

# Saturated and unsaturated hydrocarbons

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Reviewing the literature published between January 1995 and May 1996

Continuing the coverage in *Contemporary Organic Synthesis*, 1995, 2, 441

- 1 Introduction
- 2 Saturated hydrocarbons
  - 2.1 Deoxygenation
  - 2.2 Dehalogenation
  - 2.3 Desulfurisation
  - 2.4 Deamination
  - 2.5 Hydrogenation
  - 2.6 Miscellaneous
- 3 Alkenic hydrocarbons
  - 3.1 Carbonyl olefinations
  - 3.2 Alkene  $sp^2$ - $sp^2$  coupling reactions
    - 3.2.1 Heck reaction
    - 3.2.2 Stille reaction
    - 3.2.3 Suzuki reaction
  - 3.3 Rearrangements
    - 3.3.1 Cope rearrangement
    - 3.3.2 Claisen rearrangement
    - 3.3.3 Wittig rearrangement
    - 3.3.4 Miscellaneous rearrangements
  - 3.4 Alkene metathesis
  - 3.5 Miscellaneous
- 4 Alkynic hydrocarbons
  - 4.1 Alkyne metathesis
  - 4.2 Miscellaneous
- 5 References

## 1 Introduction

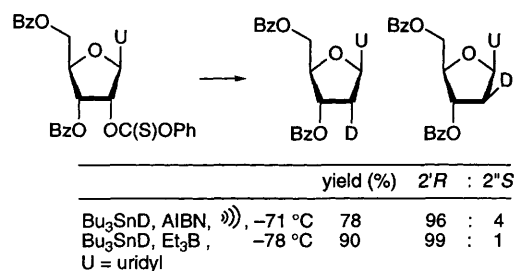
In this review particular emphasis has been placed on reductive techniques in the synthesis of saturated hydrocarbons, and on the selective synthesis and connection of the multiple bonds in unsaturated hydrocarbons. Wherever possible novel or improved methods have been emphasised as opposed to an exhaustive list of all the synthetic procedures published in the area.

## 2 Saturated hydrocarbons

### 2.1 Deoxygenation

The well documented use of tributyltin hydride still dominates the methods of deoxygenation used in synthesis. The important issue of selectivity of

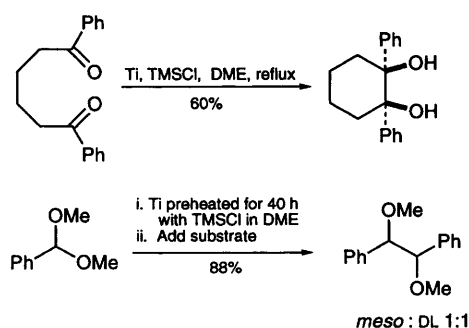
reduction, especially in the incorporation of deuterium into organic molecules, was raised in a study of the selectivity of deoxygenation of nucleoside 2'-phenoxythiocarbonates using tributyltin deuteride (**Scheme 1**).<sup>1</sup> The highest selectivity was elicited with tributyltin deuteride and triethylborane at  $-78^\circ\text{C}$  leading to a 99:1 mixture of 2'*R*:2'*S* deuteriated 2'-deoxy[2'-*D*]uridines. Sonochemical tributyltin deuteride activation with azoisobutyronitrile (AIBN) gave a 96:1 ratio, this being only slightly more selective than standard thermal conditions.



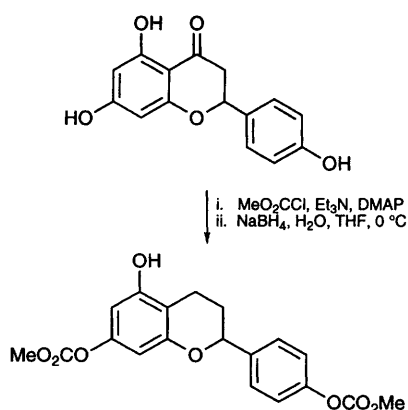
**Scheme 1**

Titanium has been widely used stoichiometrically in deoxygenation reactions and carbon-carbon bond forming reactions.<sup>2</sup> Fürstner *et al.* have detailed the first catalytic use of titanium to effect these types of reaction. The key observation for successful reaction was found to be the addition of trimethylsilyl chloride (TMSCl) which activates the metal surface by removal of the inert oxide layer.<sup>3</sup> The same research group have also used stoichiometric amounts of commercial titanium powder as a reagent for reactions previously thought to be poorly mediated by this inactive form of the metal. These reactions, which include pinacol couplings (**Scheme 2**), McMurry couplings and epoxide deoxygenations (*vide infra*), also use trimethylsilyl chloride activation.<sup>3</sup>

A variation of a one pot hydroxy group protection and ketone reduction of acyl resorcinols and coumarins has been reported.<sup>4</sup> In this method the phenolic hydroxy groups are masked as methyl carbonates and then sodium borohydride reduction in a mixture of water and THF provided alkyl resorcinols and coumarins bearing no *ortho* hydroxy group protection (**Scheme 3**). Water was found to be vital for the reduction to proceed as desired.



**Scheme 2**

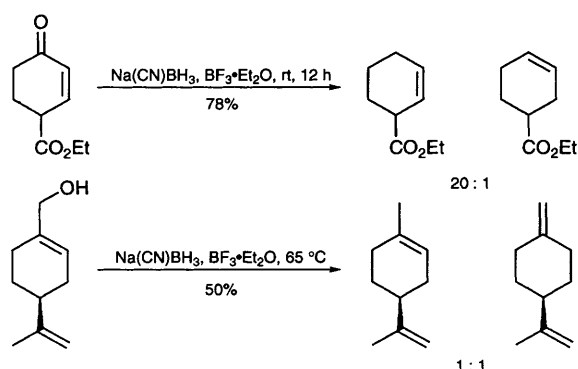


**Scheme 3**

$\alpha,\beta$ -Unsaturated enones and allylic alcohols have been reduced successfully to the corresponding alkenes using a boron trifluoride–diethyl ether and sodium cyanoborohydride mixture (**Scheme 4**).<sup>5</sup> These potentially useful reactions tend to give mixtures of isomerised alkene products.

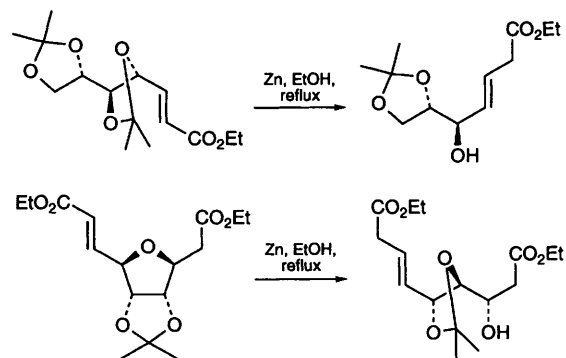
Various Lewis acid–hydride reagent mixtures, such as boron trifluoride–sodium cyanoborohydride,<sup>6</sup> titanium tetrachloride–, aluminium trichloride–, boron trifluoride– and iron trichloride–borane dimethylamine complex have been used for the complete reduction of aryl ketones to alkylbenzenes.<sup>7</sup>

A reductive elimination of  $\gamma$ -alkoxy- $\alpha,\beta$ -unsaturated esters using ethanolic activated zinc has been



**Scheme 4**

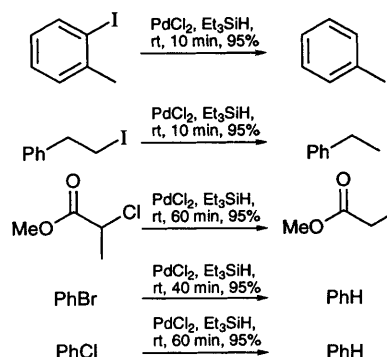
developed which yields  $\beta,\gamma$ -unsaturated esters. These synthons are of potential use in the stereospecific synthesis of natural products (**Scheme 5**).<sup>8</sup>



**Scheme 5**

## 2.2 Dehalogenation

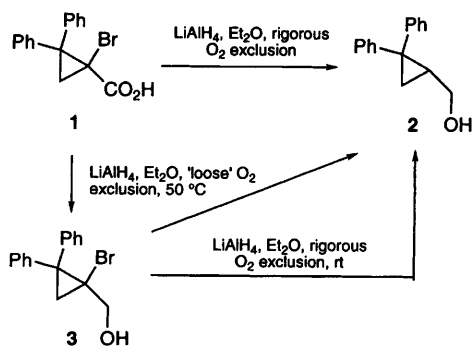
Chatgililoglu *et al.* have reported the dehalogenation of a wide variety of halides including alkyl, aryl, benzyl and  $\alpha$ -alkoxy chlorides, bromides and iodides using catalytic amounts of palladium(II) chloride in triethylsilane (**Scheme 6**).<sup>9</sup> The reactions occur in high yield at ambient temperature with the exception of 1- and 2-bromoadamantane which both require heating at 80 °C.



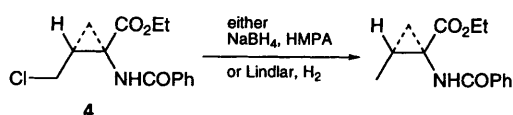
**Scheme 6**

Lithium aluminium hydride is often used for dehalogenations and a recent report has identified that when the cyclopropane acid **1** was reduced under *strictly* anaerobic conditions a dehalogenation product **2** was obtained (**Scheme 7**).<sup>10</sup> When ‘loosely’ anaerobic conditions were applied no debromination was observed.<sup>10</sup> In fact, an excess of lithium aluminium hydride and elevated temperatures were required to reduce the bromides **1** and **3** under the non-rigorous anaerobic conditions. Even small quantities of oxygen are thought to retard the dehalogenation, by inhibiting the formation of key radical intermediates.

Hydrogenolysis of the chlorine–carbon bond in the cyclopropane **4** has proved difficult under



**Scheme 7**

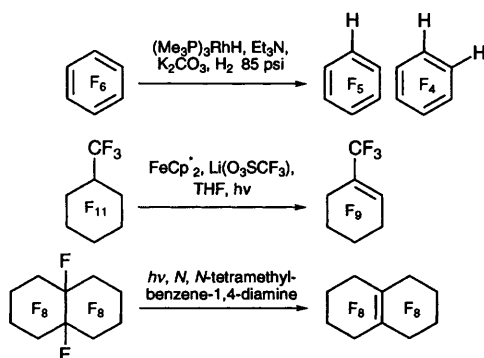


**Scheme 8**

standard catalytic hydrogenolytic conditions due to the lability of the strained three membered ring (**Scheme 8**).<sup>11</sup> Successful dehalogenation has now been brought about by either sodium borohydride reduction in hexamethylphosphoramide (HMPA) or by hydrogenolysis over Lindlar's catalyst.<sup>11</sup>

Hydrogenolysis over palladium on carbon was found to effectively dehalogenate bromo- and chloro-thiazoles that were poorly reduced by a number of other reagents.<sup>12</sup>

Of the halogens, fluorine can be the most difficult to remove when unactivated.<sup>13</sup> Heterogeneous methods for the hydrogenolysis of the carbon–fluorine bond are in general harsh and unselective,<sup>14</sup> but recently inroads have been made towards mild defluorination techniques using homogeneous transition metal catalysts.<sup>13</sup>  $(\text{Me}_3\text{P})_3\text{RhC}_6\text{H}_5$  and  $(\text{Me}_3\text{P})_3\text{RhH}$  have been used as catalysts for the monohydrogenation of a carbon–fluorine bond in hexafluorobenzene in the presence of triethylamine and potassium carbonate under 85 psi hydrogen (**Scheme 9**).<sup>15</sup> Perfluoroalkanes have



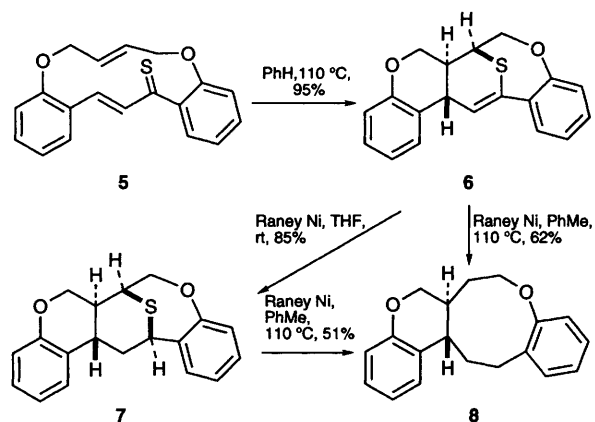
**Scheme 9**

been reduced to give fluoroalkenes by irradiating in the presence of decamethylferrocene<sup>16</sup> and other electron donors (**Scheme 9**).<sup>17</sup>

### 2.3 Desulfurisation

When incorporated into organic molecules, sulfur is a versatile element allowing, amongst others, many novel carbon–carbon bond forming reactions to take place.<sup>18</sup> In many cases the sulfur-containing functional group is not required in the final product and requires removal.

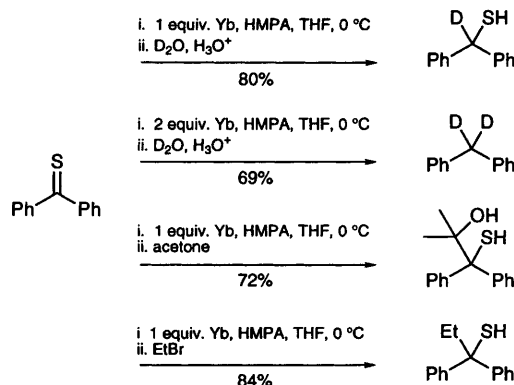
Saito *et al.* have described a hetero Diels–Alder annulation reaction using the thioetone **5** (**Scheme 10**).<sup>19</sup> Treatment of the cyclised product **6** with Raney nickel was found to selectively hydrogenate the thioenol ether to the thioether **7** which was subsequently desulfurised to reveal the nine membered cyclic ether **8**.



**Scheme 10**

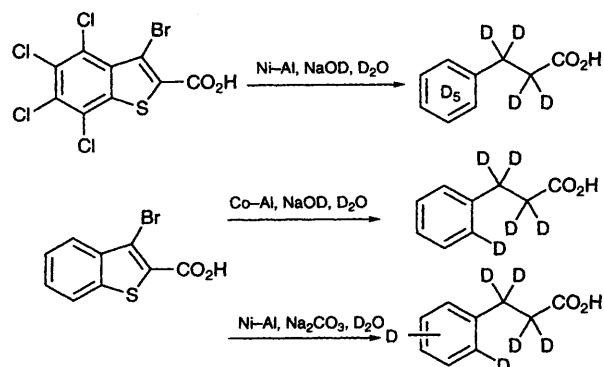
Raney nickel is the most common way of reductively removing sulfur from organic molecules, but ytterbium in HMPA has also been shown to reduce thioetones selectively to either the thiol or the fully reduced methylene compound (**Scheme 11**).<sup>20</sup> Work has also progressed to trap the intermediate radical anion with electrophiles.

Substituted and fully deuteriated phenylpropionic acids have been synthesised by the action



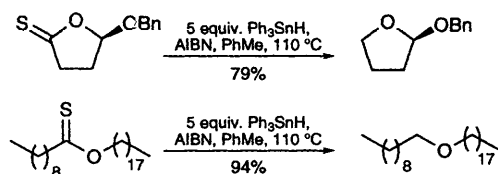
**Scheme 11**

of Raney alloy on perhalogenated benzofurans and 10% sodium deuterioxide in deuterium oxide (Scheme 12).<sup>21</sup> Interestingly a cobalt–aluminium alloy in the same solvent (or Raney alloy in 10% sodium carbonate in deuterium oxide) has been shown to selectively cleave the sulfur and bromine atoms from some unsubstituted benzofurans but give no extra incorporation of deuterium on the aromatic nucleus (Scheme 12).<sup>21</sup>



Scheme 12

During studies towards the synthesis of natural polyethers Nicolaou *et al.* published a method for the selective reduction of thioesters and thiolactones to ethers using triphenyltin hydride (Scheme 13).<sup>22</sup> This method has proved to be high yielding and extremely general.

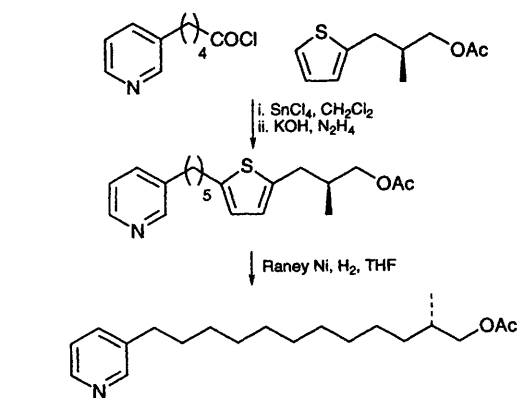


Scheme 13

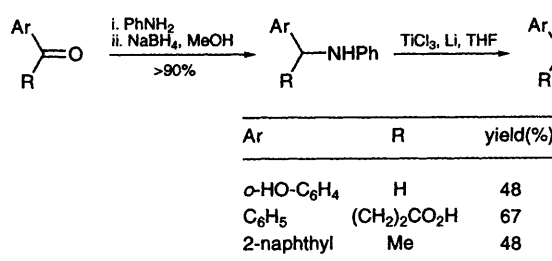
In their synthesis of niphatesine C, Bracher *et al.* used a Friedel–Crafts reaction to couple an acyl pyridine to a substituted thiophene (Scheme 14). After Wolff–Kishner reduction of the ketone, the thiophene was exhaustively hydrogenated to give the saturated product.<sup>23</sup>

## 2.4 Deamination

Benzylic phenylamines are readily reduced to alkylbenzenes and aniline when treated with low valent titanium (Scheme 15).<sup>24</sup> This is also a convenient two step method for the exhaustive reduction of aromatic ketones and aldehydes, as they are readily converted into benzylic phenylamines by reductive amination with aniline and sodium borohydride.



Scheme 14



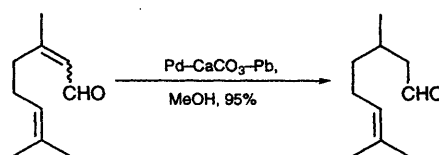
Scheme 15

## 2.5 Hydrogenation

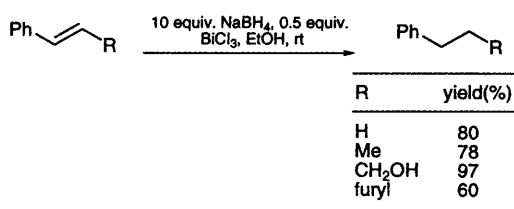
Asymmetric homogeneous catalytic hydrogenation by optically active transition metal complexes is now a vitally important area of organic synthesis and has recently been reviewed.<sup>25</sup> A recent development in this field has been the use of supercritical carbon dioxide as reaction solvent.<sup>26</sup>

The Lindlar catalyst, more commonly used for the heterogeneous partial reduction of alkynes to alkenes, has been used to selectively hydrogenate the double bond of  $\alpha,\beta$ -unsaturated carbonyl compounds (Scheme 16).<sup>27</sup> Esters, ketones and aldehydes are left unreduced, as are non-conjugated alkenes. Similarly, a water soluble rhodium catalyst has been developed for the homogeneous saturation of  $\alpha,\beta$ -unsaturated aldehydes,<sup>28</sup> and metallic samarium and iodine in ethanol has been used to hydrogenate  $\alpha,\beta$ -unsaturated carboxylic acid derivatives.<sup>29</sup>

In the same vein, sodium borohydride and bismuth trichloride mixtures have been used to selectively reduce not only alkenes conjugated to



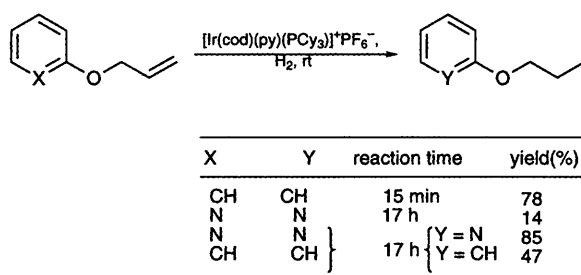
Scheme 16



**Scheme 17**

carbonyl groups,<sup>30</sup> but also alkenes conjugated to aromatic groups (**Scheme 17**).<sup>31</sup>

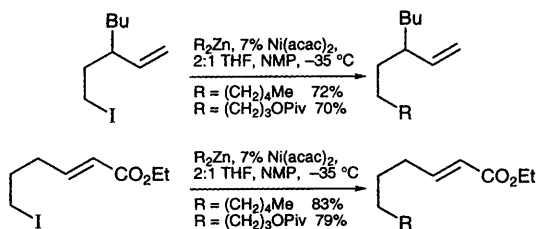
The cationic Crabtree iridium hydrogenation catalyst has been shown to selectively reduce alkenes that have a tethered 2-pyridyl group (**Scheme 18**).<sup>32</sup> When the reductions of the tethered 2-pyridyl and phenylalkenes are performed in separate flasks the phenyl alkene is reduced the most rapidly. When a competition reaction is performed in one pot however the tethered 2-pyridyl alkene is reduced up to 100 times more quickly. The proposed pyridine complexation to the iridium complex and intramolecular hydrogen delivery accounts well for these observations.



**Scheme 18**

## 2.6 Miscellaneous

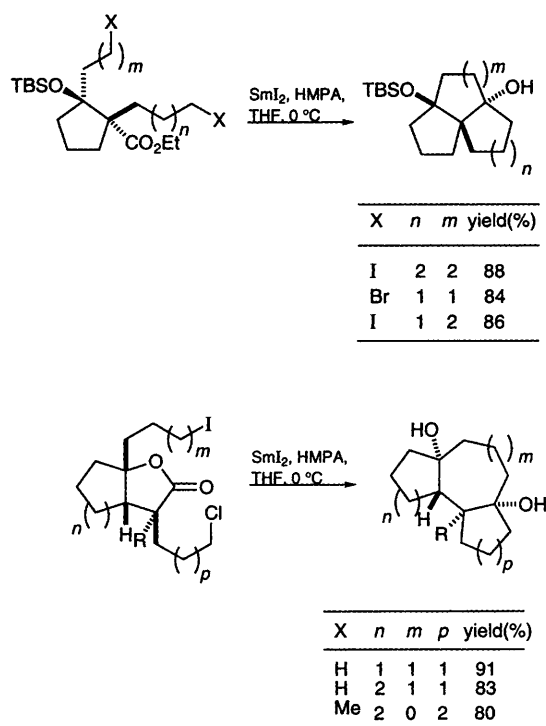
A recent review of transition metal catalysed carbocyclisations listed by the metals covers cobalt, iron, molybdenum, nickel, palladium, rhodium, ruthenium, titanium and zirconium examples.<sup>33</sup> In a novel nickel catalysed process Knochel *et al.* brought about the coupling of two sp<sup>3</sup> hybridised carbon centres (**Scheme 19**).<sup>34</sup> This mode of reactivity is dependent on the alkyl iodide having unsaturation at either the 4- or 5-position to facilitate a nickel



**Scheme 19**

centred reductive elimination. Absence of unsaturation leads to the predominance of a transmetalation and the formation of alkylnickel halides.

Molander *et al.* have used samarium diiodide promoted tandem intramolecular Barbier type reactions to synthesise a large range of bi- and tricyclic hydrocarbons (**Scheme 20**).<sup>35</sup> Metal halide exchange occurs giving an organosamarium reagent which adds initially to the ester or lactone to give a ketone which is then attacked further by the second organosamarium giving various polycyclic alcohols on work up.

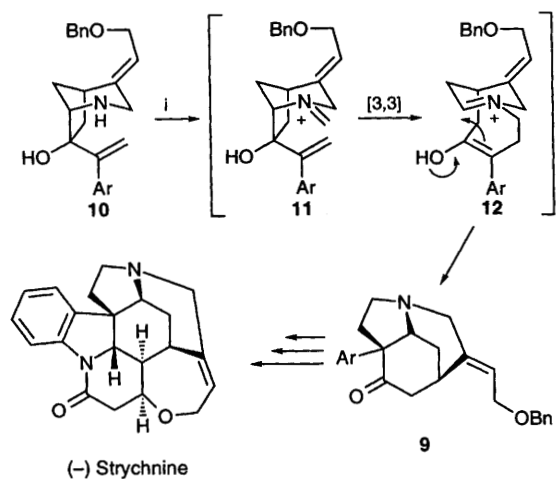


**Scheme 20**

In their enantioselective synthesis of (–)-strychnine Overman *et al.* used an aza-Wittig rearrangement to construct the enantiomerically pure tricyclic portion **9** from a bicyclic precursor **10** (**Scheme 21**).<sup>36</sup> The free amine **10** was treated with formaldehyde to give the iminium ion **11** which underwent a [3,3] sigmatropic rearrangement revealing the enol **12** which then attacked the newly formed iminium ion intramolecularly to give the tricycle **9**.

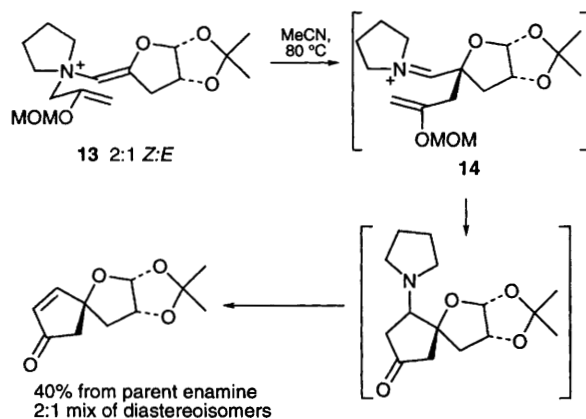
Similarly, in their work towards pungalandine IV, Florent *et al.* performed an aza-Cope rearrangement on the allyl enaminium salt **13** giving the transient iminium ion **14** which became trapped to form (after amine elimination) a spirocyclopentenone (**Scheme 22**).<sup>37</sup>

Another highly selective ring forming reaction type, a [3 + 4] annulation, has been published by Takeda *et al.* (**Scheme 23**).<sup>38</sup> Reaction of *tert*-butyldimethyl[β-(trimethylsilyl)acryloyl]silane **15**

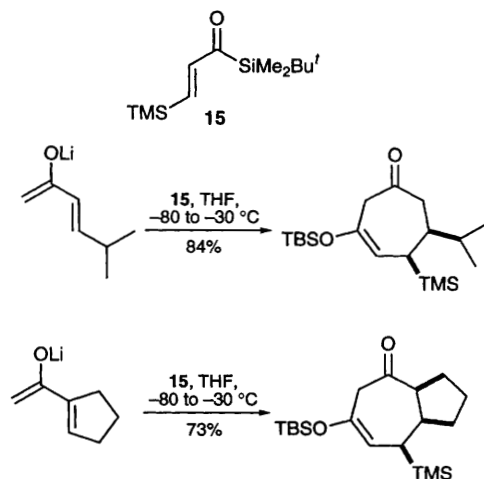


Reagent; i. HCHO, TsOH, heat, 98%.

Scheme 21



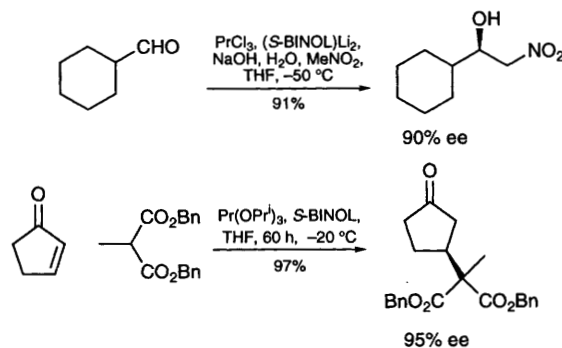
Scheme 22



Scheme 23

with various enolates of unsaturated methyl ketones led to high yields of highly functionalised cycloheptane rings.

Rare earth binaphthols have been used successfully in the first asymmetric nitro-aldol reaction, europium binaphthols in general giving the best asymmetric induction (**Scheme 24**).<sup>39</sup> The same rare earth binaphthols when prepared under halide free conditions made excellent catalysts for asymmetric Michael reactions of enones and malonates (**Scheme 24**).<sup>39</sup> A review of asymmetric catalysis, by Noyori, lists many reactions catalysed by chiral transition metal complexes.<sup>40</sup>

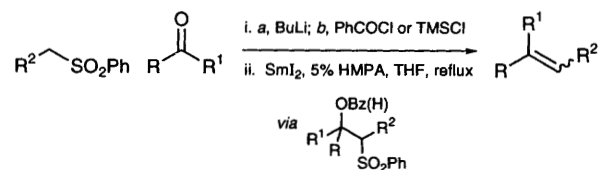


Scheme 24

### 3 Alkenic hydrocarbons

#### 3.1 Carbonyl olefinations

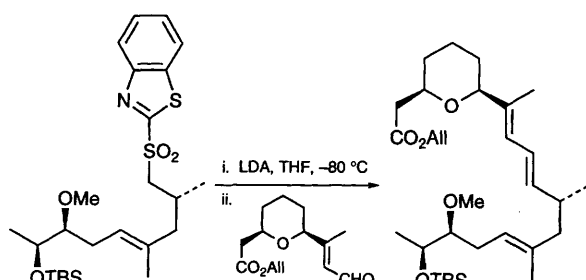
Recent modifications made to the Julia olefination procedure have allowed more efficient syntheses of trisubstituted alkenes from ketones.<sup>41</sup> This was achieved firstly by trapping intermediate alkoxides *in situ* to form either  $\beta$ -sulfonyl benzoates or  $\beta$ -hydroxy sulfones and by using samarium diiodide and 1–5% HMPA in THF to perform the reductive elimination step (**Scheme 25**).<sup>42</sup> Magnesium in ethanol with a catalytic amount of mercuric chloride has also been employed successfully for the reductive elimination of  $\beta$ -sulfonyl benzoates.<sup>43</sup>



Scheme 25

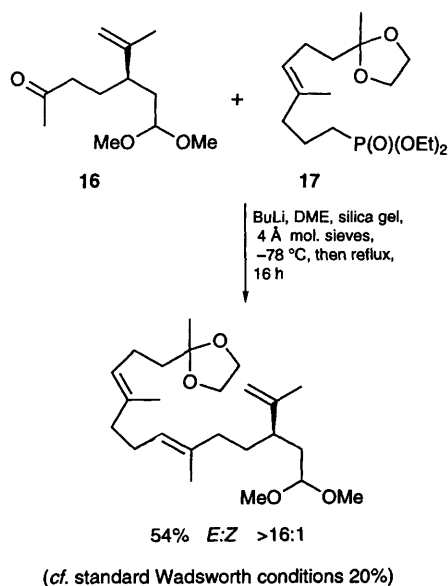
In 1993 Sylveser Julia published a major variation of the Julia olefination procedure employing lithiated benzothiazolyl sulfones.<sup>44,45</sup> The one step method gives *E*-vicinal disubstituted alkenes in an extremely stereoselective fashion, and has more recently been used successfully by Kocienski *et al.* in their synthesis of herboxidiene (**Scheme 26**).<sup>46</sup>

One of the most common methods of alkene synthesis, the Wittig reaction, has been performed



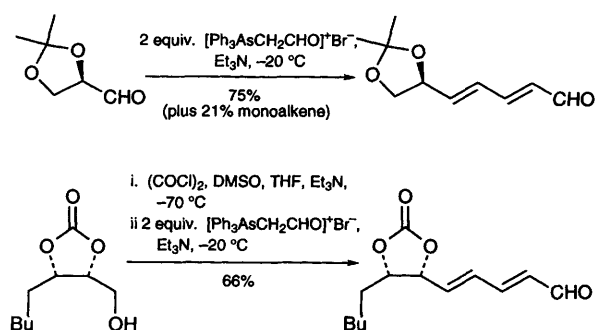
**Scheme 26**

in the presence of silica gel in hexane.<sup>47</sup> The method was found to accelerate the rates of reaction, give slightly improved *E:Z* selectivities and also greatly improve isolation and purification of the products by simply filtering off the silica adsorbed phosphine oxide by-product. Activated alumina has been used similarly as an additive in the analogous reactions with much the same effects.<sup>48</sup> Wittig and Horner–Emmons olefinations have also been achieved with immobilised aldehydes.<sup>49</sup> Standard Wadsworth–Emmons phosphonate anion olefination of the ketone **16** with the phosphonate **17** gave poor yields of the desired trisubstituted alkene (**Scheme 27**). In this case silica gel and molecular sieve additives enhanced reaction yields and gave higher stereoselectivities over more standard methodologies.<sup>50</sup>



**Scheme 27**

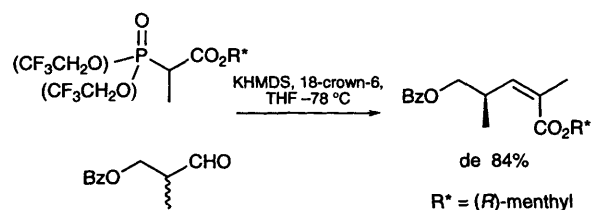
Selective homologations of aldehydes to *E,E*-dienyl aldehydes have been achieved by the Wittig-like reaction with formylmethylene-(triphenyl)arsane formed *in situ* from the arsonium bromide salt (**Scheme 28**).<sup>51</sup> The reaction is most selective with  $\alpha$ -oxygenated aldehydes, with no triene formation, and also has been employed successfully on alcohols in a one pot Swern–homologation process (**Scheme 28**).<sup>51</sup>



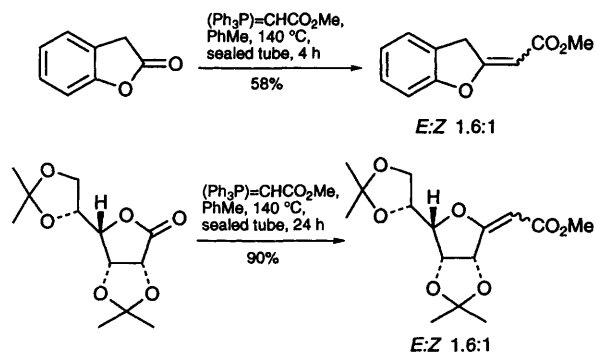
**Scheme 28**

Developments in the asymmetric Wittig and Wittig variant reactions have recently been reviewed.<sup>52</sup> To date kinetic and dynamic resolution of racemates and desymmetrisation of *meso* substrates have been achieved (**Scheme 29**).

In the majority of cases the Wittig reaction fails when attempted on ester substrates, but by heating with methoxycarbonyl(triphenyl)phosphorane in a sealed tube some carbohydrate lactones have been olefinated (**Scheme 30**).<sup>53</sup>

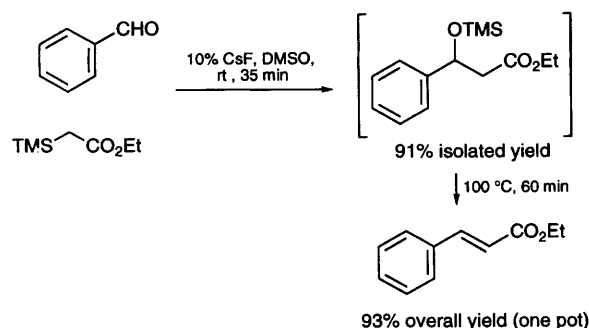


**Scheme 29**



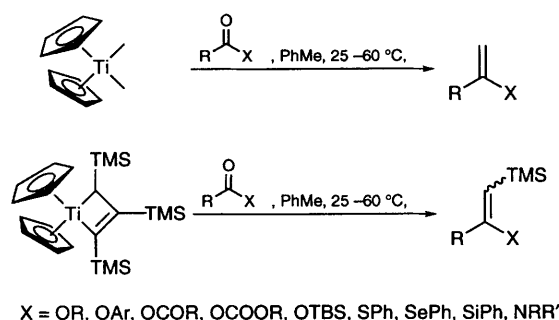
**Scheme 30**

In a variant of the Peterson olefination reaction, ethyl  $\alpha$ -(trimethylsilyl)acetate when treated with non-enolisable aldehydes and a catalytic amount of caesium fluoride in dimethyl sulfoxide (DMSO) was shown to form silyl ethers. On heating these silyl ethers selectively furnished ethyl *trans*-prop-2-enoates in good yields (**Scheme 31**).<sup>54</sup> Ethyl  $\alpha$ -(trimethylsilyl)acetate can be replaced with ethyl  $\beta$ -(trimethylsilyl)ethylamines giving  $\alpha,\beta$ -unsaturated imine products.<sup>54</sup>



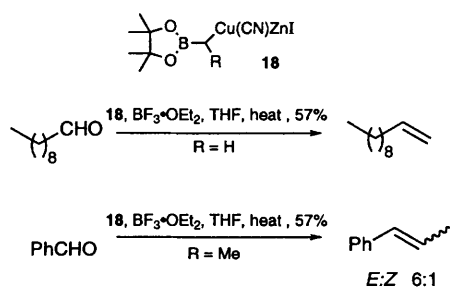
**Scheme 31**

The use of dimethyltitanocene as a less reactive alternative to the Tebbe reagent has been reviewed.<sup>55</sup> This versatile reagent is able to olefinate aldehydes, ketones, esters, thioesters, selenoesters, acylsilanes, carbonates, anhydrides, amides and imides in toluene at 70 °C.<sup>55</sup> In a related reaction tris(trimethylsilyl)titanacyclobutene has been shown to be an effective and mild reagent for the formation of vinyltrimethylsilanes from ketones, aldehydes, thioesters, esters and lactones at room temperature (**Scheme 32**).<sup>56</sup>



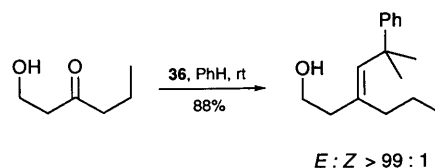
**Scheme 32**

Methylenation of aliphatic,  $\alpha,\beta$ -unsaturated and aromatic aldehydes using Knochel's (dialkoxyboryl)methylcopper reagent (**18**, R = H) and boron trifluoride–diethyl ether in THF at reflux has recently been reported (**Scheme 33**).<sup>57</sup> This reaction has been repeated using a related reagent (**18**, R = Me) forming methyl substituted alkenes in good yields and with moderate *E*:*Z* selectivity.



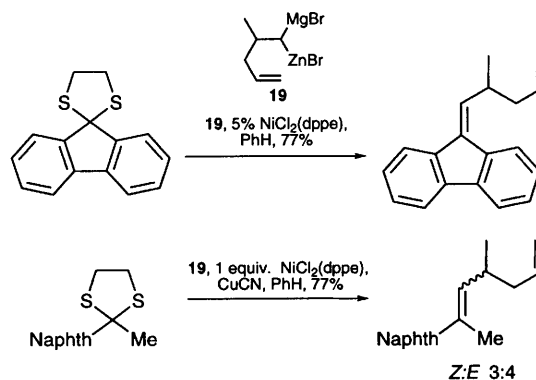
**Scheme 33**

Unsymmetrical ketones, where one chain bears an ethereal oxygen atom can be olefinated using a molybdenum alkylidene complex **36** (*vide infra*) with extremely high stereoselectivities (**Scheme 34**).<sup>58</sup> The attached alkylidene group resides *trans* to the chain bearing the directing group.



**Scheme 34**

Dithioacetals of diaryl ketones are smoothly converted into alkenes by treatment with the  $\alpha,\alpha$  magnesium–zinc reagent **19** under nickel catalysis with poor selectivities (**Scheme 35**).<sup>59</sup> Dithioacetals of aryl–alkyl ketones, or aryl aldehydes can be transformed similarly with a stoichiometric amount of nickel in the presence of a copper(I) salt.



**Scheme 35**

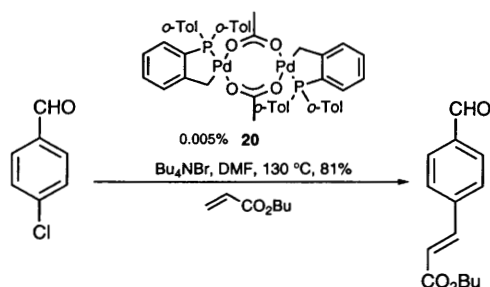
## 3.2 Alkene $sp^2$ – $sp^2$ coupling reactions

### 3.2.1 Heck reaction

The Heck reaction is now a widely used synthetic method for the assembly of polyenes and has been extensively reviewed.<sup>60</sup> Due to the size of the subject area, even during the present period of coverage, attention has been focused on only the use of new catalysts, regioselective reactions, enantioselective reactions and modified reactions.

The isolated palladacycle **20** formed by the action of three equivalents of tri-*o*-tolylphosphine on palladium diacetate is an extremely active catalyst for the Heck reaction at levels as low as 0.005% (**Scheme 36**).<sup>61</sup> The catalyst is extremely stable at temperatures of 130 °C with no evidence of phosphorus–carbon bond cleavage which occurs with reactions using palladium diacetate and tri-*o*-tolylphosphine mixtures. The addition of tetrabutylammonium bromide (TBAB) or alkali metal salts increases the stability of the catalyst in

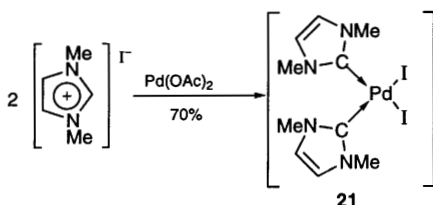




**Scheme 36**

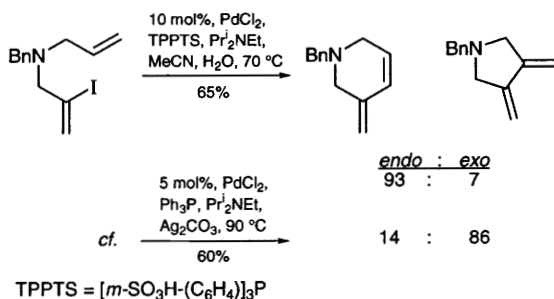
the presence of aryl chlorides and allow the Heck reaction of 4-chlorobenzaldehyde (**Scheme 36**).<sup>61</sup>

The same authors have developed the carbene palladium catalyst **21** which is not as active as the extremely active palladacycle catalyst **20** but is however very stable against heat, hydrolysis and oxidation (**Scheme 37**).<sup>62</sup> As with the palladacycle catalyst the carbene catalyst also promotes the Heck reaction of chloroarenes in the presence of TBAB.



**Scheme 37**

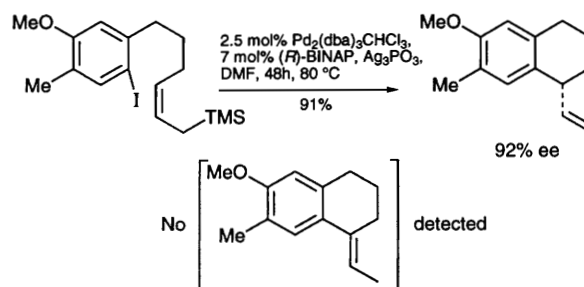
The usual *exo*-selectivity witnessed in the Heck reaction has been reversed to *endo*-selectivity in two cases of intramolecular reactions<sup>63,64</sup> using the Jeffery catalyst system.<sup>65</sup> The same reversal of regioselectivity was observed in intramolecular Heck reactions using catalytic palladium(II) salts and the water soluble tris(*m*-sulfonophenyl)phosphine (TSPPS) ligand in aqueous acetonitrile (**Scheme 38**).<sup>66</sup>



**Scheme 38**

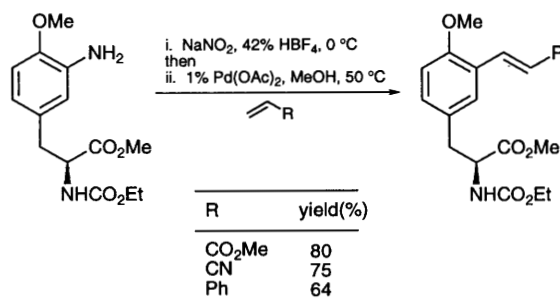
The asymmetric Heck reaction has become an extremely efficient method for the construction of chiral sp<sup>3</sup> carbon centres.<sup>66,67</sup> In the 'standard' and asymmetric Heck reactions where a tertiary sp<sup>3</sup> centre is formed there is always the potential for

occurrence of alkene regioisomers, due to competing palladate reductive elimination pathways. This problem has been successfully avoided by the incorporation of an allylsilane into the starting material, so that final reductive elimination ejects trimethylsilane (**Scheme 39**).<sup>68</sup>



**Scheme 39**

The Heck reaction is usually performed with vinylic or aromatic halides or trifluoromethanesulfonates and, to a much lesser extent, aromatic diazonium salts. Two recent reports have successfully used the latter, the first employing heterogeneous palladium on carbon catalysis,<sup>69</sup> and the second using an *in situ* method of diazonium salt formation and subsequent Heck reaction (**Scheme 40**).<sup>70</sup>

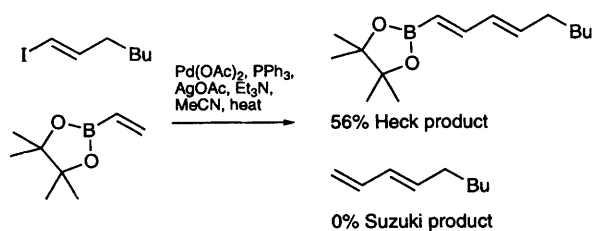


**Scheme 40**

Cascades involving Heck–Friedel–Crafts,<sup>71</sup> Heck–aldol<sup>72</sup> and Heck–Michael reactions<sup>72</sup> have found synthetic utility. Solid phase Heck reactions have also been reported which have been used to build libraries of cinnamate derivatives.<sup>73,49</sup> Finally, vinylboronate esters have been selectively converted into dienylboronate esters in a Heck fashion in the presence of silver or thallium acetate avoiding the competing Suzuki reaction, albeit in poor yields (**Scheme 41**).<sup>74</sup> The method holds promise for polyene synthesis as the dienylboronate products have then been further used in Suzuki couplings to form conjugated trienes stereoselectively.<sup>74</sup>

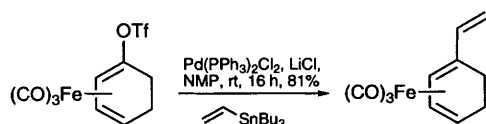
### 3.2.2 Stille reaction

Like the Heck, the Stille reaction has enjoyed widespread use in organic synthesis and the area has



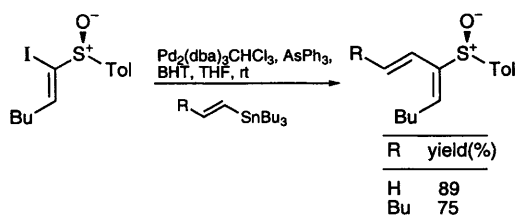
**Scheme 41**

been reviewed extensively.<sup>75</sup> Here again the focus will be on new or unusual aspects of the reaction. The first case of a Stille reaction of  $\eta^4$  tricarbonyl iron complexed cyclohexadienyl trifluoromethanesulfonate and vinylstannane has been reported (**Scheme 42**).<sup>76</sup> The same complex has also been coupled to an alkynyl fragment.



**Scheme 42**

Poor yields of dienylyl sulfoxides were obtained under many of the modified Stille conditions, and only when the radical inhibitor 2,6-di-*tert*-butyl-4-methoxyphenol (BHT) was included was the product obtained in 70% yield (**Scheme 43**).<sup>77</sup>

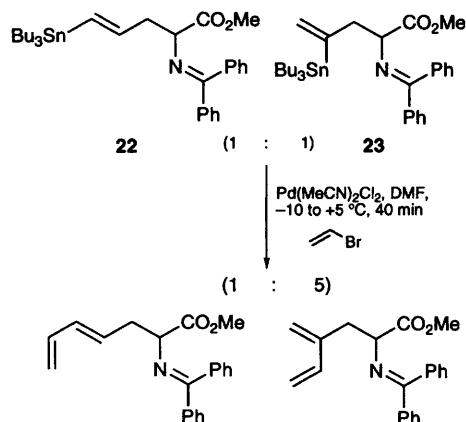


**Scheme 43**

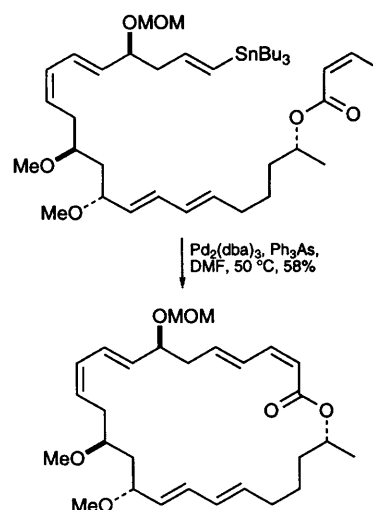
An extremely interesting accelerated Stille reaction of the more hindered vinylstannane **23** over the vinylstannane **22** is reported to be controlled by the chelation of a palladium intermediate species to a proximal imino functional group (**Scheme 44**).<sup>78</sup>

Fully aqueous versions of the Stille reaction have been reported using aryl and vinyl trichlorostannanes and 3 mol% palladium chloride in degassed 10% aqueous potassium hydroxide.<sup>79</sup> The Stille reaction has been performed in the solid phase<sup>49</sup> yielding benzodiazepine libraries<sup>80</sup> and also biaryls.<sup>81</sup> Heterogenous catalysis with palladium on charcoal has also been realised.<sup>82</sup>

Solution phase macrocyclic ring closure of several antibiotic natural products such as macrolactin A and anhydropristinamycin II<sub>B</sub> have been achieved successfully using the Stille reaction (**Scheme 45**).<sup>83</sup>



**Scheme 44**



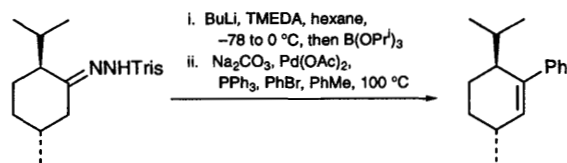
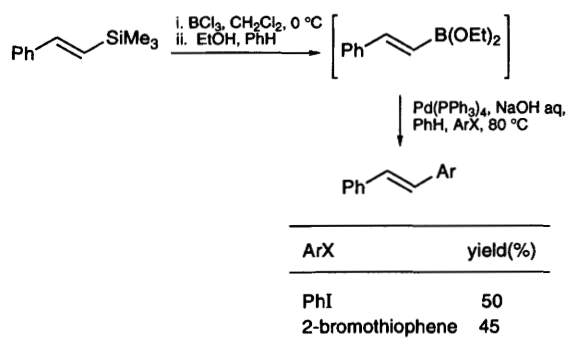
**Scheme 45**

### 3.2.3 Suzuki reaction

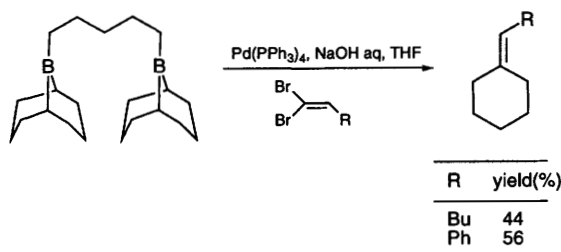
As for the Heck and Stille reactions, this coverage of the Suzuki reaction summarises novel and unusual variations on the well preceded reaction.<sup>84</sup> An *in situ* method for the synthesis of vinylboronate esters from vinylsilanes for subsequent Suzuki reaction gives moderate yields of arylated alkenes (**Scheme 46**).<sup>85</sup> Another *in situ* vinylboronate synthesis has been employed to effect a one pot Shapiro–Suzuki reaction.<sup>86</sup> A series of aromatic and aliphatic hydrazones have been converted into vinyl aromatics in reasonable yields (**Scheme 46**).

In the borane variant of the Suzuki reaction, geminal vinyl dibromides have been reacted with  $\alpha,\omega$ -diborylalkanes, derived from  $\alpha,\omega$ -dienes, under palladium(0) catalysis to give carbocycles with exocyclic double bonds (**Scheme 47**).<sup>87</sup>

The water soluble catalyst system previously described for use in the Heck reaction (**Scheme 38**) has also been used successfully in the Suzuki cross-

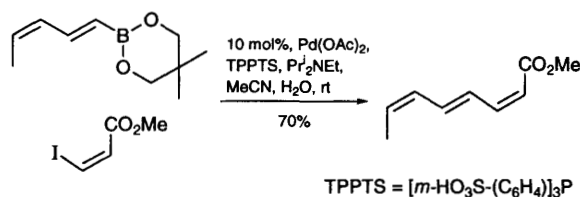


Scheme 46



Scheme 47

coupling reactions of vinylboronate esters with vinyl iodides in the presence of Hünig's base yielding a variety of functionalised dienes and trienes (Scheme 48).<sup>88</sup>



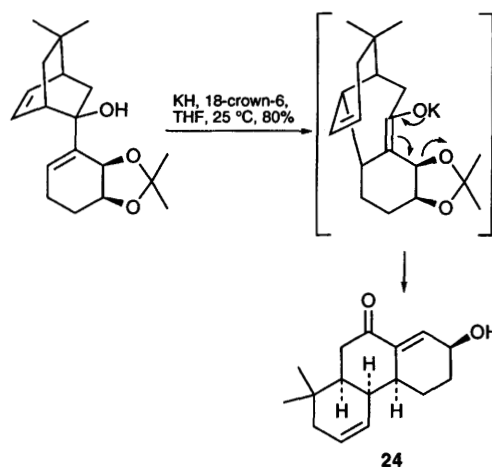
Scheme 48

Similarly the palladacycle catalyst described previously for use in the Heck reaction<sup>61</sup> has also been used in the Suzuki reaction in the synthesis of biaryls in 0.05 mol%.<sup>89</sup> The use of potassium *tert*-butoxide in the tetrakis(triphenylphosphine)palladium(0) coupling of bulky boronic acids and aryl halides has been found to give much improved yields of biaryls.<sup>90</sup> Suzuki reactions have also been performed successfully in the solid phase.<sup>49</sup>

### 3.3 Rearrangements

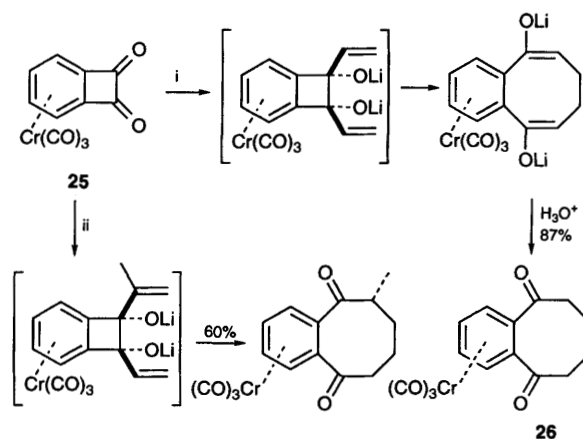
#### 3.3.1 Cope rearrangement

The oxy-anion Cope rearrangement has been used most noticeably by Paquette *et al.* in the stereo-selective construction of a whole host of densely packed polycyclic hydrocarbons.<sup>91</sup> The example depicted here involves a [3,3] Cope rearrangement followed by  $\beta$  elimination of the acetonide to give the tricyclic diene **24** (Scheme 49).<sup>91a</sup> This fragment has been further elaborated to a pentacyclic structure which is closely related to the kaurane diterpenoid natural products.



Scheme 49

The synthesis of chromium tricarbonyl complexed 1,2-dioxobenzocyclobutene **25** has recently been described by Butenschön *et al.*<sup>92</sup> Addition of excess vinylolithium to this complex at  $-78^\circ\text{C}$  gives, after acidic work up, the complexed benzocyclooctadiene **26** which is readily decomplexed (Scheme 50). The reaction is postulated to pass through a *syn* divinyl

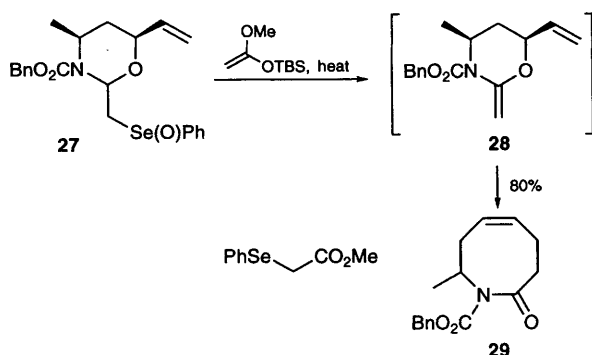


Scheme 50

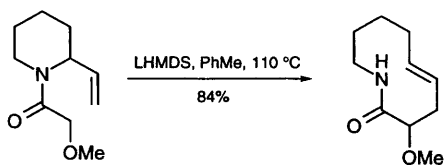
complex which then undergoes a double anionic oxy-Cope rearrangement giving the product. This reaction is of particular note as the same reaction of uncomplexed 1,2-dioxobenzocyclobutene gives only traces of the desired product. The majority of the product subsequently undergoes an undesired transannular aldol reaction. Reactions where there is branching on one or more of the reacting alkenes have also been reported but in much poorer yields.

### 3.3.2 Claisen rearrangement

The Claisen rearrangement is an extremely powerful method for the construction of carbon-carbon bonds and has been used extensively in the synthesis of a number of natural products. Here again the synthesis of unusual terpenes by Paquette *et al.* has demonstrated the applicability of the rearrangement for the production of medium ring compounds.<sup>93</sup> Two other applications of the Claisen rearrangement for the synthesis of medium ring lactams have been reported.<sup>94,95</sup> The first employed an *in situ* preparation of the diene **28** from the selenoxide **27**. The diene **28** subsequently rearranged to give the eight membered lactam **29** containing a *cis* double bond (Scheme 51).<sup>94</sup> The addition of a soft nucleophile trap, such as a silyl ketene acetal, was found to be crucial in preventing further reactions of selenic by-products.



Scheme 51



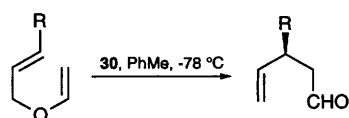
Scheme 52

The enolate aza-Claisen rearrangement depicted in Scheme 52 gives access to medium ring lactams with the thermodynamically more unstable *trans* double bond.<sup>95</sup>

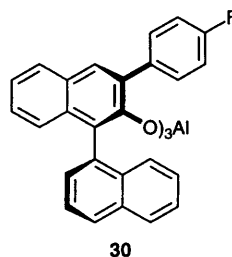
An asymmetric variation of the Claisen reaction has been developed using (*s*)-(-)-2-(methoxymethyl)pyrrolidine (SAMP) hydrazone as a chiral auxiliary for the synthesis of contiguous quaternary

and tertiary centres.<sup>96</sup> The same approach has also been successfully applied to the Wittig rearrangement (*vide infra*).<sup>119</sup>

Good to excellent *ees* have also been obtained from the use of chiral Lewis acids such as the binaphthol derivative **30** (Scheme 53).<sup>97</sup>

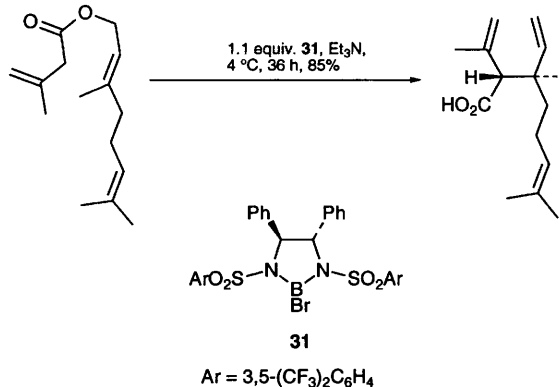


R	<i>ee</i> %	yield (%)
Bu <sup>t</sup>	91	70
Cy	86	85
Ph	97	76
TMS	92	78



Scheme 53

Corey *et al.* have used a highly enantioselective Claisen rearrangement of chiral boron enol ethers derived from the diazaborolidine **31** in their total synthesis of  $\beta$ -elemene and fuscil (Scheme 54).<sup>98</sup> A more recent synthesis of dolabellatrienone describes substantial increases in yield using pentaisopropylguanidine in the formation of the boron enol ether.<sup>99</sup>

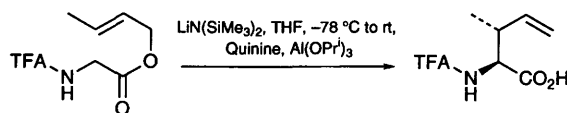


Scheme 54

The bulky Lewis acid complex of diethylaluminum chloride and triphenylphosphine has given moderate levels of diastereoselectivity in the rearrangement of an allyl vinyl ether from a remote asymmetric centre.<sup>100</sup> A urea soluble in organic solvents has given up to 22-fold acceleration of simple rearrangements. A stabilised bis-hydrogen

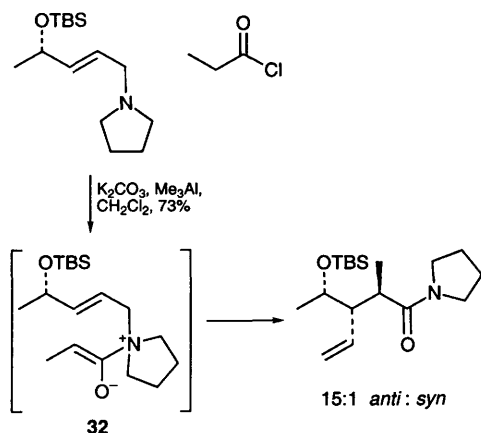
bonded transition state is suggested to be the cause of the rate increase.<sup>101</sup>

Chelation control has played an important part in directing the stereochemical outcome of the Claisen rearrangement.  $\beta$ -Oxygenation in the ester enolate variant has allowed efficient '1,4-chirality transfer',<sup>102</sup> whereas oxygenation on the allylic position has allowed the highly *E*-selective synthesis of alkenes.<sup>103</sup> Reactions involving amino acid derivatives have led to the stereoselective synthesis of alkylated amino acids<sup>104</sup> which have been made enantioselective in the presence of quinine (Scheme 55).<sup>104b</sup>



Scheme 55

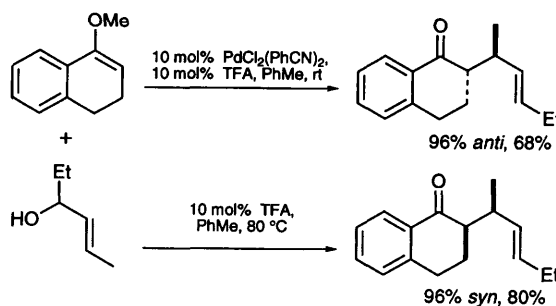
1,2 Asymmetric induction has been witnessed in the rearrangement of allylamine derived zwitterionic species **32** giving good des of the tertiary centres formed (Scheme 56).<sup>105</sup>



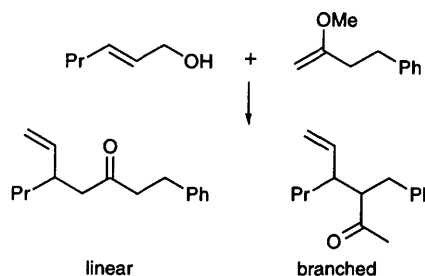
Scheme 56

Cyclic enol ether Claisen substrates, made *in situ* by the action of trifluoroacetic acid, rearrange in the presence of palladium(II) salts to give products with extremely high *anti* selectivity (Scheme 57).<sup>106,107</sup> Interestingly this palladium catalysed process gives the opposite stereochemical bias to that of the *syn* selective thermal rearrangement. Homogeneous palladium catalysed 'vinylogous acetylenic Claisen rearrangements' have also been reported<sup>108</sup> as well as immobilised rhodium catalysed rearrangements followed by intramolecular alkene hydroacylation.<sup>109</sup>

A modification of the thermal acid catalysed ketal Claisen rearrangement to a one pot procedure promoted by triisobutylaluminium has been implemented by Rychnovsky (Scheme 58).<sup>110a</sup> Yields and *E:Z* selectivities are high. In contrast to the thermal reaction<sup>110b</sup> this low temperature (0 °C) procedure



Scheme 57

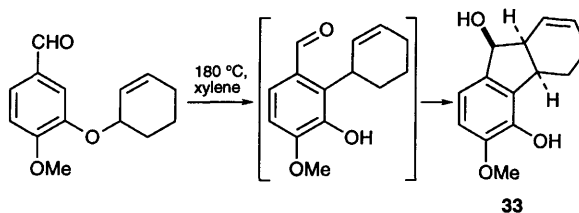


Conditions	yield(%)	linear : branched
i, PPTS, ii, Et <sub>3</sub> N, iii, Bu <sub>3</sub> Al, 0 °C.	58	94 : 6
PPTS, thermal <sup>110b</sup>	79	9 : 91

Scheme 58

gives predominantly linear products when unsymmetrical ketals are used.

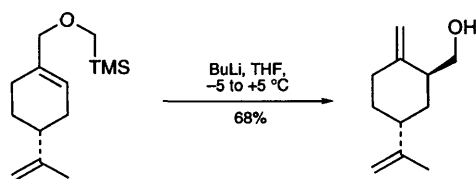
The Claisen rearrangement has been incorporated successfully into a tandem Claisen–hetero-ene reaction yielding a tetrahydro-5*H*-fluorene derivative **33** (Scheme 59).<sup>111</sup>



Scheme 59

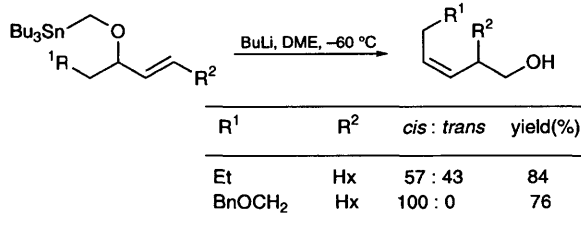
### 3.3.3 Wittig rearrangement

Trialkylsilanes have been used as an alternative to using the potentially toxic stannanes in the Wittig–Still rearrangement.<sup>112</sup> (Trimethylsilyl)methyl ethers have been transmetallated successfully with excess butyllithium to give lithiomethylallyl ethers which then undergo the [2,3] sigmatropic rearrangement (Scheme 60).



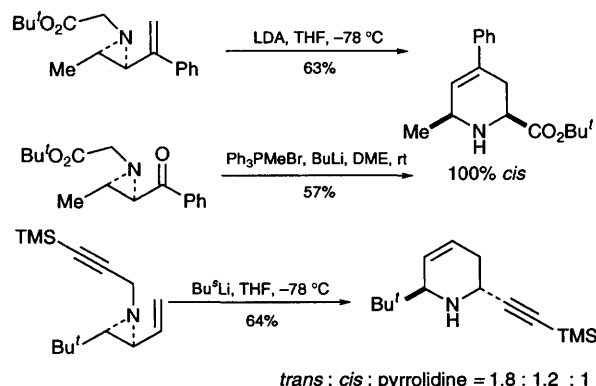
**Scheme 60**

The Wittig–Still rearrangement of *E*-alkenes, in general, is moderately selective in favour of the production of *E*-disubstituted alkenes.<sup>113,114</sup> When either a benzyloxy or (methoxymethyl)oxy moiety is placed  $\beta$  to the (tributylstannyl)methoxy group, however, the reaction becomes 95–100% *Z* stereo-selective (**Scheme 61**).<sup>113</sup> The choice of 1,2-dimethoxyethane (DME) as solvent was found to be crucial in obtaining high yields of products in these reactions.



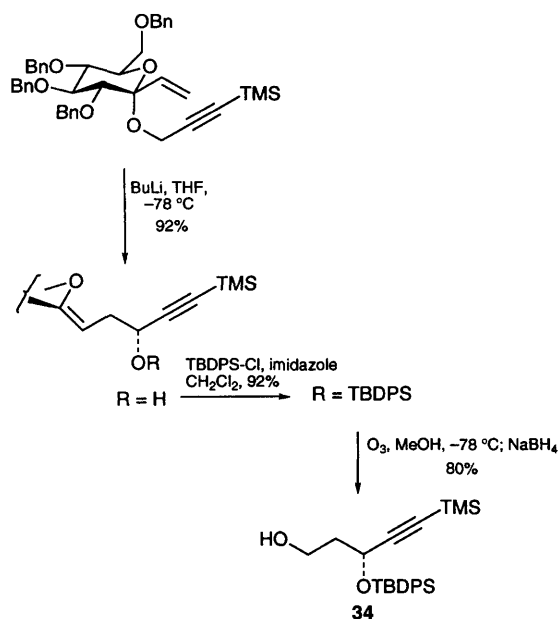
**Scheme 61**

The aza-Wittig rearrangement of *N*-[(*tert*-butoxycarbonyl)methyl]vinylaziridines is a highly selective method for the synthesis of unsaturated *cis*-2,6-disubstituted piperidines (**Scheme 62**).<sup>115</sup> The selectivity is reversed leading to *trans*-2,6 substitution when *N*-prop-2-ynyl(vinyl) aziridines are used.<sup>116</sup> Wittig olefination of keto *N*-[(*tert*-butoxycarbonyl)methyl]aziridines with two equivalents of ylide also yields *cis*-piperidines with total selectivity and in good yield; here the excess ylide acts as base for the [2,3] rearrangement of the vinyl aziridine intermediate (**Scheme 62**).<sup>117</sup>



**Scheme 62**

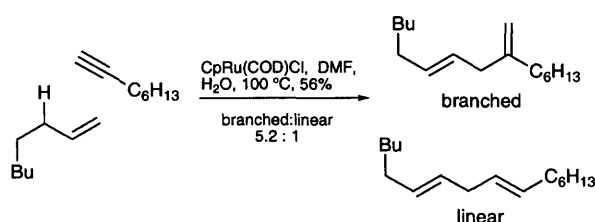
Several chiral auxiliaries have been appended to the carbanionic carbon atom, rendering the rearrangement diastereoselective. Notable among these approaches are the chiral 1,3,2-oxazaphosphorinane method of Denmark<sup>118</sup> and the prolinol derived hydrazone method of Enders,<sup>119</sup> both of which, after auxiliary cleavage, give products of >99% ee. Glucose has also been used as a chirality transfer agent, where the attachment is an acetal linkage at the anomeric centre and the allylic carbon. Rearranged products are obtained in >99% de and the auxiliary is readily cleaved by ozonolysis giving alk-2-ynyl alcohol **34** in high ee (**Scheme 63**).<sup>120</sup>



**Scheme 63**

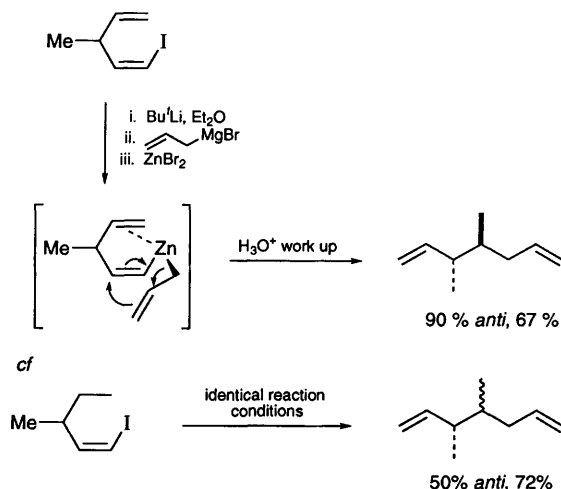
### 3.3.4 Miscellaneous rearrangements

Extensive studies by Trost into the transition metal catalysed Alder-ene type coupling of alkynes and alkenes have shown that CpRu(COD)Cl is in general the most efficient catalyst (**Scheme 64**).<sup>121</sup> The reaction tolerates a number of functional groups such as alcohols, silyl ethers and esters, and gives excellent stereochemical control at the newly formed double bonds. Regiochemical selectivities between branched and linear type coupling are in general of the order of 4:1.



**Scheme 64**

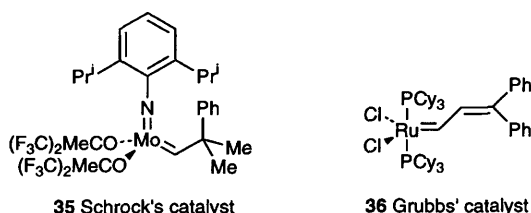
The [3,3] sigmatropic rearrangement of allyl-(vinyl)zincs is known to be highly diastereoselective when coordinating atoms such as oxygen are attached to the carbon backbone.<sup>122</sup> Normant *et al.* have recently shown that a neighbouring alkene can act as a chelating group by  $\pi$ -donation to the zinc centre resulting in excellent diastereomeric induction (Scheme 65).



Scheme 65

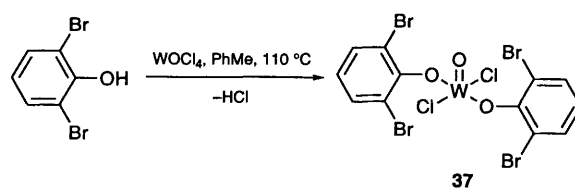
### 3.4 Alkene metathesis

Since the early 1990s ring closing metathesis, 'the metal catalysed exchange of the alkylidene of two olefins', has enjoyed increasing popularity in organic synthesis.<sup>123</sup> The most frequently used catalysts **35** and **36** devised by Schrock and Grubbs respectively (Scheme 66), have been exploited to great effect in many natural product syntheses.<sup>124</sup>



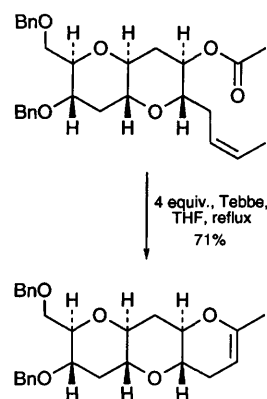
Scheme 66

Although extremely versatile, the Schrock and Grubbs catalysts have to be made in the laboratory in multistep sequences. The use of a catalyst readily made from commercially available materials in a single step is therefore an attractive goal that has been realised in the synthesis of the tungsten complex **37** (Scheme 67).<sup>125</sup> The catalyst is made simply by heating tungsten(VI) oxychloride and 2,6-dibromophenol in toluene, followed by evaporation of solvent and recrystallisation. Tetraethyllead and 2 mol% of **37** catalyses ring closing metathesis of dienes in good yields.<sup>125</sup>



Scheme 67

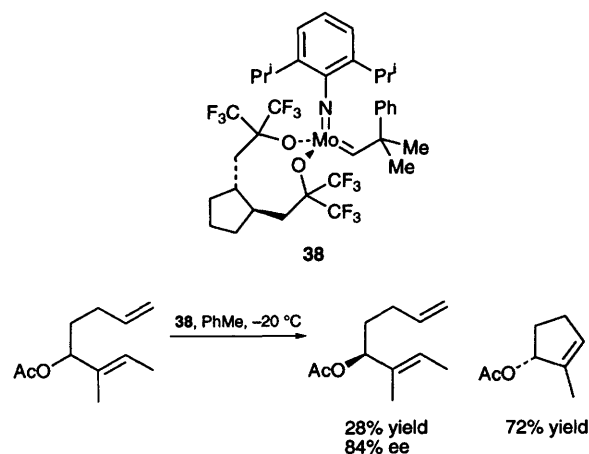
Nicolaou *et al.* have adapted the earlier work of Grubbs and reported that a fourfold excess of the Tebbe reagent brings about olefination of esters which on further heating *in situ* undergo ring closing metathesis to give cyclic enol ethers (Scheme 68).<sup>126</sup> Some Lewis acid promoted hydrolysis of the products was noted but this was prevented by the use of dimethyltitanocene in place of the Tebbe reagent.



Scheme 68

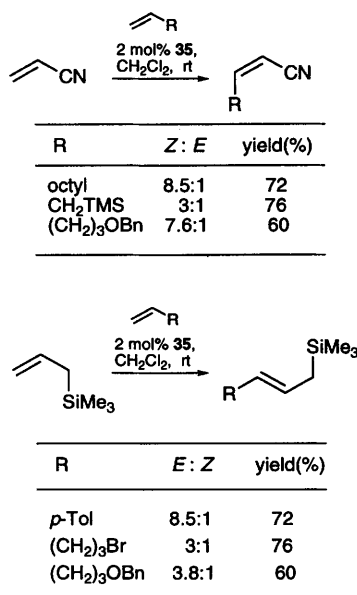
Grubbs has reported the first instance<sup>127</sup> of kinetic resolution of racemic substrates by a metathesis reaction with the chiral molybdenum catalyst **38** (Scheme 69).<sup>128</sup> This preliminary report quotes low to moderate ees of recovered uncyclised material.

Monosubstituted allylsilanes have been synthesised by metathesis of terminal alkenes with tri-



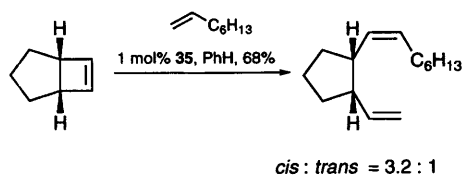
Scheme 69

methyl(allyl)silane in the presence of the Shrock catalyst (**Scheme 70**).<sup>129</sup> The reaction is tolerant of a wide range of functionality and is moderately *trans* selective. A similar synthesis of  $\alpha,\beta$ -unsaturated cyanides has been brought about by the cross metathesis of terminal alkenes with the usually unreactive acrylonitrile (**Scheme 70**).<sup>130</sup> In contrast this reaction is quite selective for the formation of *cis*-alkenes.



**Scheme 70**

With carefully controlled reaction conditions the cross metathesis of bicyclic cyclobutenes and terminal alkenes catalysed by the Schrock catalyst has been realised (**Scheme 71**).<sup>131</sup> The reaction gives a mild excess of *cis*-substituted alkenes.

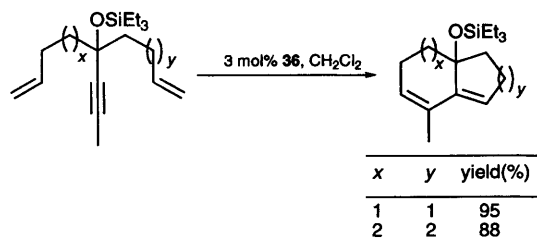


**Scheme 71**

The Grubbs catalyst **36** has been used successfully in the intramolecular metathesis of non-conjugated dieneynes to give [*n.m.0*] fused bicyclic hydrocarbons (**Scheme 72**).<sup>132</sup> The reaction allows the formation of five, six and seven membered rings but fails with halogen, trimethylsilyl and tributylstannyl substituted alkynes.

### 3.5 Miscellaneous

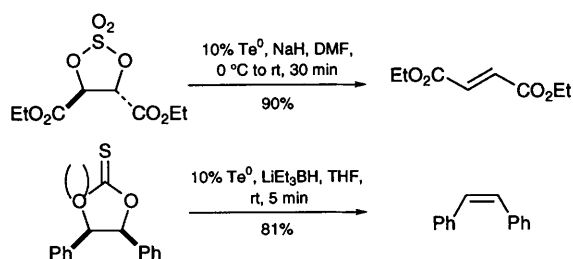
The need for petrochemical feedstocks from non-hydrocarbon sources such as carbon dioxide



**Scheme 72**

continues to be a scientific and socially very important area of research.<sup>133,134</sup> Dodecacarbonyltrirron supported on zeolite ZSM-5 has been shown to be a very active catalyst for the conversion of carbon dioxide into methane and light alkenes with a high selectivity for ethene.<sup>134</sup>

There are numerous methods for the deoxygenation of 1,2-diol derivatives.<sup>135</sup> A method has recently been described for the stereospecific synthesis of alkenes by the treatment of cyclic sulfates and thiocarbonates with a catalytic amount of telluride (**Scheme 73**).<sup>136</sup> The telluride is regenerated by the action of a stoichiometric amount of either sodium hydride or lithium triethylborohydride.



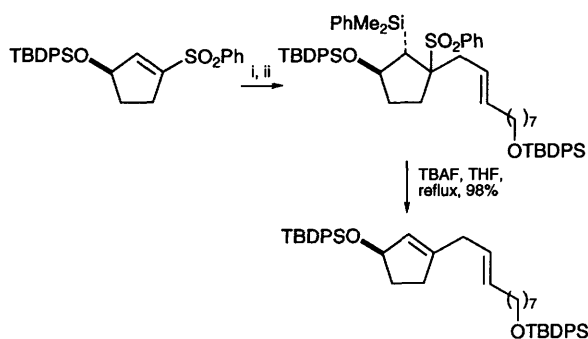
**Scheme 73**

Deoxygenation has also been reported to be facilitated by titanium metal activated by trimethylsilyl chloride.<sup>3</sup> This activation procedure, described in Section 2.1 for the pinacol reaction, has also been used in the deoxygenation of epoxides and in the McMurry reaction.<sup>3</sup>

Attempts to form vinyl anions by treatment of vinyl sulfones with lithium naphthalenide have been shown to give the undesired phenyllithiums.<sup>137a</sup> In a communication by Fuchs *et al.* the problem was circumvented by adding a silyl anion in a Michael sense to vinyl sulfones and trapping the  $\alpha$ -lithio sulfone with an electrophile. The double bond is then regenerated simply by treating the  $\beta$ -silyl sulfone with fluoride (**Scheme 74**).<sup>137b</sup> If the substrate has a potential leaving group  $\beta$  to the silane, such as a protected hydroxy group, some  $\beta$ -elimination can arise to give allylic sulfones.

Terminal alkynes bearing a nitrogen-containing functional group at the 3-position have been stannylcuprated and silylcuprated selectively using

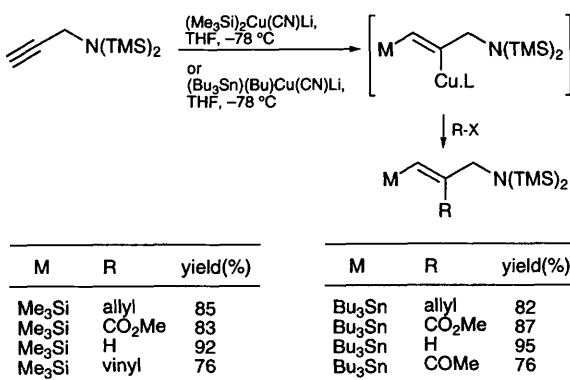




Reagents: i,  $\text{PhMe}_2\text{SiLi}$ , THF; ii,  $\text{TP(SO(CH}_2)_7\text{CHCH}_2\text{)Br}$ , HMPA,  $-78^\circ\text{C}$ , 69%

**Scheme 74**

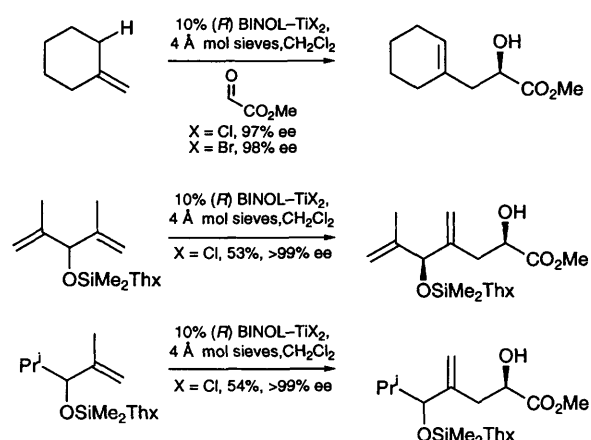
the appropriate metalocuprate to give the *syn*-metalocuprate in a highly regioselective manner (**Scheme 75**).<sup>138</sup> These intermediates react smoothly with a broad range of carbon electrophiles and the products have been used as partners in Heck and Stille type reactions.



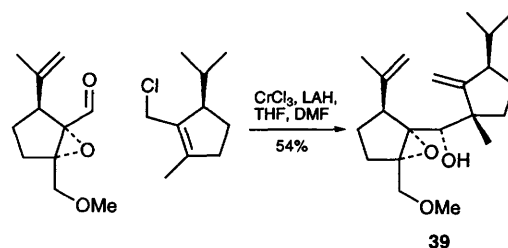
**Scheme 75**

Novel titanium binaphthol dihalides have found use as chiral catalysts in the highly enantioselective glyoxalate-ene reaction.<sup>139</sup> The reaction is highly dependent on the presence of molecular sieves and exhibits a strong positive non-linear effect. The catalysts have also been used to desymmetrise *meso* substrates and kinetically resolve racemic substrates with high ees (**Scheme 76**). The catalysts have also been used successfully in the asymmetric carbonyl-ene cyclisation, Mukaiyama aldol condensation, hetero Diels-Alder and allylic stannane/silane addition to glyoxaldehyde.<sup>139</sup>

Tankeshita and Kato used three interesting reactions for the formation of double bonds in their enantioselective synthesis of cotylenol.<sup>140</sup> The first reaction used the increasingly popular Nozaki<sup>141</sup> chromium catalysed addition of an allyl chloride to aldehyde to give the alcohol **39** in 54% yield (**Scheme 77**). In this case the addition to the aldehyde was highly diastereoselective and also



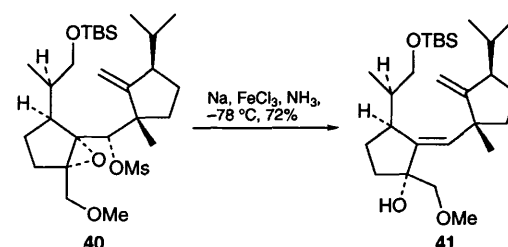
**Scheme 76**



**Scheme 77**

regioselective, reacting on the most hindered end of the allylchromium species.

Multistep elaboration of the allylchromium addition product **39** gave the epoxy methanesulfonate **40** which when subjected to sodium and iron(III) chloride in liquid ammonia gave the alkene **41** in 72% yield (**Scheme 78**).<sup>140</sup> Addition of the iron salt was found to be vital, over-reduction being seen otherwise.



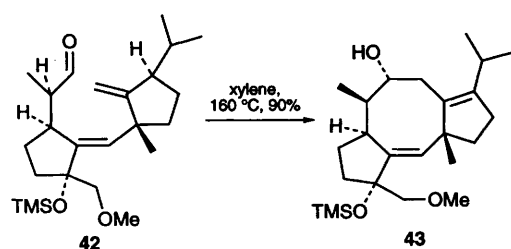
**Scheme 78**

Finally, after protecting group manipulation of **41** and primary hydroxy group oxidation the key ring closing ene reaction was successfully achieved by heating the aldehyde **42** in xylene, giving the core tricyclic ring system **43** in 90% yield (**Scheme 79**).<sup>140</sup>

## 4. Alkynic hydrocarbons

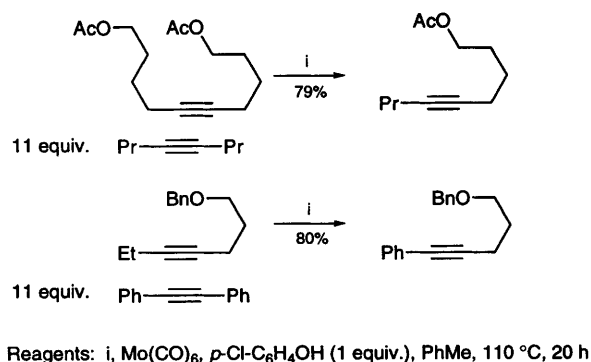
### 4.1 Alkyne metathesis

The rapidly expanding area of alkene metathesis has been described previously.<sup>123,124</sup> A mixture of molyb-



**Scheme 79**

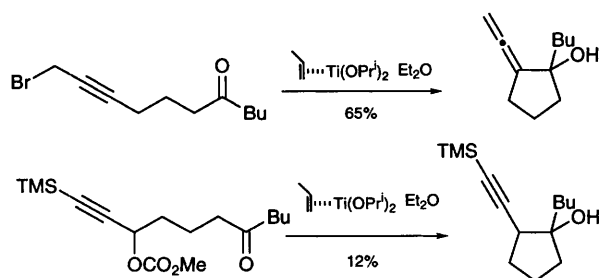
denum hexacarbonyl and *p*-chlorophenol in boiling toluene has been shown to be an effective catalyst for cross alkyne metathesis (**Scheme 80**).<sup>142</sup> This reaction is brought about by shifting the reaction equilibrium towards products by the use of an excess of one alkyne component.



**Scheme 80**

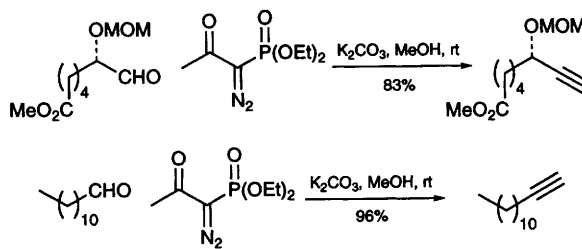
#### 4.2 Miscellaneous

The  $\text{Ti}(\text{OPr}^i)_2$  equivalent ( $\eta^2$ -propene) $\text{Ti}(\text{OPr}^i)_2$  formulated by Sato<sup>143</sup> has been used to form alkynes and allenes from prop-2-ynyl bromides and carbonates by cyclisation onto ketones and aldehydes (**Scheme 81**).<sup>144</sup> The low yields of alkynes are improved if the carbonyl function is masked as a cyclic acetal.<sup>144</sup>



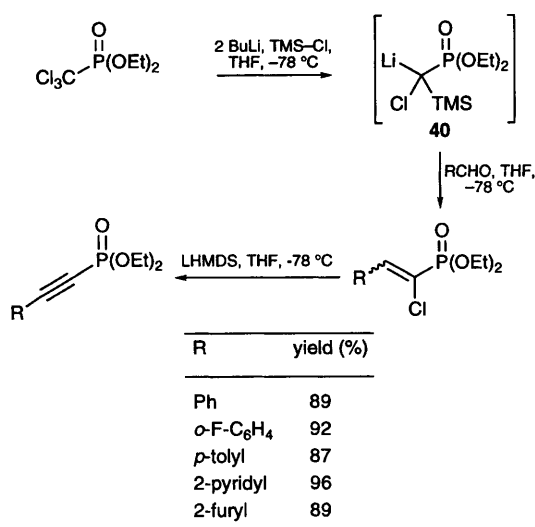
**Scheme 81**

A high yielding one step procedure for the conversion of aldehydes into terminal alkynes that avoids the use of strong alkyl lithium bases or inert atmosphere has been adapted by Bestmann *et al.* (**Scheme 82**).<sup>145</sup>



**Scheme 82**

The reaction of diethyl trichloromethylphosphonate with two equivalents of butyllithium and trimethylsilyl chloride gives the silylphosphonate anion **40**.<sup>146</sup> Peterson type reaction of **40** with aldehydes then gives  $\alpha$ -chlorovinylphosphonates which after isolation are cleanly eliminated with lithium bis(trimethylsilyl)amide (LHMDS) to give phosphonate substituted alkynes in very high yields (**Scheme 83**).<sup>146</sup>



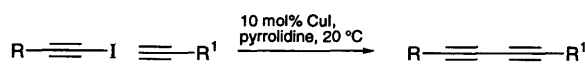
**Scheme 83**

1,2-Diarylalkenes have been oxidised directly to 1,2-diarylalkynes by treatment with  $\text{Bu}^t\text{OK}$  in DMF under air although no yields were reported.<sup>147</sup>

Unsymmetrical diynes have been constructed successfully by the cross coupling of a terminal alkyne with an iodoalkyne catalysed by copper(I) iodide in pyrrolidine at room temperature (**Scheme 84**).<sup>148</sup> Addition of palladium salts improved the yields of the sluggish reactions with bromoalkynes.

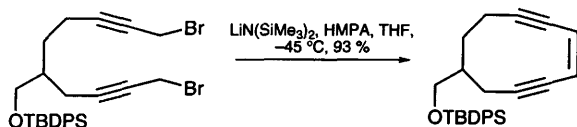
The area of enediyne natural products constantly brings to the fore new methods for the construction and joining of alkynes and alkenes. Cyclic enediynes have been constructed by the joining of two prop-2-ynyl bromides in the presence of LHMDS and HMPA (**Scheme 85**).<sup>149</sup>

In the synthesis of dynemicin analogues an improved route for the coupling of the dienyn portion has been published involving the intra-



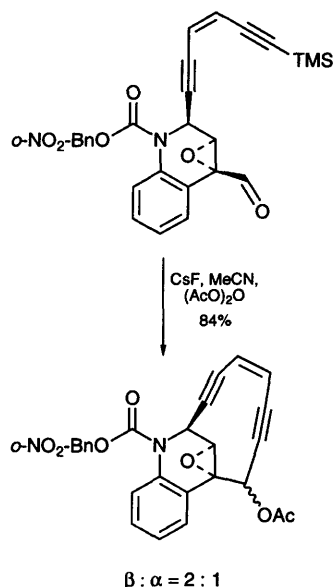
R	R <sup>1</sup>	yield(%)
C <sub>5</sub> H <sub>11</sub>	Ph	95
C <sub>5</sub> H <sub>11</sub>	(CH <sub>2</sub> ) <sub>3</sub> Cl	61
C <sub>5</sub> H <sub>11</sub>	CH <sub>2</sub> OH	95
Ph	CH <sub>2</sub> OH	95

**Scheme 84**



**Scheme 85**

molecular caesium fluoride catalysed addition of a trimethylsilylalkyne to an aldehyde (**Scheme 86**).<sup>150</sup> The addition of an *in situ* alkoxide trap such as an anhydride, acyl halide or chloroformate was found to be crucial in obtaining high yields avoiding the formation of other by-products.



**Scheme 86**

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