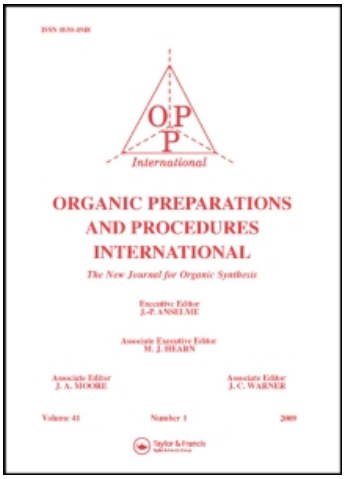

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ELECTROPHILE MEDIATED HETEROATOM CYCLIZATIONS ONTO C-C π-BONDS. PART 2: METAL ION MEDIATED CYCLIZATION

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ELECTROPHILE MEDIATED HETEROATOM CYCLIZATIONS ONTO C-C π-BONDS. PART 2: METAL ION MEDIATED CYCLIZATION

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INTRODUCTION AND SCOPE

In Part 1 we reviewed the literature from 1989 through 1995 pertaining to halogen and chalcogen mediated cyclization of nucleophilic moieties onto an unsaturated C-C linkage (alkene, alkyne, allene).[1] Prior to 1989 the literature has been covered in a number of excellent reports and reviews.[2-6] This review concentrates on the use of transition metal species as electrophilic reagents with which to induce the cyclization of heteroatom functionality onto unsaturated C-C linkages and aims to update those published previously within this area[6-8] with particular emphasis being paid to the application of these methods in the syntheses of natural products and other related compounds possessing interesting biological properties.

There are a range of electrophilic metal ions which effect cyclization on nucleophiles onto unsaturated C-C linkages. The more commonly used metal ions are Pd(II) (chloride, acetate and tetrafluoroborate), Hg(II) (nitrate, acetate, trifluoroacetate, triflate, chloride), Cu(II) (chloride), Ag(I) (isocyanate, carbonate, tetrafluoroborate), Au(III) (chloride), Tl(III) (nitrate, acetate), Ru(II) (chloride) and Rh(I) (chloride). As expected the metal counter-ion is "hard" resulting in a more electrophilic metal ion.

The metal ions differ in their potential for achieving further manipulation after the initial cyclization. Some are immediately protolysed whilst others remain attached and can be further manipulated by either ionic or free radical processes [Hg(II)] or by insertion of carbon monoxide or alkenes [Pd(II)]. Further synthetic flexibility is provided by *in situ* generation of RPd(II)X species by oxidative addition of Pd(0) to R-X (X= halide, triflate) and subsequent addition of RPd(II)X to an alkyne or allene which, in turn, produces the palladated species which undergoes the cyclization process.

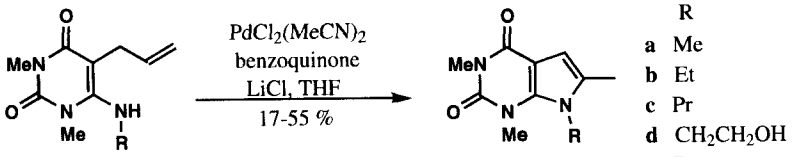
In this review, as in Part 1,[1] we have surveyed the literature from 1989 through 1995 and have organized the material in terms of the unsaturated linkage involved in the cyclization.

I. CYCLIZATION ONTO ALKENES

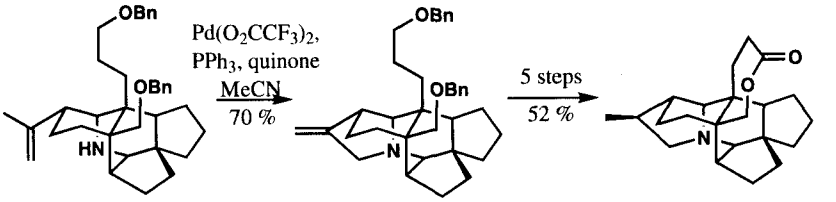
1. Nitrogen Nucleophiles

a) Amines

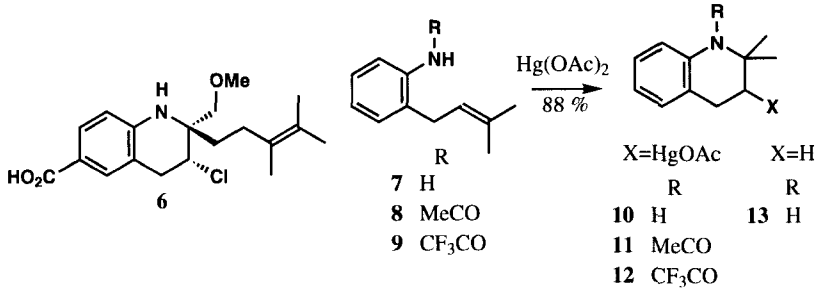
The mild conditions under which palladium (II) salts effect ring closure of secondary amines onto intramolecular alkenes has been has been applied to the preparation of a series of pyrrolo[2,3-*d*]pyrimidines **2a-f** in low to moderate yield (17-55%) by treating the appropriately substituted uracils **1a-f** with catalytic amounts (typically 10 mol%) of bis(acetonitrile) palladium (II) chloride.[9]



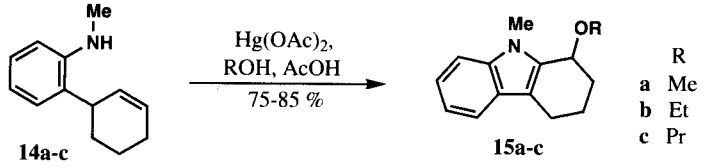
Palladium (II) catalysis has also proved effective for the construction of more complex polycyclic frameworks and has been elegantly exploited[10] in a synthesis of (±)-bukittinggine **5**, (an alkaloid from the leaves and branches of *Sapium baccatum*). Thus treatment of the advanced intermediate **3** with palladium (II) trifluoroacetate (15 mol%) in tetrahydrofuran afforded the cyclized product **4** (70%) which was subsequently transformed into the required natural product **5** in 52% yield over five steps. The source of palladium (II) was found to be crucial to the success of this procedure. In model studies, compounds akin to **3** cyclized only when treated with the trifluoroacetate salt; similar reactions using $PdCl_2/CuCl_2$ in acetic acid failed to afford cyclized products.



Mercuric ions induce similar cyclizations of both primary and secondary alkenylamines. Mercury (II) induced 6-*endo*-trig cyclization of unsaturated anilines has been identified as potentially allowing the rapid assembly of the skeleton of virantmycin **6** (a novel antibiotic from certain strains of *Streptomyces* bacilli).[11] Treatment of 2-dihydroisoprenylaniline **7** with mercuric acetate followed by immediate *in situ* reduction of the organomercurial **10** with alkaline sodium borohydride afforded the tetrahydroquinoline derivative **13** (88%). Unfortunately this reaction sequence could not be extended to the simple *N*-protected anilines required for the chlorination of the intermediate organomercurial; amides **8** and **9** did not cyclize to **11** and **12** under similar conditions, instead mercuric induced hydration of the alkene occurred.

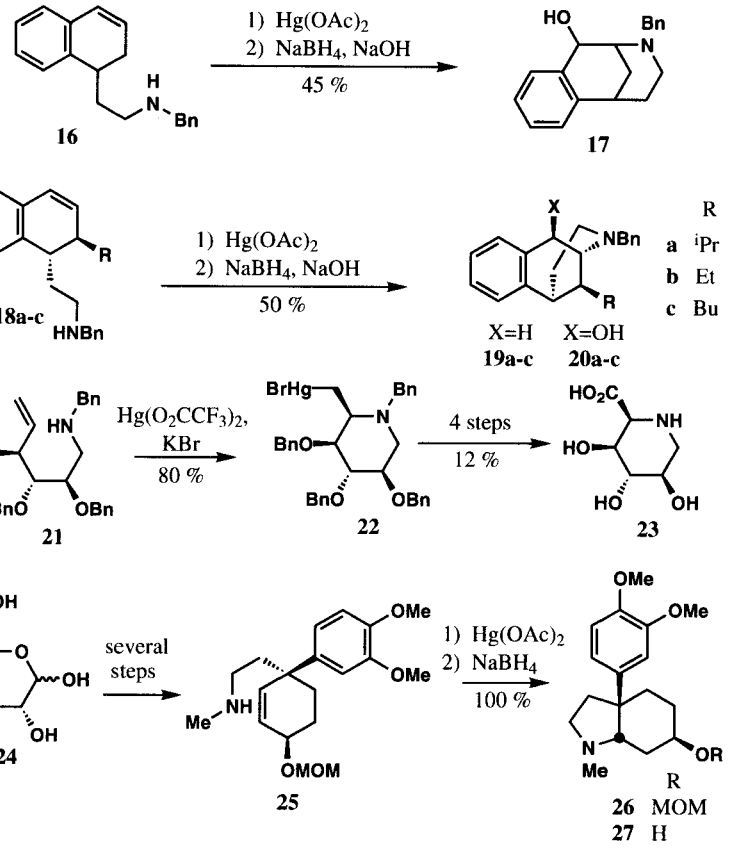


A similar protocol but using nucleophilic alcoholic solvents has been used to prepare the tetrahydrocarbazole derivatives **15a-c**[12] from the aniline precursors **14a-c** *via* 5-*exo*-trig cyclization.



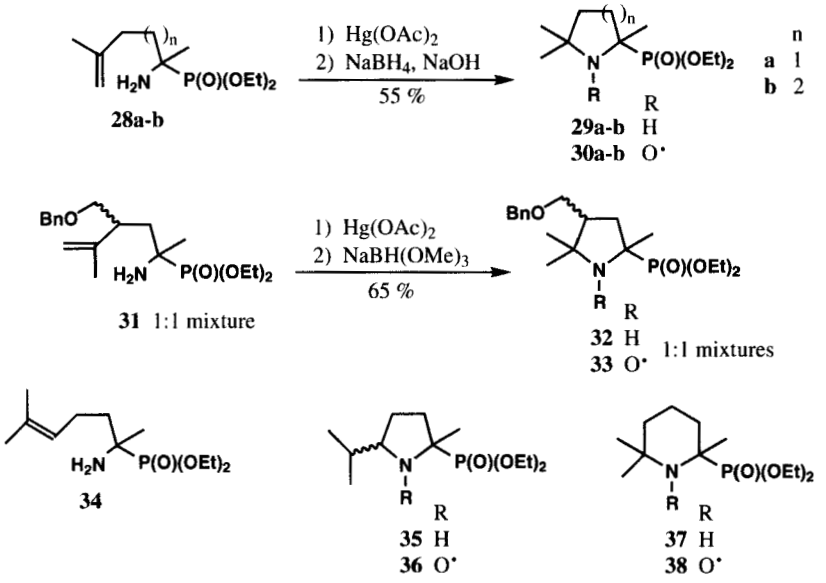
14a-c 15a-c

Others have used similar strategies involving mercury (II) salts to construct piperidine and pyrrolidine containing ring systems including 6,7-benzomorphanes (**16**→**17**),[13] the skeletons of several active opioids (**18a-c**→**19a-c** and **20a-c**),[14,15] a potent α-galactosidase inhibitor[16] (**21**→**22**→**23**) and the alkaloid (-)-mesembranol from D-glucose (**24**→**27**).[17]

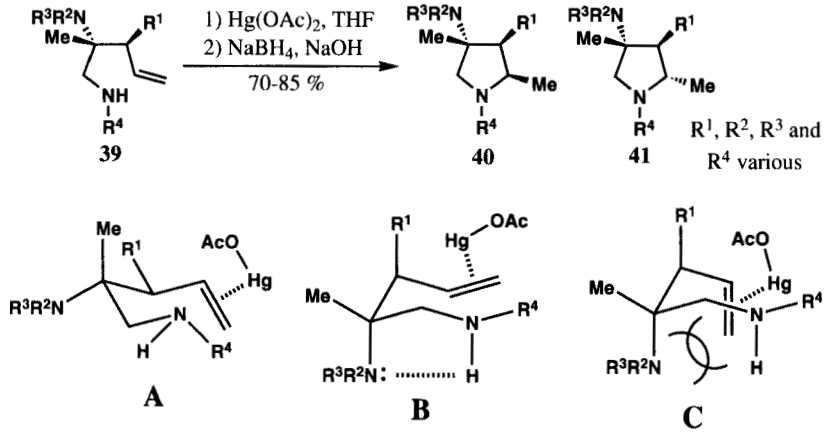


Tordo and co-workers[18-20] have used mercuric ion to induce the cyclization of a series of terminally unsaturated α-aminophosphonates. The resulting pyrrolidines and piperidines were utilized as precursors of novel stable nitroxide radicals (used extensively as spin-labels and spin-traps in ESR studies). Thus phosphonates **28a-b** and **31** afford pyrrolidines **29a** and **32** and piperidine **29b** upon

treatment with mercuric acetate followed by *in situ* reduction;[18,19] *N*-oxidation with MCPBA afforded the required radicals **30a-b** and **33**.



In a later paper[20] the same group were able to prepare amines **35** and **37** (and the corresponding nitroxide radicals **36** and **38**) directly from **34** solely by altering the mercuration conditions. Mercuration of **34** with mercuric acetate in acetone followed by borohydride reduction preferentially afforded **35** (*via* a 5-*exo*-trig cyclization) whereas treatment of **34** with the same combination of reagents in a mixture of tetrahydrofuran and water (1:1) yielded solely the product **37** derived from 6-*endo*-trig cyclization.

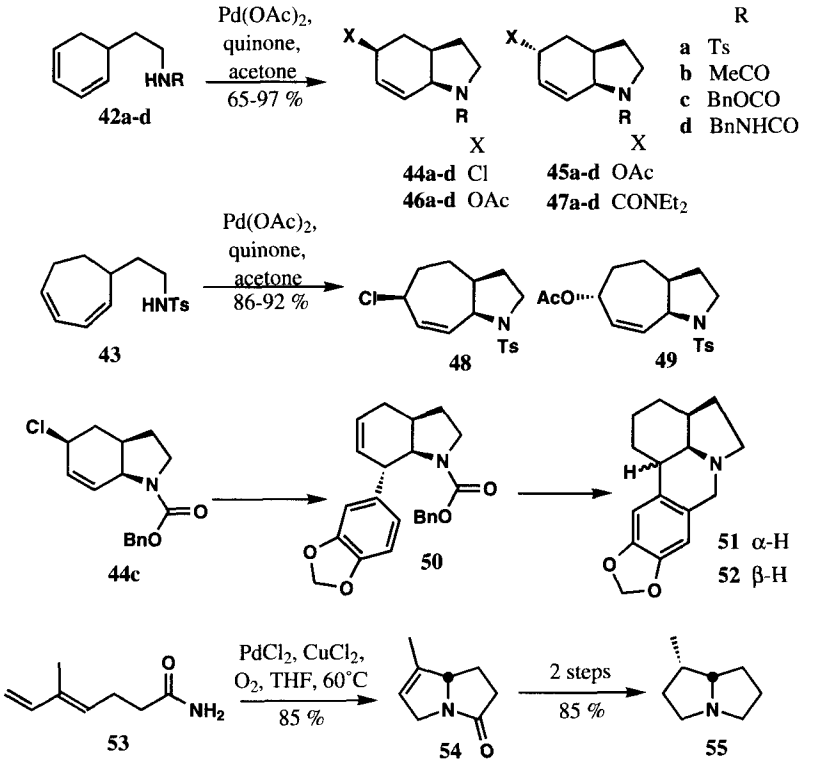


Barluenga and co-workers[21] have observed similar 5-*exo*-trig cyclizations in a series of ω-unsaturated pentenamines **39** (and their carbamate derivatives). Their results suggest that Hg(II) induced cyclizations of such compounds occur in high yield (70-85% after subsequent reduction of

the organomercurial) and with high degrees of stereoselectivity (d.e. >90%); thus **39** affords **40** and **41** (ratio >95:5). These workers suggest that cyclization occurs almost exclusively *via* the most favorable of three conformers **A-C**, **A** and **C** being somewhat disfavored relative to **B** because of developing 1,3-diaxial interactions in **C** and because of the inability to stabilize **A** by an intramolecular hydrogen bond as in **B**.

b) Amides, Carbamates, Sulfonamides And Ureas

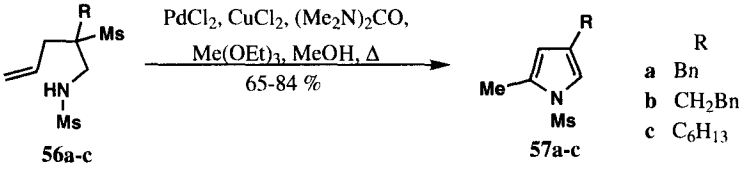
Palladium (II) salts are effective catalysts for the cyclization of nitrogenous derivatives of unsaturated acids. In particular, the extensive studies of Bäckvall and Anderson[22-27] have shown that various *N*-protected amino dienes can be efficiently cyclized with Pd(II) to afford fused heterocycles. Treatment of *N*-protected amines **42a-d** and **43** with catalytic amounts of palladium acetate (5 mol%) and a quinone re-oxidant at room temperature afforded heterocycles **44-49** in high yield.[22] The reactions were highly stereospecific (>93% *cis* or *trans*) and could be readily controlled as required by the addition of quantities of LiCl and $LiOAc{\cdot}2H_2O$. Chloride ions in excess complex strongly to palladium and stop the *cis* migration of acetate from the palladium center in the intermediate trans π-allyl complex thus controlling the preferential formation of the *cis*-isomers **44a-d, 46a-d** and **48**; exclusion of chloride ions from the reaction mixture affords solely the *trans*-isomers **45a-d** and **49**. A recent extension[23] of these ideas relying upon the interception of the intermediate π-allyl palladium complex



with diethylamine and carbon monoxide has been reported and permits the synthesis of amides **47a-d**. Further studies showed that copper (II) acetate and molecular oxygen act as a palladium re-oxidant system in these reactions.[24]

This cyclization strategy has been utilized by the same workers to prepare the alkaloids α- and γ-lycorane **51** and **52** and heliotridane **55** in racemic form. Thus carbamate **44c** undergoes a stereospecific S_N2' displacement with a methylenedioxyphenyl organocuprate reagent to afford **50** which was transformed into both **51** and **52** *via* separate reaction sequences.[25] Similarly amide **53** cyclized and underwent intramolecular trapping of the π-allyl palladium intermediate to generate lactam **54** which was reduced over two steps to heliotridane **55**.[26]

Pyrroles have also been prepared in good yield by the palladium (II) catalyzed cyclization of unsaturated sulfonamides.[28] Treatment of **56a-c** with catalytic $PdCl_2$ in refluxing methanol in the presence of base, a water scavenger and $CuCl_2$ as a re-oxidant afforded a range of 2,4-disubstituted pyrroles **57a-c** in high yield presumably *via* the expected exocyclic olefins which undergo subsequent isomerization and base catalyzed oxidation reactions.

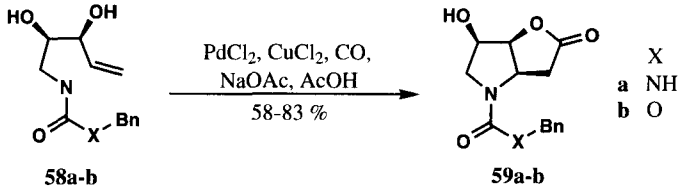


56a-c 57a-c

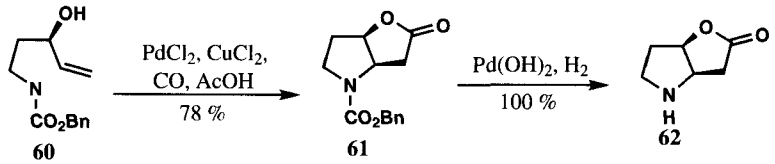
Palladium (II) catalyzed cyclization coupled with carbon monoxide insertion has allowed the preparation of a series of more highly functionalized homologated heterocycles.[29-31] Treatment of ureas and carbamates **58a-b** with catalytic palladium (II) salt and a copper (II) re-oxidant under a carbon monoxide atmosphere affords the cyclized products **59a-b** which were utilized as precursors to glycosidase inhibitors.[29] A similar procedure[30] allowed the conversion of the homochiral carbamate **60** into the lactone **61** in high yield which upon reduction afforded the Geissman-Waiss lactone **62** quantitatively. Cyclization/carbon monoxide capture in methanol allowed for the conversion of a series of sulfonamides **63a-b** into the corresponding five and six-membered heterocycles **64a-b** in good yield with a high degree of stereoselectivity; in all cases *trans*-disubstituted products predominated (*trans*:*cis* 3:1→50:1).[31]

Mercuric salts are particularly useful for the cyclization of unsaturated *N*-protected amides.[32-44] A series of papers by Takahata and Momose demonstrates that cyclization of unsaturated carbamates with mercuric salts constitutes a versatile method for the synthesis of alkaloids and related compounds.[36-44]

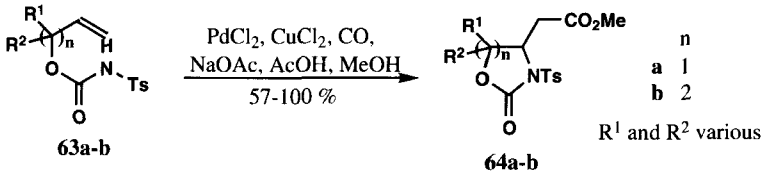
A conformationally restricted substance P antagonist **67** has been prepared from carbamate **65** by sequential treatment with mercuric trifluoroacetate and sodium borohydride which afforded the 2-azabicyclo[3.3.1]nonane derivative **66** in low yield. Conversion of **66** to the required bis-amine **67** required a further four steps.[32]



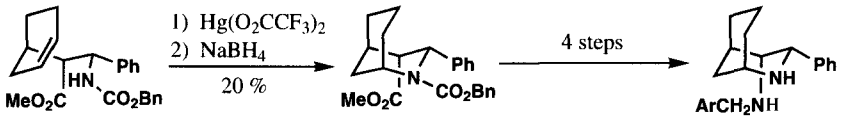
58a-b 59a-b



60 61 62

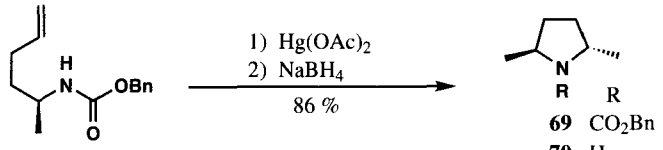


63a-b 64a-b



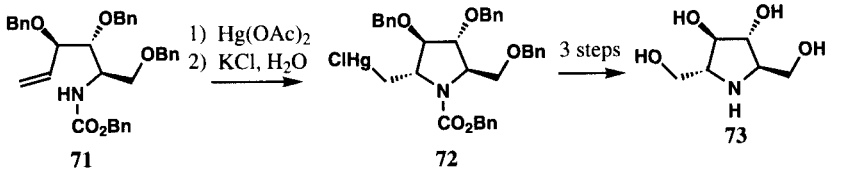
65 66 67

Homochiral C_2 symmetric 2,5-*trans*-disubstituted pyrrolidines are highly sought after ligands for use in asymmetric synthesis and mercury (II) induced cyclizations have proved particularly useful for their synthesis. Carbamate **68** (four steps from L-alanine) undergoes stereospecific cyclization with Hg(II)/$NaBH_4$ to afford the C_2 symmetric carbamate **69** in high yield;[33] acid catalyzed deprotection affording the amine **70** as its highly crystalline hydrochloride salt (89%).



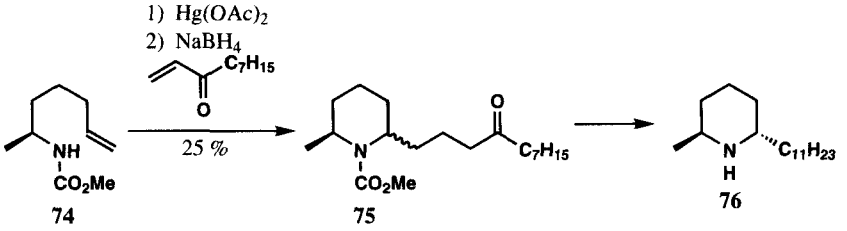
68

Likewise carbamate **71** readily cyclizes stereospecifically in the presence of Hg(II).[34] The resulting 2,5-*trans* organomercurial **72** was converted (three steps) to the homochiral C_2 symmetric amino tetraol **73** which shows activity as an inhibitor of the enzyme pyrophosphate-D-fructose-6-phosphate-1-phosphotransferase.



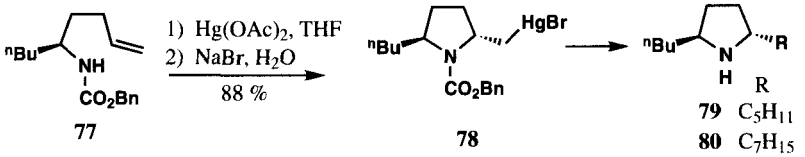
71 72 73

Utilization of mercury (II) salts permits rapid synthesis of piperidines and pyrrolidines that are active constituents of fire ant venom and poison frog toxins. Thus carbamate **74** was cyclized and radically coupled with dec-1-en-3-one to afford the piperidine **75** (25%; isomeric ratio 4:3). Subsequent reduction and deprotection afforded the fire ant venom constituent solenopsin A **76**.[35]



74 75 76

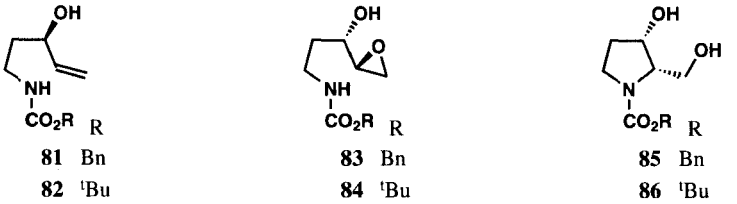
Carbamate **77** undergoes efficient Hg(II) induced cyclization with almost complete stereocontrol (*trans*:*cis* 25:1). The resulting organomercurial **78** was converted cleanly into both pyrrolidine 197B **79** (a toxin isolated from both ant venom and poison frogs) and **80** (from ant venom).[36]



77 78

79 C_5H_{11}
80 C_7H_{15}

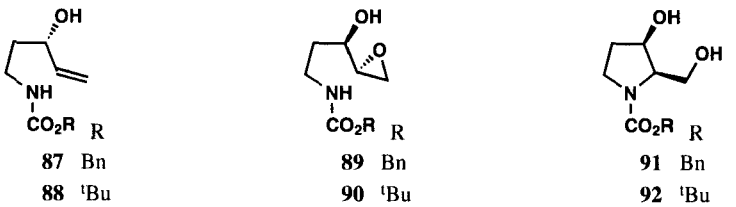
Carbamates **81-92** have been utilized by Japanese workers to prepare several natural products; Sharpless epoxidation of a racemic mixture of alkenes **81** and **87** or **82** and **88** affords a separable mixture of alkene, epoxide and diol. Extensive synthetic studies have shown that **81,82,87** and **88** can be rapidly and stereospecifically transformed into a series of compact *cis*-2,3-disubstituted intermediates by mercury (II) induced cyclization.



81 Bn
82 ^{t}Bu

83 Bn
84 ^{t}Bu

85 Bn
86 ^{t}Bu

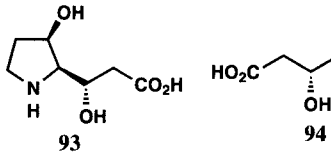


87 Bn
88 ^{t}Bu

89 Bn
90 ^{t}Bu

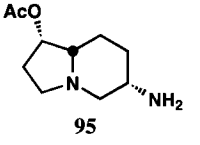
91 Bn
92 ^{t}Bu

This strategy is extremely flexible and has been applied to the synthesis of a variety of pyrrolizidine and indolizidine alkaloids, amino acids and related compounds such as (-)-detoxinine **93**,[37,39] (+)-3-hydroxyglutamic acid **94**,[37,39] bioprecursors of the toxic alkaloids slaframine **95**[37,38] and swainsonine **96**,[38] (-)-anisomycin **97**,[39] (+)-galantinic acid **98**,[39] and (-)-supinidine **99**.[40]



93

94



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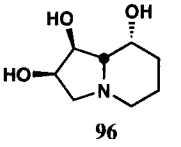

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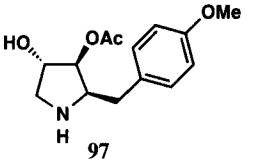

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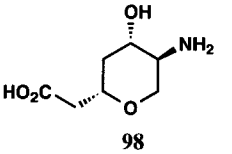

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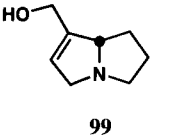
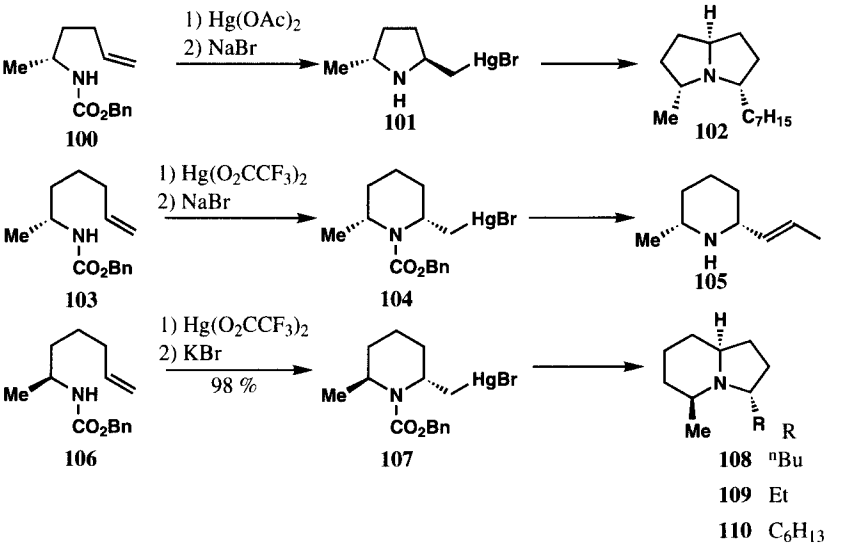


99

Mercuration of the homochiral unsaturated carbamates **100**, **103** and **106** (readily prepared from either L- or D-alanine) in the presence of bromide ion afforded the organomercurials **101**, **104** and **107** which have been used to prepare the ant venom alkaloids **102**, **109** and **110**,[41,42,44] (-)-pinidine **105**[43] and (+)-monomorine I **108**.[44] The 2 aminohexene derivative **100** cyclizes stereospecifically to the 2,5-*trans* product **101** whereas both 2-aminoheptenes **103** and **106** afford mostly the 2,6-*cis*-substituted products **104** and **107**.

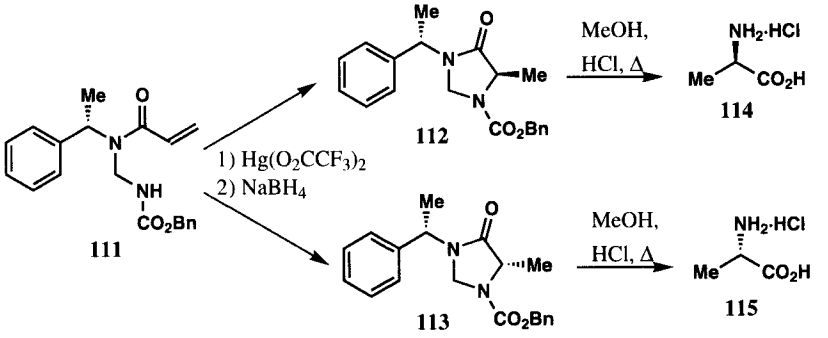


100 **101** **102** **103** **104** **105** **106** **107** **108** **109** **110**

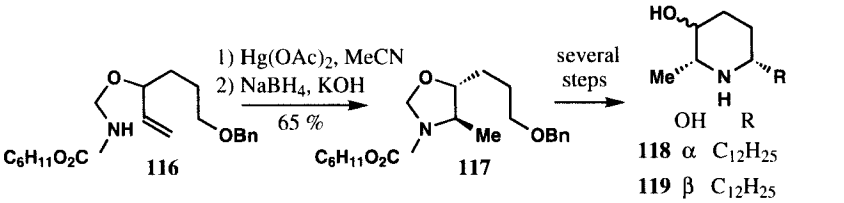
c) Amidals

The metal catalyzed cyclization of unsaturated amidals has been studied by several groups[45-52] who have shown mercury (II) salts to be useful in the synthesis of homochiral α-amino acids, 1,2-

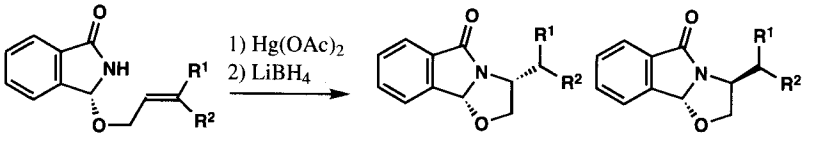
aminoalcohols and 3-hydroxy-2,6-dialkylpiperidines. Thus cyclization of amidal **111** with mercuric trifluoroacetate in dry dichloromethane at 0° followed by sodium borohydride reduction afforded a 1:1 mixture of cyclized products **112** and **113** quantitatively. Acid catalyzed hydrolysis of **112** and **113** afforded pure samples of the hydrochloride salts of D- and L-alanine **114** and **115** respectively (73%).[45] Similar procedures utilizing other related substrates have allowed the synthesis of a wider range of α-amino acids.[46,47]



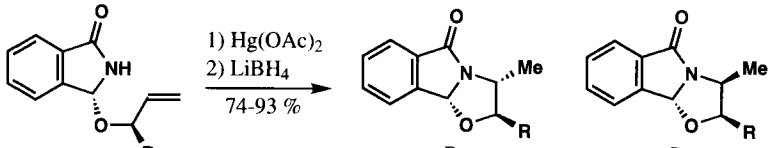
Harding and Jones have used a similar strategy to prepare stereospecifically substituted 3-hydroxypiperidines.[48] Cyclization/reduction using Hg(II)/$NaBH_4$ afforded the required *trans*-substituted oxazolidine **117** (65%) together with the *cis*-isomer (13%); subsequent synthetic transformation yielded both α- and β- 3-hydroxypiperidines **118** and **119**, (deoxygenated analogues of the natural alkaloids (-)-cassine **120** and (-)-prosafrinine **121**).



Tacaks has shown that amidals derived from phthalimide and an allylic alcohol readily undergo mercuric induced cyclization reactions in which the chiral amidal center can be used to induce high degrees of 1,3-stereoinduction.[49] Treatment of the amidals **122-124** with mercuric acetate/lithium borohydride afforded the resulting cyclized products **125-127** and **128-130** in 45-65% yield with high degrees of stereocontrol in favor of the *endo*-isomers **125-127** (12:1→200:1).

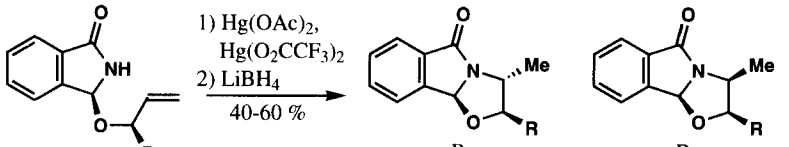


	R^1	R^2		R^1	R^2		R^1	R^2
122	H	H	**125**	H	H	**128**	H	H
123	Me	H	**126**	Me	H	**129**	Me	H
124	H	^{i}Pr	**127**	H	^{i}Pr	**130**	H	^{i}Pr

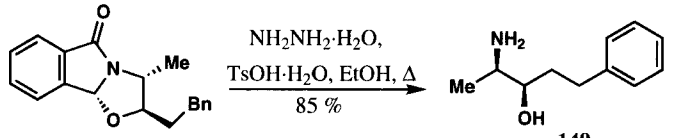


	R	R	R
131	Me	**134** Me	**137** Me
132	CH_2Bn	**135** CH_2Bn	**138** CH_2Bn
133	Bn	**136** Bn	**139** Bn

Analogous cyclization/reduction of **131-133** containing an additional stereocenter afforded almost exclusively (d.e. >98%) the *endo,trans*-isomers **134-136** in good to excellent yield (74-93%); the high levels of stereoinduction in these reactions were rationalized on the basis of the synergistic effect of the 1,3-*cis* directing amidal center and the 1,2-*trans* directing allylic R group.

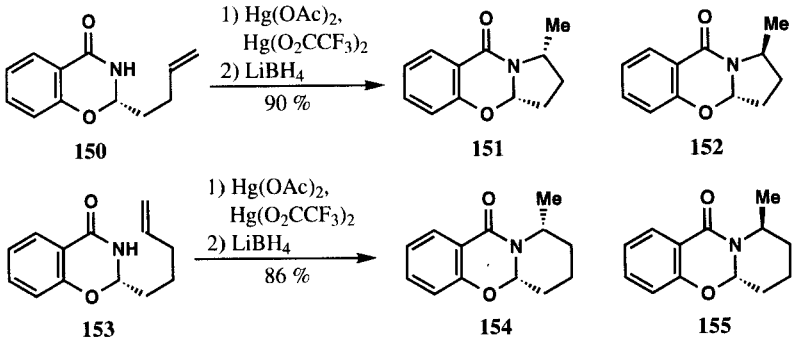


	R	R	R
140	Me	**143** Me	**146** Me
141	CH_2Bn	**144** CH_2Bn	**147** CH_2Bn
142	Bn	**145** Bn	**148** Bn

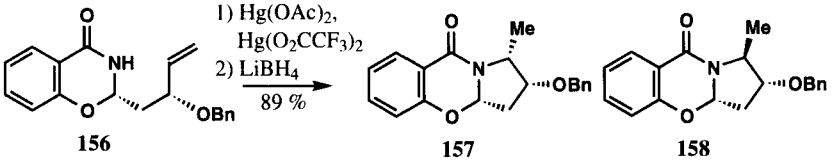


135 **149**

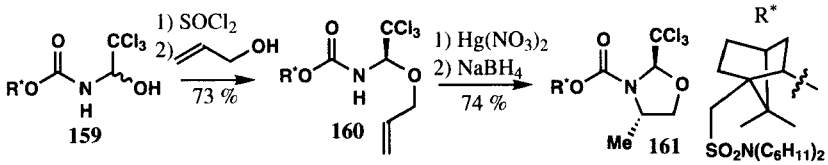
In contrast, the epimeric amidals **140-142** cyclized only under more forcing conditions and gave lower yields of reduction products **143-148** with reduced levels of stereoselectivity (2:1→4:1), the amidal center is thus the center with most stereodirecting influence. The chiral auxiliary was readily removed from **135** upon treatment with excess hydrazine hydrate in boiling acidic ethanol to afford the *syn*-1,2-amino alcohol **149** (85%). Later studies[50,51] by the same research group showed that amidals derived from salicylamide undergo mercury (II) mediated cyclization processes with high degrees of stereoselection.



Thus amidal **150** cyclizes smoothly to afford **151** and **152**, (95%; 12:1 ratio) whereas the homologous amidal **153** affords **154** and **155** (86%; 1:12 ratio).[49] A series of more highly substituted analogues of **150** and **153** were similarly cyclized and their diastereoselectivities noted; substitution patterns leading to both *trans*-2,4- and 2,5-piperidines as well as *trans*-2,3- and *cis*-2,4-piperidines were found to afford practical levels of stereodifferentiation. Likewise the stereodifferentiating effect of incorporating allylic alkoxy functionality in these systems has been investigated;[51] in certain cases, very high diastereoselectivities have been observed, (e.g. **156→157** and **158**; 89%, 50:1 ratio).

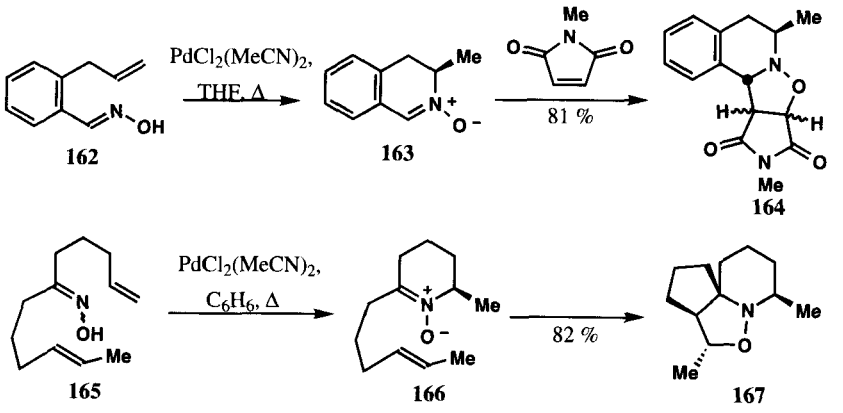


These results have been extended by Harding to double sequential transfer of chirality in intramolecular mercuration reactions.[52] Thus treatment of **159** with thionyl chloride followed by allyl alcohol afforded **160** (73%; d.e. 72%) in which the chiral auxiliary effectively controls the newly formed stereogenic center. Mercuric ion induced cyclization followed by borohydride reduction afforded homochiral *N*-protected oxazolidine **161** (74%); the newly formed amidal stereocenter thus offers complete stereocontrol upon cyclization.



d) Oximes

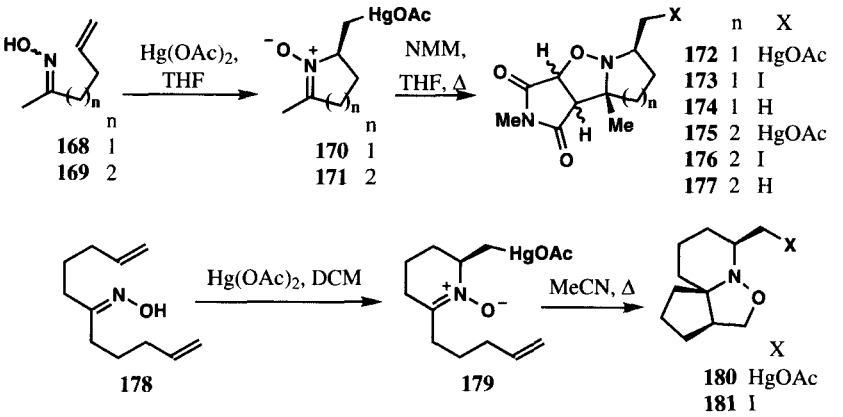
The known ready coordination of oximes with metal centers has been exploited by Grigg and co-workers[53,54] to effect the cyclization of unsaturated oximes thus giving access to a series of complex heterocycles containing the relatively easily cleaved N-O bond. Catalytic amounts of palladium (II) salts have been found to be useful in this respect and induce the formation of cyclic nitrones that can



162 163 164 165 166 167

take part in 1,3-dipolar cycloaddition reactions.[53] Treatment of oxime **162** with Pd(II) (10 mol%) at 64° affords the cyclic nitrone **163** that reacts highly stereoselectively with *N*-methylmaleimide (NMM) to yield the cycloadduct **164** (81%) as a 10:1 mixture of *exo*- and *endo*-isomers. Similarly, treatment of oxime **165** with $PdCl_2(MeCN)_2$ results in regiospecific cyclization to afford nitrone **166** which undergoes regio- and stereo-specific intramolecular cycloaddition to yield the tricycle **167** in 82% yield.

Mercuric salts also generate cyclic nitrones by the cyclization of unsaturated oximes.[54] Treatment of **168** and **169** with $Hg(OAc)_2$ at 20° afforded the nitrones **170** and **171** which underwent cycloaddition with NMM to afford cycloadducts **172** and **175** as *endo:exo* mixtures; subsequent iodination or hydride reduction affording **173** and **176** or **174** and **177** respectively. Similarly oxime **178** affords nitrone **179** which is converted to **180** at 80° (65%) whilst iodination of **180** at 20° affords **181** (55%).



	n	X
172	1	HgOAc
173	1	I
174	1	H
175	2	HgOAc
176	2	I
177	2	H

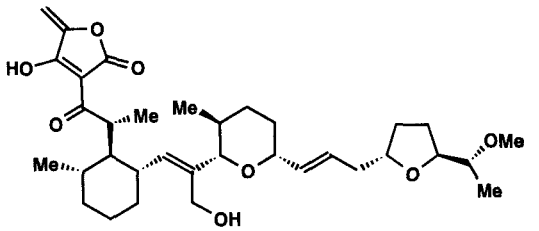
168 1, **169** 2 **170** 1, **171** 2 **178** **179** **180** HgOAc, **181** I

2. Oxygen Nucleophiles

a) Alcohols and Phenols

Palladium (II) salts induce the cyclization of alkenols to afford specifically substituted tetrahydrofurans and tetrahydropyrans. Semmelhack[55-59] has concentrated on subunits **183** and **184** which are frequently found in naturally occurring polyethers and has used this methodology to explore

the synthesis of the antibiotic tetronomycin **182**.



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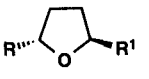

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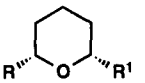
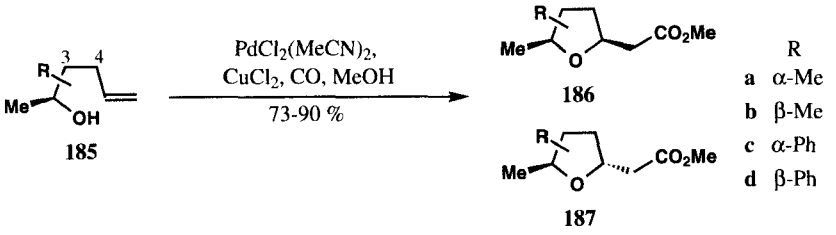
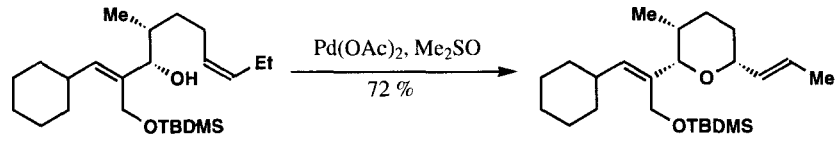


184

A study of the cyclization/carbomethoxylation of alkenols **185** with Pd(II) in methanol showed that in many cases stereoselectivity could be controlled in favor of the required *trans*-isomer **187** by a substituent attached to the allylic carbon atom (C-4) (d.e. 74-100%), C-3 substituents afforded increased amounts of the minor *cis*-isomer **186** (d.e. 0-24%).[55,57] In contrast the homologous alcohols (giving rise to tetrahydropyran products) afforded exclusively the required *cis*-isomers when treated with $Pd(OAc)_2$ in dimethylsulfoxide,[56-58] thus alcohol **188** gave the cyclized product **189** (72%) when treated with palladium acetate at room temperature. A later paper describes a similar approach to the synthesis of the framework of tetronomycin **182**.[59]

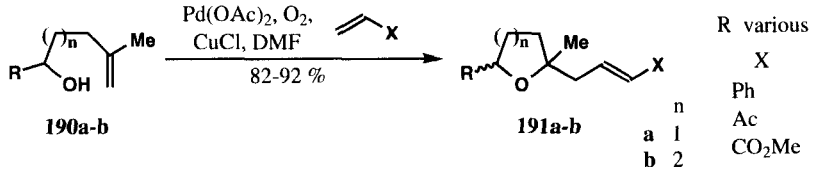


185 **186** **187**



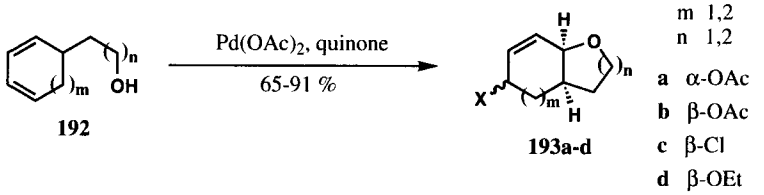
188 **189**

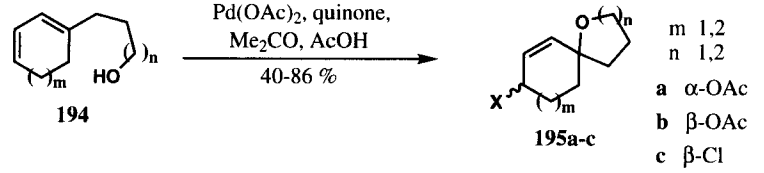
These processes can be extended to substrates which cannot undergo a final β-hydride elimination step because of the introduction of a methyl group onto the double bond. This allows chain extension *via* a Heck reaction with a second component containing a suitable vinyl unit.[59] Treatment of **190a-b** with $Pd(OAc)_2$ (10 mol%) in *N,N*-dimethylformamide at 20° afforded high yields of **191a-b** (82-92%) with a variety of activated ethylenes (X=Ph, Ac, CO_2Me).



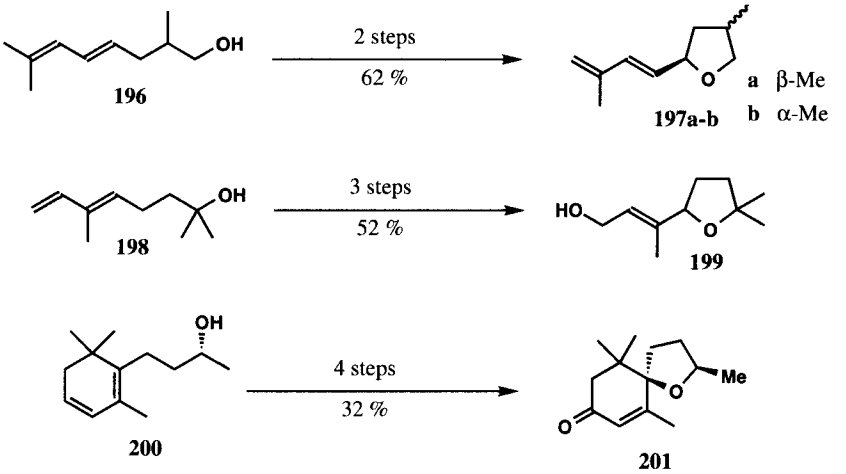
190a-b **191a-b**

A report on the synthesis of specifically substituted tetrahydrofurans extended the scope of the cyclization/ carbomethoxylation process to substrates containing more highly substituted double bonds.[60] The rate of Pd(II) mediated cyclization was found to diminish drastically with an increase in substitution at the double bond such that trisubstituted olefins were found to be essentially unreactive under standard conditions ($PdCl_2$, $CuCl_2$, CO, MeOH). Addition of 10-20 mol% of triethylamine to the reaction mixture was found to cause a dramatic increase in the rate of cyclization and trisubstituted olefins were found to react smoothly under these modified conditions, this phenomenon being attributed to the ability of the amine to break the sterically encumbered bridged chloride dimers of the Pd(II) adduct to form kinetically more labile olefin-palladium-amine monomers.

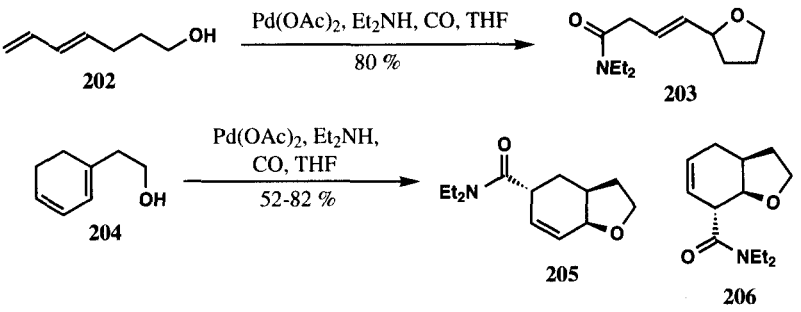




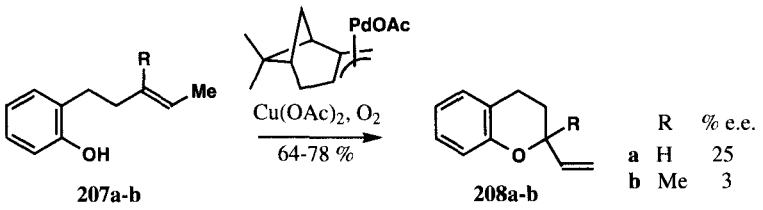
A series of papers by Bäckvall and Andersson demonstrates the ability of Pd(II) salts to cyclize enols to afford both fused and spiro bicycles.[23,24,27,61-65] Thus alcohols **192** can be cyclized with $Pd(OAc)_2$ (5 mol%) under a variety of conditions to afford the both *cis*- and *trans*-fused bicycles **193a-d** in good to high yield;[61] extension of these ideas leads to the formation of spirocyclic ethers **195a-c** from alcohols **194** in similar yield.[62-63]



These fused and spirocyclization procedures have been exploited in concise stereoselective syntheses of naturally occurring tetrahydrofurans marmello oxides A and B **197a** and **197b** and a constituent of peppermint oil **199** (from **196** and **198** respectively)[61,64] as well as theaspirone **201** (from **200**).[63]

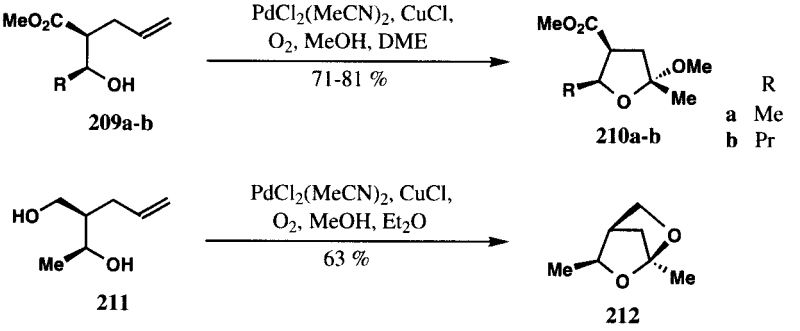


Similar reaction conditions using $Pd(OAc)_2$ under a carbon monoxide atmosphere in the presence of a secondary amine (diethylamine) results in the interception of the π-allyl palladium (II) intermediate and so extends this methodology to allow aminocarbonylation.[23] Thus dienol **202** cyclizes to afford tertiary amide **203** and 1,3-cyclohexadiene **204** affords a 77:23 mixture of amides **205** and **206**.

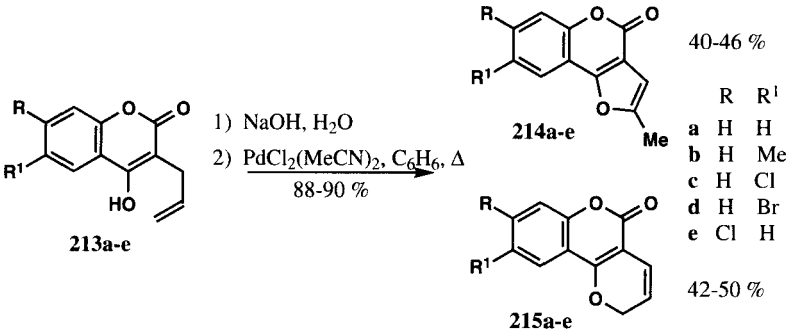


The enantioselective cyclization of 2-allylphenols **207a-b** has been explored. Catalytic quantities (10 mol%) of $[(\eta^3\text{-pinene})PdOAc)_2]$ induce a very low to moderate degree of enantiomeric excess in the resulting cyclic ethers **208a-b**.[66-67,69] Cyclization of the trisubstituted olefin **207b** was comparatively slow due to increased steric compression around the palladium center upon olefin complexation. The extremely low enantioselectivity can be explained accordingly and probably results from the competitive dissociation of the bulky pinene ligand from the chiral palladium species to afford small quantities of achiral $Pd(OAc)_2$ which in turn catalyses the subsequent cyclization of **207b**.

Pd(II) Salts can be used to prepare cyclic acetals and more complex homochiral acetals.[68-69] Catalytic amounts of $PdCl_2(MeCN)_2$ (5-10 mol%) in methanol in combination with a $CuCl/O_2$ reoxidant results in the cyclization of esters **209a-b** to afford the cyclic acetals **210a-b** in high yield (71-81%) *via* methanolysis of the intermediate enol ether selectively *anti* to the bulky alkyl and ester substituents (d.e. 80-88%). In contrast the homochiral diol **211** cyclizes under similar conditions to afford the homochiral 1,6-dioxabicyclo[2.2.1]heptane **212** in good yield by alcoholysis of the analogous vinyl ether intermediate by the second alcohol functionality.

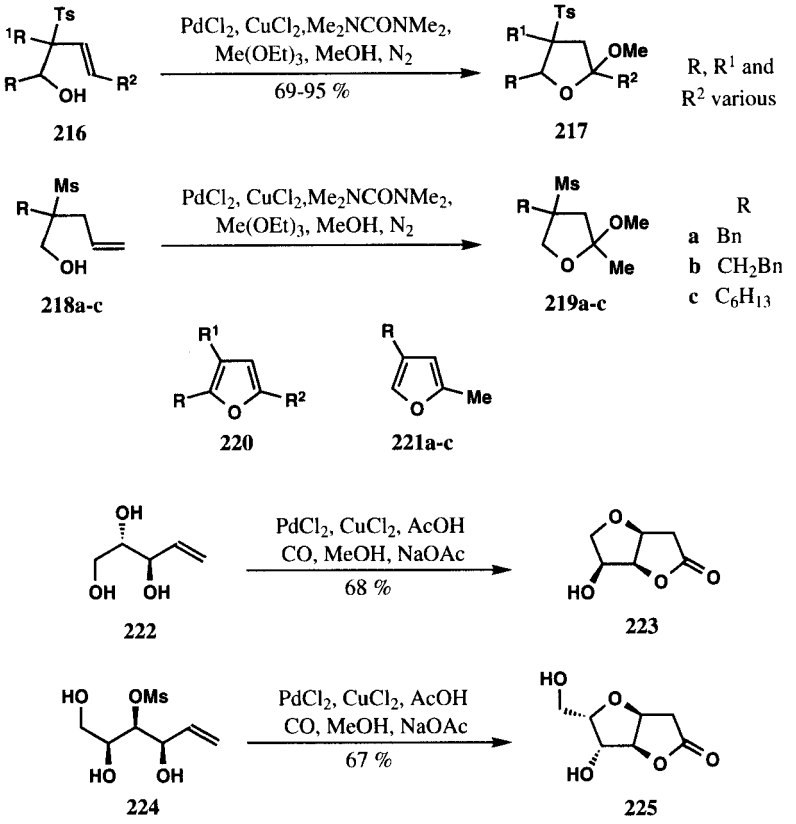


bis(Acetonitrile)palladium (II) chloride has been successfully exploited in the synthesis of furo- and pyrano[3,2-*c*][1]benzopyran-4- and 5-ones from simple 4-hydroxy-2*H*-[1]benzopyran-2-one precursors **213a-e**,[70] alcohols **213a-e** (as their sodium salts) cyclize readily at 80° over 2 hrs to afford high yields (88-90%) of the furan **214a-e** and pyran derived products **215a-e** with little or no regioselectivity in the cycloaddition step (*ca.* 1:1 mixtures in all cases).

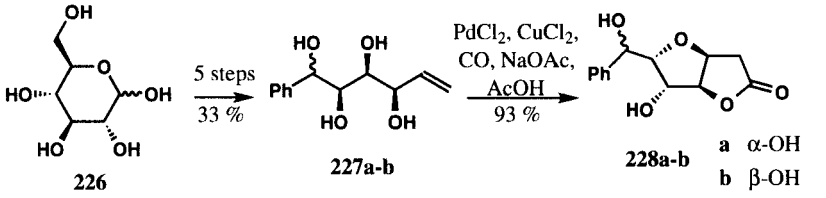


Palladium mediated cyclization has been investigated for the synthesis of furans. Inomata and co-workers have shown that 2-sulfonylated alkenols can be readily cyclized with Pd(II) salts to afford cyclic acetals in high yield (69-95%) which can be readily aromatized ($TsOH{\cdot}H_2O$, PhMe, Δ, 3 hrs) to afford furans **220** and **221a-c** in 71-90% yield;[28] thus alcohols **216** and **218a-c** can be smoothly cyclized to **217** and **219a-c** which readily aromatize when heated with catalytic quantities of acid.

Palladium mediated cyclization/carboalkoxylation has been examined for the synthesis of 2-substituted γ-lactones and has been employed in the synthesis of several useful intermediates for nucleoside and nucleotide synthesis[71] as well as in the syntheses of several natural products.[72-75] Jäger has shown that C_5- and C_6-enitols can be homologated using a Pd(II)/Cu(II) catalytic system under an atmosphere of carbon monoxide with concomitant interception of the intermediate alkylpalladium (II) species by an intramolecular hydroxyl group to afford homochiral bicyclic γ-lactones with high degrees of stereoselectivity.[71] Alkenols **222** and **224** cyclize readily at room temperature over 16-48 hrs to afford lactones **223** and **225** in good yield.

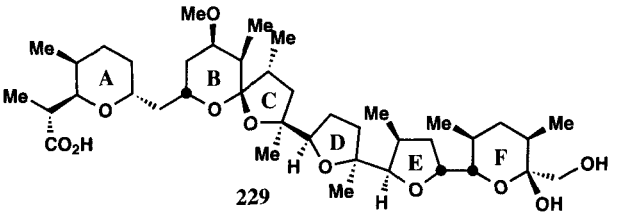


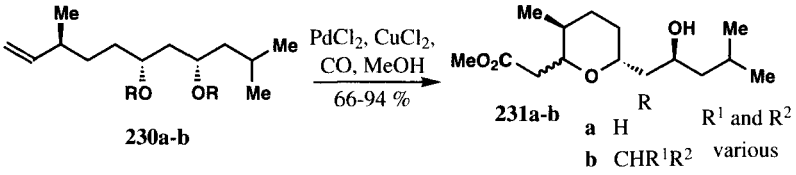
Notably in each case the kinetically preferred 5-*exo*-trig cyclization product is formed exclusively even though in the latter case involving alkenol **224** a more hindered secondary alcohol is involved in the initial Pd(II) mediated cyclization step. Later work by the same research group utilized these ideas in the assignment of absolute configuration of (+)-goniofufurone by synthesis of its unnatural (-)-enantiomer **228a** directly from D-glucose **226**.[72,73] D-Glucose **226** was converted over five steps to a mixture of epimeric polyols-**227a-b** which were cyclized, carbonylated and lactonized to afford the chromatographically separable lactones **228a-b**, lactone **228a** proving to be identical to (+)-goniofufuranone in all respect except for the sign of its specific rotation.



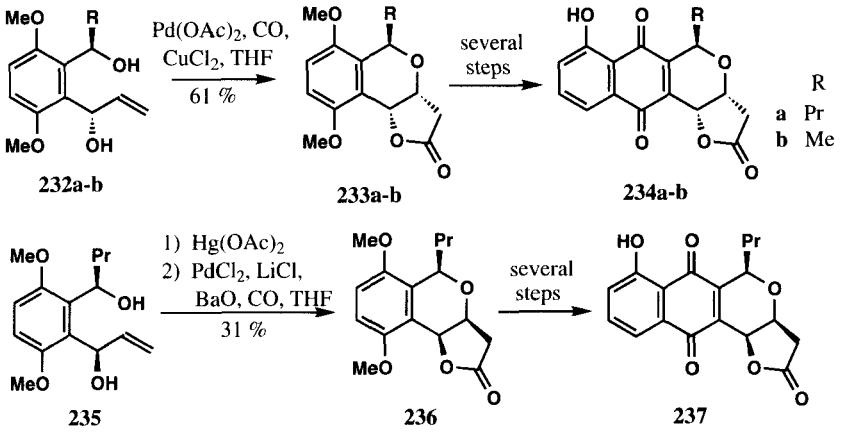
Bartlett's group have described the use of cyclization/carbomethoxylation methodology in the synthesis of the tetrahydropyran subunit (ring **A**) of the polyether antibiotic Nigericin **229**.[74] Their

studies showed that diol **230a** (and various benzylidene derivatives **230b**) could be readily cyclized with a palladium (II)/copper (II) catalytic system and carbon monoxide. The mixtures of products **231a-b** isolated had mostly the unnatural stereochemistry in which all three substituents on the tetrahydropyran ring are equatorial (α:β ratios for CH_2CO_2Me substituent between 2:1 and 8:1).



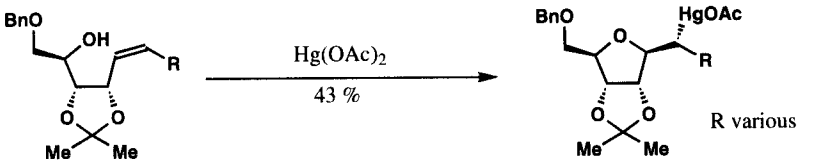


Similar conditions have been utilized in a synthesis of both frenolicin A **234a** and kalfungin **234b** *via* a the cyclization/carbonylation of the benzylic alcohols **232a-b**. The products **233a-b** were each subsequently converted over three steps to the tetracyclic lactones **234a-b** in good yield.[75] In the same paper a mercuric/palladium (II) coupled cyclization strategy allowed for the synthesis of the isomeric product **237** from the epimeric alcohol **235** *via* **236**.



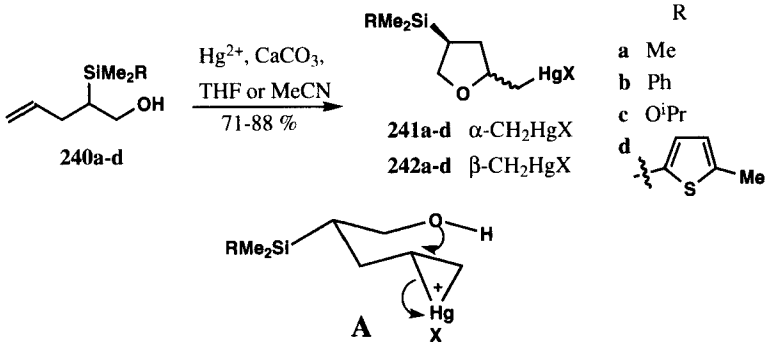
The stereoselectivity in these reactions has been explored. Cyclization of a series of sugar derived hept-2-enitols with $Hg(OAc)_2$ and other electrophiles and has shown that in certain cases the stereochemistry of the product can be predicted based upon the structural features of the alkenol.[76] In general cyclization of (*Z*)-olefins akin to **238** afforded mostly β-furanosides **239** together with some of the corresponding α-isomer and varying amounts of pyranoside derivatives although the degree of

stereoselectivity was highly dependent upon the nature of both the electrophile and the R substituent.

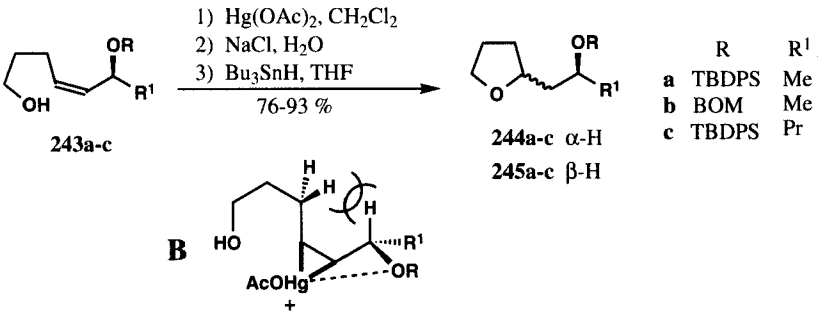


238 239

Appropriately positioned silyl functionalities result in good diastereomeric excess. Thus 2,4-*cis* products **242a-d** are preferred (d.e. 60-88%) over the 2,4-*trans* isomers **241a-d** upon cyclization of silanols **240a-d**.[77] This has been rationalized by a transition state in which the bulky silyl functionality occupies a *pseudo*-equatorial site around in the chair like transition state **A**.



240a-d

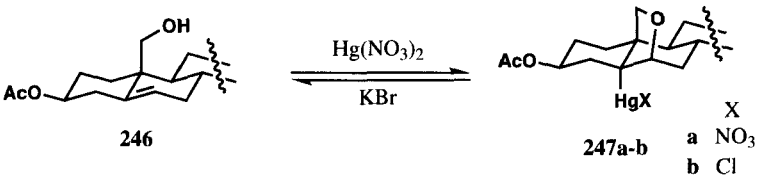


243a-c

Participation of an allylic alcohol functionality in mercury induced cyclization of alkenols.[78] results in a fair degree of diastereoselectivity. Thus treatment of **243a-c** with mercuric acetate followed by anion interchange and radical demercuration afforded tetrahydrofurans **244a-c** and **245a-c** in high yield (76-93%; ratio **244**:**245** 1:4→1:5). Transition state **B**, in which the allylic hydrogen is eclipsed with the carbon skeleton to minimize steric strain and the mercury cation is directed to the olefin *syn* to the hydroxylated functionality, is proposed leading to the preferred **245a-c**.

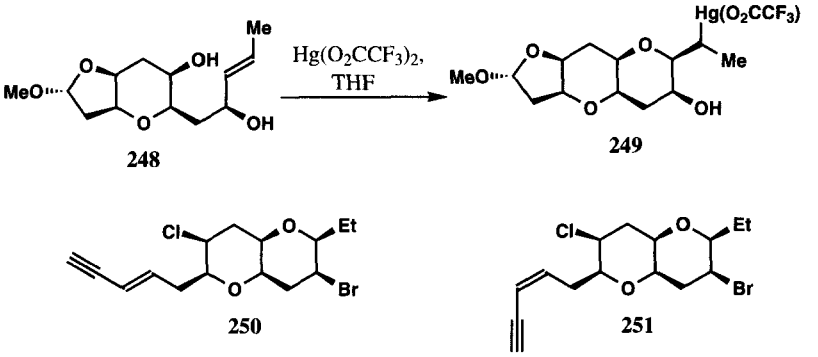
Research by Kocovsky has shown that oxymercuration products with a fixed antiperiplanar arrangement of the C-Hg and C-O bonds (which are prone to reversion to the alkenol) can be obtained in much higher yield if the initial Hg(II) counterion is replaced by halide ion from a 'soft source'.[79]

Thus the cyclization of 5-cholestene-3β-19-diol 3-monoacetate **246** with mercuric nitrate gives **247a** but addition of potassium bromide (or other group I metal halides) results in instantaneous reversion to **246**. In contrast, treatment with halides of softer metals (e.g. K_2PdCl_4) afforded quantitative yields of **247b** with no sign of transmetallated products [exchange of Hg(II) by Pd(II)].



246 **247a-b**

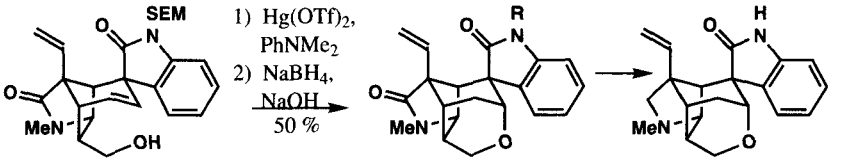
Mercuric ion induced cyclization has been utilized as a key step in the synthesis of both (3*E*)- and (3*Z*)-dactomelyne **250** and **251** (isolated from the digestive glands of the sea hare *Aplysia dactylomela*). Treatment of alcohol **248** with mercuric trifluoroacetate afforded **249** which was further elaborated over several steps into both **250** and **251**.[80]



248 **249**

250 **251**

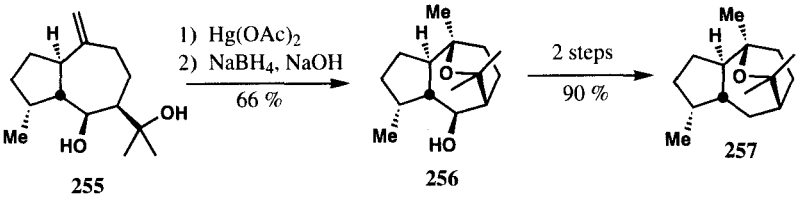
Dutch workers have shown that cyclization of the advanced synthetic intermediate **252** with mercuric ion followed by *in situ* reduction of the organomercurial intermediate with borohydride afforded the hexacycle **253** in good yield. This compound was subsequently transformed (two steps, 45%) to racemic gelsemine **254**.[81,82]



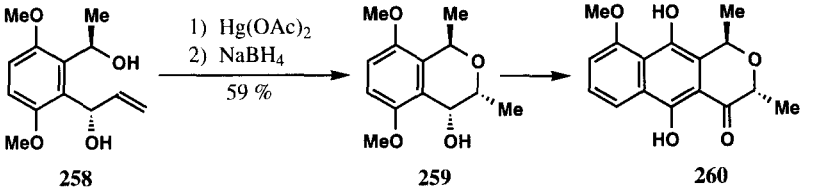
252 **253** **254**

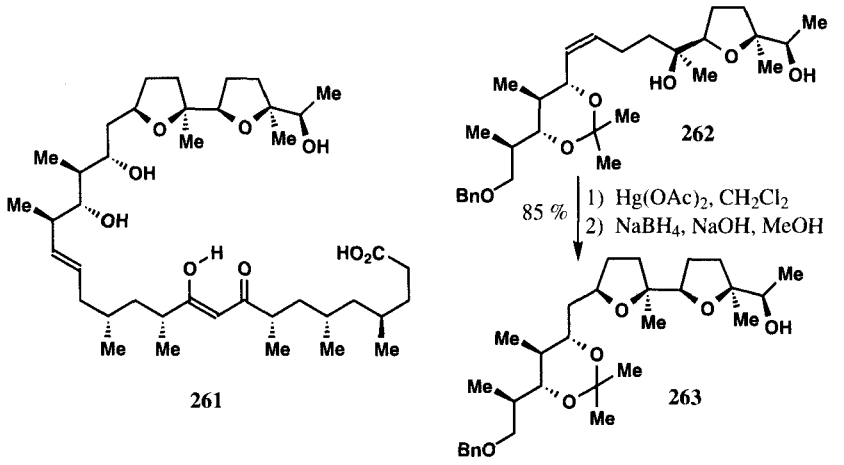
The oxido-framework of naturally occurring (-)-kessane **257** (from several plant species) has been prepared from a synthon **255** derived from naturally occurring (+)-aromadendrene. Treatment of the diol **255** with mercuric acetate followed by reduction afforded the tricycle **256** which was readily converted in high yield to the natural product **257**.[83] Mercuric ion mediated cyclization

has also recently been utilized for the synthesis of similar complex polycycles akin to the potent anti-malarial artemisinin.[84]



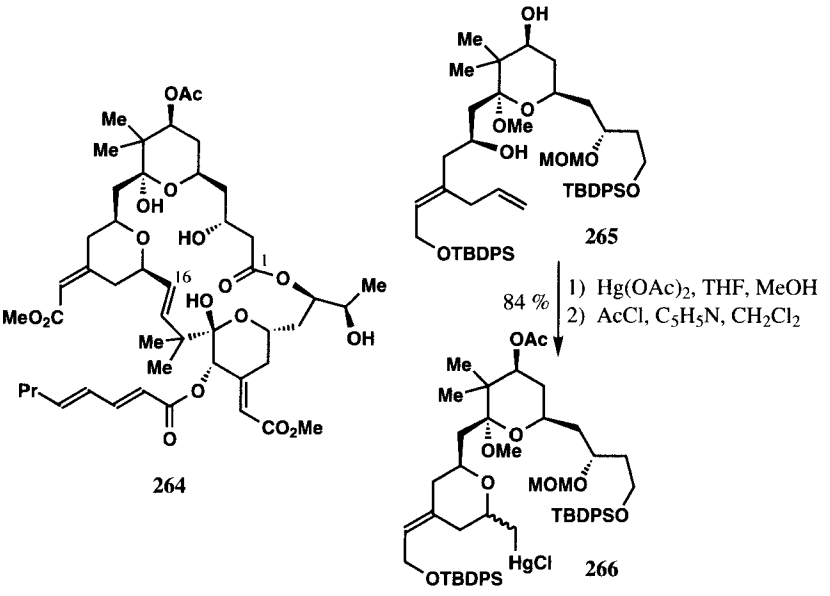
Hongcocin **260** (a constituent of the chinese medicinal plant *Eleutherine americana*) has been prepared using a cyclization/Diels-Alder sequence. Mercuric induced cyclization of **258** afforded the tetrahydropyran derivative **259** after reductive demercuration and this was subsequently converted to the racemic natural product **260**.[85] Benzotetrahydropyran construction by mercury induced cyclization facilitated the synthesis of the HIV-1 reverse transcriptase inhibitors calanolides A and B.[86]



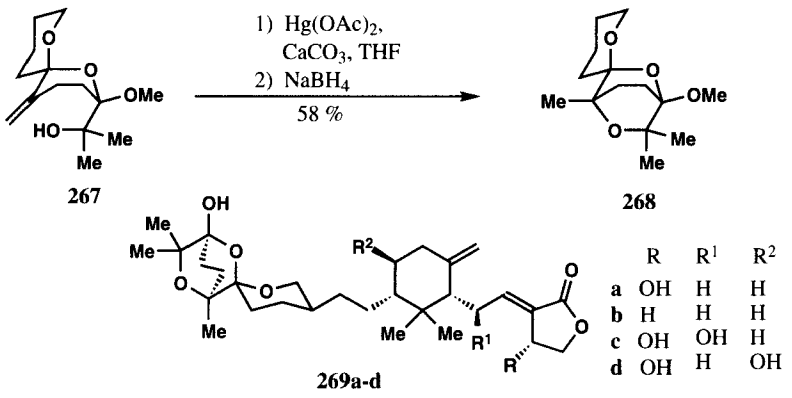


The synthesis of the Ca^{2+} and Mg^{2+} transporting polyether antibiotic ionomycin **261** has been realized by Evans using a mercuric ion induced cyclization as a key step in the formation of the advanced bis-furanoside intermediate **263**.[87] Subjection of **262** to a highly stereoselective (93:7) cyclization/reduction sequence with mercuric acetate and sodium borohydride afforded the required intermediate **263** in high yield (85%).

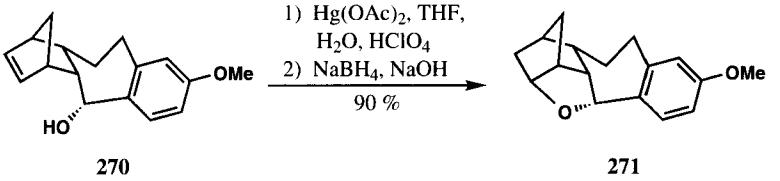
Mercury mediated cyclization has allowed a synthesis of the C_1-C_{16} fragment of bryostatin 1 **264** *via* cyclization of **265** which afforded an isomeric mixture of the tetrahydropyrans **266** in high yield.[88]



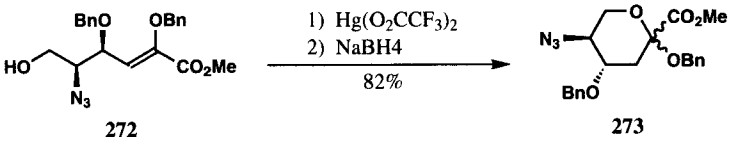
The synthesis of the trioxa-tricyclic subunit of a series of the novel fungal metabolites saponaceolides A-D **269a-d** has been recently reported, the key ring formation step being Hg(II) induced. Thus alkenol **267** cyclizes to afford an organomercurial which on reduction gave tricycle **268** in good yield (58%).[89]



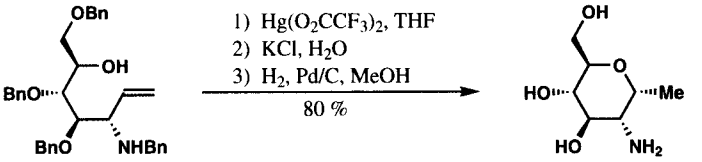
Mercury (II) induced cyclization of alkenol **270** followed by reduction afforded pentacycle **271** which is a potential intermediate for diterpenoid synthesis.[90]



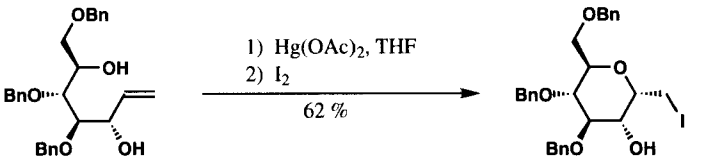
Neuraminic acid analogues have been prepared by similar cyclizations . Alcohol **272** affords **273**,[91] the amino sugar **275** has been prepared by the cyclization of **274** followed by hydrogenolysis[92,93] and the sugar derivative **277** is isolated in high yield upon treatment of **276** with Hg^{2+} followed by radical iodination of the organomercurial intermediate.[94]



272 **273**

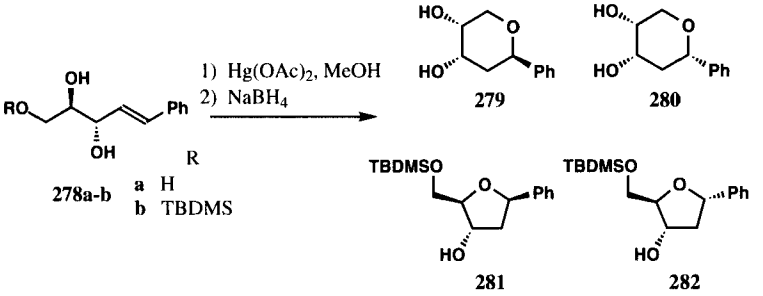


274 **275**

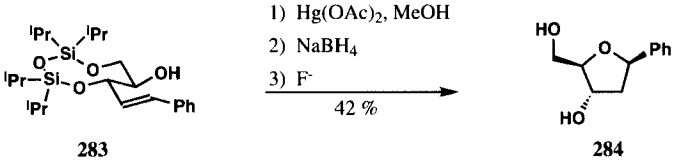


276 **277**

C-Nucleosides have also been prepared by a procedure involving mercuric ion induced cyclization.[95] Treatment of alcohol **278a** with mercuric acetate followed by reduction afforded a 1:1 mixture of the pyranose derivatives **279** and **280** whereas the *O*-silyl ether **278b** afforded a 2:3 mixture of tetrahydrofurans **281** and **282** *via* 5-*endo*-trig cyclization. In contrast the protected triol **283** underwent smooth cyclization to afford a single isomeric product which upon reduction and desilylation afforded the *C*-nucleoside **284**.

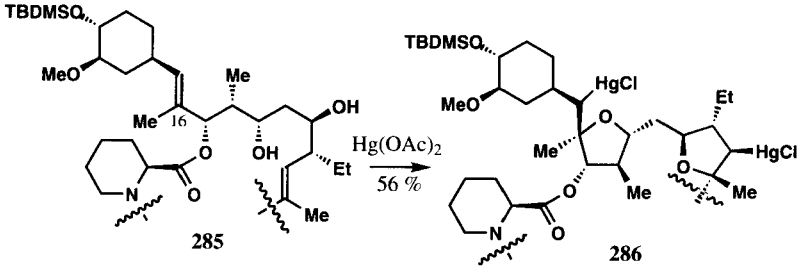


278a-b a H b TBDMS **279** **280** **281** **282**

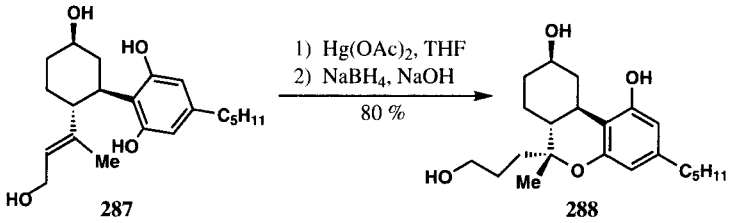


283 **284**

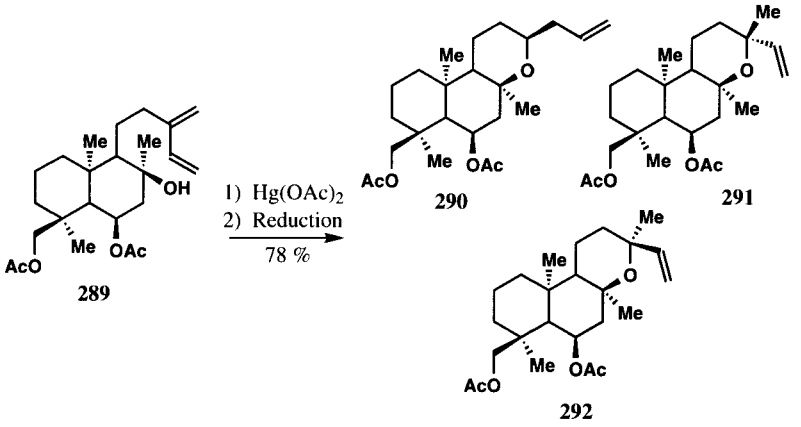
Mercuric ion induced cyclization has been utilized to explore routes to chemically modified analogues of ascomycin (the 21-ethyl analogue of the potent macrolide immuno-suppresant FK506). Treatment of diol **285** with mercuric acetate afforded the bis-tetrahydrofuran derivative **286** in good yield. The latter was subsequently transformed into a series of analogues of ascomycin lacking the cyclohexylmethylene residue at C_{16}.[96]



Conformationally restricted hybrids of CP-55,940 and HHC (a pair of non-classical cannabinoids with analgesic properties greater than those of morphine) have been prepared using mercuric ion induced cyclization of alkenols. Terpene derivative **287** cyclizes upon treatment with Hg^{2+} to afford high yields of **288**, after borohydride reduction, together with its epimer (~85:15 ratio) epimeric at the newly formed quaternary center.[97] The stereoselectivity derives from the kinetic preference for the axial organomercurial upon cyclization to pyranoside derivatives and this selectivity is believed to be similar in nature to the anomeric effect.[98]

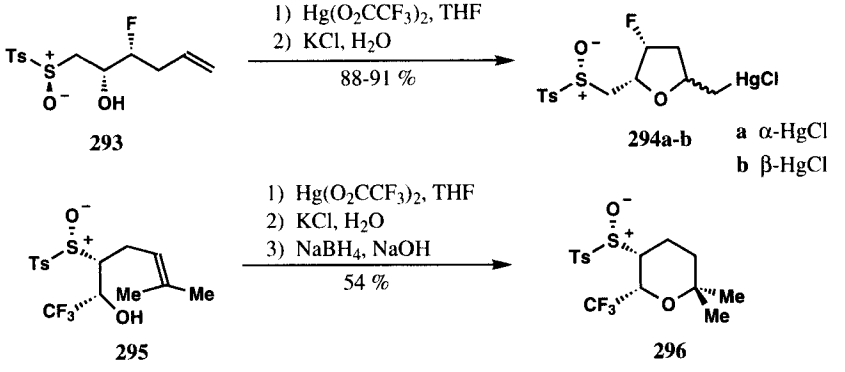


Several mannoyl oxides isolated from plant roots have been found to have ionotropic, hypotensive, bronchospasmolytic and cardiotonic activity and their synthesis from dienols by mercuric

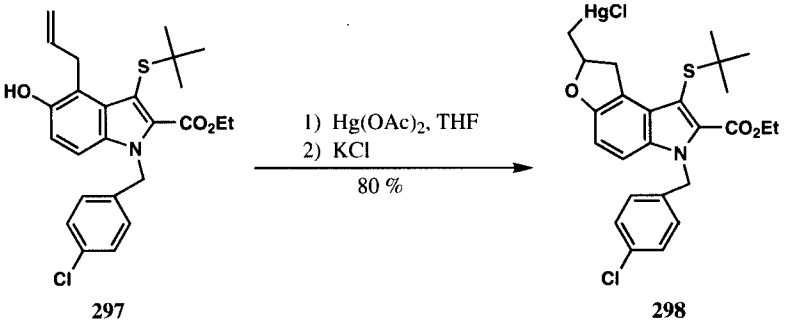


ion cyclization has been studied.[99] Mercuration of **289** afforded a mixture of **290-292** in yields that varied according to the exact conditions used, reduction conditions proving to be particularly crucial to the outcome of the reaction; the organomercurial precursors to **291** and **292** were isolated in good yield (78% after ligand interchange with chloride ion). Cyclization of **289** with $TiCl_4$ (CH_2Cl_2, -78°) was shown to be extremely efficient and afforded only **291** and **292** in 27% and 57% yield respectively.

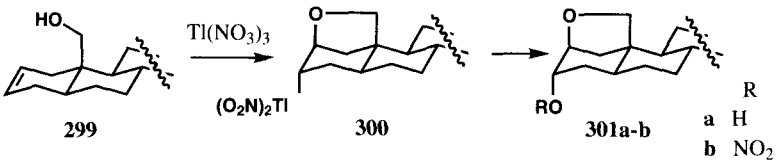
A key step in the synthesis of homochiral fluorinated tetrahydrofurans and tetrahydropyrans involved mercuric ion induced cyclization.[100-102] The five and six-membered rings formed in these reactions are, as expected, sensitive to olefin substitution. Thus **293** affords both **294a-b** in high yield (88-91%), whilst alkenol **295** affords **296** in moderate yield after reduction.



As part of a study to delineate the structural features required in a series of novel 5-lipoxygenase inhibitors researchers at Merck have noted[103] that cyclization of 2-allyl phenol **297** occurs readily in tetrahydrofuran to afford the novel organomercurial **298** in good yield. Protection of the phenol as its methyl ether allowed the alternative cyclization process through sulfur.

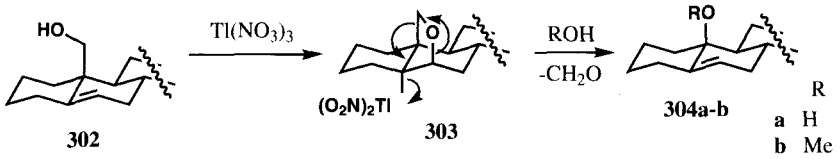


A series of metal ions (Pd^{2+}, Hg^{2+} Tl^{3+}) have been used to cyclize steroidal and terpenoid alcohols.[104-108] Kocovsky has shown that thallium (III) nitrate is effective for the cyclization of steroidal alkenols.[104-105] Treatment of 2-alken-19-ol **299** with thallium (III) nitrate trihydrate in 1,4-dioxane results in regiospecific cyclization to afford the triaxially substituted thallated product **300** which undergoes rapid dethallation to afford a mixture of alcohol **301a** (47%) and its nitrate ester **301b** (41%).[104]



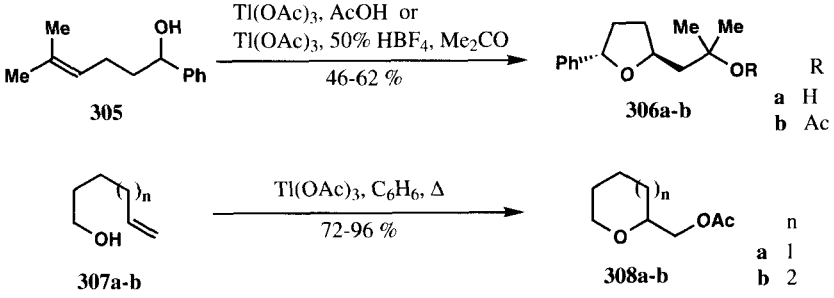
299 300 301a-b

This procedure has been successfully exploited for the synthesis of 19-norsteroids.[105] In certain cases (where the thallium substituent becomes directly attached to the newly formed tetrahydrofuran) a novel fragmentation pathway becomes possible and a facile formaldehyde elimination ensues. Thus treatment of the isomeric 5-ene-19-ol **302** under identical conditions affords thallated product **303** which rapidly eliminates formaldehyde to form the 19-norsteroid derived product **304a** by addition of water to the resulting allylic cation specifically at the more stable tertiary center (81%); in alcoholic solvents ethers are formed albeit in much lower yield (**304b** 27%).



302 303 304a-b

Cyclization of simple alkenols has been studied by a number of researchers who have shown that both the olefin substitution pattern and reaction solvent can have a dramatic effect upon the regioselectivity of thallium (III) induced cyclization. Pentenols afford both tetrahydrofuran and tetrahydropyran products (although 5,5-dialkylated cases afford solely tetrahydrofurans), hexenols and heptenols afford mostly six and seven membered rings. Alkenol **305** affords solely **306a** or **306b** depending on the reaction conditions (**306a** 46%, **306b** 62%)[106] whereas **307a-b** afford high yields of **308a-b** in refluxing benzene (96% and 72% respectively).[107]

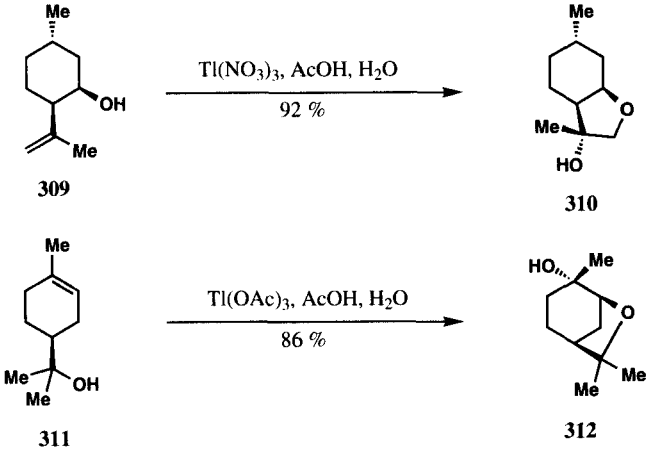


305 306a-b

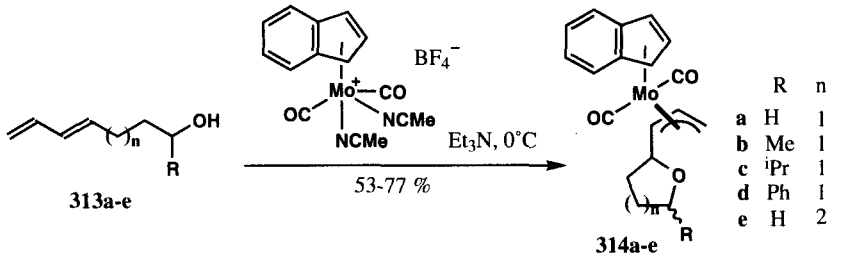
307a-b 308a-b

Thallium (III) salts have been utilized[108] in the cyclization of terpene alcohols in aqueous acetic acid. The high degree of stereocontrol in these reactions led to the suggestion that the cyclic thallium containing intermediate is broken down *via* a process involving neighboring group participation of the oxygen atom to afford a highly strained cationic intermediate that is quenched by a molecule of water. Thallium (III) nitrate induces cyclization much faster than thallium (III) acetate

although in both cases yields are similar. Neo-isopulegol **309** thus affords the fused bicyclic ether **310** whilst α-terpineol **311** affords the bridged bicycle **312** over 1 hr in high yield.

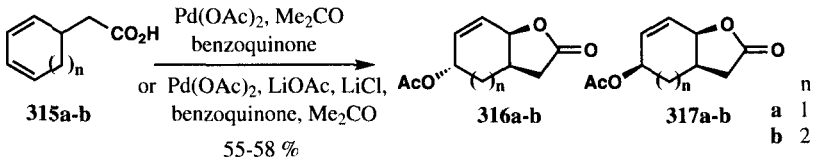


Molybdenum (II) salts effect the cyclization of unsaturated alcohols. Treatment of **313a-e** with an (η^5-indenyl)molybdenum dicarbonyl complex under basic conditions at 0° affords good to high yields of the corresponding metal complexed allylic cyclic ethers **314a-e** which can be subjected to further synthetic manipulation with external nucleophiles.[109]



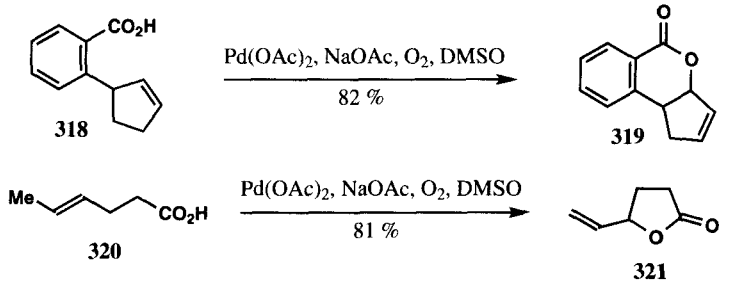
b) Carboxylic Acids

Bäckvall has shown that dienyl acids can be lactonized with catalytic quantities of palladium (II) acetate and that product stereochemistry can be easily controlled by the presence (or absence) of lithium salts.[27,110]



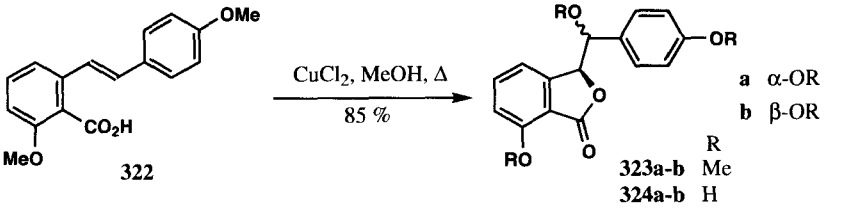
Treatment of acids **315a-b** with $Pd(OAc)_2$ (5 mol%) and a re-oxidant in acetone affords solely the *trans*-acetates **316a-b** (58% and 78% respectively). Addition of lithium acetate and catalytic lithium chloride to the reaction mixture (to suppress the facile *cis* migration of acetate anion from the

trans-palladium (II) center by replacement of acetate with chloride) affords mostly the all *cis*-isomers **317a-b** (57% and 55% respectively).

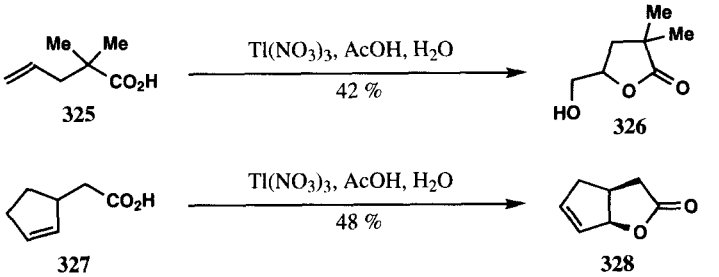


Larock's group have shown that similar cyclizations of mono-olefins can be induced with catalytic $Pd(OAc)_2$ in the presence of sodium acetate under an oxygen atmosphere [Pd(0) re-oxidant]. Thus benzoic acid **318** reacts at room temperature to afford lactone **319** (82%) and the acyclic acid **320** cyclizes to γ-lactone **321** in high yield (81%).[111]

Copper (II) salts have also been shown to be effective as lactonization catalysts for some olefinic acids. Thus acid **322** is cyclized by copper (II) chloride [or copper (II) bromide] in refluxing methanol to afford the lactones **323a-b** (70% and 15% yield).[112] The structural elucidation of hydramacrophyllols A and B (**324b** and **324a** respectively) was accomplished by this means.

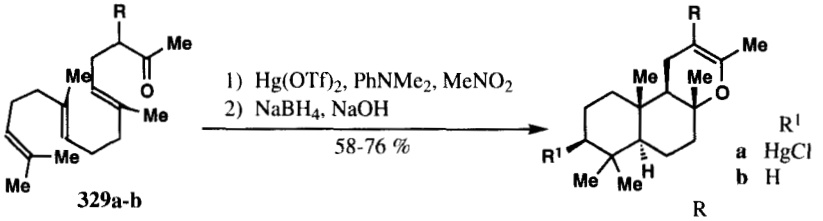


Thallium (III) salts (acetate, nitrate and trifluoroacetate) have also proved effective for similar lactonizations.[113] 4-Pentenoic acid **325** cyclizes at room temperature in aqueous acetic acid when treated with thallium (III) nitrate to afford the hydroxylated lactone **326** in moderate yield whilst acid **327** undergoes lactonization to afford **328** in similar yield *via* the corresponding hydrated lactone intermediate. Attempts to isolate this intermediate were unsuccessful.



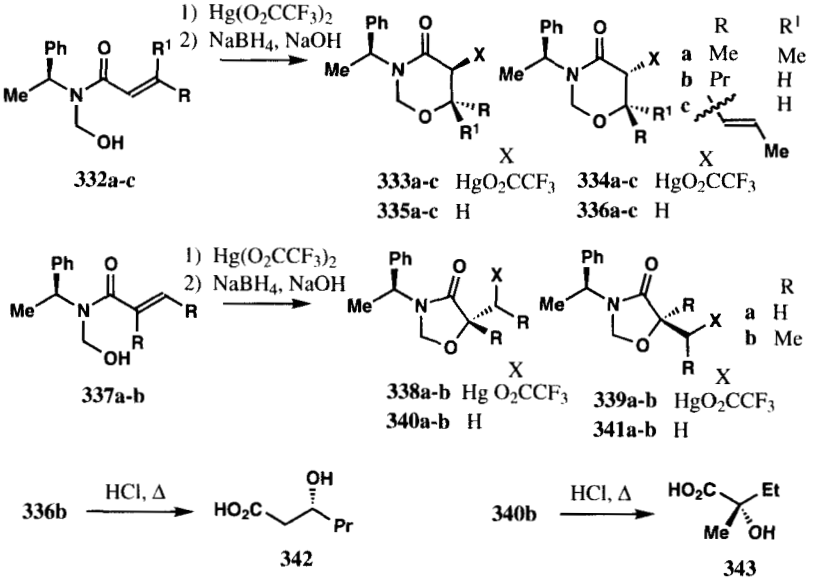
c) Ketones

Polyene cyclization (commonly promoted by Lewis acids and an important route to polycyclic terpenoids) has been reported utilizing the chemistry of mercuric ions. A series of linear trienones (and β-ketoesters) have been successfully cyclized.[114] For example, treatment of ketones **329a-b** with mercuric triflate and base affords organomercurials **330a** and **331a** which were reduced with borohydride/hydroxide to yield the tricyclic enol ethers **330b** and **331b** in 58% and 76% yield respectively.



d) Hemiamidals

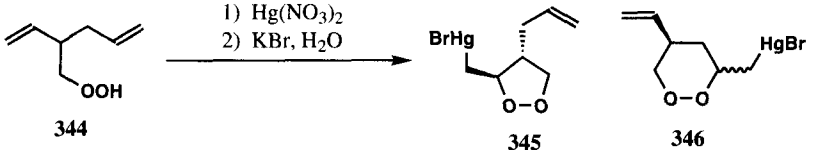
Mercuric trifluoroacetate induced cyclization of hemiamidals has been utilized for the synthesis of homochiral α- and β-hydroxy acids.[115] Homochiral amidals **332a-c** cyclized smoothly to afford diastereomeric organomercurials **333a-c** and **334a-c** which were reduced *in situ* to afford high yields of the chromatographically separable cyclized products **335a-c** and **336a-c** (70%, d.e. 0-33%).



Cyclization of hemiamidals **337a-b** occurred readily under identical conditions to afford the corresponding 5-membered ring organomercurials **338a-b** and **339a-b** which were reduced to both **340a-b** and **341a-b**. Acid catalyzed deprotection of **336b** at 100° gave the homochiral β-hydroxy acid **342**; similar treatment of **340b** afforded homochiral tertiary α-hydroxy acid **343**.

e) Hydroperoxides

Bloodworth has shown that a series of dienylhydroperoxides show a low degree of regioselectivity upon cyclization under ionic conditions in contrast to radical cyclizations which occur regiospecifically to afford 1,2-dioxolanes.[116,117] Mercuric induced cyclization of **344** followed by anionexchange afforded a mixture of 1,2-dioxolane **345** and isomeric 1,2-dioxanes **346** (in which the *trans*-3,5-dialkylated product predominated) with only a low degree of regioselectivity (1,2-dioxolane:1,2-dioxane *ca.* 2:1).

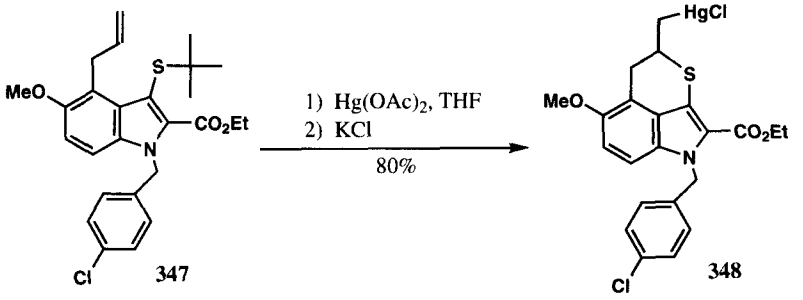


344 **345** **346**

3. Sulfur Nucleophiles

a) Sulfides

Their are few reports of the use of metal salts to catalyze the cyclization of sulfur containing alkenes because of the pronounced tendency of sulfur either to cause precipitation of or to poison heavy metal based catalysts. Nevertheless examples of the use of mercuric salts to induce cyclization in alkenylsulfides do exist; treatment of the *tert*-butyl sulfide **347** with mercuric acetate in tetrahydrofuran results in the smooth cyclization (with loss of 2-methylpropene) to afford the novel tricycle **348** in high yield (80%).[103]



347 **348**

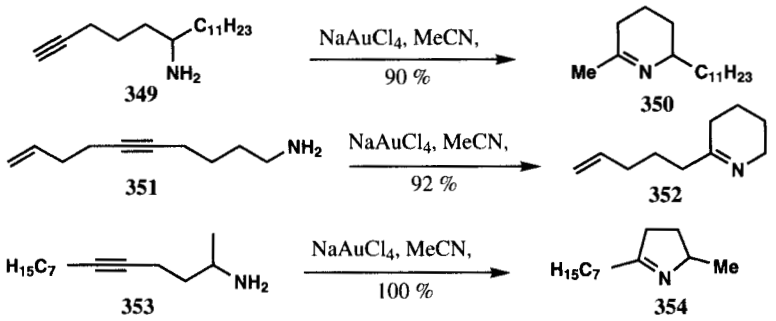
II. CYCLIZATION ONTO ALKYNES

1. Nitrogen Nucleophiles

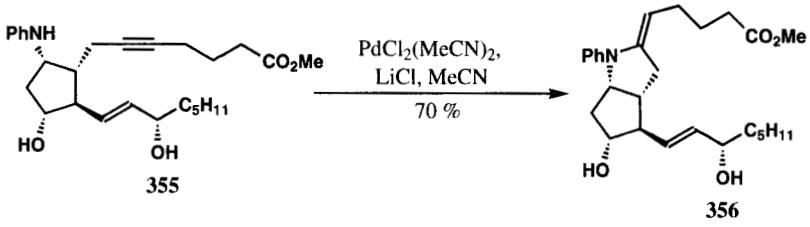
a) Amines

There are several recorded examples of the use of metal salts to induce the cyclization of aminoalkynes. In the majority of cases Pd(II) is the active species, however in certain cases more exotic catalytic systems have been documented. One of these involves the use of gold (III) salts to cyclize aminoalkynes to afford naturally occurring tetrahydropyridines and dihydro-3*H*-pyrroles.[118] Thus treatment of amines **349**, **351** and **353** with catalytic $NaAuCl_4$ in acetonitrile at 80° rapidly (1 hr)

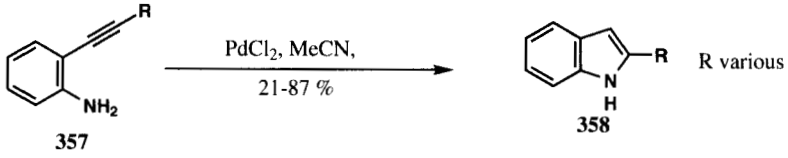
afforded excellent yields (90-100%) of the cyclized products **350**, **352** and **354** (both **350** and **352** are constituents of the venoms of various ant species).



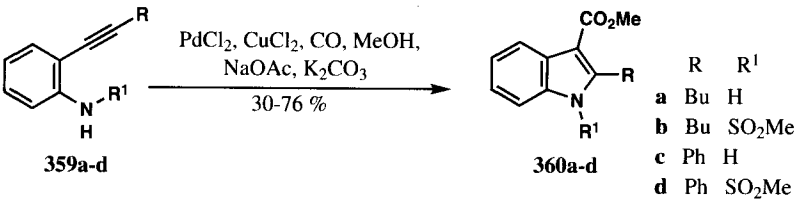
$PdCl_2(MeCN)_2$ Can also be used to catalyze the same transformations although reaction times are longer (10-20 hrs) and yields were not usually so high (63-75%).[119] A similar cyclization catalyzed by $PdCl_2(MeCN)_2$ has been elegantly employed in the synthesis of prostanoids in the I series.[120] Cyclization of **355** in acetonitrile afforded the exocyclic olefin **356** (6,9α-anilino-PGI_2) in good yield (70%).



Italian workers have shown that 2-substituted indoles can be synthesized under similar conditions by the palladium (II) catalyzed cyclization of the appropriately substituted 2-alkynylanilines.[121,122] Thus treatment of anilines **357** with $PdCl_2$ (5 mol%) in acetonitrile at 80° affords the corresponding indoles **358** in low to good yield over three to 6 hrs.

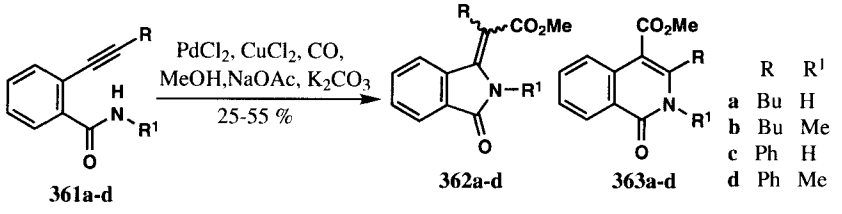


Cyclization with concomitant carbomethoxylation can also be achieved. Thus amines (and sulfonamides) **359a-d** were readily transformed into 2,3-substituted indoles **360a-d** at room temperature in methanol under a carbon monoxide atmosphere, yields being highest in the case of the two *N*-protected products **360b** and **360d**. Addition of excess copper (II) chloride was necessary as a reoxidant for the Pd(0)→Pd(II) step.[123,124]

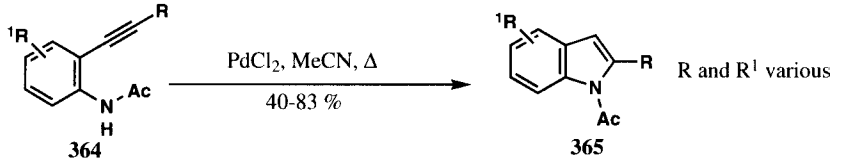


b) Amides, Carbamates And Sulfonamides

Palladium (II) salts have been extensively utilized to induce the cyclization of *N*-protected alkynylamines. Sakamoto has shown that $PdCl_2$ catalyses the cyclization-carbomethoxylation of 2-alkynylbenzamides **361a-d** regiospecifically *via* the 5-*exo*-dig mode to afford the γ-lactams **362a-d** in low to moderate yield (25-55%), no δ-lactam products **363a-d** derived from the alternative 6-*endo*-dig cyclization mode could be isolated.[124]

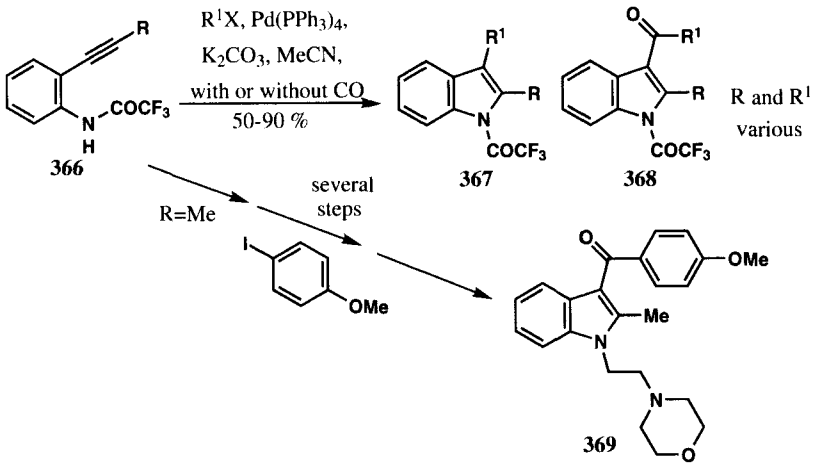


Stille[125] has shown that acetanilides can be efficiently and smoothly converted into indoles. Thus a wide range of 2-alkynylacetanilides **364** upon treatment with $PdCl_2$ in refluxing acetonitrile are converted into the corresponding 2-substituted indoles **365** (40-83%, 1-4 hrs). These processes occur without the need for an added excess of copper (II) chloride as a re-oxidant. Yields are highest in the cases where the R substituent on the alkynyl terminus is aliphatic in nature.



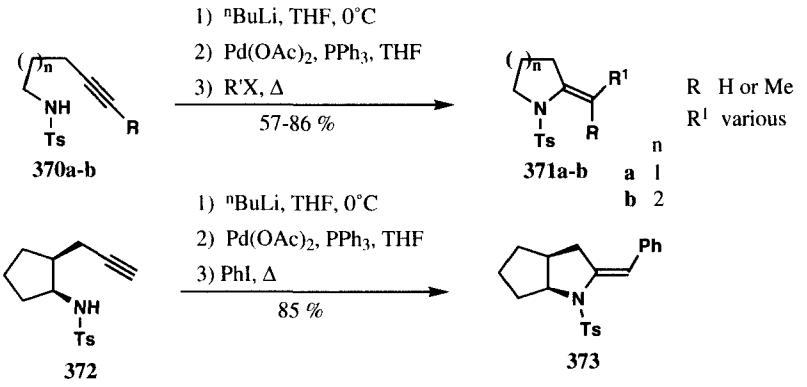
Cacchi's group have shown that these ideas can be extended to allow the preparation of 2,3-disubstituted indoles **367** and **368**;[126,127] their approach relies upon the use of a Pd(0) catalyst with an aryl halide or alkyl triflate to generate and alkyl palladium (II) halide or triflate *in situ* prior to cyclization. Additionally the use of a carbon monoxide atmosphere allows for the synthesis of acylated products.

Thus treatment of **366** with $Pd(PPh_3)_4$, aryl halide (at 80°) or alkyl triflate (at 20°) and potassium carbonate as base in acetonitrile (1-22 hrs) afforded the 2,3-dialkylated products **367**;[126] addition of a carbon monoxide atmosphere afforded the corresponding 3-acylated products **368** in similar



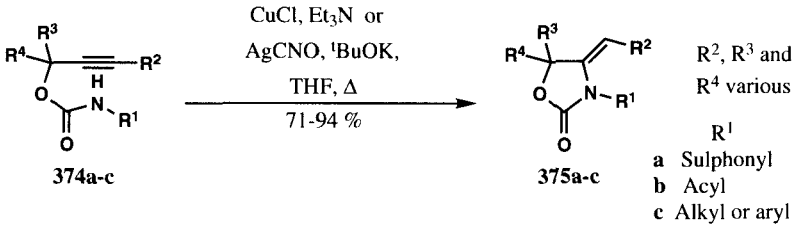
yield.[127] This latter work has allowed for a facile and high yielding synthesis of pravadoline **369** (a drug that shows a post-operative analgesic effect).

A similar strategy using vinyl or aryl halide and catalytic amounts of Pd(0) has been reported for the synthesis of several 2-alkylidene pyrrolidines and piperidines from alkynylsulfonamides.[128] Pre-treatment of the toluene-4-sulfonamides **370a-b** in tetrahydrofuran with n-butyl lithium (to generate the more nucleophilic nitrogen anion) followed by the addition of $Pd(OAc)_2$ and PPh_3 (5 and 10 mol% respectively) and excess or aryl of vinyl halide (R^1X) at reflux (8 hrs) leads to the formation of 2-alkylidenepyrrolidines and piperidines **371a-b** in good to high yield. Similarly the cyclopentyl derived analogue **372** afforded the 2-azabicyclo[3.3.0]octane derivative **373** in high yield upon treatment with iodobenzene under identical conditions.



Both copper (I) and silver (I) salts have also been utilized for cyclizations involving *N*-protected akynylcarbamates;[129] the choice of catalyst required appears to depend upon the protecting group on nitrogen. Thus *N*-sulfonyl cases **374a** require the use of copper (I) chloride and triethylamine (10 mol% of each) whereas *N*-acyl examples **374b** work best with silver isocyanate (13 mol%)

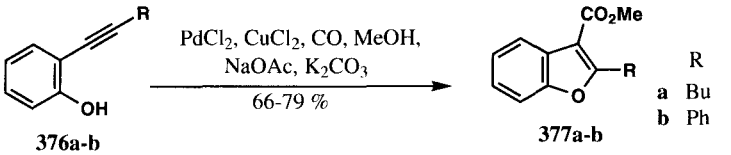
and *tert*-butoxide as base (20 mol%), both classes **374a-b** failing to cyclize in the absence of catalyst although the non-acylated carbamate **374c** cyclized to **375c** under basic conditions at room temperature (91-99%).



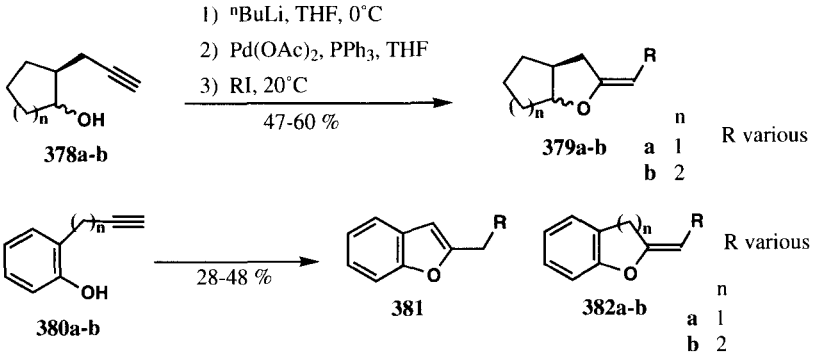
2. Oxygen Nucleophiles

a) Alcohols and Phenols

Yamanaka and Sakamoto have shown that methodology suitable for the cyclization of 2-alkynylanilines is also applicable to 2-alkynylphenols,[123,124] thus upon treatment with Pd(II), Cu(II), CO and methanol **376a-b** afford high yields of the 2,3-disubstituted benzofurans **377a-b**.

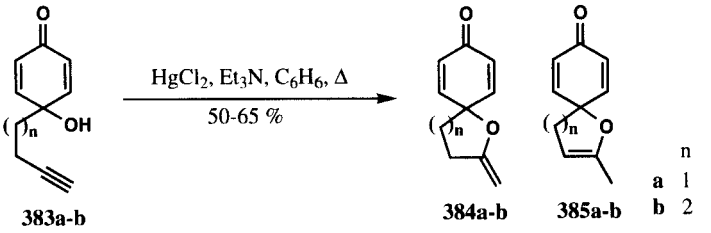


Similarly the Pd(II) based technology of Luo for the cyclization of alkynylamines[128] has been extended to the corresponding alcohols.[130] Treatment of **378a-b** under the same conditions using Pd(0) and various aryl or vinyl iodides as a source of a Pd(II) catalyst results in the formation of the 5,5- and 5,6-bicycles **379a-b** in moderate yield. Likewise, treatment of phenols **380a-b** under identical conditions afforded benzofurans **381** and/or their allylic isomers **382a-b** in low to moderate yield.

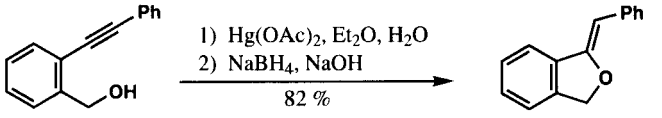


Mercuric salts cyclize alkynols and a method for the synthesis of spiro-oxabicyclic dienones from quinone derived precursors has been developed. Treatment of **383a-b** with mercuric chloride and triethylamine in boiling benzene results in either a regiospecific *exo*-dig cyclization to afford **384a** and **385a** (37% and 13% respectively) and **384b** (65%); in the latter case involving the formation of a

six membered ring none of the isomeric endocyclic olefin **385b** could be isolated. Subsequent photochemical isomerization of **384a-b** and **385a** afforded spiro bis-ketones.[131] Likewise, treatment of the benzylic alcohol **386** with mercuric acetate followed by *in situ* reduction of the resulting organomercurial species afforded **387** in 82% yield.[132]

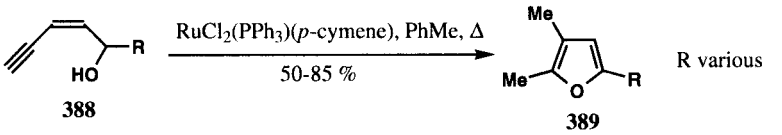


383a-b **384a-b** **385a-b**



386 **387**

Examples of cyclization of alkynols by ruthenium (II) species are also known. In particular, $RuCl_2(PPh_3)$(*p*-cymene) has been shown to be an extremely effective catalyst for such processes allowing the synthesis of 2,3,5-trisubstituted furans.[133] Thus under the influence of $RuCl_2(PPh_3)$(*p*-cymene) (1 mol%) in boiling toluene over 1-2 hrs **388** is converted to the substituted furans **389** in good to high yield.

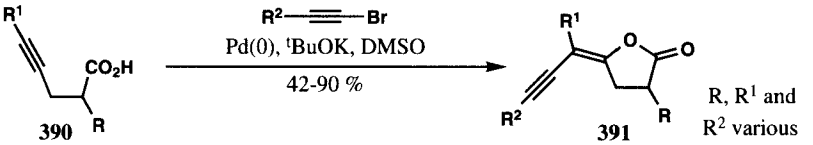


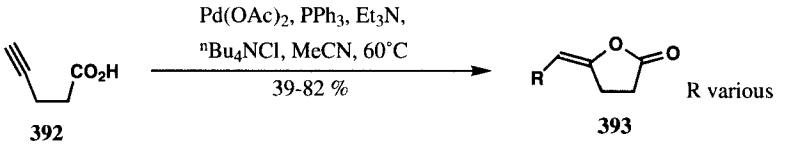
388 **389**

b) Carboxylic Acids

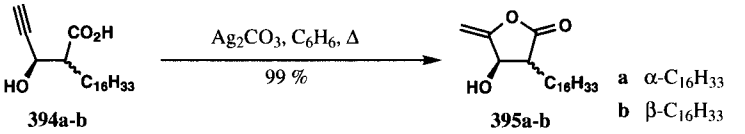
γ-Lactones containing exocyclic double bonds are compact structures that show, in many cases, interesting biological properties including antibiotic, ichthyotoxic and insecticidal activities. Palladium (0) catalysts have been cleverly utilized to cyclize alkynoic acids to prepare these highly sought after compounds. Thus acids **390** and **392** undergo rapid and regiospecific cyclization in the presence of an acetylenic, aryl or vinylpalladium (II) species (generated *in situ* from an acetylenic, aryl or vinyl iodide or triflate and a Pd(0) source) to afford the γ-lactones **391** and **393** in good to excellent yield.[134,135] The nature of the phosphine utilized to prepare the Pd(0) species is crucial to the outcome of the reaction and the acid must first be derivatized as its potassium salt; best results were obtained with tri(2-furyl)phosphine.[134]

Silver salts are exceptionally efficient catalysts with which to induce the cyclization of such alkynols.[136] French workers utilized this methodology for the first synthesis of the natural product



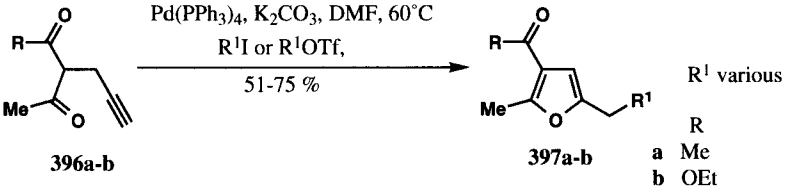


395b together with its unnatural stereoisomer **395a**. Treating both *trans*- **394a** and *cis*-β-hydroxy acids **394b** with silver carbonate (10 mol%) in boiling benzene for ten minutes generated the isomeric γ-lactones **395a** and **395b** virtually quantitatively.

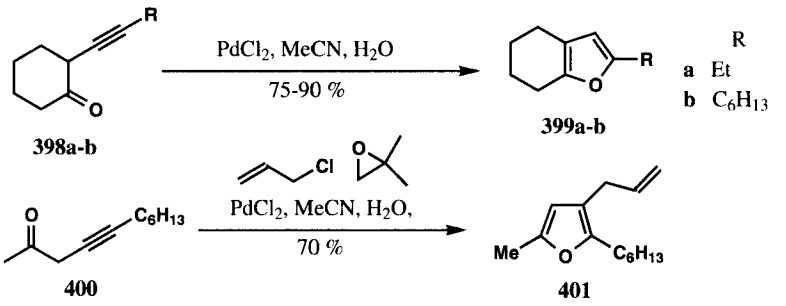


c) Ketones

Palladium (II) salts have been shown to be active catalysts for the cyclization of alkynones. Cacchi and Larock have shown that acetylenes **396a-b** can be readily cyclized to 2,3,5-trisubstituted furans **397a-b** upon treatment with potassium carbonate and an aryl or vinyl halide or triflate.[137] Catalytic quantities of a preformed Pd(0) catalyst were used to generate the necessary aryl or vinylpalladium (II) species *in situ*. Thus in *N,N*-dimethylformamide at 60° the required furan **397a-b** is formed over 2-7 hrs in good yield (51-75%).



A similar strategy has been employed by Utimoto who has shown that catalytic quantities of $PdCl_2$ can be used to cyclize similar alkynones.[69,138] Treatment of **398a-b** with $PdCl_2$ (5 mol%) in boiling aqueous acetonitrile over 2 hrs afforded the 4,5,6,7-tetrahydro-benzofurans **399a-b** in high yield. In this case no complex mixture of additives were required to complete the catalytic cycle, the intermediate vinylpalladium intermediate being destroyed by protodemetallation. Addition of an allyl halide and proton scavenger allowed the synthesis of specifically substituted products (e.g. **400→401**; 70%) by direct interception of the vinylpalladium intermediate.

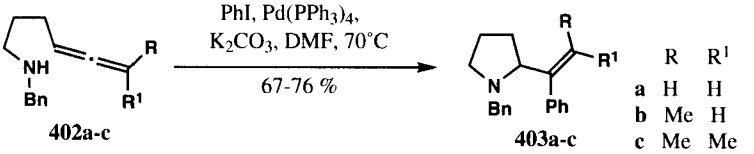


III. CYCLIZATION ONTO ALLENES

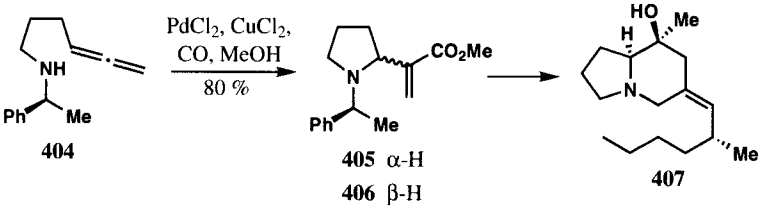
1. Nitrogen Nucleophiles

a) Amines

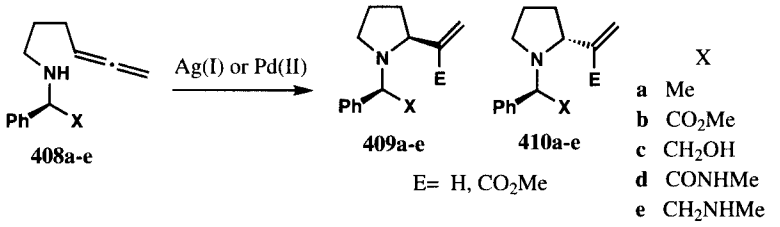
Gallagher has extensively utilized both palladium (II) and silver (I) salts to induce the cyclization of allenylamines.[139-143] Palladium (II) sources have been used both to cyclize and alkylate [palladium (II) generated *in situ* from an aryl halide or triflate and $Pd(PPh_3)_4$] and to cyclize and carbonylate (using $PdCl_2$ and a carbon monoxide atmosphere). Thus treatment of amines **402a-c** (and several carbamate and sulfonamide derivatives) with Pd(0) and iodobenzene in hot DMF (1-3 hrs) afforded the piperidines **403a-c** in high yield.[139]



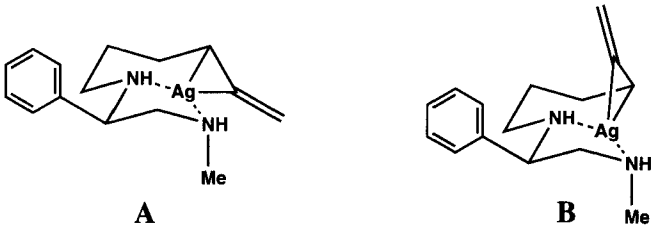
Pd(II) Catalyzed cyclization/carbonylation technology has been cleverly used in a stereoselective synthesis of pumiliotoxin 251D **407**, (an indolizidine alkaloid isolated from "poison-arrow" frogs). Cyclization/carbonylation of homochiral **404** afforded a mixture of both **405** and **406** (80%, 1:1 ratio); further manipulation of **405** (8 steps) afforded dextrorotatory **407** in good yield.[140]



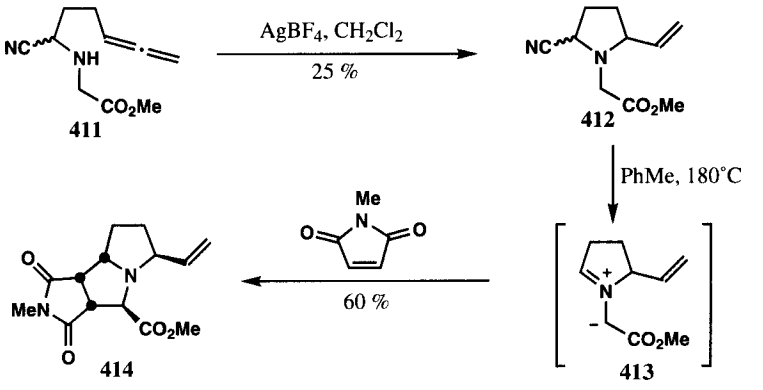
A more extensive study into the use of chiral substituents on nitrogen to control cyclization stereochemistry has shown that Pd(II) catalyzed processes can be performed with moderate levels of diasteromeric excess (up to 43% d.e.) and that silver salts can offer much higher degrees of stereocontrol (**408a-e**→**409a-e** and **410a-e**; d.e. up to 81%).[141,142]



For silver (I), stereoselectivity mirrors the ability of the coordinating side-chain X (**a-e**) to complex the electrophile, thus side-chains **d** (CONHMe) and **e** (CH_2NHMe) were preferred. Pd(II) Mediated cyclizations in general afford very low degrees of stereoselection. The authors suggest that the factors controlling the stereoselectivity are complex and that the ability of the side-chain to complex to the metal ion cannot alone explain their results since the nucleophilic amino group must attack the π-complex *anti-* to the silver ion in complexes such as **A** and **B** and thus bimolecular complexes involving two molecules of the aminoallene may be implicated to explain the observed diastereoselectivities.



The extension of these ideas to stoichiometric catalysis by mercuric salts was suggested[134] and briefly examined[142] but results were disappointing in terms of stereoselectivity (**408b→409b** and **410b**; E= HgOAc, 1:1 mixture).

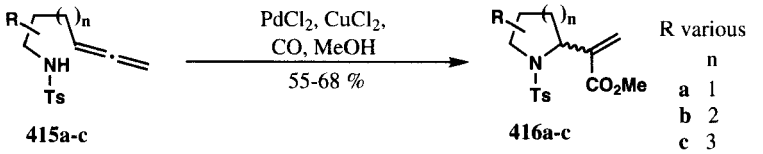


Silver mediated cyclization of allenylamines have been successfully coupled with azomethine ylide generation and 1,3-dipolar cycloaddition to allow the synthesis of more complex heterocycles.[143]

Thus treatment of amino ester **411** with $AgBF_4$ resulted in the low yielding cyclization to **412**. Heating **412** in toluene (sealed tube) in the presence of *N*-methylmaleimide resulted in the thermal elimination of hydrogen cyanide to yield the intermediate azomethine ylide **413** which underwent 1,3-dipolar cycloaddition with the maleimide derived dipolarophile with complete stereoselectivity, a single *endo*-isomer **414** being isolated (60%).

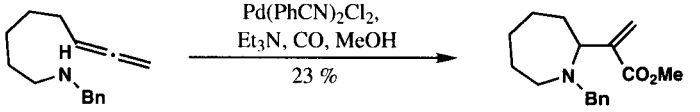
b) Carbamates and Sulfonamides

Suitably *N*-protected allenylamines can be cyclized using Pd(II) catalysis.[144-146] Treatment of several sulfonamides **415a-b** with a Pd(II)/Cu(II) system in methanol under carbon monoxide allowed the synthesis of a series of pyrrolidines **416a** and piperidines **416b** at room temperature (2-12 hrs), the intermediate alkylpalladium (II) species undergoing rapid carbonylation and the resulting eliminated Pd(0) species (after addition of methanol) being re-oxidized by the excess of copper (II) chloride. All successful reactions were regiospecific and involved cyclization by the kinetically preferred n-*exo*-trig mode (n=5 or 6).



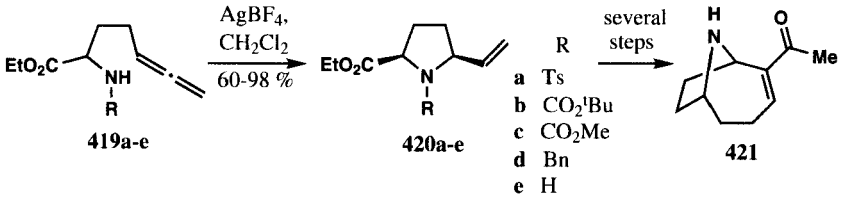
415a-c **416a-c**

Extension of these ideas to generate 7-membered rings (**415c→416c**) failed except in a single case involving an *N*-benzyl precursor **417** that afforded a low yield of **418** (23%).[144]



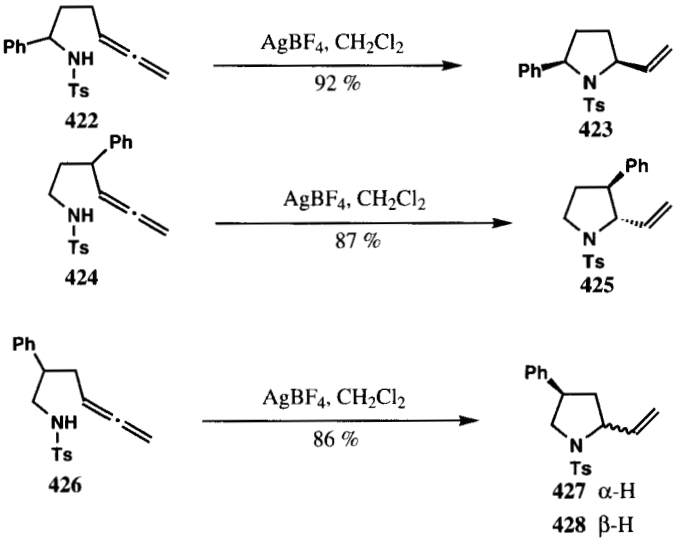
417 **418**

Gallagher has also utilized silver salts to cyclize sulfonamides as well as carbamates and has exploited this in a synthesis of (±)-anatoxin-a **421**.[145] Silver mediated cyclization of allenic amine derivatives **419a-d** occurred in excellent yield (83-98%) at room temperature to afford solely the 2,5-*cis*-disubstituted products **420a-d**. Interestingly the free primary amine **419e** afforded a 1:1 mixture of **420e** and the corresponding *trans*-isomer in somewhat lower yield (60%). Sulfonamide **420a** was subsequently converted into racemic anatoxin-a **421** over several steps.



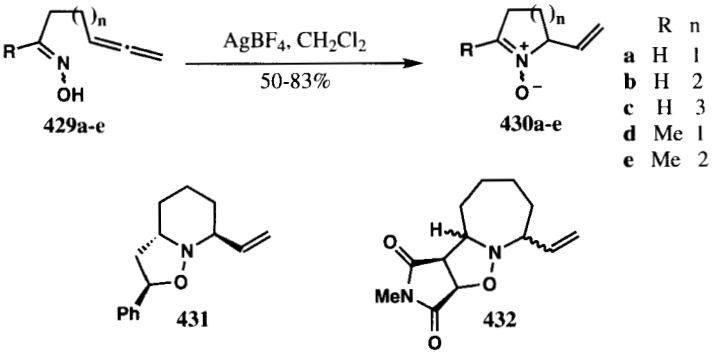
419a-e **420a-e** **421**

A later paper by Gallagher showed that the substitution pattern in allenic sulfonamides **422**, **424** and **426** could be used to control the *cis/trans* selectivity upon silver promoted cyclization.[146] 2,5-Disubstituted products favored *cis*-stereochemistry **423** whereas the 2,3-disubstitution pattern afforded *trans*-isomers **425**. 2,4-Disubstitution stereochemistry proved impossible to control under the reaction conditions, thus **426** afforded a 1:1 mixture of **427** and **428**.



c) Oximes

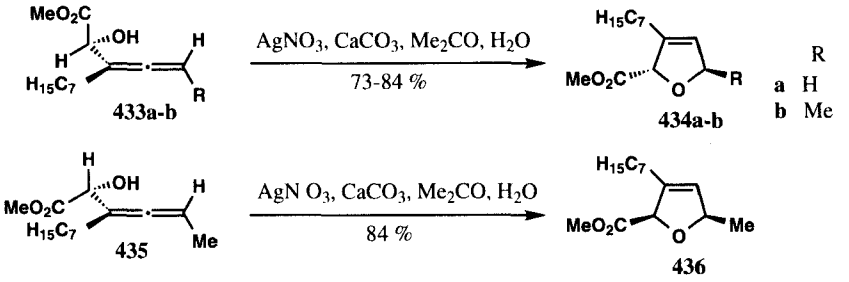
Silver tetrafluoroborate has also proved useful as a catalyst with which to cyclize allenyl oximes to cyclic nitrones of varying ring size that have been subsequently trapped in 1,3-dipolar cycloaddition reactions to afford a wide range of heterocycles.[147,148] Thus when oximes **429a-e** were treated with $AgBF_4$ at 20° they afford good yields of nitrones **430a-e**. In several cases these were isolated but more often than not, due to their inherent instability, they were reacted *in situ* with several added dipolarophiles (with varying electronic character) to afford the corresponding cycloadducts. For example, **430b** when reacted with styrene afforded a high yield of **431** (83%),[147] whereas **430b** and *N*-methylmaleimide afforded the 7,5,5-linearly fused tricyclic system **432** as a 2:2:1 mixture of diastereomers (60% yield).[148]



2. Oxygen Nucleophiles

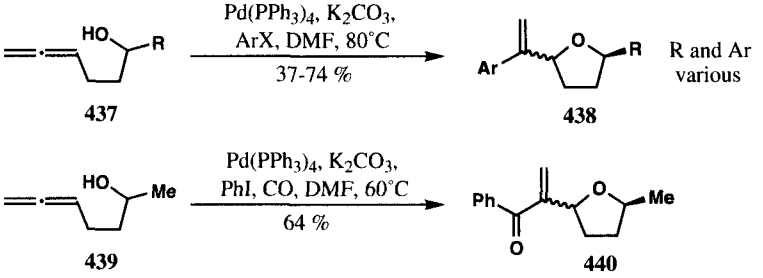
a) Alcohols

Marshall's group have shown that allenic alcohols can be regiospecifically cyclized using silver nitrate as a catalyst to afford 2,5-dihydrofurans in high yield.[149] The allenols **433a-b** and **435** were treated with Ag(I) under basic conditions at room temperature in aqueous acetone to afford the



trans- and *cis*-isomeric dihydrofurans **434a-b** and **436** respectively (73-84%), all reactions proceeding regio- and stereo-specifically.

This idea has been extended by Walkup who has shown that palladium (II) catalysts (generated *in situ* from a pre-formed Pd(0) species and an aryl halide) can also be used in these reactions and allow the formation of specifically arylated products.[150] Thus treatment of allenic alcohols **437** with Pd(0) and an aryl halide and potassium carbonate in hot *N,N*-dimethylformamide afforded tetrahydrofurans **438** in moderate to good yield (37-74%); stereoselectivity was in general quite poor with *cis*:*trans* ratios for the isolated products **438** being around 40:60 in favor of the *trans*-product.

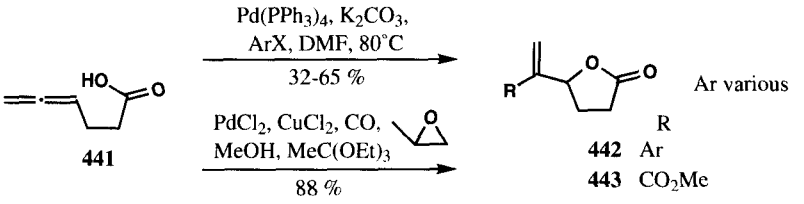


This approach also allows for the formation of specifically acylated products. Thus treatment of alcohol **439** with iodobenzene in hot *N,N*-dimethylformamide under a carbon monoxide atmosphere results in carbonylation of the intermediate cyclic vinylpalladium (II) species to afford the α,β-unsaturated ketone **440** in good yield (64%).

b) Carboxylic Acids

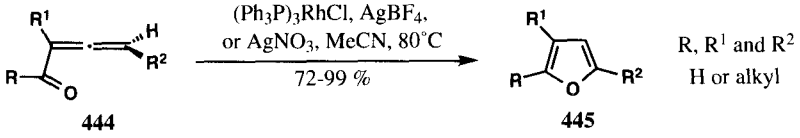
Walkup has extended his approach for the cyclization of allenic alcohols to the corresponding carboxylic acids.[150,151] Allenic acid **441** can be cyclized under identical conditions to those used for the corresponding alcohols to afford the γ-lactones **442** in moderate to good yield. Additionally by

using a Pd(II)/Cu(II) catalytic system under a carbon monoxide atmosphere in methanol results in cyclization/methoxycarbonylation to give acrylyl substituted lactones **443**.

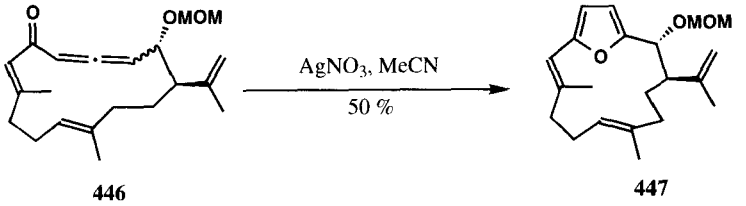


c) Aldehydes and Ketones

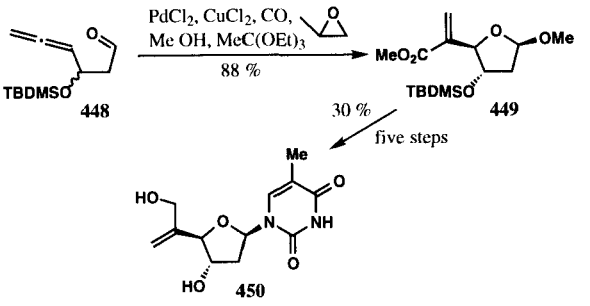
Several papers[152-154] have described the utility of metal ion induced cyclization of allenals and allenones, Rh(I),[152] Ag(I)[152,153] and Pd(II) species[154] have all proved to be applicable to such transformations. Aldehydes[152] and ketones **444**[152,153] have been cyclized using catalytic amounts of Wilkinson's catalyst, silver tetrafluoroborate or silver nitrate in hot acetonitrile. Reactions proceed rapidly (1 hr) and yields of the furans **445** are excellent (72-99%), silver tetrafluoroborate proving to be the most effective catalyst in terms of yield and reaction time.



These processes have been shown to be applicable to the synthesis of 2,5-bridged furanocembranoids.[152] Thus macrocycle **446** underwent silver catalyzed furan formation to afford the bicyclic 2,5-furanocembranoid skeleton **447** in good yield.

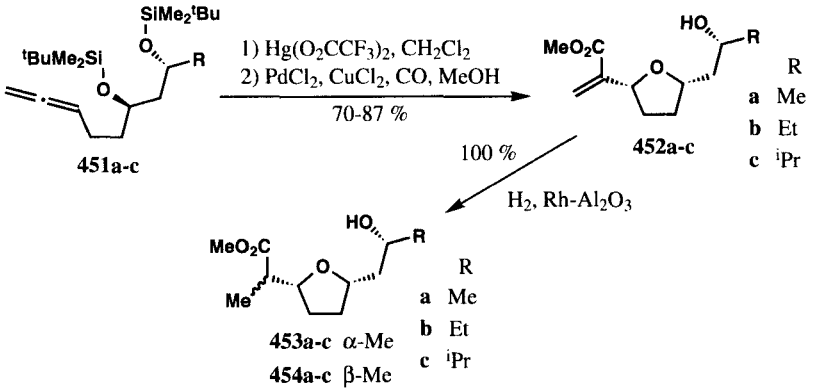


Walkup and co-workers have shown that allenals can be cyclized with Pd(II)/Cu(II) under a carbon monoxide atmosphere to give methyl furanosides in high yield.[151,154] Thus allenal **448** undergoes stereospecific cyclization/methoxycarbonylation in the presence of scavengers for acid (propylene oxide) and water (triethyl orthoacetate) followed by onium ion quenching by methanol to afford solely the 2'-deoxy-β-methyl furanoside **449** in excellent yield. Similar reactions of the corresponding allenones afforded complex mixtures of products; this was felt to be due to their much slower rate of cyclization;[151] in a subsequent paper[154] methyl β-furanoside **449** was utilized in a synthesis of a nucleoside analogue of D-2'-deoxythymidine bearing a difunctional side-chain **450**.



d) Silyl Ethers

A route involving mercury (II)/palladium (II) induced cyclization of allenes bearing silyl ethers has been cleverly incorporated by Walkup's group into syntheses of the methyl esters of (±)-nonactic **453a**, (±)-homononactic **453b** and (±)-bishomononactic acids **453c** (the subunits of the wide range of nactin antibiotics).[155] These processes [involving oxymercuration followed by transmetallation with palladium (II)] proceed smoothly at room temperature to afford high yields (70-87%) of the 2,5-*cis*-disubstituted products. Silyl ethers **451a-c** were cyclized with mercuric trifluoroacetate to afford an organomercurial intermediate which underwent transmetallation/methoxycarbonylation to afford the cyclic alcohols **452a-c**. Hydrogenation afforded the required esters **453a-c** together with their epimers **454a-c**.



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