Acc. Chem. Res. **1998,** *31,* 584−592

New Synthetic Methodologies for Carbon−Carbon Double Bond Formation

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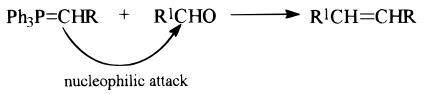
Received October 7, 1997

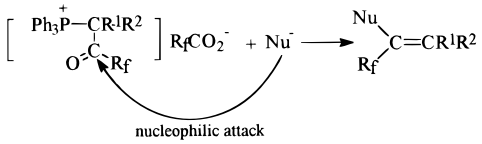
Carbon−carbon double bond formation is one of the useful and fundamental reactions in synthetic organic chemistry, particularly in the synthesis of complex natural products with biological activity. In 1953 Wittig and Geiser found that methylenetriphenylphosphorane reacted with benzophenone to give 1,1-diphenylethene and triphenylphosphine oxide, leading to the development of a new olefination methodology universally known as the Wittig reaction.[1] Since then the Wittig olefination has found widespread application in synthetic organic chemistry, and numerous papers and reviews have detailed the progress of the Wittig reaction.[1] Therefore, an investigation of the new synthetic methodology for carbon−carbon double bond formation should be valuable, and this Account reviews recent developments in our laboratory.

Synthetic Utility of Fluorinated β-Ketophosphonium Salts

The well-known Wittig reaction involves a nucleophilic attack by the ylide carbon of the Wittig reagent on electrophiles, forming a carbon−carbon double bond.



Alternatively, in our reaction the β-ketophosphonium salts as reagents are attacked by nucleophiles, resulting in the formation of a fluorinated carbon−carbon double bond.



Yanchang Shen, born in Shanghai, China, in 1931, received his B.S. (1953) in chemistry from Fu Dan University and did his graduate study (1963−1967) at the Shanghai Institute of Organic Chemistry, Academia Sinica (with Professor Y. Z. Huang). He was a postdoctoral associate at the University of Massachusetts (with Professor Ernest I. Becker, 1981−1982) and a Visiting Professor at Clemenson University (1989−1990). He was appointed Associate Professor and Professor at the Shanghai Institute of Organic Chemistry, Academia Sinica, in 1981 and 1986, respectively. He became Editor-in-Chief of *Acta Chim. Sin.*, Chinese Chemical Society, in 1994. In 1995 he received the Natural Science Award (first class) of Academia Sinica for creative work in new synthetic methodology for carbon−carbon double bond formation. His research interests include development of new synthetic methodology using phosphorus, arsenic, and organometallic reagents.

This reaction is a new contribution to carbon−carbon double bond synthesis, particularly useful for the synthesis of fluorinated functionalized carbon−carbon double bond compounds, which are useful intermediates in the synthesis of fluorinated biologically active compounds and would be difficult to prepare otherwise. Usually, fluorinated ylides are unable to react with aldehydes or ketones because of the strong electron-withdrawing effect of the perfluoroalkyl group.[2] The new idea of this reaction is to make clever use of the strong electron-withdrawing property of the perfluoroalkyl group, resulting in the formation of a δ positive charge on the neighboring carbonyl carbon. Easy attack of nucleophiles at the carbonyl carbon, followed by elimination of triphenylphosphine oxide, leads to the formation of a carbon−carbon double bond. The nucleophiles can be a variety of organometallic reagents, leading to a reaction of wide scope.

The phosphoranes **1**, generated from the corresponding phosphonium salts and phenyllithium, were acylated by the addition of perfluoroalkanoic anhydride to give fluorinated β-ketophosphonium salts **2**, which in the reaction medium were attacked by nucleophiles (RLi) (Scheme 1). Elimination of the triphenylphosphine oxide gave tetrasubstituted fluoroolefins **3** in 42−70% yields.[3] When substituted lithium acetylides were utilized as nucleophiles, fluoroenynes **4** were obtained in 43−80% yields.[4] This reaction is of broad scope since R^1 and R^2 may be alkyl, aryl, allylic, benzylic, or alicyclic groups. They would be expected to be useful intermediates in the synthesis of fluorine-containing biologically active compounds.

When methylenetriphenylphosphorane as a nucleophile attacked fluorinated β-ketophosphonium salts, after deprotonation and elimination of triphenylphosphine oxide, new ylides **7** were formed which reacted with aldehydes to give fluorodienes **8** with exclusively *E*-isomers in 20−58% yields (Scheme 2).[5] After the addition of $Ph_3P{=}CH_2$ to **5**, the temperature of the reaction mixture must be maintained at −78 °C to avoid elimination of triphenylphosphine oxide, prior to deprotonation of **6**. After addition of PhLi to **6**, the reaction mixture was gradually brought to 25 °C wherein the triphenylphosphine oxide was spontaneously eliminated. If the reaction mixture containing **6** is warmed before the addition of PhLi, a mixture of elimination products **9** and **10** results via two alternative pathways (a and b in Scheme 3). Thus, the regiocontrolled elimination of triphenylphosphine oxide from deprotonated **6** is important for forming **7** exclusively.

The ylides **11,** generated by the same method as **7,** were acylated by the addition of perfluoroalkanoic anhydride, after transylidation, to give the stabilized ylides **12** (Scheme 4). Vacuum pyrolysis of **12** gave conjugated diperfluoroalkyl enynes **13** in 85−94% yields which would be difficult to prepare otherwise.[6]

Methylenetriphenylarsorane also readily added to the carbonyl group of fluorinated β-ketophosphonium salt **5**

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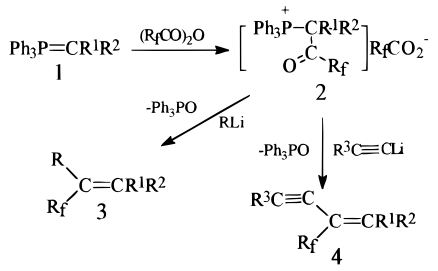
Published on Web 06/13/1998

Scheme 1

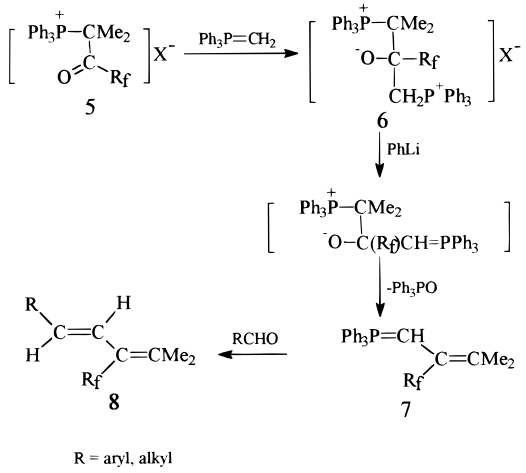


R_f=CF_3, C_2F_5, n-C_3F_7

R^1, R^2 = alkyl, aryl, allylic, benzylic, alicyclic

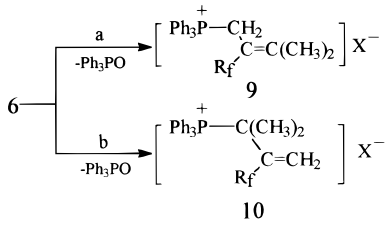
R^3 = Ph, n-Bu

Scheme 2

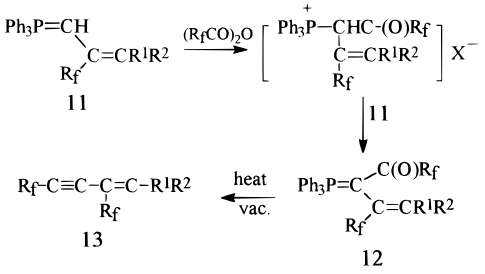


R = aryl, alkyl

Scheme 3



Scheme 4

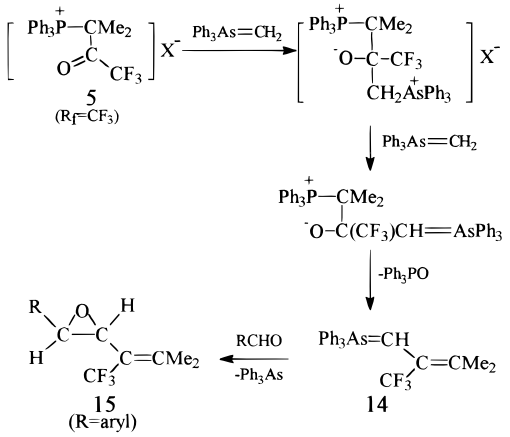


R^1=CH_3, R^2=CH_3; R^1R^2= -$[CH_2]_4$-, -$[CH_2]_5$-

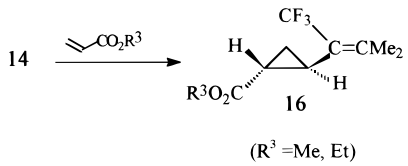
(R_f = CF_3),[7] after deprotonation and elimination of triphenylphosphine oxide, giving ylide **14**, which reacted with aldehydes to give *trans*-fluorovinylic epoxides **15** stereospecifically in 35−63% yields (Scheme 5).

Upon reaction of ylide **14** with acrylates, trifluoromethylated vinylcyclopropanes **16** were obtained exclusively

Scheme 5

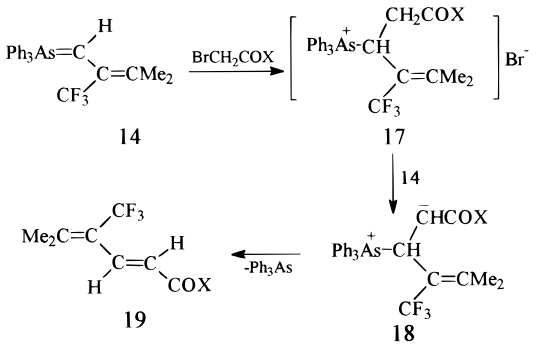


Scheme 6



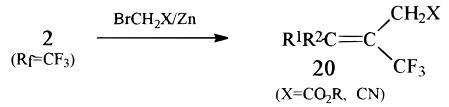
(R^3 =Me, Et)

Scheme 7



X=OMe, OEt, OBu-n, NR^1R^2

Scheme 8

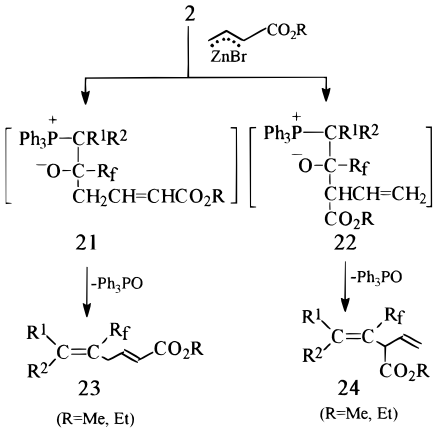


as the *trans*-isomer in 43−62% yields (Scheme 6).[8a] Ylide **14** could also be utilized in the synthesis of fluorinated diene esters or amides as shown in Scheme 7. Treatment of bromoacetic esters or amides with ylide **14** gave trifluoromethylated 2,4-dienyl carboxylates in 43−69% yields[8b] or 2,4-dieneamides in 45−85% yields,[8c] respectively, exclusively as the *E*-isomers.

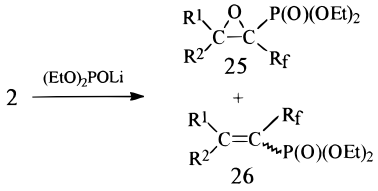
In addition to lithium reagents zinc reagents are also useful as nucleophiles to attack fluorinated β-ketophosphonium salts. Reaction of organozinc compounds with fluorinated β-ketophosphonium salts **2** gave trifluoromethylated β,γ-unsaturated esters and nitriles **20** in 26−84% yields (Scheme 8).[9]

Use of unsaturated organozinc compounds with fluorinated β-ketophosphonium salts **2** provides a route to perfluoroalkylated 1,4-alkadienes.[10] In the case of R_f =

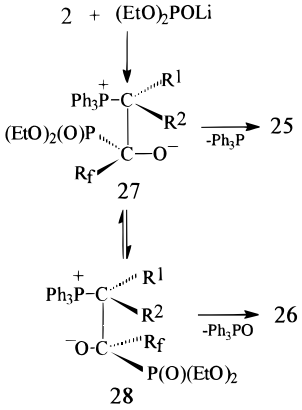
Scheme 9



Scheme 10



Scheme 11

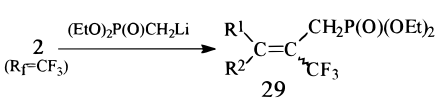


CF_3, two regioisomers, **23** and **24**, were isolated (41−55% yields; **23**:**24** = 73−95:27−5), while in the case of salts with longer chain perfluoroalkyl groups, only one isomer, **23**, was obtained (37−43% yields) (Scheme 9). Thus, steric effects are clearly important in the regioisomer distribution.

The nucleophiles employed to attack fluorinated β-ketophosphonium salts are not limited to carbon, and heteronucleophiles can also be utilized. When diethyl lithium phosphite was reacted with **2**, (α-fluoroalkylvinyl)-phosphonates or (α-fluoroepoxyalkyl)phosphonates were isolated depending upon the groups R^1 and R^2 in **2** and the base used (Scheme 10).[11] Usually the (α-fluoroalkylvinyl)phosphonates **26** were obtained exclusively in 41−78% yields, but in the case of $R^1 = R^2 = CH_3$ and with methyllithium as a base, (α-fluoroepoxyalkyl)phosphonates **25** were isolated exclusively in 42% yields.

The mechanism may be rationalized as shown in Scheme 11.[11] The reaction is initiated by nucleophilic attack of diethyl lithium phosphite on the carbonyl carbon

Scheme 12



atom of **2** to give the intermediates **27** and **28**. There is a dynamic equilibrium in **27** and **28**, and the formation of **25** against **26** is in direct proportion to the relative transition state energies for the two reactions. If $R^1 = R^2 = CH_3$, the transition state energy of **27** is low and the oxygen anion with the least sterically hindered position attacks the neighboring carbon atom, followed by elimination of triphenylphosphine to give **25**. In the other cases, with a more bulky R^1 group, the transition state energy of **28** is low and subsequent decomposition of the betaine **28** with elimination of triphenylphosphine oxide in a *syn* fashion affords **26**.

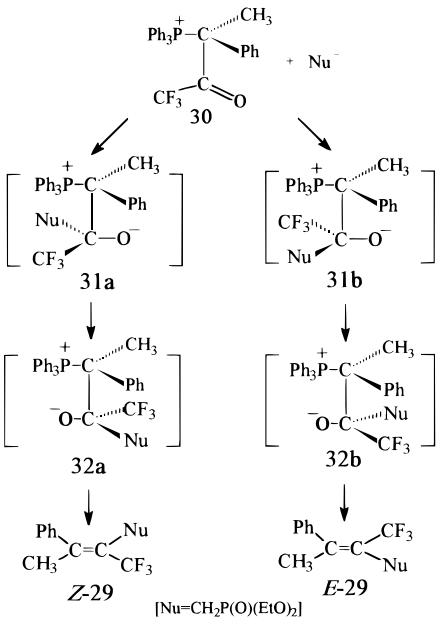
Among phosphoryl-stabilized carbanions, allylic phosphonates occupy an important position.[12a] Trifluoromethylated allylic phosphonates are of special interest. They can be synthesized by a one-pot reaction of [(dialkoxyphosphinoyl)methyl]lithium with trifluoromethylated β-ketophosphonium salts in 56−72% yields (Scheme 12).[12a]

When R^1 = Ph and $R^2 = CH_3$, the *Z*-isomer is obtained exclusively. The high stereoselectivity of the reaction can be rationalized. Thus, the oxygen of the carbonyl group orientates itself between the small (CH_3) and medium (Ph) sized groups, and the large group (Ph_3P^+) orientates itself *anti* to the carbonyl oxygen. The reaction is initiated by nucleophilic attack of a nucleophile on the carbon−oxygen double bond of the carbonyl group and for the additions containing an asymmetric α-carbon, the Felkin−Anh model of asymmetric induction[12b] predicts the predominant diastereomer. The incoming nucleophile preferentially attacks the less hindered side of the plane containing the C=O bond. Therefore, the relative steric bulks of Ph and CH_3 play an important role in the stereoselectivity. The relative steric bulk of CH_3 is smaller than that of Ph. The attack is from the rear (the side of the plane containing the small group) of **30**, forming the intermediate **31a**, and after rotation at the C−C bond, intermediate **32a** is formed, while the reverse is true for the attack from the front, forming intermediates **31b** and then **32b**. Each of those intermediates decomposes via a *syn* elimination, affording (***Z***)-**29** or (***E***)-**29** (Scheme 13). In our cases, formation of **31a** was favored over **31b** and the *Z*-isomer was obtained exclusively.

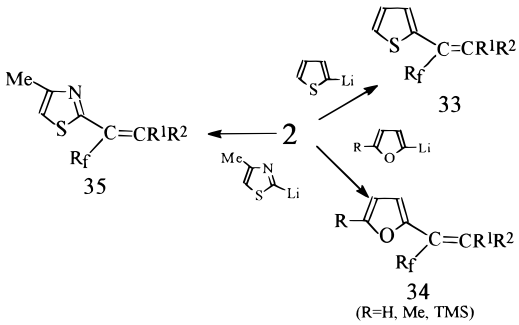
Due to their useful biological activity in medicinal and agricultural chemistry, heterocyclic compounds containing fluorine have received much attention.[13,14] However, only a few reports have appeared in the literature concerning the fluoroalkylation of heterocyclic rings.[15] We found that heterocyclic lithium compounds could attack β-ketophosphonium salts, leading to the regiospecific introduction of a fluorovinyl group into the heterocyclic rings in 51−84% yields (Scheme 14).[15,16]

Sulfur-containing nucleophiles were also useful in attacking β-ketophosphonium salts. The ease of synthesis

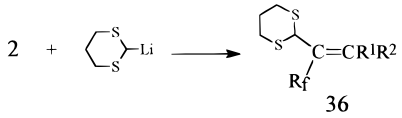
Scheme 13



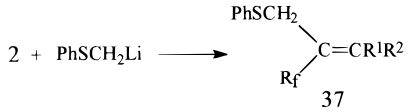
Scheme 14



Scheme 15



Scheme 16

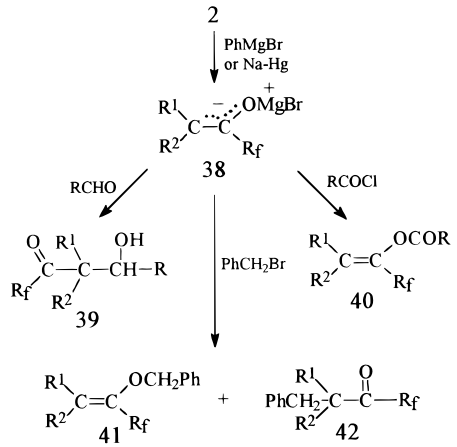


of 1,3-dithiane derivatives combined with their versatile chemistry has attracted much attention in their use as synthons.[17] We found that the reaction of 2-lithio-1,3-dithiane with fluorinated β-ketophosphonium salts **2** gave a new fluorinated synthon, perfluoroalkylated vinyl 1,3-dithianes **36**, in 52−92% yields (Scheme 15).[17]

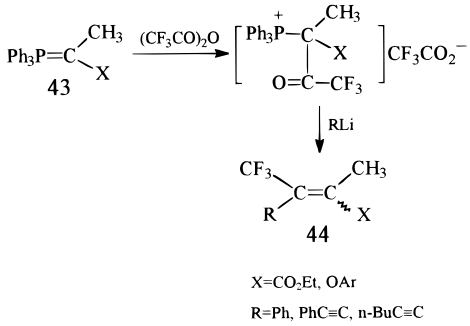
Allylic sulfides are potentially useful intermediates in organic synthesis and can undergo many useful organic transformations.[18] Perfluoroalkylated allylic sulfides **37** could be synthesized conveniently by the reaction of (thiophenoxymethyl)lithium with fluorinated β-ketophosphonium salts in 51−72% yields (Scheme 16).[19]

Grignard reagents, such as Bu^{n}MgBr, PhC≡MgBr, and $PhCH_2MgCl$ gave the tetrasubstituted fluoroolefins when

Scheme 17



Scheme 18



used with fluorinated β-ketophosphonium salts,[20] similar to organolithium compounds. However, when phenyl Grignard reagent or Na−Hg was used, reductive cleavage of the fluorinated β-ketophosphonium salts **2** occurred instead of nucleophilic addition.[20,21] The enolates **38** have been successfully trapped by suitable electrophiles and exhibit normal enolate reactivity in relation to their O- and C-nucleophilicity. Compounds **38** react with acyl chlorides and aldehydes to give unique fluorinated β-hydroxy ketones **39** in 82−88% yields or vinyl esters **40** in 56−94% yields, respectively (Scheme 17). Reaction with benzyl bromide gave fluorinated vinyl ether **41** and ketone **42** in 65% yields.

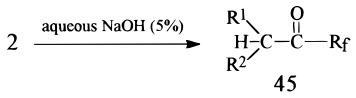
When one of the groups (R^1, R^2) in the alkylidene moiety of **2** is an electron-withdrawing group (**43**, X = CO_2-Et) or electron-donating group (**43,** X = OAr), the lithium reagents regiospecifically attack the carbonyl group attached to the trifluoromethyl group, affording trifluoromethylated α,β-unsaturated esters in 40−66% yields[22] or vinyl ethers in 40−85% yields[23] as the *E*-isomer exclusively or as the major product (*E*:*Z* = 95−61:5−39) (Scheme 18).

Treatment of fluorinated β-ketophosphonium salts **2** with aqueous sodium hydroxide (5%) gave perfluoroalkyl alkyl ketones **45** in 37−78% yields (Scheme 19).[24]

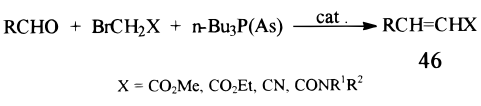
"One-Pot" Carbon−Carbon Double Bond Formation

The well-known Wittig reaction can provide olefins with both regio- and stereoselectivity, especially in the synthesis

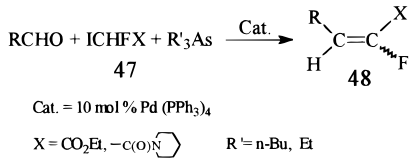
Scheme 19



Scheme 20



Scheme 21

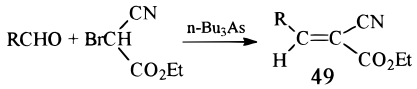


of a variety of naturally occurring substances. However, this reaction requires three steps, i.e., preparation of salts, ylide formation, and reaction with carbonyl compounds. We found that, in the presence of suitable catalysts (Pd, Zn, or Cd), trialkylphosphines and arsines are effective reagents for "one-pot" carbon−carbon double bond formation between α-bromo carboxylic derivatives (esters, amides, and nitriles) and aldehydes (Scheme 20). α,*β*-Unsaturated esters in 52−97% yields,[25,26,27,28] amides in 30−86% yields,[29,30] and nitriles in 55−77% yields[31] were obtained. The geometry of the newly formed double bond in **46** was exclusively *E* [25,26,28−30] or predominantly *E* (*E*:*Z* = 88−68:12−32)[27] in the esters and amides. In the absence of trialkylphosphine (arsine) or catalyst (Pd, Zn, or Cd), olefination did not occur at all. It is noteworthy that this reaction greatly simplifies the traditional Wittig reaction into a stereospecific alkenylation methodology and compresses the three steps of a Wittig reaction into a one-step, one-pot synthesis.[25,32]

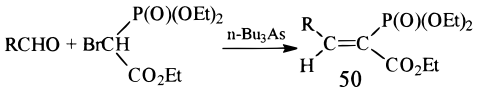
α,*β*-Unsaturated nitriles could also be synthesized from the iodine-catalyzed reaction of chloroacetonitrile with aldehydes promoted by tri-*n*-butylarsine and magnesium in 73−81% yields.[33] Our approach was successfully extended to the synthesis of fluorinated analogues, α-fluoro α,*β*-unsaturated esters in 52−90% yields[34] and amides in 45−68% yields.[35] On treatment of α-fluoro α-iodo ester or amide with aldehydes in the presence of trialkylarsine and a catalytic amount (10 mol %) of $Pd(PPh_3)_4$, α-fluoro α,*β*-unsaturated esters or amides were obtained (Scheme 21). In the case of esters, a mixture of *E*- and *Z*-isomers was obtained (*E*:*Z* = 33−46:67−54), while in the case of amides, the *Z*-isomer was obtained predominantly (*Z*:*E* = 95−71:5−29).

Without catalyst, active bromo compounds readily reacted with aldehydes in the presence of tri-*n*-butylarsine in a one-pot reaction, forming a carbon−carbon double bond in 68−96% yields.[36] The reaction of bromocyanoacetic ester with aldehydes in the presence of tri-*n*-butylarsine under neutral conditions gave α,*β*-unsaturated cyano esters exclusively as the *E*-isomer in 76−98% yields (Scheme 22).[37]

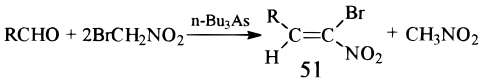
Scheme 22



Scheme 23



Scheme 24



Treatment of aldehydes and ethyl (α-diethoxyphosphoryl)bromoacetate with an equivalent amount of tri-*n*-butylarsine gave α-carboethoxy α,*β*-unsaturated phosphonates in 62−92% yields (Scheme 23). The geometry of the newly formed double bond in **50** was exclusively *E*.[38]

It is of interest that aldehydes reacted with bromonitromethane in the presence of tri-*n*-butylarsine to afford substituted 1-bromo-1-nitroalkenes in 62−69% yields with *Z*-stereoselectivity (Scheme 24).[39]

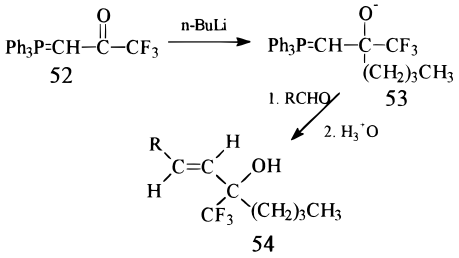
A Novel Ylide-Anion Formation Resulting from Nucleophilic Addition

Ylide-anions with high reactivity were first reported by Corey and King, using *sec*- or *tert*-butyllithium as a base to deprotonate the ylide, methylenetriphenylphosphorane, and then to react with substrates of low reactivity such as epoxides or hindered ketones.[40] We found that a novel fluorinated ylide-anion formation with high reactivity results from nucleophilic addition of organometallic reagents (lithium reagents, Grignard reagents). This new method is different from Corey's method (deprotonation method) since it results from nucleophilic addition of organometallic reagents and it provides a method for the utilization of the very stable fluorinated ylide in alkene synthesis.

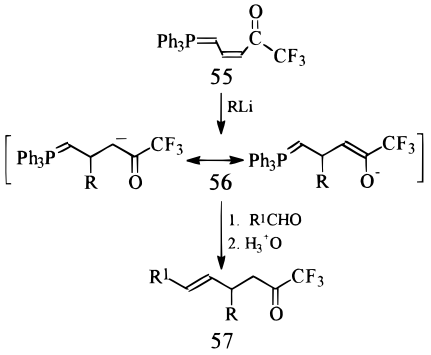
Due to the powerful electron-withdrawing effect of the trifluoroacetyl group, [(trifluoroacetyl)methylene]triphenylphosphorane **52**, the more reactive arsorane is very stable and unable to react with aldehydes.[2] An attempt to activate this phosphorane by nucleophilic addition of *n*-butyllithium to a carbonyl group succeeded because the reactivity of the carbonyl group neighboring the trifluoromethyl is enhanced. In this case the *n*-butyllithium attacks **52** to give an ylide-anion **53** which reacts with aldehydes to afford *trans*-α-trifluoromethyl allylic alcohol **54** exclusively in 46−55% yields after hydrolysis (Scheme 25).[41]

[3-(Trifluoroacetyl)allylidene]triphenylphosphorane **55** was very stable and unreactive with aldehydes due to the strong electron-withdrawing effect of the trifluoroacetyl group. The use of *n*-butyllithium or phenyllithium to activate ylide **55** resulted in a reaction different from the previous case. Thus, the nucleophiles attack in a conju-

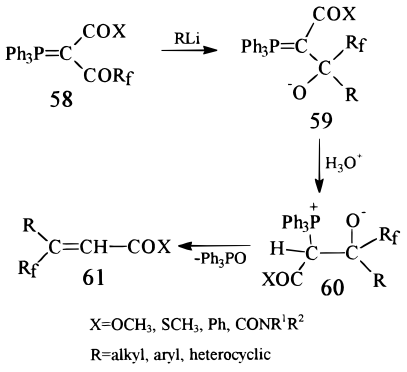
Scheme 25



Scheme 26



Scheme 27



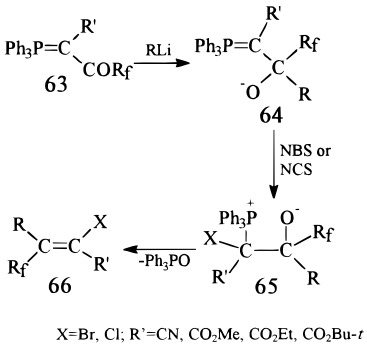
X=OCH_3, SCH_3, Ph, $CONR^1R^2$

R=alkyl, aryl, heterocyclic

gate manner to give ylide-anions **56** which react with aldehydes, after hydrolysis, to afford *trans*-α,*β*-unsaturated trifluoromethyl ketones **57** exclusively in 46−92% yields (Scheme 26).[42] An allylic ylide-anion, generated from allylidenetriphenylphosphorane and *n*-BuLi−TMEDA reacted readily with carbonyl compounds, affording *β*-hydroxy 1,3-dienes as the unique *E*,*E*-isomers in 39−58% yields.[43] 1-Iodo-1-(trimethylsilyl) 1,3-dienes could be conveniently synthesized with high stereoselectivity by consecutive reaction of allylidenetriphenylphosphorane in 47−85% yields.[44]

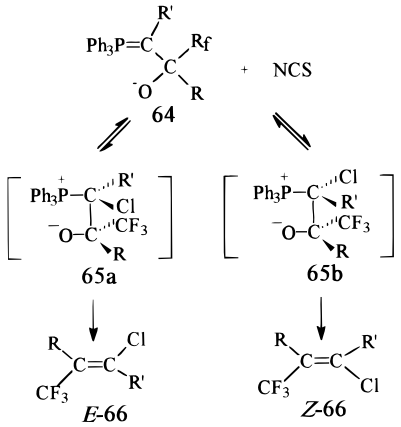
(Dicarbonylmethylene)triphenylphosphoranes are very stable because of the strong electron-withdrawing effect of the two carbonyl groups and are unreactive with aldehydes or ketones. A means to use the fluorinated (dicarbonylmethylene)triphenylphosphoranes as reagents in Wittig reactions was of interest. Fluorinated (dicarbonylmethylene)triphenylphosphoranes **58** could be regiospecifically attacked at the perfluoroacyl groups by various lithium reagents to form ylide-anions **59** (Scheme 27). After protonation, the intramolecular Wittig reaction took place spontaneously to give perfluoroalkylated α,*β*-

Scheme 28



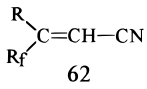
X=Br, Cl; R'=CN, CO_2Me, CO_2Et, CO_2Bu-*t*

Scheme 29



unsaturated carbonyl compounds **61** in 90−97% yields with high *E*-stereoselectivity (*E*:*Z* = 100−67:0−33)[45] and perfluoroalkylated α,*β*-unsaturated amides in 74−90% yields.[46] α,*β*-Unsaturated acids **61** (X = OH) are readily synthesized via ylide-anion formation and hydrolysis (KOH/H_2O−MeOH) from **58** (X = OMe) in 90−95% yields.[47]

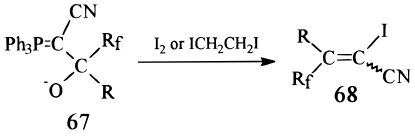
Similarly perfluoroalkylated α,*β*-unsaturated nitriles **62** could be synthesized via ylide-anion formation from [(perfluoroacyl)cyanomethylene]triphenylphosphoranes in 90−98% yields with high *E*-stereoselectivity (*E*:*Z* = 100−86:0−14).[48]



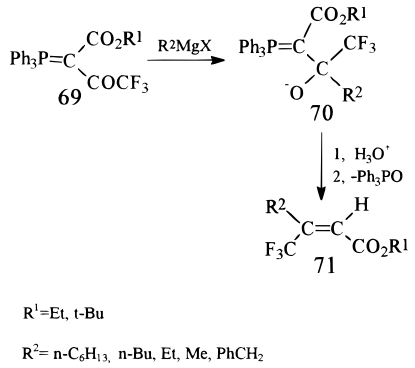
The ylide-anions **64** resulting from nucelophilic addition of lithium reagents react with *N*-bromosuccinimide or *N*-chlorosuccinimide, affording perfluoroalkylated α-bromo or α-chloro α,*β*-unsaturated esters or nitriles **66** in 62−90% yields (Scheme 28).[49,50]

The nature of the substituents in the chloroalkenes may play an important role in determining the stereoselecivity of the reaction. It can be rationalized as shown in Scheme 29. The reaction is initiated by electrophilic attack of NCS on the ylide-anion, forming two diastereoisomeric betaines **65a** and **65b** in equilibrium. The energies of the betaines depend on the steric interference between the individual pairs of "eclipsed" substituents. As a result of the different energies of betaines the equilibrium can shift

Scheme 30



Scheme 31



R^1=Et, t-Bu

R^2= n-C_6H_{13}, n-Bu, Et, Me, $PhCH_2$

toward isomer **65a** or **65b**. The relative steric bulk of CF_3 and R groups, and hence their interaction with Cl and R′, seems to control the stereochemical results.

In the case where R′ = CO_2Bu-*t*, a bulky group, the ratio of *E*-isomer decreases as the group size R is decreased (R = *sec*-Bu, *E*:*Z* = 100:0; R = *n*-Bu, *E*:*Z* = 73:27; R = PhC≡C, *E*:*Z* = 30:70). In the first case, the largest groups (*sec*-Bu, CO_2Bu-*t*) are located *trans* with respect to one other in intermediate **65a**, and the resulting preferred conformation with lower energy undergoes decomposition to give the *E*-isomer, while in the last case the location of the largest groups (CF_3 and CO_2Bu-*t*) in a *trans* configuration in intermediate **65b** resulted in the conformation with somewhat lower energy which undergoes decomposition to give a mixture of two isomers.

An attempt to react ylide-anions **67** with *N*-iodosuccinimide failed. However, they did react with either iodine or 1,2-diiodoethane, giving perfluoroalkylated α-iodo-α,β-unsaturated nitriles in 70−97% yields (Scheme 30).[51]

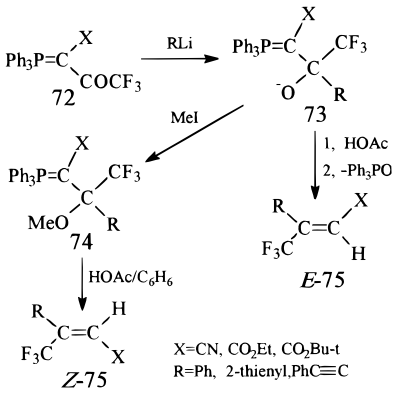
Stereocontrolled Olefination Methodology

Control of the stereochemistry is very important in the synthesis of unsaturated natural products with biological activity.[52] Therefore, the development of an effective method for stereocontrolled olefination should be valuable.

Fluorinated dicarbonyltriphenylphosphoranes **69** reacted with a variety of Grignard reagents to give the ylide-anions **70** (Scheme 31). Treatment of **70** with saturated aqueous methylamine hydrochloride, followed by elimination of triphenylphosphine oxide, gave trifluoromethylated α,β-unsaturated esters **71**, with the *Z*-isomers being the major products in 85−94% yields (*Z*:*E* = 94−90:6−10), while treatment of **70** with 5% aqueous hydrochloric acid under the same conditions afford predominantly the *E*-isomer of **71** in 72−95% yields (*E*:*Z* = 100−75:0−25).[53]

Perfluoroalkylated α,β-unsaturated esters with the *E*-isomers as the major products could be conveniently

Scheme 32



synthesized by way of fluorinated β-ketophosphonium salts (Scheme 18)[22] and via the formation of ylide-anions (Scheme 27).[45] Similarly the *E*-isomer was obtained as the major product in the preparation of perfluoroalkylated α,β-unsaturated nitriles.[48] Further, only *E*-stereoselectivity was observed in the synthesis of perfluoroalkylated α,β-unsaturated esters from ylide-anions **70** generated from phenyl Grignard reagent and fluorinated dicarbonyltriphenylphosphoranes.[53] All these methodologies gave predominantly *E*-isomers.

Recently we found a novel conversion of *E*-stereoselectivity to *Z*-stereoselectivity in the synthesis of trifluoromethylated α,β-unsaturated esters and nitriles by way of O-methylation of an ylide-anion.[54] Reaction of fluorinated phosphoranes **72** with organolithium reagents gave the ylide-anions **73**, which, after protonation and elimination of triphenylphosphine oxide, afforded (***E***)-**75** as the major products (*E*:*Z* = 100−88:0−12) in 88−98% yields (Scheme 32). Before protonation, the ylide-anions **73** were allowed to react with methyl iodide to afford O-methylated products **74** which could be hydrolyzed by acetic acid to give (***Z***)-**75** as the major products (*Z*:*E* = 92−62:8−38) in 85−94% yields. The *Z*- and *E*-isomers could be separated conveniently by column chromatography on silica gel or by fractional distillation.

Concluding Remarks

The fluorinated β-ketophosphonium salts can be utilized as reagents for the synthesis of a great variety of functionalized perfluoroalkylated alkenes. Examples are fluoroalkenes, fluoro enynes, fluoro dienes, bis(perfluoroalkyl) enynes, fluorovinylic epoxides, trifluoromethylated vinylcyclopropanes, trifluoromethylated α,β- and β,γ-unsaturated esters, perfluoroalkylated alkadienoic esters and amides, perfluoroalkyl alkyl ketones, perfluoroalkylated vinyl and allylic phosphonates, phosphoryl fluoroepoxides, fluoroalkyl phenyl sulfides, fluorovinyl heterocyclic compounds, fluorovinyl dithianes, perfluoroalkylated vinyl esters, perfluoroalkylated β-hydroxy ketones, perfluoroalkylated vinyl ethers, and perfluoroalkylated 1,4-dienes. These compounds would be difficult to prepare by other methods. A fluorine atom or perfluoroalkyl group substituted in compounds can often enhance their biological activity, and organofluorine compounds have been ap-

plied increasingly in pharmaceuticals, agrochemicals, and other fields, as exemplified in vitamin A and pheromone chemistry.[8b,c,34,54b] α-Fluoro α,β-unsaturated esters (**48**) have been used successfully as intermediates in the synthesis of monofluorinated retinoids, insect sex pheromones, and pyrethroids.[34,54b] Therefore, they would be useful intermediates for the synthesis of fluorine-containing biologically active compounds, particularly in the field of medicinal and agricultural chemistry.

"One-pot" carbon−carbon double bond formation methodology greatly simpifies the traditional Wittig reaction into a stereospecific alkenylation methodology and compresses the three steps of a Wittig reaction into a one-step, one-pot synthesis. A novel ylide-anion formation, which is different from Corey's deprotonation method and results from nucleophilic addition of organometallic reagents, was found. This method provides a means of using very stable fluorinated ylides in the synthesis of functionalized perfluoroalkylated alkenes. Stereocontrolled olefination methodology includes a conversion of *E*-stereoselectivity to *Z*-stereoselectivity in the synthesis of trifluoromethylated α,β-unsaturated esters and nitriles by way of O-methylation of a ylide-anion.

In summary, all these new synthetic methodologies for carbon−carbon double bond formation with high stereoselectivity are potentially a useful approach in organic synthesis particularly in the fields of medicinal and agricultural chemistry for the synthesis of biologically active compounds.

I much appreciate my able graduate students and colleagues, whose names are cited in the references, for their contributions, which made all of this possible. The funding for this research has come from the National Natural Science Foundation of China, Laboratory of Organometallic Chemistry, and Academia Sinica.

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AR970060I