Saturated oxygen heterocycles

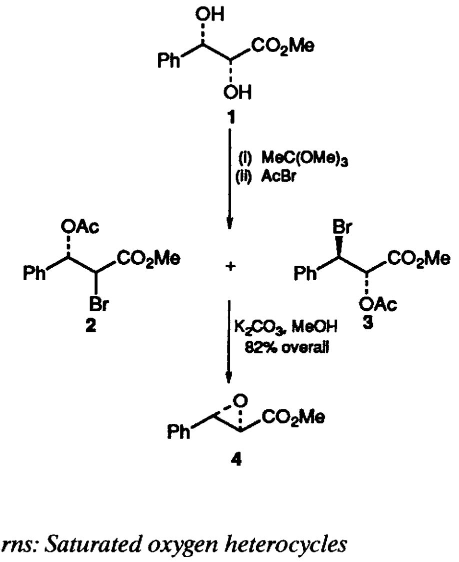
CHRISTOPHER J. BURNS

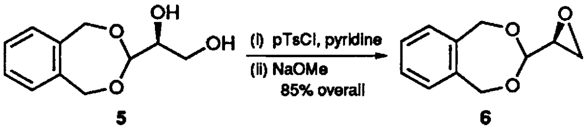
Pfizer Central Research, Sandwich, Kent CT13 9NJ

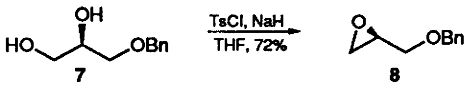
Reviewing the literature published between January 1992 and March 1993

1 Three-membered rings

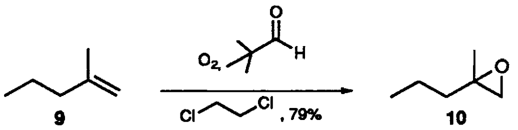
Significant progress has been made in the synthesis of chiral epoxides from unfunctionalized olefins. Kolb and Sharpless have shown that chiral vicinal diols, prepared by Sharpless' asymmetric dihydroxylation protocol,[1] can be efficiently converted into chiral epoxides *via* a three-step one-pot procedure.[2] Thus, the diol **1** yields the epoxide **4** *via* the intermediate acetoxy bromides **2** and **3** in 83% overall yield. In related work the protected chiral glyceraldehyde epoxide **6** was prepared from the chiral diol **5** by mono-tosylation and subsequent base-promoted cyclization.[3] An analogous one-pot procedure has been reported by Rao and co-workers wherein treatment of the diol **7** with a mixture of tosyl chloride and sodium hydride affords the enantiomerically pure epoxide **8** in 72% yield.[4]

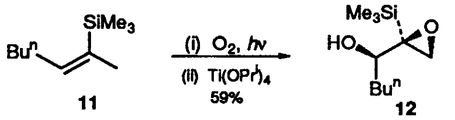




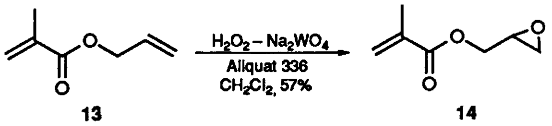


Of numerous reports detailing the use of molecular oxygen as oxidant in epoxidations, the work of the group of Kaneda is particularly noteworthy.[5] They have shown that a combination of molecular oxygen and an aldehyde, particularly pivalaldehyde, efficiently epoxidizes olefins, as exemplified by the formation of the epoxide **10** from 2-methyl-1-pentene **9**. Molecular oxygen has also been used in the synthesis of epoxy-alcohols directly from vinyl silanes.[6] Thus, photo-oxygenation of the vinyl silane **11** followed by treatment with titanium tetra-isopropoxide gave the product **12** in 59% overall yield.

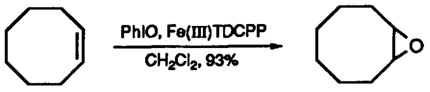




Caubere and his co-workers have shown that a combination of hydrogen peroxide and sodium tungstate under phase transfer conditions is the method of choice for the epoxidation of olefins containing the sensitive methacrylate moiety.[7] Using this method the epoxide **14**, for example, could be generated from allyl methacrylate **13** in good yield.



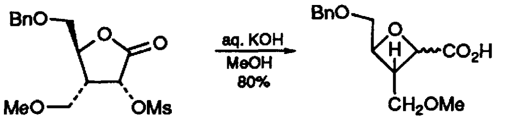
Cooke and Lindsay Smith have reported the use of polymer bound iron (III) tetra(2,6-dichlorophenyl)porphyrin ($\mathrm{Fe^{III}}$ TDCPP) as an efficient catalyst in the epoxidation of cyclooctene **15**.[8] The procedure uses iodosylbenzene as the oxidant, with a catalyst turnover of 7900, giving the epoxide **16**.



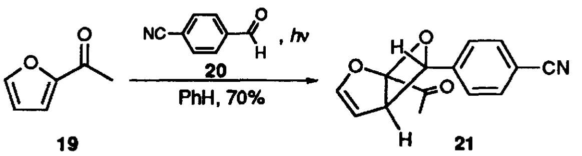
15 **16**

2 Four-membered rings

Saksena *et al.* have reported a much improved route to substituted oxetane-2-carboxylic acids.[9] Thus, they have demonstrated that ring contraction of a furanone bearing a mesylate at the three position can be affected in aqueous base, as shown in the preparation of the oxetane **18** from the glucose-derived lactone **17**. The [2 + 2] photocycloaddition between a 2-substituted furan and an aldehyde generally gives a mixture of regioisomeric bicyclic oxetanes. Carless and Halfhide have now shown, however, that 2-acetylfuran **19** undergoes highly regioselective [2 + 2] cycloadditions, with the reactions occurring on the more substituted furan double bond, as exemplified by the reaction of **19** with *p*-cyanobenzaldehyde **20** leading to the bicycle **21**.[10]

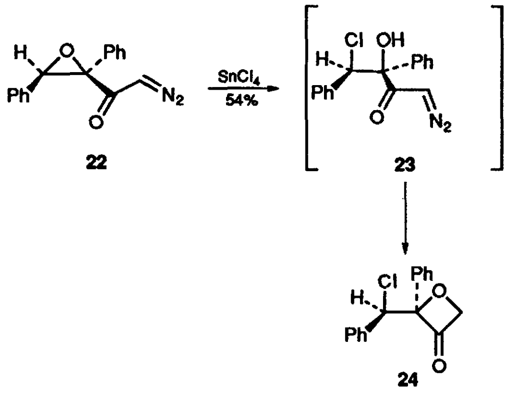


17 **18**



19 **21**

α,β-Epoxy diazomethylketones have been shown to yield oxetanones on treatment with tin tetrachloride.[11] The reaction proceeds through a chlorohydrin intermediate **23** (which in certain instances can be isolated) as shown in the transformation of **22** to the product **24**.



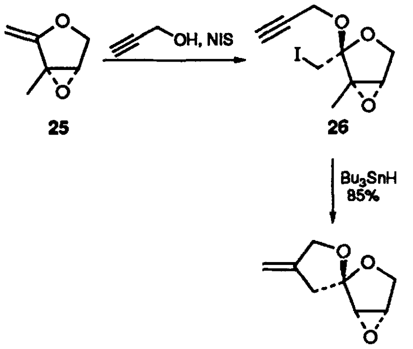
22 **23** **24**

3 Five-membered rings

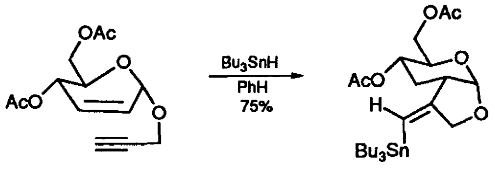
3.1 Tetrahydrofurans

Progress in the synthesis of natural and unnatural furanosides has been partly covered in a review (317 references) entitled 'AIDS-Driven Nucleoside Chemistry',[12] while the applications of palladium (II) catalysis in tetrahydrofuran synthesis has been reviewed (54 references) by Hosokawa and Murahashi.[13]

The use of free-radical chemistry to gain access to substituted tetrahydrofurans continues to be an active area of research. For example, Dalla and Pale, have reported the first synthesis of spiroketals using a free-radical approach, wherein a 2-methylene tetrahydrofuran **25** is converted in two steps *via* the iodide **26** into the spirocycle **27** in good yield.[14] The addition of tributyltin hydride to carbohydrate derived propargyl ethers has been shown to be an efficient route into fused bicyclic ketals.[15] The conversion of **28** into **29** is representative, though in some instances a mixture of *E* and *Z* isomers of the vinyl stannane product results.

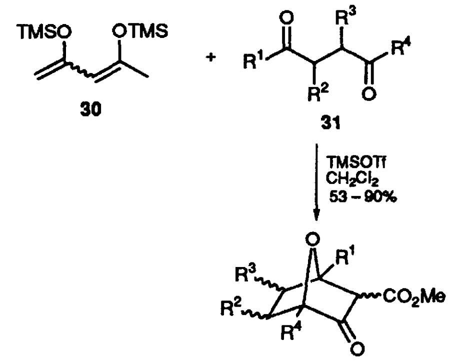


25 **26** **27**



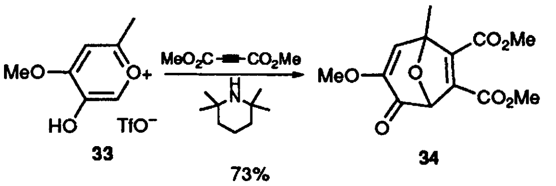
28 **29**

A highly regioselective [3 + 4] annulation reaction for the synthesis of bridged cyclic ethers has been reported by Molander and Cameron.[16] Thus, the bis(trimethylsilyl) enol ether **30** adds to the diketones **31** under Lewis acid catalysis to give the product ethers **32** in fair to excellent yields.

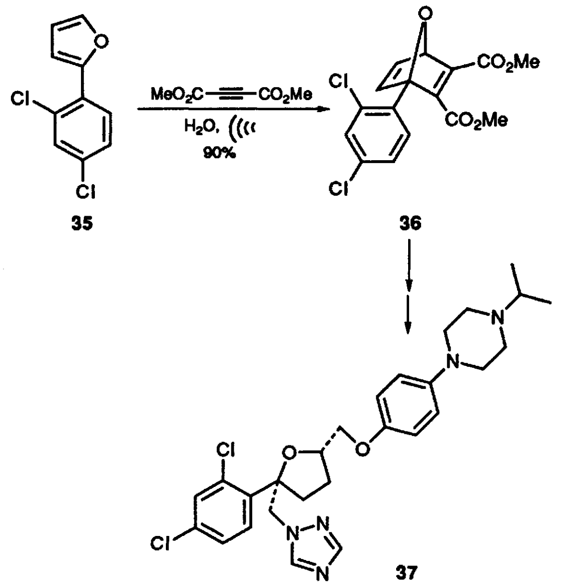


30 **31** **32**

Wender *et al.* have extended their work on [5 + 2] cycloaddition reactions and shown that the pyrylium salt **33** reacts with dimethyl acetylenedicarboxylate, in the presence of base, to provide the cyclic ether **34**.[17] The aqueous Diels–Alder reaction between the arylfuran **35** and dimethyl acetylenedicarboxylate offers a highly efficient route to the cyclic ether **36** which has then been converted in several steps into the unusual antifungal agent **37**.[18]

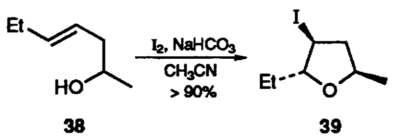


33 **34**

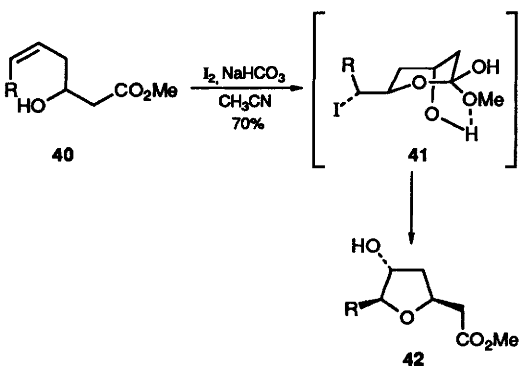


35 **36** **37**

Iodoetherifications and related processes continue to offer efficient routes to tetrahydrofuran derivatives. Thus, Knight and his group have shown that *E*-homoallylic alcohols readily cyclize to *trans*-iodotetrahydrofurans in anhydrous acetonitrile, as exemplified by the formation of **39** from **38**; the corresponding *Z*-homoallylic alcohols furnish the *cis* products.[19] Interestingly, the *Z*-hydroxyalkenoates **40** cyclize under identical conditions to give the hydroxytetrahydrofurans **42**, presumably *via* the intermediate orthoester **41**.[20]

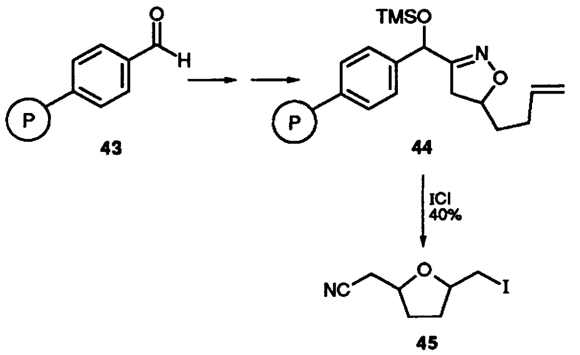


38 **39**

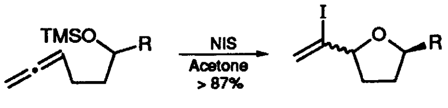


40 **41** **42**

Beebe *et al.* have shown that the polymer-bound isoxazole **44** liberates the tetrahydrofuran **45** upon treatment with iodine monochloride, regenerating in the process the starting aldehyde **43**.[21] Treatment of γ-silyloxyallenes **46** with *N*-iodosuccinimide has been shown to efficiently generate iodovinyl tetrahydrofuran derivatives **47**, with the *cis* isomer predominating by greater than nine to one.[22]

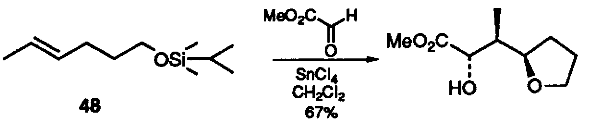


43 **44** **45**

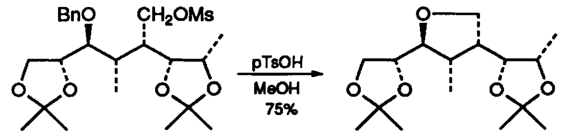


46 **47**

In a synthetic process related to iodoetherification, Mikami and Shimizu have shown that the bis-homoallylic silyl ether **48** undergoes an intramolecular cyclization on treatment with methyl glyoxylate and tin tetrachloride to provide the substituted tetrahydrofuran **49**.[23] Another interesting route to highly functionalized tetrahydrofurans, *e.g.* **51**, involves the treatment of the protected polyol benzyl ether **50** bearing a leaving group at the γ-carbon with very mild acid.[24]

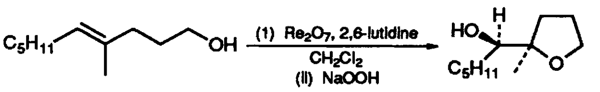


48 **49**



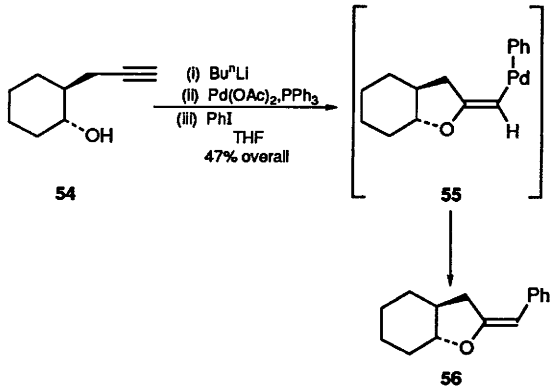
50 **51**

Kennedy and Tang have shown that treatment of 5-hydroxyalkenes with rhenium (VII) oxide is an efficient route to 2-hydroxymethyl-tetrahydrofurans.[25] Thus, for example, the tetrahydrofuran **53** is formed in 86% yield from the hydroxyalkene **52**, with oxidative cyclization occurring stereospecifically *syn* to the double bond.[26]

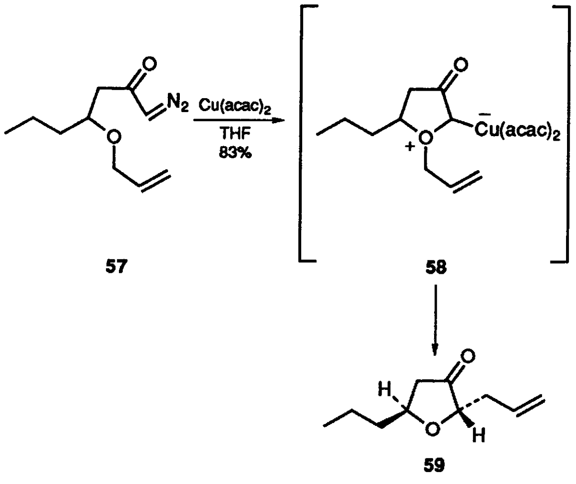


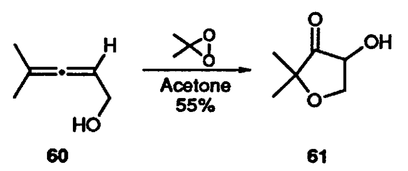
52 **53**

A novel three component palladium catalysed process for the synthesis of 2-alkylidene-tetrahydrofurans has been reported by Luo and associates.[27] The reaction presumably proceeds through the vinylpalladium intermediate **55**, as shown for the synthesis of **56** from the hydroxy acetylene **54**.



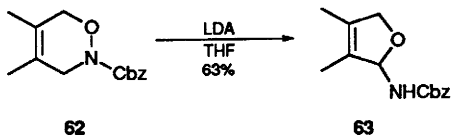
Clark has shown that copper acetylacetonate is the catalyst of choice for the conversion of the α-diazo ketone **57** into the *trans*-furanone **59**, a reaction which appears to proceed through the metal-bound ylide **58**.[28] Crandall *et al.* have extended their earlier work on the epoxidation of allenes and demonstrated that the hydroxy-allene **60** can be converted into the hydroxyfuranone **61** on treatment with dimethyldioxirane.[29]



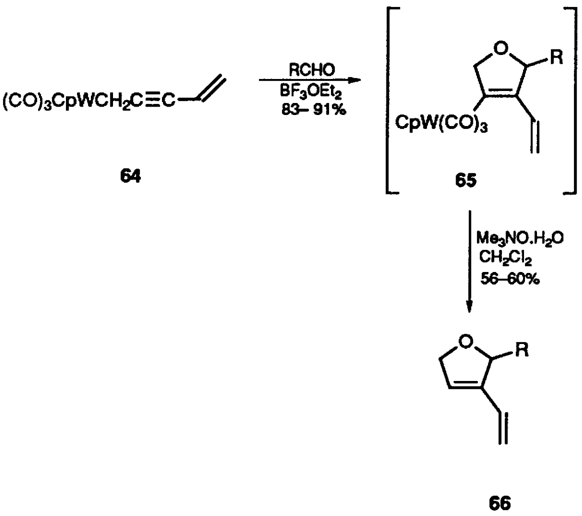


3.2 Dihydrofurans

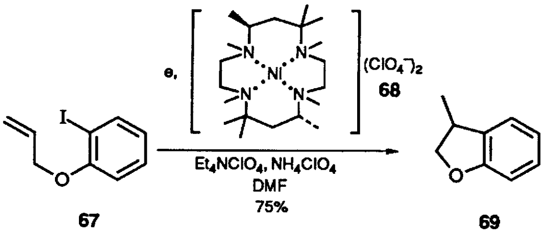
Desai and co-workers have uncovered an interesting base-induced rearrangement reaction of 3,6-dihydro-1,2-oxazines which provides an efficent route to 2-amino-2,5-dihydrofurans.[30] Thus, treatment of the protected oxazine **62** with lithium diisopropylamide generates the dihydrofuran **63** in 63% yield.



The tungsten η^1-propynyl compound **64** has been shown to react with a range of aldehydes leading to the cyclized intermediates **65**, which can then be demetallated in reasonable yields to provide the corresponding dihydrofurans **66**.[31]



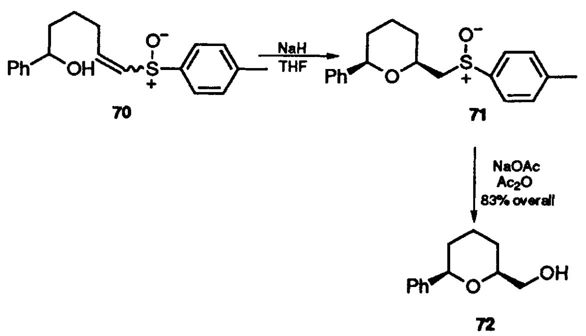
Ozaki and co-workers have demonstrated that the nickel (II) catalyst **68** can induce intramolecular free-radical cyclization reactions under electrochemical conditions;[32] the synthesis of the dihydrobenzofuran **69** from the allyl ether **67** in 75% yield is representative of the procedure.



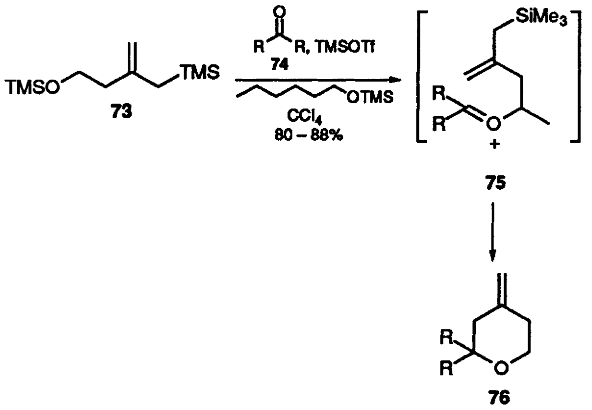
4 Six-membered rings

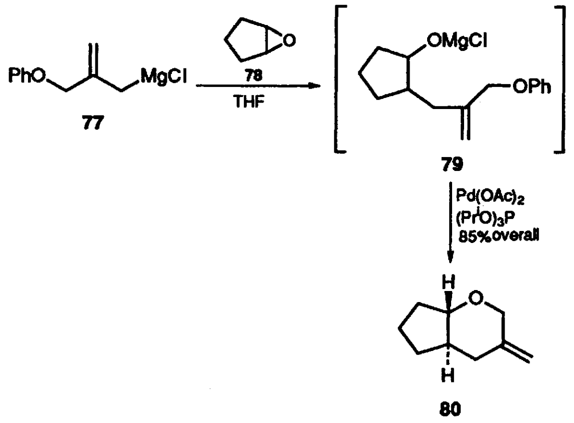
4.1 Tetrahydropyrans

A highly stereoselective route to *cis*-2,6-disubstituted tetrahydropyrans has been reported by Mandai and co-workers, whereby intramolecular addition of an hydroxyl to an α,β-unsaturated sulfoxide proceeds under thermodynamic conditions.[33] The product sulfoxide **71** can then be converted into the corresponding alcohol, as shown in the overall transformation of **70** into the pyran **72**.



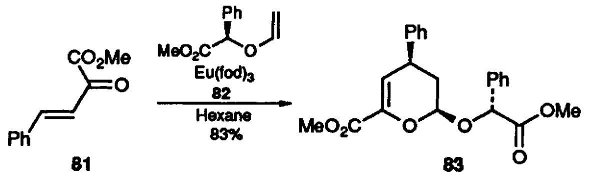
Markó *et al.* have developed an efficient one-pot synthesis of tetrahydropyrans based on an intramolecular Sakurai reaction.[34] Thus, reaction of the allylsilane **73** with ketones (or aldehydes) **74** leads to the pyrans **76** presumably *via* the oxonium cation **75**. The isomeric 3-methylene-tetrahydropyrans can be prepared in a two-step, one-pot reaction sequence reported by Klumpp and his group.[35] Addition of the allyl Grignard reagent **77** to cyclopentene oxide **78** first affords the intermediate **79** which then undergoes palladium catalysed cyclization to the desired pyran **80**.

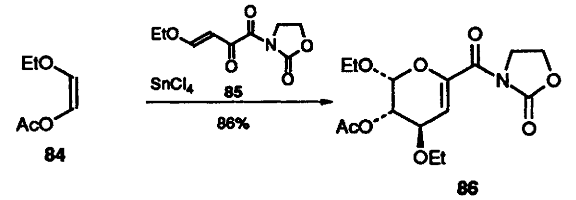


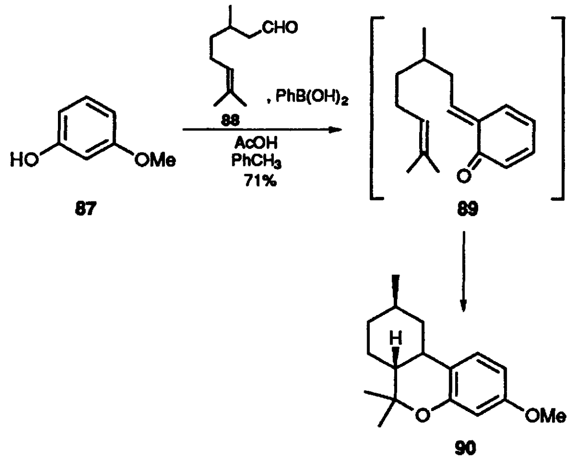


4.2 Dihydropyrans

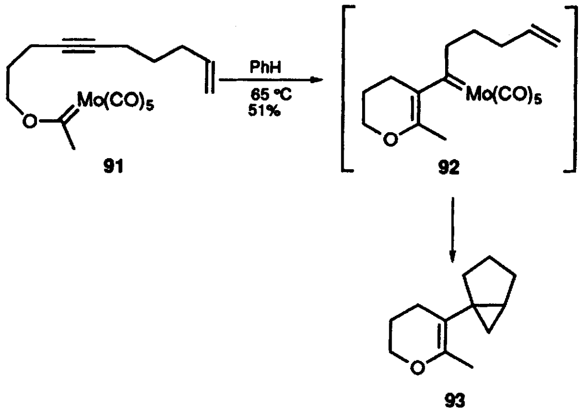
The syntheses of dihydropyrans *via* hetero Diels–Alder reactions offers a rapid entry into this ring system. Dujardin, Molato, and Brown have undertaken a systematic investigation of the europium catalysed Diels–Alder reaction of the pyruvate **81** with numerous chiral enol ethers, and have shown that use of the chiral enol ether **82** gives the best asymmetric induction (d.e. 72%) affording the *endo*-product **83** in a highly *endo* selective reaction.[36] Tietze and Schneider have demonstrated that reaction of the enol ether **84** with the heterodiene **85** can be controlled to give either the *exo* or *endo* product.[37] Thus, the reaction catalysed by the strong Lewis acid tin tetrachloride gives the *exo* product **86** in 86% yield, whereas trimethylsilyl triflate as catalyst affords the corresponding *endo* adduct. Phenylboric acid has been shown to catalyse the hetero Diels–Alder reaction of citronellal **88** with activated phenols.[38] The reaction is presumed to proceed through a quinone methide intermediate such as **89**, as shown in the synthesis of **90** from the phenol **87**.



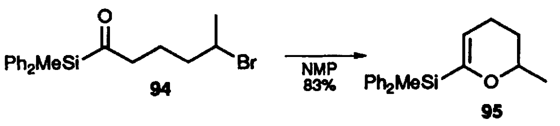




The use of molybdenum carbene complexes in the synthesis of dihydropyrans has been reported by Harvey and Brown,[39] as exemplified in the synthesis of the dihydropyran **93** *via* the intermediate **92**, on thermolysis of the Fischer carbene complex **91**.

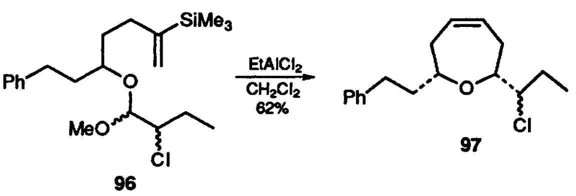


Tsai and his co-workers have reported a novel cyclization process using acylsilanes to generate 2-silyldihydropyrans.[40] Thus, simply heating the δ-bromo acylsilane **94** in *N*-methylpyrrolidine yields the dihydropyran **95** in 83% yield.

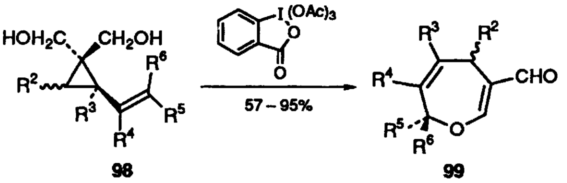


5 Medium and large ring ethers

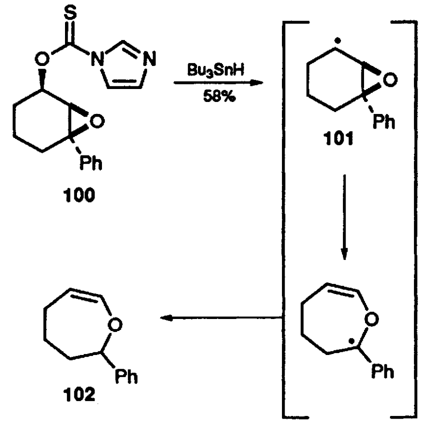
Berger and Overman have reported a simple route to oxepenes bearing an halogenated side chain at the two position, *via* a Prins-type cyclization.[41] The reaction yields only the *cis*-2,7-disubstituted oxepene, as a mixture of stereoisomers at the halogen bearing carbon, as shown for the synthesis of **97** from the mixed ketal **96**.

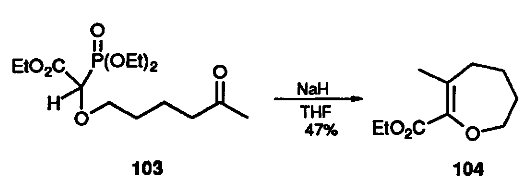


Boeckman and his co-workers have described an elegant entry into seven- and eight-membered cyclic ethers based on an intramolecular retro-Claisen rearrangement of substituted cyclopropanes.[42] Thus, oxidation of the cyclopropane diols **98** with Dess–Martin reagent provided the desired products **99** in fair to excellent yield.



An interesting free-radical ring-expansion approach to oxepenes has been reported by Marples *et al.* whereby treatment of the thiocarbonylimidazolide **100** with tributyltin hydride gives the ring expanded product **102** *via* the oxiranyl radical **101**.[43] Moody *et al.* have shown that the intramolecular Wadsworth–Emmons reaction of the ketone phosphonate **103** affords the cyclic enol ether **104** in 47% yield.[44]





6 References

1 K.B. Sharpless, W. Amberg, Y.L. Bennani, G.A. Crispino, J. Hartung, K.-S. Jeong, H.-L. Kwong, K. Morikawa, Z.M. Wang, D. Xu, and X.-L. Zhang, *J. Org. Chem.*, 1992, **57**, 2768.
2 H.C. Kolb and K.B. Sharpless, *Tetrahedron*, 1992, **48**, 10515.
3 R. Oi and K.B. Sharpless, *Tetrahedron Lett.*, 1992, **33**, 2095.
4 V.S. Murthy, A.S. Gaitonde, and S.P. Rao, *Synth. Commun.*, 1993, **23**, 285.
5 K. Kaneda, S. Haruna, T. Imanaka, M. Hamamoto, Y. Nishiyama, and Y. Ishii, *Tetrahedron Lett.*, 1992, **33**, 6827.
6 W. Adam and M. Richter, *Tetrahedron Lett.*, 1992, **33**, 3461.
7 Y. Fort, A. Olszewski-Ortar, and P. Caubere, *Tetrahedron*, 1992, **48**, 5099.
8 P.R. Cooke and J.R. Lindsay Smith, *Tetrahedron Lett.*, 1992, **33**, 2737.
9 A.K. Saksena, A.K. Ganguly, V.M. Girijavallabhan, R.E. Pike, Y.-T. Chen, and M.S. Puar, *Tetrahedron Lett.*, 1992, **33**, 7721.
10 H.A.J. Carless and A.F.E. Halfhide, *J. Chem. Soc., Perkin Trans. 1*, 1992, 1081.
11 L. Thijs, P.J.M. Cillissen, and B. Zwanenburg, *Tetrahedron*, 1992, **48**, 9985.
12 D.M. Huryn and M. Okabe, *Chem. Rev.*, 1992, **92**, 1745.
13 T. Hosokawa and S.-I. Murahashi, *Heterocycles*, 1992, **33**, 1079.
14 V. Dalla and P. Pale, *Tetrahedron Lett.*, 1992, **33**, 7857.
15 N. Moufid, Y. Chapleur, and P. Mayon, *J. Chem. Soc., Perkin Trans. 1*, 1992, 999.
16 G.A. Molander and K.O. Cameron, *J. Am. Chem. Soc.*, 1993, **115**, 830.
17 P.A. Wender and J.L. Mascareñas, *Tetrahedron Lett.*, 1992, **33**, 2115.

18 A.K. Saksena, V.M. Girijavallabhan, Y.-T. Chen, E. Jao, R.E. Pike, J.A. Desai, D. Rane, and A.K. Ganguly, *Heterocycles*, 1993, **35**, 129.

19 S.B. Bedford, K.E. Bell, G. Fenton, C.J. Hayes, D.W. Knight, and D. Shaw, *Tetrahedron Lett.*, 1992, **33**, 6511.

20 F. Bennett, S.B. Bedford, K.E. Bell, G. Fenton, D.W. Knight, and D. Shaw, *Tetrahedron Lett.*, 1992, **33**, 6507.

21 X. Beebe, N.E. Schore, and M.J. Kurth, *J. Am. Chem. Soc.*, 1992, **114**, 10061.

22 R.D. Walkup, L. Guang, S.W. Kim, and Y.S. Kim, *Tetrahedron Lett.*, 1992, **33**, 3969.

23 K. Mikami and M. Shimizu, *Tetrahedron Lett.*, 1992, **33**, 6315.

24 H. Dehmlow, J. Mulzer, C. Seilz, A.R. Strecker, and A. Kohlmann, *Tetrahedron Lett.*, 1992, **33**, 3607.

25 R. Kennedy and S. Tang, *Tetrahedron Lett.*, 1992, **33**, 3729.

26 R. Kennedy and S. Tang, *Tetrahedron Lett.*, 1992, **33**, 5299.

27 F.-T. Luo, I. Schreuder, and R.-T. Wang, *J. Org. Chem.*, 1992, **57**, 2213.

28 J.S. Clark, *Tetrahedron Lett.*, 1992, **33**, 6193.

29 J.K. Crandall, D.J. Batal, F. Lin, T. Reix, G.S. Nadol and R.A. Ng, *Tetrahedron*, 1992, **48**, 1427.

30 M.C. Desai, J.L. Doty, L.M. Stephens, and K.E. Brighty, *Tetrahedron Lett.*, 1993, **34**, 961.

31 M.-H. Cheng, G.-M. Yang, J.-F. Chow, G.-H. Lee, S.-M. Peng, and R.-A. Liu, *J. Chem. Soc., Chem. Commun.*, 1992, 934.

32 S. Ozaki, H. Matsushita, and H. Ohmori, *J. Chem. Soc., Chem. Commun.*, 1992, 1120.

33 T. Mandai, M. Ueda, K. Kashiwagi, M. Kawada, and J. Tsuji, *Tetrahedron Lett.*, 1993, **34**, 111.

34 I.E. Markó, A. Mekhalfia, D.J. Bayston, and H. Adams, *J. Org. Chem.*, 1992, **57**, 2211.

35 J. van der Louw, J.L. van der Baan, G.J.J. Out, F.J.J. de Kanter, F. Bickelhaupt, and G.W. Klumpp, *Tetrahedron*, 1992, **48**, 9901.

36 G. Dujardin, S. Molato, and E. Brown, *Tetrahedron: Asymmetry*, 1993, **4**, 193.

37 L.F. Tietze and C. Schneider, *Synlett.*, 1992, 755.

38 W.S. Murphy, S.M. Tuladhar, and B. Duffy, *J. Chem. Soc., Perkin Trans. 1*, 1992, 605.

39 D.F. Harvey and M.F. Brown, *J. Org. Chem.*, 1992, **57**, 5559.

40 Y.-M. Tsai, H.-C. Nieh, and C.-D. Cherng, *J. Org. Chem.*, 1992, **57**, 7010.

41 D. Berger and L.E. Overman, *Synlett*, 1992, 811.

42 R.K. Boeckman, M.D. Shair, J.R. Vargas, and L.A. Stolz, *J. Org. Chem.*, 1993, **58**, 1295.

43 D.A. Corser, B.A. Marples, and R.K. Dart, *Synlett*, 1992, 987.

44 C.J. Moody, E.-R.H.B. Sie, and J.J. Kulagowski, *Tetrahedron*, 1992, **48**, 3991.