Recent synthetic applications of the non-classical Wittig reaction

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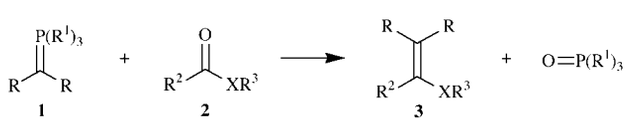
1 Introduction

As a synthetic process the Wittig reaction is probably without equal. Its use in the synthesis of naturally occurring molecules[1] and as a general method for the preparation of alkenes[2] in a predictable manner has led to it becoming one of the cornerstones of synthetic chemistry. In its simplest form the reaction can be considered as the reaction of a phosphorane (ylide) with either an aldehyde or a ketone leading to the formation of an alkene and a phosphine oxide. In 1988 we published[3] a review entitled "The Wittig Olefination Reaction with Carbonyl Compounds other than Aldehydes and Ketones", which was the first to detail the reaction of phosphoranes **1** with carboxylate derivatives **2**. This 'non-classical' variant of the traditional process leads to the formation of heterosubstituted alkenes **3**, including enol ethers and related functional groups (Scheme 1).

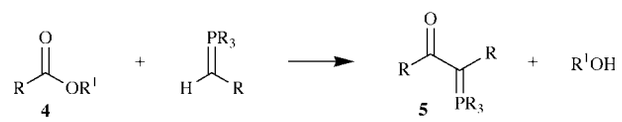


Scheme 1 R = H, alkyl, aryl, EWG; R^1 = alkyl, aryl; R^2 = H, alkyl, aryl, EWG; R^3 = alkyl, aryl, -COR, X = O, S, NH, NR.

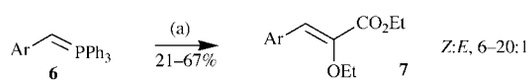
In this original work we detailed the general methodology that had been developed, several synthetic applications and a mechanistic consideration of the reaction. The aim of this current work is to provide an update on new developments and applications of this reaction and to present a more comprehensive overview of the area; the majority of the work covered will be from 1986 to the present. The reader is also directed to reviews by Heron[4] which details the synthesis of heterocycles from intramolecular Wittig and Horner–Wadsworth–Emmons (HWE) reactions and by Cristeau[5] who has detailed the synthetic applications of metalated phosphonium ylides.

2 Wittig reactions with esters

The Wittig reaction with esters can be considered under the general headings intra- and intermolecular processes and the former can be divided into reactions that form heterocyclic or carbocyclic products. The reaction of simple esters **4** with phosphoranes is known to lead to the formation of β-ketophosphoranes **5** by displacement of alkoxide[3] (Scheme 2). In order for the formation of Wittig products to occur it is known that a strong electron withdrawing substituent at the carbonyl group is required. One example of this can be found[6] in the reaction of the semi-stabilised ylides **6** with diethyl oxylate which leads to the formation of enol ethers **7** in 21–67% yield and *Z*:*E* selectivity of 6:1 to 20:1; in this example the reacting ester is activated by the presence of the second ester function (Scheme 3).

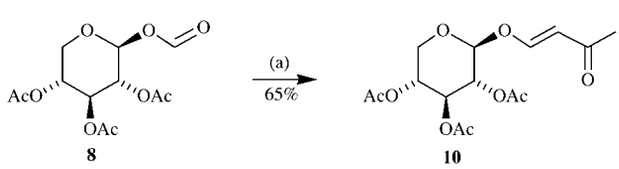


Scheme 2 R, R^1 = alkyl, aryl.



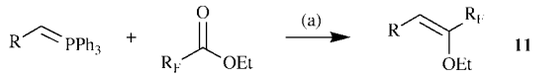
Scheme 3 *Reagents and conditions*: (a) $(CO_2Et)_2$, THF, rt, 12–18 h; Ar = Ph, substituted Ph, 1-naphthyl, 2-naphthyl, 2-thienyl.

Wittig reactions with formates are also generally successful and one recent example is the reaction of the 1-*O*-formylpyranose **8** with acetylmethylenetriphenylphosphorane **9** which led to the formation of the synthetically useful Wittig product **10** in 65% yield[7] (Scheme 4).



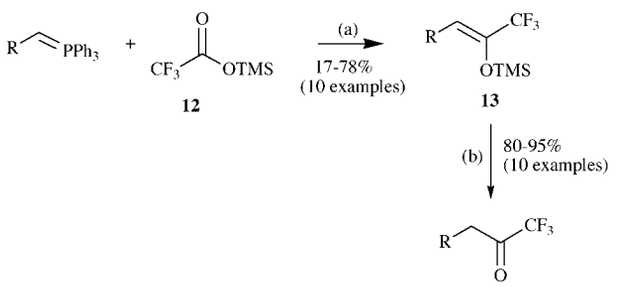
Scheme 4 *Reagents and conditions*: (a) $CH_3COCHPPh_3$ **9**, EtOAc, Δ, 18 h.

Polyfluorinated esters **11** are also known to be good substrates for the reaction and Bégué and co-workers have investigated the reaction in detail.[8] It was found that the reactions are best performed under salt free conditions (ylides generated using $NaNH_2$) and that best yields were obtained where R was alkyl or aryl (33–70%), however where R = COOEt the yield was diminished (30%). In addition it was found that if the ylides were generated using BuLi it was found that the formation of β-ketophosphoranes was the preferred reaction pathway[8a] (Scheme 5). The products of this reaction are resistant to hydrolysis and to circumvent this Bégué has reported the reaction of phosphoranes with trimethylsilyl trifluoroacetate **12** to give silyl enol ethers **13** which are readily hydrolysed to the

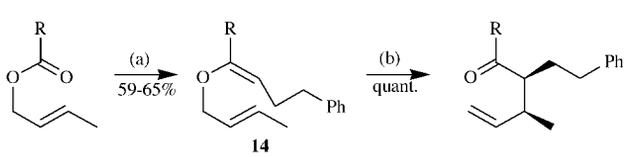


Scheme 5 *Reagents and conditions*: (a) THF, PhH, rt or Δ, 4–6 h; R = alkyl, aryl, CO_2Et; $R_F = CF_3$, C_2F_5, C_3F_7, C_7F_{15}.

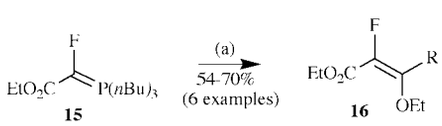
corresponding ketone[8b,c] (Scheme 6). Bégué has also reported the Claisen rearrangement of fluorinated enol ethers **14** which had been prepared *in situ* using Wittig methodology[8c] (Scheme 7). This is not a unique application of this tandem methodology as earlier reports by Suda and Carpenter report a similar process using *O*-allyl formates.[9] Other examples are also known, for example the formation of the fluorinated enol ethers **16** by treatment of the corresponding esters with the ylide **15**[10] (Scheme 8).



Scheme 6 *Reagents and conditions*: (a) THF or PhH, R = Alkyl, Ph.

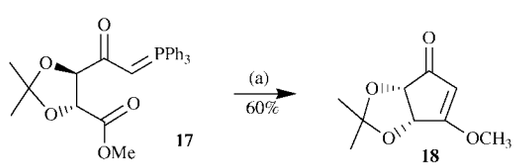


Scheme 7 *Reagents and conditions*: (a) $PhCH_2CH_2CHPPh_3$, THF; (b) 100 °C, $PhCH_3$, 2 h. R = CF_3, C_2F_5.



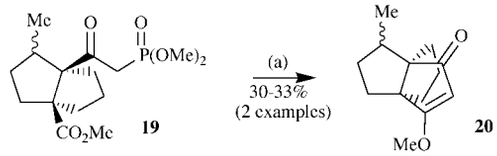
Scheme 8 *Reagents and conditions*: (a) RCO_2Et, THF, −78 °C to rt, 6 h; R = CF_3, C_2F_5, C_3F_7, CF_2Cl, CF_2Br.

Simple esters show better reactivity when used in intramolecular reactions, for example Bestmann and co-workers have reported the interesting cyclisation of the tartrate-derived phosphorane **17**, which proceeds in 60% yield to give cyclopentenone **18**, the starting material in his synthesis of the carbocyclic nucleoside (−)-neplanocin A. It is however worthy of note that the reaction, which proceeds with epimerisation at C-3, requires highly forcing conditions[11] (Scheme 9). In a related process Kraus and Shi reported the synthesis of the tricycles **20** by cyclisation of the phosphonates **19** in modest yield (Scheme 10).[12]

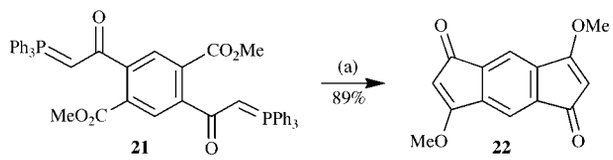


Scheme 9 *Reagents and conditions*: (a) PhMe, 150 °C, 110 bar, N_2, 80 h.

A similar reaction can be used in the synthesis of indanones[13] and a recent example is the synthesis of the indacenedione **22** by a double Wittig cyclisation of phosphorane **21** which proceeds in an excellent 89% yield[14] (Scheme 11).

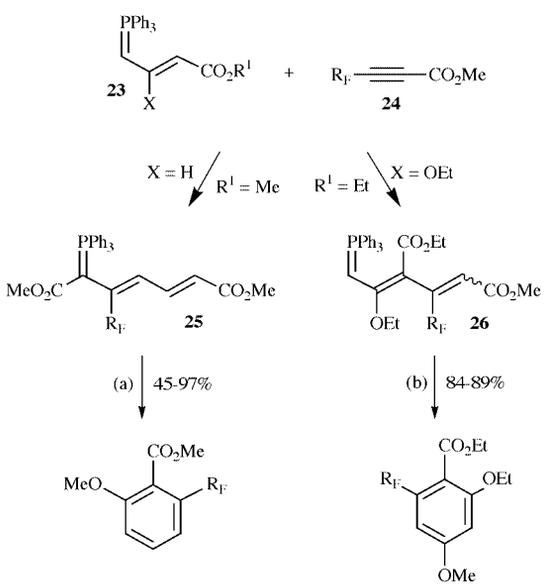


Scheme 10 *Reagents and conditions*: (a) Me = α, KOtBu, 18-crown-6, $PhCH_3$, 80 °C, 15 h; (a) Me = β, KH, 18-crown-6, $PhCH_3$, Δ, 6 h.



Scheme 11 *Reagents and conditions*: (a) Δ.

Ding and co-workers have reported that the intramolecular non-classical Wittig reaction of esters is also a method for the preparation of polysubstituted aromatics.[15] They reported that reaction of phosphorane **23** with the perfluorinated acetylenic esters **24** proceeded with net insertion into the C=P bond to give **25** where X = H, whereas insertion into the C–H bond occurred where X = OEt to give **26**. On heating at reflux in xylene, in the case of **25** or in benzene at 160–210 °C (sealed tube) for **26**, both these adducts cyclised to give the corresponding polysubstituted benzene in good to excellent yields (Scheme 12). By a similar sequence of events the arylphosphoranes **27** where converted into the naphthalenes **28**[15c] (Scheme 13).

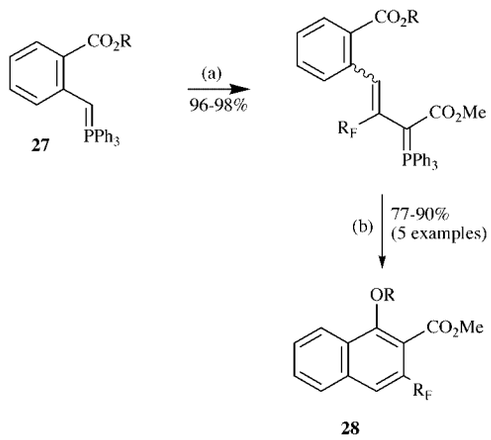


Scheme 12 *Reagents and conditions*: (a) Δ, xylenes, 10 h; (b) Δ, PhH, sealed tube 160–210 °C, 30–40 h; $R_F = CF_3$, C_2F_5, C_3F_7.

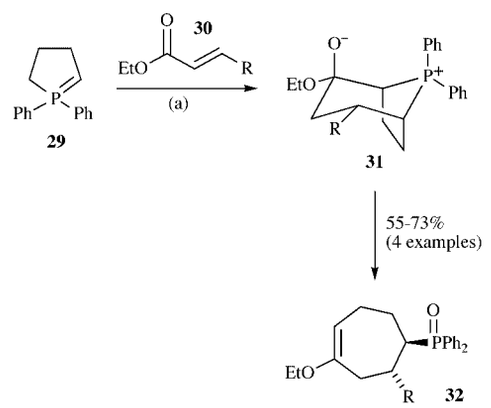
The reaction of ylide **29** with α,β-unsaturated esters **30** leads to an interesting example of the intramolecular Wittig reaction in which the phosphine oxide and alkene products are retained in the same molecule. The reaction proceeds by 1,4-addition of the ylide to the enoate leading to intermediate **31** which undergoes elimination to give the product **32**[16] (Scheme 14).

Intramolecular reactions of esters have found considerable application in the synthesis of heterocycles and several examples detailing the formation of benzofurans, chromenes, isochromenes, dihydrofurans and dihydropyrans have been reported.[3,4]

A recent example of the synthesis of 2-styryl-4*H*-[1]benzopyran-4-ones **36** involves the commonly used strategy[17] of reacting the ester function of aromatic ester such as **33** with non-stabilised ylides leading to the β-ketophosphoranes **34**,

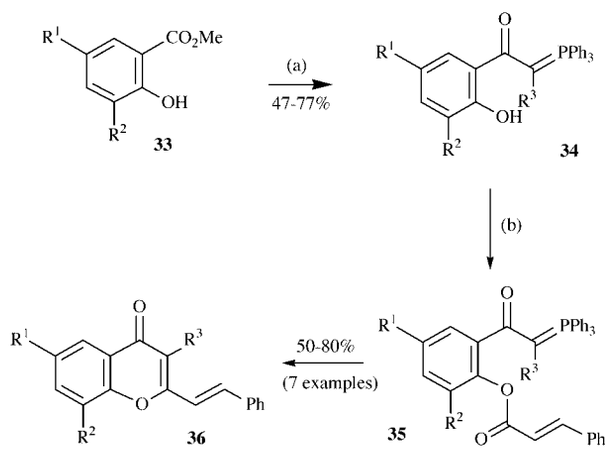


Scheme 13 *Reagents and conditions*: (a) **24**, K_3CO_3, DME, 48 h; (b) Δ, xylenes, sealed tube 250 °C, 10–20 h; R = Me, Et; $R_F = CF_3$, C_2F_5, C_3F_7.



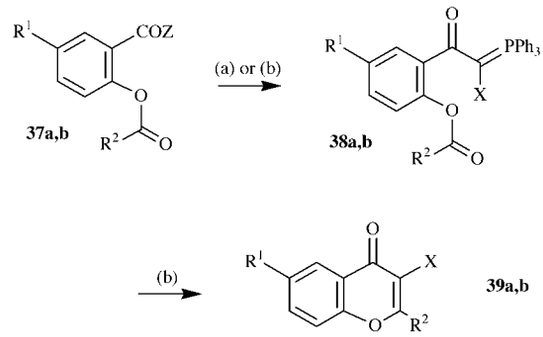
Scheme 14 *Reagents and conditions*: (a) Δ, THF, 16 h. R = Me, n-Pr, i-Pr, Ph.

followed by acylation of the free hydroxy group with an excess of cinnamyl chloride in pyridine to give the intermediates **35** which undergo cyclisation on heating to give **36**[18] (Scheme 15).



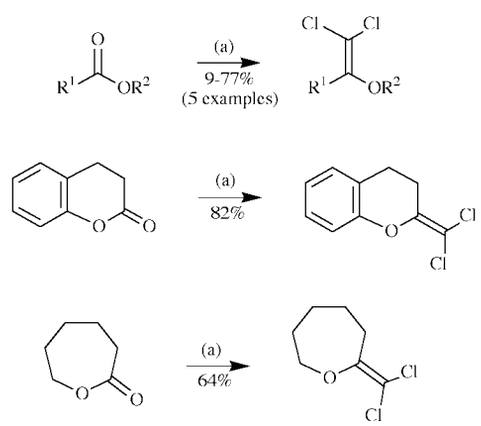
Scheme 15 *Reagents and conditions*: (a) R^3CHPPh_3, THF, 50–60 °C, 3 h; (b) PhCH=CHCOCl, Py, 70 °C, 20–24 h; R^1 = H, OMe; R^2 = H, Me, Pr, allyl; R^3 = H, Me.

The alternative strategy is to reverse these two steps and begin with an acylsalicylic acid and convert the acid function into a phosphorane.[19] For example the heterocycles **39a** (X = Cl) are easily prepared by treatment of the arylcarboxylic acids **37a** (Z = OH) with triphenylphosphine in the presence of carbon tetrachloride.[20] This reaction is thought to proceed *via* an acid chloride and then the intermediate chloro ylide **38a**; evidence is offered by the isolation of the cyano ylide **38b** (X = CN) prepared from the acid chloride **37b** (Z = Cl), which undergoes cyclisation under forcing conditions to give **39b**[20] (Scheme 16).



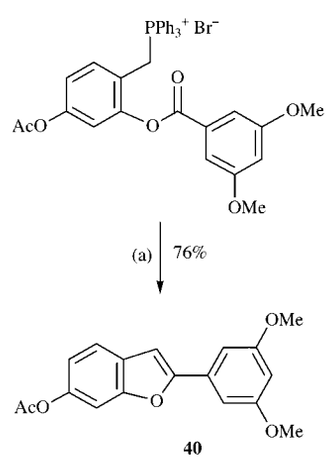
Scheme 16 *Reagents and conditions*: (a) Z = OH, X = Cl, R^1 = H, Cl, R^2 = Ar; PPh_3, NEt_3, CH_2Cl_2, CCl_4; 43–60%; (b) Z = Cl, X = CN, R^1 = H, R^2 = CH_3; Cl_3CCN, PPh_3, CH_2Cl_2, rt; 48%, then $C_6H_4Cl_2$, Δ, 180 °C; 65%.

The combination of triphenylphosphine and carbon tetrachloride was originally developed[21] by Suda and Fukushima to effect the dichloromethenylation of simple esters and lactones (Scheme 17) and as we shall see later this methodology has been employed to good effect in several synthetic protocols.



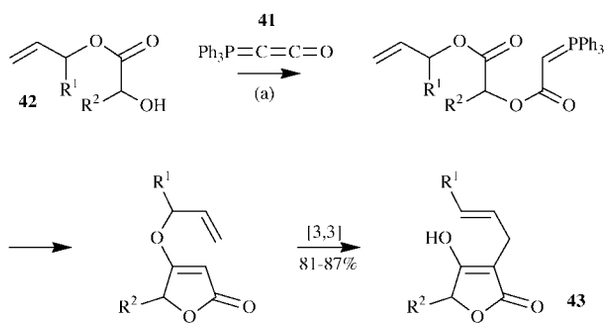
Scheme 17 *Reagents and conditions*: (a) PPh_3, CCl_4, Δ, 3–20 h; R^1 = H, Bn, Ph, 2-thienyl; R^2 = Bn, allyl.

Benzofurans are easily accessed by the intramolecular Wittig reaction with esters and several recent examples have been reported.[22] The most noteworthy of these demonstrates the synthesis of the highly oxygenated system **40** *via* a Wittig cyclisation, a key step in the total synthesis of the naturally occurring antifungal benzofuran moracin C[23] (Scheme 18).



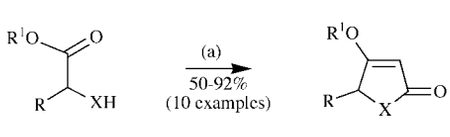
Scheme 18 *Reagents and conditions*: (a) NEt_3, dioxane, Δ.

Perhaps the most important progress in this area of research has been reported by Schobert and Bestmann who have utilised the versatile keteneylidene(triphenyl)phosphorane **41** in the domino synthesis of a range of heterocycles.[24] Initially Schobert and Bestmann reported a one pot synthesis of α,γ-disubstituted tetronic acids **43** from α-hydroxy esters **42** *via* a tandem Wittig–Claisen reaction.[24a] The reaction proceeds *via* the addition of the alcohol function to **41** followed by an intramolecular Wittig cyclisation and finally the Claisen rearrangement. In most cases it was found that the stereochemistry at C-5 of the tetronic acid was retained, however in some cases partial racemisation was observed (Scheme 19).



Scheme 19 *Reagents and conditions*: (a) **41**, Δ, $PhCH_3$, 24 h; R^1 = H, Me, R^2 = Me, Ph.

Schobert later[24b,c] developed this reaction to give a general synthesis of tetronates **45** (X = O), tetramates (X = NH) and thiotetronates (X = S) by a similar reaction of α-hydroxy, α-amino or α-sulfanyl carboxylates **44** (Scheme 20). This reaction was then extended to the synthesis of the annulated systems **46** and **47**, the δ-lactam **48** and the coumarin **49**, quinolone **50** and thiocoumarin **51** (Scheme 21). The methodology has also been applied to the synthesis of the seven membered heterocycles **52** and **53** and in the synthesis of the 1,2-oxazin-6-ones **54**, in addition reaction of the related ylide **55** or **41** with hydrazines **56** has also been shown to give the pyridazines **57** and **58** in good yield (Scheme 22). Interestingly in the formation of **57a** the Wittig reagent shows preference for reaction with an ester function in the presence of a ketone.

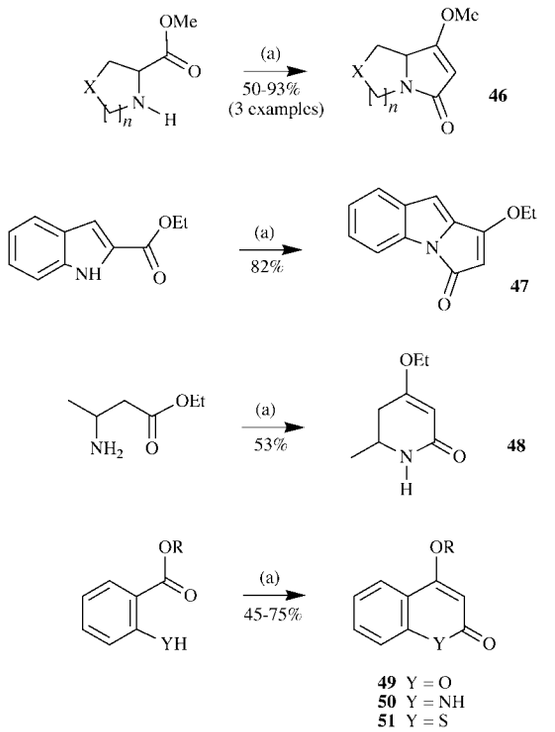


Scheme 20 *Reagents and conditions*: (a) **41**, $PhCH_3$ or xylenes, Δ; R^1 = H, Me, Bn, $–CH_2CO_2Me$, $–CH_2CH_2SMe$, $CH_2CH(OMe)_2$; R^2 = Me, Et, i-Pr, Bn.

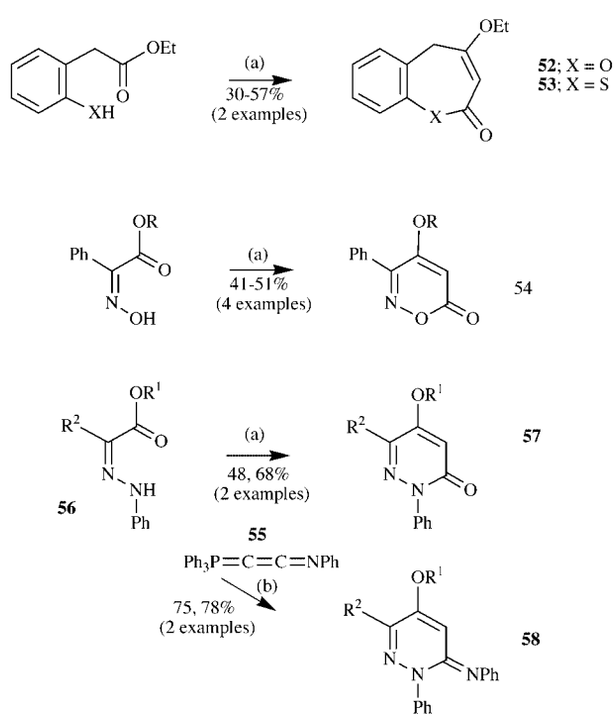
A further interesting example demonstrates the cyclisation of phosphonium salt **59** to the bicyclic β-lactam **60** in good yield under relatively mild conditions (Scheme 23).[25]

3 Wittig reactions with lactones

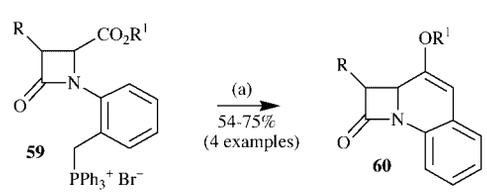
This area of the subject has again attracted considerable recent interest with both inter- and intramolecular examples of the reaction with lactones being investigated. Chapleur and co-workers have investigated[26] in great detail the intermolecular reaction and have shown that it is possible to effect the dichloromethylidenation of a variety of lactones using the combination of PPh_3 and CCl_4 previously reported by Suda and Fukushima.[21] Several systems were investigated and best yields (45–95%, 7 examples) were found with bicyclic γ-lactones such as **61** which gave the enol ether **62a**; other γ-lactones including γ-butyrolactone were also good substrates for this reaction (38–90% yield, 4 examples). Interestingly the acetate



Scheme 21 *Reagents and conditions*: (a) **41**, $PhCH_3$ or xylenes, Δ; X = S, $–CH_2–$; *n* = 1, 2; Y = O, S, NH; R = Me, Et.

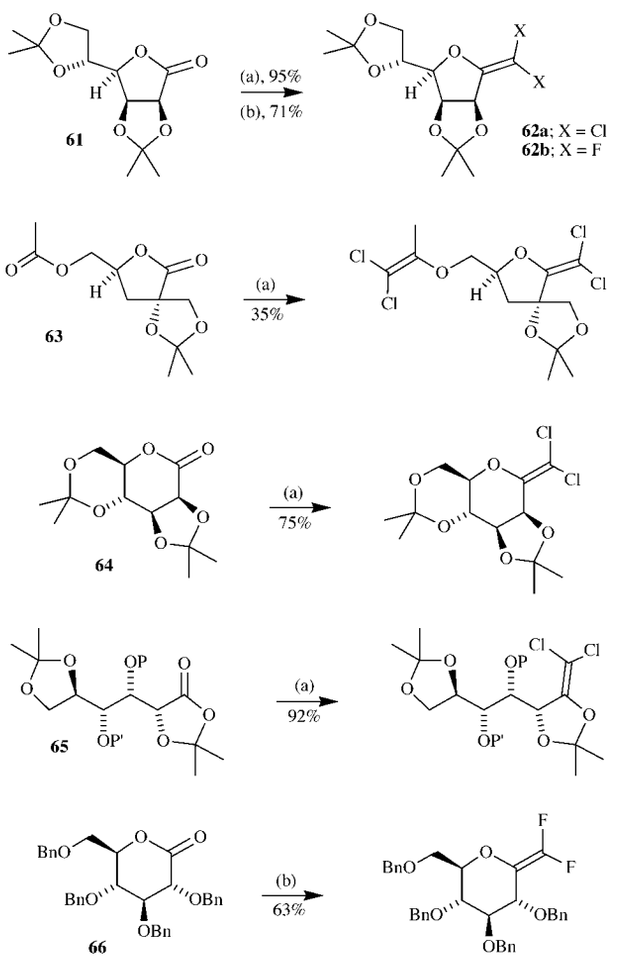


Scheme 22 *Reagents and conditions*: (a) **41**, xylenes, Δ; (b) **55**, PhH, Δ, 3 h; R = Et, *i*-Pr, Bn, *c*-C_6H_5; R^1 = Me, Et; R^2 = Ac, CO_2Me, CN.



Scheme 23 *Reagents and conditions*: (a) DIPEA, THF or CH_3CN, Δ, 40–70 h; R = H, OPh; R^1 = Me, Bn.

substituted γ-lactone **63** underwent dichloromethylidenation at the acetate function as well as at the lactone position. δ-Lactones were also effective substrates for this reaction (38–90% yield 4 examples), for example **64**, as was the dioxolanone **65**. Subsequent to this work, Motherwell and co-workers reported a similar difluoromethylidenation reaction of lactones using a combination of HMPT, zinc dust and dibromodifluoromethane.[27] Using this method several γ-lactones gave products of difluoromethylidenation (61–78%, 5 examples), for example the conversion of **61** to **62b**, as well as δ-lactones including **66** (Scheme 24).



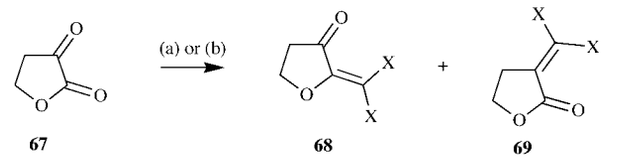
Scheme 24 *Reagents and conditions*: (a) PPh_3, CCl_4, THF, Δ; (b) $(Me_2N)_3P$, CF_2Br_2, Zn, THF, Δ; P–P′ = $(CH_3)_2C$.

The dihalomethylidenation of the α-oxolactone **67** has also been investigated and an interesting selectivity was observed which was dependent on the sequence of addition of the reactants (Table 1, Scheme 25). It was found that if the ylide [PPh_3=CX_2] was pre-formed by the addition of the phosphine to the tetrahalide the major product **68** resulted from methylidenation at the lactone carbonyl (entries 1, 3) whereas if the substrate was present whilst the phosphine was being added the ketone carbonyl was found to be methylidenated to give **69** (entries 2, 4). The authors explained this by suggesting that the intermediate phosphonium salt [PPh_3–X]$^+$[CX_3]$^-$ was reacting with the ketonic function whilst the ylide showed a preference for reactivity at the lactone function.[28]

Wittig reactions of similar α-ketolactones have also been the subject of study by three groups. Koz'minykh has reported[29] that the Wittig olefination of 5-arylfuran-2,3-diones **70** proceeds exclusively at the lactone carbonyl with stabilised phosphoranes in fair to excellent yields and is predominantly *Z*-selective. Similarly Schweizer *et al*. reported[30] the reaction of the phosphoranes **73** with lactones **71** or **72** led to olefination at

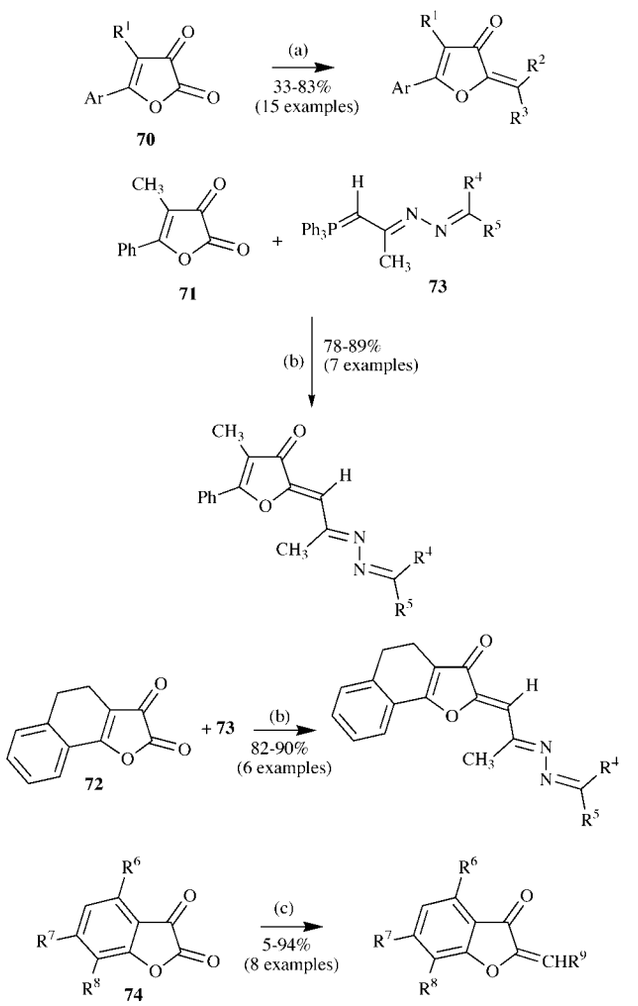
Table 1

Entry	Method	X	**68**:**69**
1	(a)	Cl	44:38
2	(b)	Cl	05:59
3	(a)	Br	57:13
4	(b)	Br	21:58



Scheme 25 *Reagents and conditions*: (a) PPh_3 and CCl_4, in CH_2Cl_2, then **67**; (b) **67** and PPh_3 in CH_2Cl_2, then CCl_4.

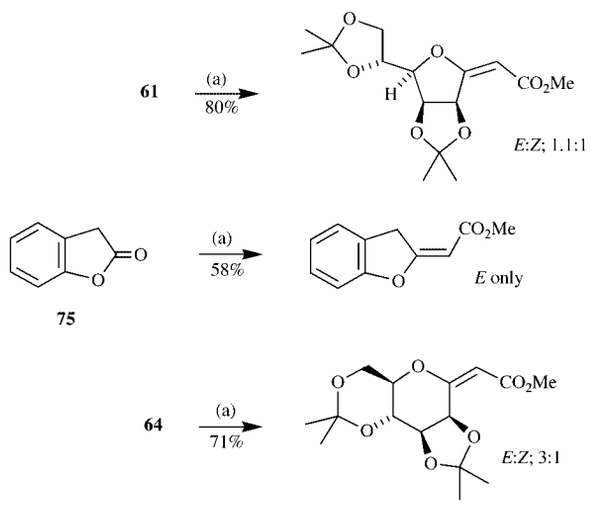
the lactone carbonyl and Yamato and co-workers reported[31] that benzofurandiones **74** also reacted with stabilised and semi-stabilised phosphoranes predominantly at the lactone carbonyl (Scheme 26).



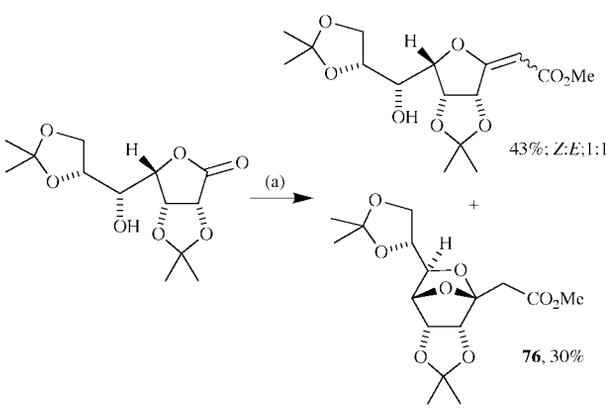
Scheme 26 *Reagents and conditions*: (a) R^2R^3C=PPh_3, PhH, Δ, 5–15 min; (b) PhH, rt, 15 h; (c) R^8CH=PPh_3, THF or PhH, Δ, 0.5–3 h; R^1 = H, Me, Br, Cl; R^2 = H, Me, Br, I; R^3 = CO_2Me, CO_2Et, CN, COPh; R^4 = H, Me, Ph, Ar, COPh; R^5 = Ph, Ar; R^6, R^7, R^8 = H, Me, OMe, Cl; R^9 = CO_2Et, Ph, CN.

Chapleur and Lakhrissi have also investigated the general reaction of lactones with methoxycarbonylmethylenetriphenylphosphorane and have found that if forcing conditions are employed (toluene, 140 °C, sealed tube) both γ-lactones

(27–90% yield, 6 examples) for example, **61** and **75**, as well as δ-lactones, such as **64**, react to give alkenes as predominantly the *E*-isomer (Scheme 27).[32] Similar olefinations of galactono- and glucono-δ-lactones, including some containing acetylated amino groups, have been reported to proceed in good yields in either refluxing toluene or in one case THF.[33] Chapleur *et al.* have also reported that reaction of partially protected sugar lactones is possible and leads to the formation of product of addition to the double bond formed in the Wittig process, for example **76**[34] (Scheme 28).



Scheme 27 *Reagents and conditions*: (a) $PhCH_3$, 140 °C, sealed tube 4–48 h.

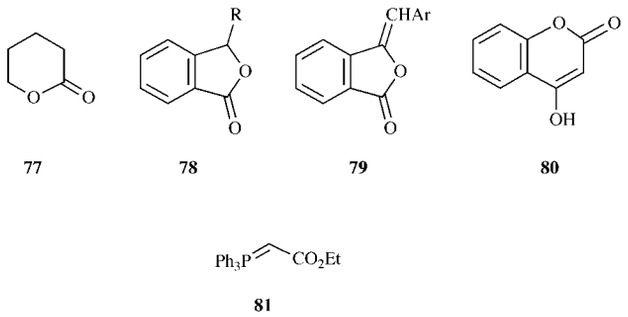


Scheme 28 *Reagents and conditions*: (a) $PhCH_3$, 140 °C, sealed tube.

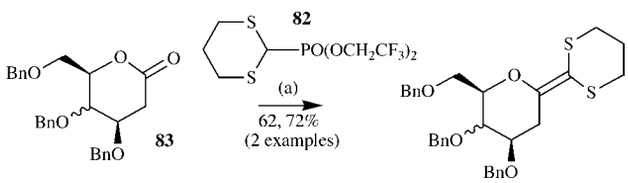
Possibly the most important discovery in this area was recently reported by Sabitha and co-workers and concerned the microwave assisted Wittig olefination of lactones and amides (see later). They found[35] that the effective olefination of γ- and δ-lactones was possible when a mixture of the lactones **77**–**80** and ethoxycarbonylmethylenetriphenylphosphorane **81** were mixed and heated to 90 °C in a microwave oven for 1–2 min (Scheme 29). The yields for this process were good (66–89%) and the products predominantly *Z* (*E*:*Z* 25:75 to 10:90).

The reaction of the phosphonate substituted 1,3-dithiane **82** with sugar lactones **83** has been reported to give ketene dithioacetals in excellent yield; the trifluoroethyl groups of **82** are thought to play a key role in this reaction by accelerating the elimination step of the HWE reaction[36] (Scheme 30). Further evidence of the activating effect of fluorine substituents is given by the reaction of the difluorolactone **84**, which on treatment with a nonstabilised ylide at room temperature in THF gave the enol ether **85**, a precursor employed in the synthesis of prostacyclin analogues[37] (Scheme 31).

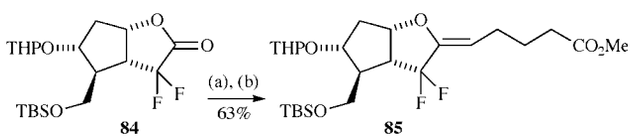
Several other reports of Wittig reactions of lactones have been reported,[38] however two of note are the reaction of



Scheme 29 R = H, Bn.

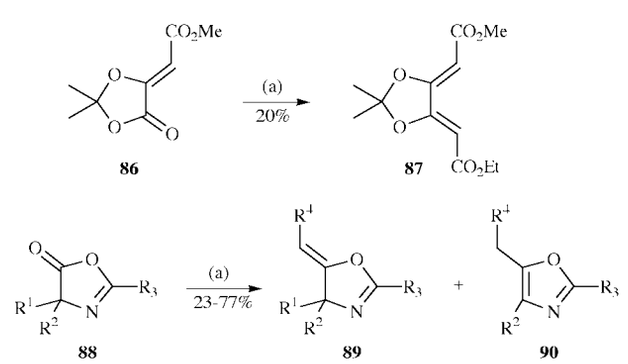


Scheme 30 *Reagents and conditions*: (a) KHDMS, THF, −78 to 0 °C.



Scheme 31 *Reagents and conditions*: (a) $HO_2C(CH_2)_4PPh_3^+$ Br^-, NaHMDS, THF, rt; (b) MeI, DIPEA, DMSO.

the 1,3-dioxolane **86** with phosphorane **81** which leads to the formation of the interesting diene **87** in 20% yield[39] and also the reaction of oxazolones **88** with stabilised and semistabilised ylides led to the Wittig products **89** or the rearrangement products, the oxazoles **90** in reasonable yields[40] (Scheme 32).

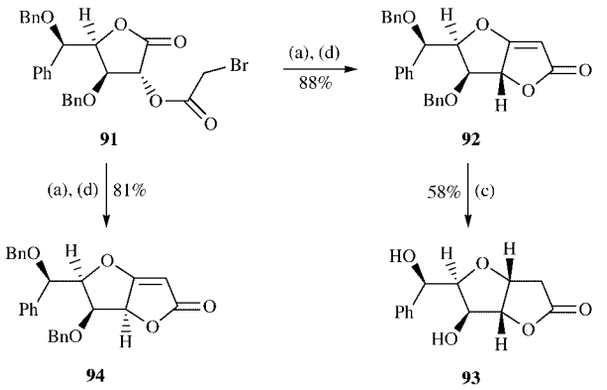


Scheme 32 *Reagents and conditions*: (a) **81**, xylenes, Δ, 24 h; (b) $R^4CH{=}PPh_3$, anisole, PhH or $PhCH_3$; R^1 = Me, i-Pr, Ph, Ar; R^2 = H, Me, Ph; R^3 = Ar; R^4 = CO_2Et, Ph.

Within our own group we have investigated[41] the intramolecular Wittig reaction of γ-lactones and have focused our efforts on the synthesis of natural products, including the cytotoxin goniofufurone **93**.[41b,c] This was effected *via* the two stage cyclisation of the glucose-derived lactone **91** with subsequent hydrogenation of the intermediate tetronate **92**. Interestingly, if this reaction is repeated using an excess of base to generate the intermediate phosphorane the reaction proceeds with epimerisation to give **94** as the major product (Scheme 33).

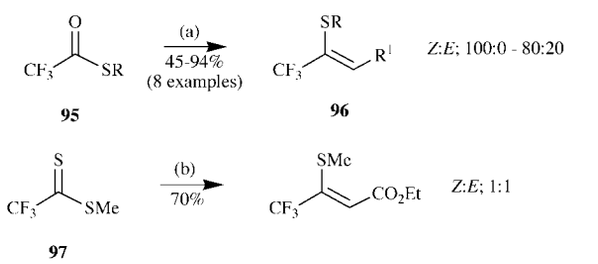
4 Wittig reactions with thiol esters

The non-classical Wittig reaction of thiol esters continues to be of considerable synthetic value. Intermolecular examples of the reaction are however limited with formation of the β-keto-



Scheme 33 *Reagents and conditions*: (a) PPh_3, CH_3CN, Δ, 2 h; (b) DBU, CH_3CN, Δ, 30 min; (c) H_2, Pd/C, EtOAc; (d) excess DBU, CH_3CN, Δ, 30 min.

phosphorane product being preferred.[42] A notable exception to this is the reaction of trifluoroacetyl thiol esters **95** which react readily with stabilised, semi-stabilised and reactive ylides to give the vinyl sulfides **96** as predominantly the *Z* isomer.[43] A similar olefination of methyl trifluorodithioacetate **97** has also been reported, however this proceeds with no stereoselection[44] (Scheme 34).

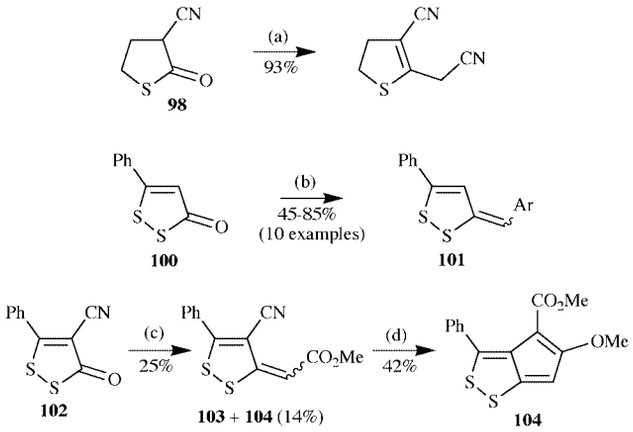


Scheme 34 *Reagents and conditions*: (a) $R^1CH{=}PPh_3$, THF, 2 h, rt; (b) **31**, THF, rt, 24 h; R = Et, *n*-hexyl; R^1 = alkyl, Ph, CO_2Et.

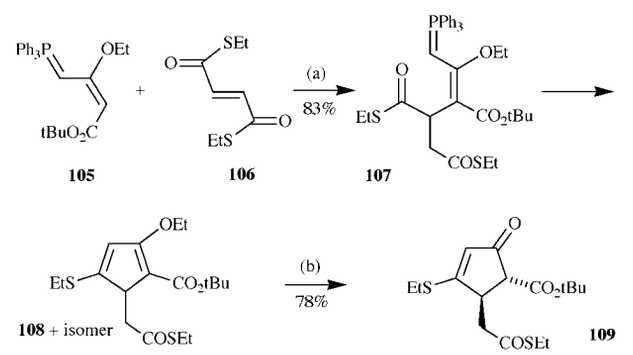
The Wittig olefination of thiolactones is a viable process, for example the thiolactone **98** has been reported to undergo olefination, with concomitant rearrangement, in 93% yield on refluxing in toluene with an excess of the stabilised ylide **99**.[45] Two groups have also reported the Wittig olefination of the 1,2-dithiol-3-ones, for example **100** reacts readily with semi-stabilised phosphoranes to give **101** in good yields.[46] Similarly the 1,2-dithiol-3-ones **102** (and the corresponding 1,2-dithiole-3-thiones) also react with a range of stabilised and semi-stabilised ylides leading to the Wittig product, for example **103**, which interestingly undergoes cyanide displacement with a further equivalent of phosphorane and further intramolecular Wittig reaction with the ester function to give **104** in reasonable yield (Scheme 35).[47]

Despite the scarcity of intermolecular examples the intramolecular version of this reaction is a very common procedure. One recent example is the novel cyclisation of the phosphorane **107**, prepared from **105** and **106**, the reaction leading to the synthesis of cyclopentadienes, for example **108**, which are readily hydrolysed to the corresponding enone **109**, the example shown being a synthetic precursor of (±)-methyl dihydrojasmonate[48] (Scheme 36).

This methodology continues to attract attention in the synthesis of heterocyclic systems and the classic Woodward methodology for the synthesis of penem[49] and carbapenem[50] β-lactam antibiotics is still a popular method. A recent publication on this theme reports an efficient method for preparing the intermediate phosphoranes **111**, which are typical precursors for the cyclisation. It was found[51] that treatment of the imide **110** with diethyl methylphosphonite in the presence of triphenyl- or diphenylmethylphosphine at ambient temperature



Scheme 35 *Reagents and conditions*: (a) Ph_3PCHCN (**99**), Tol, Δ, 7 h; (b) $ArCH{=}PPh_3$, PhH, rt; (c) Ph_3PCHCO_2Me, Δ, $PhCH_3$, 10 h; (d) Ph_3PCHCO_2Me, Δ, $PhCH_3$, 18–20 h.



Scheme 36 *Reagents and conditions*: (a) THF, −30 to 0 °C, 48 h; (b) AcOH, H_2O, THF, 48 h.

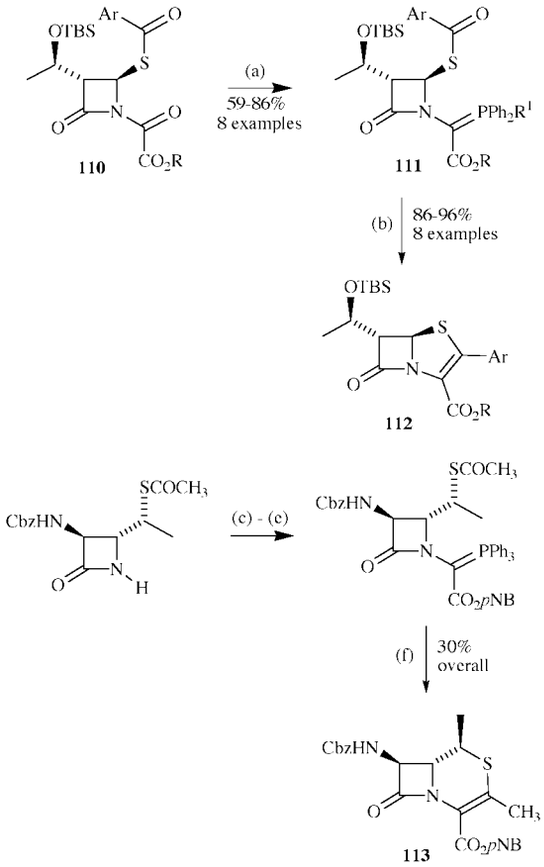
led to the formation of **111** in good yields which on purification and heating led to the penems **112** in excellent overall yield. The synthesis of the interesting isocephem **113** has also been reported which proceeds *via* the more traditional approach to these systems[52] (Scheme 37).

A further example of the Wittig reaction with thiol esters from within our own group illustrates the preparation of a series of dihydrothiophenes **116** from the cyclopropane phosphonium salt **114**.[53] We found that treatment of a thiol acid salt with **114** in refluxing THF leads to the formation of the dihydrothiophene in high yields, the reaction proceeding *via* the phosphorane **115** (Scheme 38). A similar reaction has been used in the preparation of the benzothiophene **120** where treatment of the anhydride **118** with the sodium thiolate **117** led to the Wittig cyclisation *via* the intermediate **119**[54] (Scheme 39).

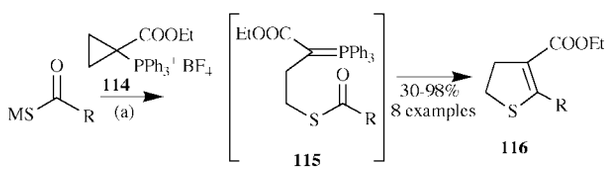
By using a strategy that mirrors that developed for the formation of benzopyran-4-ones,[19] Kumar and co-workers have reported the reaction of the *S*-acylthiosalicylic acids **121** with *N*-phenyl(triphenylphosphoranylidene)ethenimine **55** to give benzothiopyran-4-ones in high yield. The reaction is thought to proceed *via* the intermediate ylide **122** which on heating in toluene eliminates phenyl isocyanate to give **123** which in turn undergoes intramolecular Wittig cyclisation[55] (Scheme 40).

5 Wittig reactions with amides

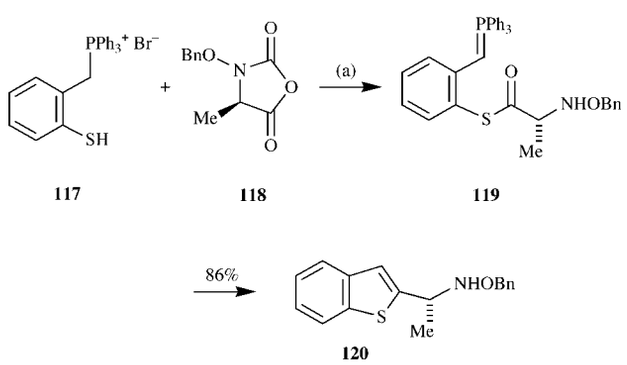
Intramolecular Wittig reactions involving simple amides have to date not been reported. Where examples have arisen there are usually special factors at work which influence the effective conjugation of the lone pair of the nitrogen with the amide carbonyl. This is illustrated in the Wittig reaction of the highly twisted amide **124**,[56] where amide resonance is disrupted by



Scheme 37 *Reagents and conditions*: (a) PPh_2R^1, $(EtO)_2PMe$, rt, 1 h; (b) $PhCH_3$, 80–110 °C; (c) $EtO(HO)CHCO_2pNB$, molecular sieves; (d) polymeric Hünig's base, $SOCl_2$, dioxane; (e) polymeric Hünig's base, PPh_3, dioxane; (f) $PhCH_3$, Δ; R = allyl, Me, R^1 = Ph, Me, Ar = Ph, 3-Py.



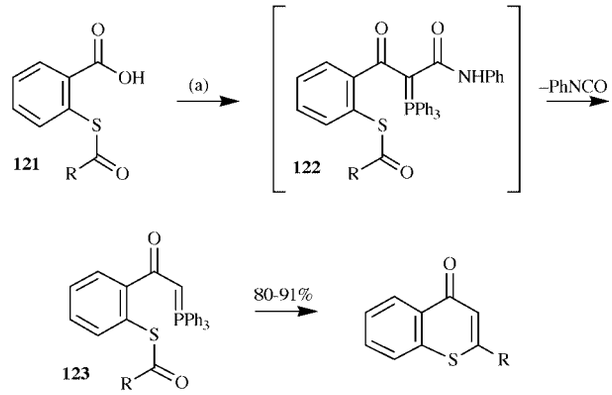
Scheme 38 *Reagents and conditions*: (a) THF, Δ, 48–72 h; M = Na, K; R = Me, Ph, OEt, n-Pr, i-Pr, t-Bu, 2-Furyl, CO_2Et.



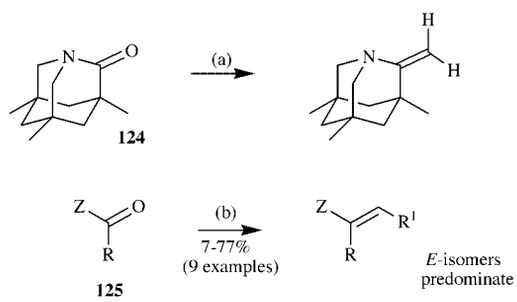
Scheme 39 *Reagents and conditions*: (a) NaH, THF DMF, rt, 12 h.

the structural features present and in the case of the 1-acylazoles **125**[57] where competing resonance plays a role in increasing reactivity (Scheme 41).

Considerable interest has been focused on the Wittig reaction with fluorinated amides. Bégué and Mesureur have reported[58] the Wittig reaction of trifluoroacetamides with the morpholine amide **126** giving the best yields. Further investigation indicated that yields were diminished when other perfluoroalkyl groups ($-C_2F_5$, $-C_3F_7$) were employed in the reaction, which was

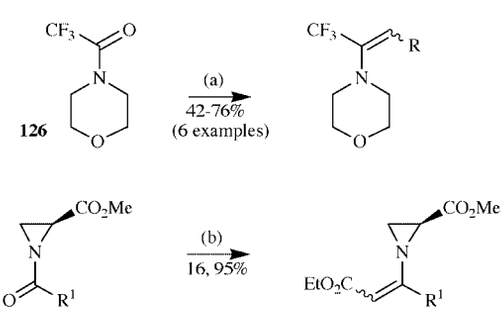


Scheme 40 *Reagents and conditions*: (a) **55**, $PhCH_3$ or dioxane, Δ, 6–15 h; R = Me, Et, Ph, Ar.



Scheme 41 *Reagents and conditions*: (a) $CH_2{=}PPh_3$; (b) $R^1CH{=}PPh_3$, $R^1 = CO_2Me$, CO_2tBu, $COCH_2C(CH_3)_3$, CN, THF, rt, 30 min; R = Ph, Ar; Z = imidazol-1-yl, 1,2,4-triazol-1-yl, benzimidazol-1-yl.

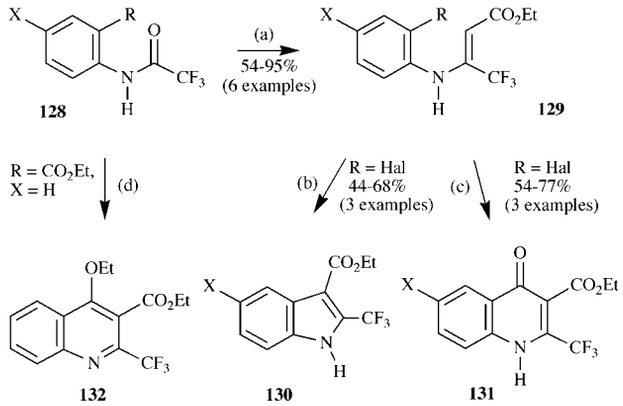
explained by the lower electron withdrawing character of these groups in comparison with $-CF_3$ and also by increased steric hindrance.[8a] The Wittig reaction of the activated aziridines **127** with stabilised phosphorane **81** has also been reported and as can be seen the trifluoromethyl has a dramatic effect on the nature and efficiency of the reaction giving mostly the enamine product, whereas in the case of the *p*-nitrobenzene substituent a low yield of the enamine product was formed, with ring opening of the aziridine being a competing process[59] (Scheme 42).



Scheme 42 *Reagents and conditions*: (a) $RCH{=}PPh_3$, Δ, THF, 24 h; (b) **81**, Δ, $PhCH_3$, 2–6 h; R = n-C_6H_{13}, Ph, $PhCH_2CH_2$, $R^1 = CF_3$, p-$NO_2C_6H_4$.

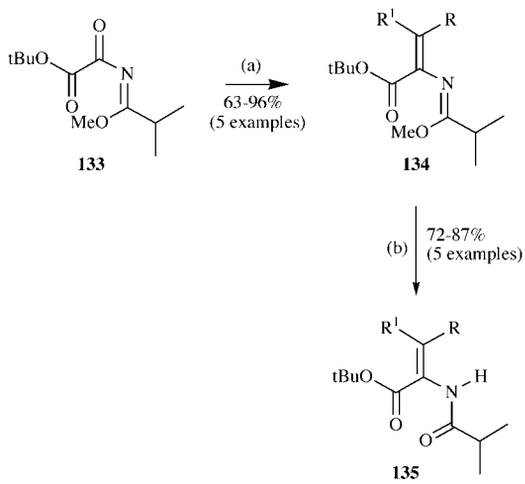
Stanforth and co-workers have also reported the Wittig reaction of trifluoroacetanilides **128** with stabilised phosphorane **81**; they found that the Wittig products **129** were formed in high yield and were further utilised in the synthesis of indoles **130**, and quinolones **131** *via* Heck reactions. They also found that where **128** contained an α-ester group the intermediate product was converted under the reaction conditions to the quinoline **132**; similar examples utilising thiophene carboxylates were also reported[60] (Scheme 43).

Two groups have reported an interesting alternative solution to effect the olefination of amide carbonyls and that is to react



Scheme 43 *Reagents and conditions*: (a) **81**, $PhCH_3$, Δ; (b) DMF, $Pd(OAc)_2$, PPh_3, $N(i\text{-}Pr)_3$, 120 °C; (c) DMF, $Pd(OAc)_2$, PPh_3, Na_2CO_3, CO, 120 °C; (d) **81**, melt, 180–200 °C; R = Hal, CO_2Et; X = CO_2Et, CN, NO_2.

tert-butyl oxalyl imidates, such as **133** with non-stabilised, semi-stabilised and stabilised ylides to give the azadienes **134** which are readily hydrolysed to the corresponding enamines **135**[61] (Scheme 44).

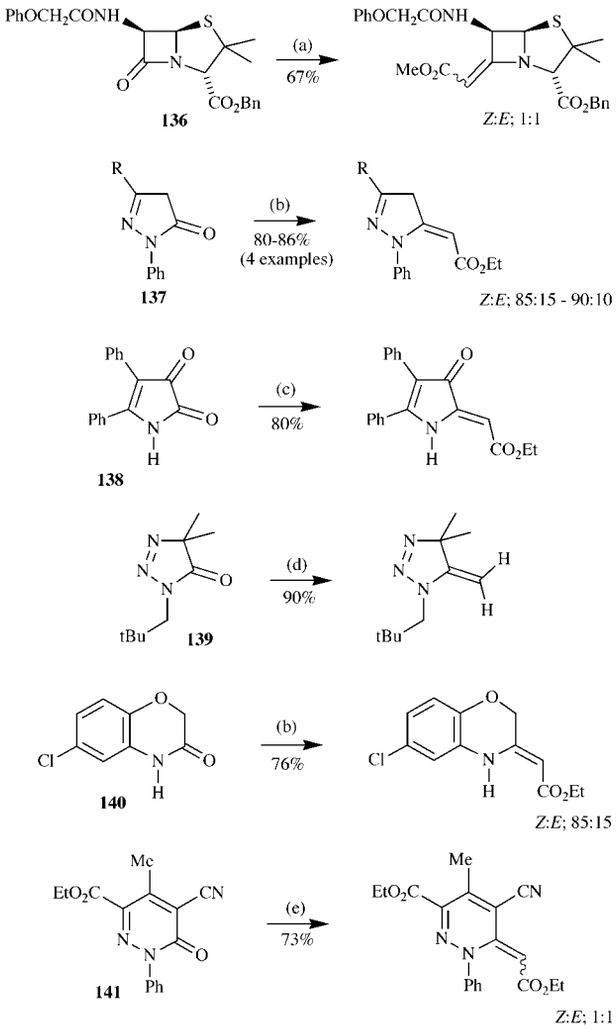


Scheme 44 *Reagents and conditions*: (a) $PhCH_3$, 0 °C, 30 min; (b) $CHCl_3$, aq. HI; R = Me, n-Pr, R^1 = H and R–R^1 = –$(CH_2)_3$–.

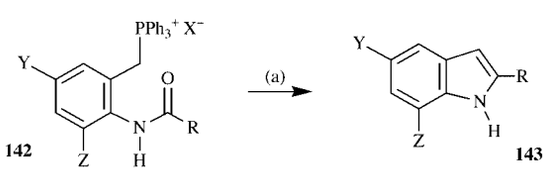
Lactams offer more scope for reactivity, indeed β-lactams such as **136**[62] are excellent substrates for the reaction with stabilised phosphoranes. In addition several γ- and δ-lactams (**137**–**141**) have been reported to undergo Wittig reactions,[38b,63] indeed a recent publication has shown that the Wittig reaction with both types of lactams is accelerated considerably by microwave irradiation[35] (Scheme 45).

A useful synthesis of indoles which is applicable to large scale preparations utilises the intramolecular Wittig reaction of amides. This reaction has continued to be applied to numerous syntheses of indoles **143** from the phosphonium salts **142** on treatment with a base (typically KOtBu) and has become one of the accepted standard routes to this heterocyclic system.[64] The reaction is tolerant of some functional groups including vinyl (entry 8) and ester (entries 9–15) functions and is generally high yielding (Scheme 46, Table 2). In addition, Capuano and co-workers have reported the synthesis of bis-indoles **144** (and one example of a bis-benzofuran) from the corresponding phosphonium salts[65] (Scheme 47).

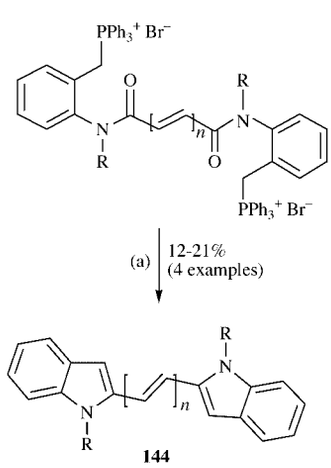
It is interesting to note that in Scheme 46 the Wittig cyclisation occurs at the amide function even when an ester group is present and in the proximity of the reacting ylide (entries 9–11). A similar situation arises when the competing group is a ketone, as found in structures **145**, in which it has been shown[64g,66] that some reaction will occur at the amide carbonyl in preference to



Scheme 45 *Reagents and conditions*: (a) MeO_2CHPPh_3, $PhCH_3$, Δ, 18 h; (b) **81**, microwave irradiation, 90 °C, 90–100 s; (c) **81**, PhH, Δ, 30 min; (d) CH_2PPh_3, Et_2O, rt, 3 days; (e) **81**, $PhCH_3$, Δ, 1 h; R = Me, Ph, CF_3, Ar.



Scheme 46 *Reagents and conditions*: (a) KOtBu, $PhCH_3$, Δ, see Table 2; X = Cl or Br.

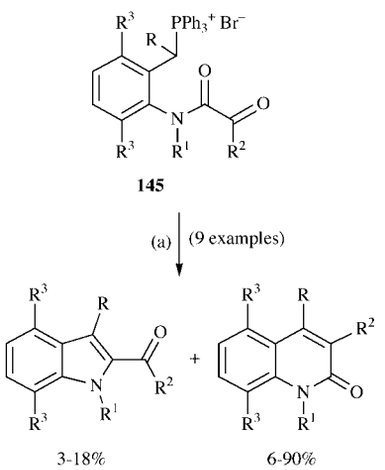


Scheme 47 *Reagents and conditions*: (a) KOtBu, $PhCH_3$, Δ, n = 0, 1; R = H, Me.

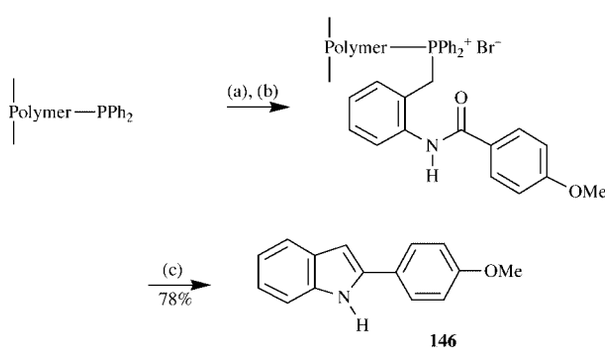
Table 2

Entry	R	Y	Z	Time/min	Yield (%)	Ref.
1	n-Pr	H	H	180	81	64*l*
2	$(CH_2)_3Ph$	H	H	30	88	64*d*
3	$(CH_2)_4Ph$	H	H	30	78	64*d*
4	$(CH_2)_3Ph$	Br	H	30	83	64*d*
5	$(CH_2)_4Ph$	Br	H	30	62	64*d*
6	cyclohexyl	H	H	30	38	64*c*
7	Bn	H	H	30	65	64*c*
8	vinyl	H	H	40	38	64*h*,*i*
9	CO_2Et	H	H	15	50	64*g*
10	CH_2CO_2Me	H	H	180	70	64*k*
11	CH_2CO_2Et	H	H	15	72	64*g*
12	$CH(Me)CO_2Et$	H	H	210	64	64*b*
13	$C(Me)_2CO_2Me$	H	H	15	35	64*g*
14	$(CH_2)_2CO_2Me$	H	OMe	30	58	64*j*
15	$(CH_2)_6CO_2Me$	H	H	45	49	64*g*

the ketone (Scheme 48). A new development of the reaction is also found in the rapidly growing area of solid phase synthesis and Hughes has reported that it is possible to prepare indole **146** using a polymer supported phosphonium salt[67] (Scheme 49).



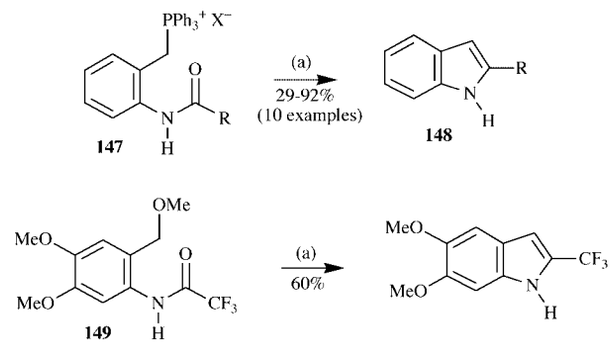
Scheme 48 *Reagents and conditions*: (a) NEt_3, Δ, 5 h, R = H, Me, Ph; R^1 = H, Et; R^2 = Me, Et, Ph, Ar; R^3 = H, OMe.



Scheme 49 *Reagents and conditions*: (a) 2-nitrobenzyl bromide, DMF, 70 °C, 48 h; $Na_2S_2O_4$, EtOH, Δ, 90 min; HBr, MeOH, dioxane; (b) 4-methoxybenzoyl chloride, Py, CH_2Cl_2, 5 h; (c) $PhCH_3$, DMF, distil; KO^{t}Bu, Δ, 45 min.

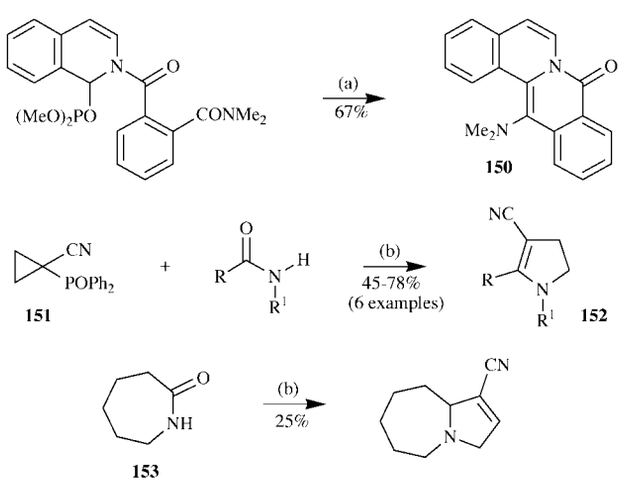
Imanishi *et al*. have reported an interesting observation in the cyclisation of phosphonium salts **147**, which proceeded to the indoles **148** in the absence of any base.[68] The reaction appears to be general in nature and the authors suggest that it might not proceed through a traditional Wittig mechanism; in addition it is possible to effect a similar transformation of benzyl methyl ethers such as **149** in the presence of triphenylphosphine and a catalytic amount of toluenesulfonic acid (Scheme 50).

Other heterocycles are accessible *via* Wittig cyclisations



Scheme 50 *Reagents and conditions*: (a) Δ, DMF, *o*-DCB, DMSO, 1–15 h; X = Br, Cl; R = CF_3, C_2F_5, Bn, Ph, Ar, Ac, EtO_2C; (b) PPh_3, TosOH (cat), $PhCH_3$, Δ, 180 °C (sealed tube), 12 h.

involving amides, for example the quinolizinone **150** was prepared using HWE methodology.[12b] In addition a flexible synthesis of dihydropyrroles **152** utilising the cyclopropylphosphine oxide **151** has been reported, in which treatment of **151** with the sodium salt of mono-substituted amides effects ring opening and subsequent Wittig cyclisation to give the products in reasonable yield. A similar reaction was also observed using caprolactam **153** (Scheme 51).[69]



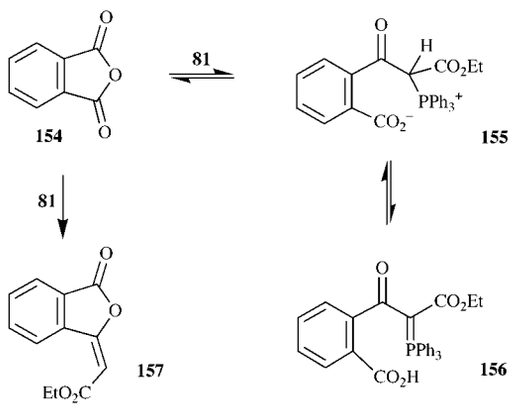
Scheme 51 *Reagents and conditions*: (a) LDA, THF, −78 to 40 °C, 1 h; (b) NaH, xylenes, 130–165 °C, 1–4 h; R = H, Me, Et; R^1 = Ph, n-Bu, C_5H_{11}.

6 Wittig reactions with anhydrides and thioanhydrides

Wittig reagents generally react to give products of acylation when treated with acyclic anhydrides even when they are fluorinated.[8a] However the Wittig olefination of stabilised

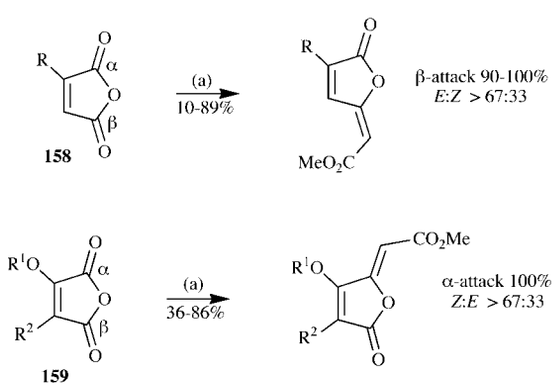
phosphoranes with cyclic anhydrides continues to be of synthetic interest and the two research groups of Kayser[70] and Abell[71] have made significant recent contributions.

Kayser has focused on the mechanistic aspects of the reaction and has cast some doubt upon the accepted mechanism of this process.[70] It is known that anhydrides, for example **154** react with stabilised phosphoranes to give the acyclic intermediates **155** and **156** and it was thought that these were precursors of the Wittig products **157**. Kayser has shown[70d,e] that the formation of these intermediates is a reversible low energy process which is sterically controlled and that the Wittig product is probably derived from a more organised higher energy transition state possibly *via* an "oxaphosphetane like" intermediate (Scheme 52). In the reaction of phthalic anhydrides there is a strong preference for the *E*-product **157**.



Scheme 52

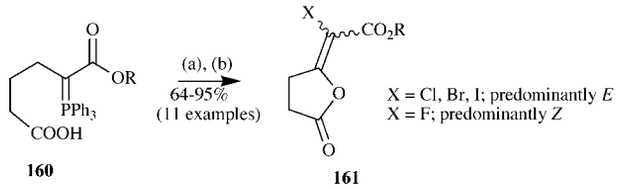
Kayser has also reported that the Wittig reaction of maleic anhydrides is controlled by firstly a strong steric effect as illustrated by the reaction of anhydrides **158** which undergo attack at the β-carbonyl preferentially. In contrast the anhydrides **159** undergo preferential attack at the α-carbonyl which was explained as being due to a combination of the electronic effect of the alkoxy group and the possibility of the formation of a donor–acceptor complex between the alkoxide group and the electron deficient phosphorus[70i] (Scheme 53).



Scheme 53 *Reagents and conditions*: (a) $MeO_2CCHPPh_3$; R = Me, Ph, Ar, Br; R^1 = Me, Et; R^2 = Me, H.

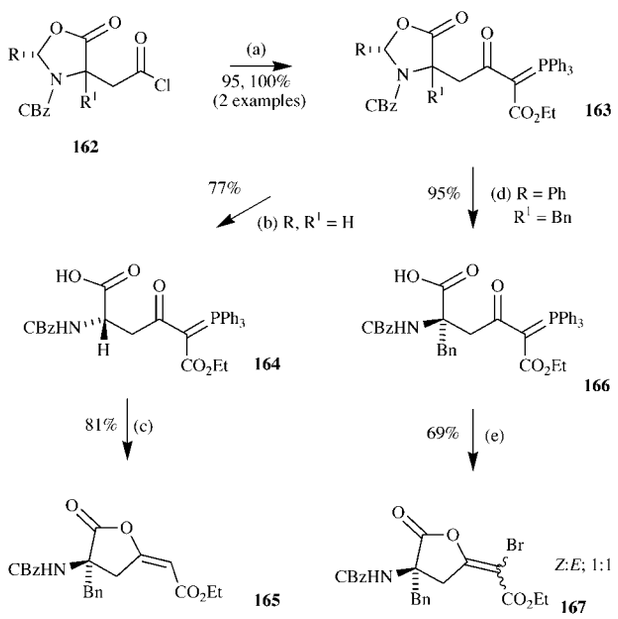
From the recent developments in this area it has been found that the acyclic intermediates found in this reaction, for example, the easily isolated ketophosphorane intermediates **160** react with halogenating agents, particularly *N*-halosuccinimides and *N*-fluorodiphenylsulfonamide to give the halogenated enol lactones **161**[70b] (Scheme 54).

Work by Abell and co-workers[71a–d] has also exploited the chemistry of these intermediates and applied it to synthesis. They have found it possible to prepare these intermediates by the reaction of phosphoranes with acid chlorides such as **162**.



Scheme 54 *Reagents and conditions*: (a) NXS, THF, 0 °C, 2–4 h; (b) *N*-fluorophenylsulfonamide, THF, −20 °C; R = Me, Et, tBu; X = F, Cl, Br, I.

These intermediates (**163**) can be hydrolysed to liberate the corresponding carboxylates **164** and **166** which can then be cyclised to form enol lactones **165** or brominated to give bromoenol lactones **167** (Scheme 55). Numerous other general reports of the Wittig reaction of phthalic,[72] aspartic,[73] succinic[74] and glutaric anhydrides[75] have appeared together with some applications in synthesis.[76,77]

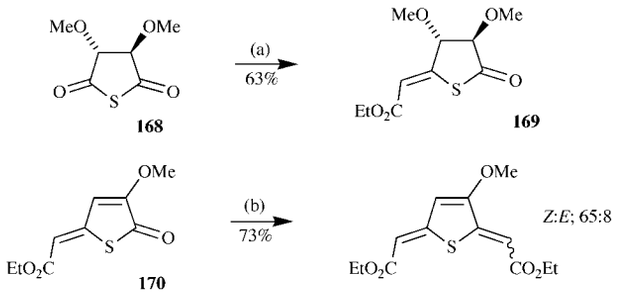


Scheme 55 *Reagents and conditions*: (a) **81** (2 equiv.), CH_2Cl_2, 0 °C to rt, 6 h; (b) NaOH, H_2O, MeOH, Δ; (c) THF, Δ; (d) LiOH, THF, MeOH, Δ, 4 h; (e) Br_2, NEt_3, CH_2Cl_2, 0–20 °C.

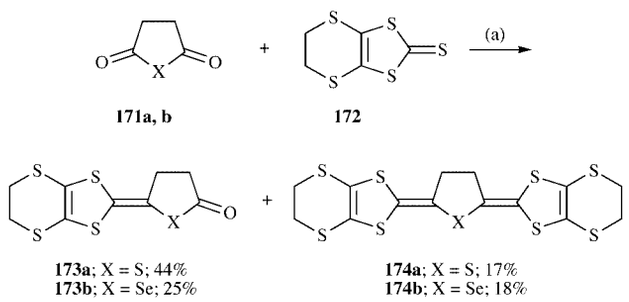
The Wittig reaction of thioanhydride **168** has been reported to give predominantly the *Z*-isomer **169** on reaction with methoxycarbonyltriphenylphosphorane. In addition, reaction of the thiolactone **170** with the same reagent but under more forcing conditions also led to Wittig olefination[78] (Scheme 56). Takahashi and co-workers have reported[79] a Wittig like condensation between the thioanhydride **171a** and the 1,3-dithiole-2-thione **172** in the presence of trimethyl phosphite leading to a mixture of the mono- and bis-olefinated compounds **173a** and **174a**. A similar reaction also produced the corresponding selenium analogues **173b** and **174b** from the selenoanhydride **171b** (Scheme 57).

7 Wittig reactions with imides, thioimides and related systems

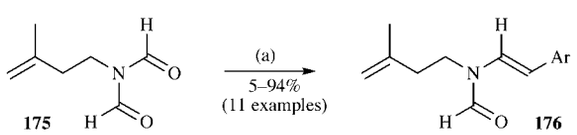
The Wittig reaction of imides and thioimides has been known for some time and many examples,[3,80] are known in synthesis. A recent intermolecular example is the reaction of γ,δ-unsaturated diformamides *i.e.* **175** with semi-stabilised ylides leading to the *N*-formylenamines **176**[81] (Scheme 58). Cyclic imides are particularly applicable to this reaction, as reported by Pattenden and co-workers, who published a detailed study of the Wittig reaction of maleimides[82] and found that steric



Scheme 56 *Reagents and conditions*: (a) **81**, THF, Δ, 3.5 h; (b) Δ, $PhCH_3$, 5 h.



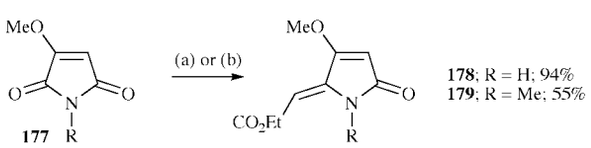
Scheme 57 *Reagents and conditions*: (a) $P(OMe)_3$, PhH, Δ, 6 h.



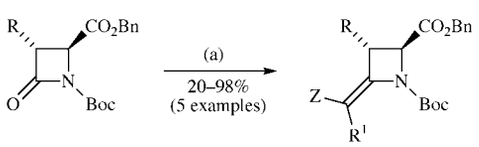
Scheme 58 *Reagents and conditions*: (a) $ArCHPPh_3$, THF, rt, 1.5–4 h.

and electronic effects play a considerable role in the product outcome of the reaction. For example, the reaction of **177** (R = H) gave the compound **178** in excellent yield under very mild conditions, whereas the methyl substituted analogue **177** (R = Me) gave the same regio-product (electronic control) **179**; however the increased steric hindrance present required more forcing conditions and led to a lower yield (Scheme 59). Whilst not strictly an imide example, it is worthy of note that Baldwin and co-workers have reported that the Wittig reaction of monocyclic-β-lactams is easily effected when the amide is Boc-protected[83] (Scheme 60). Other examples include Wittig reactions with the imide carbonyl of the heterocycles **180**[38b] which proceeds with concomitant cyclisation to give **181** and the selective olefination of the piperazine-2,5-diones **182**,[84] the imide **183** and thioimide and dithioimide **184a/b**[85] (Scheme 61).

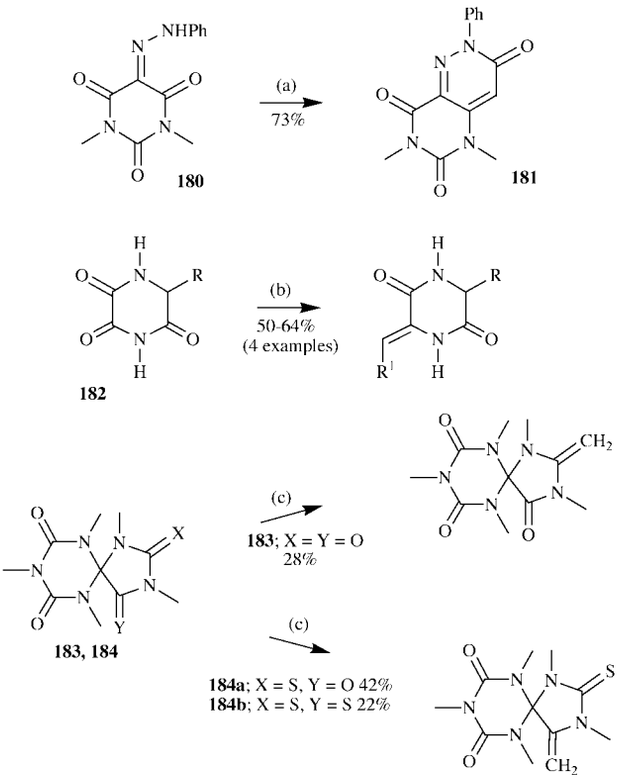
The intermolecular Wittig reactions of thioimides continues



Scheme 59 *Reagents and conditions*: (a) **81** (1 equiv.), $PhCH_3$, Δ, 26 h; (b) **81** (8 equiv.), $PhCH_3$, Δ, 24 h.

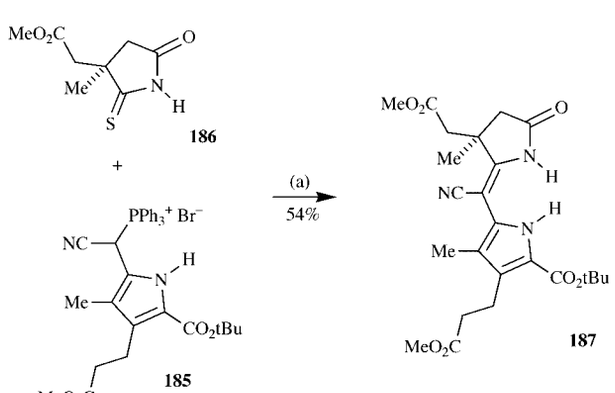


Scheme 60 *Reagents and conditions*: (a) ZR^1CHPPh_3, $PhCH_3$, Δ, 4–48 h; R = H, allyl; R^1 = H, Me; Z = CN, CO_2E, CO_2tBu.

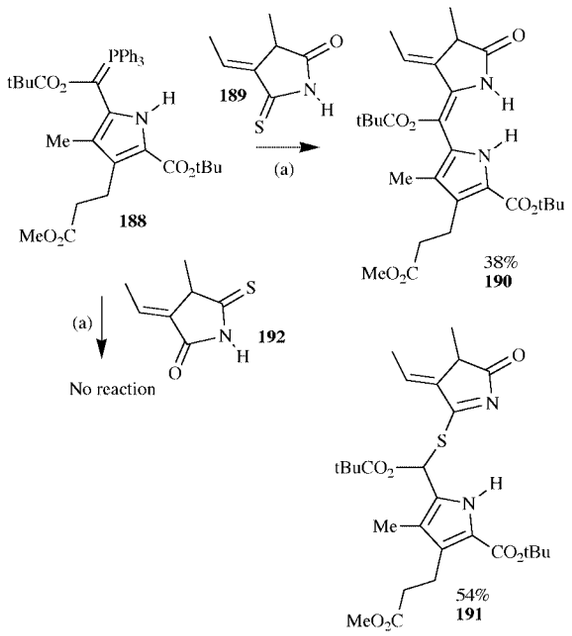


Scheme 61 *Reagents and conditions*: (a) $PhCH_3$, Δ, 10 h; (b) R^1CHPPh_3, $PhCH_3$, Δ, 16–24 h; R = Bn, Ph; R^1 = CN, CO_2Me, CNH_2; (c) CH_3PPh_3, DME, rt, 16 h.

to be of interest mainly due to the benefits of less forcing reaction conditions when compared to imides and also because of the predictability of reaction site. The reaction has found impressive applications in Battersby and co-workers' synthetic studies towards vitamin B_{12} and related metabolites.[86] For example, the ylide derived from **185** reacts with thioimide **186** selectively at the thiocarbonyl to give the enamine **187** in reasonable yield under relatively non-forcing conditions[86a] (Scheme 62). Rapoport and co-workers have reported an in depth study of the reaction of similar thioimides with stabilised phosphoranes and have found that the reactivity of these systems is highly dependent on the structure of the thioimide used.[87] They reported that reaction of phosphorane **188** with imide **189** led to the formation of the Wittig product **190** in 38% yield together with the S-alkylation product **191** in 54% yield. In contrast reaction with the isomeric thioimide **192** gave no Wittig or S-alkylation product (Scheme 63). This result was mirrored in the reaction of several other ylides with thioimides and theoretical calculations performed suggested that this result could be explained by the fact that the conjugated substrate **189** has a considerably lower LUMO energy than the unconjugated **192**.

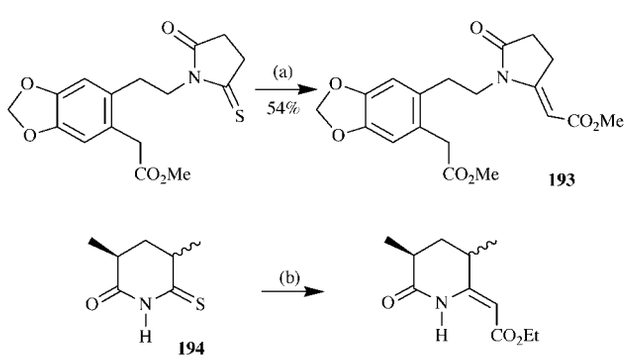


Scheme 62 *Reagents and conditions*: (a) KOtBu, Δ, $PhCH_3$, 4 h.



Scheme 63 *Reagents and conditions*: (a) Δ, *p*-xylene, 5 h.

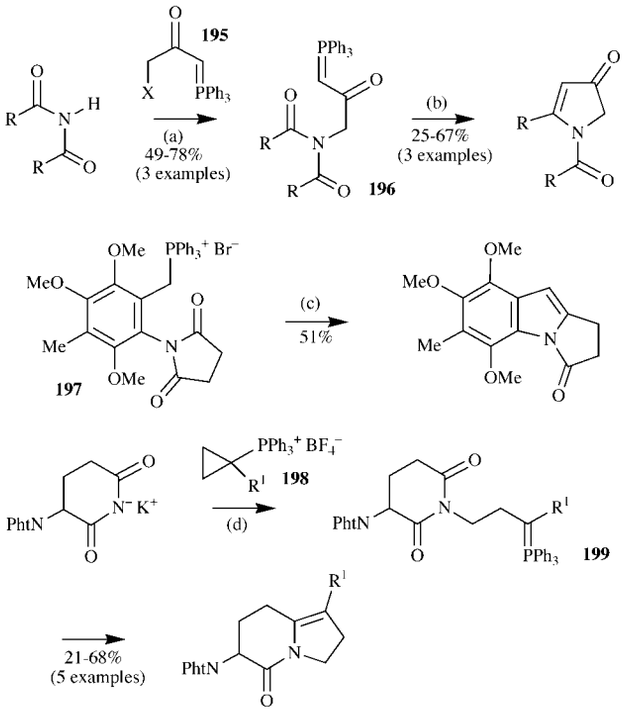
Other notable synthetic applications of this reaction are the formation of **193** *via* a Wittig reaction performed under high pressure conditions[88] and the Wittig olefination of the six-membered thioimide **194**[89] (Scheme 64).



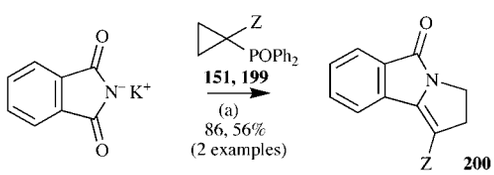
Scheme 64 *Reagents and conditions*: (a) $MeO_2CCHPPh_3$, CH_2Cl_2, 14 kbar, 3 days, 45 °C; (b) **81**, $PhCH_3$, Δ, 22 h.

The Wittig reaction of imides is particularly applicable to intramolecular processes and has been employed in the preparation of a wide range of heterocyclic systems. Flitsch and co-workers have reported several applications of the reaction in the synthesis of pyrroles and related heterocycles.[90] Examples include the reaction of the sodium salts of imides with the phosphorane **195** which leads to the intermediates **196** which cyclise on heating in mesitylene,[90a] the cyclisation of phosphonium salt **197**[90c] and the cyclisation of phosphoranes **199** derived from the ring opening of cyclopropane phosphonium salts **198** by imide sodium salts[90d] (Scheme 65). HWE variants of this type of reaction have been reported, however yields are generally not as good.[90d,91] The cyclopropane **151** and the related structure **199** were also found to react with the potassium salt of phthalimide to give the heterocycles **200**[69] (Scheme 66). A similar reaction of the oxamate **201** with a range of phosphonium bromides under basic conditions has proved to be an efficient method for the synthesis of a range of 5- and 6-membered nitrogen heterocycles[92] (Scheme 67).

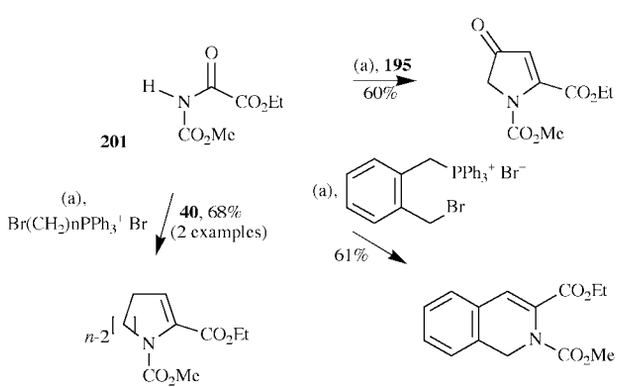
Several similar syntheses utilising intramolecular imide reactions have been reported including the reaction of keteneiminylphosphorane **55** with the *N*,*N*-diacylamino acids **202** which leads to the formation of phosphoranes **203** *via* elimination of phenyl isocyanate, which then cyclise to give pyrrolizidinediones **204**[93] (Scheme 68). Aitken and co-workers also reported the synthesis of similar systems using FVP.[94] Yamada and co-workers have also reported a novel synthesis of the Geissmann–Waiss lactone **206**, a key precursor to the synthesis of several pyrrolizidine alkaloids, which featured as the key step in the two stage cyclisation of the imide **205**[95] (Scheme 69).



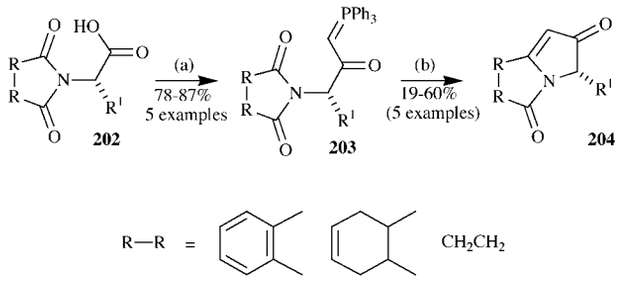
Scheme 65 *Reagents and conditions*: (a) DMF, NaH, 80 °C, 4 h; (b) Δ, mesitylene, 12 h; X = Cl, Br, R = H, Me, $–CH_2CH_2–$; (c) DMF, KOtBu, 80 °C, 3 h; (d) Δ, $PhCH_3$ or xylenes, 5–24 h; R^1 = H, SMe, SiPr, SPh, SBOM.



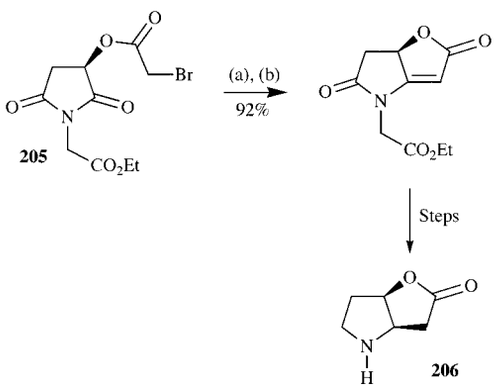
Scheme 66 *Reagents and conditions*: (a) Δ, melt; Z = CN, CO_2Et.



Scheme 67 *Reagents and conditions*: (a) DME, K_2CO_3, 85 °C, 8 h; *n* = 3, 4.

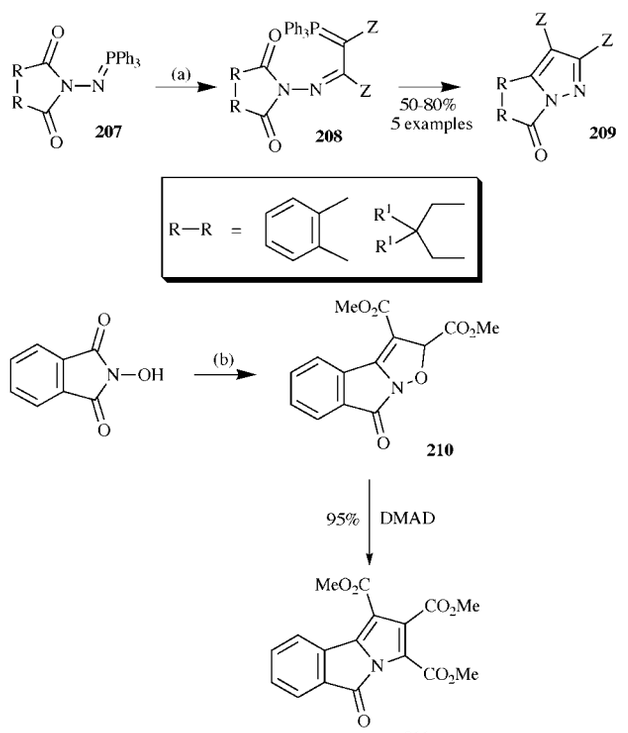


Scheme 68 *Reagents and conditions*: (a) **55**, Δ, EtOAc, then Δ, $PhCH_3$, EtOH; (b) Δ, $PhCH_3$, 12–24 h.



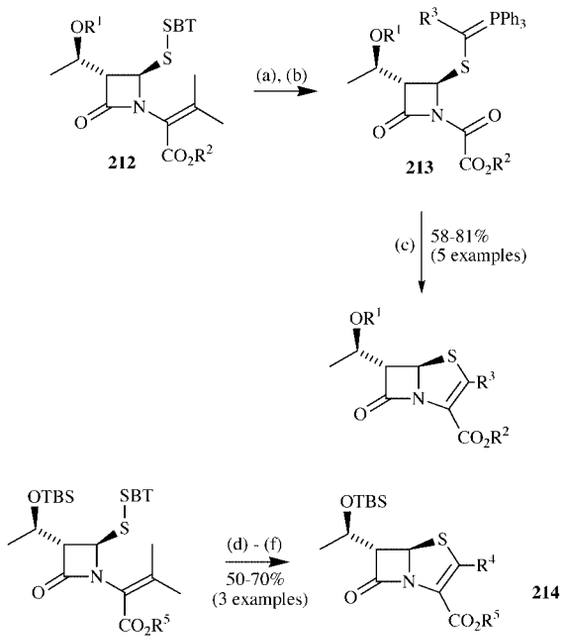
Scheme 69 *Reagents and conditions*: (a) PPh_3, CH_3CN, Δ, 3 h; (b) NEt_3, CH_3CN, Δ, 13 h.

is unstable to the reaction conditions and reacts with further DMAD to give pyrrole **211** *via* rearrangement and fragmentation[97] (Scheme 70).



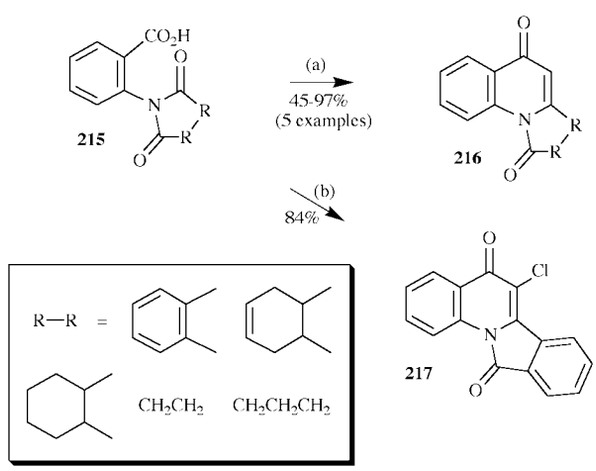
Scheme 70 *Reagents and conditions*: (a) ZCCZ, PhH, Δ, 3 h; X = CO_2Me, COPh; R^1 = Ph, Bn; (b) DMAD, PPh_3, CH_2Cl_2, rt, 24 h.

The cyclisation of the phosphoranes **213** represents an interesting variant of the Woodward penem synthesis involving an intramolecular Wittig reaction with an imide. The requisite phosphoranes are prepared by reaction of the disulfide **212** with a stabilised phosphorane followed by ozonolysis of the alkene substituent and heating to effect cyclisation. The methodology is flexible in so much as these two steps can be reversed when using more reactive phosphoranes leading to the synthesis of penems **214**[98] (Scheme 71).



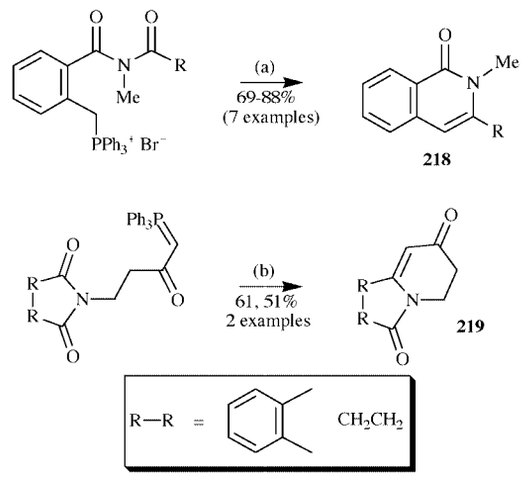
Scheme 71 *Reagents and conditions*: (a) R^3CHPPh_3; (b) CF_3CO_2H, then O_3, then DMS, $NaHCO_3$; (c) PhH, Δ; (d) O_3 then DMS; (e) R^4CHPPh_3, −50 °C; (f) warm to rt; R^1 = H, TBS; R^2 = Me, PNB; R^3 = CO_2Et, CO_2NH_2, COMe, COPh. R^4 = Ph, SPh, CH=CHPh, R^5 = PNB, TCE.

Other heterocyclic systems have been prepared *via* intramolecular Wittig reactions of imides, indeed the previously mentioned *N*-phenyl(triphenylphosphoranylidene)ethenimine **55** has been reported to react with carboxylic acids **215** to give the quinolones **216** by an identical mechanism to that reported for the formation of benzothiopyran-4-ones **124**.[99] Vorbrüggen and co-workers also effected a Wittig cyclisation of **215** to give **217** by treatment with triphenylphosphine in the presence of carbon tetrachloride; again this reaction is thought to proceed *via* an acid chloride and a chloro-ylide intermediate[20] (Scheme 72).



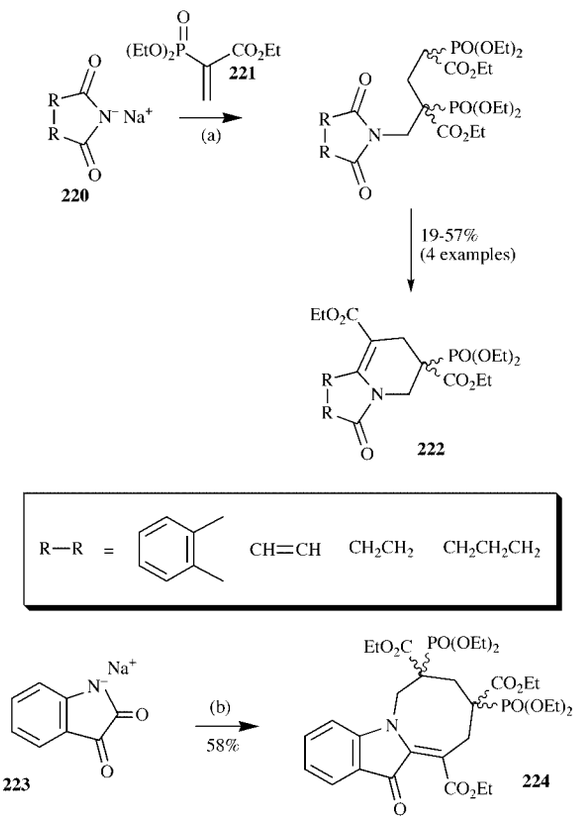
Scheme 72 *Reagents and conditions*: (a) **124**, Δ, $PhCH_3$, 6–8 h; (b) PPh_3, CH_2Cl_2, CCl_4, rt.

Similar syntheses of quinolones have been reported[100] together with the synthesis of isoquinolines **218**[101] and the synthesis of the 6-membered heterocycles **219**[102] (Scheme 73). The



Scheme 73 *Reagents and conditions*: (a) Δ, xylenes, 7 days; (b) Δ, $PhCH_3$, NEt_3, 1 h; R = Ph, Ar, 2-thienyl, i-Pr, styryl.

related heterocycles **222** were formed when sodium salts of imides **220** were reacted with two equivalents of the vinyl phosphonate **221**, the reaction proceeding *via* a two stage Michael addition and subsequent HWE reaction. Interestingly sodium isatin **223** required three equivalents to effect cyclisation and led to the unusual 8-membered heterocycle **224**[103] (Scheme 74).

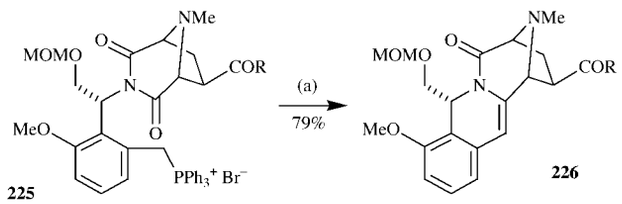


Scheme 74 *Reagents and conditions*: (a) **221** (2 equiv.), DMF, THF, 1 h, then Δ, 5 h; (b) **221** (3 equiv.), DMF, THF, 1 h, then Δ, 5 h.

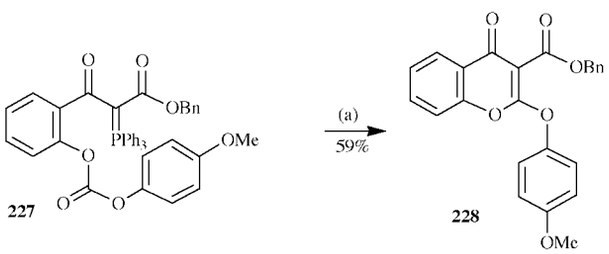
One particularly noteworthy application of this reaction is the cyclisation of phosphonium salt **225** to give the dihydroisoquinoline **226**, a key intermediate in the synthesis of the antitumour antibiotic quinocarcin, which was effected in 79% yield on heating in DMF[104] (Scheme 75).

8 Wittig reactions with carbonates, trithiocarbonate, thioureas and related systems

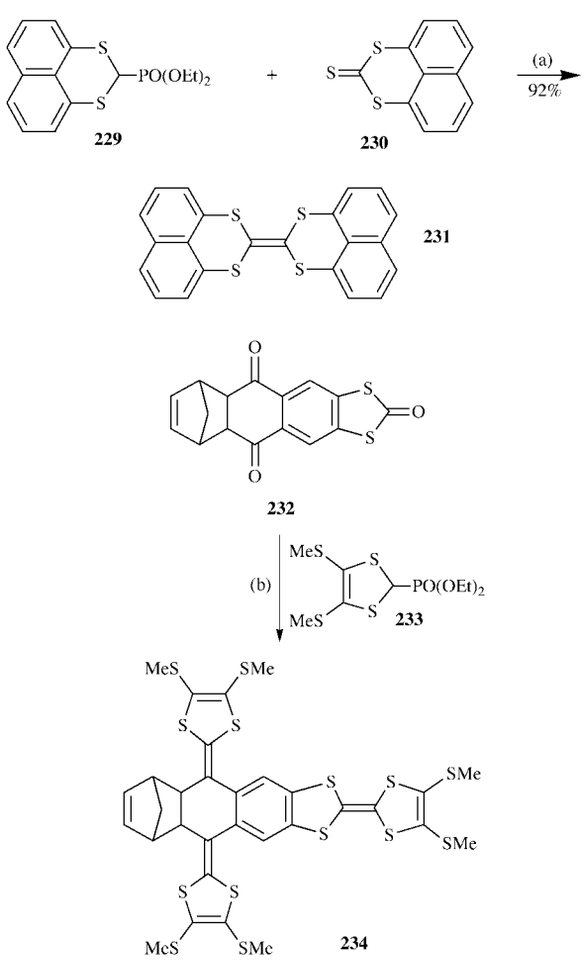
Some Wittig reactions of carbonates and trithiocarbonates have both been reported, for example the synthesis of the chromone **228** from the cyclisation of phosphorane **227**[105] (Scheme 76). Several examples of intramolecular Wittig reactions of trithiocarbonates have been reported previously, for example in the synthesis of penem β-lactams.[3,106] More recently intermolecular variants have gained importance, for example in the HWE reaction of the phosphonate **229** with trithiocarbonate **230** yielding **231**[107] and the reaction of dithiocarbonate **232** with excess phosphonate **233** led to the interesting TTF **234**[108] (Scheme 77). An example of a Wittig reaction of



Scheme 75 *Reagents and conditions*: (a) KOtBu, Δ, DMF, 120 °C, 10 h.

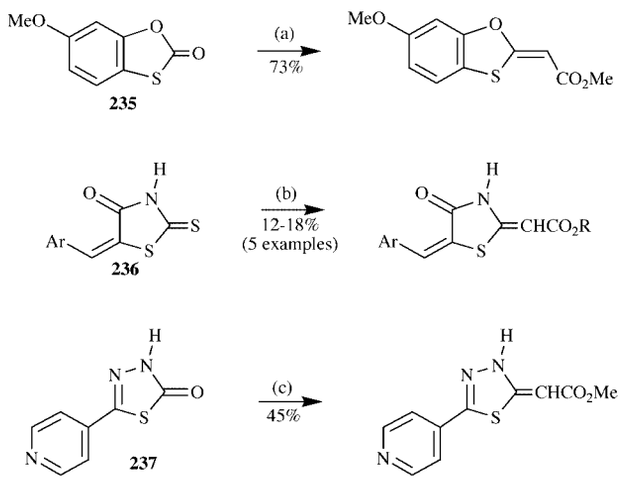


Scheme 76 *Reagents and conditions*: (a) Δ, DMF, $PhCH_3$, 28 h.



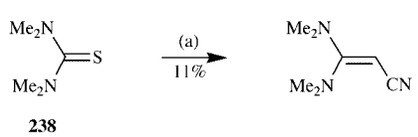
Scheme 77 *Reagents and conditions*: (a) LDA, THF, −78 to 0 °C; (b) **233** (10 equiv.), BuLi, THF, −78 °C.

methoxycarbonyltriphenylphosphorane with the thiocarbonate **235** has also been reported[109] and the much lower yielding Wittig reaction of the 2-thioxo-4-thiazolidinones **236** and the oxadiazole-2-thione **237** are also of note (Scheme 78).[110]



Scheme 78 *Reagents and conditions*: (a) $MeO_2CCHPPh_3$; (b) Δ, EtOAc or $PhCH_3$, 18–24 h; (c) $MeO_2CCHPPh_3$, Δ, $PhCH_3$, 3 h; R = OMe, OEt, Me.

Wittig reaction of urea derivatives are rare, however an exception is the reaction of tetra-*N*,*N*,*N*′,*N*′-methylthiourea **238** with cyanomethylenetriphenylphosphorane[111] (Scheme 79).



Scheme 79 *Reagents and conditions*: (a) $NCCHPPh_3$, Δ, $PhCH_3$, 60 h.

9 Conclusion

As can be seen from the examples discussed in this review the scope of the Wittig reaction continues to grow and the methods employed to effect the transformation of a carbonyl species into an alkene are becoming more diverse. When considering the more recent applications of the non-classical Wittig reaction it can be seen that a wide range of carbonyls are open to the reaction and the applications in synthesis are significant. These factors will serve to create more interest in the process which will no doubt generate many new synthetic applications in the coming years.

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