alkenyl bromide 153 was cyclized to produce only the bicyclo [5.2.0] systems 154 and 155 albeit in modest yields. Both products were converted with DBU into the tricyclic β-lactams 156 and 157. Since 153 is readily available from vinyl acetate, the Mori approach should find use in the concise synthesis of novel antibiotics. The method has been extended to the cyclization of the acetylene 158 to provide 159 and 160. Additionally, the two homocephams 161 were prepared and converted into the tricyclic system 163. In this case the palladium(0) cyclization was complicated by dimer 162 formation. Parsons has also applied similar methodology to the methodology to the cyclization of 164 (Scheme 35). Both the bicyclic system 165 and the dimer 166 were formed in this reaction.[47] In a mechanistically similar reaction Bachi has prepared 167b (81%) from 167a by reaction with iodobenzene, tetrakis-(triphenylphosphine)palladium(0), copper(I) iodide and triethylamine.[48]

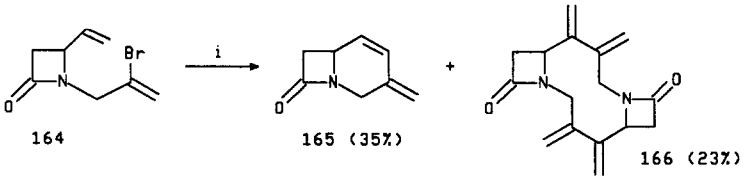
SCHEME 34



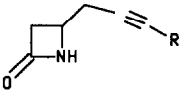
Reagents: (i) $Pd(PPh_3)_4$ (10 mol %), KI, "proton sponge", HMPA, 65°C; (ii) DBU, PhH; (iii) $Pd(PPh_3)_4$, $EtN^{iso}Pr_2$, Bu_4NI, dioxan; (iv) silica, $CHCl_3$.



SCHEME 35



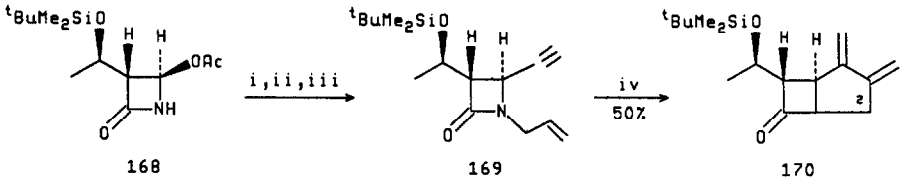
Reagent: (i) $Pd(OAc)_2$ (10 mol %), Ph_3P (20 mol %), K_2CO_3, MeCN, 80°C



167
a R=H
b R=Ph

Recently Trost has applied a palladium(II) catalyzed cyclization of a 1,6-enyne to the elaboration of a carbapenam.[49] Thus standard homologation of the Merck intermediate 168 gave 169, and this was cyclized by reaction with bis-triphenylphosphine palladium(II) acetate to produce 170. This is clearly a mechanistically intriguing reaction that presumably involves palladacyclic intermediates. Nonetheless, the approach may not be valid for molecules bearing the crucial (protected) carboxylic acid entity at C-2 (see 170).

SCHEME 36



168 169 170

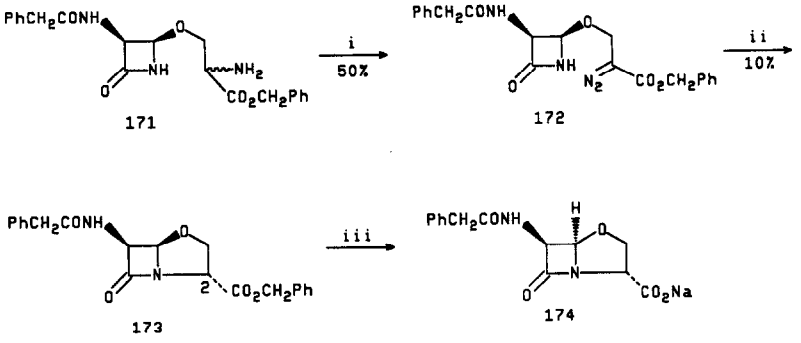
Reagents: (i) $LiC{\equiv}CSiMe_3$, THF; (ii) $BrCH_2CH{=}CH_2$, NaH, THF; (iii) $AgNO_3$, H_2O, EtOH; KCN, H_2O; (iv) $(Ph_3P)_2Pd(OAc)_2$, PhH, 60°C

9. Dirhodium Tetraacetate in β-Lactam Synthesis

(a) The Construction of Bicyclic β-Lactams via α-Diazo-β-Keto Esters

In 1978 Cama and Christensen of Merck Sharp and Dohme reported a synthesis of (±)-1-oxabisnorpenicillin G (174). Although the target 174 was of low antibiotic activity, the paper is of immense significance in that it describes an elegant strategy for the synthesis of bicyclic β-lactams (Scheme 37).[50] Diazotization of the amino ester 171 gave the corresponding α-diazo ester. Subsequent reaction of this with dirhodium tetraacetate in benzene solution resulted in an intramolecular insertion of the metal carbene into the N-H bond to produce 173 (10%) and its C-2 epimer (4.5%). Although the yield of 173 was only modest, the reaction had a major impact on synthetic strategy in the β-lactam area. Dirhodium tetraacetate has the structure 175 in which S are weakly bonded solvent molecules. Dissociation of S followed by

SCHEME 37

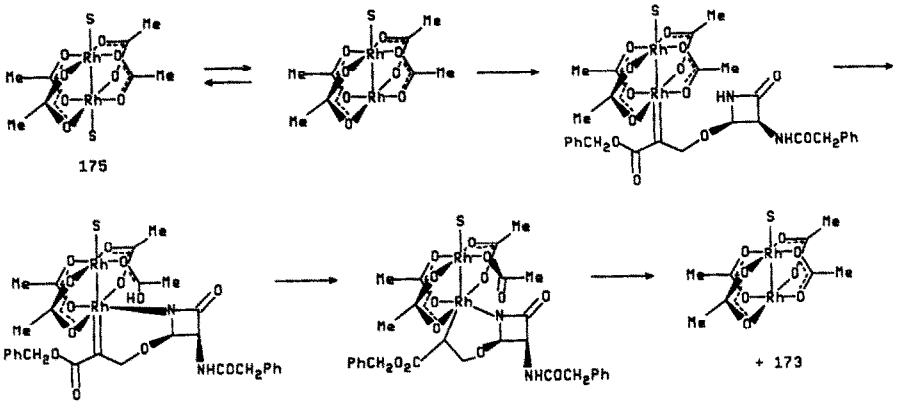


171 172 173 174

Reagents: (i) $NaNO_2$, $TsOH.H_2O$, H_2O, CH_2Cl_2, 0°C; (ii) $Rh_2(OAc)_4$ (1%), PhH, 25°C; (iii) H_2, Pd/C, $NaHCO_3$, dioxan, H_2O

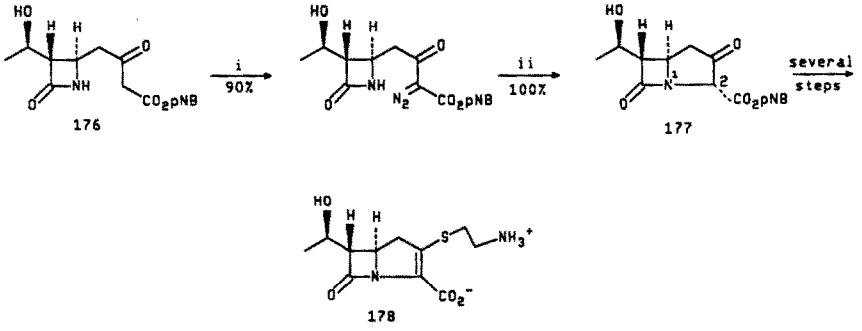
reaction with the diazo alkane produces the rhodium carbene and this inserts into the N-H bond. Whilst the details of the mechanism are obscure, the steps in Scheme 38 are based in part on known metathesis reactions of metal-carbenes[3] and on the mechanistic discussions of Doyle.[51]

SCHEME 38



The dirhodium tetraacetate methodology has proved particularly useful in the synthesis of thienamycin 178 and related carbabicyclic β-lactams. Thus Merck chemists have discovered that the insertion reaction is particularly efficient using α-diazo-β-keto ester intermediates. Examples of this crucial ring closure reaction are presented in Schemes 39,[52,53] 40,[54] 41[55], 42[56], 43[57] and 44[58]. Reaction of the β-keto ester 176 with 4-carboxybenzenesulfonyl azide gave the corresponding diazo keto ester. Subsequent reaction with dirhodium tetraacetate produced the bicyclic β-lactam 177 (Scheme 39). The crucial cyclization reaction is noteworthy on two counts. Firstly, the reaction was quantitative, which is remarkable for a reaction that gives rise to a bicyclic β-lactam via N^1-C^2 formation. Secondly the product 177 was obtained exclusively as the more stable exo isomer, presumably on account of facile isomerization of the C-2 epimer via enol formation. The keto ester 177 was subsequently converted into the potent antibiotic thienamycin 178.

SCHEME 39

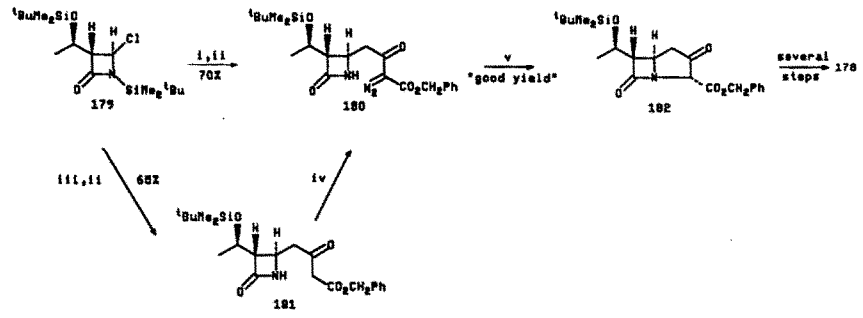


Reagents: (i) $HO_2CC_6H_4$-4-SO_2N_3, Et_3N, MeCN, 0-20°C; (ii) $Rh_2(OAc)_4$ (0.1 mol %), PhH, 80°C

pNB = $O_2NC_6H_4$-4-CH_2

Karady and coworkers from Merck used the key dirhodium tetraacetate catalyzed closure in an elegant preparation of thienamycin 178 from penicillin. The key steps are outlined in Scheme 40. Of particular note is the elaboration of the α-diazo-β-keto ester 180 via direct S_N1 displacement of the chloride 179 using a four carbon diazo fragment or via 181. Such displacement reactions of C-4 substituted 2-azetidinones are of considerable importance in β-lactam chemistry.[59] Again, in this case, catalyzed diazo insertion gave 182 and this was converted into thienamycin 178.

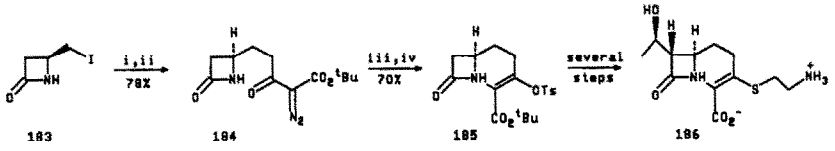
SCHEME 40



Reagents: (i) CH_2=C(OSiMe$_3$)C(=N_2)CO_2CH_2Ph, $AgBF_4$, MeCN, 0°C; (ii) MeOH, THF, HCl; (iii) CH_2=C(OSiMe$_3$)C=C(OSiMe$_3$)OCH_2Ph, $AgBF_4$, MeCN, 0°C; (iv) 2-naphthalenesulfonyl azide; (v) $Rh_2(OAc)_4$ (0.3%), PhH, 80°C

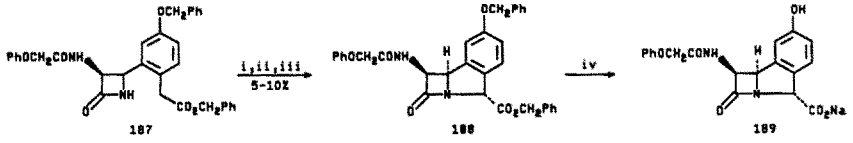
The versatility of the diazo methodology is underscored by four further examples from the Merck laboratories. Iodide **183** was easily transformed, via the diazo compound **184**, into the carbacephem **185** and subsequently into the novel homothienamycin **186**, a molecule of low antibiotic activity (Scheme 41).[55] The method was used by Heck and Christensen[56] to elaborate the nocardicin analog **189** via **187** and **188** (Scheme 42). In this example the low overall yield in the key closure resulted from difficulties in the diazo transfer step. Andrus and coworkers[57]

SCHEME 41



Reagents: (i) CH_2=C(OLi)CH=C(OLi)O^{t}Bu, THF, -78°C; (ii) $HO_2CC_6H_4$-4-SO_2N_3, Et_3N, MeCN, 0°-25°C; (iii) $Rh_2(OAc)_4$, PhH, 75°C; (iv) Ts_2O, Et_3N, CH_2Cl_2, 0°C

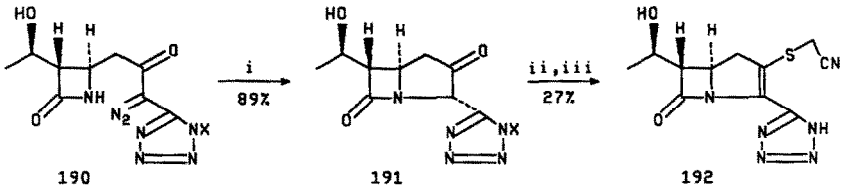
SCHEME 42



Reagents: (i) CF_3C(=NSiMe$_3$)OSiMe$_3$, Me_3SiCl, DMAP, MeCN; (ii) $O_2NC_6H_4$-4-SO_2N_3, LiO^{t}Bu, THF, -50°C; (iii) $Rh_2(OAc)_4$, PhMe, 80°C; (iv) $Pd(OAc)_2$, H_2, THF, H_2O, EtOH, $NaHCO_3$

applied the methodology for the conversion of the diazo-tetrazole **190** to produce **191** and subsequently the thienamycin analog **192** (Scheme 43). Interestingly, the product **192** was a potent antibiotic stable to deactivation by renal dehydropeptidase. Lastly Shih and coworkers[58] prepared 1β-methyl thienamycin **195** using again the dirhodium tetraacetate ring closure of **193** to give **194** as a key process (Scheme 44). Antibiotic **195** is of note in that it is stable to deactivation by renal dehydropeptidase-I. This enzyme rapidly deactivates the parent antibiotic thienamycin **178** in vivo.

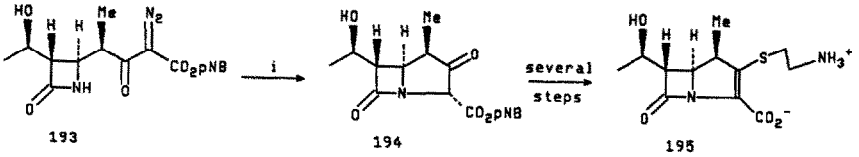
SCHEME 43



Reagents: (i) $Rh_2(OAc)_4$, CH_2Cl_2, Δ ; (ii) DBU, THF, -78°C; $(CF_3SO_2)_2O$; NaHS, $EtN^{iso}Pr_2$, -20°C; $ClCH_2CN$, $EtN^{iso}Pr_2$; (iii) Pd/C, H_2, K_2HPO_4, KH_2PO_4, H_2O, THF, EtOH

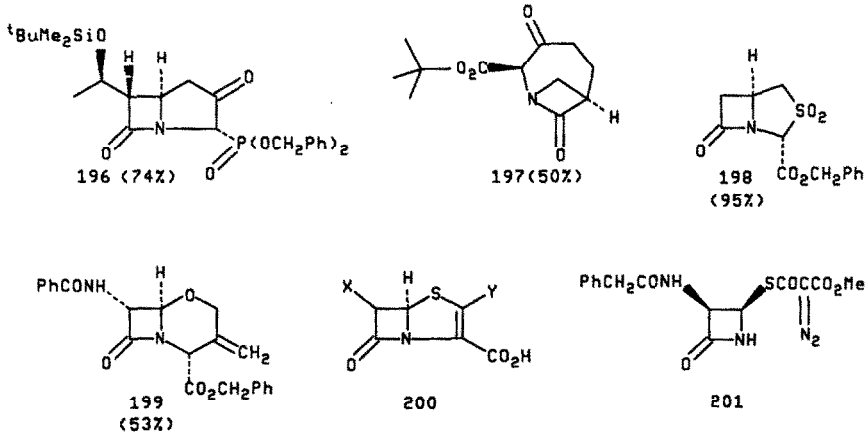
X = $CH_2OCO_2CH_2C_6H_4$-4-NO_2

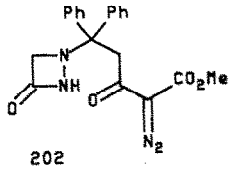
SCHEME 44



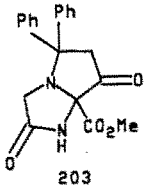
Reagent: (i) $Rh_2(OAc)_4$. pNB = $O_2NC_6H_4CH_2$

The Merck dirhodium tetraacetate N-H insertion chemistry has been extensively utilized by many groups in the syntheses of carbapenem systems.[60] Additionally the method has proved of use in the elaboration of the bicyclic β-lactams 196[61], 197[62], 198[63] and 199[64]. In each of these cases the yields of the diazo insertion reactions are given in parenthesis. It is clear from all these examples that the synthesis of bicyclic β-lactams from the dirhodium tetraacetate catalyzed closure of diazo esters is a versatile procedure. Does this paragon of β-lactam methodology have limitations? Unfortunately the procedure is not applicable to the synthesis of penems including 200. Thus, for example, Ghosez reported that the diazo malonate derivative 201 gave intractable mixtures on treatment with dirhodium tetraacetate.[65] No doubt the reaction is complicated by sulfur ylide chemistry (See section 9c). Additionally, Taylor and Davies[66] showed that the method failed for the 1,2-diaziridin-3-one derivative 202. Reaction of 202 with dirhodium tetraacetate gave 203 (37%) and 204 (24%). These authors invoked the intermediacy of the nitrogen ylide 205 to explain the formation of 203 and 204. Clearly, in order for the Merck protocol to work, soft nucleophilic heteroatoms must be absent.

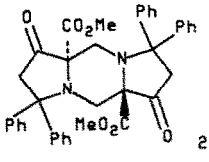




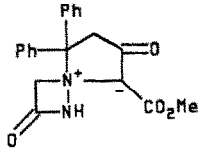
202



203



204

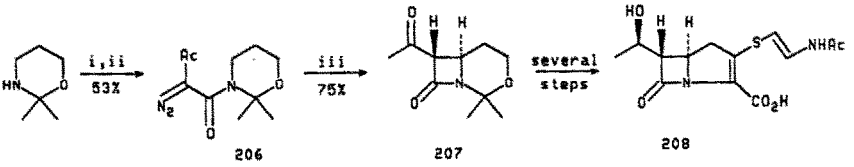


205

(b) **Dirhodium Tetraacetate Catalysis in the Construction of the β-Lactam Ring**

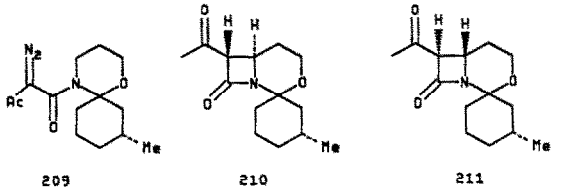
Beecham chemists have utilized a dirhodium tetraacetate catalyzed ring closure of a α-diazo-β-keto amide as a key step in their synthesis of carbapenem antibiotics.[67] The procedure is an extension of earlier photochemical routes to β-lactams described by Corey and Lowe.[68] The Beecham methodology is exemplified by Scheme 45. Reaction of the diazo keto amide 206 with dirhodium tetraacetate gave the β-lactam 207. Photolytic ring closure of 206 or copper mediated ring closure to provide 207 were both less efficient (55% and 25% respectively). The product 207 was converted in several steps into the carbapenem antibiotic olivanic acid (208).[69] Since 208 prepared by this procedure was racemic, Smale[70] studied the cyclization of 209 using dirhodium tetraacetate (0.1 equiv, PhH, 20°C). Two diastereoisomeric products 210 and 211 were formed and the required compound 210 (22%) was isolated by fractional recrystallization. Unfortunately, stereoselectivity in this process was only modest (210:211 = 3:2). Smale reported that 209 was predominantly a single (undefined) spirane epimer. The product 210 was subsequently transformed into thienamycin analogs. It is possible that a chiral dirhodium tetracarboxylate or related species may prove useful in catalytic enantioselective C-H insertions.

SCHEME 45



206 207 208

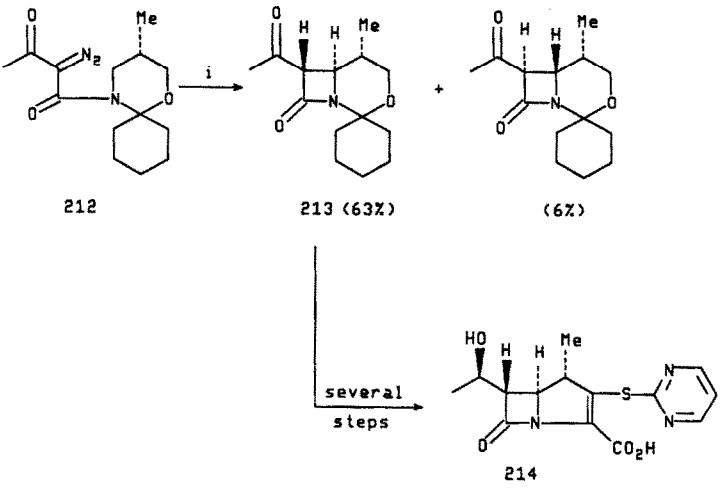
Reagents: (i) diketene; (ii) Et_3N, TsN_3; (iii) $Rh_2(OAc)_4$, CH_2Cl_2, 25°C



209 210 211

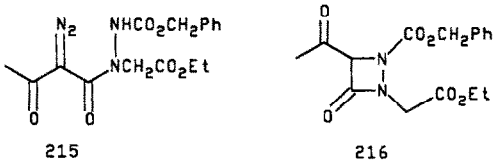
Brown and Southgate observed that 212 smoothly underwent ring closure upon reaction with dirhodium tetraacetate.[71] The α-methyl substituent, which was adjacent to the C-H bond undergoing insertion, efficiently controlled the diastereoselectivity of reaction (10:1). The product 213 was converted into the thienamycin analog 214 (Scheme 46).

SCHEME 46



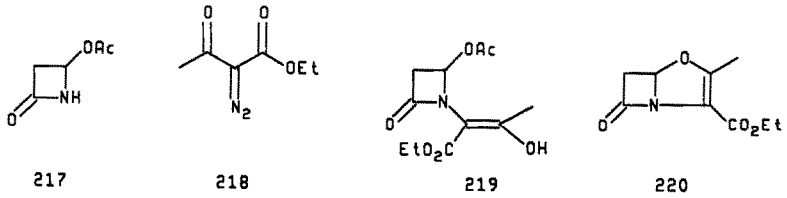
Reagent: (i) $Rh_2(OAc)_4$

In a variation of the Beecham-Lowe-Corey chemistry, Moody utilized an insertion reaction to construct several 1,2-diaziridin-3-one derivatives.[72] Thus, for example, the diazo keto hydrazide 215 was cyclized using dirhodium tetraacetate (5%, PhH, Δ) to produce 216.

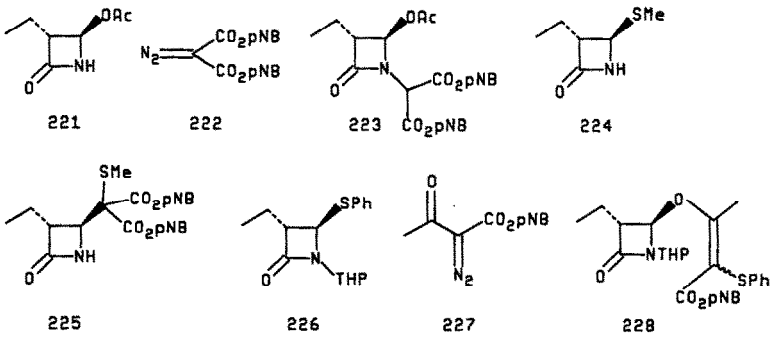


(c) **Other Dirhodium Tetraacetated Catalyzed β-Lactam Reactions and Related Copper Catalyzed Processes**

In a variation of the Merck diazo keto ester chemistry, Hunt and coworkers observed that 4-acetoxy-2-azetidinone (217) reacted with 218 in the presence of dirhodium tetraacetate to produce 219 (8%)[73] and not 220 as previously reported.[74] Kametani has also studied such



intermolecular N-H insertion chemistry. Interestingly he observed that simple β-lactam derivatives reacted via one of two distinct pathways with diazo malonates depending on the nature of the C-4 substituent. Thus, for example, 221 reacted with 222 to produce 223 (22%) and this reaction closely follows the Beecham study with 219. In contrast 224 reacted to produce 225 (30%).[75] This reaction, which undoubtly involved a sulfur ylide mechanism, is of use in the attachment of carbon functionality at the 2-azetidinone C-4 center. When applied to N-alkylated (or silylated) β-lactam sulfides and α-diazo-β-keto esters, the corresponding C-4 enol ethers were produced. The reaction of 226 and 227 to produce 228 is an example.



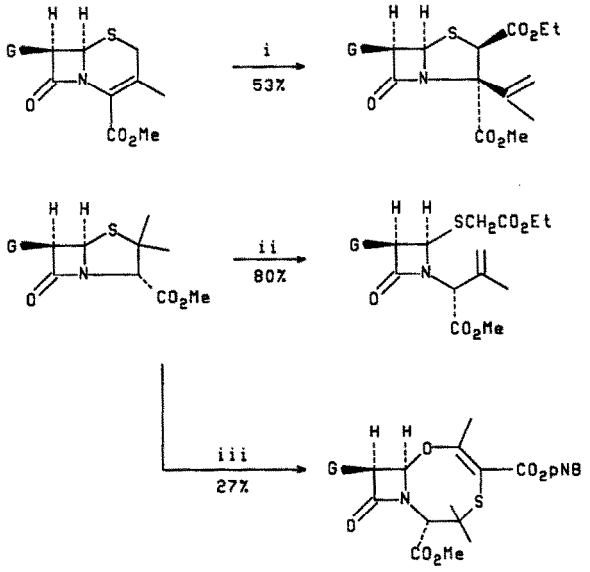
221 222 223 224

225 226 227 228

pNB = $CH_2C_6H_4$-4-NO_2

Both Sankyo and Takeda chemists and subsequently Kametani[76] reported that penicillin or cephasporin esters could be cleaved, ring contracted or expanded by reaction with diazo esters (Scheme 47). All of these reactions involve initial sulfur ylide formation.

SCHEME 47

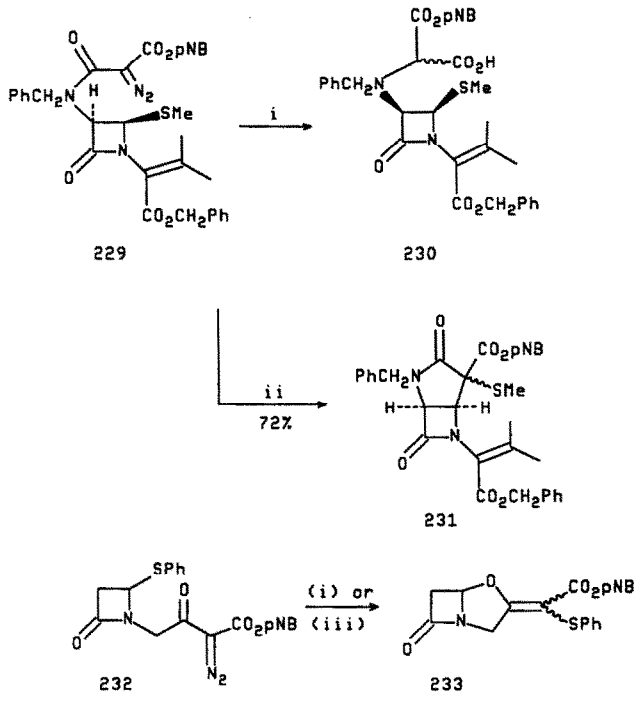


Reagents: (i) Cu, xylene, $EtO_2CCH{=}N_2$, 130°C; (ii) $Cu(acac)_2$, PhH, $EtO_2CCH{=}N_2$, Δ ; (iii) $Rh_2(OAc)_4$, $AcC(N_2)CO_2pNB$

G = $PhCH_2CONH$; pNB = $CH_2C_6H_4$-4-NO_2

Kametani, Prasad and Oida[77,78] have utilized the intramolecular reaction between sulfides and carbenes as a method for elaborating bicyclic β-lactams (Scheme 48). Surprisingly the rhodium catalyzed fragmentation of 229, in contrast to photolysis, did not produce the insertion compound 231. Instead a compound tentatively assigned as the Wolff rearrangement product 230 was detected. Sandoz workers have prepared a large number of clavulanic acid derivatives by dirhodium tetraacetate mediated cyclization. The process is illustrated by the conversion of 232 into 233.

SCHEME 48

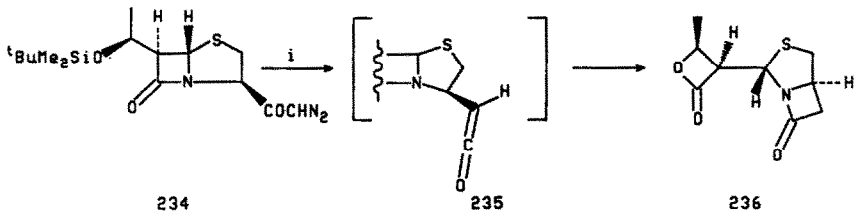


Reagents: (i) $Rh_2(OAc)_4$; (ii) hν, CCl_4, 0-10°C; (iii) $Cu(acac)_2$

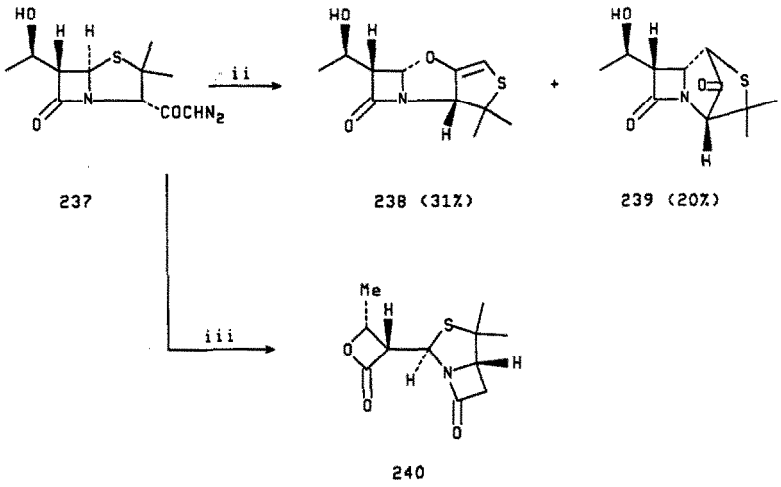
pNB = $4\text{-}O_2NC_6H_4CH_2$

Sandoz workers have studied a series of bizarre rearrangement reactions of penicillin 3-diazoketones 234 and 237 (Scheme 49).[79] Reaction of 234 with dirhodium tetraacetate gave an unstable product tentatively assigned as the β-lactone-β-lactam 236. This material was stated to arise via Wolff rearrangement and the ketene 235. In contrast the diazo ketone 237, which contains a geminal dimethyl substituent, was converted into 238 and 239 on reaction with bis-acetoacetylcopper(II). Clearly these products are derived via the intermediacy of sulfur ylides. Photolysis of 237 gave 240 which was presumably formed via Wolff rearrangement. The authors argued that the presence of the gem dimethyl substituents were essential for observing the formation of products derived from sulfur ylide intermediates since the S- carbene distance would be shorter in carbene 241a than 241b.

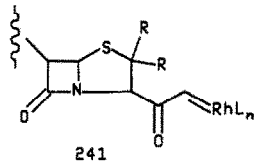
SCHEME 49



SCHEME 49 CONTINUED



Reagents: (i) $Rh_2(OAc)_4$, PhH, Δ ; (ii) $Cu(acac)_2$, PhH, Δ ; (iii) hν, PhH

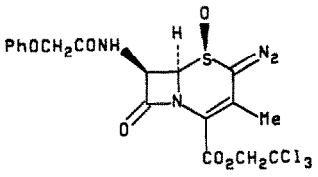


241

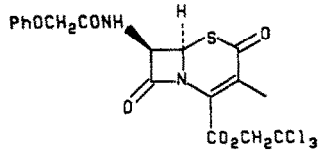
a R=Me

b R=H

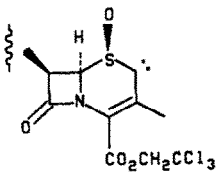
Rosati and coworkers from Pfizer discovered that dirhodium tetraacetate was particularly effective in the conversion of C-diazo-cephalosporin sulfoxides into the corresponding 2-oxocephalosporin.[80] For example, 242 was converted into 243 (40%). The authors speculated that the reaction involved the carbene 244 and zwitterion 245. Whilst the details of the mechanism are obscure it is highly likely that the reaction involves a rhodium complex (for example 246), rather than a free carbene.



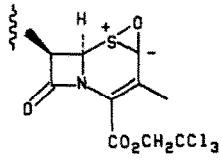
242



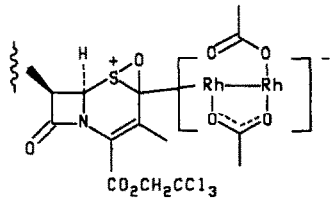
243



244



245

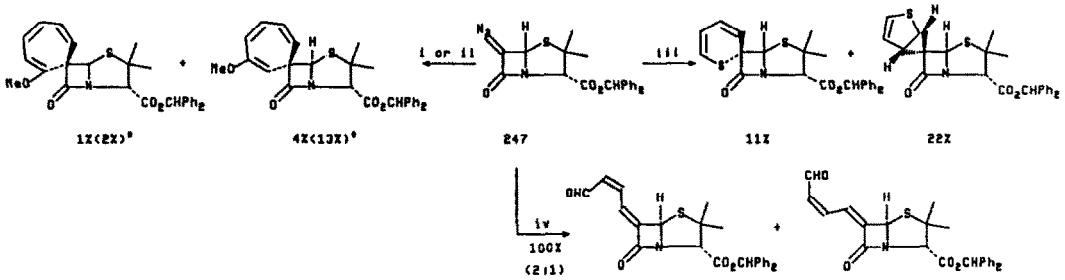


246*

*(for simplicity only 2 acetates are shown)

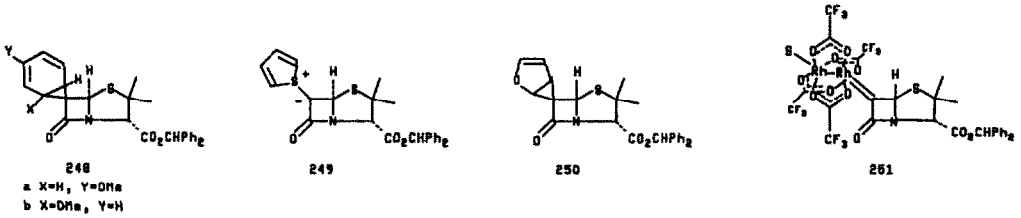
Matlin and Chan have studied the dirhodium tetraacetate mediated reaction of benzhydryl 6-diazopenicillinate 247 in the presence of anisole, thiophene and furan.[81,82] The diverse products (Scheme 50) clearly resulted from the initial formation of the cyclopropane derivatives 248 and 250 or the thiophenium ylide 249. It is germane to note that, in the reaction with anisole, yields of the adducts were better using the dirhodium tetrakis-trifluoroacetate. This is probably in consequence of the fact that the resultant rhodium carbene intermediate 251 is more electrophilic.

SCHEME 50



Reagents: (i) $Rh_2(OAc)_4$, PhOMe, CH_2Cl_2, 25°C; (ii) $Rh_2(OCOCF_3)_4$, PhOMe, CH_2Cl_2, 25°C; (iii) thiophene, $Rh_2(OAc)_4$; (iv) furan, $Rh_2(OAc)_4$

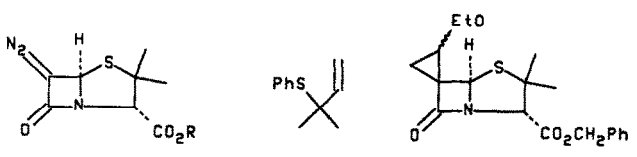
Yields in parenthesis refer to $Rh_2(OAc)_4$



248
a X=H, Y=OMe
b X=OMe, Y=H

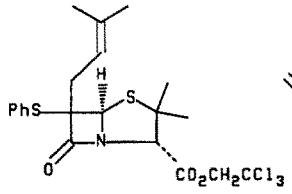
249 250 251

Further copper bis-(acetoacetonate) mediated reactions of 6-diazo penicillanic esters have been reported by Campbell[83] and John.[84] Of particular note are the reactions of 252 or 253 with ethyl vinyl ether, sulfide 254 and allyl bromide to respectively produce 255 (73% all 4 isomers), 256 (36% PhS α:β = 2:3) and 257 (48%).

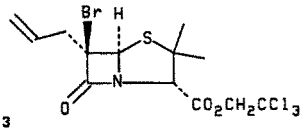


252 R=$PhCH_2$
253 R=CH_2CCl_3

254 255



256

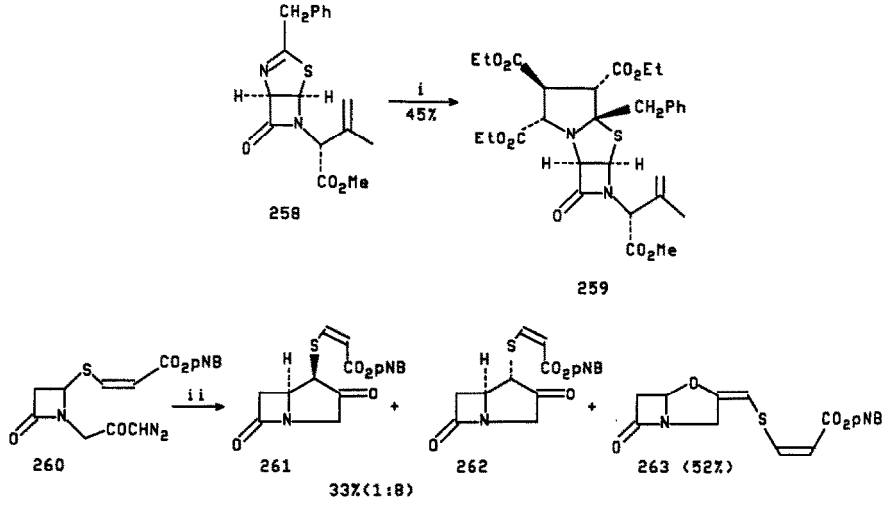


257

Thomas, John and coworkers have extensively studied the application of diazo alkane chemistry in the β-lactam area. They have observed that the thiazoloazetidinone 258 reacted with ethyl diazoacetate on copper(II) bis-(acetoacetonate) catalysis to produce 259 (Scheme 51).[85] The authors speculated that 259 was formed via a 1,3-dipolar cycloaddition between 264 and diethyl fumarate, a byproduct from the decomposition of the diazoester.

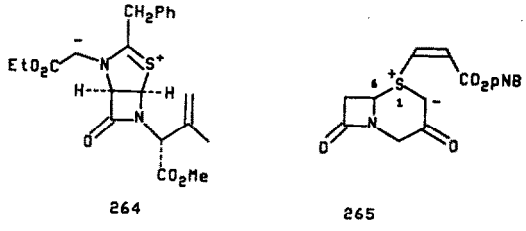
Prasad et al. have reported that the intramolecular reaction between a sulfide and a diazo ketone may be used to prepare the penam or clavam bicyclic β-lactam system.[86] Thus 260 reacted with copper(II) bis-(acetoacetonate) to produce the penams 261 and 262 (1:8) and the clavam 263 (Scheme 51). All these products are clearly derived from the sulfur ylide 265 via S1-C6 cleavage and recyclization.

SCHEME 51



Reagents: (i) $EtO_2CCH{=}N_2$, CH_2Cl_2, $Cu(acac)_2$, Δ ; (ii) $Cu(acac)_2$, PhH, Δ

pNB = $4\text{-}O_2NC_6H_4CH_2$



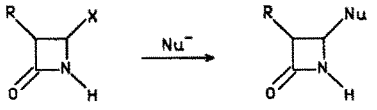
264 265

10. The Application of Cuprate Reagents in β-Lactam Chemistry

The displacement reaction of monocyclic β-lactams 266 using carbon centered nucleophiles (Scheme 52) is a versatile method in the construction of carbabicyclic β-lactams including thienamycin 178 and analogs. Chemists at Shionogi,[87] Sankyo[88] and others[89] have shown that

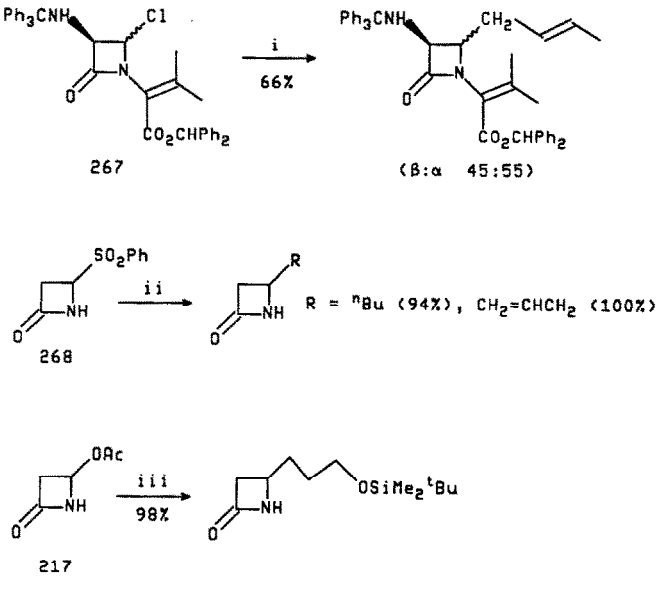
cuprate reagents are especially useful in the elaboration of 266. For example the chloride 267, sulfone 268 and acetate 217 have been converted in good yields into the corresponding alkylated derivatives (Scheme 53). Although such reactions proceed in good yield, displacement reactions using enol silanes are more useful in carbapenem synthesis (see section 9a).

SCHEME 52



266

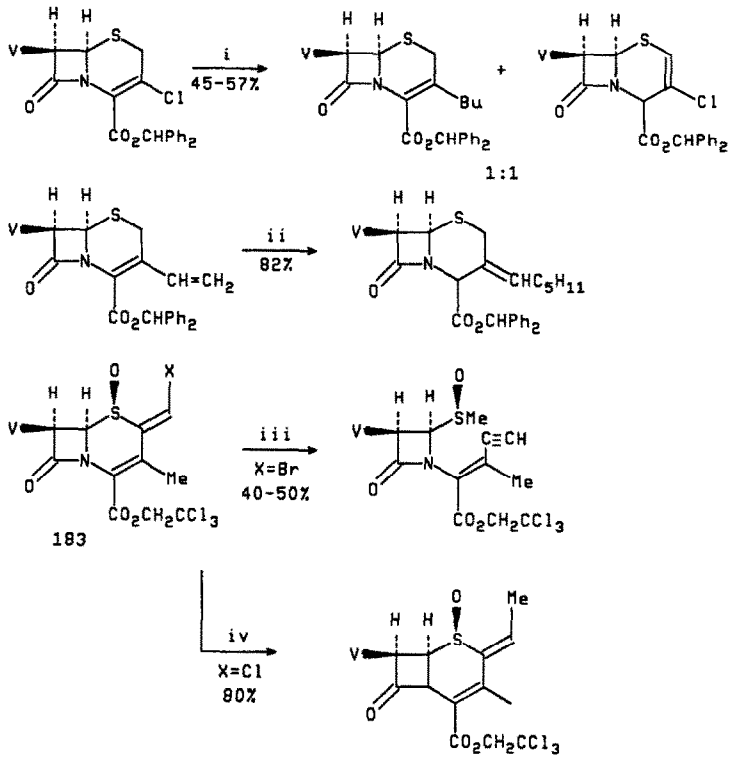
SCHEME 53



Reagents: (i) (E)-MeCH=CHCH$_2$Cu, THF, -35 to 0°C; (ii) R$_2$CuLi, THF, -78 to 0°C; (iii) LiCu(CH$_2$CH$_2$CH$_2$OSiMe$_2$^{t}Bu)$_2$, Et$_2$O, -50°C

Other uses of copper reagents in β-lactam chemistry are in the elaboration of cephalosporin derivatives (Scheme 54),[90] the surprising N-alkylation of a β-lactam iodide (Scheme 55),[91] and the production of bicyclic β-lactams via N-arylation (Scheme 56).[92] In the functionalization of cephem derivative 183 (Scheme 54) it is curious that the Grignard but not the cuprate reaction proceeded with fragmentation under very mild conditions. Additionally Oida[93]

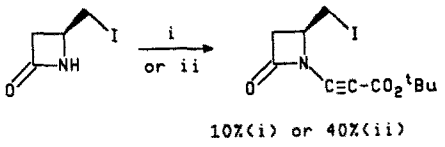
SCHEME 54



Reagents: (i) Bu_2CuLi, THF, -78°C; (ii) Bu_2CuLi, THF, -30°C; (iii) MeMgBr, THF; (iv) Me_2CuLi, THF

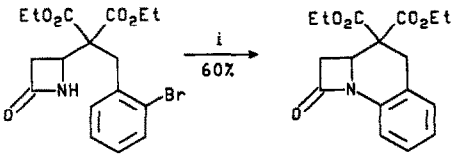
V = $PhOCH_2CONH$

SCHEME 55



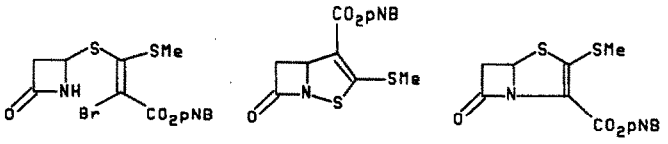
Reagents: (i) $CuC{\equiv}CCO_2{}^tBu$, HMPA, 25°C; (ii) $HC{\equiv}CCO_2{}^tBu$, CuCl, O_2, HMPT, 0°C

SCHEME 56



Reagent: (i) Cu powder, DMF, 100°C

and McCombie[94] have shown that the reaction of 269 with lithium di-isopropylamide and (tributylphosphine)copper(I) iodide gave the isopenem 270 and not the penem 271 as originally reported.[95]

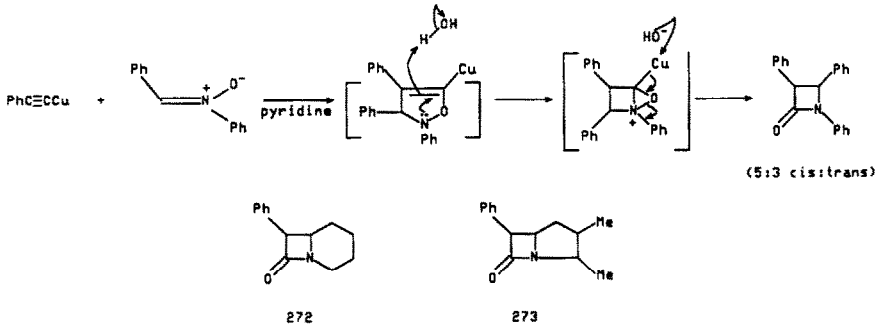


269 270 271

pNB = $CH_2C_6C_4$-4-NO_2

In 1972 Kinugasa and Hashimoto reported that β-lactams could be prepared from the reaction of copper acetylides with nitrones. The reaction was further studied by Ding and Irwin. An example of this intriguing reaction is given in Scheme 57. The English authors speculated that the reaction involved a 1,3-dipolar cycloaddition, followed by ring contraction and loss of copper.[96] Curiously Sandhu's group[97] discovered the same reaction in 1986 and suggested a graphically identical mechanism without reference. Ding and Irwin claimed that the method could be extended to bicyclic β-lactams including 272 and 273. We consider the mechanism in Scheme 57 to be very unlikely. It is more reasonable to suggest that the reaction involves oxidation of the copper acetylide to produce a ketene or N-acyl pyridinium salt followed by the classical ketene-imine "cycloaddition".

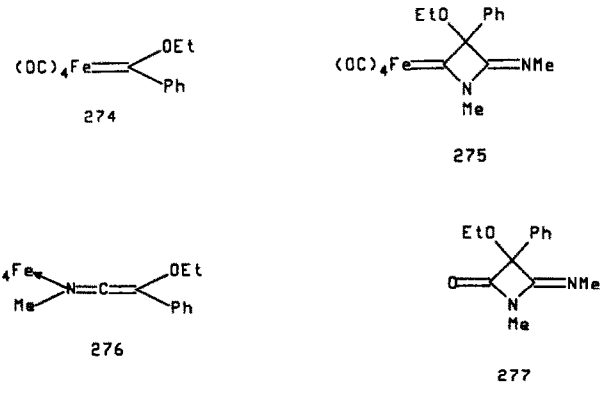
SCHEME 57



272 273

11. **Other Examples of Transition Metal Complexes in β-Lactam Chemistry**

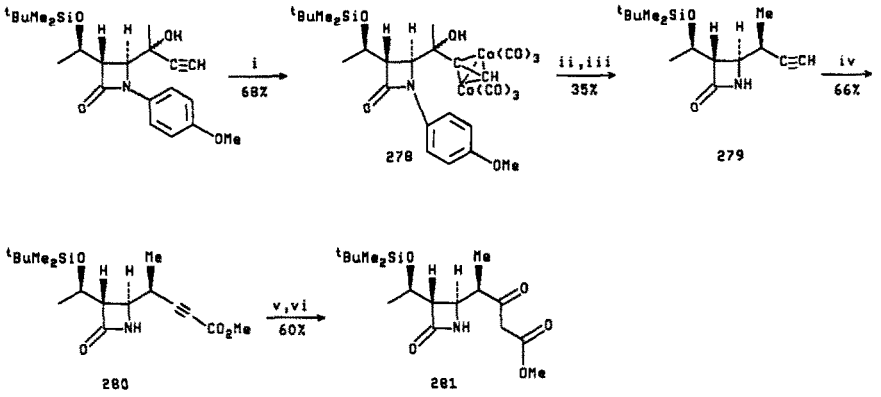
Aumann has recently described a method for converting an iron carbene complex into 3-imino-azetidinylidene iron carbenes.[98] For example reaction of 274 with methyl isonitrile gave 275 (94%). Oxidation of the product with potassium permangamate gave the corresponding β-lactam derivative 277 (95%). The authors suggested that the reaction proceeded via sequential C-alkylation of the isonitrile carbon via 276.



274 275 276 277

Complexation of an alkyne functionality has been employed by Liebeskind as a method for stereospecifically preparing a β-methyl thienamycin precursor.[99] Thus using a variation of the Nicholas reaction, 278 was converted into 279. The ceric ammonium nitrate reagent cleaved both the dicobalt octacarbonyl and the 4-methoxyphenyl groups. Subsequently, Liebeskind used a palladium mediated carbonylation in chain homologation (Scheme 58).

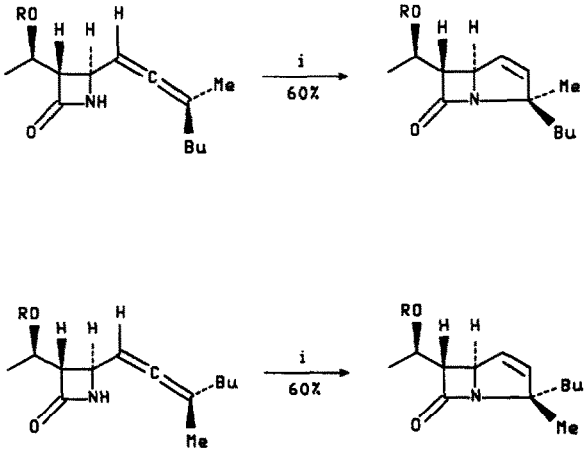
SCHEME 58



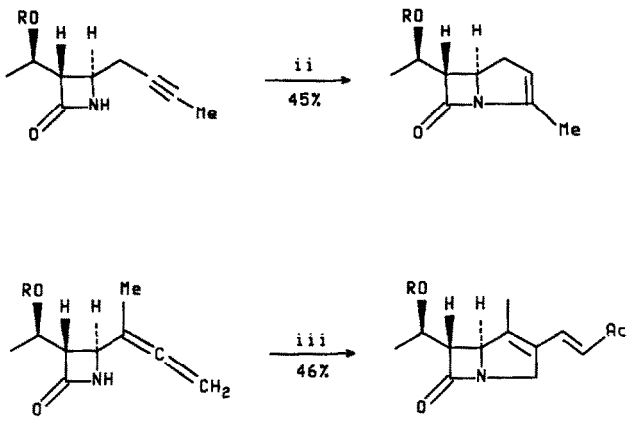
Reagents: (i) $Co_2(CO)_8$, hexane, 25°C; (ii) CF_3CO_2H, $Me_2S.BH_3$; (iii) $(NH_4)_2[Ce(NO_3)_6]$; (iv) $PdCl_2$, NaOAc, CO, MeOH; (v) PhSH, Et_3N, THF; (vi) N-bromoacetamide, dioxan, H_2O; Na_2SO_3

Recently Prasad and Liebeskind[100] have reported a stereospecific silver induced cyclization of 4-allenyl-2-azetidinones to produce Δ^1-carbapenems. Additionally, the chemistry was extended to palladium(II) catalyzed ring closure and Heck Functionalization of the resultant vinyl palladium species. These processes are exemplified in Scheme 59.

SCHEME 59



Scheme 59 continued



Reagents: (i) $AgBF_4$ (0.5 equiv.), CH_2Cl_2, 18h; (ii) $AgNO_3$, $CaCO_3$, H_2O, Me_2CO; (iii) $PdCl_2$, Et_3N, CH_2Cl_2, CH_2=CHAc

R = $^tBuMe_2Si$

Acknowledgement

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