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Conjugated enynones: preparation, properties and applications in organic synthesis

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Published data on the preparation methods, properties and chemical transformations of linear- and cross-conjugated enynones are integrated. The molecular and crystal structures, spectral characteristics and non-linear optical properties of these compounds are considered. Data on the reduction of enynones to alcohols and on electrophilic, nucleophilic and pericyclic reactions involving them are described systematically. Primary attention is paid to the regioselectivity and mechanisms of transformations of conjugated enynones. Examples of their application in the targeted organic synthesis of carbo- and heterocyclic compounds are given.
The bibliography includes 250 references.

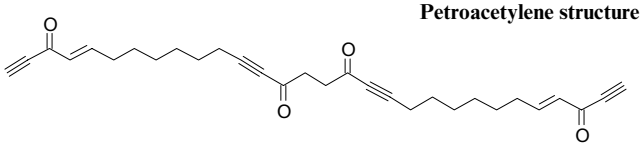
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1. Introduction

The number of studies devoted to the syntheses based on enyne ketones (vinylacetylenic ketones, enynones) — compounds containing double and triple carbon – carbon bonds conjugated with an oxo group — has considerably increased in recent years. The interest in these polyfunctional substrates is caused, first of all, by their availability and reactivity towards a broad range of nucleophiles and dipoles, which makes them valuable building blocks for the targeted organic synthesis of practically significant compounds, including natural products [1–3] and their analogues.[4,5] It is noteworthy that the enynone moiety is also present in the living nature, mainly in plants, fungi and some sea organisms.[6] For example, a 30-carbon polyacetylene compound, petroacetylene, was recently isolated from the sea sponge *Petrosia solida*.[7]

Petroacetylene structure



Owing to the presence of several chemically different reaction centres in the molecule, conjugated enynones are efficiently used for selective preparation of complex oxygen-,[8–10] nitrogen-[11–14] and sulfur-containing [15–17] heterocycles and carbocycles.[18,19] In addition to synthetic applications, there compounds are promising materials for non-linear optics.[20,21] Despite the large synthetic potential of conjugated enynones, the extensive literature on the methods for their synthesis, physical properties and chemical transformations has not yet been integrated. The only exceptions are reviews [22,23] addressing the transition metal (copper and gold)-catalyzed reactions of enyne alcohols, aldehydes and ketones and a chapter in a book.[24] A survey paper [6] gives a systematic account of the antitumour properties of natural compounds with this type of structure.

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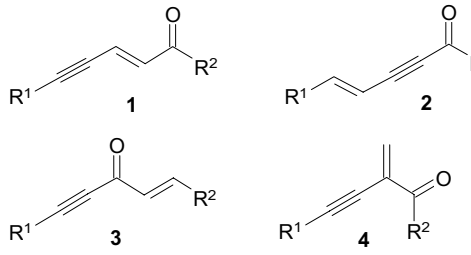
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This review is devoted to the syntheses and chemical transformations of compounds containing alk-2-en-4-yn-1-one and alk-4-en-2-yn-1-one moieties (linear-conjugated enynones **1** and **2**, respectively) and also an alk-1-en-4-yn-3-one moiety (cross-conjugated enynones **3**).

We consider the spectral and non-linear optical properties of these compounds, reduction to alcohols, electrophilic and nucleophilic reactions, cyclocondensation with polynucleophiles, cycloaddition and transformations in superacid media. The attention is focused on the data gained in the last 15 years; earlier publications are cited only if they are of prime importance. It is noteworthy that the chemistry of enynones **3** is described in most detail; this is apparently attributable to their higher availability in preparative quantities. Linear-conjugated analogues **1** and **2** are much less studied. 2-Methylenebut-3-yn-1-ones **4** are beyond the scope of this review, as they differ in the reactivity from classical enynones **1** – **3** ; systematization of the methods for their synthesis and chemical behaviour may form the subject of a separate publication. The published data on the chemical reactivity of compounds **4** under the action of gold compounds are summarized in a review.[23]

Structures 1 – 4



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

The following abbreviations are used:

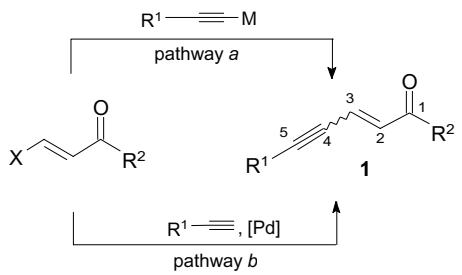
acac — acetylacetonate,
BINAL-H — binaphthyl-lithium aluminium hydride,
Boc — *tert*-butoxycarbonyl,
BrettPhos — (2′,4′,6′-triisopropyl-3,6-dimethoxybiphenyl-2-yl)dicyclohexylphosphine,
cod — cycloocta-1,5-diene,
Cp — cyclopentadienyl,
CPME — cyclopentyl methyl ether,
CPVAP — calcium phosphate-vanadate apatite,
Cy — cyclohexyl,
DABCO — 1,4-diazabicyclo[2.2.2]octane,
dba — dibenzylideneacetone,
DBU — 1,8-diazabicyclo[5.4.0]undec-7-ene,
DCE — 1,2-dichloroethane,
DDQ — 2,3-dichloro-5,6-dicyano-1,4-benzoquinone,
DFT — density functional theory,
DMA — dimethylacetamide,
DMAP – 4-dimethylaminopyridine,
DMP — Dess – Martin periodinane,
dppp — 1,3-bis(diphenylphosphino)propane,
dr — diastereomeric ratio,
ee — enantiomeric excess,
EWG — electron-withdrawing group,
Fu — furyl,
IBX — 2-iodoxybenzoic acid,
Me-CBS — 1-methyl-3,3-diphenyltetrahydro-3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole,
MW — microwave radiation,
NaOAs — sodium ascorbate,
Naph — naphthyl,
NOESY — nuclear Overhauser effect spectroscopy,
NuH — nucleophile,
PCC — pyridinium chlorochromate,
PhthN — phthalimido,
PIDA — phenyliodonium diacetate,
PIFA — phenyliodonium bis(trifluoroacetate),
ProPhenol — 2,6-bis({2-[hydroxy(diphenyl)methyl]pyrrolidino}methyl)-4-methylphenol,
Py — pyridyl,
Red-Al — sodium bis(2-methoxyethoxy)aluminium hydride,
rt — room temperature,
Solv — solvent,
TBAT — tetra-n-butylammonium difluorotriphenylsilicate,
TBDPS — *tert*-butyldiphenylsilyl,
TBS — *tert*-butyldimethylsilyl,
TEMPO — (2,2,6,6-tetramethylpiperidin-1-yl)oxyl,
Tf — trifluoromethanesulfonyl (triflyl),
TFA — trifluoromethyl acetate,
TFE — 2,2,2-trifluoroethanol,
Th — thienyl,
THP — tetrahydropyran-2-yl,
TIPS — triisopropylsilyl,
TMS — trimethylsilyl,
TPPMS — potassium 3-(diphenylphosphino)benzenesulfonate,
Ts — *p*-toluenesulfonyl (tosyl).

2. Synthesis of enynones

2.1. Alk-2-en-4-yn-1-ones

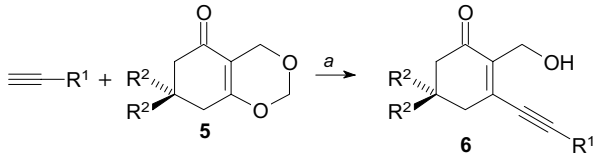
Most methods for the synthesis of alk-2-en-4-yn-1-ones **1** are based on the formation of the C(2) – C(3) or C(3) – C(4) bond of the conjugated enynone system. Usually, this is done by direct cross-coupling of 3-substituted enones and their analogues with organoelement acetylene derivatives[25 – 31] or directly with terminal alkynes[32 – 44] (Scheme 1).

Scheme 1



Lithium acetylenides or Iotzich complexes smoothly react with 3-dimethylaminoenones[25, 26, 30] and 3-alkoxyenones[28, 42] in THF or in ether (path *a*); the yields of enynones normally vary from satisfactory to good. These methods are applicable for the synthesis of alkyl-, aryl- and 1-trifluoromethyl-substituted enynones.[26, 28, 30] Cyclic derivatives can be used as analogues of 3-alkoxyenones. For

Scheme 2



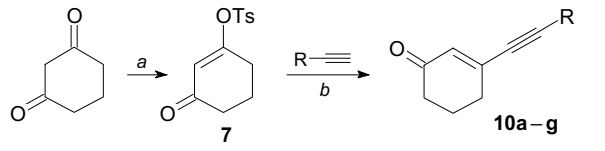
(*a*) 1) Bu^nLi, THF, −78 °C → rt; 2) H^+;
R^2 = H: R^1 = Ph (76% yield), 4-MeC_6H_4 (50%), 4-$MeOC_6H_4$ (72%), 4-$F_3CC_6H_4$ (58%), 3,4-$(MeO)_2C_6H_3$ (78%), 3-Pr^i-4-$MeOC_6H_3$ (75%), Bu^n (75%), cyclo-C_3H_5 (79%); R^2 = Me: R^1 = Ph (69%), 4-MeC_6H_4 (71%), 4-$MeOC_6H_4$ (67%), 4-$F_3CC_6H_4$ (62%)

example, the reaction of 4,6,7,8-tetrahydro-5*H*-1,3-benzo[*d*]dioxin-5-ones **5** with lithium acetylenides gave linear-conjugated enynones **6** with an endocyclic double bond in 50%–79% yields (Scheme 2).[37]

The direct reaction of acetylenes with 3-halo-substituted enones (see Scheme 1, pathway *b*) proceeds in the presence of palladium catalysts such as $Pd(PPh_3)_2Cl_2$,[1,32,33,35] $Pd(PPh_3)_4$ (Ref. 34) and $Pd(OAc)_2$ (Ref. 1) combined with CuI or in the presence of the $Pd(OAc)_2-PPh_3$ system.[45,46] The reaction takes place under mild conditions and gives, in most cases, good yields of products. When *trans*-3-substituted enones are used, configuration of the double bond in enynone does not change.[26,28] *cis*-Enones react non-selectively: for example, the reaction of (*Z*)-3-chloro-1-phenylprop-2-en-1-one with trimethylsilylacetylene catayzed by $Pd(PPh_3)_4$, CuI and Et_3N in toluene at room temperature affords (*E*)- and (*Z*)-5-trimethylsilyl-1-phenylpent-2-en-4-yn-1-ones (12% and 57% yields, respectively).[34]

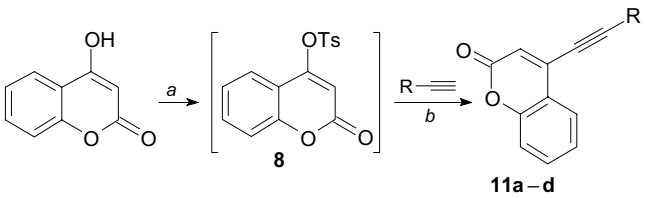
The cross-coupling of acetylenes with 3-hydroxycyclohex-2-enone (**7**) and 4-hydroxy-2*H*-chromen-2-one (**8**) tosylates and with 4-bromofuran-2(5*H*)-one (**9**) was used to prepare enyne ketones **10a–g**, **11a–d** and **12a–j** with an endocyclic double bond (Schemes 3–5).[1,45,47]

Scheme 3



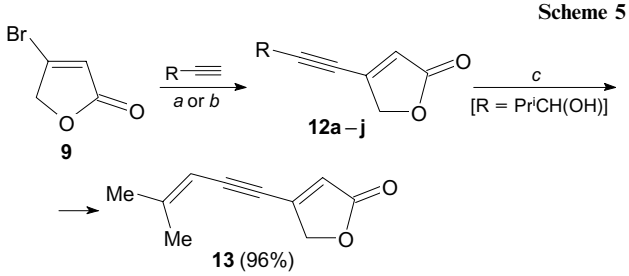
(*a*) TsCl, Et_3N, PhMe; (*b*) $Pd(OAc)_2$, PPh_3, Et_3N, DMA, DMF, rt;
R = Ph (**a**, 91% yield), 1-hydroxycyclohexyl (**b**, 94%), cyclohexen-1-yl (**c**, 91%), MeCH(OH) (**d**, 77%), $HO(CH_2)_2$ (**e**, 93%), $Cl(CH_2)_2$ (**f**, 91%), TMS (**g**, 88%); Ts is *p*-toluenesulfonyl (tosyl), TMS is trimethylsilyl, DMA is dimethylacetamide

Scheme 4



(*a*) TsCl, Et_3N, PhMe; (*b*) $Pd(OAc)_2$, PPh_3, Et_3N, DMA, DMF, rt;
R = Ph (**a**, 65% yield), $HO(CH_2)_2$ (**b**, 72%), $HO(CH_2)_3$ (**c**, 59%), Bu^n (**d**, 75%)

Scheme 5



(*a*) 1) $PdCl_2(PPh_3)_2$ (10 mol.%), CuI (2 mol.%), THF, rt, 0.5 h; 2) Pr^i_2NH, 16 h, rt; (*b*) $Pd(OAc)_2$ (3 mol.%), TPPMS (5 mol.%), Et_3N, $MeCN-H_2O$ (15 : 1), rt, 20 h; (*c*) P_2O_5, PhH, 80 °C, 1 h;
THP is tetrahydropyran-2-yl, TPPMS is potassium 3-(diphenylphosphino)benzenesulfonate

Compound **12**	R	Yield (%)	
		conditions *a*	conditions *b*
a	Ph	71	–
b	4-FC_6H_4	74	–
c	n-C_8H_{17}	80	–
d	Bu^n	73	–
e	Cyclohexen-1-yl	65	–
f	$THPOCH_2$	77	–
g	$Bu^tOCH(Me)$	86	–
h	$HO(CH_2)_2$	50	63
i	1-Hydroxycyclopentyl	62	78
j	$Pr^iCH(OH)$	–	81

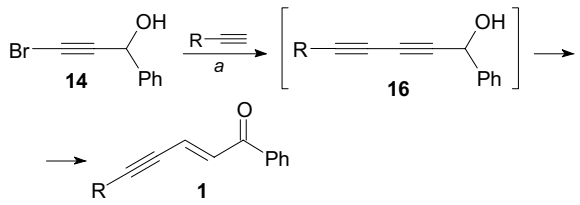
Compound **12j** was used in the synthesis of the natural monoterpenoid lactone, cleviolide (**13**) (see Scheme 5).

The direct palladium-catalyzed cross-coupling of enones with terminal acetylenes is also possible;[42,48] however, in this case, the reaction is accompanied by formation of the corresponding diacetylenes.[42] 1,5-Disubstituted pent-2-en-4-yn-1-ones have been prepared[49,50] using the Cadiot–Chodkiewicz reaction, that is, the reaction of propargyl alcohols **14** and **15** with terminal alkynes or (bromoethynyl)benzene catalyzed by CuCl in the presence of piperidine. The reaction involves the intermediate formation of diacetylene alcohols **16** or **17** (Scheme 6).

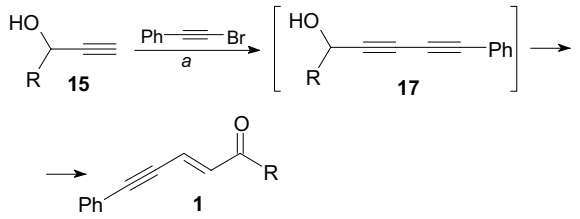
tert-Butyldimethylsilyl ethers of diacetylenic alcohols isomerize in a similar way under the action of bases.[51] This gives enynones in good yields; however, unlike the above cases, they are formed as mixtures of *E*- and *Z*-isomers with the latter predominating.

The reaction of (2-triphenylphosphoranylidene)alkanones **18** with propargyl aldehydes **19** is often used to form the C(2)–C(3) bond in enynones (Scheme 7, Table 1).[8,27,29,52,53] This method is employed to prepare alkyl-, aryl- and hetaryl-substituted enynones. The reaction is conducted either by heating the reactants in benzene,[29] or at room temperature in CH_2Cl_2,[8] or on cooling in THF.[27] Enynones are usually formed in good yields and, in some cases,[8] in nearly quantitative yields. A drawback of this method is the necessity to separate the products from triphenylphosphine oxide formed as a by-product.[8,27]

Scheme 6

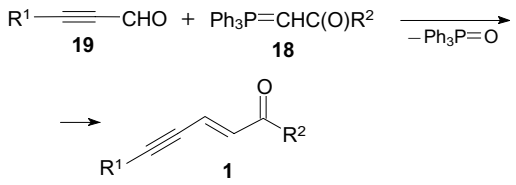


(*a*) CuCl, piperidine, 8 °C, 8 h; R = 4-$MeOC_6H_4$ (56% yield), 3-$MeOC_6H_4$ (63%), 4-PhC_6H_4 (59%), 2-$MeO_2CC_6H_4$ (32%), 3,5-$Me_2C_6H_3$ (49%), 1-hydroxy-1,2,3,4-tetrahydronaphthalen-1-yl (45%), 1-hydroxycyclohexyl (67%), cyclohexen-1-yl (64%), 3,4-dihydronaphthalen-1-yl (32%), $TBSOCH_2$ (48%), n-$C_9H_{19}CH$(TBS) (57%); TBS is *tert*-butyldimethylsilyl

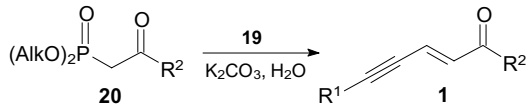


(*a*) CuCl, piperidine, 0 °C → rt, 3 – 8 h; R = 2-Fu (43% yield), 2-Th (38%), 3-Py (41%), 1-Naph (45%), 2-FC_6H_4 (55%), 4-FC_6H_4 (78%), 4-ClC_6H_4 (92%), 2-BrC_6H_4 (65%), 3-BrC_6H_4 (81%), 4-BrC_6H_4 (75%), 2-IC_6H_4 (53%), 4-$MeOC_6H_4$ (73%), 2-MeC_6H_4 (70%), 2-BocNHC_6H_4 (67%), 3-$O_2NC_6H_4$ (36%); Fu is furyl, Th is thienyl, Py is pyridyl, Naph is naphthyl

Scheme 7



Scheme 8



Alk = Me, R^1 = $TBSOCH_2$, R^2 = TBDPSO$(CH_2)_4$ (79% yield);[54]
Alk = Et, R^1 = Bu^n, R^2 = Bu^t (96%);[55]
TBDPS is *tert*-butyldiphenylsilyl

Apart from the Wittig ylides, the reaction with acetylenic aldehydes **19** can be carried out for dialkoxyphosphoryl ketone derivatives **20**. The reaction proceeds in the presence of potassium carbonate and gives products in good yields (Scheme 8).[54, 55]

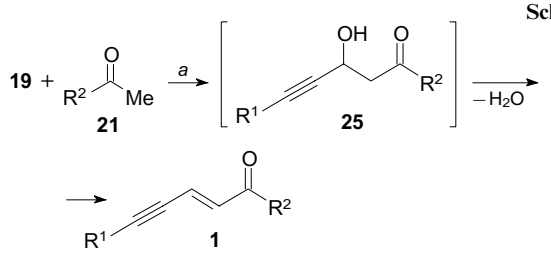
The formation of the C(2) – C(3) bond in enynones is attained *via* the Claisen – Schmidt aldol condensation[56] involving α-acetylenic aldehydes **19** and acetone (**21a**)[57] or aryl methyl ketones **21**,[4, 57, 58] 2-acetylthiophenes,[59] cyclohexanone (**22**), tetrahydrothiopyran-4-one (**23**)[8] (Scheme 9) or 1,3-diketones.[60 – 62] Bases are normally used as catalysts;[4, 56 – 59] the reactions are carried out in alcohols[4] or in

Table 1. Synthesis of enynones **1** by the reaction of (2-triphenylphosphoranylidene)alkanones **18** with propargyl aldehydes **19** (see Scheme 7).

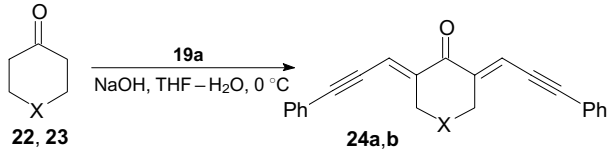
R^1	R^2	Yield (%)	Ref.
4-MeC_6H_4	Ph	92	8
4-$MeOC_6H_4$	Ph	89	8
3,5-$(MeO)_2C_6H_3$	Ph	94	8
3-$F_3CC_6H_4$	Ph	84	8
4-ClC_6H_4	Ph	94	8
2-IC_6H_4	Ph	88	8
4-$O_2NC_6H_4$	Ph	85	8
2-Naph	Ph	92	8
2-Th	Ph	95	8
(*E*)-PhCH=CH	Ph	79	8
n-C_8H_{17}	Ph	89	8
Bu^n	Ph	79	27
Bu^n	Me	82	27
Ph	Ph	69	27
Ph	Me	75	27
TMS	Me	76	52
Bu^t	Me	79	52
Ph	1-Phenyl-1*H*-imidazol-2-yl	–	29
TIPS[a]	1-Phenyl-1*H*-imidazol-2-yl	–	29
Bu^t	Me	79	53

Note. A dash means that the yield is not indicated in the original publication. [a] TIPS is triisopropylsilyl.

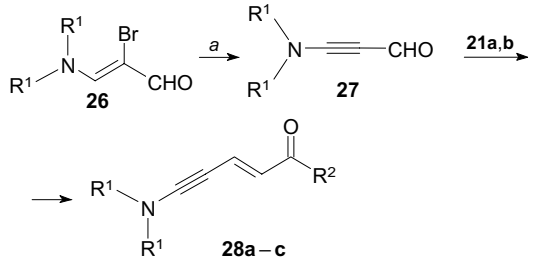
Scheme 9



(*a*) NaOH, EtOH, H_2O, 0 – 5 °C; R^1 = Ph: R^2 = Ph (89% yield), 4-MeC_6H_4 (71%), 4-$Pr^iC_6H_4$ (64%), 4-$MeOC_6H_4$ (50%), 4-$EtOC_6H_4$ (76%), 4-ClC_6H_4 (89%), 3-BrC_6H_4 (30%), 4-BrC_6H_4 (76%), 3-$H_2NC_6H_4$ (10%), 2-Fu (69%); R^1 = 4-MeC_6H_4: R^2 = Ph (50%), 4-MeC_6H_4 (40%), 4-ClC_6H_4 (68%); R^1 = 4-BrC_6H_4: R^2 = Ph (54%), 4-BrC_6H_4 (30%), 2-Fu (20%)



X = CH_2 (**a**, 65% yield), S (**b**, 62%)



(*a*) Bu^tOK, −10 °C; **21**: R^2 = Me (**a**), Ph (**b**); **28**: R^1 = R^2 = Me (**a**, 52% yield); R^1 = Et, R^2 = Me (**b**, 53%); R^1 = Me, R^2 = Ph (**c**, 49%)[57]

alcohol – water mixtures.[58] The reaction products are enynones **1** (Ref. 58) or, in the case of aldehyde **19a** (R^1 = Ph), dimers **24a**,**b**.[8]

The reactions of aromatic α-acetylenic aldehydes with acetophenones should better be carried out with cooling in a water – alcohol mixture, which ensures the removal of the enynone precipitate from the reaction sphere and prevents side reactions (nucleophilic addition of alcohol and retro aldol reaction).[58] Intermediate aldols **25** are completely dehydrated under the reaction conditions. Ostroumov *et al.*[57] proposed using 2-bromo-3-dialkylaminopropynals **26** as the source of the carbonyl component. Compounds **26** eliminate HBr under the action of potassium *tert*-butoxide, thus generating acetylenic aldehyde **27**, which reacts with the methylene component to give dialkylamino-substituted enynones **28a – c** (49% – 53% yield). The condensation of α-acetylenic aldehydes with 1,3-diketones proceeds in the presence of acids and affords only *E*-configured enynones.[60, 62]

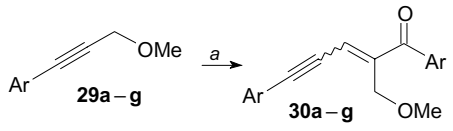
When the conditions of the condensation are properly selected, good product yields are usually obtained. The success of the aldol crotonic condensation in the synthesis of enynones is mainly determined by the availability of the starting aldehydes **19**; the reaction is *E*-stereoselective.[63, 64]

There are data indicating that in the absence of a methylene component, α-acetylenic aldehydes are capable of self-condensation to give 2-formylpent-2-en-4-yn-1-ones. For example, according to Dong *et al.*,[65] phenylpropynal is converted to 2-benzoyl-5-phenylpent-2-en-4-ynal in the presence of diphenyl-L-proline (20 mol.%) and trifluoroacetic acid (20 mol.%) catalysts.

Several methods for the synthesis of alk-2-en-4-yn-1-ones based on oxidation of acetylene derivatives have been reported. Pent-2-en-4-yn-1-ones can be obtained by careful oxidation of secondary alkynylvinyl alcohols by Dess – Martin periodinane (DMP)[66] or Swern reagent [$(COCl)_2$ – DMSO].[67] The best yield (81%) was obtained in the oxidation of (*Z*)-1,5-diphenylpent-2-en-4-yn-1-ol on treatment with 2-iodoxybenzoic acid (IBX).[68]

Furthermore, the oxidation of methyl propargyl ethers **29a – g** with a mixture of 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) with $FeCl_3$ resulted in the formation of 2-methoxymethyl-substituted pent-2-en-4-yn-1-ones **30a – g**.[69] It is noteworthy that this reaction affords a mixture of *E*- and *Z*-isomers of enynones in which the former predominates (Scheme 10).

Scheme 10

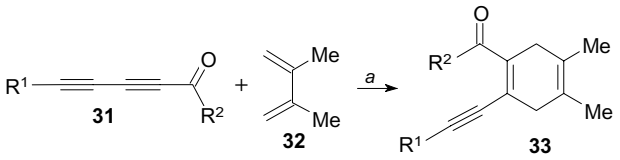


(*a*) $FeCl_3$, DDQ, CH_2Cl_2, air, 30 °C, 15 h

Compounds **29**, **30**	Ar	Yield (%)	*E* : *Z* ratio
a	Ph	57	93 : 7
b	2-MeC_6H_4	38	82 : 18
c	3-MeC_6H_4	51	92 : 8
d	4-MeC_6H_4	45	60 : 40
e	4-ClC_6H_4	35	93 : 7
f	4-BrC_6H_4	43	91 : 9
g	4-FC_6H_4	51	86 : 14

The reaction of diacetylenic ketones **31** with 2,3-dimethylbuta-1,3-diene (**32**) induced by dimethylaluminium chloride at room temperature gives enynones **33** with a double bond in the cyclohexadiene moiety (Scheme 11).[70]

Scheme 11



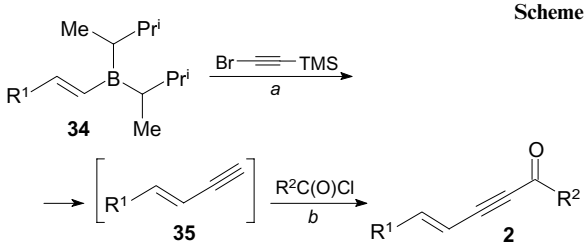
(*a*) Me_2AlCl, CH_2Cl_2; R^1 = TMS: R^2 = Me (61% yield), Ph (88%), 2-BrC_6H_4 (57%), 4-BrC_6H_4 (79%), 2-$MeOC_6H_4$(51%), 4-$MeOC_6H_4$ (59%); R^2 = Ph: R^1 = Ph (68%), Et (94%)

A number of specific reactions give rise to the linear-conjugated 2-en-4-yn-1-one pentads, for example, the rearrangement of furylcarbenes generated by pyrolysis[71] or photolysis[72, 73] of diazo furans; elimination of EtOH from 3-ethoxy-1-phenylpent-4-yn-1-one[74] under the action of Et_2NLi at −78 °C; and the reaction of 1-arylethynylcyclobutan-1-ols with 1-ethynyl-1,2-benzodioxol-3(1*H*)-ones in the presence of $K_2S_2O_8$ at 60 °C.[75] These methods, however, are hardly applicable for the preparative synthesis of enyne ketones **1** because of the poor accessibility of the starting compounds.

2.2. Alk-4-en-2-yn-1-ones

Enynones **2** can be obtained *via* the formation of the C(1) – C(2) or C(3) – C(4) bonds. For example, a one-pot synthesis of **2** includes the cross-coupling of vinylboranes **34** with (bromoethynyl)trimethylsilane followed by palladium-catalyzed acylation of the resulting enynes **35** with aryl- and hetarylcarboxylic acid chlorides. Using this approach, it is possible to avoid the isolation of labile intermediate enynes **35** (Scheme 12).[76]

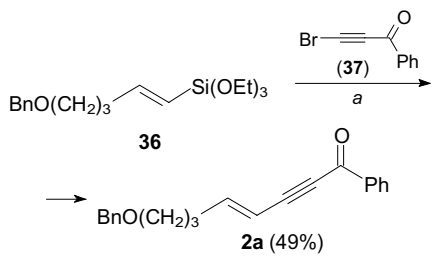
Scheme 12



(*a*) $Cu(acac)_2$, 1 M MeONa, –15 °C → rt; (*b*) $Pd(OAc)_2$, PPh_3, Et_3N, rt; R^1 = n-C_6H_{13}: R^2 = Ph (86% yield), 2-MeC_6H_4 (90%), 4-MeC_6H_4 (79%), 4-ClC_6H_4 (78%), 2-Naph (87%), 2-Fu (76%), 2-Th (79%); R^1 = Ph: R^2 = Ph (90%), 2-MeC_6H_4 (85%), 4-MeC_6H_4 (77%), 4-ClC_6H_4 (82%), 2-Naph (77%), 2-Fu (86%), 2-Th (79%); R^2 = Ph: R^1 = $Cl(CH_2)_2$ (88%), cyclohexen-1-yl (92%); acac is acetylacetonate

The C(3) – C(4) bond can also be formed *via* coupling of [5-(benzyloxy)pent-1-en-1-yl]triethoxysilane (**36**) with 3-bromo-1-phenylprop-2-yn-1-one (**37**); however, product **2a** is formed in a lower yield than in the previous cases.

Scheme 13

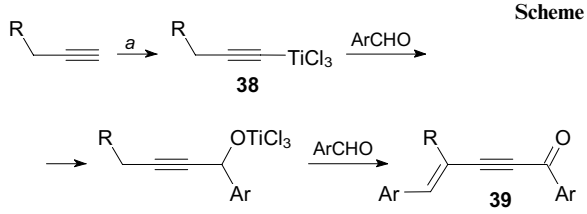


(*a*) $Cu(MeCN)_4PF_6$, TBAT, MeCN, 40 °C, 16 h;
TBAT is tetra-n-butylammonium difluorotriphenylsilicate

A benefit of this method is the lack of necessity for using palladium catalysts (Scheme 13).[77]

Alkynyltitanium trichlorides **38** obtained *in situ* from terminal acetylenes in the presence of the $TiCl_4 - Et_3N$ system (2 equiv.) react with aromatic aldehydes to give enynones **39** in 78% – 92% yields (Scheme 14). A limitation of this method is the necessary use of alkynes with a methylene group at the triple bond. Benzaldehyde reacts with phenylacetylene under the same conditions to give a mixture of 1,3-diphenylprop-2-yn-1-one with (*E*)-hexa-3-en-1,5-diyne-1,3,4,6-tetrayltetrabenzene.[78]

Scheme 14



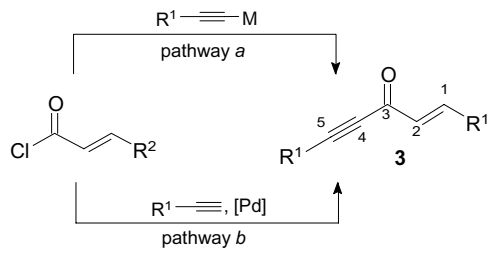
(*a*) $TiCl_4$, Et_3N, CH_2Cl_2, 0 °C; Ar = Ph: R = Bu^n (87% yield), n-C_5H_{11} (92%), n-C_7H_{15} (91%); Ar = 1-Naph, R = Bu^n (78%)

Apart from the considered methods, alk-4-en-2-yn-1-ones **2** can be prepared by oxidation of the corresponding alcohols with active manganese dioxide[19,79,80] and pyridinium chlorochromate (PCC);[81] treatment of the enyne lithium derivative with the Weinreb amide;[82] and the reaction of ethyl 5-(benzo[*d*][1,3]dioxol-5-yl)pent-4-en-2-ynoate with *tert*-butyl acetate and lithium diisopropylamide in THF at −78 °C.[83]

2.3. Alk-1-en-4-yn-3-ones

The most popular method for the synthesis of cross-conjugated enyne ketones **3** is the reaction of chlorides of unsaturated acids with alkynes (Scheme 15).

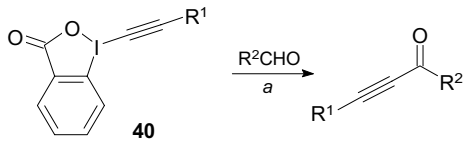
Scheme 15



Here, like in the synthesis of linear-conjugated enynones **1**, reactions of acid chlorides or related compounds[84,85] with acetylene derivatives (pathway *a*) or direct catalytic cross-coupling (pathway *b*) are possible. In the former case, metal acetylenides are normally used; higher yields of enynones are attained with copper and manganese acetylides.[86] Trimethylsilyl-substituted acetylenes[87–89] and diacetylenes[90] can be employed (in the presence of $AlCl_3$) as the acetylene components in the reaction with acid chlorides.

Acetylenic, in particular, enyne ketones are synthesized by coupling of alkyne derivatives of hypervalent iodine **40** with unsaturated aldehydes. The reaction occurs on heating in acetonitrile in the presence of di-*tert*-butyl peroxide, but the yield of enyne ketones in this reaction is only 20% – 32% (Scheme 16).[91]

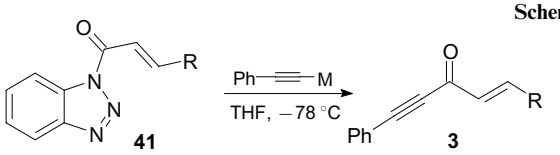
Scheme 16



(*a*) Bu^tOOBu^t, MeCN, N_2, 80 °C, 24 h;
R^1 = TIPS, R^2 = (*E*)-PhCH=CH (20% yield);
R^2 is cyclohex-1-enyl: R^1 = TIPS (32%), Ph (30%)

Katritzky *et al.*[84] showed that 1-(1*H*-benzo[*d*][1,2,3]triazol-1-yl)-substituted prop-2-en-1-ones **41** are applicable, instead of carboxylic acid chlorides, for the reaction with phenylacetylenides (Scheme 17).

Scheme 17



M = Li, MgBr; R = H (69% yield), 2-Th (32%)

A similar reaction takes place when lithium phenyl- or *tert*-butylacetylenide is added to 1-ethoxy-2,3-diphenylcyclopropenylium tetrafluoroborate in a THF – hexane mixture at −70 °C. The yields of 1,2,5-triphenylpent-1-en-4-yn-3-one and 6,6-dimethyl-1,2-diphenylhept-1-en-4-yne-3-one thus formed are 78% and 85%, respectively; however, the authors do not mention anything about the configuration of the double bond in the reaction products.[92]

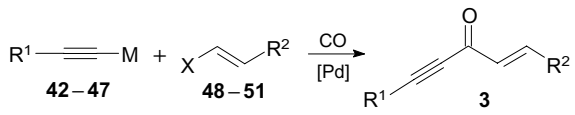
Despite their simplicity and availability, this group of methods (pathway *a* in Scheme 15) has now been displaced almost completely by the palladium-catalyzed cross-coupling of acyl chlorides with terminal acetylenes (pathway *b*). The catalyst systems used for this reaction include $Pd(PPh_3)_4$ with $ZnCl_2$ or $ZnBr_2$,[93] $Pd/BaSO_4$ under the same conditions,[94] Pd/C,[95] $Pd(OAc)_2$,[96] $Pd(PPh_3)_2Cl_2 - CuI$,[97] $KF/Al_2O_3 - Pd(PPh_3)_2Cl_2 - CuI$ with microwave activation,[98] palladium nanoparticles embedded into the poly-1,4-phenylene sulfide polymer matrix[99] and more complex palladium-based catalyst systems.[100] The reaction is carried out in toluene[93,99,100] or dichloromethane[84] with addition of amine, in triethylamine[93–95] or without a solvent.[98] The reaction proceeds under mild conditions and gives products in good and, in some cases,[93–95,98,100] nearly quantitative yields. This method is

used to prepare 5-alkyl-, 5-aryl- and 5-ferrocenyl-substituted [98] pent-1-en-4-yn-3-ones.

Copper(I) iodide in triehylamine can also be employed as a catalyst for phenylacetylene cross-coupling with cinnamoyl chloride; however, the yield of 1,5-diphenylpent-1-en-4-yn-3-one is lower in this case than in Pd-catalyzed reactions.[101–103] The reaction can be assisted by microwave radiation.[101, 102]

A number of synthetic methods are based on catalytic carbonylation of alkyne (**42**–**47**) and alkene (**48**–**51**) components. These reactions can be carried out for terminal acetylenes and for their derivatives (Scheme 18).

Scheme 18



R^1 = Ph: M = $SiMeF_2$ (**42**), $SnBu^n_3$ (**43**), In (**44**), H (**45**);
R^1 = Bu^n, M = H (**46**); R^1 = H, M = CO_2H (**47**);
R^2 = Ph: X = $I^+PhBF_4^-$ (**48**), Br (**49**), OTf (**50**), H (**51**);
Tf is trifluoromethanesulfonyl (triflyl)

For example, carbonylation of a mixture of difluoromethyl(phenylethynyl)silane (**42**) with a styrene hypervalent iodine derivative **48** proceeds at room temperature in dimethoxyethane in the presence of the allylic complex $(\eta^3\text{-}C_3H_5PdCl_2)_2$ with addition of tetra-n-butylammonium fluoride.[104] Compound **48** also easily reacts with tri-n-butyl(phenylethynyl)tin (**43**) under the action of $PdCl_2$ in a dimethoxyethane–water mixture.[105] In both cases, the reaction gave 1,5-diphenylpent-1-en-4-yn-3-one in 78%–79% yield. The same product is formed upon $Pd(PPh_3)_4$-catalyzed carbonylation of a mixture of β-bromostyrene (**49**) with phenylethynylindium (**44**) in THF at 70 °C (75% yield).[106] In the case of styryl (**50**) and analogous cycloalkenyl trifluoromethanesulfonates [107] and styrene (**51**),[108] carbonylation can be accomplished directly using terminal alkynes **45** and **46**, without the intermediate formation of their organoelement derivatives, but the yield of enynones decreases. A mixture of β-iodostyrene with phenylacetylene was shown to be carbonylated in the presence of a Cu catalyst (PPh_3–CuI system); however, apart from 1,5-diphenylpent-1-en-4-yn-3-one, this reaction gives a considerable amount of 1,4-diphenylbut-1-en-3-yne formed as the cross-coupling product.[109] 1,7-Diphenylhepta-1,6-dien-4-yn-3-one is obtained by carbonylation of a mixture of propiolic acid (**47**) with β-bromostyrene (**49**) in the presence of a $Pd(PPh_3)_2Cl_2$–CuI system in acetonitrile containing triethylamine at 80 °C.[110] The reaction of acid **47** is accompanied by Sonogashira cross-coupling and by build-up of an additional C(6)–C(7) multiple bond. It is noteworthy that the double bond configuration is retained in the carbonylation reactions.

A widely used method for the synthesis of cross-conjugated enynones is oxidation of secondary vinylethynyl alcohols **52**.[90, 111–127] The latter are prepared from organometallic acetylene derivatives and the corresponding α,β-unsaturated aldehydes (Scheme 19, Table 2). The oxidation is accomplished by active manganese dioxide in dichlorome-

Scheme 19

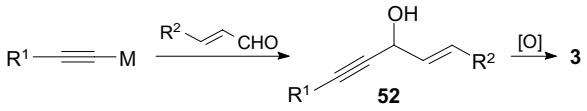


Table 2. Synthesis of cross-conjugated enyne ketones **3** by oxidation of alcohols **52** (see Scheme 19).

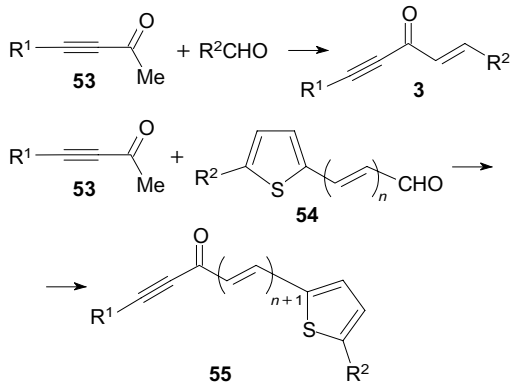
R^1	R^2	Oxidant	Reaction conditions	Yield (%)	Ref.
Ph	Ph	MnO_2	CH_2Cl_2, 23 °C	96	114
Ph	Ph	I_2, Bu^tOK	CH_2Cl_2, 10 °C	90	122
3,4-$(MeO)_2C_6H_3$	Ph	MnO_2	CH_2Cl_2, 23 °C	84	114
3-EtO-4-$MeOC_6H_3$	Ph	MnO_2	CH_2Cl_2, 23 °C	99	114
2-$F_3CC_6H_4$	Ph	MnO_2	CH_2Cl_2, 23 °C	99	114
2,4-$F_2C_6H_3$	Ph	MnO_2	CH_2Cl_2, 23 °C	99	111, 114
2-Th	Ph	MnO_2	CH_2Cl_2, 23 °C	99	114
2-Py	Ph	MnO_2	CH_2Cl_2, 23 °C	75	114
Bu^t	Ph	MnO_2	CH_2Cl_2, 23 °C	99	114
TMS	Ph	MnO_2	CH_2Cl_2, 23 °C	97	114
3,4-$(MeO)_2C_6H_3$	H	MnO_2	CH_2Cl_2, 23 °C	77	114
3-EtO-4-$MeOC_6H_3$	H	MnO_2	CH_2Cl_2, 23 °C	62	114
2,4-$F_2C_6H_3$	H	MnO_2	CH_2Cl_2, 23 °C	99	114
Pr^n	4-$MeOC_6H_4CH_2O(CH_2)_2$	MnO_2	CH_2Cl_2, rt	83	116
4-$MeOC_6H_4CH_2O(CH_2)_3$	H	MnO_2	CH_2Cl_2, rt	54	119
TMS	$MeO_2C(CH_2)_7$	DMP	CH_2Cl_2, rt	95	121
TMS	Me	PCC	CH_2Cl_2, rt	89	90
2-Py	Me	PCC	CH_2Cl_2, rt	35	90
2-Py	Me	$BaMnO_4$	CH_2Cl_2, rt	82	90
TMS	Ph	PCC	CH_2Cl_2, rt	96	90
H	Ph	O_2 (1 atm)	CPVAP, Pr^nCN, 100 °C	31	126
H	Ph	O_2 (1 atm)	Propargyl alcohol, $VO(acac)_2$, MeCN, 3 Å zeolite	65	127

Note. CPVAP is calcium phosphate vanadate.

thane [111–119] or chloroform [120] at room temperature. This oxidant acts under very mild conditions and, in most cases, provides high yields. Beneficial results were obtained using DMP,[121] I_2-Bu^tOK system,[122] pyridinium chlorochromate,[90] $BaMnO_4$ [90] and IBX [123] in DMSO. In addition, oxygen in the presence of cobalt [124] or vanadium compounds [125–127] was proposed for oxidation of alcohols **52**; however, the yield of enyne ketones **3** did not exceed 65% in any of these experiments.

The aldol crotonic condensation of ethynyl methyl ketones **53** with aromatic and heteroaromatic aldehydes is successfully used in the synthesis of *E*-isomers of cross-conjugated enynones **3**.[59,128–130] The condensation is carried out on cooling in THF in the presence of the $Et_2Zn-(S,S)$-ProPhenol catalytic system (ProPhenol is 2,6-bis({2-[hydroxy-(diphenyl)methyl]pyrrolidino}methyl)-4-methylphenol) [128] or in ethanol in the presence of alkalis (Scheme 20, Table 3).[129,130] Using this procedure, aldehydes **54** were converted, in moderate yields, to polyunsaturated ketones **55** containing a thiophene ring (see Scheme 20).[59] The condensation of 5-nitrofurfural with 4-phenylbut-3-yn-2-one in ethanol in alkaline medium is accompanied by pronounced resinification. 1-(5-Nitrofuran-2-yl)-5-phenylpent-1-en-4-yn-3-one can be obtained only in glacial acetic acid under acid catalysis (concentrated H_2SO_4).[130] Generally, this method has the same features as the synthesis of linear-conjugated enynones **1** (see above).

Scheme 20



R^1	R^2	*n*	Yield (%)	R^1	R^2	*n*	Yield (%)
Me	H	0	50	Ph	O_2N	0	46
Bu^n	H	0	48	Ph	H	1	41
Ph	H	0	45	Ph	H	2	43

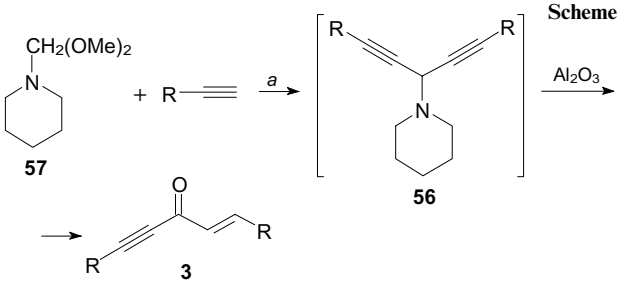
Synthetic routes to symmetrically disubstituted pent-1-en-4-yn-3-ones based on diyne derivatives have been developed. It was shown, for example, that passing of solutions of 1-[1,5-di(het)aryl-1,4-diyn-3-yl]piperidines **56**, obtained from acetal **57**, through a neutral Al_2O_3 layer affords 1,5-di(het)arylpent-1-en-4-yn-3-ones in 52% – 73% yields (Scheme 21).[131]

Several efficient syntheses of cross-conjugated enynones are based on the formation of the C(1)–C(2) double bond *via* elimination of alkoxy and aryloxy groups. For instance, Babu *et al.*[132] described cross-conjugated enyne ketones with diverse substituents in positions 1 and 5 (Scheme 22, Table 4). The palladium-catalyzed cross-coupling of acetylenic alcohols **58** and presynthesized alkynes affords phenoxy-substituted alkylvinyl alcohols **59a–m**, which are converted to enynones **60a–m** under very mild conditions, namely, at room temperature in the presence of 30 mol.% of *p*-toluenesulfonic acid. Compounds **60** are formed in

Table 3. Synthesis of cross-conjugated enyne ketones **3** by condensation of ethynyl methyl ketones **53** with aldehydes (see Scheme 20).

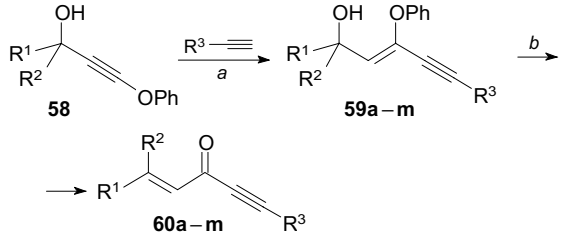
R^1	R^2	Reaction conditions	Yield (%)	Ref.
Ph	Ph	NaOH, EtOH, rt, 2–3 h	65	129
Ph	2-$O_2NC_6H_4$	NaOH, EtOH, rt, 2–3 h	20	129
Ph	3-$O_2NC_6H_4$	NaOH, EtOH, rt, 2–3 h	54	129
Ph	4-$O_2NC_6H_4$	NaOH, EtOH, rt, 2–3 h	57	129
Ph	3-BrC_6H_4	NaOH, EtOH, rt, 2–3 h	70	129
Ph	4-BrC_6H_4	NaOH, EtOH, rt, 2–3 h	69	129
Ph	4-ClC_6H_4	NaOH, EtOH, rt, 2–3 h	56	129
Ph	2-FC_6H_4	NaOH, EtOH, rt, 2–3 h	60	129
Ph	4-MeC_6H_4	NaOH, EtOH, rt, 2–3 h	58	129
Ph	4-$MeOC_6H_4$	NaOH, EtOH, rt, 2–3 h	61	129
Ph	2-$Cl(CH_2)_2OC_6H_4$	NaOH, EtOH, rt, 2–3 h	53	129
Ph	4-$Me_2NC_6H_4$	NaOH, EtOH, rt, 2–3 h	47	129
4-BrC_6H_4	Ph	NaOH, EtOH, rt, 2–3 h	44	129
4-BrC_6H_4	3-BrC_6H_4	NaOH, EtOH, rt, 2–3 h	60	129
4-BrC_6H_4	4-$MeOC_6H_4$	NaOH, EtOH, rt, 2–3 h	44	129
4-$MeOC_6H_4$	Ph	NaOH, EtOH, rt, 2–3 h	50	129
4-$MeOC_6H_4$	3-BrC_6H_4	NaOH, EtOH, rt, 2–3 h	55	129
4-$MeOC_6H_4$	4-$MeOC_6H_4$	NaOH, EtOH, rt, 2–3 h	60	129
TMS	n-C_7H_{15}	(*S*,*S*)-ProPhenol (10 mol.%), Et_2Zn (50 mol.%), THF, 4 °C	69	128
TMS	5-Methyl-2-oxo-2,3-dihydrofuran-3-ylmethyl	(*S*,*S*)-ProPhenol (10 mol.%), Et_2Zn (50 mol.%), THF, 4 °C	64	128
Ph	5-Bromofuran-2-yl	NaOH, EtOH, H_2O, rt, 1.5 h	69.2	130
Ph	5-Iodofuran-2-yl	NaOH, EtOH, H_2O, rt, 1.5 h	58.4	130
Ph	5-Nitrofuran-2-yl	AcOH, H_2SO_4, 3 days	40.7	130

Scheme 21



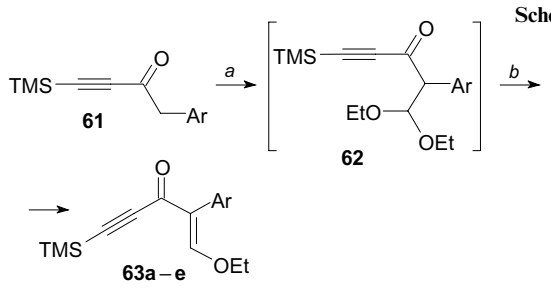
(*a*) CuBr (10 mol.%), dppp (10 mol.%), 3 Å zeolite, PhMe, N_2, 10 h; R = Ph (62% yield), 4-MeC_6H_4 (73%), 3-MeC_6H_4 (54%), 4-$MeOC_6H_4$ (52%), 4-FC_6H_4 (52%), 3-Th (68%); dppp is 1,3-bis(diphenylphosphino)propane

Scheme 22



(*a*) $Pd(PPh_3)_2Cl_2$ (10 mol.%), Et_3N, THF, rt, 12 h; (*b*) TsOH, THF, rt, 3 h

Scheme 23



(*a*) $HC(OEt)_3$, Ac_2O, Δ; (*b*) Ac_2O, 140 °C; Ar = Ph (**a**, 47% yield), 4-$O_2NC_6H_4$ (**b**, 68%), 4-$MeOC_6H_4$ (**c**, 50%),[133] 4-ClC_6H_4 (**d**, 53%), 4-MeC_6H_4 (**e**, 41%) [134]

87% – 96% yields; also, polyunsaturated ketones **60j**,**m** are obtained by this method in high yields.

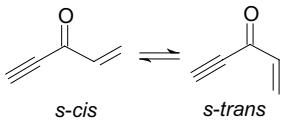
Heating of alkyne ketones **61** with triethyl orthoformate in acetic anhydride gives rise to diethoxy derivatives **62**, which eliminate an ethanol molecule to give 2-aryl-1-ethoxypent-5-(trimethylsilyl)-1-en-4-yn-3-ones **63a – e** (Scheme 23).[133, 134]

3. Properties and structure of enynones

3.1. Spectral characteristics

The conjugated system of multiple bonds is responsible for characteristic features of the IR spectra of cross-conjugated enynones **3**. The stretching bands of the keto group are shifted to lower frequencies due to the conjugation. In solutions ($CHCl_3$, CCl_4) of these compounds, *s-cis* – *s-trans* conformational equilibrium is established; therefore, their IR spectra show two stretching bands for the keto group in the 1660 – 1630 cm^{-1} range, with the lower frequency band corresponding to the *s-trans*-conformer and the higher frequency band corresponding to the *s-cis*-form (Scheme 24).[129]

Scheme 24



In the crystalline state, cross-conjugated enynones tend to mainly exist in the *s-trans*-conformation of the enone group, as indicated by the single ν_{CO} band at about 1630 cm^{-1}. The stretching band at 1660 – 1590 cm^{-1} for the double bond ($\nu_{C=C}$) can be strictly interpreted only in the IR spectra of pent-1-en-4-yn-3-one and alkyl-substituted enynones; in the spectra of aryl-substituted enynones, this band can be overlapped by the absorption bands of the aromatic groups. The $\nu_{C\equiv C}$ band occurs at 2224 – 2175 cm^{-1} and has a relatively low intensity.[129] The stretching bands of the multiple bonds of linear conjugated enynones **1** and **2** are manifested in approximately the same ranges.[20, 30, 57] It was shown that a CF_3 group introduced in the vicinity of the oxo group induces a shift of the

Table 4. Synthesis of cross-conjugated enyne ketones **60** from compounds **59** (see Scheme 22).[132]

Compounds **59, 60**	R^1	R^2	R^3	Yield of **59** (%)	Yield of **60** (%)
a	Ph	Ph	Ph	84	96
b	Ph	Ph	4-MeC_6H_4	81	94
c	Ph	Ph	4-$MeOC_6H_4$	79	95
d	Ph	Ph	cyclo-C_3H_5	71	91
e	Ph	Ph	2-Py	76	92
f	Ph	H	Ph	82	89
g	Ph	H	3-$MeOC_6H_4$	81	94
h	n-C_6H_{13}	H	Ph	79	92
i	Pr^i	H	Ph	76	90
j	(*E*)-PhCH=CH	H	Ph	72	88
k	Ph	Me	Ph	81	93
l	Ph	Et	Ph	78	93
m	(*E*)-PhCH=CH	Me	Ph	71	87 [a]

[a] Mixture of *cis*- and *trans*-isomers in 2 : 3 ratio.

ν_{CO} and $\nu_{C\equiv C}$ bands to higher frequency.[28, 30] According to IR spectroscopy data (a single ν_{CO} band at 1670 – 1630 cm^{-1}), enynones **1** have an *s-cis*-conformation of the enone group both in the crystalline state and in solutions.[58]

The most comprehensive information about the structures of conjugated enynones is gained from the NMR spectra. The protons at the double bond of enynones **1**, **2** and **3** resonate at 6 – 8 ppm in the ^{1}H NMR spectra; however, in the presence of aryl and hetaryl substituents, the low-field signal is often overlapped by multiplets for the aromatic protons.[28, 30, 86, 104, 126] The double bond configuration does not considerably affect the position of the vinylic proton signals. This configuration may be identified from the spin-spin coupling constants, which usually amount to 15 – 16 Hz for the *E*-isomers of linear- and cross-conjugated enynones. Published data concerning *Z*-enynones are not abundant, but it is known, for example, that the spin-spin coupling constants of the H – C(2) and H – C(3) linear-conjugated enynones — 5-trimethylsilyl-1-phenylpent-2-en-4-yn-1-one and 1-phenylpent-2-en-4-yn-1-one — range from 11.7 to 12.0 Hz.[34] The keto group carbon signal in the ^{13}C NMR spectra of linear-conjugated enynones **1** is usually manifested at 185 – 190 ppm, while in the case of cross-conjugated enynones **3**, it shifts upfield (175 – 180 ppm).[58, 86]

3.2. X-Ray diffraction data and non-linear optical properties

Currently, the Cambridge Crystallographic Data Centre (CCDC) contains information about the molecular and crystal structures of several dozens of *E*-isomers of conjugated enynones; the structures of 1,5-diaryl-substituted enynones **1** were studied most comprehensively. X-Ray diffraction data confirm the planar structure of ketones **1** and the *cis*-conformation of the enone group in the solid phase. The conjugation in the multiple bond pentad of enynones **1** causes some shortening (1.41 – 1.43 Å) of the C(3) – C(4) bond in comparison with the analogous bond in the vinylacetylene molecule (1.43 Å).[58]

A structural study of a set of linear-conjugated enynones with various aryl groups in positions 1 and 5 showed that five of these compounds (ketones **1** with R^1 = Ph: R^2 = 4-MeC_6H_4, 4-$MeOC_6H_4$, 4-$EtOC_6H_4$; R^2 = Ph: R^1 = Ph, 4-BrC_6H_4) crystallize in chiral space groups. The crystallization in the chiral groups is due to the formation of symmetrical dimers. Analysis of the intermolecular contacts revealed the C=O···H structure-forming motifs (Fig. 1) and competing Hal···Hal interactions. The generation of the second optical harmonics was experimentally found for these compounds. Taking into account the fact that the compounds crystallize in chiral space groups and the possibility to prepare a broad range of derivatives with both electron-donating and electron-withdrawing substituents, linear-conjugated enynones **1** can be considered as promising compounds, not inferior to *N*-(4-nitrophenyl)-L-prolinol, for potential non-linear optical applications.[20]

The presence of non-linear optical properties is predicted also for cross-conjugated enynones **3**.[21]

4. Chemical reactivity of enynones

4.1. Reduction to alcohols

The enantioselective reduction of the keto group of enynones is one of the most important reactions for this type of compounds, as it is utilized for total synthesis[3, 135 – 137] and for structure determination[138] of natural compounds. In particular, *R*- or *S*-vinylacetylenic alcohols **64a – f** are obtained in good yields by the reduction of cross-conjugated enynones with $BH_3 \cdot Me_2S$[136, 137, 139 – 141] or $BH_3 \cdot THF$[142] in the presence of (*R*)- or (*S*)-Me-CBS (Me-CBS is 1-methyl-3,3-diphenyltetrahydro-3*H*-pyrrolo[1,2-*c*][1,3,2]oxazaborole), which ensures a high enantiomeric excess (Scheme 25, Table 5). The asymmetric reduction of linear-conjugated enynone **65** to alcohol **66** was accomplished in the presence of binaphthyl lithium aluminium hydride [(*S*)-BINAL-H].[135]

The reactions of enynones **67** containing an endocyclic double bond with sodium bis(2-methoxyethoxy)aluminium hydride (Red-Al) in THF do not stop after keto group

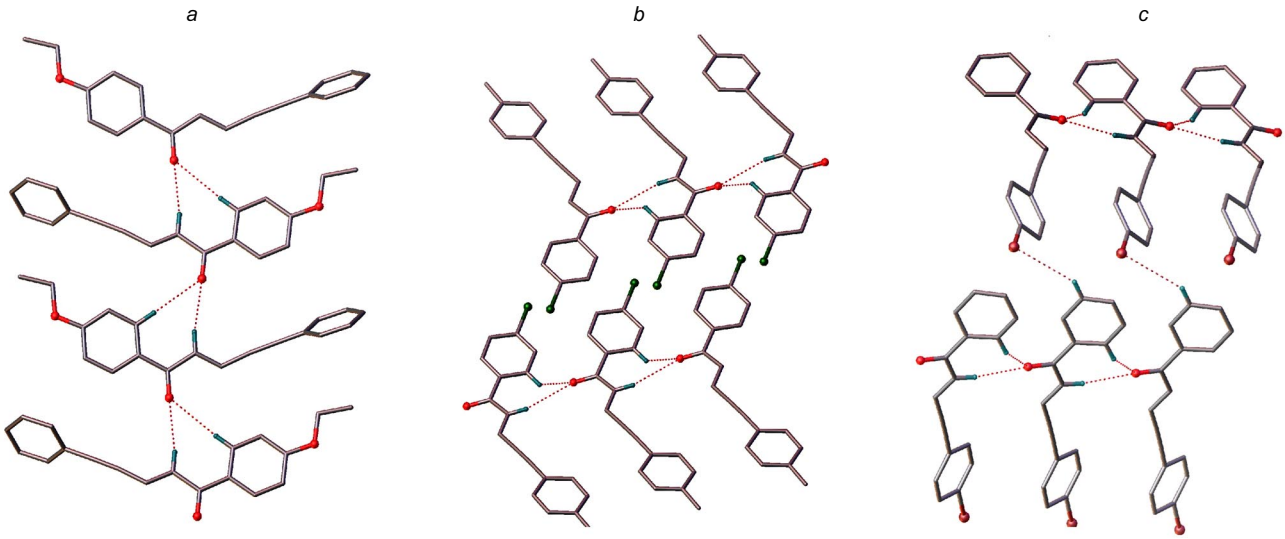
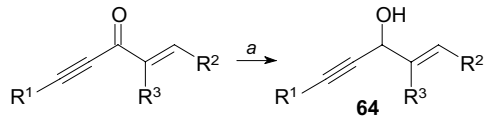
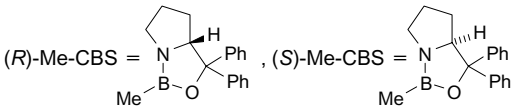


Figure 1. Intermolecular interactions in the crystals of linear-conjugated enynones: 1-(4-ethoxyphenyl)-5-phenylpent-2-en-4-yn-1-one (*a*), 1-(4-chlorophenyl)-5-(4-methylphenyl)pent-2-en-4-yn-1-one (*b*) and 5-(4-bromophenyl)-1-phenylpent-2-en-4-yn-1-one (*c*).[20]

Scheme 25



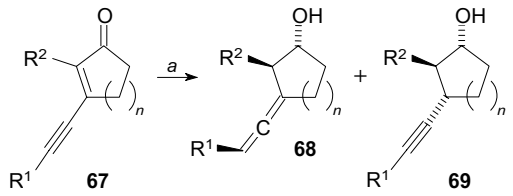
(*a*) (*R*)- or (*S*)-Me-CBS, $BH_3 \cdot Me_2S$ or $BH_3 \cdot THF$, THF;



(*b*) (*S*)-BINAL-H, THF, –100 → 180 °C

hydrogenation. This reaction gives mainly allene alcohols **68**. Acetylenes **69** are formed in minor amounts; the product **68** to **69** ratio is affected by the nature of substituent R^1: in the case of trimethylsilyl groups, a product mixture is formed, whereas the phenyl substituent results in the formation of pure allenes **68** (Scheme 26).[143]

Scheme 26



(*a*) 1) Red-Al, THF, 0 °C → rt, 2 h; 2) H_2O

R^1	R^2	*n*	Yield of **68** (%)	Yield of **69** (%)
TMS	Me	1	69	15
TMS	Me	2	64	14
TMS	H	2	54	5
Ph	Me	1	54	0
Ph	Me	2	96	0
Ph	H	2	56	0

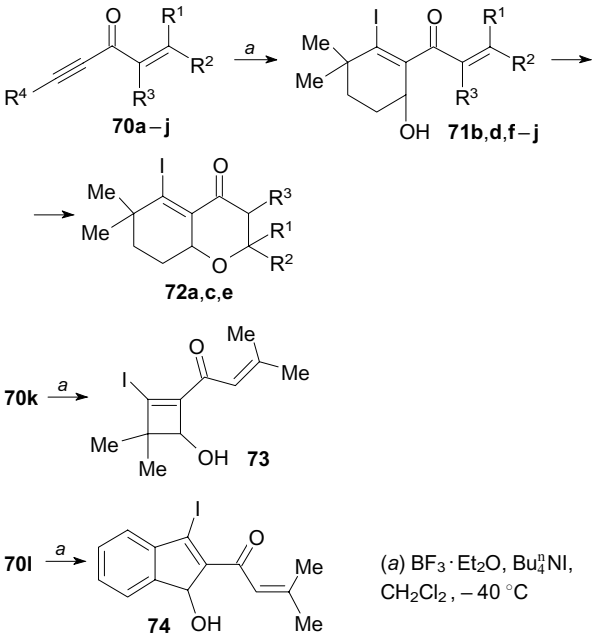
4.2. Reactions induced by electrophiles

Despite the presence of the electron-withdrawing keto group, which decreases the electron density of the carbon – carbon conjugated bonds, enyne ketones can react rather actively with electrophiles. It is noteworthy that in recent years, primary attention has been devoted to reactions of conjugated enynones with transition element compounds (see reviews [22, 23]) and to their transformations in superacid media. Reactions of this type are accompanied, in almost all cases, by cyclization and formation of carbo- and heterocyclic compounds.

4.2.1. Reactions in the presence of metal compounds and iodine

On treatment with boron trifluoride etherate in the presence of Bu^n_4NI, formyl-substituted enynones **70a – j** cyclize at the triple bond α-carbon atom to give cyclohex-2-en-1-ols **71b**,**d**,**f – j**. Some of these compounds undergo the 6-*endo-trig* oxa-Michael cyclization, resulting in products **72a**,**c**,**e**. Under these conditions, 2,2,7-trimethyl-5-oxooct-6-en-3-ynal (**70k**) is converted to cyclobutenone **73**, while 2-(5-methyl-3-oxohex-4-en-1-yn-1-yl)benzaldehyde (**70l**) is converted to indene **74** (Scheme 27, Table 6).[118] When boron trifluoride etherate is replaced by $TiCl_4$ or $AlCl_3$, only cycloalkenols like **71** are formed in 59% – 82% yields; by varying the number of carbon atoms in the substituent R^4 of the starting enynone **70**, it is possible to prepare

Scheme 27



(*a*) $BF_3 \cdot Et_2O$, Bu^n_4NI, CH_2Cl_2, – 40 °C

Table 5. Synthesis of vinylacetylene alcohols **64** by the reduction of the corresponding ketones (see Scheme 25).

Enynol	R^1	R^2	R^3	Reducing agent	Temperature °C	Yield (%)	*ee* (%)	Ref.
(*R*)-**64a**	$TBDPSO(CH_2)_2$	H	H	$BH_3 \cdot Me_2S$	–60	66	90	136
(*R*)-**64b**	TMS	H	H	$BH_3 \cdot Me_2S$	–30	75	>99	137
(*S*)-**64c**	H	See [a]	H	$BH_3 \cdot Me_2S$	–30	94	>98	139
(*R*)-**64e**	$PhS(CH_2)_2CH(OAc)CH_2$	$Boc(CH_2)_2$	H	$BH_3 \cdot Me_2S$	0	86	94 – 97	140
(*S*)-**64f**	Pr^i	Pr^i	H	$BH_3 \cdot Me_2S$	–60	85	–	141
(*S*)-**64d**	TMS	H	Bu^n	$BH_3 \cdot THF$	–30	100	90	142

Note. *ee* is enantiomeric excess; [a] 1-(triisopropylsilyloxymethyl)-3,5-dioxan-1-yl.

Table 6. Cyclization of formyl-substituted enynones **70** (see Scheme 27).[118]

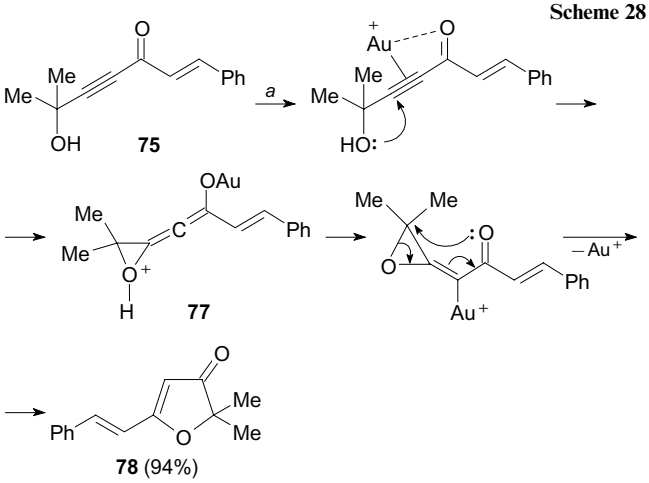
Enynone	R^1	R^2	R^3	R^4	Product	Yield (%)
70a	Me	Me	H	$CMe_2(CH_2)_2CHO$	**72a**	77 [a]
70b	Me	Ph	H	$CMe_2(CH_2)_2CHO$	**71b**	85
70c	Me	4-$MeOC_6H_4$	H	$CMe_2(CH_2)_2CHO$	**72c**	74 [a, b]
70d	Me	Bu^t	H	$CMe_2(CH_2)_2CHO$	**71d**	85
70e	H	Me	H	$CMe_2(CH_2)_2CHO$	**72e**	60 [c]
70f	H	Ph	H	$CMe_2(CH_2)_2CHO$	**71f**	77
70g	H	4-$O_2NC_6H_4$	H	$CMe_2(CH_2)_2CHO$	**71g**	86
70h	H	4-$MeOC_6H_4$	H	$CMe_2(CH_2)_2CHO$	**71h**	86
70i	Me	Me	Me	$CMe_2(CH_2)_2CHO$	**71i**	50
70j	Me	$(CH_2)_4$		$CMe_2(CH_2)_2CHO$	**71j**	88
70k	Me	Me	H	CMe_2CHO	**73**	64
70l	Me	Me	H	2-$OCHC_6H_4$	**74**	98

[a] The reaction mixture was warmed up to 0 °C; [b] tetrahydropyranone **72c** was obtained as a diastereomer mixture (*dr* = 3.2 : 1); [c] the reaction mixture was warmed up to room temperature for 39 h; and tetrahydropyranone **72e** was isolated as a pure diastereomer.

compounds with five, six or seven carbon atoms in the ring.[144]

6-Hydroxy-6-methyl-1-phenylhept-1-en-4-yn-3-one (**75**) cyclizes on treatment with a mixture of gold complex **76** with silver triflate.[145] In the authors' opinion, the reaction starts with coordination of enynone **75** by the cationic gold(I) complex formed *in situ* from complex **76** and AgOTf; this is followed by the formation of the intermediate epoxide compounds **77**, which rearranges (with liberation of the gold cation) to give the target furanone **78** (Scheme 28).

Scheme 28

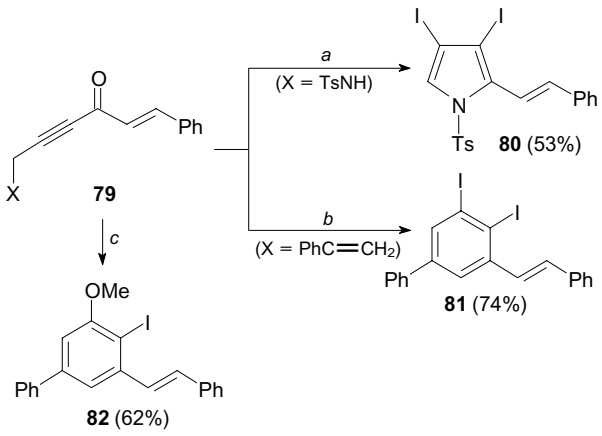


(*a*) $(4\text{-}F_3CC_6H_4)_3PAuCl$ (**76**) (5 mol.%), AgOTf (5 mol.%), PhMe, rt, 3 h

Iodocyclization of cross-conjugated enynones **79** has been reported.[117, 146] The reaction involves the triple bond, with the product structure being determined, first of all, by the substituent nature: the aminotosyl derivative undergoes ring closure to give pyrrole derivative **80**,[146] while the vinyl derivative is converted to arenes **81** and **82** (Scheme 29).[117] In the latter case, the authors did not indicate the reaction time, as the reaction was monitored by TLC.

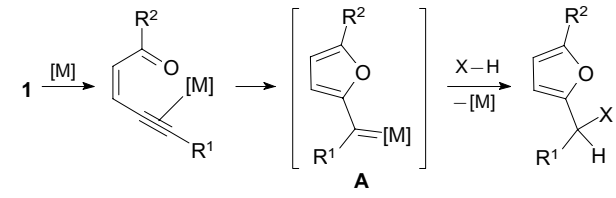
The electrophilic activation of the multiple bonds of enynones of type **1** is attained *via* π-coordination to transition metal compounds.[61, 147 – 150] The carbenoid **A** formed

Scheme 29



(*a*) I_2 (3 equiv.), MeOH, rt, 12 h; (*b*) I_2 (1.1 equiv.), $MeNO_2$, 65 °C, 7 h; (*c*) I_2 (1.5 equiv.), MeOH, 65 °C (X = PhC═CH_2)

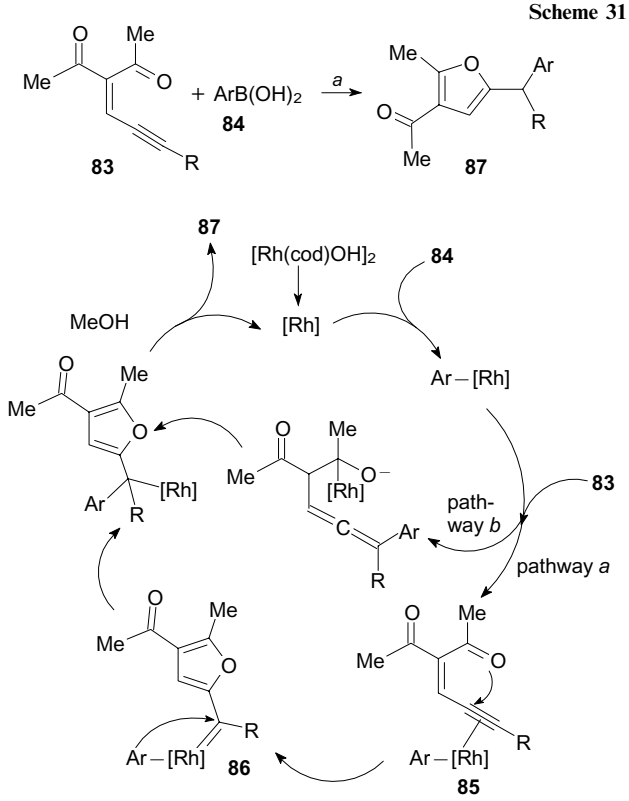
Scheme 30



after that reacts with the X – H reagent to give the product (Scheme 30).[151 – 154]

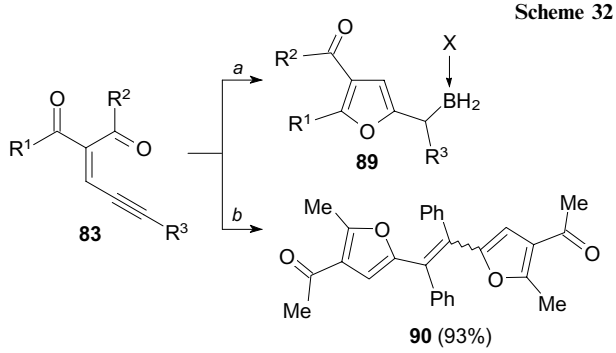
For example, enyne diketones **83** react with arylboronic acids **84** in the presence of the hydroxy(cycloocta-1,5-diene)rhodium(I) dimer (2 mol.%). The catalytic cycle of rhodium(I) for this reaction is shown in Scheme 31. Presumably, the reaction proceeds *via* the formation of rhodium enynedione complex **85**, which is then converted to 2-furylcarbenoid **86**; the subsequent migration of the Ar group results in the recovery of rhodium(I) and gives furans **87** in 32% – 70% yield (pathway *a*). An alternative mechanism (pathway *b*) implies electrophilic activation of the keto group of enynones **83**.[149]

Scheme 31



(*a*) [Rh(cod)OH]$_2$ (2 mol.%), Bu^{t}OK (1 equiv.), MeOH, 80 °C;
R = Ph: Ar = Ph (74% yield), 4-MeC$_6$H$_4$ (70%), 4-Bu^{t}C$_6$H$_4$ (64%), 4-ClC$_6$H$_4$ (71%), 4-BrC$_6$H$_4$ (57%), 4-MeO$_2$CC$_6$H$_4$ (58%), 4-AcC$_6$H$_4$ (56%), 4-H$_2$C=CHC$_6$H$_4$ (62%), 2-MeOC$_6$H$_4$ (66%), 3-MeOC$_6$H$_4$ (74%), 4-MeOC$_6$H$_4$ (69%), 3-BrC$_6$H$_4$ (60%), 3,5-Me$_2$C$_6$H$_3$ (68%), 2-Naph (71%), 2-Th (34%), 3-Th (48%);
Ar = 4-MeC$_6$H$_4$: R = 4-MeOC$_6$H$_4$ (57%), 4-MeC$_6$H$_4$ (66%), 4-F$_3$CC$_6$H$_4$ (62%), 4-ClC$_6$H$_4$ (64%), 4-IC$_6$H$_4$ (65%), 4-PhC$_6$H$_4$ (63%), 3-MeOC$_6$H$_4$ (68%), 3-FC$_6$H$_4$ (61%), 2-Th (50%);
cod is cycloocta-1,5-diene

Scheme 32



(*a*) X → BH$_3$ (**88**) (X = Bu$^n_3$P, Me$_3$N, Bu$^n_3$N, 1,3-dimethyl-2,3-dihydro-1*H*-imidazol-2-yl), CuCl (5 mol.%), Solv, 60 °C, 10 min;
(*b*) pinacolborane, CuCl (5 mol.%), DCE, 60 °C; Solv is solvent

The reaction of enynones **83** with borane complexes **88** in the presence of gold or rhodium compounds, $PtCl_2$, $ZnCl_2$, $[Rh(TFA)_2]_2$ (TFA is trifluoromethyl acetate), CuCl and $CuCl_2$ proceeds in a similar way. The highest yields of furans **89** (up to 99%) are achieved with CuCl as the catalyst in 1,2-dichloroethane (DCE) at 60 °C over a period of 10 min (Scheme 32, Table 7).[150] Under these conditions, pinacolborane reacts to give dimer **90** as a mixture of *E*- and *Z*-isomers in 3 : 2 ratio.

Table 7. Synthesis of furan-containing complexes **89** by the reaction of enynones **83** with borane complexes **88** (see Scheme 32).[150]

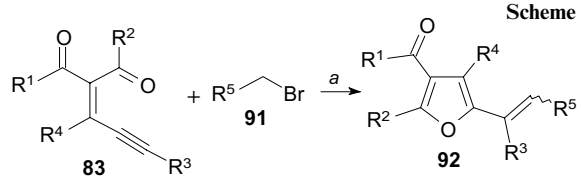
R^1	R^2	R^3	X	Yield (%)
Me	Me	Ph	Bu$^n_3$P	89
Me	Me	Ph	Bu$^n_3$N	88
Me	Me	Ph	Me$_3$N	98
Me	Me	Ph	See [a]	60
Me	Me	2-MeC$_6$H$_4$	Me$_3$N	98
Me	Me	3-MeC$_6$H$_4$	Me$_3$N	98
Me	Me	4-MeC$_6$H$_4$	Me$_3$N	99
Me	Me	4-ClC$_6$H$_4$	Me$_3$N	99
Me	Me	3-MeOC$_6$H$_4$	Me$_3$N	98
Me	Me	4-MeOC$_6$H$_4$	Me$_3$N	98
Me	Me	4-F$_3$CC$_6$H$_4$	Me$_3$N	98
Me	Me	2-Naph	Me$_3$N	98
Me	Me	Me	Me$_3$N	89
Me	Me	n-C$_6$H$_{13}$	Me$_3$N	99
Me	Me	Cy [b]	Me$_3$N	99
Me	Me	Bu^t	Me$_3$N	99
Me	Me	TMS	Me$_3$N	99
Et	Et	Ph	Me$_3$N	99
Ph	Ph	Ph	Me$_3$N	96 [c]
2-Th	2-Th	Ph	Me$_3$N	95 [d]

[a] 1,3-Dimethylimidazolin-1-yl; [b] Cy is cyclohexyl; [c] the reaction time is 1 h; [d] the reaction time is 30 min.

It was founds[150] that in the presence of CuCl, the reaction has the first partial orders with respect to enynone **83** and the catalyst and the zero order with respect to borane **88**; no kinetic isotope effect is observed. These results, in combination with density functional theory (DFT) data indicate that the reaction is rate-limited by the formation of Cu carbenoid.

The cyclization of enyne diketones like **83** and substituted benzyl bromides **91** catalyzed by palladium complexes, $Pd_2(dba)_3$ (dba is dibenzylideneacetone) and $Pd(PPh_3)_4$, forms the basis of a general method for the synthesis of furans **92** (Scheme 33, Table 8).[155] In most cases, the reaction is stereoselective and gives *Z*-isomers. Here, as in the previous examples, the authors believe that this reaction proceeds *via* the formation of carbenoids.

Scheme 33



(*a*) Pd(PPh$_3$)$_4$ (5 mol.%), Pr$^i_2$NEt (3 equiv.), DMF, 90 °C, 2 h

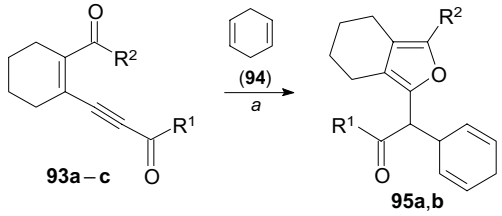
Subsequently, the cyclization of enyne diketones **83** catalyzed by copper(I),[60] copper(II),[62] zinc[147,156] and gold[157,158] compounds has often been used to prepare various functional derivatives of furans. Enynones **83** containing the *m*-propargyloxy moiety in the aromatic ring of

Table 8. Synthesis of furans **92** by cyclization of enynones **83** with benzyl bromides **91** (see Scheme 33).[155]

R^4	R^1	R^2	R^3	R^5	Yield (%)
H	Ac	Me	Bu^t	4-MeC_6H_4	79
H	Ac	Me	TMS	4-MeC_6H_4	82 [a]
H	Ac	Me	TIPS	4-MeC_6H_4	66 [b]
H	Ac	Me	Ph	4-MeC_6H_4	53 [c]
H	Bz	Ph	Bu^t	4-MeC_6H_4	67 [d]
H	EtO_2C	Me	Bu^t	4-MeC_6H_4	77
H	MeO_2C	Et	Bu^t	4-MeC_6H_4	77
Ph	H	Me	H	4-MeC_6H_4	35
$(CH_2)_3$		Ph	H	4-MeC_6H_4	52
$(CH_2)_4$		Ph	H	4-MeC_6H_4	65
H	Ac	Me	Bu^t	Ph	85
H	Ac	Me	Bu^t	4-PhC_6H_4	82
H	Ac	Me	Bu^t	4-$MeO_2CC_6H_4$	76
H	Ac	Me	Bu^t	4-$O_2NC_6H_4$	72
H	Ac	Me	Bu^t	3-ClC_6H_4	84
H	Ac	Me	Bu^t	3-NCC_6H_4	93
H	Ac	Me	Bu^t	3-$MeOC_6H_4$	95
H	Ac	Me	Bu^t	2-BrC_6H_4	79
H	Ac	Me	Bu^t	1-Naph	59

[a] The *E*- and *Z*-isomer ratio is 8 : 1; [b] the reaction time is 30 h; [c] the *E*- and *Z*-isomer ratio is 3 : 2; [d] the reaction time is 10 h.

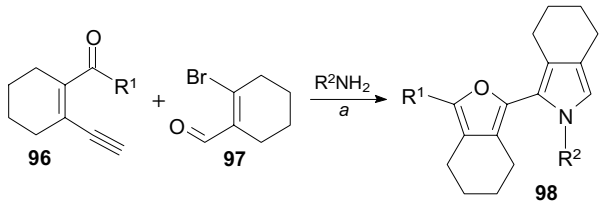
Scheme 34



(*a*) $[Rh_2(OAc)_4]$ (2.5 mol.%), CH_2Cl_2, Δ

Compound **93**	R^1	R^2	Reaction time /h	Yield (%)
a	Me	H	8	35
b	Ph	H	72	20
c	H	Ph	24	0

Scheme 35



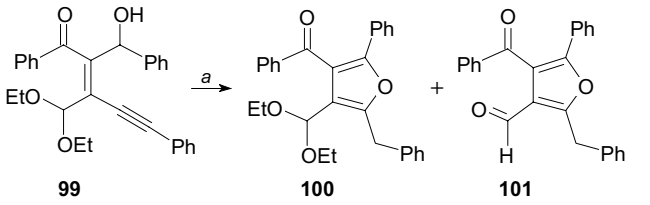
(*a*) $Pd(dba)_3$ (3 mol.%), PPh_3 (18 mol.%), CuI (9 mol.%), PhMe, rt, 24 h; R^2 = Bu^t: R^1 = 4-$MeOC_6H_4$ (53% yield), 4-$Ph_2NC_6H_4$ (87%), 4-$F_3CC_6H_4$ (86%), 2-Th (68%); R^1 = Ph: R^2 = Bn (71%), All (54%)

substituent R^1 readily undergo a cascade reaction in the presence of palladium complexes, which results in the formation of fused oxygenated polyheterocycles.[159]

Enynones with an endocyclic double bond **93a**,**b** react with cyclohexa-1,4-diene (**94**) in the presence of rhodium acetate (Scheme 34).[160] This gives compounds **95a**,**b** in moderate yields. When enynone **93c** containing a benzoyl group is used, the reaction does not take place. The reaction of enynones **96** with 2-bromocyclohex-1-enecarbaldehyde (**97**) in the presence of *tert*-butyl-, benzyl- or allylamine proceeds at room temperature in toluene and affords heterocycles **98** (Scheme 35).[161]

When the enynone molecule contains a hydroxymethyl moiety in the α-position to the keto group, cyclization is intramolecular and involves this moiety (Scheme 36). The reaction of enynone **99** proceeds in the presence of $Pd(MeCN)_2Cl_2$ (20 mol.%) on refluxing in THF. This gives the diethyl acetal derivative (**100**, 18% yield) and, as a result of partial hydrolysis, formyl derivative (**101**, 36%) of furan.[162, 163]

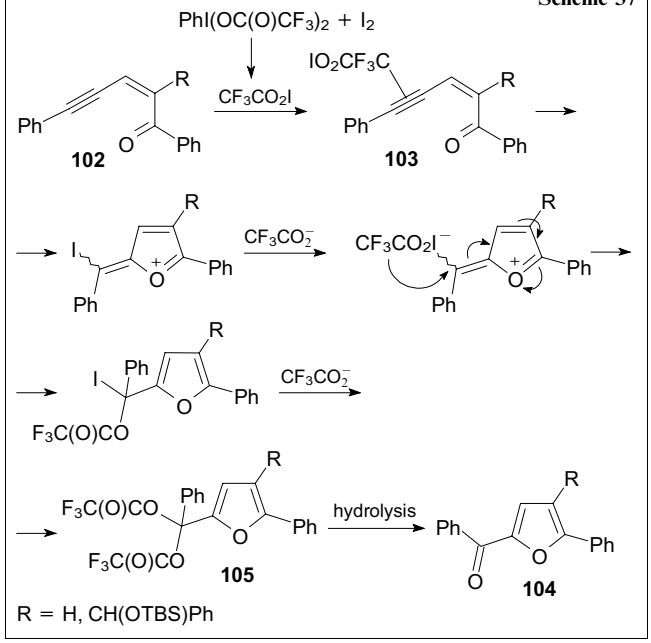
Scheme 36



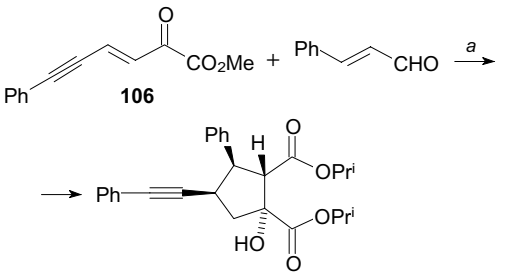
(*a*) $Pd(MeCN)_2Cl_2$ (20 mol.%), THF, Δ, 2 h

Not only transition metal compounds can serve as catalysts for cyclization of enynones to furans. For example, the electrophilic activation of the triple bond of *cis*-enynones **102** is attained *via* coordination of the phenyliodonium bis(trifluoroacetate) (PIFA)$-I_2$ system to the triple bond to form complexes **103** (Scheme 37).[9]

Scheme 37

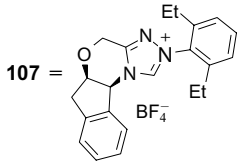


Scheme 38

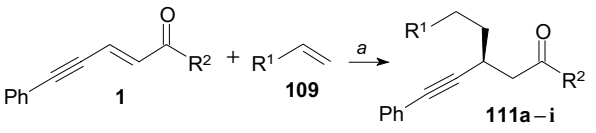


108 (62%, *dr* 20 : 1, *ee* 94%)

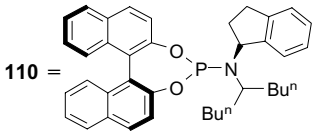
(*a*) **107** (20 mol.%), DBU (40 mol.%), $Ti(OPr^i)_4$ (5 equiv.), Pr^iOH, THF, 23 °C; DBU is 1,8-diazabicyclo[5.4.0]undec-7-ene;



Scheme 39



(*a*) **110** (10 mol.%), $[Cp_2ZrHCl]\cdot CH_2Cl_2$, CuCl (140 mol.%), AgOTf (11 mol.%), TMSCl (5 equiv.), Et_2O, 0 °C, 12 h; Cp is cyclopentadienyl;



The reaction is carried out in the presence of PIFA–I_2 (2 equiv.) and $NaHCO_3$ (4 equiv.) at room temperature in THF. The yield of benzoylfurans **104** after hydrolysis of compounds **105** under these conditions reaches 87%–92%. Apart from furans, six-membered rings can be generated in the electrophilic cyclization of enynones.[164]

The reactions of linear-conjugated enynones in the presence of titanium and zirconium compounds have been studied.[165, 166] The reaction of enyne keto ester **106** with cinnamaldehyde is promoted by tetraisopropoxytitanium. Chiral agent **107** ensures the stereoselective formation of the reaction product **108** (Scheme 38).[165]

Table 9. Synthesis of chiral alkynones **111** by the condensation of enynones with alkenes **109** (see Scheme 39).[166]

Compound **111**	R^1	R^2	Yield (%)	*ee* (%)
a	Bu^n	Me	70	94
b	Cy	Me	87	95
c	Cyclohex-3-en-1-yl	Me	87	95
d	$H_2C{=}CH(CH_2)_2$	Me	69	92
e	$TBSO(CH_2)_2$	Me	66	94
f	$TMSCH_2$	Me	75	94
g	$Br(CH_2)_5$	Me	76	96
h	$Br(CH_2)_5$	SEt	66	97
i	Cyclohex-3-en-1-yl	SEt	75	96

Enynones **1** react entantioselectively with alkenes **109** on treatment with the Schwartz reagent and the ligand **110**–CuCl–AgOTf–TMSCl system in diethyl ether. The reaction involves the enynone double bond and gives compounds **111a**–**i** in good yields (Scheme 39, Table 9).[166]

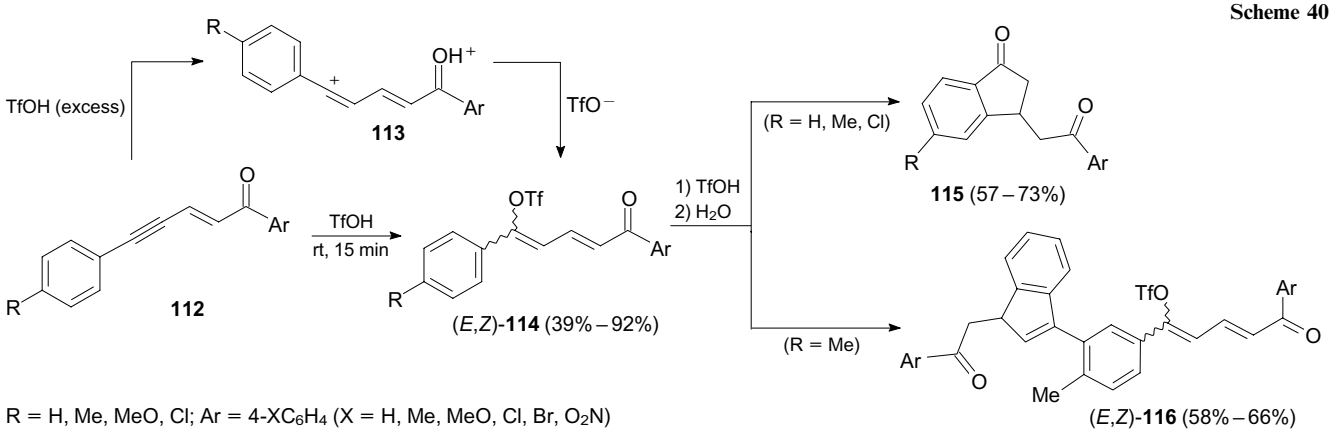
4.2.2. Reactions in superacid media

In recent years, considerable attention has been paid to reactions of conjugated enynones in superacids.[18, 19, 167] In trifluoromethanesulfonic acid, 1,5-diarylpent-2-en-4-yn-1-ones **112** are first coverted to cations **113** (as shown by NMR spectroscopy) and then to dienone triflates **114**, which undergo intramolecular electrophilic substitution on further acid activation, thus being cyclized to indanone derivatives **115**. The reaction is accompanied by the formation of dimeric products **116** (Scheme 40).[18]

In the presence of arenes, the reaction follows the alkenylation pathway and affords indene derivatives **117** and **118** (Scheme 41, Table 10). The addition of pyridine to the reaction medium results in the formation of 1,5,5-triarylpenta-2,4-dien-1-ones.[19]

Similarly, in a superacid medium (TfOH, conc. H_2SO_4), cross-conjugated aromatic enynones **3**, first, add presumably the anion of the acid to their triple bond, thus giving protonated enynones **119** and dienones **120**. Treatment of the reaction mixture with water affords dienones **121** (in the case of TfOH) or α,β- unsaturated diketones **122** (in the case of concentrated H_2SO_4). As the contact time with concentrated H_2SO_4 increases, salt **123** is converted to dihydro-

Scheme 40



R = H, Me, MeO, Cl; Ar = 4-XC_6H_4 (X = H, Me, MeO, Cl, Br, O_2N)

Scheme 41

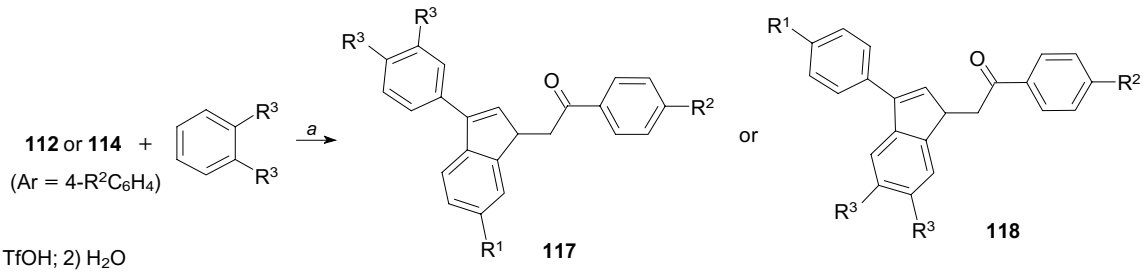


Table 10. Synthesis of indene derivatives **117** and **118** by alkenylation (see Scheme 41).[18]

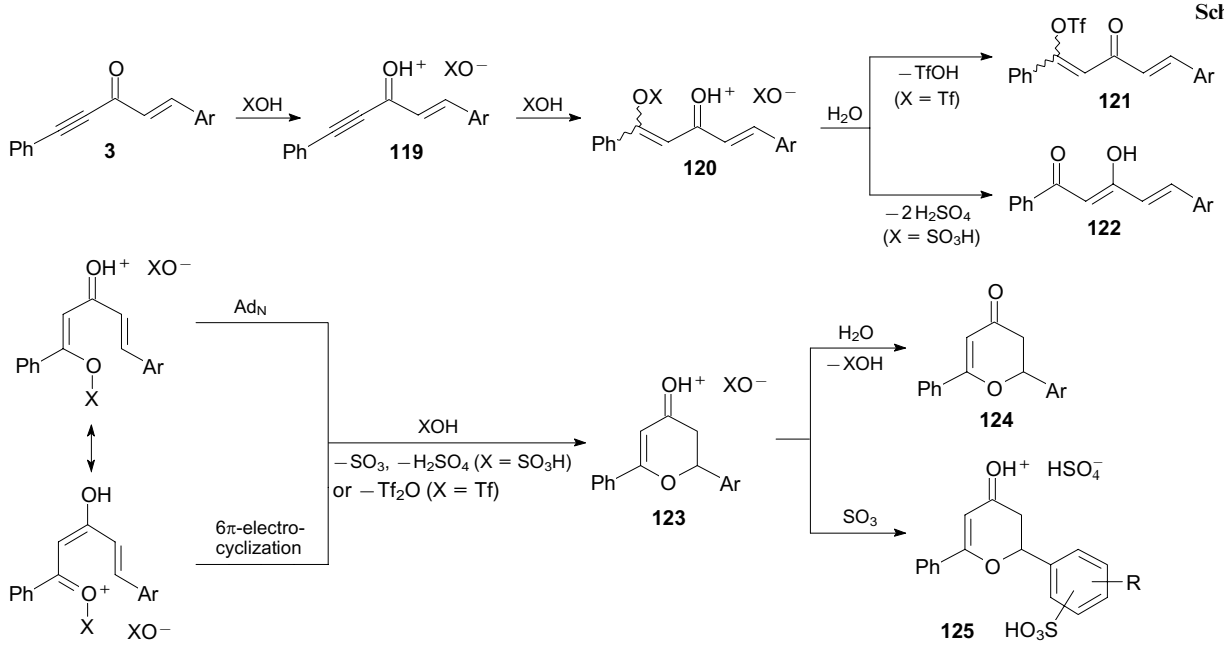
Starting compound [a]	R^1	R^2	R^3	Temperature °C	Time /h	Total yield (%) (see [b])	Major product	
							No.	mole fraction [c]
114	H	H	Cl	0	6	73	**117**	0.76
114	H	H	MeO	0	6	85	**118**	0.90
114	H	Me	MeO	0	6	68	**118**	0.89
114	Cl	H	Cl	rt	16	74	**117**	0.78
114	Cl	H	Me	rt	12	81	**118**	0.88
114	Cl	H	MeO	rt	12	71	**118**	0.48
114	Cl	H	MeO	0	6	17	**118**	0.93
114	Me	Cl	Cl	−38 → rt	6	30	**117**	0.84
114	Me	Cl	Me	−38 → rt	6	46	**118**	0.69
114	Me	Cl	MeO	−38 → rt	6	45	**118**	0.85
112	MeO	H	Cl	rt	12	23	**117**	0.60
112	MeO	H	Me	rt	12	95	**118**	0.63

[a] Triflates **114** were generated *in situ* from the corresponding enynones **112**; [b] yields for all regioisomers in the mixtures after chromatographic separation; [c] mole fraction of the major product in the mixture after separation (according to ^{1}H NMR data).

pyran-4-ones **124** and the products of their sulfonation **125** (Scheme 42).[167]

The protonated forms of compounds **120** were characterized, as in the previous case, by ^{1}H and ^{13}C NMR spectra.

Scheme 42



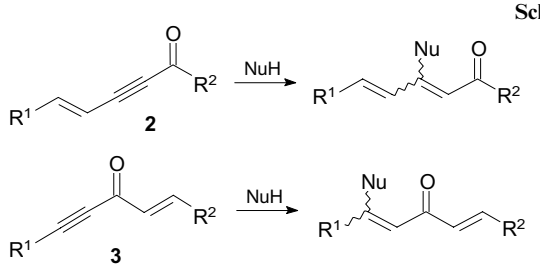
4.3. Nucleophilic reactions

The carbonyl group has a potent electron-withdrawing effect on the double and triple bonds and, hence, increases the enynone affinity to nucleophiles.[168, 169] For this reason, nucleophilic addition is the most general type of reactions of enynones. However, it is noteworthy that the multicentre nature of the substrates considerably influences the reaction pathways. The key factors determining the reaction regioselectivity are the relative positions of the double bonds in the conjugated pentad and the nature of substituents at its terminal atoms. Apart from the substrate structure, a considerable role may be played by the nature of the nucleophile and the reaction conditions.

4.3.1. Alk-1-en-4-yn-3-ones and alk-4-en-2-yn-1-ones

Enyne ketones in which the triple bond directly adjoins the keto group behave, most often, similarly to α,β-acetylenic ketones: they add N- and S-nucleophiles, first of all, at the β-carbon atom of the triple bond (Scheme 43).[123, 170–172]

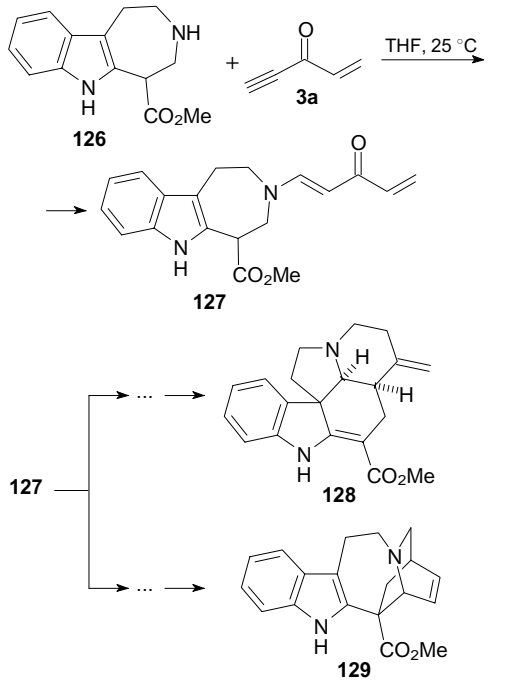
Scheme 43



NuH is nucleophile

This fact is used in the synthesis of nitrogen-containing heterocycles. For example, the addition of azepinoindole **126** to pent-1-en-4-yn-3-one (**3a**) giving adduct **127** is one of the steps towards the synthesis of indole alkaloids — desethylvincadifformine (**128**) and desethylcatharanthine (**129**) (Scheme 44).

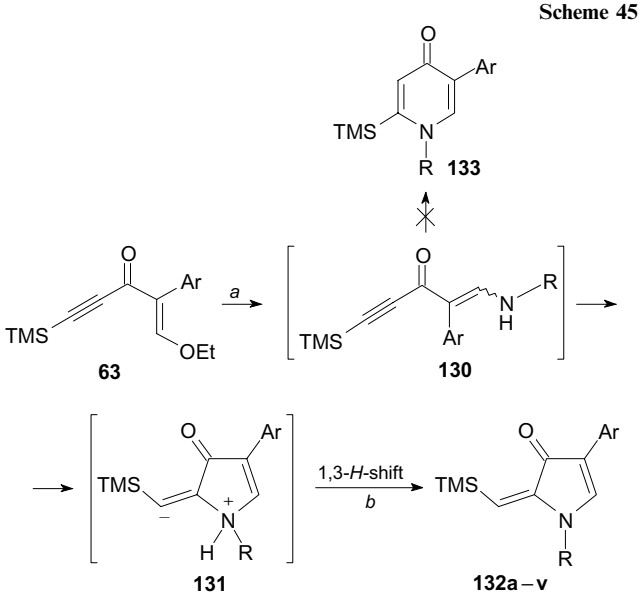
Scheme 44



It is notable that the whole conjugated pentad of the initial enynone becomes a building block for the subsequent steps of this synthesis.[2]

Golubev *et al.*[173] reported the use of the enynone pentad in the synthesis of nitrogen heterocyclic compounds. The reaction of 2-aryl-1-ethoxy-5-(trimethylsilyl)pent-1-en-4-yn-3-ones **63** with primary amines in diphenyl ether yields, first, amino ketones **130**, which generate anions **131** on further heating to 200 °C and are converted to pyrrolones **132a–v**. The unusual cyclization pathway of amino ketones **130** (5-*exo*-*dig*-reaction involving the triple bond α-atom) was attributed to the efficient stabilization of the initial anion **131** due to the presence of the trimethylsilyl group. 4-Pyridones **133** are not formed in this reaction (Scheme 45). When 1,1-dimethylhydrazine was used (40 °C, THF), only ketone of type **130** was obtained. Pyrrolones **132a–v** exhibit pronounced fluorescence.

Scheme 45



(*a*) RNH_2, Ph_2O, 80 °C; (*b*) Ph_2O, 200 °C;
Ar = 4-$O_2NC_6H_4$: R = 4-$MeOC_6H_4$ (**a**, 90% yield), Ph (**b**, 88%), 4-$O_2NC_6H_4$ (**c**, traces), 4-FC_6H_4 (**d**, 90%), 4-$MeO_2CC_6H_4$ (**e**, 68%), 4-$F_3CC_6H_4$ (**f**, 68%), 2-$F_3CC_6H_4$ (**g**, 62%), 4-NCC_6H_4 (**h**, 65%), 4-MeC_6H_4 (**i**, 84%), 1,3,5-$Me_3C_6H_2$ (**j**, 84%), 2,6-$Pr^i_2C_6H_3$ (**k**, 80%), 2-Th (**l**, 45%), 3-(4-chlorophenyl)-1-phenyl-1*H*-pyrazol-5-yl (**m**, 75%), Pr^n (**n**, 90%), cyclo-C_5H_9 (**o**, 77%), Bu^t (**p**, 73%), Bn (**q**, 90%), furfuryl (**r**, 80%); Ar = Ph: R = Ph (**s**, 65%), 4-$MeOC_6H_4$ (**t**, 66%); Ar = 4-$MeOC_6H_4$: R = Ph (**u**, 70%), 4-$MeOC_6H_4$ (**v**, 74%)

Cross-conjugated enynones **3** are successfully employed in the synthesis of six-membered sulfur-[111, 114, 170] and selenium-containing[171] heterocycles as a result of both unsaturated carbon–carbon bonds being involved in the reaction. Indeed, the reaction of enynones **3** with sodium sulfide or sodium hydrogen sulfide in a THF–water mixture or with sodium hydrogen sulfide in 2-methoxyethanol serves as a convenient synthetic route to 2,3-dihydrothiopyran-4-ones **134**, the yields of which vary from 8% to 96% (Scheme 46, Table 11).[111, 114]

Scheme 46

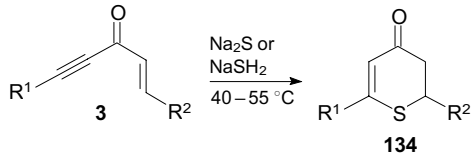


Table 11. Synthesis of 2,3-dihydrothiopyran-4-ones **134** by cyclization of enynones **3** induced by sulfides (see Scheme 46).

R^1	R^2	Conditions	Yield (%)	Ref.
Ph	Ph	$Na_2S \cdot 9H_2O$, THF, H_2O	94	111, 114
3,4-$(MeO)_2C_6H_3$	Ph	$NaSH \cdot 1.2H_2O$, $MeO(CH_2)_2OH$	96	114
3-EtO-4-$MeOC_6H_3$	Ph	$NaSH \cdot 1.2H_2O$, $MeO(CH_2)_2OH$	92	114
2-$F_3CC_6H_4$	Ph	$NaSH \cdot 1.2H_2O$, $MeO(CH_2)_2OH$	84	111, 114
2,4-$F_2C_6H_3$	Ph	$Na_2S \cdot 9H_2O$, THF, H_2O	65	114
2,4-$F_2C_6H_3$	Ph	$NaSH \cdot 1.2H_2O$, $MeO(CH_2)_2OH$	43	114
2-Th	Ph	$NaSH \cdot 1.2H_2O$, $MeO(CH_2)_2OH$	81	111, 114
2-Py	Ph	$NaSH \cdot 1.2H_2O$, $MeO(CH_2)_2OH$	60	111, 114
Bu^t	Ph	$NaSH \cdot 1.2H_2O$, $MeO(CH_2)_2OH$	85	111, 114
TMS (see [a])	Ph	$Na_2S \cdot 9H_2O$, THF, H_2O	34	114
TMS (see [a])	Ph	$NaSH \cdot 1.2H_2O$, $MeO(CH_2)_2OH$	70	114
3,4-$(MeO)_2C_6H_3$	H	$NaSH \cdot 1.2H_2O$, $MeO(CH_2)_2OH$	36	114
3-EtO-4-$MeOC_6H_3$	H	$NaSH \cdot 1.2H_2O$, $MeO(CH_2)_2OH$	16	111, 114
2,4-$F_2C_6H_3$	H	$Na_2S \cdot 9H_2O$, THF, H_2O	8	111, 114

[a] The TMS group in the product with R^1 = H is eliminated under the reaction conditions.

2,3-Dihydrothiopyran-4-one derivatives are also formed when thioester **135** reacts with 2-methylbut-3-yn-2-ol (**136**). The reaction starts with Pd/Cu-catalyzed cross-coupling of the initial thioester with alcohol **136**, while enynone **137** and *p*-nitrobenzenethiol thus formed give nucleophilic addition product **138**. This product is deprotonated to anion **139**, followed by rearrangement to anion **140**, cyclization of which affords 2,3-dihydrothiopyran-4-one derivative **141** (Scheme 47). The reaction of enynone **137** prepared by an alternative route with *p*-nitrobenzenethiol as well as heating of adduct **138** under the reaction conditions (Et_3N, DMF, 80 °C) lead to product **141**, which confirms the proposed mechanism of the reaction.[170]

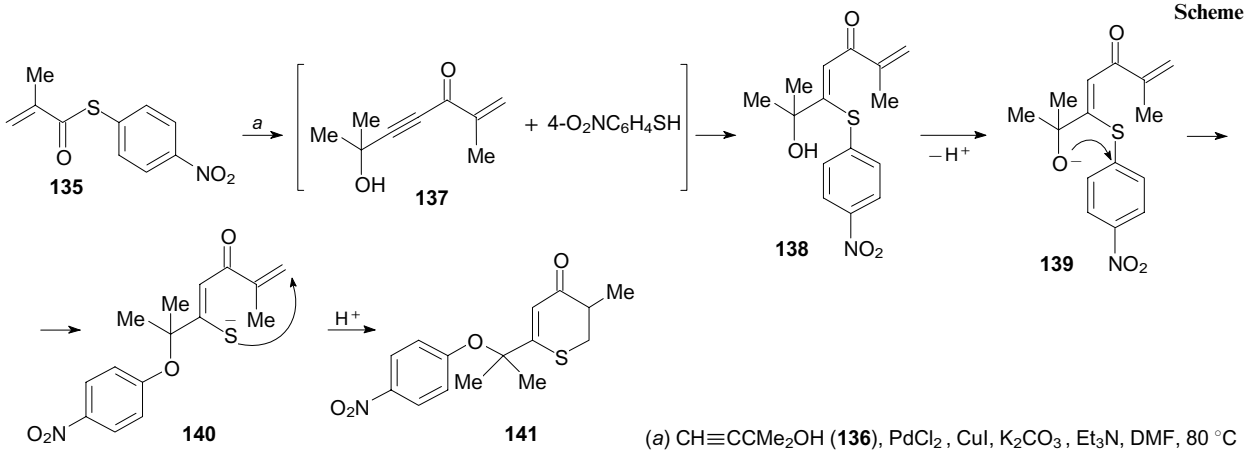
Attention is attracted by the fact that even so sterically crowded triple bond of enynone **137** is more reactive towards S-nucleophile than the double bond.

The reaction of cross-conjugated enynones with CH-acids is successfully used in the synthesis of complex carbocyclic systems.[174 – 176] For example, the Michael reaction of 5-ethoxyenynone **142** with diethyl malonate in the presence of potassium *tert*-butoxide in *tert*-butyl alcohol involves both multiple bonds to give cyclohexenone **143**.[174] Homologous 5-methoxyenynone **144** reacts with 7-chloro-4,6-dimethoxybenzofuran-3(2*H*)-one (**145**) to give the DL-griseofulvin (**146**), an antifungal agent, in a moderate yield.[174] The reaction of enynone **3b** with dimedone (**147**) also involves both carbon – carbon multiple bonds, thus giving spiro[5.5]undec-7-ene derivative **148** (Scheme 48).[175]

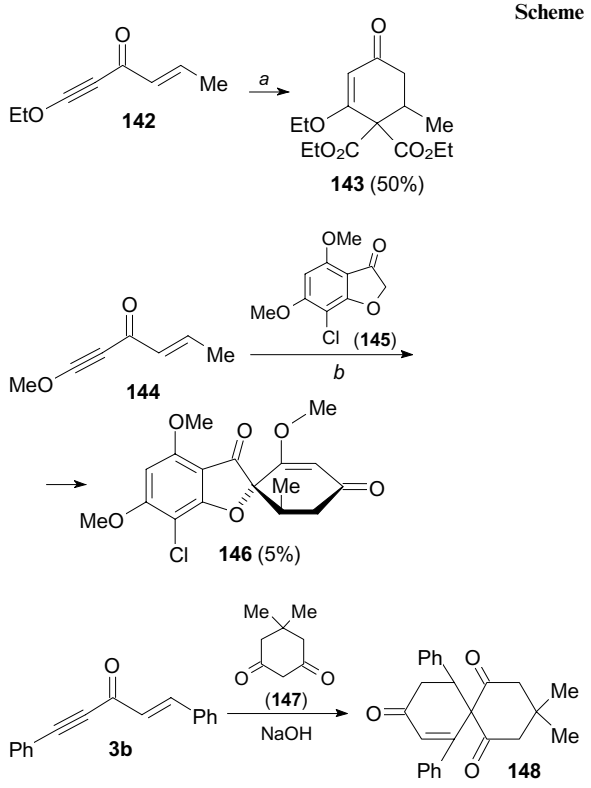
Under the action of Lewis acids, the enynone complex with $Co_2(CO)_6$ (**149**) undergoes intramolecular cyclization to give bridged compound **150** as a single stereoisomer, which was studied by X-ray diffraction (Scheme 49). Despite the fact that this cyclization can formally be classified as [4 + 2]-cycloaddition, the authors believe that the reaction mechanism actually includes two successive Michael reactions. Apart from the target compound **150**, by-products **151** and **152** are formed (Michael adduct and the product of hydrolysis of the initial enynone complex, respectively), with the reaction selectivity being considerably affected by the Lewis acid used and the contact time (Table 12). The highest yield of the target compound **150** is attained when $MeAlCl_2$ is employed as the catalyst. This reaction was extended to enynone complexes **153** and **154**; this yielded products **155** and **156**. However, in the latter case, a large excess of the catalyst is needed due to pronounced distortion of the bond angles in the complex; under these conditions, the yield of the target compound is markedly lower.[176]

The reaction of cross-conjugated enynone **3c** with β-naphthol derivative **157** catalyzed by di-n-butylmagnesium in the presence of (*S*)-2-[(4-benzyl-4,5-dihydrooxazol-

Scheme 47



Scheme 48



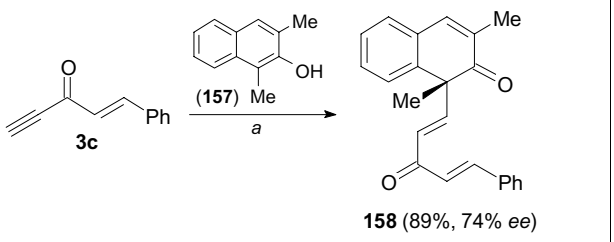
(*a*) $CH_2(CO_2Et)_2$, Bu^tOK, Bu^tOH, rt; (*b*) Bu^tOK, diglyme, rt

Table 12. Yields of products **150** – **152** with the use of various Lewis acids (see Scheme 49).[176]

Lewis acid	Time /h	Yield of **150** (%)	Yield of **151** (%)	Yield of **152** (%)
$BF_3 \cdot Et_2O$	0.5	0	0	34
$AlCl_3$	25	34	12	26
Et_2AlCl	3.5	27	0	0
$MeAlCl_2$	3.0	40	30	17
$MeAlCl_2$ (see [a])	0.33	75	1	2

[a] With the addition of 2,6-di-*tert*-butylpyridine.

Scheme 50



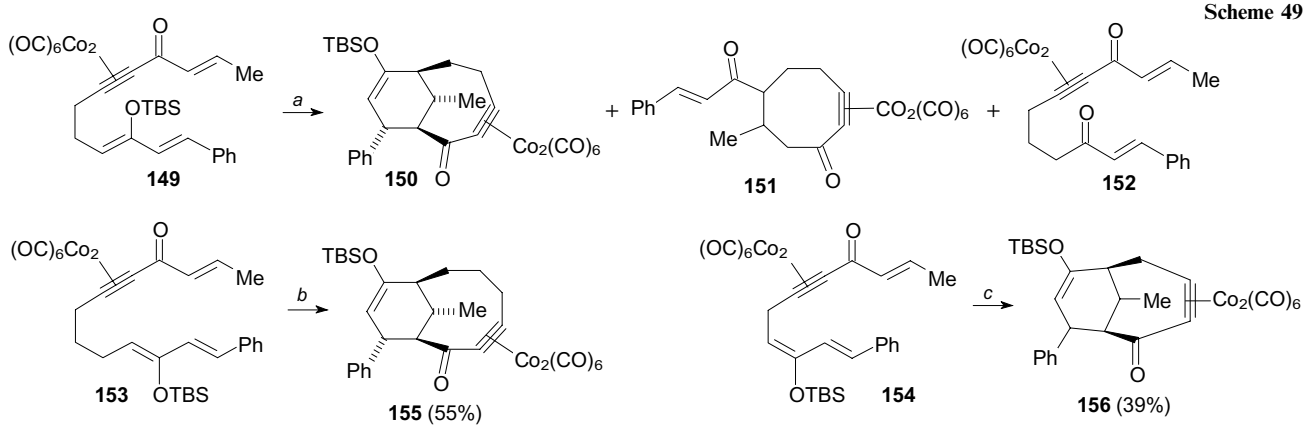
(*a*) Bu^n_2Mg/L, CPME, 0 °C, 1 h

2-yl)methyl]phenol (L) as a chiral ligand in cyclopentyl methyl ether (CPME) involves the triple bond. Adduct **158** is formed in a good yield as a mixture of *E*- and *Z*-isomers in 15 : 1 ratio (Scheme 50).[177]

Reactions of enynones with indole,[115, 178] furan[179] and 5*H*-oxazol-4-one[180] derivatives have been studied. Cross-conjugated enynones **3c** and **159** ($R^3 \neq H$) react with substituted indoles **160**, at the double bond upon the CH-activation with sodium tetrachloroaurate. The initially formed adducts **161** undergo a cascade process and thus cyclize to 9,10-dihydrocyclohepta[*b*]indol-8(5*H*)-ones **162** in high yield (Scheme 51, Table 13).[115] Under these conditions, more complex cross-conjugated enyne systems also react at the double bond;[178] in the presence of gold compounds, the same reaction proceeds for 2-methylfuran.[179] However, unlike the previous examples,[115, 178, 179] the enantioselective reaction of 1-phenylpent-1-en-4-yn-3-one (**3e**) with 2-(2-chlorophenyl)-5-methyloxazol-4(5*H*)-one **163** in the presence of chiral compound **164** involves the triple bond and gives product **165** (see Scheme 51).[180]

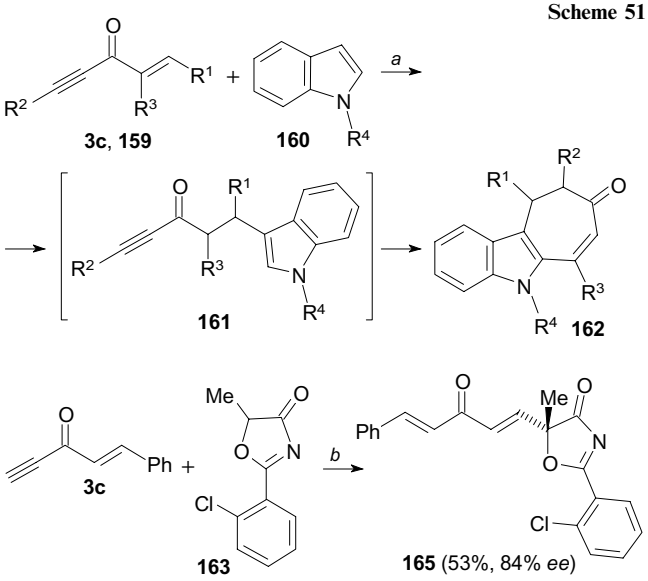
The nucleophilic reaction centre can also be located in the starting enynone substrate molecule. For example, (2-aminophenyl)-substituted enynones **166a** – **d** undergo intermolecular cyclization in the presence of gold complex **167**; this is utilized for the synthesis of 5,6,11,12-tetrahydrodibenzo[*b*,*f*][1,5]diazocines **168a** – **c** (Scheme 52, Table 14).[181] Presumably, two enynone molecules react initially to form an adduct at the β-carbon atom of the triple bond, and the subsequent 8-*exo*-*dig*-cyclization gives the target products. The catalytic function of Au^I consists in π-coordination to the triple bond, which increases its electrophilicity. Recently, it was shown[182] that in the

Scheme 49

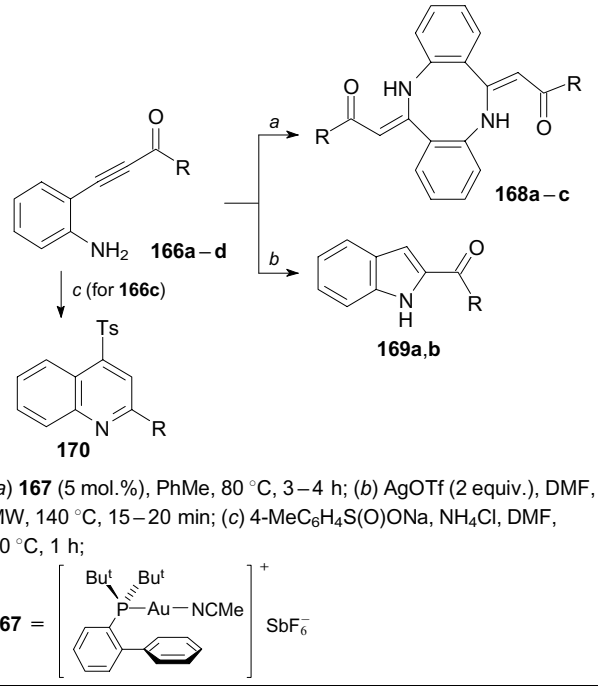


(*a*) Lewis acid (2 equiv.), CH_2Cl_2, – 78 °C; (*b*) $MeAlCl_2$ (2 equiv.), CH_2Cl_2, rt, 2.5 h; (*c*) $MeAlCl_2$ (5.25 equiv.), 2,6-di-*tert*-butylpyridine, CH_2Cl_2, rt, 10 min

Scheme 51



Scheme 52



presence of silver compounds [under microwave (MW) irradiation], anti-Michael cyclization of enynones **166** takes place to give indoles **169a**,**b**. Like in the pyrrole formation reaction,[173] the triple bond α-atom is the site of attack by the nucleophile. According to quantum chemical calculations for the model reaction of substrate **166e** (R = Ph), the thermodynamically most stable transition state is a state of type **A**, which includes a silver ion coordinated to a solvent molecule and both atoms of the triple bond (Fig. 2). According to DFT data, in this transition state, the α-carbon atom is more electrophilic

Table 14. Cyclization products of (2-aminophenyl)-substituted enynones **166** (see Scheme 52).

Compound **166**	R	Reaction product	Yield (%)	Ref.
a	Cyclooct-1-en-1-yl	**168a**	62	181
b	4-*tert*-Butylcyclohex-1-en-1-yl	**168b**	79	181
c	(*E*,*E*)-Bu^n(CH=CH)$_2$	**168c**	56	181
b	4-*tert*-Butylcyclohex-1-en-1-yl	**169a**	56	182
d	(*E*)-(2-Fu)CH=CH	**169b**	66	182
c	(*E*,*E*)-Bu^n(CH=CH)$_2$	**170**	72	183

Table 13. Synthesis of 9,10-dihydrocyclohepta[*b*]indol-8(5*H*)-ones **162** (see Scheme 51).[115]

R^1	R^2	R^3	R^4	Time /h	Temperature /°C	Yield (%)
Me	H	4-MeC$_6$H$_4$	H	6	23	98
Me	H	4-MeOC$_6$H$_4$	H	24	23	82
Me	H	4-F$_3$CC$_6$H$_4$	H	16	23	73
Ph	H	Ph	H	24	82	77
Ph	£	Ph	H	3	82	100
Me	H	2-Naph	H	8	23	81
Ph	H	2-Naph	H	24	23	97
Ph	H	Bu^n	H	72	82	47
Ph	H	Bu^n	H	18	82	69
Me	H	Bu^n	H	24	82	79
Me	H	Bu^n	H	4	82	82
H	H	Bu^n	H	96	82	60
H	H	Ph	H	12	23	99
Pr^i	H	Ph	H	18	23	72
H	Me	Ph	H	8	23	76
Me	Me	Ph	H	8	82	15
Me	Me	Ph	H	18	23	73
Ph	H	H	H	18	82	0
Me	H	Ph	Me	20	23	71

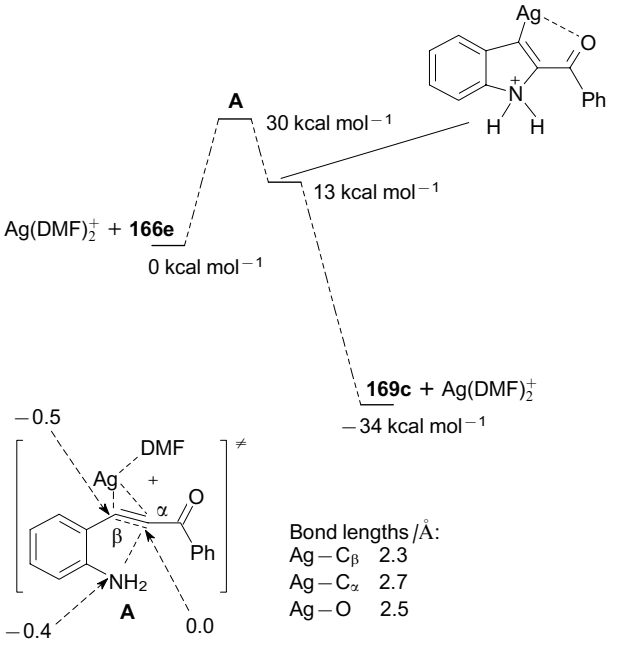


Figure 2. Energy profile of the cyclization of 3-(2-aminophenyl)-1-phenylprop-2-yn-1-one (**166e**) in the presence of AgOTf according to DFT data (the numerals at the dashed arrows are atomic charges).[173]

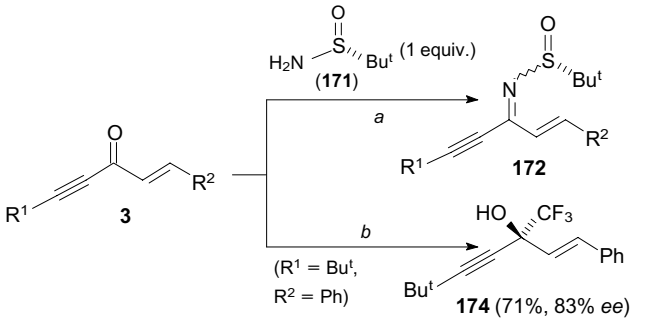
than the β-carbon atom. The intramolecular cyclocondensation involving the keto group occurs on heating of 1-(2-aminophenyl)undeca-4,6-dien-1-yn-3-one (**166c**) in toluene in the presence of sodium toluenesulfinate to give 4-(4-methylphenylsulfonyl)quinoline (**170**) (see Scheme 52).[183]

Apart from the example reported by Rode *et al.*,[183] nucleophilic addition to the keto group of cross-conjugated enynones is utilized in the synthesis of precursors of biologically active products.[184, 185] For example, the reaction of enynones **3** with (*R*)-2-methylpropane-2-sulfinamide (**171**) catalyzed by tetraethoxytitanium involves the keto group and gives *Z*- and *E*-isomer mixtures of imines **172** , as follows from the ^{1}H NMR spectra recorded in C_6D_6 at 25 °C (Scheme 53).[184] The enantioselective trifluoromethylation of enynone **3d** (R^1 = Bu^t, R^2 = Ph) proceeds in the presence of cinchona alkaloid **173** and Me_4NF. The trimethylsilyl ether formed initially (not indicated in the Scheme) is converted to the target product **174** on treatment of the reaction mixture with an aqueous solution of Bu^n_4NF. It is noteworthy that such propargyl alcohols are of considerable interest as chiral building blocks for the synthesis of anti-HIV-active compounds.[185]

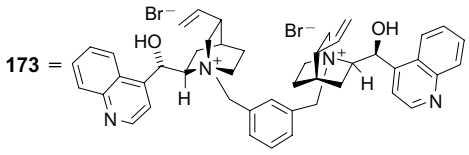
The pathway of reaction between cross-conjugated enynones and organometallic reagents is determined by the nature of the reagent: for example, dialkyl lithium cuprates add at the triple bond,[100] while lithium 1,3-dithiane adds at the keto group.[186, 187]

In linear-conjugated enynones **2**, the double bond is less reactive than in cross-conjugated analogues because of the 'isolation effect' of the acetylene bridge; therefore, nucleophilic reagents such as benzene- and phenylmethanethiols usually add to these ketones (in the presence of Et_3N) only at the triple bond.[188]

Scheme 53



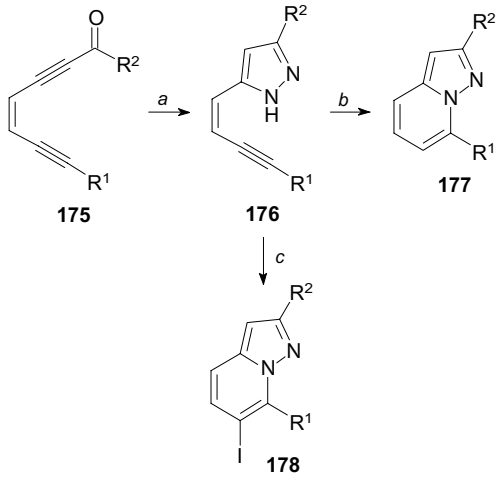
(*a*) Ti(OEt)$_4$ (2 equiv.), THF, 60 °C, 24 h; (*b*) 1) $TMSCF_3$, **173** (10 mol.%), Me_4NF (20 mol.%), PhMe, CH_2Cl_2, −60 → −50 °C, 2 h; 2) Bu^n_4NF, H_2O;



R^1	R^2	Yield of **172** (%)	*Z*:*E*
TMS	Me	87	3.7:1
TMS	H	70	4.5:1
Pr^n	Me	75	>20:1

The conjugated system of multiple bonds of ynenynones **175** is involved in the synthesis of fused nitrogen heterocycles.[79, 80] Heating of ketones **175** with hydrazine in acetonitrile affords enyne pyrazole derivatives **176**, which undergo intramolecular addition to the triple bond, being converted to pyrazolo[1,5-*a*]pyridines **177** (Scheme 54, Table 15). The cyclization of pyrazoles **176** gives good product yields only when a gold complex in the presence of $AgSbF_6$ is used as the catalyst. Compounds **177** can also be obtained from ketones **175** in one step (induced by CuCl on refluxing in acetonitrile), but the yields of the target products are much lower in this case (13%–80%).[79] In addition, 6-iodopyrazolo[1,5-*a*]pyridines **178** were prepared in good yields *via* iodocyclization (see Scheme 54).[80] Com-

Scheme 54



(*a*) N_2H_4, MeCN, 60 °C, 30 min; (*b*) Ph_3PAuCl (3 mol.%), $AgSbF_6$ (10 mol.%), THF, rt, 5 h; (*c*) I_2 (2 equiv.), CH_2Cl_2, rt, 4 h

Table 15. Yields of cyclization products of ynenynones **175** (see Scheme 54).[79, 80]

R^1	R^2	Yield of **176** (%)	Yield of **177** (%)	Yield of **178** (%)
H	Ph	93	98	97
n-C_6H_{13}	Ph	94	99	98
Bu^n	Ph	93	99	99
n-C_5H_{11}	Ph	95	99	99
Bu^i	Ph	92	86	86
Bu^t	Ph	88	46	72
Ph	Ph	82	97	99
2-MeC_6H_4	Ph	86	98	92
3-MeC_6H_4	Ph	89	94	90
4-MeC_6H_4	Ph	84	96	99
2-$MeOC_6H_4$	Ph	83	95	94
3-$MeOC_6H_4$	Ph	86	94	95
4-$MeOC_6H_4$	Ph	86	98	98
4-$O_2NC_6H_4$	Ph	80	94	68
4-NCC_6H_4	Ph	80	92	60
2-$MeSC_6H_4$	Ph	80	92	–
n-C_6H_{13}	4-$MeOC_6H_4$	75	91	88
Ph	4-$MeOC_6H_4$	78	96	85
4-$MeOC_6H_4$	4-$MeOC_6H_4$	76	90	78
4-NCC_6H_4	4-$MeOC_6H_4$	78	97	68
n-C_6H_{13}	4-$F_3CC_6H_4$	76	95	64
H	4-FC_6H_4	87	90	82
n-C_5H_{11}	Me	90	92	90

pounds **178** served for the synthesis of various biologically active functional derivatives, in particular, a p38 kinase inhibitor — 2-(4-fluorophenyl)-3-(4-pyridyl)pyrazolo[1,5-*a*]pyridine.[80]

4.3.2. Alk-2-en-4-yn-1-ones

The nucleophilic addition to linear-conjugated ketones **1** can be directed towards either the double bond (2,3-addition) or the triple bond (4,5-addition). In the latter case, the addition yields 1,3-dienes.[189 – 191] The reaction can be accompanied by closure of the enynone pentad to a furan or pyran ring.[8, 10, 192, 193] It is worth noting that this is the most characteristic and significant feature for the preparative chemistry of compounds containing an alk-2-en-4-yn-1-one moiety.

The nucleophilic addition of thiols to the double bond of 1,5-diarylpent-2-en-4-yn-1-ones **112** is a reversible kinetically controlled reaction, while the addition to the triple bond is irreversible, being a thermodynamically controlled process. The regioselectivity is determined by the substituent in the reagent: in the case of phenylmethanethiol, the equilibrium is shifted to the right due to the absence of resonance stabilization of the $PhCH_2S^-$ ion, and acetylenic keto sulfides **179** are formed. In the case of substituted benzenethiols (R = Ar), the RS^- ion occurring in equilibrium with acetylenic keto sulfide **179** slowly adds to the triple bond to give a mixture of *E*,*E*- and *E*,*Z*-isomeric diene keto sulfides **180** (Scheme 55, Table 16).[194, 195]

The reactions of enyne ketones with nucleophiles do not always end in the formation of adducts at the multiple bonds.[10, 196] Indeed, the reaction of enynones **112** with 2-sulfanylbenzothiazole (**181a**) catalyzed by a base {KOH, K_2CO_3, Et_3N, *N*-methylmorpholine, DBU, 1,4-diazabicyclo[2.2.2]octane (DABCO)} is accompanied by furan ring closure to give products **182** (Scheme 56).[10] Note that a

Scheme 55

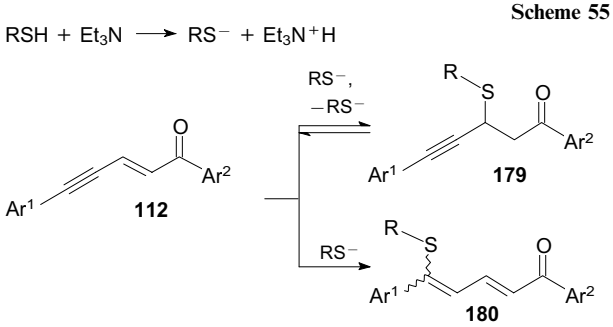
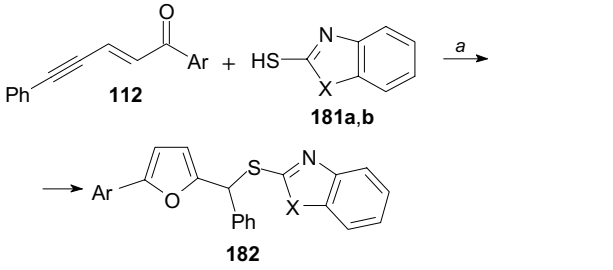


Table 16. Synthesis of sulfides from enynones **112** (see Scheme 55).[194, 195]

Ar^1	Ar^2	R	Product	Yield (%)
Ph	Ph	Bn	**179a**	57
4-MeC_6H_4	Ph	Bn	**179b**	75
4-ClC_6H_4	Ph	Bn	**179c**	89
4-BrC_6H_4	Ph	Bn	**179d**	90
2-Fu	Ph	Bn	**179e**	81
Ph	4-BrC_6H_4	Bn	**179f**	78
Ph	Ph	4-BrC_6H_4	**180a**	63
4-MeC_6H_4	Ph	4-BrC_6H_4	**180b**	82
4-$MeOC_6H_4$	Ph	4-BrC_6H_4	**180c**	43
4-ClC_6H_4	Ph	Ph	**180d**	82
4-ClC_6H_4	Ph	4-MeC_6H_4	**180e**	66
4-ClC_6H_4	Ph	4-BrC_6H_4	**180f**	83

Scheme 56



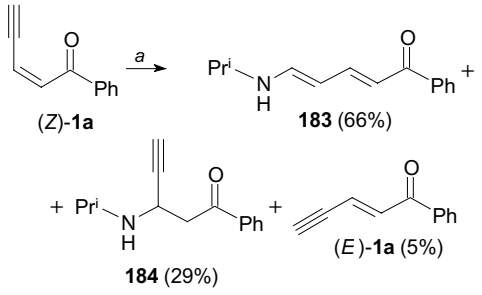
(*a*) DBU, MeOH, rt, 24 h; X = S: Ar = Ph (56% yield), 4-MeC_6H_4 (50%), 4-ClC_6H_4 (90%), 4-BrC_6H_4 (87%); X = NH, Ar = 4-BrC_6H_4 (53%)

similar reaction with 2-sulfanylbenzimidazole (**181b**) takes place when the potassium salt of the reagent is used.

The reaction of linear-conjugated enynones with amines proceeds by an analogous mechanism. For example, (*Z*)-1-phenylpent-2-en-4-yn-1-one [(*Z*)-**1a**] reacts with 2-aminopropane in $CDCl_3$ at room temperature to give adducts **183** and **184** at both multiple C – C bonds. In addition, the product of isomerization of the initial ketone is detected in the reaction mixture, which provides more evidence for the reversibility of 2,3-addition reactions (Scheme 57).[34]

The reactions of enynones **112** with secondary amines — piperidine (**185**), morpholine (**186**), piperazine (**187**) and diethanolamine — have been studied most comprehensively.[197 – 199] Depending on the reaction conditions, substituents in positions 1 and 5 and the nature of the amine, both 2,3- and 4,5-adducts may be formed. Morpholine (**186**) reversibly adds to the double bond of ketone **112a**

Scheme 57



(*a*) Pr^iNH_2, $CDCl_3$, rt

($Ar^1 = Ar^2 = Ph$) under mild conditions to afford adduct **188** (Scheme 58, Table 17). Long-term heating of solutions of ketones **112** with amines **185**, **186** or morpholine ketone **188** gives rise to penta-2,4-dien-1-ones **189a – d** and **190a – e**. In the case of piperazine (**187**) addition, the regioselectivity of the reaction is determined by the nature of substituents in the aryl ring: 1,5-diphenylpent-2-en-4-yn-1-one (**112a**) ($Ar^1 = Ar^2 = Ph$), like enynones containing electron-donating substituents (Ar^2 = 4-MeC_6 H_4, 4-$MeOC_6H_4$), forms bis-adducts at the double bond **191a – c**, whereas enynones with electron-withdrawing substituents (Ar^2 = 4-ClC_6H_4, 4-$O_2NC_6H_4$) are converted to bis-adducts at the triple bond **192a**,**b**. In the case of ketones containing electron-donating groups in the substituent Ar^2, the equilibrium **112** ⇄ **191** is largely shifted towards product **191**, as in the case of phenylmethanethiol,[194] and the reaction stops at this step. In the enynones activated by electron-withdrawing groups, the triple bond is sufficiently reactive for the formation of 4,5-addition products **192** under drastic conditions (long-term refluxing of the reactants in EtOH).

Generally, it is obviously correct that linear-conjugated enynones **112** react with thiols and amines according to a general mechanism in which the 2,3-addition is a reversible kinetically controlled process, while the 4,5-addition is an irreversible thermodynamically controlled process.

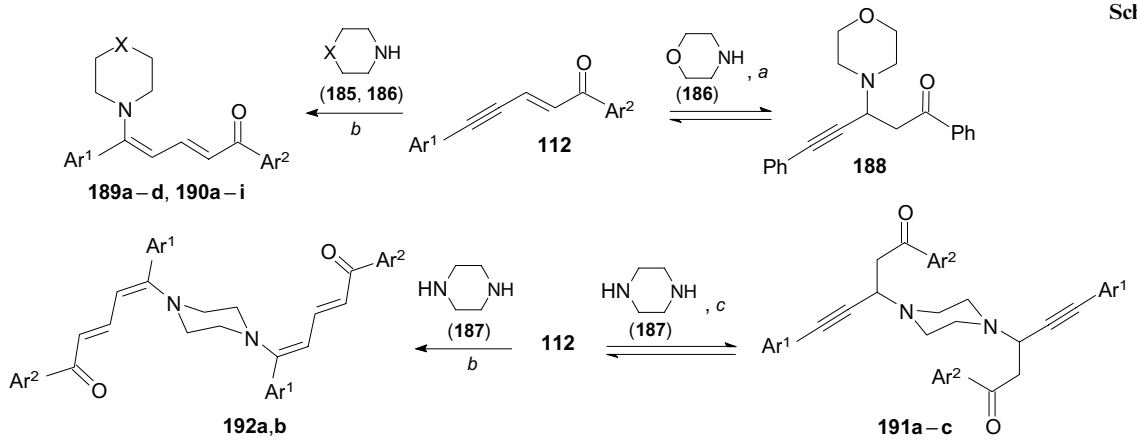
The reactions of linear-conjugated enynones of type **1** with C-nucleophiles have been studied.[8, 200 – 203] These reactions are often accompanied by heterocyclization and can serve as a convenient method for the synthesis of furan derivatives.[8, 201] For example, disubstituted enynones **1** undergo the Michael reaction with CH-acids **193** in the presence of bases [K_2CO_3, Cs_2CO_3, 4-dimethylaminopyridine (DMAP), DBU]. The subsequent intramolecular attack on the triple bond by the keto group oxygen in intermediate 2,3-adducts **194** leads to furan ring closure yielding compounds **195**. The applicable CH-acids **193** include 1,3-dicarbonyl compounds, 3-oxocarboxylic acid esters and nitriles and 1-phenyl-2-(phenylsulfonyl)ethanone; when 1,3-cyclohexanediones are used under the same conditions, annulated furans are formed. Apart from enynones **1**, other electrophilically activated enynes such as alkenynecarboxylic acid esters, amides and nitriles and nitro derivatives of a similar structure can also participate in analogous reaction. The reaction proceeds under mild conditions and gives products in good yields (Scheme 59, Table 18).[8]

The reactions of hydroxycoumarin and its derivatives **196** with 6-substituted hex-3-en-5-yn-2-ones **1** in the presence of chiral catalysts — quinine, cinchonidine and cinchonine derivatives (*e.g.*, compounds **197**) — with addition of (*S*)-*N*-Boc-alanine (Boc is *tert*-butoxycarbonyl) and trifluoroacetic or mandelic acid proceed in a similar way,

Table 17. Products of reactions of enynones **112** with cyclic secondary amines (see Scheme 58).

Ar^2	Ar^1	Reagent	Product	Yield (%)	Ref.
Ph	Ph	**186**	**188**	89	197
4-MeC_6H_4	Ph	**185**	**189a**	83	198
4-$MeOC_6H_4$	Ph	**185**	**189b**	65	198
4-ClC_6H_4	Ph	**185**	**189c**	89	198
4-BrC_6H_4	Ph	**185**	**189d**	87	198
Ph	Ph	**186**	**190a**	91	198
4-MeC_6H_4	Ph	**186**	**190b**	90	198
4-$MeOC_6H_4$	Ph	**186**	**190c**	64	198
4-$EtOC_6H_4$	Ph	**186**	**190d**	62	198
4-ClC_6H_4	Ph	**186**	**190e**	93	198
4-BrC_6H_4	Ph	**186**	**190f**	86	198
4-$O_2NC_6H_4$	Ph	**186**	**190g**	89	198
Ph	4-MeC_6H_4	**186**	**190h**	85	198
4-BrC_6H_4	4-BrC_6H_4	**186**	**190i**	48	198
Ph	Ph	**187**	**191a**	75	197
4-MeC_6H_4	Ph	**187**	**191b**	64	197
4-$MeOC_6H_4$	Ph	**187**	**191c**	71	197
4-ClC_6H_4	Ph	**187**	**192a**	47	197
4-$O_2NC_6H_4$	Ph	**187**	**192b**	46	197

Scheme 58



(*a*) EtOH, rt, 30 min; (*b*) EtOH, Δ, 3 – 4 h; (*c*) EtOH, 30 – 40 °C, 30 – 40 min; X = CH_2 (**185**, **189**), O (**186**, **190**)

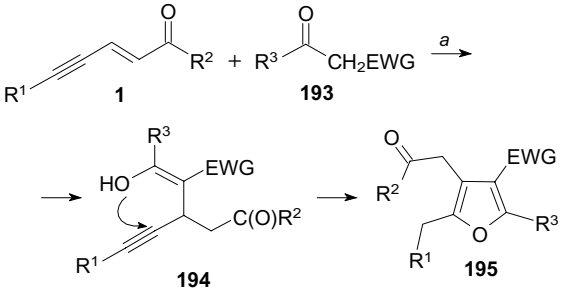
Table 18. Synthesis of furans **195** by the condensation of enynones **1** and ketones **193** (see Scheme 59).[8]

R^1	R^2	R^3	EWG	Time h	Yield (%)	R^1	R^2	R^3	EWG	Time h	Yield (%)
Ph	Ph	$CH_2CMe_2CH_2C(O)$		15	98	Ph	Ph	4-$MeOC_6H_4$	CN	15	91
Ph	Ph	$(CH_2)_3C(O)$		16	93	Ph	Ph	3-ClC_6H_4	CN	18	86
Ph	Ph	$CH_2CH(Me)CH_2C(O)$		15	97	Ph	Ph	4-$MeO_2CC_6H_4$	CN	18	79
Ph	Ph	$CH_2CH(Pr^i)CH_2C(O)$		19	91	Ph	Ph	4-FC_6H_4	CN	16	72
Ph	Ph	$CH_2CH(Ph)CH_2C(O)$		16	99	Ph	Ph	Ph	SO_2Ph	20	73
Ph	Ph	$CH_2CH(4\text{-}MeOC_6H_4)CH_2C(O)$		15	97	4-MeC_6H_4	Ph	$CH_2CMe_2CH_2C(O)$		20	95
Ph	Ph	$CH_2CH(4\text{-}Me_2NC_6H_4)CH_2C(O)$		16	99	4-$MeOC_6H_4$	Ph	$CH_2CMe_2CH_2C(O)$		18	97
Ph	Ph	$CH_2CH(R)CH_2C(O)$		15	97	2,4-$(MeO)_2C_6H_3$	Ph	$CH_2CMe_2CH_2C(O)$		21	90
Ph	Ph	$CH_2CH(2\text{-}Fu)CH_2C(O)$		15	82	4-$F_3CC_6H_4$	Ph	$CH_2CMe_2CH_2C(O)$		23	95
Ph	Ph	Me	Ac	15	71	4-ClC_6H_4	Ph	$CH_2CMe_2CH_2C(O)$		20	96
Ph	Ph	Ph	Bz	20	95	2-IC_6H_4	Ph	$CH_2CMe_2CH_2C(O)$		20	96
Ph	Ph	Me	CO_2Et	15	67	4-$O_2NC_6H_4$	Ph	$CH_2CMe_2CH_2C(O)$		20	86
Ph	Ph	Ph	CO_2Et	15	79	1-Naph	Ph	$CH_2CMe_2CH_2C(O)$		18	97
Ph	Ph	2-Fu	CO_2Et	20	76	2-Th	Ph	$CH_2CMe_2CH_2C(O)$		22	96
Ph	Ph	Ph	CN	19	89	PhCH=CH	Ph	$CH_2CMe_2CH_2C(O)$		22	90
Ph	Ph	4-MeC_6H_4	CN	17	88	n-C_8H_{17}	Ph	$CH_2CMe_2CH_2C(O)$		24	74
						Ph	Me	$CH_2CMe_2CH_2C(O)$		18	96

Note. EWG is the electron-withdrawing group, R is benzo[*d*][1,3]dioxol-4-yl.

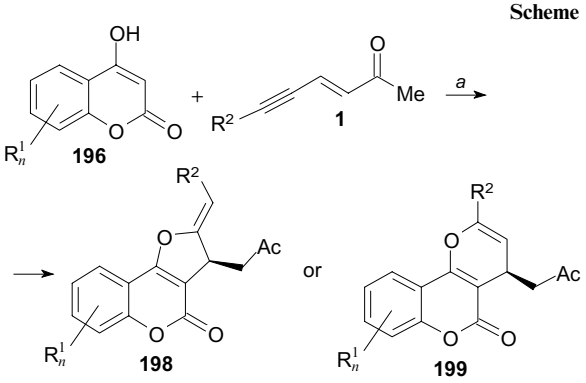
involving the double bond and position 3 of compounds **1**. The subsequent cyclization of the intermediately formed Michael adducts proceeds in the presence of Ag, Au, Pt and Cu compounds in toluene (Scheme 60, Table 19).[201]

Scheme 59

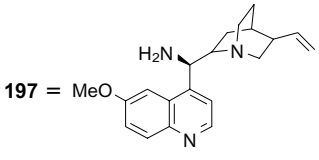


(*a*) DBU, MeCN, 85 °C

Scheme 60



(*a*) 1) **197** (20 mol.%), (*S*)-*N*-Boc-alanine (40 mol.%), THF, 4 °C; 2) Ag_2CO_3 (10 mol.%), PhMe, rt;



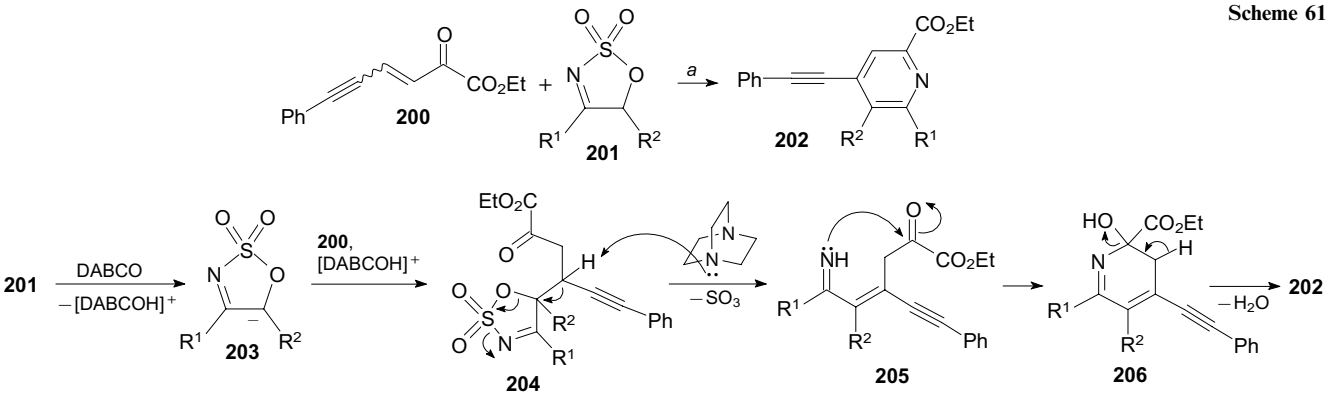
The reaction of aromatic ketones **1** (R^2 = Ar) gives 2,3-dihydro-4*H*-furo[3,2-*c*]chromen-4-ones **198**; the use of alkyl or cycloalkyl ketone **1** (R^2 = Alk, cyclo-Alk) results in the formation of 4*H*,5*H*-pyrano[3,2-*c*]chromen-5-ones (*e.g.*, compound **199**), but their yields are considerably lower, although the enantiomeric excess barely decreases.[201]

Ethyl 2-oxo-6-phenylhex-3-en-5-ynoate (**200**) reacts with 5*H*-1,2,3-oxathiazole 2,2-dioxides **201** under microwave irradiation and affords ethyl 4-(phenylethynyl)picolinates

Table 19. Synthesis of annulated chromenones from hydroxycoumarins **196** (see Scheme 60).[201]

R^1_n	R^2	Product	Yield (%)	*ee* (%)
H	Ph	**198**	84	88
H	4-FC_6H_4	**198**	76	89
H	4-BrC_6H_4	**198**	76	85
H	4-$F_3CC_6H_4$	**198**	75	93
H	2,3-Dihydro-benzo[*b*]furan-4-yl	**198**	67	81
H	3-MeC_6H_4	**198**	80	89
H	3-$MeOC_6H_4$	**198**	82	93
H	2-Naph	**198**	79	92
H	2-ClC_6H_4	**198**	81	94
H	1-Naph	**198**	75	80
H	2-Fu	**198**	78	99
H	2-Th	**198**	76	77
6-Me	4-BrC_6H_4	**198**	54	92
6,7-(CH_2OCH_2)	4-FC_6H_4	**198**	56	94
7-MeO	1-Naph	**198**	74	94
6-Cl	3-$MeOC_6H_4$	**198**	60	98
6-Cl	Ph	**198**	91	73
7-MeO	Ph	**198**	58	93
6,7-(CH_2OCH_2)	Ph	**198**	72	83
H	H	**198**	84	70
H	Bu^n	**199**	52	90
H	cyclo-C_5H_9	**199**	32	89

Scheme 61

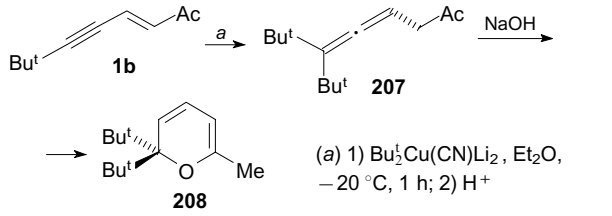


(*a*) DABCO (1 equiv.), MW, 70–80 °C; R^2 = H: R^1 = Ph (85% yield), 4-$MeOC_6H_4$ (80%), 4-ClC_6H_4 (86%), 2-Fu (82%), 2-Th (83%); R^1 = Ph, R^2 = Me (58%)

202. Dioxides **201** act as C-nucleophiles in this reaction. The reaction starts with activation of position 5 of compound **201** on treatment with a base (DABCO) and addition of the resulting anion **203** to the double bond of enyne ketoester. The subsequent reaction of Michael adduct **204** with DABCO gives rise to imine **205**, the cyclization of which furnishes 2,3-dihydropyridine **206**. Aromatization of the latter completes the formation of compounds **202** in good yields. The introduction of the methyl group at position 5 of reagent **201** markedly decreases the yield of the product (Scheme 61).[202]

The reactions of nucleophiles with enynones can generate allenes. 7,7-Dimethyloct-3-en-5-yn-2-one (**1b**) adds lithium di-*tert*-butyl(cyano)cuprate yielding allene **207**, which cyclizes to 2,2-di-*tert*-butyl-6-methyl-2*H*-pyran (**208**) on treatment with a solution of alkali (Scheme 62).[203]

Scheme 62

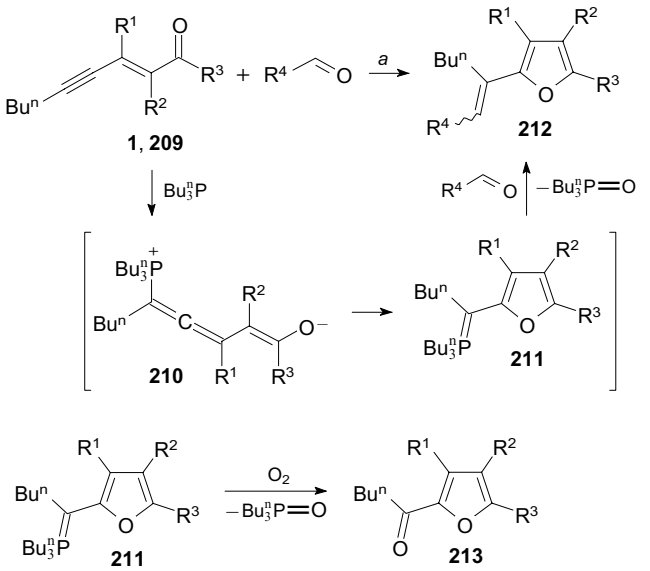


(*a*) 1) $Bu^t_2Cu(CN)Li_2$, Et_2O, −20 °C, 1 h; 2) H^+

Presumably, allene structures can also be formed upon the reaction with P-nucleophiles.[27,204–206] The 1,6-addition of tri-n-butylphosphine to ketones **1** (R^1 = R^2 = H) and **209** (R^1, $R^2 \neq$ H) gives, first, allene structures **210**, which then undergo cyclization to furan derivatives **211**. The reactions of compounds **1** and **209** with aldehydes yield furans **212** (Scheme 63, Table 20).

A general method for the synthesis of α-vinylfurans **212** was developed on the basis of this reaction. Good yields are obtained only when the initial ketones have aliphatic substituents at the triple bond (*e.g.*, Bu^n). The transformation of 5-phenyl-substituted enynones affords a mixture of products. When aldehydes are replaced by 4-methylacetophenone, the reaction does not proceed.[27,204] Later it was shown that the tri-n-butylphosphorane moiety of intermediate compounds **211** can be eliminated on treatment with

Scheme 63



(*a*) Bu^n_3P, CH_2Cl_2, rt, 5 h

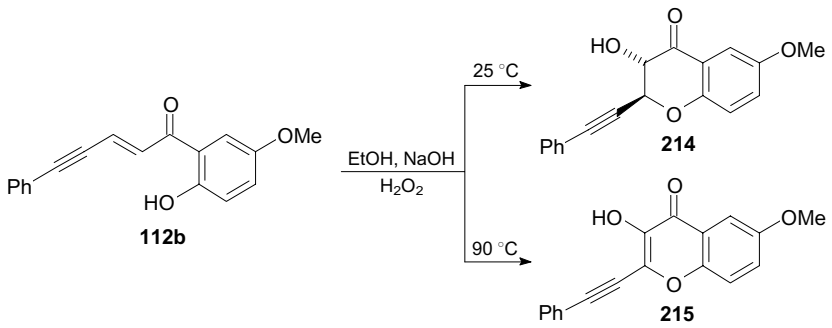
Table 20. Synthesis of furans **212** by the condensation of enynones with aldehydes induced by tri-n-butylphosphine (see Scheme 63).[27]

R^1	R^2	R^3	R^4	Yield (%)	*E*:*Z*
H	H	Ph	Ph	83	90:10
H	H	Me	Ph	56	>90:10
Bu	H	Me	Ph	64	91:9
Ph	H	Me	Ph	63	93:7
H	Ph	Ph	Ph	70	90:10
H	H	Ph	Et	92	80:20
H	H	Ph	(*E*)-PhCH=CH	90	79:21
H	H	Ph	4-MeC_6H_4	89	92:8

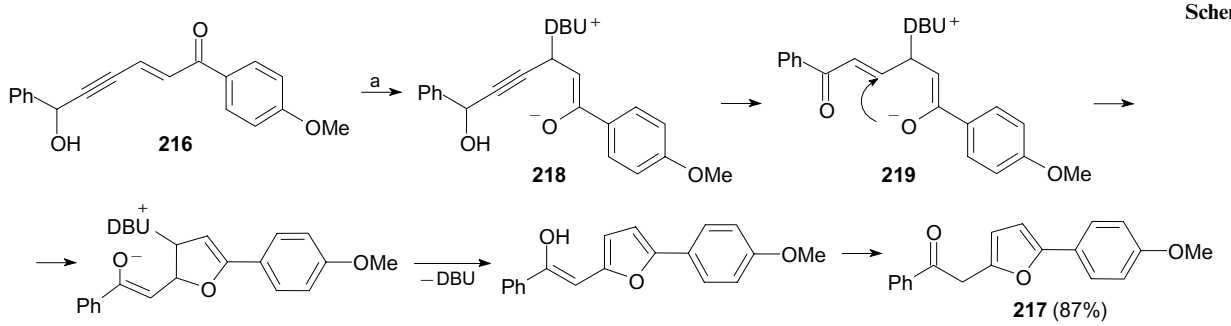
molecular oxygen; this gives furyl-containing ketones **213** (see Scheme 63).[205]

The reactions of linear-conjugated enynones with O-nucleophiles are used to obtain functional derivatives of furan, chromanone and chromenone.[4,206] It was found, for example, that the *ortho*-hydroxy group in the benzoyl

Scheme 64



Scheme 65



(*a*) DBU (20 mol.%), THF, 60 °C, 2 h

moiety of the enynone can be used as the nucleophile. A solution of NaOH in ethanol with some H_2O_2 added can serve as the catalyst for the intramolecular cyclization (with simultaneous hydroxylation) of 1-(2-hydroxy-5-methoxyphenyl)-5-phenylpent-2-en-4-yn-1-one (**112b**) (Scheme 64).

At room temperature, chromanone **214** is formed, while on heating to 90 °C, the reaction gives chromenone **215**.[4]

Hydroxymethyl-substituted enynone **216** cyclizes to furan **217** under the action of DBU. In the opinion of Wang *et al.*,[207] the reaction starts with the catalyst addition to the double bond of enynone to give zwitter-ion **218**. The 1,3-hydride shift generates zwitter-ion **219**, and the subsequent intramolecular Michael reaction closes the furan ring (Scheme 65).

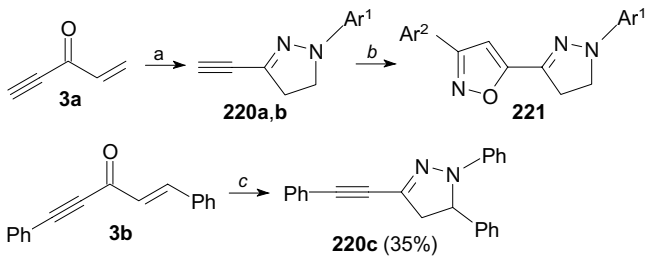
4.4. Cyclocondensation

This part of the review mainly integrates data about reactions of enynones with dinucleophiles at the keto group and one of the carbon – carbon multiple bonds (cyclocondensation). Acetalization with diols is also covered in this Section. These reactions usually furnish heterocyclic systems containing unsaturated substituents, which are of interest as potential biologically active and fluorescent materials.

4.4.1. Alk-1-en-4-yn-3-ones

Data on the reactions of alk-1-en-4-yn-3-ones with 1,2-N,N-, 1,2-N,O-, 1,3-N,N- and 1,4-N,S-dinucleophiles are available from the literature. The regioselectivity of reactions of cross-conjugated enynones with substituted hydrazines is mainly determined by the nature of substituents in the reagent and the substrate and the cyclocondensation conditions. The simplest cross-conjugated enynone **3a** reacts with phenyl- or *p*-tolylhydrazine at the double bond and the keto group to give 1-aryl-3-ethynyl-4,5-dihydro-1*H*-pyrazoles **220a**,**b**, which possess relatively high reactivity towards arylnitrile oxides and are used in the synthesis of bis-azoles **221**.[208] The cyclocondensation of phenylhydrazine with enynone **3b** proceeds in a similar way to give pyrazoline derivative **220c** (Scheme 66).[103]

Scheme 66



(*a*) Ar^1NHNH_2, Et_2O, rt; (*b*) $Ar^2C(Cl)=NOH$, Et_3N, dioxane;
(*c*) $PhNHNH_2$, H^+, EtOH, 78 °C;
220: Ar^1 = Ph (**a**, 40% yield), 4-MeC_6H_4 (**b**, 43%);
221: Ar^1 = Ph: Ar^2 = Ph (91%), 4-$MeOC_6H_4$ (75%), 4-ClC_6H_4 (95%), 4-$O_2NC_6H_4$ (95%); Ar^1 = 4-MeC_6H_4, Ar^2 = Ph (94%)

The reaction of enynone **3b** with anhydrous hydrazine in anhydrous ethanol involves both carbon – carbon multiple bonds and gives a mixture of 3-(1-hydrazono-2-phenylethyl)-5-phenyl-1*H*-pyrazole and 3-(2-hydrazono-2-phenylethyl)-5-phenyl-1*H*-pyrazole. The same enynone reacts with hydroxylamine hydrochloride (under reflux in ethanol in the presence of NaOH) in a similar way to give a mixture of isoxazoles.[209, 210]

When the ethoxy group, which is a good leaving group, occurs in the β-position (5-trimethylsilyl-substituted enynones **63**), cyclization at the carbon – carbon double bond is

Scheme 67

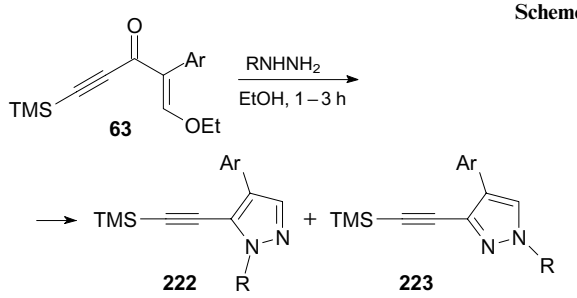


Table 21. Synthesis of pyrazole derivatives **222** and **223** by the reaction of enynones **63** with hydrazines (see Scheme 67).[133]

Ar	R	Temperature /°C	Yield of **222** (%)	Yield of **223** (%)
4-$O_2NC_6H_4$	4-$MeOC_6H_4$	20 [a]	94	–
4-$O_2NC_6H_4$	Ph	80	84	–
4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	80	65	–
Ph	4-$MeOC_6H_4$	20 [a]	80	6
Ph	Ph	80	74	–
Ph	4-$O_2NC_6H_4$	80	48	–
4-$MeOC_6H_4$	4-$MeOC_6H_4$	20 [a]	61	3
4-$MeOC_6H_4$	Ph	80	63	–
4-$MeOC_6H_4$	4-$O_2NC_6H_4$	80	62	–
4-$O_2NC_6H_4$	H	rt	74	
4-$O_2NC_6H_4$	Pr	rt	28	45
4-$O_2NC_6H_4$	Pr^i	rt	60	15
4-$O_2NC_6H_4$	Bn	rt	46	33

[a] 4-Methoxyphenylhydrazine hydrochloride with the addition of Et_3N.

accompanied by elimination of this group to afford isomeric pyrazole derivatives **222** and **223** (Scheme 67, Table 21).[133]

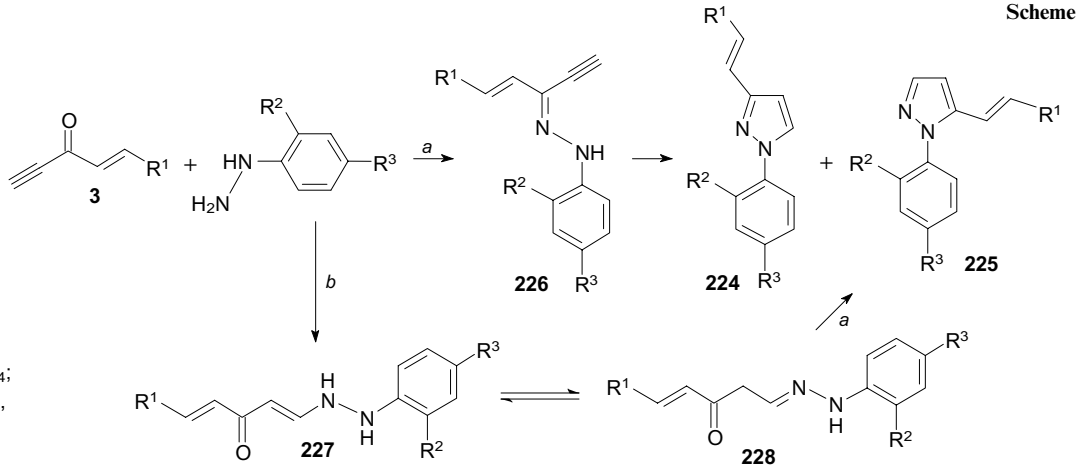
In the case of enynones with a substituted double bond, the regioselectivity of cyclocondensation changes. For example, the reaction of terminal enynones **3** with arylhydrazines proceeds at the ethynyl group and results in the formation of isomeric 1-aryl-3-(β-styryl)pyrazoles **224** and 1-aryl-5-(β-styryl)pyrazoles **225** in a total yield of up to 84% (Scheme 68). The ratio of products **224** and **225** depends on the reaction conditions: on heating in acidified MeOH, the reaction gives a mixture of isomers **224** (probably, *via* intermediate **226**) and **225**. Meanwhile, if prior to acidification and heating, the reactants are stirred at room temperature, arylhydrazine first adds to the triple bond to give enamine **227**, which exists in tautomeric equilibrium with hydrazone **228**, and the latter is converted to pyrazole **225** on heating in acidified MeOH.[87]

The condensation of 5-phenylpent-1-en-4-yn-3-one with phenyl- and *p*-tolylhydrazines in ethyl alcohol at room temperature results in the formation of 1-aryl-3-phenylethynyl-4,5-dihydro-1*H*-pyrazoles.[211] Thus, summarizing the known literature data on the reactions of cross-conjugated enynones with hydrazines provides the conclusion about the crucial effect of substituents in positions 1 and 5 on the reaction regioselectivity: the cyclization involves the less crowded carbon–carbon bond. When substituents in positions 1 and 5 are identical (enynone **3b**) or missing (enynone **3a**), the double bond is more reactive towards arylhydrazines. The chemical nature of the hydrazine also influences the cyclocondensation route. For example, acetylhydrazine reacts with enynone **3b** to give the cyclization product at the triple bond, namely, [1-(5-hydroxy-3-phenyl-5-styryl-4,5-dihydro-1*H*-pyrazol-1-yl)ethanone],[212] while 2,4-dinitrophenylhydrazine[103] gives the corresponding hydrazone, which does not undergo cyclization.

Cyclocondensation of cross-conjugated enynones with 1,3-N,N-dinucleophiles has been studied by Golubev *et al.*[134,213] The reaction of β-ethoxy-substituted enynones **63** with amidines **229** conducted in the presence of $MgSO_4$ in dichloromethane proceeds in the same way as the reaction with arylhydrazines,[133] *i.e.*, involves the ethoxyvinyl and carbonyl groups and results in the formation of trimethylsilylacetylene pyrimidine derivatives **230**. In a basic medium, the trimethylsilyl group is eliminated to give ethynylpyrimidines **231** (Scheme 69, Table 22).[134] The reaction of enynones **63** with 5-aminopyrazoles **232** was used to develop an efficient synthetic protocol to obtain a series of fluorescent 7-(trimethylsilylethynyl)pyrazolo[1,5-*a*]pyrimidines **233** (see Scheme 69, Table 23).[213]

The cyclocondensation of cross-conjugated enynones with N,S-dinucleophiles makes it possible to obtain sulfur heterocycles with unsaturated substituents. For example, on refluxing in ethanol, 4-amino-4*H*-1,2,4-triazole-3-thiol (**234**) adds to the triple bond of enynones **3** (R^1 = Ph, R^2 = Ar). The cyclization of adducts **235** formed in the first step is induced by heating in DMF and gives 1,2,4-triazolo[3,4-*b*]-1,3,4-thiadiazepines **236a–c**. It was found

Scheme 68



(*a*) HCl, MeOH, Δ;
(*b*) MeOH, rt;
R^1 = Ph, 4-$MeOC_6H_4$, 4-$MeSC_6H_4$, 4-$O_2NC_6H_4$;
R^2 = H, O_2N; R^3 = O_2N, $MeSO_2$, MeO

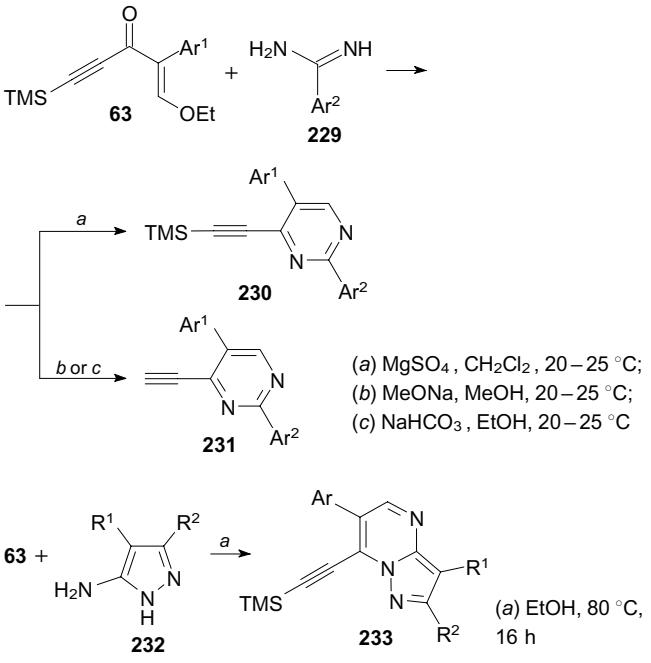
Table 22. Synthesis of pyrimidines **230** and **231** by condensation of enynones **63** with amidines **229** (see Scheme 69).[134]

Ar^1	Ar^2	Conditions	Product	Yield (%)	Ar^1	Ar^2	Conditions	Product	Yield (%)
4-$O_2NC_6H_4$	Ph	*a*	**230**	15	Ph	4-ClC_6H_4	*c*	**231**	56
Ph	Ph	*a*	**230**	61	Ph	Ph	*c*	**231**	48
4-$MeOC_6H_4$	Ph	*a*	**230**	75	Ph	4-MeC_6H_4	*c*	**231**	57
4-$O_2NC_6H_4$	4-$O_2NC_6H_4$	*b*	**231**	81	Ph	4-$MeOC_6H_4$	*c*	**231**	57
4-$O_2NC_6H_4$	4-ClC_6H_4	*c*	**231**	66	4-MeC_6H_4	4-$O_2NC_6H_4$	*b*	**231**	65
4-$O_2NC_6H_4$	Ph	*c*	**231**	73	4-MeC_6H_4	4-ClC_6H_4	*c*	**231**	54
4-$O_2NC_6H_4$	4-MeC_6H_4	*c*	**231**	50	4-MeC_6H_4	Ph	*c*	**231**	62
4-$O_2NC_6H_4$	4-$MeOC_6H_4$	*c*	**231**	73	4-MeC_6H_4	4-MeC_6H_4	*c*	**231**	48
4-ClC_6H_4	4-$O_2NC_6H_4$	*b*	**231**	60	4-MeC_6H_4	4-$MeOC_6H_4$	*c*	**231**	63
4-ClC_6H_4	4-ClC_6H_4	*c*	**231**	85	4-$MeOC_6H_4$	4-$O_2NC_6H_4$	*b*	**231**	43
4-ClC_6H_4	Ph	*c*	**231**	67	4-$MeOC_6H_4$	4-ClC_6H_4	*c*	**231**	61
4-ClC_6H_4	4-MeC_6H_4	*c*	**231**	79	4-$MeOC_6H_4$	Ph	*c*	**231**	55
4-ClC_6H_4	4-$MeOC_6H_4$	*c*	**231**	60	4-$MeOC_6H_4$	4-MeC_6H_4	*c*	**231**	52
Ph	4-$O_2NC_6H_4$	*b*	**231**	48	4-$MeOC_6H_4$	4-$MeOC_6H_4$	*c*	**231**	45

Table 23. Synthesis of pyrazolopyrimidines **233** by condensation of enynones **63** with 5-aminopyrazoles **232** (see Scheme 69).[213]

Ar	R^1	R^2	Yield (%)	Ar	R^1	R^2	Yield (%)
4-$O_2NC_6H_4$	H	4-ClC_6H_4	94	4-$MeOC_6H_4$	H	4-ClC_6H_4	85
4-$O_2NC_6H_4$	H	Ph	91	4-$MeOC_6H_4$	H	Ph	61
4-$O_2NC_6H_4$	H	4-MeC_6H_4	85	4-$MeOC_6H_4$	H	4-MeC_6H_4	61
4-$O_2NC_6H_4$	H	4-$MeOC_6H_4$	81	4-$MeOC_6H_4$	H	4-$MeOC_6H_4$	65
4-ClC_6H_4	H	4-ClC_6H_4	93	Ph	H	H	44
4-ClC_6H_4	H	Ph	89	4-$MeOC_6H_4$	H	H	48
4-ClC_6H_4	H	4-MeC_6H_4	88	Ph	H	3-FC_6H_4	64
4-ClC_6H_4	H	4-$MeOC_6H_4$	85	4-$MeOC_6H_4$	H	3-FC_6H_4	55
Ph	H	4-ClC_6H_4	87	Ph	NC	H	66
Ph	H	Ph	87	4-$MeOC_6H_4$	NC	H	72
Ph	H	4-MeC_6H_4	88	Ph	EtO_2C	H	75
Ph	H	4-$MeOC_6H_4$	82	4-$MeOC_6H_4$	EtO_2C	H	80
4-MeC_6H_4	H	4-ClC_6H_4	91	Ph	Ph	Me	61
4-MeC_6H_4	H	Ph	84	4-$MeOC_6H_4$	Ph	Me	52
4-MeC_6H_4	H	4-MeC_6H_4	96	Ph	NC	$NCCH_2$	50
4-MeC_6H_4	H	4-$MeOC_6H_4$	82	4-$MeOC_6H_4$	NC	$NCCH_2$	50

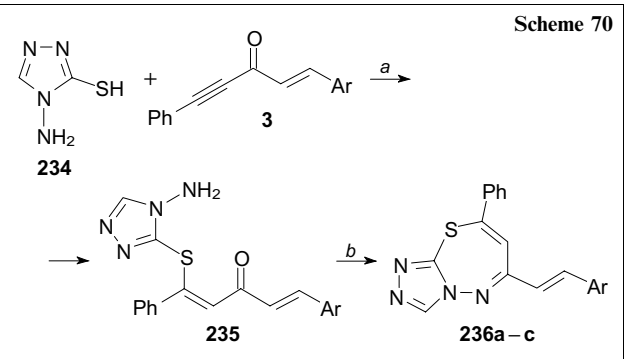
Scheme 69



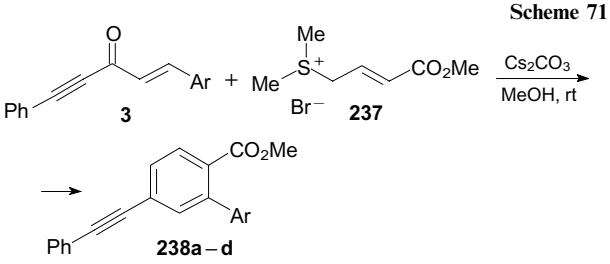
that enynones **3** are more reactive in this reaction than chalcones or α-acetylenic ketones (Scheme 70).[214]

The reaction of enynones **3** (R^1 = Ph, R^2 = Ar) with (4-methoxy-4-oxobut-2-en-1-yl)dimethylsulfonium bromide (**237**) also follows the cyclocondensation pathway; however, in this case, a benzene ring is formed. Methyl 2-aryl-

Scheme 70



Scheme 71



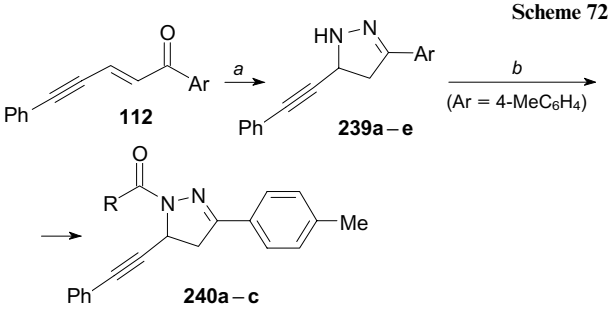
Compound **238**	Ar	Reaction time /min	Yield (%)
a	Ph	10	29
b	4-ClC_6H_4	10	36
c	4-BrC_6H_4	15	34
d	4-$MeOC_6H_4$	40	25

4-(phenylethynyl)benzoates **238a–d** are produced in moderate yields (Scheme 71).[215]

4.4.2. Alk-2-en-4-yn-1-ones

The reactions of linear-conjugated enynones with dinucleophiles have been very little studied. Odin *et al.*[216] showed that hydrazine reacts with diaryl-substituted pentenynones **112** (Ar^1 = Ph) at the propenone moiety. Pyrazolines **239a–e** formed in this reaction are easily acylated with carboxylic acid chlorides to give acylated derivatives, *e.g.*, compounds **240a–c**. No hydrazine adducts at the triple bond of enynones **112** were detected (Scheme 72).

Scheme 72

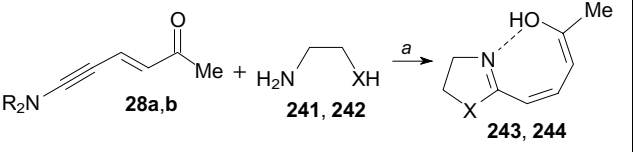


(*a*) $N_2H_4 \cdot H_2O$, EtOH, rt; (*b*) RC(O)Cl, Py, Et_2O;
239: Ar = Ph (**a**, 84% yield), 4-MeC_6H_4 (**b**, 81%), 4-$MeOC_6H_4$ (**c**, 46%), 4-ClC_6H_4 (**d**, 83%), 4-BrC_6H_4 (**e**, 81%);
240: R = Me (**a**, 84%), Ph (**b**, 81%), 2-Fu (**c**, 46%)

Dialkylamino-substituted enynones **28a**,**b** react with ethylenediamine (**241**) and ethanolamine (**242**) with twice repeated attack on the electrophilic centre of the substrate and elimination of the dialkylamino group to furnish imidazoline **243** and oxazoline **244** derivatives containing a completely enolized vinylacetyl moiety. The enol tautomer of compounds **243** and **244** is so stable that neither variation of the solvent nor a change in the solution concentration leads to detection of the ketone tautomer (Scheme 73).[217,218]

The keto group in enynone **1b** is sufficiently reactive for acetalization: under reflux in toluene with ethylene glycol in the presence of *p*-toluenesulfonic acid, the 1,3-dioxolane derivative is formed in 75% yield.[52]

Scheme 73



(*a*) THF, 65–70 °C; X = NH (**241**; **243**, 36% yield), O (**242**; **244**, 32%)

Published data on the cyclocondensation of enynones **1** can be found only in a few publications.[52,214–218]

4.5. Pericyclic reactions

Back in 1966–1967, A.A.Petrov's research team[219,220] showed that the carbon–carbon multiple bonds of cross-conjugated pentenynones possess high reactivity in the diene synthesis and 1,3-dipolar cycloaddition with nitrile oxides and diphenylnitrile imine. More recently, pericyclic reactions of conjugated enyne ketones have been successfully employed to prepare complex azaheterocyclic systems.

4.5.1. Alk-1-en-4-yn-3-ones

Cross-conjugated enynones react with buta-1,3-diene as dienophiles on heating to 140 °C in benzene. The diene synthesis pathway is determined by the substituents in enynone positions 1 and 5, in particular, hex-2-en-5-yn-4-one predominantly reacts, while hex-1-en-4-yn-3-one exclusively reacts at the unsubstituted carbon–carbon multiple bond irrespective of its nature. Hept-2-en-5-yn-4-one reacts only at the double bond. No isomerization with multiple bond migration takes place.[219]

Enynones **3** (X = H) and **245** (X ≠ H) undergo thermally activated [2+2]-cycloaddition with ketene silyl acetals **246**. As in the case of buta-1,3-diene,[219] the reaction involves the unsubstituted multiple bond. First (at 60 °C), cyclobutene derivatives **247** are formed; on further heating (140–165 °C) in xylene they are converted to cyclohexadienes **248a–e** or salicylic acid derivatives **249a–c**, depending on the nature of substituents R^3 and R^4 in compounds **246** (Scheme 74, Table 24).[221]

Scheme 74

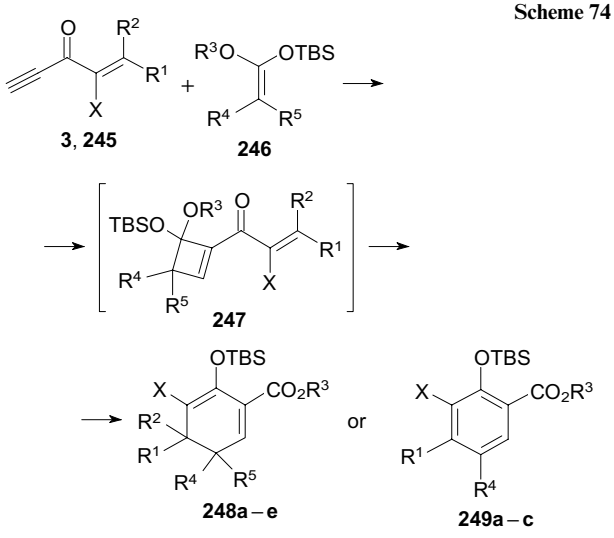
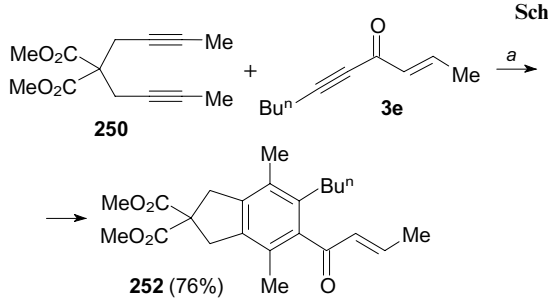


Table 24. Synthesis of compounds **248**, **249** by cycloaddition of alkynones to silyl acetals **246** (see Scheme 74).[221]

R^1	X	R^2	R^3	R^4	R^5	Reaction conditions	Product	Yield (%)
Ph	H	H	Me	H	MeO	60 °C, 1 h; 140 °C, 3 h [a]	**248a**	86 [b]
Ph	H	H	Et	H	H	140 °C, 3 h [a]	**248b**	62
Me	Me	H	Me	H	MeO	60 °C, 7 h; 140 °C, 2 h [a]	**248c**	56 [c]
$(CH_2)_4$		H	H	H	MeO	80 °C, 5 h; 140 °C, 8 h [a]	**248d**	50 [c, d]
Me	H	Me	Me	H	MeO	60 °C, 10 h; 140 °C, 5 h [a]	**248e**	60
Ph	H	H	Me	MeO	MeO	60 °C, 1 h; 165 °C, 14 h [e]	**249a**	75
Me	Me	H	Me	MeO	MeO	60 °C, 5 h; 165 °C, 12 h [e]	**249b**	71
$(CH_2)_4$		H	Me	MeO	MeO	60 °C, 8 h; 165 °C, 12 h [e]	**249c**	66

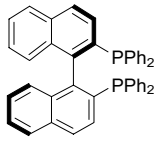
[a] In xylene; [b] the *cis*- to *trans*-isomer ratio is 6 : 1; [c] single isomer; [d] stereochemistry was not determined; [e] in mesitylene.

Scheme 75



(*a*) **251** (1 mol.%), $[Ir(cod)Cl]_2$ (2 mol.%), PhH, Δ;

251 =



The reactions of enynones with acetylene compounds may also give arenes. For example, the [2 + 2 + 2]-cycloaddition of dimethyl 2,2-di(but-2-yn-1-yl)malonate (**250**) to enynone **3e** is catalyzed by an iridium complex in the presence of (*R*)-2,2′-bis(diphenylphosphino)-1,1′-binaphthalene (**251**). This reaction involves the enynone triple bond and two triple bonds of reagent **250**; this results in benzene ring closure in product **252** (Scheme 75).[222]

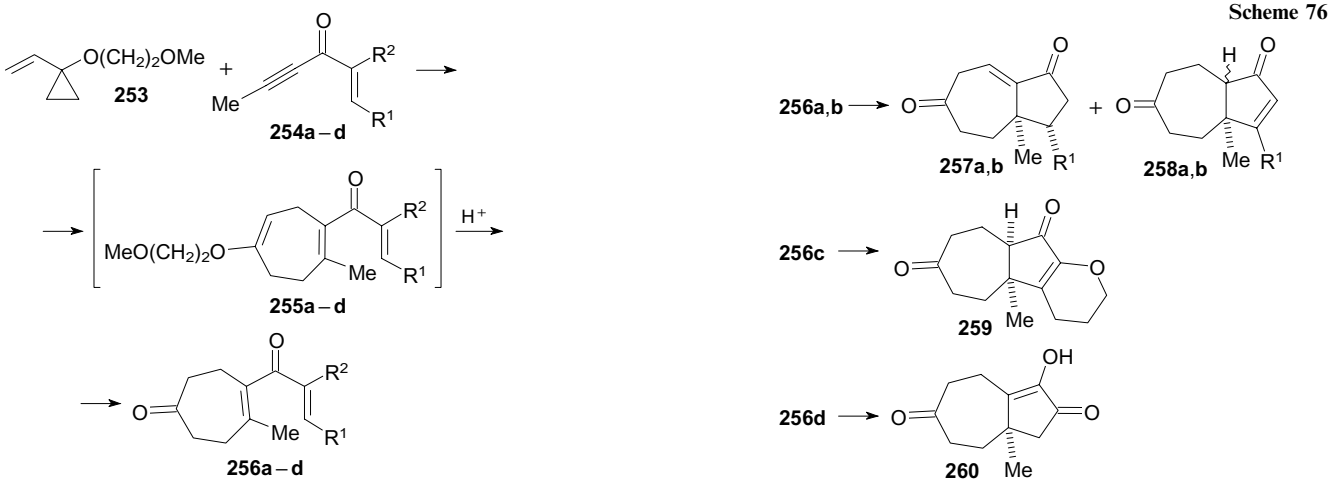
The [5 + 2]-cycloaddition of 1-(2-methoxyethoxy)-1-vinylcyclopropane (**253**) to enynones **254a – d** catalyzed by rhodium compounds involves exclusively the triple bond. The reaction takes place in a mixture of 1,2-dichloroethane and 2,2,2-trifluoroethanol (TFE) on heating for 16 – 20 h *via* the formation of enol ethers **255a – d**, which are hydrolyzed (in a one-pot procedure) to give cycloheptenone derivatives **256a – d**. Compounds **256a – d** readily undergo the Nazarov reaction, which is utilized in the synthesis of bicyclo[5.3.0]decenes **257 – 260** (Scheme 76, Table 25).[223]

Table 25. Synthesis of cycloheptenone **256** and bicyclo[5.3.0]decenes **257 – 260** (see Scheme 76).[223]

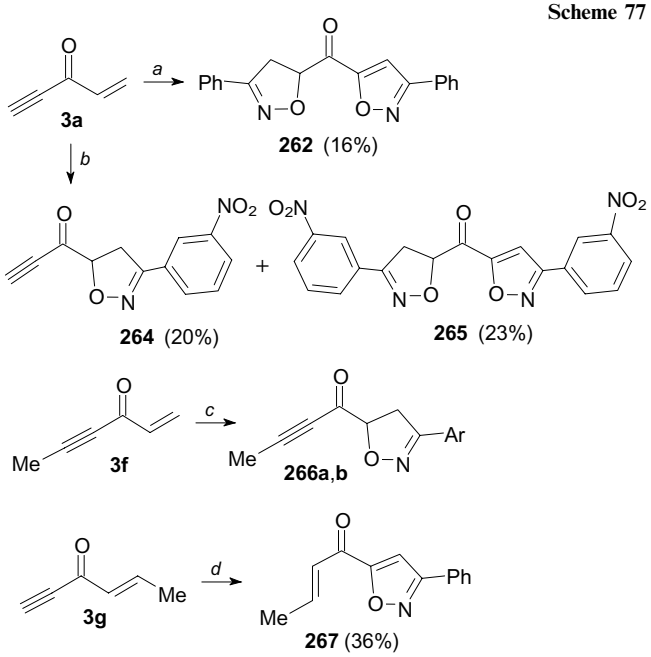
R^1	R^2	Reaction conditions	Product	Yield (%) (ratio)
Me	H	$[Rh(CO)_2Cl]_2$ (2.5 mol.%), 16 h [a]	**256a**	74
Ph	H	$[Rh(CO)_2Cl]_2$ (2.5 mol.%), 20 h [a]	**256b**	65
$(CH_2)_3O$		$[Rh(CO)_2Cl]_2$ (5 mol.%), 16 h [a]	**256c**	90
H	EtO	$[Rh(CO)_2Cl]_2$ (5 mol.%), 20 h [a]	**256d**	82
Me	H	TMSOTf (1.1 – 2.0 equiv.), CH_2Cl_2, rt, 1 h	**257a** + **258a**	85 (2 : 1)
Ph	H	TMSOTf (1.1 – 2.0 equiv.), CH_2Cl_2, rt, 0.5 h	**257b** + **258b**	53 (5 : 1)
$(CH_2)_3O$		$AgSbF_6$ (10 mol.%), DCE, rt, 2.5 h	**259**	95 [b]
H	EtO	$AgSbF_6$ (10 mol.%), DCE, 50 °C, 16 h	**260**	90

[a] The reaction was carried out in a DCE and TFE mixture at 80 °C; [b] *cis* : *trans* > 20 : 1.

Scheme 76



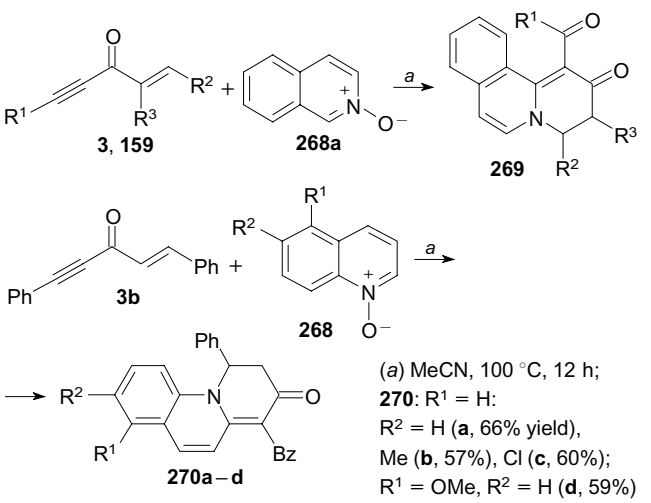
Scheme 77



(*a*) PhC≡N$^+$O$^-$ (**261**), Et_2O, 35 °C, 2 h;
(*b*) 3-$O_2NC_6H_4C{\equiv}N^+O^-$ (**263**), PhH, 80 °C, 5 h;
(*c*) **261** or **263**, Et_2O; (*d*) **261**, Et_2O;
266: Ar = Ph (**a**, 85% yield), 3-$O_2NC_6H_4$ (**b**, 55%)

It was shown [220] that the 1,3-dipolar cycloaddition of nitrile oxides to cross-conjugated enynones can be directed to both the double and triple bonds. Ketone **3a** reacts with benzonitrile oxide (**261**) yielding bis-azole **262** (Scheme 77). 3-Nitrobenzonitrile oxide (**263**) is less reactive, being converted to a mixture of isoxazoline **264** with bis-azole **265**. Monosubstituted enynones **3f,g** react with benzonitrile oxides **261** and **263** at the unsubstituted multiple bond; this affords isoxazolines **266a**,**b** and isoxazole **267**, respectively. It was noted that the nitrile oxide cycloaddition to the double bond gives higher yields of products than the cycloaddition to the triple bond. Analogous regiochemical trends were identified for the cycloaddition of diphenylnitrile imine.[220]

Scheme 78



(*a*) MeCN, 100 °C, 12 h;
270: R^1 = H:
R^2 = H (**a**, 66% yield),
Me (**b**, 57%), Cl (**c**, 60%);
R^1 = OMe, R^2 = H (**d**, 59%)

Table 26. Synthesis of 3,4-dihydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-ones **269** (see Scheme 78).[224]

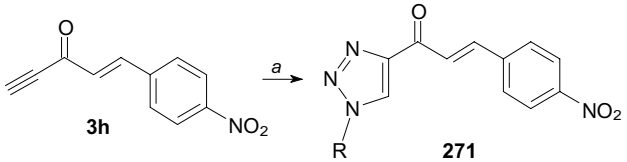
R^1	R^2	R^3	Yield (%)
Ph	Ph	H	85
3-MeC_6H_4	Ph	H	74
4-MeC_6H_4	Ph	H	81
4-$MeOC_6H_4$	Ph	H	74
4-FC_6H_4	Ph	H	88
4-ClC_6H_4	Ph	H	93
4-BrC_6H_4	Ph	H	76
4-$F_3CC_6H_4$	Ph	H	87
4-PhC_6H_4	Ph	H	67
3,5-$(MeO)_2C_6H_3$	Ph	H	72
2-Th	Ph	H	93
3-Th	Ph	H	41
1-Naph	Ph	H	65
Bu^n	Ph	H	48
TMS [a]	Ph	H	52
cyclo-C_3H_5	Ph	H	55
Ph	4-MeC_6H_4	H	69
Ph	4-$MeOC_6H_4$	H	62
Ph	4-ClC_6H_4	H	76
Ph	Et	H	71
Ph	2-Fu	H	61
Ph	Ph	Me	89[b]

[a] The TMS group in the product R^1 = H is eliminated under the reaction conditions; [b] diastereomeric ratio (*dr*) = 1.6 : 1.

The whole conjugated pentad of enynones **3** and **159** ($R^3 \neq H$) participates in the reaction with isoquinoline oxide (**268a**), which gives rise to a series of 3,4-dihydro-2*H*-pyrido[2,1-*a*]isoquinolin-2-one derivatives **269** (Scheme 78, Table 26). Enynone **3b** reacts with substituted quinoline oxides **268** to afford dihydro-1*H*-pyrido[1,2-*a*]-quinolin-3(2*H*)-ones **270a – d** (see Scheme 78). Compounds **269** and **270** exhibit weak fluorescence.[224]

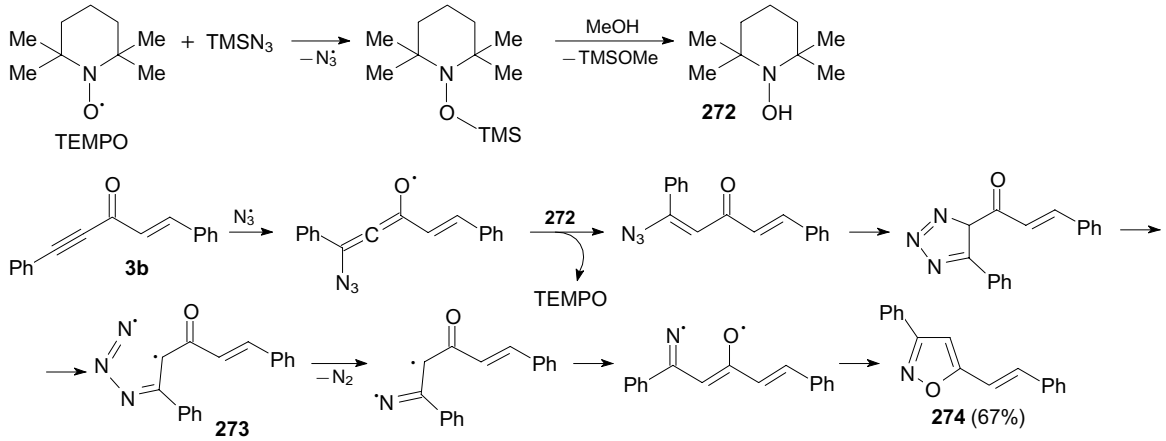
The reactions of cross-conjugated enynones with azides are addressed in a number of studies.[14, 225 – 228] 1-(4-Nitrophenyl)pent-1-en-4-yn-3-one (**3h**) undergoes the azide – alkyne cycloaddition reaction with alkyl and aryl azides under standard conditions in the presence of sodium ascorbate (NaOAs). This gives moderate yields (19% – 52%) of 1,2,3-triazole chalcones **271** (Scheme 79), which show an inhibitory effect towards guinea pig liver transglutaminase.[225, 226] Subsequently, this reaction was extended to a

Scheme 79



(*a*) RN_3, $CuSO_4$, NaOAs, H_2O, Bu^tOH, 75 °C, 16 h;
R = Bn (23% yield), n-C_9H_{19} (20%), Cy (38%), $CyCH_2$ (32%), 2-$MeOC_6H_4CH_2$ (23%), 4-$O_2NC_6H_4CH_2$ (19%), 3-$O_2NC_6H_4CH_2$ (19%), 2-$O_2NC_6H_4CH_2$ (24%), $C_6F_5CH_2$ (33%), 3,5-$(F_3C)_2C_6H_3CH_2$ (52%), 1-phenethyl (48%), Ph_2CH (39%), 2-$PyCH_2$ (30%), (1*H*-1,2,3-triazol-5-yl)methyl (23%)

Scheme 80



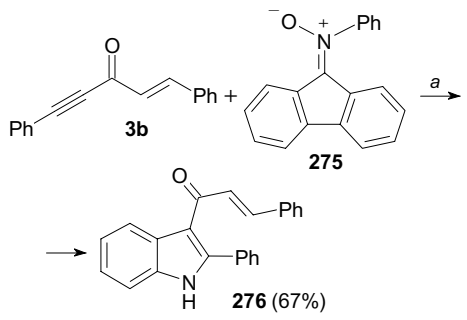
broad range of 1,5-diaryl-substituted pent-1-en-4-yn-3-ones.[14]

When enynones **3** contain one more triple bond (R^1 = HC≡C), the unsubstituted bond proves to be more reactive in the azide – alkyne cycloaddition. Indeed, the reaction of 1-(2-thienyl)hepta-1-en-4,6-diyn-3-one with benzyl azide in the presence of $CuSO_4 \cdot 5H_2O$ and ascorbic acid in DMF proceeds at room temperature at the terminal triple bond to give 5-(1-benzyl-1*H*-1,2,3-triazol-4-yl)-1-(2-thienyl)pent-1-en-4-yn-3-one.[228]

In the opinion of He *et al.*,[229] the reaction of enynone **3b** with trimethylsilyl azide initiated by (2,2,6,6-tetramethylpiperidin-1-yl)oxyl (TEMPO) is consecutive. On treatment with TEMPO, trimethylsilyl azide generates the azide radical and intermediate **272** (Scheme 80). The reaction is accompanied by elimination of a nitrogen molecule from biradical **273** and leads to 3-phenyl-5-styrylisoxazole (**274**).

1,3-Dipolar cycloaddition of nitrone **275** to enynone **3b** is also initially directed to the triple bond, but ends in the formation of indole derivative **276** (Scheme 81).[230]

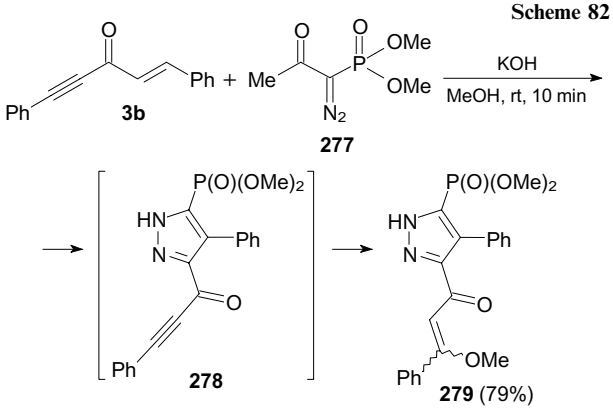
Scheme 81



(*a*) 1) MeCN, Δ, 4 h; 2) $H_2C_2O_4 \cdot SiO_2$, CH_2Cl_2, rt

Unlike azides and nitrones, the cycloaddition of dimethyl (1-diazo-2-oxopropyl)phosphonate (Bestmann – Ohira reagent, **277**) to ketone **3b** in an alkaline solution proceeds at positions 1 and 2 of the C=C bond. Pyrazole **278** thus formed undergoes nucleophilic addition of alcohol at the triple bond being converted to adduct **279** (Scheme 82).[231]

Scheme 82



4.5.2. Alk-2-en-4-yn-1-ones

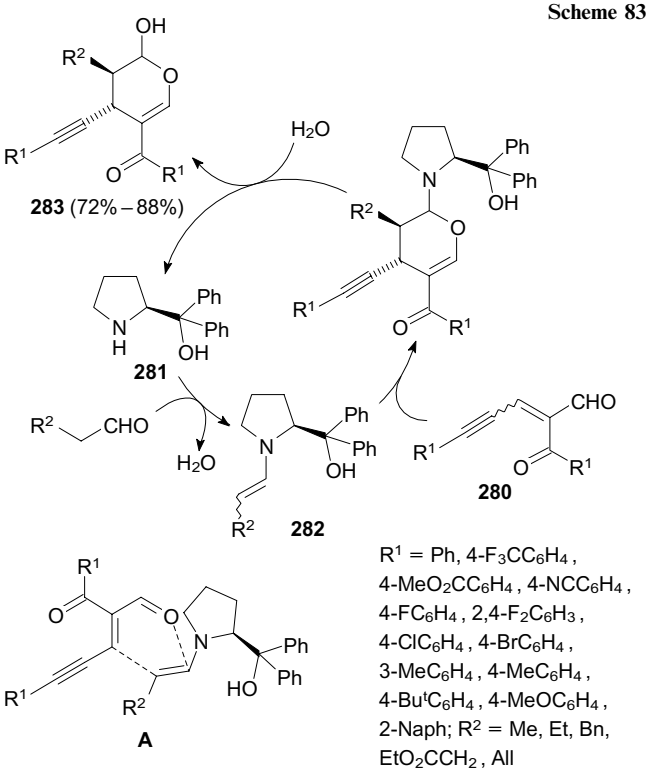
Data on the pericyclic reactions of compounds containing the alk-2-en-4-yn-1-one moiety are few and are mainly limited to 1,3-dipolar cycloaddition reactions. There are publications describing reactions of linear-conjugated enynones with dienophiles,[9, 65, 232] nitrile imines[233] and azides.[11 – 13, 234]

The oxo Diels – Alder reaction of 2-aroylpent-2-en-4-ynals **280** with unsaturated derivatives **282**, generated in a cascade process from diphenyl-L-proline (**281**) and aliphatic aldehydes, gives 3,4-dihydropyrans **283**. The propenal group of enynal acts as the diene in this reaction, see structure **A** (Scheme 83).[65]

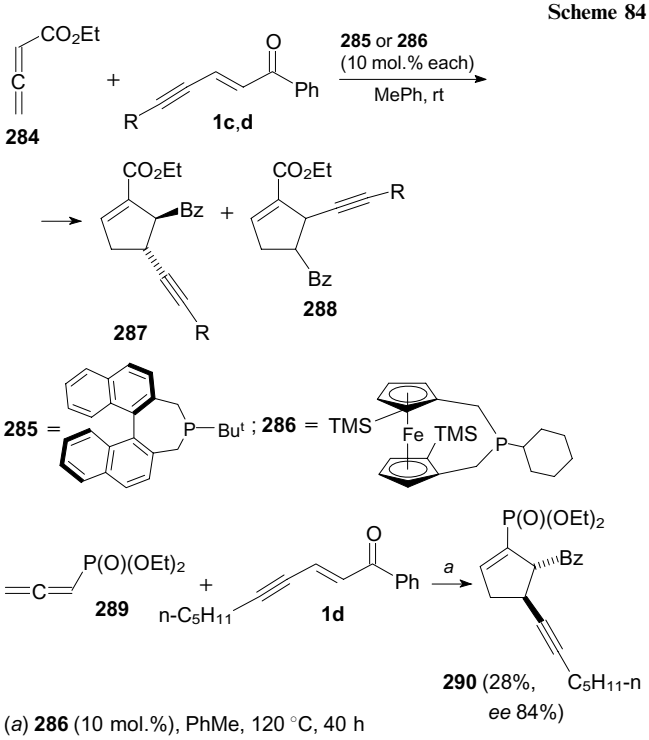
The reactions of enynones with allenes have been reported.[235 – 237] The [3 + 2]-cycloaddition of ethyl buta-2,3-dienoate (**284**) to enynones **1c**,**d** takes place at room temperature in the presence of chiral agents **285** or **286** and affords cyclopentene **287** and by-product **288** (Scheme 84, Table 27). The ratio of the reaction products is affected by the substituent R in the substrate: higher selectivity is observed for 5-phenyl-substituted enynone **1c** in the presence of phosphepine **285**.[235] In the case of 5-pentyl-substituted enynone **1d**, high selectivity is attained when ferrocenyl derivative **286** is used as the chiral agent.[236] Diethyl propa-1,2-dien-1-ylphosphonate (**289**) reacts with enynone **1d** under more drastic conditions and gives a markedly lower yield of product **290** (see Scheme 84).[237]

Linear-conjugated 6-diethylaminoenynone **28b** (R^1 = Et, R^2 = Me) selectively adds nitrile imines **291** at the triple bond. The reaction occurs in the presence of Et_3N

Scheme 83



Scheme 84



in anhydrous diethyl ether at room temperature and furnishes pyrazoles **292**. The p,π-conjugation with the amino group brings about a specific pathway of 1,3-cycloaddition (Scheme 85).[233]

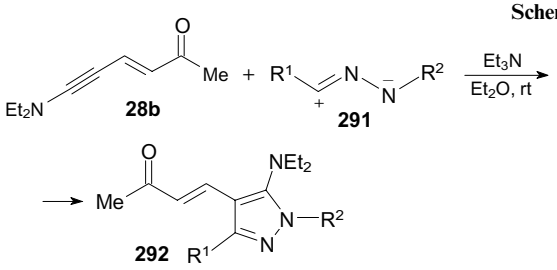
1,5-Diarylpent-2-en-4-yn-1-ones **112** react with the azide ion in DMF at room temperature. 1,2,3-Triazole chalcones **293** formed in this reaction easily react with hydrazine or phenylhydrazine hydrochloride to give 4-(4,5-dihydro-1*H*-pyrazol-5-yl)-1,2,3-triazoles **294**. Bis-azaheterocycles **294** are oxidized to pyrazoles **295** under reflux in glacial acetic acid (Scheme 86, Table 28).[14,234] An alternative synthetic route to 1,2,3-triazole chalcones is the Claisen–Schmidt reaction.[238,239]

Table 27. Cycloaddition of ethyl buta-2,3-dienoate to enynones **1c**,**d** (see Scheme 84).

Substrate	R	Catalyst	Yield of **287** + **288** (%)	*ee* (%) (see [a])	**287** : **288**	Ref.
1c	Ph	**285**	70	87	> 20 : 1	235
1d	n-C_5H_{11}	**285**	65	85	6 : 1	235
1d	n-C_5H_{11}	**286**	70	90	15 : 1	236

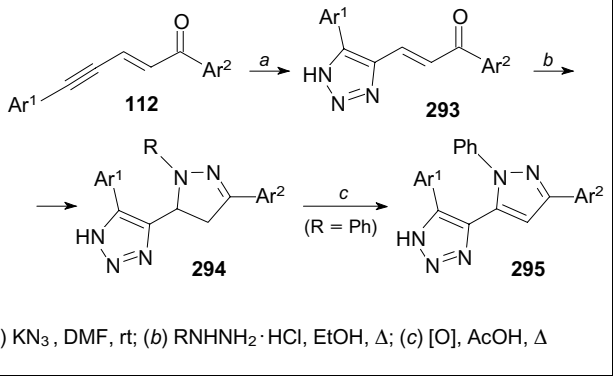
[a] Enantiomeric excess for cyclopentene **287**.

Scheme 85



R^1	R^2	Time /h	Yield (%)
Ac	Ph	18	33
Ac	4-BrC_6H_4	30	48
Ph	Ph	24	45

Scheme 86



The intramolecular 1,3-dipolar cycloaddition of enynones **296a**,**b** containing an azide group yields tricyclic derivatives **297a**,**b**.[12] In the case of ketones **298** in which the azide group occurs on the side of the triple bond, the cycloaddition in the presence of gold complexes with the BrettPhos ligand [BrettPhos is (2′,4′,6′-triisopropyl-3,6-dimethoxybiphenyl-2-yl)dicyclohexylphosphine] proceeds *via* the intermediate elimination of N_2. The reaction is conducted in toluene for 3–40 h and results in the closure of the 2,3-dihydro-1*H*-pyrrolizine system **299** (Scheme 87, Table 29).[13] In the case of substrate **298a** (R^1–R^2 = $CH_2CMe_2CH_2$, R^3–R^4 is benzo, R^5 = H), heterocycle **299a** is formed within 16 h (65% yield).

Table 28. Transformations of 1,5-diarylpent-2-en-4-yn-1-ones **112** (see Scheme 86).

Ar^1	Ar^2	R	Product	Yield (%)	Ref.
Ph	Ph		**293**	97	234
Ph	4-MeC_6H_4		**293**	96	234
Ph	4-ClC_6H_4		**293**	95	234
Ph	4-$MeOC_6H_4$		**293**	90	14
Ph	4-BrC_6H_4		**293**	98	14
Ph	2-Th		**293**	91	14
4-MeC_6H_4	Ph		**293**	87	14
4-BrC_6H_4	4-BrC_6H_4		**293**	91	14
Ph	Ph	Ph	**294**	83	234
Ph	4-MeC_6H_4	Ph	**294**	87	234
Ph	4-ClC_6H_4	Ph	**294**	93	234
Ph	4-BrC_6H_4	Ph	**294**	84	14
Ph	2-Th	Ph	**294**	72	14
Ph	Ph	H [a]	**294**	85	14
Ph	4-MeC_6H_4	Ph	**295**	82	14
Ph	4-BrC_6H_4	Ph	**295**	89	14

[a] Hydrazine (a base) was used.

Scheme 87

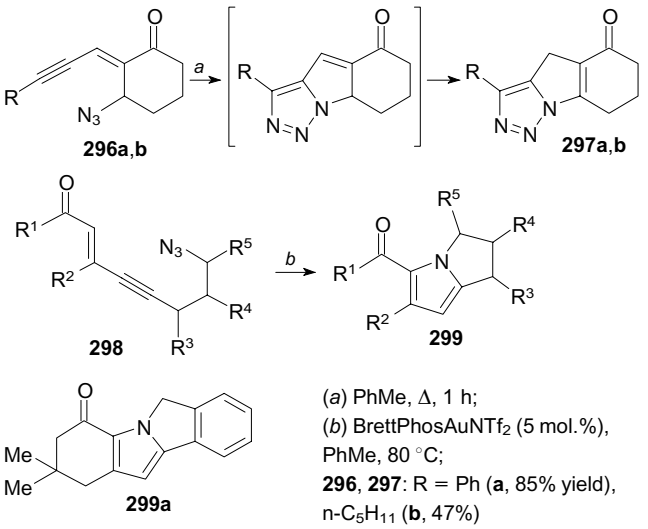


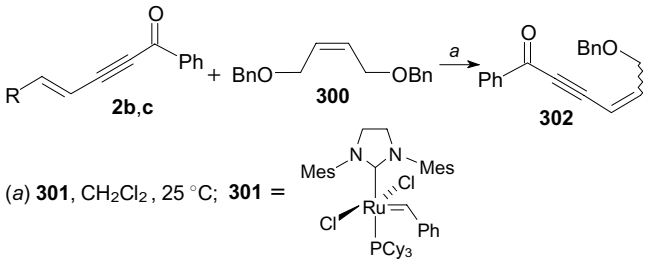
Table 29. Synthesis of 2,3-dihydro-1*H*-pyrrolizines **299** by cyclization of enynones **298** (see Scheme 87).[13]

R^1	R^2	R^3	R^4	R^5	Reaction time /h	Yield (%)
Me	Me	H	H	Me	24	76
Ph	H	H	H	Me	16	81
$(CH_2)_3$		H	H	H	14	86
$CH_2CH(Me)CH_2$		H	H	H	11	84
$CH(Me)(CH_2)_2$		H	H	H	40	71
$(CH_2)_2CH(Me)$		H	H	H	12	91
$CH_2CMe_2CH_2$		H	BnO	H	11	80
$CH_2CMe_2CH_2$		H	H	Me	11	92
$CH_2CMe_2CH_2$		Pr^n	H	H	3	87

4.6. Miscellaneous reactions

Conjugated enynones **2b**,**c** undergo cross-metathesis with 1,4-bis(benzyloxy)but-2-ene (**300**) catalyzed by ruthenium complexes **301** (Grubbs II catalyst). The reaction gives product **302** with *cis*-selectivity (according to ^{1}H NMR data) (Scheme 88).[240]

Scheme 88



Enynone	R	Reaction time /h	Yield (%)	*E*:*Z*
2b	H	18	34	1:7
2c	$AllOCH_2$	6	63	1:4

Boukouvalas *et al.*[1] and Meng *et al.*[241] considered the reactions of conjugated enynones at the terminal substituents (in positions 1 and 5) in which the enynone pentad remains intact. On treatment with iodine in the presence of potassium carbonate in dichloromethane at 0 °C, 1-phenylpent-1-en-4-yn-3-one substitutes the terminal proton at the triple bond; this affords 5-iodo-1-phenylpent-1-en-4-yn-3-one in 89% yield.

An example of a radical reaction of enynones of type **1** has been reported by Ren *et al.*[242] Heating of enynones **83** with sulfinic acids **303** in water in the presence of air oxygen generates furans **304** in 32% – 94% yields (Scheme 89, Table 30). It is assumed that, as in reactions with some nucleophiles,[10, 27, 203] allene structures **305** are initially formed. To confirm the reaction mechanism, the researchers [242] carried out a number of experiments with addition of TEMPO under inert atmosphere; as a result, the intermediate formation of structures **305** and/or **306** was demonstrated by high-resolution mass spectrometry. Hydroxyl

Scheme 89

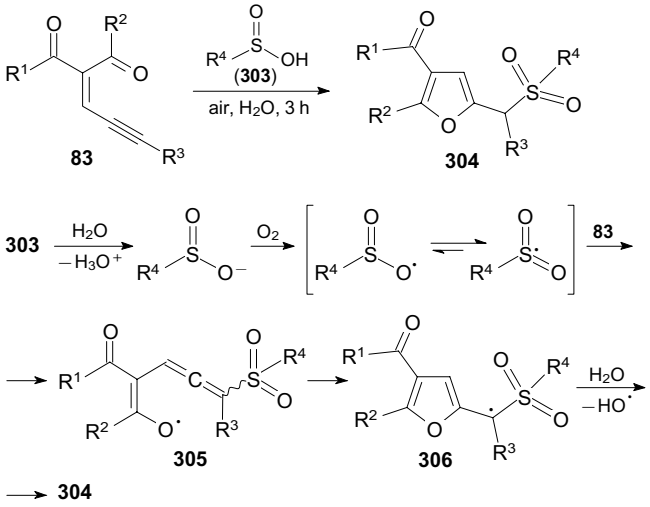


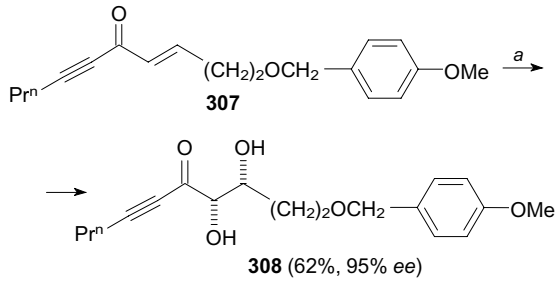
Table 30. Synthesis of sulfonyl-substituted furans **304** (see Scheme 89).[242]

R^1	R^2	R^3	R^4	Temperature /°C	Yield (%)	R^1	R^2	R^3	R^4	Temperature /°C	Yield (%)
Me	Me	Ph	Me	80	84	Me	Me	Ph	4-$AcHNC_6H_4$	80	82
Me	Me	Ph	Ph	80	78	Me	Me	Ph	2,4-$F_2C_6H_3$	120	77
Me	Me	Ph	4-MeC_6H_4	80	94	Me	Me	Ph	3,5-$F_2C_6H_3$	80	88
Me	Me	Ph	4-$MeOC_6H_4$	80	41	Me	Me	Ph	2,4-$Cl_2C_6H_3$	80	89
Me	Me	Ph	3-FC_6H_4	80	72	Me	Me	Ph	3,4-$Cl_2C_6H_3$	80	80
Me	Me	Ph	4-FC_6H_4	80	70	Me	Me	Ph	3,5-$Cl_2C_6H_3$	80	50
Me	Me	Ph	2-ClC_6H_4	80	90	Me	Me	Ph	4-Me-3-FC_6H_3	80	82
Me	Me	Ph	3-ClC_6H_4	80	85	Me	Me	Ph	2-Me-3-ClC_6H_3	80	71
Me	Me	Ph	4-ClC_6H_4	80	86	Me	Me	Ph	Bn	80	70
Me	Me	Ph	2-BrC_6H_4	80	84	Me	Me	4-MeC_6H_4	4-MeC_6H_4	120	86
Me	Me	Ph	4-BrC_6H_4	120	77	Me	Me	4-FC_6H_4	4-MeC_6H_4	120	76
Me	Me	Ph	4-IC_6H_4	80	73	Me	Me	4-ClC_6H_4	4-MeC_6H_4	120	90
Me	Me	Ph	3-NCC_6H_4	80	80	Et	Et	Ph	4-MeC_6H_4	120	81
Me	Me	Ph	4-NCC_6H_4	120	78	Ph	Ph	Ph	4-MeC_6H_4	120	32
Me	Me	Ph	2-Naph	80	79	Ph	Me	Ph	4-MeC_6H_4	120	46
						EtO	Me	Ph	4-MeC_6H_4	120	57

radicals were detected in additional experiments using EPR spectroscopy.

The Sharpless asymmetric dihydroxylation of enynones has been reported.[116,243] The oxidation of enynone **307** is the first step in the synthesis of propargyl alcohols — chiral building blocks for the preparation of analogues of natural products.[116] The reaction is induced by the commercial chiral catalyst AD-mix-β and proceeds under mild conditions to give product **308** in good yield and with high stereoselectivity (Scheme 90).[244]

Scheme 90



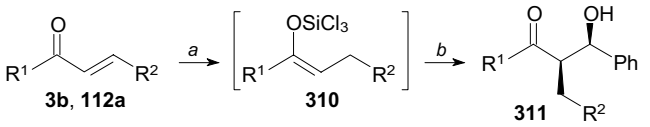
(*a*) AD-mix-β, $MeSO_2NH_2$, Bu^tOH, H_2O, 0 °C

A stereoselective method has been developed for the synthesis of keto alcohol derivatives based on α,β-unsaturated ketones, including enynones.[245] The one-pot synthesis includes successive treatment of enynones **3b** and **112a** with trichlorosilyl triflate and benzaldehyde in the presence of (*S*)-(1,1′-binaphthyl)-2,2′-diylbis(diphenylphosphine oxide) (**309**) as a chiral agent. According to 2D NMR spectroscopy with nuclear Overhauser effect (NOESY), the first step yields Z-configured trichlorosilyl enol ethers **310**, which ensures high *syn*-selectivity of the subsequent step giving the target products **311** (Scheme 91).

The oxidative aziridination of conjugated enynones **3** (R^3 = C≡CTMS) and **112a** has been studied[11,89] (see †). The reaction proceeds under mild conditions and does not affect the triple bond (Scheme 92, Table 31). *N*-Phthalimidoaziridines **312a–k** and **313** are used in the synthesis of five-membered heterocyclic derivatives.

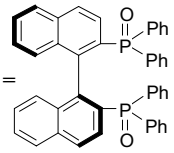
† Oxidative aziridination of conjugated enynones was also considered in a review by Kuznetsov *et al.*[246]

Scheme 91



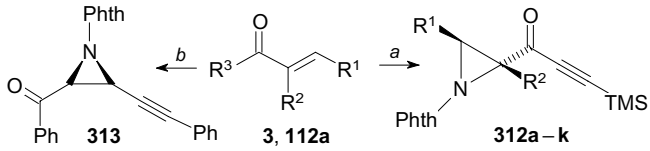
(*a*) Cl_3SiOTf (1.5 equiv.), Bu^iCy_2N (2 equiv.), CH_2Cl_2, −40 °C; (*b*) **309** (10 mol.%), PhCHO, CH_2Cl_2, −40 °C;

309 =



R^1	R^2	Yield (%)	*syn* : *anti*	*ee* (*syn*) (%)
Ph	PhC≡C	82	95 : 5	80
PhC≡C	Ph	56	89 : 11	84

Scheme 92



(*a*) PhthNH, $Pb(OAc)_2$, CH_2Cl_2, 0 °C; (*b*) PhthNH, PIDA, CH_2Cl_2, rt; PhThN is phthalimido, PIDA is phenyliodonium diacetate

Some enynones can participate in photochemical reactions.[247–250] For example, Um *et al.*[247] observed light-induced *cis–trans*-isomerization of 3-methyl-2-(4-nitrophenyl)-1,5-diphenylpent-2-en-4-yn-1-one. It was shown that irradiation of a benzene solution of ketone **314** at ~365 nm induces ring closure to give 5,6-dihydro-4*H*-cyclopenta[*c*]furan **315** (Scheme 93).[248,249] The reaction of linear-conjugated enynones **316a**,**b** with 2-chloroacrylonitrile, 2,3-dimethylbuta-1,3-diene and methacrylonitrile at

Scheme 93

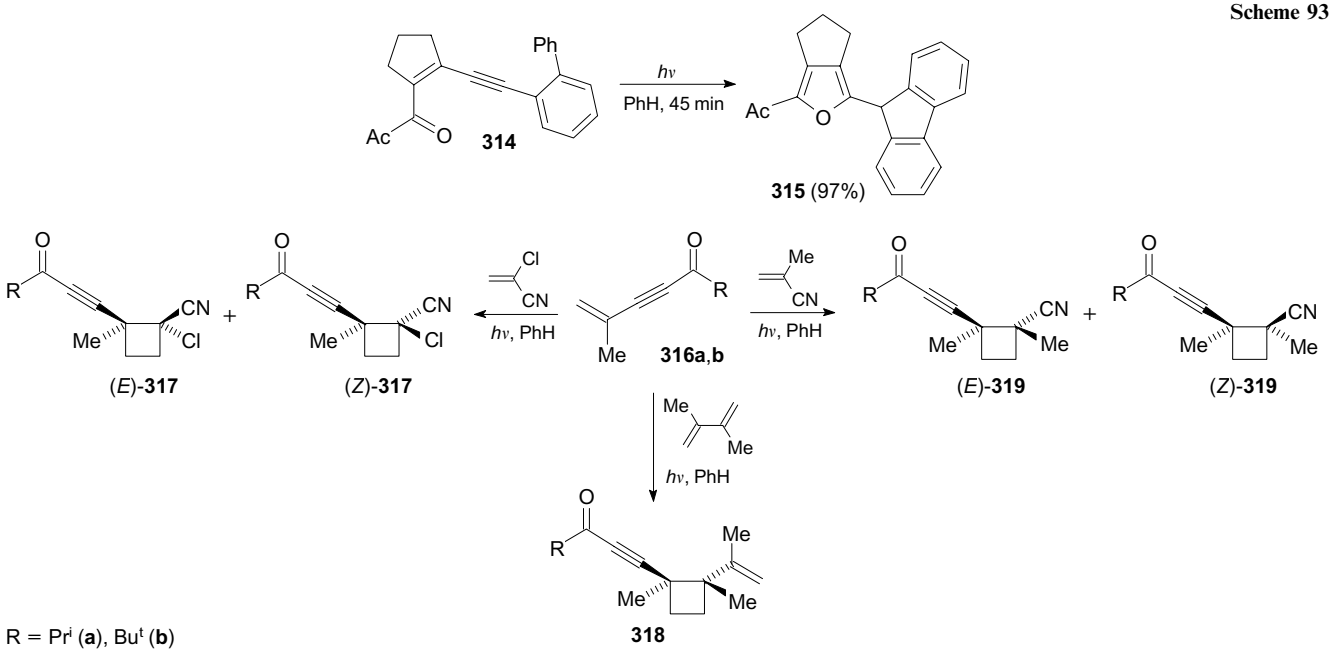


Table 31. Synthesis of aziridines from enynones (see Scheme 92).

R^1	R^2	Product	Yield (%)	Ref.
4-$O_2NC_6H_4$	H	**312a**	89	89
4-ClC_6H_4	H	**312b**	76	89
Ph	H	**312c**	72	89
4-MeC_6H_4	H	**312d**	76	89
4-$MeOC_6H_4$	H	**312e**	72	89
2-Th	H	**312f**	65	89
3-Th	H	**312g**	62	89
1-Phenylpyrazol-4-yl	H	**312h**	66	89
Ph	Ph	**312i**	78	89
Ph	4-$MeOC_6H_4$	**312j**	74	89
Ph	4-$O_2NC_6H_4$	**312k**	81	89
PhC≡C	H	**313**	67	11

the double bond induced by irradiation at 350 nm leads to cyclobutanes **317** – **319**.[250]

5. Conclusion

The material presented in the review demonstrates the considerable progress made in the last 15 years in the chemistry of linear- and cross-conjugated enyne ketones. First of all, this refers to new applications of these compounds in the synthesis of complex carbo- and heterocyclic structures. These compounds are also of interest as nonlinear optical materials. Highly efficient synthetic routes to conjugated enynones have now been developed, making them synthetically accessible. However, some issues of the chemistry of conjugated enynones remain unsolved, in particular, features of their reactions with polynucleophiles and 1,3-dipoles. The reactions of these compounds with free radicals have been scarcely studied.

Thus, conjugated enyne ketones are accessible and fairly convenient building blocks for the synthesis of complex molecules, the synthetic potential of which is far from being exhausted. It is quite promising to study the properties of these compounds with the goal to develop new highly efficient strategies of organic synthesis.

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