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Olefination of carbonyl compounds: modern and classical methods

V N Korotchenko, V G Nenajdenko, E S Balenkova, A V Shastin

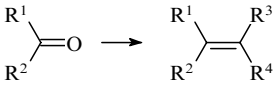
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Abstract. The published data on the methods for alkene synthesis by olefination of carbonyl compounds are generalised and systematised. The main attention is given to the use of transition metals and organoelement compounds. The review covers the data on both classical and newly developed methods that are little known to chemists at large. The bibliography includes 276 references.

I. Introduction

Olefination of carbonyl compounds, *i.e.*, conversion of the carbonyl group into a double carbon – carbon bond, is one of the paramount strategies in the regioselective synthesis of substituted alkenes.[1 – 3]



Thus many total syntheses of complex molecules, including natural compounds, involve the formation of a C = C bond by this particular route.[4] Olefination is the construction of an alkene from two different components, *viz.*, a carbonyl compound and an olefinating agent, which allows broad variation of the nature of substituents at the double bond.

Numerous reviews and monographs deal with separate classical olefination procedures; however, their collective description is virtually absent. A systematic consideration of the existing olefination methods is given only in *Comprehensive Organic Synthesis,* which covers the literature up to the year of 1999.[2] The handbook *Comprehensive Organic Transformations* contains a large set of olefination reactions with no comments.[5] The book *Preparation of Alkenes*[1] published in 1996 provides a brief description of the main olefination procedures, such as the Wittig, Peterson, Julia, Johnson and McMurry reactions, aldol condensation and reductive coupling of polyhaloalkanes with carbonyl compounds in the presence of chromium derivatives. In addition, this book describes some standard procedures for the synthesis of alkenes. Other reviews are devoted to the methods for the synthesis of individual types of unsaturated compounds. Thus the review[6] published in 1983 considers the use of various olefination procedures for the synthesis of stilbenes. The review[7] describes the McMurry and Barton – Kellog reactions and their application in the synthesis of sterically hindered alkenes. The review[8] deals with the addition reactions of CH-acids to aldehydes under conditions of phase transfer catalysis which sometimes yield alkenes. One of the chapters in the review[9] published in 2001 and devoted to the synthesis of conjugated dienes considers the use of olefination in the synthesis of dienes.

The striking progress in this field of organic synthesis is associated first of all with the use of various transition metals, reagents based on them and organoelement compounds; however, many novel olefination procedures are not mentioned in the reviews and monographs published so far. Besides, new modifications, reagents and catalysts of the classical reactions are being constantly developed, which has made it possible to extend the range of their practical applications and ensures higher yields, greater selectivity and milder reaction conditions.

The present review provides a comparative analysis of methods used for the olefination of carbonyl compounds and covers the literature published up to the end of 2003.

The carbonyl carbon atom bears a partial positive charge; therefore, general olefination procedures include, as a rule, the addition of various C-nucleophiles (both preformed and prepared *in situ*) to the carbonyl group. In this review, the methods used for converting the carbonyl group into the C = C bond are classified according to the type of nucleophilic species that attack the carbonyl carbon atom. Correspondingly, all olefination methods are divided into four groups, *viz.*, addition of ylides or carbanions stabilised by heteroatoms in the α-position to the carbonyl group (Section II); condensation of carbonyl compounds with various CH-acids (Section III); olefination with reagents based on metals (Section IV). Reactions not involving direct synthesis of alkenes, *e.g.*, the Grignard reaction, are excluded from consideration where possible. The methods not included in the first three groups are considered in Section V.

In describing the olefination reactions, we placed the main emphasis on both the preparative aspects and reaction mechanisms. The review displays the most recent modifications of the olefination reactions, since the traditional methods are considered

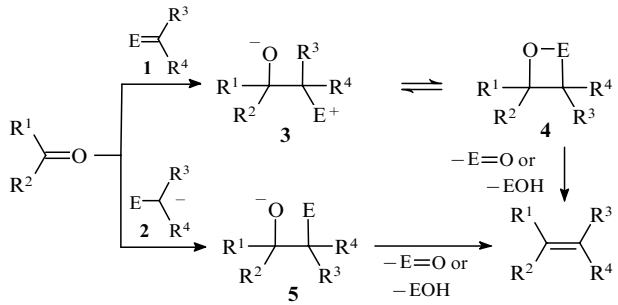
V N Korotchenko, V G Nenajdenko, E S Balenkova Department of Chemistry, M V Lomonosov Moscow State University, Leninskie Gory, 119992 Moscow, Russian Federation. Fax (7-095) 932 88 46. Tel. (7-095) 939 22 76. E-mail: vassili_k@mail.ru (V N Korotchenko), nen@acylium.chem.msu.ru (V G Nenajdenko, E S Balenkova)
A V Shastin Institute of Problems of Chemical Physics, Russian Academy of Sciences, 142432 Chernogolovka, Moscow Region, Russian Federation. Fax (7-096) 514 32 44. E-mail: shastin@icp.ac.ru

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in sufficiently great detail in the reviews.[10–35] The generally known data are cited only if they are of critical importance.

II. Addition of ylides or carbanions stabilised by heteroatoms in the α-position

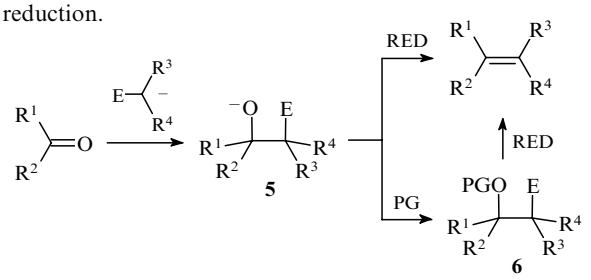
This Section is devoted to the olefination methods based on the addition, to the carbonyl group, of ylides of the type **1** or of carbanions of the type **2** stabilised either by elements from Groups IIIA–VIIA of the Periodic System or by functional groups containing heteroatoms. Reactions of ylides **1** with carbonyl compounds yield the intermediates **3** with a betaine structure or the cyclic intermediates **4**. The addition of the carbanions **2** to the carbonyl group results in alkoxides of the corresponding β-hydroxy organoelement compounds **5**.



E is heteroatom or functional group.

Depending on the nature of the heteroatom, further transformations of the intermediates into the target alkenes occur in two routes. It is of note that the loss of the organoelement fragment usually occurs in the above-described reactions, which points to its subsidiary role. Elements with electronegativities lower than that of carbon (Table 1) and with high affinities for oxygen are eliminated from the intermediate compounds as the corresponding oxygen-containing products, *viz*., organoelement oxides and hydroxides. Thus, the olefinating agents can simultaneously act as the reducing agents.

If the electronegativity of an element is close to that of carbon or exceeds it (Cl, Br), the conversion of intermediate alkoxides of the type **5** into alkenes requires the use of additional reducing agents. In this case, the formation and reduction of the intermediate compounds **5** are carried out in succession. Very often, this is preceded by protection of the hydroxy group by silylation or acylation; in this case, it is protected compounds **6** that are subject to reduction.



RED is a reducing agent, PG is protecting group.

The reaction of carbonyl compounds with isocyanides (Section II.3.a) is a special case. Here, the role of a reducing agent is played by the carbon atom of isocyanide, although the corresponding carbanion is stabilised by the nitrogen-containing functional group.

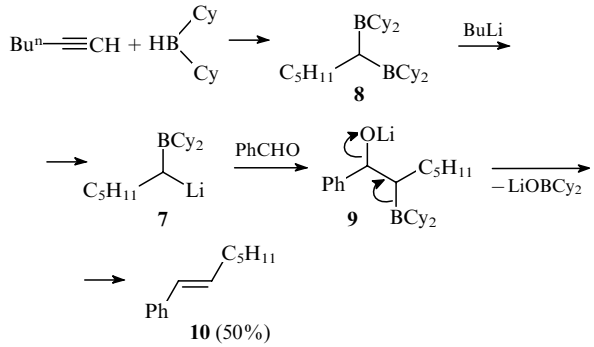
Table 1. The electronegativity and energy of the single bond E–O of Group IIIA–VIIA elements of the Periodic System.

Element	Group	Electronegativity [a]	Energy of the E–O bond /kcal mol^{-1} (see [b])	Reaction type
B	IIIA	2.01	124.3 (125.0)	addition with subsequent elimination
C	IVA	2.50	85.6	the same
Si	IVA	1.74	111.4 (108.0)	"
Ge	IVA	2.02	92.0 (86.8)	"
Sn	IVA	1.72	(85.5)	"
Pb	IVA	1.55	(95.1)	"
P	VA	2.06	86.0 (97.3)	"
N	VA	3.07	51.1	see [c]
As	VA	2.20	77.9 (114.0)	addition with subsequent elimination
Sb	VA	1.82	(75.0)	the same
Bi	VA	1.67	92.0 (81.0)	"
Te	VIA	2.01	(64.1)	"
S	VIA	2.44	(63.3)	use of an additional reducing agent
Se	VIA	2.48	(82.0)	the same
Cl	VIIA	2.83	49.2 (49.2)	"
Br	VIIA	2.74	(55.9)	"

[a] Data from Ref. 36; [b] data from Refs 37, 38, the data from Ref. 36 are given in parenthesis; [c] for details see Section II.3.a.

1. Reagents based on Group IIIA elements

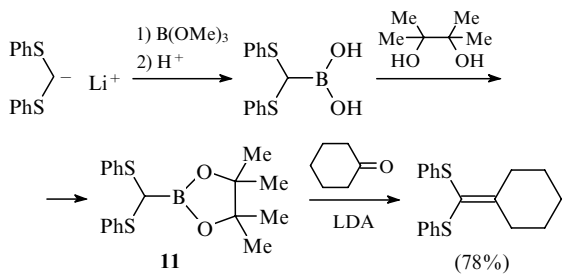
A series of olefinating agents for the synthesis of alkenes based on organoboron compounds have been prepared.[1, 2, 10, 39] Thus the *gem*-lithioorganoboron reagent **7** synthesised *in situ* by metallation of *gem*-diborane **8** adds to benzaldehyde, aliphatic ketones and diaryl ketones to give an intermediate of type **9**.[40]



Cy is cyclo-C_6H_{11}.

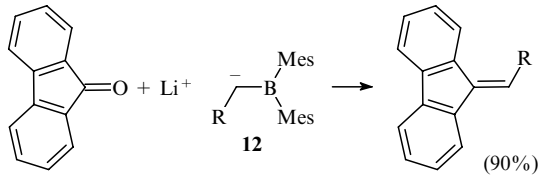
Subsequent β-elimination of dialkyl borinate gives alkenes in 20%–50% yields; the *trans*-isomer of alkene **10** is formed predominantly from benzaldehyde. The high affinity of boron for oxygen is the driving force of this elimination (see Table 1). Thus, the organoboron reagent **7** acts simultaneously as the reducing agent. The necessity for the preliminary synthesis of *gem*-diborylalkane **8** is a significant disadvantage of this method.

The use of cyclic boronate **11** as an olefinating agent allows conversion of aldehydes and ketones into dithioacetals of homologous ketenes.[41]



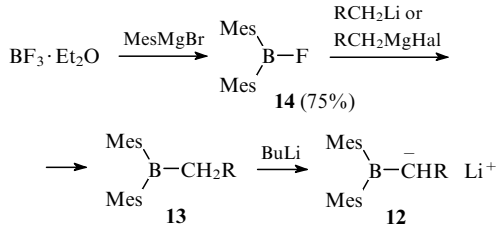
LDA is lithium diisopropylamide.

The addition of carbanions of type **12** stabilised by an α-boron atom to aromatic carbonyl compounds gives alkenes in good yields.[42,43]



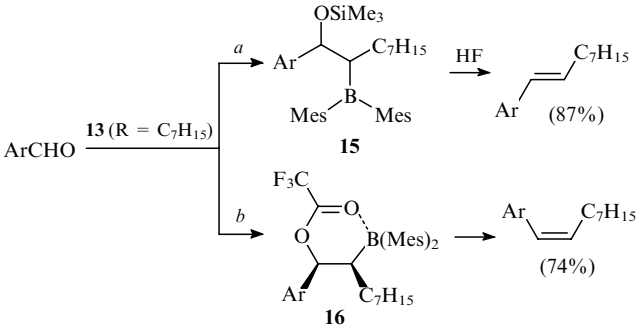
R = Me.

The carbanions **12** are prepared from dimesitylalkylboranes **13**, which in turn are synthesised from boron trifluoride etherate by successive addition of two equivalents of mesitylmagnesium bromide and subsequent treatment of compound **14** with Grignard reagents or organolithium compounds.[44]



R = H, Alk.

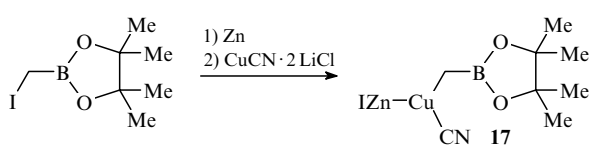
In the case of aromatic aldehydes, the stereochemistry of alkene formation can be controlled by modifying the reaction conditions. Silylation of an intermediate alcohol and subsequent treatment of the silyl derivative **15** with hydrofluoric acid afford *E*-isomers of alkenes in high yields and with good stereoselectivity.

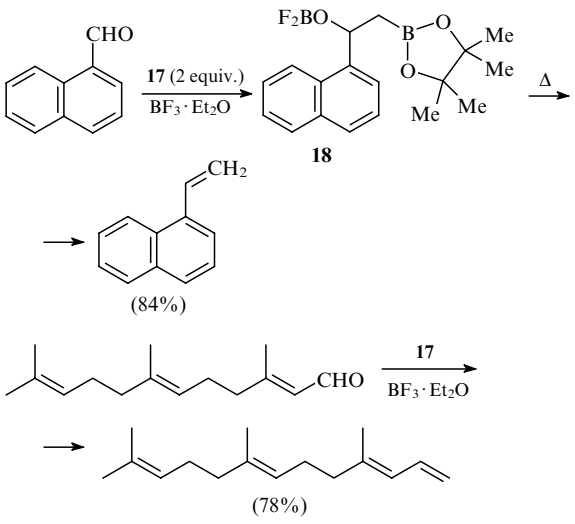


Ar = 4-MeOC$_6$H$_4$; (*a*) BuLi, Me$_3$SiCl; (*b*) BuLi, (CF$_3$CO)$_2$O.

Treatment of the intermediate alcohol with trifluoroacetic anhydride results in *Z*-isomers of alkenes; aromatic aldehydes containing electron-withdrawing groups in the *para*-position are an exception.[42] Presumably, the stereochemistry of this reaction is determined by coordination of the acyl oxygen atom to the boron atom in the intermediate **16**.

It was found that α-boron-substituted zinc organocyanocuprate **17**,[45] which reacts with a vast variety of electrophiles including carbonyl compounds, can be used as a convenient methylenating reagent. Its reactions with aldehydes in the presence of Lewis acids and subsequent thermolysis of the intermediate **18** yield terminal alkenes. The area of application of the reagent **17** includes aliphatic, aromatic and α,β-unsaturated aldehydes.

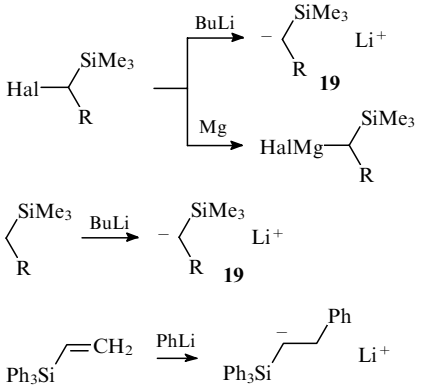




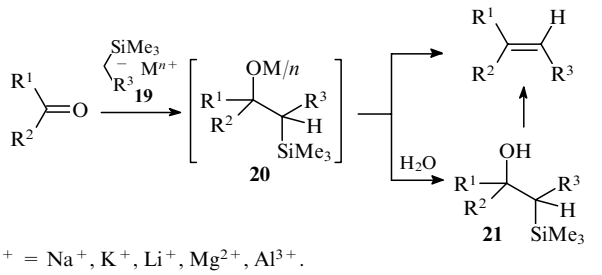
2. Reagents based on Group IVA elements

a. Silicon-based reagents: the Peterson olefination and related methods

The reaction of carbonyl compounds with carbanions stabilised by α-triorganylsilyl groups and subsequent elimination of the intermediate silanol is a general olefination method (the Peterson olefination).[1,2,11–15] Since the moment of its discovery in 1968,[46] this reaction has been used, along with the Wittig and the Julia reactions, in the synthesis of diverse alkenes. Silyl carbanions R$\overline{\text{C}}$HSiMe$_3$ **19** are employed as the olefinating agents. These are prepared by the Grignard reaction or by metallation of α-halogenosilanes, by deprotonation of silanes with strong bases as well as by addition of organometallic compounds to vinylsilanes. The deprotonation of silanes is favoured by the presence of other electron-withdrawing groups in the molecule. Aromatic, aliphatic and unsaturated aldehydes and ketones can be used as the carbonyl components.

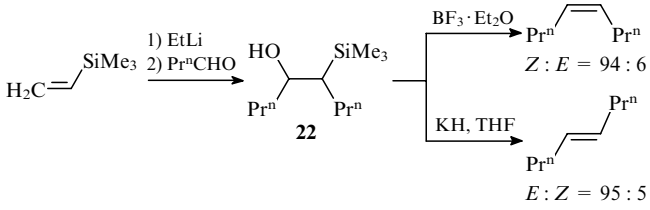


The addition of the α-silyl carbanion **19** to the carbonyl group yields the alkoxide intermediate **20**, which eliminates silanol and is converted into an alkene. The formation of a stable Si—O bond is a driving force of this reaction (see Table 1). If the intermediate **20** has an ionic nature (*e.g.*, if the role of a counterion is played by Na$^+$ or K$^+$, or the substituent R^3 represents an anion-stabilising group), silanol is spontaneously eliminated and an alkene is formed.[46,47] If the intermediate **20** has a covalent nature, *i.e.,* the role of a counterion is played by Li$^+$, Mg^{2+} or Al^{3+}, the corresponding β-hydroxy silanes **21** can be isolated.

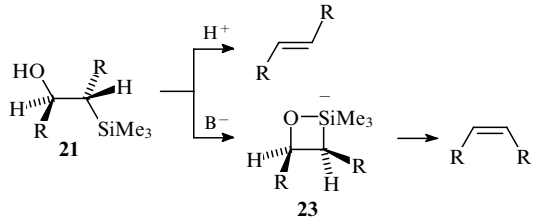


M^{n+} = Na^+, K^+, Li^+, Mg^{2+}, Al^{3+}.

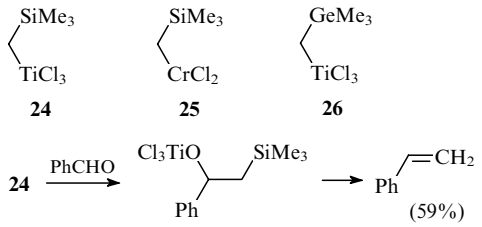
The elimination of silanol from β-hydroxy silanes in the presence of acids or bases occurs according to different mechanisms and yields opposite alkene isomers.[13, 14, 48] Thus treatment of the β-hydroxy silane **22** with boron trifluoride etherate yields an *E*-isomer of oct-4-ene, whereas a *Z*-isomer is formed predominantly in the presence of KH.[48]



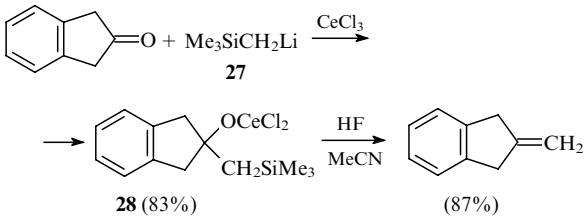
Such a stereoselectivity of the Peterson reaction is due to the fact that elimination of hydroxy- and trialkylsilyl groups in acidic media occurs from the thermodynamically most favourable *anti*-periplanar conformation of the *O*-protonated form of β-hydroxy silane **21**. In the presence of bases, alkenes having opposite geometries are formed from the intermediate siloxetane **23** by *syn*-elimination of silanol. The possibility of control over the geometry of reaction products is a main advantage of the Peterson olefination; however, the formation of β-hydroxy silanes **21** should be put under control in order to achieve stereoselectivity. Otherwise, the diastereomers formed have to be separated.



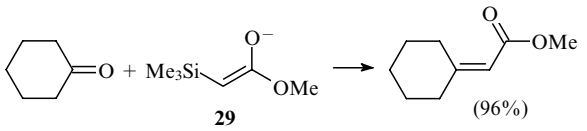
Lithium or magnesium salts of silicon-containing compounds are commonly used as the olefinating agents; however, several modern modifications of the Peterson reaction have been developed on the basis of transition-metal derivatives. In one of them, organometallic compounds **24**, **25** and **26** obtained *in situ* from transition-metal halides ($TiCl_4$, $CrCl_3$) and metallated silane (Me_3SiCH_2MgCl) or germane (Me_3GeCH_2MgCl) are used as the methylenating reagents.[49] Thus, the modified reagent actually represents an α-trimethylsilyl(germyl)-carbanion with a transition metal as a counterion. This family of reagents was used for the conversion of some aliphatic and aromatic aldehydes into terminal alkenes in high yields. Ketones do not enter into this reaction.



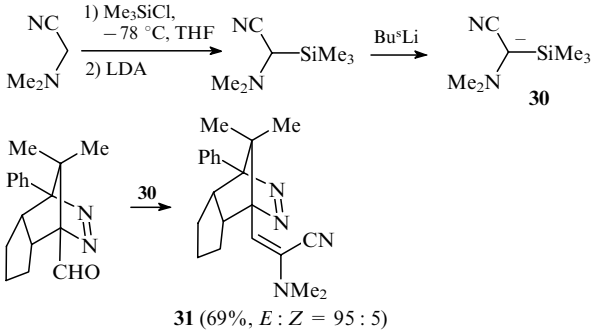
Apparently, the Peterson reaction with the system (trimethylsilyl)methyllithium (**27**) – cerium(III) chloride proceeds in a similar way.[50, 51] This system allows methylenation of a broad range of aldehydes and ketones including easily enolisable ones, since the basicities of organocerium reagents are much lower than that of the lithium derivative. Silanol is eliminated from the intermediate **28** under the action of HF or KF; the yields of the terminal alkenes are usually high (80% – 90%).



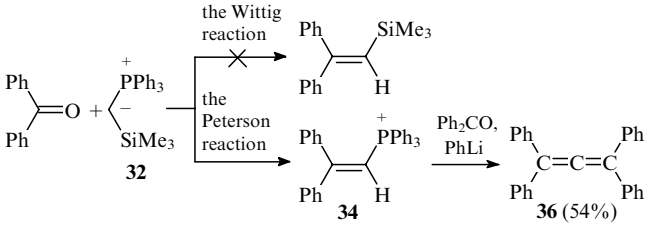
Some methods for the synthesis of various functionalised alkenes are based on the Peterson reaction. Thus a stabilised Peterson reagent, *viz*., ester α-silylenolate **29**, was used for the synthesis of α,β-unsaturated esters.[52] Compound **29** is easily prepared by deprotonation of the corresponding α-silylcarboxylates with strong bases like lithium diisopropylamide.

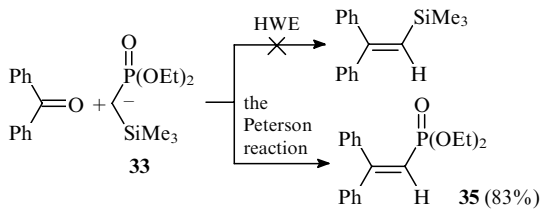


The polyfunctional anion **30** stabilised by trimethylsilyl and cyano groups is used in the synthesis of captodative alkenes of the type **31,** which contain both the donor (dimethylamino group) and acceptor (cyano group) substituents.[53] In the case of aliphatic aldehydes, this reaction occurs with high stereoselectivity and yields predominantly *E*-isomers of alkenes, whereas in the case of aromatic aldehydes and ketones the stereoselectivity of the reaction is lower.

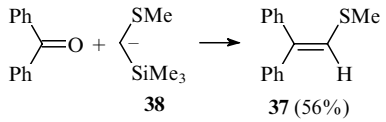


A comparison of the Peterson and the Wittig reactions, on the one hand, and the Peterson and the Horner – Wadsworth – Emmons (HWE) reactions, on the other hand, was carried out using the olefinating agents **32** and **33** stabilised by both silicon and phosphorus atoms. It was found that the reaction with benzophenone yields exclusively phosphorus-containing alkenes **34** and **35**.[12, 54, 55] Thus, the silyl groups are more prone to elimination than the phosphate groups. The vinyltriphenylphosphonium salt **34** can be used in particular in the synthesis of allenes of type **36**.

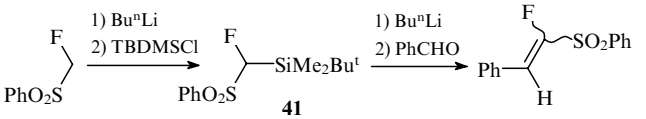


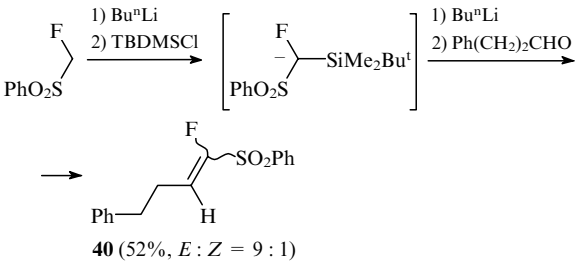


The mixed reagent **38**, which represents a carbanion stabilised simultaneously by sulfur and silicon atoms, was used in the synthesis of vinyl sulfides **37**.[55]



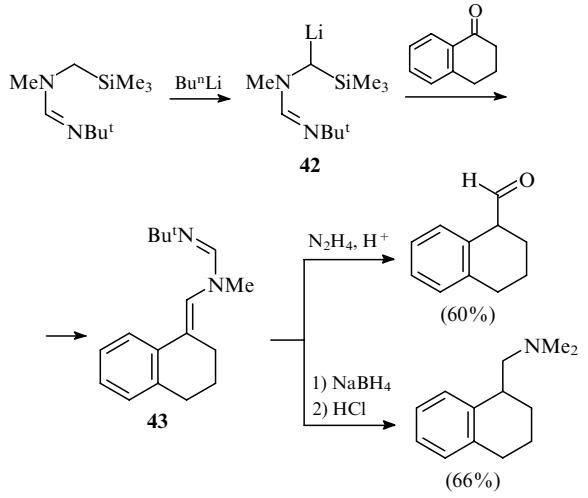
Stereoselective synthesis of unsaturated fluorine-containing sulfones **39** and **40** has been carried out using the organosilicon reagent **41**.[56] The olefination procedures make use of the previously synthesised reagent **41** or that prepared *in situ*.



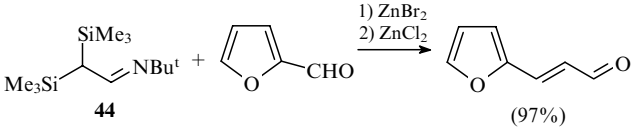


TBDMS is Bu^tMe_2Si.

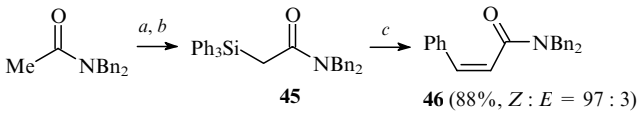
The lithium salt of formamidine **42** containing a trimethylsilyl group was used in homologisation of carbonyl compounds.[57, 58] The reaction of the salt **42** with carbonyl compounds yields enamines **43** which can be further reduced to saturated amines or converted into the corresponding aldehydes.



The use of the disilyl derivative **44** for olefination allows the preparation of α,β-unsaturated aldehydes.[59] The reactions with aldehydes yield *E*-isomers.

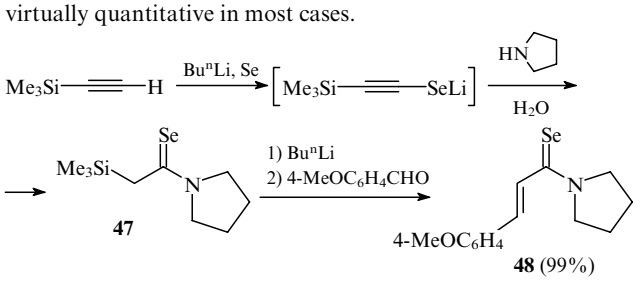


Triphenylsilylacetamides **45** can also be used as the olefinating agents. The reactions with aldehydes afford predominantly *Z*-isomers of the corresponding α,β-unsaturated amides **46**.[60]

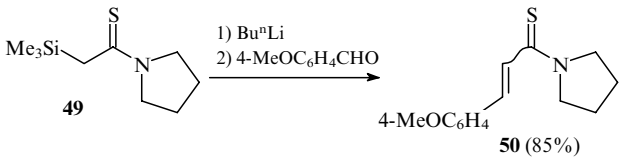


(*a*) LDA; (*b*) Ph_3SiCl; (*c*) PhCHO, KHMDS, THF, −78 °C;
KHMDS is potassium hexamethyldisilazanide.

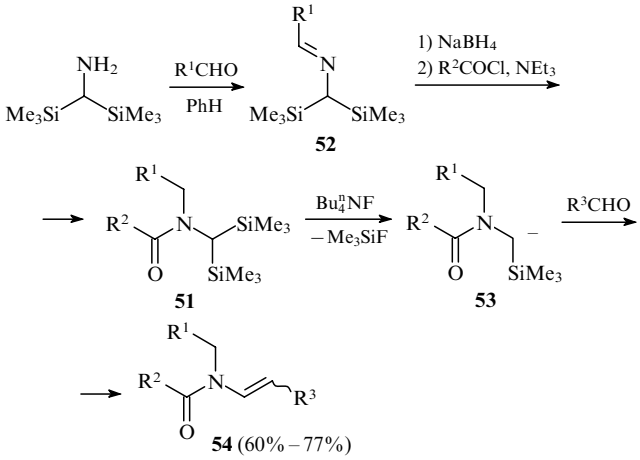
The reagent **47** synthesised from trimethylsilylacetylene was used for the preparation of selenoamides of substituted cinnamic acids **48**.[61] The reactions of the selenoamide **47** with aromatic aldehydes in the presence of Bu^nLi result in *E*-isomers of unsaturated selenoamides **48**; the yields of the reaction products are virtually quantitative in most cases.



The reactions of aldehydes with α-silylthioacetamide **49** yield unsaturated thioamides **50** (*e.g.*, as 1 : 1 mixtures of isomers).[61]

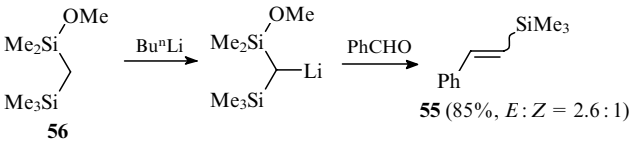


The olefination by *gem*-disilyl reagents **51** derived from imines **52** has been described.[62] This reaction occurs in the presence of tetrabutylammonium fluoride. Substituted benzaldehydes, pivalic and 2-methylcinnamic aldehydes were assayed as candidates for the carbonyl components. The carbanion **53** formed upon cleavage of a trimethylsilyl group under the action of the fluoride ion seems to play the role of an olefinating agent. The corresponding enamides **54** are obtained in good yields; however, the selectivity of the reaction is low.



R^1 = Ar; R^2, R^3 = Alk, Ar.

Carbonyl compounds can be transformed into vinylsilanes **55** using *gem*-disilylmethane **56** containing a methoxy group at one of the silicon atoms.[63] Deprotonation of compound **56** and addition of the carbanion to the carbonyl group result in silicon-substituted alkenes. It is only the methoxysilyl group that is eliminated due to coordination of lithium to the oxygen atom in the intermediate.

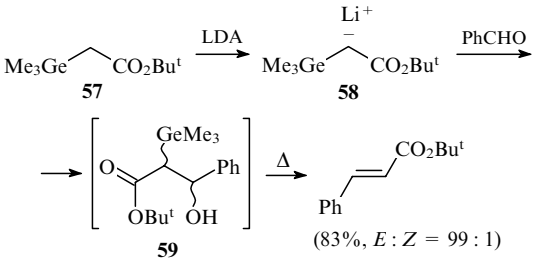


56

55 (85%, $E:Z = 2.6:1$)

b. Germanium-based reagents

An analogue of the Peterson reaction, which makes use of (trimethylgermyl)acetates **57**, has been described.[64] Their deprotonation affords carbanions **58** stabilised by the germanium atom, which add to aldehydes and ketones. Elimination of germanol (thermal or acid-induced) from intermediate diastereomeric β-hydroxy germanes **59** yields *E*-isomers of α,β-unsaturated esters. The reaction occurs with high stereoselectivity; both *threo*- and *erythro*-isomers **59** are converted into *E*-isomers of unsaturated compounds.

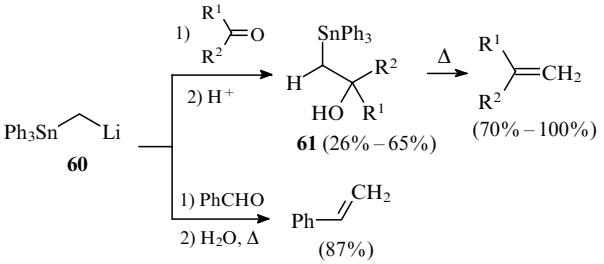


57 **58** **59**

(83%, $E:Z = 99:1$)

c. Tin- and lead-based reagents

A series of olefinating agents have been prepared based on organotin and -lead compounds.[65–76] Metallation of triphenylstannylmethyl iodide leads to triphenylstannylmethyllithium **60**, which adds to aldehydes and ketones to yield 2-triphenylstannylethanols **61**.[65] Subsequent thermal elimination of Ph_3SnOH gives terminal alkenes. This reaction may involve isolation of intermediate compounds **61** or be carried out as a one-pot synthesis. The total yield of alkenes is usually low (18%–62%), but can significantly be increased if the isolation step of intermediate stannyl ethanols **61** is excluded.



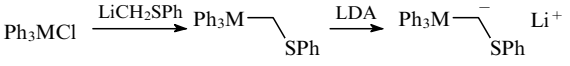
60

61 (26%–65%) (70%–100%)

(87%)

R^1 = Alk, Ar; R^2 = H, Alk.

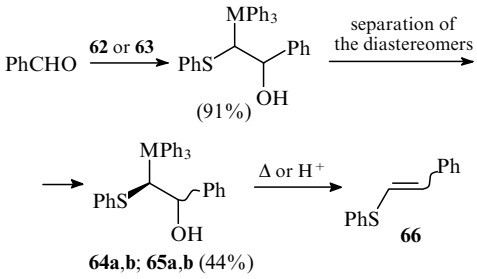
The anions **62** and **63** stabilised simultaneously by the trimethylstannyl (**62**) or trimethylplumbyl (**63**) and phenylthio groups were used as olefinating agents.[66, 67]



62, **63**

M = Sn (**62**), Pb (**63**).

The reagents **62** and **63** react with benzaldehyde to give diastereomeric pairs of phenylthio(triphenylstannyl)ethanols **64a**,**b** and phenylthio(triphenylplumbyl)ethanols **65a**,**b**. Separation of the diastereomers and subsequent thermal elimination or acid treatment yields *E*- or *Z*-isomers of β-(phenylthio)styrene **66**.

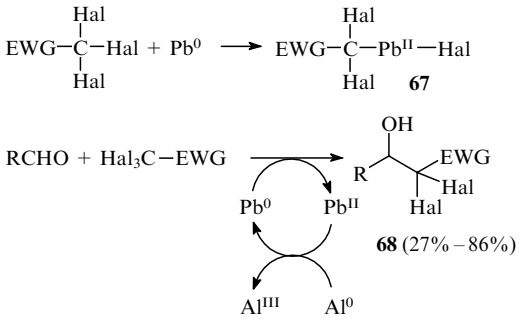


(91%)

64a,**b**; **65a**,**b** (44%) **66**

M	Alcohol	Configuration of **66** [yield (%)]	
		Δ	H^+
Sn	*threo*-**64a**	*E* (93)	*Z* (100)
	erythro-**64b**	*Z* (100)	*E* (95)
Pb	*threo*-**65a**	*E* (87)	*E* + *Z* (67)
	erythro-**65b**	*E* + *Z* (98)	*E* (83)

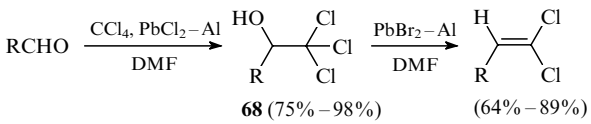
A method for the conversion of aromatic and aliphatic aldehydes into substituted alkenes by reductive addition of polyhalogeno compounds, such as tetrachloro- or tetrabromomethane, bromotrichloromethane, trichloroacetamide and trichloroacetonitrile, to aldehydes in the presence of a bimetallic system Pb–Al, has been developed.[68] This utilises aluminum foil as a reducing agent and lead halide as a catalyst. It was suggested[68] that the reaction proceeds *via* the organolead compound **67** formed upon oxidative addition of Pb^0 to the polyhalogenoalkane; subsequent reaction of the intermediate **67** with the carbonyl group yields the hydroxy derivatives **68**.



68 (27%–86%)

Hal = Cl, Br; EWG = Cl, Br, CN, $CONH_2$.

Reductive 1,2-elimination of the vicinal chlorine atom and the hydroxy group, which yields alkenes, was studied in the example of alcohols **68** based on CCl_4. The system $PbBr_2$–Al has proved to be an efficient reducing agent.[68]

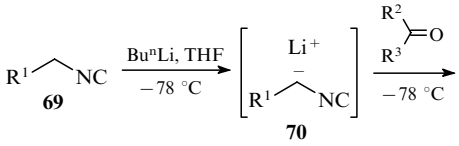


68 (75%–98%) (64%–89%)

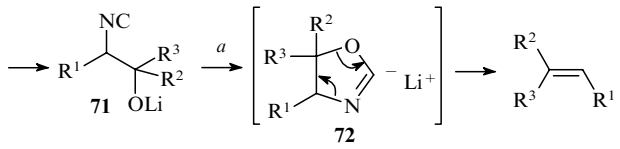
3. Reagents based on Group VA elements

a. Carbanions stabilised by the isocyanide group

The isocyanide group can stabilise carbanions in the α-position.[69] The isocyanides **69** generate the carbanions **70** that add to the carbonyl groups of aldehydes and ketones to give the adducts **71**. Subsequent elimination of lithium cyanate, which proceeds *via* the oxazoline carbanion **72**, yields alkenes.

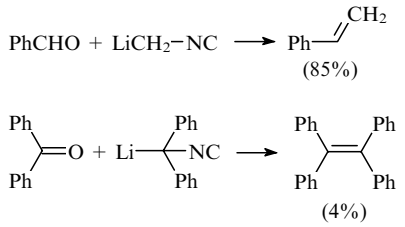


69 **70**



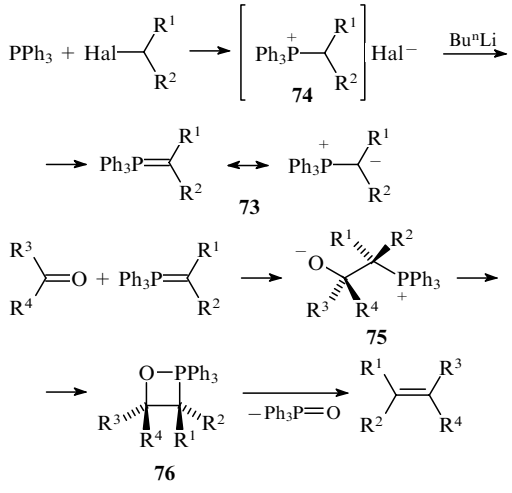
(*a*) from −78 to −20 °C.

This reaction usually proceeds with low yields and is highly sensitive to steric hindrance in both metallated isocyanide and the carbonyl compound. Thus the yield of tetraphenylethylene is much lower than that of styrene.



b. The Wittig reaction

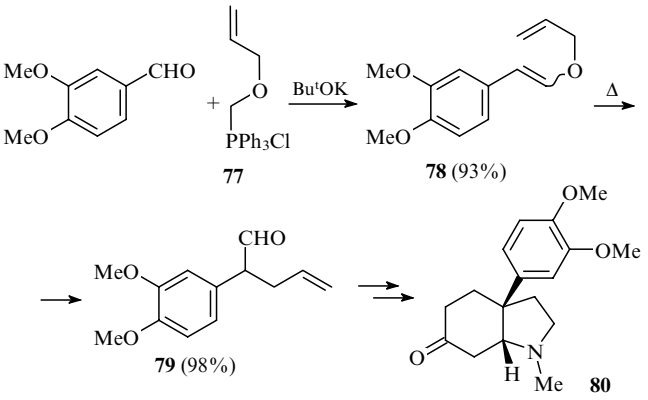
A related group of methods is based on the Wittig reaction with phosphorus ylides and its modifications involving phosphonate anions (the Horner–Wadsworth–Emmons modification) or phosphine oxides (the Horner method).[2] The formation of P–O bonds, which proceeds with a considerable gain of energy, is the driving force of these reactions (see Table 1). At present, this methodology is the most general and efficient approach to the synthesis of alkenes. From the moment of its discovery in 1953, the Wittig reaction has been the subject of intense studies; its synthetic applications, the olefination mechanism and effects of various factors on its direction and stereochemistry have been rather extensively studied and are documented in many reviews and monographs.[2,16–21] In addition, the description of the Wittig reaction and its applications have been included in manuals of organic chemistry, therefore, there is no need to dwell upon them. This reaction has been used in the syntheses of numerous compounds including natural products.[70] A great number of publications are devoted to the theoretical studies of the reaction mechanism.[71,72] The Wittig reaction is general and applicable to aldehydes and ketones containing various functional substituents, such as nitro, hydroxy, alkoxy, amino and alkoxycarbonyl groups as well as halogen. The presence of double and triple bonds conjugated with the carbonyl group does not prevent the reaction. Phosphorus ylides (phosphoranes) **73** prepared by the treatment of phosphonium salts **74** with strong bases are used as the olefinating agents in the Wittig reaction; the phosphonium salts **74** are usually synthesised from phosphines and alkyl halides.



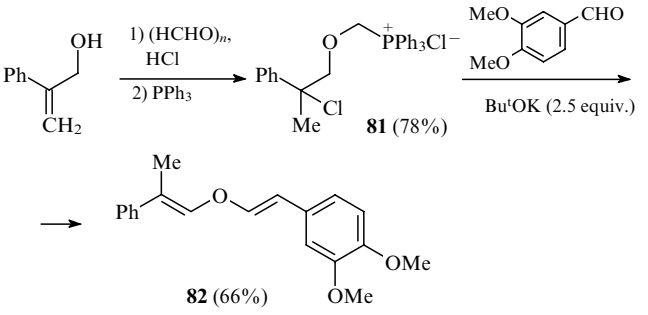
An alternative method for the synthesis of ylides includes reactions of phosphines with carbenes generated *in situ* upon catalytic decomposition of diazoalkanes [the so-called salt-free phosphorus ylides (Section V.3)]. Simple ylides (R^1, R^2 = H or Alk) are highly reactive and react with low active carbonyl substrates, such as ketones and esters, whereas the presence of electron-withdrawing groups (COR, CN, CO_2R, CHO) in the α-position of ylides makes these compounds more stable, but less reactive. It was found that the Wittig reaction proceeds through the formation of betaine **75**, its cyclisation into oxaphosphetane **76** and subsequent elimination of triphenylphosphine oxide.

Special mention should be made of the stereochemical result of the Wittig reaction. The so-called 'non-stabilised' phosphoranes react with aldehydes to yield predominantly (*Z*)-1,2-disubstituted alkenes. This method underlies a basic strategy in the synthesis of such compounds. In contrast, stabilised phosphoranes of the type Ph_3P = CH(EWG) yield *E*-isomers in reactions with aldehydes. These regularities have been reviewed in detail elsewhere.

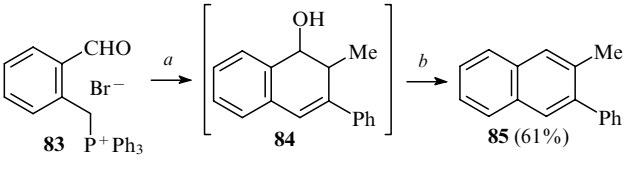
In this Section, we consider the most recent applications of the Wittig reaction. The allyl vinyl ether **78** is the olefination product of veratric aldehyde with the olefinating agent **77** containing the allyloxy group.[73] Subsequent Claisen rearrangement gives the aldehyde **79**, which is further converted into the alkaloid mesembrine (**80**).



The phosphonium salt **81** was used in the synthesis of non-symmetrical divinyl ethers **82**.[74] The use of an excess base in the Wittig reaction ensures high yields of the target products.

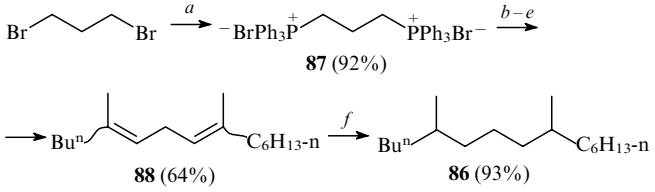


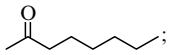
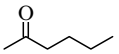
The use of the Wittig reaction in the synthesis of various cyclic systems is a promising methodology. Thus the reaction of the ylide **83** containing an aldehyde group with propiophenone enolate results in annelation and formation of the alcohol **84**, which is further dehydrated to give the substituted naphthalene **85**.[75] Various aromatic and aliphatic aldehydes and ketones were used as the carbonyl components in this reaction.



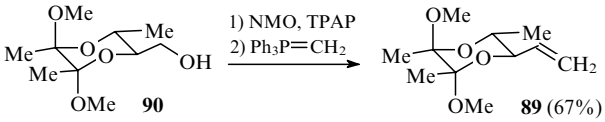
(*a*) PhCOEt, LDA; (*b*) TsOH.

The double Wittig reaction was used in the synthesis of the pheromone **86** (5,9-dimethylpentadecane).[76] The bisphosphonium salt **87** was sequentially introduced into a one-pot reaction with octan-2-one and hexan-2-one. Subsequent hydrogenation of the diene **88** yielded the pheromone **86** in the form of a racemic mixture of diastereomers.



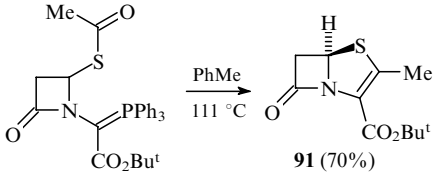
(*a*) PPh_3 (2.1 equiv.), DMF; (*b*) Bu^nLi (1.1 equiv.); (*c*) ;
(*d*) Bu^nLi (1.1 equiv.); (*e*) ; (*f*) H_2, Pd/C.

Preparation of aldehydes *in situ* by the oxidation of primary alcohols with *N*-methylmorpholine *N*-oxide in the presence of a catalytic amount of tetrapropylammonium perruthenate is a recent modification of the Wittig reaction.[77] This approach was used in the synthesis of the terminal alkene **89** from the alcohol **90**.

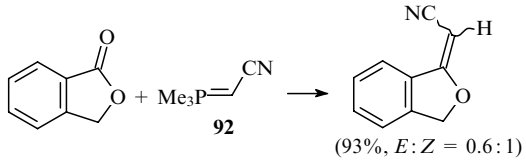


NMO is *N*-methylmorpholine *N*-oxide;
TPAP is tetrapropylammonium perruthenate.

It is not only aldehydes and ketones, but also esters, thiol esters, carboxylic anhydrides, amides and imides that can sometimes be used as substrates in the Wittig reaction.[16] Thus the intramolecular Wittig reaction was used by Woodward for the synthesis of the penicilline derivative **91**.[16,78]



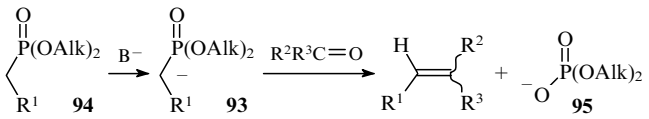
Cyanomethylenetrimethylphosphorane **92** was used in the synthesis of unsaturated nitriles from esters, lactones and imides.[79]



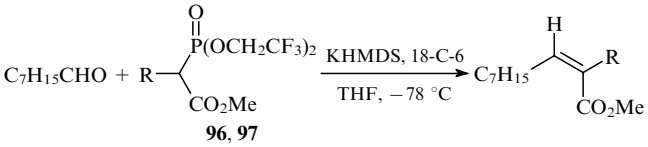
Despite its obvious versatility, the Wittig reaction has one disadvantage, *viz*., the necessity to use stoichiometric amounts of phosphines. Separation of reaction products from phosphine oxides complicates the experimental procedure. Other disadvantages include low stereoselectivity (in the case of allylic and benzylic ylides) and low reactivity of α,β-unsaturated and sterically hindered ketones.[80]

c. The Horner – Wadsworth – Emmons reaction

The Horner – Wadsworth – Emmons reaction (HWE) also known as a phosphonate modification of the Wittig reaction is widely employed in the synthesis of substituted alkenes.[1,2,16,18,22] In this case, the role of the nucleophile is played by the phosphonate anions **93** formed upon deprotonation of phosphonates **94** by strong bases, *e.g*., sodium hydride or potassium *tert*-butoxide. Anions of the type **93** are stronger nucleophiles than phosphorus ylides; therefore, the Horner – Wadsworth – Emmons method is efficient in the synthesis of alkenes from sterically hindered ketones which are not olefinated under the conditions of the classical Wittig reaction.[18] The second reaction product is dialkyl phosphate **95**, which is readily soluble in water; this, in turn, significantly facilitates the isolation of the target alkenes. However, the necessary presence of an anion-stabilising group in the α-position of the phosphonate reagent is a limitation of the method, which significantly narrows the area of its application in comparison with the classical Wittig reaction. Most commonly, the role of the stabilising group is played by the carboxy group; however, aryl or alkenyl groups and even halogens sufficiently stabilise the phosphonate anion.

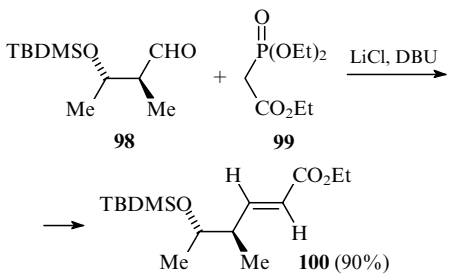


The mechanism of the Horner – Wadsworth – Emmons reaction is similar to that of the Wittig reaction and includes the formation of cyclic oxaphosphetanes. Variation of the olefination conditions and reagents allows one to synthesise *E*- and *Z*-alkenes with a high degree of stereoselectivity. *Z*-Isomers of alkenes are predominantly formed under conditions of kinetic control, *e.g*., at low temperatures, in weakly polar solvents (THF, CH_2Cl_2), under the action of strong bases containing a potassium atom (KHMDS, $KOBu^t$) for deprotonation and in the presence of crown ethers.[81] The use of bis(trifluoroethyl)phosphonates **96** and **97** also favours the formation of alkenes having a *Z*-configuration.



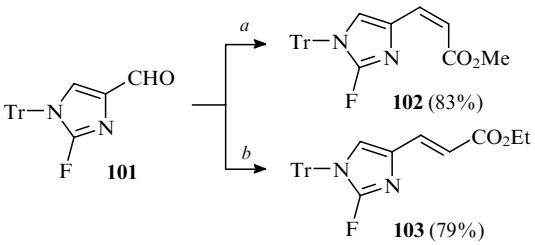
R = H (90%, *Z*:*E* = 12:1); R = Me (88%, *Z*:*E* = 46:1).

The optimum conditions for the synthesis of thermodynamically more stable *E*-isomers of alkenes are as follows: the reaction is to be carried out at 20 °C in polar solvents in the presence of lithium halides, amines are used as bases and phosphonates should contain bulky substituents.[82] Thus the olefination of aldehyde **98** with diethyl phosphonate **99** yields the *E*-isomer of the α,β-unsaturated ester **100**. Treatment of ketones with phosphonate anions under the conditions of the Horner – Wadsworth – Emmons reaction also yields both *E*- and *Z*-alkenes, although with lower stereoselectivity than in the case of aldehydes.



DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene.

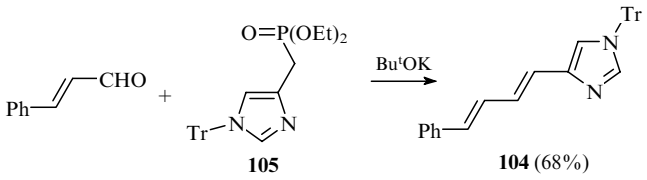
Thus by varying the reaction conditions and the structure of the phosphonate fragment, one can effectively control the stereochemistry of the olefination reaction.[83] The olefination of imidazolecarbaldehyde **101** with bis(trifluoroethyl) phosphonate **96** gives the unsaturated ester **102** with *Z*-configuration, whereas diethyl phosphonate **99** yields the *E*-isomer of the ester **103**.



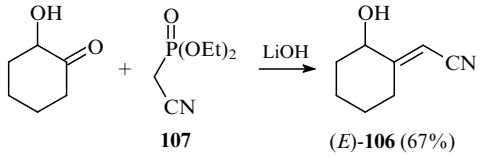
(*a*) $(CF_3CH_2O)_2P(O)CH_2CO_2Me$ (**96**), KHMDS, 18-C-6 (1.5 equiv.);

(*b*) $(Et_2O)_2P(O)CH_2CO_2Et$ (**99**), KHMDS, 18-C-6 (5 equiv.); Tr = Ph_3C.

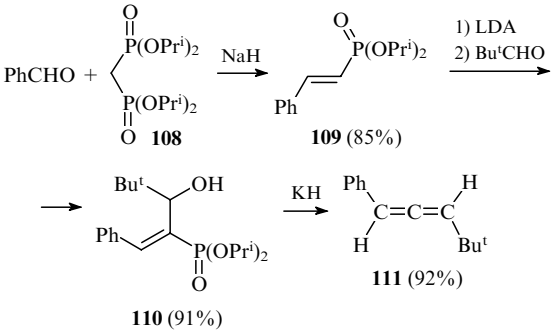
Synthesis of dienylimidazoles **104** was effected using the reagent **105** containing an imidazole nucleus.[84] Alkenes are formed stereospecifically and the configuration of the newly formed double bond of diene **104** was *E*.



The use of potassium carbonate[85] or lithium hydroxide as promoters is a convenient modification of the Horner–Wadsworth–Emmons reaction.[86] Thus the addition of LiOH increases the stereoselectivity and prevents side reactions in the synthesis of unsaturated esters and nitriles.[86] This approach was used in the stereospecific synthesis of unsaturated nitriles **106**, where diethylphosphonoacetonitrile (**107**) was used as the olefinating agent. High stereoselectivity of this reaction is due to coordination of lithium in the transition state to the hydroxy group in the α-position of the substrate.

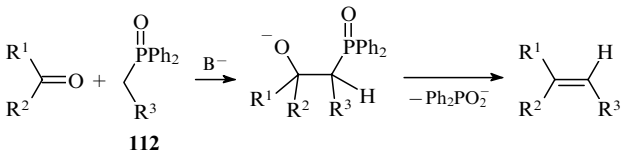


The reaction of benzaldehyde with methylenedi(phosphonate) **108** was used in the synthesis of allenes from carbonyl compounds.[87] The reaction of compound **108** with aldehydes gave the corresponding alkenylphosphonates **109**. Their subsequent treatment with LDA and the addition of the second carbonyl compound afford hydroxyalkenylphosphonates **110**, which can be converted into allenes **111** by treatment with potassium hydride.

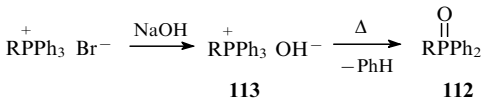


d. The Horner–Wittig reaction

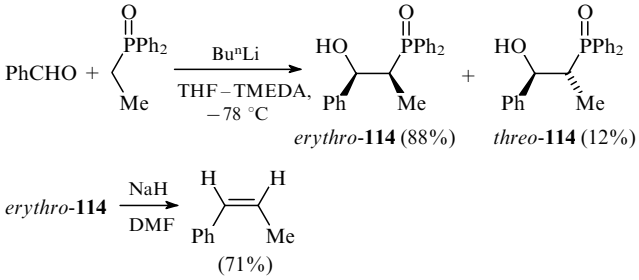
The use of the reaction of phosphine oxides **112** with aldehydes in the presence of potassium *tert*-butoxide or sodium amide for the synthesis of alkenes was recommended by Horner.[2, 18, 88] In this case, the role of the olefinating agent is played by the phosphine oxide anion generated upon deprotonation of compound **112**. Its addition to the carbonyl group yields β-hydroxy phosphineoxide, which undergoes further *syn*-elimination of the anion $Ph_2PO_2^-$.



The corresponding phosphine oxides **112** can be prepared by thermal decomposition of alkyltriphenylphosphonium hydroxides **113**.[18]

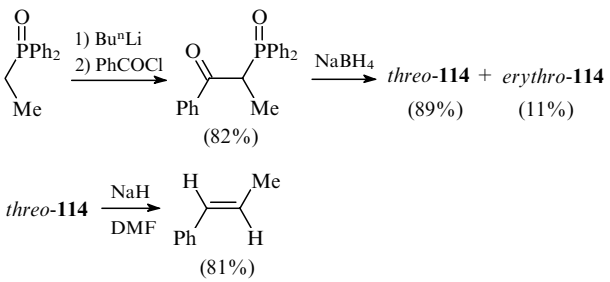


If sodium or potassium bases are used in the Horner–Wittig reactions, the elimination of $Ph_2PO_2^-$ from hydroxy phosphine oxide occurs *in situ*, whereas in the case of lithium bases β-hydroxy phosphine oxides can be isolated.[89] Upon subsequent treatment with other bases (NaH, KOH, $KOBu^t$), β-hydroxy phosphine oxides undergo *syn*-elimination resulting in alkenes, *Z*-isomers from the *erythro*-adducts and the corresponding *E*-isomers from the *threo*-adducts. Similar transformations were described for the adducts **114**.[89]



TMEDA is *N,N,N′,N′*-tetramethylethylenediamine.

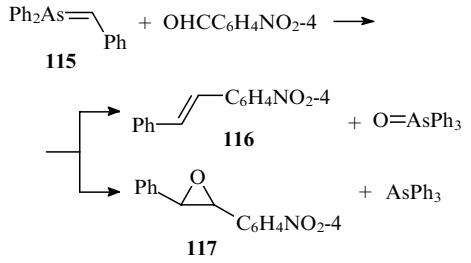
The ratio of diastereomers of β-hydroxy phosphine oxides **114** can be changed by varying the nature of the solvent, the base and the reaction temperature.[89] In weakly polar solvents (THF, ether), *erythro*-diastereomers are formed predominantly at low temperatures (−78 °C) and in the presence of the system Bu^nLi–TMEDA, while mixtures of isomeric β-hydroxy phosphine oxides are usually formed at elevated temperatures and in more polar solvents. β-Hydroxy phosphine oxides enriched in the *threo*-stereomer are formed upon reduction of the corresponding β-oxophosphine oxides with sodium borohydride.[90]



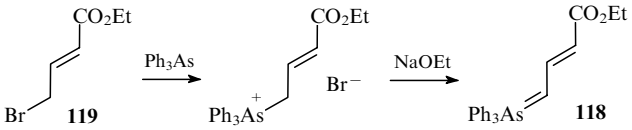
e. Arsenic-based reagents

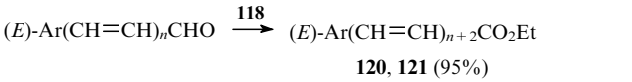
Carbanions stabilised by arsenic and antimony are less commonly used in olefination reactions in comparison with their phosphorus analogues. Arsenic and antimony ylides containing electron-withdrawing groups are more reactive than the corresponding phosphoranes. Their reactions with aldehydes were used for the development of effective methods for the synthesis of some substituted alkenes the preparation of which by the Wittig reaction is either difficult or impossible. The properties and

applications of arsenic ylides (arsoranes) are described in a review.[91] The corresponding ylides are formed upon alkylation of triphenylarsine and subsequent deprotonation of the resulting arsonium salts. As a rule, olefination with arsenic ylides occurs stereospecifically. Arsenic ylides react with carbonyl compounds to give both alkenes and epoxides (this reaction route is more typical of sulfur ylides). Presumably, this is due to a lower affinity of arsenic for oxygen in comparison with phosphorus (see Table 1). Thus the reaction of arsorane **115** with 4-nitrobenzaldehyde yields a mixture of stilbene **116** and epoxide **117**.



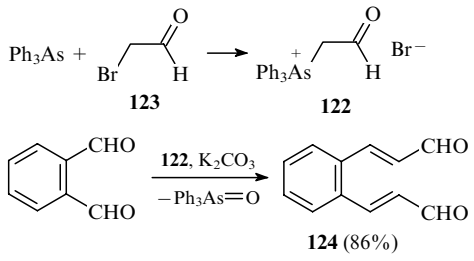
Ylides stabilised by electron-withdrawing groups manifest higher proneness for olefination, whereas more reactive ylides react with the predominant formation of epoxides.[91] Thus the ylide **118** derived from the ethyl 4-bromocrotonate **119** is used in the stereoselective synthesis of alka-2,4-dienoates **120** and 2,4,6-trienoates **121**.[92]



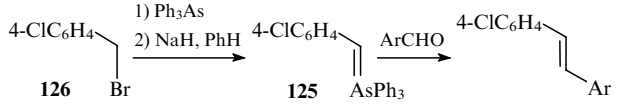


Ar = 4-ClC$_6$H$_4$, n = 0 (**120**); Ar = Ph, n = 1 (**121**).

Arsenic ylide **122**, the reaction product of triphenylarsine and bromoacetaldehyde **123**, reacts with phthalic aldehyde in the presence of potassium carbonate, to give the α,β-unsaturated aldehydes **124** in high yields; the nature of the carbonyl components can be varied over a broad range. This reaction is stereoselective; the ratio of the *E*- and *Z*-isomers of the target alkenes is no less than 97 : 3.[93]

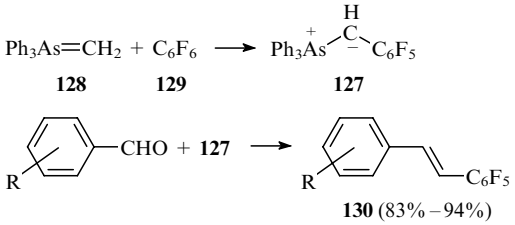


Arsenic ylide **125** generated from 4-chlorobenzyl bromide **126** was used in the stereoselective synthesis of *trans*-isomers of nonsymmetrical stilbenes [94] from diverse aromatic aldehydes containing both donor and acceptor substituents in the aromatic nucleus. The yields vary from 40% to 80%; it is the corresponding *trans*-stilbenes that were obtained in all cases.



Ar = Ph, 3-NO$_2$C$_6$H$_4$, 4-NO$_2$C$_6$H$_4$, 4-MeC$_6$H$_4$, 4-MeOC$_6$H$_4$, 4-ClC$_6$H$_4$, 4-Me$_2$NC$_6$H$_4$, 3,4-(MeO)$_2$C$_6$H$_3$, 3,4-(MeO)$_2$-6-BrC$_6$H$_2$, 2-furyl.

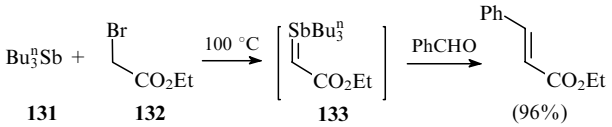
(Pentafluorophenylmethylene)triphenylarsorane **127** obtained *in situ* by a reaction of methylenetriphenylarsorane **128** with hexafluorobenzene **129** gives stereospecifically non-symmetrical *E*-stilbenes **130** containing a perfluorophenyl substituent.[95]



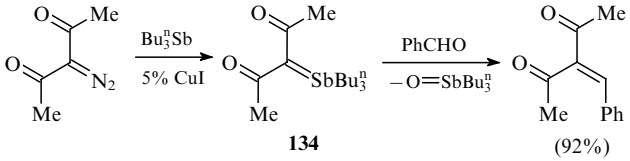
130 (83% – 94%)

f. Antimony-based reagents

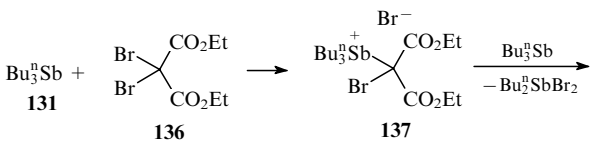
The use of the system tributylstibine – ethyl bromoacetate as an olefinating agent allows transformation of some aromatic and aliphatic aldehydes and ketones into α,β-unsaturated esters.[96] A significant advantage of this method is the possibility to conduct the reaction in the absence of strong bases. A mixture of stibine **131** and ethyl bromoacetate (**132**) plays the role of an olefinating agent. Unfortunately, the mechanism of this reaction has not been reported, [96] but it is assumed that it resembles that of the Wittig reaction and involves the formation of antimony ylide **133**.

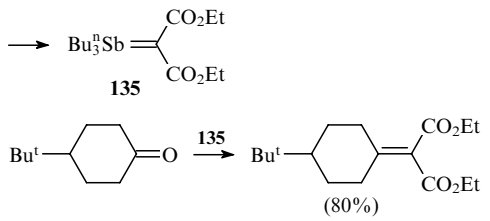


The reaction of antimony ylides **134** prepared by the copper(I) iodide-catalysed decomposition of α-diazo-β-dicarbonyl compounds with aromatic and aliphatic aldehydes and ketones yields α,β-unsaturated esters and ketones. As regards its outcome, this reaction is similar to the Knoevenagel reaction. In most cases, the yields are nearly quantitative. Studies of a relationship between the oxidation state of copper and the nature of the catalyst counterion and the yields of the target products revealed that copper(I) halides are the catalysts of choice.[97] Triphenylstibine should be used in equimolar amounts, and triphenylstibine oxide is formed as a second reaction product. A salient advantage of this method is that the ylide does not require strong bases for its generation. The use of derivatives of other Group VA elements (Ph_3As, Ph_3Bi) in this reaction is less efficient, whereas in the case of triphenylphosphine the target product is not formed at all. These results are different from the literature data on the olefination of carbonyl compounds by diazoalkanes in the presence of triphenylphosphine catalysed by such metals as rhodium and ruthenium (see Section V.3).



An alternative approach to the synthesis of antimony ylides **135** includes a reaction of tributylstibine **131** with *gem*-dibromomalonates **136**.[98] The quarternary antimonium salts **137** formed react with the second equivalent of stibine to yield stiboranes **135**. The latter play the role of olefinating agents which can be introduced into reactions with aliphatic ketones.



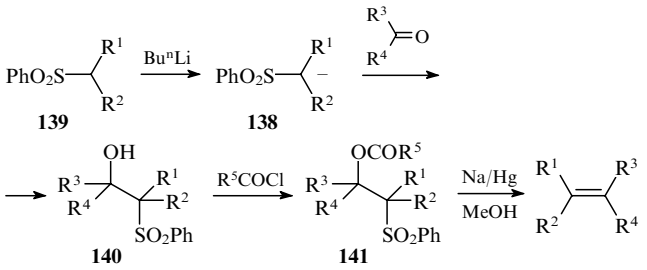


4. Reagents based on Group VIA elements

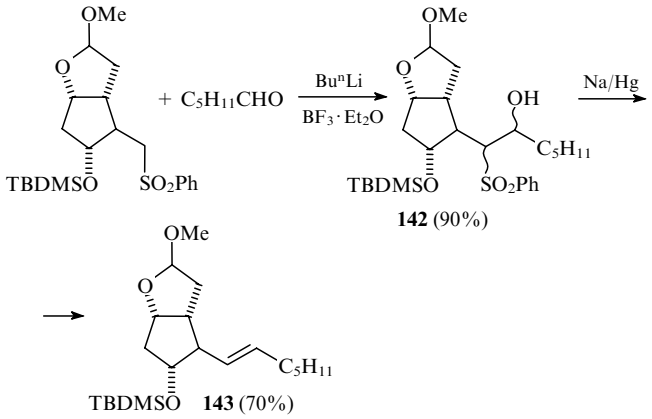
The olefination reactions considered in this Section include the addition, to the carbonyl group, of carbanions stabilised by a sulfo- or a sulfoximino group in the α-position as well as by selenium and tellurium.

a. The Julia reaction

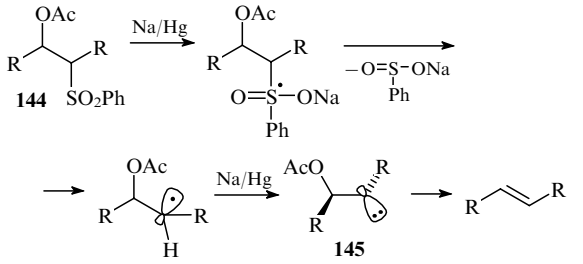
The Julia reaction (also referred to as the Julia – Lythgoe reaction in the English-language literature) consists of the generation of carbanions **138** upon deprotonation of sulfones **139** by strong bases.[1, 2, 99–101] Subsequent addition of the anion **138** to the carbonyl group yields a mixture of diastereomeric β-hydroxy sulfones **140**. The reaction is accelerated in the presence of Lewis acids, such as boron trifluoride etherate[102] and magnesium bromide.[103] Then, the hydroxy group of β-hydroxy sulfones **140** is converted into a good leaving group (acetate, benzoate, *p*-toluenesulfonate); subsequent reduction of α-acyloxy sulfones **141** with sodium amalgam in methanol gives alkenes.[23]



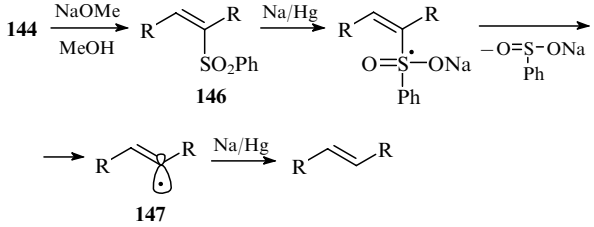
Sometimes, the modification step of the hydroxy group is omitted and β-hydroxy sulfones **140** are subjected to reductive elimination.[102] Thus the reduction of the adduct **142** with sodium amalgam gives the alkene **143** in high yield.



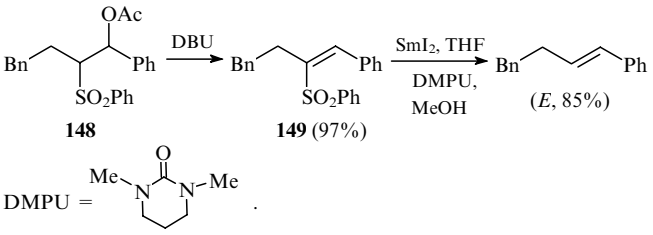
Reductive elimination occurs with high stereoselectivity: 1,2-disubstituted alkenes are formed exclusively as *E*-isomers.[2] It was shown that the geometry of the resulting alkene does not depend on the stereochemistry of the intermediate β-hydroxy sulfone; diastereomeric *erythro*- and *threo*-acetoxysulfones **144** are converted into the same *trans*-alkene,[104] which is one of the main advantages of the Julia reaction. High *E*-selectivity is explained by the fact that the intermediate anion **145** formed in the reductive elimination step has time to acquire a thermodynamically more favourable *trans*-configuration prior to the elimination of the acetate ion.



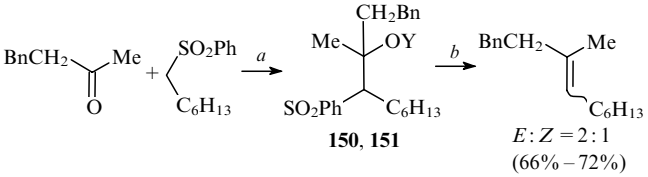
An alternative mechanism of reductive elimination includes preliminary formation of vinyl sulfones **146** and their subsequent reduction first to the vinyl radicals **147** and then to alkenes.[105]



Toxic sodium amalgam can be replaced by other reducing reagents, such as magnesium or samarium iodide (the latter is generated *in situ* from samarium and iodine).[2, 105] In the latter case, β-acetoxy sulfone **148** is converted into vinyl sulfone **149** and then reduced with samarium iodide. Such a reduction usually occurs with high yields (69% – 95%) and high stereoselectivity and affords 1,2-disubstituted alkenes; however, the necessity to use nine equivalents of samarium iodide makes this method extremely expensive.

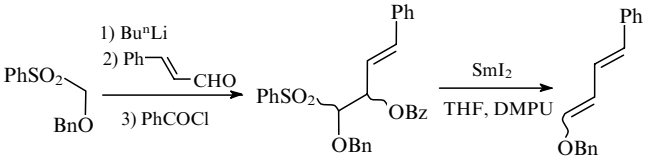


The Julia method is a convenient tool for the synthesis of alkenes; however, its main disadvantage is its multistep character. In addition, the synthesis of tri- and tetra-substituted alkenes proceeds in low yields. The use of disubstituted sulfones and aldehydes (rather than monosubstituted sulfones and ketones) is more preferable for the preparation of trisubstituted alkenes[1] due to reversibility of the reaction of a sulfone-derived anion with a ketone.[106, 107] A modified one-pot procedure, which includes acylation or silylation of β-hydroxy sulfones and reduction of the intermediates **150** and **151** with samarium iodide, allows the involvement of ketones into the reaction.[106, 107] However, the stereoselectivity of formation of trisubstituted alkenes is usually low; the *E* : *Z* ratio is ~2 : 1.



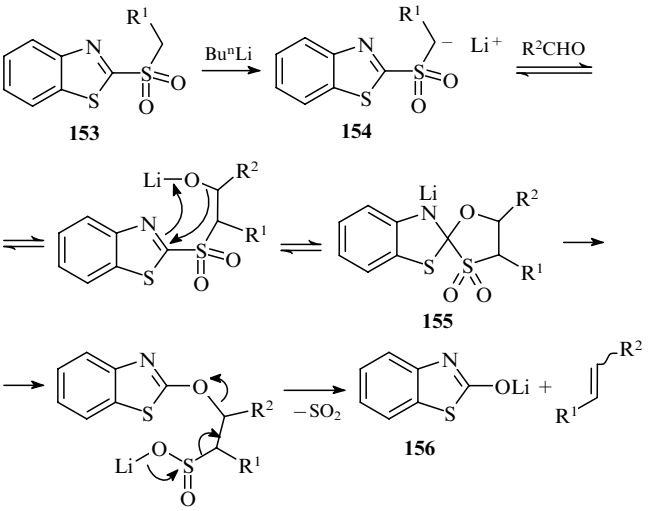
150: Y = Me_3Si (69%); **151**: Y = Bz (85%);
(*a*) 1) Bu^nLi, 2) Me_3SiCl or PhCOCl; (*b*) SmI_2, THF, HMPA;
HMPA is hexamethylphosphoramide.

This approach was used in the synthesis of the diene **152**, which contains a benzyloxy group at the terminal atom of the diene system.[107] Dienes like compound **152** are promising substrates for the Diels–Alder reaction.

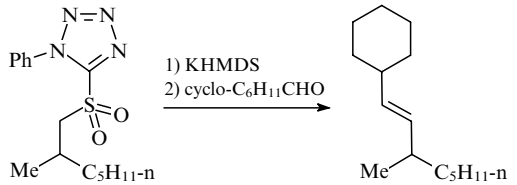


152 (82%, $E,E:E,Z = 1.7:1$)

The modification of the Julia reaction based on the use of benzothiazol-2-yl sulfones **153** as olefinating agents, has been named the Julia–Kocienski reaction. Upon addition of anions **154** to aldehydes, the adducts **155** are formed which undergo elimination of SO_2 resulting in the *trans*-isomers of 1,2-disubstituted alkenes and a lithium salt of 1,3-benzothiazol-2-one **156** as a side product.[108] The use of heteroaryl sulfones allows one to exclude the reductive elimination step.

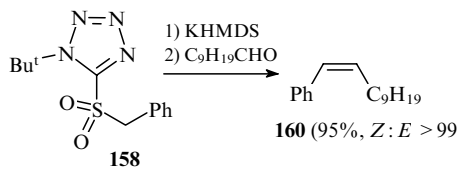


In a more recent study,[109] Kocienski suggested the use of sulfones **157** containing a phenyltetrazole system. These sulfones are more stable; the stereoselectivity of the reaction and the yields of the alkenes are higher than in the case of reagents containing a benzothiazole substituent.[109]



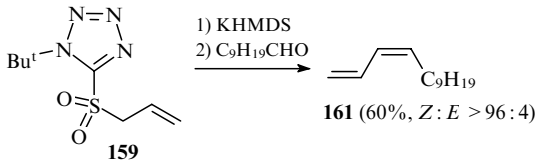
157 (59%, $E:Z = 99:1$)

Analogous reagents **158** and **159** contain a 1-*tert*-butyl-1*H*-tetrazol-5-yl system; the carbanion formed is additionally stabilised by a phenyl or vinyl group.[110] With these reagents, the yields of 1,2-disubstituted alkenes are higher than in the case of the reagent **157**; the formation of alkenes **160** and **161** proceeds with high *Z*-stereoselectivity.



158

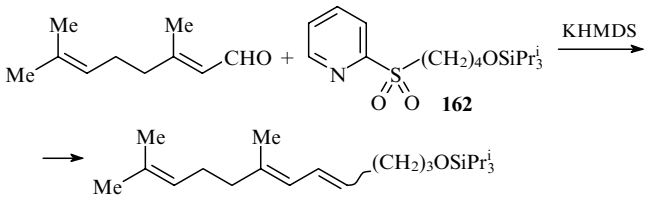
160 (95%, $Z:E > 99:1$)



159

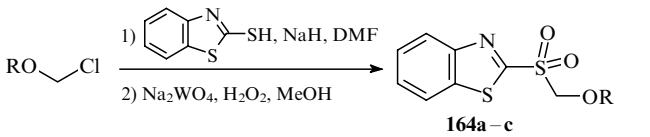
161 (60%, $Z:E > 96:4$)

The condensation of 2-pyridylsulfone **162** with α,β-unsaturated aldehydes occurs with predominant formation of *E,Z*-isomers of dienes. Compound **163** was obtained in 64% yield.[111]



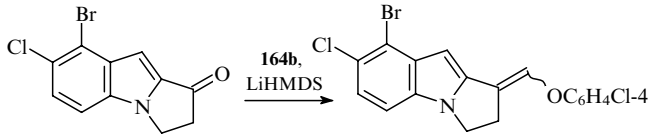
163 (64%; $E,Z:E,E = 88:12$)

β-Alkoxy sulfones **164a–c** can be used in the synthesis of enol ethers from aldehydes and ketones by the Julia–Kocienski reaction.[112] The formation of the ethers **165** occurs with low stereoselectivity, albeit in good yields.



164a–c

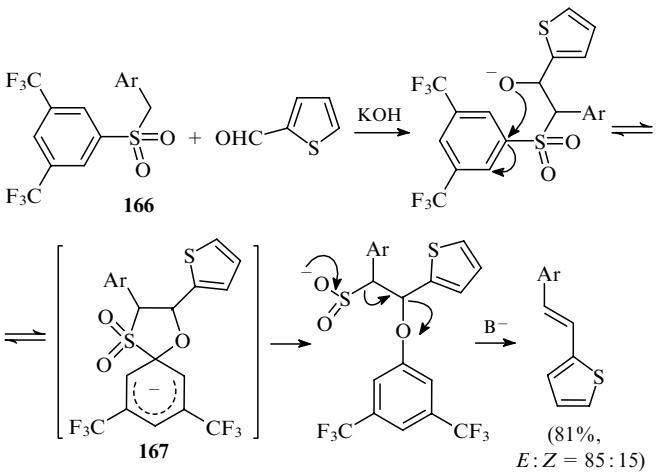
R = Bn (**a**, 68%); 4-ClC_6H_4 (**b**, 80%); $MeOCH_2CH_2$ (**c**, 75%).



165 (85%, $E:Z = 74:26$)

LiHMDS is lithium hexamethyldisilazanide.

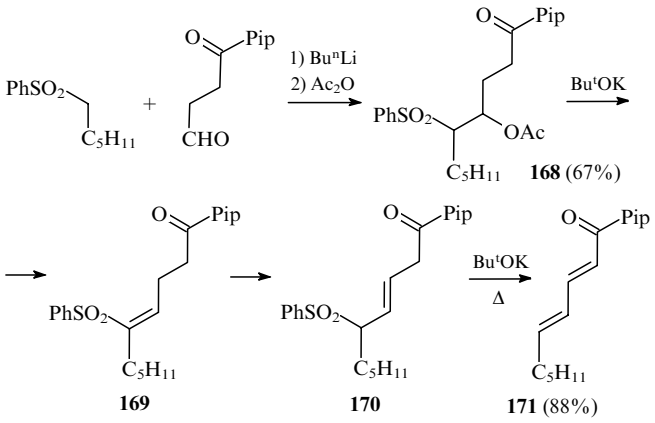
The sulfone **166** containing an electron-deficient arene fragment was used in yet another modification of the Julia–Kocienski reaction.[113] The addition of a carbanion generated from compound **166** to aldehydes and subsequent β-elimination of 3,5-bis(trifluoromethyl)phenoxide from the adduct **167** upon treatment with a base with concomitant liberation of SO_2 afford alkenes in high yields and with high *E*-stereoselectivities.



Ar = 3,5-$(MeO)_2C_6H_3$.

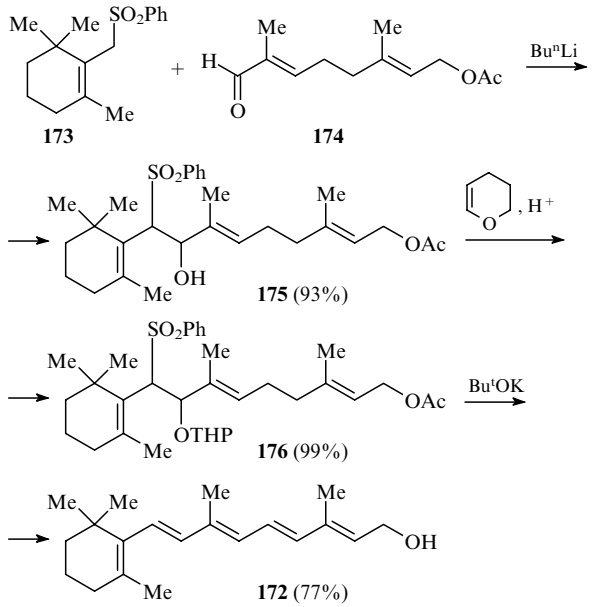
The Julia reaction can be used in the synthesis of conjugated polyenes from carbonyl compounds. Thus compound **168** prepared from hexylphenyl sulfone and the corresponding aldehyde was treated with a strong base, such as potassium *tert*-butoxide.[114]

The first step includes elimination of acetic acid and formation of the vinylic sulfone **169** which is rearranged into the allylic sulfone **170**. The latter undergoes 1,4-elimination to give a diene **171** (usually, with *E*,*E*-configuration).[115, 116] The intermediate vinylic sulfone **169** can be isolated upon treatment of **168** with an equimolar amount of a base. Subsequent cleavage of the sulfone requires a fourfold excess of potassium *tert*-butoxide and heating.



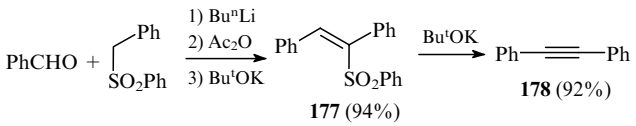
PiP is piperidin-1-yl.

The Julia method was used in the synthesis of many natural compounds including muscone and some retinoids.[2, 101, 117] Thus synthesis of retinol **172** involved the addition of β-cyclogeranyl sulfone **173** to the aldehyde **174**. The resulting β-hydroxy sulfone **175** was protected with a tetrahydropyranyl group; the product **176** was treated with potassium *tert*-butoxide. Subsequent elimination of the protected hydroxy group and the sulfone with concomitant rearrangement of multiple bonds yields the target compound **172** in which all the double bonds have a *trans*-configuration.

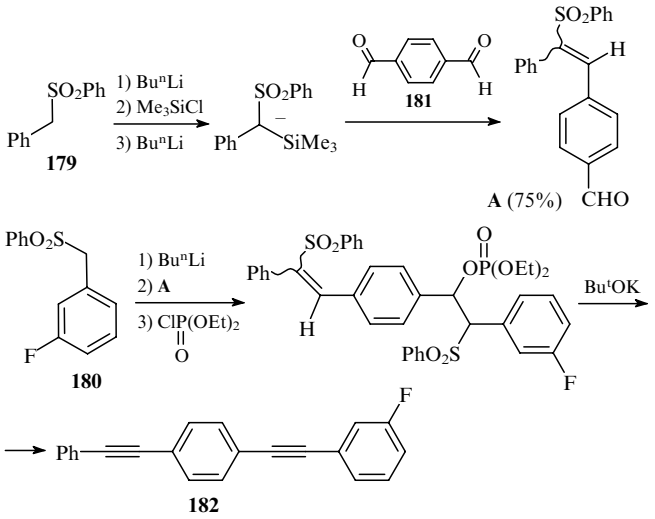


THP is tetrahydropyran-2-yl.

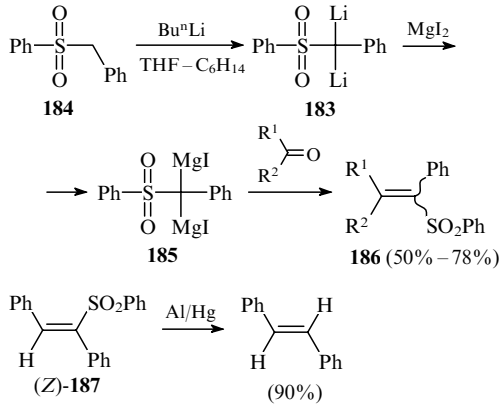
If the shift of double bonds in vinylic sulfones, *e.g.*, in compound **177**, is impossible, subsequent elimination yields acetylene **178**.[115]



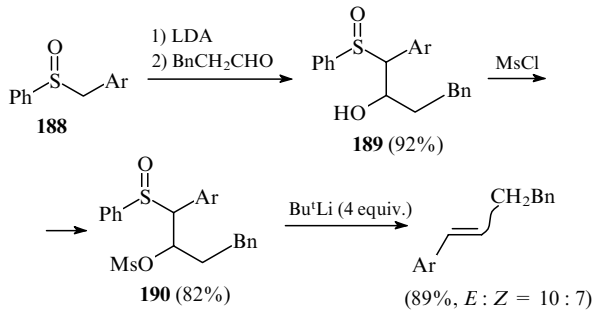
The addition of sulfones to dialdehydes allows one to synthesise non-symmetrical polyacetylenes.[118] Thus consecutive addition of two different sulfones (**179** and **180**) to the carbonyl groups of the dialdehyde **181** and elimination of the sulfonyl groups yield diacetylene **182** with different substituents.



Benzyl phenyl sulfone α,α-dilithium derivative **183**, which is easily prepared by the double metallation of benzyl phenyl sulfone **184**, can be converted into an organodimagnesium compound **185** *in situ* using lithium – magnesium exchange upon treatment with magnesium iodide. The dimetallated sulfone **185** is a convenient olefinating agent, which reacts with aliphatic, aromatic and unsaturated aldehydes or ketones to give α,β-unsaturated sulfones **186** in good yields.[119] The sulfonyl group is removed using aluminium amalgam or the system $LiAlH_4 - CuCl_2$.[120] Unfortunately, in the majority of cases this reaction occurs non-stereoselectively and yields first a mixture of *E*- and *Z*-isomers of sulfones and then a mixture of the corresponding alkenes. The desulfonylation occurs in good yields (40% – 90%). Thus *trans*-stilbene is formed in 90% yield from the *Z*-sulfone **187**.[120]

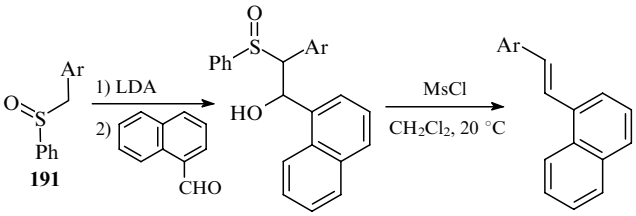


A sulfoxide modification of the Julia-type olefination reaction has been developed.[121, 122] In the case of sulfoxides **188,** the acidity of α-hydrogen atoms is lower than that of sulfones; this makes the corresponding carbanions more reactive as a result of which even ketones can be used as the carbonyl components in this reaction. Mesylation of the intermediate β-hydroxy sulfoxides **189** and reduction of the intermediates **190** by Grignard reagents or *tert*-butyllithium result in alkenes. In the case of an aliphatic substrate (*e.g.*, 3-phenylpropanal), the stereoselectivity of the reaction with all arylmethyl phenyl sulfoxides studied was low.



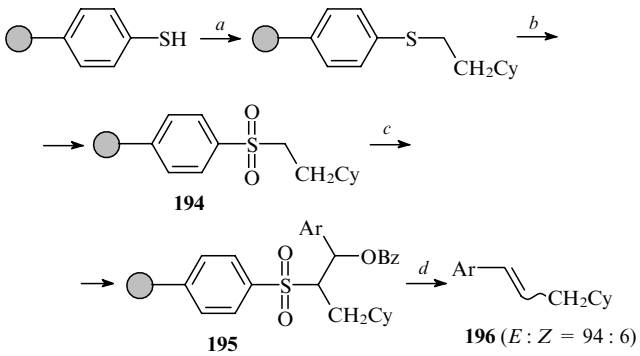
Ms = $MeSO_2$.

On going to aromatic aldehydes, non-symmetrical stilbenes are formed in this reaction exclusively as *trans*-isomers.[122] For example, the addition of sulfoxide **191** to 1-naphthaldehyde and mesylation of β-hydroxy sulfoxide **192** result in spontaneous elimination and formation of the *trans*-alkene **193**.



Ar = 4-$MeOC_6H_4$.

A recent modification of the Julia reaction consists of solid-phase synthesis.[123] A polymer containing pendent benzenethiol units is converted into the olefinating agent **194** by sequential *S*-alkylation and oxidation of the sulfide. Subsequent deprotonation and addition of anisaldehyde followed by benzoylation of the resulting β-hydroxy sulfone and reduction of compound **195** with samarium iodide yield the alkene **196** in 27% yield (starting from benzenethiol). The stereoselectivity of this reaction depends on the type of the acylating reagent (Ac_2O or PhCOCl) and the solvent used for reductive elimination.

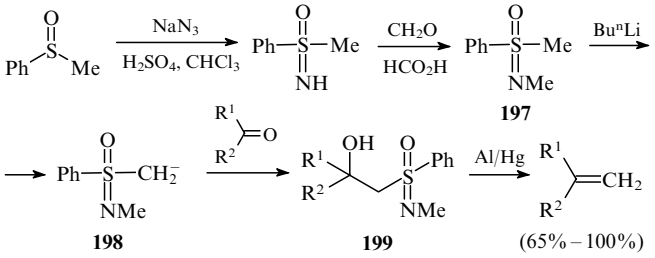


(*a*) 1) Bu^{t}OK (12 equiv.), 2) $CyCH_2CH_2OTs$ (2 equiv.), THF – DMSO (2 : 1), 20 °C; (*b*) *m*-CPBA (4 equiv.), CH_2Cl_2, 20 °C; (*c*) 1) Bu^{n}Li, 2) ArCHO, 3) PhCOCl; (*d*) SmI_2 (7 equiv.), THF, DMPU, 20 °C; Ar = 4-$MeOC_6H_4$; *m*-CPBA is *m*-chloroperbenzoic acid;

 — polymeric support.

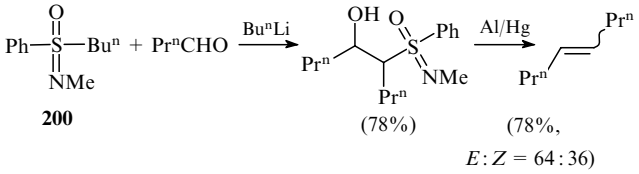
b. The Johnson reaction

In 1973, Johnson proposed to use sulfoximine **197** for methylenation of carbonyl compounds.[124, 125] The carbanion **198** prepared by deprotonation of the imine **197** with n-butyllithium appeared to be a strong C-nucleophile. Its addition to the carbonyl group of ketones yields β-hydroxy sulfoximine **199** which is further reduced with aluminium amalgam to the corresponding terminal alkene. The starting sulfoximine **197** can easily be prepared from methyl-phenyl sulfoxide.[124] The reaction can be carried out in a one-pot manner, without isolation of the intermediate **199**.[124] The Johnson reaction proved to be effective in the synthesis of terminal alkenes from both ketones and aldehydes. The carbanion **198** was found to be more nucleophilic than methylene triphenylphosphorane, this can be used in the synthesis of alkenes that cannot be prepared by the Wittig reaction.[2, 126]

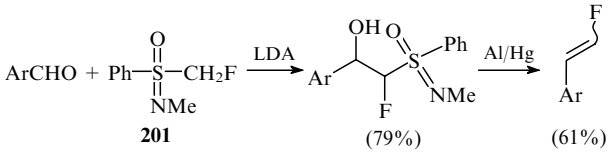


R^1 = Alk, Ar; R^2 = H, Alk.

The use of higher homologues of sulfoximines, *e.g.*, compound **200**, in reactions with aldehydes and ketones allows one to synthesise non-terminal alkenes; however, in this case the reaction occurs with low stereoselectivity.[125]

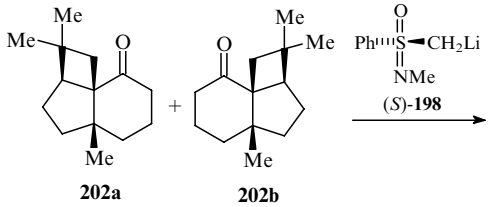


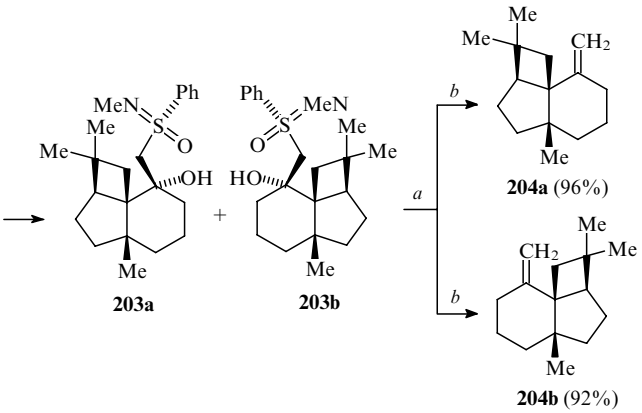
α-Fluoromethyl sulfoximine **201** was recommended as a convenient fluoromethyenating agent.[127] It was employed in the synthesis of a series of vinyl fluorides from aromatic and aliphatic aldehydes and ketones. This reaction is non-stereoselective and yields a mixture of alkene isomers in a 1 : 1 ratio.



Ar = 4-$MeOC_6H_4$.

It should be noted that the Johnson reagent (sulfoximine **197**) contains an asymmetrical sulfur atom. The reaction of an individual *S*-enantiomer of the carbanion **198** with a racemic mixture of the ketone **202** (**202a**, **202b**), chromatographic separation of the intermediate diastereomeric β-hydroxy sulfoximines **203a**,**b** and subsequent reductive elimination of sulfoximine resulted in the alkene enantiomers **204a**,**b** in the optically pure state.[128]

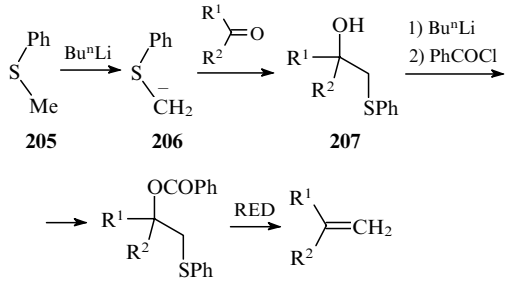




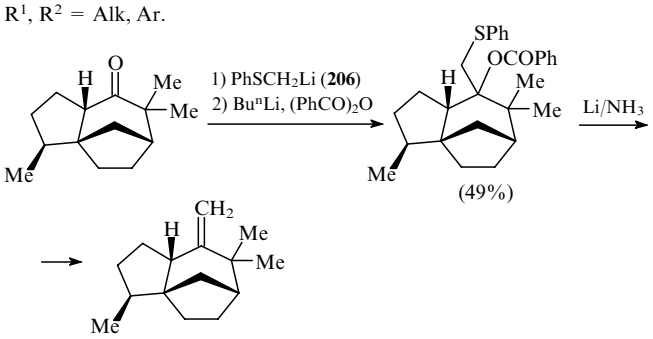
(*a*) separation of diastereomers; (*b*) Al/Hg.

c. Other sulfur-containing reagents

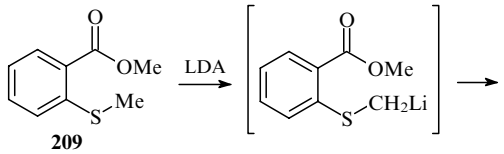
The carbanion **206** generated from thioanisole (**205**) adds to the carbonyl group of aliphatic and aromatic ketones to give β-phenylthioethanol **207**.[129] Benzoylation of the hydroxy group and subsequent reductive elimination of the ester and phenylthio groups yield terminal alkenes. Lithium in liquid ammonia,[129] the system $TiCl_4-Zn$ [2] or metallic titanium are used as the reducing agents.[130] Cage ketones can also be employed as the carbonyl components.[129]

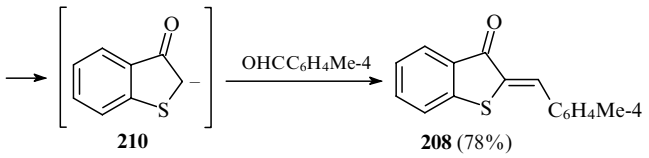


R^1, R^2 = Alk, Ar.



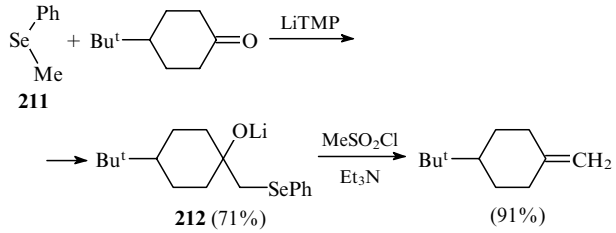
In the synthesis of thioaurones, *e.g.*, 2-(arylmethylidene)benzothiophen-3-ones **208**, 2-methylthiobenzoic acid or its methyl ester **209** were used as the olefinating agents.[131] This reaction is accompanied by anionic intramolecular cyclisation of the ester **209**, which yields the intermediate **210**; subsequent addition of the latter to the carbonyl group gives the alkene **208**. It should be noted that this reaction occurs stereospecifically and yields exclusively the *Z*-isomer of the alkene **208**. Other aliphatic and aromatic aldehydes can also enter into this reaction.[131]



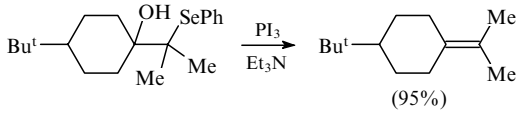


d. The Krief–Reich reaction

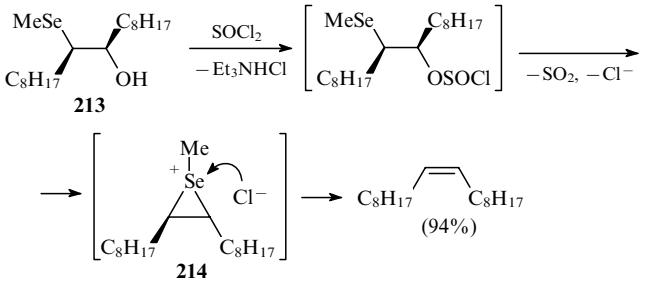
The olefination of carbonyl compounds by carbanions stabilised by selenium atoms is referred to as the Krief–Reich reaction.[2, 24, 132–134] The addition of carbanions prepared by deprotonation of alkyl aryl selenides **211** (see Ref. 3) or treatment of diselenoacetals with butyllithium,[135] to the carbonyl group results in β-hydroxy selenides **212**, which can further be converted into various products. In particular, alkenes are prepared by elimination of the hydroxy and selenyl fragments using methanesulfonyl chloride, $SOCl_2$ [134] or PI_3 in the presence of triethylamine.[135]



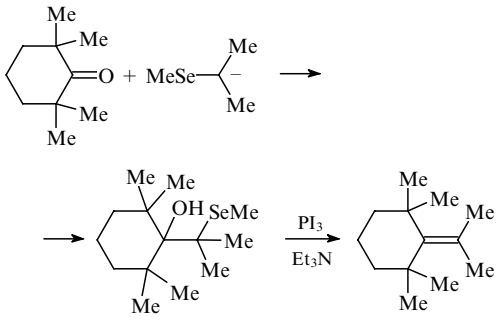
TMP is 2,2,6,6-tetramethylpiperidin-1-yl.



The modification of the OH-group of β-hydroxy selenide **213** by treatment with thionyl chloride results in its conversion into a good leaving group; elimination of the latter yields the selenonium cation **214**. An attack by an external nucleophile at the selenium atom of the cation **214** yields alkenes.[2, 136]

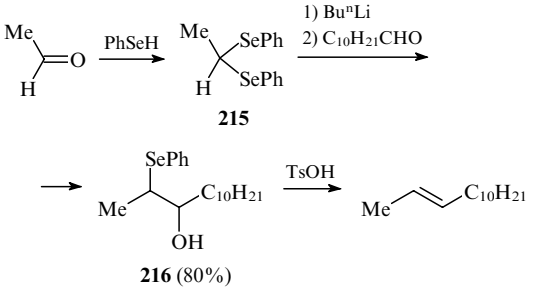


The Krief–Reich reaction was used in the synthesis of various types of alkenes including sterically hindered ones.[137]



The Krief–Reich methodology can be used for cross-coupling of two different aldehydes.[132] Conversion of one of them into selenoacetal **215,** treatment of the latter with n-butyllithium and addition of the resulting carbanion to the second aldehyde result

in β-hydroxy selenide **216**. Subsequent elimination of the hydroxy and selenyl fragments yields alkenes.

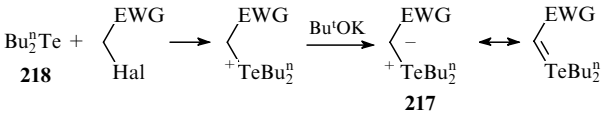


215

216 (80%)

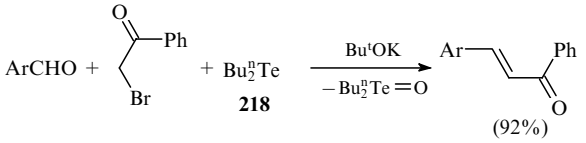
d. Tellurium-based reagents

Tellurium ylides **217** containing an electron-withdrawing group (ester, cyano, keto, *etc.*) in the α-position are used in the synthesis of α,β-unsaturated esters, nitriles and ketones.[138, 139] To this end, aromatic aldehydes are treated with α-halo-substituted esters or nitriles in the presence of equimolar amounts of dibutyl telluride **218**. The corresponding tellurium ylides **217** are generated *in situ* by deprotonation of telluronium salts. This reaction results in good yields, it is highly stereoselective and gives predominantly *E*-isomers of alkenes. It is of note that reactions of tellurium ylides with carbonyl compounds yield olefination products, whereas reactions of sulfur ylides with the carbonyl group give epoxides.



218 **217**

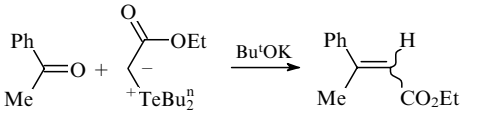
EWG = CO_2R, COR, CN; Hal = Cl, Br.



(92%)

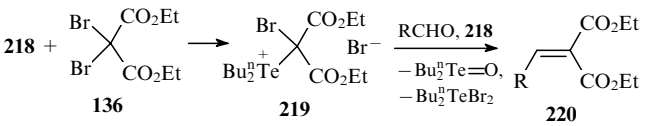
Ar = 4-$NO_2C_6H_4$.

Both aldehydes and ketones can be used as the carbonyl components; however, in the case of non-symmetrical ketones the stereoselectivity of alkene formation is low.[139]



(68%, *E* : *Z* = 11 : 1)

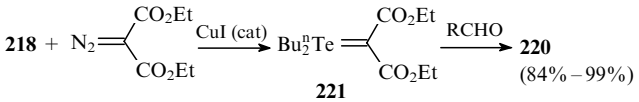
In the presence of dibutyl telluride **218**, dibromomalonate **136** can be used as the olefinating agent in reactions with aromatic aldehydes.[140] The reaction mechanism is similar to that considered above for the olefination with tributylstibine (Section II.3.e) and includes the formation of the telluronium salt **219** as a result of the alkylation of dibutyl telluride. In the presence of a second equivalent of dibutyl telluride, the salt **219** reacts with aldehydes to give α,β-unsaturated malonates **220**.



136 **219** **220** (84%–99%)

R = Alk, Ar, Het.

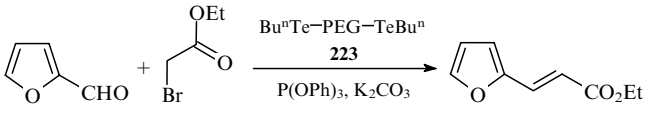
The copper-catalysed decomposition of diazo compounds in the presence of dialkyl or diaryl tellurides yields tellurium ylides **221**, which react with aldehydes to give alkenes.[141]



221 **220** (84%–99%)

R = Alk, Ar, Het.

A method for the synthesis of α,β-unsaturated esters, *e.g.*, the furan derivative **222**, has been developed where the telluride is coupled to polyethylene glycol (**223**).[142, 143] The tellurium derivative was used in catalytic amounts (2 mol.%), and equimolar amounts of triphenyl phosphite are required for the reduction of tellurium oxide formed. The yields of the target alkenes are usually close to quantitative; the stereoselectivity of the reaction is extremely high.



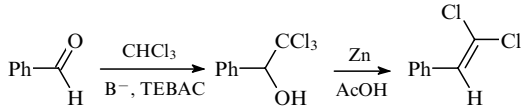
222 (96%, *E* : *Z* = 99 : 1)

PEG is polyethylene glycol.

5. Reagents based on Group VIIA elements

Addition of anions generated from tri-, di- and monohalomethanes to aldehydes and ketones $R^1R^2C{=}O$ and subsequent reduction of β-halogeno alcohols yields *gem*-dihaloalkenes $R^1R^2C{=}CHal_2$, vinyl halides $R^1R^2C{=}CHHal$ or terminal alkenes $R^1R^2C{=}CH_2$. This group of olefination methods was developed relatively recently, but nevertheless has rather a broad range of synthetic applications.

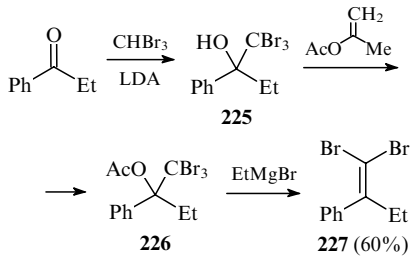
Reduction of aryltrichloromethylmethanols of the type **224** or their acetates,[144] with zinc in acetic acid (2–4 equiv.) or electrochemically is a convenient route to the synthesis of dichloroalkenes.[145] The corresponding alcohols are prepared by condensation of aldehydes with chloroform in the presence of phase-transfer catalysts [8, 145] or by a reaction of aldehydes with the trichloromethyl anion generated from trichloroacetic acid.[146]



224 (87%)

TEBAC is triethylbenzylammonium chloride.

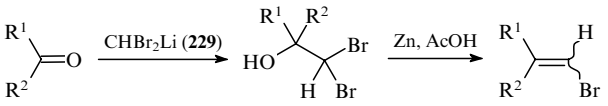
gem-Bromochloroalkenes and *gem*-dibromoalkenes can be prepared by a similar procedure using dibromochloromethane and bromoform, respectively.[147] Thus the addition of the tribromomethyl anion to ethyl phenyl ketone results in tribromomethylpropanol **225**. Subsequent acylation of the hydroxy group and reduction of the resulting ester **226** with Grignard reagent yield the dibromoalkene **227**. Other alkyl aryl and dialkyl ketones are also used as the carbonyl substrates.[147]



225 **226** **227** (60%)

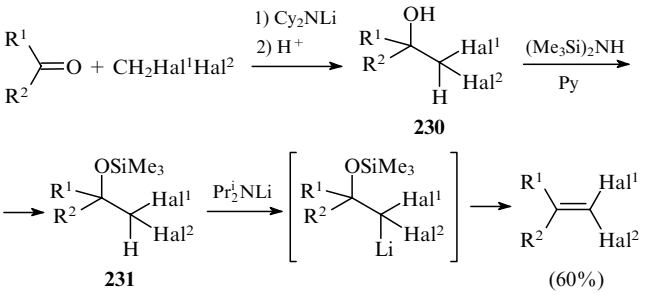
Bromoalkenes **228** can be obtained from carbonyl compounds by treatment with dibromomethyllithium **229** generated *in situ* from dibromomethane and lithium dicyclohexylamide.[148] This reaction is applicable to a vast variety of aromatic and aliphatic aldehydes and ketones including α,β-unsaturated aldehydes and

ketones, which afford the corresponding bromo-substituted dienes. However, the stereoselectivity of the formation of bromoalkenes is usually low.



R^1, R^2 = Alk, Ar.

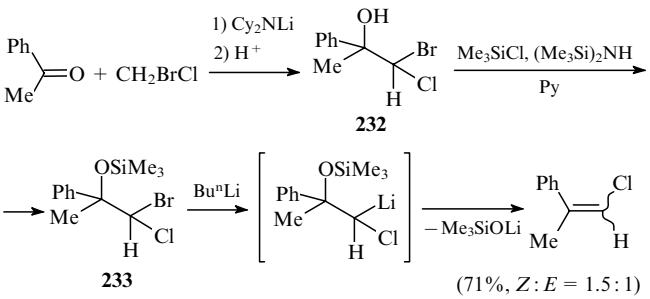
The reactions of carbonyl compounds with dihalomethanes (CH_2Cl_2, CH_2Br_2, CH_2BrCl) in the presence of lithium dicyclohexylamide and subsequent acidification of the reaction mixture yield the corresponding β,β-dihalo-substituted alcohols **230**; treatment of the latter with chlorotrimethylsilane in the presence of hexamethyldisilazane and pyridine gives the silylated derivatives **231**.[149] This reaction occurs with good yields and can be applied to both aliphatic and aromatic carbonyl substrates.



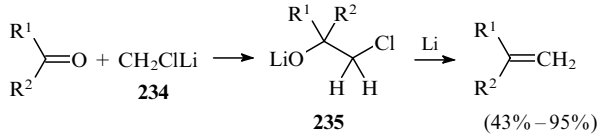
R^1 = H, Me, Et; R^2 = Et, C_7H_{15}, Ph; R^1–R^2 = $(CH_2)_3$, $(CH_2)_5$; Hal^1, Hal^2 = Cl, Br.

Subsequent treatment of compounds **231** with lithium diisopropylamide yields dihaloalkenes through C-deprotonation and β-elimination of silanol.

Silylation of an intermediate **232** derived from bromochloromethane and subsequent treatment of the silyl derivative **233** with n-butyllithium results in the chemoselective exchange bromine–lithium; elimination of silanol yields monohaloalkenes. However, the stereoselectivity of the synthesis of vinylic halides is very low: the isomer ratio is close to equimolar.



The use of chloromethyllithium **234** generated from chloroiodomethane as the olefinating agent in reactions with ketones results in terminal alkenes.[150] This reaction occurs *via* the intermediate **235**; subsequent reduction of the latter with lithium yields the target products.

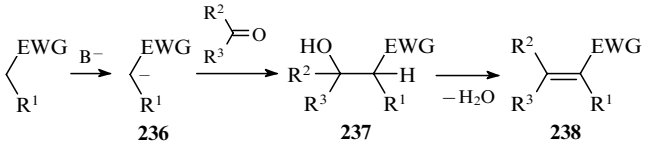


R^1, R^2 = Alk, Ar.

Thus condensation of polyhalomethyl anions with carbonyl compounds followed by acylation or silylation of intermediate alcohols and their subsequent reduction or elimination yield terminal alkenes or vinylic halides. However, the multistep character of this method is its disadvantage.

III. Condensation of carbonyl compounds with CH-acids

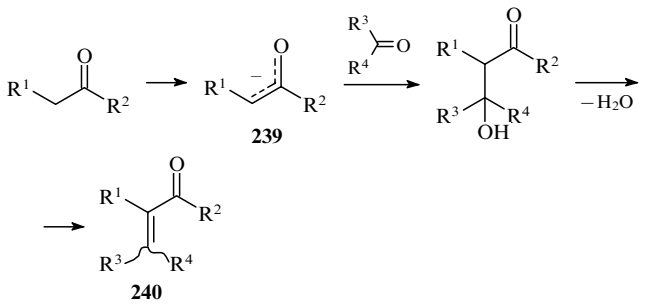
Compounds containing one or several electron-withdrawing groups at one carbon atom (CH-acids) are deprotonated in the presence of bases; the carbanions **236** formed add to the electrophilic carbon atom of the carbonyl group to give the alcohols **237**. If a CH-acid contains more than one hydrogen atom in the α-position relative to the electron-withdrawing group, the condensation products undergo dehydration resulting in the formation of alkenes **238** containing electron-withdrawing substituents. The presence of electron-withdrawing groups favours elimination according to the E1cb mechanism.



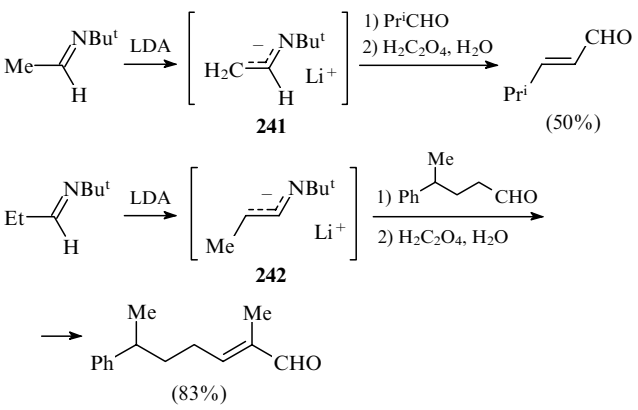
Many of the reactions described in this chapter were discovered as early as the 19th century; however, this branch of organic chemistry is still developing and novel modifications of the known reactions, reagents and catalysts continue to appear. A method for the synthesis of alkenes using carbanions stabilised by an electron-deficient aromatic system has been developed recently. Reactions of carbanions, which differ in the nature of substituents at the CH-acidic centre, are used in organic synthesis; these will be described in the chapters that follow.

1. Aldol condensation and its modifications

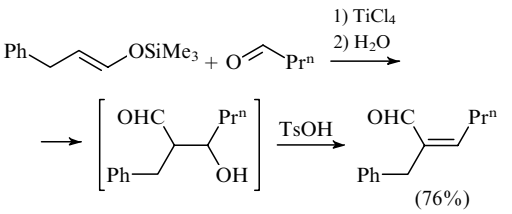
Reactions of enolate anions **239** generated from aldehydes and ketones with carbonyl compounds yield enals or enones **240**.[1,2] In these reactions, aldehydes and ketones play the role of both nucleophiles (the methylene component) and electrophiles (the carbonyl component). This allows both self-condensation and cross-coupling. Both bases and acids can be used as catalysts.



At present, direct chemo- and regioselective aldol condensation is based on the use of specially prepared metal enolates as well as of enol silyl ethers [151] and azaenolates.[152–154] Methods for the synthesis of enols and enolates as well as asymmetric syntheses based on them are documented in numerous reviews and monographs.[2,155–166] Thus conversion of one of the carbonyl compounds into an imine or a dimethylhydrazone by treatment with a primary amine or 1,1-dimethylhydrazine is a convenient procedure for modification of the aldol condensation.[2,152–154] Subsequent deprotonation of imines by non-nucleophilic bases yields azaenolates **241** and **242**, which act as the olefinating agents in the reaction with aldehydes and ketones.[3] The β-hydroxyimines formed are converted into α,β-unsaturated carbonyl compounds upon acid treatment. The condensation occurs stereospecifically and gives usually *trans*-isomers of alkenes.

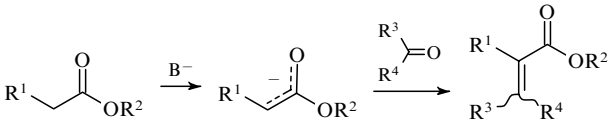


Preliminary conversion of a carbonyl compound, which plays the role of a nucleophilic component, into an enol silyl ether is yet another method for selective aldol cross-coupling.[151] In the case of non-symmetrical carbonyl compounds, enol ethers can be prepared regioselectively. Under conditions of kinetic control, a less substituted enol is formed predominantly, whereas under conditions of thermodynamic control a more stable substituted enol is the main product. Further reactions of enol silyl ethers with carbonyl compounds in the presence of Lewis acids yield β-hydroxy ketones or α,β-unsaturated ketones.[151]



2. Condensation of aldehydes and ketones with esters

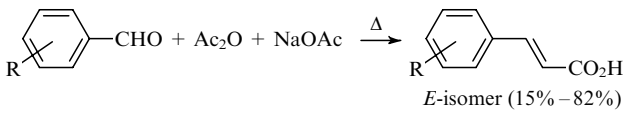
Esters $R^1CH_2COOR^2$ are used as nucleophilic components in condensations with carbonyl compounds, which yield α,β-unsaturated acids or esters.



Esters usually require stronger bases for the generation of enolates than in the aldol condensation due to lower CH-acidity of hydrogen atoms in the α-position. This method is of a rather historical significance; the range of its application is fairly narrow due to drastic reaction conditions.[3] Modern approaches are based on the use of stronger bases of the LDA type, which allows complete deprotonation of the ester.

3. The Perkin reaction

Condensation of aromatic aldehydes and ketones with carboxylic anhydrides or their analogues is referred to as the Perkin reaction.[3,25] This reaction requires heating, sometimes rather significantly (up to 200–250 °C), of the reaction mixture. If an anhydride contains more than one α-hydrogen atom, dehydration takes place; the intermediate salt of β-hydroxy acid is never isolated. The role of a base in the Perkin reaction is always played by a sodium or potassium salt of the acid corresponding to the anhydride introduced into the reaction; however, in some versions, ammonia, triethylamine and some other amines are used. Aromatic aldehydes and their vinylogues ArCH=CHCHO are used as the carbonyl components. The Perkin reaction is a convenient procedure for the synthesis of substituted cinnamic acids from accessible aromatic aldehydes, the predominant formation of *E*-isomers is observed. However, at present this reaction has a rather historical significance, since it requires drastic conditions and often the yields of target products are low.

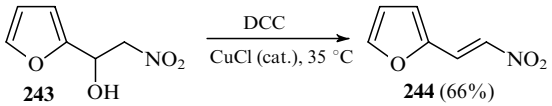


R = OH, OAlk, Hal, NO_2.

4. The Henry reaction

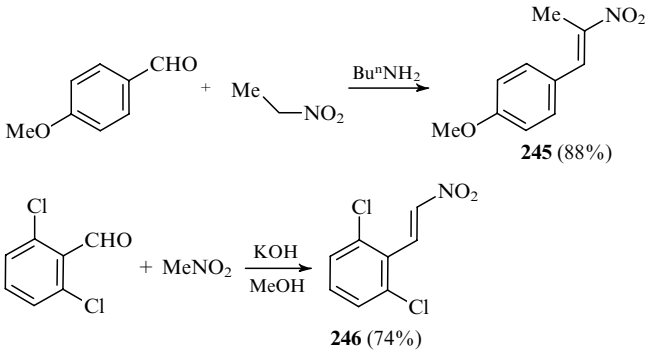
Condensation of carbonyl compounds with nitro derivatives is called the Henry reaction or the nitroaldol reaction.[2] It represents the most convenient method for the synthesis of nitro alcohols and nitro alkenes.[26–29,167] The nitroaldol reaction employs weak bases, since aliphatic nitro compounds are characterised by high CH-acidity. Amines, alkalis, carbonates and alkali metal alkoxides are usually employed as catalysts.

The reaction is often stopped at the step of a nitro alcohol; subsequent dehydration is carried out with dehydrating agents, such as dicyclohexylcarbodiimide, pivaloyl chloride, phthalic anhydride or methanesulfonyl chloride.[27] Thus the dehydration of the β-nitro alcohol **243** with dicyclohexylcarbodiimide in the presence of catalytic amounts of CuCl yields the nitro alkene **244**.[168]

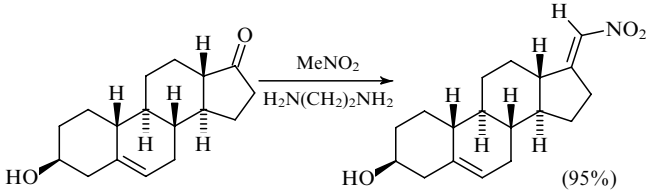


DCC is dicyclohexylcarbodiimide.

Aromatic aldehydes are directly converted into nitro alkenes **245** and **246** due to a considerable energy gain upon formation of the double bond conjugated to an aromatic system. The synthesis of alkenes **245** and **246** occurs in a stereoselective manner.[3]



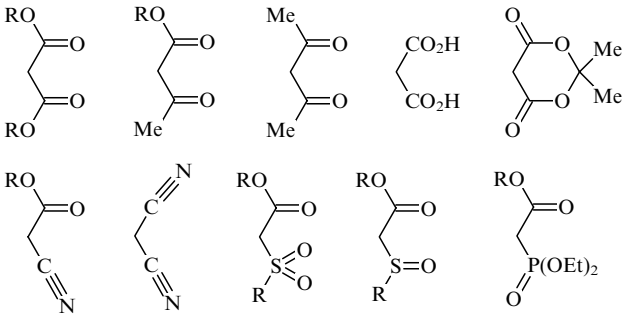
The olefination of ketones with nitromethane in the presence of ethylenediamine also results in unsaturated compounds.[27]



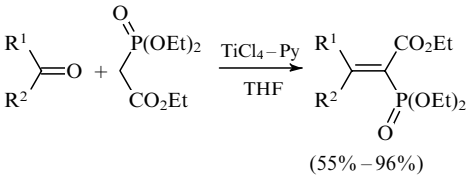
5. The Knoevenagel reaction

Reactions of aldehydes and ketones with compounds of the type $(EWG)_2CH_2$, which contain a reactive methylene group (1,3-diketones, 1,3-keto esters, malonates, ethyl cyanoacetate, malononitrile, *etc.*), are usually referred to as the Knoevenagel reaction,[3] although this definition is not quite correct.

In addition to 1,3-dicarbonyl compounds,[169,170] the Knoevenagel reaction widely employs alkyl cyanoacetates,[171] sulfonyl[172] and sulfinyl acetates,[173] as well as phosphonoacetates.[174]



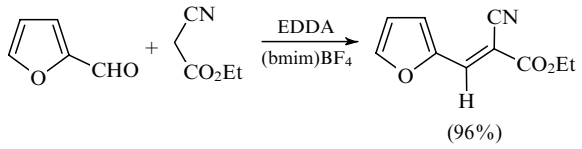
The generation of enolates from compounds containing two electron-withdrawing groups allows the use of weaker bases than the traditional aldol condensation, *viz*., amines, acetates as well as a mixture of $TiCl_4$ and pyridine.[174]



(55%–96%)

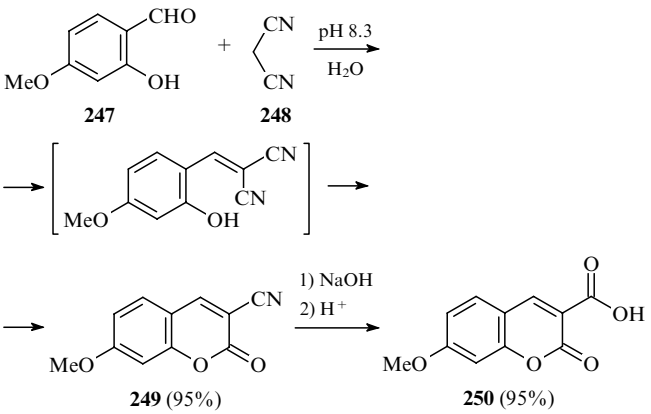
R^1, R^2 = Alk, Ar.

In one of the most recent modifications of the Knoevenagel reaction, ionic liquids are used as solvents. Thus condensation of diverse aromatic and aliphatic carbonyl compounds with ethyl cyanoacetate, acetylacetone and ethyl acetoacetate in 1-butyl-3-methylimidazolium tetrafluoroborate [(bmim)BF_4] was studied in the presence of ethylene diammonium diacetate (EDDA) as the catalyst.[173] This reaction is stereospecific and gives *E*-isomers of alkenes; in most cases, the yields of reaction products are virtually quantitative.



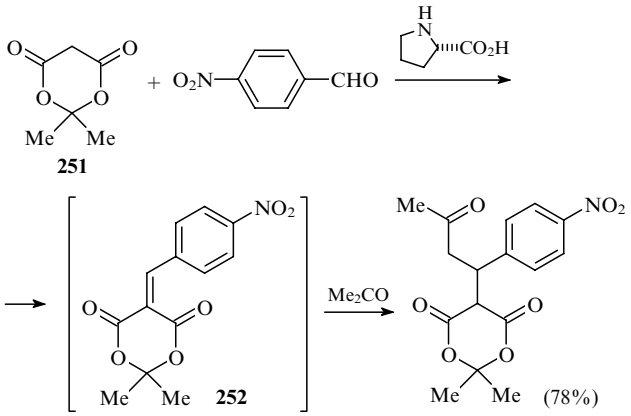
(96%)

The condensation of salicylic aldehydes with Meldrum's acid or malonic acid is widely used in the synthesis of substituted coumarin-3-carboxylic acids.[3] Its most recent version consists of a reaction of salicylic aldehydes of the type **247** with malononitrile **248** under heterogeneous conditions in the presence of an aqueous alkali or sodium hydrogen carbonate.[175] This results in substituted 3-cyanocoumarin **249**; its subsequent alkaline hydrolysis gives the coumarin-3-carboxylic acid derivative **250**. Both reaction steps occur in high yields.

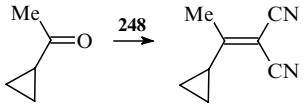


249 (95%) **250** (95%)

A three-component reaction representing the proline-catalysed condensation of aldehydes with Meldrum's acid **251** and subsequent Michael addition of ketone enolates to the adduct **252** formed, has been developed.[176] In this reaction, two C–C bonds are formed.

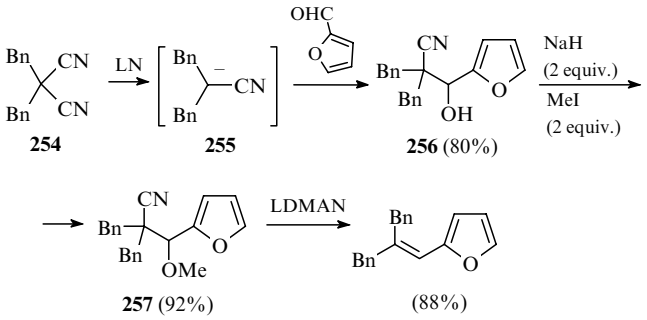


The use of malononitrile **248** in organic synthesis has been surveyed;[177–179] its condensation with carbonyl compounds is widely used in the synthesis of alkylidene- and arylidenemalononitriles. In particular, cyclopropyl-substituted dinitrile **253** was prepared in this manner.



253 (81%)

And finally, special mention should be made of an original olefination procedure based on reductive addition, to the carbonyl group, of *gem*-dinitrile **254**, which is prepared by bisalkylation of malononitrile.[180] Reduction of *gem*-dinitrile **254** with lithium naphthalenide leads to the loss of one cyano group.The carbanion formed **255**, which is stabilised by the residual cyano group, is an effective nucleophile which reacts with a broad range of electrophiles including carbonyl compounds. The intermediate β-hydroxy nitrile **256** is further *O*-alkylated. Reductive elimination of the vicinal alkoxy- and cyano fragments by treatment of compound **257** with lithium 1-(dimethylamino)naphthalenide yields the corresponding alkene. This reaction results in the loss of both cyano groups. It is noteworthy that the possibility of synthesising tetrasubstituted alkenes from ketones is a significant advantage of this method.



254 **255** **256** (80%)

257 (92%) (88%)

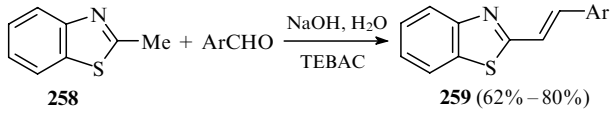
LN is lithium naphthalenide;
LDMAN is lithium 1-(dimethylamino)naphthalenide.

6. Condensation of carbonyl compounds with other CH-acids

Carbanions stabilised by an electron-deficient aromatic system can be used as olefinating agents.[2, 6, 181] Condensation of the corresponding CH-acids with aromatic aldehydes in the presence of bases is used for the preparation of non-symmetrical stilbenes or their heterocyclic analogues.[6] Pyridine, piperidine, alkali metal alkoxides and, less frequently, alkalis are commonly used as the bases.

Thus the reaction of aromatic aldehydes with 2-methylbenzothiazole **258** in the presence of aqueous alkali and a phase-transfer

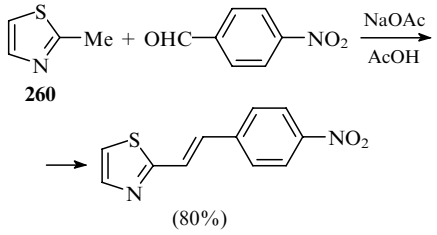
catalyst yields olefination products, *viz*., 2-styrylbenzothiazoles **259**.[181]



258 **259** (62% – 80%)

Ar = Ph, 2-ClC_6H_4, 4-ClC_6H_4, 4-MeC_6H_4, 4-$MeOC_6H_4$.

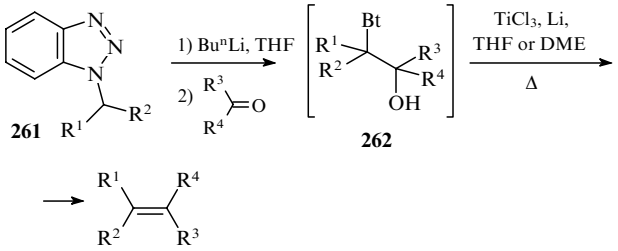
Synthesis of styrylthiazole is carried out in acetic acid in the presence of sodium acetate.[182] Protonation of the nitrogen atom of the heterocyclic base **260** increases the CH-acidity of the methyl group and favours its reaction with benzaldehydes. Lewis acids ($ZnCl_2$) and protic acids (HCl, H_3BO_3) can be used as catalysts.



260

(80%)

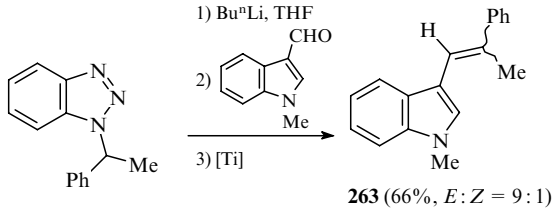
Katritzky *et al*.[80, 183, 184] have proposed the use of *N*-alkylbenzotriazole anions **261** in the condensation of carbonyl compounds for the synthesis of allyl- and benzyl-substituted alkenes. The alcohols **262** formed containing a benzotriazole system are reduced to alkenes upon treatment with low-valence titanium derivatives; the heterocyclic system is thereby eliminated.



261 **262**

Bt is benzotriazol-1-yl.

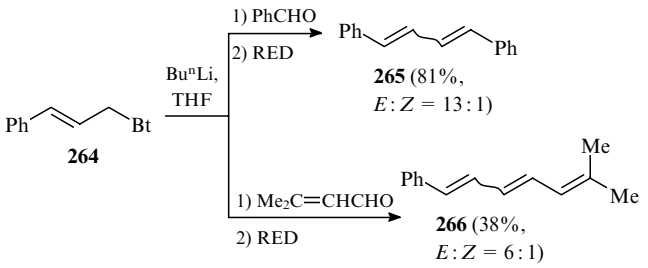
The olefination proceeds in good yields (53% – 81%) and high *E*-stereoselectivity not only in the case of 1,2-disubstituted, but also tri- and tetrasubstituted alkenes. Thus stereoselectivity of the formation of the trisubstituted alkene **263**, which represents a heterocyclic analogue of stilbene, was fairly good.



263 (66%, $E:Z = 9:1$)

Aliphatic and aromatic aldehydes and ketones as well as α,β-unsaturated carbonyl compounds were used as the carbonyl substrates. Unfortunately, the range of olefinating agents is limited to *N*-allyl- and *N*-benzylbenzotriazole derivatives.

This approach is used in the stereoselective synthesis of some conjugated dienes and trienes.[183, 184] Thus the reagent **264** was used to yield conjugated diene **265** and triene **266**:



264

IV. Reagents based on transition and non-transition metals

A great diversity of methods for the olefination of carbonyl compounds is known which make use of reagents based on metals, in the first place, transition metals.[1, 3] In these reactions, metal compounds usually play the role of reducing agents. Reagents based on titanium, zinc and chromium are especially popular.

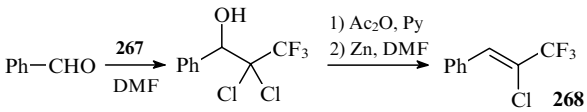
1. Reagents based on Group IIB metals

a. Zinc-based reagents

Reductive coupling of polyhaloalkanes with carbonyl compounds in the presence of zinc was used in the synthesis of various halogen-substituted alkenes.[185 – 187] It was shown that treatment of zinc with 1,1,1-trichloro-2,2,2-trifluoroethane gives a stable organozinc reagent **267**, its addition to aromatic and aliphatic aldehydes yields the corresponding alcohols. The latter can be reduced to trifluoromethyl-substituted alkenes by excess zinc. In the case of benzaldehyde, the yield of the reaction product **268** (over three steps) was 84%.[186, 187]

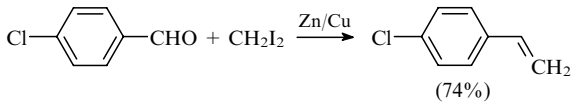


267



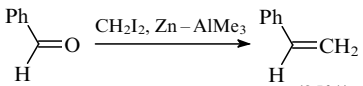
268

Diiodomethane was used as a methylenating agent in the synthesis of terminal alkenes from aromatic aldehydes in the presence of a zinc – copper couple.[188]

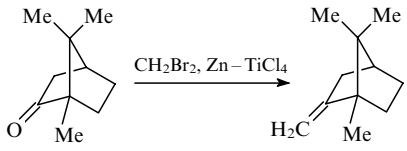


(74%)

The Oshima – Lombardo reaction includes methylenation of carbonyl compounds by dihalomethanes (CH_2I_2, CH_2Br_2) catalysed by $Zn-TiCl_4$ or $Zn-AlMe_3$ systems.[1, 189] A *gem*-organodizinc compound of the type $HalZnCH_2ZnHal$ (**269**, Hal = I, Br) is used as the olefinating agent.

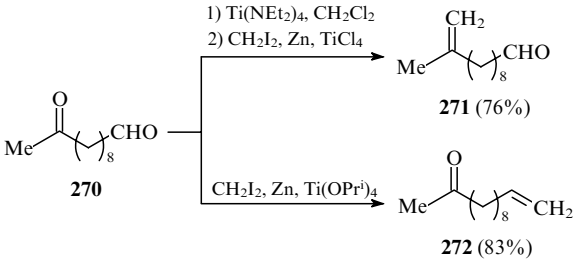


(85%)



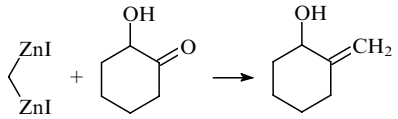
(92%)

It should be noted that the presence of ester or lactone fragments does not prevent methylenation of carbonyl groups.[190] Selective methylenation of the aldehyde group in the presence of the keto group and *vice versa* is a salient advantage of the Oshima – Lombardo reaction.[191] Thus the methylenation of a keto group, which does not affect an aldehyde group, can be performed following treatment of the substrate with tetrakis(diethylamino)titanium (this results in selective protection of the aldehyde group due to complex formation). The chemoselective methylenation of an aldehyde in the presence of a ketone is carried out using titanium isopropoxide or trimethylaluminium. This approach was demonstrated in a spectacular way in the selective methylenation of either keto or aldehyde groups of the keto aldehyde **270** to give isomeric oxo alkenes **271** and **272**, respectively.



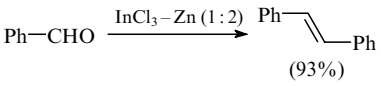
270 **271** (76%) **272** (83%)

The *gem*-organodizinc reagent **269** (Hal = I) was used in the synthesis of substituted allylic alcohols and amines from α-hydroxy and α-amino ketones.[192] Presumably, in this case coordination of the heteroatom to zinc takes place, which favours the methylenation reaction. The methylenation of substrates containing no such substituents in the α-position requires the presence of titanium salts.



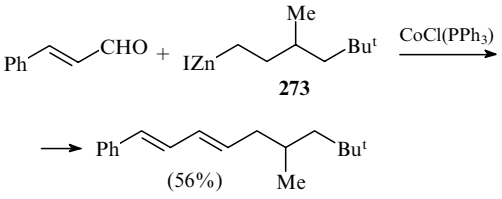
269 (90%)

Reductive coupling of carbonyl compounds in the presence of the system $InCl_3$ – Zn yields symmetrical alkenes; this reaction occurs stereospecifically and yields *E*-isomers.[193] Aromatic and aliphatic aldehydes and ketones are used as substrates. This process is similar to the McMurry reaction (see Section IV.3.a).



(93%)

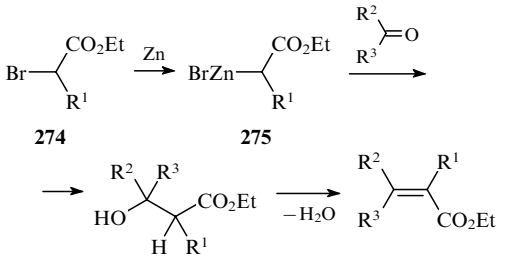
The organozinc compound **73** was used in the stereoselective olefination of aromatic and unsaturated aldehydes. In the presence of a cobalt(I) complex, the reaction occurs under mild conditions and yields *E*-isomers of alkenes.[194]



273

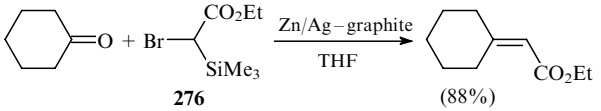
(56%)

The Reformatsky reaction represents the reaction of carbonyl compounds with α-halo-substituted esters **274** or their vinilogues $RCHHalCH=CHCO_2Et$ in the presence of zinc.[195] Its first step includes insertion of zinc into the C—Hal bond and formation of the organozinc intermediate **275** (the Reformatsky reagent), which represents zinc enolate. The intermediate organozinc compound is not isolated. β-Hydroxy esters are usually formed from aliphatic carbonyl compounds, which can easily be dehydrated into α,β-unsaturated esters. In the case of aromatic aldehydes and ketones, dehydration usually takes place directly in the reaction mixture.



274 **275**

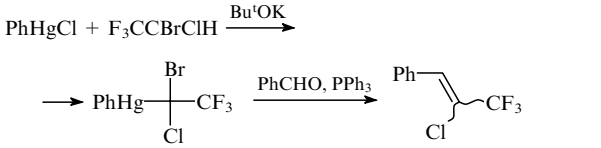
A mixed-type version of the Reformatsky and Peterson reactions based on the use of (halogeno)trimethylsilylacetate **276** is known.[196] The use of this reagent allows direct preparation of alkenes avoiding β-hydroxy derivatives.



276 (88%)

b. Mercury-based reagents

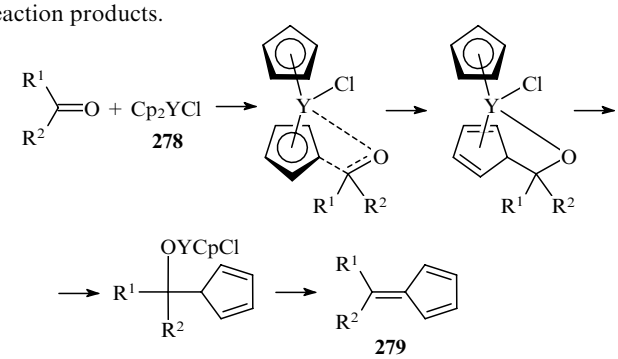
A multistep synthesis of trifluoromethyl-substituted alkenes **268** using organomercurials as CF_3-group sources has been developed.[197] The organomercuric compound **277** prepared by treatment of phenylmercury chloride with halothane $CF_3CBrClH$ in the presence of potassium *tert*-butoxide served as the olefinating agent. Treatment of benzaldehyde with the reagent **277** in the presence of triphenylphosphine yields a mixture of *E*- and *Z*-isomers of the trifluoromethyl-substituted alkene **268** in an equimolar ratio. Low yields and high toxicities of the mercury compounds make this method inconvenient for application in synthetic practice.



277 **268** (38%, $E:Z = 1:1$)

2. Reagents based on Group IIIB metals

The use of dicyclopentadienylyttrium chloride **278** as the olefinating agent yields fulvenes **279**.[198] Thus the reagent **278** acts as a synthetic equivalent of the cyclopentadienyl anion. The first step includes coordination of yttrium to the oxygen atom of the carbonyl group. Subsequent addition of cyclopentadienyl to the carbon atom and elimination of yttrium oxide give fulvenes **279**. Both aldehydes and ketones give high yields (57% – 96%) of reaction products.



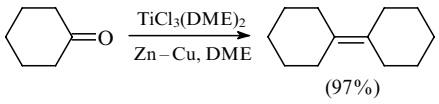
278 **279**

Cp is cyclopentadienyl.

3. Reagents based on Group IVB metals

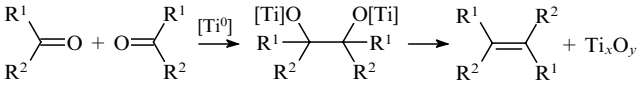
a. The McMurry reaction

The McMurry reaction is the olefination of carbonyl compounds in the presence of low-valence titanium derivatives yielding various alkenes.[1] The formation of very strong Ti—O bonds is the driving force of this reaction. This reaction consists of reductive dimerisation of carbonyl compounds and gives symmetrical alkenes. The mechanism of the McMurry reaction and its synthetic applications have become the subject of intense studies which have been reviewed.[30–35] Both aldehydes and ketones are employed. Dimerisation of aromatic aldehydes is used for the synthesis of substituted stilbenes.[6]



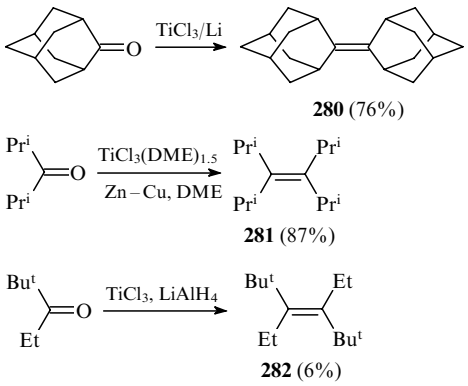
DME is 1,2-dimethoxyethane.

Various titanium derivatives playing the role of reducing agents can be prepared by *in situ* reduction of $TiCl_4$ or $TiCl_3$ with zinc, a zinc–copper alloy, lithium aluminium hydride and alkali metals. It is believed that zero-valent titanium is formed under these conditions. The first step of the McMurry reaction actually represents pinacol condensation; however, the *vic*-diols formed undergo further reduction to alkenes.

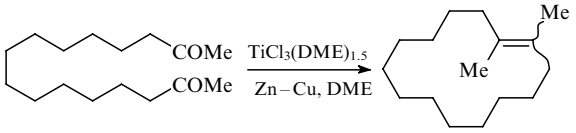


Functional groups, such as nitrile, amide, ester, *p*-toluenesulfonyl, *etc*., are not affected under the conditions of the McMurry reaction.[30] An epoxide or a *vic*-diol fragment present in the substrate is reduced to the alkene. Nitro groups, oximes and sulfoxides do not withstand the reaction conditions and are reduced.[30]

Reductive dimerisation according to McMurry was used for the preparation of a series of crowded alkenes containing bulky substituents, *e.g.,* adamantylideneadamantane (**280**),[30] tetraisopropylethylene (**281**)[199] and even di-*tert*-butyldiethylethylene (**282**).[200] Unfortunately, tetra-*tert*-butylethylene could not be prepared by this method.[30]

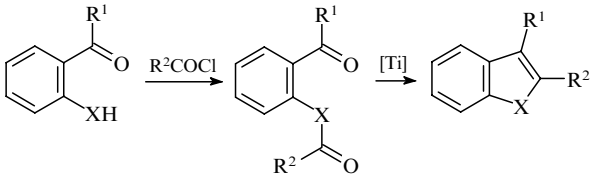


Reductive dimerisation of dicarbonyl compounds is a convenient method for the synthesis of cyclic alkenes with ring size varying from 3 to 36.[201] The synthesis of medium and large rings from dicarbonyl derivatives is carried out under high dilution; the ring closure proceeds in high yields and is highly stereoselective. Medium and large rings are usually formed with *E* configuration of the double bond.[199] Thus the endocyclic alkene **283** was prepared by the McMurry reaction.



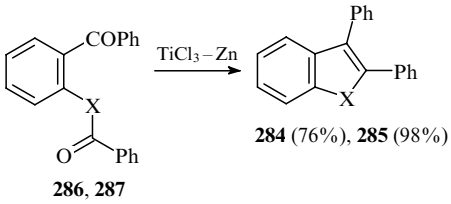
283 (82%, $E:Z = 92:8$)

It is unreasonable to prepare non-symmetrical alkenes by the McMurry reaction, since dimerisation of two carbonyl compounds gives all three possible alkenes. However, intramolecular coupling of substrates containing non-equivalent carbonyl groups represents a smooth access to non-symmetrical cycloalkenes. Thus the cyclisation of *o*-acylamino- or acyloxy-substituted benzophenones yields various indole and benzofuran derivatives.[202]



X = O, NH, NAlk; R^1 = Alk, Ar; R^2 = H, Alk, Ar, OAlk, $NAlk_2$.

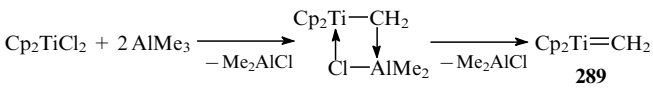
The use of the McMurry reaction in the synthesis of substituted furans **284** and indoles **285** from compounds **286** and **287** has been described by Furstner *et al*.[203, 204]

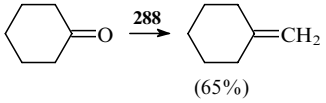


X = O (**284**, **286**); NH (**285**, **287**).

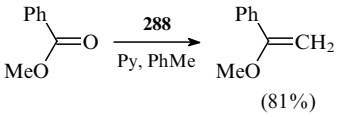
b. The Tebbe reaction

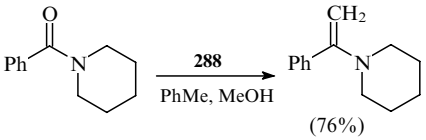
In 1978, Tebbe *et al*.[205] proposed to use metallacyclobutane **288** as a C_1-synthon, which became a popular reagent for olefination of carbonyl compounds. The Tebbe reagent is prepared *in situ* by the addition of commercially available titanocene dichloride to trimethylaluminium in toluene.[206] Under olefination conditions, the reagent **288** is converted into a highly reactive methylene-titanocene complex **289**. Donor ligands (*e.g*., THF or pyridine) are beneficial for the reaction, they favour elimination of the Lewis acid (Me_2AlCl) from the ring.[207]





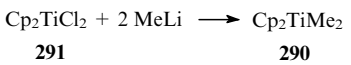
Carboxylic acid derivatives, *viz*., esters[208] and amides,[209] can be used as carbonyl components along with aldehydes and ketones. Thus, vinyl ethers and enamines can be obtained by the Tebbe reaction.

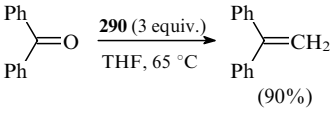


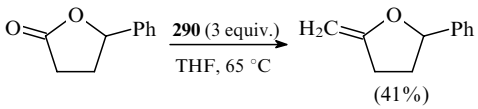


c. Dialkyltitanocenes

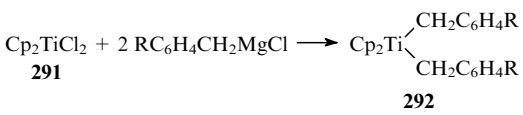
In 1990, Petasis and Bzowej[210] developed a new methylenating agent, *viz*., dimethyltitanocene Cp_2TiMe_2 (**290**), as an alternative to the Tebbe reagent. The advantages of this reagent include its stability and availability; besides, it does not contain aluminium. The Petasis reagent is prepared by mixing titanocene dichloride **291** with methyllithium. The area of its synthetic applications practically coincides with that of the Tebbe reagent.[211]





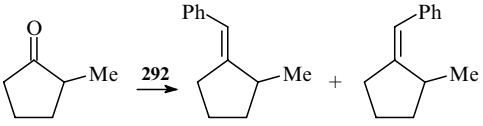


Several more olefinating agents have been developed based on titanocene dichloride **291**.[212,213] Thus the reactions of complex **291** with substituted benzylmagnesium chlorides yield dibenzyltitanocenes **292**.



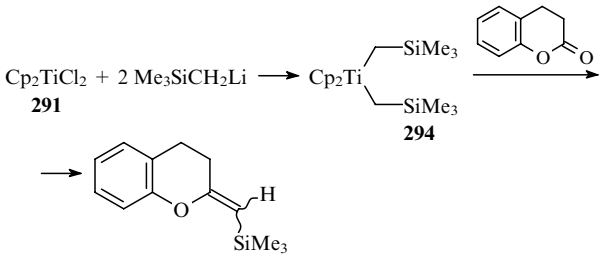
R = H, F, Cl, OMe.

The reactions of carbonyl compounds with the reagent **292** (R = H) yield aryl-substituted alkenes **293**.[212] Low stereoselectivity of this reaction is its main disadvantage.



293 (75%, $E:Z$ = 1 : 1)

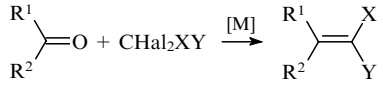
The reactions of a silicon-containing reagent **294** prepared from titanocene dichloride **291** with carbonyl compounds and carboxylic acid derivatives yield vinylsilanes **295**.[213,214]



295 (83%, $Z:E$ = 2.5 : 1)

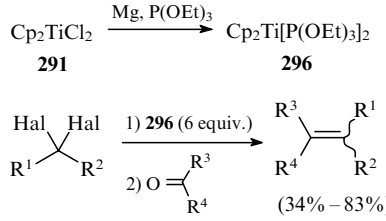
d. Miscellaneous titanium-based reagents

Reductive coupling of polyhalogeno compounds $CHal_2XY$ (Hal, X, Y = Cl, Br) with aldehydes and ketones is widely used in the synthesis of various substituted alkenes.



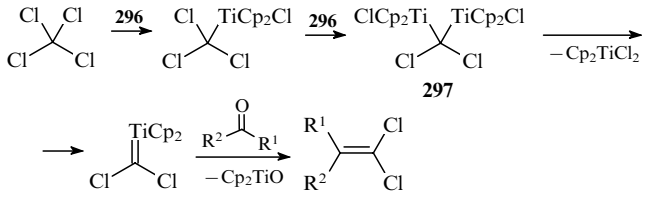
[M] is a reducing metal derivative in lower oxidation states.

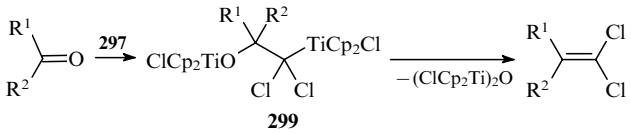
Thus the olefination of aromatic and aliphatic aldehydes and ketones by *gem*-dihalo compounds has been described.[215–217] The titanium derivative **296** prepared *in situ* by reduction of titanocene dichloride **291** with magnesium in the presence of triethyl phosphite was used as the reducing agent.



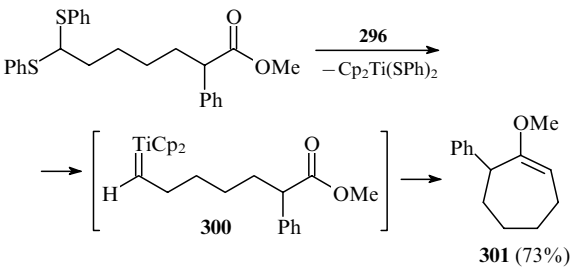
R^1, R^2 = H, Alk, Hal; Hal = Cl, Br; R^3 = Alk; R^4 = H, Alk, OAlk.

Aliphatic and aromatic aldehydes and ketones as well as esters and lactones can be used as carbonyl components. This is an undisputable advantage of the reaction, since it allows one to synthesise acyclic and cyclic vinyl ethers with different types of substitution at the double bond. Dichloro- and dibromoalkanes as well as chloroform and carbon tetrachloride are used as polyhaloalkane components. As a rule, the reaction proceeds stereoselectively and results in the predominant formation of a less sterically hindered alkene isomer. The reaction mechanism includes consecutive insertion of two molecules of the titanium derivative **296** into the C–Hal bond of the polyhaloalkane resulting in the intermediate **297**. Elimination of the Cp_2TiCl_2 molecule affords the titanium-carbene complex **298** which reacts with the carbonyl compound to give a dichloroalkene. The synthesis of dichloroalkenes can proceed in a different route, namely, *via* intermediate complexes of the type **299** prepared by addition of the organotitanium compound **297** to the carbonyl group. The necessity of using six equivalents of the reducing agent (compound **296**) is a serious disadvantage of this method.



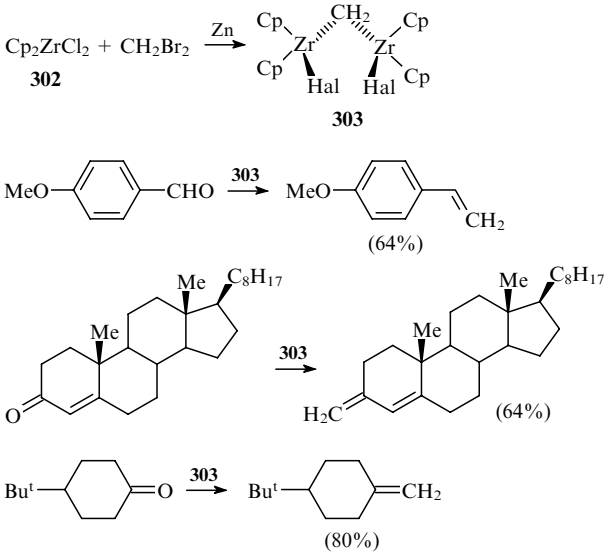


The use of the system dithioacetal – $Cp_2Ti[P(OEt)_3]_2$ (**296**) for olefination allows the transformation of carbonyl compounds into alkenes.[218,219] As in the case of polyhaloalkanes, the titanium-carbene complex is the key intermediate in this reaction. Intramolecular cyclisation of the titanium-carbene complex **300**, which contains simultaneously a dithioacetal fragment and an ester group, resulting in the cyclic vinyl ether **301**, is an example of such a reaction.[218]

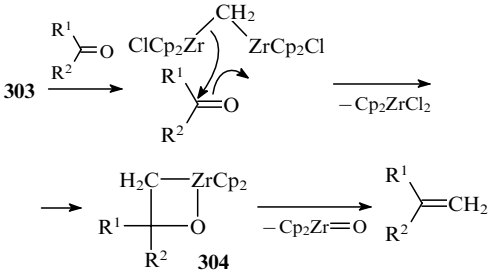


d. Zirconium-based reagents

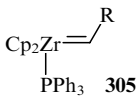
The reaction of zirconocene dichloride **302** with dibromomethane in the presence of zinc yields a methylene-zirconium complex **303**, which was used as a methylenating agent in the synthesis of terminal alkenes.[220] Aliphatic, aromatic and α,β-unsaturated aldehydes and ketones were used as the carbonyl components.



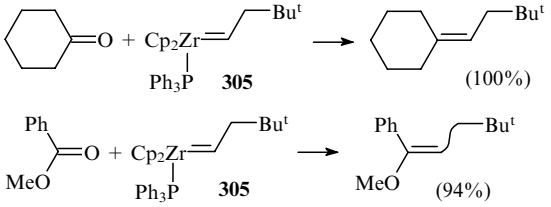
The hypothetical mechanism of this reaction includes coordination of the zirconium atom to the carbonyl oxygen atom and an attack of the nucleophilic carbon atom on the carbon atom of the carbonyl group. This reaction yields metallaoxacyclobutane **304**; subsequent rapid elimination of zirconocene oxide gives the target alkenes.[220]



Alkylidenezirconium complexes **305** were used as olefinating agents for the introduction of longer-chain carbon fragments.[221,222] In contrast to the methylene complex **303**, these can be used in the synthesis of alkenes not only from ketones, but also from esters, lactones [222] and imidates.[223]

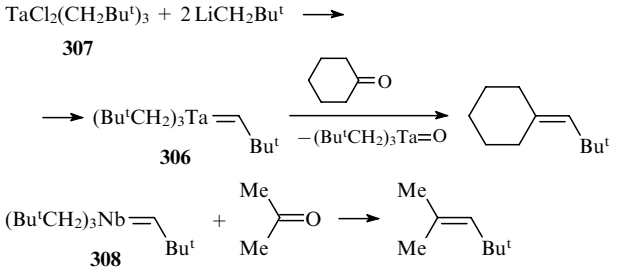


R = Bu^n, Bu^s, CH_2Bu^t, cyclo-C_5H_{11}.



4. Reagents based on Group VB metals

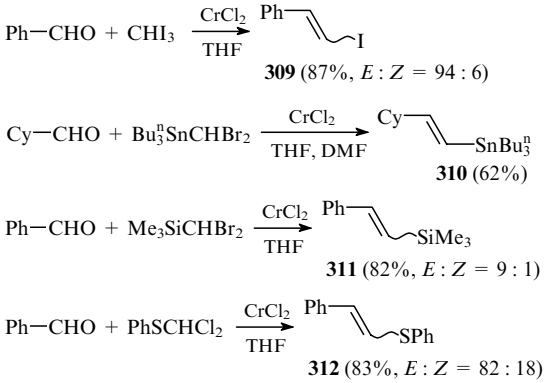
Alkylidene complexes of nyobium and tantalum (the Schrock carbenes) manifest nucleophilic properties.[223,224] It was shown that the neopentylidenetantalum complex **306** formed upon reduction of compound **307** with neopentyllithium can be used for the introduction of the neopentylidene group into a broad range of carbonyl compounds.[225] Aldehydes, ketones, amides and esters were used as the carbonyl components of this reaction. The yields of alkenes varied from 35% to 90%. The neopentylideneniobium complex **308** manifests similar reactivity.



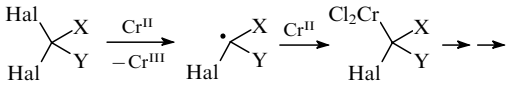
5. Reagents based on Group VIB metals

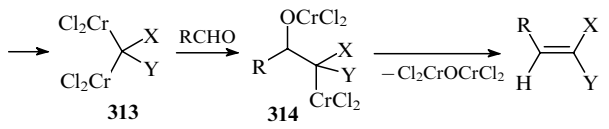
a. Chromium-based reagents

Reductive coupling of *gem*-dihalo compounds $CHal_2XY$ with aldehydes in the presence of chromium(II) chloride as the reducing agent is widely used in the synthesis of various alkenes.[1] It was found that reactions of such dihaloalkanes with aldehydes are stereoselective and give predominantly *E*-isomers of alkenes. Various substituted dihaloalkanes including those containing heteroatoms can be used as the olefinating components. This yields vinyl halides **309**,[226] vinylstannanes **310**,[227] vinylsilanes **311** and vinyl sulfides **312**.[228]



The mechanism of this reaction consists of substitution of chromium for two halogen atoms resulting in *gem*-organodichromium compounds **313**, which further add to the aldehyde. Subsequent elimination of a chromium(III) salt from the intermediate **314** yields alkenes.[1,226,229]





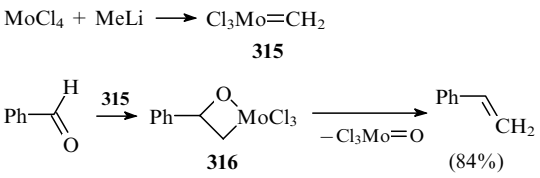
313 314

Hal = Cl, Br, I; X, Y = H, Alk, Hal, SR, $SnAlk_3$, $SiAlk_3$; R = Alk, Ar.

High yields and high stereoselectivity are indisputable advantages of this method. The disadvantages include the necessity of using six equivalents of the reducing agent and conducting the reaction in an inert atmosphere in dry solvents. The use of this method for the olefination of ketones has not been reported so far.

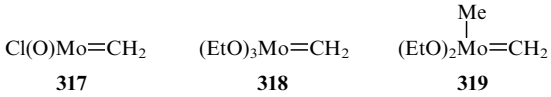
b. Molybdenum-based reagents

The methylene-molybdenum complex $Cl_3Mo{=}CH_2$ (**315**) prepared by treatment of molybdenum(V) chloride with methyllithium is a very mild methylenating agent. This reacts with aldehydes and ketones to give terminal alkenes in good yields.[230]



315 316 (84%)

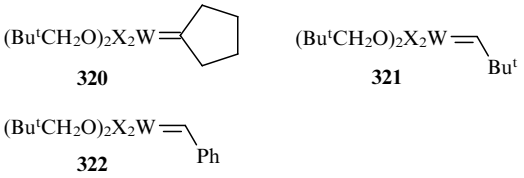
Presumably,[230] this methylenation occurs *via* metallacyclobutane **316**. A family of methylenating agents **317**–**319** based on molybdenum have been synthesised. Reagents **315** and **317** have proved to be the most reactive.



317 **318** **319**

c.Tungsten-based reagents

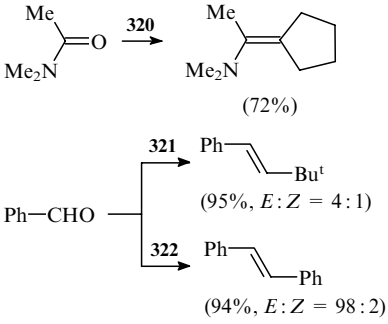
The tungsten-carbene complexes **320**–**322** are convenient reagents for the synthesis of sterically hindered (including exocyclic) alkenes.[231]



320 **321** **322**

X = OCH_2Bu^t, Cl, Br, I.

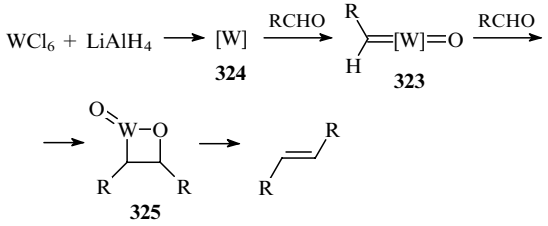
The role of a carbonyl component can be played by aromatic and aliphatic aldehydes, ketones, lactones and amides. The reaction is carried out using stoichiometric amounts of tungsten-carbene complexes. The yields are good in all cases.



(72%) (95%, *E*:*Z* = 4:1) (94%, *E*:*Z* = 98:2)

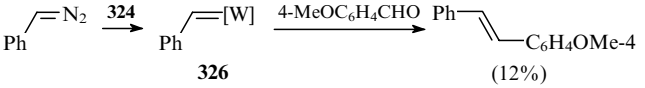
Reductive dimerisation of aromatic aldehydes and ketones, which gives good yields of symmetrical alkenes, is carried out in the presence of low-valence tungsten derivatives (the so-called 'tungsten' version of the McMurry reaction)[232] prepared *in situ* by treatment of WCl_6 with butyllithium.

It was recommended[233] to perform the coupling of aldehydes and ketones with a reagent formed upon reduction of WCl_6 with lithium aluminium hydride (its structure is not reported by the authors) as a reducing agent. Coupling was shown to occur in moderate yields with both aliphatic and aromatic substrates. Studies of the reaction mechanism suggest that the tungsten-carbene complex **323** formed as a result of insertion of the reagent **324** (marked as [W] in the scheme) into the carbonyl group is involved in the formation of alkenes. Subsequent addition of the second aldehyde molecule to the complex **323** and fragmentation of the metallacyclobutane intermediate **325** results in alkenes.



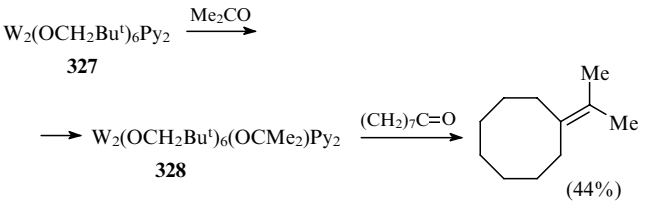
324 **323** **325**

The reaction of anisaldehyde with phenyldiazomethane in the presence of the reagent **324** gives *p*-methoxystilbene in low yield. In this case, the role of the olefinating agent is played by the diazo compound, while the tungsten-carbene complex **326** is a putative intermediate.[233]



326 (12%)

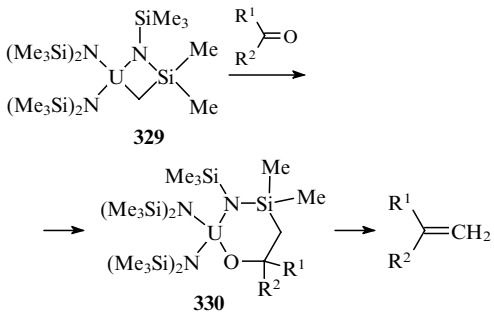
The binuclear tungsten complex $W_2(OCH_2Bu^t)_6Py_2$ (**327**) was proposed for cross-coupling of two different carbonyl compounds.[234] Its reaction with acetone yields the complex $W_2(OCH_2Bu^t)_6(OCMe_2)Py_2$ (**328**). Subsequent treatment of aldehydes and ketones with the reagent **328** converts the carbonyl group into the isopropylidene group, *i.e.*, affords reductive cross-dimerisation products.



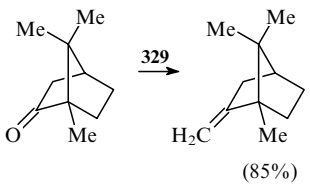
327 **328** (44%)

6. Uranium-based reagents

The metallacycle **329** based on uranium was proposed as a mild methylenating agent for cyclic and sterically hindered ketones as the carbonyl components.[235] It was shown that the olefination proceeds *via* intermediate six-membered metallacycles of the type **330**. High sensitivity of these complexes to moisture and air is a disadvantage.



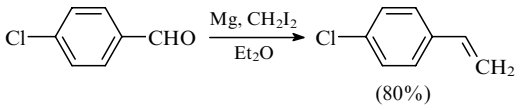
329 **330**



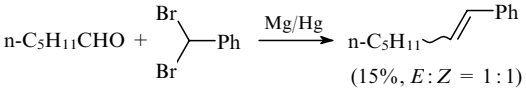
7. Reagents based on non-transition metals

Reductive coupling of carbonyl compounds with dihaloalkanes in the presence of non-transition reducing metals is also used in the synthesis. Presumably, the reactions of reducing metals with *gem*-dihaloalkanes afford *gem*-organodimetallic derivatives CH_2M_2, which yield the corresponding terminal alkenes in reactions with aldehydes and ketones.[39]

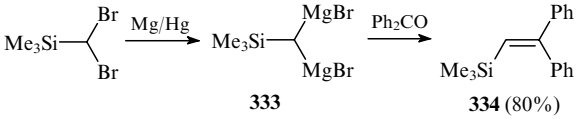
Dibromomethane and diiodomethane react with magnesium or magnesium amalgam to give *gem*-organodimagnesium compounds $CH_2(MgBr)_2$ (**331**) and $CH_2(MgI)_2$ (**332**). The latter proved to be convenient methylenating agents in the transformations of diverse carbonyl compounds into alkenes. These reactions usually give the products in high yields.[236]



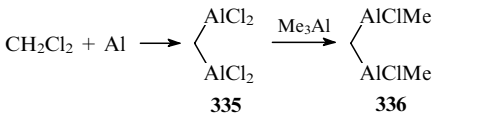
If benzylidene bromide $PhCHBr_2$ is used as the olefinating agent, the yield of the alkene is low. Therefore, this method can be used only for the incorporation of a methylene fragment.[236]

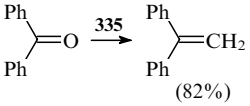


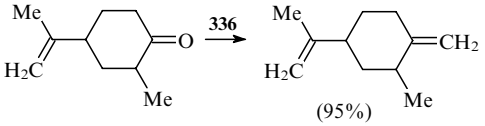
gem-Organodimagnesium compound **333** containing a trimethylsilyl group was successfully used in the synthesis of 1,1-diphenyl-2-trimethylsilylethylene **334** from benzophenone.[237] However, the yield of the expected reaction product with cyclohexanone was only 13%.



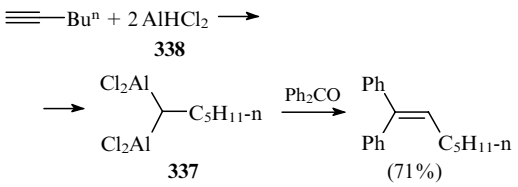
A method for the synthesis of terminal alkenes from ketones (including easily enolisable ones) using a family of *gem*-organodialuminium reagents of the type **335** and **336** has been developed.[238] The reagent **335** was prepared by boiling aluminum powder in dichloromethane in the presence of catalytic amounts of CH_2Br_2 as a primer.







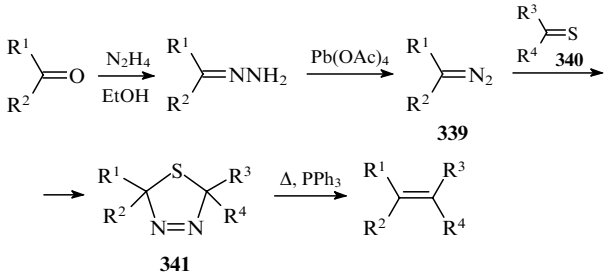
1,1-Bis(dichloroaluminio)hexane (**337**) prepared by the addition of two molecules of dichloroalane **338** to hex-1-yne was used in the synthesis of non-terminal alkenes from aromatic ketones.[39, 238]



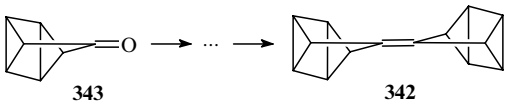
V. Miscellaneous olefination methods

1. The Barton – Kellogg reaction

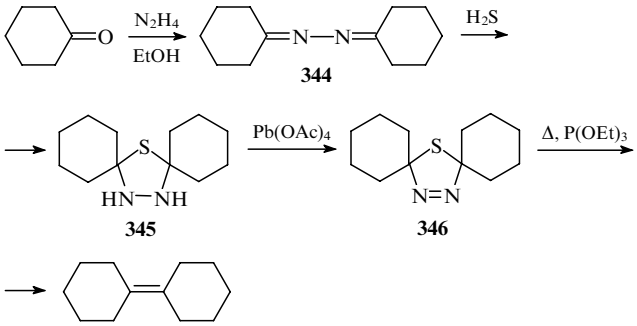
The Barton – Kellogg olefination represents the condensation of diazo compounds **339** with carbonyl derivatives **340** resulting in thiadiazolines **341**. Subsequent heating of the latter in the presence of triphenylphosphine yields alkenes.[239] The Barton – Kellogg reaction can be regarded as a reductive coupling of two different carbonyl compounds, since diazo compounds **339** are usually prepared by oxidation of hydrazones.



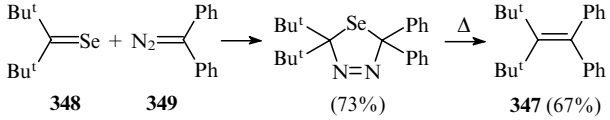
The Barton – Kellogg reaction was employed in the synthesis of sterically hindered alkenes. Thus bi(quadricyclylidene) **342** was prepared from the ketone **343** using this reaction sequence.[7]



A version of the Barton – Kellogg reaction is known where the carbonyl compound is converted into a symmetrical azine **344**.[240, 241] Subsequent cyclisation upon treatment with hydrogen sulfide yields thiadiazolidine **345**; the latter is further oxidised to thiadiazoline **346** with lead tetraacetate. Thermolysis of compound **346** with simultaneous desulfurisation with triethyl phosphite yields a symmetrical alkene.

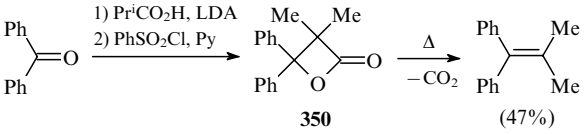


A procedure based on the use of selenocarbonyl compounds was effective in the synthesis of sterically hindered alkenes.[7, 24] Thus 2,2-di-*tert*-butyl-1,1-diphenylethylene (**347**) was prepared from di-*tert*-butylselone **348** and diphenyldiazomethane **349**.[24]



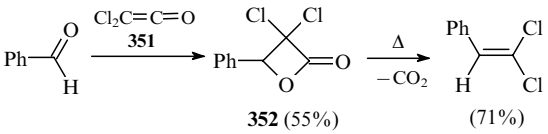
2. Thermal splitting of β-lactones

Thermal splitting of β-lactones **350** is a convenient method for the preparation of alkenes containing alkyl and aryl substituents at the double bond.[242] The corresponding lactones are formed by cyclisation of β-hydroxy acids under the action of benzenesulfonyl chloride in the presence of pyridine, while β-hydroxy acids are, in turn, prepared either by the condensation of dilithium derivatives of carboxylic acids with aldehydes and ketones or by the Reformatsky reaction. Thermolysis of β-lactones at 140–160 °C gives the corresponding alkenes in yields varying from moderate to quantitative.



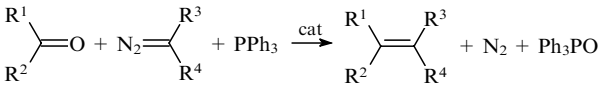
Sometimes, the formation of alkenes from β-hydroxy acids may take place *in situ* even in the step of lactone formation. It was found that the cyclisation of β-hydroxy acids in the presence of pyridine on gentle heating (45–55 °C) is accompanied by simultaneous decarboxylation of lactones, which yields almost exclusively *E*-stereoisomers of alkenes. Since the cyclisation of β-hydroxy acids results in the formation of the least sterically hindered lactones, *cis*-elimination of carbon dioxide yields the least hindered alkenes.

A two-step procedure for the synthesis of dichlorostyrenes from the corresponding aldehydes has been proposed.[243] The first step includes the [2 + 2]-cycloaddition of dichloroketene **351** to an aldehyde. The lactone **352** undergoes thermal decarboxylation to give the corresponding dichlorostyrene. The yields in the first step are 29%–83%, those in the second step are 23%–86%. In the case of aldehydes containing electron-withdrawing substituents, the yields are higher than from aldehydes containing donor groups.



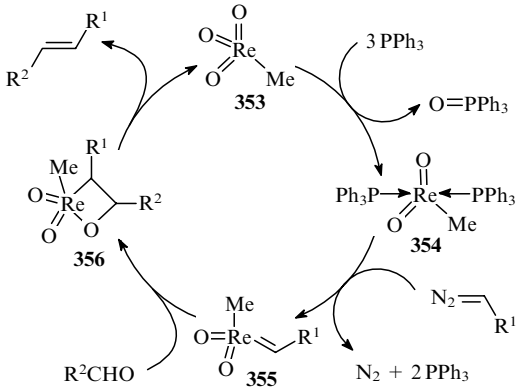
3. Olefination of carbonyl compounds by diazoalkanes in the presence of metal-complex catalysts

A method for the olefination of carbonyl compounds by stable diazoalkanes in the presence of stoichiometric amounts of triphenylphosphine catalysed by metal complexes based on rhenium,[244–251] ruthenium,[252,253] rhodium,[253] iron,[254–258] cobalt [259] and molybdenum,[260] has been developed.

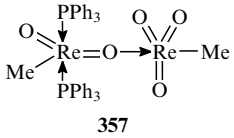


This reaction, which is analogous to the Wittig reaction, does not require strong bases for the synthesis of phosphorus ylides.[253] In the majority of cases, ylides are synthesised from stable diazoalkanes containing an electron-withdrawing group, although trimethylsilyldiazomethane was also employed.[253] The necessity to use stable diazocompounds and stoichiometric amounts of triphenylphosphine in this reaction poses certain restrictions on its synthetic application.

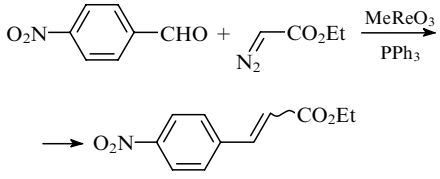
This version of olefination widely employs rhenium catalysts, *e.g.*, methyltrioxorhenium (**353**).[244,245] The olefination of carbonyl compounds upon treatment with ethyl diazoacetate or ethyl diazomalonate in the presence of equimolar amounts of triphenylphosphine and catalytic amounts of $MeReO_3$ has been described.[245] In the absence of the catalyst, no olefination occurs; the diazo compound reacts with the aldehyde to give a nonsymmetrical azine. It has been shown [246] that the rhenium(V) derivative **354** formed upon reduction of methyltrioxorhenium with triphenylphosphine plays the role of a true catalyst. Presumably, this reaction proceeds *via* the rhenium-carbene complex **355** as a key intermediate.[245,246] Subsequent [2 + 2]-cycloaddition of the carbonyl group to the carbene complex **355** results in metallacyclobutane **356**, the fragmentation of the latter yields an alkene.



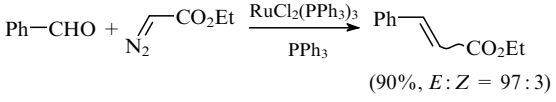
A binuclear rhenium(VII)–rhenium(V) complex **357** formed in the reaction of methyltrioxorhenium with triphenylphosphine [246] and an η^2-alkyne methyldioxorhenium complex [248] can be used as catalysts.



This method was used in the synthesis of α,β-unsaturated acid esters starting from aliphatic, aromatic and α,β-unsaturated aldehydes and cyclic ketones as the carbonyl components. *E*-Isomers of alkenes are formed in this reaction in high yields (80%–97%). In the case of aromatic aldehydes, the presence of electron-withdrawing substituents in the *para*-position relative to the carbonyl group favours the reaction.

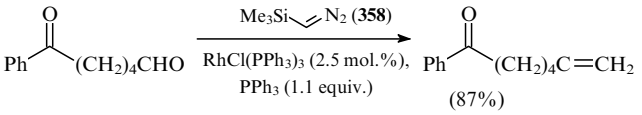


The ruthenium complex $RuCl_2(PPh_3)_3$ is yet another convenient catalyst for the olefination of aldehydes with ethyl diazoacetate in the presence of triphenylphosphine.[252] The mechanism of this reaction is not specified, but the formation of a ruthenium–carbene complex is conjectured. The stereoselectivity of this reaction is high both in the case of aliphatic and aromatic substrates; the ratio of *E*- and *Z*-isomers of α,β-unsaturated esters is no less than 9 : 1.

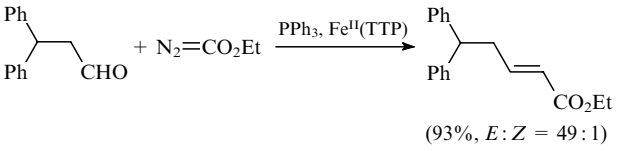


Trimethylsilyldiazomethane (**358**), in the presence of equimolar amounts of triphenylphosphine, was proposed for the methylation of aldehydes.[253] The choice of an optimum catalyst for this reaction, *viz.*, the Wilkinson catalyst $RhCl(PPh_3)_3$, was made based on the results of studies of catalytic activities of several rhodium and ruthenium complexes. This method proved to be suitable for the synthesis of terminal alkenes from various aldehydes. Functional or protective groups do not interfere with

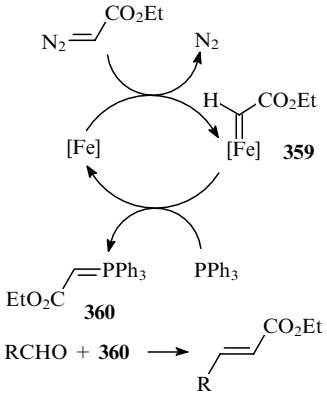
this reaction. It is of note that the keto group of the substrate is not involved in the reaction. The yields of the alkenes are 60% – 98%.



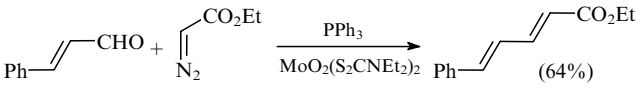
The olefination of aldehydes with ethyl diazoacetate in the presence of an iron(II) complex with tetra(*p*-tolyl)porphyrin [Fe^{II}(TTP)] proceeds with very high *trans*-stereoselectivity and in nearly quantitative yields.[254]



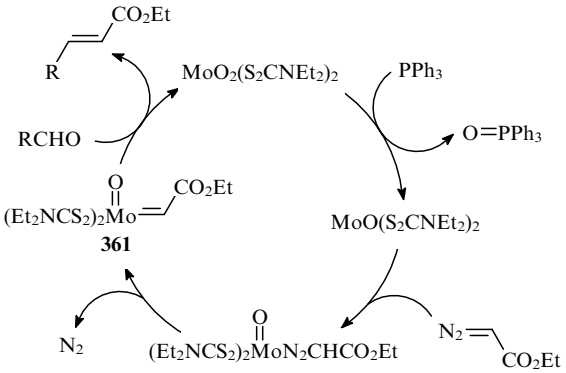
Presumably,[254] the mechanism of this reaction includes the formation of the iron carbene complex **359**, which is further involved in the transfer of carbene to triphenyl phosphine resulting in the ylide **360**. The olefination step itself is not included in the catalytic cycle.



A similar olefination reaction is catalysed by the molybdenum complex $MoO_2(S_2CNEt_2)_2$.[260] This reaction proceeds with high stereoselectivity, but the yields of the corresponding alkenes are lower than in the catalysis by other metals. Aromatic, aliphatic and α,β-unsaturated aldehydes were used as the carbonyl components.

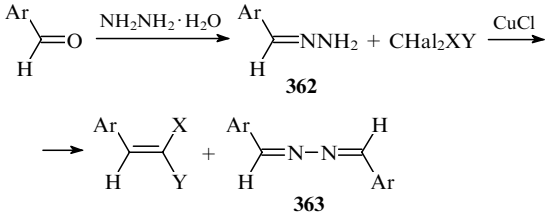


The reaction mechanism involves the formation of the molybdenum-carbene complex **361** which plays the role of the olefinating agent.



4. Catalytic olefination of hydrazones

A new, in principle, reaction of the catalytic olefination of hydrazones of carbonyl compounds was discovered in 1999.[261] It was found that the reaction of *N*-unsubstituted hydrazones of aromatic aldehydes **362** with *gem*-dihalo compounds $CHal_2XY$ in the presence of catalytic amounts of copper(I) chloride yields substituted alkenes. Symmetrical azines of the carbonyl derivatives **363** are formed as side products of transformations of hydrazones; this reaction is accompanied by evolution of nitrogen. Thus, a new double carbon – carbon bond is formed in this reaction.

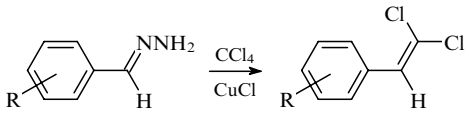


Ar = 4-$NO_2C_6H_4$, 4-ClC_6H_4, 4-$MeOC_6H_4$; Hal, X, Y = F, Cl, Br, I.

Since hydrazones are readily available, this reaction can be used as a simple two-step procedure for the synthesis of alkenes from carbonyl compounds.

In addition to copper salts, the oxidation of hydrazones with tetrachloromethane is catalysed by salts of other transition metals, such as silver, lanthanum, titanium, manganese, cobalt, rhodium, palladium and platinum. However, the highest yields of alkenes are obtained in the presence of CuCl.

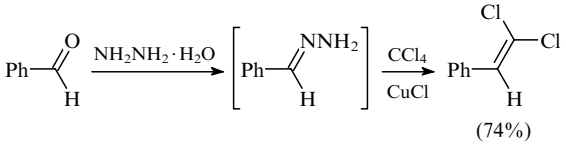
This reaction served as the basis for the development of novel methods for the synthesis of various substituted alkenes. Thus the use of CCl_4 as the olefinating agent allows one to synthesise the corresponding dichloroalkenes.[262]



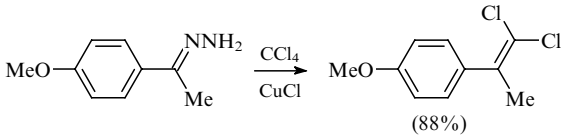
R = H (27%); 4-Cl (82%)

Substrates containing electron-withdrawing substituents in the aromatic nucleus (*e.g.*, chlorine, bromine, nitro and cyano groups) are converted into β,β-dichlorostyrenes in high yields. If hydrazones containing donor substituents or benzaldehyde hydrazone are used, the yields of dichloroalkenes are low. Low stabilities of the corresponding hydrazones are the main reason for the low yields of dichlorostyrenes in these cases.

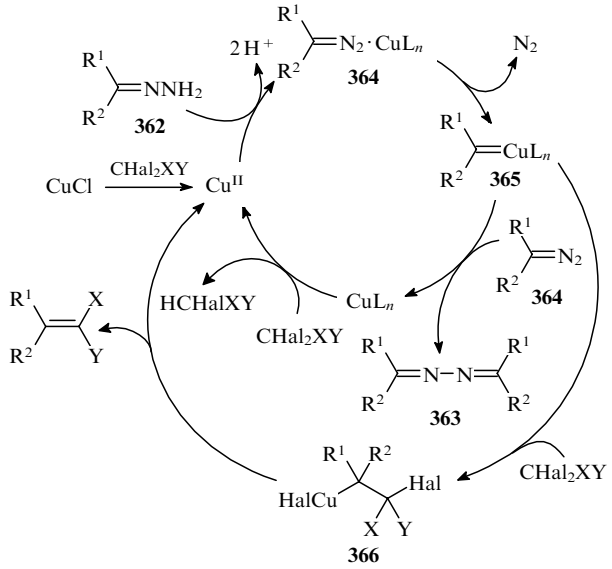
A simplified procedure for the one-pot synthesis of dichloroalkenes directly from aldehydes, which obviates the preparation and isolation of hydrazones, has been developed.[263] Besides, in the case of donor substrates the yields of dichloroalkenes are significantly higher.



The area of synthetic applications of the catalytic olefination reaction is not confined to hydrazones of aromatic aldehydes; alkyl aryl ketone hydrazones can be converted into tetrasubstituted alkenes in good yields.[264]

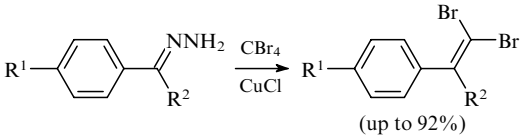


A mechanism of this reaction, which describes its catalytic cycle, has been proposed.[265–267] The first step includes oxidation of hydrazones **362** to the corresponding diazoalkanes **364** with copper(II) formed upon oxidation of CuCl with polyhaloalkanes. The diazo compounds **364** undergo further copper-catalysed fragmentation to give the copper-carbene complex **365**, the key intermediate of the olefination reaction. Further transformations of the complex **365** can proceed in two different routes. The reaction with polyhaloalkanes gives alkenes and is accompanied by regeneration of the catalyst (Cu^{II}) (the outer cycle). This reaction proceeds through oxidative addition of copper across the C—Hal bond and formation of the organocopper intermedate **366**. The side reaction, *i.e.*, the formation of azines **363**, occurs upon reaction of the complex **365** with the second molecule of diazoalkane **364** (the inner cycle).

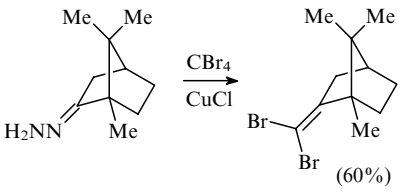


A salient advantage of this reaction is that the preparation of alkenes from carbonyl compounds does not require the use of external reducing agents, since this function is in fact fulfilled by hydrazine.

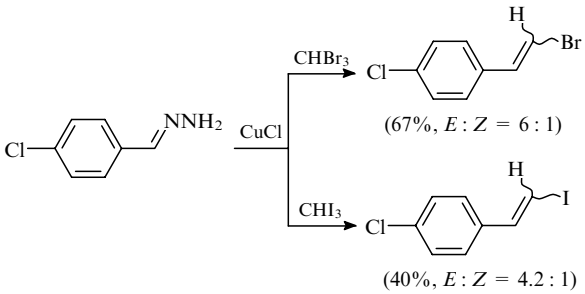
In addition to CCl_4, other polyhaloalkanes can be used as the olefinating agents; by varying the latter, one can obtain various types of alkenes. In particular, with CBr_4 as the olefinating agent, hydrazones of carbonyl compounds are converted into the corresponding dibromoalkenes.[264, 268, 269]



R^1 = H, MeO, Br; R^2 = H, Et.

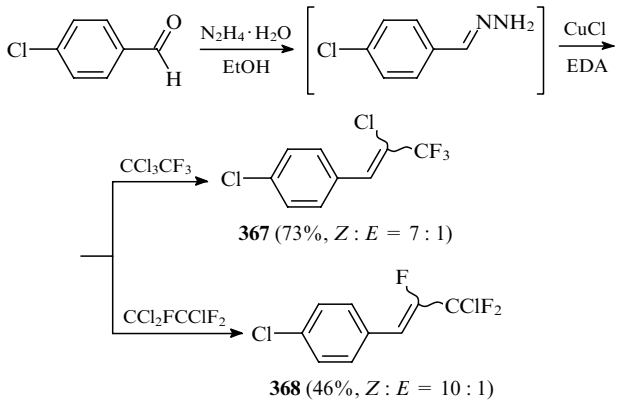


In the case of trihalomethanes (haloforms), the reaction with hydrazones yields monohalogenoalkenes. The reaction of the hydrazones of aromatic aldehydes with $CHBr_3$ leads to β-bromostyrenes stereoselectively (predominantly, *E*-isomers).[270]



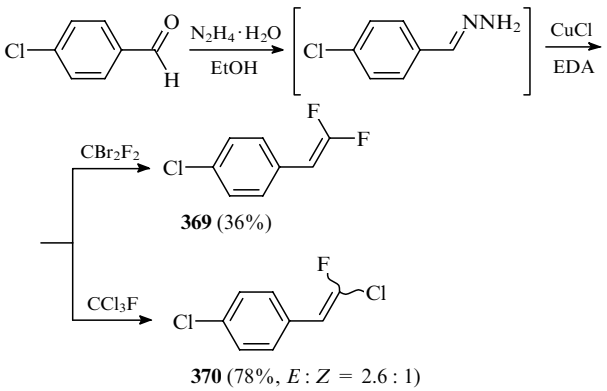
Reactions of hydrazones with iodoform proceed in a similar way. In this case, the corresponding vinyl iodides are formed as the reaction products.[271]

Fluorine-containing alkenes are formed if fluorochloroalkanes (Freons) are used as the olefinating agents. Thus reactions of hydrazones of aromatic aldehydes prepared *in situ* synthesised with Freons CCl_2FCClF_2 and CCl_3CF_3 yield fluoro alkenes **367** and **368**[272] (predominantly, less sterically hindered *Z*-isomers). The stereoselectivity of this reaction is rather high; the ratio of the isomers depends on the nature of the aromatic system and the position of the substituents in the benzene ring. Thus the stereoselectivity of the reaction increases in the case of donor substrates and decreases in the case of substrates containing electron-withdrawing groups.

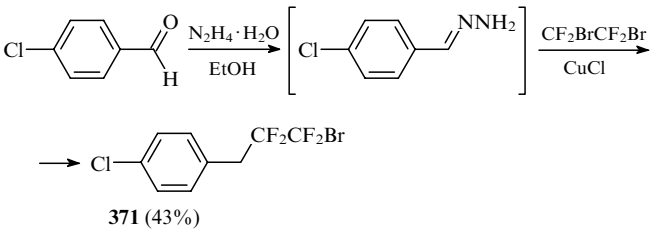


EDA is 1,2-ethylenediamine.

Dibromodifluoromethane and trichlorofluoromethane were used as fluorine-containing C_1-synthons in the catalytic olefination reaction, which afforded the corresponding *gem*-difluorostyrenes **369** (see Ref. 273) and chlorofluorostyrenes **370**.[274]

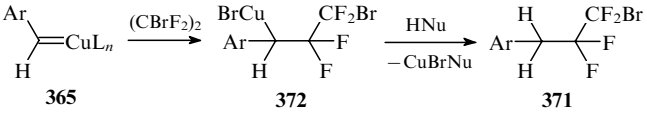


In the case of dibromotetrafluoroethane $CBrF_2CBrF_2$, the corresponding arylbromotetrafluoropropanes **371** (rather than unsaturated compounds) are formed as reaction products.



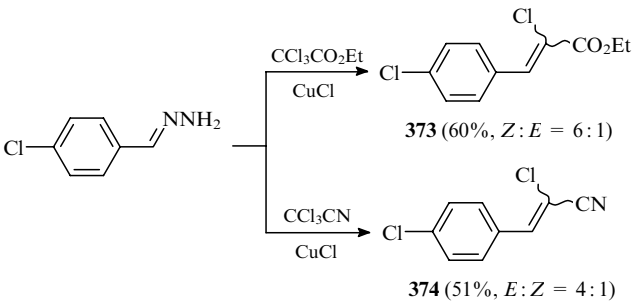
371 (43%)

It was found that in this case the abnormal course of this reaction is due to the high stability of the C—F bond. The reaction of the copper-carbene complex **365** with $CBrF_2CBrF_2$ yields the corresponding organocopper intermediate **372**; elimination of CuBrF from this intermediate is hardly likely and only the saturated compound **371** is formed.



365 **372** **371**

Polyhalogenated reagents, such as CCl_3CO_2Et and CCl_3CN, are used in the synthesis of functionalised unsaturated compounds. Thus the reactions of hydrazones with ethyl trichloroacetate and trichloroacetonitrile give α-chlorocinnamates **373**[275] and α-chlorocinnamonitriles **374**.[276]



373 (60%, $Z:E$ = 6:1)

374 (51%, $E:Z$ = 4:1)

VI. Conclusion

A survey of the current literature demonstrates that the methods for olefination of carbonyl compounds are quite numerous and differ in the nature of the olefinating agents, reaction conditions, types of carbonyl substrates and, correspondingly, types of unsaturated compounds formed.

It is of note that the correct comparison of efficiencies of various olefination procedures is difficult, since many exotic chemical methods are more captivating than practical and have not received wide application because of their high cost, low availability of the corresponding reagents and certain inertiality of thought inherent in some synthetic chemists. Nevertheless, the present review gives an idea about both the wide arsenal and explosive development of this branch of synthetic organic chemistry.

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