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The Wittig Olefination Reaction with Carbonyl Compounds other than Aldehydes and Ketones

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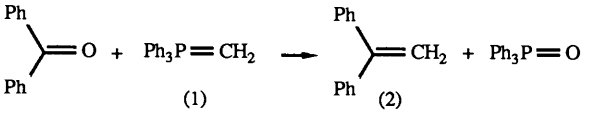
1 Introduction

Since the original observation by Wittig and Geissler[1] that methylenetriphenylphosphorane (1) reacted with benzophenone to give diphenylethylene (2) (Scheme 1) the Wittig reaction has been used countless times as a preparative organic reaction.[2,3] In general terms the Wittig reaction is considered as a condensation between a phosphorus ylide (3) and an aldehyde or ketone (4), giving rise to an olefin (5) and a phosphine oxide (6) (Scheme 2). Numerous reviews on the Wittig reaction have been published[2–4] covering both the synthetic and mechanistic aspects of the reaction and reflecting its importance as a chemical procedure. In contrast to such reviews it is the aim of this article to illustrate the increasing use in organic synthesis of the reaction of phosphoranes and related reagents with functional groups such as esters, amides, and anhydrides, to form olefins in a manner analogous to that more commonly observed with aldehydes and ketones. Mechanistic evidence for the possible intermediate species involved in such reactions and the factors influencing the ultimate yields of olefinic products will also be discussed.

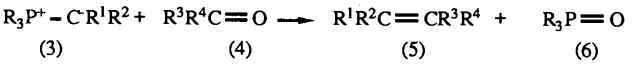
It was originally reported[5] that reactions between esters and reactive phosphoranes gave rise to β-ketophosphoranes such as (7) (Scheme 3). Subsequent reinvestigation of the general reaction have shown that it is possible to obtain the Wittig olefination product (8) with a wide variety of ester-type compounds using stabilized, semi-stabilized, and even reactive phosphoranes (Scheme 4).

This 'non-classical' Wittig reaction has found numerous applications in the synthesis of natural products containing enol-ether, enamine, and related functionalities.

[1] G. Wittig and G. Geissler, *Liebigs Ann. Chem.*, 1953, **580**, 44.
[2] H. J. Bestmann and O. Vostrowsky, *Top. Curr. Chem.*, 1983, **109**, 85.
[3] H. Pommer and P. C. Thieme, *Top. Curr. Chem.*, 1983, **109**, 165.
[4] (*a*) M. Schlosser, *Top. Stereochem.*, 1970, **5**, 1; (*b*) I. Gosney and A. G. Rowley in 'Organophosphorus Reagents in Organic Synthesis', ed. J. I. G. Cadogan, Academic Press, New York, 1979, p. 17; (*c*) M. Schlosser and B. Schaub, *Phosphorus Sulfur*, 1983, **18**, 171.
[5] (*a*) S. Trippett and D. M. Walker, *J. Chem. Soc.*, 1961, 1266; (*b*) G. Wittig and U. Schollkopf, *Chem. Ber.*, 1954, **87**, 1318.

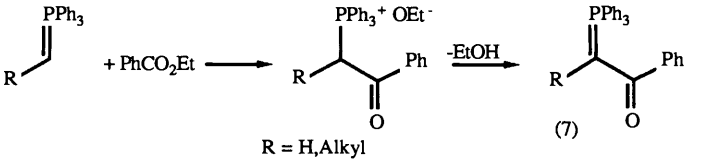


Scheme 1



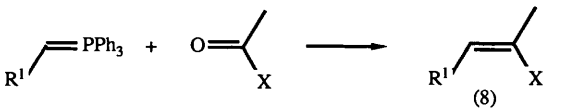
R,R^1,R^2,R^3,R^4 = H,Alkyl,Aryl

Scheme 2



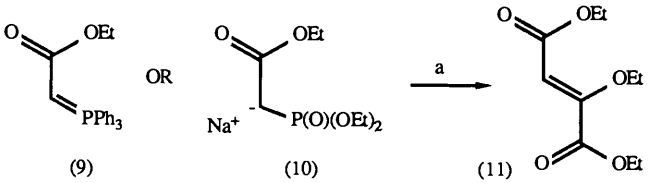
R = H,Alkyl

Scheme 3



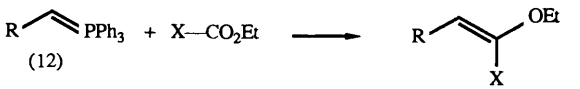
R^1 = COR,CO_2R,Ph; R = Alkyl,Aryl; X = OR,OAc,SR,NHR,NHCOR

Scheme 4



(a) $(CO_2Et)_2$

Scheme 5



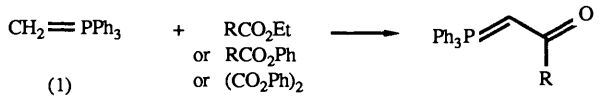
R = Ph,Alkyl; X = CH_2F,CF_3

Scheme 6

2 Wittig Reaction with Esters

Machleidt *et al.*[6] reported the reaction of ethyl oxalate with stabilized phosphoranes (9) and phosphonates (10) leading to the formation of vinyl ester (11)

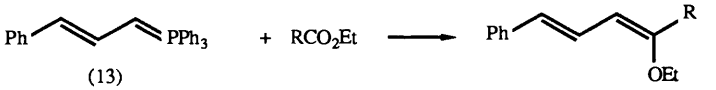
[6] W. Grell and H. Machleidt, *Liebigs Ann. Chem.*, 1966, **693**, 134.



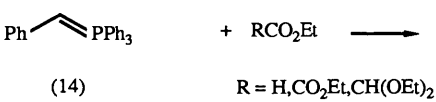
(1)

R = H,CO_2Et,$CH(OEt)_2$,CN,OPh

Scheme 7

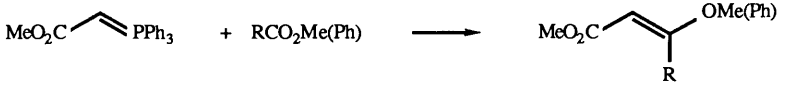


(13)



(14) R = H,CO_2Et,$CH(OEt)_2$

Scheme 8



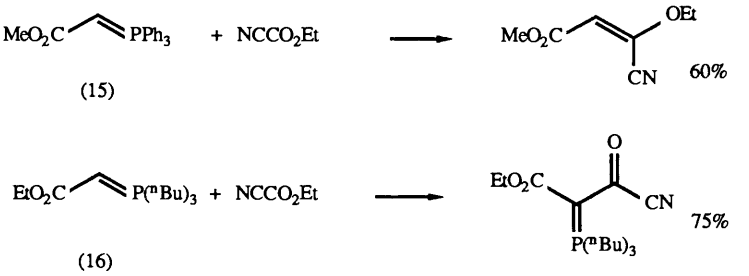
R = H,CN,CO_2Et,OPh

Scheme 9

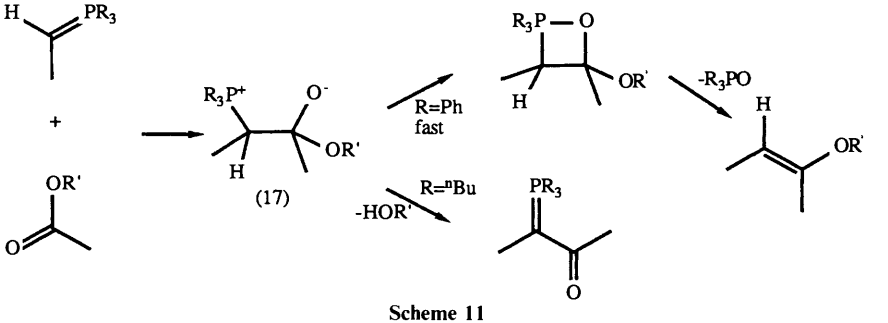
(Scheme 5). In the same paper and also in a communication by Bestmann *et al.*[7] the condensation of phosphoranes (12) with fluorinated acetates was reported (Scheme 6). The yields for the reaction are best, (65—82%) when R is semi-stabilizing (*e.g.* R = Ph) and X is highly electron withdrawing (*e.g.* X = CF_3). However, the yields for non-stabilized phosphoranes are by no means low (45—76%); this is in stark contrast to previous reports.[5]

Le Corre reinvestigated the reaction of phosphoranes with esters and drew several conclusions from his work.[8] Firstly, he reported that the reaction of methylenetriphenylphosphorane (1) with esters gave β-keto phosphoranes as the only product (Scheme 7). He did show, however, that semi-stabilized phosphoranes (13) and (14) gave vinylic products with esters. Best yields were obtained when R was H or CO_2Et (67—91% over 1—3 hours); however with R = $CH(OEt)_2$ yields were low (25—32% over 3 hours) (Scheme 8). Vinylic products were also observed with stabilized phosphoranes, yields of 60—85% being obtained (Scheme 9). Le Corre also reported that replacement of the phenyl groups on the phosphine with *n*-butyl groups leads to the formation of β-keto phosphoranes as the reaction

[7] H. J. Bestmann, K. Rostock and H. Dornauer, *Angew. Chem., Int. Ed. Engl.*, 1966, **5**, 308.
[8] M. Le Corre, *Bull. Soc. Chim. Fr.*, 1974, 2005.



Scheme 10



Scheme 11

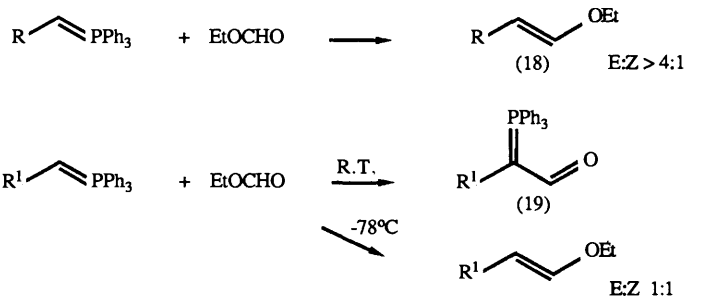
product—compare, for example, the reactions of phosphoranes (15) and (16) (Scheme 10).

From the work of Le Corre, it is possible to conclude that electron withdrawing groups (CN, CO_2Et) (or, as in the case of formates, the lack of an electron donating group) attached to the ester carbonyl increase the tendency for the formation of olefinic products. The difference in product composition for the different phosphorus substituents was explained by assuming that the alkyl groups (*e.g.* Bu^n) stabilize any intermediate betaine (17) formed in the reaction by electron donation to the phosphorus. This allows the intermediate to exist for longer periods of time and undergo decomposition by both routes. In contrast electron-withdrawing groups on the phosphorus have the opposite effect, in that the electron deficient phosphorus will increase the rate of formation of the oxaphosphetane and thus product formation will be rapid (Scheme 11).

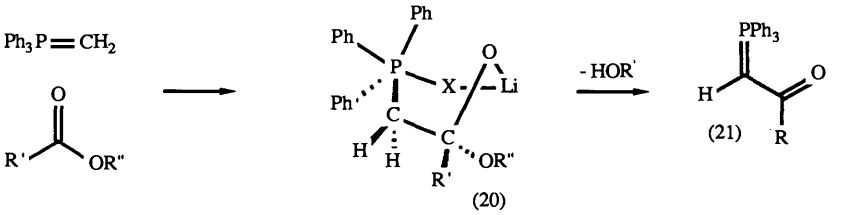
Further investigation was performed by Subramanyan *et al.*[9] who reacted all three types of phosphorane with ethyl formate. Stabilized phosphoranes (R = CO_2Et, Ph) gave in excess of 90% yield of vinylethers (18). With reactive ylides (R^1 = alkyl) the results of Le Corre were confirmed, the products obtained being β-keto phosphoranes (19). However, if this reaction was carried out at −78 °C low yields of vinyl ethers were obtained (Scheme 12).

The difference in results of the workers with regard to reactive phosphoranes, *i.e.*

[9] V. Subramanyan, E. H. Silver, and A. H. Soloway, *J. Org. Chem.*, 1976, **41**, 1272.



Scheme 12



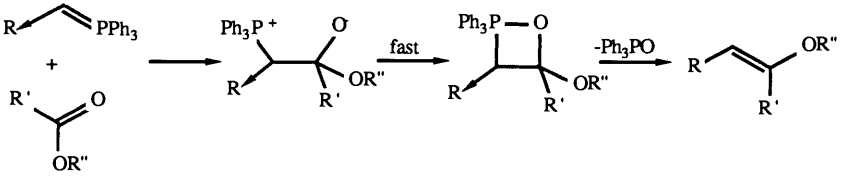
R',R" = H,Alkyl,Aryl; X = Halide

Scheme 13

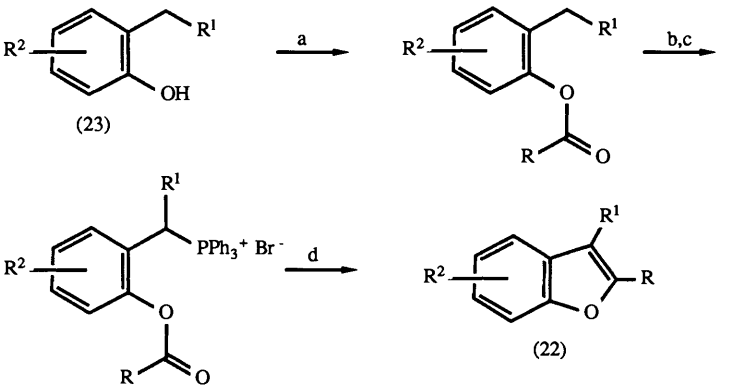
Bestmann obtaining good yields of olefins[7] whereas Le Corre[8] and Subramanyan[9] obtained β-keto phosphoranes, can be explained by differing experimental procedure. In a communication by Van der Gen *et al.*[10] some discussion of differences in reaction pathways was mentioned: if lithium bases are used to generate the reactive phosphoranes the formation of salt-stabilized betaine intermediates with twist boat structures (20) (as proposed by Schlosser[4a]) is expected (Scheme 13).

Formation of an intermediate which gives rise to an olefinic product is inhibited by the presence of the lithium cation; it has been reported that complexed oxygen has a low tendency to form triphenylphosphine oxide.[4a] From this evidence it would appear that the formation of β-keto phosphoranes (21) is favoured by the presence of alkali metal salts; this is indeed demonstrated by the work of Le Corre[8] and Subramanyan.[9] Bestmann used salt-free conditions in his reactions and obtained better yields of olefins.[7] With stabilized phosphoranes it is further suggested[10] that the electron withdrawing substituent (R) that stabilizes the phosphorane also stabilizes and encourages the formation of the double bond of the product (Scheme 14). Factors such as the absence of metal salts and higher reaction temperatures could also play a role in the different product outcome obtained with stabilized phosphoranes.

[10] U. J. Uijttewaal, F. L. Jonkers, and A. Van der Gen, *J. Org. Chem.*, 1978, **43**, 3306.



Scheme 14



(a) RCOCl, (b) Br_2, (c) PPh_3, (d) sodium-t-amylate; R = Et,Pr,Bu,Ph,Ar; R^1 = H,Me; R^2 = H,PhCO

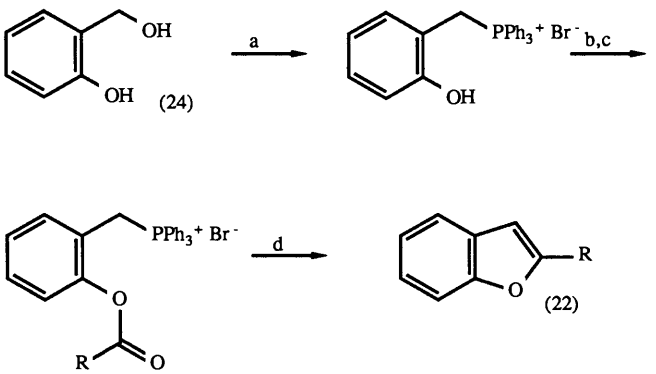
Scheme 15

The synthetic applicability of the reaction between phosphoranes and esters has been investigated, in particular by Le Corre. In his definitive paper[11] he described the preparation of numerous benzofurans (22) by two routes from phenols, both involving a Wittig cyclization. Firstly, *o*-alkylphenols (23) are esterified, and then brominated and converted into phosphonium salts; subsequent cyclization by treatment with base gave benzofurans (22) in excellent yields (72—94%) (Scheme 15). In the second route *o*-hydroxybenzyl alcohol (24) is converted into the corresponding benzylic phosphonium salt with triphenylphosphonium hydrobromide, esterified and cyclized to benzofurans (22), again in excellent yields (70—93%) (Scheme 16).

Le Corre reported[12] the preparation of chromenes (25) by an analogous process involving reaction of benzyl bromides with preformed phosphoranes, followed by intramolecular cyclization. Isochromenes (26) were also prepared[13] from α,α'-dibromoxylenes in overall yields of 50—80% (Scheme 17).

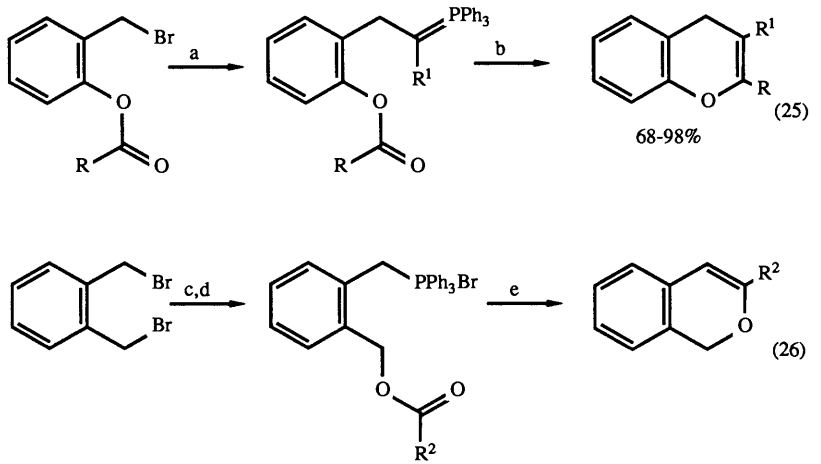
Several reports of the synthesis of naturally occurring benzofurans have

[11] A. Hercouet and M. Le Corre, *Tetrahedron*, 1981, **37**, 2867.
[12] A. Hercouet and M. Le Corre, *Tetrahedron Lett.*, 1979, 2995.
[13] B. Begasse, A. Hercouet, and M. Le Corre, *Tetrahedron Lett.*, 1979, 2149.



(a) PPh_3.HBr, (b) RCOCl, (c) NEt_3 (d) sodium-t-amylate/heat ; R = Et,Pr,Bu,Ph,Ar, cyclopropyl,$C(CH_3)=CH_2$, 2-furyl,CH=CHPh

Scheme 16



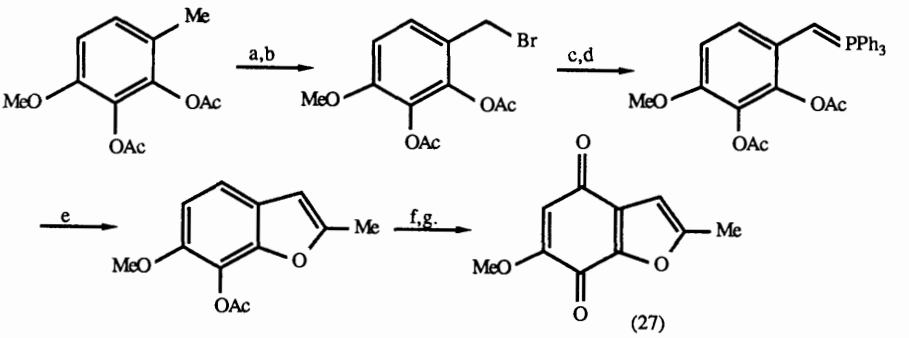
(a) 2 eqv. $R^1CH=PPh_3$, (b) reflux/toluene, (c) PPh_3, (d) R^2CO_2 Na, (e) sodium-t-amylate/heat; R = Me,Et,Ph, R^1 = Ac,Ph,CO_2Me, R^2 = H,Me,Ph

Scheme 17

appeared in recent literature all using this approach.[14] For example the natural product acamelin (27), an allergy-induced extract of the Australian blackwood, has been prepared *via* this methodology[14a] (Scheme 18).

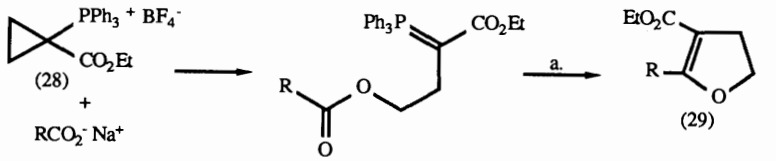
Dihydrofurans and dihydropyrans have also been prepared from acyclic

[14] (*a*) B. A. McKittrick and R. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1983, 2423; (*b*) B. A. McKittrick and R. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1983, 475; (*c*) B. A. McKittrick, and R. Stevenson, *J. Chem. Soc., Perkin Trans. 1*, 1984, 709.



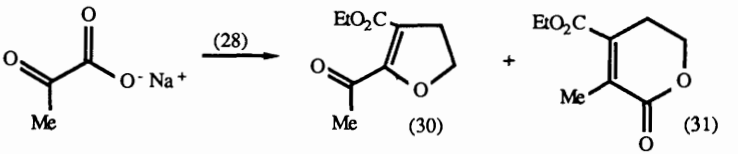
(a) Ac_2O, (b) NBS, (c) PPh_3, (d) NEt_3, (e) reflux/toluene/4hrs, (f) $LiAlH_4$, (g) $(KSO_3)_2NO$

Scheme 18



(a) reflux/29-144hrs; R = H,Me,Ph,CH_2F,CH=CHPh

Scheme 19



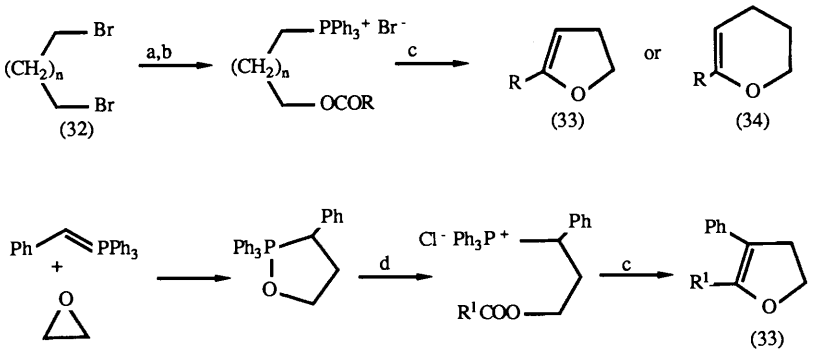
Scheme 20

precursors using the Wittig cyclization. Dauben and Hart reported[15] that reaction of carboxylic acid salts with carboethoxycyclopropyltriphenylphosphonium fluoroborate (28) gave dihydrofurans (29) in good yields 70—93% (Scheme 19). An interesting result was obtained when sodium pyruvate was reacted with (28); a mixture of two products, a dihydrofuran (30) and a dihydropyran (31), was obtained in a 5:1 ratio respectively (Scheme 20). This represented the first example of a phosphorane reacting selectively with an ester in the presence of a ketone. The authors suggested that carbonyl electrophilicity and steric factors govern the course of the reaction.[15]

Le Corre also reported the preparation of dihydrofurans and dihydro-2,3-pyrans by two routes.[16] Reaction of terminal dibromoalkanes (32) with triphenylphosphine

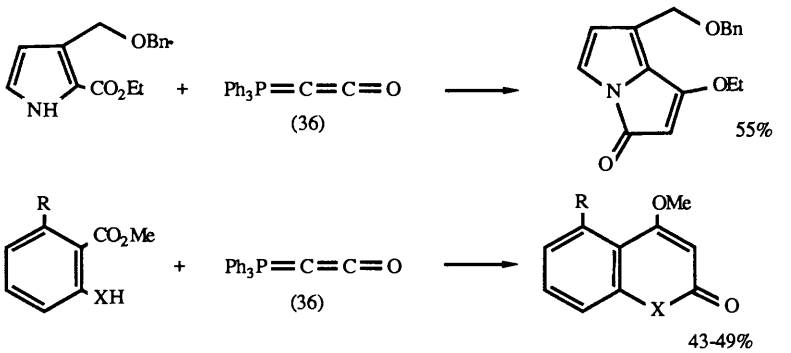
[15] W. G. Dauben and D. J. Hart, *Tetrahedron Lett.*, 1975, 4353.

[16] (*a*) A. Hercouet and M. Le Corre, *Tetrahedron*, 1981, **37**, 2855; (*b*) A. Hercouet and M. Le Corre, *Tetrahedron*, 1981, **37**, 2861.



(a) PPh_3, (b) $RCO_2^-Na^+$, (c) sodium-t-amylate, (d)R^1COCl; n = 1,2; R = Ph, 4-pyridyl,2-furyl, n-heptyl; R^1 = H,Pr

Scheme 21



X = O,NH; R = H,Me

Scheme 22

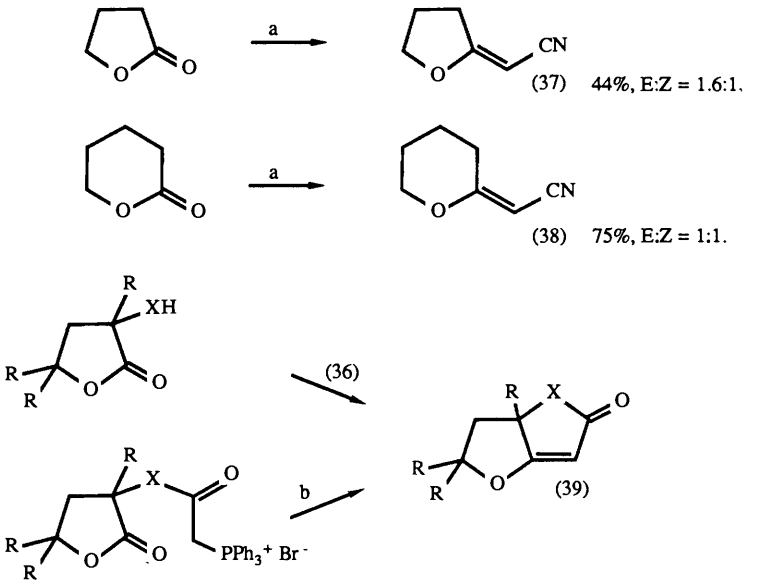
and sodium carboxylates followed by base-mediated cyclization led to dihydrofurans (33) and dihydro-2,3-pyrans (34). A similar route, using ethylene oxide and phenylmethylenetriphenylphosphorane (35) also gave dihydrofurans (33) (Scheme 21).

The use of triphenylphosphoranylidene ketene (36) in the synthesis of heterocycles has been recently reviewed by Bestmann *et al.*[17] Several examples of this reagent reacting with esters have been reported[18] (Scheme 22).

Only two examples have been reported of reaction between Wittig reagent with a lactone carbonyl; this is somewhat surprising considering the many literature

[17] H. Bestmann, G. Schmid, D. Sandmeier, G. Schade, and H. Oechsner, *Chem. Ber.*, 1985; **118**, 1709.

[18] (*a*) W. Kose, K. Nickisch, and F. Bohlmann, *Chem. Ber.*, 1980, **113**, 2694; (*b*) K. Nickisch, W. Klose, E. Nordhoff, and F. Bohlmann, *Chem. Ber.*, 1980, **113**, 3086.



(a) $(EtO)_2P(O)CH_2CN/NaH$, (b) DBN/THF/reflux; R = H,Me; X=NH,O,S

Scheme 23

reports involving cyclic anhydrides and imides. First, reaction of both γ-butyrolactone and δ-valerolactone with the sodium enolate of diethylcyanomethylphosphonate gave the vinylic products (37) and (38) in 40% and 75% yield respectively (mixture of *E* and *Z* isomers).[19] More recently the preparation of bicyclic heterocycles (39) has been reported[20] *via* two routes, one of which utilizes (36) (Scheme 23).

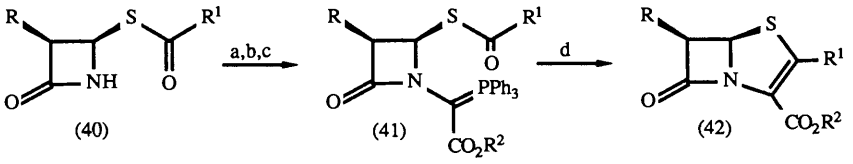
3 Wittig Reaction with Thiolesters

Probably the most frequently reported and well known of the 'non-classical' Wittig reactions is found in the Woodward synthetic approach to the penem β-lactams. First fully reported in 1978,[21] it involved modification of 4-thioacetylazetidinones (40) *via* a procedure developed by Woodward's group, into stabilized phosphoranes (41). Cyclization of (41) in hot toluene gave penems (42) (Scheme 24). Certain general trends can be concluded with respect to the rate and ease of reaction (Table 1).

[19] A. J. Duggan, M. A. Adams, P. J. Brynes, and J. Meinwald, *Tetrahedron Lett.*, 1978, 4323.

[20] J. Brennan and P. J. Murphy, *Tetrahedron Lett.*, submitted for publication.

[21] (*a*) I. Ernest, J. Gosteli, C. W. Greengrass, W. Holick, D. E. Jackman, H. R. Pfaendler, and R. B. Woodward, *J. Am. Chem. Soc.*, 1978, **100**, 8214; (*b*) H. R. Pfaendler, J. Gosteli, and R. B. Woodward, *J. Am. Chem. Soc.*, 1979, 101, 6306; (*c*) M. Lang, K. Prasad, W. Holick, J. Gosteli, I. Ernest, and R. B. Woodward, *J. Am. Chem. Soc.*, 1979, **101**, 6296; (*d*) I. Ernest, J. Gosteli, and R. B. Woodward, *J. Am. Chem. Soc.*, 1979, **101**, 6301; (*e*) I. Ernest, A. J. Main, and R. B. Woodward, *Helv. Chim. Acta*, 1981, **64**, 1303.



(a) R^2O_2CCHO, (b) $SOCl_2$, (c) $PPh_3/KHCO_3$, (d) heat/Toluene;
R = $NHCOCH_2OPh$, R^1,R^2 = see Table 2

Scheme 24

Table 1 *Conditions and yields for the preparations of compound* (42)*

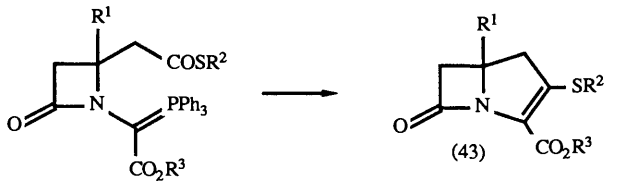
	Entry		*Conditions*		
	R^1	R^2	*Temperature*	*Time*	*Yield*
1	Me	Bu^t	111 °C	10 h	70%
2	Pr^i	Bu^t	80—100 °C	8 d	6%
3	Ph	PNB†	90 °C	3 d	53%
4	*p*-$NO_2C_6H_4$	Bu^t	55 °C	17 h	90%
5	Me	Me	80 °C	46 h	57%
6	Me	PNB	80 °C	4—5 d	70%
7	Me	CH_2CCl_3	80—100 °C	3 d	10%

* Data tabulated from reference 21*a*. † *p*-Nitrobenzyl

The ease of reaction can be considered as a function of the time required to effect transformation, the reaction yield, and the temperature at which the reaction is performed. For variations in R^1 it is clear that a change from Me to Pr^i (entry 1, 2) greatly decreases the ease of reaction. Two factors could account for this; firstly, increased steric hindrance between the phosphorane and carbonyl caused by the isopropyl group; secondly, the increased electron donating effect of the isopropyl group decreasing the reactivity of the carbonyl to nucleophilic attack. Introduction of a phenyl group (entry 3) again has a steric effect, but its electron withdrawing effect enhances the rate of reaction to a certain extent. Increased electron withdrawing ability such as with *p*-nitrophenyl (entry 4), further increases the ease of reaction.

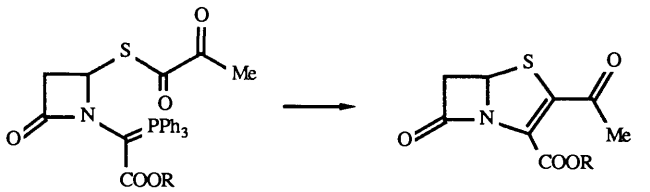
As far as R^2 is concerned an opposite effect is observed. Electron donating groups such as Bu^t and Me (entries 1,5) give best results, whereas electron withdrawing groups (*p*-nitrobenzyl and 2,2,2-trichloroethyl (entries 6,7) require long periods of heating to effect transformation. One can postulate that the electron donation makes the phosphorane more nucleophilic towards the ester carbonyl and that this effect increases the rate of reaction.

Having said this it is then important to consider other factors—for example, in a report relating to the synthesis of carbapenams (43) the workers involved noticed that in the cases where R^1 = Me yields for the reaction were typically around 50%, whereas if the position was unsubstituted (R^1 = H) yields were low, typically



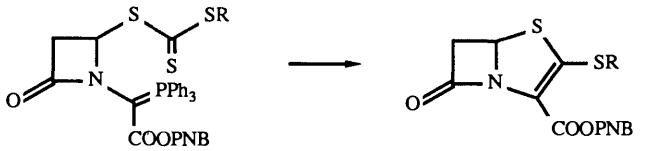
R^1 = H,Me, R^2 = Ph,PNB, R^3 = ^{t}Bu,Bn,PNB

Scheme 25



R = ^{t}Bu,PNB

Scheme 26



R = Et,-$(CH_2)_2$NHAc

Scheme 27

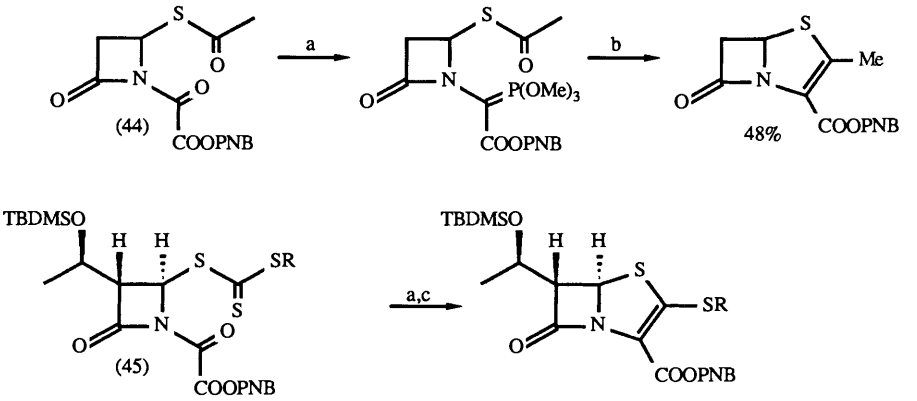
around 10%) (Scheme 25). The instability of some thiolesters was cited as a possible explanation for this observation.[22]

Woodward *et al.* also reported a cyclization in the β-lactam series which showed a preference for an ester in the presence of a ketone[21e] (Scheme 26). This observation taken with that of Dauben and Hart[15] (Scheme 20) would appear to suggest a marked preference for the formation of five- rather than six-membered rings in reactions of this type.

Woodward's group was also the first to report cyclization involving a trithiocarbonate[23] (Scheme 27).

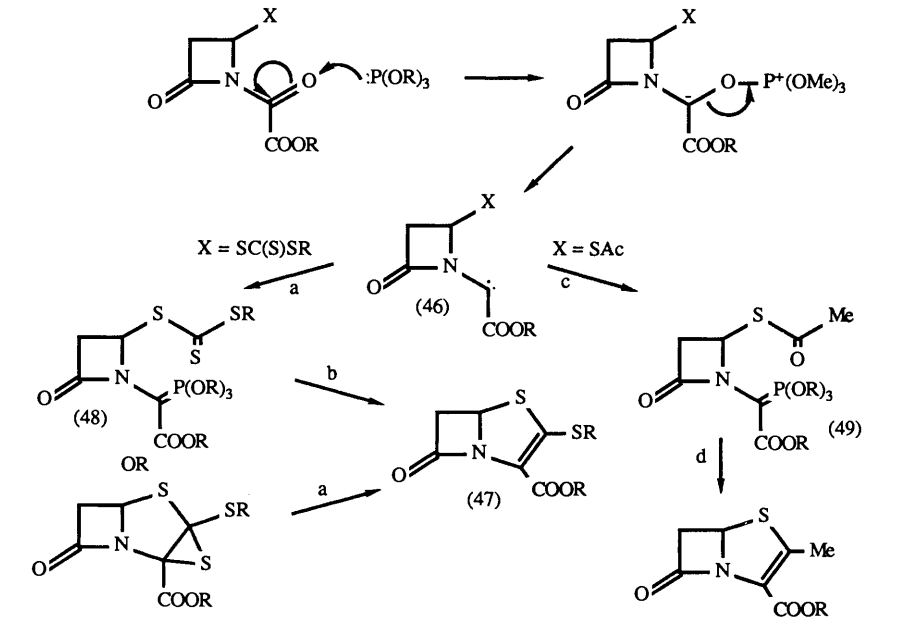
In recent years, both methods of synthesis developed by Woodward, thiolester and trithiocarbonate, have been modified by Yoshida *et al.*[24] Reaction of oxalimides (44), (45) with two equivalents of a trialkylphosphite gave β-lactams as

[22] R. J. Ponsford, P. M. Roberts, and R. Southgate, *J. Chem. Soc., Chem. Commun.*, 1979, 847.
[23] M. Lang, K. Prasad, J. Gosteli, and R. B. Woodward, *Helv. Chim. Acta*, 1980, **63**, 1093.
[24] (*a*) T. Hayashi, A. Yoshida, N. Takeda, and S. Oida, *Chem. Pharm. Bull.*, 1983, **31**, 768; (*b*) A. Yoshida, Y. Tajima, N. Takeda, and S. Oida, *Tetrahedron Lett.*, 1984, **25**, 2793.



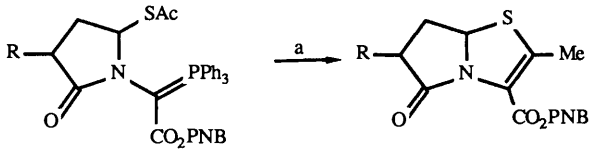
(a) heat/65°C/$P(OMe)_3$, (b) heat/toluene/105°C/20hrs, (c) reflux/xylene/15hrs;
R = ^{i}Pr,Ph,$CH_2CH_2NHCO_2PNB$

Scheme 28



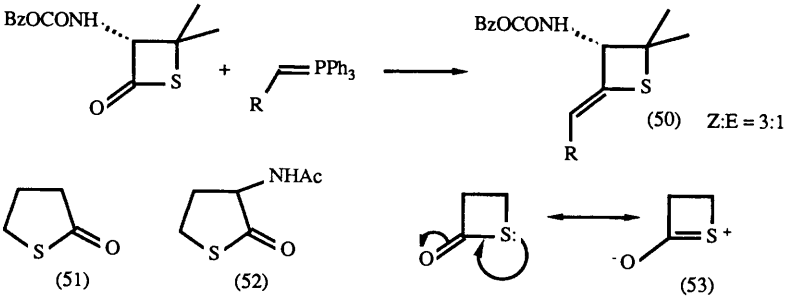
(a) $P(OR)_3$/80°C, (b) heat/125°C, (c)$P(OR)_3$/65°C,
(d) heat/105°C; R = alkyl

Scheme 29



(a) heat/toluene; R = H,^{t}BuCONH

Scheme 30



R = CO_2Et,CN,COMe

Scheme 31

products (Scheme 28). The mechanism of the reaction[25] is generally assumed to be *via* a nucleophilic attack of phosphorus at the amide oxygen, followed by decomposition of the intermediate species formed into the carbene (46). In the case of the trithiocarbonate the carbene is able to undergo insertion into the C=S bond; subsequent desulphurization with another equivalent of trialkylphosphite forms the final product (47). Condensation between the carbene and trialkylphosphite gives rise to the ylide (48): this will also undergo cyclization, but only on stronger heating.[24b] In the case of the thiolester, the carbonyl is not reactive enough towards the carbene and thus undergoes addition of trialkylphosphites to give ylides (49); these undergo cyclization on further heating (Scheme 29).

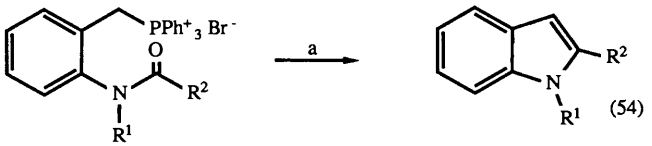
Woodward's methodology has recently been used in the synthesis of γ-lactam analogues of the penems[26] (Scheme 30).

Stoodley *et al.*[27] reported that the condensation of stabilized phosphoranes with thietan-2-ones gave rise to vinylthioethers (50) in good yields. The authors also reported that attempted reactions of phosphoranes with five-membered thiolactones (51) and (52) were unsuccessful. It was concluded that thietan-2-ones have enhanced ketonic character imposed upon them by the geometry of the four-membered ring. It is probable that resonance overlap in thietan-2-ones is diminished, as any resonance form containing an internal double bond (53) will

[25] (*a*) E. Perrone, M. Alpegiani, A. Bedeschi, F. Giudici, and G. Franceschi, *Tetrahedron Lett.*, 1984, 25, 2399. (*b*) A. Afonso, F. Hon, J. Weinstein, A. K. Gangaly, and A. T. McPhail, *J. Am. Chem. Soc.*, 1982, **104**, 6138.

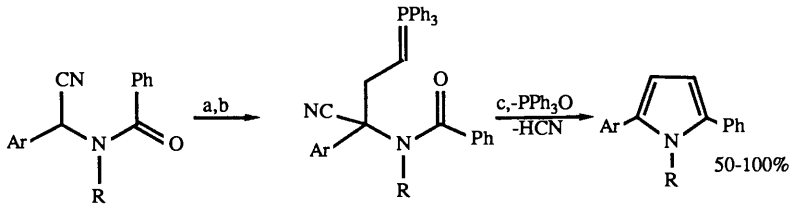
[26] D. B. Boyd, T. K. Elzey, L. D. Hatfield, M. K. Kinnick, J. M. Morin, Jr., *Tetrahedron Lett.*, 1986, **27**, 3453.

[27] S. Al-Zaidi and R. J. Stoodley, *J. Chem. Soc., Chem. Commun.*, 1982, 995.



(a) Toluene/reflux/base; R^1 = H,Ph;R^2 = Me,$H_2C{=}CH_2$,Ph,Ar

Scheme 32



(a) NaH, (b) $CH_2{=}CHPPh_3^+$ Br^-, (c) heat/DMF/20-24hrs;
R = Alkyl,Aryl

Scheme 33

cause added ring strain; this will increase the ketonic character of the carbonyl (Scheme 31).

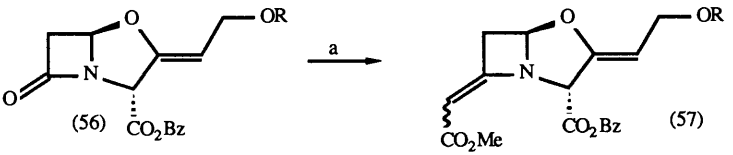
4 Wittig Reactions with Amides

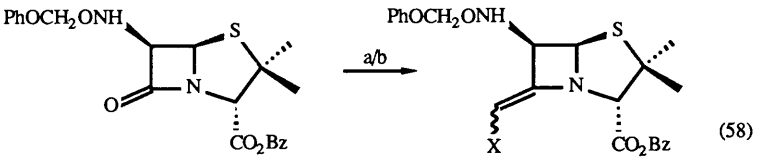
Only a few examples are known of amides being reactive towards phosphoranes; this is probably due to the low reactivity of amides towards nucleophilic attack. Those that have been reported have utilized either semi-stabilized or reactive phosphoranes or highly reactive amides.

Le Corre, reported the synthesis of a number of indoles (54) *via* an intramolecular Wittig condensation;[28] the reaction was remarkably facile, reaction times of only 10—15 min being required and yields were excellent (80—97%) (Scheme 32). Similarly, pyrroles (55) have also been prepared in 50—100% yield (Scheme 33).[29]

It is also possible to react the carbonyl of β-lactam ring systems with stabilized phosphoranes. Reaction of clavulanic acid derivatives (56) with methoxycarbonylmethylenetriphenylphosphorane gave low yields of olefinic products (57), whilst the benzyl ester of penicillin V gave an almost quantitative yield of (58) as a 60:40 ratio of *Z*:*E* isomers (Scheme 34).[30] Ozonolysis of the double bond formed leads to regeneration of the original compound; thus the reaction can be considered as a method of protection for the β-lactam system.[30]

[28] M. Le Corre, A. Hercouet, and H. Le Baron, *J. Chem. Soc., Chem. Commun.*, 1981, 14.
[29] J. V. Cooney and W. E. McEwen, *J. Org. Chem.*, 1981, **46**, 2570.
[30] M. L. Gilpin, J. B. Harbridge, T. T. Howarth, and T. J. King, *J. Chem. Soc., Chem., Commun.*, 1981, 929.





(a) $MeO_2CCH{=}PPh_3$/reflux/toluene, (b) $XCH = PPh_3$; R = Phthalimido,H; X = CO_2Me,CN,CO_2Bz

Scheme 34

5 Wittig Reaction with Anhydrides

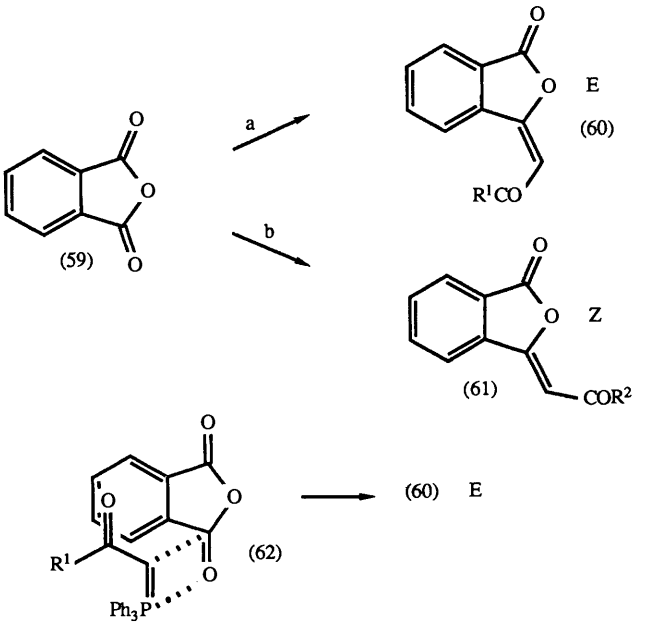
It has been well established that the reaction between cyclic anhydrides and stabilized phosphoranes proceeds well and leads to the formation of enol-lactones.[31]

The first reported reaction involving an anhydride was by Chopard *et al.* in 1965; reaction of phthalic anhydride (59) with stabilized phosphoranes led to enol lactones (60) and (61) in approximately 60% yield (in all cases) (Scheme 35).[32]

It was observed that for the alkoxycarbonyl and amide stabilized phosphoranes predominantly *E*-products (60) were formed (pathway a), whilst for the acyl-phosphoranes *Z*-products (61) predominated (pathway b). The authors, in explaining this difference, put forward an intermediate (62), in which the electron rich π-orbitals in the ester carbonyl overlap with the electron deficient π-orbitals in the aromatic system in a $\pi \longrightarrow \pi^*$ fashion. The overlap would be at its greatest when the electron donating group R^1 was alkoxy or alkylamino in nature and thus *E* olefins would be expected to predominate. These results were later shown to be incorrect and other theories on stereochemical outcome have been offered. In an investigation, by Knight *et al.* into the reaction of phosphoranes with phthalic anhydrides, a different reason for the preferential formation of *E*-alkenes was suggested.[33] Consideration of the two diastereomeric intermediates (63) and (64) shows that intermediate (63) is the least sterically hindered and thus would probably be the preferred betaine; subsequent formation of the oxaphosphetane and loss of triphenylphosphine oxide would then lead to *E*-alkenes as products (Scheme 36).

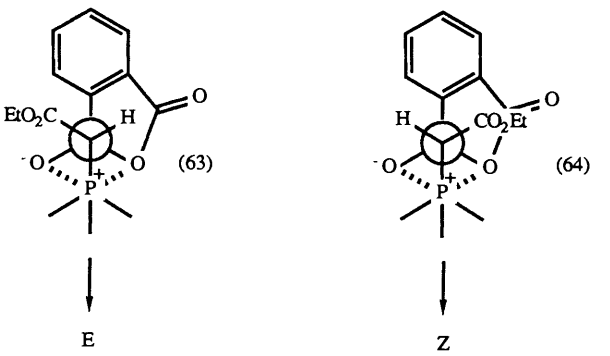
Wittig reactions of this type have been extensively studied by Massy-Westropp *et al.* who have performed reactions involving succinic, maleic, glutamic, and phthalic

[31] A. D. Abell and R. A. Massy-Westropp, *Aust. J. Chem.*, 1982, **35**, 2077.
[32] P. A. Chopard, R. F. Hudson, and R. J. G. Searle, *Tetrahedron Lett.*, 1965, 2357.
[33] A. Allahdad and D. W. Knight, *J. Chem. Soc., Perkin Trans. 1*, 1982, 1855.



(a) $R^1COCH{=}PPh_3$; R^1 = OMe,OEt,N(Alkyl)$_2$, (b) $R^2COCH{=}PPh_3$; R^2 = Me,Ph

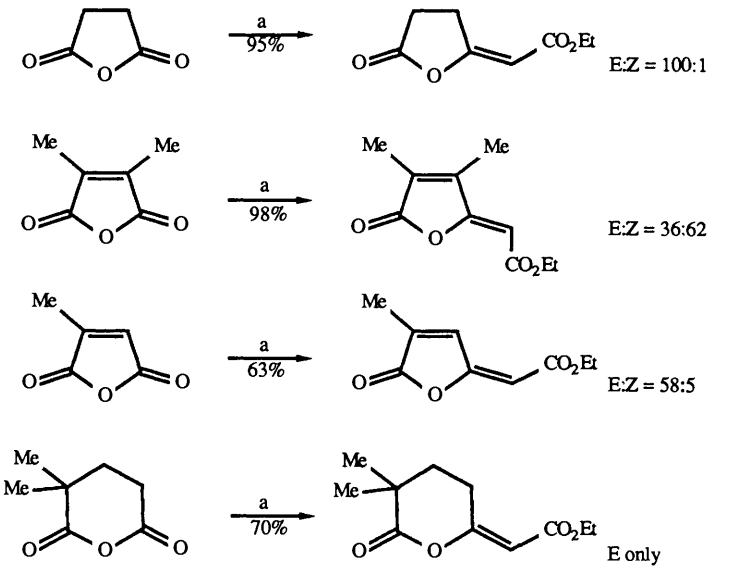
Scheme 35



Scheme 36

anhydrides.[31,34] The products obtained are predominantly the *E*-isomers (Scheme 37). The Wittig methodology was used in the synthesis of the natural

[34] (*a*) A. P. Gara, R. A. Massy-Westropp, and G. D. Reynolds, *Tetrahedron Lett.*, 1969, 4171; (*b*) C. F. Ingham, R. A. Massy-Westropp, G. D. Reynolds, and W. D. Thorpe, *Aust. J. Chem.* 1975, **28**, 2499; (*c*) P. J. Babidge and R. A. Massy-Westropp, *Aust. J. Chem.*, 1977, **30**, 1629; (*d*) R. A. Massy-Westropp and M. F. Price, *Aust. J. Chem.*, 1980, **33**, 333; (*e*) I. R. Doyle and R. A. Massy-Westropp, *Aust. J. Chem.*, 1982, **35**, 1903; (*f*) A. D. Abell, I. R. Doyle, and R. A. Massy-Westropp, *Aust. J. Chem.*, 1982, **35**, 2277.



(a) $EtO_2CH{=}PPh_3$

Scheme 37

Table 2 *Stereochemical outcome of reaction between phthalic anhydride and stabilized phosphoranes* (Scheme 39)*

Phosphorane $Ph_3P{=}CHCOR$	*Chopard*	*Massy-Westropp*
R	*E*:*Z*	*E*:*Z*
OEt	10:1	9:2
Ph	1:4	10:1
Me	1:10	5:2

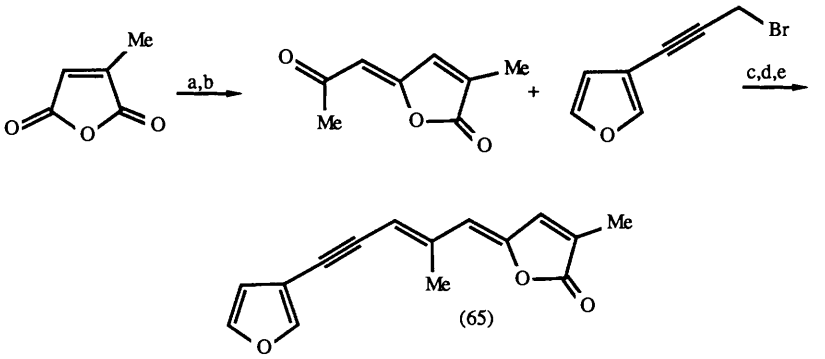
* Data taken from refs. 32 and 34b

product freelingyne (65) (Scheme 38).[35]

Massy-Westropp's group performed their own investigation into the mechanistic aspects of the Wittig reaction with anhydrides.[31] Initially they repeated the work of Chopard *et al.*[32] and obtained results inconsistent with those previously reported: Table 2, (Scheme 39).[34b]

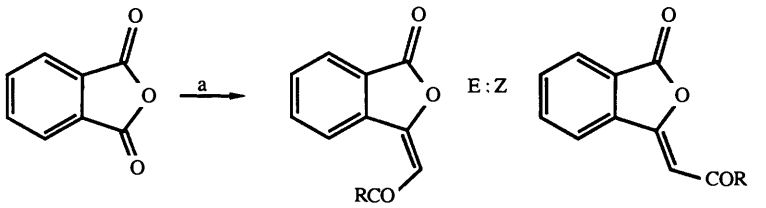
In all cases the *E*-isomer was predominant when the work was repeated; this result was rationalized by differences in reaction conditions between the two groups. The initial work was performed at temperatures of 100—120 °C which could cause isomerization of the products of the reaction. Massy-Westropp's

[35] (*a*) C. F. Ingham, R. A. Massy-Westropp, and G. D. Reynolds, *Aust. J. Chem.*, 1974, **27**, 1477; (*b*) C. F. Ingham and R. A. Massy-Westropp, *Aust. J. Chem.*, 1974, **27**, 1491.



(a) $MeCOCH{=}PPh_3$, (b) I_2/Benzene, (c)$Zn/HgCl_2$, (d) AcCl, (e) flash vacuum pyrolysis

Scheme 38



(a) $RCOCH{=}PPh_3$; For yields and R see Table 2

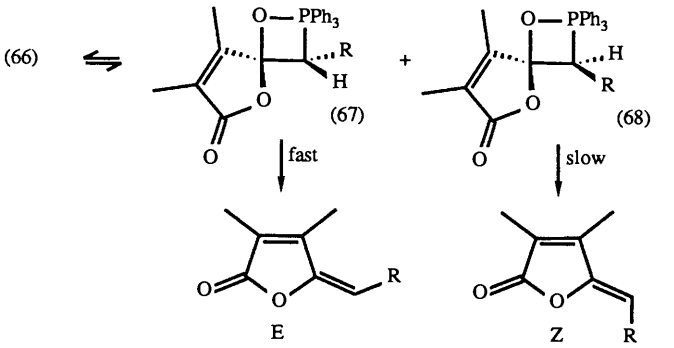
Scheme 39

group performed their tranformations at 40 °C and demonstrated that no isomerization occurs at this temperature.

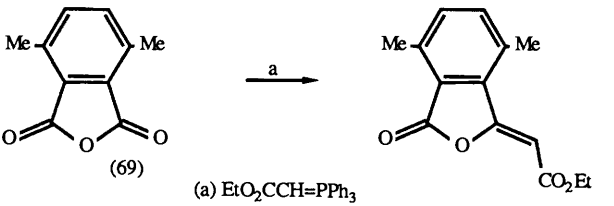
Further work elucidated the fact that an equilibrium occurs between the starting materials, the Wittig intermediates, and an acyclic intermediate (66)[31] (Scheme 40). They concluded that, because the equilibrium occurs readily, the most thermodynamically stable product should eventually be formed; as this is not the case, however, the reaction must be under kinetic control. These results (greater production of the thermodynamically less stable product) were rationalized by consideration of the reaction intermediates. They suggested that an equilibrium existed between the acyclic intermediate (66) and the isomeric oxaphosphetanes (67) and (68) and that the more sterically crowded oxaphosphetane (67) decomposes at a faster rate than (68); this results in predominantly *E* stereochemistry (Scheme 41).

The authors also stated that if a betaine intermediate only precedes the formation of (66) then the product stereochemistry would be dependent upon either the rates of decomposition of the isomeric oxaphosphetans or upon the mode of cyclization of (66).

Scheme 40



Scheme 41



Scheme 42

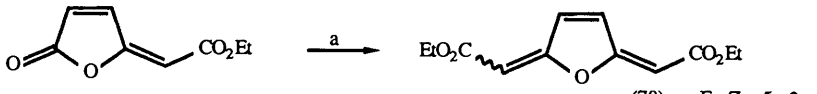
The reaction was performed on 3,6-dimethylphthalic anhydride (69) and the product ratio was completely reversed in that the *E*:*Z* ratio was 1:15. Here the steric interactions of the methyl groups reverse the rates of decomposition or formation of the isomeric oxaphosphetans (Scheme 42).

Enol lactones formed in these reactions can react further to give bis-adducts (70).[34c] The lactone carbonyl is relatively reactive due to the delocalization of the electrons of the ring oxygen (Scheme 43).

Reactions involving acyclic anhydrides and stabilized phosphoranes generally give only acylated phosphoranes;[36] two notable exceptions were reported, however, both in the field of β-lactam chemistry. Woodward reported the preparation of the cephalosporin derivative (71) by treatment of the acid precursor with acetic anhydride[37] (Scheme 44). Subsequently Hamashima *et al.* reported the

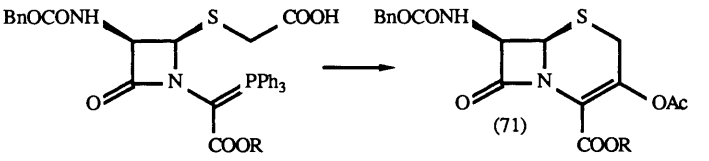
[36] P. A. Choppard, R. J. G. Searle, and F. H. Devitt, *J. Org. Chem.*, 1965, **30**, 1015.

[37] R. B. Woodward in 'Recent Advances in the Chemistry of β-Lactam Antibiotics', ed. J. Elks, The Chemical Society, Burlington House, London, 1977, p. 167.

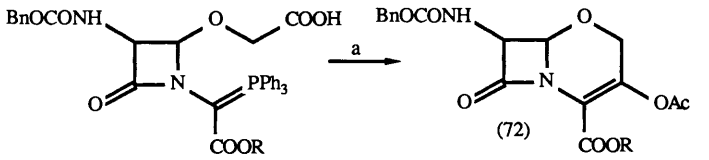


(a) $EtO_2CCH{=}PPh_3$

Scheme 43



Scheme 44



(a) Ac_2O/Me_2NCOCH_3/reflux/Toluene; R=$CHPh_2$, ^tBu

Scheme 45

preparation of oxacephems (72) *via* a similar route[38] (Scheme 45). Reaction was smoothest for R = Bu^t (69%, 90 °C, 3 hours), whereas when R = $CHPh_2$ lower yields were obtained (48%, 105 °C, 16 hours); this again demonstrates that electron donating groups on the phosphorane ester increase the favourability of reaction.

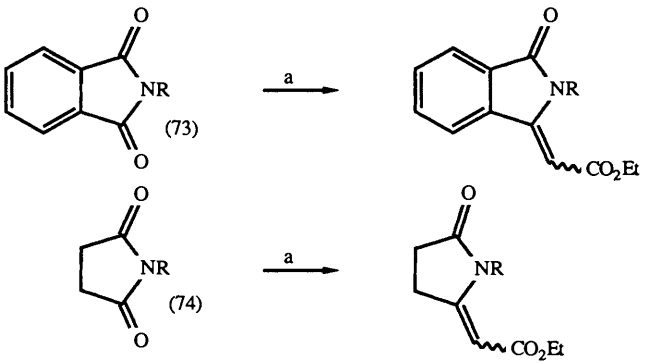
6 The Wittig Reaction with Imides

The intermolecular Wittig reaction of imides and phosphoranes was first reported by Flitsch *et al.* in 1969 with the reaction of phthalimides (73) and succinimides (74) to give olefinic products[39] (Scheme 46). The early work performed on imides, including open chain imides, cyclic imides, *N*-acylimides, *N*-sulphonolactams, and *N*-acylpyrroles, has been reviewed by Flitsch.[40]

Reaction temperatures used in the olefination are generally high (approx. 200 °C) and thus the reaction is performed either as a melt or in a high boiling solvent. *N*-Substituted imides give predominantly *E*-olefins whereas unfunctionalized imides produce *Z*-olefins. Reactive and semi-stabilized phosphoranes give low yields of olefinic products, whereas stabilized phosphoranes give high yields. It is also possible, as in the case of anhydrides, to obtain bis-adducts from the reaction by using excess phosphorane, for example in the reactions of *N,N*-diformylmethylamine (75) (Scheme 47).

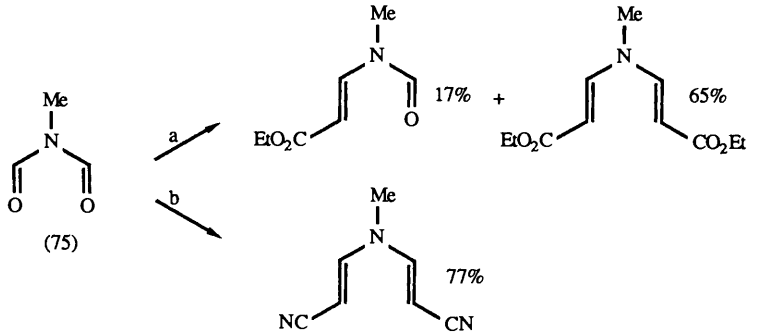
Reactions with cyclic imides generally give mixtures of mono- and bis-adducts,

[38] Y. Hamashima, S. Yamamoto, T. Kubota, K. Tokura, K. Ishikura, K. Minami, F. Matsubara, M. Yamaguchi, I. Kikkawa, and W. Nagata, *Tetrahedron Lett.*, 1979, 4947.
[39] W. Flitsch and H. Peters, *Tetrahedron Lett.*, 1969, 1161.
[40] W. Flitsch and S. R. Schindler, *Synthesis*, 1975, 685.



(a) $EtO_2CCH{=}PPh_3$; R = H,stereochemistry = Z, R = Me,stereochemistry = E

Scheme 46



(a) $EtO_2CCH{=}PPh_3$, (b) $NCCH{=}PPh_3$/heat/160°C/4hrs

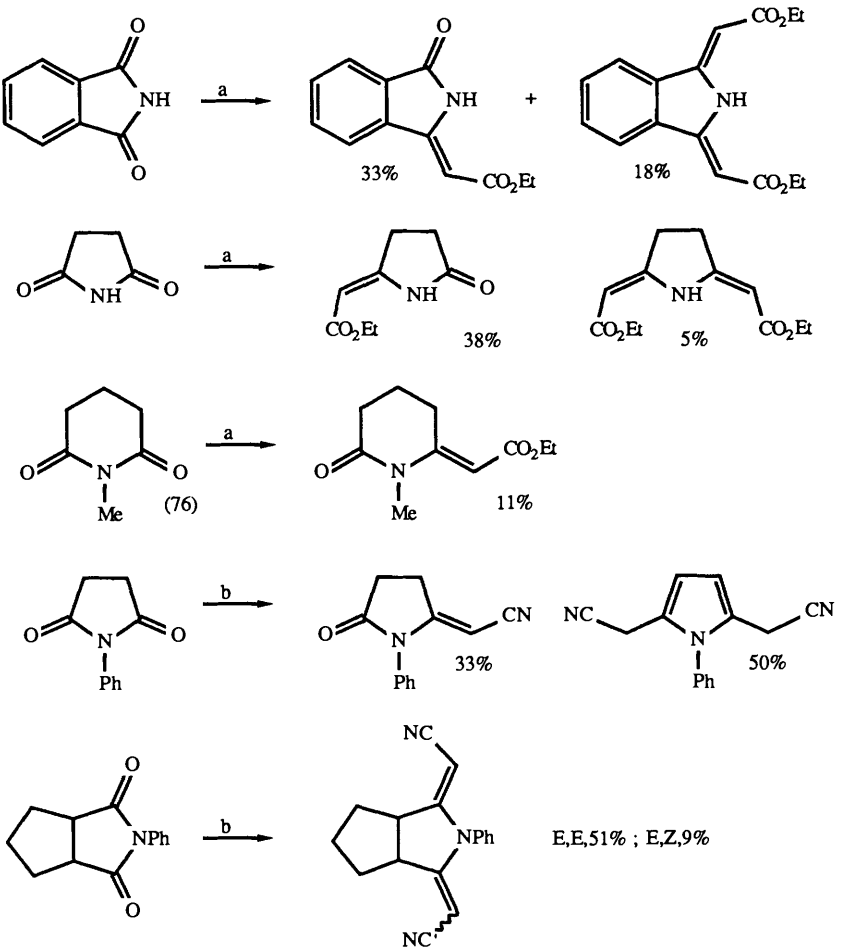
Scheme 47

some of which isomerize to give pyrroles (Scheme 48). Of the six-membered imides only *N*-methylglutarimide (76) was found to react, and then only in a low yield (11%).

N-Acylation of imides increases the reactivity of the imide-carbonyl (this is reflected in the change of the C=O stretching frequency, in the i.r. spectrum, to 1 820 cm^{-1}, a 50—100 cm^{-1} shift to higher wavenumber in comparison to unsubstituted imides). This tends to lower the temperature of reaction and increase yields (Scheme 49).

Indirect Wittig olefination of amides is possible by reaction of *N*-sulphonyllactams with stabilized phosphoranes followed by reductive deprotection[41] (Scheme 50). *N*-Acylpyrroles also give Wittig olefination products under

[41] M. Natsume, M. Takahashi, K. Kiuchi, and H. Sugaya, *Chem. Pharm. Bull.*, 1971, **19**, 2648.

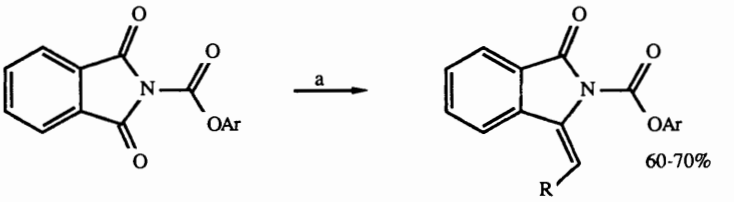


(a) $EtO_2CCH{=}PPh_3$, (b) $NCCH{=}PPh_3$

Scheme 48

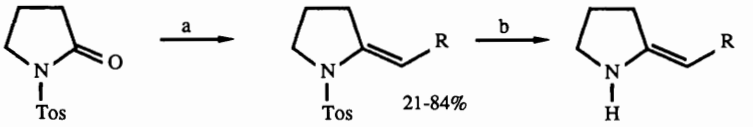
similar conditions (Scheme 51) and this reaction has been used in recent years in the preparation of heterocycles *via* intramolecular cyclization. Flitsch *et al.*[42] reported the preparation of dihydropyrroles (77) by reaction of imides with phosphonium salt (28) (Scheme 52). Similarly the intramolecular cyclization of succinimide and glutarimide was easily accomplished in good yields[43] (Scheme 53). In contrast to

[42] W. Flitsch, K. Pandl, and P. Rubkamp, *Liebigs Ann. Chem.*, 1983, 529.
[43] W. Flitsch and P. Rubkamp, *Liebigs Ann. Chem.*, 1983, 521.



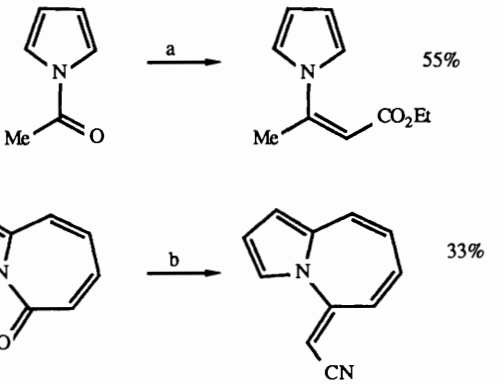
(a)RCH=PPh_3/THF/reflux/24hrs; R = CN,CO_2Et

Scheme 49



(a)RCH=PPh_3/140-180°C/15-50hrs, (b) Na/NH_3 ; R = COPh,COMe,CN,CO_2Et

Scheme 50

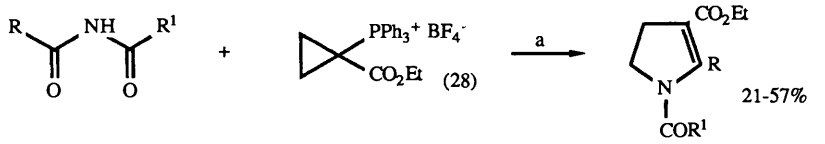


(a) $EtO_2CCH=PPh_3$/140°C/2hrs, (b)NCCH=PPh_3/140°C/12hrs

Scheme 51

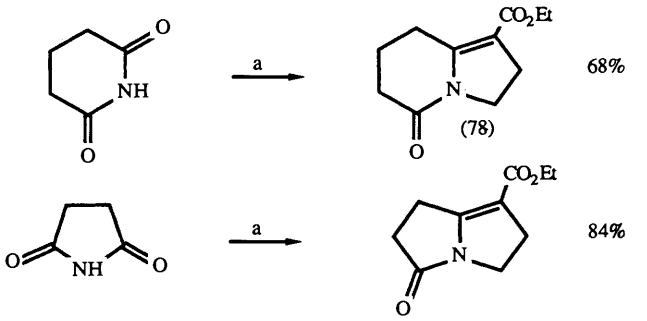
the reaction of *N*-methylglutarimide (76) with stabilized phosphoranes, which gave 11% yield at 200 °C after 4 hours,[40] the intramolecular reaction to (78) proceeded in 68% yield at 125 °C after $2\frac{1}{2}$ hours. This demonstrates the role that proximity of reactants plays in the cyclization reaction. The adduct from succinimide was further modified to isoretronecanol (79)[43] (Scheme 54).

Battersby *et al.* used the Wittig approach in reaction of a thioimide with a stabilized phosphorane in the synthesis of the 'Western half' (80) of the



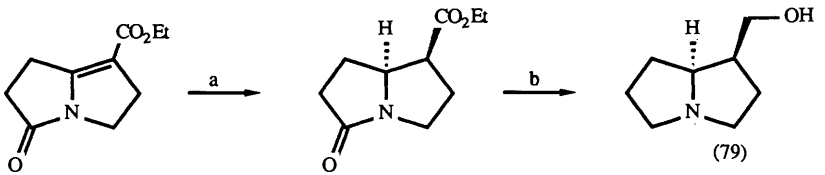
(a) NaH/xylene/reflux/2hrs; R = H,Me,Ph, R^1 = H,Me,Ph

Scheme 52



(a) NaH/(28)/xylene/reflux/3.5hrs

Scheme 53



(a) PtO_2/H_2, (b) $LiAlH_4$

Scheme 54

isobacteriochlorins; these compounds are important in biosynthetic studies of vitamin B_{12} (Scheme 55).[44]

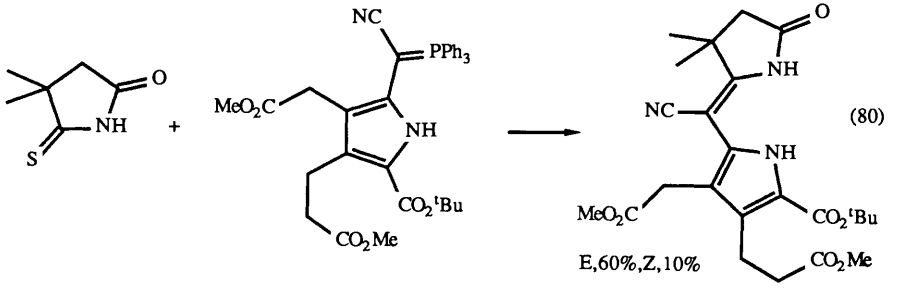
The tetramate natural product pukeleimide A (81) has also been prepared *via* a Wittig condensation with an imide[45] (Scheme 56).

7 Summary

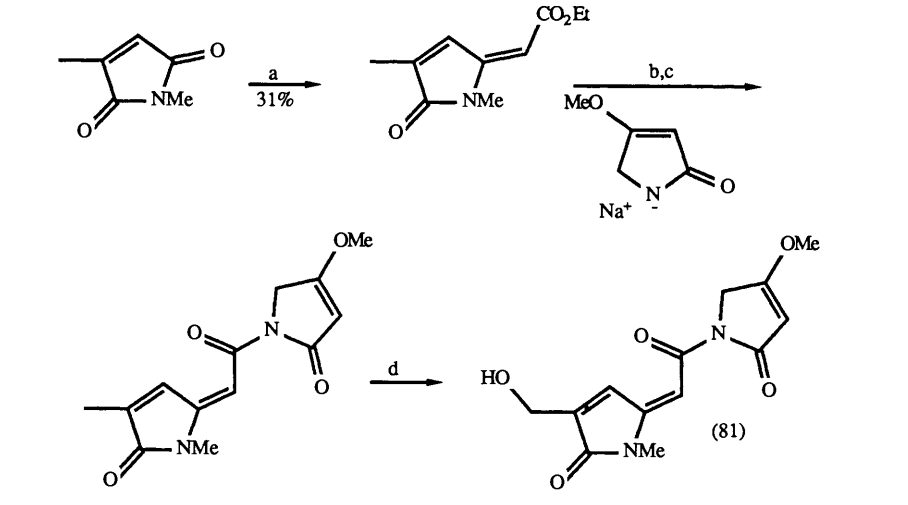
The mechanism of the Wittig reaction is still, some thirty years after its discovery,

[44] D. M. Arnott, A. R. Battersby, P. J. Harrison, G. B. Henderson, and Z. C. Sheng, *J. Chem. Soc., Chem. Commun.*, 1984, 525.

[45] G. D. James, G. Pattenden, and S. D. Mills, *Tetrahedron Lett.*, 1985, **26**, 3617.



Scheme 55

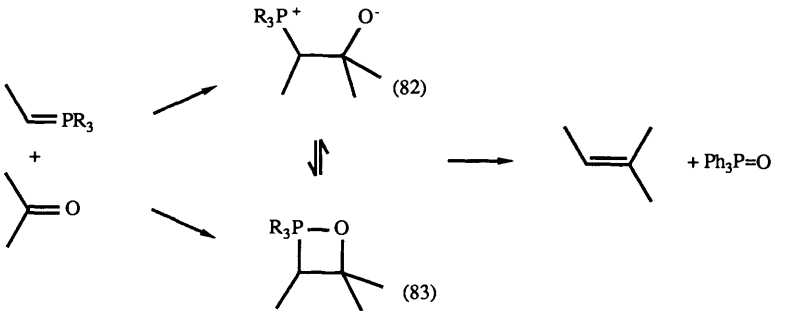


(a) $EtO_2CCH{=}PPh_3$/Toluene/reflux/36hrs, (b) KOH, (c) $SOCl_2$, (d)SeO_2

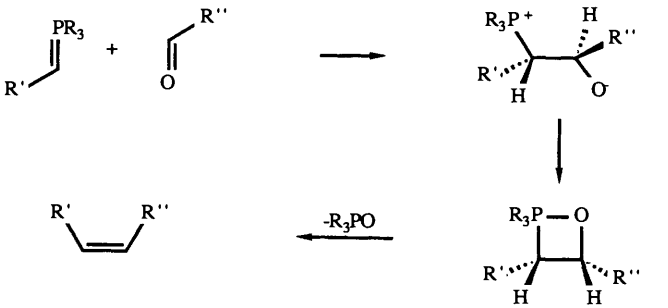
Scheme 56

somewhat controversial.[46–54] Numerous studies have been performed in order to elucidate the nature of the intermediates. It was long assumed that a zwitterionic intermediate, a betaine (82), was present, as proposed by Wittig.[5b] More recent studies support the formation of an oxaphosphetane (83) *via* a concerted pathway[47,49,51–54] (Scheme 57).

[46] (*a*) E. Vedejs, G. P. Meier, and K. A. J. Snoble, *J. Am. Chem. Soc.*, 1981, **103**, 2823; (*b*) E. Vedejs and K. A. J. Snoble, *J. Am. Chem. Soc.*, 1973, **95**, 5778.
[47] (*a*) H. J. Bestmann, *Pure Appl. Chem.*, 1979, **51**, 515; (*b*) H. J. Bestmann, *Pure Appl. Chem.*, 1980, **52**, 717.
[48] M. Schlosser and H. B. Tuong, *Angew. Chem., Int. Ed. Engl.*, 1979, **18**, 633.
[49] B. Giese, J. Schoch, and C. Ruchardt, *Chem. Ber.*, 1978, **111**, 1395.
[50] E. Vedejs, T. Fleck, and S. Hara, *J. Org. Chem.*, 1987, **52**, 4637.
[51] D. W. Allen, *Z. Naturforsch., Teil B*, 1980, **35**, 1455.
[52] M. Schlosser and B. Schaub, *J. Am. Chem. Soc.*, 1982, **104**, 5821.
[53] A. B. Reitz, M. S. Mutter, and B. E. Maryanoff, *J. Am. Chem. Soc.*, 1984, **106**, 1873.



Scheme 57



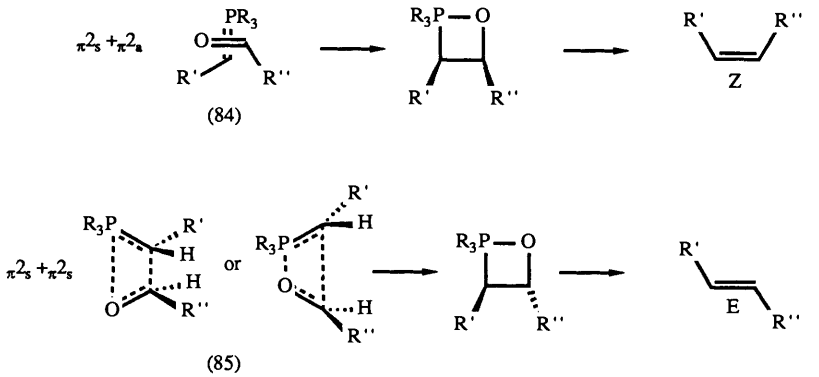
Scheme 58

The reversibility of intermediate formation has long been quoted as the reason behind the greater amounts of *E*-olefins observed in reactions involving stabilized phosphoranes and stabilized aldehydes (thermodynamic equilibrium).[4a] With reactive phosphoranes the initial step was considered to be irreversible and thus product formation was kinetically controlled by the initial mode of addition which on steric grounds gives rise to a *Z*-olefin[52,55] (Scheme 58).

Betaines were postulated as the intermediates in these reactions;[4a] however evidence has been presented which suggests that direct oxaphosphetane formation is the rate determining step in the reactions of stabilized phosphoranes with aldehydes,[49] and also that oxaphosphetane formation is non-reversible.[50] The mode of cyclization of the phosphorane and aldehyde is dependent upon the nature of the substituent on the phosphorane. An orthogonal ($_{\pi}2_s + {}_{\pi}2_a$) condensation has been suggested[46] for reactive phosphoranes (84), whereas a coplanar ($_{\pi}2_s + {}_{\pi}2_s$) cycloaddition has been proposed for stabilized phosphoranes (85), the P–O and

[54] B. E. Maryanoff, A. B. Reitz, M. S. Mutter, R. R. Inners, and H. R. Almond, Jr., *J. Am. Chem. Soc.*, 1985, **107**, 1068.

[55] J. V. Cooney and W. E. McEwen, *J. Org. Chem.*, 1983, **48**, 983.



Scheme 59

C–C bonds possibly forming to different extents, depending on the aldehyde and phosphorus substituents[49-51] (Scheme 59).

The existence of betaines as intermediates cannot be ruled out in conditions where salts are present.[46,50] In so far as the reactions between ester moieties and reactive phosphoranes are concerned the existence of a salt–betaine complex has been put forward to explain the low yields of olefinic products.[10] It is also worth noting that in the work of Bestmann *et al.* with fluorinated esters, salt-free conditions were used and appreciably better yields were obtained.[7] Interchanging the phenyl groups on the phosphorus for alkyl groups increases the yields of β-ketophosphoranes;[8] again if the intermediate is a betaine the alkyl groups would impose a stabilizing effect on the positive charge on the phosphorus. Efforts have been made to enhance the yields of β-ketophosphoranes by using phenyl esters, phenyl thiolesters, or acylimidaziolides[56] Two notable synthetic examples are a modification of the Fujimoto–Belleau reaction with phosphoranes or phosphonates in the preparation of steroid (86)[57] and also in the synthesis of glyoxalase-I inhibitors (87) (Scheme 60).[58]

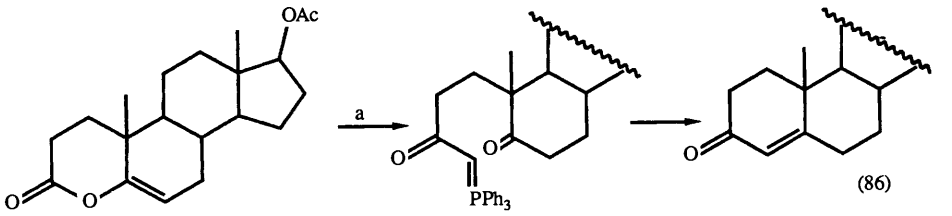
It would appear, from the limited amount of information available, that conditions which stabilize the intermediate in the reaction lead to diminished yields of olefinic products.

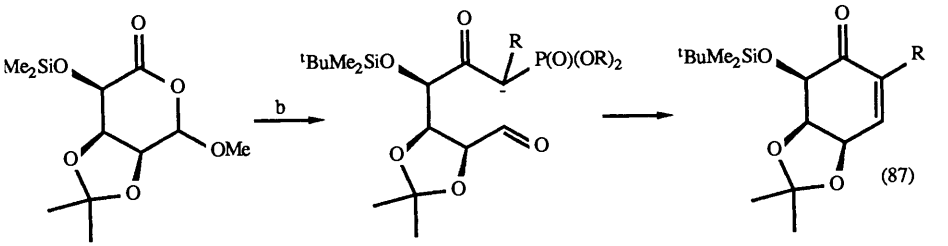
From the results reported concerning stabilized phosphoranes certain generalizations can be made. In assuming that the only intermediates in the reaction between (88) and (89) are betaines and/or oxaphosphetanes (which is not the case with cyclic anhydrides) the role of R^1—R^4 and X can be considered (Scheme 61). As previously mentioned R^1, if alkyl, will tend to give lower yields of olefin than if it is aryl.[8] It has been shown that R^2 has to be electron withdrawing,

[56] (*a*) H. J. Bestmann and B. Arnason, *Chem. Ber.*, 1962, **95**, 1513; (*b*) H. J. Bestmann, N. Sommer, and H. A. Stabb, *Angew. Chem., Int. Ed. Engl.*, 1962, **1**, 270; (*c*) N. Sommer and H. A. Stabb, *Angew. Chem., Int. Ed. Engl.*, 1962, **1**, 270.

[57] C. A. Henrick, E. Bohme, J. A. Edwards, and J. H. Fried, *J. Am. Chem. Soc.*, 1968, **90**, 5926.

[58] S. Mirza, L. P. Molleyres, and A. Vasella, *Helv. Chim. Acta*, 1985, **68**, 988.





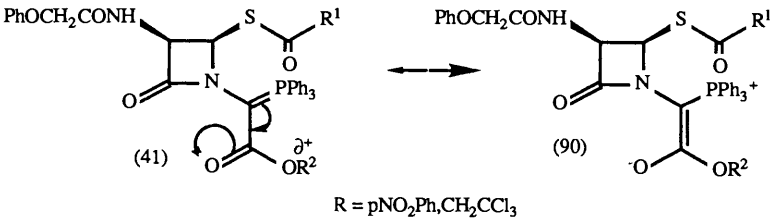
(a) CH_2=PPh_3/heat, (b) $(RO)_2P(O)CH_2R$/nBuLi ; R = H,Me

Scheme 60

Scheme 61

and therefore resonance stabilizing, in order for the reaction to yield olefinic products. However, if R^2 is too electron withdrawing, as is the case with some examples of Woodward's penem work,[21] the reaction is sluggish and yields are low. The electron withdrawing *p*-nitrobenzyl and 2,2,2-trichloroethyl ester groups (42) considerably diminished the rates and yields of reactions; this probably stems from the increased contribution from the resonance form (90) which will predominate with strongly electron withdrawing substituents (Scheme 62). The nucleophilicity of (90) will be significantly lower than that of the phosphorane (42) and so the ease of reaction will decrease. It has also been suggested that R^2 stabilizes the formation of the double bond in the case of stabilized phosphoranes.[10] It would appear that the reactivity of phosphoranes with esters is dependent upon the nucleophilicity of the phosphorane, and overly stabilized phosphoranes are not particularly reactive.

Substituents on the ester R^3, R^4, and X are required to enhance the reactivity of



Scheme 62

the ester carbonyl or to make it more ketonic in character. Electron withdrawing groups at R^3 (*e.g.* phenyl, fluoroalkyl, alkoxy) give best results; this is probably due to the enhanced susceptibility of the carbonyl group to nucleophilic attack which aids the formation of the reaction intermediates. The substituent XR^4 is also required to activate the carbonyl group towards attack. This can be achieved in several ways: electron withdrawing groups (*e.g.* phenyl, aryl, vinylic) increase the positive charge on the carbonyl carbon. Similarly, in anhydrides and imides the carbonyl is made more reactive by the diminished resonance available to each carbonyl by the linking heteroatom.

Other factors include ring size, for example of cyclic imides: of the six-membered imides only one is known to react intermolecularly whereas five-membered heterocycles readily react.[40] This is due to the diminished contribution of internal resonance forms in the ring systems as ring size decreases. This is well exemplified by the work performed by Stoodley on thietan-2-ones.[27]

The carbonyl group in thiolesters is reactive since, again resonance between the sulphur and the carbonyl is not as strong as is experienced with esters owing to the character of the orbitals involved. The π-bond overlap in the C=O bond is $2p\pi$—$2p\pi$, which is much stronger than the $2p\pi$—$3p\pi$ overlap of the C=S bond; this diminished resonance tends to increase the ketonic character of the thiolester.

As far as cyclizations are concerned, the close proximity of the two reactants quite probably has some effect on the favourability of the reaction.

In general the reactions of stabilized phosphoranes with carboxylic acid derivatives have been performed at considerably higher temperatures than analogous reactions with ketones in which the methylene group takes the place of the heteroatom bound to the carbonyl function; this would suggest that a higher activation energy is involved in the former reactions.

As can be seen by the variety of reactions and the breadth of their synthetic utility, the formation of hetero-substituted olefinic linkages by the reaction of carboxylic acid derivatives with phosphoranes and related species has become an important approach to the synthesis of compounds of general and commercial interest; indeed for a number of applications it appears that they have become the method of choice. Finally, it is hoped that an increased awareness of these reactions will stimulate further applications of this valuable extension to classical Wittig methodology.