The oxa-Michael reaction: from recent developments to applications in natural product synthesis

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In marked contrast to Michael reactions, oxa-Michael reactions have not been used as standard transformations in organic synthesis until quite recently. This was mainly due to a lack of reactivity and selectivity, although the potential products of such reactions are valuable intermediates. This *tutorial review* presents recent major advances in the field of oxa-Michael (sometimes called oxo-Michael or oxy-Michael) reactions and applications in the total synthesis of complex natural products.

Introduction

The addition of carbon-nucleophiles to conjugate acceptor systems (Michael addition) has become one of the most important C–C bond forming reactions in organic synthesis. Various anionic carbon synthons (derived from nitroalkanes or malonates for example) can be reacted with a diverse set of acceptor molecules such as α,β-unsaturated ketones and esters or nitroalkenes. In many cases, a high degree of stereocontrol together with good yields can be achieved so that these reactions not only belong to the standard repertoire of organic synthesis but are also frequently used in the context of natural product synthesis.[1] In marked contrast, the addition of non-carbon nucleophiles such as amines,[2] thiols,[3] phosphorus[4] and alcohols (hetero-Michael addition) has gained considerably less interest in the past decades. This holds especially true for the conjugate addition of alcohols, the oxa-Michael addition (Scheme 1).[5] The addition of alcohols leads to intermediate enolates which can then serve as starting points for further reactions (domino reactions) or can be protonated to give β-hydroxy carbonyl (or carboxyl) compounds. It is important to note that these final products can in principle also be obtained by aldol reactions. Therefore, the oxa-Michael reaction represents a valuable synthetic alternative to the established aldol methodology in cases where suitably substituted alcohols can be employed. For a long time however, this reaction has suffered from major drawbacks such as low reactivity and reversibility issues as well as a lack of control in stereoselectivity. Consequently, reports concerning the oxa-Michael reaction have remained quite scarce and no general reaction protocols for this transformation have been reported until quite recently.[6] This is even more astonishing since the first oxa-Michael reaction was reported as early as 1878 (earlier than the carbon Michael reaction) by Loydl in his work towards the synthesis of malic acid.[7] Moreover, the products accessible by this reaction are key intermediates in organic synthesis (Fig. 1).

The structural motifs of β-hydroxy ketones and β-amino alcohols can be found in a variety of natural products and important synthetic intermediates.[8] Besides, oxa-Michael reactions often grant efficient access to heterocycles and natural products, especially when incorporated in domino reactions.[9] Due to these reasons, considerable effort has been directed towards the synthetic problems mentioned above. This has led

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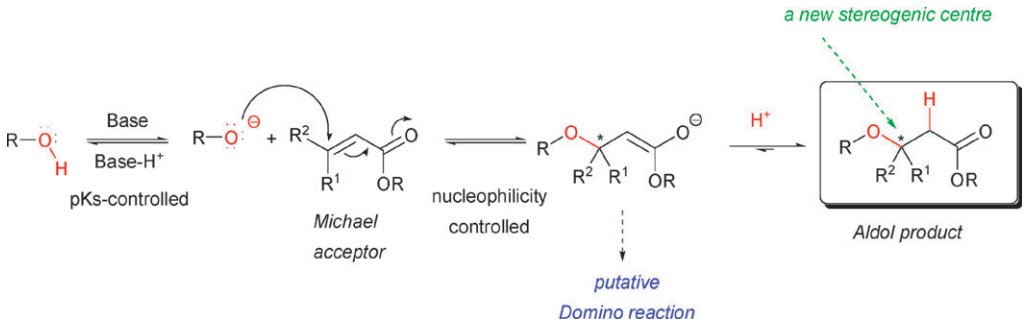


Scheme 1 The oxa-Michael reaction.

to major breakthroughs within the past years regarding general reaction protocols as well as stereoselective variants. Besides, organocatalysis has been frequently used to develop enantioselective oxa-Michael reactions.

Therefore, the aim of this review is to give an instructive overview of recent major developments within the fields of general reaction procedures, diastereoselective and enantioselective oxa-Michael reactions as well as their application in the synthesis of heterocycles and natural products.

General reaction protocols

In order to develop more broadly applicable protocols for the oxa-Michael reaction, the above mentioned problems of reactivity and reversibility have to be suitably addressed. Apart from intramolecular reactions, two major ways of activation are possible. Carefully selected bases can be used for the deprotonation of alcohols, thereby enhancing their nucleophilicity. Besides, Lewis or Brønsted acids can be applied for the activation of the conjugate acceptor and both ways have indeed been realized.

Verkade and co-workers reported on the oxa-Michael addition of primary alcohols to various acceptors using a proazaphosphatrane catalyst (**1**, Scheme 2).[6]

Primary and allylic alcohols are suitable substrates as are cyclic and acyclic acceptor systems. The reaction can be performed under mild conditions and yields are good to excellent. However, higher order and thus more hindered alcohols are not suitable substrates for this reaction. A somewhat similar approach was recently developed by Bergman, Toste *et al.*[10] It was found that simple trialkylphosphines such as trimethylphosphine efficiently catalyze the oxa-Michael addition of primary, secondary and aryl alcohols with various acyclic acceptors under mild conditions (Scheme 3).

Interestingly, mechanistic studies indicate that the phosphine itself probably does not merely act as a base but undergoes conjugate addition to the acceptor, thereby creating a basic enolate that then serves as base. A similar observation was made by Bhuniya and co-workers who developed a protocol for the addition of oximes to different Michael acceptors.[11] These oximes represent versatile synthons for oxa-Michael reactions since they possess higher acidity and nucleophilicity compared to alcohols and can easily be transformed into the desired alcohols by reductive cleavage. The reaction employs triphenylphosphine as catalyst and is suitable for both aldoximes and ketoximes as well as a variety of conjugate acceptors (Scheme 4).

However, a disadvantage of these methods is the air- and moisture sensitivity of the phosphorus-catalysts, which requires working under an inert atmosphere. Recently, Connon and co-workers published an amine-catalyzed hydroxyalkylation of diverse conjugate acceptors that can be performed under ambient atmosphere.[12] The scope of this reaction in terms of substrates is comparable to the phosphine-catalyzed reactions mentioned above.

As discussed in the introduction to this section, a complementary approach for catalyzing oxa-Michael reactions consists of the activation of the acceptor by acids. To this end, an

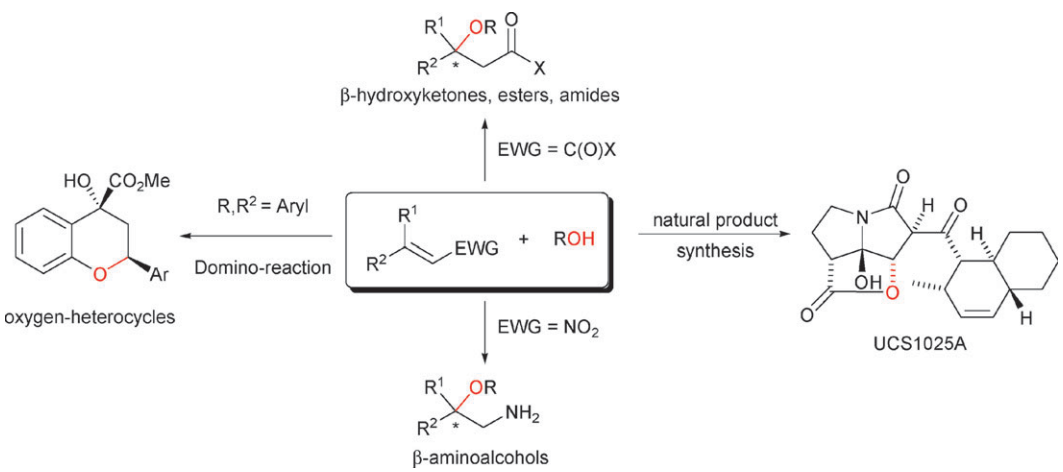
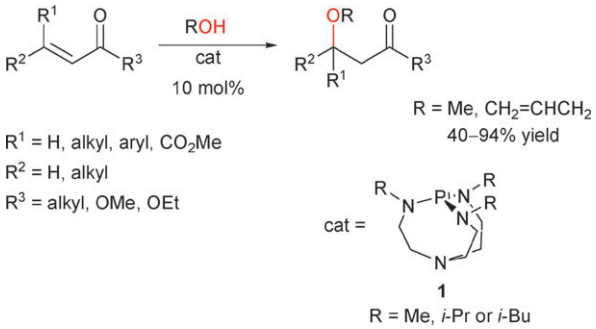
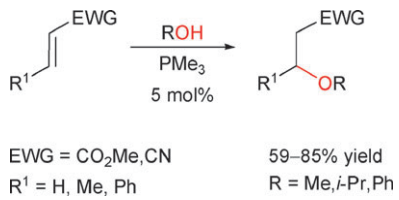


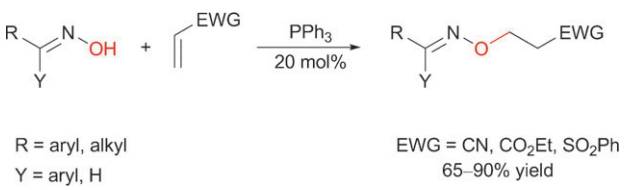
Fig. 1 Scope of the oxa-Michael reaction.



Scheme 2 Proazaphosphatrane-catalyzed oxa-Michael reaction.



Scheme 3 Phosphine-catalyzed oxa-Michael reaction.

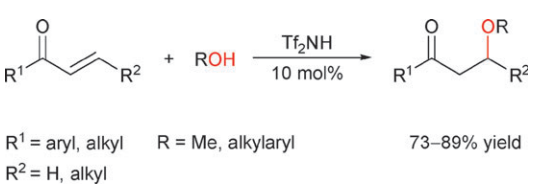


Scheme 4 Oxa-Michael addition of oximes.

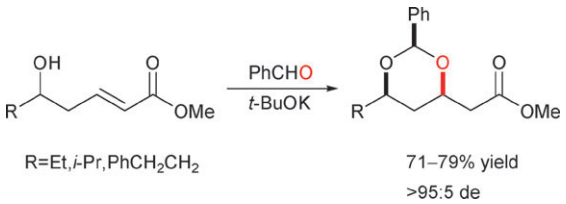
interesting reaction employing bis(trifluoromethane)sulfonimide (Tf_2NH) as a strong acid catalyst was recently developed (Scheme 5).[13]

The reaction can be applied to various α,β-unsaturated ketones as acceptors and alkyl as well as benzyl alcohols. However, aryl alcohols are not suitable substrates due to competing Friedel–Crafts-type reactions triggered by the strong acid.

Contrary to intermolecular oxa-Michael reactions, intramolecular versions have been far more prominent, especially within the context of natural product synthesis. This is mainly due to the fact that reversibility and a lack of reactivity in the nucleophiles can be overcome more easily by tethering both reactants. An instructive example for such an intramolecular reaction has been developed by Evans and Gauchet-Prunet.[14] Aiming at the stereoselective construction of *syn*-1,3-diols for the synthesis of polyene macrolide antibiotics, they employed easily accessible homoallylic alcohols as starting materials (Scheme 6).



Scheme 5 Acid catalyzed oxa-Michael reaction.



Scheme 6 Stereoselective acetalization of esters.

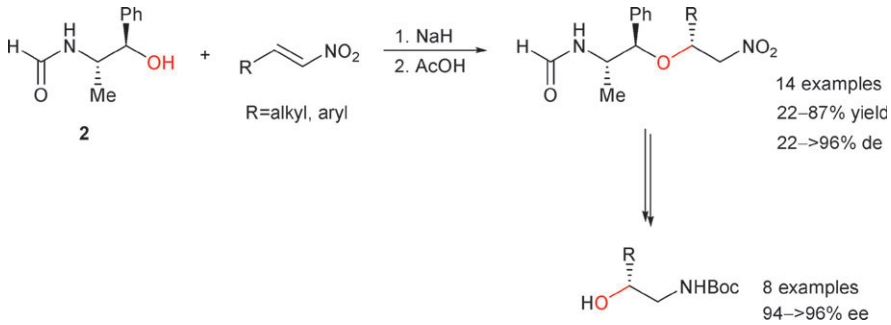
Reaction of these alcohols with benzaldehyde in the presence of potassium *tert*-butoxide (*t*-BuOK) furnishes the corresponding benzylidene acetals in high yield and diastereoselectivity. Addition of the deprotonated alcohol to benzaldehyde yields an acetal alkoxide which then serves as a tethered oxygen nucleophile in the conjugate addition step. The stereochemical outcome of the reaction can be explained on the basis of thermodynamic control and the fact that the *syn*-diastereomer is energetically favoured due to all substituents on the dioxane ring being equatorial. Regarding the scope of the substrate, the reaction is not limited to α,β-unsaturated esters. Unsaturated Weinreb-type amides and, even more interestingly, γ-substituted substrates can be used with equal efficiency. This transformation does not only represent an early example of an intramolecular oxa-Michael addition but can also be regarded as a role model for more recent developments in the field of organocatalytic versions of this reaction, which will be discussed later in this review. Moreover, this transformation has been frequently used within the context of natural product synthesis.[15]

Stereoselective oxa-Michael reactions

Chiral hydroxide equivalents

Considerable progress has been made in the field of stereoselective intermolecular oxa-Michael reactions within the past years. One way of achieving such a reaction consists of the use of chiral auxiliaries, thus transforming the nucleophiles into chiral hydroxide equivalents. After performing diastereoselective oxa-Michael reactions, the auxiliaries can be cleaved, thereby liberating enantiomerically enriched products. Seminal work in this field has been performed by Enders and coworkers who established *N*-formylnorephedrine (**2**) as a suitable *ex*-chiral pool auxiliary for the diastereoselective oxa-Michael reaction (Scheme 7).[16] The enantiomerically pure auxiliary can be deprotonated with strong bases such as sodium hydride and undergoes highly diastereoselective additions to a variety of substituted nitroalkenes. The products are typically isolated in good to excellent yields and with diastereomeric excesses of more than 90%.

However, the reaction is not without drawbacks since aromatic nitroalkenes (R = aryl) lead to lower yields and diastereomeric excesses as do substituents in the α-position of the nitroalkene. The resulting products from the oxa-Michael addition can be transformed into *N*-protected amino alcohols in a two-step sequence involving reduction–protection of the nitroalkene as well as cleavage of the benzylic ether moiety. 2-Amino alcohols available by this sequence are important synthetic intermediates for natural products and drugs as well



Scheme 7 Oxa-Michael addition of *N*-formylnorephedrines.

as for chiral auxiliaries.[17] The same group also extended this methodology to the synthesis of *N*-protected amino diols by the combination of the diastereoselective oxa-Michael addition with subsequent diastereoselective inter- and intramolecular 1,3-dipolar cycloadditions.

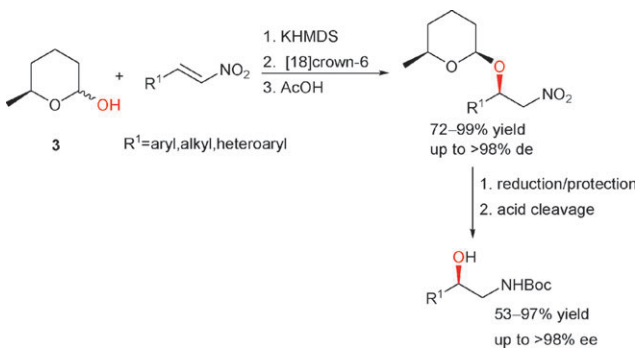
A complementary approach to diastereoselective oxa-Michael additions using chiral auxiliaries was developed by Dixon *et al*. They employed readily available 6-alkyl-δ-lactol (**3**) in enantiopure form as a chiral hydroxide equivalent.[18] The advantage of this strategy is that the auxiliary represents a chiral version of the commonly used tetrahydropyranyl protecting group and can easily be removed under acidic conditions to yield the desired oxa-Michael product (Scheme 8).

It is important to note in Scheme 8 that the addition of [18]crown-6 as a complexing agent is essential for achieving high diastereoselectivities. This is presumably due to the tight ion pairing between the metal ion and the alkoxide formed in the first step, which has a negative influence on the reaction outcome.

Although this oxa-Michael reaction was originally developed for nitroalkenes as acceptors, it was recently extended to other systems such as α,β-malonate esters, unsaturated α-keto esters, α,β-disubstituted nitroolefins and activated α,β-unsaturated esters. The scope of these transformations is outlined in Scheme 9.

By varying the acceptor system, a diverse set of useful intermediates can be obtained in good to excellent yields and enantiomeric/diastereomeric excesses. Moreover, the short and efficient access to chiral butenolides, which form part of various natural products, is especially noteworthy.

A third approach to diastereoselective oxa-Michael additions that shall be discussed in this review was developed by



Scheme 8 Oxa-Michael addition with 6-methyl-δ-lactol.

Watanabe and his group.[19] Following the intramolecular oxa-Michael reactions of acetals discussed in the previous section, they employed chiral ketones derived from D-fructose and D-glucose for an asymmetric version of this reaction.

As depicted in Scheme 10, the best results can be obtained with glucose derived ketone **4** and δ-hydroxy enones. In this case, the corresponding product can be obtained in high yield and diastereoselectivity, although minor amounts of a side product which is epimeric in both the β-hydroxy position and the spiro ketal are also isolated. The reaction presumably proceeds through hemiacetal formation between the ketone and the δ-hydroxy ketone (mediated by the base *n*-hexadecyltrimethylammonium hydroxide) followed by diastereoselective oxa-Michael addition. Extension of this protocol to γ-hydroxy enones led to the desired five-membered cyclic acetals, albeit in low diastereoselectivity. However, this problem could be overcome by stereoselective oxa-Michael addition to the corresponding acetylene derivatives followed by hydrogenation.

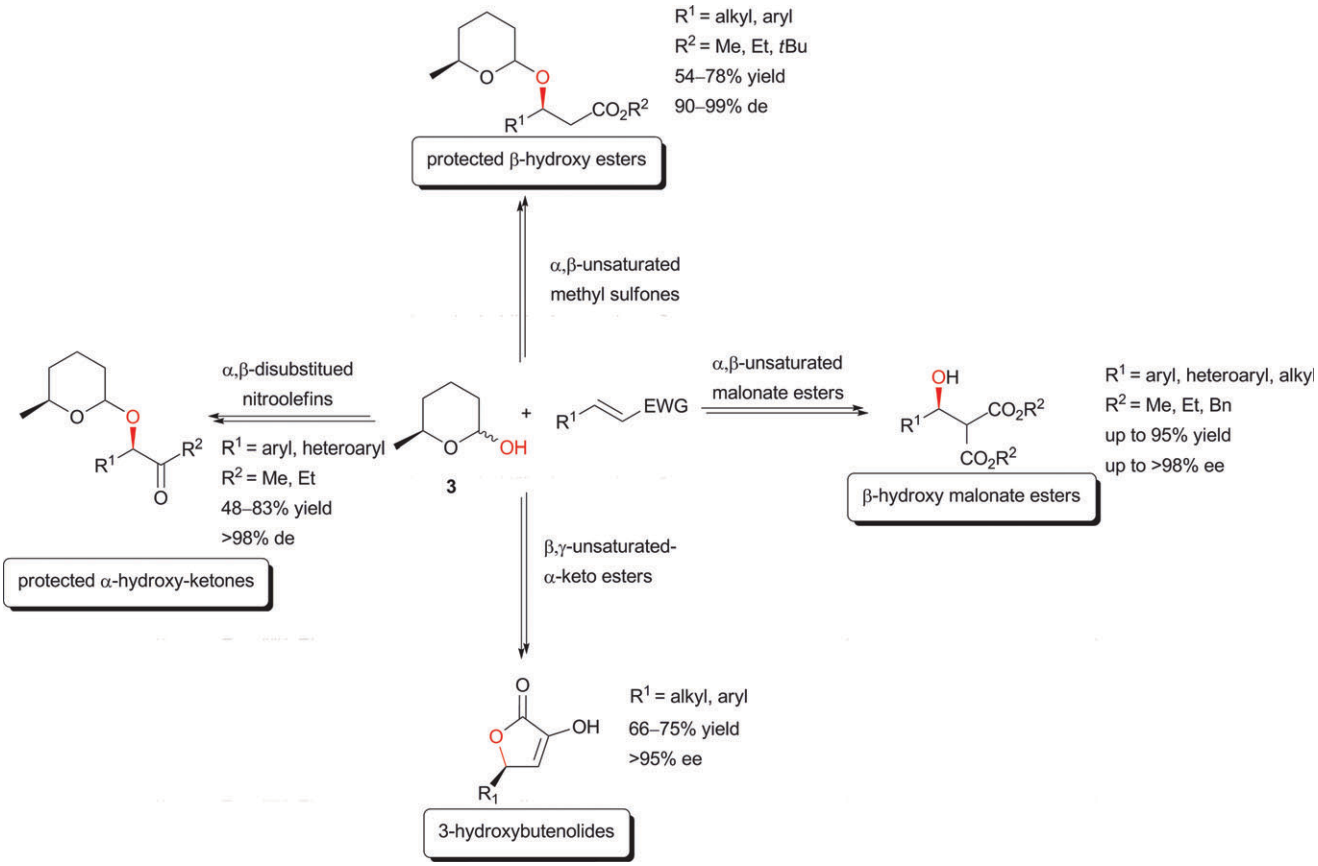
Enantioselective (organocatalytic) oxa-Michael reactions

As an alternative to the aforementioned diastereoselective reactions, catalytic enantioselective oxa-Michael reactions offer another straightforward access to chiral hydration products. As mentioned earlier, a common strategy for catalysing this reaction consists of Michael acceptor activation by Lewis or Brønsted acids. Indeed, chiral Lewis acids as well as various organocatalysts have been developed to achieve high levels of asymmetric induction. Both approaches will be discussed in this section.

Jacobsen and his group applied their well-established (salen)aluminium complexes to the addition of oximes to α,β-unsaturated imides (Scheme 11).[20]

The dimeric salen catalyst effects the addition of salicylaldoxime to imides in high yield and excellent enantiomeric excess. Although the reaction only tolerates aliphatic substituents in the imide moiety (R = alkyl), it is compatible with different functional groups such as esters, acetals and silyl ethers. This allows the reaction to be used as an alternative to acetate aldol reactions in the synthesis of polyketide natural products. Besides, the strong catalyst control of enantioselectivity enables diastereoselective additions to chiral imide substrates as outlined in Scheme 12.

Oxime addition to the Roche ester derived imide yields the desired hydration product in high yield and enantiomeric excess. By employing both enantiomers of the catalyst, the *syn* as well as the *anti*-addition products can be obtained. Since the imide group is readily converted into other carboxylic acid



Scheme 9 Scope of 6-alkyl-δ-lactol (**3**) addition.

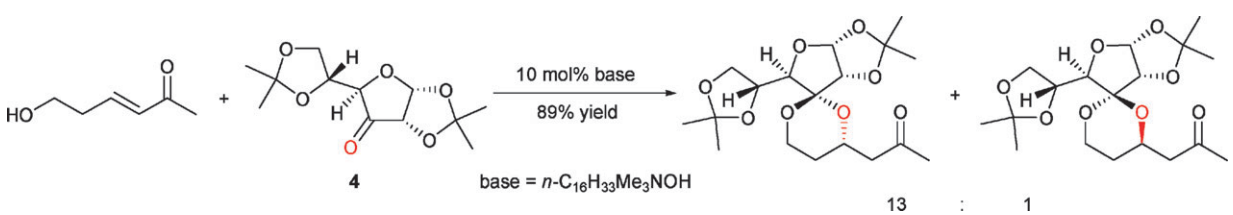
derivatives, the method represents a valuable synthetic tool for natural product synthesis.

The rapidly developing field of organocatalysis has recently been extended to oxa-Michael reactions. Jørgensen and his group used diaryl prolinol ethers for the activation of the Michael acceptor in the addition of benzaldoxime to α,β-unsaturated aldehydes (Scheme 13).[21] This reaction presumably proceeds through the well established LUMO-activation of the aldehyde by intermediate iminium ion formation.

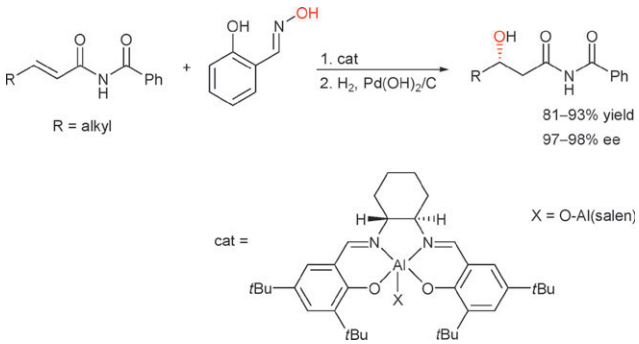
Under optimised conditions, benzaldehyde oxime adds to various aliphatic and ester substituted α,β-unsaturated aldehydes in high yield and enantiomeric access. However, cinnamic aldehyde derivatives turned out to be unreactive in this transformation. Due to the lability of the resulting aldehyde, the reaction products were reduced directly to give the protected alcohols. Again, the oxime moiety can easily be cleaved to yield the corresponding diols without loss of optical purity.

Recently, biphenyl diamine based catalysts for oxa-Michael additions of aliphatic alcohols to α,β-unsaturated aldehydes were developed by Maruoka and co-workers.[22] Having developed suitable reaction conditions for the racemic reaction, they also developed a chiral version of their biphenyl catalyst (Scheme 14). This system catalyses the addition of methanol, ethanol and allyl alcohol to aliphatic α,β-unsaturated aldehydes, albeit in moderate yield and enantiomeric excess. The reaction is believed to proceed through iminium activation whereby the sulfonamide moiety in the catalyst is key for assisting the iminium ion formation.

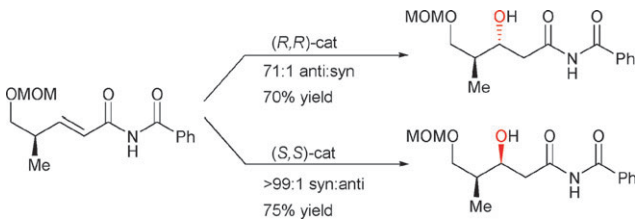
As described in the first section of this review, the intramolecular oxa-Michael addition of hemiacetals derived from δ-hydroxy-α,β-enones offers an alternative way of achieving highly stereoselective oxa-Michael reactions. Consequently, various efforts have been made to develop organocatalytic versions of this reaction. A major breakthrough in this context was achieved by Falck and co-workers who reported an enantioselective intramolecular oxa-Michael addition of boronic acid hemiesters triggered by thiourea type bifunctional organocatalysts.[23] As outlined in Scheme 15, aliphatic as well



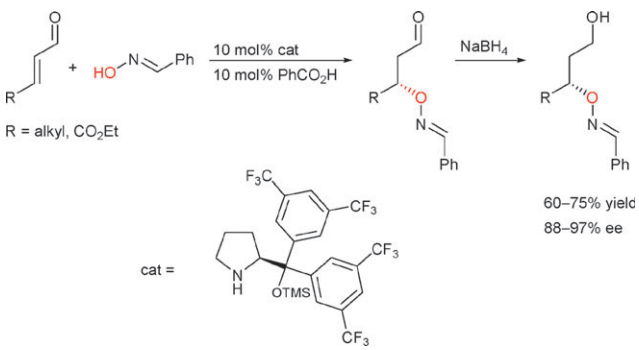
Scheme 10 Oxa-Michael reaction with glucose-derived ketone.



Scheme 11 Lewis acid catalyzed oxa-Michael reaction.

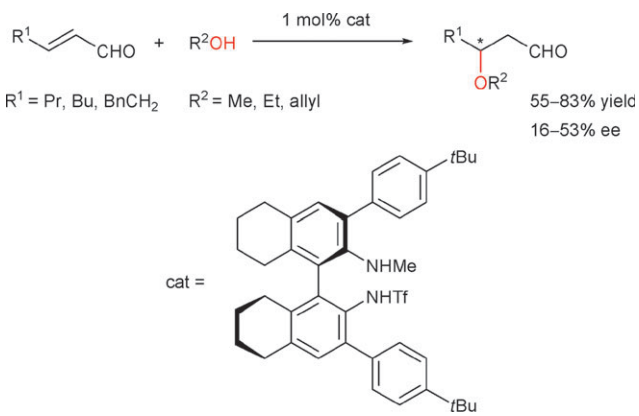


Scheme 12 Synthesis of acetate aldol products by oxa-Michael reaction.

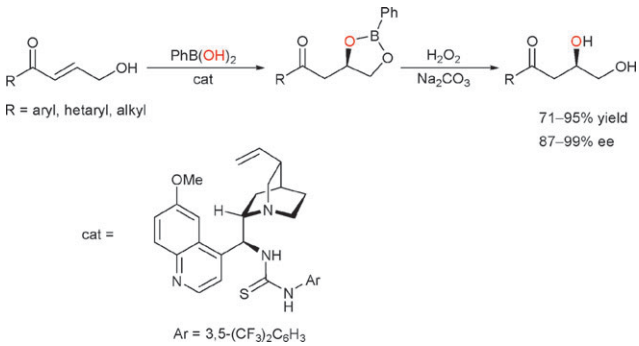


Scheme 13 Organocatalytic oxa-Michael addition of benzaldoxime.

as aromatic γ-hydroxy enones react with phenylboronic acid to give the corresponding boronic acid hemiesters, which then undergo intramolecular oxa-Michael addition under the influence of the catalyst. Oxidative cleavage of the resulting dioxaborolane consequently gives rise to chiral 1,2-diols in high yield and enantiomeric excess.



Scheme 14 Biaryl diamine mediated oxa-Michael addition.



Scheme 15 Organocatalytic oxa-Michael reaction of boronic acid hemiesters.

Interestingly, the thiourea catalyst combines both modes of activation mentioned in the introduction of the general reaction protocols section. The thiourea moiety activates the enone system by coordination to the carbonyl oxygen whereas the tertiary quinine nitrogen enhances the nucleophilicity of the boronic acid hemiester by complexation (''push–pull'', Fig. 2).

By slight changes to the reaction conditions, δ-hydroxy-α,β-enones could also be used as substrates, giving rise to chiral 1,3-diols.

It can be expected from these exciting results, that boronic acids will find further use as hydroxyl synthons in oxa-Michael additions, especially since their applications in the context of conjugate addition reactions are scarce.

Synthesis of heterocycles and natural products

The preceding paragraphs have given ample evidence that the oxa-Michael reaction is becoming a more and more versatile method in organic synthesis. It is therefore not surprising, that this reaction has been applied to the synthesis of heterocycles and natural products. Regarding the wealth of oxygen heterocycles representing the core of many important natural products, the following examples shall give an impression of the synthetic utility of this reaction.[24]

Heterocycles

Chromanes represent bicyclic oxygen heterocycles that have considerable importance in medicinal chemistry. Derivatives have been used as enzyme inhibitors or multidrug transporter inhibitors for example. Besides, chromanes represent the core of important natural products such as vitamin E. Jørgensen and co-workers recently developed an elegant access to chiral chromanes by embedding an oxa-Michael reaction in a

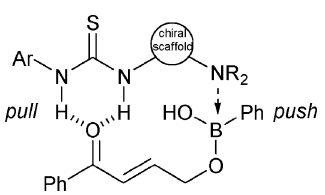
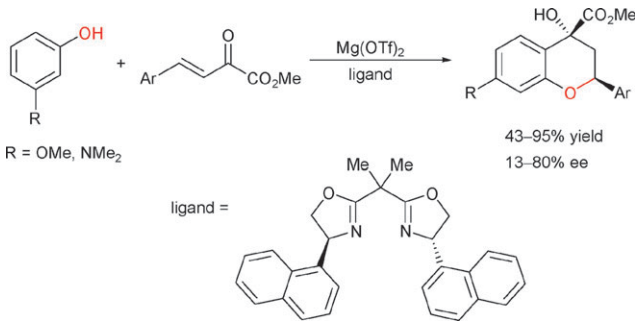


Fig. 2 Proposed mode of action of thiourea catalyst.

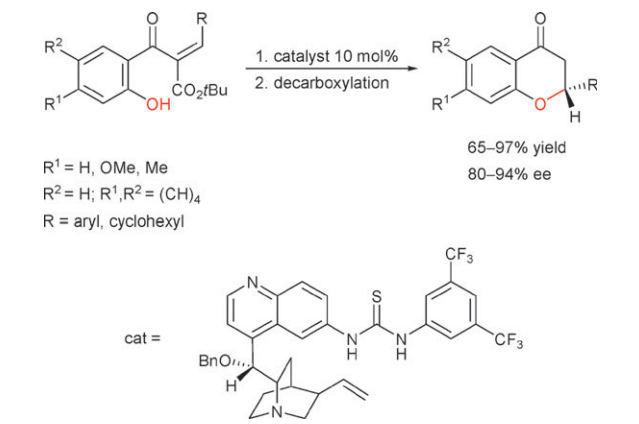
domino process (Scheme 16).[25] In this transformation, electron rich phenols react with β,γ-unsaturated α-keto esters in a Lewis acid-catalysed oxa-Michael reaction. Under the reaction conditions, the resulting products directly undergo Friedel–Crafts alkylation to form the desired chromanes in high yield and enantioselectivity.



Scheme 16 Synthesis of chiral chromanes.

Optimization of the reaction conditions revealed that magnesium triflate as a Lewis acid together with a bulky bisoxazoline ligand gave the best results. Besides, it turned out that the substrate scope is somewhat limited since both an electron donating group on the phenol and the aromatic moiety on the acceptor are essential for high yield and enantioselectivity.

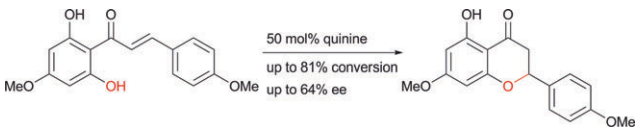
Recently, Scheidt and co-workers developed an organocatalytic intramolecular oxa-Michael addition for the synthesis of chiral flavanones and chromanones.[26] Flavanones are important structures in the context of anti-tumor and anti-inflammatory therapeutic agents. Besides, they often serve as colourful pigments in nature. Despite considerable efforts, their asymmetric synthesis has remained a challenge due to the reversibility of the oxa-Michael reaction. As shown in Scheme 17, a chiral thiourea catalyst is used for the cyclization of α-substituted chalcones to give 3-carboxy flavanones (not shown) in high enantiomeric excess.



Scheme 17 Organocatalytic synthesis of flavanones.

Again, the catalyst has a dual role in both activating the Michael-acceptor by hydrogen bonding and deprotonating the phenol by means of its tertiary amine moiety. In this context, the *tert*-butyl ester group in the substrate is of key importance for catalyst binding and therefore high enantioselectivity. The β-keto ester substrates are easily accessible by Knoevenagel condensation and the ester group is easily cleaved in a one-pot decarboxylation to give the desired flavanones.

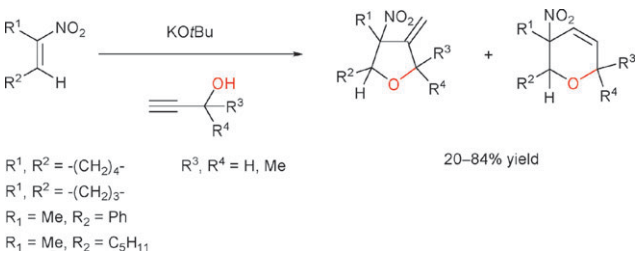
The by far more challenging direct cyclization of 2′-hydroxychalcone to flavanone, which lacks the need for further activation by means of an ester group, has recently been investigated by Hintermann *et al.*[27] Whereas chiral Brønsted acids such as camphor sulfonic acid were shown to be unsuitable catalysts, they were able to produce flavanones in up to 64% ee and in good yields by employing activated substrates and quinine as a chiral Brønsted base (Scheme 18).



Scheme 18 Direct organocatalytic synthesis of flavanone.

However, the reaction is not general and is limited to activated chalcone substrates. In this context, 4,4′-dimethoxy-2′,6′-dihydroxychalcone turned out to be an especially suitable substrate.

A straightforward access to methylenetetrahydrofurans was recently reported by Dulcère and co-workers.[28] As shown in Scheme 19, base induced oxa-Michael addition of propargylic alcohols to nitroalkenes followed by 5-*exo* cyclization onto the triple bond leads to the corresponding methylenetetrahydrofurans in good yield. The ring expanded homologues could also be obtained as side products due to competing 6-*endo* cyclization.



Scheme 19 Synthesis of methylenetetrahydrofurans.

Natural product synthesis

The oxa-Michael addition has also found application in the synthesis of complex natural products. However, it is important to note that intramolecular versions of this reaction can be found far more often, due to the already discussed problems with reversibility and lack of reactivity. Only recently, intermolecular reactions have gained more attraction when they were used in highly efficient domino reactions to yield various oxygen heterocycles.[24]

A pioneering application of an intramolecular oxa-Michael reaction was developed by Nicolaou and co-workers during

5 6

Scheme 20 Pyran assembly in the total synthesis of Brevetoxin B.

their total synthesis of the marine neurotoxin Brevetoxin B.[29] In this impressive synthesis, the oxa-Michael addition was used for the stereoselective synthesis of tetrahydropyran moieties. One of the key transformations is shown in Scheme 20: Deprotection of the C11-alcohol in precursor **5** followed by base-induced oxa-Michael addition stereoselectively yields the desired pyran moiety (C-ring).

Compound **6** represents a late stage intermediate in the total synthesis of Brevetoxin B. Interestingly, the transformation is highly diastereoselective due to the reversibility of the oxa-Michael addition and the resulting thermodynamically controlled ring closure.

Various studies have been published dealing with the use of quinine and related *Cinchona* alkaloids as catalysts in asymmetric intramolecular oxa-Michael reactions. Ishikawa and co-workers have applied this method to the synthesis of chromanone moieties in chromanone-coumarin type natural products.[30] In their synthesis of (+)-calanolide A, a quinine catalyzed intramolecular oxa-Michael addition of tigloylphenol **7** leads to a mixture of the *cis*- and *trans*-isomers of chromanone-coumarin **8** (Scheme 21). The *cis*-isomer was formed with an enantiomeric excess of 98% ee and could be transformed into the natural product (+)-calanolide A in three further synthetic steps.

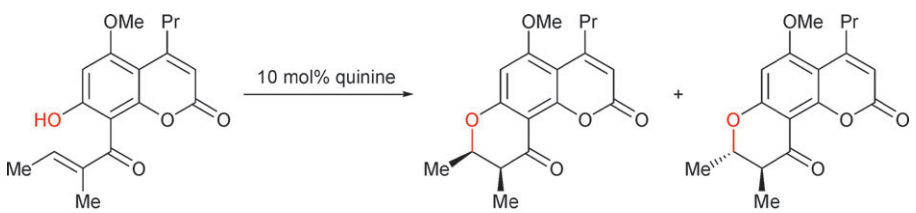
An unusual intramolecular addition of a carboxylic acid to a Michael acceptor was recently used for a kinetic resolution by Christmann *et al.* in their total synthesis of UCS1025A.[31] They discovered that treatment of racemic pyrrolizidine **9** with quinine led to selective cyclization of (−)-**9** (Scheme 22). Both lactone **10** and unreacted starting material (+)-**9** can then be isolated in enantioenriched form.

By employing deuterated dichloromethane as solvent, the resolution could conveniently be monitored by ^{1}H-NMR spectroscopy. Lactone **10** could be converted back to optically active **9** by base induced β-elimination. The latter compound then served as a starting point for the successful total synthesis of UCS1025A.

Another key application of oxa-Michael reactions can be found in the field of spiroketal natural products. The complex natural product azaspiracid-1 contains a synthetically challenging trioxadispiroketal moiety and has long withstood all attempts directed towards its total synthesis. During their synthetic efforts, Forsyth and co-workers developed an efficient synthesis of the spiroketal moiety involving a double intramolecular oxa-Michael addition (Scheme 23).[32]

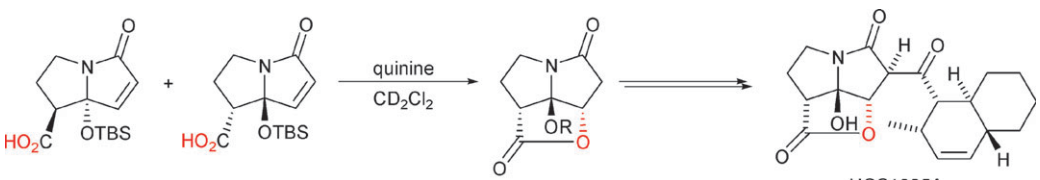
Deprotection of both TES-ethers in **11** leads to hemiketal formation at the C13 carbonyl moiety (tetrahydrofuran ring closure) followed by double oxa-Michael addition of the generated hemiketal together with the C6-alcohol onto the alkynone moiety. Interestingly, the stereogenic centre at C6 efficiently controls the configuration at C10 and C13 under thermodynamic ketalization conditions.

The same strategy was further extended to the solid phase synthesis of spiroketal libraries by Waldmann and Sommer.[33]



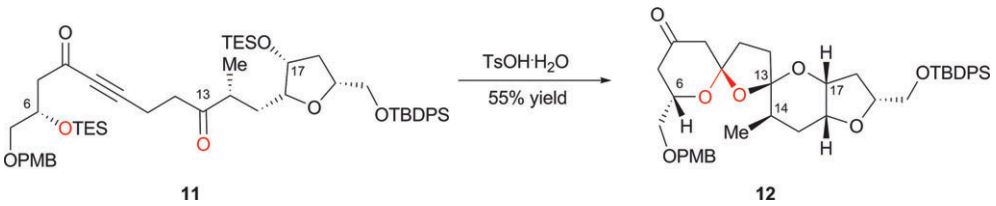
7 *cis*-**8** 67% yield 98% ee *trans*-**8** 21% yield 39% ee

Scheme 21 Catalytic asymmetric intramolecular oxa-Michael addition.



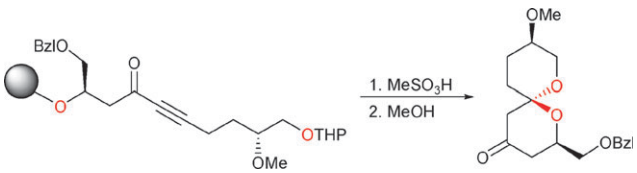
rac-**9** (−)**10** 62% ee UCS1025A

Scheme 22 Kinetic resolution of pyrrolizidine **9**.



Scheme 23 Spiroketal synthesis by double oxa-Michael reaction.

Their efforts were in part motivated by the observation that spiroketals not only form part of many natural products, but that structurally simplified spiroketals often retain considerable biological activity. Therefore, libraries containing such natural product fragments could be of potential interest in the field of chemical biology. As exemplified in Scheme 24, key features of this strategy are the application of acid labile solid phase linkers and protecting groups.

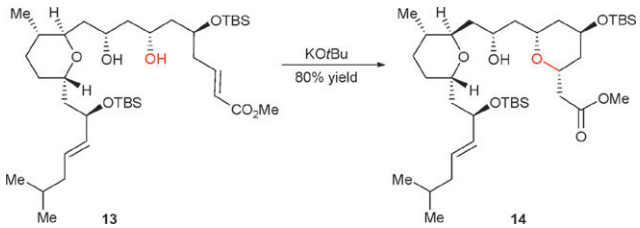


Scheme 24 Spiroketal solid phase synthesis.

Thus, acid cleavage from the solid phase and cleavage of the THP group in one pot set the stage for a double intramolecular oxa-Michael reaction, directly yielding the spiroketal moiety. Using this methodology, a library of 91 structurally diverse spiroketals was synthesized.

Another example of a late-stage oxa-Michael reaction within a multistep natural product synthesis can be found in the case of the marine natural product leucascandrolide A. Due to its significant cytotoxicity and antifungal activity combined with its fascinating architecture, various synthetic groups directed their efforts towards a total synthesis of this compound. During their total synthesis of leucascandrolide A macrolactone, Crimmins and Siliphaivanh employed an intramolecular oxa-Michael-addition for the establishment of one of the tetrahydropyran moieties.[34] A late stage intermediate in the synthesis (**13**) smoothly cyclized to give the desired 2,6-*cis*-disubstituted tetrahydropyran moiety in **14** (Scheme 25).

The resulting product could be transformed into leucascandrolide A macrolactone in just four further steps. The compatibility of the oxa-Michael methodology with a highly functionalized substrate like **13** underlines the importance of this reaction as a powerful tool for carbon–oxygen bond formation, even within complex molecules.



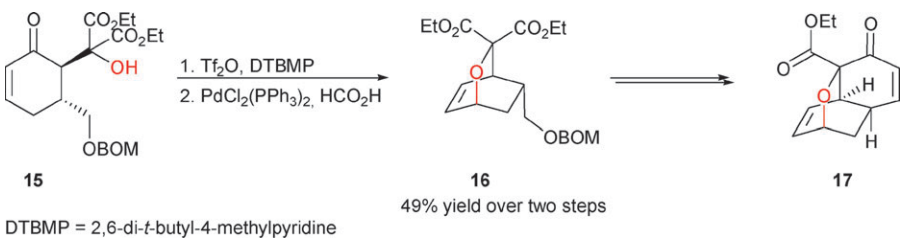
Scheme 25 Tetrahydropyran synthesis by oxa-Michael reaction.

A very interesting synthesis of an oxa-bridged decalin system involving intramolecular oxa-Michael addition was recently reported by Ōmura *et al.*[35] This synthesis formed part of a synthetic endeavour towards the bismacrolactone antibiotics luminamicin and lustromycin. As shown in Scheme 26, the key reaction starts with tertiary alcohol **15**, which is itself available in an eight step sequence. Interestingly, all attempts towards a base-catalyzed oxa-Michael reaction were unsuccessful since a spontaneous retro-Michael addition could be observed. However, trapping of the enolate resulting from oxa-Michael addition with triflic anhydride resulted in an intermediate enol triflate which was directly reduced to olefin **16**. Further elaboration of this compound led to the octalin core (**17**) of luminamicin and lustromycin.

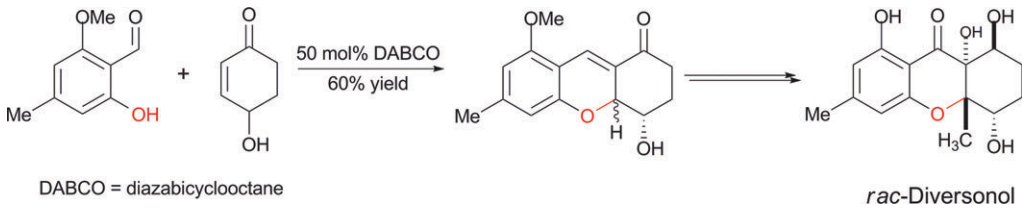
This reaction sequence serves as an instructive example that one of the various possibilities to overcome the reversibility of oxa-Michael reactions consists of acceptor activation and subsequent intermediate trapping by strong Lewis acids like triflic anhydride.

Recently, we were able to accomplish the total synthesis of the fungal metabolite diversonol.[36] The key step in this synthetic endeavour was an intermolecular oxa-Michael reaction between a suitably substituted salicylic aldehyde and racemic 4-hydroxycyclohexenone (Scheme 27).

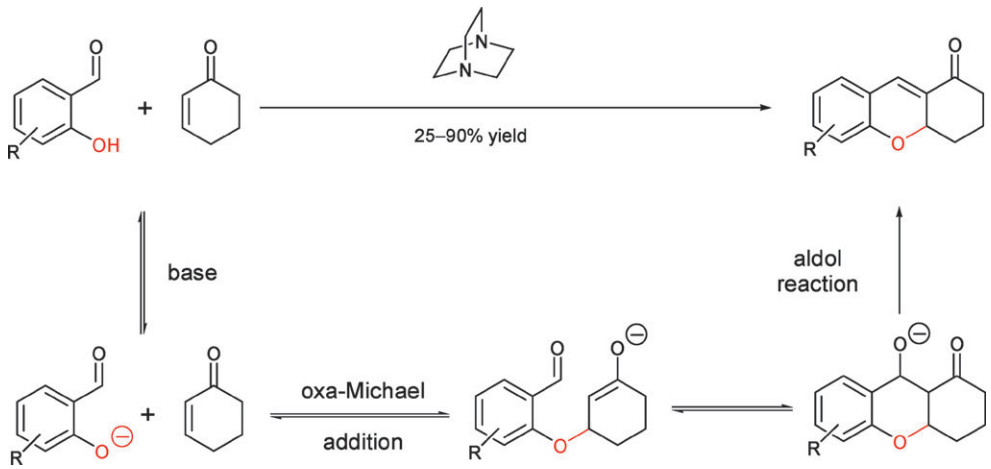
This reaction directly leads to the tetrahydroxanthenone core of diversonol in good yield and the natural product can be elaborated from this intermediate in few additional steps. Earlier studies of the reaction mechanism revealed that tetrahydroxanthenones are formed by a domino reaction involving oxa-Michael addition and aldol condensation (Scheme 28).[37]



Scheme 26 Synthesis of oxa-bridged decalin system **17**.



Scheme 27 Total synthesis of diversonol.



Scheme 28 Domino oxa-Michael reaction.

Base-induced deprotonation of salicylic aldehydes leads to the more nucleophilic phenolate anions which then undergo oxa-Michael addition with the cyclohexenone. The resulting enolates are trapped by intramolecular aldol condensation, thereby preventing retro-oxa-Michael reactions. The resulting tetrahydroxanthenones can be obtained in moderate to excellent yields.

Conclusions

This review has given ample evidence that the oxa-Michael addition, once seldom used in the organic synthesis laboratory has turned into a useful synthetic tool over the recent years. Major progress has been made in terms of substrate scope and the development of efficient catalysts. Moreover, high levels of stereocontrol can often be achieved by using chiral auxiliaries, chiral Lewis acids or bases and, more recently, organocatalysts. All these developments have led to extensive use of the oxa-Michael reaction in the field of total synthesis and the reaction even turned out to be a key tool for the preparation of spiroketals or tetrahydropyrans for instance. However, the reaction is still not without its drawbacks, since intermolecular reactions are by far more difficult to realize, often due to reaction reversibility. Only very recently could this problem partly be overcome by embedding oxa-Michael reactions in domino processes and therefore trapping the intermediates. However, there is still a need for even more general reaction protocols, especially in the field of intermolecular reactions. It can be expected that the true value of this reaction for the synthesis of carbon–oxygen bonds and heterocyclic moieties has only started to be revealed.

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