Pergamon

SCIENCE DIRECT®

Tetrahedron 59 (2003) 1369–1380

TETRAHEDRON

Tetrahedron report number 632

Synthetic methods for α-substituted cyclic α,β-enones

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Received 16 December 2002

Contents

1. Introduction

The introduction of a functional group at the α-position of α,β-unsaturated carbonyl derivatives and related compounds is an important protocol in organic chemistry. The resulting adducts such as **1**–**3** are useful intermediates in organic synthesis[1–3] and, moreover, a number of them exhibit biological activities[4] (Fig. 1).

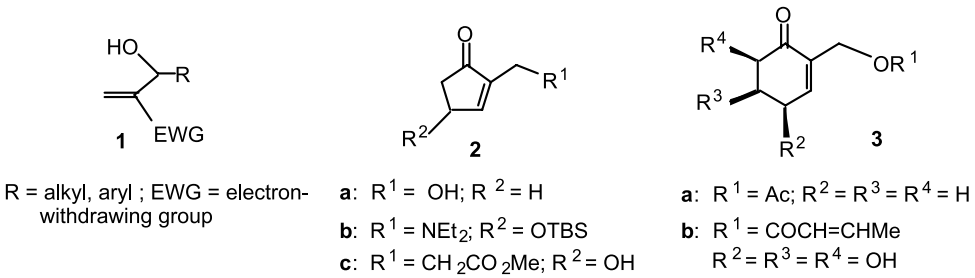

Figure 1.

Keywords: α-substituted cyclic α,β-enones; β-dicarbonyl compounds; carbon–carbon bond.

Abbreviations: Ac, acetyl; 9-BBN, 9-borabicyclo[3.3.1]nonane; *m*-CPBA, *m*-chloroperbenzoic acid; DABCO, 1,4-diazabicyclo[2.2.2]octane; DBU, 1,8-diazabicyclo[5.4.0]undec-7-ene; DDQ, 2,3-dichloro-5,6-dicyano-1,4-benzoquinone; Dibal, diisobutylaluminium hydride; DMAP, 4-*N*,*N*-dimethylaminopyridine; DMF, *N*,*N*-dimethylformamide; E^+, electrophile; EWG, electron-withdrawing group; L, ligand; NMP, *N*-methyl-2-pyrrolidinone; Nu^-, nucleophile; PCC, pyridinium chlorochromate; Ph, phenyl; Py, pyridine; TBDMS, *t*-butyldimethylsilyl; Tf, trifluoromethylsulfonyl; TMSCl, trimethylsilyl; Ts, tosyl (*p*-toluenesulfonyl).

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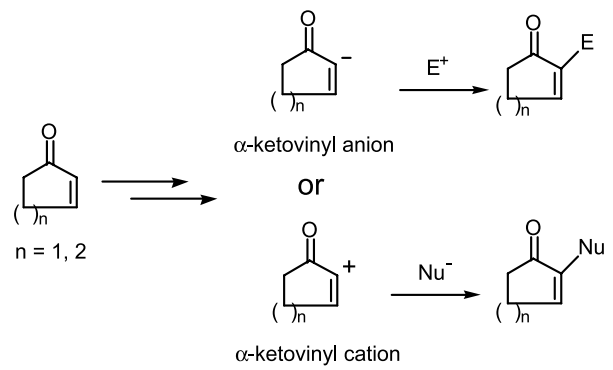
doi:10.1016/S0040-4020(03)00035-8



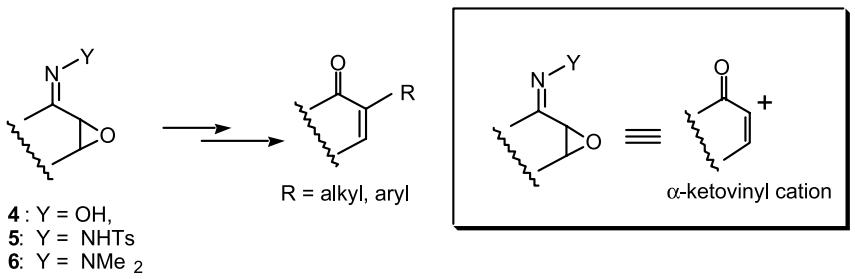
Scheme 1.

The α-hydroxyalkylation of various non-cyclic Michael acceptors (i.e. acrylates, acrylonitrile, methyl vinyl ketone, vinyl sulfones and vinyl phosphonates), via the Baylis–Hillman reaction, allowed an efficient access to polyfunctional derivatives **1** and has recently been reviewed by Basavaiah.[1] Although the popularity of β′-functionalised cyclic α,β-enones, as useful synthons in organic syntheses has been increasing during the last decade, their preparation has never been reviewed. In this paper, we wish to report various methods allowing access to α-substituted cyclic α,β-enones.

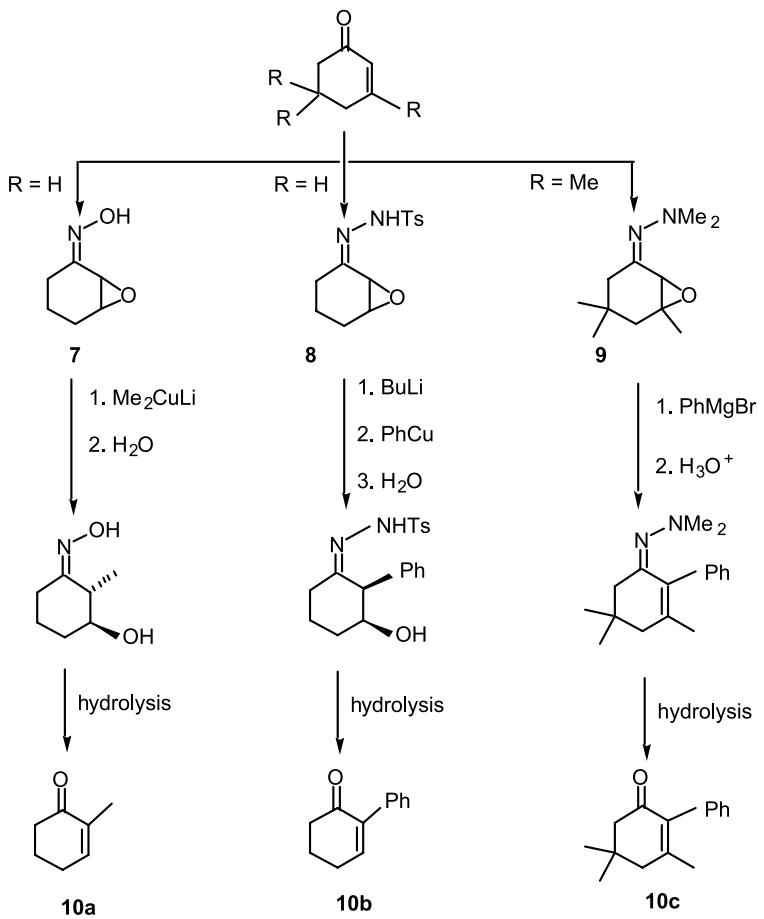
2. Synthesis of α-substituted cyclic α,β-enones

2.1. Using a latent α-ketovinyl anion (cation) equivalent

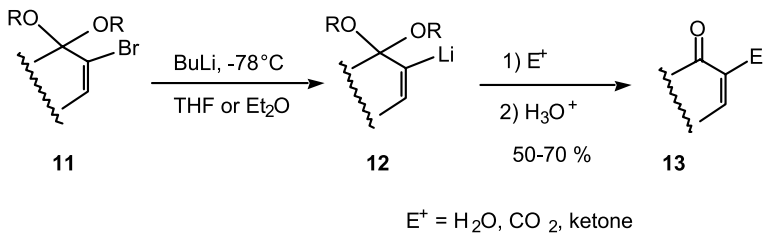
An ideal synthetic approach for α-substituted cyclic



Scheme 2.



Scheme 3.

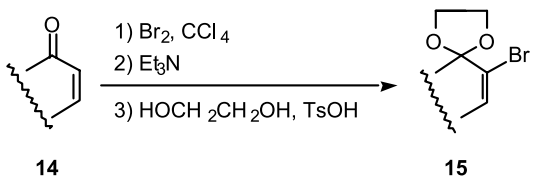


Scheme 4.

α,β-enones would be accomplished directly from the corresponding parent enones without the intervention of the thermodynamic dienolate. This protocol required the generation of the corresponding α-ketovinyl cation or the α-ketovinyl anion, followed by its capture by an appropriate nucleophile (Nu^-) or electrophile (E^+), respectively (Scheme 1).

In this regard, three groups (Corey,[5] Fuchs[6] and Stork[7]) have developed a reverse polarity (umpolung) strategy for α-alkylation and α-arylation of α,β-enones. They have independently demonstrated that α,β-epoxyketone derivatives (oximes **4**, tosylhydrazones **5** and *N*,*N*-dimethylhydrazones **6**) are versatile latent equivalents for the α-ketovinyl cation and may be converted to α-alkylated- and α-arylated cyclic α,β-enones (Scheme 2).

Indeed, the α,β-epoxyoxime **7**, α,β-epoxytosylhydrazone **8** and α,β-epoxy-*N*,*N*-dimethylhydrazone **9** reacted with organometallic reagents (RMgX, RLi and R_2CuLi) to produce the corresponding α alkyl- or α-aryl-β-hydroxy-nitrogen derivatives which may be dehydrated to give the desired α-alkylated or α-arylated enones **10** (Scheme 3).



Scheme 5.

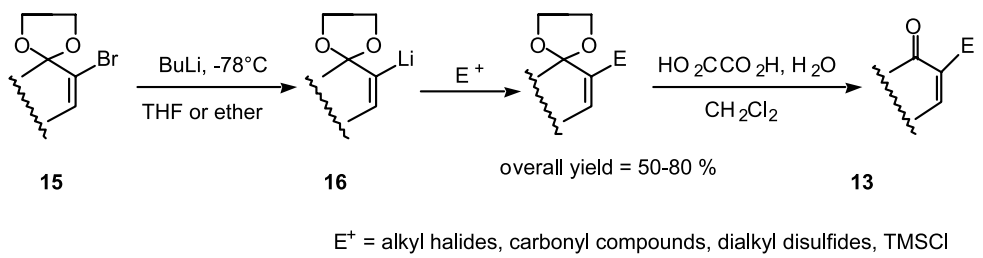
On the other hand, Ficini,[8a] House[8b] and Swenton[8c] have showed that α-bromoketals **11** could be used as a latent equivalent for the α-ketovinyl anion and metallation of the functionalised vinyl bromide derivatives **11** with BuLi at −78°C afforded the required α-ketovinyl anion **12**. Subsequent electrophilic capture gave, after hydrolysis, the desired α-substituted α,β-enones **13** (Scheme 4).

Accordingly, Smith et al.[9] have, more recently, developed a ketovinyl anion methodology for the conversion of cyclic enones **14**, in numerous steps, to their respective α-substituted enones **13**. Towards this end, firstly, the α-bromoketals **15** were prepared in a three-step sequence: (a) bromination (b) dehydrobromination and (c) ketalisation of the resulting α-bromoenone (Scheme 5).

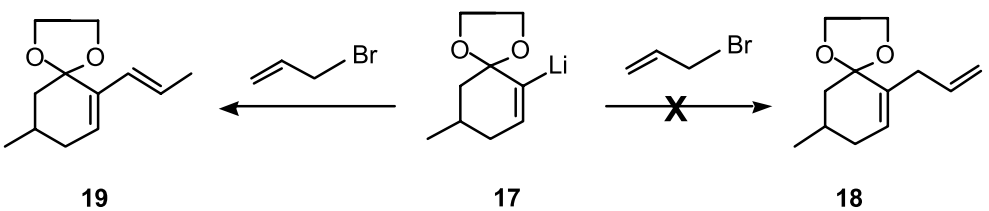
Treatment of **15** with BuLi in THF at −78°C led smoothly to the α-ketovinyl anions **16** which were trapped by various electrophiles (alkyl halides, carbonyl compounds, TMSCl and dimethyl disulfide) to give, after acidic hydrolysis, the corresponding α-substituted enones **13** in moderate to good yields (Scheme 6).

Unfortunately, this procedure did not represent a general solution for the construction of various α-substituted cyclic α,β-enones. Kraus and co-workers[10] have observed that the coupling reaction of the α-ketovinyl anion **17** with allyl bromide did not furnish the desired compound **18** but the corresponding isomerised ketal **19** (Scheme 7).

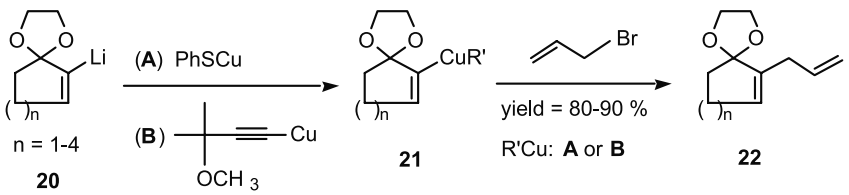
Majetich[11] encountered the same difficulties when he has



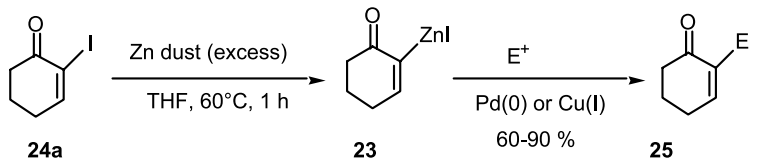
Scheme 6.



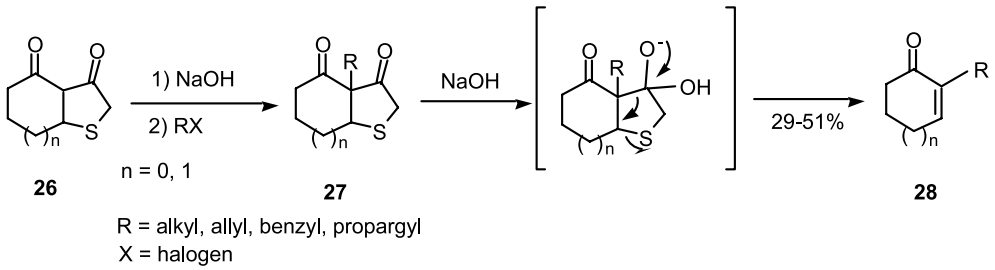
Scheme 7.



Scheme 8.



Scheme 9.



Scheme 10.

attempted to prepare 1,4-dienes by coupling α-ketovinyl anion equivalents with functionalised allylic iodides. A solution to this synthetic problem was developed by transmetallation of the vinyl lithium derivative **20** with organocopper reagents. Indeed, **20** reacted with either phenylthiocopper (**A**) or 3-methyl-3-methoxy-1-butynyl-copper (**B**) to afford the Gilman reagents **21** which, in its turn, reacted with allyl bromide to generate the desired α-allylated cyclic enones as their ethylene ketals **22** in good yields (Scheme 8).

This methodology was successfully applied to various electrophiles such as benzylic, allylic and propargylic halides as well as allyl acetates, alkyl iodides, bromo-acetaldehyde diethyl acetal, acetyl chloride and some Michael acceptors.

Recently, Knochel[12] has showed that Pd(0)- or Cu(I)-catalysed cross-coupling reactions between 6-oxocyclo-hexen-1-ylzinc iodide **23**, prepared from the reaction of the vinyl iodide derivative **24a** and zinc dust (10 equiv.) in THF at 60°C, with various activated allyl, vinyl or aryl iodides (bromides), furnished the polyfunctional 2-alkenylated- or 2-arylated 2-cyclohexenones **25** in 60–90% yield (Scheme 9).

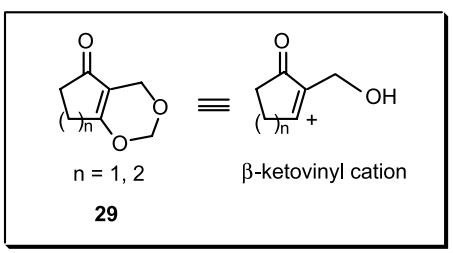
Besides these organometallic methodologies, the bicylic β-diketones **26**[13] can be employed as latent α-ketotovinyl anion equivalents. In fact, these carbonyl compounds reacted with reactive halides, in the presence of K_2CO_3 in refluxing ethanol, to afford the 2-alkylated intermediates **27**. Further treatment of these derivatives with 50% aqueous NaOH in heterogenous media (Et_2O–H_2O), furnished through a tandem reversed Dieckman–Michael addition, the 2-substituted cyclic enones **28** in moderate yields (Scheme 10).

This protocol was found successful with various halide and sulfide derivatives as well as ethylbromoacetate.

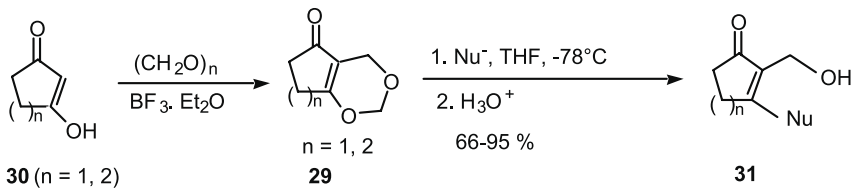
2.2. From a β-ketovinyl cation equivalent

Smith and co-workers[14] have reported that the 1,3-dioxin vinylogous esters **29** are versatile β ketovinyl cation equivalents for α-hydroxymethylated cyclic enones (Scheme 11).

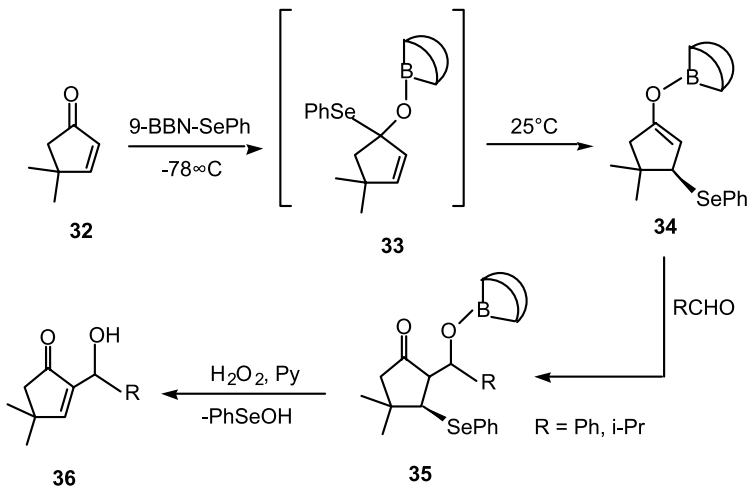
This synthetic approach involves the $BF_3{\cdot}Et_2O$-catalysed Prins[15] reaction of the cyclic 1,3-diketones **30** and either formaldehyde or trioxane. The resulting 1,3-dioxins **29** underwent, in the presence of organolithium derivatives and DIBAL, a reductive and alkylative 1,3-transposition to



Scheme 11.



Scheme 12.

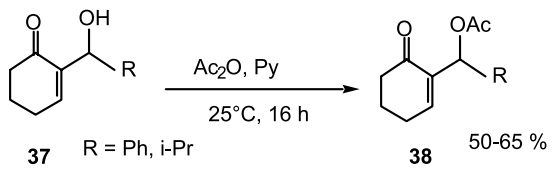


Scheme 13.

give a variety of β-substituted α-(hydroxymethyl) cyclic enones **31** (Scheme 12).

2.3. Via a tandem conjugate addition–aldol reaction

In 1985, it was found that α,β-unsaturated ketones reacted with 9-(phenylseleno)-9-borabicyclononane (9-BBN-SePh).[16] Accordingly, treatment of 4,4-dimethylcyclopent-2-en-1-one **32** with this reagent at −78°C led in quantitative yield to the 1,2-adduct **33**, which was converted at 25°C to the thermodynamically more stable 1,4-Michael adduct **34**. Subsequent aldol condensation, employing benzaldehyde or *i*-PrCHO to give **35**, followed by elimination of phenylselenic acid (H_2O_2, C_5H_5N, 0–30°C), gave the ketol derivatives **36** in 67% yield (Scheme 13).

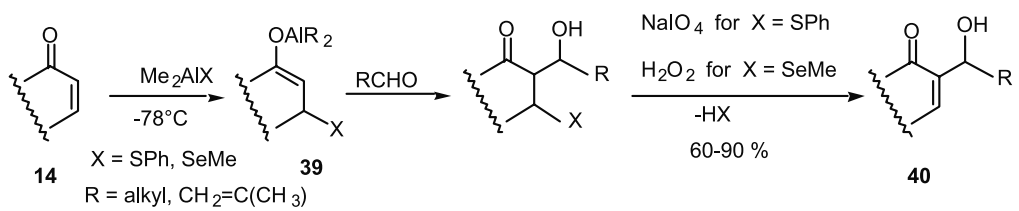


Scheme 14.

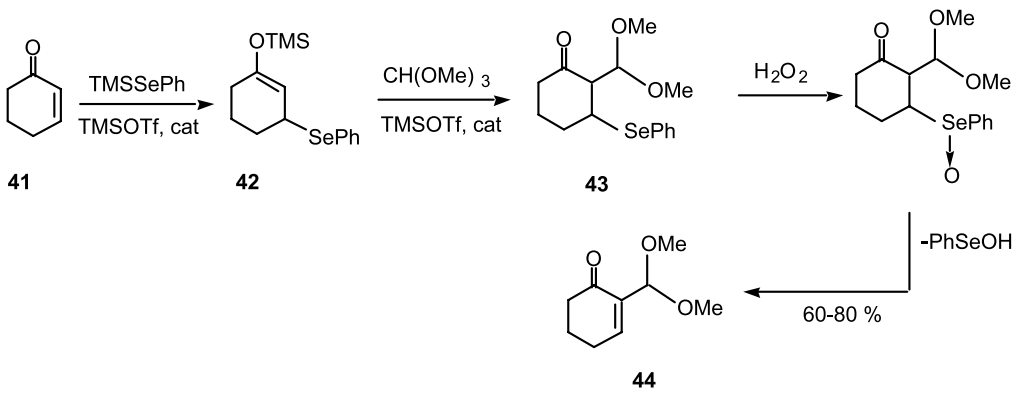
Surprisingly, when this protocol was applied to 2-cyclohexenone, it was found that the resulting ketol adduct **37** was unstable towards chromatographic separation and the crude product was acetylated (Ac_2O, C_5H_5N, 25°C, 16 h) to the stable ketoacetate **38** in good overall yields (Scheme 14).

Furthermore, Oschima et al.[17] have reported that the Michael addition of Me_2AlSPh or $Me_2AlSeMe$ on α,β enones **14** gave the corresponding aluminium enolates **39**, which were trapped by aliphatic aldehydes and methacrolein to afford, after elimination of PhSH or MeSeH, the ketol adducts **40** in moderate to good yields (Scheme 15).

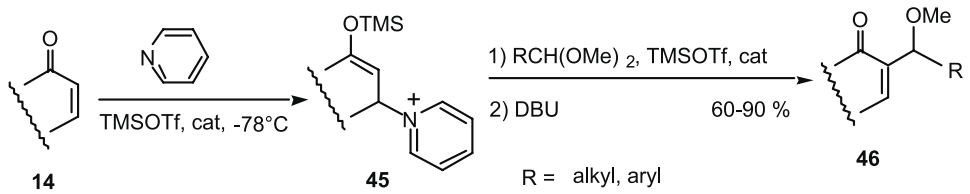
In addition, the reaction of cyclic enones such as **41**[18] with trimethylsilyl phenyl selenide in the presence of a catalytic amount of TMSOTf in CH_2Cl_2 generated the silylated enolate **42**, which was coupled with orthoesters and acetals to give the aldol-type product **43**. Oxidation of **43** with H_2O_2 gave, after elimination of PhSeOH, the desired β′-functionalised enone **44**. This process is represented as



Scheme 15.



Scheme 16.



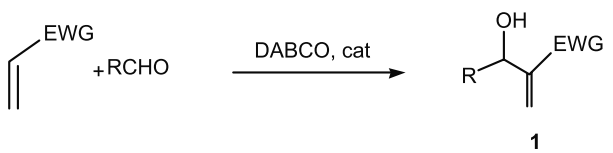
Scheme 17.

an indirect α-dimethoxymethylation of 2-cyclohexenone **41** (Scheme 16).

More recently, Kim and co-workers[19] have described a novel procedure for the α-alkoxyalkylation of α,β-enones through pyridiniosilylation in a three-step sequence. It began with a TMSOTf-promoted Michael addition of pyridine to the α,β-unsaturated ketones **14** at −78°C. Subsequently, the coupling reaction of the resulting silyl enol ethers **45** with acetals in the presence of TMSOTf, followed by the β-elimination of pyridine with DBU, generated the α-(alkoxyalkyl) enones **46** (Scheme 17).

2.4. Baylis–Hillman reaction

The Baylis–Hillman reaction[1] is considered to be one of the most facile coupling protocols between activated alkenes and aldehydes, allowing the introduction of an hydroxyalkyl moiety at the α-position of Michael acceptors. Tertiary amines such as 1,4-diazabicyclo[2.2.2]octane (DABCO) or 3-hydroxyquinuclidine (3-HQ) are usually used as catalysts in this process (Scheme 18).



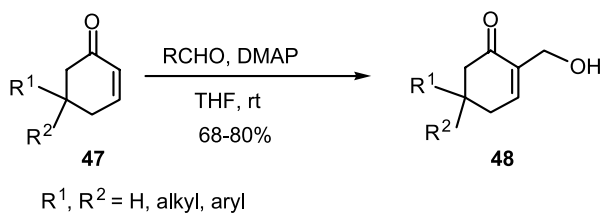
Scheme 18.

During the last decade, several authors[20] have, however, showed that the standard reaction conditions (i.e. DABCO or 3-HQ at room temperature) usually employed to functionalise non-cyclic Michael acceptors failed when they were applied to cyclic enones.

The first examples concerning the α-hydroxymethylation of 2-cyclohexenones **47** were reported recently by El Gaïed et al.[21] who showed that these enones reacted with aqueous formaldehyde, in the presence of DMAP as a catalyst, in THF to generate the 2-(hydroxymethyl)-2-cyclohexenones **48** in fair to good yields (Scheme 19).

In addition, the same authors have observed that, under these conditions, a Baylis–Hillman reaction did not occur when the 2-cyclohexenones **49** are bearing, at the β-position, an electron-withdrawing or -donating group (Fig. 2).

Although the Baylis–Hillman methodology produced highly functionalised adducts such as **1**–**3** which may serve as the starting materials for the synthesis of useful targets, the reaction rate is generally very slow. In order to enhance the reactivity of cyclic enones towards aldehydes,



Scheme 19.

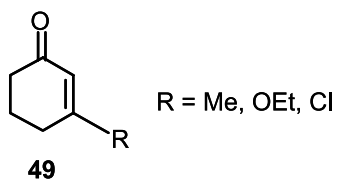
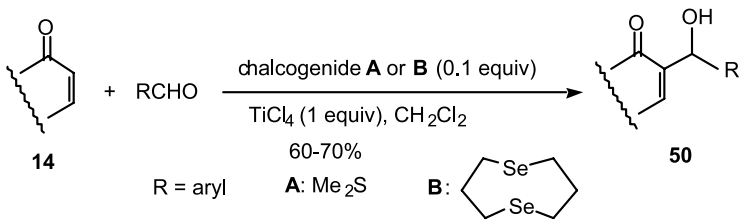
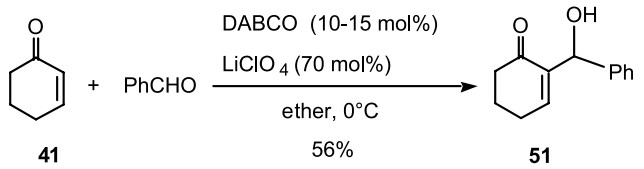


Figure 2.



Scheme 20.



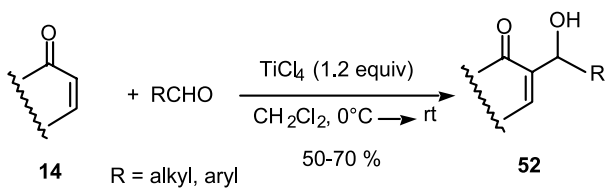
Scheme 21.

much effort has been undertaken using Lewis acids and especially $TiCl_4$. Aggarwal and co-workers[22] have shown that Lewis acids such as $TiCl_4$ and $BF_3{\cdot}OEt_2$ decelerated the Baylis–Hillman reaction conducted in the presence of DABCO, due to the formation of amine–Lewis acid complexes. Kataoka et al.[23] have shown, however, that the chalcogeno-Baylis–Hillman reaction catalysed by sulfides **A** and selenides **B** was accelerated by the addition of Lewis acids and the best results were obtained when a such reaction was catalysed by the bis-selenide **B** in the presence of 1 equiv. of $TiCl_4$ in CH_2Cl_2 (Scheme 20).

Unfortunately, under these conditions, only some functionalised allylic alcohols **50** were prepared by the coupling reaction between the cyclic enone **41** and especially activated aromatic aldehydes.

Similarly, Kabayachi[24] has reported, in 1999, that among cyclic enones, only 2-cyclohexenone **41** reacted with benzaldehyde at 0°C, by using DABCO (10–15%) in the presence of 70 mol% of lithium perchlorate ($LiClO_4$), as a co-catalyst, to afford the 2-(hydroxybenzyl)-2-cyclohexenone **51** in moderate yields (Scheme 21).

More recently, Li and co-workers[25] have found that the $TiCl_4$-mediated Baylis–Hillman reaction between cyclic enones **14** (2 equiv.) and both aliphatic or activated aromatic aldehydes (1 equiv.) did not need a catalytic amount of a tertiary amine such as DABCO, and afforded the required compounds **52** in fair yields (Scheme 22).



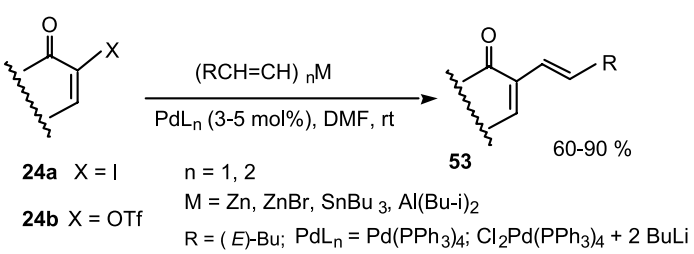
Scheme 22.

2.5. Pd-Catalysed α-alkylation and α-arylation of cyclic enones

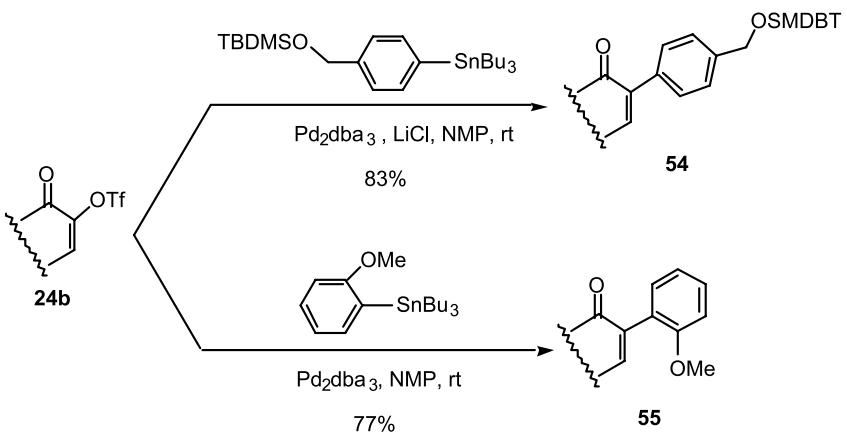
Pd(0) and Pd(II) catalysts are widely employed to produce new carbon–carbon bonds, which are required in a number of important synthetic applications.[26] In the course of the functionalisation of cyclic enones, Negishi[27] has described, in 1981, a direct method allowing the introduction of an (*E*)- or (*Z*)-alkenyl group at the α-position of α-iodo- or α-triflyloxyenones **24** with strict control of the regiochemistry. α-Iodo (α-triflyloxy) cyclic enones can be coupled with alkenylmetal derivatives containing Zn, Al or Sn, in the presence of a palladium catalyst, to generate the corresponding α-alkylated enones **53** in modest to good yields (Scheme 23).

Similarly, Roth and Farina[28] have reported, more recently, that the Pd-mediated cross coupling reaction of α-triflyloxy cyclic enones **24b** with arylstannanes, in NMP (*N*-methyl-2-pyrrolidinone) instead of THF, gave the α-arylated enones **54** and **55** in 77–83% yields (Scheme 24).

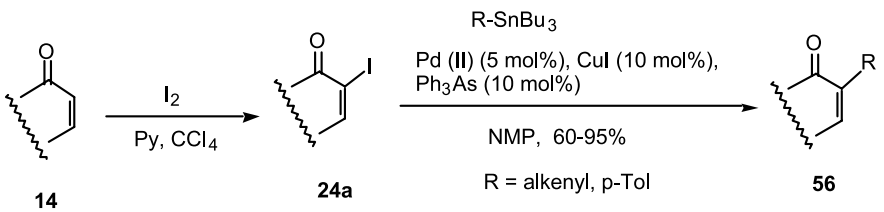
In 1992, Johson and co-workers[29] developed a direct preparation of α-iodocyclic enones **24a** by the reaction between iodine, dissolved in a 1:1 mixture of pyridine–carbon tetrachloride, and the corresponding enones **14**. These α-iodoenones underwent Pd-catalysed coupling reactions with alkenyl- and arylstannanes to afford the α-substituted enones **56** in moderate to excellent yields (Scheme 25).



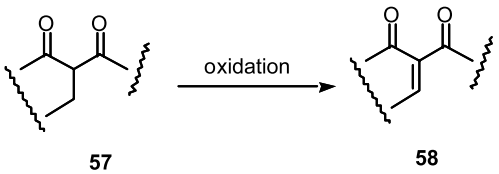
Scheme 23.



Scheme 24.



Scheme 25.



Scheme 26.

2.6. Conversion of β-dicarbonyl compounds to their corresponding α,β-unsaturated derivatives

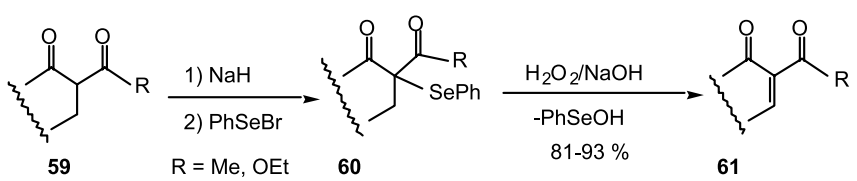
There are a number of methods for the direct introduction of α,β-double bonds into the saturated β-dicarbonyl compounds **57** (Scheme 26).

The most important methods are halogenation–dehalogenation, selenoxide *syn* elimination procedures and DDQ oxidation.

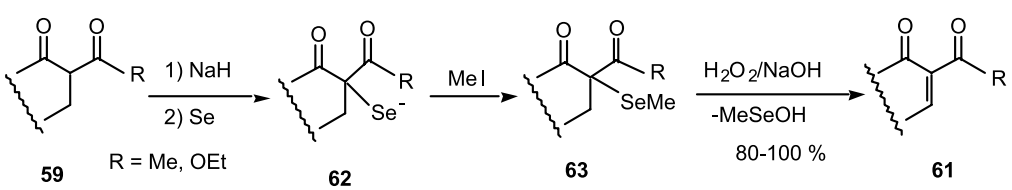
2.6.1. Reich procedure and its modification. In 1975, Reich and co-workers[30] have reported that the reaction of 2-acetyl- and 2-ethoxycarbonyl-2-cyclohexenone **59** with PhSeBr is conveniently carried out at room temperature in the presence of a suspension of NaH in THF. The resulting α-seleno-β-dicarbonyl compounds **60** were oxidised in situ either by H_2O_2–NaOH or by m-CPBA and even by ozonolysis, to afford the desired α,β-unsaturated derivatives **61** in high yields (Scheme 27).

Some years later, Liotta[31] developed a modification of the Reich procedure, which represents the most efficient method available for the synthesis of unsaturated β-dicarbonyl compounds **61**.

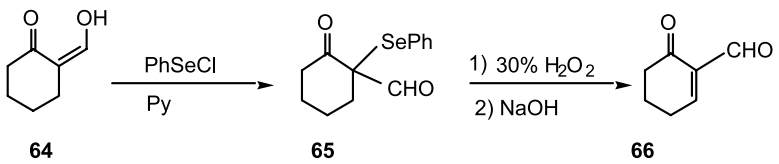
This process involved the conversion of the β-dicarbonyl compounds **59** in the presence of NaH–selenium–RI, instead of NaH–PhSeBr via **62** to their corresponding 2-methylselenyl derivatives **63**. As previously described,



Scheme 27.



Scheme 28.

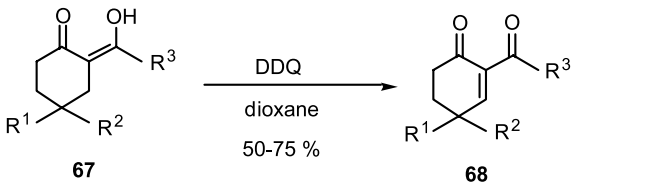


Scheme 29.

these intermediates underwent oxidation, followed by *syn* elimination of the selenoxides, to afford the α,β-unsaturated derivatives **61** (Scheme 28).

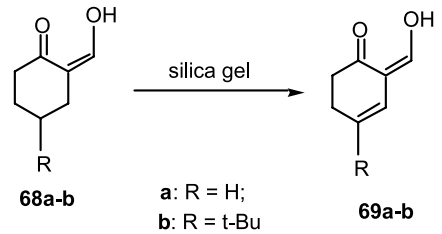
Liotta[32] reported that enolisable β-dicarbonyl compounds (keto-aldehydes and keto-esters) such as α-(hydroxymethylene)cyclohexanone **64** could be also β-selenated in the presence of PhSeCl/pyridine. After removal of the pyridine, the selenated intermediate **65** was oxidised in situ with 30% H_2O_2 to afford the desired compound **66** in good to excellent yields (85–100%). This reaction sequence is illustrated in Scheme 29.

2.6.2. DDQ oxidation. 1,3-Dicarbonyl compounds **67** were rapidly dehydrogenated by 1 equiv. of DDQ in dioxane,

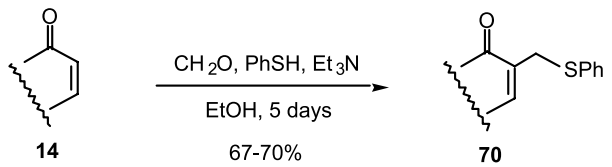


a: R^1, R^2, R^3 = H; **b**: R^1 = t-Bu; R^2 = R^3 = H; **c**: R^1, R^2, R^3 = Me

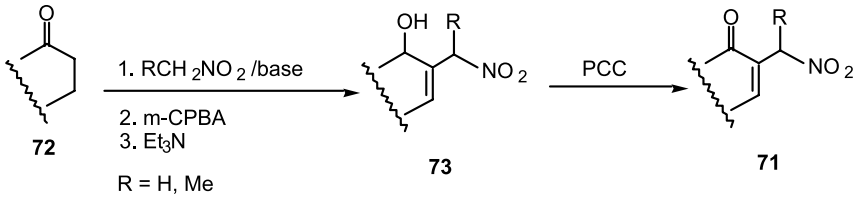
Scheme 30.



Scheme 31.



Scheme 32.



Scheme 33.

with no use of a catalyst, to afford the unsaturated derivatives **68** in modest yields.[33] Indeed, the α-formylenones **68a** and **b** were difficult to isolate without significant loss and they were more sensitive than their homologous 4,4-disubstituted derivative **68c** (Scheme 30).

The authors of this protocol suggested that this sensitivity is at last partly due to their enolisation during purification on column chromatography into the 2-(hydroxymethylene)-3-enones **69a** and **b** which are retained on alumina (Scheme 31).

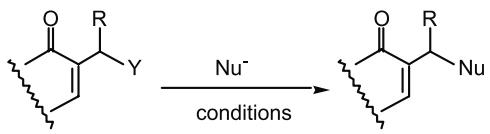
2.7. Other methods

2.7.1. Direct α-phenylthiomethylation of cyclic enones. Phenylthiomethylation of the cyclic enones **14** was carried out in the presence of 1 mol equiv. each of thiophenol, 37% aqueous formaldehyde and triethylamine in refluxing ethanol during 5 days[34] and the allylic sulfur compounds **70** were prepared in fair yields (Scheme 32).

2.7.2. Indirect α-(nitroalkylation) of cycloalkanones. Allylic nitro compounds **71**[35] are readily available from the cycloalkanone parents **72**. This protocol starts with a coupling reaction of these ketones with 1-nitroalkanes in basic conditions, followed by dehydration, to give 1-(nitroalkyl) cycloalkenes, the epoxidation os which using *m*-CPBA in methylene chloride afforded the corresponding nitro-oxiranes. Further oxirane ring opening by triethylamine generated the allylic alcohols **73** which are oxidised by PCC in methylene chloride, to provide the required allylic nitroalkyl enones **71** (Scheme 33).

2.7.3. Reactions of various nucleophiles with β′-functionalised cyclic enones. Tamura et al.[36] have reported that the regioselective substitution of the nitro- and sulfonyl groups in α-(nitroalkyl)- and α-(phenylsulfonyl) enones **74** by various nucleophiles such as amines, $PhSO_2Na$ and stabilised carbanions derived from dimethyl malonate in DMF afforded the corresponding β′-functionalised cyclic enones **75** (Scheme 34).

More recently, we have shown[3a,b,37] that α-(acetoxymethyl)-2-cyclohexenone **74** underwent in THF a regioselective replacement of the acetoxy group by amines and



74 75

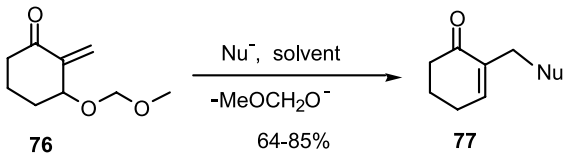
Ref. 36: R = H, Me; Y = NO_2, $PhSO_2$; Nu^- = amines, $PhSO_2Na$, dimethyl malonate; solvent: DMF

Ref. 37, 3a,b: R = H; Y = OAc; Nu^- = amines, β-dicarbonyl compounds; solvent: THF

Scheme 34.

stabilised carbanions derived from various β-dicarbonyl compounds to provide the overall S_N2-type products **75** (Scheme 34).

2.7.4. Reactions of various nucleophiles on 2-methylene-3-(methoxymethyloxy) cyclohexanone. The 1,4-addition of a variety of nucleophiles (i.e. amines, stabilised carbanions and Gilman reagents) on the exocyclic enone **76**[38] in an appropriate solvent (THF or benzene) led after elimination of the alkoxy group to the α-substituted 2-cyclohexenones **77** in 64–85% yields (Scheme 35).



76 77

Nu^- = amines, enolates, R_2CuLi

Scheme 35.

3. Conclusions

Since the discovery of interesting targets in which cyclic enone derivatives represent the main structural feature, much attention has been directed to the development of new routes to these polyfunctional compounds. Most of the synthetic alternatives reviewed in this paper are based on coupling reactions between cyclic enones and a wide variety of electrophiles. Among these methods, the Baylis–Hillman reaction has emerged during the last decade because of its efficiency and its facile use in mild conditions. A more systematic investigation of this process is, however, needed to permit its successful application to useful targets and in asymmetric synthesis.

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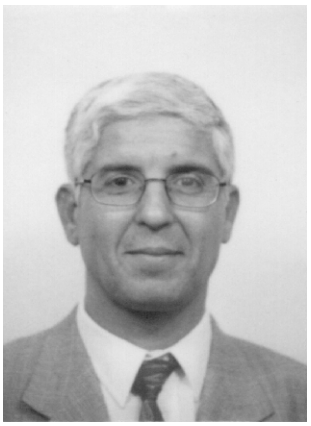
Biographical sketch



Farhat Rezgui was born in Bou Salem, Tunisia. In 2000, he received his Doctorat d'Etat from the University of Tunis, under the direction of Professor M. M. El Gaïed. In the course of the collaboration with Professor J. F. Normant's group, Paris 6, he worked (1996–1999) with Dr P. Mangeney and Professor A. Alexakis on the chiral dihydroquinolines. In 2000, he moved to the IPEST, Tunis where he currently is a Professor of Organic Chemistry. His research interests concentrate on the development of new methods in organic synthesis and include the functionalisation of cyclic enones as well as the preparation and reactivity of cyclic Baylis–Hillman adducts.

Hassen Amri was born in Tabarka, Tunisia. He studied chemistry at the University of Tunis El Manar and received his doctorat de troisième cycle in 1983 from this university. From 1985 to 1988 he worked in the group of Villiéras (DR, CNRS) at the University of Sciences et Techniques de Nantes (France) to obtain his doctorat d'Etat. In 1992 he became Professor of organic chemistry at the University of Tunis El Manar, and since 1996 he is full Professor. His current interests include the development of new methodologies in Organic synthesis in the area of organometallic chemistry, with special focus on the synthesis of new synthons and their further transformations into biological active compounds: ± sarkomycin, methylenomycin B, ± mitsugashiwalactone and functional α-alkylidene γ-lactams. In 1998, he is elected to the leading committee of the Tunisian Chemical Society as vice president and in 2000 he became Editor-in-Chief of the Journal of the same Society.

Mohamed Moncef El Gaïed obtained his Maitrise es-sciences in chemistry from the Faculty of Sciences of Tunis in 1967 and his Doctorat de Spécialité in 1971 and his Doctorat d'Etat in 1973 from the University of Paris VI under the direction of Dr Yvonne BESSIERE (Directeur de Recherche, Laboratoire de l'Ecole Normale Supérieure, Paris). In December 1973, he came back to Tunis and started his career in the Faculty of Sciences, first as Maître de Conférences and then as Professor. His research interests concentrate mainly on the study of monoterpenes reactions and synthesis of fluorinated compounds and the discovery of easily accessible reagents leading to Baylis–Hillman adducts from cyclic substrates. He has previously held senior research fellow (October 1980–September 1981) at the University of Southampton where he worked with Professor Richard. C. COOKSON on an approach towards the total synthesis of an unusual antibiotic, known only by the code number k-76, which has the interesting property of inhibiting the complement system. He is the recipient of the Ordre National du Mérite (deuxième classe) for Education and Sciences and the Ordre de la République (Chevalier).