DOI: 10.1070/RCR4679

ortho-Quinone methides as key intermediates in cascade heterocyclizations

Dmitry V. Osipov,[a] Vitaly A. Osyanin,[a, b] Yuri N. Klimochkin [a]

[a] *Samara State Technical University*
ul. Molodogvardeiskaya 244, 443100 Samara, Russian Federation
[b] *People's Friendship University of Russia (RUDN University)*
ul. Miklukho-Maklaya 6, 117198 Moscow, Russian Federation

Development of new methods of heterocyclic synthesis is still a topical issue. In this connection, the trend related to the use of highly reactive *o*-quinone methides for the synthesis and functionalization of heterocycles appears rather promising. Since most of *o*-quinone methides are unstable, the choice of precursors and generation conditions is highly important for subsequent transformations involving them. Various methods of generation of *o*-quinone methides and cascade heterocyclizations in which the formation of these compounds is a key step are surveyed in the review. The trends of using *o*-quinone methides in the synthesis of various heterocycles are analyzed and the heterocyclization reactions involving these compounds are classified.
The bibliography includes 395 references.

Contents

I. Introduction 625
II. The reactivity and generation methods of *o*-quinone methides 627
III. Cascade processes initiated by 1,4-addition 629
IV. Diels – Alder reaction 654
V. Electrocyclic reactions 672
VI. Heterocyclizations initiated by sigmatropic shifts 680
VII. Miscellaneous types of cascade transformations involving *o*-quinone methides 681
VIII. Conclusion 683

I. Introduction

Development of efficient synthetic routes with elucidation of the design patterns for oxygen-containing fused heterocycles is currently an important fundamental problem of organic chemistry. The efforts of synthetic chemists are aimed, on one hand, at searching for reaction conditions that would provide nearly quantitative yields in each step and, on the other hand, at minimizing the number of separate steps. Modern methods for the synthesis of organic compounds should not only be based on simple and commercially available substrates and reagents and decrease the cost of target products, but also considerably mitigate the environmentally adverse consequences of process implementation.

These requirements are reflected in the interest of organic chemists in one-pot syntheses, which has sharply increased in recent years.[1, 2] Among transformations of this type are cascade reactions, which are also called domino or tandem reactions in the literature.

Also, the choice of an accessible substrate offering a great synthetic potential has been and is still a key problem

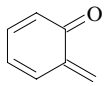
D.V.Osipov. Candidate of Chemical Sciences, Associate Professor of the Department of Organic Chemistry at the SamSTU.
Telephone: +7(846)332 – 2122, e-mail: osipovdv25@mail.ru
Current research interests: chemistry of heterocyclic compounds, synthesis of natural products, cascade reactions.
V.A.Osyanin. Doctor of Chemical Sciences, Professor of the Department of Organic Chemistry at the SamSTU, Chief Researcher of the Joint Institute for Chemical Research at the RUDN University.
Telephone: +7(846)332 – 2122, e-mail: vosyanin@mail.ru
Current research interests: chemistry of heterocyclic compounds, chemistry of nitrogen- and oxygen-containing heterocycles, cascade and multicomponent reactions, chemistry of cage compounds.
Yu.N.Klimochkin. Doctor of Chemical Sciences, Professor, Head of the Department of Organic Chemistry at the SamSTU.
Telephone: +7(846)332 – 2122, e-mail: orgchem@samgtu.ru
Current research interests: chemistry of cage compounds, antiviral properties of organic compounds, chemistry of adamantane.

Received 2 July 2016
Translation: Z.P.Svitanko

© 2017 Russian Academy of Sciences and Turpion Ltd.

of the molecular design of novel heterocyclic systems.[3] Owing to the presence of several reaction centres, *ortho*-quinone methide (*o*-QM, **1**) and its derivatives are valuable intermediates in the synthesis of benzannulated oxygen-containing systems, which are of interest as photochromic materials[4] and biologically active compounds.[5–7] The presence of 1-oxabutadiene moiety with an invariable cisoid conformation in *o*-QMs and the formation of stable aromatic products from these species account for their high reactivity towards a broad range of dienophiles and nucleophiles.

Structure 1



1

The properties and the synthetic potential of *o*-QMs have been vigorously studied in recent years; most of all, this is related to their specific structure, high reactivity and an important role in many chemical and biochemical processes. The key aspects of *o*-QM reactivity were covered in the pioneering studies of Turner[8,9] back in the 1960s. However, a considerable increase in the number of publications on this topic took place only in the last two decades. Several reviews consider various aspects of the synthesis and application of these intermediates. Classic reviews[10,11] describe the key methods for generation and chemical reactivity of *o*-QMs. Being potent electrophiles, *o*-QMs can alkylate many nucleophiles, including carbohydrates, nucleophilic sites of enzymes and DNA, and this has also been considered in the literature.[12,13]

The accumulated knowledge on the application of *o*-QMs, including the aspects described above, and on investigation of their properties and use in medicinal chemistry and biology have been covered most comprehensively in a book[14] edited by Rokita. The paper of Bolton,[15] describing QM bioactivation routes essential for medicinal chemistry deserves attention; however, it is mainly devoted to *para*-isomers. A review of Basarić *et al.*[16] demonstrates the pathways of photochemical generation of quinone methides and their applications in medicinal chemistry. Analysis of the role of QMs in the lignin chemistry is also noteworthy.[17] Finally, the most recent reviews illustrate the methods for *o*-QM generation[18] and stabilization *via* complex formation,[19] the use of these intermediates in asymmetric synthesis,[20–23] preparation of chromenes and chromans,[24] total synthesis of natural compounds[25] and in some other reactions.[26] However, the publications noted above present only a superficial consideration of the cascade heterocyclization reactions involving *o*-QMs. The large amount of accumulated information concerning the preparation of various fused heterocycles from *o*-QMs brings about the necessity to systematically describe these reactions.

Many authors use the terms 'tandem', 'cascade' and 'domino' reactions interchangeably, without drawing a borderline between them. However, there are actually different views on how the reactions of this type should be classified. According to Ho,[27] tandem processes are combinations of two or more reactions that occur in a definite order; if the addition of extra reagents is required, their fragments are integrated into the product. According to Nicolau *et al.*,[28] cascade reactions include several transformations in one process operation; this is done using only one solvent (solvent system) and a single isolation of the product. According to Denmark and Thorarensen,[29] tandem reactions can be divided into three types:

1) all reactions occur without addition of extra reagents or catalysts and the reaction conditions do not change (domino or cascade reactions);

2) the intermediates formed in the first reaction have all necessary functional groups for the subsequent steps to proceed, but additional energy (heating or irradiation) is required to overcome the energy barrier;

3) intermediates formed in the first reaction also have the necessary functional groups, but extra reagents or catalysts are needed for the subsequent transformations.

Reactions of the first type usually involve the formation of highly reactive intermediates, which are very difficult or impossible to isolate. In the second and third cases, the intermediate compounds are, most often, relatively stable.

In the opinion of Tietze *et al.*,[30–32] a domino reaction is a reaction consisting of two or more bond-forming transformations, which occur under the same conditions without addition of any other reagents or catalysts, the subsequent reactions involving the reaction centres formed in the previous steps. According to this definition, most of domino reactions fall into the more extensive class of tandem processes.

An important advantage of cascade reactions is the possibility of participation of sensitive and unstable intermediates. Since the reactive intermediates do not decompose as they are generated, because they are further consumed, the final products are most often formed in good yields. Thus, the cascade strategy as applied to the synthesis of heterocycles is a potent tool for increasing the complexity of a molecular structure starting from simple initial compounds.

In this review, we adhered to the definition of domino reactions proposed by Tietze's group and used it as a synonym for cascade reactions. The *o*-QM generation step, which is often the retro-Michael reaction, was not taken into account as a separate process. Most of the cascade reactions involving *o*-QMs reported in the literature can formally be assigned to one of three groups (Fig. 1).

However, we do not use this classification, because transformations that are similar in essence are often classified as different types. The classification based on the mechanism of separate steps of a domino process is also hardly suitable, because of the large diversity of chemical transformations even within one cascade. Therefore, in this review, the cascade reactions are grouped together in terms of the type of transformations of *o*-QMs that directly result in the construction of a heterocyclic system. This classification gives a clear view of the synthetic applicability of *o*-QMs and can be useful for selection of the lines for further research.

The approach of complementary coupling of two ambiphiles also appears promising for the synthesis of cyclic structures.[33] According to a definition,[34] ambiphilic reagents are compounds containing reaction centres of the opposite nature in one molecule. In a publication of Yudin and co-workers,[35] ambiphilic reagents are called amphoteric compounds; among them, the authors distinguish thermodynamic amphoteric organic compounds (for example, α-amino acids) and kinetic amphoteric compounds, which have both electrophilic and nucleophilic centres with no

1. One-component reactions:

$$A \longrightarrow [o\text{-QM}] \longrightarrow X_1 \longrightarrow X_2 \longrightarrow \cdots$$

$$A \longrightarrow X_1 \longrightarrow [o\text{-QM}] \longrightarrow X_2 \longrightarrow \cdots$$

$$A \longrightarrow [o\text{-QM}] \xrightarrow{[o\text{-QM}]} X_1 \xrightarrow{[o\text{-QM}]} X_2 \text{ (trimerization)}$$

2. Two-component reactions:

$$A \longrightarrow [o\text{-QM}] \xrightarrow{B} X_1 \longrightarrow X_2 \longrightarrow \cdots$$

$$A + B \longrightarrow X_1 \longrightarrow [o\text{-QM}] \longrightarrow X_2 \longrightarrow \cdots$$

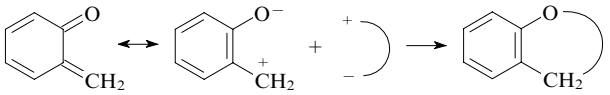
3. Three-component reactions:

$$A + B \longrightarrow X_1 \longrightarrow [o\text{-QM}] \xrightarrow{C} X_2 \longrightarrow \cdots$$

(for C = B pseudo-three-component reaction)

Figure 1. Types of cascade reactions involving reactants A – C and generation of *o*-quinone methides (*o*-QMs), resulting in products X_n.

proton transfer between them. *o*-Quinone methides can be regarded as 1,4-ambiphilic reagents, which allows them to be used in cascade heterocyclizations to give five-, six-, seven- and eight-membered oxygen-containing heterocycles (Fig. 2). However, the range of appropriate ambiphilic substrates for *o*-QMs still remains rather narrow. Since no systematic analysis of *o*-QMs as 1,4-ambiphiles in the construction of benzannulated heterocycles has been carried out to date, we considered many reactions also from this standpoint.

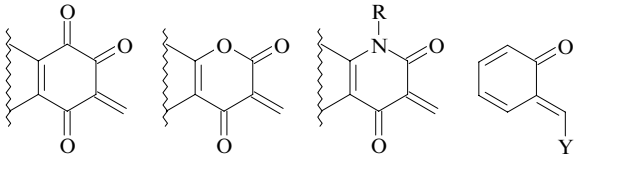


o-QM (**1**) 1,4-ambiphile 1,*n*-ambiphile

Figure 2. Scheme of the synthesis of oxygen-containing cyclic systems involving *o*-quinone methide as a 1,4-ambiphile.

It should be mentioned that this review almost exclusively describes the transformations of *o*-QMs that have a 6-alkylidenecyclohexa-2,4-dien-1-one moiety distinguishable in the molecule. We do not consider unsaturated substrates **A** – **C**, including heterocyclic ones, which contain an additional carbonyl group, because their reactivity differs substantially from the behaviour of classic *o*-QMs. For the same reason, structures **D** with a heteroatom at the exocyclic carbon atom are barely considered; in particular, the review does nor cover the insertion reactions of arynes into formamides followed by the formation of heterocycles, which are described in detail by Miyabe.[36]

Structures A – D



A **B** **C** **D** (Y = OR, SR, NR_2)

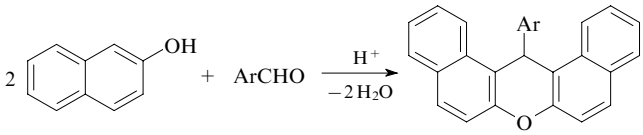
This review addresses cascade reactions giving rise to cyclic structures based on *o*-QMs and starts with the brief description of the most efficient methods for generation of *o*-QMs and their chemical properties (Section II). Section III presents the cascade reactions initiated by 1,4-addition. Section IV deals with the cascade processes based on Diels – Alder reactions, including oligomerization of *o*-QMs. Section V covers the cascade reactions that comprise electrocyclization. Section VI describes the heterocyclizations initiated by sigmatropic shifts. The domino reactions that do not fall into any of the above types are considered in Section VII.

II. The reactivity and generation methods of *o*-quinone methides

As has already been noted, *o*-QMs can alkylate many nucleophiles, including those occurring in nature.[11] For example, willow bark and leaves contain salicortin, which inactivates the pest β-glucosidase *via* the formation of *o*-QMs. The antitumour action of natural antibiotics, daunomycin, adriamycin and menogaril, is ascribed to *o*-QM generation *in vivo* during their reductive bioactivation. Vitamin K_1 and ubiquinones (coenzyme Q_n) play a key role in the electron transfer and energy transport by means of their *o*-quinone methide tautomers.[11] Also, *o*-QM generation underlies the use of some linkers in the solid-phase synthesis.[37] Worthy of note are the key role of these intermediates in the production of phenol formaldehyde resins [38] and their increasing significance in the development of new bioorthogonal and click reactions.[39]

o-Quinone methides were mentioned for the first time in a publication of Fries and Kann [40] (1907) in relation to oligomerization of 2-halomethylphenols. Meanwhile, the synthesis of 14*H*-dibenzo[*a*, *j*]xanthenes **2** from 2-naphthol and aromatic aldehydes reported back in 1883 is one of the first cascade transformations involving *o*-QMs and giving a heterocycle (Scheme 1).[41]

Scheme 1



2

Apart from the non-charged structure **1**, *o*-QM can be depicted as a singlet form representing resonance-stabilized benzyl carbocation **1′** and as triplet biradical form **1″** (Fig. 3). In addition to the aromatic conjugation, the dipolar species is stabilized by the field effect. The electron-donating effect of the oxygen atom makes *o*-QMs less electrophilic, but kinetically more stable and more selective towards nucleophiles as compared with benzyl carbocations.

Unlike *o*-benzoquinones, *o*-QMs are highly polarized, which accounts for their higher reactivity.[42] Apart from the lack of participation in radical reactions, these compounds differ from *o*-quinodimethane **3** by the very small number of known cases of cyclization. For example, irradiation of substituted salicyl alcohol **4a** (*o*-QM precursor) at 6.5 K

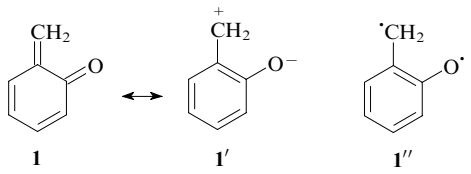
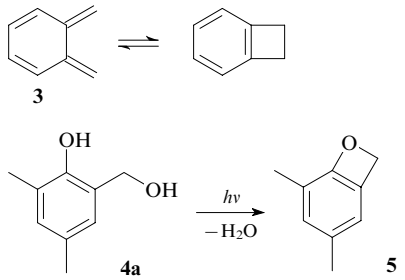


Figure 3. Singlet dipolar and triplet biradical forms of *o*-quinone methide.

with a high-pressure mercury lamp yields benzoxete **5**, which is thermodynamically less stable than *o*-QMs (Scheme 2).[43]

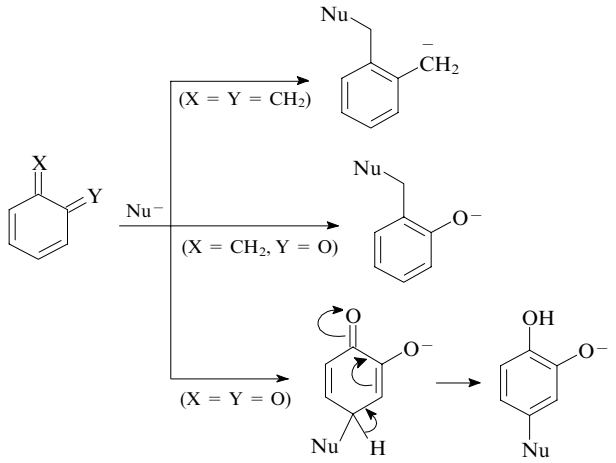
Scheme 2



A direct spectroscopic investigation of the unsubstituted *o*-QM (**1**) is possible only in an argon matrix at 10 K or by using laser flash photolysis technique. The simplest *o*-QMs are too unstable and rapidly polymerize as their dilute solutions are concentrated. However, the *o*-QM stability is increased in the presence of electron-withdrawing or aryl groups at the exocyclic carbon atom, upon elongation of the conjugation chain, in particular, as a result of benzannulation, in the presence of several electron-donating groups in the ring and/or sterically bulky substituents in the vicinity of the carbonyl group as well as the possibility of intramolecular hydrogen bonding.[44] Furthermore, *o*-QMs can be stabilized as transition metal (Ir, Os, Rh) complexes; however, the reactivity of these complexes usually markedly differs from that of free *o*-QMs.[19] As examples of stable *o*-QMs, including naturally occurring ones, consider compounds **6**–**14** (the *o*-QM moiety is marked by bold lines).[45–52]

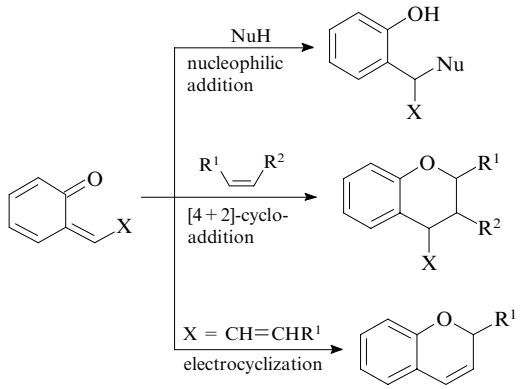
o-Quinone methides occupy a unique place among Michael acceptors. The addition of nucleophiles (NuH) to these species directly gives an aromatic system and, therefore, it is thermodynamically favourable. In the related benzoquinones and quinodimethanes, the formation of an aromatic system requires an additional enolization step in the former case, while in the latter case, the conjugate addition of nucleophiles affords benzyl carbanions, which are less stable than phenoxide ions (Scheme 3).

Scheme 3

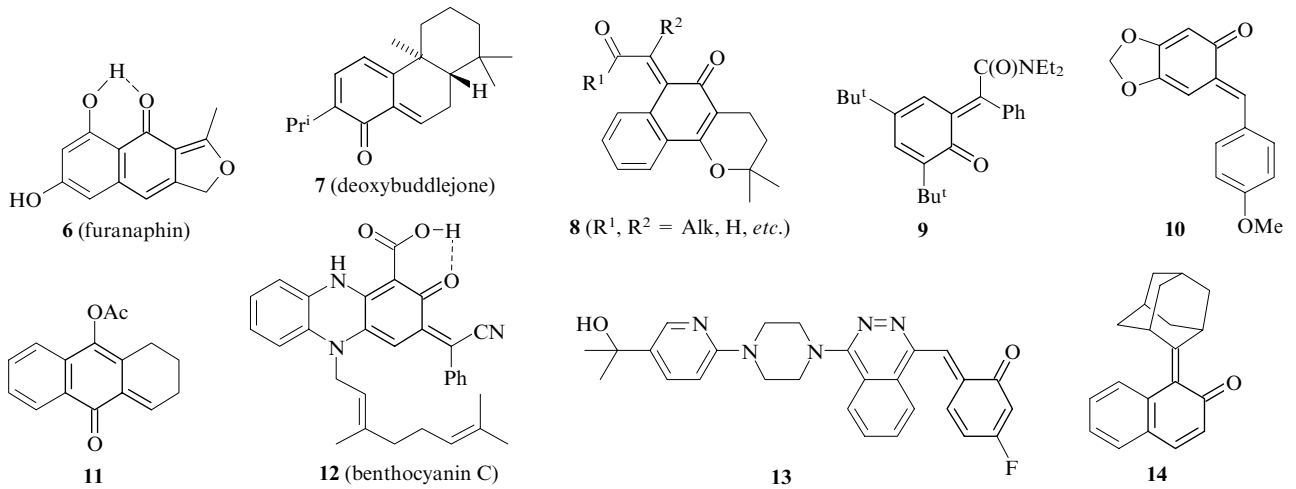


When there are appropriate substituents, the adducts initially formed from *o*-QMs can undergo subsequent cyclization to give fused heterocyclic systems. Furthermore,

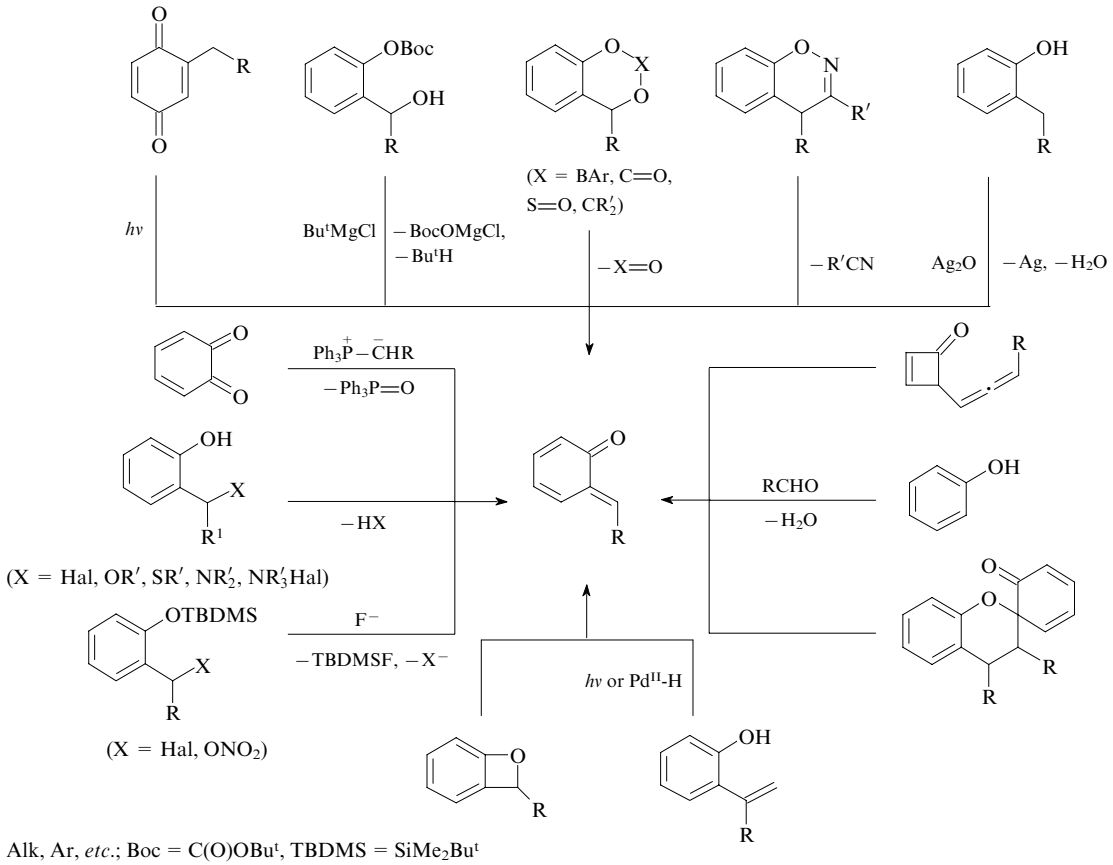
Scheme 4



Structures 6 – 14



Scheme 5



R, R′ = Alk, Ar, *etc.*; Boc = C(O)OBu^t, TBDMS = $SiMe_2Bu^t$

o-QMs can be stabilized by cycloaddition and α-vinyl derivatives are stabilized *via* electrocyclization (Scheme 4).[21]

The chemical properties of *o*-QMs and phenols are tightly connected, which is manifested most clearly in the methods for *o*-QM generation from phenol derivatives and in *o*-QM conversion to phenol derivatives upon reactions with nucleophiles and dienophiles. As compared with the *para*-isomers, *o*-QMs are formed, as a rule, under more drastic conditions due to higher polarization and lower stability.[44] The generation of *o*-QMs is performed by chemical (on treatment with oxidants, acids or bases), thermal, photochemical, electrochemical or enzymatic routes. Most often, *o*-QMs are generated by thermolysis of various precursors, such as salicyl alcohols and ethers, Mannich bases, quaternary ammonium salts, 2-halomethylphenols, 2-mercaptomethylphenols, 2-allylphenols, 4*H*-benzo[*e*][1,2]oxazines, 4*H*-benzo[*d*][1,3,2]dioxaborinines and so on (Scheme 5).

Most of the methods developed to date provide good results if the generated *o*-QMs are involved in subsequent intramolecular reactions. However, the application of these species in intermolecular reactions is usually complicated by the formation of oligomerization products.

The use of high temperature often induces undesirable side reactions, in particular, decomposition of nucleophiles and/or final products or change in the reaction stereochemistry. Since *o*-QMs are electrophilic, their generation is facilitated by electron-donating substituents and impeded by electron-withdrawing ones. In addition, thermolysis proceeds under milder conditions if the resulting *o*-QMs are stabilized by additional conjugation. The ease of generation of *o*-QMs is markedly affected by the nature of the leaving group at the benzyl carbon atom in the precursor. For each precursor, there is an optimal temperature range for the generation of *o*-QMs, which depends on the nature of substituents in the molecule.

III. Cascade processes initiated by 1,4-addition

A major route of *o*-QM stabilization in a nucleophilic medium is the conjugate addition of various Michael donors. The Michael donors used most often include CH-acids, allylsilanes, aliphatic and aromatic amines, amino acids, electron-enriched arenes and heterocycles, phenols, carboxylic acids, alcohols and some other compounds. An important factor for these reactions is the choice of the solvent, which, on the one hand, can compete with the nucleophile in the addition reactions and, on the other hand, can facilitate the *o*-QM generation step. The nucleophile addition to *o*-QMs is formally reversible, but the equilibrium is considerably shifted, almost in all cases, towards the products, and this dictates the ultimate outcome at any equilibrium constant of the *o*-QM generation step. The reported cascade reactions that include the Michael addition as one of the steps afford, most often, five- and six-membered heterocycles.

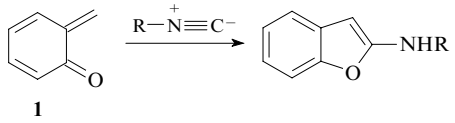
III.1. Michael reaction – nucleophilic addition

III.1.a. Synthesis of benzofurans

The carbon atom of the isonitrile group possesses simultaneously electrophilic and nucleophilic properties; therefore, isonitriles can be considered as 1,1-ambiphilic reagents for

the synthesis of fused furans in the reactions with *o*-QM precursors (Scheme 6).

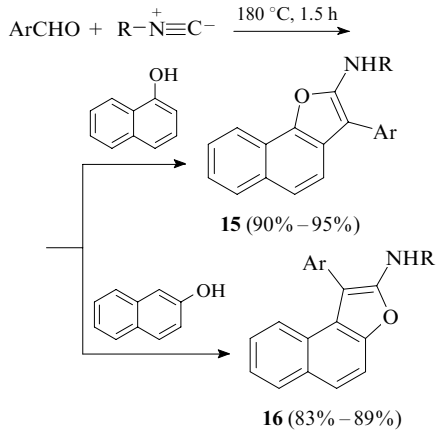
Scheme 6



1

It was found that heating of a mixture of 1- and 2-naphthols with aromatic aldehyde and aliphatic isonitrile gives the corresponding 2-alkylaminonaphthofurans **15** and **16** in high yields (Scheme 7).[53]

Scheme 7



15 (90%–95%)

16 (83%–89%)

R = cyclo-C_6H_{11}, Bu^t

The mechanism of this reaction is similar to that of the transformation of phenolic Mannich bases **17** into aminobenzofurans **18** under the action of aliphatic isonitrile in the presence of 1,2-dibromoethane and catalytic amounts of lithium perchlorate (Scheme 8).[54] Under these conditions, the retro-Michael reaction takes place to give the corresponding *o*-QM, which undergoes the Michael addition to isonitrile, and the subsequent cyclization furnishes 2-aminobenzofurans **18**.

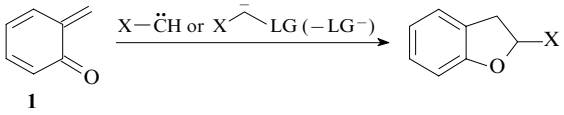
The ambiphilic nature of the cyanide ion allows the use of inorganic cyanides in the synthesis of 2-aminobenzofurans unsubstituted at the amino group (Scheme 9). The thermolysis of 2,4-di-*tert*-butylphenol Mannich bases **19** in sulfolane results in generation of *o*-QMs **20**, which undergo the Michael addition to the cyanide anion. *o*-Hydroxybenzyl cyanides **21** thus formed are converted to 2-aminobenzofurans **22** as a result of the intramolecular Pinner cyclization followed by tautomerization.[55]

Attention is attracted by the fact that this method for the preparation of 2-aminobenzofurans has been applied only to sterically hindered Mannich bases.

III.1.b. Synthesis of dihydroarenofurans

Dihydroarenofurans can formally be obtained from *o*-QMs and 1,1-ambiphiles complementary to them (Scheme 10); these may be singlet carbenes or carbenoids or their synthetic equivalents, in particular, diazo compounds.

Scheme 10

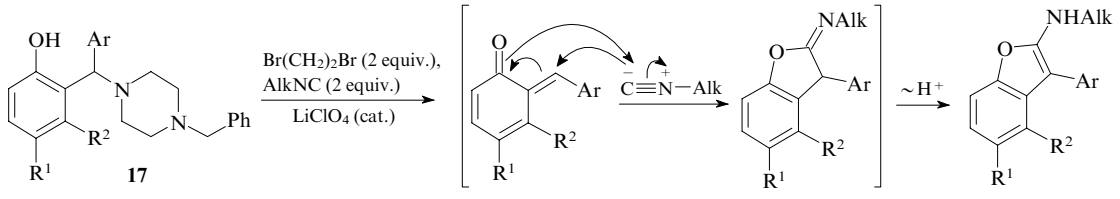


1

Various precursors of *o*-QMs, in particular, Mannich bases obtained by aminomethylation of 1- and 2-naphthols, 4-hydroxyacetanilide, 2,4-dimethylphenol and their quaternary salts, react with diazomethane or dimethylsulfoxonium methylide to give the corresponding 2,3-dihydronaphthofurans.[56] The product yields depend considerably on the nature of the leaving group in the *o*-QM precursor. Usually, the yields increase when quaternized derivatives of Mannich bases are employed. In addition, dimethylsulfoxonium methylide is a much more efficient reagent for the preparation of various dihydrofuran systems than diazomethane. However, the latter is applicable if the initial substrate contains functional groups sensitive to bases.

As an example of such transformation, consider the reaction of quaternary ammonium salts **23** and **24** with dimethylsulfoxonium methylide in the presence of dimsyl

Scheme 8

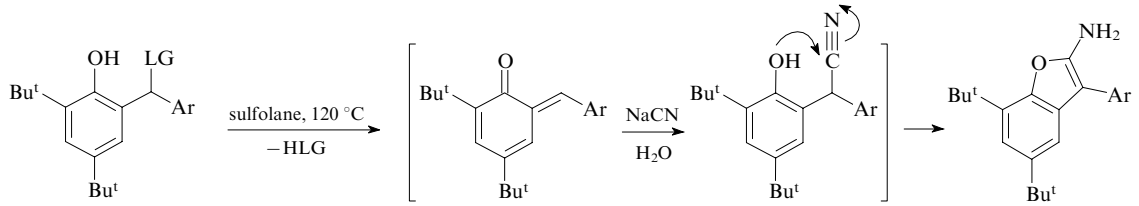


17

18 (25%–76%)

R^2 = H: R^1 = H, Me, CO_2Me; R^1–R^2 is benzo

Scheme 9



19

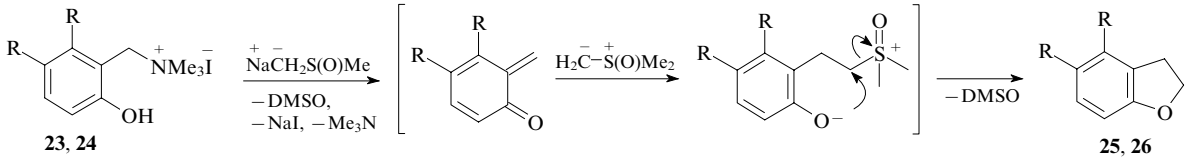
20

21

22 (77%–99%)

LG (leaving group) = NMe_2, cyclo-$N(CH_2)_5$

Scheme 11

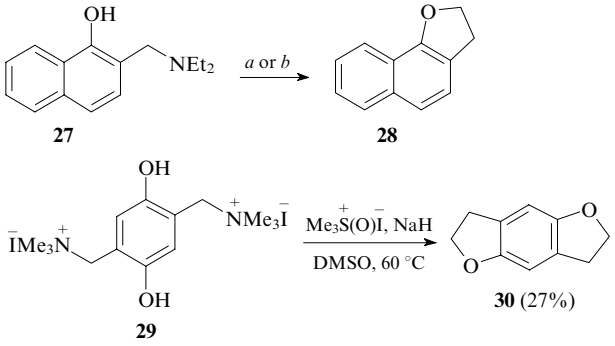


R = H (**23**; **25**, 47% yield); R – R is benzo (**24**; **26**, 50%)

sodium, resulting in the synthesis of dihydrobenzo- (**25**) and naphthofurans (**26**) (Scheme 11).[57]

Treatment of 2-diethylaminomethyl-1-naphthol (**27**) with diazomethane or dimethylsulfoxonium methylide generated from trimethylsulfoxonium iodide gives rise to 2,3-dihydronaphtho[1,2-*b*]furan (**28**) (Scheme 12).[56] However, whereas the reaction of 2,5-bis(dimethylaminomethyl)-hydroquinone dimethiodide (**29**) with trimethylsulfoxonium iodide in the presence of NaH afforded tetrahydrobenzo[1,2-*b*:4,5-*b*′]difuran (**30**), no such reaction took place with diazomethane.

Scheme 12

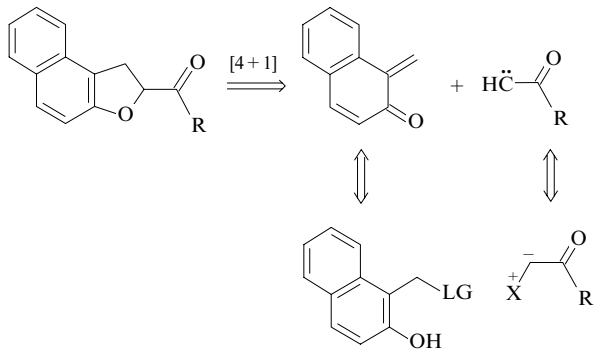


(*a*) CH_2N_2, 3 °C, 24 h (4% yield); (*b*) $Me_3\overset{+}{S}(O)\overset{-}{I}$, NaH, 60 °C, 16 h (53%)

Bladé-Font[58] investigated the reaction of colchicine derivative **31** with excess diazomethane. The author proposed several possible reaction mechanisms involving the corresponding *o*-QM (Scheme 13). One option includes conjugate addition of diazomethane to *o*-QM followed by intramolecular nucleophilic substitution. An alternative mechanism implies [2 + 1]-cycloaddition of the carbene generated from diazomethane at the exocyclic double bond of *o*-QM to give a spirocyclic adduct, which is stabilized *via* cyclopropane ring opening and rearrangement to a dihydrofuran system **32**.

Retrosynthetic analysis of 2-acyl-2,3-dihydronaphtho[2,1-*b*]furans indicates that these compounds can be prepared from *o*-QMs and acyl carbenes by formal [4 + 1]-cycloaddition (Scheme 14). Nitrogen or sulfur ylides, which are usually generated from the appropriate salts by the action of bases, can serve as synthetic equivalents (shown by double-headed arrows) of acyl carbenes.

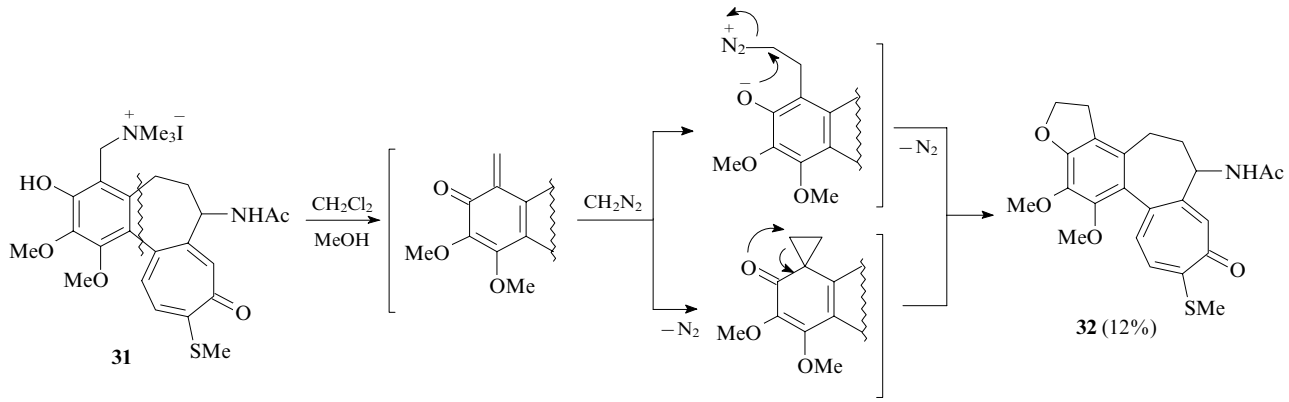
Scheme 14



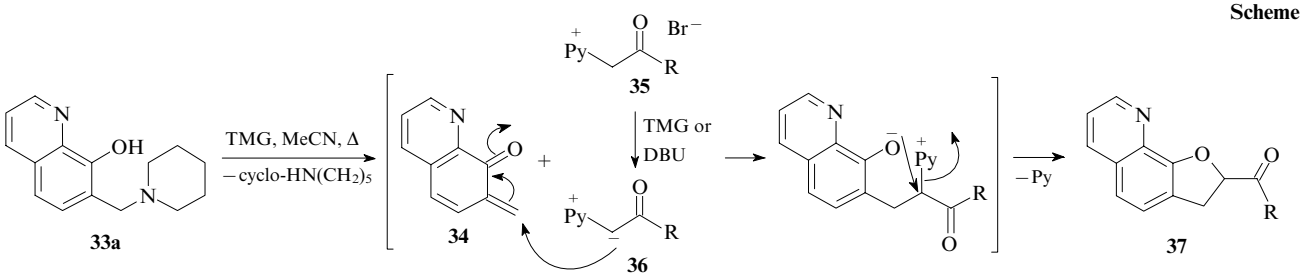
Carbonyl-stabilized pyridinium ylides can be utilized as 1,1-ambiphiles in the construction of *trans*-disubstituted dihydroarenofurans. The successful use of this approach was first illustrated in relation to 7-methylenequinolin-8-one (**34**) generated from 7-(piperidinomethyl)quinolin-8-ol (**33a**) (Scheme 15).[59] Pyridinium ylides **36** formed *in situ* from pyridinium salts **35** under the action of 1,1,3,3-tetramethylguanidine (TMG) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU) react with *o*-QM **34** according to Michael addition pathway; the subsequent intramolecular nucleophilic substitution gives rise to 2-acyl-2,3-dihydrofuro[3,2-*h*]-quinolines **37**.

Later this approach was extended to various *o*-QM precursors such as Mannich bases derived from 2-naphthol (**38**) and phenol (**39**), Mannich base methiodides (**23**), 2-hydroxybenzyl (salicyl) alcohol (**4b**, R^2 = H) and its

Scheme 13

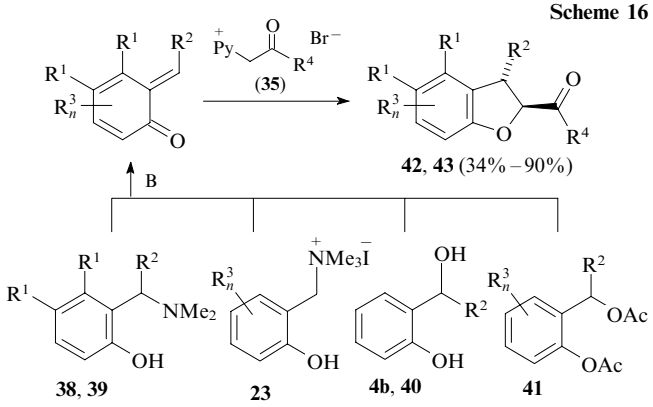


Scheme 15



R = 1-Ad (55% yield), Bu^t (42%), cyclo-C_3H_5 (34%); Ad is adamantyl, Py is pyridine

Scheme 16



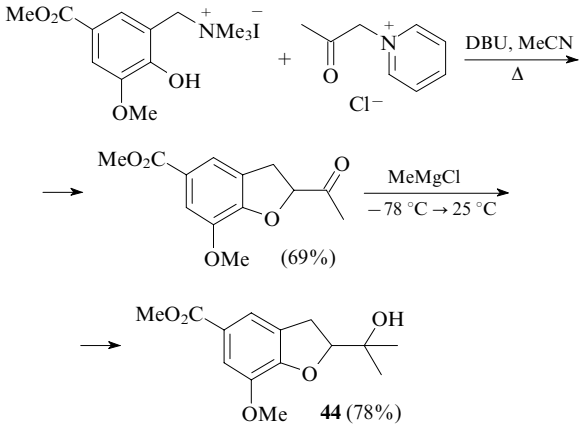
R^1–R^1 is benzo (**38**, **43**), R^1 = H (**39**, **42**); R^2 = H, Ar; R^3_n = H, 5-CHO, 5-NO_2, 5-CO_2Me, 6-CO_2Me, 5-Ac, 5,6-Me_2, 7-OMe, 5-Br, 6-Br; R^4 = Alk, Ar, NH_2; B is base

analogues **40** (R^2 = Alk, Ar), as well as their diacetates **41**.[60] The reactions diastereoselectively give dihydrobenzo- (**42**) and dihydronaphthofurans (**43**) (Scheme 16; here and below the positions of substituents in the product are indicated).

The developed method was successfully tested in the total synthesis of a natural product, (±)-7-methoxyanodendroate (**44**) (Scheme 17).[60]

Aryl methylides containing electron-withdrawing groups in the benzene ring can be utilized in this cascade reaction instead of carbonyl-stabilized pyridinium ylides (Scheme 18). The reaction of pyridinium salts **45** with compounds **38a**,**b** [R^2 = H (**a**), Ph (**b**)] gave 2-aryl-2,3-dihydronaphtho[2,1-*b*]furans **46a**–**c**, while using the appropriate heterocyclic precursors of *o*-QMs provided dihydrofurans **47** and **48**.[60]

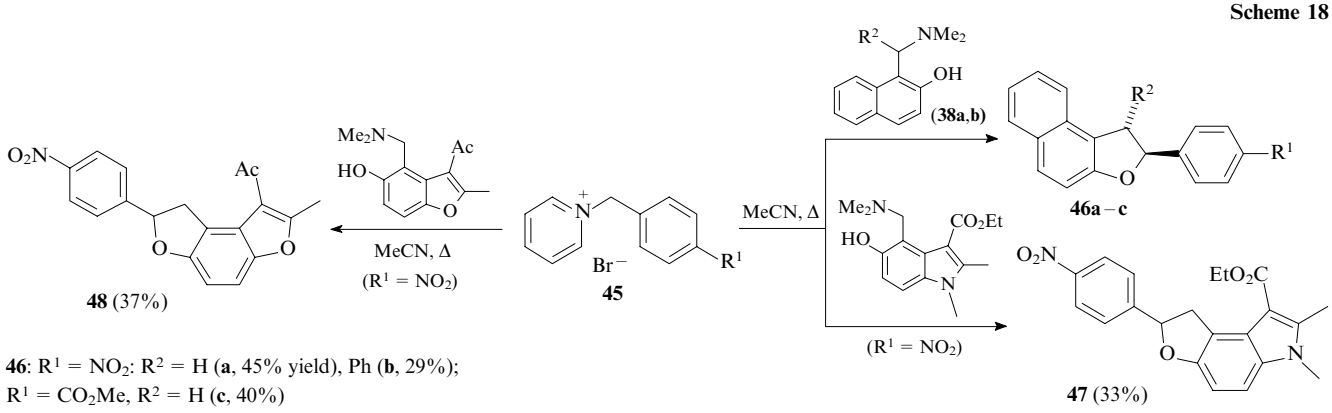
Scheme 17



Carbonyl-stabilized sulfur ylides, which can be both preformed and generated *in situ* from the appropriate sulfonium salts, can also function as efficient synthetic equivalents of acyl carbenes in the synthesis of *trans*-2,3-dihydrobenzofurans **42** (Scheme 19). Several more synthetic routes to substituted 2,3-dihydrobenzofurans have been developed, starting from 2-(1-tosylalkyl)phenols **49**,[61] *o*-alkylphenols **50** under oxidative conditions[62] (the presence of electron-donating groups in the *o*-QM precursor molecule is necessary) or [2-(bromomethyl)phenoxy](*tert*-butyl)dimethylsilane **51** with the participation of sulfur ylides **52**.[63] When dimethylsulfonium methylide was introduced in this reaction, 2-unsubstituted 2,3-dihydrobenzofurans were obtained.

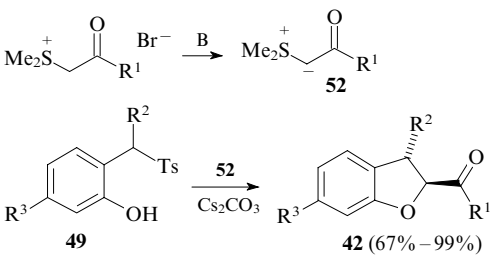
It is worth noting that a moderate enantioselectivity was attained when chiral sulfonium salt **53** was used in the synthesis of 2,3-dihydrobenzofuran **54** (Scheme 20).[63]

Scheme 18

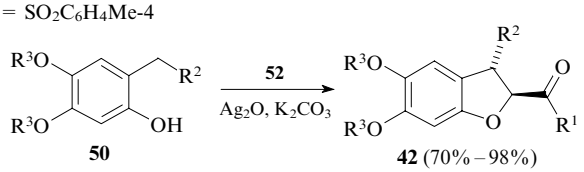


46: R^1 = NO_2: R^2 = H (**a**, 45% yield), Ph (**b**, 29%); R^1 = CO_2Me, R^2 = H (**c**, 40%)

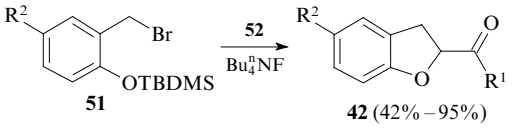
Scheme 19



R^1 = OEt, OMe, OBn, Ph, NEt_2; R^2 = Alk, Ar; R^3 = H, Br, OMe; Ts = $SO_2C_6H_4Me$-4



R^1 = OEt, OMe, Ph, NEt_2; R^2 = Ar, CH=CHPh; $R^3 - R^3$ = $(CH_2)_2$, CH_2



R^1 = Ar, Het, OEt, Ph, NH_2; R^2 = H, Br

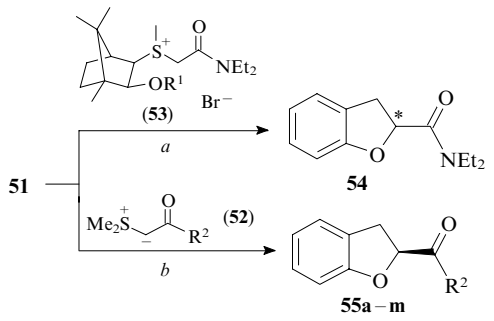
A high enantiomeric excess (*ee*) was attained in the synthesis of dihydrobenzofurans **55a – m** directly from carbonyl-stabilized sulfur ylides **52** in the presence of urea-based chiral catalyst **56**.[64]

It should be mentioned, however, that the use of carbonyl-stabilized sulfur ylides together with *o*-QM precursors in the synthesis of 2-acyl- or 2-aroyl-2,3-dihydrobenzofurans and 1,2-dihydronaphtho[2,1-*b*]furans was demonstrated by Cadona and Croce[65] back in 1976. This approach was also successfully used to prepare some other fused dihydrofurans,[66,67] including naturally occurring ones.[68,69]

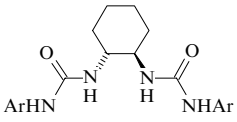
1,2a-Disubstituted tetrahydro-3*H*-cyclobuta[*c*]chromen-3-ones **57** and 1-substituted dihydrocyclopropa[*c*]chromen-2-ones **58** containing electron-withdrawing substituents in positions 2a and 1a react with dimethylsulfoxonium methylide to give tetrahydrodibenzo[*b*,*d*]furan-4-ols **59** and dihydro-1*H*-cyclopenta[*b*]benzofuran-3-ols **60**, respectively (Scheme 21).[70 – 72] Presumably, *o*-QMs are key intermediates in this rearrangement, higher yields being observed in the case of naphthoquinone methides ($R^2 - R^2$ is benzo).

An attempt to perform the Wittig reaction with 9,10-phenanthrenequinone (**61**) and benzylidenetriphenylphosphorane (**62a**) resulted in the isolation of *o*-QM **63a** as an unstable solid, which was rapidly converted to dimer **64** on

Scheme 20



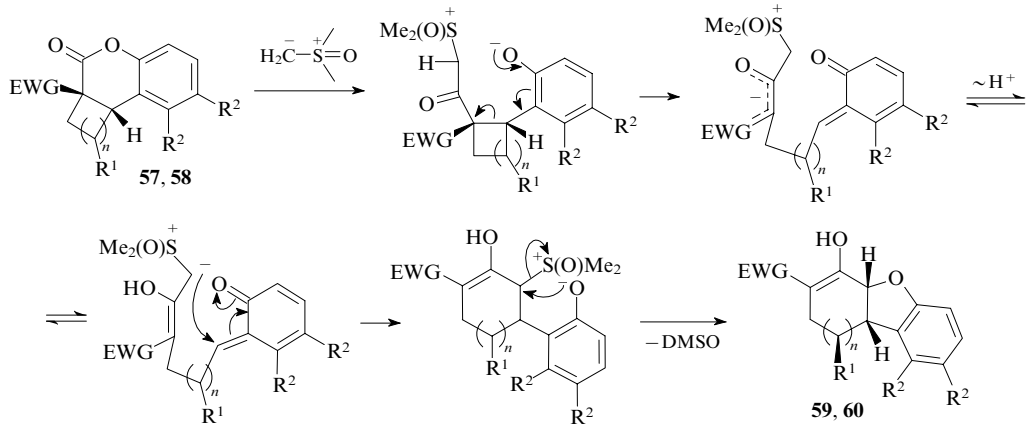
(*a*) Bu^n_4NF, Cs_2CO_3, CH_2Cl_2, rt;
(*b*) **56** (20 mol.%), CsF, 18-crown-6, PhMe, −20 °C;

56 =  [Ar = 3,5-$(CF_3)_2C_6H_3$];

R^1 = H (25% yield, 63% *ee*), Me (69%, 60% *ee*);
Th is thienyl, Fu is furyl

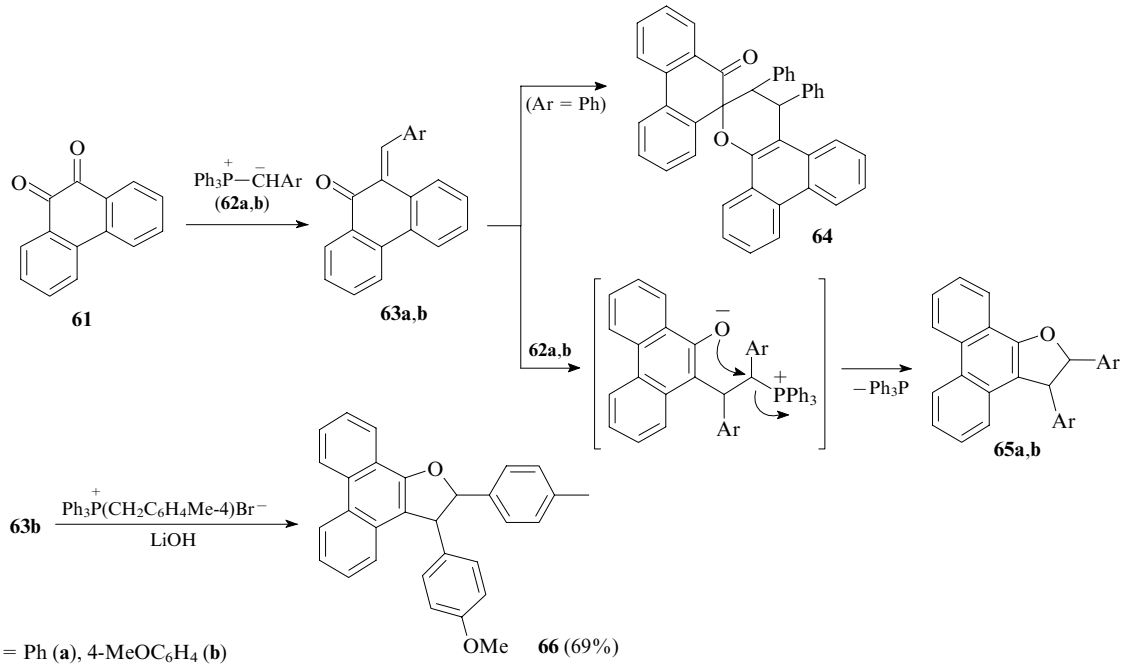
Compound **55**	R^2	Yield (%)	*ee* (%)
a	Ph	96	78
b	4-MeC_6H_4	95	78
c	4-$MeOC_6H_4$	93	66
d	4-FC_6H_4	96	66
e	4-ClC_6H_4	96	54
f	3-ClC_6H_4	98	68
g	3-BrC_6H_4	98	82
h	2,4-$F_2C_6H_3$	96	4
i	2-Th	97	46
j	2-Fu	70	44
k	Bu^t	98	50
l	PhCH=CH	70	40
m	Et_2N	90	50

Scheme 21



n = 1 (**57**; **59**, 21% – 93% yield), 0 (**58**; **60**, 26% – 89%); R^1 = Ar, Alk; R^2 = H, $R^2 - R^2$ is benzo; EWG = CO_2Alk, C(O)Ar, C(O)Alk, CN; EWG is an electron-withdrawing group

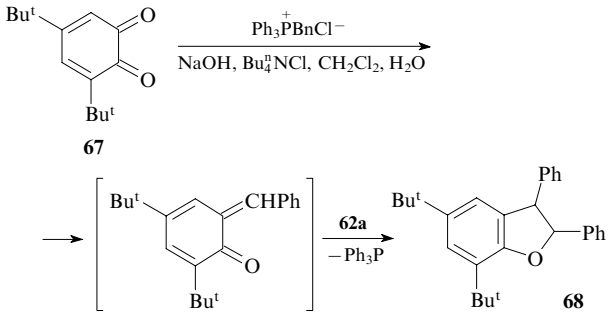
Scheme 22



heating (Scheme 22).[73] However, treatment of phenanthrenequinone **61** with excess phosphorane **62a** afforded 2,3-diphenyldihydrophenanthrofuran (**65a**) in 86% yield. A similar transformation was also observed in the case of 4-methoxybenzylidene(triphenyl)phosphorane (**62b**): keeping of an equimolar mixture of **62b** with *o*-QM **63b** (or a mixture of 9,10-phenanthrenequinone **61** and phosphorane **62b** in 1 : 2 ratio) for 5 days resulted in the isolation of *cis*-2,3-bis(4-methoxyphenyl)-2,3-dihydrophenanthro[9,10-*b*]furan (**65b**). Treatment of a mixture of *o*-QM **63b** and 4-methylbenzyl(triphenyl)phosphonium bromide with an aqueous solution of LiOH afforded compound **66** in 69% yield.[74]

Sterically hindered 3,5-di-*tert*-butyl-*o*-benzoquinone (**67**) reacts with benzylidenetriphenylphosphorane **62a**, generated *in situ* from the corresponding salt in a two-phase system, to also afford dihydrobenzofuran derivative **68** (Scheme 23).[75]

Scheme 23



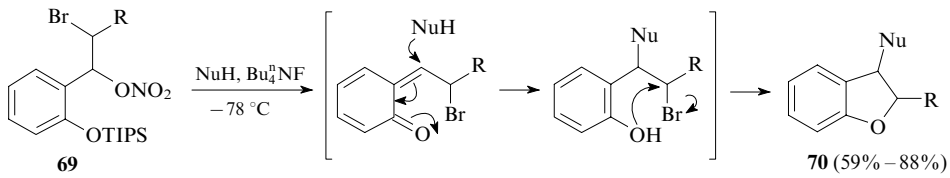
Shaikh and Varvounis [76, 77] developed a method for the synthesis of substituted 2,3-dihydrobenzofurans based on the generation of *o*-QMs from 2-bromo-1-[2-(triisopropylsilyloxy)phenyl]ethyl nitrates **69** on treatment with fluoride ions in the presence of various C-, N-, O- and S-nucleophiles (diethyl malonate, ethyl cyanoacetate, amines, alcohols, thiols, thiophenols, sodium azide) (Scheme 24). The reaction includes the Michael addition and intramolecular nucleophilic displacement of bromine to yield products **70**.

The reaction of 4-nitro-2-[(triethylammonio)methyl]-phenoxide (**71**) with 2-chloro-1,3-dicarbonyl compounds **72a–c** in the presence of triethylamine provided the synthesis of 5-nitro-2,3-dihydrobenzofurans **73a–c** (Scheme 25).[78]

Keeping aminal **74** and bromonitromethane in benzene at room temperature gives rise to 2-nitro-2,3-dihydronaphtho[1,2-*b*]furan **75**, which is then deaminated on heating to afford 2-nitronaphtho[1,2-*b*]furan **76** (Scheme 26).[79] A possible mechanism of formation of compound **75** includes the conjugate addition of the bromonitromethane anion to the generated 1,2-naphthoquinone-2-methide **77** followed by intramolecular nucleophilic substitution.

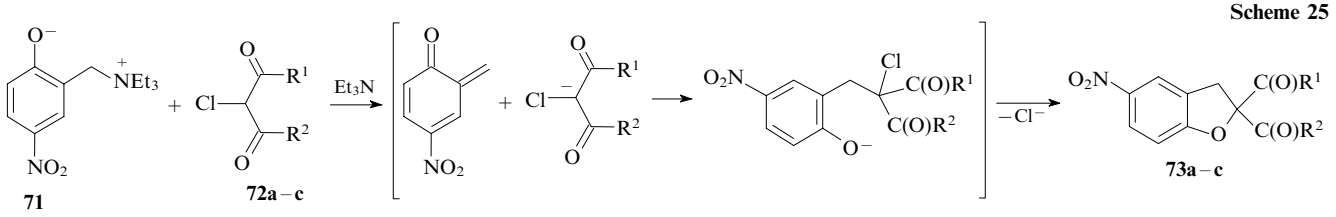
One more 1,1-ambiphilic reagent that can be used for the construction of 2-nitroarenofuran systems is potassium trinitromethanide.[80] In this case, *o*-QMs react with the trinitromethanide anion at the carbon atom as a soft

Scheme 24



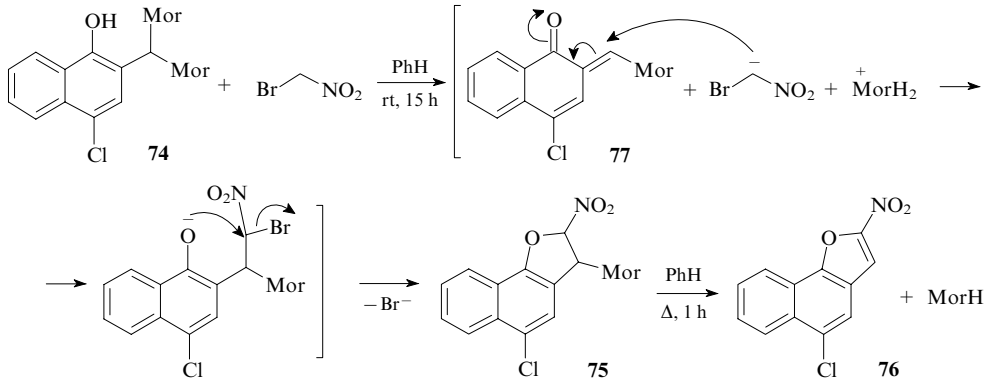
R = CO_2Et, H; NuH = cyclo-$HN(CH_2)_4$, 4-$MeOC_6H_4NH_2$, MeOH, Pr^iOH, EtSH, PhOH, PhSH, $HSCH_2CO_2Me$, $NCCH_2CO_2Et$, NaN_3; TIPS = $SiPr^i_3$

Scheme 25



R^1 = Me: R^2 = Me (**a**, 65% yield), OEt (**b**, 85%); $R^1 = R^2$ = OEt (**c**, 41%)

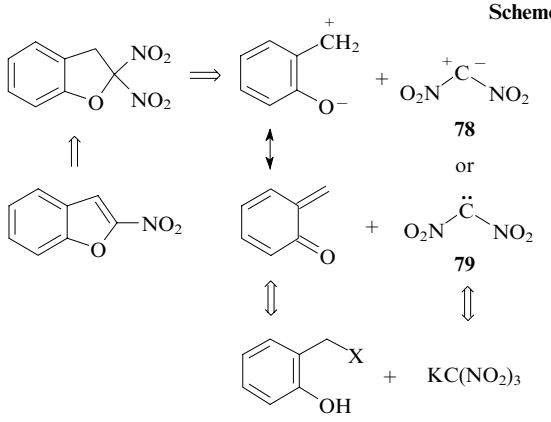
Scheme 26



Mor is morpholino

nucleophilic centre. Potassium trinitromethanide acts as a synthetic equivalent of 1,1-dipolar one-carbon synthon **78** or dinitrocarbene **79** (Scheme 27).

Scheme 27

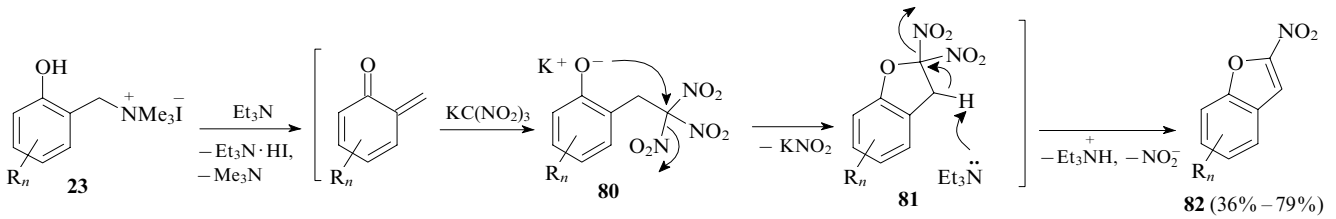


The reaction of Mannich base methiodides **23** (as *o*-QM precursors) with potassium trinitromethanide furnishes nitro-substituted benzofurans (Scheme 28). This is a cascade reaction, with the first step being the generation of *o*-QMs upon elimination of trimethylamine from quaternary salts; the subsequent Michael addition of the trinitromethanide anion gives rise to trinitromethyl derivatives **80**, which undergo 5-*exo*-*tet*-cyclization yielding 2,2-dinitro-2,3-dihydrobenzofurans **81**. The elimination of nitrous acid gives 2-nitrobenzofurans **82**. This reaction pathway is confirmed by the isolation of compounds **81a**,**b** and **83a**,**b** in the case where 2-chloromethylphenols are used as *o*-QM precursors.

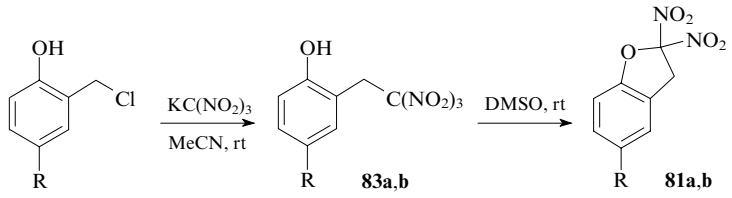
The reaction was also accomplished with some other precursors of *o*-QMs (Scheme 29).

Ashfeld's group [81] has shown that 1,2-dicarbonyl compounds **84** act as latent ambiphilic reagents in the presence of hexamethylphosphorous triamide and *o*-QMs (Scheme 30). The reaction of hexamethylphosphorous tri-

Scheme 28

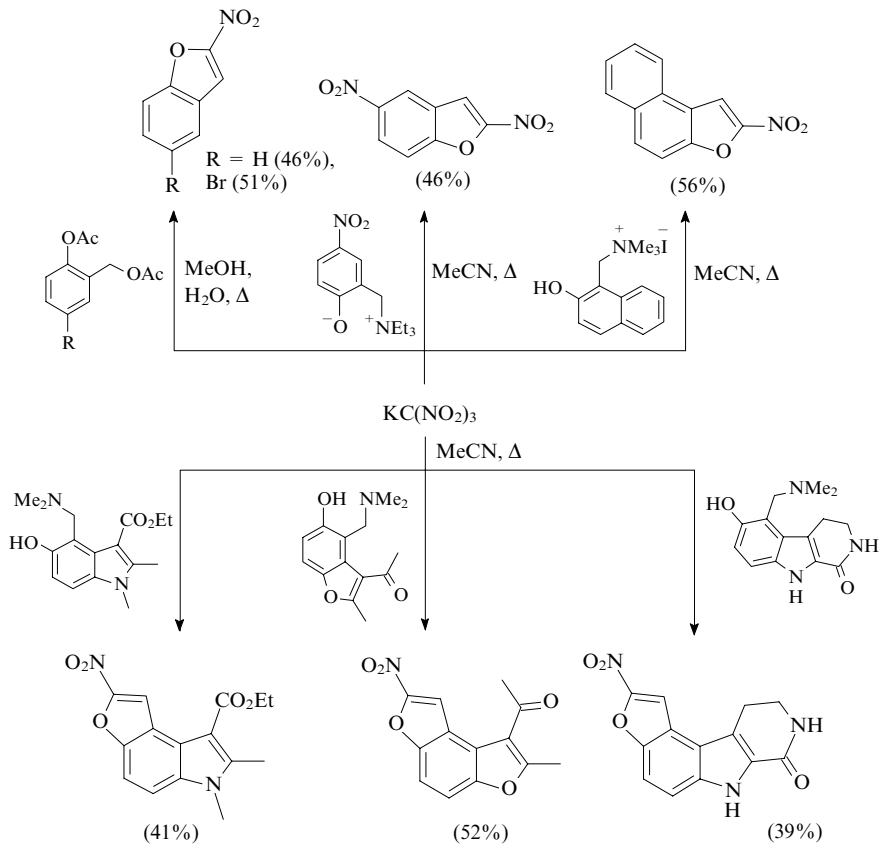


R_n = 5-Bn, 5-Ac, 5-CHO, 5-Cl, 5-NO_2, 5,6-Me_2, 5-CO_2Me, 6-CO_2Me, 5,7-Bu^t_2, 5-(1-Ad), 7-(1-Ad), 5-OMe, 7-OMe

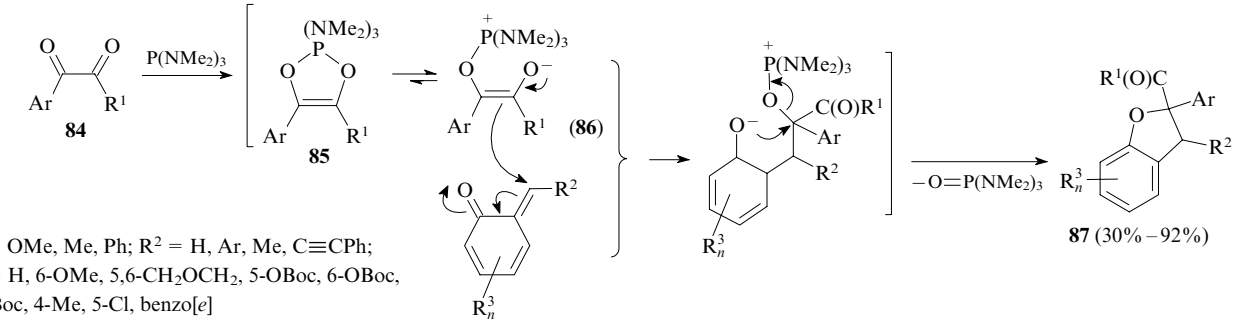


R = NO_2 (**81a**, 71% yield; **83a**, 50%), Ac (**81b**, 50%; **83b**, 43%)

Scheme 29



Scheme 30



R^1 = OMe, Me, Ph; R^2 = H, Ar, Me, C≡CPh;
R^3_n = H, 6-OMe, 5,6-CH_2OCH_2, 5-OBoc, 6-OBoc, 7-OBoc, 4-Me, 5-Cl, benzo[*e*]

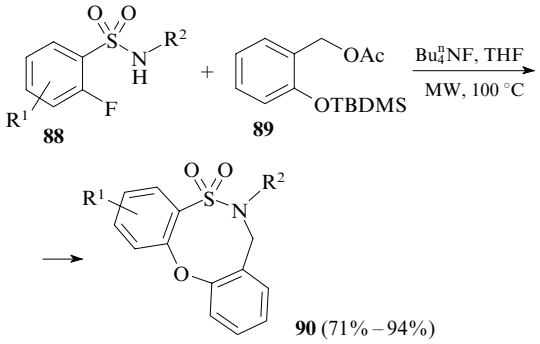
amide with compounds **84** involves the intermediate formation of dioxaphospholene **85** occurring in equilibrium with zwitter-ion form **86**, which then undergoes conjugate addition to *o*-QMs. The subsequent cyclization with elimination of phosphine oxide produces 2,3-dihydrobenzofurans **87**.

III.2. Michael reaction – nucleophilic substitution S_NAr (8-*exo-trig*-cyclization)

Microwave (MW) irradiation of *o*-fluorobenzenesulfonamides **88** and *o*-silyloxybenzyl acetate **89** in the presence of tetra-n-butylammonium fluoride generates the formal [4 + 4]-cycloaddition products — 6,7-dihydrodibenzo[*b*,*g*][1,4,5]oxathiazocine 5,5-dioxides **90** (Scheme 31).[33]

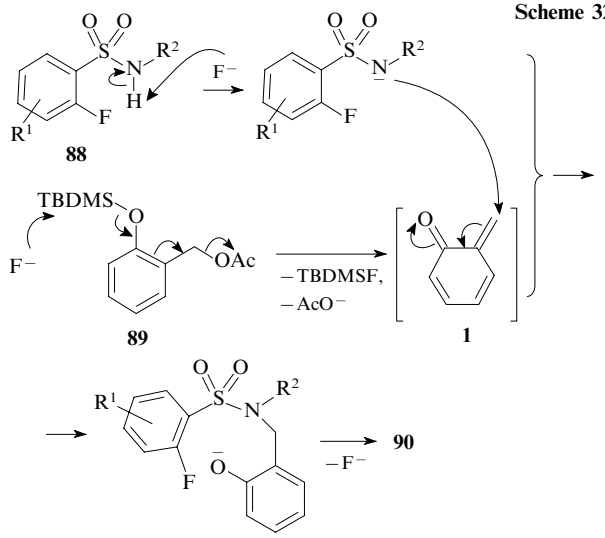
The reaction mechanism includes the following key steps: the generation of the sulfonamide anion, the formation of *o*-QM from *o*-silyloxybenzyl acetate **89** initiated by desilylation under the action of the fluoride ion, the subsequent 1,4-addition to the *o*-QM and intramolecular nucleophilic substitution proceeding *via* the formation of the Meisenheimer complex (Scheme 32).

Scheme 31



R^1 = H, 4-Br, 5-Cl; R^2 = Ar, Bu^n, Bu^i, cyclo-C_3H_5, $CH_2C{\equiv}CH$, All, $CH(Pr^i)CO_2Me$, $CH(Bu^i)CO_2Me$; All is allyl

Scheme 32

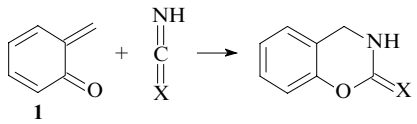


III.3. Michael reaction – 6-*exo-trig*- or 6-*exo-dig*-cyclization

III.3.a. Synthesis of 2*H*-1,3-benzoxazine-2-(thi)ones

2*H*-1,3-Benzoxazin-2-ones and -2-thiones are formally the products of addition of isocyanic or isothiocyanic acid to *o*-QM (Scheme 33).

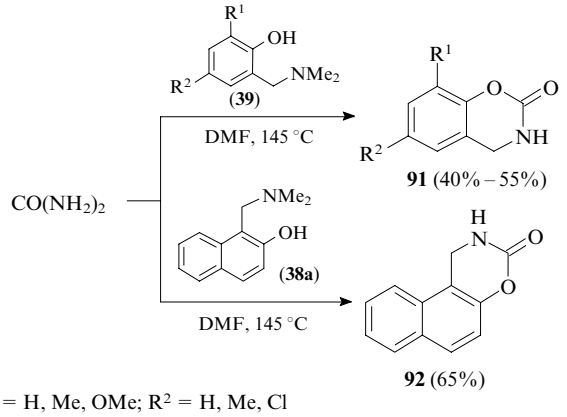
Scheme 33



X = O, S

Urea can serve as a synthetic equivalent of isocyanic acid. The condensation of urea with *o*-phenol (**39**) and naphthol (**38a**) Mannich bases in DMF yields 3,4-dihydro-2*H*-1,3-benzoxazin-2-ones **91** and 1,2-dihydro-3*H*-naphtho[1,2-*e*][1,3]oxazin-3-ones **92** (Scheme 34).[82]

Scheme 34

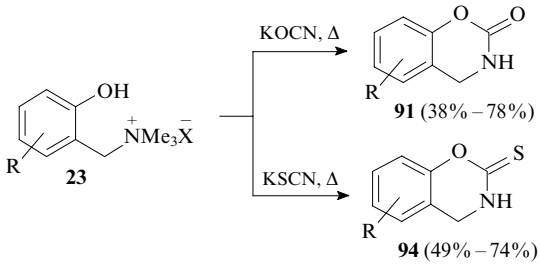


R^1 = H, Me, OMe; R^2 = H, Me, Cl

Presumably, thermolysis of Mannich base **39a** leads to generation of *o*-QM, which acts as a Michael acceptor in the reaction with urea. *N*-(*o*-Hydroxybenzyl)urea (**93**) formed intermediately undergoes 6-*exo-trig*-cyclization giving 1,3-benzoxazine **91** (Scheme 35).

Potassium cyanate can be used instead of urea, while Mannich bases can be replaced by their quaternary salts **23**. In the case of potassium cyanate, 3,4-dihydro-2*H*-1,3-benzoxazine-2-thiones **94** have been isolated (Scheme 36).[83,84] The reactions are carried out in aprotic polar solvents such as acetonitrile, nitromethane, butanone and 1,2-diethoxyethane.

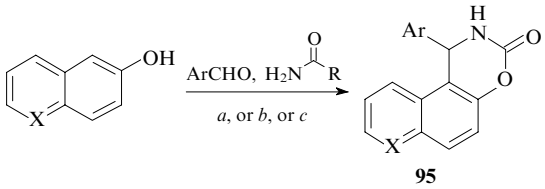
Scheme 36



R = 5-Me, 6-Me, 7-Me, 6-Cl, 7-Cl; X = I, $MeOSO_3$

The three-component condensation of 2-naphthol, aromatic aldehydes and urea or methyl carbamate carried out under various conditions results in 1,2-dihydronaphthoxazin-3-ones **95** (Scheme 37).[85–90] Instead of 2-naphthol, the reaction has also been carried out with 1-naphthol,[89] 6-hydroxyquinoline and dibenzofuran-2-ol.[91]

Scheme 37



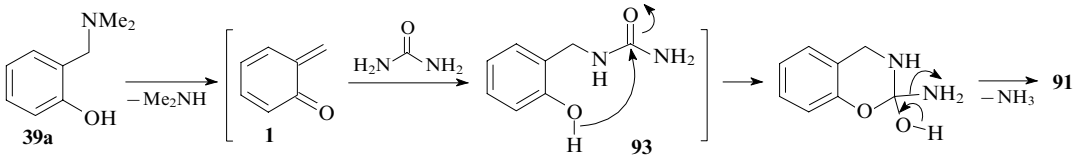
(*a*) for X = CH, R = OMe: I_2, 80 °C (90 – 96% yield);
(*b*) for X = CH, R = NH_2: TsOH (58% – 64%) or MW (69% – 82%);
(*c*) for X = CH, N; R = OMe: H_2O, Et_3BnNF, 80 °C (74% – 85%)

III.3.b. Synthesis of azolobenzoxazines

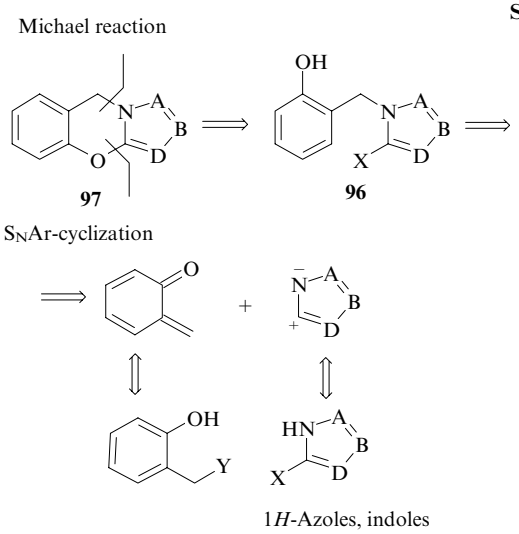
If a good leaving group is present in the nucleophilic agent molecule, the Michael adducts **96** formed initially can be further cyclized to afford benzannulated fused heterocyclic systems **97**. This type of cascade transformations involving *o*-QMs and consisting of the aza-Michael reaction and subsequent intramolecular nucleophilic substitution has been described in relation to a variety of 1*H*-azoles and indoles (Scheme 38).[92] The latter can be considered as 1,2-heteroambiphiles in reactions with *o*-QMs.

The use of 3,5-dibromo- and 3-chloro-1,2,4-triazoles as Michael donors in reactions with various *o*-QM precursors allows the preparation of 1,2,4-triazolo[5,1-*b*][1,3]benzoxazines **98a – m** (Scheme 39, Table 1).[93,94] Compounds used to generate *o*-QMs in this reaction include phenolic Mannich

Scheme 35

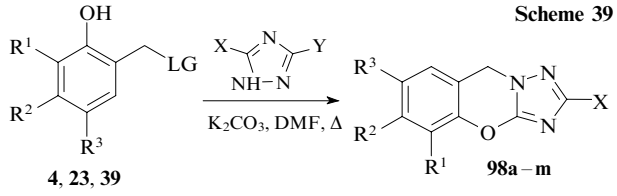


Scheme 38



A, B, D = N, CH; D = CH, A═B is benzo;
X = Cl, Br, SMe; Y = OH, NMe_2, NMe_3I

Scheme 39



bases [for example, **39b** ($R^1 = R^3 = Bu^t$, $R^2 = H$)], their quaternary salts (**23**) and salicyl alcohols [for example, **4b**,**c** ($R^2 = R^3 = H$: $R^1 = H$ (**b**), OMe (**c**)].

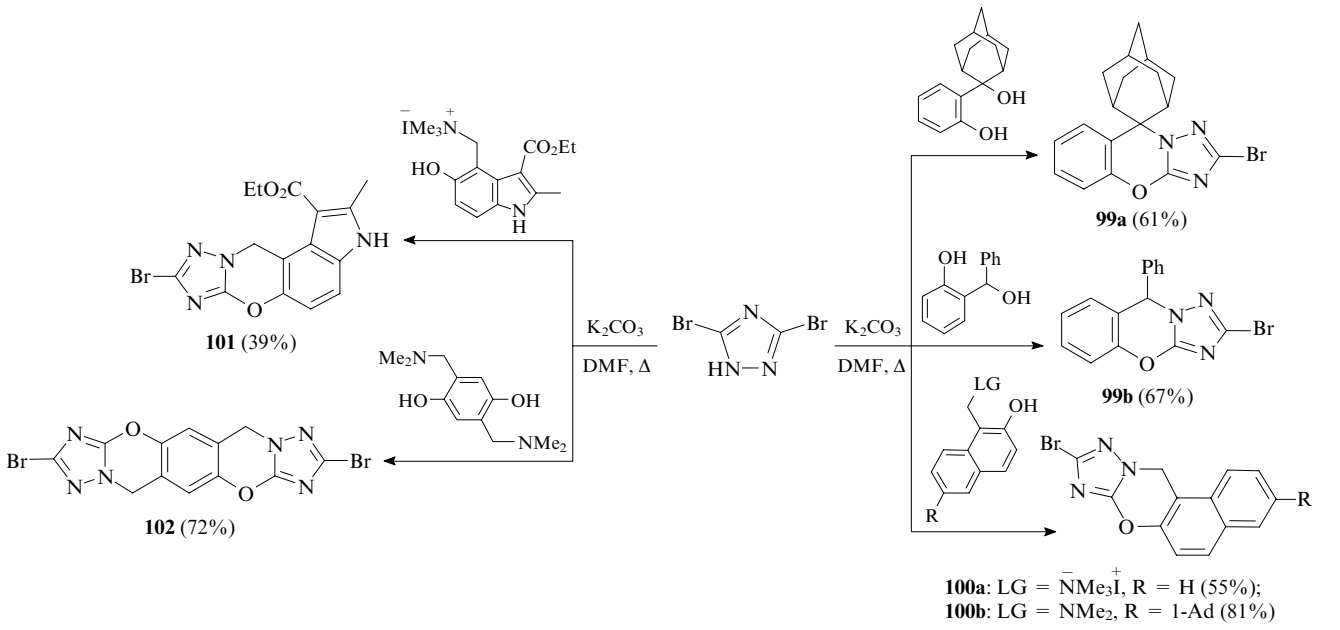
This reaction is general, it can be performed for salicyl alcohols with bulky substituents at the exocyclic carbon atom (see the preparation of compounds **99a**,**b** in Scheme 40). It is also applicable to the preparation of more complex heterocyclic systems such as naphthalene (**100**), indole (**101**) and bis(triazoloxazino)benzene (**102**) derivatives.[92, 94, 95]

Table 1. Synthesis of 1,2,4-triazolo[5,1-*b*][1,3]benzoxazines **98a**–**m** (see Scheme 39).

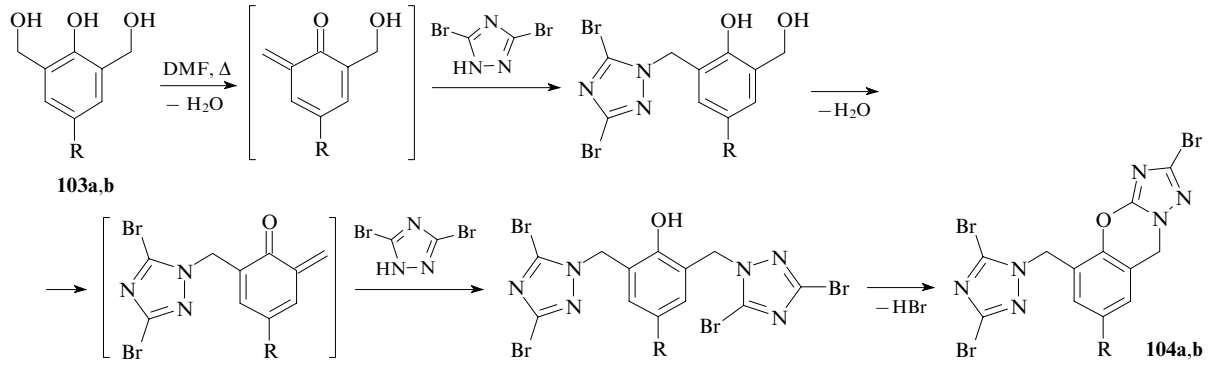
Compound **98**	R^1	R^2	R^3	X	Y	LG	Yield (%)	Ref.
a	Bu^t	H	Bu^t	Br	Br	NMe_2	47	94
b	H	Me	Me	Br	Br	NMe_3I	82	94
c	H	H	Bu^t	Br	Br	NMe_3I	77	94
d	H	H	Bn	Br	Br	NMe_3I	69	94
e	H	H	1-Ad	Br	Br	NMe_3I	80	94
f	H	H	CO_2Me	Br	Br	NMe_3I	24	94
g	H	H	OMe	Br	Br	NMe_3I	72	94
h	1-Ad	H	Me	Br	Br	NMe_3I	84	94
i	2-Ad	H	H	Br	Br	NMe_3I	79	94
j	1-Ad	H	Me	H	Cl	NMe_3I	70	94
k	H	H	H	Br	Br	OH	84	93
l	H	H	H	H	Cl	OH	87	93
m	OMe	H	H	Br	Br	OH	71	94

The cyclization is facilitated by the presence of K_2CO_3 in the reaction mixture. The reactions of 3,5-dibromo-1,2,4-triazole and 2,6-bis(hydroxymethyl)phenols **103a**,**b** in the absence of a base afford 2-bromo-5-[(3,5-dibromo-1*H*-1,2,4-triazol-1-ylmethyl]-9*H*-[1,2,4]triazolo[5,1-*b*][1,3]benzoxazines **104a**,**b** as a result of tandem generation of *o*-QMs (Scheme 41).[92, 94] This transformation is a domino process including five steps (two dehydrations, two Michael additions and one nucleophilic substitution). The reaction can be accomplished under milder conditions if 4-nitro-2-[(triethylammonio)methyl]phenolate (**71**) is used as the precursor for *o*-QM **105** (Scheme 42).[92, 94] It is noteworthy that this compound is one of the best precursors for the highly electrophilic nitro-substituted *o*-QM. The reaction gave heterocycle **106**. The reactions of salicyl alcohols[92, 96] and naphthol Mannich bases[97] with 3,4,5-tribromopyrazole afforded benzo[*e*]pyrazolo[5,1-*b*][1,3]oxazines **107a**–**d** and naphtho[1,2-*e*]pyrazolo[5,1-*b*][1,3]oxazines **108a**–**c** in up to 85% yields (Scheme 43). On heating of an equimolar

Scheme 40

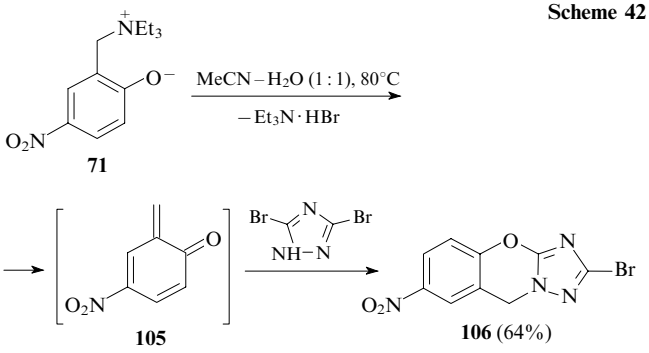


Scheme 41

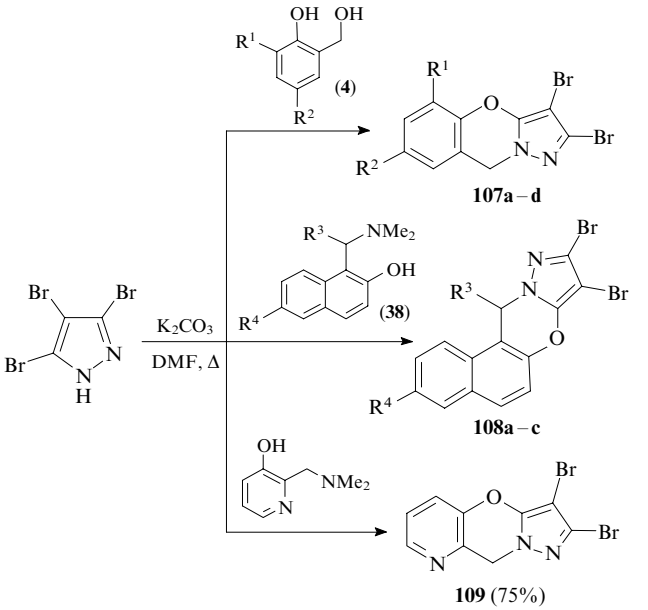


R = Cl (**a**, 55% yield), Bu^t (**b**, 65%)

Scheme 42



Scheme 43



Compound **107**	R^1	R^2	Yield (%)
a	H	H	82
b	H	Br	85
c	Br	1-Ad	53
d	CH_2OH	OMe	65

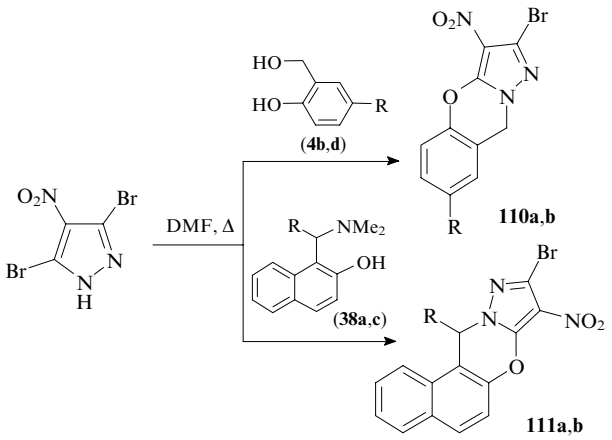
Compound **108**	R^3	R^4	Yield (%)
a	H	H	68
b	H	1-Ad	55
c	4-$MeOC_6H_4$	H	70

mixture of 3,4,5-tribromopyrazole and 3-hydroxy-2-(dimethylaminomethyl)pyridine, 9*H*-pyrazolo[5,1-*b*]pyrido[2,3-*e*][1,3]-oxazines **109** are formed.[92] The presence of K_2CO_3, first, increases the pyrazole nucleophilicity as a result of deprotonation and, second, accelerates the transformation of the intermediate 2-(3,4,5-tribromo-1*H*-pyrazol-1-ylmethyl)phenols and -naphthols into pyrazolo[5,1-*b*][1,3]oxazines.

Benzo[1,2-*e*]- (**110a**,**b**) and 12*H*-naphtho[1,2-*e*]pyrazolo[5,1-*b*][1,3]oxazines (**111a**,**b**) were prepared by the reaction of 3,5-dibromo-4-nitropyrazole with salicyl alcohols **4b**,**d** [R = H (**b**), Br (**d**)] or Mannich bases derived from 2-naphthol **38a**,**c** [R = H (**a**), 4-$MeOC_6H_4$ (**c**)], respectively (Scheme 44).[92,94] In this case, heterocyclization does not require a base, as the nitro group present in the pyrazole moiety substantially increases the nucleophilic mobility of bromine atoms.

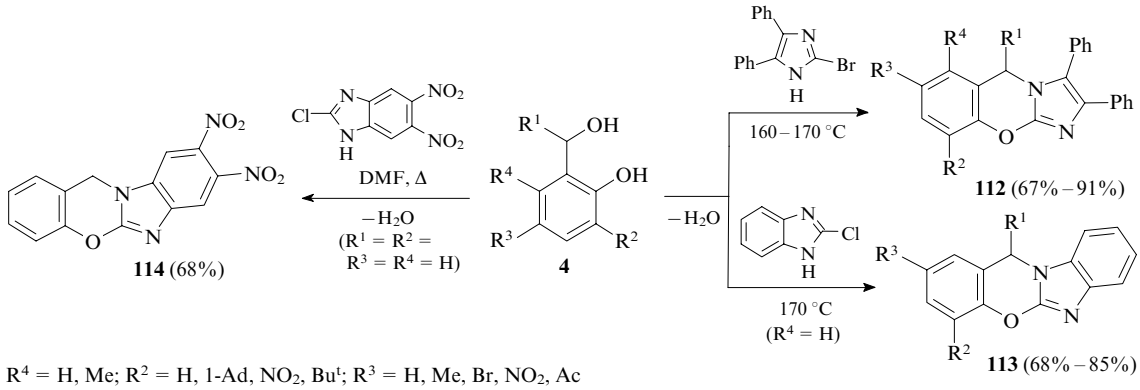
Like in the case of 1,2,4-triazole and pyrazole derivatives, if an appropriate substituent is present in the α position to the NH group of (benz)imidazole, intramolecular heterocyclization of the intermediate 2-[(benz)imidazol-1-ylalkyl]phenols is possible (Scheme 45). 5*H*-Imidazo[2,1-*b*][1,3]benzoxazines **112** were synthesized by the reaction of 2-bromo-4,5-diphenylimidazole with salicyl alcohols **4**, while a number of 12*H*-benzimidazo[2,1-*b*][1,3]benzoxazines **113** were obtained using 2-chlorobenzimidazole. Heating of 2-chloro-5,6-dinitrobenzimidazole with salicyl

Scheme 44



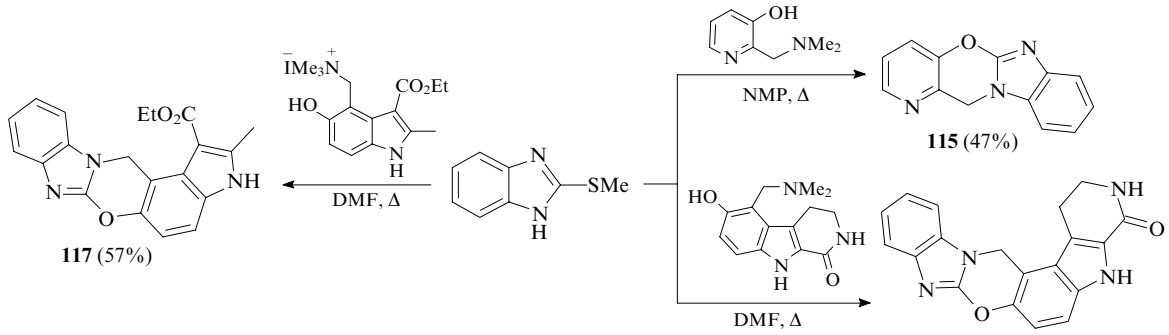
110: R = H (**a**, 80% yield), Br (**b**, 75%); **111**: R = H (**a**, 65%), 4-$MeOC_6H_4$ (**b**, 53%)

Scheme 45



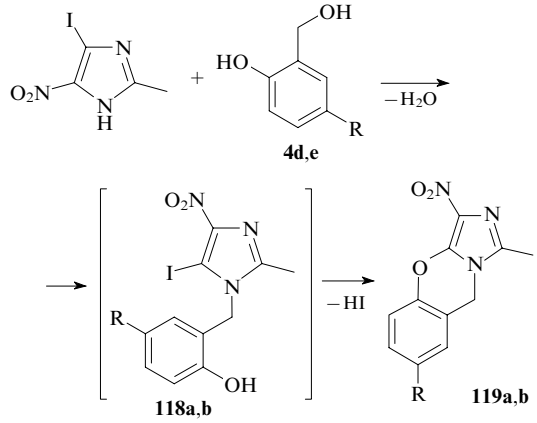
R^1, R^4 = H, Me; R^2 = H, 1-Ad, NO_2, Bu^t; R^3 = H, Me, Br, NO_2, Ac

Scheme 46



NMP is *N*-methyl-2-pyrrolidone

Scheme 47



R = Br (**4d**; **118a**; **119a**, 66% yield), NO_2 (**4e**; **118b**; **119b**, 51%)

alcohol gives rise to 8,9-dinitro-12*H*-benzimidazo[2,1-*b*][1,3]benzoxazine **114** in a moderate yield.[98–100]

2-(Methylthio)benzimidazole was found to be suitable, along with 2-chlorobenzimidazole, for the construction of benzimidazobenzoxazines **113** mentioned above and more complex heterocycles **115**–**117** (Scheme 46).[92, 101, 102]

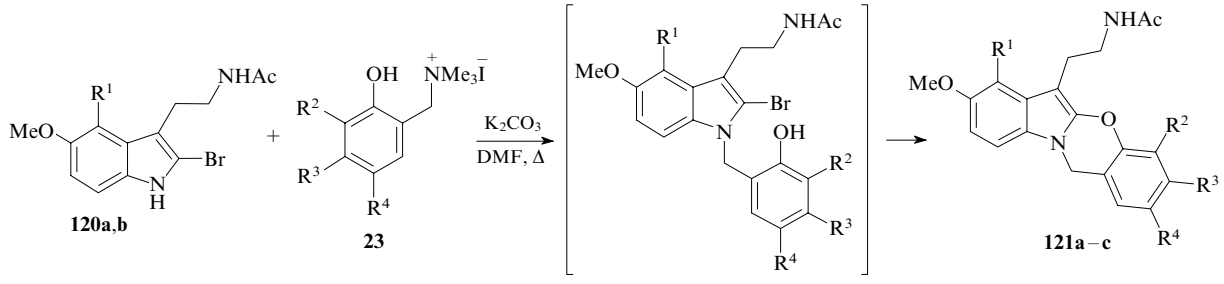
4-Iodo-2-methyl-5-nitroimidazole reacts with substituted salicyl alcohols **4d**,**e** to give addition products **118a**,**b**, which are converted to 9*H*-imidazo[5,1-*b*][1,3]benzoxazines **119a**,**b** (Scheme 47).[103]

The reactions of 2-bromo- and 2,4-dibromomelatonins **120a**,**b** with 2-(dimethylaminomethyl)phenol methiodides **23** afford substituted indolo[2,1-*b*][1,3]benzoxazines **121a**–**c** (Scheme 48).[104]

III.3.c. Reactions with CH acids

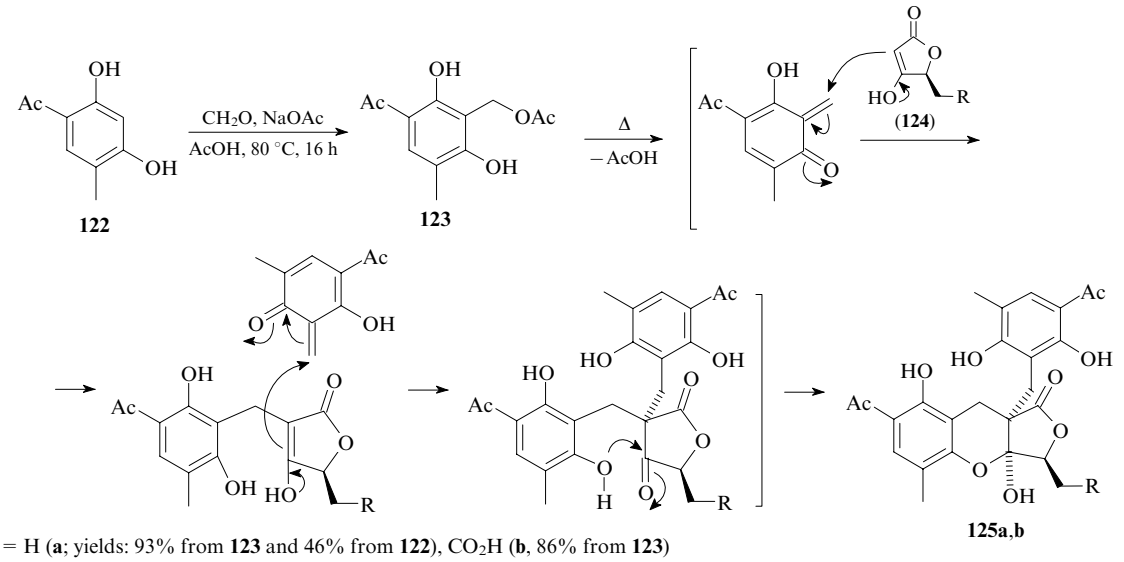
Trapping of *o*-QMs with CH-acids (1,3-dicarbonyl compounds, methylene-active nitriles and so on) is an efficient approach to the synthesis of substituted chromans and chromenes. The reactions of *o*-QMs with enamines derived from 1,3-dicarbonyl compounds functioning as 1,2-ambiphilic reagents are also considered in this Section.

Scheme 48



120: R^1 = H (**a**), Br (**b**); **121**: R^1 = R^2 = R^3 = H, R^4 = OMe (**a**, 54% yield); R^1 = Br, R^4 = Me: R^2 = H, R^3 = Me (**b**, 43%); R^2 = 1-Ad, R^3 = H (**c**, 63%)

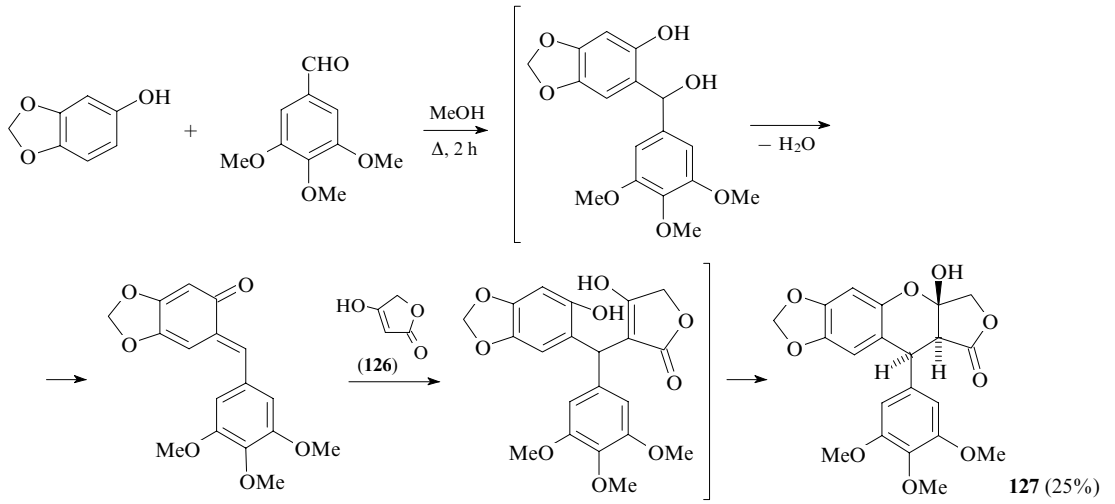
Scheme 49



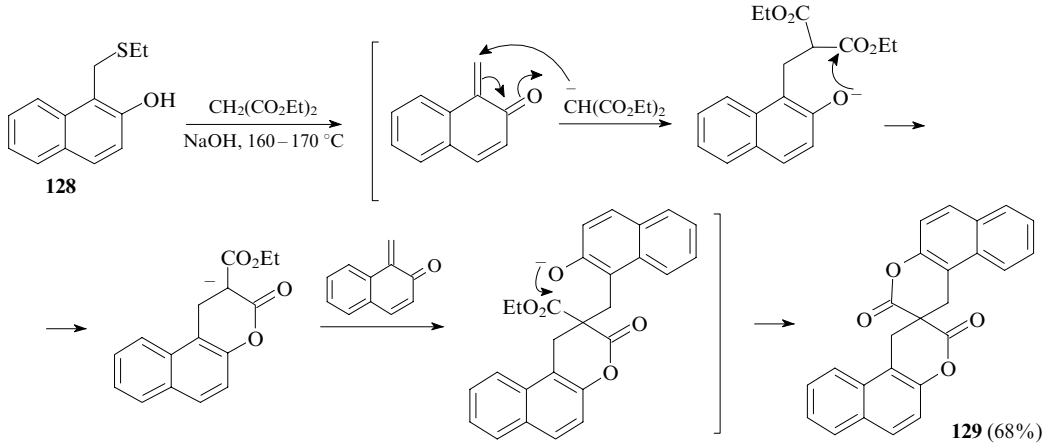
R = H (**a**; yields: 93% from **123** and 46% from **122**), CO_2H (**b**, 86% from **123**)

Spence and George [105] described the total synthesis of unusual naturally occurring polyketides from resorcinol derivative **122**. The multicomponent cascade reaction of resorcinol derivative **123**, generated from compound **122** and formaldehyde, with substituted tetronic acid **124** results in the synthesis of *ent*-penilactone A (**125a**) and penilactone B (**125b**) (Scheme 49). This process, which comprises the formation of four C – C bonds, one C – O bond and two stereo centres, includes phenol hydroxymethylation, alcohol esterification, two Michael additions and, finally, heterocyclization, which occurs *via* nucleophilic addition to the carbonyl group (formation of a hemiketal). The *o*-QM

Scheme 50



Scheme 51



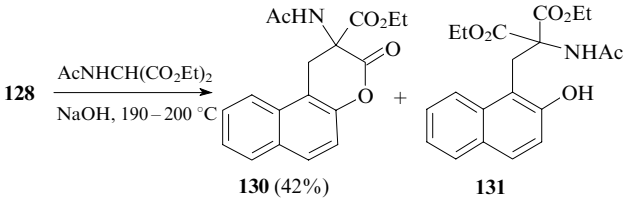
precursor formation step can be combined with the subsequent reactions, the synthesis being conducted in refluxing toluene.

The condensation of 3,4,5-trimethoxybenzaldehyde, 3,4-methylenedioxyphenol and tetronic acid **126** (Scheme 50) affords hydroxylactone **127**.[106] It is noteworthy that this reaction could not be carried out with other aromatic aldehydes.

On heating of 1-ethylthiomethyl-2-naphthol (**128**) with excess diethyl malonate, spirocyclic benzocoumarin **129** was prepared (Scheme 51).[107] The reaction includes two successive 1,4-addition and 6-*exo*-*trig*-cyclization cascades.

Under similar conditions, diethyl acetamidomalonate is converted to lactone **130**, which is formed as a mixture with 2-hydroxy-1-naphthylmethyl acetamidomalonate **131** in 3 : 1 ratio (Scheme 52).[107]

Scheme 52



130 (42%) **131**

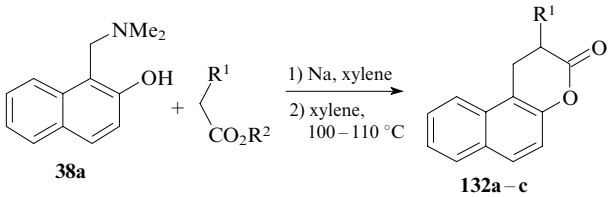
1-(Dimethylaminomethyl)-2-naphthol (**38a**) was also reacted with various CH-acids to give benzochromanones **132a–c**.[108–110] Katritzky and co-workers[111] demonstrated the possibility of using benzotriazole as the leaving group in the generation of *o*-QM from compound **133**, which reacts with dimethyl methylmalonate to give chroman **134** (Scheme 53).

The reaction of Mannich base **38a** with diethyl malonate was extended to some other β-dicarbonyl compounds; this resulted in the synthesis of heterocycles **135–137**; benzocoumarin **129** was prepared from **138** (Scheme 54).[112, 113]

o-Quinone methides generated by treatment of salicyl alcohols **40** with calcium trifluoromethylsulfonate (triflate, OTf) in the presence of tetra-n-butylammonium hexafluorophosphate react with various CH-acids to give products **139**, **140** or **141a**,**b**. An important feature of these processes is that they can be conducted in water[114] or without a solvent or catalyst with microwave activation (Scheme 55).[115]

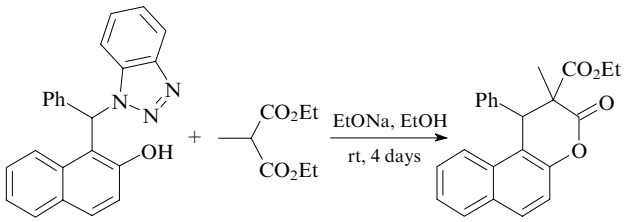
A similar reaction with naphthols resulted in the synthesis of benzoxanthenes **142**, **143**.

Scheme 53



38a **132a–c**

R^2 = Et: R^1 = CO_2Et (**a**, 78% yield), CN (**c**, 85%);
R^1 = CO_2Bn, R^2 = Bn (**b**, 62%)



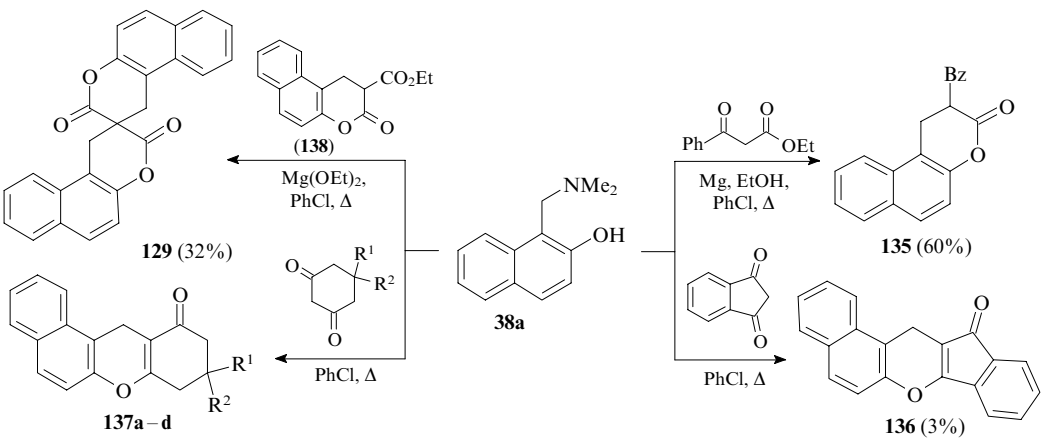
133 **134** (56%)

On treatment of 2-phenyl-4*H*-benzo[*d*][1,3,2]dioxaborinine **144** with diethyl malonate in the presence of $TiCl_4$, dihydrocoumarin **145** was isolated (Scheme 56).[116]

Monosubstituted isopropylidene malonates **146a–c** react with 1-(dimethylaminomethyl)-2-naphthol (**38a**) in the presence of acetic anhydride giving rise to benzo[*f*]-chromenones **147a–c** (Scheme 57),[117] which are structural analogues of splitomicin (R = H) modulating the histone deacetylase (HDAC) activity.[118]

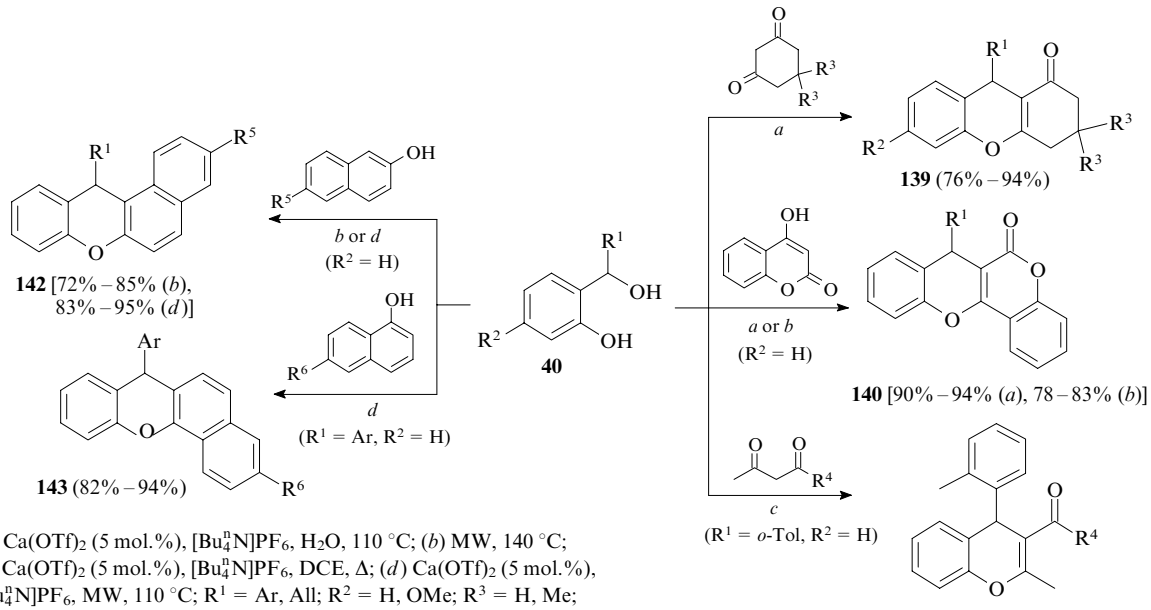
Recently, on the basis of reactions of *o*-hydroxystyrenes **148** and azlactones **149**, a method for the synthesis of chiral dihydrocoumarins **150** has been developed (Scheme 58).[119] Chiral phosphoric acid **151** and chiral guanidine **152** (a base) as catalysts provide high stereoselectivity of the reaction (*ee* up to 92%). Apparently, the action of chiral guanidine induces the formation of enolyzed azlactone, which undergoes Michael addition to *o*-QM, generated from hydroxystyrene under the action of chiral phosphoric acid. The subsequent 6-*exo*-*trig*-cyclization and opening of the intermediate thus formed afford dihydrocoumarins **150** in high yields. However, when R^1 is changed from methyl to the ethyl group, the product yield decreases. Furthermore, dihydrocoumarins are nor formed if R^1 = H or Bn and if azlactone contains non-aromatic substituents (R^3 = Me, Bn). Chen and co-workers[120] showed that *o*-hydroxybenzyl

Scheme 54



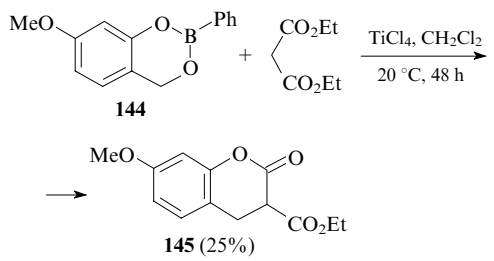
R^1 = R^2 = H (**a**, 61% yield), Me (**b**, 55%); R^1 = H: R^2 = Me (**c**, 30%), Ph (**d**, 26%)

Scheme 55

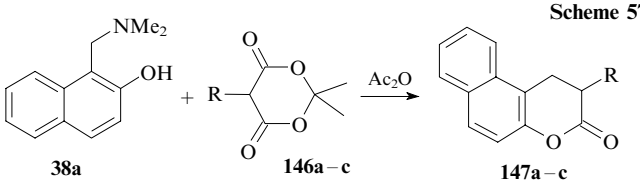


(*a*) $Ca(OTf)_2$ (5 mol.%), $[Bu^n_4N]PF_6$, H_2O, 110 °C; (*b*) MW, 140 °C; (*c*) $Ca(OTf)_2$ (5 mol.%), $[Bu^n_4N]PF_6$, DCE, Δ; (*d*) $Ca(OTf)_2$ (5 mol.%), $[Bu^n_4N]PF_6$, MW, 110 °C; R^1 = Ar, All; R^2 = H, OMe; R^3 = H, Me; R^4 = Me (**a**), OEt (**b**); R^5 = H, Br; R^6 = H, OMe; DCE is 1,2-dichloroethane; *o*-Tol = 2-MeC_6H_4

Scheme 56



Scheme 57

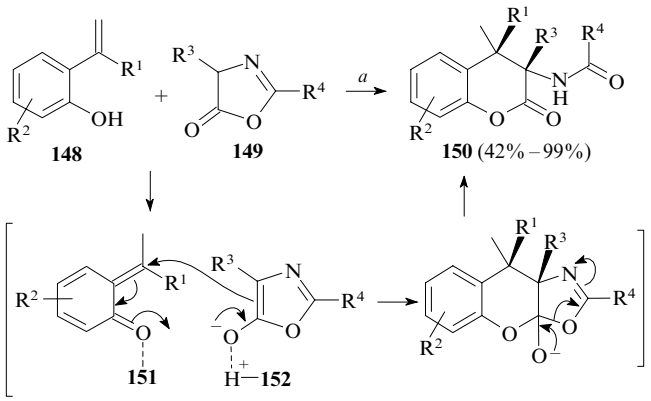


146, **147**: R = Me (**a**, 74% yield), Et (**b**, 89%), Ph (**c**, 71%)

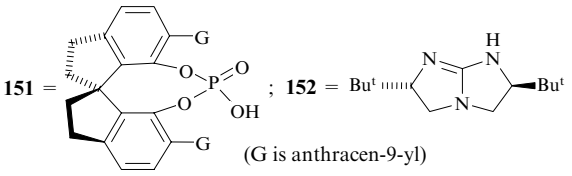
alcohols can also serve as *o*-QM precursors in the reactions with azlactones.

A related reaction of *o*-QMs generated from 2-(1-tosylalkyl)phenols **153** under the action of bases with 5-substituted 2(3*H*)-furanones **154** leads to 3,4-dihydrocoumarins

Scheme 58

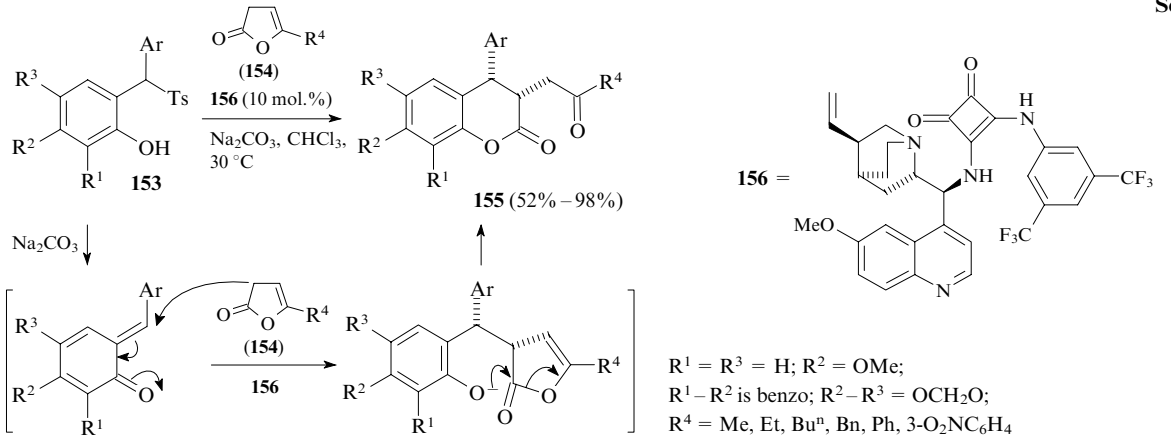


(*a*) **151** (20 mol.%), **152** (10 mol.%), $MgSO_4$, PhMe; R^1 = Me, Et; R^2 = H, 6-F, 6-Cl, 6-Br, 6-Me, 6-OEt, 6-OMe, 7-F; R^3, R^4 = Ar;



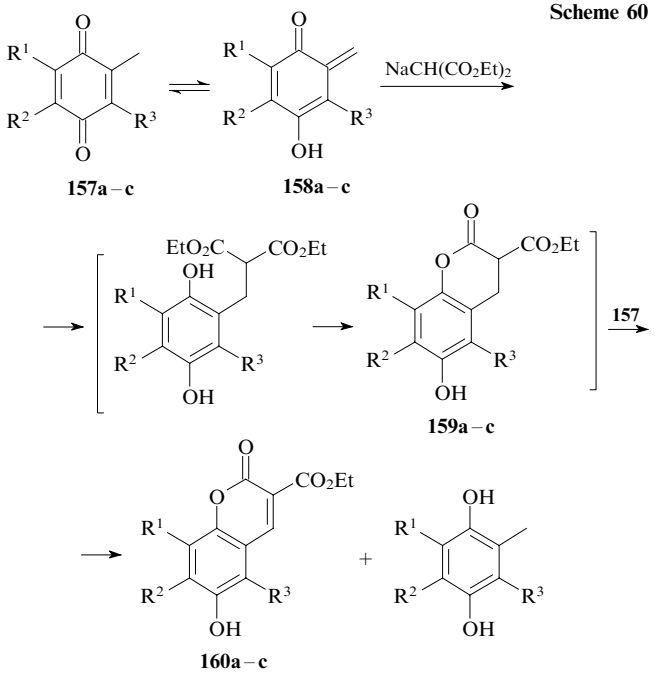
(G is anthracen-9-yl)

Scheme 59



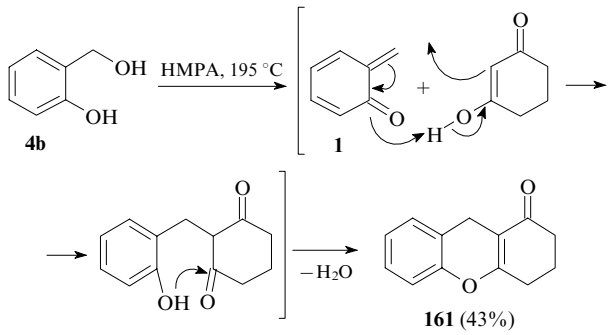
R^1 = R^3 = H; R^2 = OMe;
R^1 – R^2 is benzo; R^2 – R^3 = OCH_2O;
R^4 = Me, Et, Bu^n, Bn, Ph, 3-$O_2NC_6H_4$

Scheme 60



R^1 = Me, R^3 = Br: R^2 = Me (**a**), Br (**b**); R^1–R^2 is benzo, R^3 = Me (**c**)

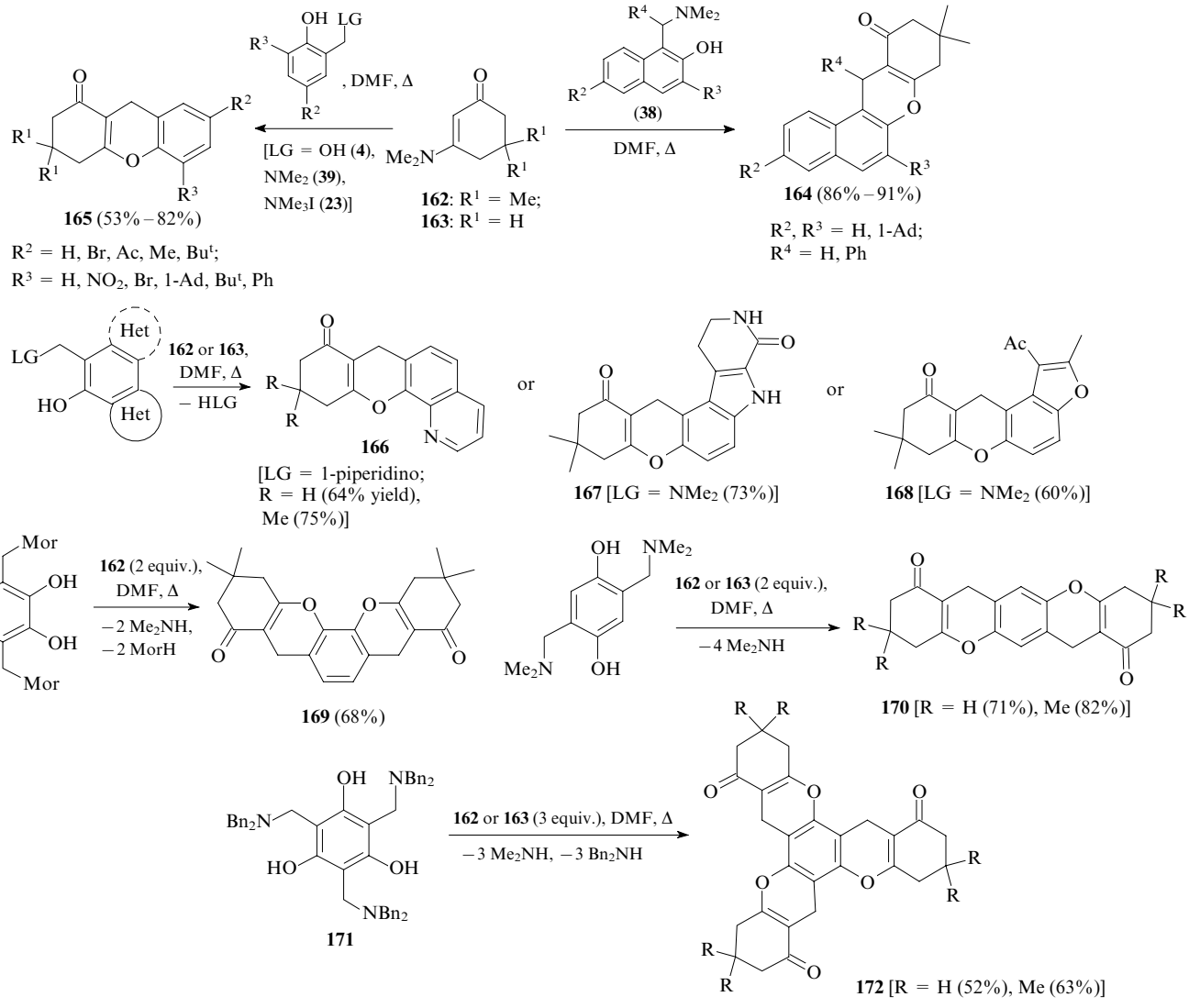
Scheme 61



155 as a result of the carbo-Michael reaction, which is catalyzed by chiral squaramide **156**, and intramolecular transesterification (Scheme 59).[121]

Smith and co-workers[122–124] demonstrated that alkyl-substituted *p*-benzoquinones **157a–c** (including 2,3-dimethyl-1,4-naphthoquinone) are tautomerized to *o*-QMs **158a–c**, which undergo the Michael condensation with the enolate of diethyl malonate to afford dihydrocoumarins **159a–c**. The latter are dehydrogenated during the reaction to coumarins **160a–c** *via* oxidation with the initial quinone (Scheme 60). Reaction of this type can also be carried out for sodium ethyl acetoacetate.[125]

Scheme 62

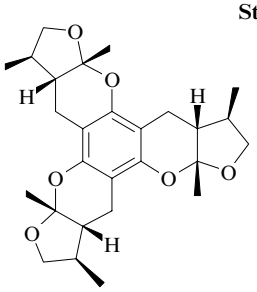


2,3,4,9-Tetrahyro-1*H*-xanthen-1-one (**161**) was prepared from salicyl alcohol (**4b**) and cyclohexane-1,3-dione in hexamethylphosphoramide (HMPA) (Scheme 61).[126] The reaction includes the intermediate generation of *o*-QM from salicyl alcohol, the addition of cyclohexane-1,3-dione enol form to it, intramolecular cyclization and dehydration. Instead of salicyl alcohol, 1-(dimethylaminomethyl)-2-naphthol (**38a**) can be used, with the reaction being carried out in chlorobenzene.[127]

β-Enamino ketones can serve as synthetic equivalents of 1,3-dicarbonyl compounds in the reactions with *o*-QMs. By reactions of enamines based on dimedone (**162**) and cyclohexane-1,3-dione (**163**) with salicyl alcohols, Mannich bases or quaternary ammonium salts, 2,3,4,9-tetrahydro-1*H*-xanthen-1-one derivatives **164** and **165**, were synthesized (Scheme 62).[92, 128]

In all cases, *o*-QMs were generated thermally. The developed procedure for the synthesis of tetrahydroxanthenes was extended to more intricate *o*-QM precursors; this resulted in the preparation of heterocycles **166**–**170**.[92, 129, 130] Heating of a mixture of tris(dibenzylaminomethyl)phloroglucinol (**171**) and enamines **162**, **163** in 1 : 3 molar ratio affords dodecahydro-1*H*,6*H*,12*H*-dichromeno[2,3-*a*:2,3-*c*]xanthene-1,7,13-triones **172**,[131] structurally related to natural xyloketal A.[132]

Structure of xyloketal A



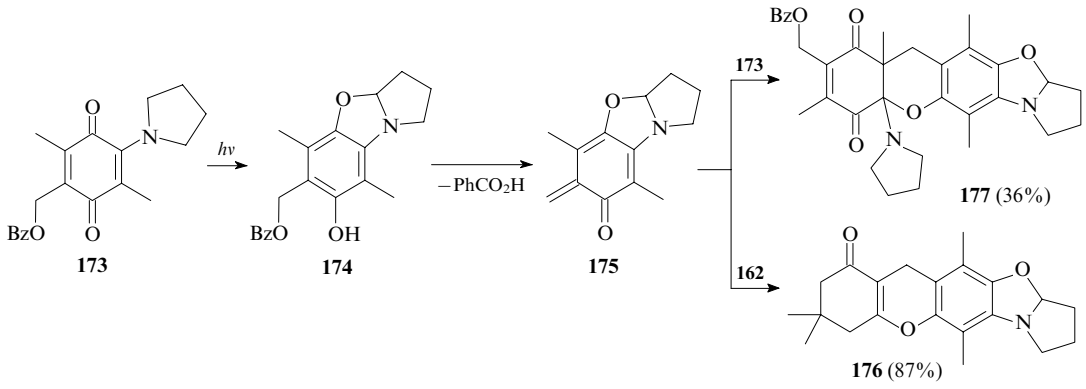
A similar reaction could be accomplished on irradiation of substituted *p*-benzoquinone **173** in the presence of enamine **162** (Scheme 63). The first step is cyclization of compound **173** to isomeric benzoxazoline **174**; this is followed by generation of *o*-QM **175**, which is trapped with enamine, resulting in the formation of hydrogenated pyrrolo[2,1-*b*]xantheno[3,2-*d*]oxazol-10-one **176**. It is noteworthy that the initial *p*-benzoquinone **173** can itself react with *o*-QM to give compound **177**.[133]

In the case of addition of cyclic enaminones to *o*-QMs catalyzed by chiral phosphoric acids **178** and **179**, the reaction can follow two alternative routes (Scheme 64): in the presence of the electron-withdrawing acetyl group at the nitrogen atom, the addition occurs at the C(2)=C(3) bond and gives tetrahydroxanthenone **180**,[134] whereas aryl substituents at nitrogen promote cyclization at the C(1)–C(2) bond to give imines **181**.[135]

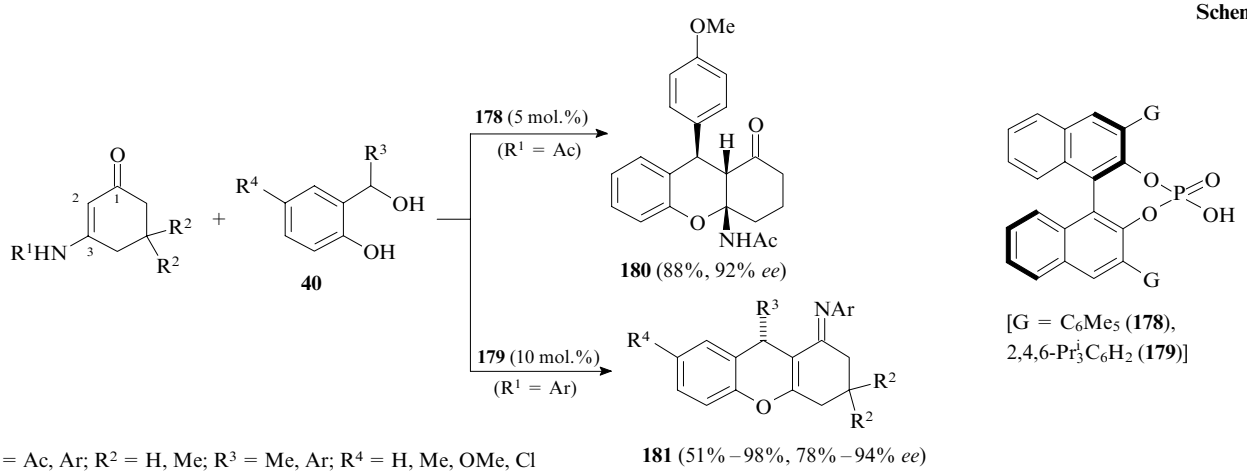
Recently, this reaction was conducted using *o*-hydroxystyrenes as *o*-QM precursors and chiral phosphoric acid **182** as the catalyst; this provided a high enantioselectivity of the formation of products **183** at temperatures of up to 130 °C (Scheme 65).[136]

The reaction of 4-hydroxycoumarin **184** with salicyl alcohols **4a**,**f**,**g** in the presence of HCl or $POCl_3$ afforded

Scheme 63

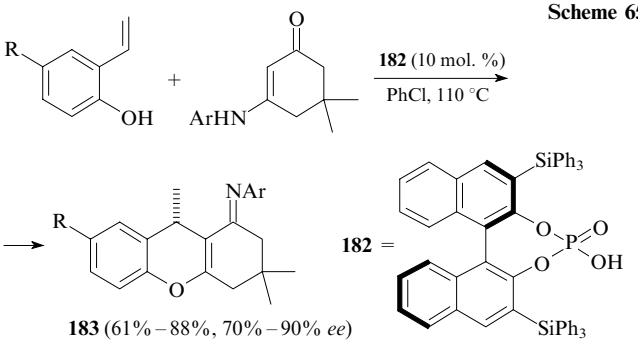


Scheme 64



R^1 = Ac, Ar; R^2 = H, Me; R^3 = Me, Ar; R^4 = H, Me, OMe, Cl

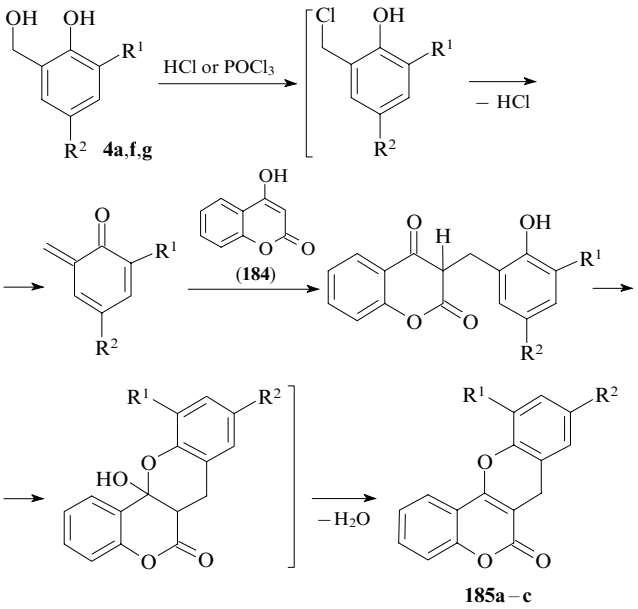
Scheme 65



R = H, Me, OMe, F, Cl

benzopyrano[2′,3′:4,3]coumarins **185a–c**, which were isolated in rather low yields (Scheme 66).[137]

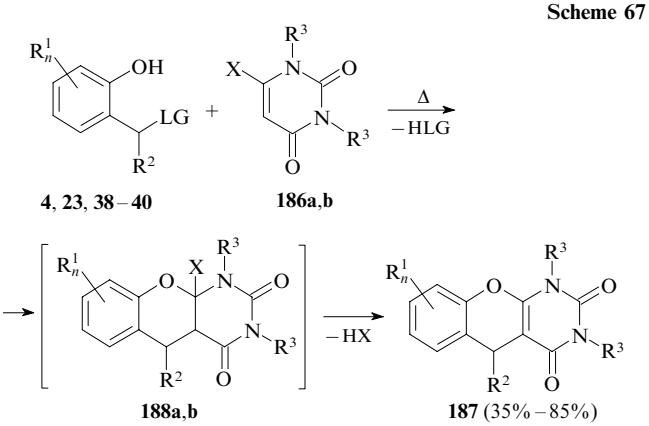
Scheme 66



$R^1 = R^2$ = Me (**4a**; **185a**, 35%); R^1 = OMe: R^2 = All (**4f**; **185b**, traces), Me (**4g**; **185c**, 6% yield);

6-Substituted uracils **186a**,**b** can serve as synthetic equivalents of 1,3-dicarbonyl compounds. Heating of their mixtures with various *o*-QM precursors (salicyl alcohols, phenol and naphthol Mannich bases and the corresponding methiodides) gives rise to 1,5-dihydrochromeno[2,3-*d*]pyrimidinediones **187** *via* the addition reaction followed by elimination of hydrogen chloride or ammonia from the initially formed adducts **188a**,**b** (Scheme 67).[92,138,139] On the other hand, the reactions of *o*-QM with uracils **186a**,**b**, and with enamines based on 1,3-dicarbonyl compounds can

Scheme 67

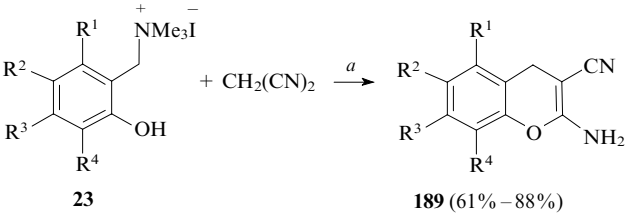


LG = OH (**4**, **40**), NMe_2 (**38**, **39**), NMe_3I (**23**); R^1_n = H, 7-NO_2, benzo[5,6], *etc.*; R^2 = H, Pr^i, Ar; R^3 = H, Me; X = Cl (**a**), NH_2 (**b**)

be regarded as asynchronous [4 + 2]-cycloaddition followed by elimination (see Section IV.1).

o-Quinone methides actively react with malononitrile to give 2-amino-4*H*-chromene-3-carbonitriles **189**, which are important for medicinal chemistry.[140,141] This cascade process was accomplished for the first time with quaternized Mannich bases **23** as *o*-QM precursors[92,142] under base catalysis; the best results were obtained using DBU (Scheme 68). An important feature of this reaction is the possibility to use 'green' solvents such as water and ethanol.

Scheme 68

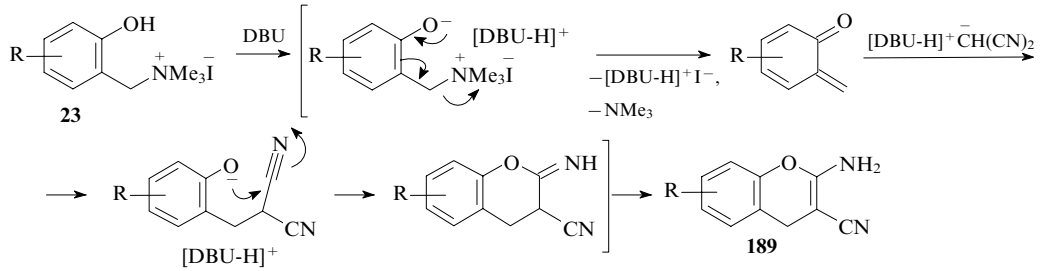


(*a*) DBU, EtOH or H_2O;
R^1 = H: R^2 = OMe, 1-Ad, Me, Bu^t, CO_2Me, Bn, Cl, CH=CHCO_2Me; R^1–R^2 is benzo; R^3 = H, Me, CO_2Me; R^4 = H, 1-Ad, OMe

The reaction mechanism includes the generation of the corresponding *o*-QM, which is formed upon thermal decomposition of quaternary ammonium salts **23** in the presence of a base. The subsequent Michael addition of the malononitrile anion furnishes 2-hydroxybenzylmalononitrile. After that, Thorpe–Ziegler heterocyclization (or the intramolecular version of the Pinner reaction) leads to generation of imine, a tautomer of the final chromene **189** (Scheme 69).

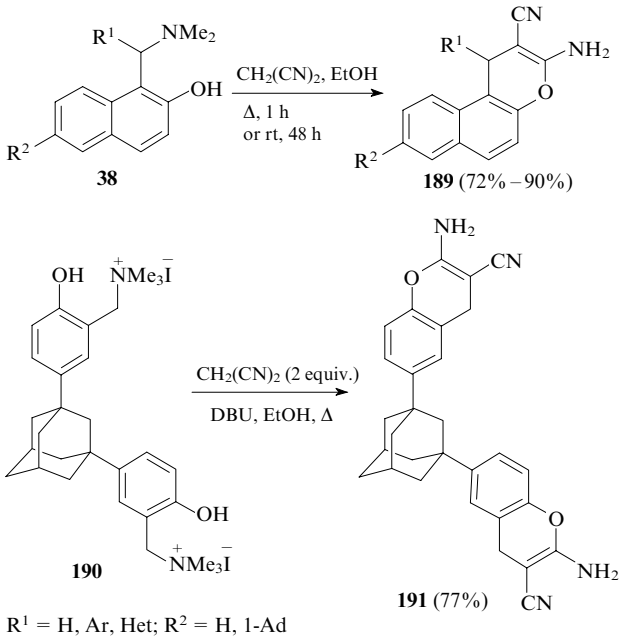
The generation of *o*-QMs from phenolic Mannich bases requires either high temperature or photochemical activa-

Scheme 69



tion. Upon irradiation of 2-(dimethylaminomethyl)phenols **39** or salicyl alcohols **40** in the presence of malononitrile, chromenes **189** were isolated in up to 90% yields.[143] However, *o*-QMs based on 2-naphthol are generated in refluxing ethanol, which is associated with their higher stability due to increasing conjugation length. It is also of interest that these precursors can be converted to *o*-QMs even at room temperature; however, the reaction time increases from 1 h to 48 h.[144] The ethanol boiling point is sufficient to generate *o*-QMs from phenolic Mannich base methiodides. Indeed, two successive generations of *o*-QM from quaternary salt **190** yield bis(2-amino-4*H*-chromene-3-carbonitrile) **191** (Scheme 70).[92]

Scheme 70

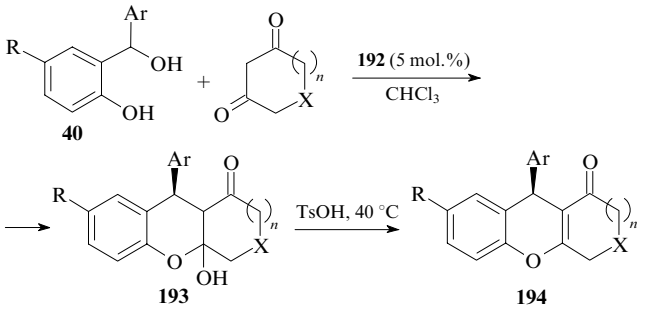


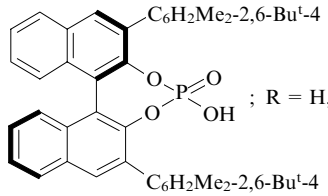
R^1 = H, Ar, Het; R^2 = H, 1-Ad

Two key approaches have been developed for asymmetric addition of malononitrile, 1,3-dicarbonyl compounds and some other CH-acids to *o*-QMs. One approach has been proposed by Schneider and co-workers [145] and consists in the use of chiral phosphoric acids [*e.g.*, acid **192** based on 1,1′-binaphthalene-2,2′-diol (BINOL)] as catalysts of asymmetric addition (Scheme 71). The CH-acids are reacted with various salicyl alcohols **40** serving as *o*-QM precursors. The main advantages of this method are the possibility of using readily accessible initial compounds and easy scalability of the process. The authors assume that the initially formed product of addition of CH-acid to *o*-QM is cyclodehydrated under the action of *p*-toluenesulfonic acid; however, the structure of the intermediate adduct **193** has not been reliably confirmed. The yields of products **194** and stereoselectivity of the reaction depend on the nature of the 1,3-dicarbonyl compound.

Rueping and co-workers [146] developed a related approach using cyclic esters and BINOL-based phosphoramides and subsequent treatment of the reaction mixture with $FeCl_3$; this approach gives similar results. The researchers proved unambiguously that the reaction proceeds *via* the formation of the corresponding cyclic hemiketal, introduction of the acid catalyst being required only for dehydration. Apparently, the reaction described by Schneider and co-workers [145] follows a similar mechanism.

Scheme 71



192 =  ; R = H, OMe, Alk, Br;

n	X	Yield (%)	*ee* (%)
1	CH_2	89 – 98	90 – 96
	O	62 – 93	90 – 98
	S	59 – 68	92 – 98
0	CH_2	62 – 94	86 – 96

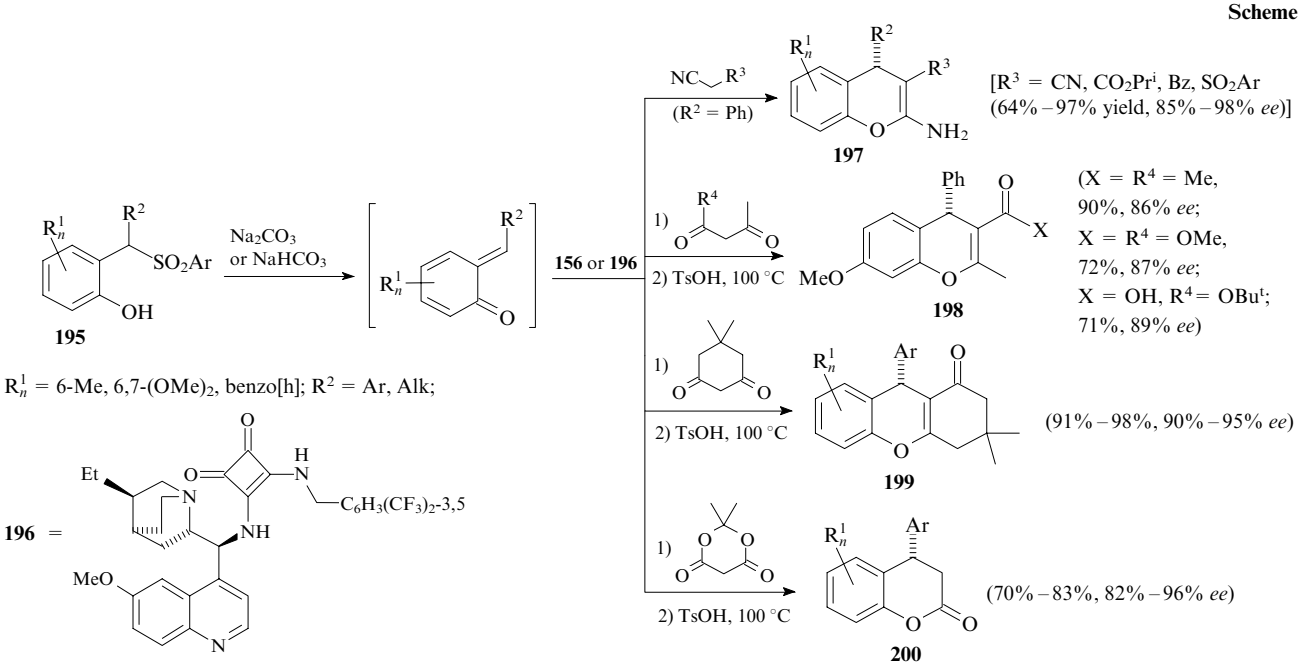
The second approach with the use of 2-(arylsulfonylmethyl)phenols **195** as the *o*-QM precursors was proposed independently by two research groups.[147, 148] The reaction is initiated by a base and proceeds at room temperature, the best results being attained with squaramide derivatives **156** and **196** as catalysts (products **197** – **199** were obtained in the highest yields and with the highest *ee*) (Scheme 72). It is noteworthy that for the use of acetylacetone, 1,3-ketoesters or dimedone, the subsequent dehydration requires that the reaction mixture be treated with *p*-toluenesulfonic acid. When Meldrum's acid is used, chroman-2-ones **200** are formed under similar conditions *via* elimination of acetone and carbon dioxide.

Later, it was shown that stable *o*-QMs can be introduced into the reaction with malononitrile catalyzed by chiral squaramide to give the corresponding 2-amino-4*H*-chromene-3-carbonitriles.[149] The reaction retains the enantioselectivity when scaled up to gramme amounts, with the catalyst amount being only 2 mol.%.

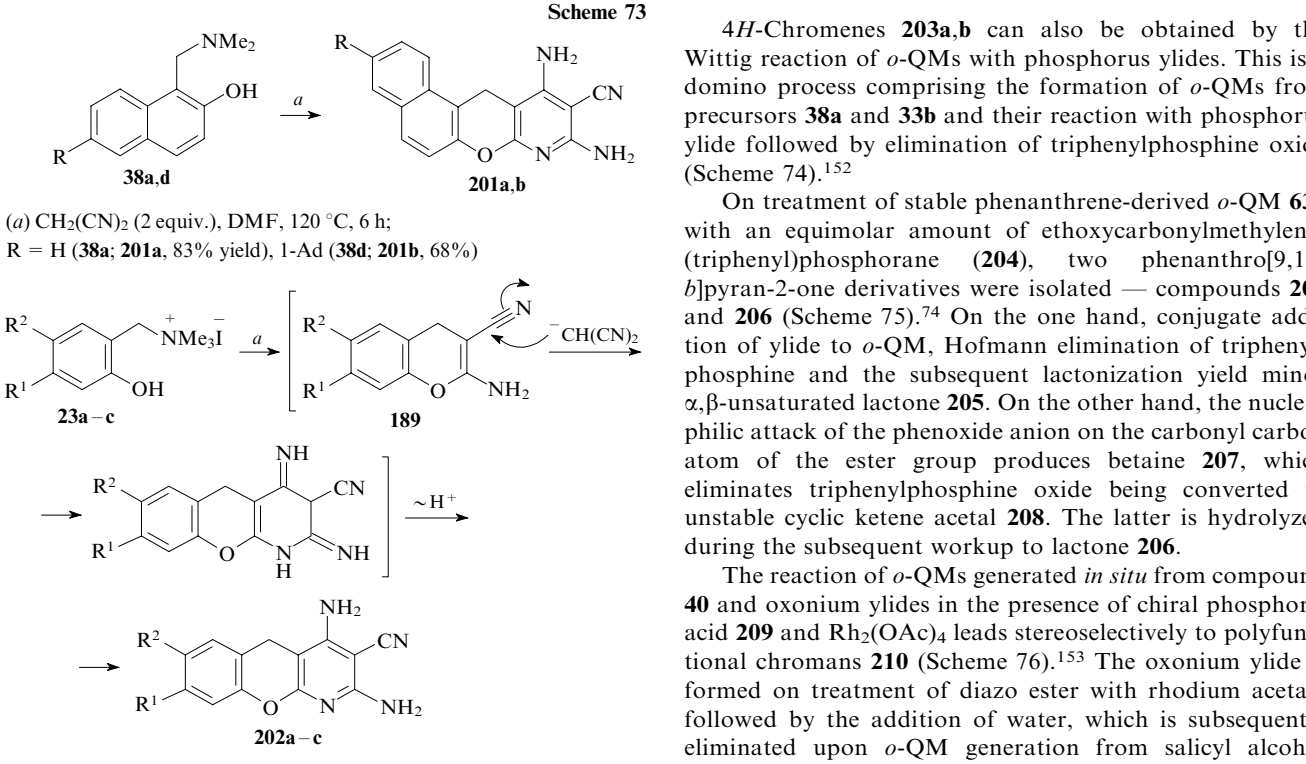
Squaramide-based catalysts are also used in the oxidative generation of *o*-QMs from 2-alkylphenols in the presence of CH-acids such as malononitrile, 2-(arylsulfonyl)acetonitrile and *tert*-butyl cyanoacetate.[150] The cascade is initiated by oxidation of the CH bond on treatment with manganese dioxide to give *o*-QMs; the subsequent Michael addition and cyclization afford 4*H*-chromenes. A drawback of the method is that only electron-enriched compounds are suitable for the generation of *o*-QMs.

The reactions of various precursors of *o*-QMs with excess malononitrile afford 9,11-diamino-12*H*-benzo[5,6]chromeno[2,3-*b*]pyridine-10-carbonitriles **201a**,**b** and 2,4-diamino-5*H*-chromeno[2,3-*b*]pyridine-3-carbonitriles **202a** – **c** (Scheme 73).[142, 151] The pseudo-three-component reaction proceeds *via* the intermediate formation of β-enaminonitriles **189**, which are then condensed with a second equivalent of malononitrile.

Scheme 72



Scheme 73

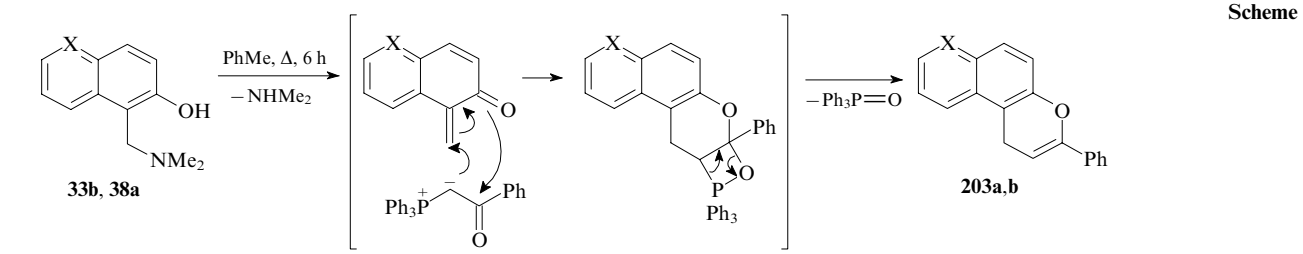


4*H*-Chromenes **203a**,**b** can also be obtained by the Wittig reaction of *o*-QMs with phosphorus ylides. This is a domino process comprising the formation of *o*-QMs from precursors **38a** and **33b** and their reaction with phosphorus ylide followed by elimination of triphenylphosphine oxide (Scheme 74).[152]

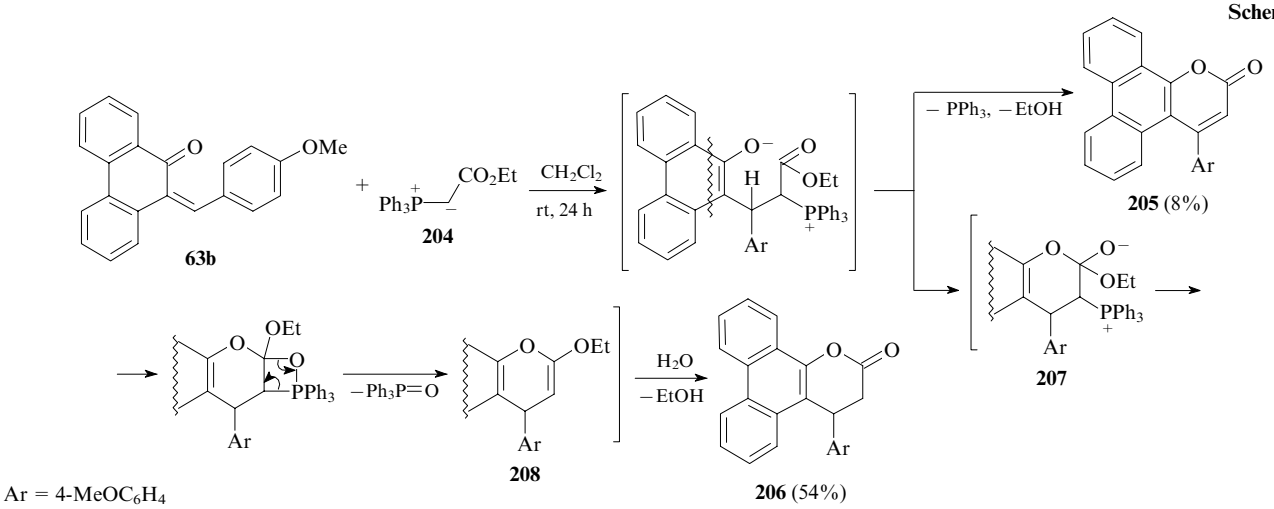
On treatment of stable phenanthrene-derived *o*-QM **63b** with an equimolar amount of ethoxycarbonylmethylene-(triphenyl)phosphorane (**204**), two phenanthro[9,10-*b*]pyran-2-one derivatives were isolated — compounds **205** and **206** (Scheme 75).[74] On the one hand, conjugate addition of ylide to *o*-QM, Hofmann elimination of triphenylphosphine and the subsequent lactonization yield minor α,β-unsaturated lactone **205**. On the other hand, the nucleophilic attack of the phenoxide anion on the carbonyl carbon atom of the ester group produces betaine **207**, which eliminates triphenylphosphine oxide being converted to unstable cyclic ketene acetal **208**. The latter is hydrolyzed during the subsequent workup to lactone **206**.

The reaction of *o*-QMs generated *in situ* from compound **40** and oxonium ylides in the presence of chiral phosphoric acid **209** and $Rh_2(OAc)_4$ leads stereoselectively to polyfunctional chromans **210** (Scheme 76).[153] The oxonium ylide is formed on treatment of diazo ester with rhodium acetate followed by the addition of water, which is subsequently eliminated upon *o*-QM generation from salicyl alcohol under the action of catalyst **209**. The conjugate addition of the ylide to the *o*-QM and the subsequent cyclization furnish the target chromans **210**. It is noteworthy that the

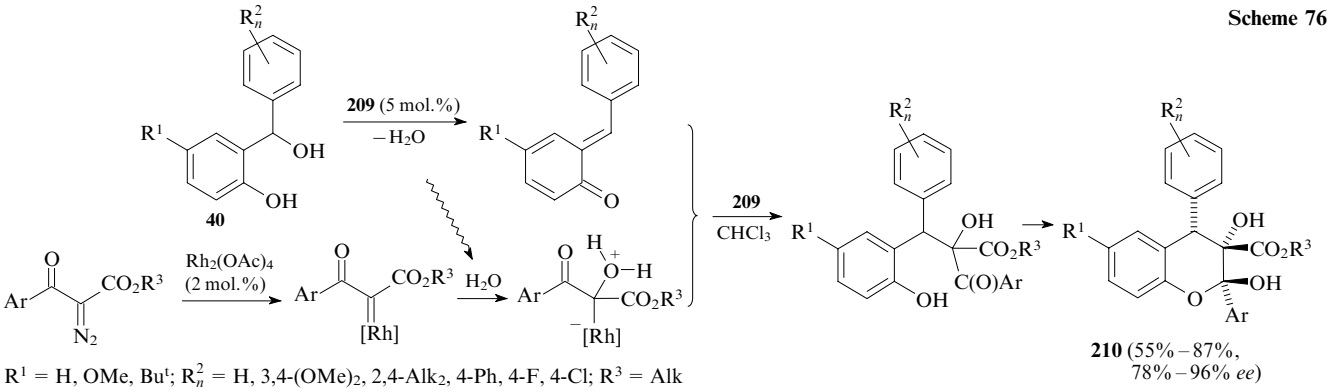
Scheme 74



Scheme 75

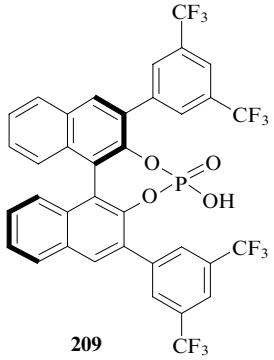


Scheme 76



reaction does not occur if there is a substituent in the *ortho*-position of the aryl group of the diazo ester.

Structure 209



209

III.4. Three-component reactions of naphthols, aromatic aldehydes and CH-acids. Synthesis of naphthopyrans

In recent years, increasing attention has been paid to the development of new three-component reactions of 2-naphthol, aldehydes (most often, aromatic) an various CH-acids (Scheme 77). Although reactions of this type do not differ fundamentally from the two-component reactions considered above, they are collected in a separate Section, because there are quite a few such reactions and they are highly valuable for the synthesis of naphtho-fused heterocycles. The nature of CH-acids is varied most often in three-component processes of this type. Published data describe condensations of 2-hydroxy-1,4-naphthoquinone,[154 – 164] 6-aminouracils,[165] barbituric acid,[166 – 169] cyanoacetic[170 – 173] and acetoacetic acid derivatives,[174, 175] 1,3-diketones (acetylacetone, cyclopentane-1,3-dione,[176 – 179] cyclohexane-1,3-dione,[180] indane-1,3-dione[181 – 183]), 4-hydroxycoumarin,[184 – 187] acetophenones[188] and some other. According to researchers cited, in most transformations presented in the Scheme, the yields of products **211** – **220** reach or exceed 90%.

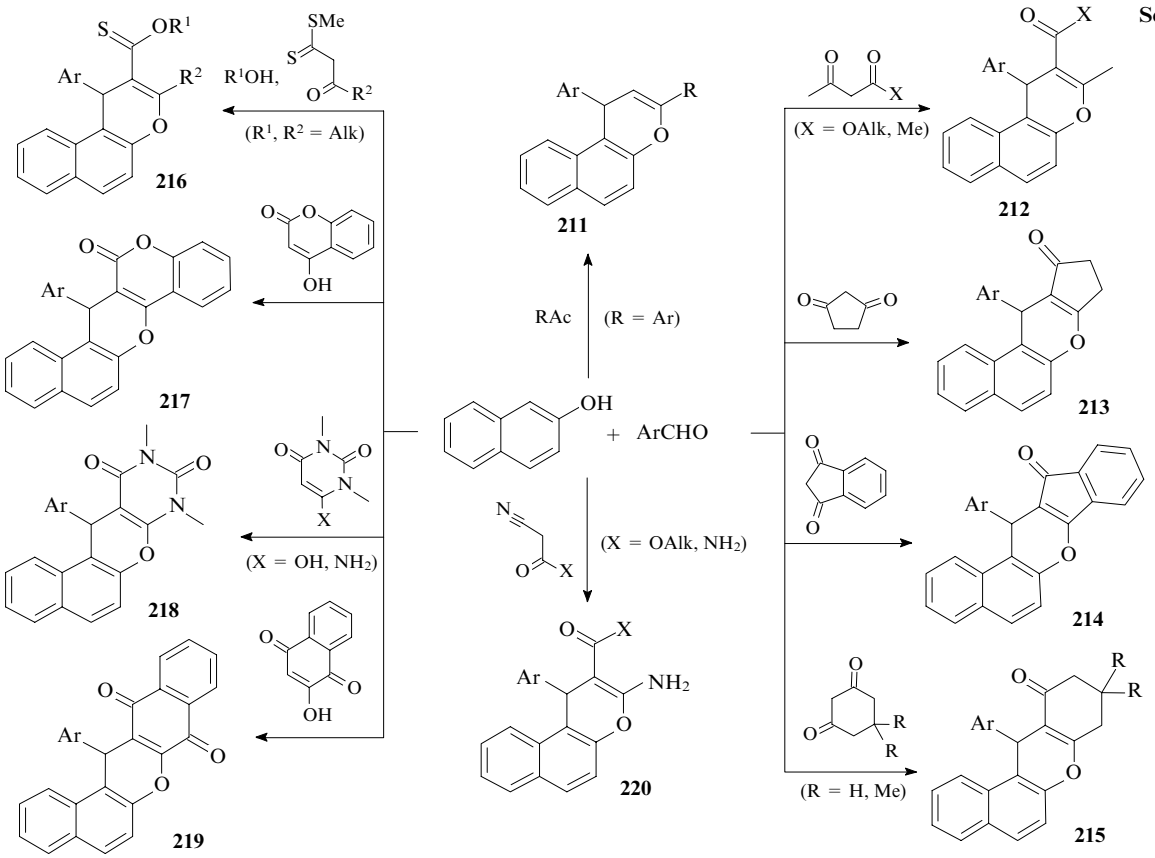
These three-component reactions proceed by similar mechanisms (Scheme 78) comprising the initial hydroxyalkylation of 2-naphthols with aromatic aldehydes. This yields unstable alcohols **221**, which are dehydrated with generation of *o*-arylidenenaphthoquinones **222**. The subsequent conjugate addition of CH-acid in the enol form to compounds **222**, heterocyclization and water or ammonia elimination afford fused and/or functionally substituted benzo[*f*]chromenes. The reactions are catalyzed, most often, by protic acids or Lewis acids.

Most researchers believe that the above-listed transformations occur *via* the intermediate generation of *o*-QMs **222**. Some other deem that the reaction starts with the Knoevenagel condensation of aldehyde with the CH-acid, and after that, the product acts as the Michael acceptor with respect to naphthol, *e.g.*, as shown in Scheme 79.

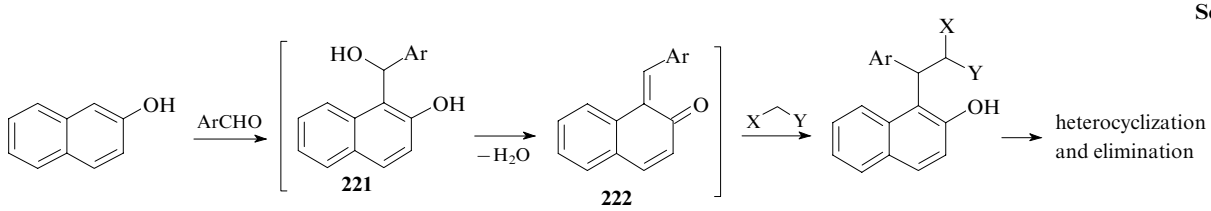
However, despite the large number of studies devoted to these reactions, in none of them, do the authors present any evidence in favour of one or another mechanism. Presumably, the first step of these cascade transformations is determined by the relative nucleophilicity of 2-naphthol and CH-acid, which varies over a broad range.

The reaction of 2-naphthol, ethyl acetoacetate and aromatic *o*-hydroxyaldehydes — salicylaldehydes and 2-hydroxynaphthaldehyde — follows a more complex path-

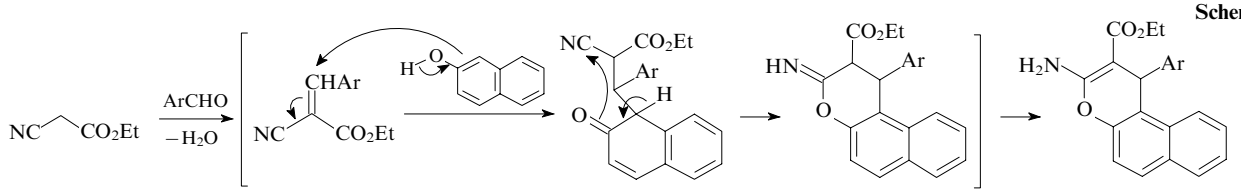
Scheme 77



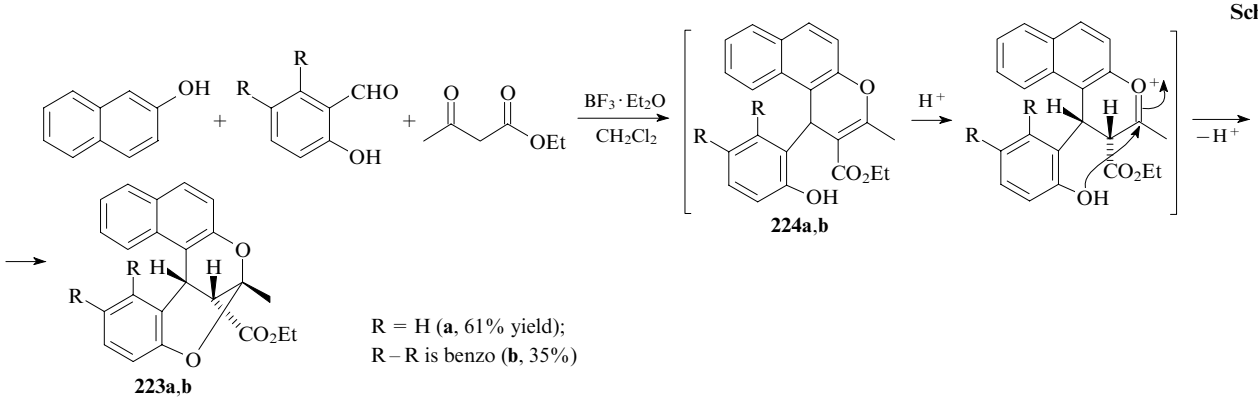
Scheme 78



Scheme 79



Scheme 80

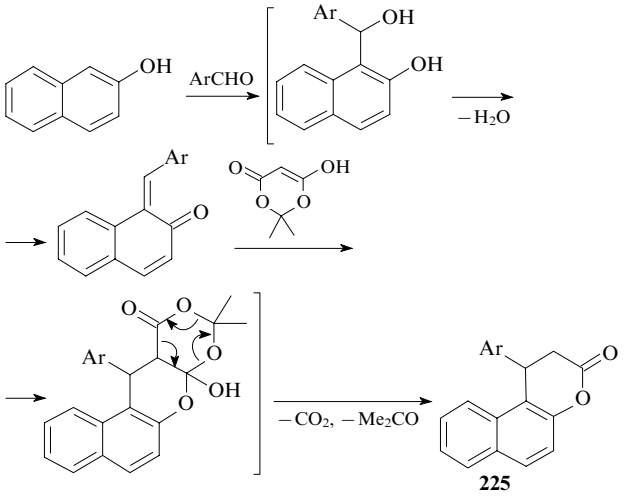


R = H (**a**, 61% yield);
R – R is benzo (**b**, 35%)

way and results in the formation of benzo[*d*]naphtho[1,2-*g*][1,3]dioxocine derivatives **223a**,**b** (Scheme 80).[189] The reaction presumably includes the formation of chromenes **224a**,**b**, which are protonated and undergo 6-*exo*-*trig*-cyclization.

Benzo[*f*]chromen-3-ones **225** were obtained by the reaction of 2-naphthol, aromatic aldehydes and Meldrum's acid in the presence of $CeCl_3$ (Ref. 190) or tetra-n-butylammonium fluoride [191] (Scheme 81).

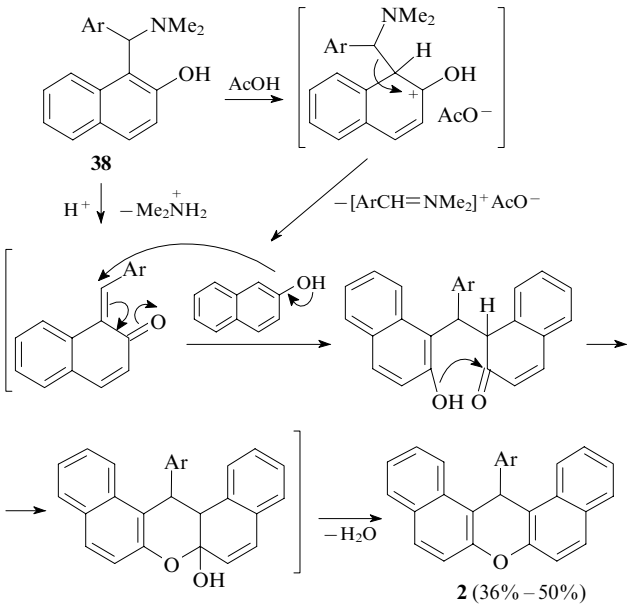
Scheme 81



225

A considerable drawback of the above methods for the synthesis of a naphtho-fused system is the competing formation of dibenzoxanthenes **2**, which is especially pronounced in the presence of electron-withdrawing substituents in aromatic aldehydes.[192] It is also noteworthy that the Betti bases, which are direct precursors of *o*-QMs, can be converted to 14*H*-dibenzo[*a*,*j*]xanthenes **2** in moderate yields in acetic acid in the absence of foreign nucleophiles (Scheme 82).[193, 194]

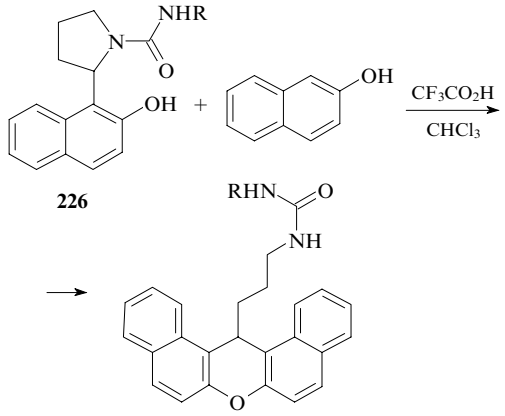
Scheme 82



2 (36% – 50%)

It was found that 2-(2-hydroxy-1-naphthyl)pyrrolidine-1-carboxamides **226** react with 2-naphthols with pyrrolidine ring opening to give dibenzoxanthenes **227** (Scheme 83).[195] Note that initial carboxamides can be prepared from nitrogen-containing acetals and 2-naphthol.[196]

Scheme 83



226

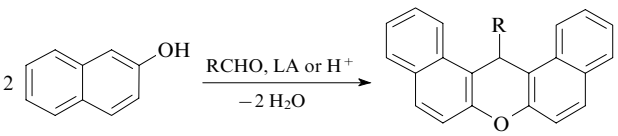
227 (53% – 83%)

R = H, Ph, Alk

Transformations of this type should be taken into account while using naphthol Mannich bases in acid medium.

14-Aryl- or 14-alkyl-14*H*-dibenzo[*a*,*j*]xanthenes **2** were prepared in rather high yields by pseudo-three-component condensation of 2-naphthol (2 equiv.) with aromatic or aliphatic aldehyde (1 equiv.) in the presence of protic acids or Lewis acids (P_2O_5, $InCl_3$, TsOH and so on) (Scheme 84).[197 – 200] The cascade process consists of consecutive steps including hydroxyalkylation of 2-naphthol, generation of *o*-QM, Michael addition of a second 2-naphthol molecule and cyclodehydration.

Scheme 84



R = Alk, Ar; LA is Lewis acid

2

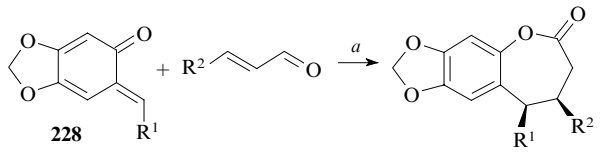
1-Naphthol is less reactive in these transformations. Nevertheless, three-component reactions of 1-naphthol and aromatic aldehydes with cyclic 1,3-diketones,[179] acetophenones [188] and ethyl cyanoacetate [172] have been reported.

III.5. Michael reaction – 7-*exo*-*trig*-cyclization

The reactions of *o*-QMs with 1,3-ambiphiles represent a promising approach to the preparation of seven-membered oxygen-containing benzannulated heterocycles. However, data on reactions of this type are scarce.

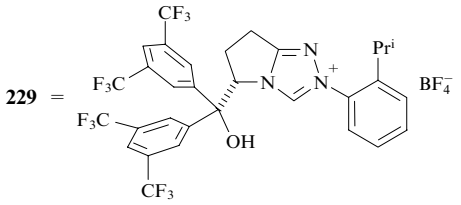
Ye's [201] and Scheidt' [202] groups independently developed similar methods for the synthesis of 2,3,4,5-tetrahydrobenzo[*b*]oxepine derivatives using N-heterocyclic carbenes (NHC). It was found that stable *o*-QMs **228** react with c α,β-unsaturated aldehydes in the presence of catalytic amounts of NHC precursor **229** and a base to give mainly the *cis*-isomers of benzo-ε-lactones **230** (Scheme 85).[201] In the other procedure,[202] 2-(*tert*-butyldimethylsilyloxy)benzyl bromides **231** are used as *o*-QM precursors in the presence of caesium fluoride and NHC precursor **232**. In the presence of substituents at the exocyclic carbon atom in *o*-QM, the *trans*-isomer of benzo-ε-lactone **233** was isolated as the major diastereomer. However, in this case, a minor side product resulting from [4 + 2]-cycloaddition of cinnamaldehyde to *o*-QM was also formed.

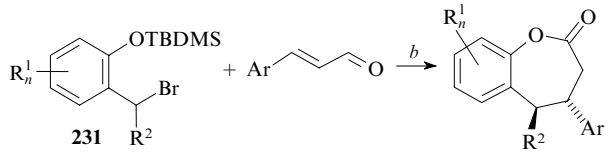
Scheme 85



228 **230** (79%–97%)

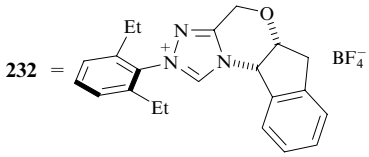
(*a*) **229** (10 mol.%), KOAc (10 mol.%), dioxane, rt;
R^1 = 4-$MeOC_6H_4$, PhC≡C; R^2 = Ar, 2-Fu, Alk;





231 **233** (56%–85%)

(*b*) **232** (20 mol.%), CsF, 18-crown-6, Bu^n_4NOAc, THF, −18 °C;
R^1_n = H, 7,8-$(OMe)_2$, 6,7-Alk_2; R^2 = H, Alk;



The reaction mechanism includes the following key steps (Scheme 86). The NHC is generated from azolium salt **232** under the action of tetra-n-butylammonium acetate, which acts as a soft base (here and below, the 1,2,4-triazole moiety of the carbene is shown for the sake of simplicity); then NHC adds to the carbonyl carbon atom of α,β-unsaturated aldehyde and, after proton transfer, vinylic Breslow intermediate **234** (a synthetic equivalent of the homoenolate ion) is formed. Meanwhile, *o*-QM is generated from precursor **231** under the action of the fluoride ion, and intermediate **234** adds to *o*-QM according to Michael. The subsequent tautomeric transformation and intramolecular O-acylation of the phenoxide ion produce benzoxepinones **233**.

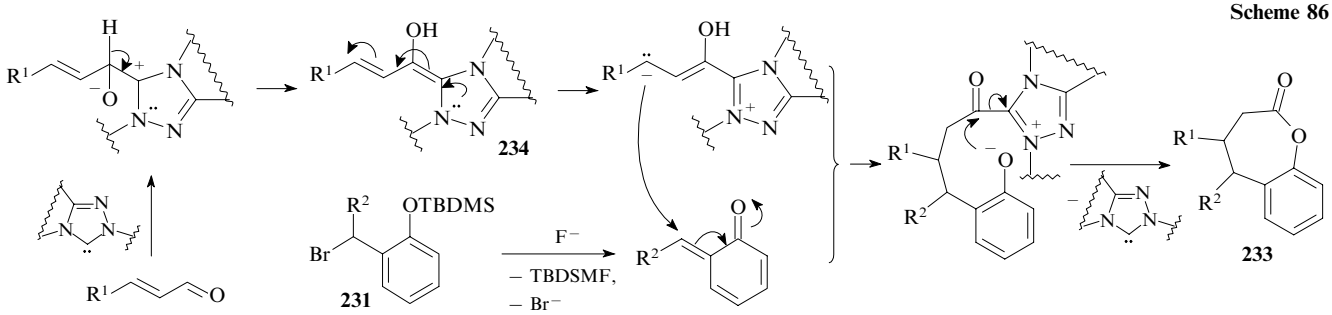
III.6. Michael reaction – 6-*exo-tet*-cyclization

Heating of 2-aminomethylphenol **235** and vinyl ethyl ether at 100 °C results in not only the classic Diels–Alder product, 2-ethoxychroman **236**, but also hemiaminal **237** in 1 : 2.5 ratio (according to ^{1}H NMR spectroscopy).[203] The hemiaminal is formed upon the Michael reaction of 2-aminomethylphenol with *o*-QM followed by the addition of dibenzylamine **238** to vinyl ethyl ether and heterocyclization (Scheme 87). At 140 °C, only ethoxychroman **236** was isolated in a low yield.

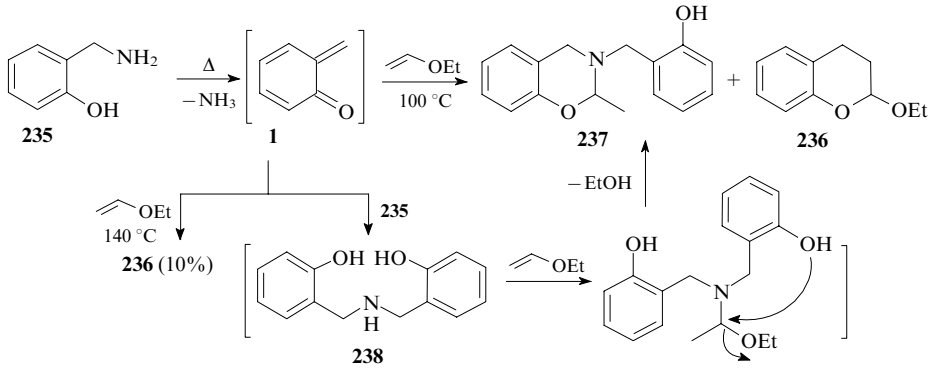
III.7. Michael reaction – oxidative dearomatization

1-Methyl-2-naphthols react with phenols in the presence of air oxygen and optically active iron complexes to give spirocyclic dihydrobenzofurans **239** in good yields and with high enantioselectivity (Scheme 88).[204] This reaction can be performed for phenols with a broad variety of substituents. However, the presence of a methyl group in position 1 of 2-naphthols is critical, and 1-ethyl-2-naphthols are unable to undergo this reaction. The aerobic generation of *o*-QM from 1-methyl-2-naphthol catalyzed by Fe complex **240**, the subsequent Michael addition of phenol and asymmetric oxidative dearomatization of the naphthol moiety lead to dihydrobenzofurans **239**. Since the naphthol moiety is oxidized more easily than the phenol group, the

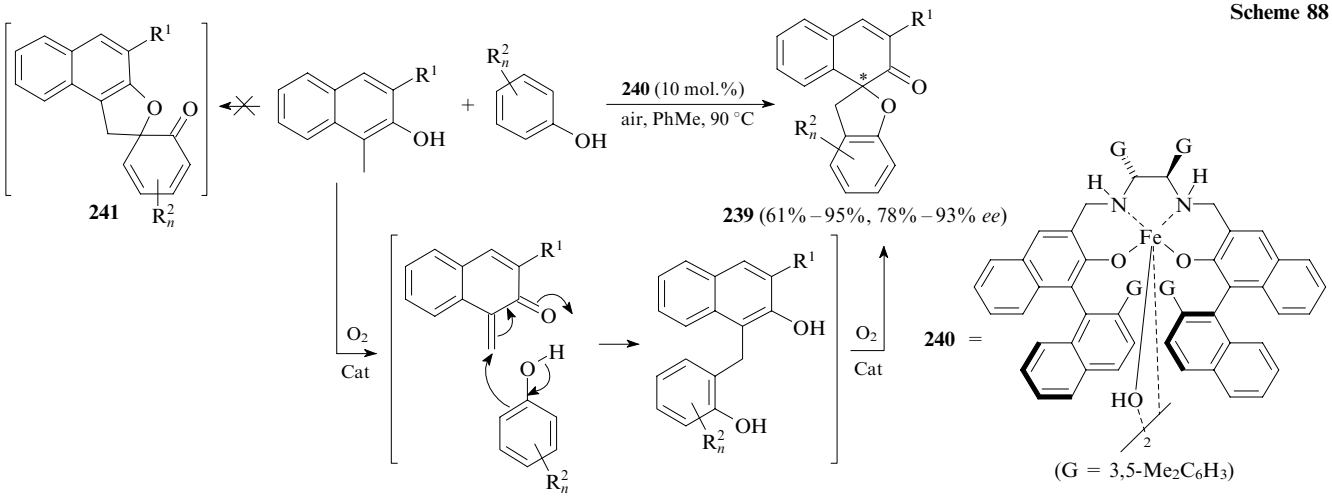
Scheme 86



Scheme 87



Scheme 88



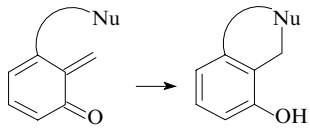
R^1 = Me, Pr^n, All; R^2_n = H, 5-Bu^t, 5-NO_2, 5-Br, 5-CO_2Me, 5-CN, 4,6-Me_2, 5,7-Me_2, *etc.*; Cat is catalyst

potentially possible formation of spirocyclic structures of type **241** does not take place.

III.8. Intramolecular Michael reaction

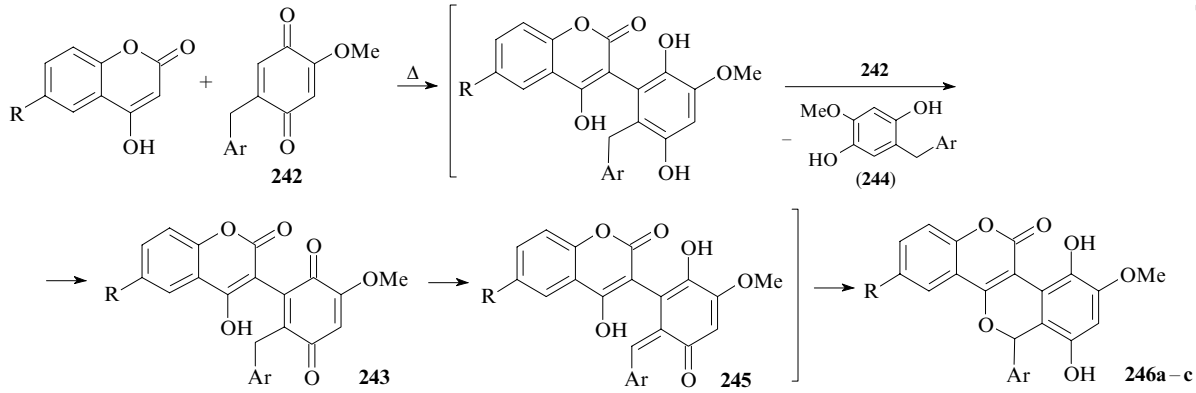
The generation of *o*-QM from a precursor containing an additional nucleophilic centre may be followed by heterocyclization (Scheme 89).

Scheme 89



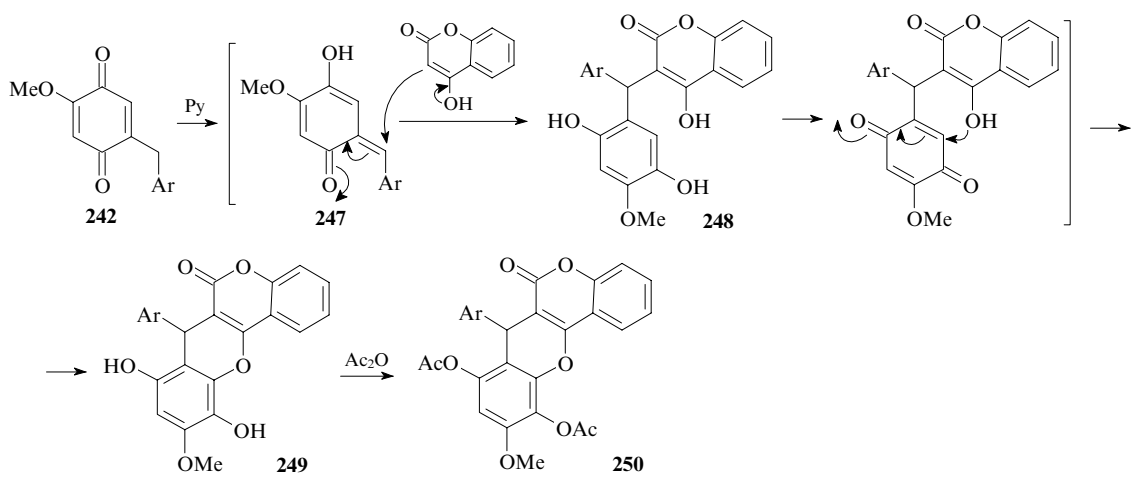
The reaction of 4-hydroxycoumarins and 2-arylmethyl-5-methoxy-1,4-benzoquinones **242** comprising a number of intermediate steps (Michael reaction, oxidation to give quinones **243** and hydroquinones **244**, isomerization of quinones **243** to *ortho*-arylidene derivatives **245** and intramolecular 6-*endo-trig*-cyclization) resulted in the synthesis

Scheme 90



R = H: Ar = 4-$MeOC_6H_4$ (**a**), 3,4-$OCH_2OC_6H_3$ (**b**); R = Me, Ar = 4-$MeOC_6H_4$ (**c**)

Scheme 91

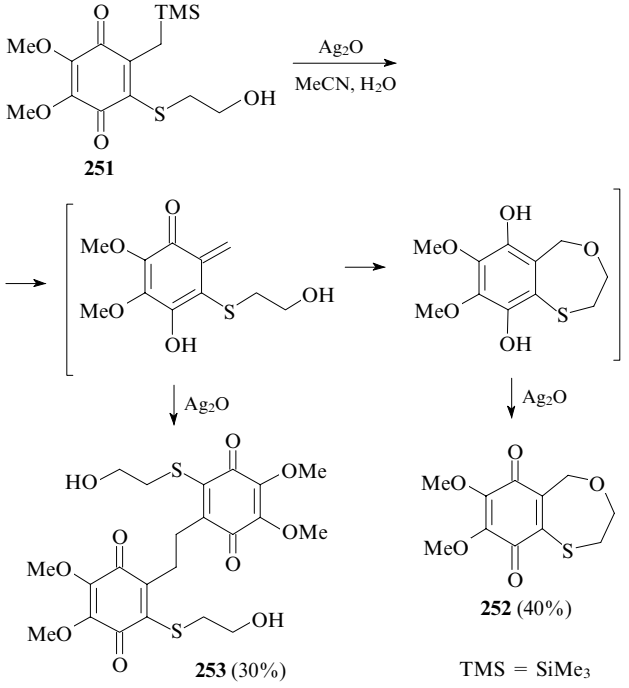


of 6*H*,11*H*-[2]benzopyrano[4,3-*c*][1]benzopyran-11-ones **246a** – **c** (Scheme 90).[205]

It is noteworthy that this reaction conducted in pyridine gives, apart from compounds of type **246**, other products isomeric to **246**. Apparently, quinone **242** isomerizes in pyridine to give *o*-QM **247**, which then adds hydroxycoumarin. The subsequent oxidation of adduct **248** and intramolecular 6-*endo*-*trig*-cyclization afford product **249** as diacetate **250** (Scheme 91).[205]

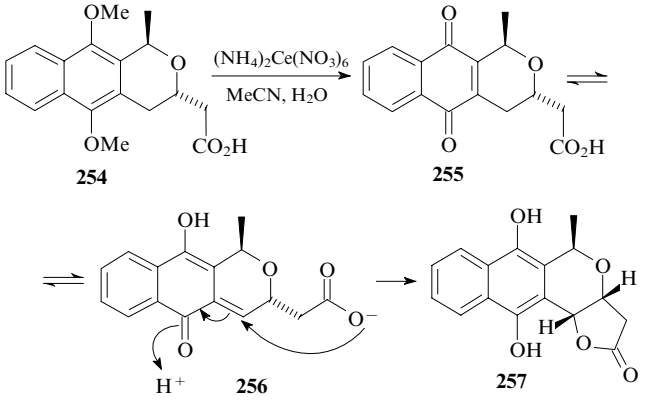
The oxidation of trimethylsilylmethyl-*p*-benzoquinone **251** with Ag_2O involving the intermediate generation of the corresponding *o*-QM and the subsequent intramolecular 7-*endo*-*trig*-cyclization and dehydrogenation give rise to 7,8-dimethoxy-2,3-dihydro-5*H*-4,1-benzoxathiepine-6,9-dione **252** and dimeric product **253** (Scheme 92).[206]

Scheme 92



The oxidative demethylation of 3,4-dihydro-1*H*-benzo[*g*]isochromene **254** on treatment with ammonium cerium(IV) nitrate, tautomerization of the resulting quinone **255** to *o*-QM **256** and intramolecular conjugate addition of the carboxylate anion give γ-lactone **257** as a result of 5-*exo*-*trig*-cyclization (Scheme 93).[207] The total yield of products **255** and **257** (1 : 4 ratio) is 89%.

Scheme 93

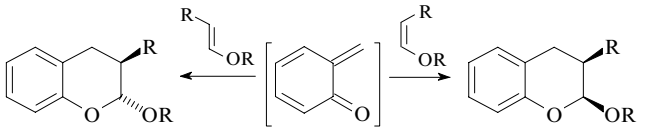


IV. Diels – Alder reaction

The inverse electron demand [4 + 2]-cycloaddition is one of the most popular reactions of *o*-QMs. The *o*-QM molecule usually functions as a heterodiene and the reactions result in the formation of various fused oxygen-containing rings. These reactions represent a convenient and general method for the synthesis of chromene and chroman systems. The high value of this approach is obvious, because a considerable complication of the carbon skeleton with a moiety encountered in many natural compounds occurs in one step. However, reactions of *o*-QMs with electron-deficient dienophiles are rare.[208 – 211]

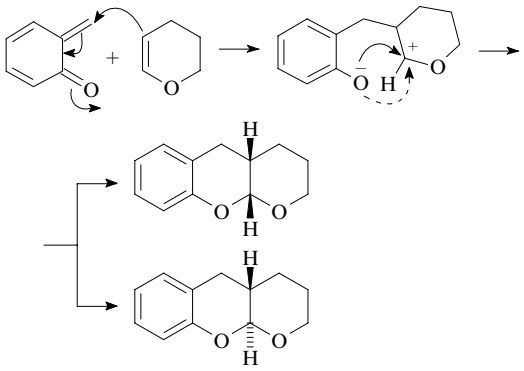
Cycloaddition is usually stereoselective and gives one adduct (Scheme 94).

Scheme 94



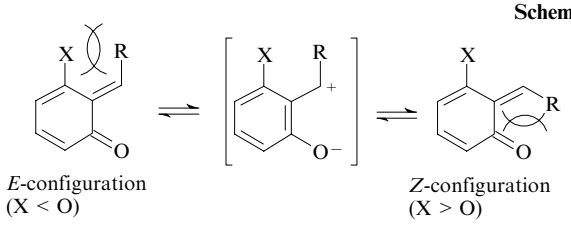
However, in some cases, especially in acid medium, the stereochemistry is violated. On the one hand, this is related to the participation of the protonated *o*-QM form in the reaction, and on the other hand, the formation of a cycloadduct can be a non-concerted process because of the high degree of polarization of reactants (Scheme 95).

Scheme 95



The selectivity of formation of Diels – Alder reaction products depends on three factors: diene and dienophile orientation in the transition state (*endo*- or *exo*-approach), *o*-QM geometry (*E*- or *Z*-configuration) and stability of the corresponding diastereomers. If the substituent X is smaller than the oxygen atom, *E*-configuration is preferred for steric reasons; otherwise, *Z*-isomer is preferred (Scheme 96).

Scheme 96



If *o*-QM in the *E*-configuration and monosubstituted alkene undergo [4 + 2]-cycloaddition, then the kinetically controlled *cis*-isomer is formed as the major product. In the case of thermodynamic control, the *trans*-isomer is formed

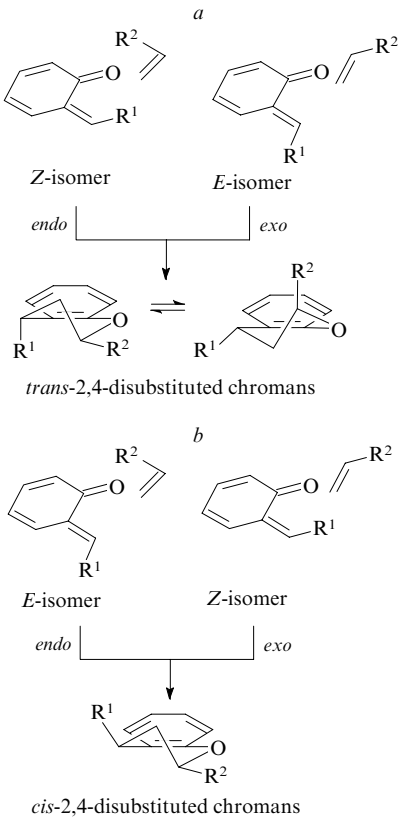
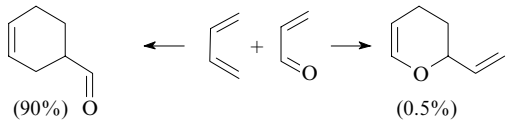


Figure 4. Schemes of formation of *trans*- (*a*) and *cis*-2,4-disubstituted chromans (*b*).

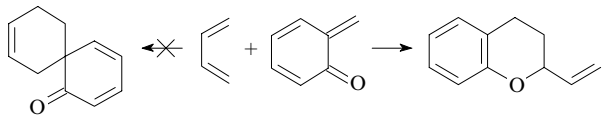
(Fig. 4).[212, 213] Usually, the higher the temperature of *o*-QM generation, the lower the diastereoselectivity of cycloaddition.

The aromatization of the quinone methide moiety is the driving force of most cycloaddition reactions. This fact represents the fundamental distinction between *o*-QMs and other α,β-unsaturated carbonyl compounds, which can be illustrated in relation to reactions of acrolein and *o*-QM with butadiene (Schemes 97, 98).[214]

Scheme 97



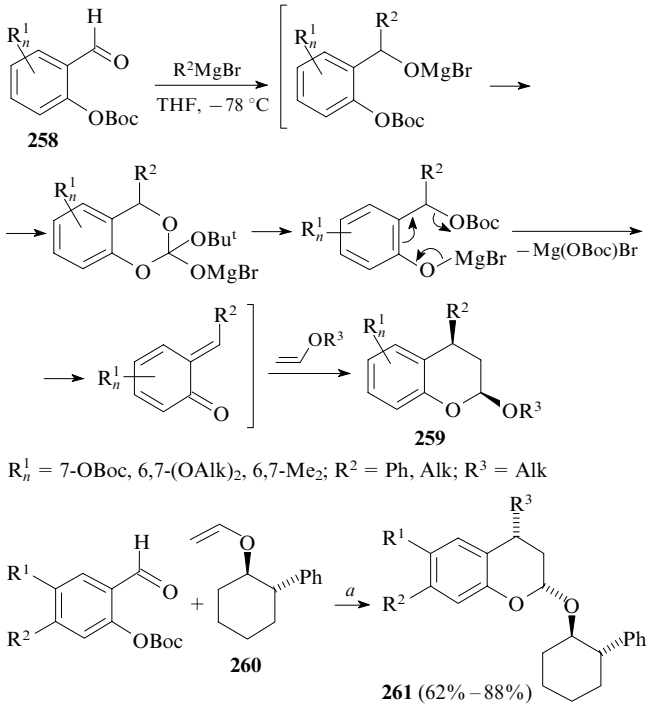
Scheme 98



IV.1. Cascade processes comprising the intermolecular version of [4 + 2]-cycloaddition

The domino processes with the hetero-Diels – Alder reaction being the final step are widely covered in the literature; their diversity is determined by the steps preceding the generation of *o*-QM. This step may be the initial nucleophilic addition to the carbonyl group. On treatment of *o*-OBoc-benzaldehydes **258** with organometallic compounds, in particular, Grignard reagents, *o*-QM is already generated at a temperature of −78 °C. The cascade includes nucleophilic addition of the organometallic compound to the carbonyl group, cyclization, migration of the Boc group and elimination of Mg(OBoc)Br, which subsequently decomposes with evolution of CO_2. If the *o*-QM is generated in the presence of a dienophile (vinyl ethers, enamines, styrene), [4 + 2]-cycloaddition products **259** are formed under very mild conditions (Scheme 99).[215 – 217] In the case where R^2 = Ph, R^3 = Et, the *cis*- to *trans*-isomer ratio is > 20 : 1. Note that using organolithium compounds it is impossible to generate the corresponding *o*-QM because of the strong coordination of the lithium ion to the oxygen atom of the phenolate from which the *o*-QM is directly generated. This sequence of transformations was also extended to the optically active vinyl ether **260** and was one of the first examples of enantioselective [4 + 2]-addition to *o*-QM to give product **261**.[218]

Scheme 99



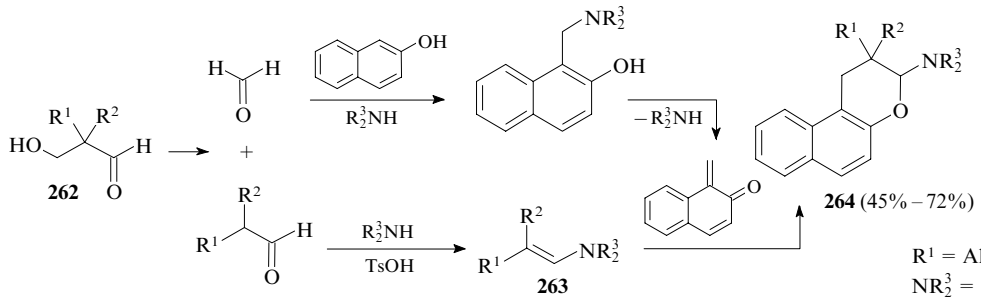
R^1_n = 7-OBoc, 6,7-$(OAlk)_2$, 6,7-Me_2; R^2 = Ph, Alk; R^3 = Alk

(*a*) R^3MgBr, Et_2O;
R^1 = H, OMe; R^2 = OBoc, $O(CH_2)_2TMS$; R^3 = Ph, Me

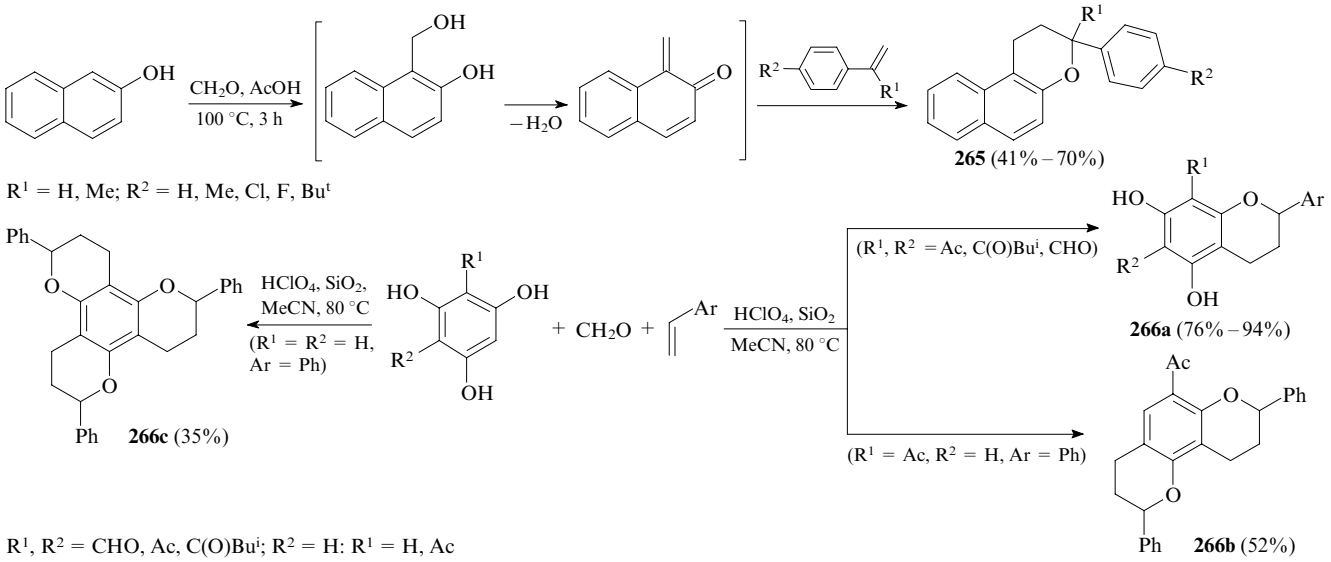
The reaction of 2-naphthol, secondary amine and 2,2-dialkyl-3-hydroxypropanals **262** proceeds in the presence of catalytic amounts of TsOH (Scheme 100).[219] This cascade reaction consists of the retro-aldol degradation of 2,2-dialkyl-3-hydroxypropanal **262** and the subsequent formation of the Mannich base from 2-naphthol, secondary amine and formaldehyde, which is formed in the retro-aldol reaction. The Mannich base undergoes the retro-Michael reaction to give *o*-QM and secondary amine, which is converted to enamine **263** upon the reaction with the second retro-aldol reaction product — 2,2-dialkylacetaldehyde. In the last step, *o*-QM reacts with enamine **263** to give the final 2,2-dialkyl-3-dialkylamino-2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans **264**. This reaction is also applicable to 1-naphthol.

The three-component reaction of 2-naphthol, formaldehyde and substituted styrenes affords 2,3-dihydro-1*H*-naphtho[2,1-*b*]pyrans **265** (Scheme 101).[220] Under similar conditions, phloroglucinols are converted to substituted flavans **266a – c**.[221]

Scheme 100



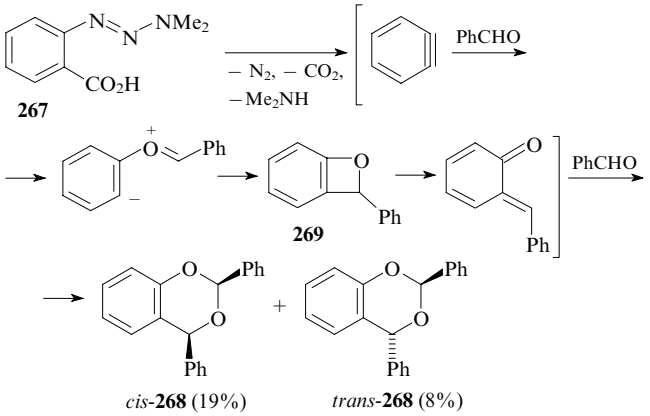
Scheme 101



Later this reaction was used for the preparation of polysubstituted chromans from 1,1-diarylethylenes, aromatic aldehydes and nucleophiles such as 2-naphthol, indoles and 1,3,5-trimethoxybenzene.[222] The process was conducted with acidic ionic liquids as catalysts without a solvent.

Heating of 1-(2-carboxyphenyl)-3,3-dimethyltriazene (**267**) with an excess of benzaldehyde leads to a mixture of *cis*- and *trans*-2,4-diphenyl-1,3-benzodioxins (**268**) in a low yield (Scheme 102).[223] Thermolysis of triazene **267** is accompanied by generation of dehydrobenzene, which undergoes [2 + 2]-cycloaddition reaction with benzaldehyde to give benzoxete **269** and then *o*-QM is formed upon

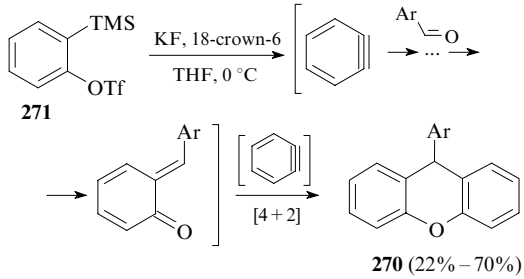
Scheme 102



cycloreversion. The [4 + 2]-cycloaddition involving a second benzaldehyde molecule gives 1,3-benzodioxins **268**. It is also noteworthy that since the synchronous thermal [2 + 2]-cycloaddition is forbidden by the Woodward–Hoffmann rules, benzoxete **269** is apparently formed in two steps *via* a zwitter-ionic intermediate.

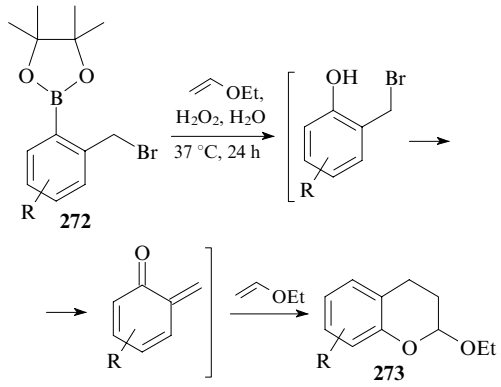
Of great interest is the synthesis of 9-arylxanthenes **270** from arynes and aromatic aldehydes. Arynes are generated *in situ* from *o*-(trimethylsilyl)phenyl triflate (**271**) under the action of the KF–18-crown-6 system (Scheme 103).[224] This

Scheme 103



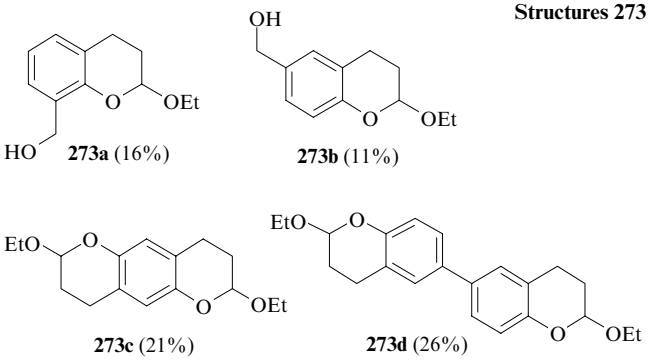
is followed by the reaction with aromatic aldehydes, which proceeds *via* zwitter-ion and benzoxete formation steps and gives *o*-QMs. The subsequent [4 + 2]-cycloaddition to a second dehydrobenzene molecule affords 9-arylxanthene **270**. The yields of xanthenes increase in the presence of electron-donating substituents in aromatic aldehydes.

Scheme 104

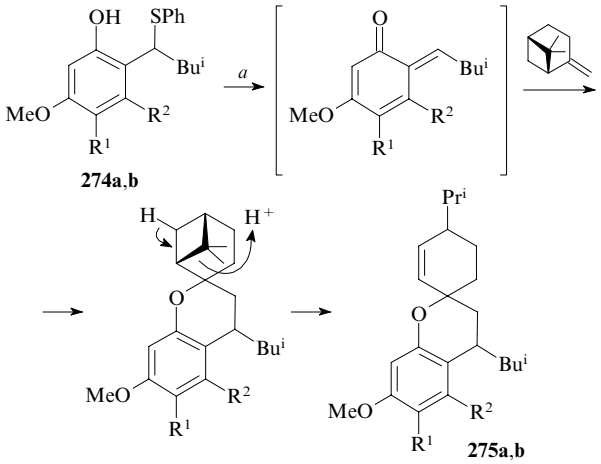


The oxidation of arylboronates **272** with hydrogen peroxide in a mixture of acetonitrile and phosphate buffer in the presence of vinyl ethyl ether gives Diels – Alder adducts **273** in moderate yields (Scheme 104).[225] Compounds **273a – d** obtained by this method are presented below.

Structures 273



Scheme 105



(*a*) $LiClO_4$, $MeNO_2$, methylene blue, 0.85 V, visible light (> 360 nm), 100 W;
R^1 = H, R^2 = OMe (**a**, 80% yield); R^1 = MeO, R^2 = H (**b**, 91%)

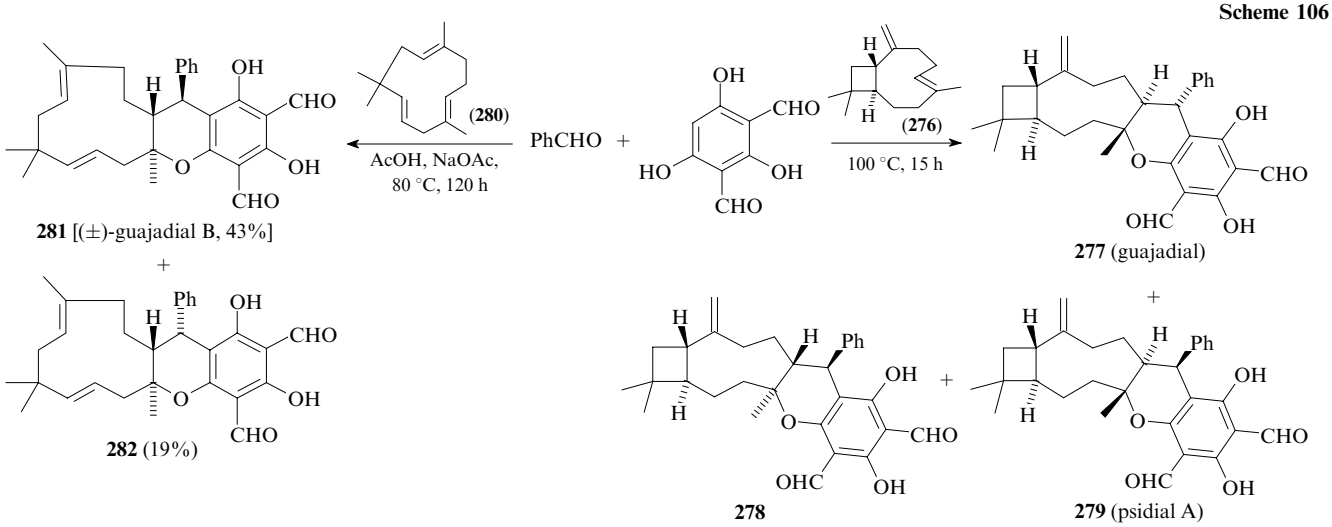
The photosensitized electrochemical oxidation of 2-(1-phenylthioalkyl)phenols **274a**,**b** in the presence of methylene blue and β-pinene provides an approach to the synthesis of spirochromans **275a**,**b** as mixtures of four diastereomers. Apparently, these compounds are formed upon skeletal rearrangement of the initially formed Diels – Alder adducts (Scheme 105).[226]

On heating of caryophyllene (**276**) (10 equiv.) with benzaldehyde (2 equiv.) and diformyl phloroglucinol (1 equiv.), three stereoisomeric products **277 – 279**, including two naturally occurring compounds, were isolated in 21% total yield (Scheme 106).[227] The initial product of benzaldehyde and diformylphloroglucinol condensation is dehydrated to give *o*-QM. The latter undergoes the Diels – Alder reaction in which the endocyclic double bond is more reactive due to the strain in the nine-membered ring. A cyclic triene, humulene (**280**), was used as the dienophile in this reaction to accomplish the biomimetic synthesis of racemic guajadial B (**281**) as a mixture with its epimer **282**.[228]

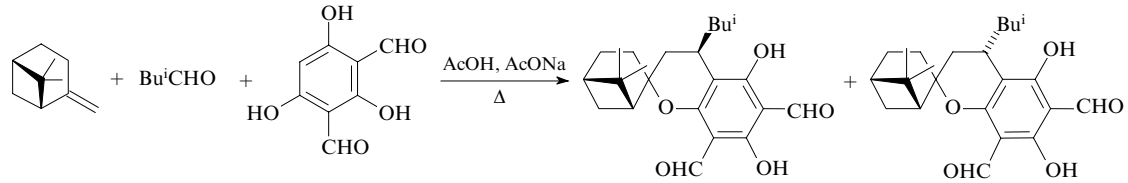
Robustadials A (**283**) and B (**284**) were synthesized by a similar chart using three-component condensation of β-pinene, isovaleraldehyde and diformylphloroglucinol (Scheme 107).[229]

The condensation of diformylphloroglucinol, benzaldehyde and bicyclogermacrene (**285**) in trifluoroethanol affords psiguadial D (**286**) in a yield of 10%. When hexafluoroisopropyl alcohol is used as the solvent, a mixture of the products of [4 + 2]-cycloaddition (**286**) (7% yield) and

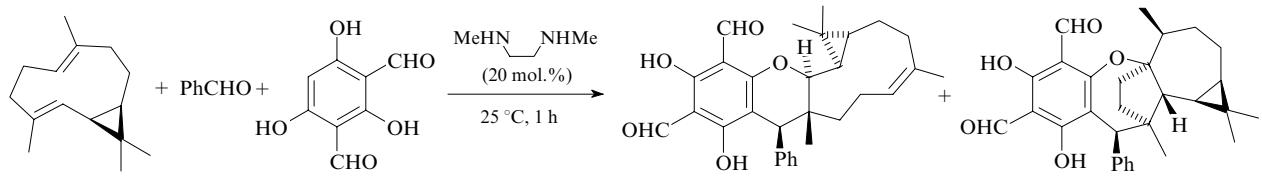
Scheme 106



Scheme 107



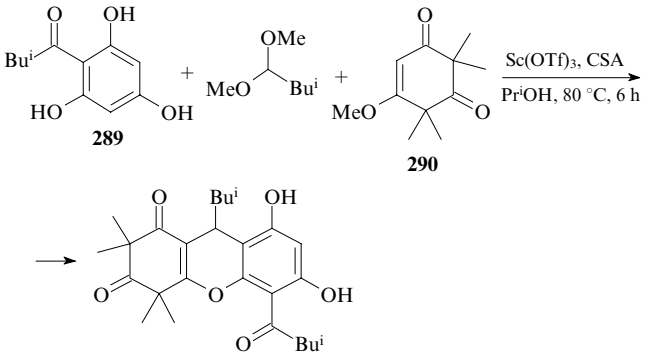
Scheme 108



formal [4 + 3]-cycloaddition (psiguadial A, **287**, 1% yield) is formed (Scheme 108).[230] Evidently, with such yields, this method requires further development; however, it is fairly promising for the synthesis of some natural compounds with a related skeleton.[231, 232]

The three-component synthesis of rhodomyrtosone B (**288**) was performed using 2,4,6-trihydroxyphenyl isobutyl ketone (**289**), isovaleraldehyde dimethyl acetal and syncarpic acid methyl ether (**290**) with scandium(III) triflate combined with camphorsulfonic acid (CSA) as the catalyst (Scheme 109).[233]

Scheme 109



Other examples of transformations of this type can be found in a review.[234]

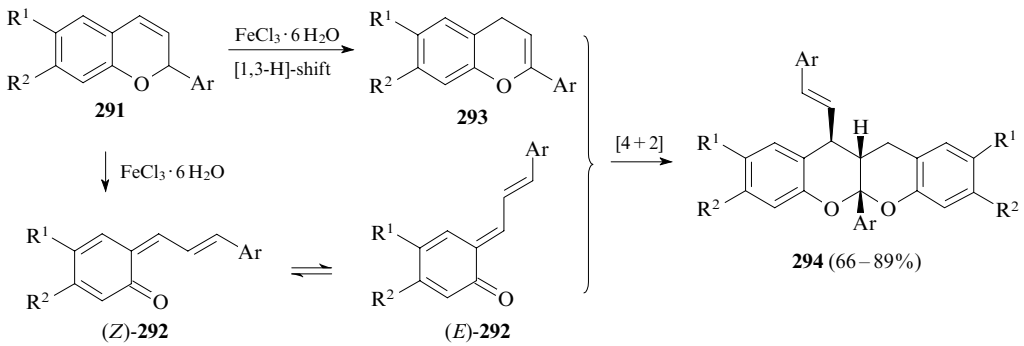
2*H*-Chromenes **291** are dimerized in the presence of $FeCl_3$ in dichloromethane (Scheme 110).[235] Under these conditions, one half of the 2*H*-chromene molecules is converted *via* oxa-6π-electrocyclic rearrangement to *o*-QMs (*Z*)-**292**, which occur in equilibrium with the *E*-isomers, while the other half undergoes a hydride shift, thus being isomerized to 2-flavene **293**, which is an active dienophile. The subsequent [4 + 2]-cycloaddition gives chromeno[2,3-*b*]chromenes **294**.

However, the use of 2*H*-chromenes containing electron-donating groups in position 7 results in the predominant formation of chromeno[4,3-*b*]chromenes **295a–e** as single diastereomers; this approach was used for the synthesis of dependensin (**295d**) (Scheme 111, Table 2).[235, 236]

It is noteworthy that the reactions of 2-(4-methoxyphenyl)-4*H*-chromenes with 2-(4-alkoxyphenyl)-2*H*-chromenes in the presence of $FeCl_3 \cdot 6H_2O$ produce chromeno[2,3-*b*]chromenes **294**, irrespective of the nature of substituent at the C(7) atom of 2*H*-chromene.[235]

A related acid-catalyzed reaction was carried out with diphenylethylene **296**.[237] The reaction starts with diphenylethylene **296** tautomerization to *o*-QM **297**, which reacts with a second equivalent of diphenylethylene **296** to afford polysubstituted chroman **298**. The subsequent protonation of chroman induces elimination of 3-methoxyphenol giving rise to chromene **299** (Scheme 112). In the case of TsOH

Scheme 110



Ar = 4-MeOC$_6$H$_4$; R^1 = H, Me, Br, O$_2$N, MeO; R^2 = H, Cl, Me$_2$NCO$_2$

Scheme 111

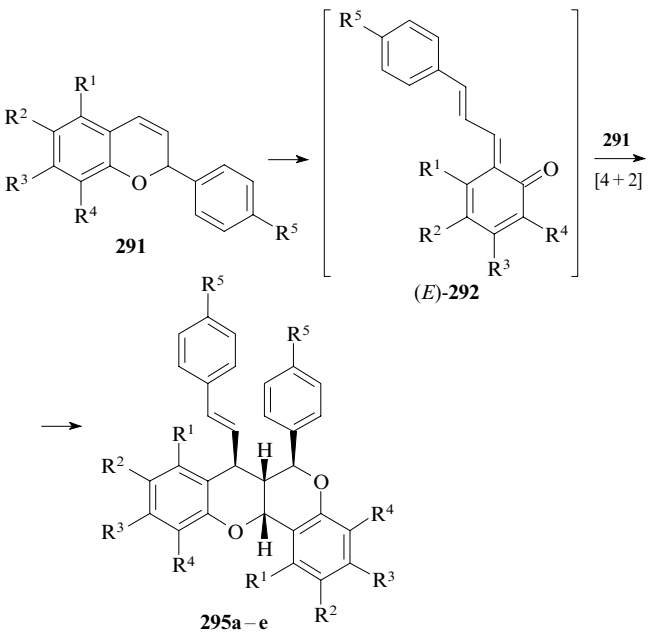


Table 2. Synthesis of chromeno[4,3-*b*]chromenes **295a – e** (see Scheme 111).[235, 236]

Compound **295**	R^1	R^2	R^3	R^4	R^5	Reaction conditions	Yield (%)
a	H	H	OMe	H	OMe	$FeCl_3 \cdot 6H_2O$	82
b	H	OCH_2O		H	OMe	$FeCl_3 \cdot 6H_2O$	64
c	OMe	H	OMe	OMe	H	$FeCl_3 \cdot 6H_2O$	62
d	OMe	H	OMe	OMe	OMe	conc. HCl, MeOH	72
e	H	H	See [a]	H	See [a]	conc. HCl, MeOH	92

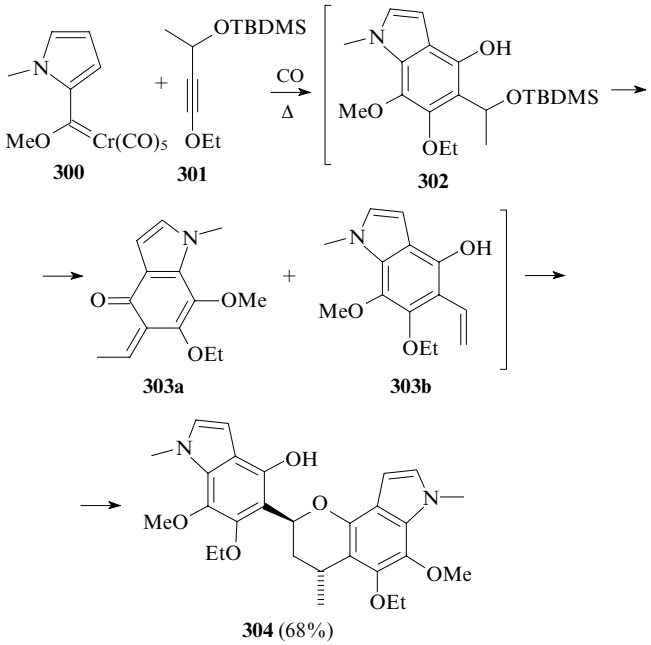
[a] OAc in the initial compound and OH in the product.

used as the catalyst, the intermediate chromans **298** can be isolated.[237]

The Dötz reaction of Fischer carbene **300** and alkyne **301** directly results in a 2,4-*trans*-substituted chroman type [4 + 2]-dimer (Scheme 113).[238] Probably, the intermediate phenol **302** is thermally degraded to give both *o*-QM **303a** in the *Z*-configuration and the corresponding styrene **303b** as a result of [1,5]-hydride shift. The subsequent *endo*-addition of styrene to *o*-QM gives cycloadduct **304**.

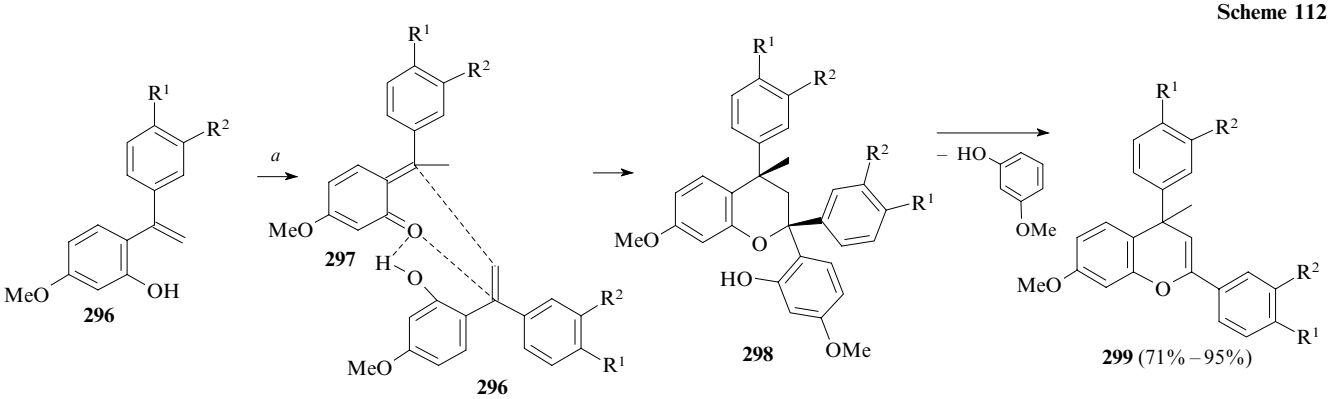
A unique cascade transformation comprising the Claisen rearrangement, generation of *o*-QM and intermolecular Diels – Alder reaction involving (−)-sabinene (**305**) resulted in the synthesis of the tetracyclic core of (−)-spirooliganones A (17*S*, **306a**) and B (17*R*, **306b**) possessing antiviral activity (Scheme 114).[239]

Scheme 113



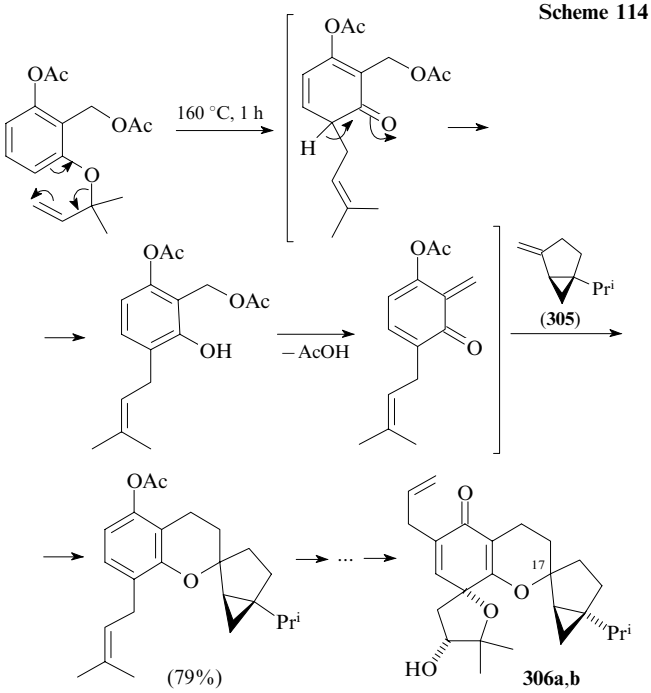
In most examples presented above, cycloaddition was the final step of the cascade process. However, if the cycloadduct formed initially is unstable, it may eliminate some small fragment. The formation of an additional multiple bond is usually thermodynamically favourable as this increases the conjugation length. Possible reagents for implementing this strategy are so-called push-pull alkenes **307**, which are compounds containing electron-donating and electron-withdrawing substituents at different ends of the double bond. The electron density redistribution caused by the substantial charge transfer from the donor to

Scheme 112



(*a*) H^+, PhCl, 50 °C, 3 h; R^1 = H, R^2 = OMe; R^2 = H: R^1 = H, F, Me, Bu^t, OMe; $R^1 - R^2$ = OCH_2O, benzo

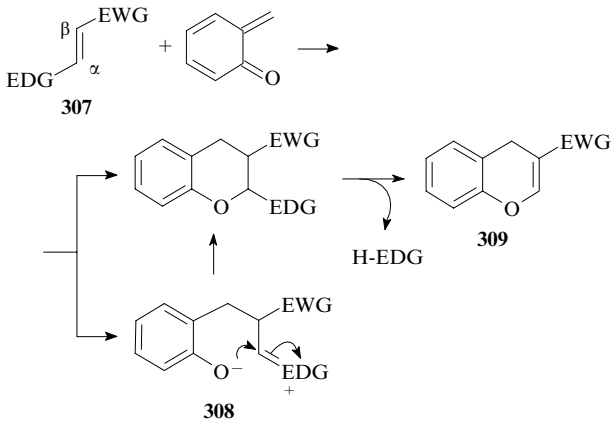
Scheme 114



Stereoisomers:: 17*S* (**a**), 17*R* (**b**)

acceptor substituent leads to C=C bond elongation, polarization and susceptibility to both nucleophilic and electrophilic attacks.[240] Therefore, alkenes of this type can be used in heterocyclization reactions.[241, 242] From the standpoint of ambiphilicity concept, the push-pull alkenes are 1,2-ambiphiles and react with *o*-QMs by the addition – elimination mechanism. The first step of the reaction may occur as either asynchronous but concerted [4 + 2]-cycloaddition or as a stepwise reaction *via* the formation of zwitter-ionic intermediate **308**, which would be converted to benzopyran derivative **309** upon 6-*exo*-*trig*-cyclization and elimination of an H-EDG group (Scheme 115).

Scheme 115



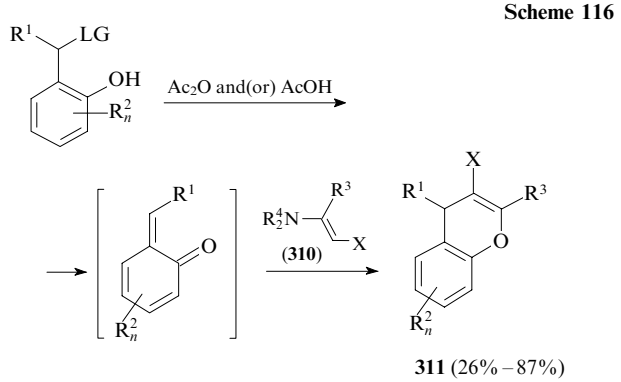
EDG is electron-donating group

For example, cycloaddition of enamines **310**, which contain various electron-withdrawing substituents (nitro, aldehyde, trifluoroacetyl or another substituent) in the β-position, to *o*-QMs generated from salicyl alcohol (**4b**) or naphthol Mannich bases **38** can be used to prepare substituted chromenes **311** (Scheme 116).[92, 243 – 247]

3-Amino-2-nitro-1*H*-benzo[*f*]chromenes **312a**,**b** were synthesized by the reaction of 1-(dimethylaminomethyl)-2-naphthol (**38a**) with nitroketene N,S-acetals **313a**,**b** combining conjugated electron-donating, electron-withdrawing and good leaving groups as well as C-nucleophilic and C-electrophilic centres in the molecule (Scheme 117).[92]

After the reaction of Mannich base **39b** (obtained from 2,4-di-*tert*-butylphenol) with malononitrile, the expected chromene **189a** and chromenopyridine **202d** were isolated together with unexpected dimer **314a** resulting from addition of the corresponding *o*-QM to chromene **189a**.[142] The

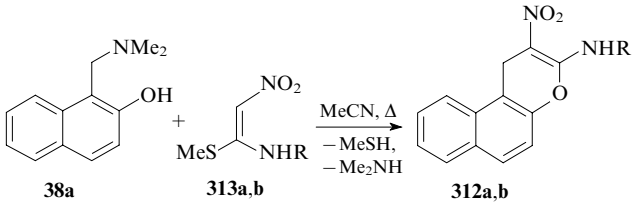
Scheme 116



311 (26% – 87%)

LG = Cl, OH, NMe_2, NMe_3I; R^1 = H, Ar; R^2_n = 6,7-Me_2, 6-OMe, 8-OMe, 6-(1-Ad), 8-(1-Ad), 6-Me, 6-Bu^t, 6-Ac, 6-NO_2, benzo[*h*], benzo[*f*], *etc.*; R^3 = H, Me; R^4_2N = Mor, NMe_2; X = NO_2, CHO, Ac, $C(O)CF_3$, C(O)Ar

Scheme 117

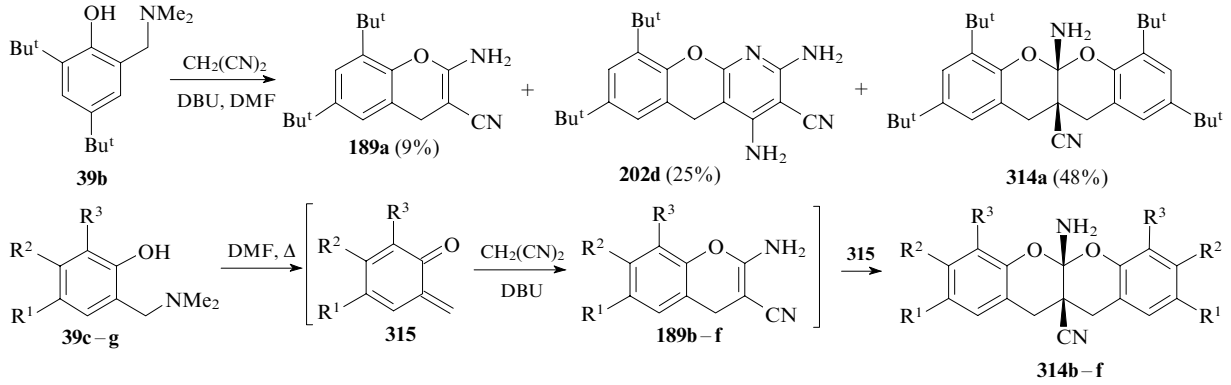


312, **313**: R = Bn (**a**, 34% yield), 4-MeC_6H_4 (**b**, 40%)

reaction was extended to other Mannich bases **39c** – **g**. The mechanism includes the thermal generation of *o*-QM **315**, its 1,4-addition to the malononitrile anion and cyclization to 2-amino-4*H*-chromene-3-carbonitrile **189**. The subsequent cycloaddition of a second equivalent of *o*-QM **315** to aminonitrile **189**, which acts as a heterodienophile, affords chromeno[2,3-*b*]chromenes **314a** – **f** as single *cis*-diastereomer (Scheme 118).[248] 2-Amino-4*H*-chromene-3-carbonitriles **189** can be regarded as push-pull alkenes.

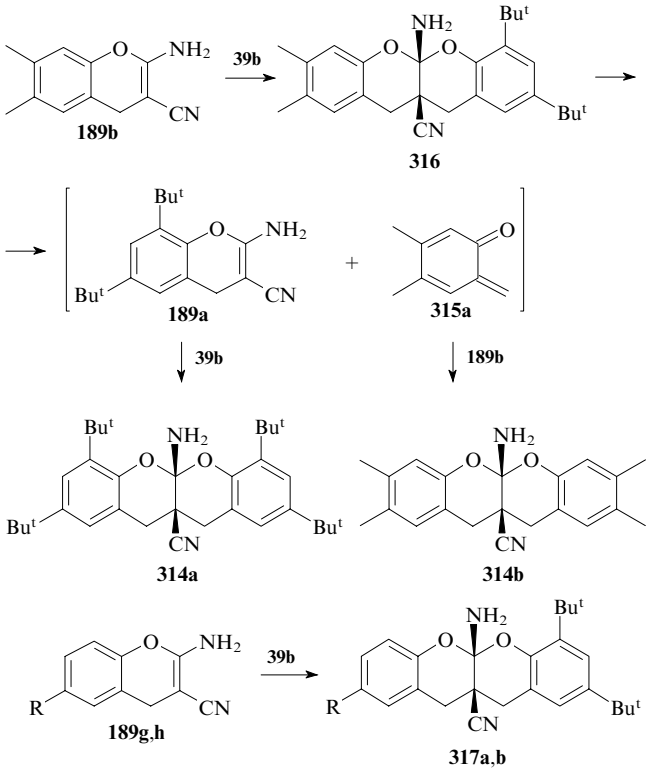
It is noteworthy that unsymmetrical chromeno[2,3-*b*]-chromene **316** cannot be isolated even in a low yield, which is attributable to its further degradation according to the retro-Diels – Alder reaction pathway to give a mixture of two symmetrical chromeno[2,3-*b*]chromenes **314a**,**b** (Scheme 119). In this case, the formation of unsymmetrical derivative **316** was detected only by chromatography – mass spectrometry of the reaction mixture.[92] Meanwhile, in the case of compounds **189g**,**h**, unsymmetrical chromeno[2,3-*b*]-chromenes **317a**,**b** were isolated in moderate yields (see Scheme 119).

Scheme 118



Compounds	R^1	R^2	R^3	Yield of **314** (%)	Compounds	R^1	R^2	R^3	Yield of **314** (%)
39c, **189b**, **314b**	Me	Me	H	44	**39f**, **189e**, **314e**	Bu^t	H	1-Ad	49
39d, **189c**, **314c**	MeO	H	H	37	**39g**, **189f**, **314f**	H	CO_2Me	H	39
39e, **189d**, **314d**	1-Ad	H	H	46					

Scheme 119

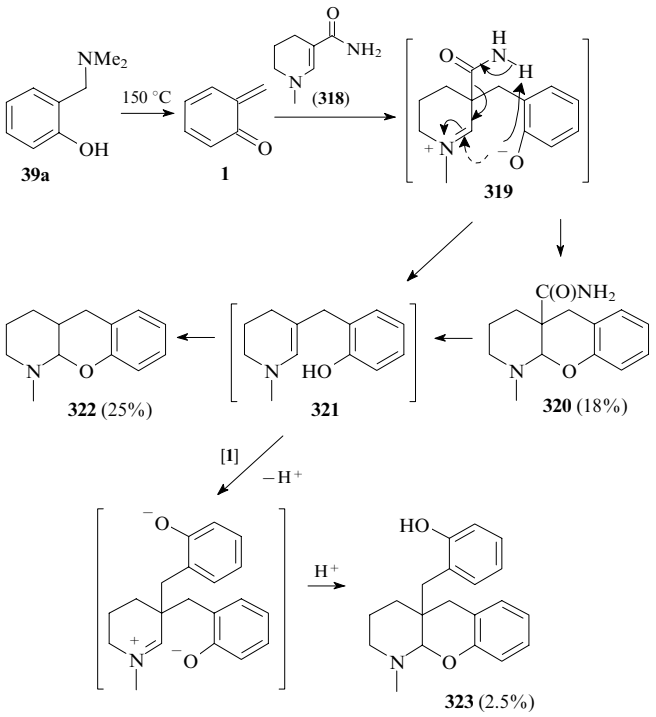


R = Bn (**189g**; **317a**, 18% yield), Bu^t (**189h**; **317b**, 20%)

The reaction of *o*-QM (**1**) generated from 2-(dimethylaminomethyl)phenol (**39a**) with tetrahydropyridine **318** affords a mixture of cyclic products. Presumably, all of the products are formed *via* phenolate **319**, which is able to cyclize directly to compound **320** or eliminate a proton from the amide group (leaving as cyanic acid) to give intermediate **321**, which is in turn converted to chromeno[2,3-*b*]piperidine **322** or its benzylated derivative **323** (Scheme 120).[249] This reaction indirectly confirms the high degree of asynchronicity of *o*-QM addition to highly polarized alkenes.

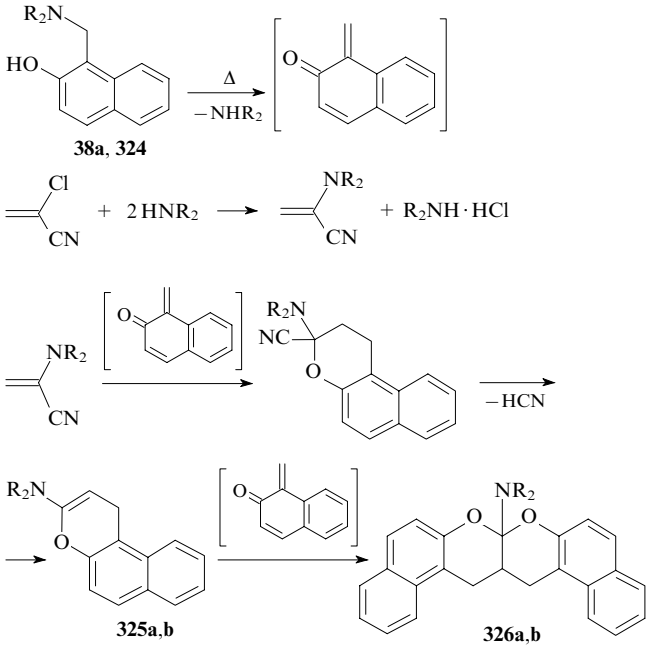
An unusual example of a [4 + 2]-cycloaddition–elimination–[4 + 2]-cycloaddition cascade is the reaction of *o*-QMs generated from naphthol Mannich bases **38a** and **324** with α-chloroacrylonitrile to give pyrano[3,2-*e*]pyrans (Scheme 121).[250]

Scheme 120



The secondary amine formed upon decomposition of the naphthol Mannich base reacts with α-chloroacrylonitrile to give α-cyanoenamine, which reacts with *o*-QM according to the Diels–Alder reaction pathway. The process is accompanied by elimination of an HCN molecule to give 3-aminonaphthopyrans **325a**,**b**, which undergo again the Diels–Alder reaction with a second *o*-QM molecule, resulting in the formation of benzannulated pyrano[3,2-*e*]pyrans **326a**,**b**.

Scheme 121



NR_2 = NMe_2 (**38a**; **325a**; **326a**, 68% yield), Mor (**324**; **325b**; **326b**, 75%)

This reaction is probably the first example of the cycloaddition of *o*-QM to a captodative alkene, represented by α-cyanoenamine.

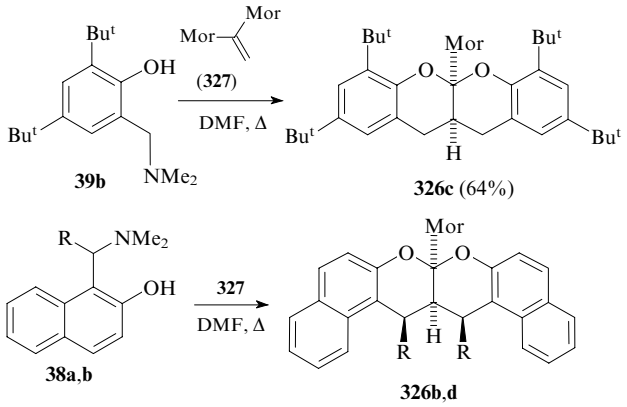
It was proposed to use 1,1-bis(morpholino)ethylene (**327**) as an alternative to toxic α-chloroacrylonitrile in the synthesis of symmetrical chromeno[2,3-*b*]chromenes **326b**–**d** (Scheme 122).[92]

The Diels–Alder reactions of 1-(dimethylaminomethyl)-2-naphthol (**38a**) or 2-(dimethylaminomethyl)phenol (**39a**) and enamines **328** yield 2,3-polymethylenebenzo(naphtho)-pyrans **329** or **330** (Scheme 123).[251]

A number of addition reactions of *o*-QMs to various enamines giving xanthene derivatives have been reported.[134, 214]

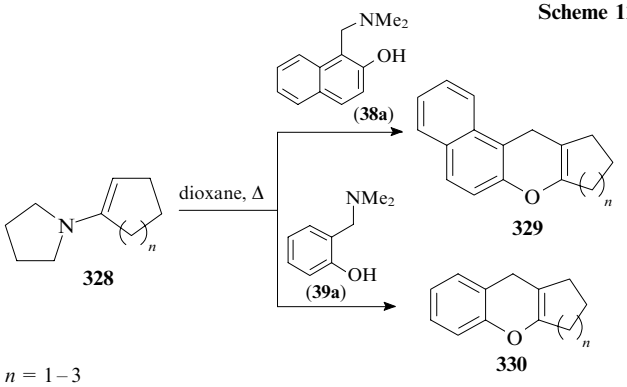
The reaction of 5-nitrosalicylaldehyde morpholinal **331** with cycloheptanone and cyclooctanone follows an intricate pathway, resulting in 3,3′-polymethylene-2,2′-spirobipyrans **332a**,**b** (Scheme 124).[252] The cascade process includes [4+2]-cycloaddition between the initially generated *o*-QM **333** and enamine, elimination of two morpholine molecules, [4+2]-cycloaddition of one more molecule of *o*-QM **333** to intermediate **334** and finally elimination of morpholine. In

Scheme 122



R = H (**38a**; **326b**, 75% yield), Ph (**38b**; **326d**, 43%)

Scheme 123



n = 1–3

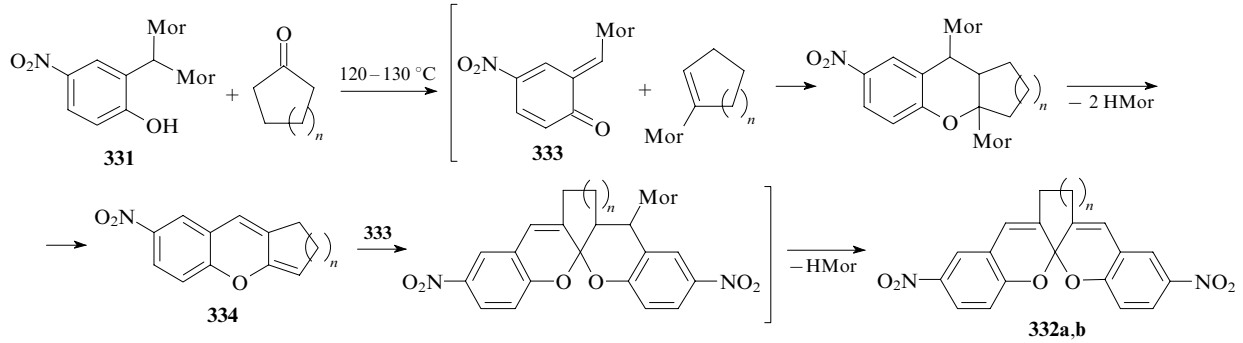
the presence of an excess of ketone, the reaction can be stopped after the formation of compound **334**.[253]

Pyrolysis of pyridoxine (**335**) in the presence of morpholinocyclohexene (**336**) resulted in the isolation of chromeno[2,3-*c*]pyridine derivative **337** in 33% yield (Scheme 125).[254] The reaction comprises the generation of pyridine-based *o*-QM, asynchronous cycloaddition of enamine to the *o*-QM, dehydrogenation and the subsequent elimination of the morpholine molecule.

Meanwhile, there are known examples of the addition of enamines generated *in situ* to *o*-QMs that is not accompanied by elimination; the reaction products formed in this case are 2-aminochromans.[255–257]

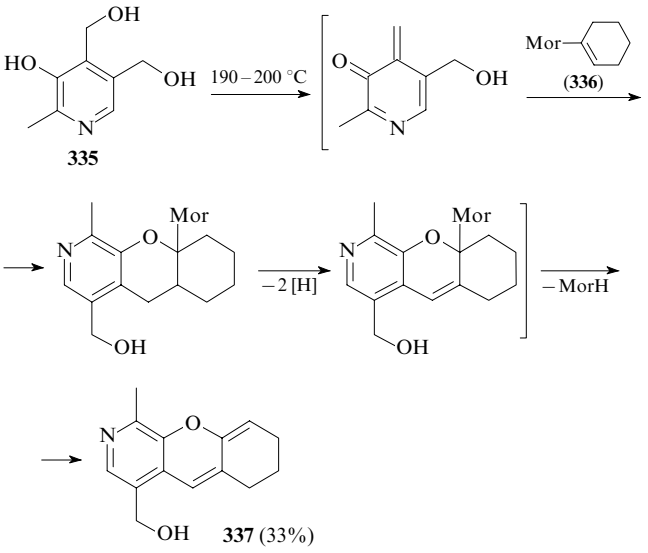
An efficient method has been proposed for the preparation of dihydrocoumarins from *o*-QMs generated *in situ* and

Scheme 124



n = 3 (**a**, 41% yield), 4 (**b**, 34 %)

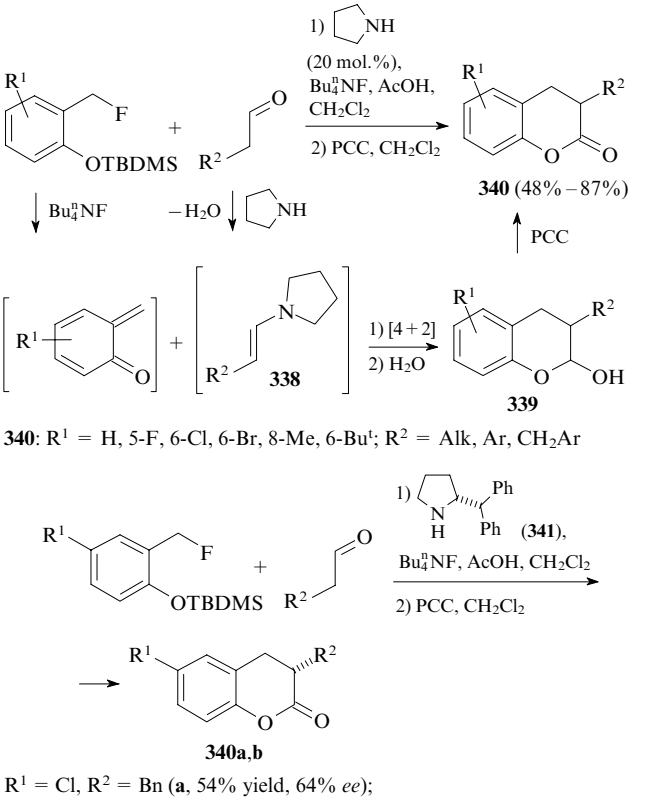
Scheme 125



enamines **338** based on substituted acetaldehydes and pyrrolidine.[258] The Diels – Alder adducts **339** formed initially are oxidized with pyridinium chlorochromate (PCC) to give dihydrocoumarins **340** in 48% – 87% yields over two steps. A similar reaction carried out with (*R*)-2-benzhydrylpyrrolidine (**341**) taken in a quantity of 20 mol.% affords dihydrocoumarins **340a**,**b** with a moderate enantioselectivity (Scheme 126).

Dihydrocoumarins **340** or **341** were successfully synthesized with the participation of NHC in the reaction of *o*-QMs with *N*-acylimidazoles[259] or carboxylic acids in the

Scheme 126



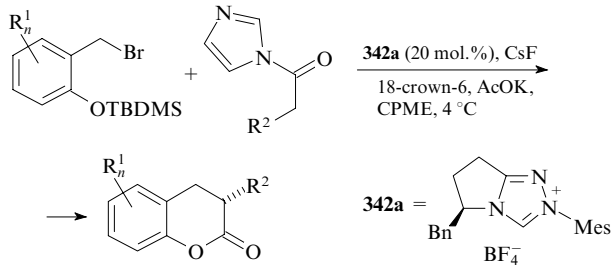
340: R^1 = H, 5-F, 6-Cl, 6-Br, 8-Me, 6-Bu^t; R^2 = Alk, Ar, CH_2Ar

340a,**b**

R^1 = Cl, R^2 = Bn (**a**, 54% yield, 64% *ee*);
R^1 = H, R^2 = Pr^n (**b**, 44%, 48% *ee*)

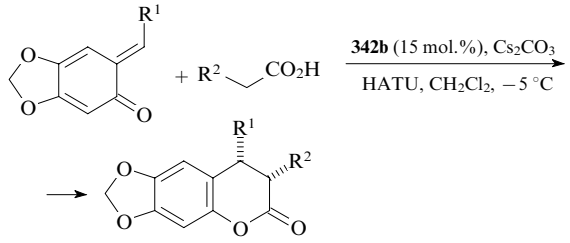
presence of condensing agents (Scheme 127).[260] The use of chiral precursors of NHC — salts **342a**,**b** — provides dihydrocoumarins with high enantio- and diastereoselectivity.

Scheme 127



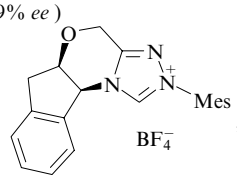
340 (56% – 80%, 50% – 86% *ee*)

R^1_n = H, 6,7-Me_2, 5-F, 6-F, 6-Cl; R^2 = Me, Pr^i, Bu^i, CH_2Ar;
CPME is cyclopentyl methyl ether

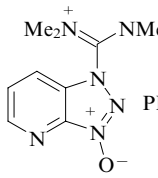


341 (53% – 80%, 79% – 99% *ee*)

R^1 = 4-MeC_6H_4, 4-$MeOC_6H_4$, PhCH=CH;
R^2 = Et, Ar;

342b = 

,

HATU = 

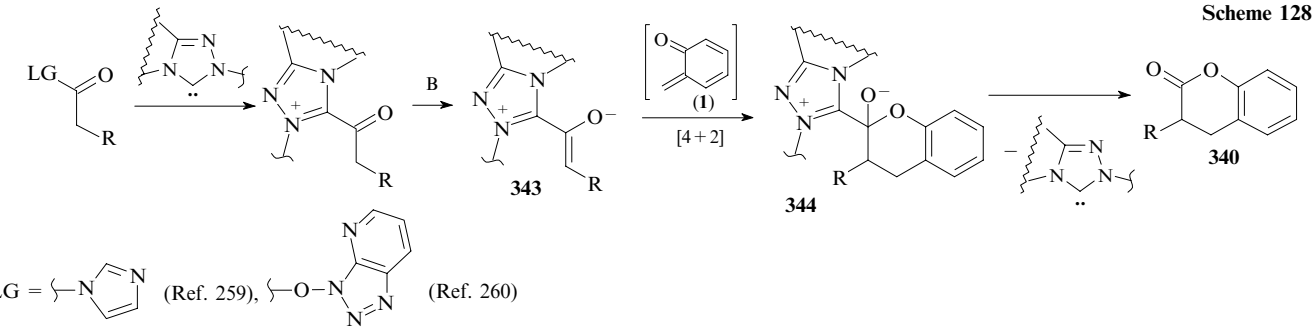
PF_6^-; Mes is 2,4,6-trimethylphenyl

The reaction of NHC generated from azolium salts **342a**,**b** under the action of bases with carboxylic acid derivatives followed by deprotonation gives rise to enolate **343**, which then reacts with *o*-QM. It has not been found out whether this reaction is concerted or stepwise, involving the conjugate addition of the enolate to *o*-QM and subsequent 6-*exo*-*trig*-cyclization. The elimination of NHC from intermediate **344** yields dihydrocoumarins **340** (Scheme 128).

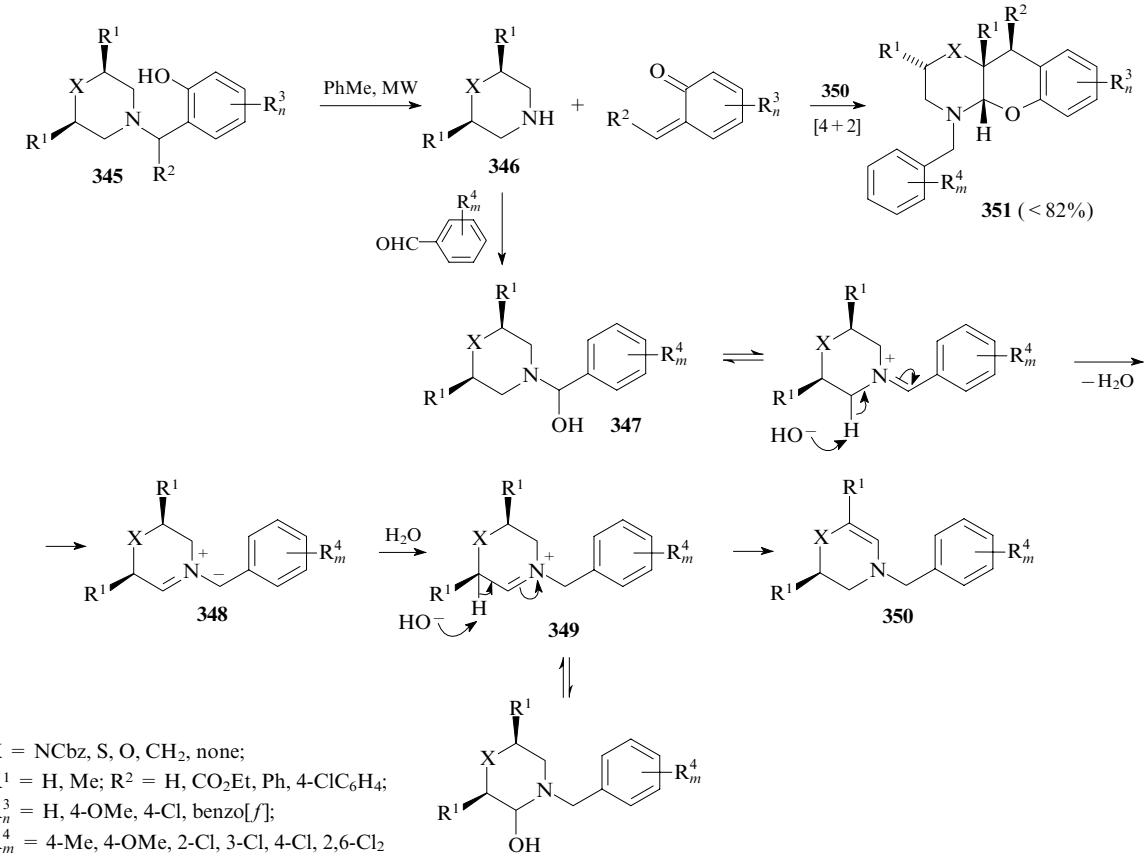
An efficient method has been developed for the synthesis of cyclic N,O-acetals; the method consists in microwave irradiation of a mixture of an aromatic aldehyde with compounds **345** — Mannich bases of phenol or 2-naphthol (Scheme 129).[261] The reaction starts with the generation of *o*-QM with elimination of cyclic amine **346**, which reacts with the aldehyde to give hemiaminal **347**, then azomethylide **348** and endocyclic iminium cation **349**, and finally enamine **350**. N,O-Acetal **351** is formed in the Diels – Alder reaction of enamine **350** with the *o*-QM.

Spirocyclic chromans containing an N,O-acetal moiety were obtained by the three-component acid-catalyzed reaction of substituted phenols, imidazolidin-4-ones **352** and paraformaldehyde (Scheme 130).[262] The domino process includes hydroxymethylation of phenol with paraformalde-

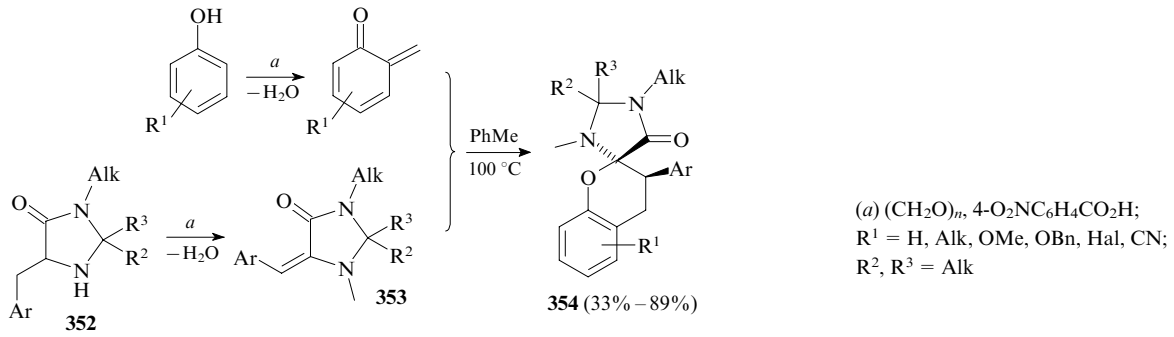
Scheme 128



Scheme 129



Scheme 130

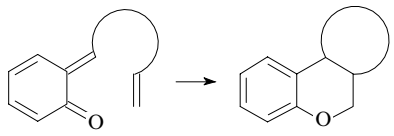


hyde and dehydration of salicyl alcohol to *o*-QM. At the same time, imidazolidin-4-ones **352** react with paraformaldehyde with elimination of water to be converted to arylideneimidazolidin-4-ones **353**, which react with *o*-QM to give spirochromans **354**.

IV.2. Intramolecular Diels – Alder reaction

The intramolecular Diels – Alder reaction involving *o*-quinone methides is shown in the general form in Scheme 131.

Scheme 131



Most of the intramolecular Diels – Alder reactions reported in the literature refer to the synthesis of natural products or structurally related compounds. For example, the reaction of methyl 2,4-dihydroxybenzoate (**355a**) with (*R*)-(+)-citronellal [(*R*)-**356**] catalyzed by ethylenediaminodiacetate (EDDA) gives rise to tricyclic product **357a** as a result of consecutive hydroxyalkylation, dehydration (with the generation of *o*-QM **358**) and intramolecular [4+2]-cycloaddition reactions (Scheme 132). It is noteworthy that since resorcinols behave similarly to cyclic 1,3-diketones in many transformations, the first step of this cascade process can be classified as the Knoevenagel reaction.[263] The stereospecific formation of only the *trans*-adduct can be attributed to the pseudo-equatorial orientation of *o*-QM **358** in the energetically more favourable *exo*-transition state.[264] The regiospecific generation of *o*-QM **358** is caused by the presence of an intramolecular hydrogen bond between the hydroxyl hydrogen atom and the ester carbonyl oxygen atom. A similar sequence of transformations was applied for the synthesis of compound **357b** from orcinol (**355b**).[265] *m*-Styrylresorcinol **359** was reacted with (*S*)-(−)-citronellal [(*S*)-**356**] to give (+)-machaeriol A (**360**),[266] which has been isolated from the bark of the *Machaerium multiflorum* tree.[267]

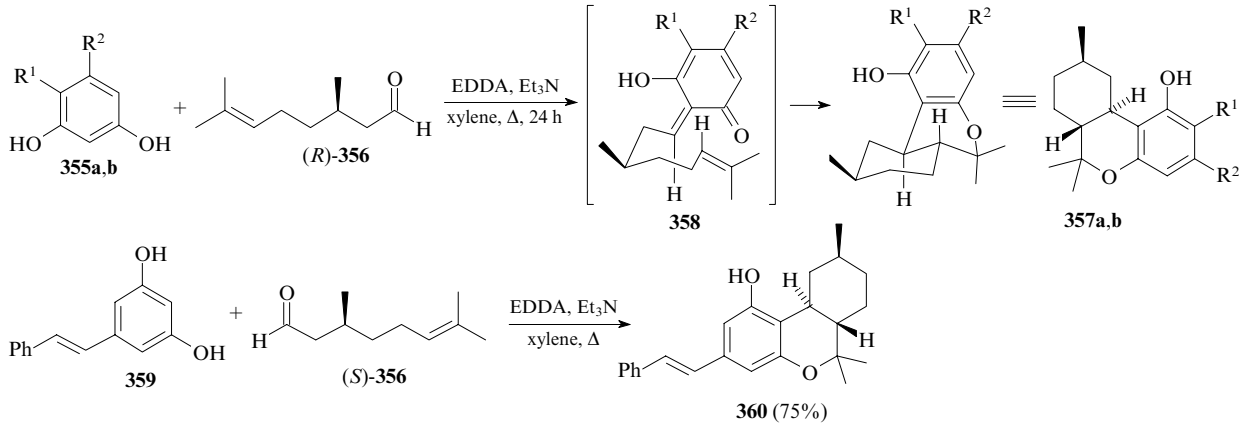
Along with resorcinols, naphthols can also be involved in this reaction to give naphthopyran derivatives. In this case, phenylboronic acid[116,268] and quinoline[269] are also used as catalysts.

Using O-allyl salicylaldehyde derivatives **361**, 6a,12b-dihydro-6*H*,7*H*-chromeno[3,4-*c*]chromenes **362** and naphthopyranobenzopyrans **363** were prepared from 4-acetylresorcinol and 1-naphthol, respectively (Scheme 133).[270] The *cis*-configuration of the products is associated with the fact that *exo*-transition state **364** is less favourable due to 1,3-allylic strain.[271]

Zhao *et al.*[272] succeeded in constructing the furo[3,2-*c*]benzopyran nucleus by condensation of various substituted salicylaldehydes and α-prenyl alcohols **365** catalyzed by benzenesulfonic acid; most often, this gave only one diastereomer **366** (Scheme 134). Hemiacetal **367** formed in the first step eliminates a water molecule to give the corresponding *o*-QM, which is then involved in the intramolecular Diels – Alder reaction.

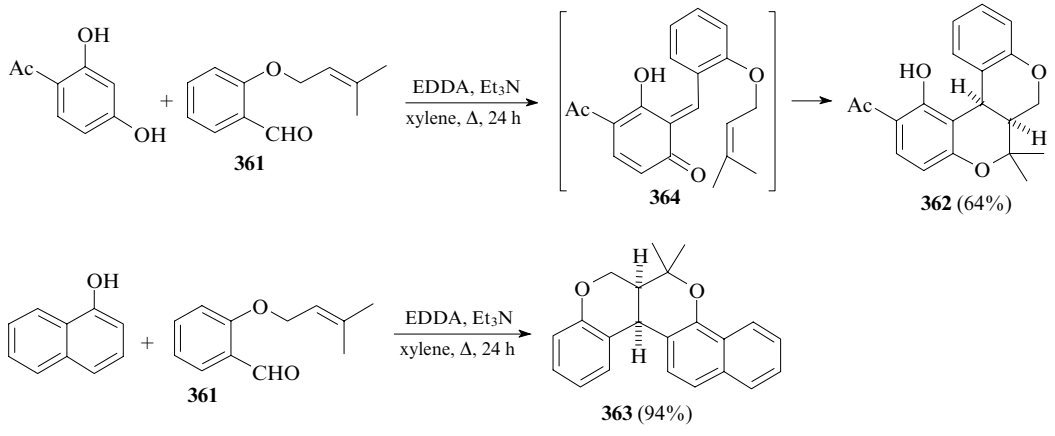
Trauner's group[273] accomplished a cascade process initiated by desilylation. The process included oxidation of compound **368** to 1,4-naphthoquinone **369**, tautomerization of the latter to *o*-QM **370** and spontaneous intramolecular [4+2]-cycloaddition. The subsequent demethylation of product **371a** afforded rubioncolin B (**371b**) (Scheme 135).

Scheme 132

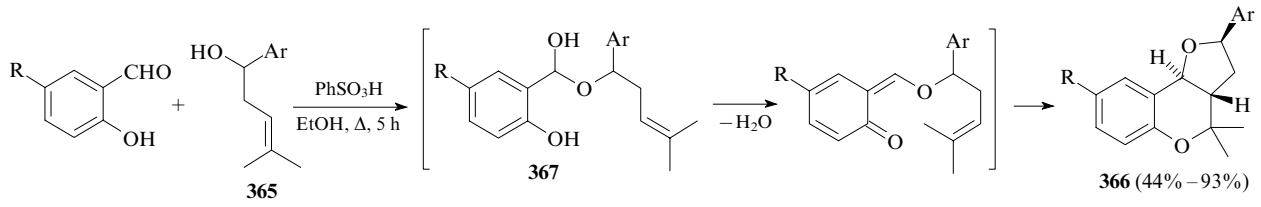


R^1 = CO_2Me, R^2 = H (**a**); R^1 = H, R^2 = Me (**b**)

Scheme 133

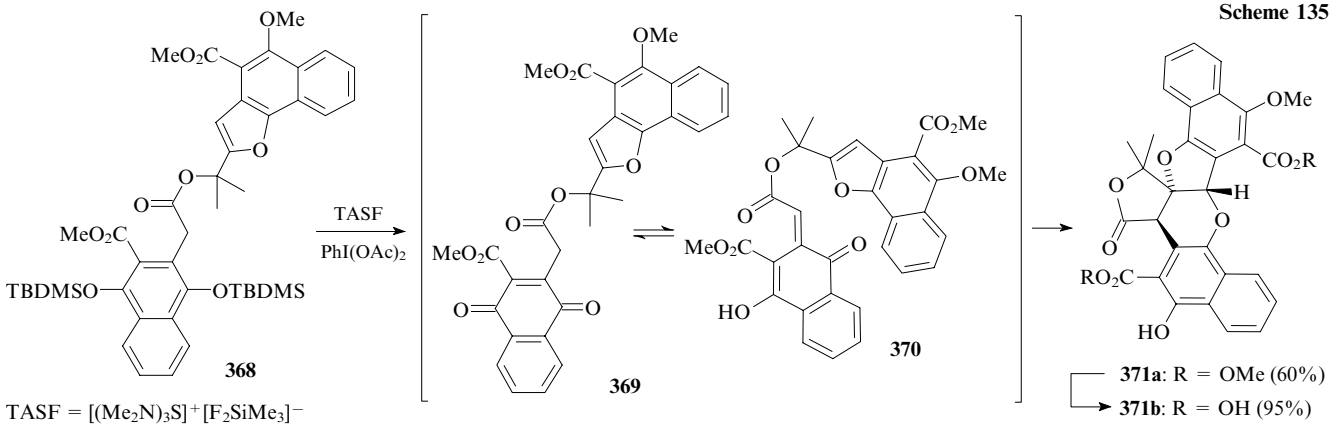


Scheme 134



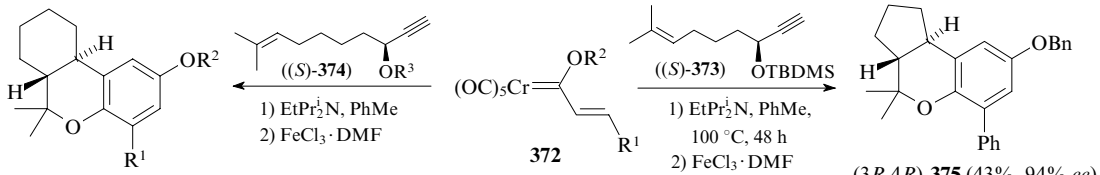
R = H, Cl, Br, Me, NO_2

Scheme 135



TASF = $[(Me_2N)_3S]^+[F_2SiMe_3]^-$

Scheme 136



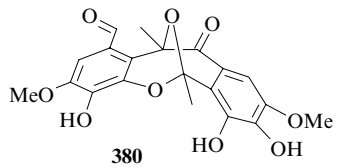
R^1 = Ph, benzofuran-2-yl; R^2 = Me, Bn; R^3 = TIPS, TBDMS, Ph_3C

The Dötz reaction involving Fischer carbenes **372** and alkynes **373** and **374** leads to tricyclic pyrans **375** and **376** *via* the generation of *o*-QMs (see Section V.3) and intramolecular Diels – Alder reaction (Scheme 136).[274]

Recently, it was shown that oxidation of 2-(2-acylphenyl)benzofurans **377** with oxone ($KHSO_4 \cdot 2\,KHSO_5 \cdot K_2SO_4$) in the presence of sodium hydrogen carbonate affords heterocyclic system **378** that is difficult to prepare by other methods. The cascade of reactions includes epoxidation, valence isomerization to *o*-QMs **379** and [4 + 2]-cycloaddition (Scheme 137).[275]

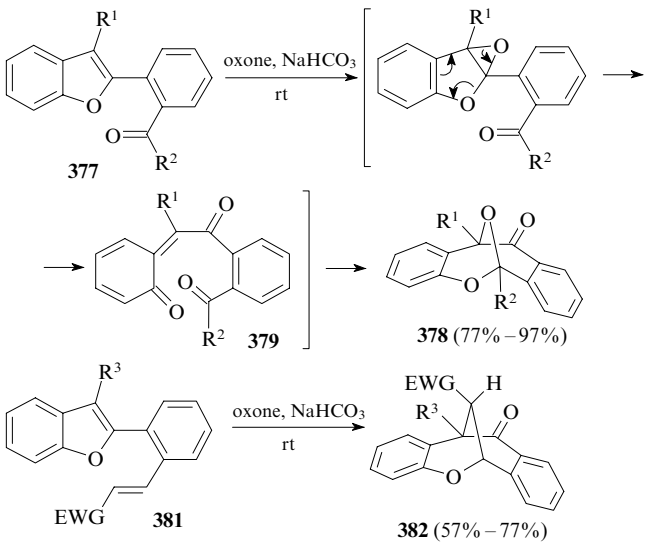
The last-mentioned reaction occurs with the participation of two electron-depleted moieties: *o*-QM as a heterodiene and the carbonyl group as a dienophile. This process was used as the key step in the synthesis of naturally occurring integrastatin B (**380**), which exhibits anti-HIV activity.[276]

Structure 380



380

Scheme 137



R^1, R^2 = H, Alk; R^3 = Me, Et; EWG = Ac, Bz, CO_2Et, NO_2

A similar cascade of transformations can also be accomplished for various 2-(2-vinylphenyl)benzofurans **381** to give products **382** (see Scheme 137).

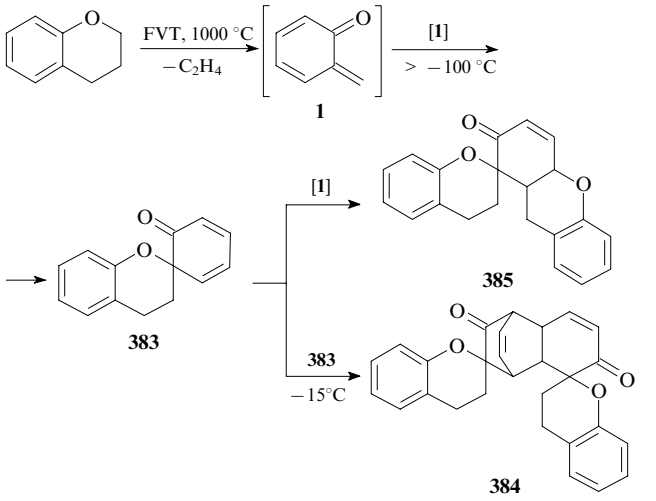
IV.3. Oligomerization of *o*-quinone methides

A key stabilization pathway of *o*-QMs in the absence of active nucleophiles or dienophiles is the Diels – Alder type self-condensation. This transformation is a typical cascade process. The first step usually includes elimination of a low-molecular-weight compound (water, secondary amine, tertiary amine hydrohalide and so on), giving rise to highly reactive *o*-QM. The intermediate formed in this step reacts, most often, with a second *o*-QM molecule at the exocyclic double bond to give a dimer. The driving force of the process is re-aromatization of one of the carbocycles. This fact accounts for the ease of this reaction as compared, for example, with acrolein dimerization. The frequently formed dimer reacts with one more *o*-QM molecule to give the corresponding trimer. Reactive *o*-QMs can also undergo further oligomerization, resulting in a complex mixture of products.

One of the first examples of *o*-QM dimerization was reported by Hultzsch[277] back in 1941. Dimerization (and subsequent oligomerization) of sterically unhindered *o*-QMs is so an active cascade process that it occurs even at low temperature. Indeed, the simplest *o*-QM (**1**) was prepared by flash vacuum thermolysis (FVT) from unsubstituted chroman.[278] The absorption bands of the monomeric *o*-QM were detected by UV spectroscopy. However, at temperatures above −100 °C, a new set of absorption bands already appears and the sample rapidly changes from yellow-coloured to colourless, which is associated with the formation of dimer **383** (Scheme 138). As the mixture warms up to −15 °C, the set of IR absorption bands for the dimer disappears, but another set appears, which corresponds to tetramer **384** according to the data of mass spectrometry. It is noteworthy that up to room temperature, the IR spectrum of the mixture always contains a weak absorption band at 1681 cm^{-1}, which has been assigned to trimer **385**.

o-Quinone methide **386** and the products of its oligomerization **387** – **389** were prepared in a similar way by flash

Scheme 138

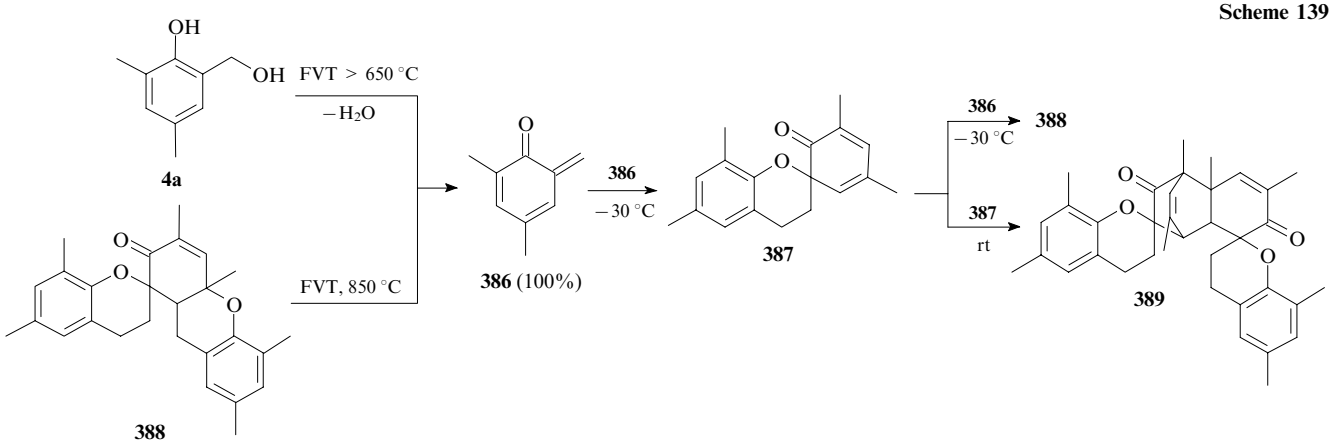


vacuum thermolysis from 4,6-dimethylsalicyl alcohol (**4a**).[279] It was shown that complete conversion of salicyl alcohol **4a** to *o*-QM takes place at 650 °C, while trimer **388** is converted to *o*-QM at 850 °C. Trimer **388** and tetramer **389** in approximately equal molar amounts (98% total yield) were isolated upon pyrolysis carried out at 800 °C (Scheme 139). Trapping of *o*-QM at −30 °C resulted in the isolation of dimer **387** and trimer **388**.

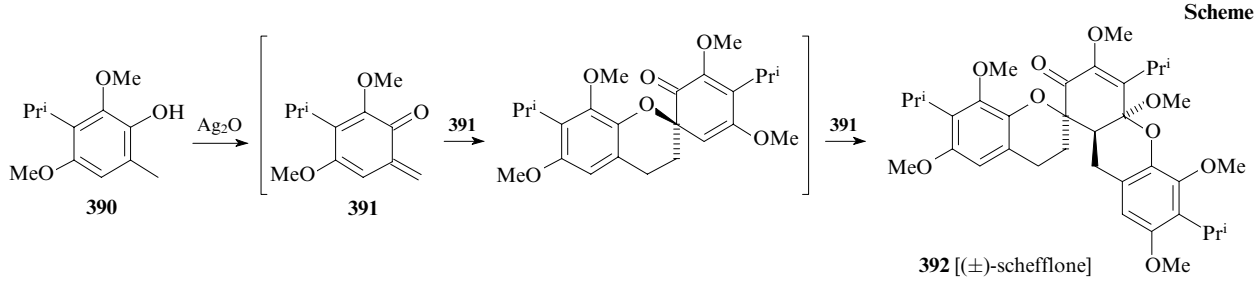
Trimerization also takes place in the oxidation of *o*-alkylphenols with Ag_2O or $K_3[Fe(CN)_6]$.[280, 281] Treatment of espintanol **390** with Ag_2O induced, first, the *in situ* generation of *o*-QM **391**, which provided the synthesis of natural triterpenoid (±)-schefflone (**392**) (Scheme 140)[282] and a number of tocopherol trimers.[283]

o-Quinone methide trimers were also prepared from unstable *o*-halomethylphenols.[284, 285] For example, heating of 2,6-bis(bromomethyl)-4-methylphenol (**393**) for 100 h affords trimer **394**. The subsequent crystallization of **394**

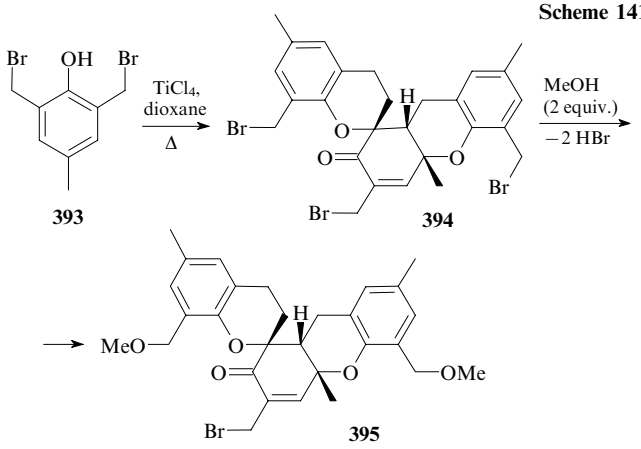
Scheme 139



Scheme 140



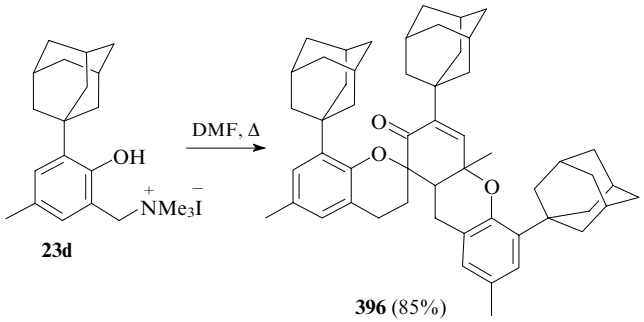
Scheme 141



from methanol leads to dimethoxy derivative **395** (Scheme 141).

Trimer **396** was prepared in a high yield by heating sterically crowded *o*-QM precursor **23d** in refluxing DMF (Scheme 142).[286] This reaction is the first example of the selective formation of *o*-QM trimerization product upon thermolysis of a quaternary ammonium salt.

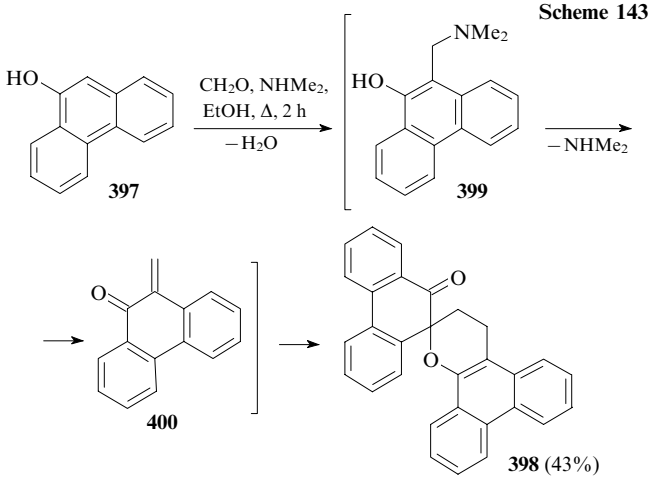
Scheme 142



Products of *o*-QM oligomerization were also isolated upon pyrolysis of 4*H*-benzo[*d*][1,3,2]dioxasilines[287] and 4*H*-benzo[*d*][1,3,2]dioxaborinines.[288]

The Mannich reaction–[4+2]-cycloaddition cascade underlies the synthesis of spirocyclic phenanthrene type dimers. For example, aminomethylation of 9-phenanthrenol **397** with dimethylamine and formaldehyde can be used for the preparation of the corresponding cycloadduct **398** in 43% yield (Scheme 143).[289] With catalytic amounts of pyridine instead of dimethylamine, the dimer can be isolated

Scheme 143

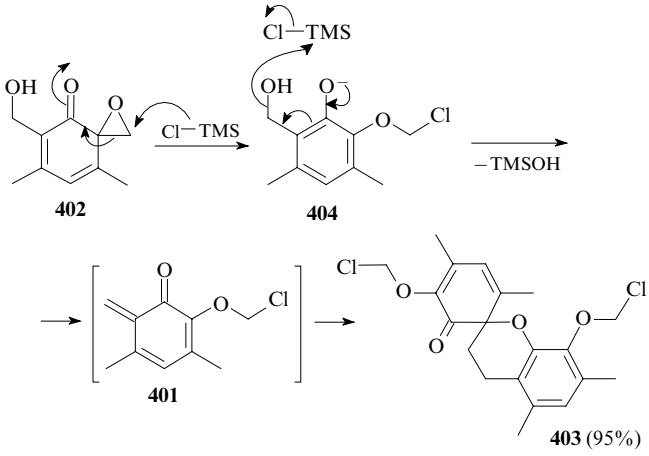


in a yield of 40%; conduction of this reaction without any base also gives the dimer (36% yield). The ease of deamination of Mannich base **399** is attributable, on the one hand, to the formation of *o*-QM **400**, which is fairly stable owing to the long conjugation chain present in the molecule, and, on the other hand, to the fact that generation of the *o*-QM does not require high energy expenditure, as two π-electron sextets are present in both the Mannich base and the corresponding *o*-QM.

When L-proline was used instead of dimethylamine, analogous spirodimers of type **398** were isolated in up to 85% yields.[290] Generally, the product yields tend to increase with increasing number of electron-donating alkoxy groups in 9-phenanthrenol.

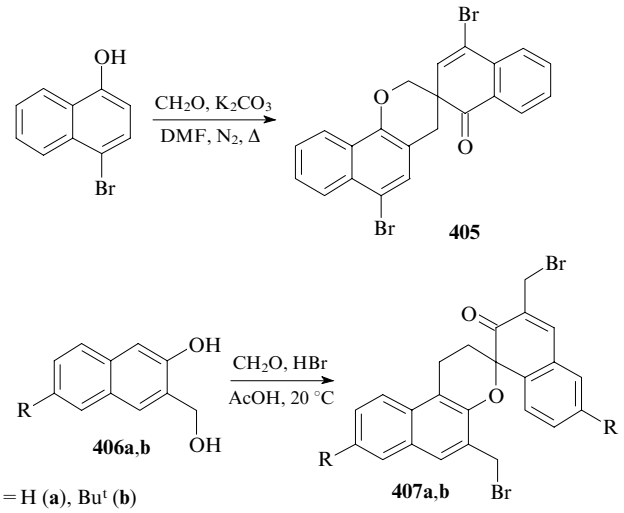
A fairly mild method for the generation of *o*-QM **401** from spirocyclic oxirane **402** and chlorotrimethylsilane has been developed (Scheme 144).[291] As a result, head-to-head dimer **403** was isolated in an almost quantitative yield. The authors assume that this domino process involves the intermediate formation of salicyl alcohol-derived phenolate **404**, which reacts with a second equivalent of Me_3SiCl to generate *o*-QM **401**.

Scheme 144



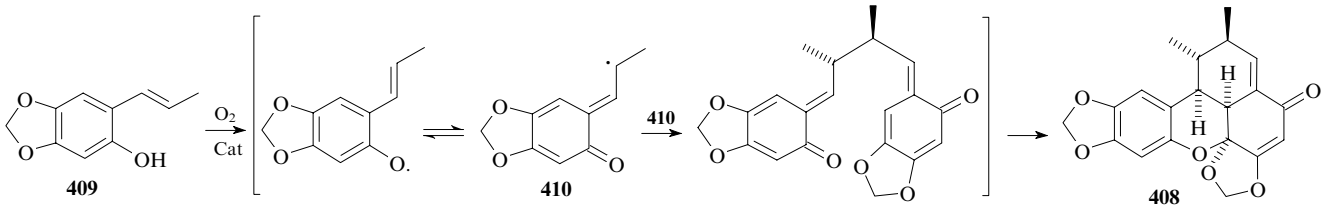
The driving force of the process is the formation of a stronger Si–O bond [bond energy (E_b) = 443 kJ mol^{-1}]

Scheme 145



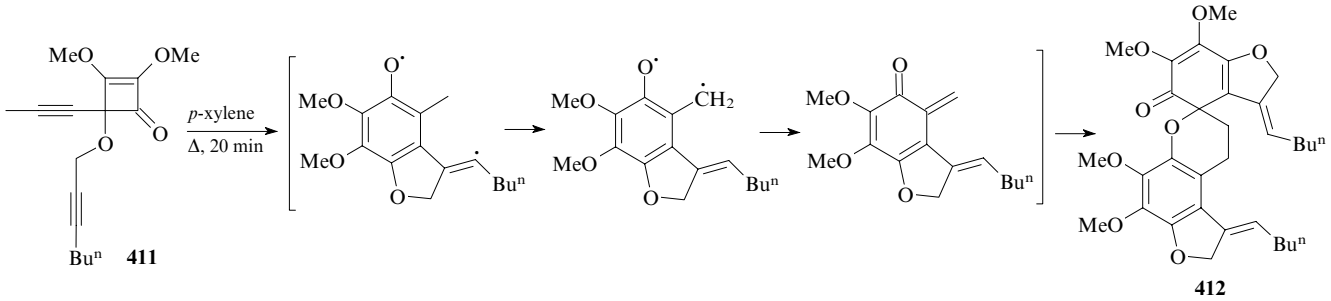
instead of the Si–C bond (E_b = 313 kJ mol^{-1}). An advantage of the method is the possibility to conduct the synthesis at room temperature without oxidants, acids or bases;

Scheme 146



Cat = Co^{II}(salpr) (90% yield), Co^{II}(salen) (94%), $PdCl_2$ (46%); salpr is bis(3-salicylideneaminopropyl)amine; salen is *N*,*N*′-bis(salicylidene)ethylenediamine

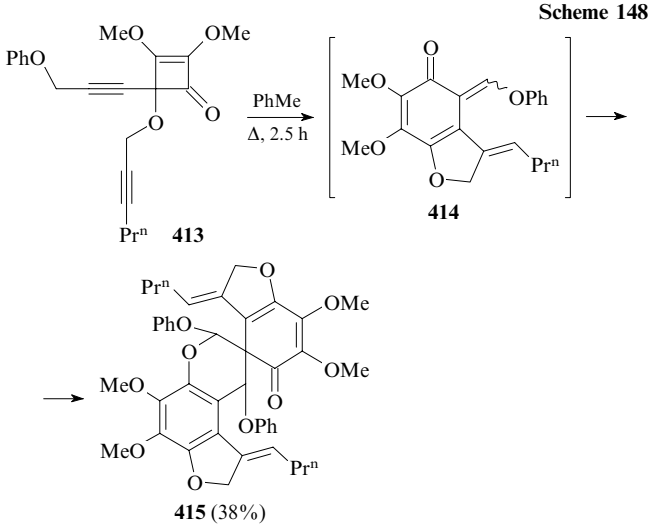
Scheme 147



however, it is obvious that the range of suitable substrates is rather limited.

Spirocyclic dimers of this type can be obtained from 4-substituted 1-naphthols. For example, Ashram *et al.*[292] prepared dimer **405** directly from 4-bromo-1-naphthol and

Scheme 148



formaldehyde (Scheme 145). This is also an example of a cascade reaction. Using a somewhat modified method, the same authors converted 3-hydroxymethyl-2-naphthols **406a**,**b** to dimers **407a**,**b**.

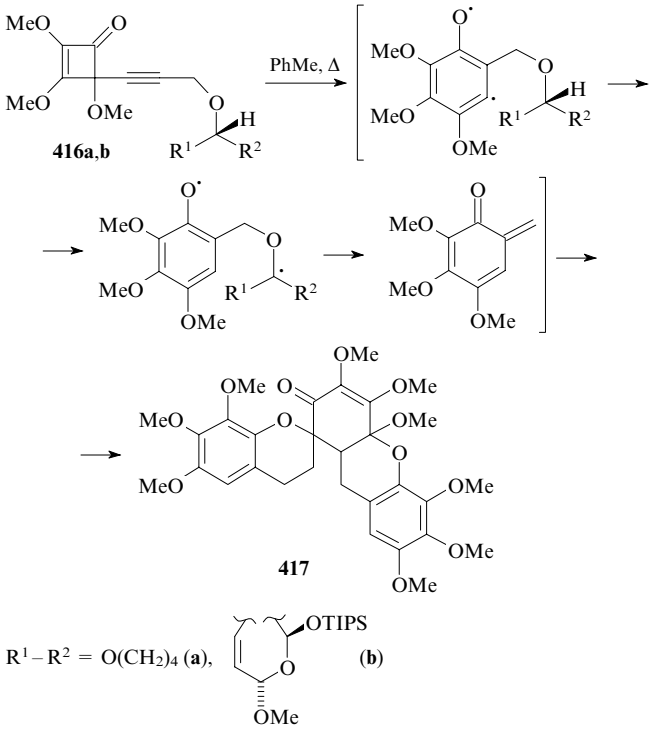
An unusual example of formation of a different type of dimer is the synthesis of carpanone (**408**) from 6-[(1*E*)-prop-1-enyl]-1,3-benzodioxol-5-ol (**409**) (Scheme 146). The process includes the recombination of radicals formed upon the oxidation of phenol and the intramolecular Diels – Alder reaction. *o*-Quinone methide **410** is generated under the action of molecular oxygen in the presence of cobalt(II) complexes[293] or $PdCl_2$.[294]

In addition, carpanone and its structural analogues, polemannones B and C, were synthesized in 79% – 91% yields in the presence of $CuCl_2$ and (−)-sparteine.[295]

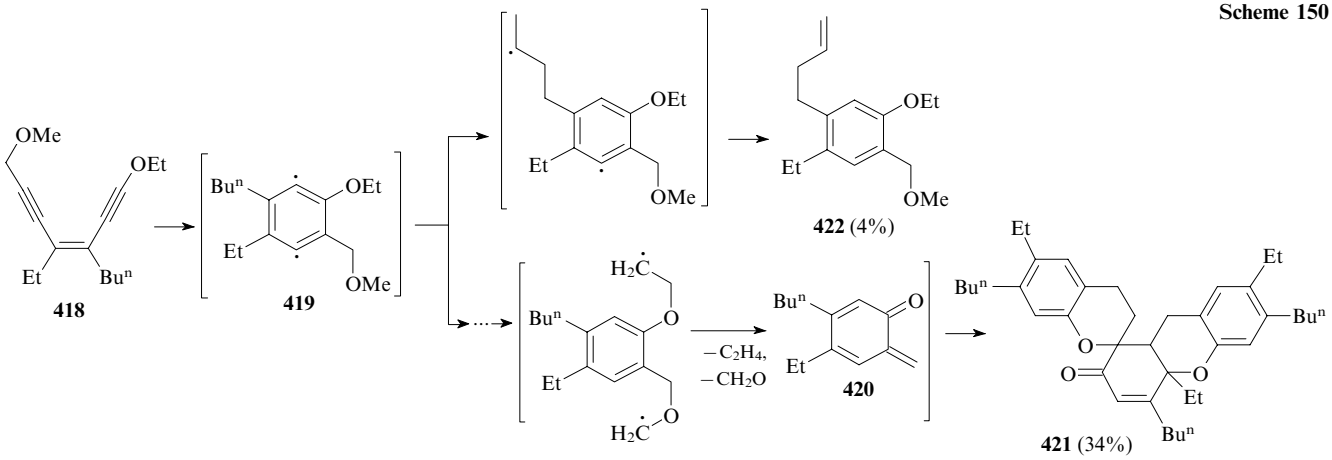
Non-trivial results were obtained on heat treatment of squaric acid derivative **411**.[296] The product of rearrangement and dimerization of the initial cyclobutenone **411** — compound **412** — was isolated in a yield of 37%. The hypothetical mechanism of the process is presented in Scheme 147.

The thermal rearrangement of cyclobutenone **413** gives *o*-QM **414** phenoxide-substituted at the methylene moiety; the [4 + 2]-cycloaddition of **414** yields head-to-tail dimer **415** (Scheme 148).[297] This route of dimerization can be explained by steric factors.

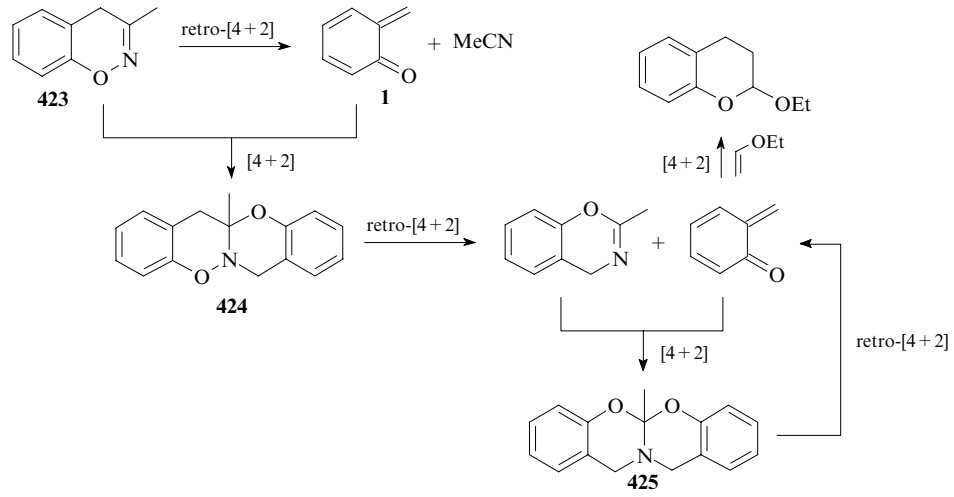
Scheme 149



Scheme 150



Scheme 151



Heating of squaric acid derivatives **416a**,**b** in refluxing toluene was used to synthesize a close analogue of the triterpenoid (±)-schefflone **417** in 49% and 72% yields, respectively (Scheme 149).[297]

On heating of enediyne **418** in refluxing chlorobenzene, Bergman type rearrangement of dehydrobenzene (**419**) takes place to give *o*-QM **420**, which is then trimerized to form compound **421** (Scheme 150).[298] Apart from the generation of *o*-QM, side reaction giving alkene **422** takes place as a result of unpaired electron transfer to the butyl group.

IV.4. Reactions of *o*-quinone methides with imino dienophiles

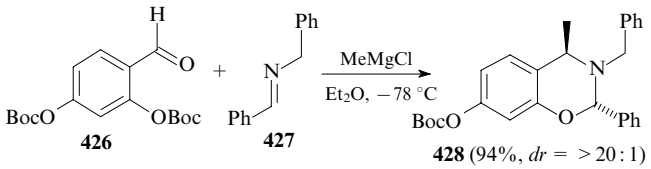
The [4 + 2]-cycloaddition reactions of *o*-QMs with azomethines represent a convenient method for the preparation of heterocyclic hemiaminals.

Thermolysis of 3-methyl-4*H*-1,2-benzoxazine (**423**) furnishes tetracyclic 1,3-benzoxazino[3,2-*b*]-1,2-benzoxazine **424**, which can further be converted to isomeric heterocycle **425**.[299] The formation of these systems includes successive retro-Diels–Alder and Diels–Alder reactions. The intermediate formation of *o*-QM was confirmed by [4 + 2]-cycloaddition with vinyl ethyl ether (Scheme 151).

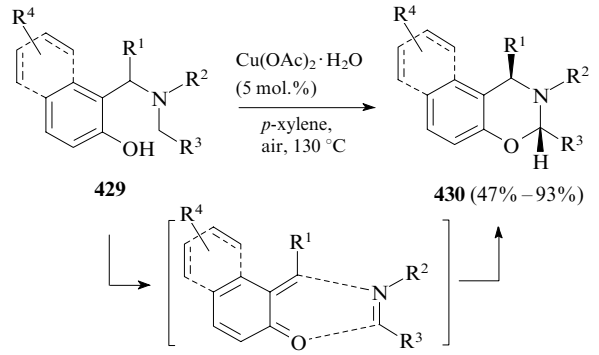
o-Quinone methide formed from *o*-OBoc-benzaldehyde **426** reacts with imine **427** to give 3,4-dihydro-2*H*-1,3-benzoxazine **428** with high diastereoselectivity (Scheme 152, *dr* is the diastereomer ratio).[215]

Various Mannich bases **429** are converted to the corresponding dihydro-1,3-oxazines **430** on treatment with copper(II) acetate in the presence of air oxygen

Scheme 152



Scheme 153



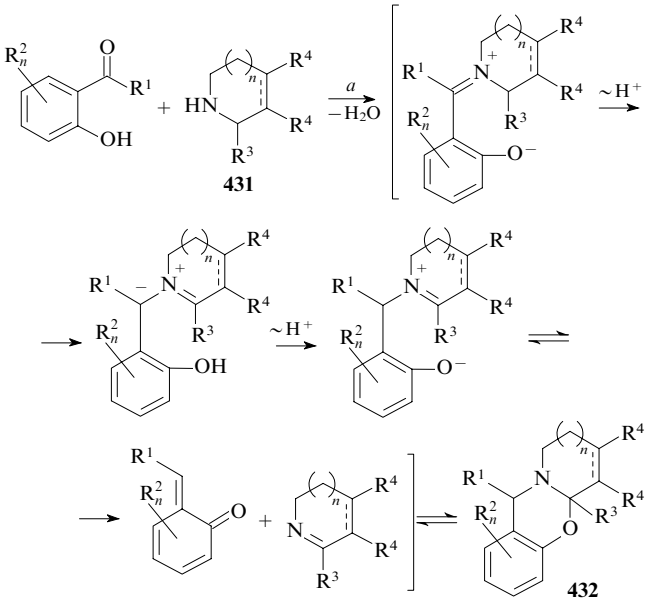
R^1 = H, Ar, Het; R^2–R^3 = $(CH_2)_n$ (n = 3, 4), $(CH_2)_2OCH_2$, *o*-[$(CH_2)_2$]C_6H_4; R^2, R^3 = H, Me, Et, Bn, Ph; R^4 = H, OAlk, Br

(Scheme 153).[300] A similar cyclization was accomplished in the presence of CuI (10 mol.%) and L-proline (20 mol.%)

as catalysts [301] and under the action of Bu^{t}OOH in the presence of molecular iodine.[302]

The redox neutral α-oxygenation of cyclic secondary amines **431** with salicylaldehydes, *o*-hydroxybenzo- or acetophenones leads to polycyclic N,O-acetals **432** *via* the possible generation of the corresponding *o*-QMs (Scheme 154).[303]

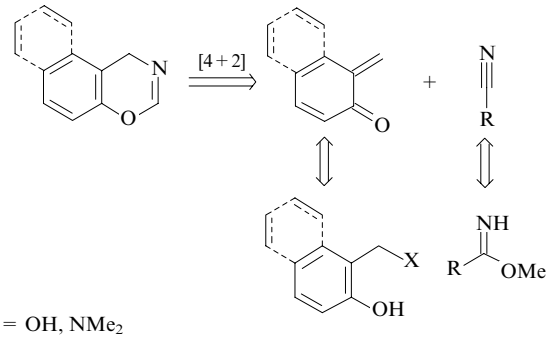
Scheme 154



(*a*) AcOH, PhMe; n = 0 – 2; R^1 = H, Me, Ph; R^2_n = H, 3-Alk, 4-Alk, 5-Alk, 6-Alk, 3-OMe, 5-OMe, 3-Br, 5-Br, 5-Cl, 5-NO_2, 5-CO_2Me, benzo[*e*]; R^3 = H, Ph; R^4 = H, R^4 – R^4 is benzo

The retrosynthetic analysis of 1,3-benzoxazines and their fused analogues indicates that they can be regarded as products of [4 + 2]-cycloaddition of *o*-QMs to nitriles. However, nitriles are, most often, poor dienophiles, while unstable *o*-QMs usually act as heterodienes only in the presence of electron-rich alkenes. These difficulties can be avoided by conducting this reaction with stable *o*-QM precursors — phenol (naphthol) Mannich bases — and carboxylic acid imino esters widely used in the synthesis of nitrogen heterocycles [304] as synthetic equivalents of nitriles (Scheme 155). The nitrogen atom in imino esters is nucleophilic and the adjacent electron-deficient carbon atom is electrophilic; hence, the initial imino compounds can be regarded as 1,2-ambiphiles.

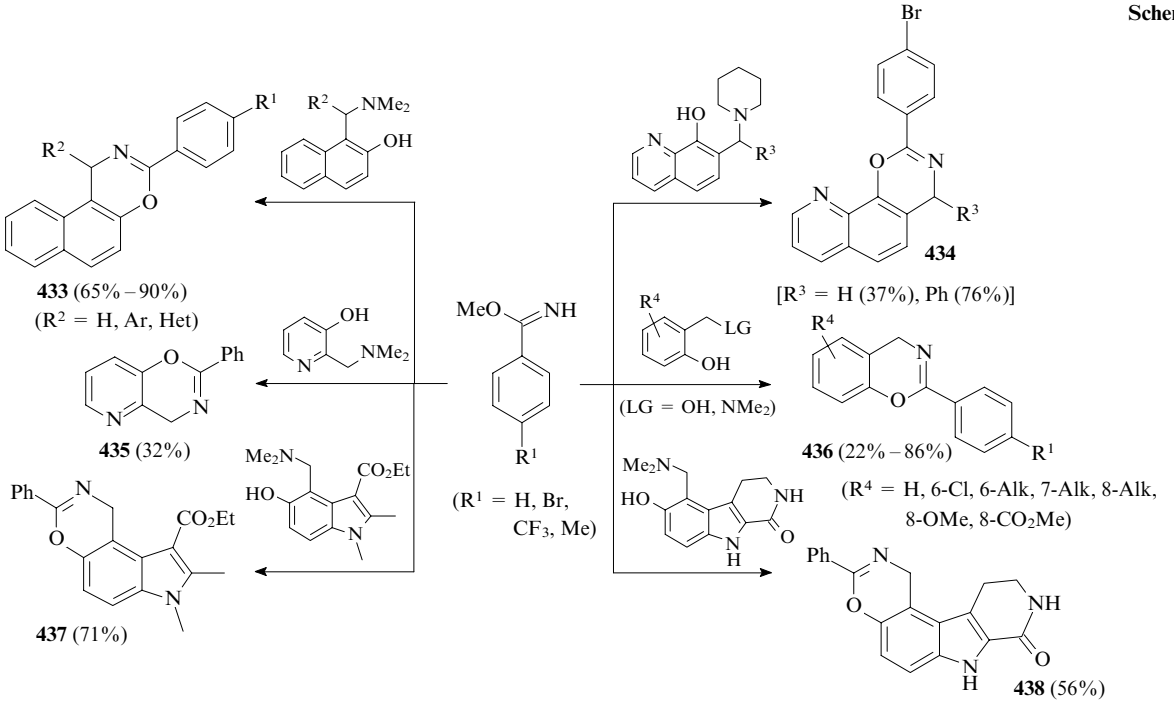
Scheme 155



X = OH, NMe_2

Heating of the imidates of aromatic carboxylic acids, including heterocyclic ones, with naphthol Mannich bases (**38**) results in the formation of 1*H*-naphtho[1,2-*e*][1,3]oxazines **433** (Scheme 156). It should be emphasized that good yields of naphthoxazines are attained by the use of even 1 equiv. of imino dienophile, whereas for attaining reasonable yields in the reactions of *o*-QMs with dienophiles, a large excess of the latter is usually required.[305, 306] The cycloadduct formed initially eliminates a methanol molecule giving rise to naphthoxazines **433**. It is noteworthy that the reaction proved to be general and was extended to several other *o*-QM precursors; this resulted in the synthesis of heterocyclic systems **434** – **438**.[92, 307] The use of ethanol as the solvent was less successful.[308]

Scheme 156



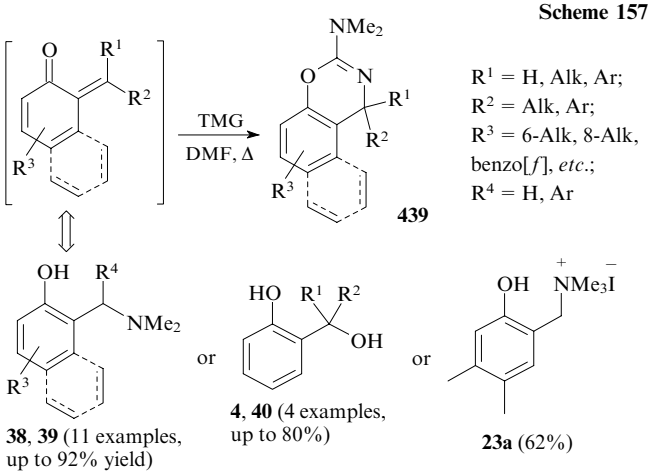
(R^1 = H, Br, CF_3, Me)

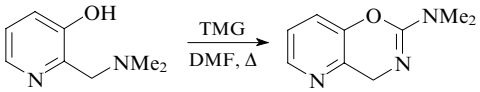
(LG = OH, NMe_2)

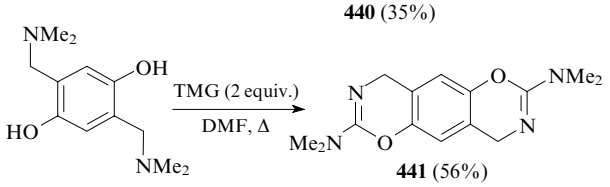
[R^3 = H (37%), Ph (76%)]

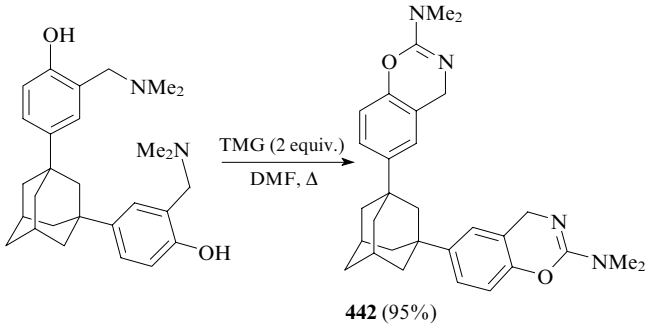
(R^4 = H, 6-Cl, 6-Alk, 7-Alk, 8-Alk, 8-OMe, 8-CO_2Me)

Scheme 157









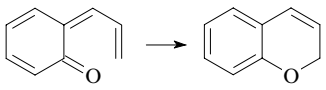
A similar reaction of *o*-QM can also be performed for 1,1,3,3-tetramethylguanidine widely used as a strong non-nucleophilic base, which formally acts as an imino dienophile; the reaction gives fused 2-dimethylamino-1,3-benzoxazines **439** (Scheme 157).[80,92] The possible *o*-QM precursors include salicyl alcohols **4** and **40** (even sterically crowded ones) and Mannich bases of phenol (**39**) and naphthol (**38**) and also of carboline, indole and pyridine (see, for example, synthesis of compound **440**). The successive generation of *o*-QM from bis-Mannich bases in the presence of TMG affords 1,3-benzoxazines **441** and **442**.[92]

In the reactions of *o*-QM with 1,1,3,3-tetramethylguanidine, the initially formed Diels–Alder adduct eliminates a dimethylamine molecule, which results in the formation of 2-dimethylamino-4*H*-1,3-benzoxazines.

V. Electrocyclic reactions

The major transformation of *o*-QMs containing an additional double bond in conjugation is the easy and, as a rule, spontaneous oxa-6π-electrocyclization to give 2*H*-benzopyrans (Scheme 158).

Scheme 158

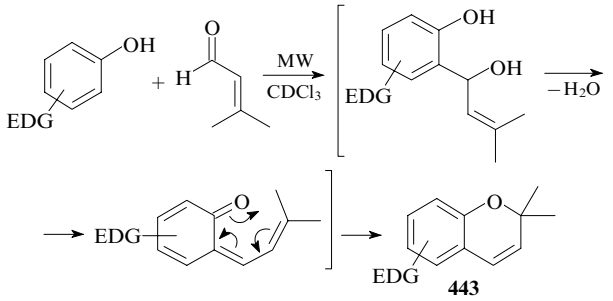


The cascade processes reported in the literature that include electrocyclic transformations of *o*-QMs are classified more conveniently in terms of the mechanisms of the steps that precede *o*-QM generation. The *o*-QMs needed for electrocyclization are prepared most often *in situ* from phenols (as a rule, containing donor substituents) or naphthols and α,β-unsaturated aldehydes. Yet another important method is the Claisen rearrangement involving aryl propargyl ethers.

V.1. Hydroxyalkylation–electrocyclization

An efficient method for the preparation of 2,2-dimethyl-2*H*-chromenes **443** is the microwave-assisted reaction of phenols and 3-methylbut-2-enal (Scheme 159).[309] The process occurs in the absence of a catalyst in a neutral medium, which allows conducting this reaction for substrates sensitive to acids and bases. Products **443** are formed as a result of phenol hydroxyalkylation, dehydration and oxa-6π-electrocyclization.

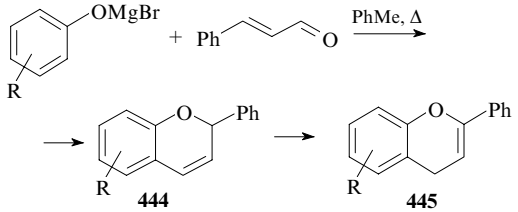
Scheme 159



EDG = OH, OMe, OCH_2OMe

The reaction involving Mg or Ti phenoxides and α,β-unsaturated carbonyl compounds in refluxing toluene resulted in the synthesis of a broad range of 2*H*-benzopyrans.[310,311] When cinnamaldehyde is used, the initially formed 2-phenyl-2*H*-1-benzopyrans **444** are often isomerized to flavenes **445** under the reaction conditions (Scheme 160).[312]

Scheme 160

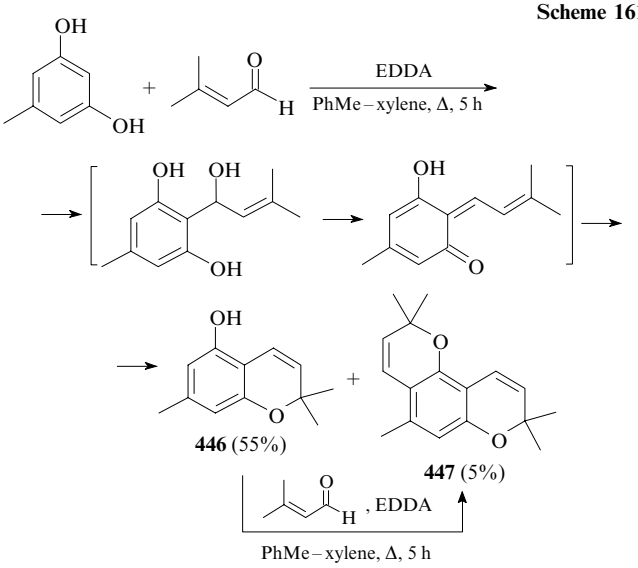


R = 5-Alk, 7-Alk, 8-Alk, 6-OH, 7-OH

The reaction of orcinol with 3-methylbut-2-enal catalyzed by ethylenediamine diacetate gave benzopyran **446** as the major product accompanied by a pyrano[2,3-*f*]chromene **447** impurity (Scheme 161).[313,314]

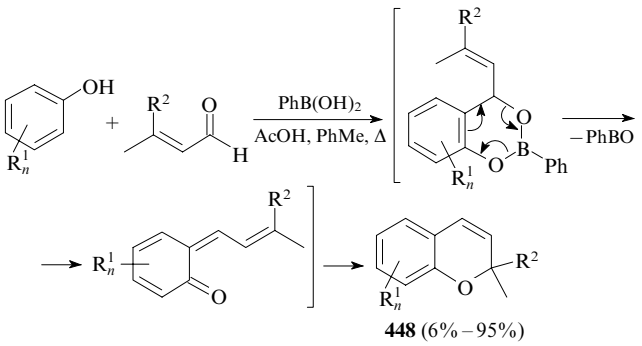
This reaction was extended to naphthols[315] and 1(4)-hydroxycarbazoles.[316] Instead of EDDA, the synthesis of the natural product siccanochromene A was catalyzed by

Scheme 161



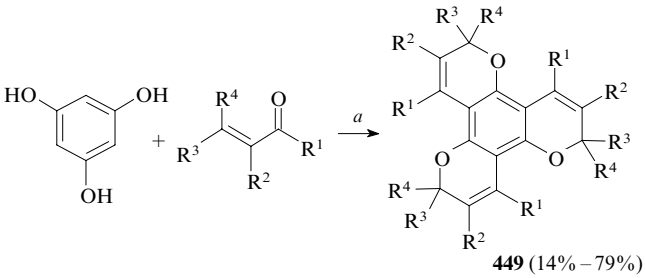
oxalic acid in aqueous THF,[317] the synthesis of pyrano- and dihydropyranoxanthones was catalyzed by $Ca(OH)_2$,[318] and for the synthesis of 2*H*-chromene derivatives **448** and **449**, montmorillonite K10,[319] phenylboronic acid in the presence of propanoic or acetic acid, and arylboronic acids in the presence of organic Brønsted acids were employed (Scheme 162).[116, 320 – 323]

Scheme 162



448 (6% – 95%)

R^1_n = 5,7-Me_2, 7-C(O)NEt_2, 6-OAlk, 7-OAlk, 8-OAlk, 6-Br, 7-OC(O)NEt_2, benzo[*f*], benzo[*h*], dibenzo[*f*,*h*]; R^2 = H, Me



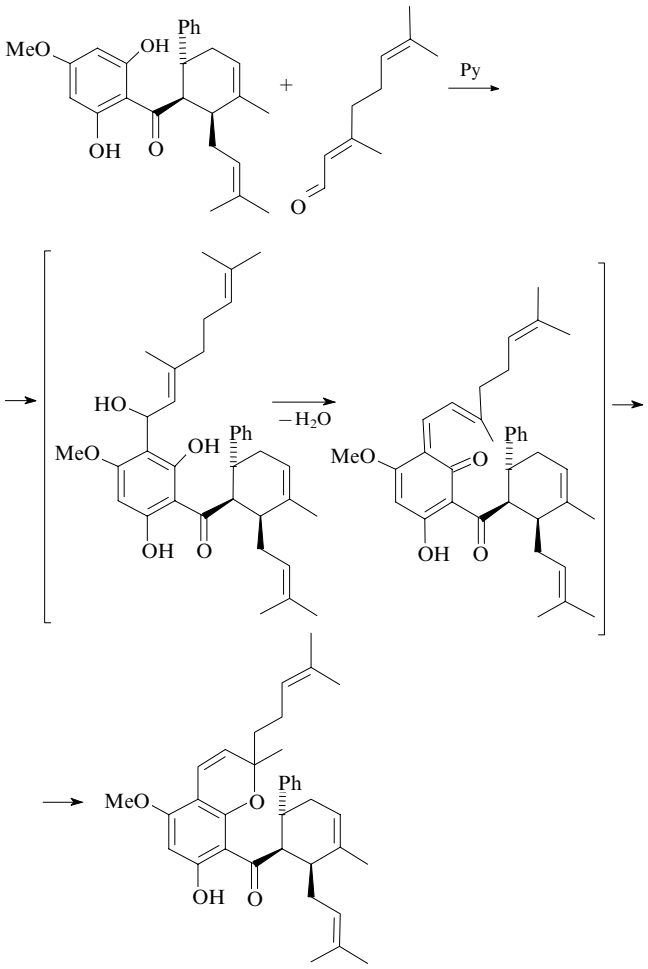
449 (14% – 79%)

(*a*) $PhB(OH)_2$, $EtCO_2H$, PhH, Δ; R^1 = H, Me; R^2 = H; R^2 – R^3 = $(CH_2)_3$; R^3 = H, Me, Ph, $(CH_2)_2CH{=}CMe_2$; R^3 – R^4 = $(CH_2)_4$, $(CH_2)_5$, ; R^4 = H, Me, Ph

Apart from α,β-unsaturated aldehydes, their synthetic equivalents can also be used in this reaction, *e.g.*, β-hydroxyacetals[324] or α,β-unsaturated acetals;[325] however, in this case, the yields of 2*H*-chromenes are often unsatisfactory.

It should be specially emphasized that most of the methods for 2*H*-chromene synthesis listed above are applicable only to highly electron-rich substrates — resorcinol, phloroglucinol and naphthol derivatives. Nevertheless, hetero-domino processes comprising hydroxyalkylation of electron-rich aromatic compounds and 6π-electrocyclization are successfully used in the synthesis of natural chromenes. As an example, consider the biomimetic synthesis of panduratin B (**450**) (Scheme 163).[326]

Scheme 163



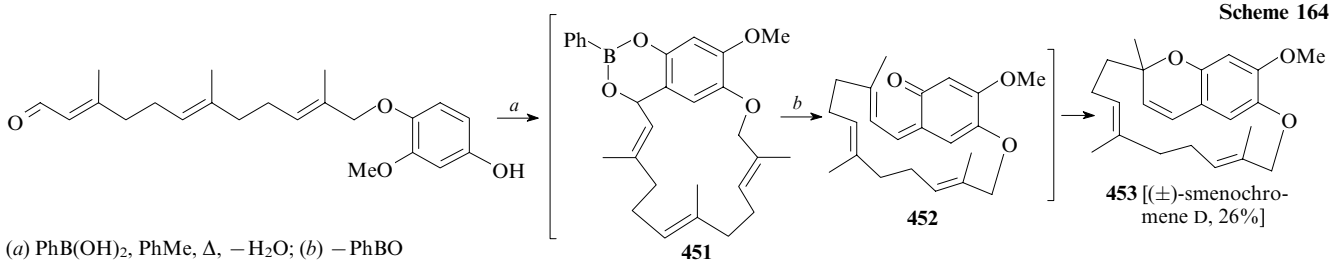
450 (panduratin B, 86%)

A reaction proceeding *via* the intermediate formation of cyclic borate **451** and vinyl *o*-QM **452** resulted in the synthesis of smenochromene D (**453**) (Scheme 164).[327]

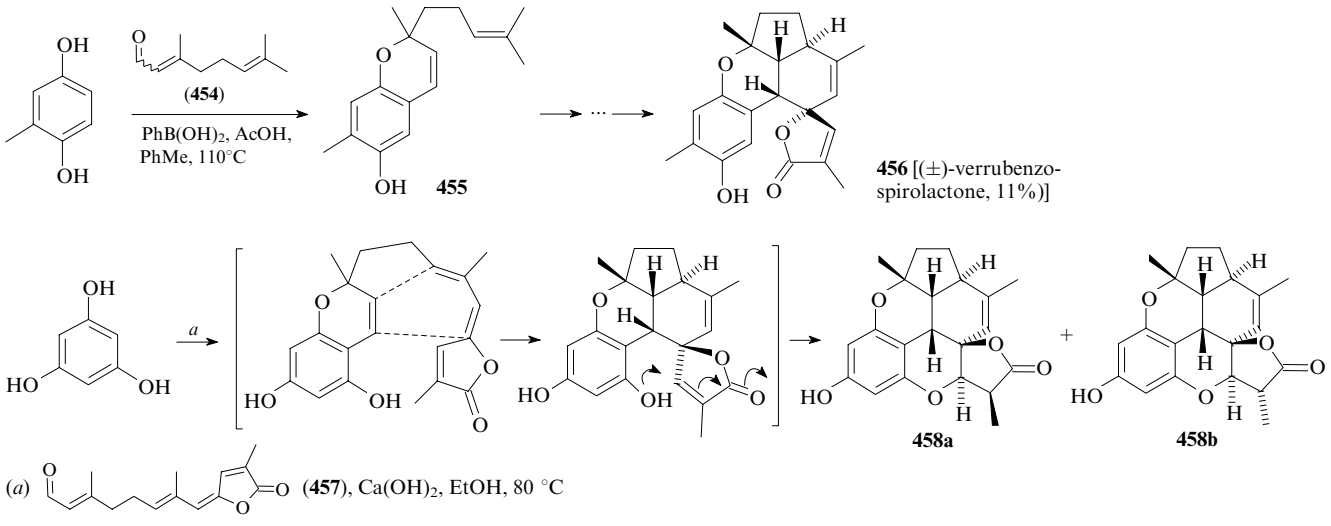
According to a similar approach, methylhydroquinone was reacted with citral **454** to give intermediate **455**, which was converted to (±)-verrubenzospirolactone (**456**) over five steps.[328] The reaction of aldehyde **457** with phloroglucinol in the presence of calcium hydroxide affords a mixture of diastereomers **458a**,**b** (3 : 1 ratio; 46% yield) *via* a unique cascade consisting of the Knoevenagel condensation (generation of *o*-QM), oxa-6π-electrocyclization, intramolecular Diels – Alder reaction and oxa-Michael reaction (Scheme 165).

The biomimetic approach was also utilized to prepare daurichromenic acid (**459**)[329] and deoxybruceol (**460**). The formation mechanism of the latter includes [1,5]-sigmatropic shift and [4 + 2]-cycloaddition (Scheme 166).[330, 331]

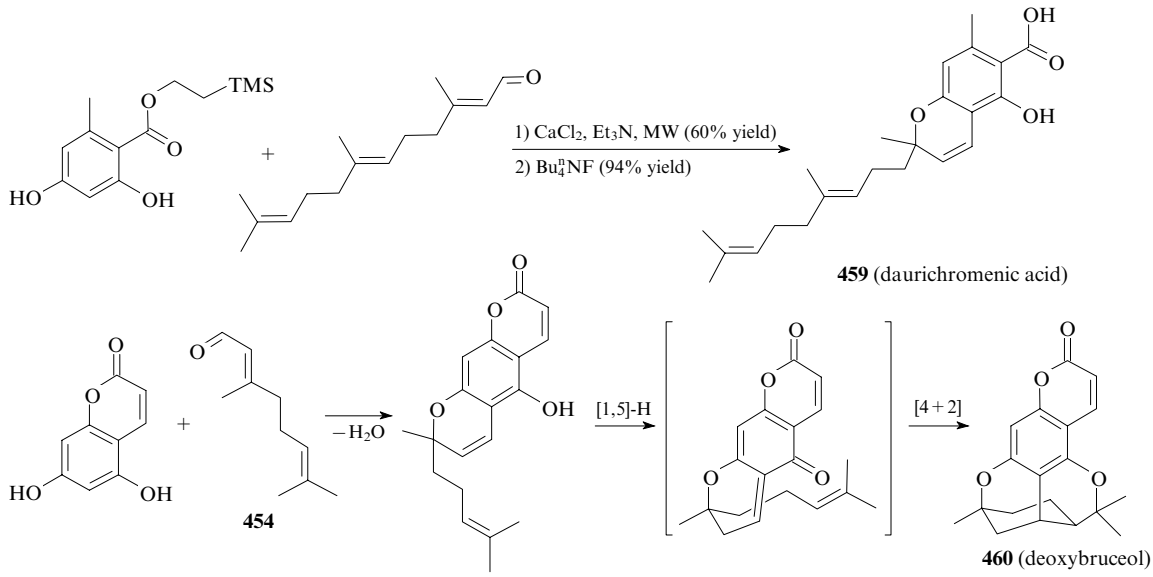
Scheme 164



Scheme 165



Scheme 166



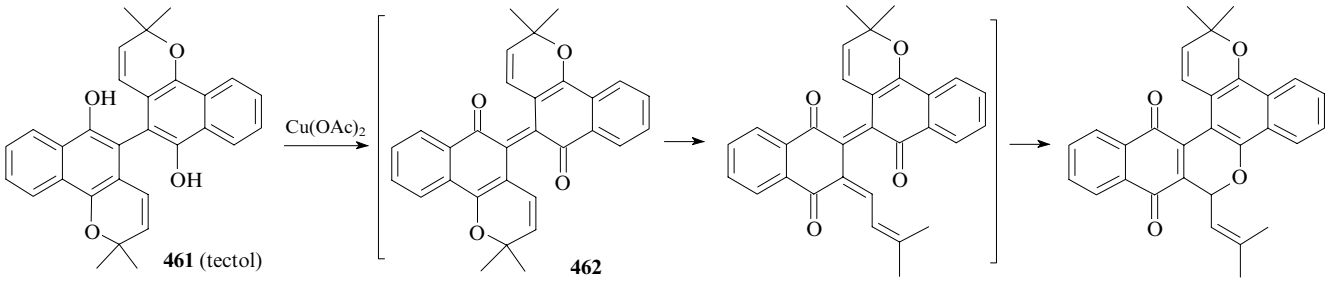
The cascade reaction of resorcinols with citral (**454**) or farnesal opens up the route to a group of polycyclic compounds related to rubranine and deoxybruceol).[331 – 333]

Treatment of tectol (**461**) with copper acetate triggers the oxidation to quinone **462**, electrocyclic opening of one 2*H*-pyran ring and finally 6π-electrocyclization involving the carbonyl group of the *o*-methylenequinone moiety to give tecomaquinone I (**463**) (Scheme 167).[334]

V.2. Sigmatropic rearrangement – electrocyclization

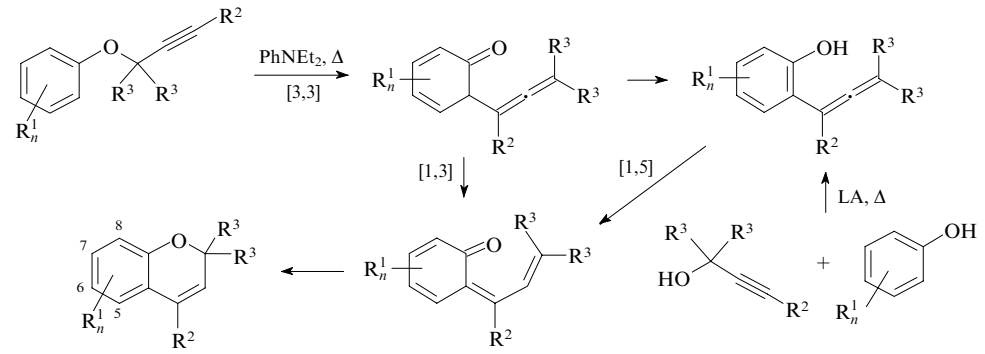
An important method for the synthesis of 2*H*-chromenes is the rearrangement of propargyl phenyl ethers,[335 – 339] which can cyclize in high-boiling solvents, for example, *N*,*N*-diethylaniline at 210 – 230 °C to give chromenes (Scheme 168).[340 – 345] The reaction mechanism includes [3,3]-sigmatropic rearrangement, tautomerization to the corresponding *o*-QM and the subsequent electrocyclization. Phenol derivatives containing electron-withdrawing groups

Scheme 167



461 (tectol) **462** **463** (tecomaquinone I, 60%)

Scheme 168



R^1_n = H, 5-OMe, 6-OMe, 7-OMe, 8-OMe, 6-Cl, 7-Cl, 8-Cl, 6-NO_2, 6-Ac, benzo[*h*]; R^2 = H, Ph, CH_2OAc; R^3 = H, Me

are usually converted to 2*H*-chromenes in moderate yields.[346] The acid-catalyzed reaction of phenols with propargyl alcohols, which occurs *via* the formation of allenes, also affords benzopyrans, with their yields usually being < 10%.[347 – 349] Upon the use of 1,1-disubstituted propargyl alcohols in the presence of $BF_3 \cdot Et_2O$, the corresponding 2*H*-chromenes were isolated in 64% – 90% yields.[350]

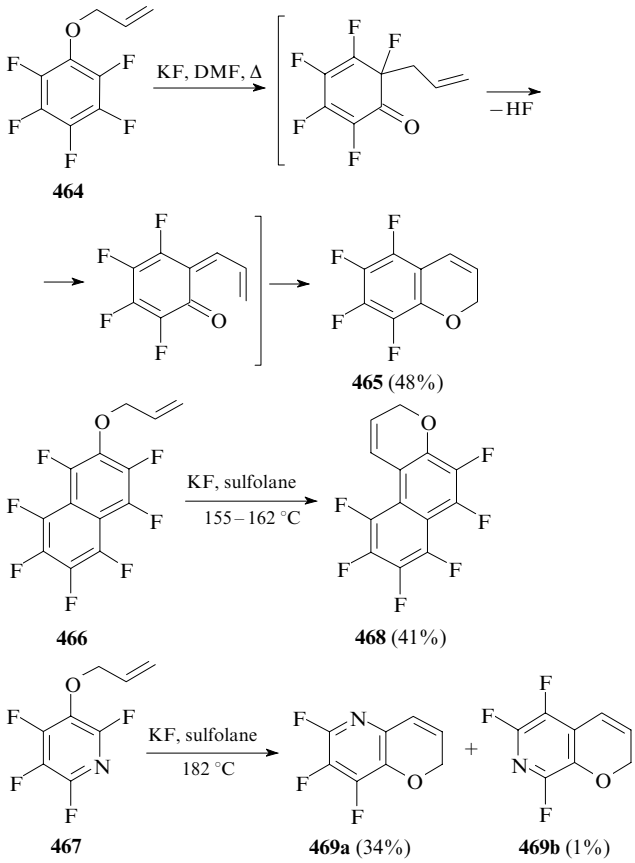
This sequence of transformations was used to prepare a natural chromene, desoxymorellin,[351] and in the synthesis of 5,8-difluoro-2*H*-chromene on heating of 2-(prop-2-yn-1-yloxy)-1,4-difluorobenzene in silicone oil.[352] A number of most recent works on the synthesis of naphtho[2,1-*b*]pyrans are considered in a review.[353]

Thermolysis of pentafluorophenyl allyl ether **464** includes the steps of Claisen rearrangement, HF elimination, resulting in the generation of *o*-QM, and the subsequent electrocyclization (Scheme 169).[354] This affords fluorinated 2*H*-benzopyran **465**. Similar naphthalene **466** and pyridine **467** derivatives can also participate in this reaction. In the former case, product **468** is formed in a satisfactory yield, while in the latter case, allyl group migration to the carbon atom adjacent to nitrogen takes place predominantly to furnish isomer **469a**. Note that thermolysis in the gas phase selectively gives a different isomer (**469b**).[355]

Heating of cyclopropa[*c*][1]benzopyrans **470** in *N*,*N*-diethylaniline at temperature > 250 °C induces a rearrangement to 2*H*-benzopyrans **471** (Scheme 170).[356] The rate-limiting step is the electrocyclic ring opening, which is followed by fast [1,5]- and [1,7]-sigmatropic shifts and 6π-electrocyclization. Similar transformations occur on refluxing 4-ethoxy derivative **472** with the subsequent distillation, giving rise to 4-ethoxy-2-methyl-2*H*-benzopyran **473** in a quantitative yield.[357]

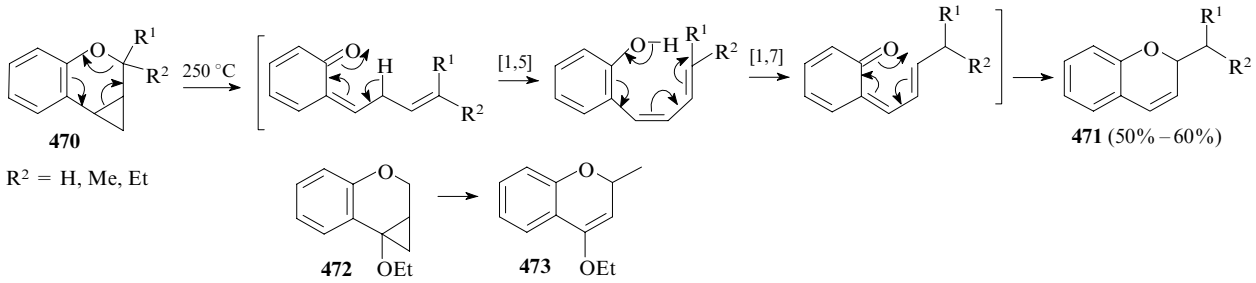
It was shown that heating of 2-(penta-1,3-dien-1-yl)phenols **474a**,**b** affords 2-ethyl-2*H*-chromenes **475a**,**b**.[358] *cis*-

Scheme 169

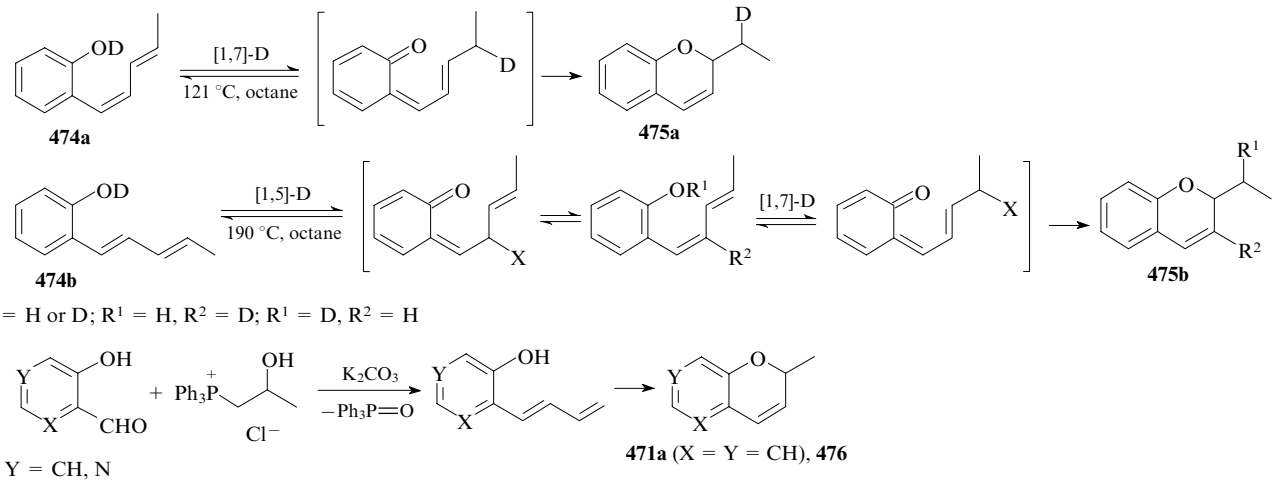


Deuterophenol **474a** is cyclized *via* [1,7]-sigmatropic shift and electrocyclization. Meanwhile, *trans*-deuterophenol **474b** can undergo successive [1,5]- and [1,7]-sigmatropic

Scheme 170



Scheme 171



shifts, which gives a mixture of deuterochromenes **475b**. Chromenes of this type can be prepared from *o*-hydroxy-substituted aromatic aldehydes and (2-hydroxyethyl)- or (2-hydroxypropyl)triphenylphosphonium chloride in the presence of a base; this reaction gives chromene **471a** (X = Y = CH) and its aza analogues **476** *via* a number of intermediate steps, the first one being the Wittig alkenylation [359] (Scheme 171).

V.3. Miscellaneous cascade processes comprising electrocyclization

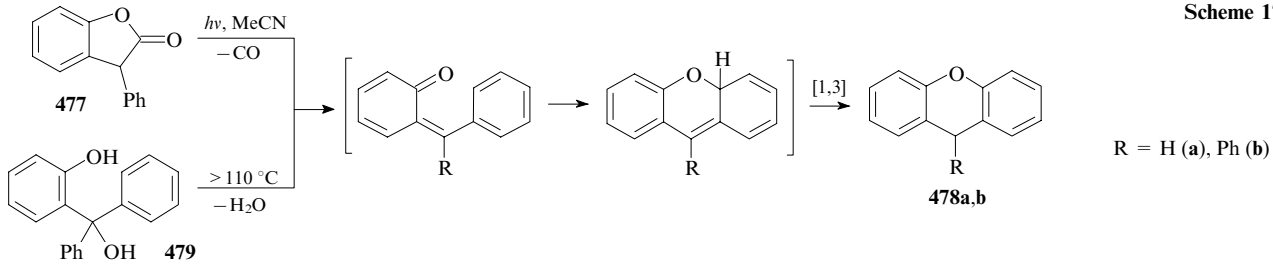
Irradiation of benzofuranone **477** leads to xanthene (**478a**) in a low yield. Probably, the reaction includes the generation of *o*-QM as a result of CO extrusion, electrocyclization and [1,3]-shift.[360] On dehydration above 110 °C, 2-hydroxytriphenylmethanol **479** is irreversibly converted to 9-phenylxanthene (**478b**) (Scheme 172).[361]

Recently, a fundamentally new method has been developed for the construction of a chromene system from α,β-unsaturated Fischer carbenes **480** (as chromium complexes) and propargyl ethers **481** containing an alkenyl group at the propargyl carbon atom (Scheme 173).[362] The cascade process includes the construction of the benzene ring by the Dötz reaction, generation of *o*-QM **482** and oxa-6π-electrocyclization. The subsequent oxidative treatment of the resulting chromium carbene complexes **483** affords chromenes **484** in average yields of 70% – 80%. This annulation method was utilized in the synthesis of several natural compounds (*e.g.*, lapachenole and vitamin E).

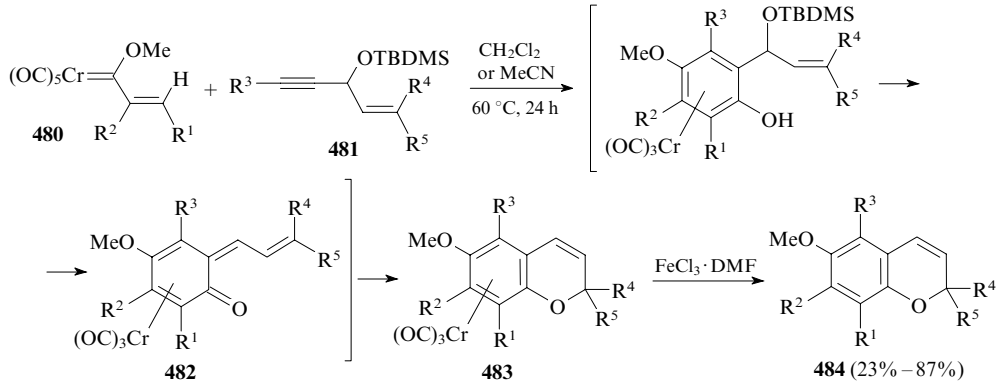
An unusual example of the cascade process is the condensation of salicylaldehydes with acetone and secondary amines in ethanol, which includes several intermediate steps (aldol-crotonic condensation, Michael reaction, addition of the secondary amine at the carbonyl groups, generation of *o*-QM, electrocyclization and cyclization to N,O-acetal) and results in the formation of chromanylmethylchromenes **485** (Scheme 174).[363]

The oxidation of *o*-propenylphenol **486** with 2,3-dichloro-5,6-dicyano-1,4-benzoquinone (DDQ) in refluxing benzene affords 3-methylspirobi[2*H*-1-benzopyran] **487** (Scheme 175).[364]

Scheme 172

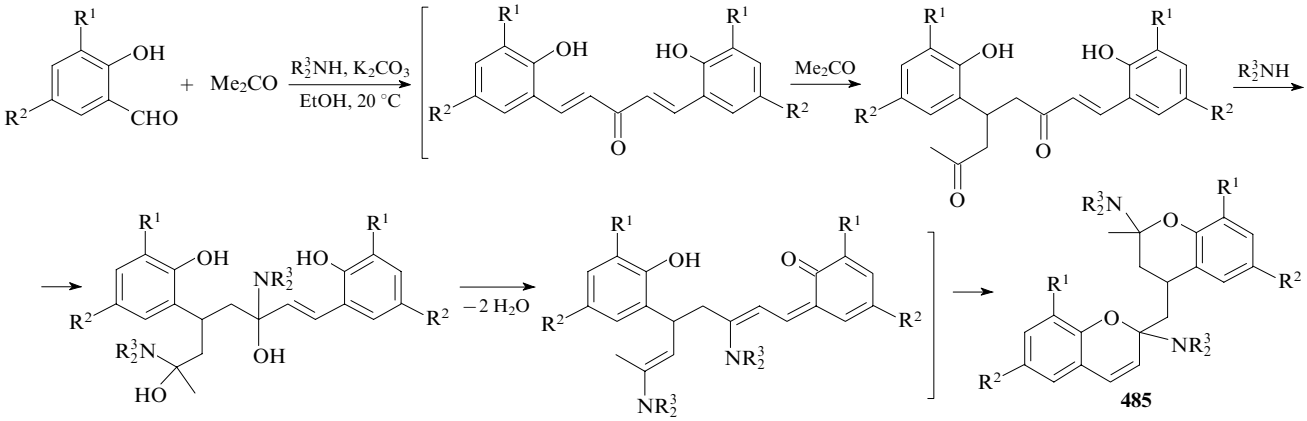


Scheme 173



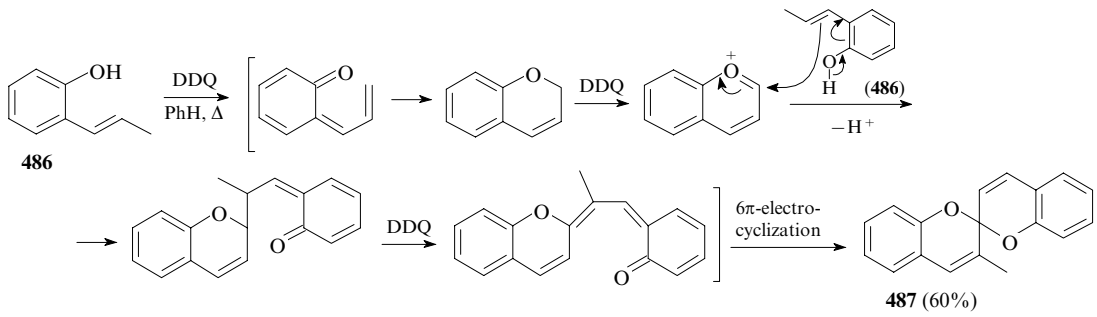
R^1 = H, Alk, Ph; R^2 = H, Alk, TMS; R^3 = H, Me; R^4, R^5 = H, Alk

Scheme 174



R^3 = Me: R^1 = R^2 = H (25% yield), Cl (36%), Br (35%); R^3 = Et: R^1 = R^2 = H (10%), Cl (20%), Br (40%); R^1 = H, R^2 = Me: R^3 = Me (11%), Et (5%); R^1 = H, R^2 = Cl: R^3 = Me (35%), Et (16%)

Scheme 175



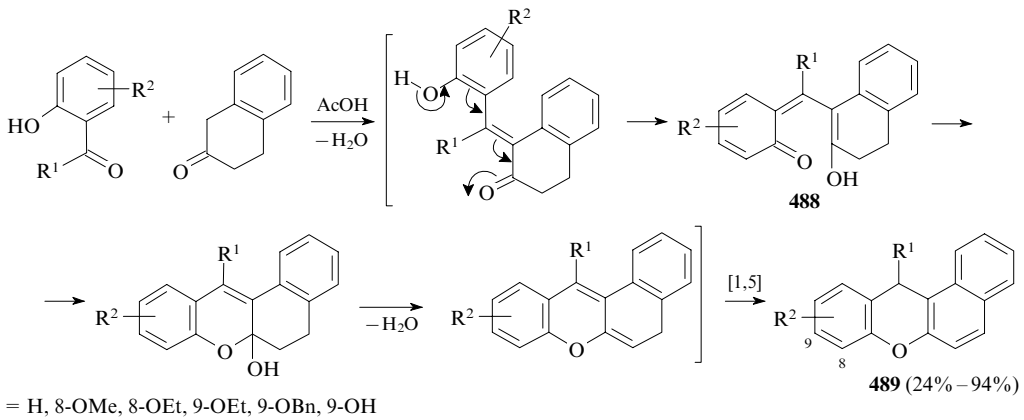
A convenient method for the synthesis of 12*H*-benzo[*a*]xanthenes has been developed on the basis of the acid-catalyzed reaction of 2-tetralone and 2-hydroxy-substituted aromatic aldehydes. The hypothetical mechanism of this reaction includes aldol-crotonic condensation, isomerization of α,β-unsaturated ketones to *o*-QM **488**, electrocyclization, elimination of water and [1,5]-sigmatropic shift to give 12*H*-benzo[*a*]xanthenes **489** (Scheme 176).[365]

On treatment of phosphonium salt **490** with sodium methoxide, benzopyran derivative **471a** was isolated (Scheme 177).[366] The reaction proceeds *via* the formation of phosphorus ylide **491** and cyclization to betaine **492**, which is then protonated and dehydrated to vinylphosphonium salt **493**. The subsequent β-elimination, protonation and electrocyclization of *o*-QM give rise to ion pair **494**, which is then converted to product **471a** as a result of Michael addition of the hydroxide anion and elimination of the Ph_3PO molecule.

Peroxide **495** obtained upon the photosensitized oxidation of 1-benzoxepine is converted to benzopyran-2-carbaldehyde **496** on treatment with trimethyl phosphite (Scheme 178).[367]

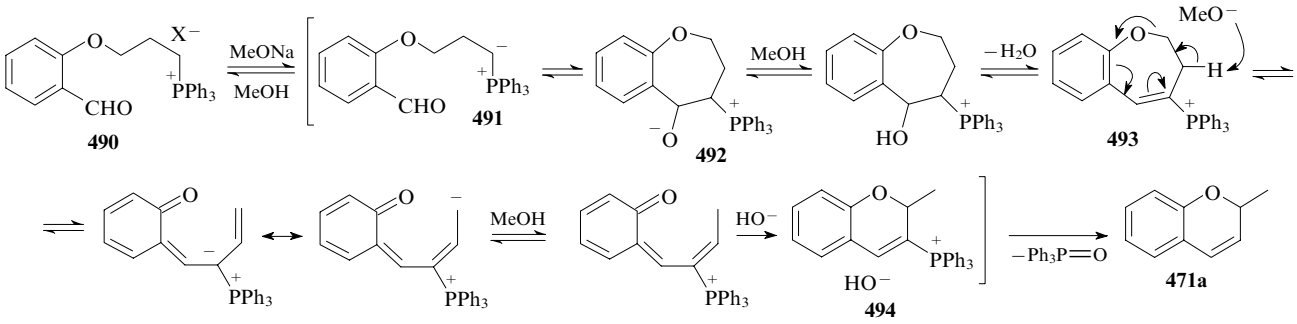
Three-component condensation of salicylaldehydes with secondary amines and alkenylboronic acids or alkenyltrifluoroborates in protic solvents can be used for the synthesis of 2*H*-chromenes. The possible mechanism of this reaction includes transfer of the alkenyl group to the iminium cation **497** (generated from amine and aldehyde)

Scheme 176

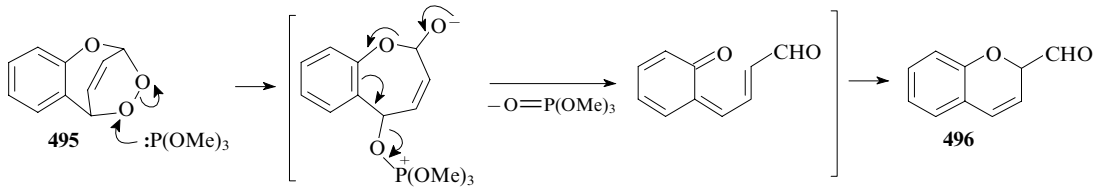


R^1 = H, Me; R^2 = H, 8-OMe, 8-OEt, 9-OEt, 9-OBn, 9-OH

Scheme 177



Scheme 178

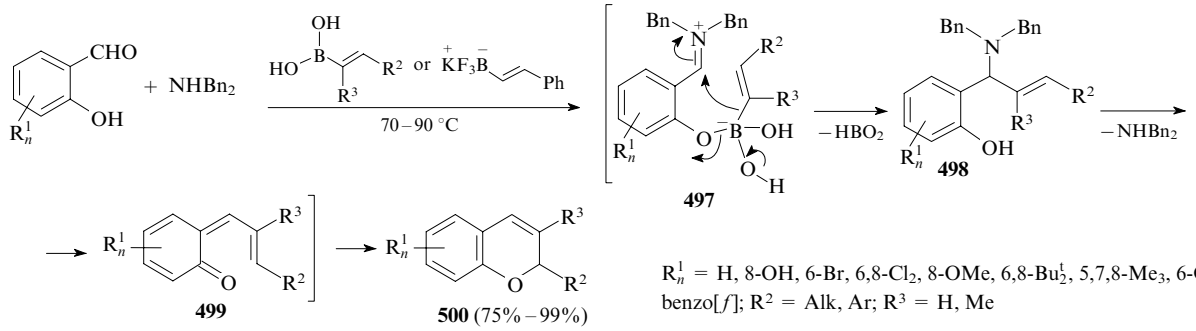


to give Mannich base **498**, which is deaminated to form *o*-QM **499**. Electrocyclization of the latter affords 2*H*-chromenes **500** (Scheme 179).[368, 369]

It was found that secondary amines can be replaced by tertiary amines. The initial product of amine addition to carbonyl group **501** reacts with alkenylboronic acid, which acts as a hydroxide ion acceptor, to yield ion pair **502** (Scheme 180). The subsequent conjugate addition of the alkenyl group to *o*-QM produces zwitter-ionic intermediate **503**, which is deaminated to give another *o*-QM **504** followed by electrocyclization of the latter.[368]

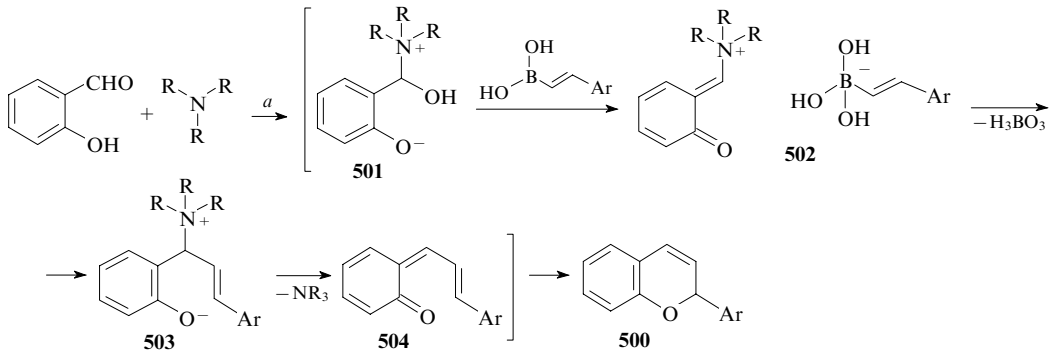
Later, the asymmetric synthesis of substituted chromans by three-component condensation of aromatic aldehydes, sesamol (**505**) and alkenylboronates **506** catalyzed by chiral binaphthol **507** was shown to be possible (Scheme 181).[370] *cis*-Chromans **508** are formed in moderate yields (49% – 72%) and with good enantio- [enantiomer ratio (*er*) up to 89 : 11] and diastereoselectivities (*dr* up to 2.8 : 1). It should be noted that the use of diisopropyl styrylboronate results in an increase in the cyclization time to 24 h, increase in the diastereoselectivity (*dr* = 20 : 1) and decrease in the product yield to 32%. This supports the assumption that

Scheme 179



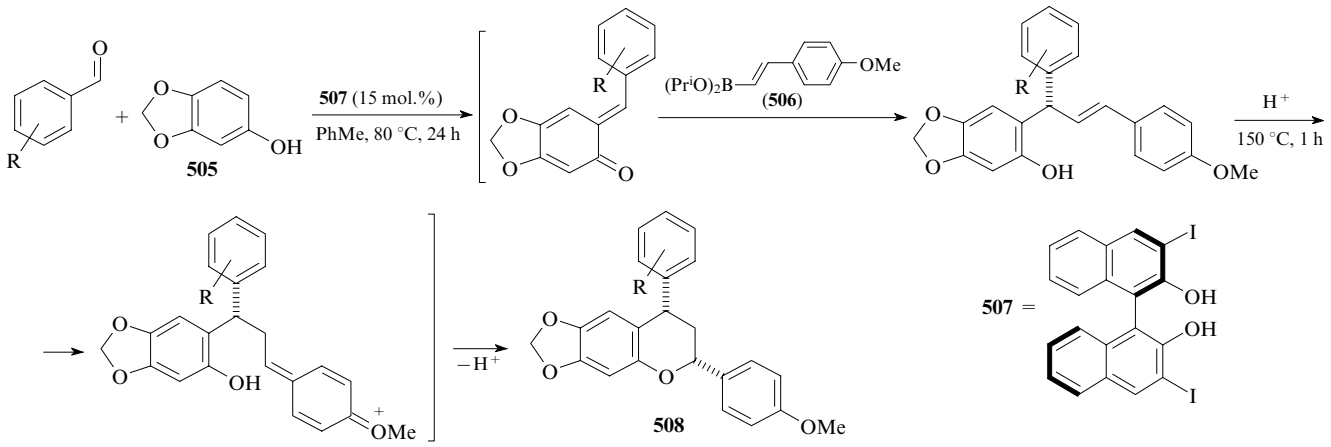
R^1_n = H, 8-OH, 6-Br, 6,8-Cl_2, 8-OMe, 6,8-Bu^t_2, 5,7,8-Me_3, 6-OBn, benzo[*f*]; R^2 = Alk, Ar; R^3 = H, Me

Scheme 180



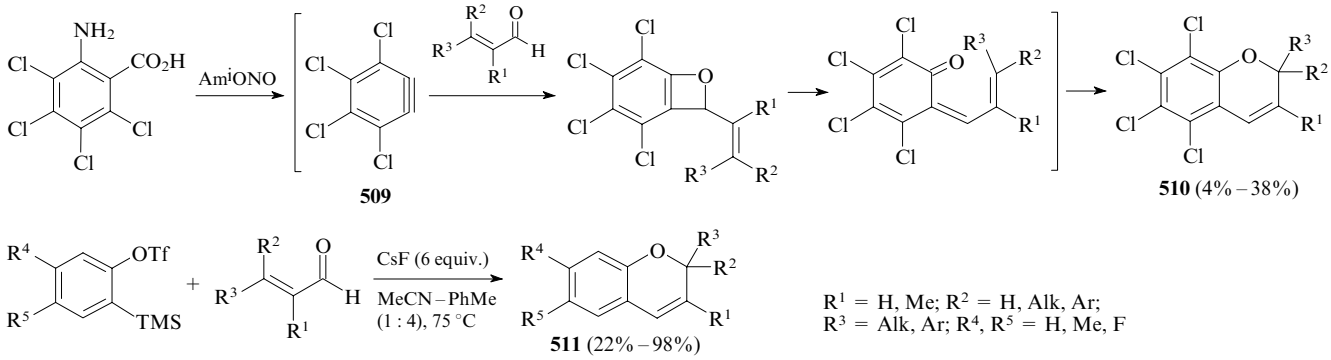
(*a*) H_2O or EtOH, 70 °C; R = Me, Et

Scheme 181



R = H, 4-CF_3, 4-OMe, 2-Br

Scheme 182



510 (4% – 38%)

511 (22% – 98%)

R^1 = H, Me; R^2 = H, Alk, Ar;
R^3 = Alk, Ar; R^4, R^5 = H, Me, F

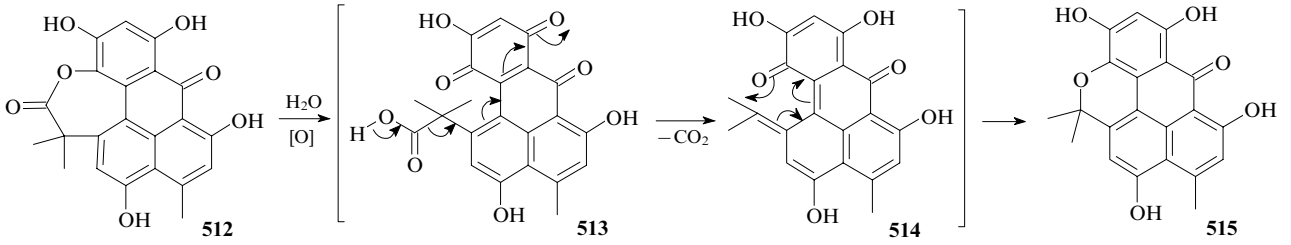
cyclization takes place after protonation of the alkene. Although this process does not include electrocyclization, a common feature of this reaction and the reaction considered above is vinyl group transfer to *o*-QM.

Tetrachlorodehydrobenzene (**509**) generated from tetrachloroanthranilic acid and isoamyl nitrite (Am^iONO) reacts with aldehydes to be converted to benzoxete, which undergoes cycloreversion followed by electrocyclization to give tetrachlorinated 2*H*-benzochromenes **510** (Scheme 182).[371, 372] According to this procedure, the yields of products **510** are 4% – 38%. A more efficient method for the preparation of 2*H*-chromenes **511** is based on generation of dehydrobenzene from *o*-trimethylsilylphenyl triflates.[373]

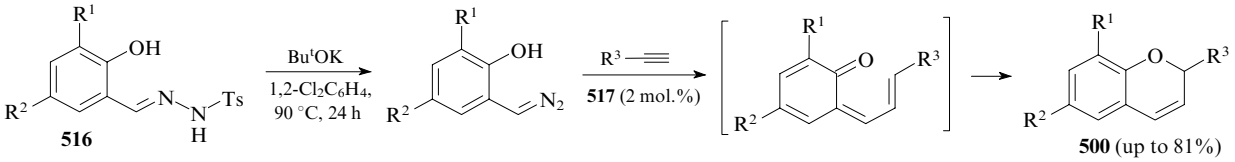
Apparently, hydrolysis of lactone **512**, which is oxidized to quinone **513** under the reaction conditions, can also be classified as a cascade reaction (Scheme 183).[374] The subsequent decarboxylation results in *o*-QM **514**, the electrocyclization of which gives resistorubone (**515**). Unfortunately, the authors did not present any experimental details.

Among cascade transformations, noteworthy is the metal radical method for the synthesis of 2*H*-chromenes (19 examples) based on the reactions of salicylaldehyde *N*-tosylhydrazones **516** with terminal alkynes in the presence of a base and a Co^{II} porphyrin metal radical catalyst **517** (Scheme 184).[375] This method offers wide opportunities for the variation of substituents and, as a rule, gives

Scheme 183

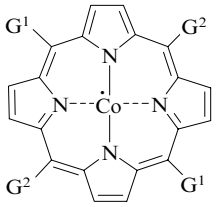


Scheme 184



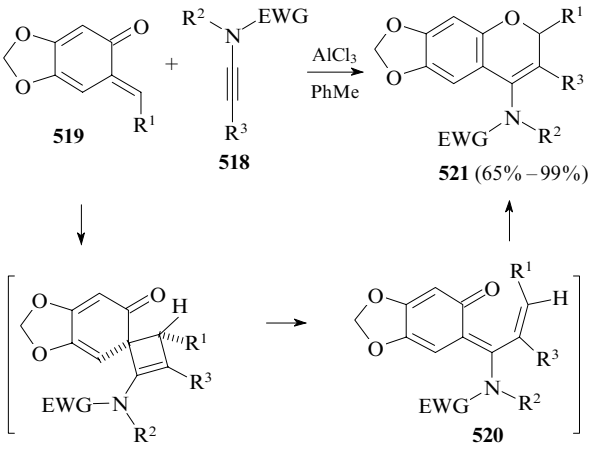
R^1 = H, Bu^t, Br, F; R^2 = H, Bu^t, NO_2, Br; R^3 = Ar, $(CH_2)_2Ph$

Structure 517



G^1 = 2,6-(Pr^{i}C(O)NH)$_2$C$_6$H$_3$;
G^2 = 3,5-Bu$^t_2$C$_6$H$_3$

Scheme 185



R^1 = 4-MeOC$_6$H$_4$, PhCH=CH; R^2 = Bn, Alk, All;
R^3 = Alk, Ar, TIPS; EWG = SO_2Ar

products in good yields. This and some other metal-catalyzed methods for 2*H*-chromene synthesis involving *o*-QMs are covered in a review.[376]

A unique example is the preparation of 4-amino-substituted 2*H*-chromenes reported by Yang *et al.*[377] The initial Lewis-acid catalyzed [2+2]-cycloaddition of ynamines **518** to *o*-QMs **519** at the exocyclic double bond is followed by 4π-electrocyclic ring opening and then 6π-electrocyclization of intermediate **520** to give 4-amino-2*H*-chromenes **521** (Scheme 185). Note that the use of ynamines with a terminal triple bond results in classical [4+2]-cycloaddition to give isomeric 2-amino-4*H*-chromenes.

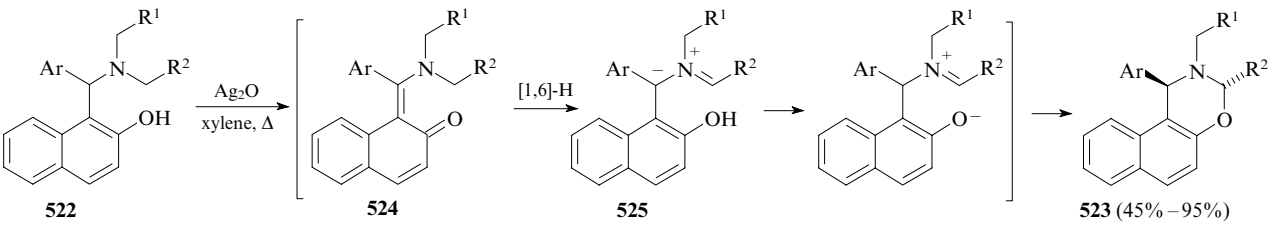
VI. Heterocyclizations initiated by sigmatropic shifts

A relatively small group of cascade reactions includes those where the heterocyclization step is preceded by sigmatropic shifts involving *o*-QMs.

The oxidation of Mannich bases of 2-naphthol **522** with silver(I) oxide in refluxing xylene (in some cases, at room temperature) resulted in the preparation of naphtho[1,2-*e*][1,3]oxazines **523** (Scheme 186). This method for α-C–H functionalization of amines, including heterocyclic ones, consists of oxidative generation of *o*-naphthoquinone methide **524**, [1,6]-hydride shift, proton transfer and diastereoselective cyclization to give oxazines **523** in the *trans*-configuration. In the case of electron-withdrawing groups in the aryl substituent, the yields of oxazines increase owing to stabilization of ylide **525**.[378]

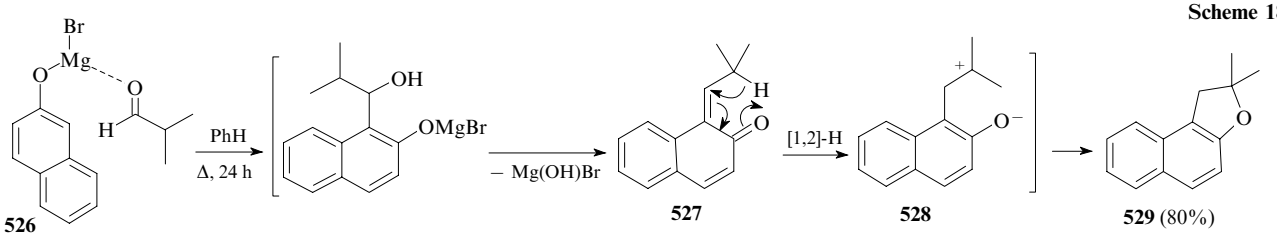
Heating of (2-naphthyloxy)magnesium bromide (**526**) with isobutyric aldehyde induces *ortho*-hydroxyalkylation followed by generation of *o*-QM **527** and [1,2]-hydride shift, resulting in the formation of zwitter-ionic intermediate **528**, the cyclization of which affords dihydronaphthofuran **529** (Scheme 187).[379] When (aryloxy)magnesium bromides of

Scheme 186

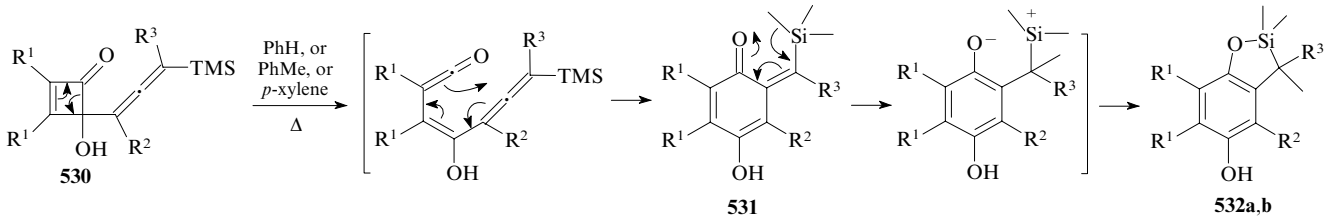


R^1, R^2 = H, Me, Ph; R^1–R^2 = $CH_2N(Me)CH_2$, CH_2OCH_2, $(CH_2)_n$ (n = 2–5)

Scheme 187



Scheme 188



R^1 = OMe, R^2 = OBu^t, R^3 = TMS (**a**, yield >90%); R^1 = OPr^i, R^2 = OMe, R^3 = Ph (**b**, 94%)

the benzene series are used, 2,2-dialkyldihydrobenzofurans are formed in <10% yields, while 2-alkenylphenols and 2,2′-alkylidenebisphenols are the major reaction products. Probably, in the case of more stable 1,2-naphthoquinone-1-methide, the [1,2]-hydride shift is more favourable than the [1,5]-shift. On the contrary, in the case of 1,2-benzoquinone methides, the [1,5]-hydride shift prevails, giving rise to 2-alkenylphenols.

Silyl-substituted 4-allenylcyclobutenones **530** undergo electrocyclic ring expansion in refluxing benzene, toluene or *p*-xylene to give *o*-QMs **531**. The subsequent migration of the methyl group from silicon to carbon and ring closure afford 2,3-dihydrobenzo[d][1,2]oxasiloles **532** (Scheme 188).[380]

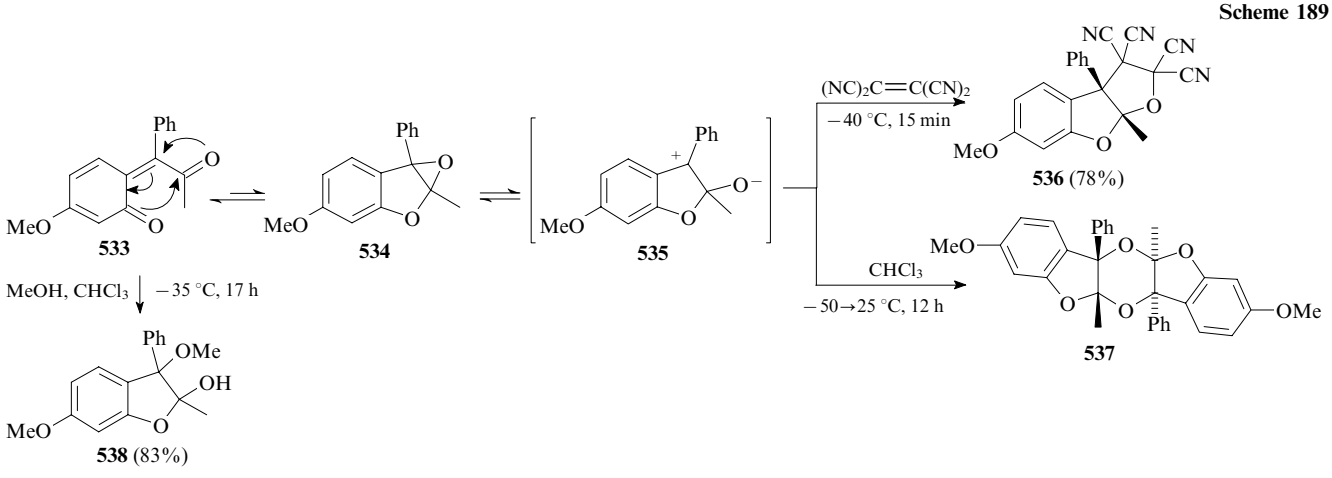
VII. Miscellaneous types of cascade transformations involving *o*-quinone methides

o-Quinone methide **533**, which is stable at reduced temperature, reacts with tetracyanoethylene, through valence isomerization to epoxybenzofuran **534** and generation of 1,3-dipole **535**, to give 1,3-dipolar cycloadduct **536**. On heating to room temperature in solution, it dimerizes to 1,4-dioxane **537** (Scheme 189). Meanwhile, the product of methanolysis of *o*-QM **533** can be formed either upon nucleophilic cleavage of the epoxide ring or upon 1,4-addition of methanol to the *o*-QM and subsequent cyclization to hemiketal **538** as a mixture of diastereomers.[381]

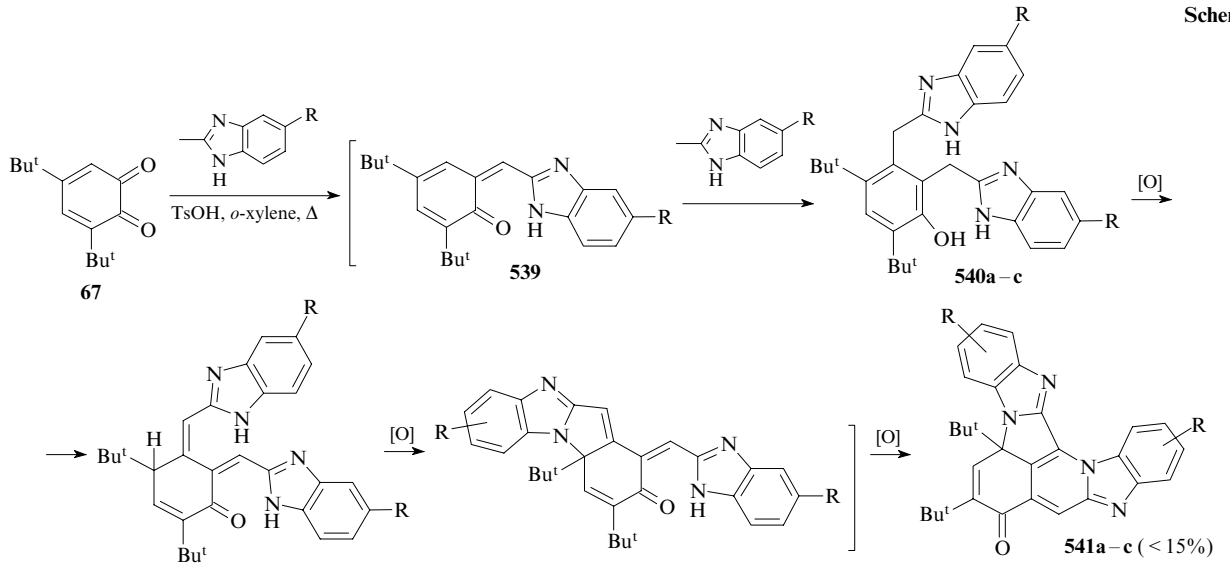
Sterically hindered *o*-benzoquinone **67** reacts with 2-methylbenzimidazole in refluxing *o*-xylene (Scheme 190).[382] It can be assumed that the initial condensation (similar to aldol-crotonic one) of quinone **67** with 2-methylbenzimidazole as the methylene component affords *o*-QM **539**. The subsequent 1,6-addition of a second 2-methylbenzimidazole molecule as a Michael donor yields bis(benzimidazole) derivative **540a**, which is oxidized with the initial *o*-benzoquinone to give polycyclic isoquinoline derivative **541a**. The use of 5-substituted 2-methylbenzimidazoles resulted in bis-products **540b**,**c**, which are oxidized to polyheterocycles **541b**,**c** (formed as mixtures of isomers).

The condensation of 1-bromomethyl-2-(tetrahydropyran-2-yloxy)naphthalenes **542** with tetrachloro- or tetrabromopyracatechol **543** in ketone type solvents in the presence of K_2CO_3 affords a mixture of spirodihydropyrans **544a**,**b** in a low yield (Scheme 191).[383] Although the tetrahydropyranyl group is stable against bases, in this case, it is eliminated with generation of 1,2-naphthoquinone-1-methide **545**. In refluxing acetone in the presence of K_2CO_3, this product is converted to a mixture of dimeric spironaphthalenones **544a**,**b**, while in the absence of a base

Scheme 189

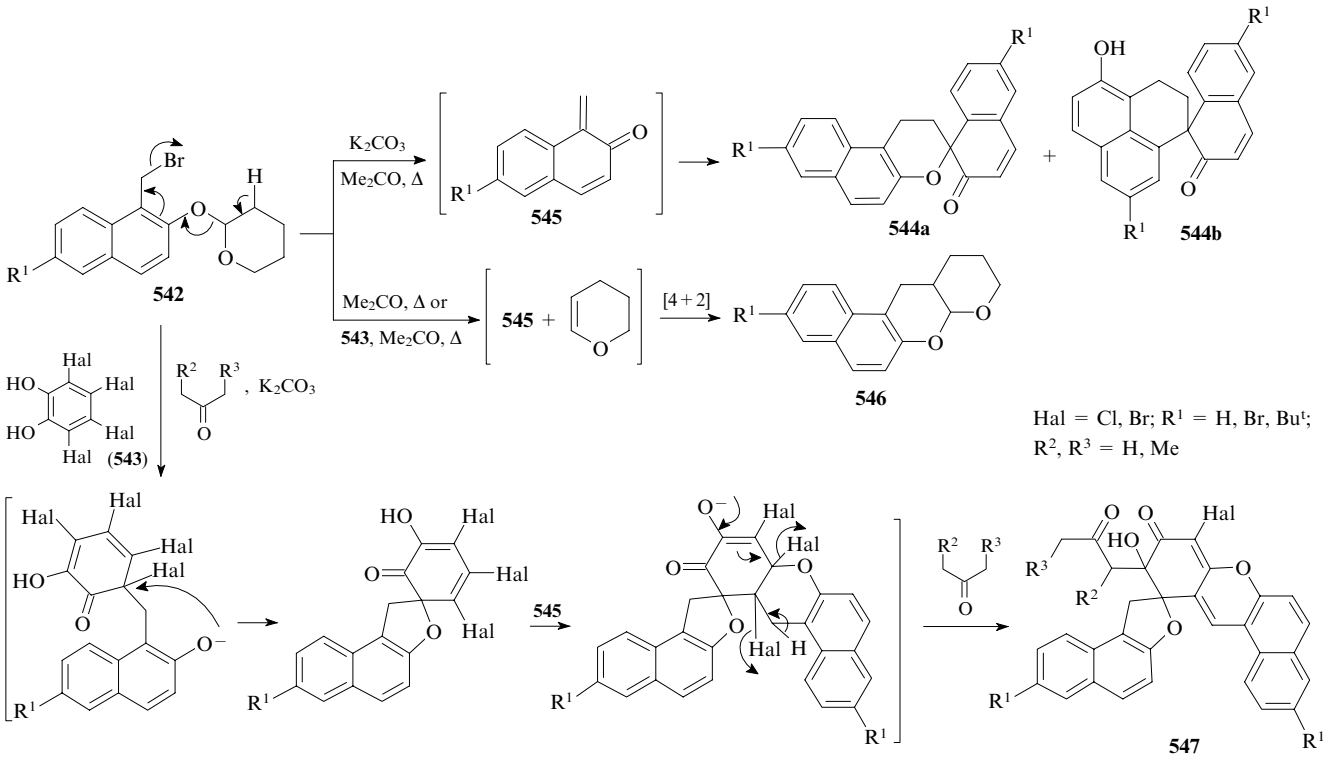


Scheme 190



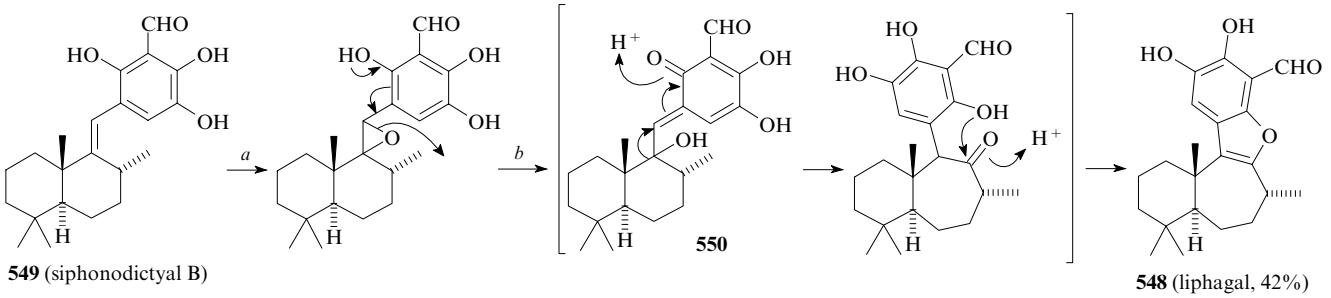
R = H (**a**), Me (**b**), Cl (**c**)

Scheme 191



Hal = Cl, Br; R^1 = H, Br, Bu^t; R^2, R^3 = H, Me

Scheme 192



549 (siphonodictyal B)

548 (liphagal, 42%)

(*a*) *m*-CPBA, $NaHCO_3$; (*b*) CF_3CO_2H

(in the presence or absence of pyrocatechols), it reacts with dihydropyran formed during the reaction to give the [4 + 2]-cycloaddition product — tetrahydrobenzo[*f*]pyrano[2,3-*b*]-chromene **546**. When all of the above-listed reagents are used together, the transformation follows a more complex route. It includes the Michael addition of tetrahalopyrocatechol anion to 1,2-naphthoquinone-1-methide **545**, intramolecular halide ion displacement by the nucleophilic substitution mechanism, conjugate addition of the resulting adduct to a second 1,2-naphthoquinone-1-methide molecule **545**, elimination of the halide ion and hydrogen halide and the subsequent nucleophilic addition of the ketone to give spiro compounds **547**.

George's research group[384] developed a biomimetic approach to the synthesis of a meroterpenoid, liphagal (**548**), from siphonodictyal B (**549**). Epoxidation of compound **549** with *m*-chloroperoxybenzoic acid (*m*-CPBA) followed by ring opening leads to generation of *o*-QM **550** (Scheme 192). The subsequent transformation of the six-membered carbocycle to a seven-membered one and 5-*exo*-*trig*-cyclization furnish benzofuran **548**. This method for liphagal synthesis supplements the range of modern synthetic routes to benzofurans.[385]

VIII. Conclusion

Analysis of the published data on cascade reactions of *o*-QMs provides the conclusion that the construction of oxygen-containing heterocyclic systems (benzopyrans, benzofurans and so on) *via* these intermediates has been studied in considerable detail.† Meanwhile, much less attention has been devoted to the use of *o*-QMs in the synthesis of fused N,O-heterocycles. This is largely related to the instability and high reactivity of *o*-QMs and to incompatibility of *o*-QM generation conditions and stability of the products formed. The reactions of *o*-QMs with heterodienophiles have been scarcely studied. Data on both the possible pathways of the reactions between *o*-QMs and nucleophilic agents and dienophiles and the mechanistic details of these reactions are currently fragmentary and contradictory. In some cases, the question of whether these reactions proceed *via* generation of the *o*-hydroxybenzyl carbocation or *via* generation of *o*-QMs remains open. The reactivity of *o*-QMs containing electron-withdrawing groups has been studied to a much lesser extent than that of their analogues with electron-donating substituents. Furthermore, persistent interest is aroused by the development of new methods for the generation of *o*-QMs from available precursors, especially with the use of chiral catalysts. Thus, the development of new approaches to the synthesis of benzannulated heterocyclic systems and polyfunctional phenol derivatives (as the initial substrates for heterocyclization) based on cascade transformations involving *o*-QMs is an important task in both the chemistry of phenols and the chemistry of heterocyclic compounds. The introduction of reactions of this type into industrial synthetic schemes would make it possible to markedly reduce in the future the number of steps in the syntheses of such compounds and, hence, the amount of hazardous emissions to the environment, which is fully compatible with the green chemistry concept.

This review was written with the financial support of the Ministry of Education and Science of the Russian Federation (Agreement No. 02.a03.21.0008) and Council for Grants at the President of the Russian Federation (Programme for the State Support for Young Russian Scientists, Grant MD-5833.2016.3).

† During the preparation of this review, several more papers on this subjects appeared.[386–395]

References

1. W Zhao, F-E Chen *Curr. Org. Synth.* **9** 873 (2012)
2. Y Hayashi *Chem. Sci.* **7** 866 (2016)
3. C Cabrele, O Reiser *J. Org. Chem.* **81** 10109 (2016)
4. *Organic Photochromic and Thermochromic Compounds* (Eds J C Crano, R J Guglielmetti) (New York: Springer, 2002)
5. H K Shamsuzzaman *Eur. J. Med. Chem.* **97** 483 (2015)
6. L Pan, J L Woodard, D M Lucas, J R Fuchs, A D Kinghorn *Nat. Prod. Rep.* **31** 924 (2014)
7. R J Nevagi, S N Dighe, S N Dighe *Eur. J. Med. Chem.* **97** 561 (2015)
8. A B Turner *Q. Rev. Chem. Soc.* **18** 347 (1964)
9. A B Turner, in *Progress in the Chemistry of Organic Natural Products* Vol. 24 (Ed. L Zechmeister) (Wien, New York: Springer-Verlag, 1966) p. 288
10. R W Van De Water, T R R Pettus *Tetrahedron* **58** 5367 (2002)
11. C Selenski, T R R Pettus *Sci. Synth.* **28** 4.28.12.1 (2006)
12. P Wang, Y Song, L Zhang, H He, X Zhou *Curr. Med. Chem.* **12** 2893 (2005)
13. M Freccero *Mini-Rev. Org. Chem.* **1** 403 (2004)
14. *Quinone Methides* (Ed. S E Rokita) (Hoboken, NJ: Wiley, 2009)
15. J L Bolton *Curr. Org. Chem.* **18** 61 (2014)
16. N Basarić, K Mlinarić-Majerski, M Kralj *Curr. Org. Chem.* **18** 3 (2014)
17. S M Shevchenko, A G Apushkinskii *Russ. Chem. Rev.* **61** 105 (1992)
18. M M Toteva, J P Richard *Adv. Phys. Org. Chem.* **45** 39 (2011)
19. H Amouri *Synlett* 1357 (2011)
20. T P Pathak, M S Sigman *J. Org. Chem.* **79** 9210 (2011)
21. L Caruana, M Fochi, L Bernardi *Molecules* **20** 11733 (2015)
22. Z Wang, J Sun *Synthesis* **47** 3629 (2015)
23. A A Jaworski, K A Scheidt *J. Org. Chem.* **81** 10145 (2016)
24. S B Ferreira, F de Carvahlo da Silva, A C Pinto, D T G Gonzaga, V F Ferreira *J. Heterocycl. Chem.* **46** 1080 (2009)
25. N J Willis, C D Bray *Chem. – Eur. J.* **18** 9160 (2012)
26. M S Singh, A Nagaraju, N Anand, A S Chowdhury *RSC Adv.* **4** 55924 (2014)
27. T-L Ho *Tandem Organic Reactions* (New York: Wiley, 1992)
28. K C Nicolaou, D J Edmonds, P G Bulger *Angew. Chem., Int. Ed.* **45** 7134 (2006)
29. S E Denmark, A Thorarensen *Chem. Rev.* **96** 137 (1996)
30. L F Tietze, U Beifuss *Angew. Chem., Int. Ed. Engl.* **32** 131 (1993)
31. L F Tietze *Chem. Rev.* **96** 115 (1996)
32. L F Tietze, G Brasche, K Gericke *Domino Reactions in Organic Synthesis* (Weinheim: Wiley-VCH, 2006)
33. T Samarakoon, M Hur, R Kurtz, P Hanson *Org. Lett.* **12** 2182 (2010)
34. E V Babaev *Chem. Heterocycl. Compd.* **29** 796 (1993)
35. H Zhi, A Zajdlik, A K Yudin *Acc. Chem. Res.* **47** 1029 (2014)
36. H Miyabe *Molecules* **20** 12558 (2015)
37. S Gnaim, D Shabat *Acc. Chem. Res.* **47** 2970 (2014)
38. K Lenghaus, G G Qiao, D H Solomon *Polymer* **41** 1973 (2000)
39. Q Li, T Dong, X Liu, X Zhang, X Yang, X Lei *Curr. Org. Chem.* **18** 86 (2014)
40. K Fries, K Kann *Justus Liebigs Ann. Chem.* **353** 335 (1907)
41. W Trzcisski *Ber. Dtsch. Chem. Ges.* **16** 2835 (1883)
42. P Wan, B Barker, L Diao, M Fischer, Y Shi, C Yang *San. J. Chem.* **74** 465 (1996)
43. H Meier *Molecules* **17** 1548 (2012)
44. W-J Bai, J G David, Z-G Feng, M G Weaver, K-L Wu, T R R Pettus *Acc. Chem. Res.* **47** 3655 (2014)
45. S B Ferreira, D T G Gonzaga, F de Carvahlo da Silva, K G de Lima Araújo, V F Ferreira *Synlett* 1623 (2011)
46. M Horikawa, T Noguchi, S Takaoka, M Kawase, M Sato, T Tsunoda *Tetrahedron* **60** 1229 (2004)

47. W Verboom, H J T Bos *Tetrahedron Lett*. **19** 1229 (1978)
48. A Y Mensah, P J Houghton, S Bloomfield, A Vlietinck, D V Berghe *J. Nat. Prod*. **63** 1210 (2000)
49. M Gunduz, U A Argikar, A Kamel, K Colizza, J L Bushee, A Cirello, F Lombardo, S Harriman *Drug Metab. Dispos*. **40** 2074 (2012)
50. K Shin-ya, K Furihata, Y Teshima, Y Hayakawa, H Seto *J. Org. Chem*. **58** 4170 (1993)
51. J Veljković, L Uzelac, K Molcanov, K Mlinarić-Majerski, M Kralj, P Wan, N Basarić *J. Org. Chem*. **77** 4596 (2012)
52. S R Angle, W Yang *J. Am. Chem. Soc*. **112** 4524 (1990)
53. M Adib, M Mahdavi, S Bagherzadeh, H R Bijanzadeh *Synlett* 2542 (2009)
54. L E Kapm, L Grimaud, J Oble *Org. Biomol. Chem*. **4** 3410 (2006)
55. M Gerster, R Wicki *Synthesis* 249 (2004)
56. A Bladé-Font, T M Rocabayera *J. Chem. Soc., Perkin Trans. 1* 841 (1982)
57. E Breuer, D Melumad *Tetrahedron Lett*. 1875 (1969)
58. A Bladg-Font *Tetrahedron Lett*. 3607 (1969)
59. V A Osyanin, D V Osipov, Yu N Klimochkin *Chem. Heterocycl. Compd*. **48** 993 (2012)
60. V A Osyanin, D V Osipov, Yu N Klimochkin *J. Org. Chem*. **78** 5505 (2013)
61. M-W Chen, L-L Cao, Z-S Ye, G-F Jiang, Y-G Zhou *Chem. Commun*. **49** 1660 (2013)
62. B Wu, M-W Chen, Z-S Ye, C-B Yu, Y-G Zhou *Adv. Synth. Catal*. **356** 383 (2014)
63. X Lei, C-H Jiang, X Wen, Q-L Xu, H Sun *RSC Adv*. **5** 14953 (2015)
64. Q-Q Yang, W-J Xiao *Eur. J. Org. Chem*. 233 (2017)
65. L Cadona, P D Croce *Synthesis* 800 (1976)
66. Patent US 5510366 (1993)
67. H Sato, T Dan, E Onuma, H Tanaka, B Aoki, H Koga *Chem. Pharm. Bull*. **39** 1760 (1991)
68. M Miyake, Y Fujimoto *Chem. Lett*. 1683 (1993)
69. M Miyake, Y Hanaoka, Y Fujimoto, Y Sato, N Takemoto, I Yokota, Y Yoshiyama *Heterocycles* **43** 665 (1996)
70. M Yamashita, K Okuyama, I Kawasaki, S Ohta *Tetrahedron Lett*. **36** 5603 (1995)
71. M Yamashita, K Okuyama, T Kawajiri, A Takada, Y Inagaki, H Nakano, M Tomiyama, A Ohnaka, I Terayama, I Kawasaki, S Ohta *Tetrahedron* **58** 1497 (2002)
72. M Yamashita, T Inaba, M Nagahama, T Shimizu, S Kosaka, I Kawasaki, S Ohta *Org. Biomol. Chem*. **3** 2296 (2005)
73. W W Sullivan, D Ullman, H Shechter *Tetrahedron Lett*. 457 (1969)
74. D N Nicolaides, S G Adamopoulos, E J Hatzigrigoriou, K E Litinas *J. Chem. Soc., Perkin Trans. 1* 3159 (1991)
75. V B Vol'eva, I A Novikova, G D Ostapets-Sveshnikova, I S Belostotskaya, V V Ershov *Izv. Akad. Nauk SSSR, Ser. Khim*. 2416 (1980)
76. A k Shaikh, G Varvounis *Org. Lett*. **16** 1478 (2014)
77. A k Shaikh, G Varvounis *RSC Adv*. **5** 14892 (2015)
78. E Fanghänel, J Böckelmann, N Grossmann, D Pfeifer *J. Prakt. Chem*. **328** 724 (1986)
79. R Royer, J-P Buisson *Eur. J. Med. Chem*. **15** 275 (1980)
80. V A Osyanin, D V Osipov, M R Demidov, Yu N Klimochkin *J. Org. Chem*. **79** 1192 (2014)
81. K X Rodriguez, J D Vail, B L Ashfeld *Org. Lett*. **18** 4514 (2016)
82. K Balasubramanian, S Selvaraj *Synthesis* 767 (1977)
83. J Arct, E Jakubska, G Olszewska *Synthesis* 314 (1977)
84. J Arct, E Jakubska, G Olszewska *Synth. Commun*. **8** 143 (1978)
85. A Nizam, M A Pisha *Synth. Commun*. **40** 2864 (2010)
86. M Dabiri, A S Delbari, A Bazgir *Synlett* 821 (2007)
87. A Kumar, A Saxena, M Dewan, A De, S Mozumdar *Tetrahedron Lett*. **52** 4835 (2011)
88. R Khavasi, A Bazgir, V Amani, R Rahimi *J. Chem. Res*. 450 (2008)
89. A Hajra, D Kundu, A Majee *J. Heterocycl. Chem*. **46** 1019 (2009)
90. M H Mosslemin, M R Nateghi, R Mohebat *Monatsh. Chem*. **139** 1247 (2008)
91. S Kantevari, T Yempala, S V N Vuppalapati *Synthesis* 959 (2010)
92. V A Osyanin, Doctoral Thesis in Chemical Sciences, Samara State Technical University, Samara, 2014
93. V A Osyanin, D V Osipov, Yu N Klimochkin *Chem. Heterocycl. Compd*. **46** 377 (2010)
94. D V Osipov, V A Osyanin, L G Voskressensky, Yu N Klimochkin *Synthesis* **49** 2286 (2017)
95. V A Osyanin, D V Osipov, Yu N Klimochkin *Chem. Heterocycl. Compd*. **47** 1607 (2012)
96. V A Osyanin, V Yu Nakushnov, D V Osipov, Yu N Klimochkin *Chem. Heterocycl. Compd*. **46** 1027 (2010)
97. V A Osyanin, V Yu Nakushnov, Yu N Klimochkin *Chem. Heterocycl. Compd*. **47** 755 (2011)]
98. N E Sidorina, V A Osyanin *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.,* **49** 91 (2006)
99. V A Osyanin, N E Sidorina *Izv. Vyssh. Uchebn. Zaved., Khim. Khim. Tekhnol.,* **48** 83 (2005)
100. N E Sidorina, V A Osyanin *Chem. Heterocycl. Compd*. **41** 1201 (2005)
101. V A Osyanin, D V Osipov, Yu N Klimochkin *Chem. Heterocycl. Compd*. **47** 108 (2011)
102. N E Sidorina, V A Osyanin *Chem. Heterocycl. Compd*. **43** 1065 (2007)
103. V A Osyanin, N E Sidorina *Chem. Heterocycl. Compd*. **42** 1499 (2006)
104. V A Osyanin, Yu N Klimochkin *Chem. Heterocycl. Compd*. **45** 833 (2009)
105. J T J Spence, J H George *Org. Lett*. **15** 3891 (2013)
106. L Jurd *J. Heterocycl. Chem*. **33** 1227 (1996)
107. F Poppelsdorf, S J Holt *J. Chem. Soc*. 4094 (1954)
108. Patent US 2693470 (1954)
109. Patent GB 731258 (1952)
110. F R Atherton, F Bergel, A Cohen, B Heath-Brown, A H Rees *Chem. Ind. (London)* 1151 (1953)
111. A R Katritzky, Z Zhang, X Lan, H Lang *J. Org. Chem*. **59** 1900 (1994)
112. H Hellmann, J L W Pohlmann *Justus Liebigs Ann. Chem*. **642** 35 (1961)
113. H Hellmann, J L W Pohlmann *Justus Liebigs Ann. Chem*. **642** 40 (1961)
114. S Yaragorla, P L Saini, P V Babu, A I Almansour, N Arumugam *Tetrahedron Lett*. **57** 2351 (2016)
115. R Dada, G Singh, A Pareek, S Kausar, S Yaragorla *Tetrahedron Lett*. **57** 3739 (2016)
116. J D Chambers, J Crawford, H W R Williams, C Dufresne, J Scheigetz, M A Bernstein, C K Lau *Can. J. Chem*. **70** 1717 (1992)
117. R T Jacobs, A D Wright, F Smith *J. Org. Chem*. **47** 3769 (1982)
118. J Posakony, M Hirao, S Stevens, J A Simon, A Bedalov *J. Med. Chem*. **47** 2635 (2004)
119. Y-C Zhang, Q-N Zhu, X Yang, L-J Zhou, F Shi *J. Org. Chem*. **81** 1681 (2016)
120. X-Y Yu, J-R Chen, Q Wei, H-G Cheng, Z-C Liu, W-J Xiao *Chem. – Eur. J*. **22** 6774 (2016)
121. B Wu, Z Yu, X Gao, Y Lan, Y-G Zhou *Angew. Chem., Int. Ed*. **56** 4006 (2017)
122. L I Smith, D J Byers *J. Am. Chem. Soc*. **63** 612 (1941)
123. L I Smith, K C Johnson *J. Am. Chem. Soc*. **59** 673 (1937)
124. L I Smith, I M Webster *J. Am. Chem. Soc*. **59** 662 (1937)
125. L I Smith, D Tenenbaum *J. Am. Chem. Soc*. **59** 667 (1937)
126. P Yates, D J Bichan *Can. J. Chem*. **33** 2045 (1975)
127. H Hellmann, J L W Pohlmann *Justus Liebigs Ann. Chem*. **642** 33 (1961)
128. V A Osyanin, E A Ivleva, Yu N Klimochkin *Synth. Commun*. **42** 1832 (2012)
129. V A Osyanin, E A Ivleva, Yu N Klimochkin *Chem. Heterocycl. Compd*. **46** 1011 (2010)
130. V A Osyanin, D V Osipov, Yu N Klimochkin *Chem. Heterocycl. Compd*. **47** 1601 (2012)
131. V A Osyanin, Yu N Klimochkin *Chem. Heterocycl. Compd*. **47** 242 (2011)

132. D Sielemann, A Winter, N Risch *Heterocycles* **63** 2615 (2004)
133. Y Chen, M G Steinmetz *J. Org. Chem.* **71** 6053 (2006)
134. S Saha, C Schneider *Chem. – Eur. J.* **21** 2348 (2014)
135. J-J Zhao, Y-C Zhang, M-M Xu, M Tang, F Shi *J. Org. Chem.* **80** 10016 (2015)
136. M Tang, J-J Zhao, Q Wu, M-S Tu, F Shi *Synthesis* **49** 2035 (2017)
137. E Ziegler, K Mayr *Monatsh. Chem.* **92** 246 (1961)
138. X Chen, M Nagata, K Tanaka, F Yoneda *J. Chem. Soc., Chem. Commun.* 44 (1989)
139. V A Osyanin, D V Osipov, S A Pavlov, Yu N Klimochkin *Chem. Heterocycl. Compd.* **50** 1195 (2014)]
140. I G Sonsona, E Marques-Lopez, R P Herrera *Symmetry* **7** 1519 (2015)
141. R Pratap, V J Ram *Chem. Rev.* **114** 10146 (2014)
142. V A Osyanin, D V Osipov, Yu N Klimochkin *Tetrahedron* **68** 5612 (2012)
143. M Fujiwara, M Sakamoto, K Komeyama, H Yoshida, K Takaki *J. Heterocycl. Chem.* **52** 59 (2015)
144. D V Osipov, V A Osyanin, Yu N Klimochkin *Russ. J. Org. Chem.* **49** 398 (2013)
145. O El-Sepelgy, S Haseloff, S K Alamsetti, C Schneider *Angew. Chem., Int. Ed.* **53** 7923 (2014)
146. C-C Hsiao, H-H Liao, M Rueping *Angew. Chem., Int. Ed.* **53** 13258 (2014)
147. B Wu, X Gao, Z Yan, W-X Huang, Y-G Zhou *Tetrahedron Lett.* **56** 4334 (2015)
148. L Caruana, M Mondatori, V Corti, S Marales, A Mazzanti, M Fochi, L Bernardi *Chem. – Eur. J.* **21** 6037 (2015)
149. A Adili, Z-L Tao, D-F Chen, Z-Y Han *Org. Biomol. Chem.* **13** 2247 (2015)
150. B Wu, X Gao, Z Yan, M-W Chen, Y-G Zhou *Org. Lett.* **17** 6134 (2015)
151. V A Osyanin, D V Osipov, Yu N Klimochkin *Chem. Heterocycl. Compd.* **47** 1460 (2011)
152. M von Strandtmann, M Cohen, C Puchalski, J Shavel Jr *J. Org. Chem.* **33** 4306 (1968)
153. S K Alamsetti, M Spanka, C Schneider *Angew. Chem., Int. Ed.* **55** 2392 (2016)
154. A K Jordão, M D Vargas, A C Pinto, F de C da Silva, V F Ferreira *RSC Adv.* **5** 67909 (2015)
155. D Liu, D Xu, J Gao, S Zhou *Chem. Sci. Trans.* **3** 455 (2014)
156. L Q Wu, Y F Wu, C G Yang, L M Yang, L J Yang *J. Braz. Chem. Soc.* **21** 941 (2010)
157. H R Shaterian, M Ranjbar, K Azizi *J. Mol. Liq.* **162** 95 (2011)
158. W Li, W Bian, L Wang *Asian J. Chem.* **25** 8289 (2013)
159. V Srinivasa, V R Rao *Synth. Commun.* **42** 388 (2012)
160. J M Khurana, A Chaudhary, A Lumb, B Nand *Can. J. Chem.* **90** 739 (2012)
161. S Chao, G Lu, L Wu *Asian J. Chem.* **23** 3865 (2011)
162. A Rahmatpour *Monatsh. Chem.* **144** 1205 (2013)
163. M Dabiri, Z N Tisseh, A Bazgir *J. Heterocycl. Chem.* **47** 1062 (2010)
164. L Wu, J Zhang, L Fang, C Yang, F Yan *Dyes Pigm.* **86** 93 (2010)
165. G C Nandi, S Samai, M S Singh *Synlett* 1133 (2010)
166. L Wu, X Wang, L Yang, F Yan *Asian J. Chem.* **22** 6178 (2010)
167. K P Kumar, S Satyanarayana, P L Reddy, G Narasimhulu, N Ravirala, B V S Reddy *Tetrahedron Lett.* **53** 1738 (2012)
168. G C Nandi, S Samai, R Kumar, M S Singh *Tetrahedron* **65** 7129 (2009)
169. X-J Sun, J-F Zhou, P-S Zhao *Synth. Commun.* **42** 1542 (2012)
170. P Das, A Dutta, A Bhaumik, C Mukhopadhyay *Green Chem.* **16** 1426 (2014)
171. X-M Wen, H-Y Wang, S-L Li *J. Chem. Res.* 776 (2006)
172. G Sabitha, M Bhikshapathi, S Nayak, R Srinivas, J S Yadav *J. Heterocycl. Chem.* **48** 267 (2011)
173. A C Shekhar, A R Kumar, G Sathaiah, K Raju, P S Rao, M Sridhar, B Narsaiah, P V S S Srinivas, B Sridhar *Helv. Chim. Acta* **95** 502 (2012)
174. P Srihari, B Ganganna, K Rajendraprasad, D C Bhunia, J S Yadav *Indian J. Chem., Sect. B* **50** 1755 (2011)
175. S Samai, G C Nandi, M S Singh *Tetrahedron* **68** 1247 (2012)
176. J Li, W Tang, L Lu, W Su *Tetrahedron Lett.* **49** 7117 (2008)
177. Jian Li, Yia Li, J Fang, W Su *Synth. Commun.* **40** 1029 (2010)
178. A Kumar, S Sharma, R A Maurya, J Sarkar *J. Comb. Chem.* **12** 20 (2010)
179. J Li, L Lu, W Su *Tetrahedron Lett.* **51** 2434 (2010)
180. A M Akondi, M L Kantam, R Trivedi, B Sreedhar, S K Buddana, R S Prakasham, S Bhargava *J. Mol. Catal. A: Chem.* **386** 49 (2014)
181. L Q Wu, W L Li, F L Yan *J. Heterocycl. Chem.* **47** 1246 (2010)
182. L-Q Wu, L-M Yang, X Wang, F-L Yan *J. Chin. Chem. Soc.* **57** 738 (2010)
183. H R Shaterian, M Mohammadnia, F Moradi *J. Mol. Liq.* **172** 88 (2012)
184. Y Xie, Y Wang, L Wu *Asian J. Chem.* **23** 5377 (2011)
185. W Ma, X Wang, F Yan, L Wu, Y Wang *Monatsh. Chem.* **142** 163 (2011)
186. Y Wan, C Wang, H-Y Wang, L-L Zhao, X-X Zhang, J-J Shi, S-Y Huang, G-X Liu, H Wu *J. Heterocycl. Chem.* **51** 1293 (2014)
187. X Wang, G Lu, F Yan, W Ma, L Wu *J. Heterocycl. Chem.* **48** 1379 (2011)
188. S Damavandi, R Sandaroos *J. Adv. Sci. Res.* **2** (3) 73 (2011)
189. S H Mashraqui, M B Patil, H D Mistry, S Ghadigaonkar, A Meetsma *Chem. Lett.* **33** 1058 (2004)
190. M Kidwai, A Jahan, N K Mishra *C. R. Chimie* **15** 324 (2012)
191. S Gao, C H Tsai, C-F Yao *Synlett* 949 (2009)
192. M Lei, L Ma, L Hu *Synth. Commun.* **41** 3424 (2011)
193. V A Osyanin, M R Demidov, Yu N Klimochkin *Russ. J. Gen. Chem.* **85** 989 (2015)]
194. W Dilthey, H Steinborn *J. Prakt. Chem.* **133** 219 (1932)
195. A S Gazizov, A V Smolobochkin, J K Voronina, A R Burilov, M A Pudovik *Tetrahedron* **71** 445 (2015)
196. A S Gazizov, A R Burilov, M A Pudovik, O G Sinyashin *Russ. Chem. Rev.* **86** 75 (2017)
197. R Kumar, G C Nandi, R K Verma, M S Singh *Tetrahedron Lett.* **51** 442 (2010)
198. W Dilthey, F Quint, J Heinen *J. Prakt. Chem.* **152** 49 (1939)
199. O Dischendorfer, E Nesitka *Monatsh. Chem.* **50** 16 (1928)
200. D Vaughan, A B Naidu, A Jha *Curr. Org. Synth.* **9** 613 (2012)
201. H Lv, W-Q Jia, L-H Sun, S Ye *Angew. Chem., Int. Ed.* **52** 8607 (2013)
202. J Izquierdo, A Orue, K A Scheidt *J. Am. Chem. Soc.* **135** 10634 (2013)
203. Y Herzig, L Lerman, W Goldenberg, D Lerner, H E Gottlieb, A Nudelman *J. Org. Chem.* **71** 4130 (2006)
204. T Oguma, T Katsuki *Chem. Commun.* **50** 5053 (2014)
205. L Jurd, R Wong *Aust. J. Chem.* **33** 137 (1980)
206. J E Ezcurra, K Karabelas, H W Moor *Tetrahedron* **61** 275 (2005)
207. P A Hume, J Sperry, M A Brimble *Org. Biomol. Chem.* **9** 5423 (2011)
208. K Wojciechowski, K Dolatowska *Tetrahedron* **61** 8419 (2005)
209. M S Chauhan, F M Dean, D Matkin, M L Robinson *J. Chem. Soc., Perkin Trans. 1* 120 (1973)
210. W Chen, S K Park, W Yu, A Xiong, B G Sanders, K Kline *Eur. J. Med. Chem.* **58** 72 (2012)
211. H Wang, Y Wang, K-L Han, X-J Peng *J. Org. Chem.* **70** 4910 (2005)
212. G Desimoni, L Astolfi, M Cambieri, A Gamba, G Tacconi *Tetrahedron* **29** 2627 (1973)
213. A Arduini, A Bosi, A Pochini, R Ungaro *Tetrahedron* **41** 3095 (1985)
214. G Desimoni, G Tacconi *Chem. Rev.* **75** 651 (1975)
215. R M Jones, C Selenski, T R R Pettus *J. Org. Chem.* **67** 6911 (2002)
216. W-J Bai, J C Green, T R R Pettus *J. Org. Chem.* **77** 379 (2012)
217. C Selenski, T R R Pettus *J. Org. Chem.* **69** 9196 (2004)
218. C Selenski, L H Mejorado, T R R Pettus *Synlett* 1101 (2004)

219. P Huang, T Cameron, A Jha *Tetrahedron Lett*. **50** 51 (2009)
220. Y Gu, J Barrault, F Jérôme *Adv. Synth. Catal*. **351** 3269 (2009)
221. S B Bharate, R Mudududdla, J B Bharate, N Battini, S Battula, R R Yadav, B Singh, R A Vishwakarma *Org. Biomol. Chem*. **10** 5143 (2012)
222. A Taheri, B Lai, J Yang, J Zhang, Y Gu *Tetrahedron* **72** 479 (2016)
223. J Nakayama, M Yoshida, O Simamura *Chem. Lett*. 451 (1973)
224. H Yoshiba, M Watanabe, H Fukushima, J Ohshita, A Kunai *Org. Lett*. **6** 4049 (2004)
225. S Cao, Y Wang, X Peng *J. Org. Chem*. **79** 501 (2014)
226. K Chiba, Y Yamaguchi, M Tada *Tetrahedron Lett*. **39** 9035 (1998)
227. A L Lawrence, R M Adlington, J E Baldwin, V Lee, J A Kershaw, A L Thompson *Org. Lett*. **12** 1676 (2010)
228. Y Gao, G-Q Wang, K Wei, P Hai, F Wang, J-K Liu *Org. Lett*. **14** 5936 (2012)
229. S B Bharate, I P Singh *Tetrahedron Lett*. **47** 7021 (2006)
230. D N Tran, N Cramer *Chem. – Eur. J*. **20** 10654 (2014)
231. M Shao, Y Wang, Y-Q Jian, X-J Huang, D-M Zhang, Q-F Tang, R-W Jiang, X-G Sun, Z-P Lv, X-Q Zhang, W-C Ye *Org. Lett*. **14** 5262 (2012)
232. Y-Q Jian, X-J Huang, D-M Zhang, R-W Jiang, M-F Chen, B-X Zhao, Y Wang, W-C Ye *Chem. – Eur. J*. **21** 9022 (2015)
233. A Gervais, K E Lazarski, J A Porko *J. Org. Chem*. **80** 9584 (2015)
234. I P Singh, J Sidana, S B Bharate, W J Foley *Nat. Prod. Rep*. **27** 393 (2010)
235. Y Luan, H Sun, S E Schaus *Org. Lett*. **13** 6480 (2011)
236. M Deodhar, D StC Black, N Kumar *Tetrahedron* **63** 5227 (2007)
237. C Qi, D Ramella, A M Wensley, Y Luan *Adv. Synth. Catal*. **358** 2604 (2016)
238. A Yamashita, T A Scahill, C G Chidester *Tetrahedron Lett*. **26** 1159 (1985)
239. L Song, H Yao, R Tong *Org. Lett*. **16** 3740 (2014)
240. E Kleinpeter *J. Serb. Chem. Soc*. **71** 1 (2006)
241. D V Dar'in, P S Lobanov *Russ. Chem. Rev*. **84** 601 (2015)
242. V G Nenajdenko, A V Sanin, E S Balenkova *Russ. Chem. Rev*. **68** 437 (1999)
243. A V Lukashenko, V A Osyanin, D V Osipov, Yu N Klimochkin *Chem. Heterocycl. Compd*. **52** 711 (2016)
244. L Reng *Synthesis* 69 (1989)
245. V A Osyanin, A V Lukashenko, D V Osipov, Yu N Klimochkin *Chem. Heterocycl. Compd*. **50** 1528 (2015)
246. A V Lukashenko, D V Osipov, V A Osyanin, Yu N Klimochkin *Russ. J. Org. Chem*. **52** 1817 (2016)
247. A V Lukashenko, V A Osyanin, D V Osipov, Yu N Klimochkin *J. Org. Chem*. **82** 1517 (2017)
248. V A Osyanin, D V Osipov, D D Borisov, Yu N Klimochkin *Chem. Heterocycl. Compd*. **49** 683 (2013)
249. F Troxler *Helv. Chim. Acta* **56** 374 (1973)
250. K K Balasubramanian, S Selvaraj *J. Org. Chem*. **45** 3726 (1980)
251. J R Mahajan, H C Araujo *Synthesis* 111 (1976)
252. L Yu Ukhin, L V Belousova, Zh I Orlova, S V Shishkina, O V Shishkin *Russ. Chem. Bull., Int. Ed*. **51** 1262 (2002)
253. L Yu Ukhin, V A Kharlanov, E V Solomovich, O V Shishkin *Russ. Chem. Bull., Int. Ed*. **48** 949 (1999)
254. M Frater-Schroder, M Mahrer-Busato *Bioorg. Chem*. **4** 332 (1975)
255. L Jurd *J. Heterocycl. Chem*. **25** 89 (1988)
256. L Jurd *J. Heterocycl. Chem*. **33** 1919 (1996)
257. L Jurd *J. Heterocycl. Chem*. **34** 601 (1997)
258. D Zhou, K Mao, J Zhang, B Yan, W Wang, H Xie *Tetrahedron Lett*. **57** 5649 (2016)
259. A Lee, K A Scheidt *Chem. Commun*. **51** 3407 (2015)
260. Y Wang, J Pan, J Dong, C Yu, T Li, X-S Wang, S Shen, C Yao *J. Org. Chem*. **82** 1790 (2017)
261. W Chen, Y Kang, R G Wilde, D Seidel *Angew. Chem., Int. Ed*. **53** 5179 (2014)
262. Y Zhou, K-D Zhou, X-P Xu, Y-N Zhu, Z Wu, S-J Ji *Tetrahedron* **70** 9644 (2014)
263. K C Majumdar, A Taher, R K Nandi *Tetrahedron* **68** 5693 (2012)
264. J J Talley *J. Org. Chem*. **50** 1695 (1985)
265. G Casiraghi, M Cornia, G Casnati, G G Fava, M F Belicchi *J. Chem. Soc., Chem. Commun*. 271 (1986)
266. L Xia, Y R Lee *Synlett* 1643 (2008)
267. J Muhammad, X-C Li, D C Dunbar, M A ElSohly, I A Khan *J. Nat. Prod*. **64** 1322 (2001)
268. W S Murphy, S M Tuladhar, B Duffy *J. Chem. Soc., Perkin Trans. 1* 605 (1992)
269. W S Murphy, A Culhane, B Duffy, S M Tuladhar *J. Chem. Soc., Perkin Trans. 1* 3397 (1992)
270. Y R Lee, Y M Kim, S H Kim *Tetrahedron* **65** 101 (2009)
271. R W Hoffmann *Chem. Rev*. **89** 1841 (1989)
272. L-M Zhao, A-L Zhang, H-S Gao, J-H Zhang *J. Org. Chem*. **80** 10353 (2015)
273. J Lumb, K C Choong, D Trauner *J. Am. Chem. Soc*. **130** 9230 (2008)
274. K A Korthals, W D Wulff *J. Am. Chem. Soc*. **130** 2898 (2008)
275. A A More, C V Ramana *Org. Lett*. **18** 612 (2016)
276. A A More, C V Ramana *Org. Lett*. **18** 1458 (2016)
277. K Hultzsch *Ber. Dtsch. Chem. Ges*. **74** 1539 (1941)
278. M Letulle, P Guenot, J-L Ripoll *Tetrahedron Lett*. **32** 2013 (1991)
279. G G Qiao, K Lenghaus, D H Solomon, A Reisinger, I Bytheway, C Wentrup *J. Org. Chem*. **63** 9806 (1998)
280. D A Bolon *J. Org. Chem*. **35** 715 (1970)
281. F M Dean, M O A Orabi *J. Chem. Soc., Perkin Trans. 1* 2617 (1982)
282. D V Osipov, V A Osyanin, Yu N Klimochkin *Synlett* **23** 917 (2012)
283. D Liao, H Li, X Lei *Org. Lett*. **14** 18 (2012)
284. C Bavoux, M Perrin, H Goldmann, V Bohmer *J. Chem. Soc., Perkin Trans. 2* 2059 (1989)
285. F M Dean, D A Matkin, M O A Orabi *J. Chem. Soc., Perkin Trans. 1* 1437 (1981)
286. V A Osyanin, Yu V Popova, Yu N Klimochkin *Russ. J. Org. Chem*. **47** 958 (2011)
287. P Kempem, T Löschner, A A Auer, A Seifert, G Cox, S Spange *Chem. – Eur. J*. **20** 8040 (2014)
288. R Faure, G Thomas-David, R Bartnik, Z Cebulska, E Graca, S Lesniak *Bull. Soc. Chim. Fr*. 378 (1991)
289. P D Gardner, H Sarrafizadeh *J. Org. Chem*. **25** 641 (1960)
290. X Wu, S Lin, M Li, T You *Synlett* 1501 (2009)
291. P Cacioli, J A Reiss *Aust. J. Chem*. **37** 2599 (1984)
292. M Ashram, D O Miller, P E Georghiou *J. Chem. Soc., Perkin Trans.1* 1470 (2002)
293. M Matsumoto, K Kuroda *Tetrahedron Lett*. **22** 4437 (1981)
294. O L Chapman, M R Engel, J P Springer, J C Clardy *J. Am. Chem. Soc*. **93** 6696 (1971)
295. O O Fadeyi, R N Daniels, S M DeGuire, G W Lindsley *Tetrahedron Lett*. **50** 3084 (2009)
296. S L Xu, M Taing, H W Moore *J. Org. Chem*. **56** 6104 (1991)
297. Y Xiong, H Xia, H W Moore *J. Org. Chem*. **60** 6460 (1995)
298. A Tarli, K K Wang *J. Org. Chem*. **62** 8841 (1997)
299. Z Goldschmidt, S Levinger, H Gottlieb *Tetrahedron Lett*. **35** 7273 (1994)
300. M L Deb, S S Dey, I Bento, M T Barros, C D Maycock *Angew. Chem., Int. Ed*. **52** 9791 (2013)
301. A Shahrisa, R Teimuri-Mofrad, M Gholamhosseini-Nazari *Synlett* **26** 1031 (2015)
302. M L Deb, C D Pegu, P J Borpatra, P K Baruah *Tetrahedron Lett*. **57** 5479 (2016)
303. M T Richers, M Breugst, A Yu Platonova, A Ullrich, A Dieckmann, K N Houk, D Seidel *J. Am. Chem. Soc*. **136** 6123 (2014)
304. V I Kelarev, V N Koshelev *Russ. Chem. Rev*. **64** 317 (1995)
305. A k Shaikh, A J A Cobb, G Varvounis *Org. Lett*. **14** 584 (2012)
306. A F Barrero, J F Q Moral, M M Herrador, P Arteaga, M Cortés, J Benites, A Rosellón *Tetrahedron* **62** 6012 (2006)
307. D V Osipov, Candidate Thesis in Chemical Sciences, Samara State Technical University, Samara, 2014
308. I Szatmári, A Heténvi, L Lázár, F Fülöp *J. Heterocycl. Chem*. **41** 367 (2004)
309. M Adler, S Baldwin *Tetrahedron* **50** 5075 (2009)

310. G Sartori, G Casiraghi, L Bolzoni, G Casnati *J. Org. Chem.* **44** 803 (1979)
311. J-L Pozzo, V A Lokshin, R Guglielmetti *J. Chem. Soc., Perkin Trans. 1* 2591 (1994)
312. G Casiraghi, G Casnati, G Salerno *J. Chem. Soc. C* 2546 (1971)
313. Y R Lee, J H Choi, S H Yoon *Tetrahedron Lett.* **46** 7539 (2005)
314. Y R Lee, L Xia *Tetrahedron Lett.* **49** 3283 (2008)
315. Y R Lee, Y M Kim *Helv. Chim. Acta* **90** 2401 (2007)
316. R P Pandit, Y R Lee *Synthesis* **44** 2910 (2012)
317. S Nozoe, K Hirai *Tetrahedron Lett.* 3017 (1969)
318. G S Hari, Y R Lee *Bull. Korean Chem. Soc.* **32** 2949 (2011)
319. M R Dintzner, T W Lyons, M H Akroush, P Wucka, A T Rzepka *Synlett* 785 (2005)
320. J D Pettigrew, J A Cadieux, S S S So, P D Wilson *Org. Lett.* **7** 467 (2005)
321. B A Chauder, C C Lopes, R S C Lopes, A J M da Silva, V Snieckus *Synthesis* 279 (1998)
322. S Bissada, C K Lau, M A Bernstein, C Dufresne *Can. J. Chem.* **72** 1866 (1994)
323. V Dimakos, T Singh, M S Taylor *Org. Biomol. Chem.* **14** 6703 (2016)
324. W J G Donnelly, P V R Shannon *J. Chem. Soc. D* 76 (1971)
325. F Camps, J Coll, A Messeguer, M A Pericás *J. Heterocycl. Chem.* **17** 1377 (1980)
326. O Pancharoen, K Picker, V Reutrakul, W C Taylor, P Tuntiwachwuttikul *Aust. J. Chem.* **40** 455 (1987)
327. B S Olson, D Trauner *Synlett* 700 (2005)
328. H C Lam, H P Pepper, C J Sumby, J H George *Angew. Chem., Int. Ed.* (2017) (in the press); doi: 10.1002/anie.201700114
329. Y Kang, Y Mei, Y G Du, Z D Jin *Org. Lett.* **5** 4481 (2003)
330. M J Begley, L Crombie, D A Slack, D A Whiting *J. Chem. Soc., Perkin Trans. 1* 2402 (1977)
331. H Zeng, D Duan, B Tang *Synlett* **26** 927 (2015)
332. Y R Lee, J H Kim *Synlett* 2232 (2007)
333. X Wang, Y R Lee *Tetrahedron* **67** 9179 (2011)
334. R N Khanna, P K Sharma, R H Thomson *J. Chem. Soc., Perkin Trans. 1* 1821 (1987)
335. F Bigi, S Carloni, R Maggi, C Muchetti, G Sartori *J. Org. Chem.* **62** 7024 (1997)
336. H J Knölker, C Hofmann *Tetrahedron Lett.* **37** 7947 (1996)
337. D Bell, M R Davies, G R Geen, I S Mann *Synthesis* 707 (1995)
338. J T North, D R Kronenthal, A J Pullokaran, S R Real, H Y Chen *J. Org. Chem.* **60** 3397 (1995)
339. N Bhuvaneswari, C S Venhatachalam, K K Balasubramanian *J. Chem. Soc., Chem. Commun.* 1177 (1994)
340. J Zsindely, H Schmid *Helv. Chim. Acta* **51** 1510 (1968)
341. B S Thyagarajan, K K Balasubramanian, R B Rao *Tetrahedron* **23** 1893 (1967)
342. Y Besace, I Marszak, J Maisse *Bull. Soc. Chim. Fr.* 2275 (1971)
343. J Hlubucek, E Ritchie, W C Taylor *Tetrahedron Lett.* 1369 (1969)
344. Patent JP 22587 (1963)
345. I Iwai, J Ide *Chem. Pharm. Bull.* **11** 1042 (1963)
346. J M Evans, C S Fake, T C Hamilton, R H Poyser, E A Watts *J. Med. Chem.* **26** 1582 (1983)
347. G Cardillo, L Merlini *Gazz. Chim. Ital.* **98** 191 (1968)
348. Patent GB 877960 (1960)
349. Patent US 3004040 (1960)
350. S Madabhushi, R Jillela, K R Godala, K K R Mallu, C R Beeram, N Chinthala *Tetrahedron Lett.* **53** 5275 (2012)
351. E J Tisdale, I Slobodov, E A Theodorakis *Org. Biomol. Chem.* **1** 4418 (2003)
352. J Kong, T Meng, J Su *Org. Process. Res. Dev.* **19** 681 (2015)
353. A Jha, P-J J Huang *J. Heterocycl. Chem.* **46** 1098 (2009)
354. G Brooke *J. Fluorine Chem.* **22** 483 (1983)
355. G M Brooke, R S Matthews, N S Robson *J. Chem. Soc., Perkin Trans. 1* 102 (1980)
356. R Hug, G Frater, H J Hansen, H Schmid *Helv. Chim. Acta* **54** 306 (1971)
357. M C Sacquet, B Graffe, P Maitte *Bull. Soc. Chim. Fr.* 2557 (1971)
358. R Hug, H J Hansen, H Schmid *Chimia* **23** 108 (1969)
359. D Billeret, D Blondeau, H Sliwa *Synthesis* 881 (1993)
360. A Padwa, D Dehn, T Oine, G A Lee *J. Am. Chem. Soc.* **97** 1837 (1975)
361. M Gomberg, D Nishida *J. Am. Chem. Soc.* **45** 190 (1923)
362. N Majumdar, K A Korthals, W D Wulff *J. Am. Chem. Soc.* **134** 1357 (2012)
363. R Kuhn, H R Hensel, D Weiser *Justus Liebigs Ann. Chem.* **611** 83 (1958)
364. G Cardillo, R Cricchio, L Merlini *Tetrahedron* **27** 1875 (1971)
365. A Jha, J Beal *Tetrahedron Lett.* **45** 8999 (2004)
366. E E Schweizer, T Minami, D M Crouse *J. Org. Chem.* **36** 4028 (1971)
367. J E Baldwin, O W Lever *J. Chem. Soc., Chem. Commun.* 344 (1973)
368. N A Petasis, A N Butkevich *J. Organomet. Chem.* **694** 1747 (2009)
369. Q Wang, M G Finn *Org. Lett.* **2** 4063 (2000)
370. K S Barbato, Y Luan, D Ramella, J S Panek, S E Schaus *Org. Lett.* **17** 5812 (2015)
371. H Heaney, J M Jablonski, C T McCarty *J. Chem. Soc., Perkin Trans. 1* 2903 (1972)
372. H Heaney, J M Jablonski *Chem. Commun. (London)* 1139 (1968)
373. T Zhang, X Huang, L Wu *Eur. J. Org. Chem.* 3507 (2012)
374. N A Bailey, C P Falshaw, W D Ollis, M Watanabe, M M Dhar, A W Khan, V C Vora *Chem. Commun. (London)* 374 (1968)
375. N D Paul, S Mandal, M Otte, X Cui, X P Zhang, B de Bruin *J. Am. Chem. Soc.* **136** 1090 (2014)
376. N Majumdar, N D Paul, S Mandal, B de Bruin, W D Wulff *ACS Catal.* **5** 2329 (2015)
377. Y Yang, H Liu, C Peng, J Wu, J Zhang, Y Qiao, X-N Wang, J Chang *Org. Lett.* **18** 5022 (2016)
378. S Mahato, S Haldar, C K Jana *Chem. Commun.* **50** 332 (2014)
379. G Casnati, A Pochini, M G Terenghi, R Ungaro *J. Org. Chem.* **48** 3783 (1983)
380. M Taing, H W Moore *J. Org. Chem.* **61** 329 (1996)
381. W Adam, L Hadjiarapoglou, K Peters, M Sauter *Angew. Chem., Int. Ed. Engl.* **32** 735 (1993)
382. Yu A Sayapin, V N Komissarov, S V Kobtsev, V I Minkin, Z A Starikova, M Yu Antipin *Dokl. Chem.* **403** 121 (2005)
383. T R Kasturi, A B Mandal, P Amruta Reddy, K B Ganesha Prasad, B Rajasekhar *Tetrahedron* **47** 5245 (1991)
384. A W Markwell-Heys, K K W Kuan, J H George *Org. Lett.* **17** 4228 (2015)
385. O A Omelchuk, A S Tikhomirov, A E Shchekotikhin *Russ. Chem. Rev.* **85** 817 (2016)
386. X-L Lian, A Adili, B Liu, Z-L Tao, Z-Y Han *Org. Biomol. Chem.* **15** 3670 (2017)
387. J Zhou, M-L Wang, X Gao, G-F Jiang, Y-G Zhou *Chem. Commun.* **53** 3531 (2017)
388. J-H Jin, X-Y Li, X Luo, J S Fossey, W-P Deng *J. Org. Chem.* **82** 5424 (2017)
389. N Meisinger, L Roiser, U Monkowius, M Himmelsbach, R Robiette, M Waser *Chem. – Eur. J.* **23** 5137 (2017)
390. Y Xie, B List *Angew. Chem., Int. Ed.* **56** 4936 (2017)
391. C Lin, H-J Du, H Zhao, D-F Yan, N-X Liu, H Sun, X Wen, Q-L Xu *Org. Biomol. Chem.* **15** 3472 (2017)
392. E E Allen, C Zhu, J S Panek, S E Schaus *Org. Lett.* **19** 1878 (2017)
393. Y Zhu, W-E Zhang, L Zhang, S Luo *Chem. – Eur. J.* **23** 1253 (2017)
394. A J Day, H C Lam, C J Sumby, J H George *Org. Lett.* **19** 2463 (2017)
395. L Song, F Huang, L Guo, M A Ouyang, R Tong *Chem. Commun.* **53** 6021 (2017)