European Journal of Organic Chemistry

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European Journal of Organic Chemistry

Chemistry Europe
European Chemical Societies Publishing

REVIEW OPEN ACCESS

Retro-*Hetero*-Michael Addition Strategies in Organic Synthesis

Dina Scarpi | Ernesto G. Occhiato

Department of Chemistry "U. Schiff", University of Florence, Sesto Fiorentino, Italy

Correspondence: Ernesto G. Occhiato (ernesto.occhiato@unifi.it)

Received: 31 March 2026 | **Revised:** 25 June 2026 | **Accepted:** 30 June 2026

Keywords: heterocycles | Michael addition | retro reactions | retro-hetero-Michael addition | total synthesis

ABSTRACT

This review covers the applications of retro-*hetero*-Michael addition reactions in organic synthesis that have appeared in the literature in the last 15 years, with a focus on the synthesis and modification of carbo- and heterocyclic compounds, including natural products. The retro-*aza*-, retro-*oxa*-, and retro-*thia*-Michael addition reactions which are dealt with in the review have been widely exploited in synthetic organic chemistry to perform functional group manipulation, controlled isomerization, isomeric amplification, racemization for dynamic kinetic resolution, intramolecular rearrangements, and ring opening/ring reconstruction sequences. The syntheses of many complex natural products have included a retro-*hetero*-Michael addition step at some stage. Thus, what was once considered a problem has now become an established tool in the hands of organic chemists, who can leverage the retro-*hetero*-Michael addition-based strategies for the preparation of intermediates in the synthesis of natural and biologically active carbo- and heterocyclic compounds.

1 | Introduction

The *hetero*-Michael addition, i.e., the 1,4-conjugate addition of heteroatom-centered nucleophiles such as amines, alcohols, and thiols to electron-deficient alkenes, is one of the most important reactions for the formation of new carbon–heteroatom bond in organic synthesis [1–7]. The reversibility of the *hetero*-Michael addition reactions, through either E2 or E1cB β-elimination mechanism, under the appropriate conditions has become an established tool to manipulate and transform molecules and materials. For instance, it is actively exploited in polymer degradation and recycling as a sustainable solution for the reduction of polymer wastes [8–13]; in cargo release (e.g., dyes, drugs) from materials and proteins [14–17]; and, of course, in synthetic organic chemistry. In small molecule synthesis, for example, although the reversibility of the *hetero*-Michael addition has often been regarded as a major drawback, robust retro-*hetero*-Michael addition-based approaches have been exploited for the preparation of natural and biologically active carbo- and heterocyclic compounds, a selection of which is shown in Figure 1. The retro-Michael addition is part of the mechanism by which the Morita–Baylis–Hillman reaction takes place (the β-elimination step); however, given the ample coverage of the literature, this specific application will not be dealt with in this review [18, 19].

As shown in Scheme 1, in small molecule synthesis, general approaches to promote a retro-*hetero*-Michael reaction are based on the generation of the enolate anion **II**, intermediate of the direct reaction, either by treatment with a base of a carbonyl compound **I** (the hetero-Michael adduct) bearing a nucleophilic β-leaving group (e.g., an amine, an alcohol, a thiol) or from related enol esters **IV** and silyl enol ethers **V** by treatment with suitable reagents to release the enolate. Generation of enol **VI** upon exposure to acids (e.g., TfOH) is also another approach to cause the β-elimination, as it is the generation of the corresponding enamine **VII**.

Dedicated to Prof. Andrea Goti on the occasion of his 70th birthday.

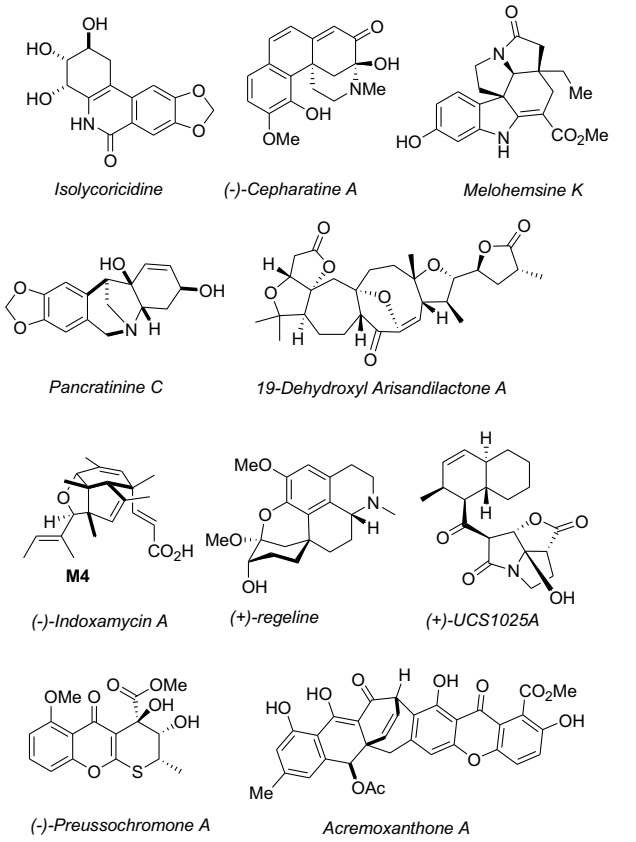
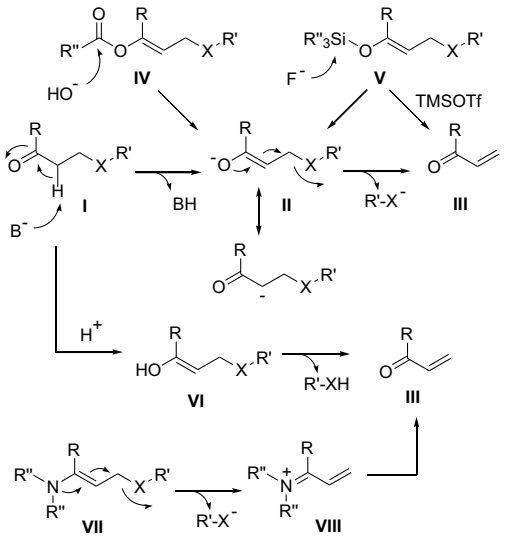


FIGURE 1 | Examples of natural products whose synthesis included a retro-*hetero*-Michael reaction.



SCHEME 1 | General approaches for retro-*hetero*-Michael additions.

Quite surprisingly, despite the many applications of retro-*hetero*-Michael additions in modern synthetic organic chemistry, only occasionally they have been mentioned in reviews focused on the direct reaction [1–7], and to our knowledge, no reviews of the recent literature dealing with the synthetic applications of the retro-*hetero*-Michael reactions have been issued. With the present work, we therefore intend to fill this gap by surveying the literature appeared in the last 15 years (2011–2025) on the synthetic applications of retro-*aza*-, retro-*oxa*-, and retro-*thia*-Michael (or retro-*sulfa*-Michael) addition reactions, focusing on the preparation and skeletal editing of carbo- and heterocyclic compounds, including natural compounds. We will show how what was once considered a problem has now become an established tool in the hands of organic chemists.

The analysis of the literature revealed that the retro-*hetero*-Michael reaction, often included in complex cascade processes, was exploited for a wide range of synthetic transformations. As for its simplest applications, the retro-*hetero*-Michael addition allowed for double bond restoration or proper installation inside a ring in the final stages of a synthesis, as well as the generation of reactive electrophiles undergoing inter- and intramolecular conjugate addition to attain ring closure, isomeric amplification, alkene isomerization, and functional group deprotection, just to mention a few cases. However, where the retro-*hetero*-Michael addition really played a key role was in processes reshaping the molecular skeleton of cyclic compounds, including their stereochemistry, by and after ring opening, from simple isomerization and vinyl shifts to elegant isomeric amplifications and racemization for metal- and enzyme-mediated dynamic kinetic resolutions (DKR), to end with often complex and sophisticated intramolecular rearrangements involving ring reconstruction.

It must be said that while in most cases the intervention of a retro-Michael addition was planned at a certain stage of the synthesis, it is also true that in a few cases, it was a fortuitous finding, which led to unexpected and interesting products.

The review is thus organized in chapters each dealing with a retro-*hetero*-Michael addition type based on the heteroatom-centered leaving group. In each section, we will discuss the applications of the various strategies mentioned above to the synthesis and transformation of carbo- and heterocyclic compounds, with a section specifically devoted to the synthesis of natural compounds. General comments on the retro-*hetero*-Michael addition types will be given under the relative chapter.

2 | Retro-*Aza*-Michael Addition Reaction

Because of the widespread presence of N-heterocycles amongst bioactive and natural compounds, together with retro-*oxa*-Michael, retro-*aza*-Michael reaction-based strategies were those mostly developed in synthetic organic chemistry. Although the *aza*-Michael addition may be reversible under specific conditions that depend on the nature of the reagents, the uncatalyzed retro-reaction generally, but not always (vide infra), requires high temperature (>110–150 °C) as the direct process is thermodynamically favored [20]. The *aza*-Michael reaction is an equilibrium that can be altered by suitable solvents at room temperature and especially with sterically hindered Michael acceptors, the retro process seems to occur more easily [20]. The same happens when the pK_b of the amine nucleophiles (>9–10) makes them better leaving groups, and when extended conjugation stabilizes the Michael acceptor. It has also been shown that in some cases, the *aza*-Michael addition reaction becomes reversible under acidic conditions (protonation of the amine subtracts the nucleophile from the equilibrium) [21],

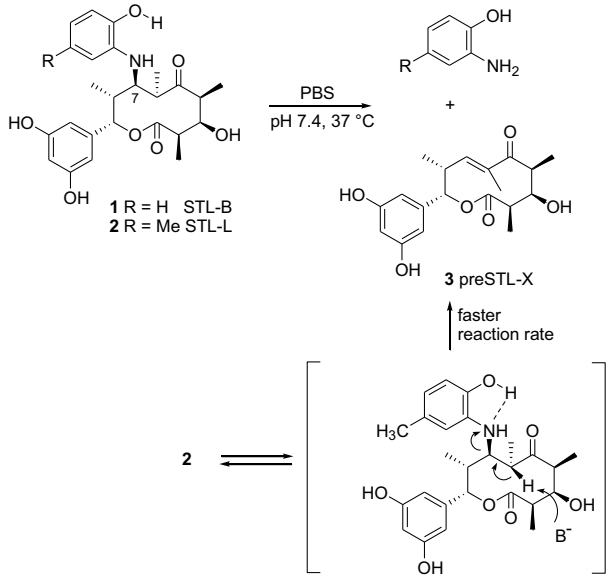
and these have in some cases been used in the past 15 years. Nevertheless, for most of the modern synthetic applications which will be discussed herein, the retro-*aza*-Michael has been promoted at relatively low temperatures using tertiary base catalysts, e.g., 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), Et_3N, 1,4-diazabicyclo[2.2.2]octane (DABCO), etc., and inorganic bases in water or alcohols, besides some of the other methods depicted in Scheme 1.

2.1 | Synthesis and Transformation of Carbo- and Heterocycles

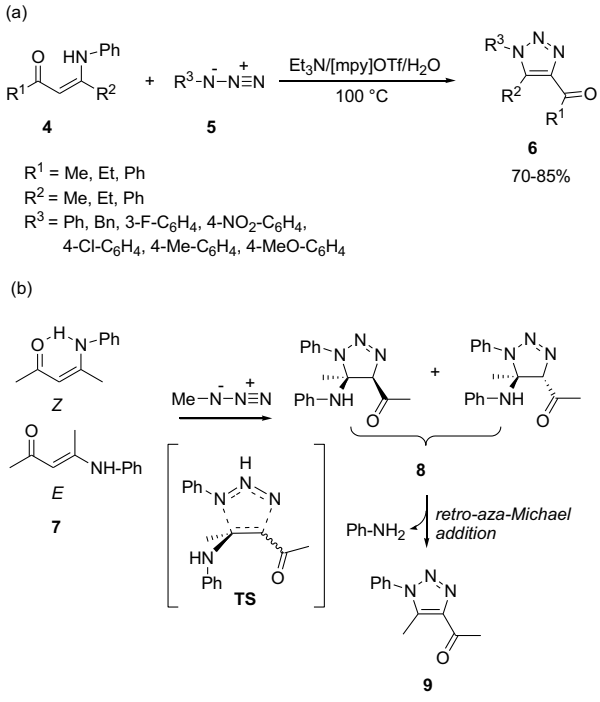
An effective masking tool for reactive α,β-unsaturated carbonyl compounds was developed by Lu et al. [22]. As Michael reaction acceptors are directly or indirectly involved in many biochemical processes [23], non-selective reactions of α,β-unsaturated carbonyl compounds with biomolecules can lead to potential harmful effects. To address this problem, masking groups such as Michael donors can be used to protect and, consequently, control the rate of release and selectivity of reactive α,β-unsaturated carbonyl groups [22].

Saccharothriolide B (STL-B, **1**) (Scheme 2) is a 10-membered macrolide isolated from the rare actinomycete *Saccharothrix sp*. A1506. Among congeners, **1** has shown the most potent cytotoxicity against human fibrosarcoma HT1080 cells. The toxicity is due to the release of the Michael acceptor presaccharothriolide X (preSTL-X, **3**), via a retro-*aza*-Michael reaction at C-7 involving *o*-aminophenol. Following a previous study on the retro-*aza*-Michael reaction undergone by **1** in protic solvents [24], Kakeya investigated the release of preSTL-X from STL-B to find an effective masking tool for this highly reactive, bioactive α,β-unsaturated carbonyl compound. The authors found that 2-amino-4-methylphenol could well serve the scope. They synthesized saccharothriolide L (STL-L, **2**) by precursor-directed in situ synthesis (PDSS) method using the culture broth of *Saccharothrix sp.* A1506 and studied by HPLC the effect of the new Michael donor on the retro-*aza*-Michael reaction at 37 °C in phosphate-buffered saline (PBS) at pH 7.4. The authors found that STL-L exhibited a much faster rate for the retro-*aza*-Michael reaction, compared with STL-B, reasonably because the electron-donating methyl group somewhat strengthens the intramolecular hydrogen bond which in turn results in a much faster E2 elimination process. Interestingly, in a previous study by the same authors [24], it was found that *o*-anisidine was not eliminated from its Michael adduct, confirming the crucial role of the H-bond. According to the authors, 2-amino-4-methylphenol may be used for masking reactive α,β-unsaturated carbonyl compounds. Also, protection of the phenolic OH group could be exploited for tissue- or microenvironment-selective release of the bioactive compounds [24].

In the next example, a base-promoted retro-*aza*-Michael addition served to restore a conjugated double bond inside a heterocycle ring. 1,2,3-Triazoles are important heterocyclic compounds due to their pharmaceutical properties and biological activities. They are also widely used in organic synthesis, in material chemistry, and for bioconjugation [25]. De Nino et al. [25] reported on a total regioselective synthesis of 1,4,5-trisubstituted-1,2,3-triazoles **6** from enaminones **4** and aryl azides **5** performed in an ionic liquid (1-methyl pyridinium trifluoromethanesulfonate, [mpy]OTf) in the presence of water and triethylamine at 100 °C (Scheme 3). The use of the combined system IL-water-triethylamine was necessary to obtain the products, as elimination of any of the three elements resulted in no reaction. The process consists of a cascade starting with a water-promoted 1,3-dipolar cycloaddition on any of the two *E* and *Z* isomers of **7** to form cycloadduct intermediates **8** which cannot be isolated, as they immediately undergo a Et_3N-promoted retro-*aza*-Michael reaction to form trisubstituted triazole **9** in a complete regioselective way (Scheme 3).



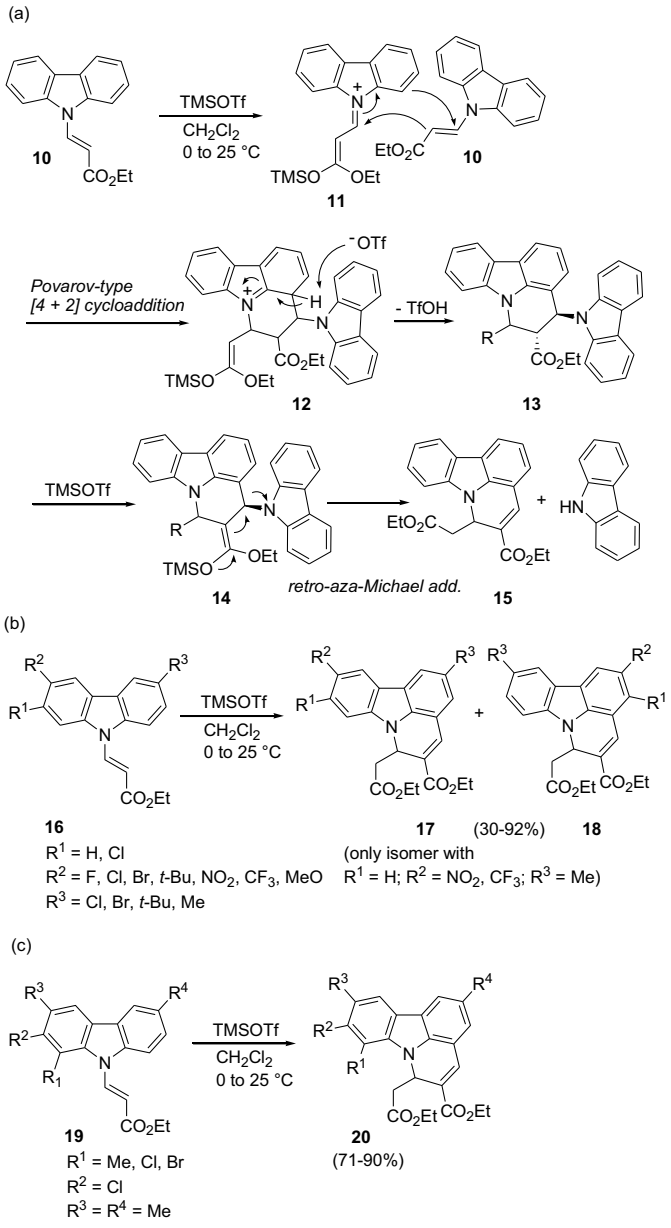
SCHEME 2 | Development of a masking tool for reactive α,β-unsaturated carbonyl compounds.



SCHEME 3 | (a) Regioselective synthesis of 1,4,5-trisubstituted-1,2,3-triazoles. (b) Proposed mechanism.

The scope of the reaction was evaluated with a series of enaminones and aryl azides (including benzyl azides) providing after 3–6 h the corresponding products in 70%–85% yield.

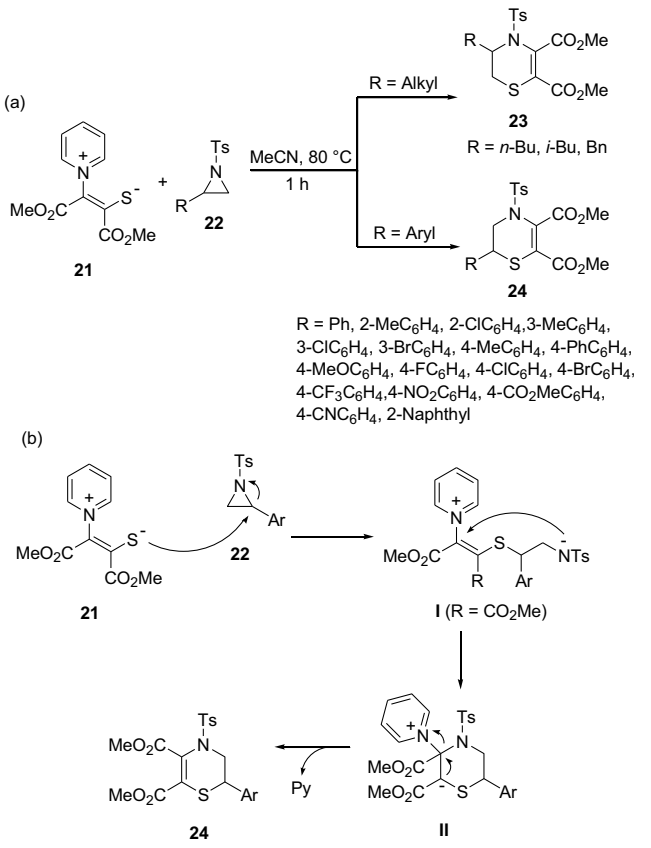
As in De Nino et al. [25], also in the synthesis of highly fluorescent pyridocarbazoles **15**, the retro-*aza*-Michael reaction allowed for the restoration of the double bond to generate the unsaturated heterocycles [26]. N-centered concave heterocycles containing the carbazole nucleus have recently attracted attention because of their π-extended conjugation, which makes them chromophores with excellent photophysical properties [27]. Gharpure et al. [26] discovered that when treating carbazole **10** (Scheme 4a) with TMSOTf in CH_2Cl_2, a cascade process involving a Povarov-type formal [4 + 2] cycloaddition [28] and a retro-*aza*-Michael took place, which led to the dimerization of the vinylogous carbamate and the formation of the product **15**. Mechanistically, TMSOTf complexes with ester carbonyl in carbamate **10** leading to the formation of iminium ion **11**.



SCHEME 4 | (a–c) Synthesis of highly fluorescent pyridocarbazoles.

Povarov-type [4 + 2] cycloaddition reaction of this iminium ion with the olefin part of vinylogous carbamate **10** generates intermediate **13** which, upon formation of silyl enol ether **14** after reaction with TMSOTf, eventually undergoes carbazole elimination through a retro-*aza*-Michael reaction. The reaction is general for a variety of substituents and gives good regioselectivity when electron-withdrawing groups (NO_2, CF_3) are present on carbazoles, while in the other cases (Scheme 4b), mixtures of isomers are obtained. Of course, C1-substituted carbazoles **19** are converted in excellent yield into one isomer only (Scheme 4c). The synthesized carbazoles were evaluated for their photophysical properties which proved excellent, with quantum yields (ΦF) up to 61%.

1,4-Thiazines (thiomorpholines) and their oxidized derivatives are found in many natural and synthetic pharmaceutical molecules such as antibacterial, anti-imflammatory, antioxidant, and 5-lipoxygenase inhibitor compounds [29]. Wang et al. developed an efficient cascade reaction between pyridinium 1,4-zwitterionic thiolate **21** and alkyl- and aryl-*N*-Ts-aziridines **22** for the synthesis of thiomorpholines **23** and **24** (Scheme 5a) which proceeds via a cascade S_N2 ring-opening/cyclization/Py extrusion process in refluxing acetonitrile (Scheme 5b) [29]. Also in this case, the retro-*aza*-Michael process (the pyridine extrusion) served to restore the double bond initially present in one of the reactants. As for the regioselectivity, ring-opening of aryl-substituted aziridines mainly occurred on the substituted carbon atom, whereas the attack on the unsubstituted carbon exclusively took place for alkyl substituted aziridines. The enantiopurity of the aziridines

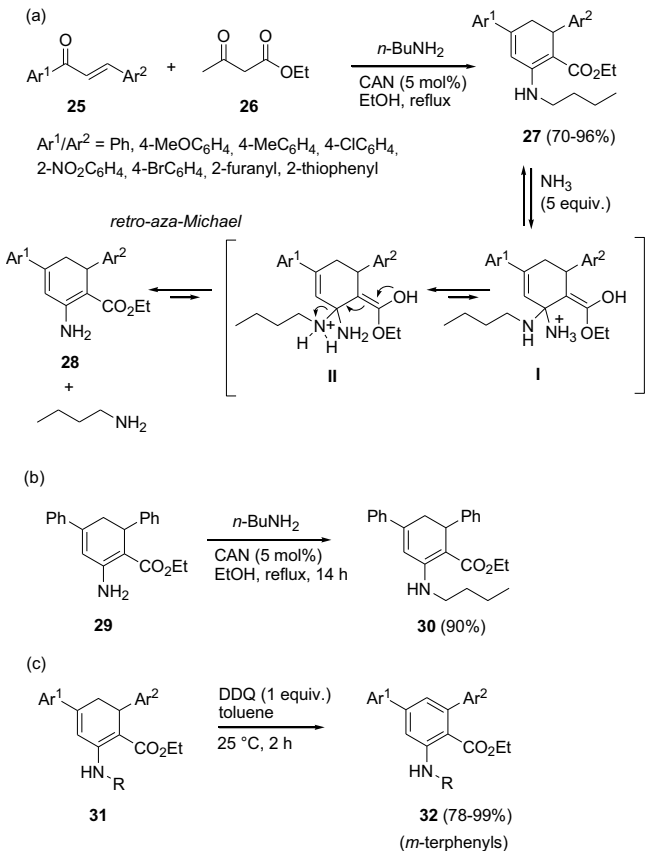


SCHEME 5 | (a) Cascade reaction for the synthesis of thiomorpholines. (b) Proposed mechanism.

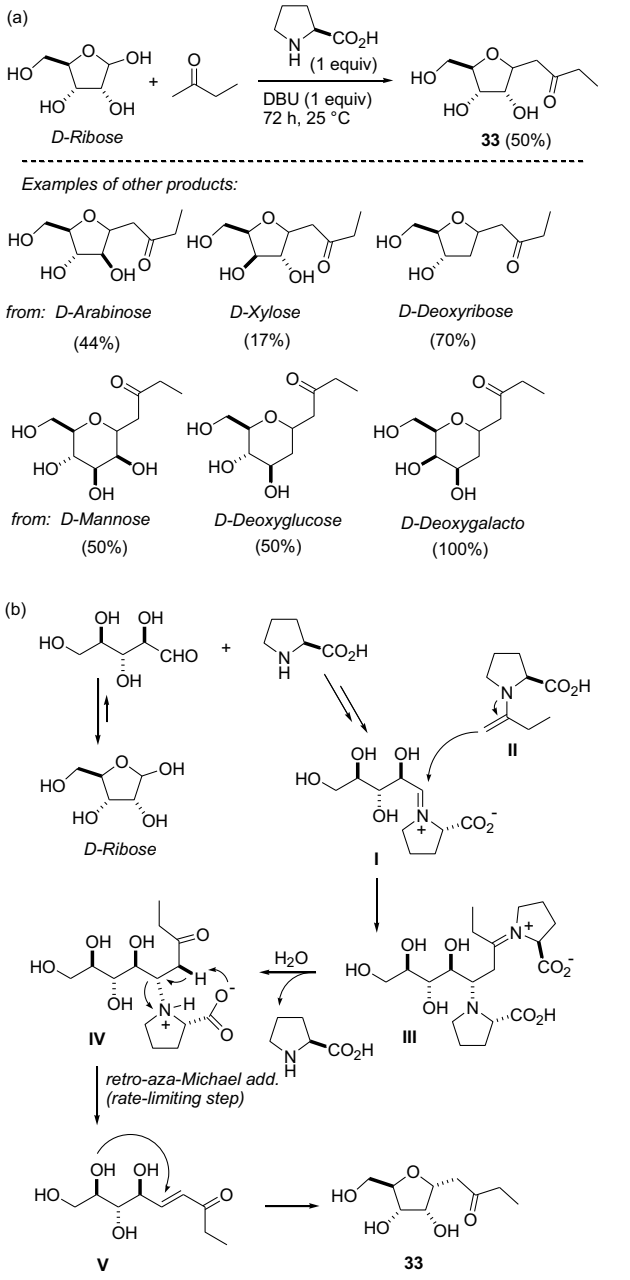
was also maintained in the final products thus making this a direct strategy for the regioselective and enantio-retained synthesis of 3,4-dihydro-2*H*-1,4-thiazines.

m-Terphenyl is an important structural motif found in many natural products and synthetic molecules that have been widely used as building blocks in medicinal chemistry and materials science [30]. Rocchi et al. recently reported on a Ce(IV) ammonium nitrate-catalyzed, three-component reaction between alkyl- or arylamines, β-ketoester **26** and chalcones **25** in refluxing ethanol for the construction of a large library of highly substituted dihydro-*m*-terphenyl derivatives containing β-alkylamino- or β-arylamino ester moieties (Scheme 6) [30]. These could then be oxidized to the corresponding *m*-terphenyls **32** by DDQ in toluene. In order to prepare *m*-terphenyls with a free β-amino group, because of the impossibility of employing ammonia as a starting material for the multicomponent reaction, the authors resorted to an indirect method in which the reversibility of the *aza*-Michael addition was the key element. They carried out the usual three-component reaction with butylamine and, without isolation, treated in situ product **27** with an excess of ammonium formate as a source of ammonia. Under these conditions the *aza*-Michael/retro-*aza*-Michael process took place leading to the exchange of the butylamino and amino substituents (Scheme 6a). This exchange was demonstrated to be reversible, as the reaction between **29** and butylamine under the reaction conditions gave the *N*-butyl derivative **30** in 90% yield (Scheme 6b). Since the *aza*-Michael/retro-*aza*-Michael pathway is reversible, the good results in the butylamino–amino exchange must be ascribed to equilibrium displacement because of the large excess of ammonium formate employed. A large number of N-unsubstituted products **28** were thus obtained by this approach.

A thorough study on proline-catalyzed aldol reaction of carbohydrates (aldopentoses and aldohexoses) with methyl ketone for the synthesis of C-glycosides **33** was carried out by Stier et al. with the aid of quantum mechanical calculations (Scheme 7a) [31], by which a coherent reaction mechanism was identified matching the experimental data (Scheme 7b). A Mannich reaction between enamine **II** and iminium ion **I** forms intermediate **III** which, after proline hydrolysis, generates β-aminoketone **IV** which set the stage for a retro-*aza*-Michael reaction. According to the calculation and experimental data this step leading to



SCHEME 6 | (a–c) Synthesis of *m*-terphenyls with a free β-amino group.

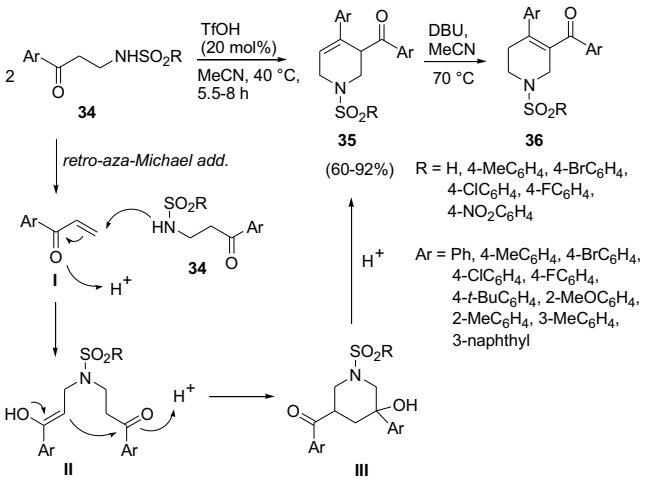


SCHEME 7 | (a) Proline-catalyzed aldol reaction of carbohydrates for the synthesis of C-glycosides. (b) Proposed mechanism.

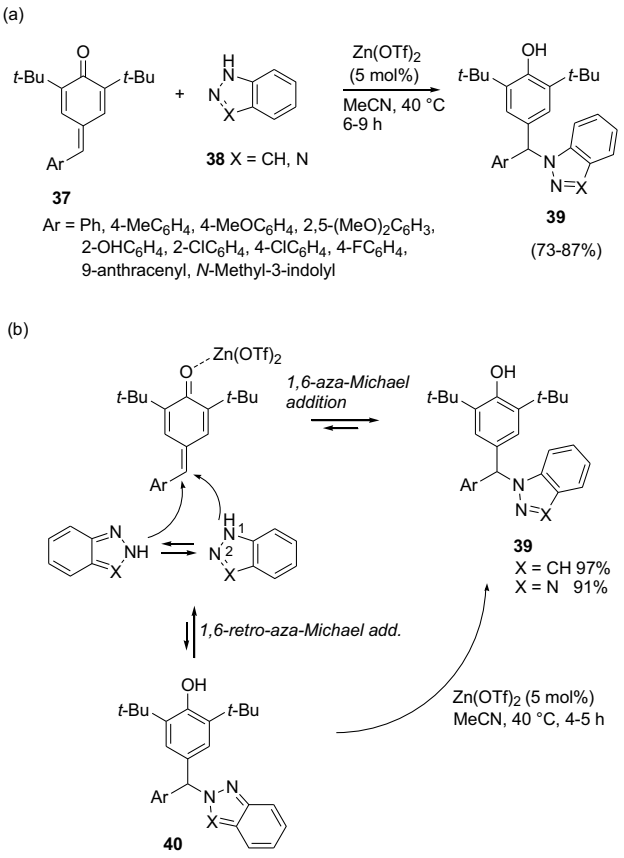
α,β-unsaturated ethyl ketone **V** determines rate and selectivity of the overall cascade reaction. Because of the cyclic nature of the transition state, strongly matched and mismatched cases were observed when used with D- or L-proline. Key precursor **V** finally yields C-glycosides **33** by an intramolecular amine-catalyzed *oxa*-Michael addition. The protocol was applied to different monosaccharides with erratic success (from 0 to 100% yield), which depended on the absolute configuration of the various stereocenters and, of course, of proline. As an example, D-glucose did not react at all when L-proline was used, while D-mannose provided the corresponding C-glycosides in 50% yield.

1,2,3,6-Tetrahydropyridine constitutes an important building block in organic synthesis and exists in numerous natural products and pharmaceutically active compounds [32]. An acid-catalyzed retro-*aza*-Michael addition was exploited by Wu et al. to generate a Michael acceptor (aryl vinyl ketone **I**) from β-*N*-sulfonyl-aminoketones **34** which underwent conjugate addition by the N atom of a second molecule of substrate (Scheme 8) [32]. Next ring closure formed piperidine intermediate **III** which eventually lose water to generate various multisubstituted 1,2,3,6-tetrahydropyridine derivatives **35** in moderate to good yields. After this novel self-condensation step, 1,2,5,6-tetrahydropyridines **36** could be obtained (in a one-pot manner, too) through DBU-promoted isomerization.

During their studies on new catalytic methods for making C—N bond via 1,6-addition between N—H containing heterocycles and enones as Michael acceptors, Guin et al. [33] recently reported on the $Zn(OTf)_2$-catalyzed regioselective C—N bond formation by reacting aryl/heteroaryl-substituted *para*-quinone methides **37** as 1,6-acceptors and various aza-heterocycles among which 1*H*-indazole and benzotriazole **38** (Scheme 9). These *para*-quinone methides (*p*-QMs) are powerful reactive intermediates as following the conjugate nucleophilic attack aromatization takes place favoring the process. In this work Guin et al. found that the high level of regioselectivity toward the formation of products **39** was due to a 1,6-retro-*aza*-Michael addition occurring on isomeric product **40**, formed after the competing attack by the N-2 atom to the *para*-quinone methide. This isomeric



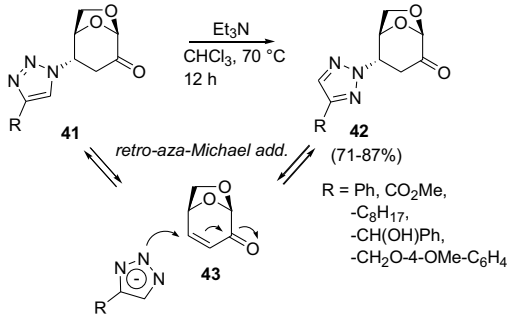
SCHEME 8 | Acid-catalyzed retro-*aza*-Michael addition for the synthesis of tetrahydropyridines.



SCHEME 9 | (a) Isomeric amplification in the synthesis of **39** by 1, 6-retro-aza-Michael addition. (b) Proposed mechanism.

amplification was demonstrated by subjecting isolated isomers **40** to the reaction conditions, which were quantitatively converted into target isomers **39** by the retro-*aza*-Michael process.

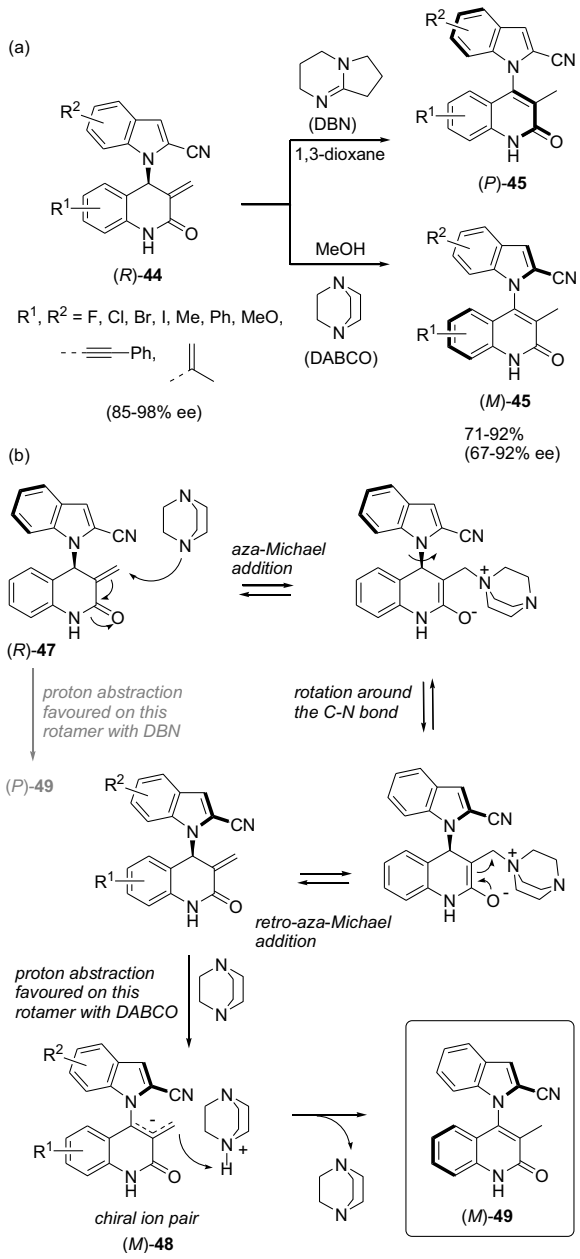
A similar rearrangement, in this case with triazole as the Michael donor, was exploited by Tsai et al. for the isomerization of levoglucosenone derivatives **41** into alternative products **42** (Scheme 10) for a preliminary screening of levoglucosenone derivatives as anticancer compounds [34]. Levoglucosenone (1,6-anhydro-3,4-dideoxy-β-D-glycero-hex-3-enopyranos-2-ulose) **43** is a highly attractive chiral synthon formed in the pyrolytic treatment of acid pretreated cellulose-containing materials. The authors stereoselectively synthesized triazoles **41** by reacting levoglucosenone with sodium azide followed by a 1,3-dipolar cycloaddition reaction with various alkynes under Cu(I)



SCHEME 10 | Isomeric amplification in the synthesis of triazole derivatives **42**.

catalysis. By treatment of **41** with Et_3N, the retro-*aza*-Michael reaction provided levoglucosenone **43** and a triazole anion which reacted with **43** with its central N atom, to form thermodynamically more stable isomers **42** in excellent yields. This represents a novel synthetic strategy for the preparation of N2-substituted 1,2,3-triazoles.

Positional isomerization of alkenes is a powerful transformation for relocating a C=C bond from one position to another. A very interesting case of stereospecific positional alkene isomerization was based on the reversibility of the *aza*-Michael addition of different tertiary bases to suitable acceptors. Liu et al. [35] achieved bidirectional chirality transfer, in particular central-to-axial chirality transfer, in the double bond positional isomerization of centrally chiral exocyclic alkenes **44** by achiral Lewis base catalysis. So, both *P* and *M* atropisomers of axially chiral

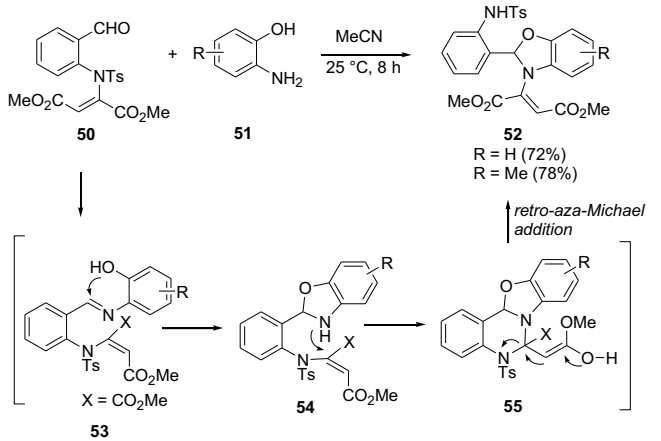


SCHEME 11 | (a) Chirality transfer in the double bond isomerization of exocyclic alkenes **44**. (b) Proposed mechanism.

N-indolylquinolinones **45** were readily obtained starting from the same *R* enantiomer of **44** (Scheme 11a). These substrates were prepared with a wide variety of substituents by an asymmetric allylic substitution-isomerization strategy by reacting 2-substituted indoles with suitable allylic alcohol derivatives in the presence of $(DHQD)_2PYR$ (0.2 equiv.) as the chiral catalyst, followed by reductive amidation [35]. Mechanistic DFT studies indicated that, starting from (*R*)-**47**, rotation around the C–N bond after the *aza*-Michael addition occurs freely at room temperatures with both DABCO and 1,5-diazabicyclo 4.3.0 non-5-ene (DBN) through the *aza*-Michael/retro-*aza*-Michael equilibrium (Scheme 11b). However, in the next proton abstraction step, the formation of chiral ion pair (*M*)-**48** is kinetically favored when DABCO (in MeOH) is used, which leads to the *M* artropisomers **49** after double bond repositioning, whereas with DBN (in 1,3-dioxane) is the (*P*)-**48** chiral ion pair which is preferentially formed and, consequently, the *N*-indolylquinolinone **49** with *P* absolute configuration. This approach was evaluated on a wide variety of enantioenriched substrates (*R*)-**44** (85%–98% ee) leading in most case to the atropisomeric products (*P*)- and (*M*)-**45** with good yields (71%–92% yield) and excellent chirality transfer (67%–92% ee).

The benzoxazole moiety is found in many biologically active molecules. Many have applications in medicinal chemistry (melatonin receptor agonists, amyloidogenesis inhibitors, rho kinase inhibitors, anticancer agents, antimicrobial, etc.), while others have been utilized in agricultural applications as herbicides. They also find applications such as dye lasers, in polymer synthesis, and as fluorescent probes for anion and metal cation sensors [36].

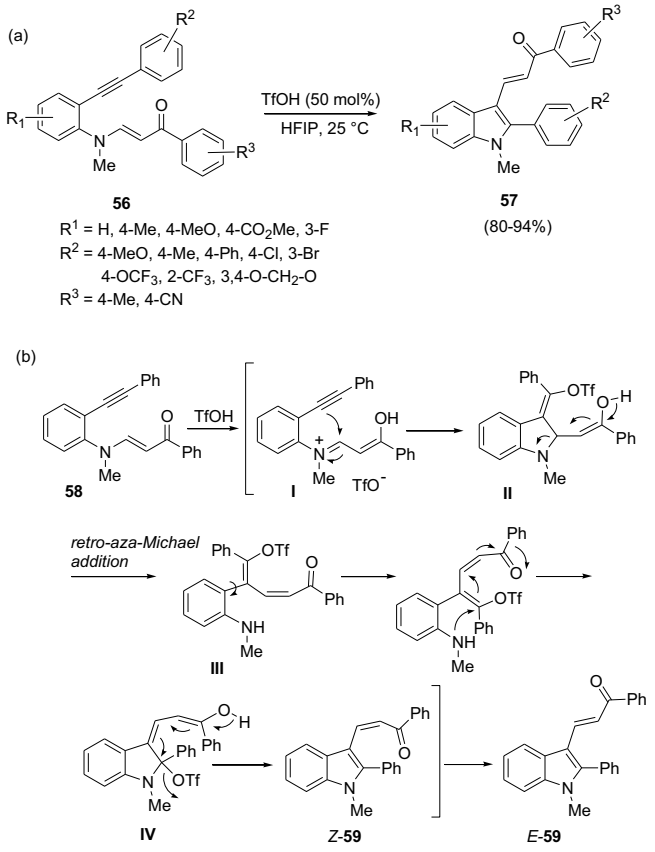
A novel strategy for the synthesis of N-vinyl benzoxazoles **52** (Scheme 12) has been disclosed by Bakhtadoss et al. in which a retro-*aza*-Michael reaction allows for an intramolecular distal 1,5-vinyl migration [36]. The process proceeds through a quadruple domino reaction by reacting at room temperature and without any catalyst, N-vinyl salicylaldehyde **50** and 2-aminophenol derivatives **51**. The initial imine formation (**53**) is followed by the oxazole **54** formation which intramolecularly reacts via *aza*-Michael addition to form enol **55** (or the enolate). This intermediate then undergoes a retro-*aza*-Michael addition which involves the N-Ts amino as the leaving group, thereby efficiently



SCHEME 12 | Synthesis of *N*-vinyl benzoxazoles **52**.

providing functionalized *N*-vinyl benzoxazoles. Only two examples were reported in which the N-vinyl shift occurs from nitrogen-to-nitrogen atom. As we will show later, this cascade process was much more extensively used by the authors to produce benzoxazoles and benzoxazines via a retro-*oxa*-Michael addition as the final step which allows for an oxygen to nitrogen atom vinyl shift. According to the authors, this protocol does not require workup and column chromatography.

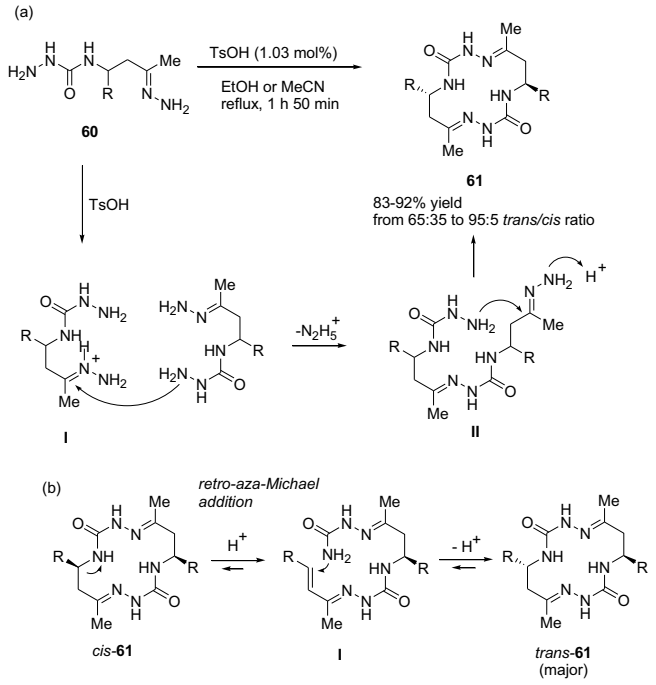
An interesting, metal-free approach to the synthesis of substituted indoles **57** with high double bond geometry control was based on a formal vinyl shift from a N to a C atom in the TfOH promoted cyclization of vinylogous amides **56** prepared from *o*-alkynylanilines (Scheme 13), as reported by Mandal and Balamurugan [37]. Mechanistically, according to the authors, formation of the electrophilic iminium/oxocarbenium ion species **I** upon addition of the TfOH triggers a 5-*endo*-*trig* attack by the triple bond with the formation of a benzo-fused five-membered ring **II** which immediately undergoes ring opening by a retro-*aza*-Michael addition, keeping the *cis* configuration of the enone double bond in **III**. A 1,6-conjugate addition of the amino group after rotation around the C2-C bond regenerates the five-membered azacycle **IV** which is converted into the target indole **59** by a 1,6-retro-*oxa*-Michael addition followed by TfOH promoted *Z*/*E* isomerization. As a consequence of this rearrangement, the aryl group originally present on the triple bond at C2 is installed at C2 of the indole moiety. This atom-economic transformation was also extended to substrates bearing different aromatic nuclei on the vinylogous amide moiety such as 9-anthracenyl, 3-furyl, 2-thienyl, 2-benzofuranyl to obtain always in excellent yield the corresponding indoles.



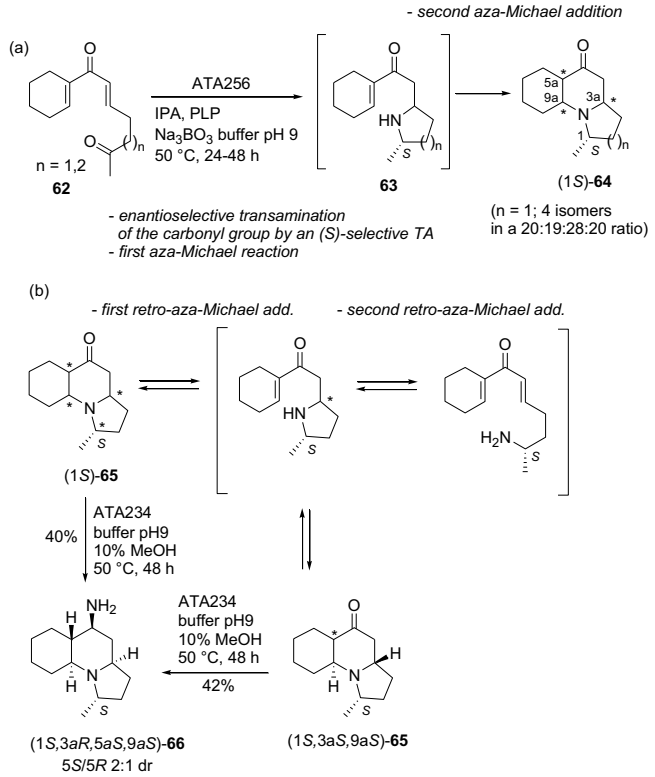
SCHEME 13 | (a) Metal-free approach to the synthesis of substituted indoles **57**. (b) Proposed mechanism.

Polyaza macrocycles are of significant interest because of their ability to bind different inorganic and organic cations, anions, and neutral molecules [38]. Their binding properties depend on their molecular structure, particularly on number of nitrogen atoms, ring size, and conformation. Polyaza macrocycles and their metal complexes, besides possessing a wide range of biological activities, find applications as contrast agents for magnetic resonance imaging, radiopharmaceuticals, sensors, NMR shift reagents, luminescent materials, and catalysts. Shutalev et al. [38] reported on the *p*-toluensulfonic acid-catalyzed cyclization of 4-(1-aryl-3-oxobutyl)semicarbazide hydrazones **60** into mixtures of *trans*- and *cis*-isomers of 14-membered cyclic bis-semicarbazones **61** which occurred in refluxing EtOH or acetonitrile (Scheme 14a). The authors found that the isomeric ratio depended on the reaction conditions but the *trans* isomer **61** was always preferentially formed, in some cases with very high stereoselectivity. The macrocyclization of the acyclic precursor **II** formed from two molecules of substrate proceeds initially with low diastereoselectivity to give mixtures of *trans*- and *cis*-macrocycles **61**. By prolonging heating, however, a slow transformation of *cis* isomers (Scheme 14b) into *trans* isomers via ring opening by a retro-*aza*-Michael reaction results in high *trans*-selectivity. The driving force of this isomerization was shown to be a lower solubility of *trans*-isomers compared with *cis* isomers.

In their study on a single-step, biocatalytic route to indolizidine and quinolizidine skeletons **64** containing four stereocenters by a double intramolecular *aza*-Michael reaction triggered by the enzyme-catalyzed transamination of the distal carbonyl group in simple substrates **62** (Scheme 15a), O'Connell et al. found a low



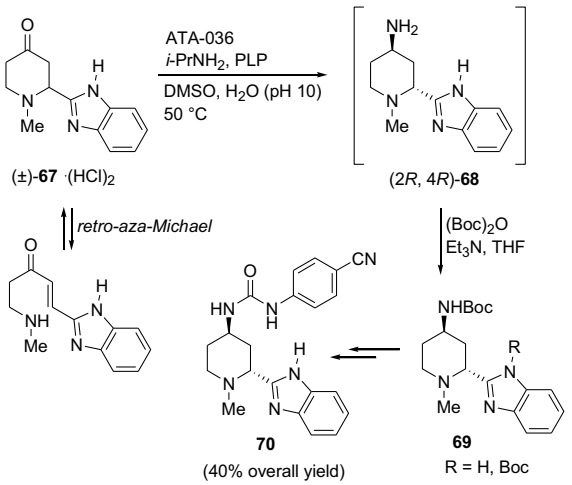
SCHEME 14 | (a–b) Cis to trans isomerization in the synthesis of polyaza macrocycles **61**.



SCHEME 15 | (a) Biocatalytic synthesis of indolizidine and quinolizidine skeletons. (b) Proposed mechanism.

level of diastereoselectivity in the synthesis of indolizidine compounds using both *S* selective ATA256 and *R* selective ATA025 transaminases [39]. However, single isomers of these sp^3-rich indolizidine compounds could be obtained (Scheme 15b) in a biocatalytic cascade with a proper transaminase (ATA234) in which a double intramolecular retro-*aza*-Michael reaction mediates a DKR. ATA234 transaminase, which irreversibly converts the carbonyl group at position 5 of the skeleton into an amino group, can discriminate between the various equilibrating diastereomers preferring the one with a *trans*-fusion between the two six-membered rings and having 9a*S* and 3a*R* absolute configuration. This preference was demonstrated by subjecting isolated (1*S*,3a*S*,9a*S*)-**65** isomer, with the opposite configuration at C3a, to the same conditions, obtaining after 48 h the *trans* (1*S*,3a*R*,5a*S*,9a*S*)-**66** isomer with 3a*R* absolute configuration. This proves the occurrence of the second retro-*aza*-Michael process forming the chiral primary amine.

The enzymatic transamination process as the discriminating final step in a DKR mediated by a single retro-*aza*-Michael reaction, has previously been reported by Peng et al. who developed a concise, asymmetric route to a smoothened receptor (SMO) inhibitor from 4-piperidinones [40]. Synthetic intermediate **68** was efficiently obtained as the desired *anti* isomer in >10:1 dr and with >99% ee by subjecting racemic piperidone **67** to the transamination/retro-*aza*-Michael conditions (Scheme 16). The enzyme ATA-036 was identified as the best catalyst for a highly efficient transamination of the 2*R* enantiomer affording the desired (2*R*,4*R*)-amine **68** with high conversion and excellent selectivity. Because 4-piperidone **67** was found to be unstable at elevated temperatures, the DKR was carried out at 50 °C

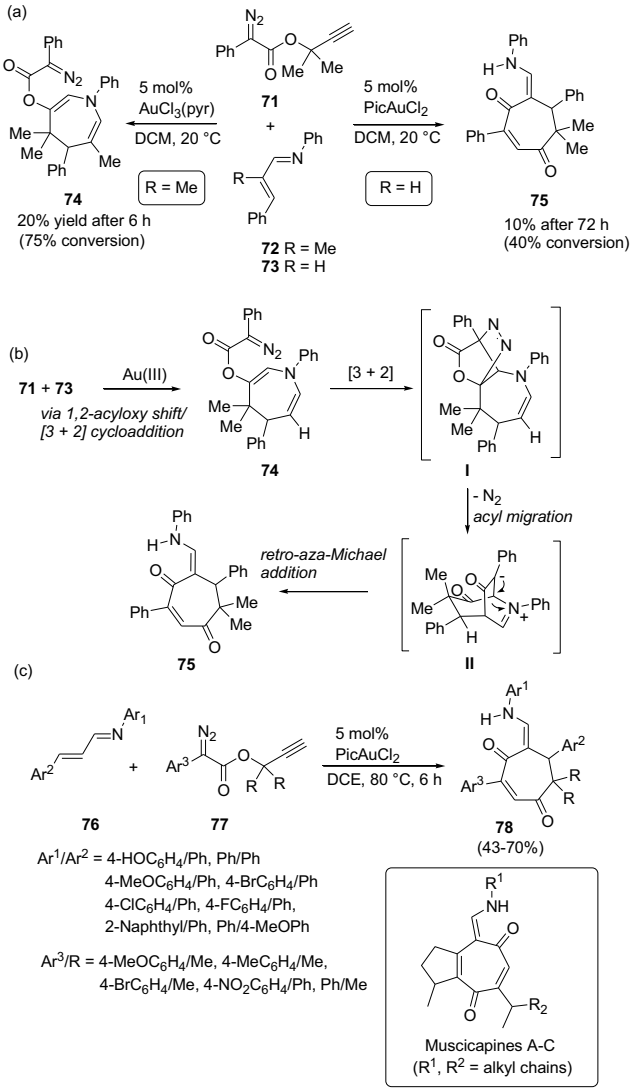


SCHEME 16 | Asymmetric route to a smoothened receptor (SMO) inhibitor **70**.

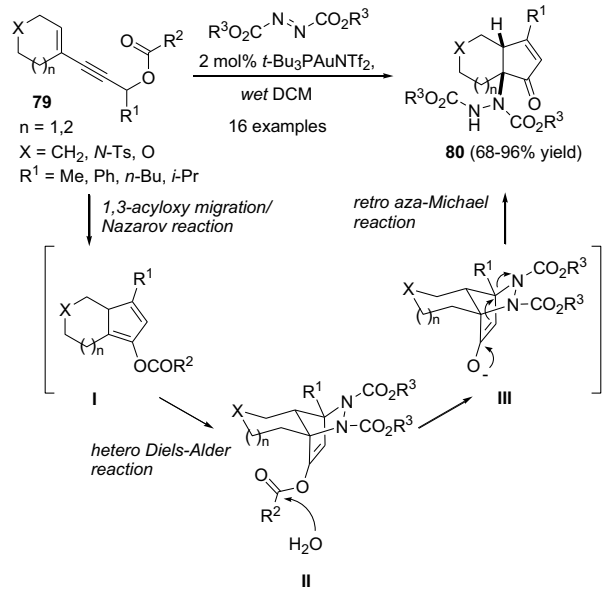
requiring 50−60 h to be complete. Also, because the transamination product **68** was highly soluble in DMSO−H_2O and thus very difficult to extract with organic solvents, N-Boc protection was performed in situ before transforming it into the target inhibitor **70**.

In the course of their studies on the catalytic [4 + 3]-cycloaddition reactions of vinylimines to form dihydroazepines with gold vinylcarbenes from propargyl ester derivatives, Qiu et al. discovered an unexpected intramolecular rearrangement leading instead to cycloheptene-1,4-diones **75** when using propargyl phenyldiazoacetate **71** as the source of the gold vinylcarbene [41]. As shown in Scheme 17a, in their preliminary experiments the authors found that vinylamine **72** reacted very slowly with the gold vinylcarbene obtained by the Au(III)-catalyzed 1, 2-acyloxy shift of **71**, furnishing in low yield the target azepine **74**. Quite surprisingly, in the attempt to improve the yields by testing different catalysts and imines, the authors found that with $PicAuCl_2$ as the catalyst and with simpler imine **73** another product was formed which was identified as cycloheptene-1,4-dione **75**, albeit in very low yield. The formation of this product can be accounted for by the initial intramolecular [3 + 2] addition in azepine **74** (Scheme 17b) of the diazo group with the double bond. The newly formed pyrazoline **I** is highly strained, which causes a spontaneous nitrogen (N_2) extrusion/acyloxy migration cascade process to afford azomethine ylide **II**. This continues the cascade via a retro-*aza*-Michael addition and tautomerization to complete the process forming 1,4-cycloheptenedione-enamine **75**. The process was optimized (in DCE as the solvent and at 80 °C) and extended to differently substituted vinylimines **76** and propargyl aryldiazoacetates **77** obtaining in most cases good yields (Scheme 17c). Although the 1,4-enedione-ketoenamine skeleton is rare, it has been identified in muscicapines A-C, sesquiterpene alkaloids recently discovered in the roots of a shrub native to Northeastern Brazil (*Croton muscicapa*) [42].

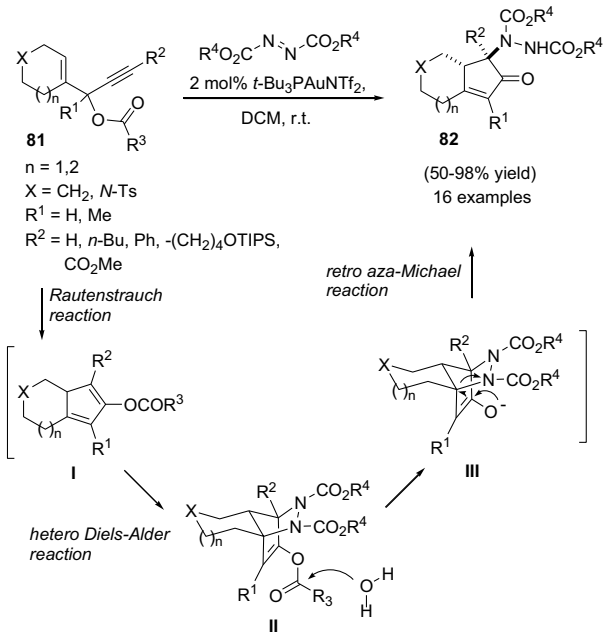
Following preceding work by the same authors on the synthesis of α-tertiary hydrazine derivatives by gold catalysis [43], Scarpi et al. [44] established an efficient method for the synthesis of α−hydrazino-2-cyclopentenones **80** which was based on a gold(I)-catalyzed cycloisomerization of propargyl acetates



SCHEME 17 | (a) Synthesis of cycloheptene-1,4-diones **75**. (b) Proposed mechanism. (c) Synthesis of cycloheptene-1,4-diones **78**.



SCHEME 18 | Synthesis of α-hydrazino-2-cyclopentenones **80**.

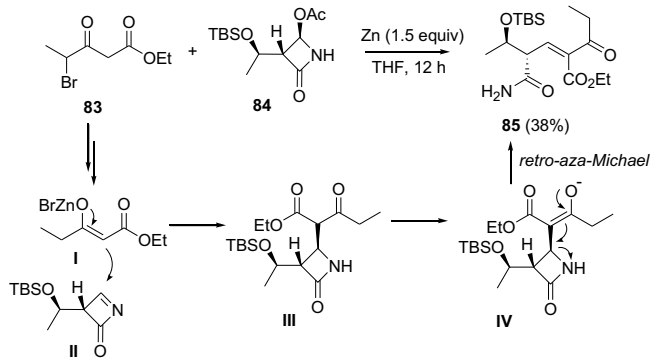


SCHEME 19 | Synthesis of α-hydrazino-2-cyclopentenones **82**.

(and pivalates) **79** (Scheme 18). By trapping with a dialkyl azodicarboxylate (R^3 = Et, i-Pr, Bn) the dienyl ester intermediate **I** which is formed in that process, a highly tensioned cycloadduct **II** is formed with complete facial selectivity. The next spontaneous, highly regioselective ring opening of this HDA cycloadduct takes place via a retro-*aza*-Michael reaction in the presence of water, which is essential not only to promote the latter step, but also to avoid the formation of N-acylated byproducts. This cascade, one-pot process, includes a sequence of four reactions (1,3-acyloxy migration, Nazarov cyclization, hetero-Diels-Alder, and retro-*aza*-Michael addition), and provides in high yields (68%–96%) unprecedented 5-hydrazino-2-cyclopentenone derivatives **80** bearing an α-tertiary hydrazine moiety.

By a similar approach, exploiting the 1,2-acyloxy migration of propargyl esters **81** (Scheme 19), Scarpi et al. [45] reported on the synthesis of regioisomeric products **82** in 50%–98% yield. In this case, the dialkyl azodicarboxylate present in situ traps the cyclopentadienyl ester intermediate **I** which is formed in the gold(I)-catalyzed Rautenstrauch rearrangement of ester **81**. As before, the next highly regioselective ring opening of the hetero-Diels–Alder cycloadducts **II** to form α-hydrazino-2-cyclopentenones **82** takes place via a retro-*aza*-Michael reaction consequent to the ester hydrolysis in the presence of the right amount of water. In this case the authors found that the gold(I) catalyst, together with water, is essential to promote ring opening, too.

During their studies on new synthetic approaches to potential precursors of carbapenems based on the Reformatsky reaction of azetidinone **84** with bromo ester **83** (Scheme 20), Valiullina et al. obtained amide **85**, instead of the target lactam, in 38% yield [46]. According to the authors, imine **II** generated in the reaction medium, undergoes nucleophilic attack by zinc enolate **I** to form azetidinone **III** which in turn, after formation of the corresponding enolate **IV**, experiences a retro-*aza*-Michael addition with consequent ring opening. Compound **85** was in the next stage

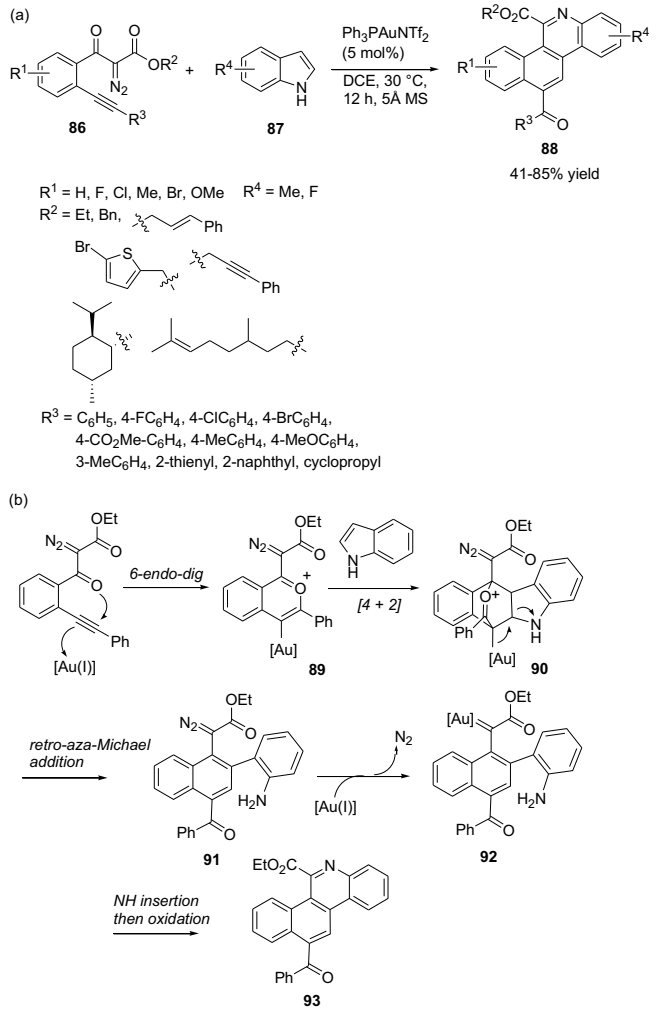


SCHEME 20 | The unexpected formation of amide **85**.

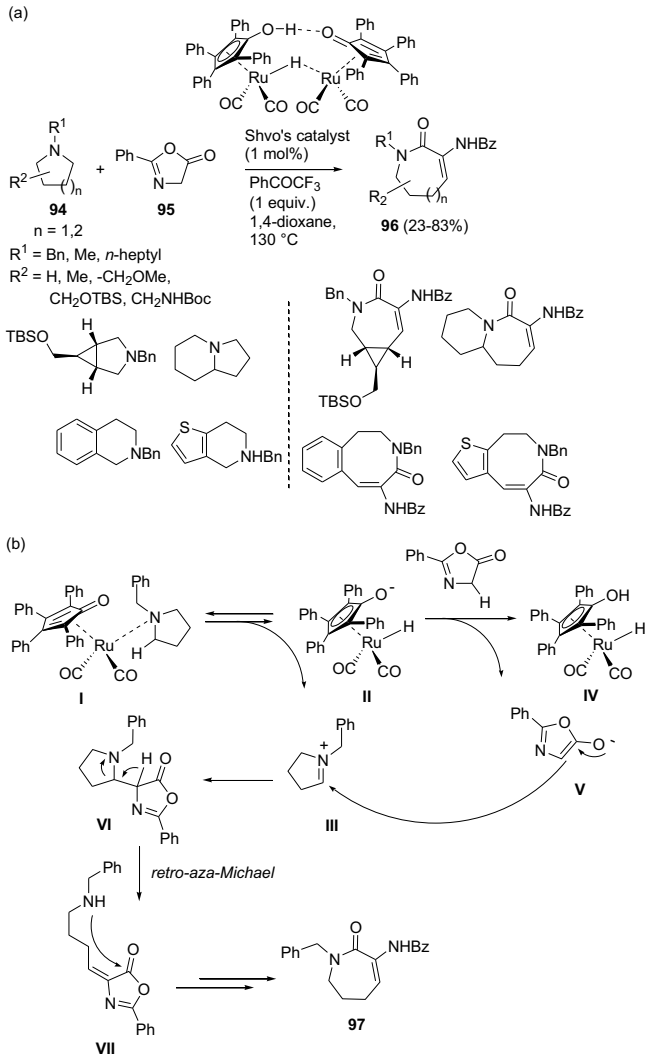
used for the synthesis of substituted 1*H*-pyridin-2-one heterocycles, albeit in low yield.

Phenanthridines, which are N-containing polycyclic aromatic hydrocarbons (PAHs), are privileged motifs in synthetic and natural biologically active compounds, pharmaceuticals, and materials [47]. An unprecedented catalyst-dependent cascade reaction of alkyne-tethered diazoketones **86** with indoles **87**, was reported by Bao et al. [47] which provides a divergent method for the synthesis of benzo[i]phenanthridines **88** and benzo[b] carbazoles. The former were obtained when using an Au(I) catalyst in good to high yields under mild reaction conditions and with broad substrate generality (Scheme 21a). The reactions were carried out in the presence of 5 mol% of $Ph_3PAuNTf_2$ as the catalyst in dichloroethane (DCE) at 30 °C. Mechanistic studies (Scheme 21b) revealed that the Au(I)-catalyzed 6-*endo*-dig cyclization of alkyne-tethered diazoketone initially forms the isobenzopyrylium intermediate **89**, followed by cycloaddition with external indole. The reaction then goes through a formal retro-*aza*-Michael reaction to give the diazo compound **91**, which forms the gold carbene intermediate **92** with the same gold catalyst and terminates by intramolecular N-H insertion and aromatization.

The development of synthetic methods for the construction of N-heterocycles is of great importance in synthetic organic chemistry. Wu et al. [48] reported on a very interesting molecular editing approach to transform the ring system of saturated, unstrained N-heterocycle motifs (pyrrolidine and piperidine) **94** into analogs with different ring sizes **96** (Scheme 22a). The direct regioselective insertion into pyrrolidine (and piperidine)



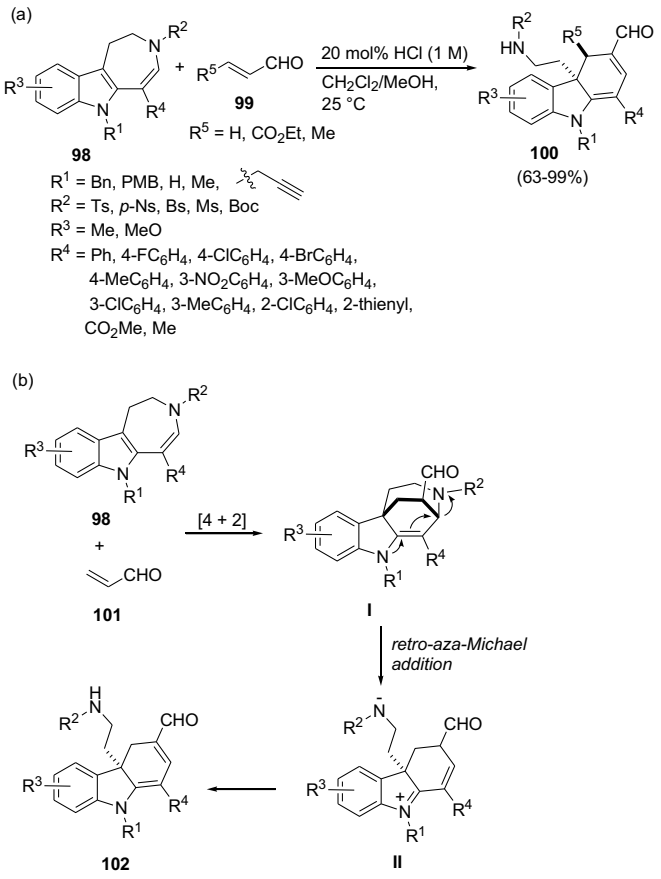
SCHEME 21 | (a) Gold(I)-catalyzed synthesis of benzo[i]phenanthridines **88**. (b) Proposed mechanism.



SCHEME 22 | (a) Molecular editing of saturated N-heterocycles by Ru(II)-catalysis; (b) Proposed mechanism.

is challenging owing to the existence of strong C—N and C—C bonds. Wu et al. demonstrated that the ring expansion reaction of these alicyclic amines was possible via an α-functionalization–deconstruction–reconstruction strategy by reacting them with readily accessible azlactone as a bifunctionalized two-carbon unit synthon (**95**) in the presence of 1 mol% of Shvo's catalyst and 1 equiv. of 2,2,2-trifluoro-1-phenyl-ethanone, in refluxing 1,3-dioxane. The initial α-functionalization of the pyrrolidine ring (Scheme 22b) was realized through the Ru-catalyzed dehydrogenation of this cyclic amine to form iminium ion **III**, which underwent nucleophilic attack by the stabilized enolate tautomer **V** of the azlactone formed by reaction of **95** with ruthenium complex **II**. The deconstruction step involving the pyrrolidine ring in **VI** then occurred through a retro-*aza*-Michael addition, which caused the C—N cleavage. Finally, the reconstruction sequence proceeded via intramolecular lactamization between the linear secondary amine and the azlactone skeleton. This process was applied to a large series of substrates, including bicyclic amines (a few examples are shown in Scheme 22a), leading to seven and eight-membered azacycles **96** in modest to excellent yield. The scope of the reaction was evaluated on the aryl ring of the azlactone **95** with yields ranging from 49% to 51% when using pyrrolidine as the amine. Finally, the synthetic utility was demonstrated through late-stage skeletal editing of commercially available drugs like probenecid and naproxen.

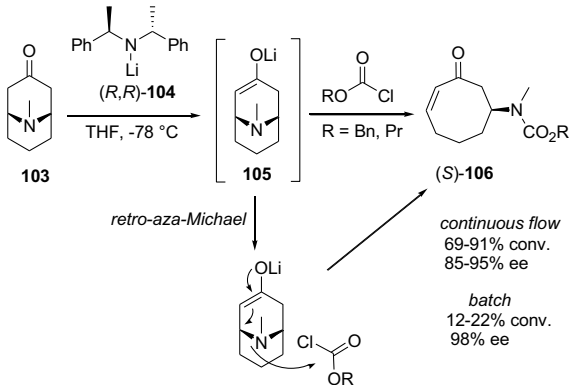
Hydrocarbazoles with an all-carbon quaternary center at C4a position are the core frameworks of many natural indole alkaloids and bioactive compounds [49]. Xie et al. reported on a Brønsted acid-initiated Diels–Alder cycloaddition/retro-*aza*-Michael addition cascade strategy from azepino[4,5-b]indoles **98** (prepared according to three different methods and bearing an electron withdrawing group on the azepine N atom) and commercially available acrolein **99** which provided target compounds **100** in 63%–99% yield (Scheme 23a) [49]. The reaction was carried out by mixing the substrate and acrolein in a dichloromethane/methanol 3:1 v/v solution at room temperature for 10 h. The initial Diels–Alder cycloaddition of azepino[4,5-b]indole **98** (Scheme 23b) and dienophile **101** provides a congested tetracyclic intermediate **I**, which undergoes a retro-*aza*-Michael addition (the enamine moiety here is the equivalent of a carbonyl group) driven by strain releasing. This yields hydrocarbazoles **102** after isomerization of the retro-*aza*-Michael intermediate product **II**. This methodology provided an entry to a series of hydrocarbazole derivatives bearing an all-carbon quaternary center at C4a position with a wide functional group tolerance, although other dienophiles such as methyl acrylate, acrylic acid, methyl vinyl sulfone, phenyl vinyl sulfone, and acrylonitrile proved unsuccessful in this cascade reaction. The synthetic utility of the method was demonstrated by a scale-up experiment and various derivatizations.



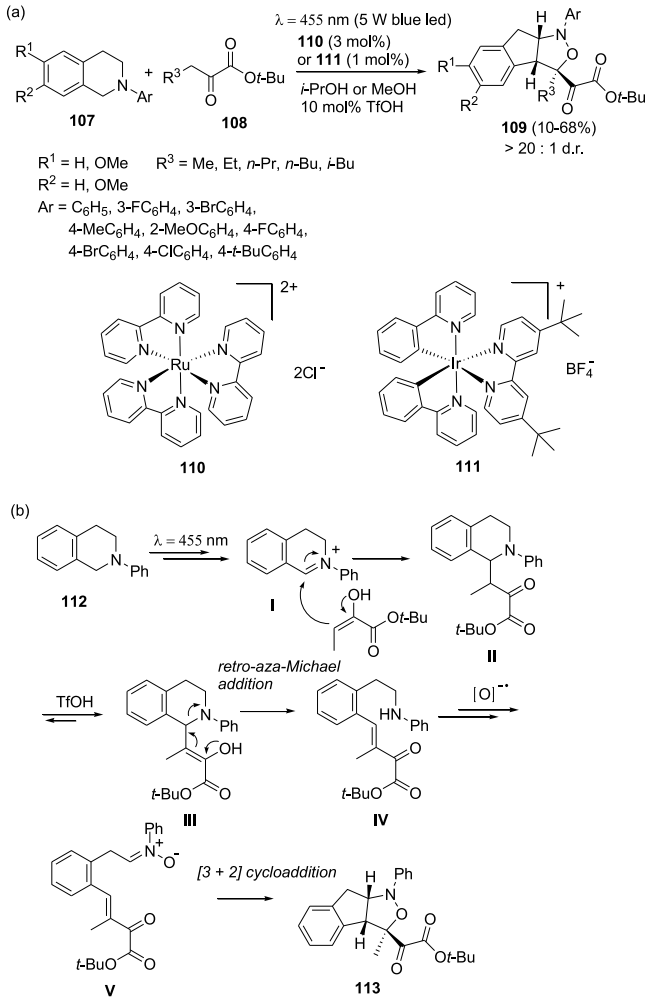
SCHEME 23 | (a) Synthesis of hydrocarbazoles **100** with an all-carbon quaternary center at C4a. (b) Proposed mechanism.

In their studies on the retro-*aza*-Michael reaction of granatanone **103** (Scheme 24) for the preparation of substituted eight-membered ring precursors of alkaloid adaline, Sienkiewicz et al. [50] demonstrated that the low temperature (−78 °C) enantioselective deprotonation with chiral lithium amide (*R*,*R*)-**104** under continuous flow conditions could provide, in the presence of a chloroformate, the ring opening products (*S*)-**106** with good conversion (69%–91%) and excellent enantioselectivity (85%–95% ee). Interestingly, while enantioselectivity was very high with both benzyl and propyl chloroformate, the reaction of granatanone **103** gave very low yields (<22%) when the same reaction was carried out in batch.

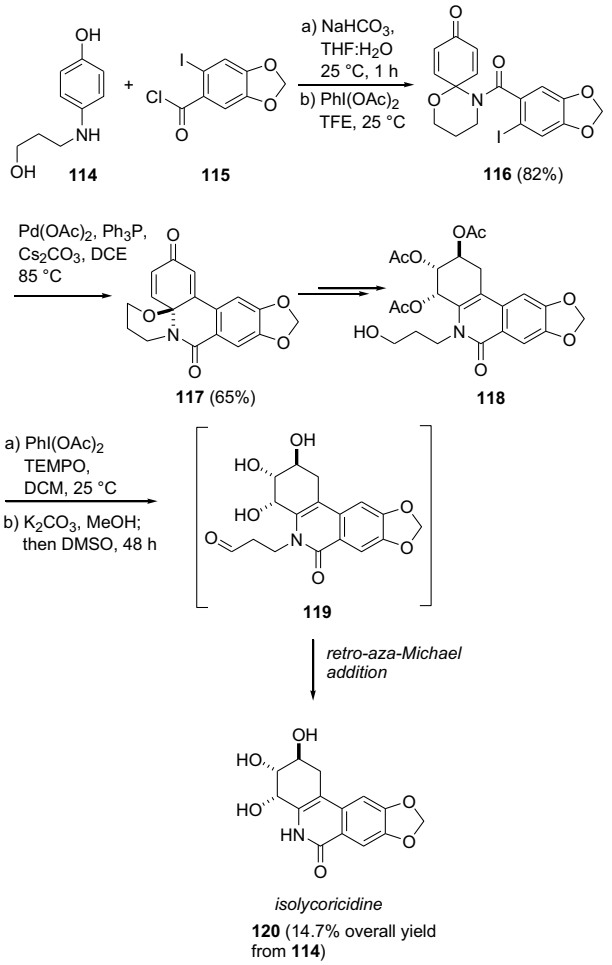
Bicyclic isoxazolidine skeletons are recurring motifs in natural products but also important building blocks for the synthesis of 1,3-difunctional amino alcohols [51]. Xie et al. reported on the highly diastereoselective synthesis of densely functionalized isoxazolidines **109** (Scheme 25a) from various tertiary amines **107** and α-ketoesters **108**, through a C–H activation/retro-*aza*-Michael-oxidation/ [3 + 2] cycloaddition tandem sequence by irradiation with visible light at 455 nm [51]. Ru(II)- and Ir(III)



SCHEME 24 | Retro-*aza*-Michael reaction of granatanone **103**.



SCHEME 25 | (a) Highly diastereoselective synthesis of densely functionalized isoxazolidines **109**. (b) Proposed mechanism.



SCHEME 26 | Synthesis of isolycoricidine.

photocatalysts **110** and **111**, respectively, were used in 1–3 mol% in alcohol as the solvent in the presence of triflic acid, providing the target products in modest to good yields. As for the mechanism (Scheme 25b), the (model) tertiary amine **112** first undergoes a single electron transfer (SET) process with the excited state of the catalyst that is formed under the irradiation by visible light, producing an aminyl radical cation which, under the reaction conditions, is then converted into reactive iminium ion **I**. This is trapped by the nucleophilic enol generated in situ from the α-ketoester under the catalysis of TfOH, to form **II**. Acid-promoted retro-*aza*-Michael reaction converts the latter into the unstable intermediate **IV**. Subsequently, this secondary amine intermediate can be quickly oxidized to imine and then to nitrile oxide **V** by the superoxide anion generated in the photochemical process. The stage is therefore set for the final [3 + 2] cycloaddition to produce the desired bicyclic isoxazolidine **113** in a process which forges two C—C, one C—O, and one N—O bonds, the construction of two new rings and the formation of one quaternary carbon center.

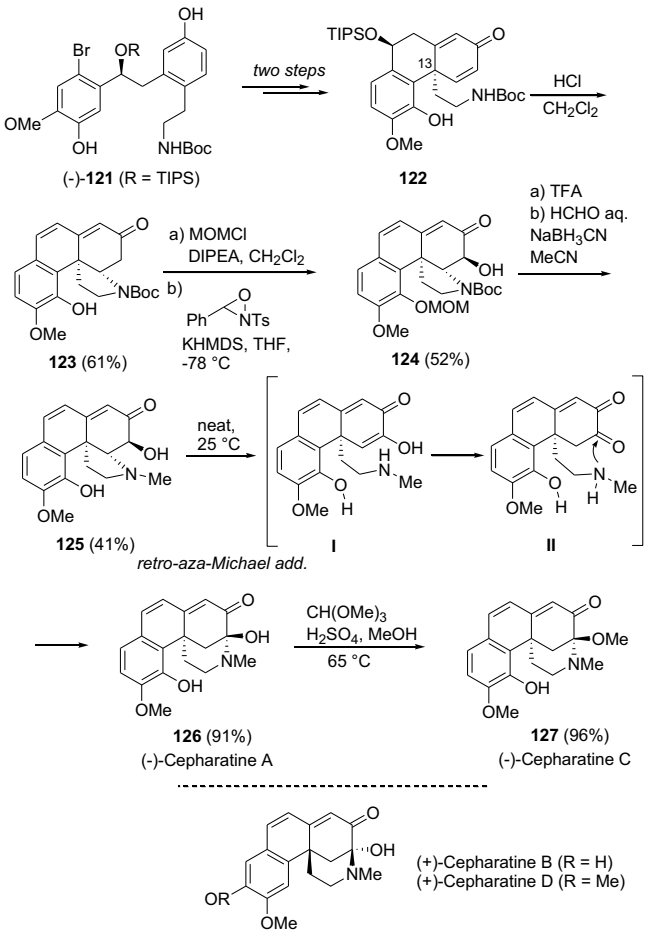
2.2 | Synthesis of Natural Products

Isolycoricidine is a natural product of the *Amaryllidaceae* alkaloid family which is known to include very active substances against a variety of diseases among which cancer and virus infections [52]. Despite its promising bioactivities, isolycoricidine has been understudied and only one total synthesis of (±)-isolycoricidine was reported in the literature [53] before the more recent synthesis by Denis et al. (Scheme 26) [52]. The synthesis started by reacting under Schotten–Baumann conditions phenol **114** and known aromatic system **115** which yielded the corresponding amide (not shown). Next, an oxidative dearomatization process attained by using (diacetoxyiodo)benzene led to the formation of spiro compound **116** in 82% yield over two steps. Interestingly, the propylamino-alcohol lateral chain in **114** served for two purposes: First, it enabled the formation of the spiranic core during the phenol dearomatization process, increasing the reactivity of the dienone **116** because of the augmented strain. Then, it functioned as a N-protecting group of the lactam segment to be removed by a retro-*aza*-Michael addition process. The Heck coupling was next carried out under standard conditions to provide tetracyclic intermediate **117** in 65% yield. After proper manipulation, the stage was set, with **118**, for the final O- and N-deprotection step which was carried out by oxidation of the primary alcohol group with (diacetoxyiodo)benzene in the presence of TEMPO, followed by acetate deprotection, to form aldehyde **119** from which the smooth released of acrolein by a retro-*aza*-Michael process produced isolycoricidine **120** in 10 steps and 15% yield from phenol **114**. The Heck coupling of **114** was carried out enantioselectively (70% ee), too, albeit

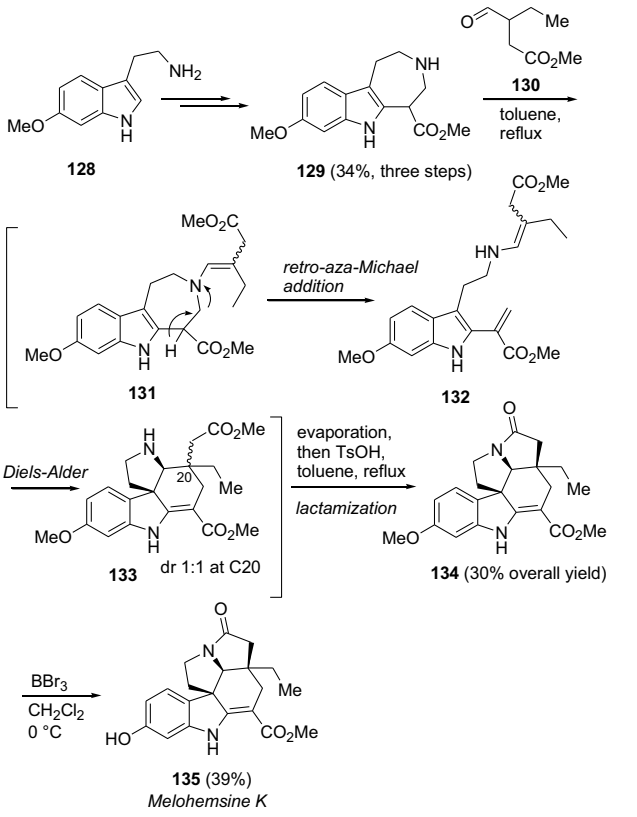
the synthesis was accomplished with the racemic material. Synthetic analogs of isolycoricidine were prepared by similar strategies in which the retro-*aza*-Michael process allowed for the N-deprotection along the synthetic route.

The deconstruction/reconstruction approach was exploited by Odagi et al. [54] in the synthesis of cepharatines A-D (Scheme 27), which are a structurally new subgroup of hasubanan alkaloids isolated from *Stephania cepharantha*. These alkaloids possess an azabicyclo [3.3.1]nonane motif and have an all-carbon quaternary stereogenic center at C13. Odagi et al. achieved the enantioselective total synthesis of these alkaloids by constructing the tetracyclic motif by means of a bioinspired cascade reaction involving a retro-*aza*-Michael reaction/hemiaminal formation as the key step [54]. The synthesis of cepharatine A is shown in Scheme 27 as an example. Optically pure phenol (−)-**121**, which was obtained by coupling of commercially available aldehydes, was converted in two steps into dienone **122**, i.e., the tricyclic core cepharatine A bearing the all-carbon quaternary stereogenic center at C13. Dienone **122** was subjected to a regioselective intramolecular *aza*-Michael reaction upon treatment with hydrochloric acid, during which the required elimination reaction of silanol to give conjugated dienone **123** occurred, too. Then, after protection of the phenol OH as methoxymethyl (MOM) ether, the hydroxylation at C6 was carried out by Davis oxaziridine, affording corresponding α-hydroxy **124** in 52% yield over the two steps. Then, the Boc protecting group was converted into a methyl group by deprotection with TFA followed by reductive amination with formaldehyde and sodium cyanoborohydride to give **125**, a putative biosynthetic intermediate, in 41% yield. Then, conversion of **125** into (−)-cepharatine A **126** via a cascade process entailing the retro-*aza*-Michael reaction/hemiaminal formation surprisingly occurred spontaneously simply upon standing at room temperature, which provided (−)-cepharatine A in 91% yield. Finally, cepharatine A was converted into cepharatine C (**127**) by reaction with trimethyl orthoformate in the presence of sulfonic acid in 96% yield. The other alkaloids B and D were prepared by a similar approach.

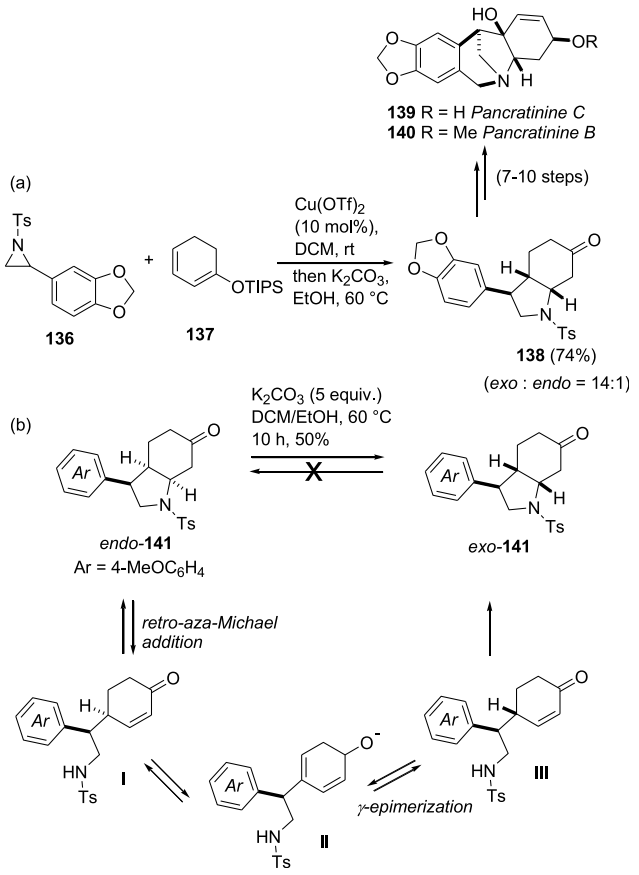
The ring opening/ring reconstruction approach was also exploited by Lin et al. for the racemic synthesis of melohemsine k (Scheme 28), a natural compound belonging to a class of alkaloids from *Melodinus hemsleyanus* exhibiting vasorelaxant activities and which contain unique 6/5/6/5/5 and 6/5/6/5/6 pentacyclic carbon frameworks [55]. The total synthesis of melohemsine K (**135**) was attained through a convergent approach in just three steps from azepine **129** in turn prepared from 6-methoxyl tryptamine **128** in three steps. The synthesis strategically relied on the formation of enamine **131** by reacting azepine with aldehyde **130** in refluxing toluene, conditions which favored the initial step of a cascade process, i.e., a temperature-promoted retro-*aza*-Michael addition reaction to form intermediate **132**. The stage was thus set for an intramolecular Diels–Alder reaction which provided tetracyclic intermediate **133** as a 1:1 diastereomeric mixture at C20. This was not isolated but instead treated, after evaporation of the solvent, with catalytic *p*-TsOH in refluxing toluene, which provided the first intermediate to be isolated



SCHEME 27 | Synthesis of cepharatines A–D.



SCHEME 28 | Synthesis of melohemsine k.



SCHEME 29 | (a) Synthesis of pancratinines B and C. (b) Mechanistic studies.

and characterized, i.e., pentacyclic compound **134** in 30% overall yield. This last reaction afforded pentacyclic compound **134** probably from the *cis* isomer of **133**, whereas the *trans* isomer proceeded through an unidentifiable pathway to give the other byproducts as indicated by thin-layer chromatography. Eventually, deprotection of phenol OH group by BBr_3 provided target compound melohemsine K (**135**) in 39% yield.

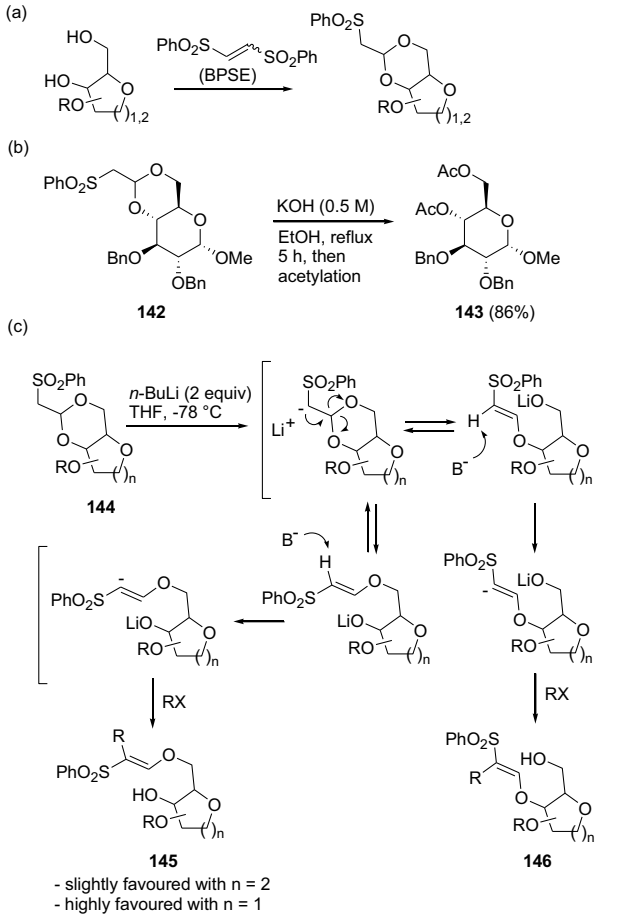
A ring opening through a retro-*aza*-Michael process was invoked by Wang et al. to explain the high diastereoselectivity in the formation of fused-[5, 6] carbocyclic pyrrolidine **138** as the key intermediate in the synthesis of montanine-type pancratinine B and C alkaloids (Scheme 29a) [56]. In their work, the authors developed a Cu-catalyzed [3 + 2] cycloaddition of 2-arylaziridines and cyclic silyl dienol ethers to diastereoselectively construct fused-[5, n] carbocyclic pyrrolidines that are commonly present in nature. In particular, the one-pot $Cu(OTf)_2$-catalyzed reaction of aziridine **136** with silyl dienol ether **137**, followed by treatment with K_2CO_3 in hot ethanol for several hours, provided six-membered ring fused pyrrolidine **138** in 74% yield as a 14:1 *exo*/*endo* diastereomeric mixture. Mechanistic studies on **141** (Scheme 29b) based on deuterium experiments suggested a stepwise process involving the initial base-promoted retro-*aza*-Michael in hot ethanol to form intermediate **I**. This undergoes epimerization of γ-enone position to form **III**, followed by recyclization which diastereoselectively provides the *exo* isomer **141**. The total syntheses of pancratinines B and C were then realized for the first time starting from *exo*-**138** in 7 and 10 steps, respectively.

3 | Retro-*Oxa*-Michael Addition Reaction

Despite in their excellent reviews on the applications of *oxa*-Michael reactions in natural product synthesis [5, 6], Nising and Bräse considered the retro-*oxa*-Michael reaction as a major drawback in that context, things have changed since, as many examples of small molecule syntheses which are instead based on such a process have been published in the last 15 years. There are some studies on the inherent reversibility of the *oxa*-Michael additions, which are surveyed and discussed by Ratzenböck et al. [9], who also carried out a nice study on the retro-*oxa*-Michael reaction in small model molecules (vinyl sulfones, acrylates, and acrylonitrile acceptors) according to which, in general, the retro-*oxa*-Michael reaction is Brønsted base catalyzed and fast when carried out at elevated temperatures (>100 °C), as demonstrated by alcohol exchange reactions. Also, the reversibility of the retro-*oxa*-Michael reaction was studied by alcohol exchange reactions with Michael adducts with primary alcohols of allylic or aliphatic nature and secondary alcohols in the presence of a base (5 mol% KOH) at 140 °C finding a correlation between exchange rate and reactant structure. Strong bases are often required for the deprotonation of the α-carbon atom when an alkoxide is the leaving group (vide infra) in the retro process, but Michael addition products embodying strong acceptors possess more acidic α-proton and dissociation becomes easier. Similarly to the retro-*aza*-Michael, for modern synthetic applications, the retro-*oxa*-Michael has been promoted at relatively low temperatures using tertiary base catalysts and aqueous bases, acids, bifunctional organocatalysts, and some of the other methods depicted in Scheme 1.

3.1 | Synthesis and Transformation of Carbo- and Heterocycles

1,3-Diol moieties in carbohydrates can be protected as phenylsulfonylethylidene (PSE) acetals through a Michael-type reaction of the diols with 1,2-bis(phenylsulfonyl)ethylene (BPSE) (Scheme 30a) [57]. These PSE acetals, compared with other acetals, are not affected by acidic conditions. Deprotection instead can be accomplished via a double retro-*oxa*-Michael reaction. Since previously reported conditions to effect PSE acetal cleavage were particularly harsh ($LiAlH_4$, $LiNH_2$ in liquid ammonia) [57], Chéry et al. performed a study on the reactivity of a standard model substrate, i.e., methyl 2,3-di-*O*-benzyl-4,6-*O*-(2-phenylsulfonyl)ethylidene-α-D-glucopyranoside **142** and other selected pyrano- and furano-type PSE acetals, to find milder deprotection conditions to restore the free 1,3-diol moiety [58]. Deprotection under various protic conditions resulted in KOH or Cs_2CO_3 in refluxing EtOH as the best approach to the total cleavage of the acetal with reasonably good yields (Scheme 30b). In one case, direct acetylation of the crude mixture led to the 4,6-di-*O*-acetyl derivative (**143**) in 86% yield. Interestingly, under aprotic, strongly basic conditions, PSE 1,3-dioxanes **144** (Scheme 30c) undergo very efficient ring cleavage through a single retro-*oxa*-Michael addition, the regioselectivity of which is dependent on the carbohydrate ring template. For example, on pyrano frames, there is a slight predominance of primary (**145**) over secondary (**146**) alkoxyvinyl sulfones, whereas a furano frame favors the formation of the primary alkoxyvinyl sulfone, as demonstrated by trapping

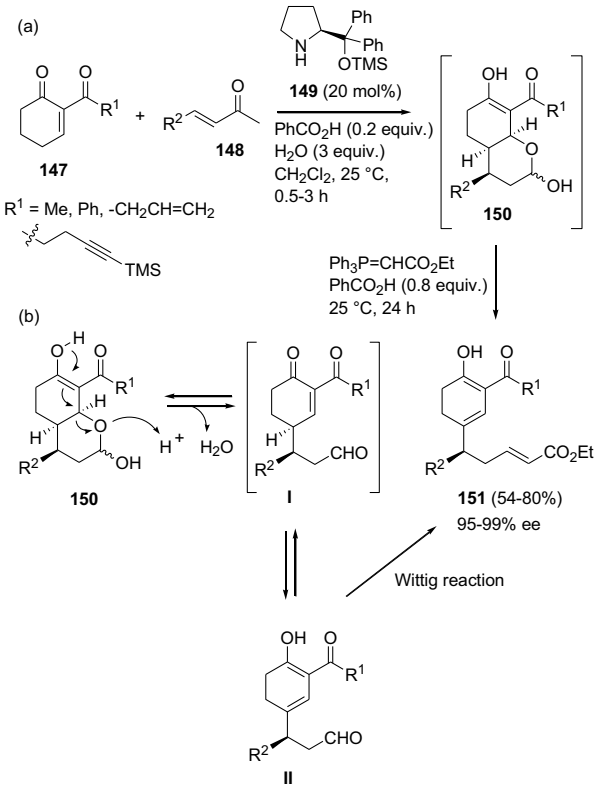


SCHEME 30 | 1,3-Diol moiety protection (a)/deprotection (b) in carbohydrates. (c) Proposed mechanism.

the anionic intermediates with an electrophile such as AcOH for proton quenching or alkyl halides.

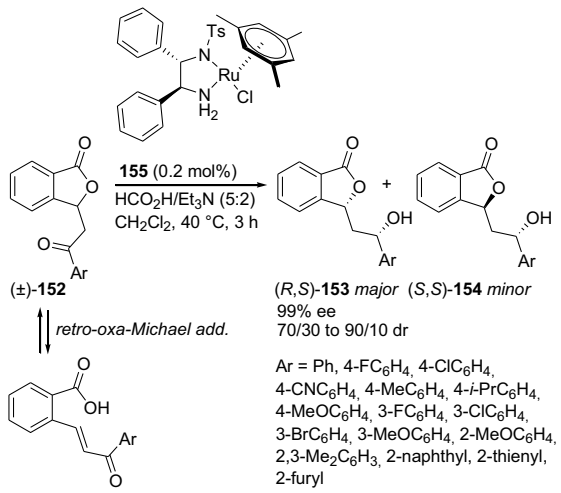
A retro-*oxa*-Michael reaction allowed for the deprotection of a carbonyl group in tetrahydrochromane derivatives **150** under acid conditions and its consequent reaction with a Wittig reagent in a domino sequence to furnish chiral functionalized cyclic 1, 3-diene derivative **151** in good yield and excellent enantioselectivities (95%–99%) (Scheme 31) [59]. The whole sequence included the selective reaction at the γ-position of diketones **147** with α,β-unsaturated aldehydes in the presence of diphenylprolinol silyl ether in dichloromethane to afford hemiacetals **150** through a sequence which included an asymmetric vinylogous Michael reaction, a hydration, and an *oxa*-Michael reaction. Without their isolation, these substituted tetrahydrochromane derivatives were reacted with $Ph_3P{=}CHCO_2Et$ in the presence of phenyl acetic acid to form product **151**. As for the mechanism, the acid-catalyzed retro-*oxa*-Michael generated aldehyde intermediate **I** which, after double bond isomerization, was consequently trapped by the Wittig reagent. The presence of the acid was crucial for this reaction, as without acid, the yields were low.

The reversibility of the *oxa*-Michael reaction has in many cases been exploited for the fast racemization of a substrate, allowing for a metal- or an enzyme-catalyzed DKR to be realized. Dynamic kinetic resolution through asymmetric transfer



SCHEME 31 | (a) Domino sequence to chiral functionalized cyclic 1,3-diene derivative **151**. (b) Proposed mechanism.

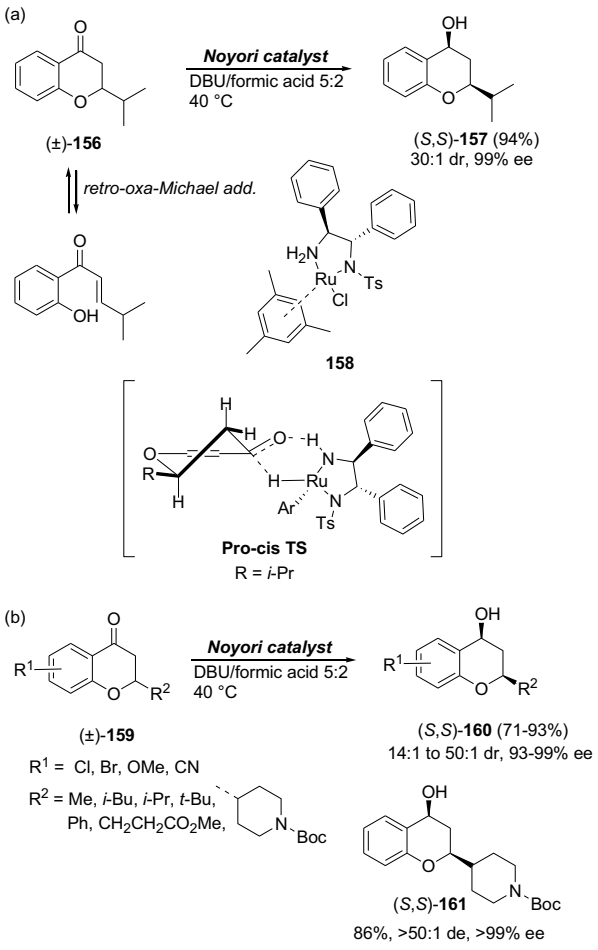
hydrogenation (DKR-ATH) is a powerful methodology to build various optically active compounds with two newly created stereocenters [60]. Cheng et al. reported on the DKR of phthalides **152**, a class of heterocycles showing a wide range of biological activity against several illnesses and physiologic conditions, through asymmetric transfer hydrogenation under mild conditions and in the presence of a tertiary base to generate 3-(2-hydroxy-2-arylethyl)isobenzofuran-1(3H)-ones **153** bearing two stereocenters in a 1,3-relative position with good enantiomeric excesses but just acceptable diastereoselectivity (Scheme 32) [60]. The DKR exploited the fast *oxa*-Michael/retro-*oxa*-Michael



SCHEME 32 | DKR for the synthesis of 3-(2-hydroxy-2-arylethyl)isobenzofuran-1(3*H*)-ones **153**.

reaction undergone at 40 °C by the substrates **152** in the presence of Et_3N as the tertiary base and the RuCl[(*S*,*S*)-TsDPEN](mesitylene) catalyst **155** for the transfer hydrogenation process in the presence of HCOOH as a hydrogen source. A variety of phthalides were used as substrates to provide optically pure phthalides with high yields, excellent enantioselectivities, and acceptable diastereomeric ratios. In all cases, the faster hydrogenation transfer occurred onto the *R* enantiomer to produce (*R*, *S*) as the major diastereomers.

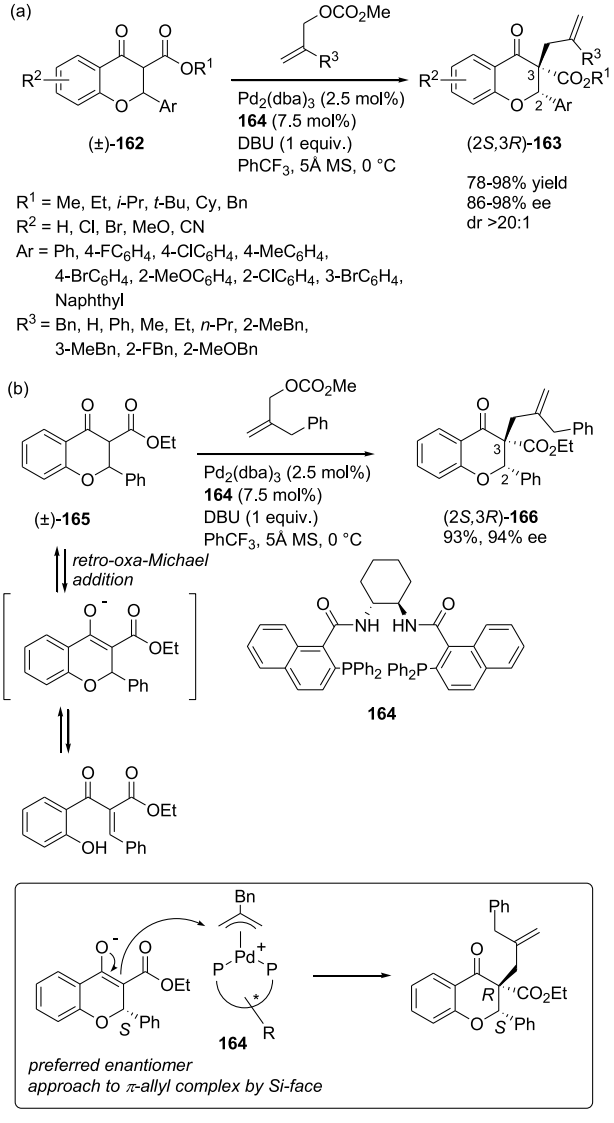
Following an analogous approach, Ashley et al. reported on the DKR of β-substituted chromanones by the ruthenium-catalyzed asymmetric transfer hydrogenation in the presence of a tertiary base, to produce valuable chromanols in high yields and with high levels of stereocontrol [61]. The reaction was studied on racemic compound **156**, and it was found to proceed by base-catalyzed racemization of the β-stereocenter through an *oxa*-Michael/retro-*oxa*-Michael process in concert with a highly selective ketone transfer hydrogenation step catalyzed by a Noyori catalyst (Scheme 33a). After screening a variety of bases and modified Noyori catalysts in the presence of formic acid, it was found that DBU allowed for a facile racemization at 40 °C of **156**, and, by using Noyori catalyst **158**, the transfer hydrogenation step was highly *cis*-diastereo- and enantioselective. Interestingly, in contrast to the results reported by Cheng et al. [60], with Et_3N amine as the base no racemization occurred, and the products were obtained in a 1:1 diastereomeric mixture.



SCHEME 33 | (a–b) DKR of β-substituted chromanones.

The faster hydrogenation transfer rate with the *S* enantiomer has been accounted for by a favored pro-*cis* transition state. A wide range of alkyl substituents were viable at the chromanone 2-position, from the small methyl to the large *tert*-butyl group as well as potentially reactive carbamates (Scheme 33b) and methyl esters. Excellent results were also obtained with a wide range of arene substitution.

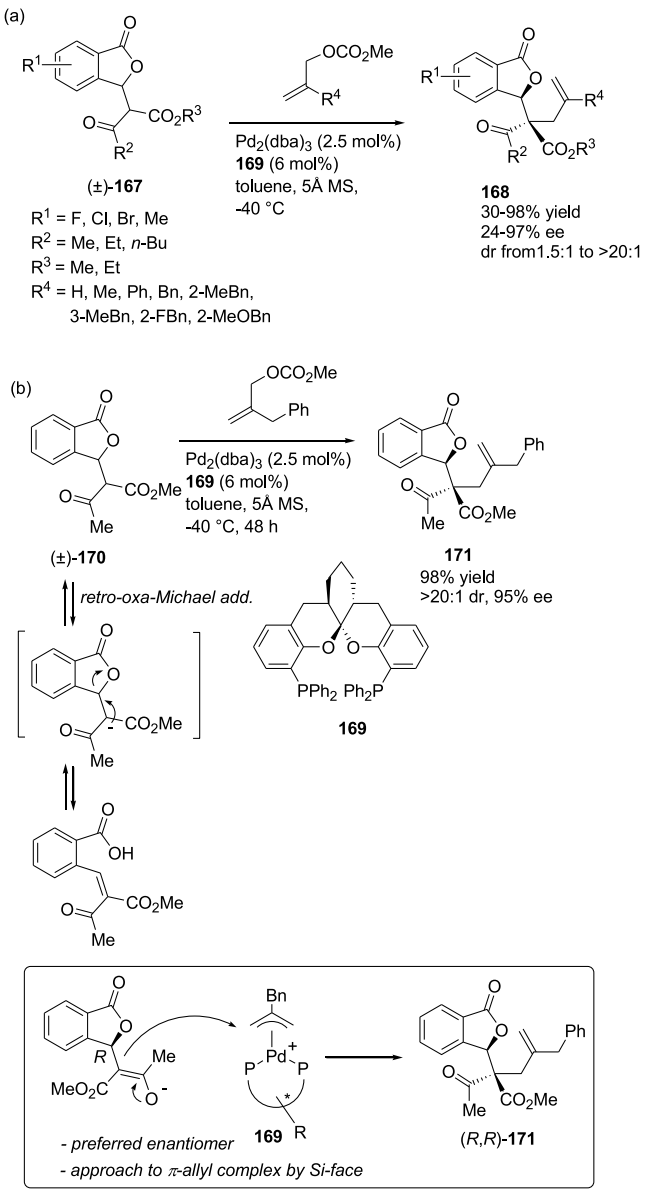
Flavonoids are a class of polyphenolic secondary metabolites found in many plants which fulfill many functions including an antioxidant role. By exploiting the propensity of flavonoids to transformation from the cyclic to the linear form under basic conditions through a retro-*oxa*-Michael addition, the Zhou's group [62] successfully combined a palladium-catalyzed asymmetric allylic alkylation (AAA) and a base-promoted retro-*oxa*-Michael addition of 2,3-disubstituted flavonoids such as **162** (Scheme 34a) to achieve an efficient DKR in the allylation process. A study of the reaction conditions with model compound **165** (Scheme 34b) resulted in **164** as the best ligand for palladium in the presence of DBU as the base in benzotrifluoride



SCHEME 34 | (a) Palladium-catalyzed asymmetric allylic alkylation in the synthesis of **163**. (b) Proposed mechanism.

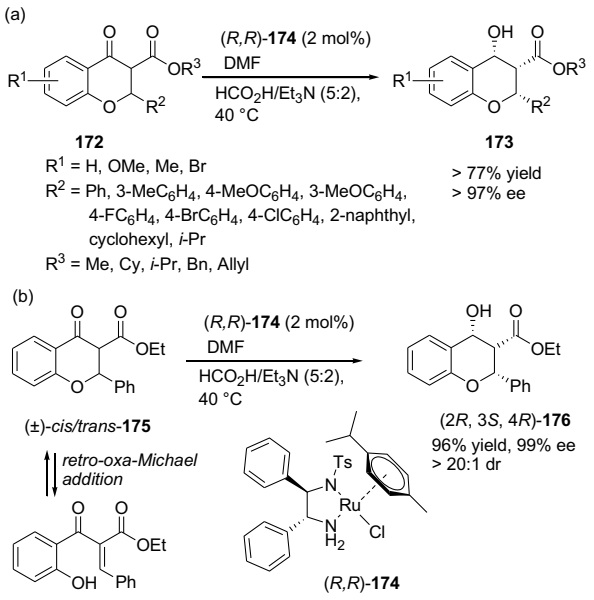
($PhCF_3$) as the solvent. Given the fast racemization of the flavonoid through the retro-*oxa*-Michael/*oxa*-Michael reaction, the reaction could be carried out even at 0 °C to improve selectivity. Under these conditions, almost enantiopure (94% ee) 2,3-disubstituted product (2*S*,3*R*)-**166** with two contiguous stereocenters, of which one a quaternary, was obtained in high isolated yield (93%). The enantioselectivity of the palladium-catalyzed AAA has been accounted for by using Trost et al.'s model [63], for which the transient enolate approaches the (π-allyl)palladium−**164** complex by its *Si* face, to avoid disfavored steric interaction between the "wall" of the ligand and the phenyl ring of the substrate.

By a similar approach, the palladium-catalyzed asymmetric allylic alkylation was employed by the Zhou's group [64] to carry out a DKR of isobenzofuranone derivatives (phthalides) **167** (Scheme 35a). Quite interestingly, the racemization step, based on the retro-*oxa*-Michael addition, did not require the addition of a base to occur reasonably because of the high acidity of the proton involved in the retro-Michael step. This was so fast that the reaction could be successfully carried out at -40 °C in toluene, in the presence of $Pd_2(dba)_3$ as the catalyst source and chiral spiroketal-based diphosphine (SKP) **169** as the ligand. As above, the transient enolate of the favored *R* enantiomer (Scheme 35b) approaches the (π-allyl)palladium−**169** complex by its *Si* face to furnish **171** with *R*,*R* absolute configuration. This process was highly efficient in providing a series of enantioenriched phthalide derivatives **171** bearing vicinal tertiary and all-carbon quaternary stereocenters with, apart from a few exceptions, high chemo-, enantio-, and diastereoselectivity, and showing good functional group tolerance. Appreciably, the reaction was also repeated on a gram scale on substrate **170** which, after 48 h, provided phthalide derivative **171** in 98% yield, 95% ee and >20:1 diastereomeric ratio.

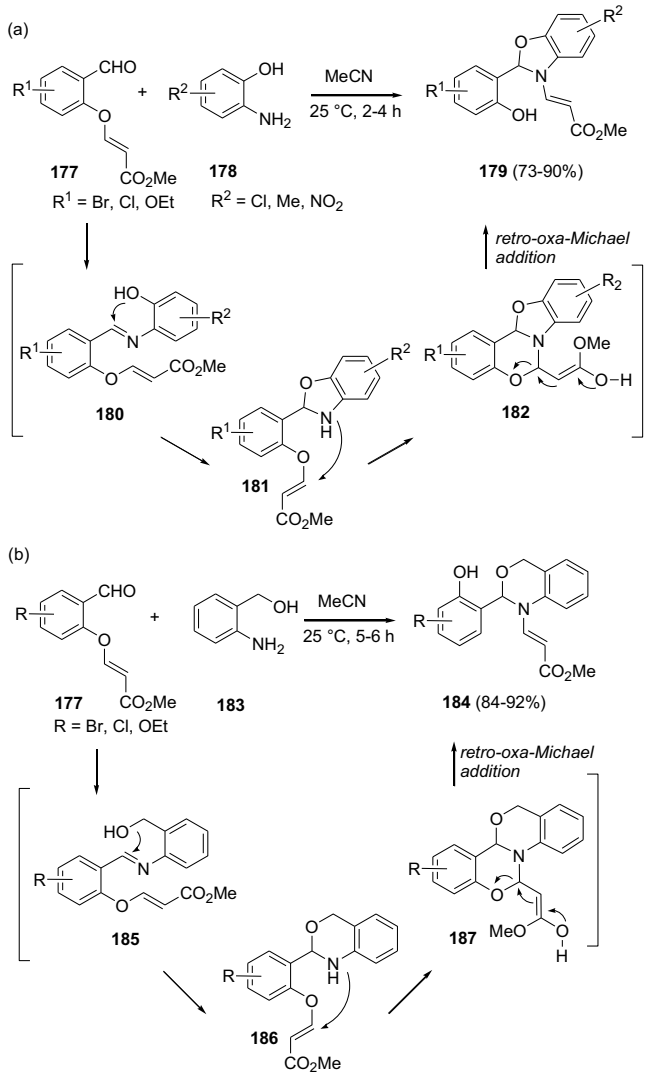


SCHEME 35 | (a) Palladium-catalyzed asymmetric allylic alkylation in the synthesis of **168**. (b) Proposed mechanism.

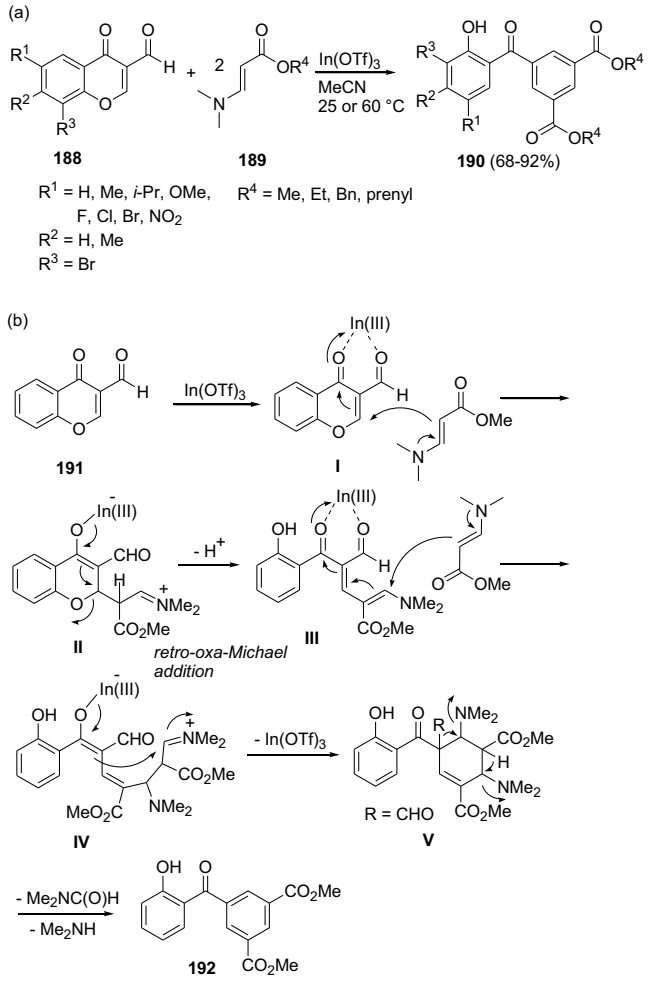
In continuation of their studies on metal-catalyzed DKR of flavonoids, and in analogy to previous work by Ashley et al. on chromanones [61] and Cheng et al. on phthalides [60], the Zhou's group developed a ruthenium-catalyzed asymmetric transfer hydrogenation of 2,3-disubstituted flavanones **172** for the construction of three contiguous stereocenters under basic conditions, through a combination of DKR and base-catalyzed retro-*oxa*-Michael addition (Scheme 36) [65]. Chiral flavanols **173**, with 2,3-*cis* relative configuration, were accordingly obtained with excellent enantioselectivities and diastereoselectivities. Differently from Ashley's substrates, the presence of a second substituent at C3 implies that four stereoisomers are generated in the retro-*oxa*-Michael/*oxa*-Michael equilibrium which can undergo the ketone metal-catalyzed transfer hydrogenation in the final resolution step. The reaction was best carried out in DMF at 40 °C by using **174** as the chiral ruthenium catalyst and could be extended to substrates bearing a wide variety of substituents (furnishing product in high yields and with impressive >97% ee). Et_3N was an efficient base-catalyst for the retro-conjugate/conjugate addition step in this



SCHEME 36 | (a) Ruthenium-catalyzed asymmetric transfer hydrogenation of 2,3-disubstituted flavanones **172**. (b) Proposed mechanism.



SCHEME 37 | (a) Synthesis of N-vinyl benzoxazoles **179** and (b) N-vinyl benzoxazines **184**.



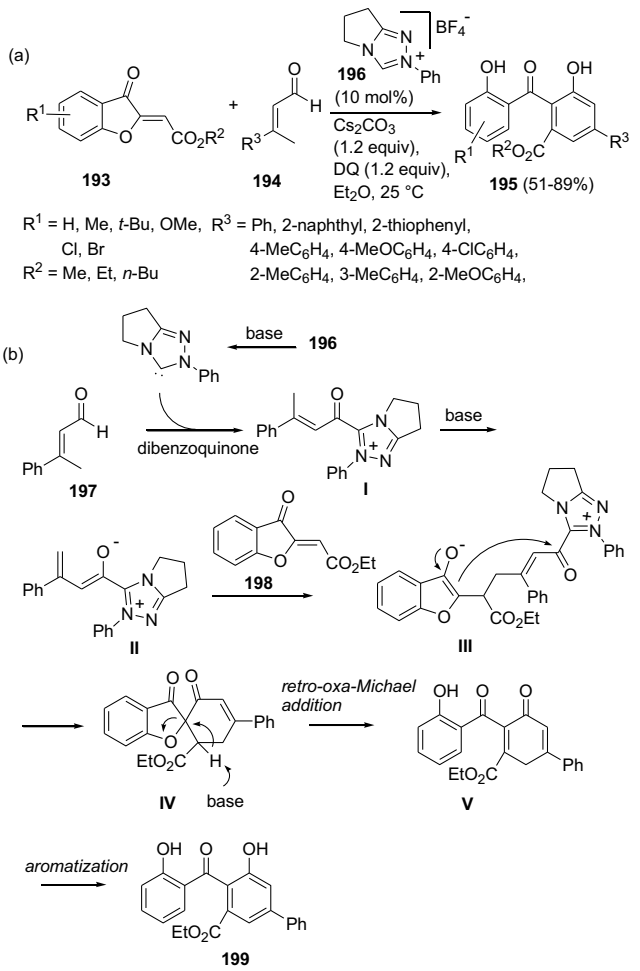
SCHEME 38 | (a) Synthesis of benzophenone derivatives **190**. (b) Proposed mechanism.

case. Importantly, the asymmetric transfer hydrogenation could be achieved at gram scale without loss of the activity and enantioselectivity.

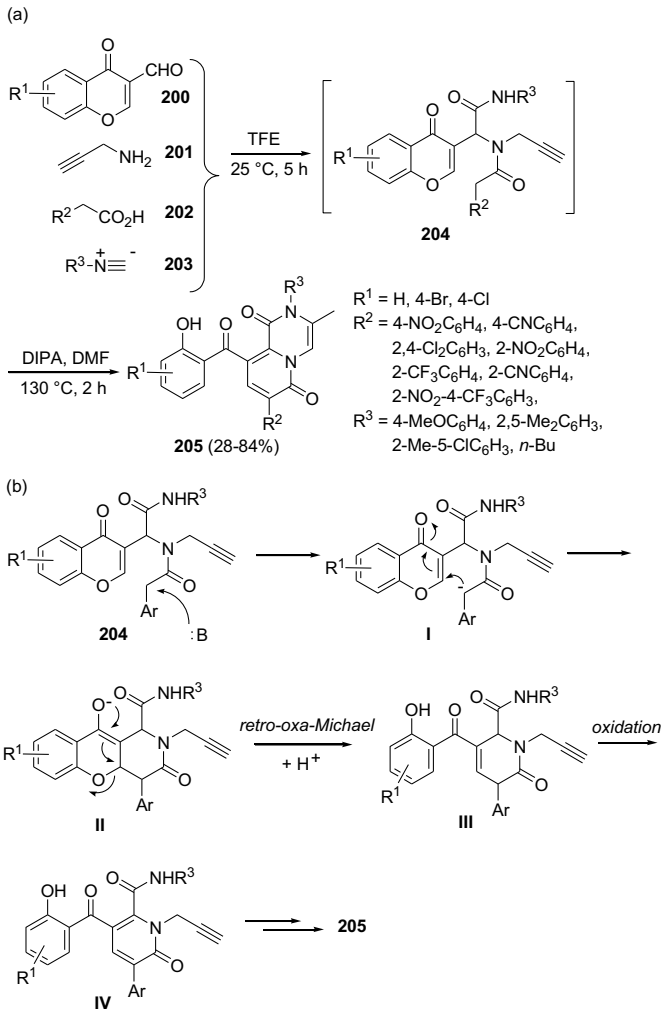
The strategy employed by Bakhthadoss and Mushaf [36] for the synthesis of *N*-vinyl benzoxazoles **179** (see the section on the retro-*aza*-Michael addition) allowed the same authors to prepare the same compounds (Scheme 37a) and *N*-vinyl benzoxazines **184** (Scheme 37b) in excellent yields. Given the different nature of the starting material **177**, an *O*-vinyl salicylaldehyde derivative, it is a retro-*oxa*-Michael reaction that now allows for an intramolecular distal 1,5-vinyl migration [36]. The use of aminophenols **178** and 2-aminobenzyl alcohol **183** as reagent partners did not require changes in the reaction conditions (with 2-aminobenzyl alcohol the reaction was just slightly slower) but determined the size of the heterocycle obtained at the end of the cascade process.

A ring opening strategy based on the retro-*oxa*-Michael was exploited by two different groups in the synthesis of benzophenone derivatives. Benzophenone is an important structural motif found in many natural products and pharmaceuticals. Among their wide range of pharmacological properties, one is sun-protection activity [66].

A variety of functionalized 2-hydroxybenzophenone derivatives **190** (Scheme 38a) were synthesized efficiently in 68%–92% yield via a highly regioselective indium(III)-catalyzed [2 + 2 + 2] benzannulation of 3-formylchromones **188** with β-enamino esters **189** [66]. The reaction is best carried out in acetonitrile in the presence of 5 mol% of indium triflate at room temperature or heating at 60 °C. This reaction proceeds via a domino Michael/retro-Michael/6π-electrocyclization/deformylation reaction (Scheme 38b). The 3-formylchromone **191** first gives complex **I** in the presence of $In(OTf)_3$ catalyst which triggers the Michael-type addition of the enamine to afford intermediate **II**. A subsequent retro-*oxa*-Michael reaction followed by double bond migration through deprotonation affords intermediate **III**, which undergoes the conjugate addition by a second molecule of enamine to give intermediate **IV**. The intramolecular cyclization of enolate motif with iminium ion forms a six-membered ring intermediate **V**, which further undergoes elimination reactions of dimethylamine and dimethylformamide to produce the final product **192**. The reaction could be extended to β-enamino ketones as the nucleophiles. One of the compounds exhibited higher sun protection activity than oxybenzone which is used in most popular sunscreens.



SCHEME 39 | (a) Synthesis of benzophenone derivatives **195**. (b) Proposed mechanism.

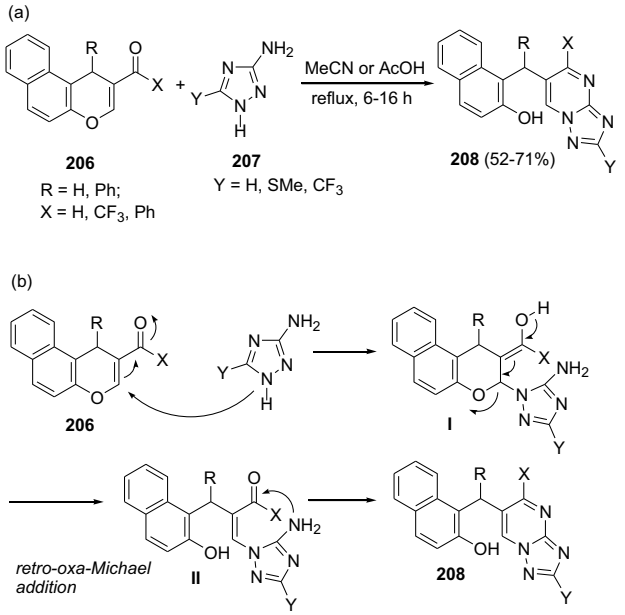


SCHEME 40 | (a) Multicomponent synthesis of functionalized pyrazinone-fused pyridines **205**. (b) Proposed mechanism.

While in the synthesis of benzophenone derivatives described by Cai et al. [66], the ring opening involved a six-membered ring (a benzo-fused 2,3-dihydro-4-pyranone) in Chen et al.'s work 2-methylene-benzofuran-3-one derivatives **193** (aurones) (Scheme 39a) were instead employed as the electrophiles undergoing a conjugate nucleophilic attack to prepare benzophenones **195** under N-heterocyclic carbene (NHC) catalysis [67]. In the presence of dibenzoquinone (DQ) as the oxidant (Scheme 39b), the addition of carbene (generated from NHC precursor **196** by the base) to enal **197** affords unsaturated acyl azolium **I**, which is γ-deprotonated to give dienolate **II**. The Michael addition of dienolate **II** to aurone **195** affords adduct **III**, followed by intramolecular C-acylation that furnishes spirocyclic compound **IV**, regenerating the NHC catalyst. In the presence of a base, the C–O cleavage in compound **IV** by a retro-*oxa*-Michael addition gives cyclohexadienone **V**, which is transformed into more stable, aromatic product **199**. This reaction was best carried out in the presence of Cs_2CO_3 as the base, at room temperature, and with **196** as the best preNHC catalyst allowing for the preparation of a variety of dihydroxybenzophenone derivatives **195** with potential cytotoxic, enzyme inhibition, and sunscreen activity.

The ring opening strategy based on the retro-*oxa*-Michael addition undergone by chromenone derivatives **200** was exploited by Lei et al. in a novel one-pot, multicomponent synthesis of highly functionalized pyrazinone-fused pyridines **205** [68]. The Ugi reaction involving 4-oxo-4*H*-chromene-3-carbaldehydes **200**, propargylamine **201**, phenylacetic acid derivatives **202**, and isocyanides **203**, in trifluoroethanol (TFE) under air, led to products **204** which, after work-up, were heated in DMF at 130 °C in the presence of diisopropylamine (DIPA) as the base (Scheme 40a). Under these conditions, the Michael/retro-*oxa*-Michael addition (Scheme 40b), followed by aromatization of intermediate **III**, generated intermediate **IV** from which the cyclization cascade for the construction of pyrazinone-fused pyridines continued. This simple procedure, which included only one purification, could be applicable to a broad scope of Ugi starting materials providing the final products in moderate to good yields.

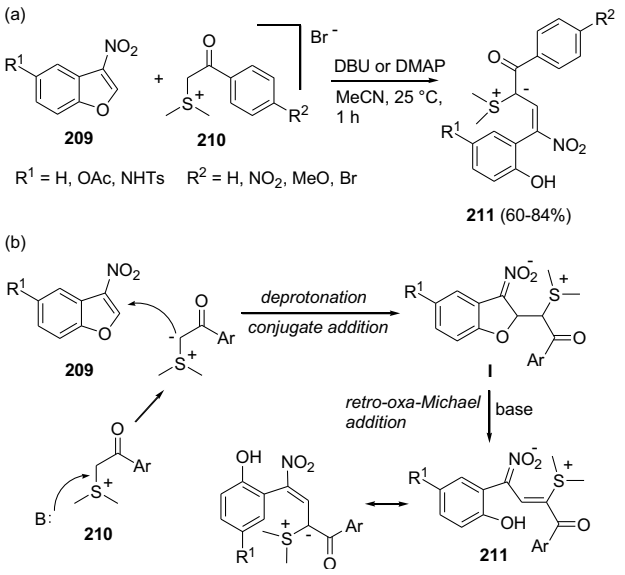
The ring opening approach based on a retro-*oxa*-Michael addition reaction following the direct conjugate addition was also exploited by Osipov et al. for the synthesis of [1, 2, 4]triazolo[1,5-a]pyrimidines **208** containing a (2-hydroxynaphthalen-1-yl) methyl group at position 6 (Scheme 41a) [69]. The reagents, chromenes **206** and aminotriazole **207**, were reacted in either refluxing acetonitrile or acetic acid for several hours. Following the initial conjugate addition on **206** by the



SCHEME 41 | (a) Synthesis of [1, 2, 4]triazolo[1,5-a]pyrimidines **208**. (b) Proposed mechanism.

bisnucleophilic 3-amino-1,2,4-triazole, intermediate **I** undergoes the expected retro-*oxa*-Michael addition, and consequent cleavage of the pyran ring, to form intermediate **II** which cyclizes following the attack of the amino group to the carbonyl group (Scheme 41b).

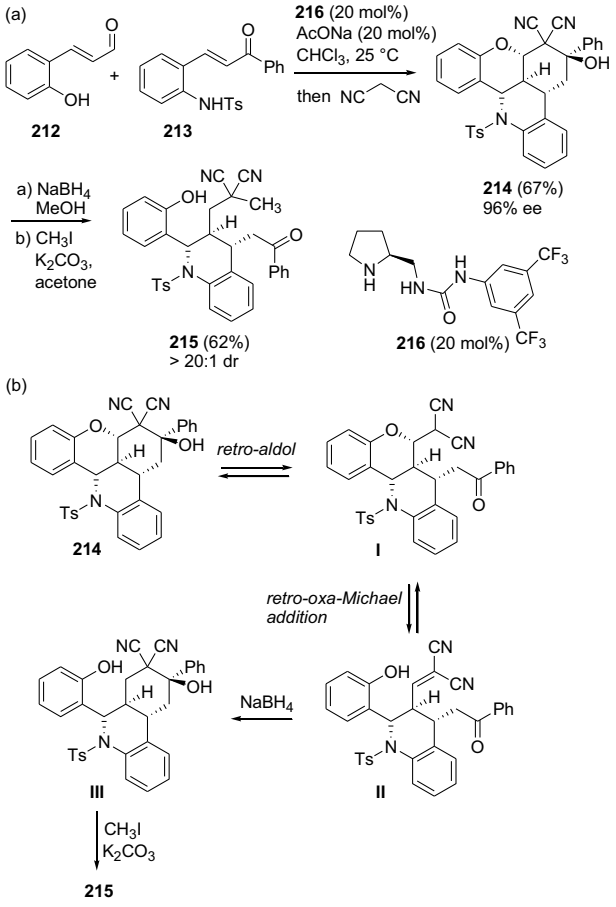
In continuation of their work on the reactivity of push-pull oxygen-containing heterocycles (benzofurans and 4*H*-chromenes) with nucleophiles, Osipov's group studied the reaction of carbonyl-stabilized sulfur ylides (from sulfonium salts **210** with 3-nitrobenzofurans **209** (Scheme 42a) for the synthesis of (E)-1-aryl-2-(dimethylsulfonio)-4-nitro-1-oxobut-3-en-2-ides **211** [70]. Also in this case, the heterocycle ring opening was possible thanks to a retro-*oxa*-Michael addition consequent



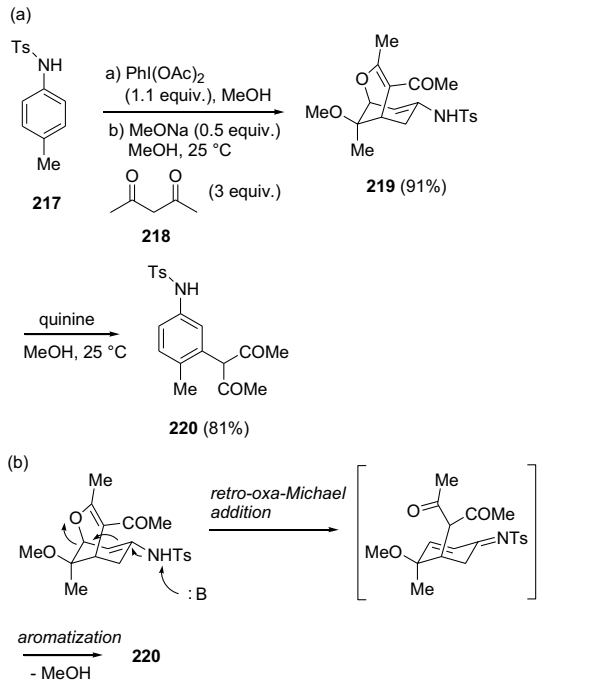
SCHEME 42 | (a) Synthesis of (*E*)-1-aryl-2-(dimethylsulfonio)-4-nitro-1-oxobut-3-en-2-ides **211**. (b) Proposed mechanism.

to the nucleophilic addition of the sulfur ylide to the activated double bond (Scheme 42b). While in other cases, the carbonyl functionality was already installed on the substrate (e.g., in chromen-4-ones, 4H-chromene-3-carbaldehydes, etc.) in this process, it is the nucleophile that brings along an aryl ketone moiety which allows the retro-*oxa*-Michael to occur. This process was best carried out in acetonitrile at room temperature with DBU or 4-(dimethylamino)pyridine (DMAP) as the base, leading to the final products in 60%–84% yield.

Many polycyclic chromane architectures exhibiting high molecular and stereogenic complexity were obtained in good yields (up to 99%) and excellent enantioselectivities (most with ≥95% ee) in the one-pot step-wise reaction of 2-hydroxycinnamaldehyde **212**, 2-aminochalcone derivative **213** and malononitrile in the presence of **216** as chiral secondary amine catalysts to form **214** (Scheme 43a) [71]. During their studies on the further elaboration of this compound, Wang et al. [71] discovered that it could be converted into structurally diverse tetrahydroquinoline derivatives such as **215** (Scheme 43b) by a very interesting retro-reaction mechanism which included a retro-*oxa*-Michael addition step in the presence of $NaBH_4$ in MeOH. A first retro-aldol reaction in **214** to form intermediate **I** was followed by the retro-*oxa*-Michael addition accompanied by reduction of the olefin group of **II**. Further aldol-type cyclization and C-alkylation under basic conditions afforded the



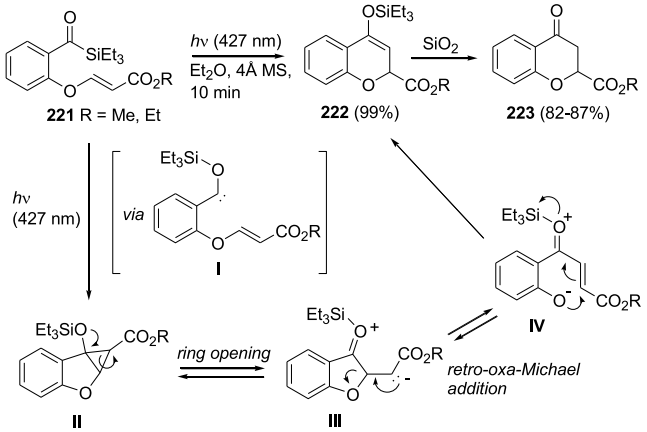
SCHEME 43 | (a) Synthesis of polycyclic chromane **214**. (b) Proposed mechanism.



SCHEME 44 | (a) Synthesis of meta carbon-functionalized aniline derivative **220**. (b) Proposed mechanism.

tetrahydroquinoline in good yield and high diastereomeric ratio.

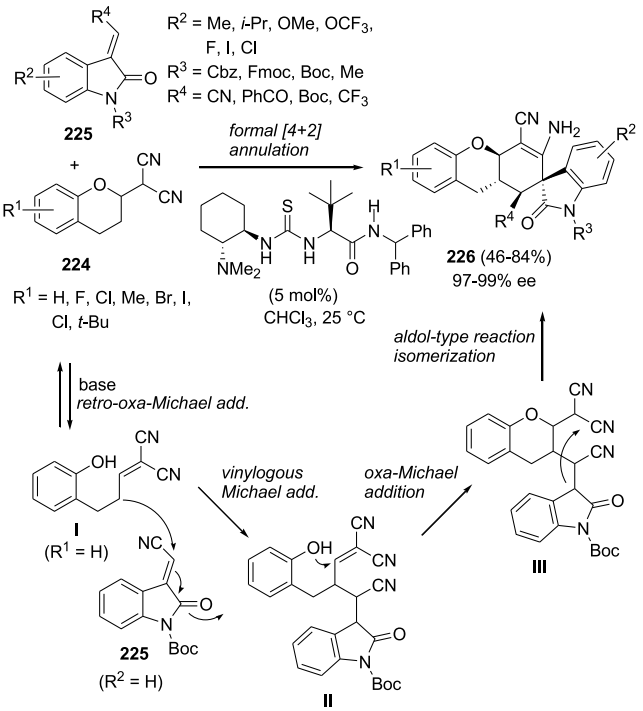
The retro-*oxa*-Michael addition of compound **219** (Scheme 44) was investigated to explore the possibility of converting bridged bicyclic compounds obtained from **217** into the corresponding meta carbon-functionalized aniline derivative **220** [72]. Both acids (TfOH, TsOH) and bases were used to promote the retro-*oxa*-Michael addition, but only quinine was an effective catalyst for both the ring opening and the next aromatization, providing *m*-substituted aniline **220** in 81% yield. The authors prepared many examples of substrates such as **217** from substituted anilines via an oxidative dearomatization and a domino Michael addition, but only the simplest example was subjected to this study by the authors as shown in Scheme 44.



SCHEME 45 | Cyclopropanation/retro-*oxa*-Michael/*oxa*-Michael cascade process to chromanones **223**.

During their studies on the [2 + 1]-cycloaddition of visible light induced singlet nucleophilic carbenes with tethered olefins to afford unique bicyclo[3.1.0]hexane and bicyclo [4.1.0]heptane scaffolds, Bunyamin et al. discovered an additional transformation involving a cyclopropanation/retro-*oxa*-Michael/*oxa*-Michael cascade process to afford, after hydrolysis, chromanones **223** in excellent yield (Scheme 45) [73]. Only two examples were reported by the authors, which involved acyl silanes **221** containing an electron deficient olefin. These quickly reacted under visible light irradiation (427 nm LED, 40 W) in diethyl ether observing a color change from bright yellow to colorless in only 10 min. Formation of silyl enol ether **222** is suggested to occur via a photochemical cascade reaction initiated by rapid cyclopropanation of carbene **I** with the proximal alkene, followed by ring opening that generates an enolate intermediate **III** that drives a retro-*oxa*-Michael reaction to afford a phenolate. This in turn undergoes Michael addition onto the activated acceptor producing **222**. Subsequent hydrolysis of silyl enol ethers **222** during silica-gel chromatography afforded chromanones **223**.

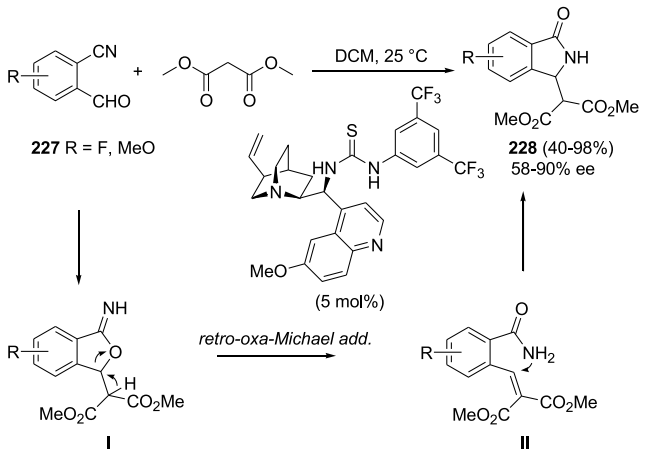
You and Liu exploited the propensity of 2-(chroman-2-yl)malononitrile moiety seen above to give a retro-*oxa*-Michael by E1cB mechanism in order to generate a vinylogous intermediate bearing two nucleophilic sites [74]. On these grounds, a novel annulation was designed and successfully applied to the asymmetric synthesis of polycyclic compounds **226** (Scheme 46) which contained both chromane and spirooxindole moieties. The products were obtained by reacting 2-(chroman-2-yl)malononitriles **224** with isatin derivatives **225** under the catalysis of a chiral bifunctional thiourea-tertiary amine (5 mol%) in chloroform, which provided a variety of products in good yields (up to 84%) and excellent enantioselectivities (>97% ee). The authors



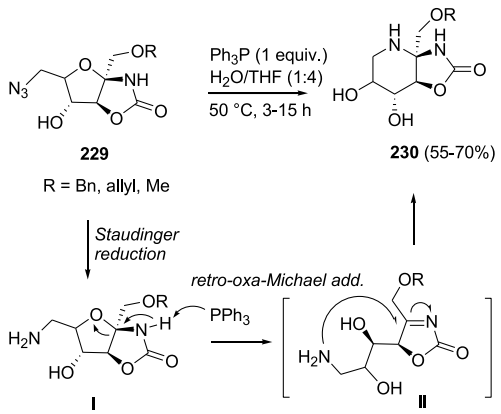
SCHEME 46 | The retro-*oxa*-Michael addition in the synthesis of polycyclic compounds **226**.

suggest that after the formation of **I** by E1cB elimination (the retro-*oxa*-Michael addition) under basic conditions, the next vinylogous Michael addition to isatin derivative **225** gives intermediate **II** with multiple nucleophilic and electrophilic sites. The recyclization of chromane to **III** is then induced by the newly generated stereocenter and is achieved by an irregular DKR. Then, the 3-position of the oxindole attacks one of CN group of the malononitrile substituent through an aldol-type reaction, followed by double bond isomerization to form the product. Other pathways would be possible, but the one leading to **226** is preferred under the reaction conditions.

Isoindolinones are interesting heterocyclic compounds because of their presence in many natural and bioactive products [75]. The ring opening/reconstruction strategy was exploited by More et al. [75] in the first asymmetric organocatalytic synthesis of 3-substituted isoindolinones **228** by reacting 2-cianobenzaldehydes **227** with dimethyl malonate (Scheme 47). After an aldol and cyclization reaction sequence leading to intermediate **I**, the next retro-*oxa*-Michael addition generates intermediate **II** which, by a cooperative action of the bifunctional thiourea catalyst, enantioselectively cyclizes through conjugate addition to produce **228** in good yield and enantiomeric excesses.



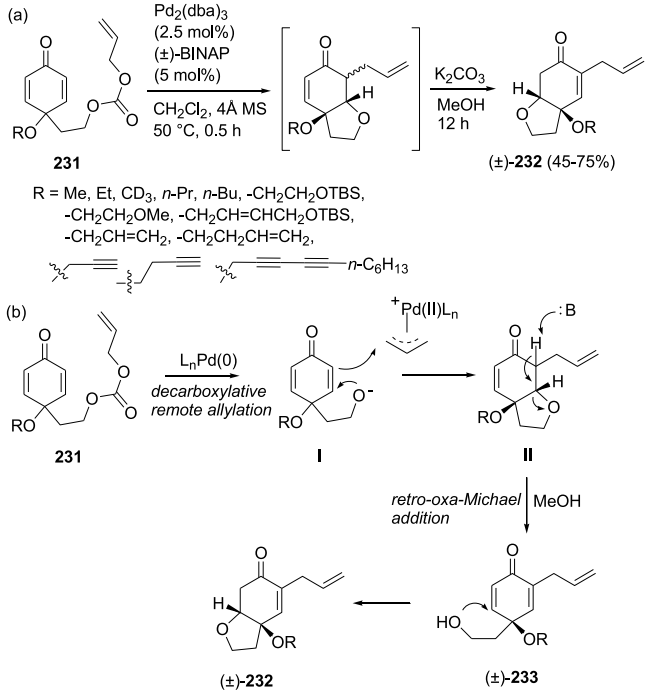
SCHEME 47 | The ring opening/reconstruction strategy in the synthesis of polycyclic compounds **228**.



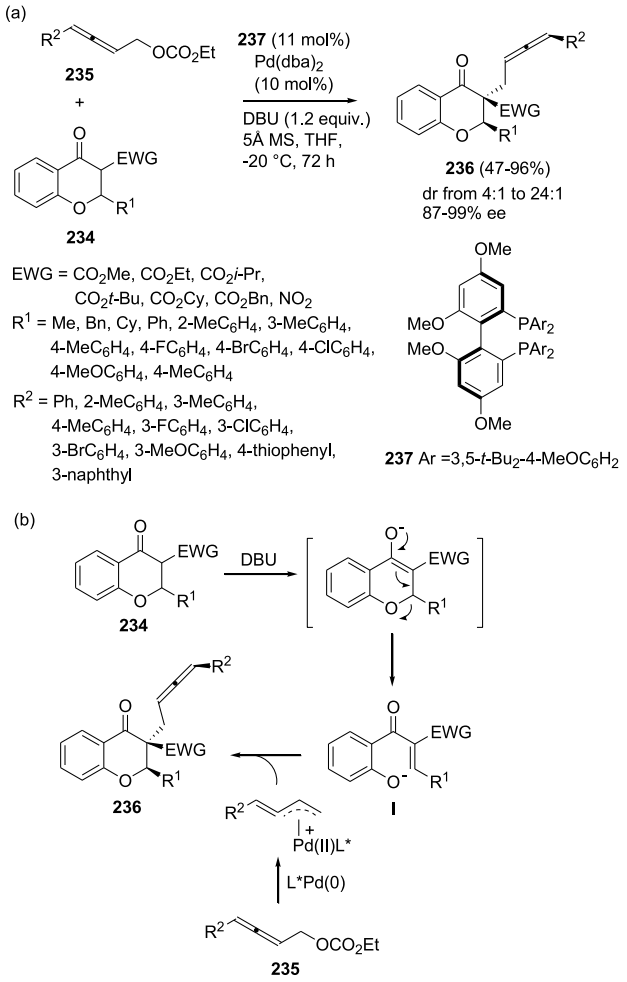
SCHEME 48 | Staudinger reduction of oxazolidin-2-ones **229**.

A retro-*oxa*-Michael addition-based ring opening/reconstruction process was serendipitously discovered by Domingues at al. during their studies on the Staudinger reduction of pentose- and ketohexose-derived oxazolidin-2-one sugars **229** (only the latter shown in Scheme 48 as examples) [76]. The authors suggest that following the Staudinger reduction of the azido into the amino group of **I**, a retro-*oxa*-Michael reaction leading to the imine intermediate **II** is followed by cyclization through a Michael addition of the amino group to the imine carbon atom to furnish iminosugars **230** which were assayed as inhibitors of a range of glycosidases. The retro-*oxa*-Michael reaction is supposed to be catalyzed by traces of base, such as triphenylphosphine or another amine residue. Interestingly, for the related oxazolidine-2-thione (OZT) azidosugars, the presence of sulfur disfavors the formation of the imine intermediate and terminates the reaction at the amino-OZT product.

A retro-*oxa*-Michael addition-based ring opening/reconstruction process was entailed during the synthesis of allyl-substituted cyclohexanone structures **232** (Scheme 49) found in some natural products such as kadsurin A, illicinone E, and bifidenone [77]. As for the mechanism (Scheme 49b), the authors suggest that both electrophilic π-allyl–Pd complex and the nucleophilic alkoxy anion **I** are generated in the Pd-catalyzed decarboxylation of allylcarbonate **231**. The intramolecular *oxa*-Michael addition of the alkoxy anion to the enone, followed by trapping of the in situ-generated enolate with π-allyl–Pd(II) complex, leads to the bicyclic enone **II** as a diastereomeric mixture. Then, upon *in situ* treatment with a base (K_2CO_3 in MeOH) the 1,3- migration occurs via a retro-*oxa*-Michael ring-opening reaction to afford cyclohexadienone **233** which subsequently undergoes intramolecular *oxa*-Michael addition on the less substituted enone functionality to give α-allyl enone **232** with exclusive *syn* selectivity. The reaction was extended to 4-alkyl



SCHEME 49 | (a) Synthesis of allyl-substituted cyclohexanone derivatives **232**. (b) Proposed mechanism.

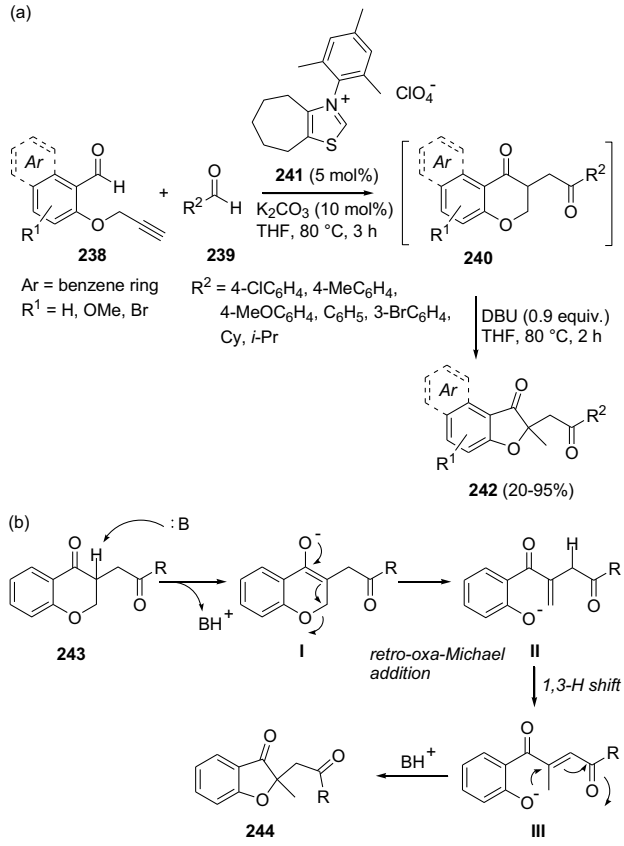


SCHEME 50 | (a) Enantio- and diastereoselective construction of substituted chiral allenes **236**. (b) Proposed mechanism.

substituted cyclohexadienones but the yields were much lower (15%–30%). The feasibility of this cascade process was demonstrated by a gram-scale reaction and further elaboration of the products.

By an analogous approach, the combination of the retro-*oxa*-Michael addition undergone by 4-chromanone derivatives **234** in the presence of a base and the formation of an electrophilic π-allyl–Pd complex generated from allenylic carbonates **235**, allowed for the enantio- and diastereoselective construction of substituted chiral allenes **236** bearing a nonadjacent stereogenic axis and two stereogenic centers (Scheme 50) [78]. The reaction, which featured a broad substrate scope, was best carried out with **237** as the chiral ligand for the palladium species in the presence of DBU as the base in THF. By carrying out the reaction at −20 °C, generally high diastereoselectivities and enantiomeric excesses (>95% ee) were achieved. The lowest diastereomeric ratios (4:1) were obtained when the EWG in **234** was a nitro group but in all the other cases (EWG = CO_2R) diastereomeric ratios were generally higher than 12:1.

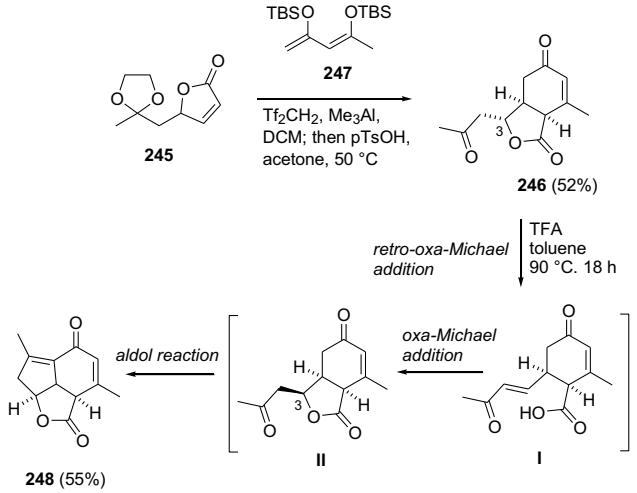
Franz et al. reported on an efficient organocatalytic one-pot cascade access to disubstituted benzofuran-3-(2*H*)-ones **242** starting from simple aldehyde precursors **238** and **239** (Scheme 51) [79]. This cascade process was based on the combination of



SCHEME 51 | (a) Organocatalytic cascade access to disubstituted benzofuran-3-(2H)-ones **242**. (b) Proposed mechanism.

an NHC-catalyzed hydroacylation/Stetter reaction cascade with a three-step Brønsted base-mediated rearrangement, the latter involving a ring opening/reconstruction by a retro-*oxa*-Michael addition. The reaction was best carried out in the presence of NHC precursor **241** and K_2CO_3 as a base in boiling THF providing intermediates **240** which were not isolated but instead treated with DBU to promote the retro-*oxa*-Michael as the first step of the ring contraction. This modular and atom-economical approach furnished the target compounds **242** in up to 95% yield. In the proposed mechanism (Scheme 51b), after the hydroacylation/Stetter reaction cascade (not shown here) which generates chroman-4-one **243**, in the presence of DBU a ring-opening by retro-*oxa*-Michael addition to form aryloxide **II** occurs, which is followed by a base-promoted 1,3-H shift to generate the conjugated internal double bond in **III**. *Oxa*-Michael addition of the oxyanion **III** to the activated olefin finally results in the formation of 2,2-disubstituted benzofuranones **244** in a 5-*exo*-*trig* ring closing fashion.

Ueda et al. exploited the reversibility of the *oxa*-Michael addition to change the relative configuration at the C3 position in compound **246** (Scheme 52), a key intermediate in their synthetic studies toward yonarolide, a natural compound extracted from soft corals of the genus *Sinuralia* which contains a tricyclic core such as **248** [80]. The construction of the dihydroisobenzofuran-1,5-dione **246** was realized via the Lewis acid-catalyzed Diels–Alder reaction between dienophile **245** and diene **247**, followed by ketal cleavage. This process led to intermediate **246** with the wrong relative configuration in 52% yield. Attempts at obtaining both

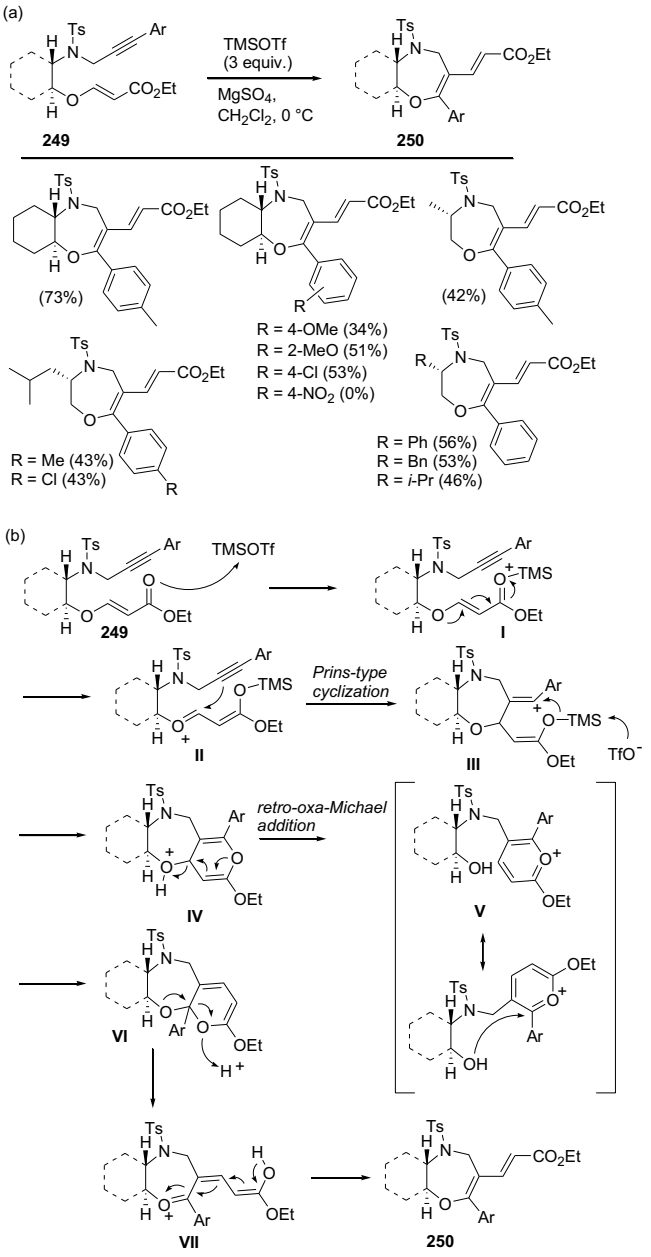


SCHEME 52 | A synthetic study towards yonarolide.

epimerization at C3 via retro-*oxa*-Michael/*oxa*-Michael reaction followed by intramolecular aldol reaction under several basic conditions (*t*-BuOK, Et_3N, DBU, K_2CO_3) were unsuccessful, but treatment of **246** with trifluoroacetic acid in toluene instead produced the desired compound **248** in 55% yield with the correct relative stereochemistry.

A serendipitous synthesis of 1,4-oxazepine dienes **250** was based on the TMSOTf-mediated reaction of alkynyl vinylogous carbonates **249** in CH_2Cl_2 which underwent an intramolecular Prins-type cyclization followed by a retro-*oxa*-Michael and, eventually, cycloisomerization upon treatment with the Lewis acid to give products **250** with *E* double bond geometry in generally modest yields (Scheme 53a) [81]. According to the authors, the alkynyl vinylogous carbonate **249** (Scheme 53b) upon treatment with TMSOTf leads to the formation of oxonium ion **II**. The tethered alkyne traps this oxonium ion in a Prins-type mode to give vinyl carbocation **III** which reacts intramolecularly to give the six member-fused bicyclic 1,4-oxazepane intermediate **IV**. Protonation (or silylation) of the seven-membered ring oxygen atom triggers the retro-*oxa*-Michael reaction which furnishes intermediate **V**. Eventually, trapping the oxonium ion in **V** with the oxygen of the alcohol moiety and next ring opening leads to the formation of 1,4-oxazepine products **250** in which the ethyl acrylate moiety has undergone migration.

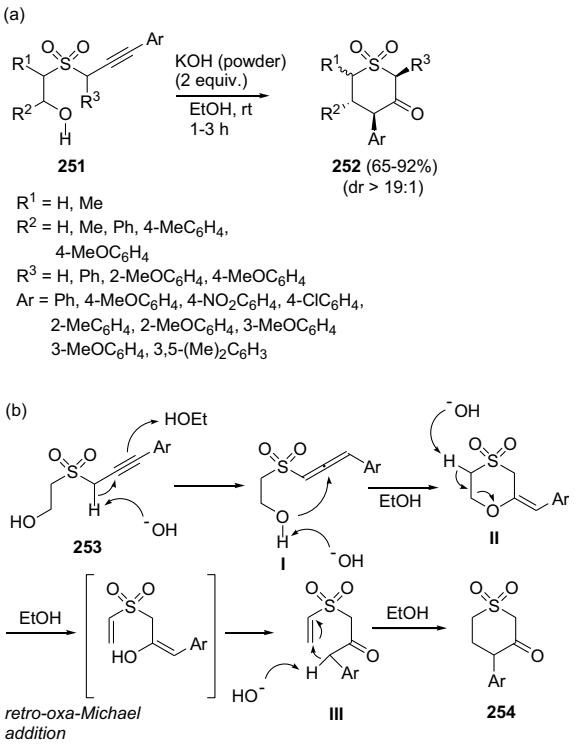
Another serendipitous synthesis of heterocyclic compounds, in which the retro-*oxa*-Michael step played a key role, was that of cyclic β-ketosulfones **252** (Scheme 54) which was observed when sulfone-tethered arylalkynols **251** were reacted with a base such as KOH in ethanol [82]. The reaction provided a varied of β-ketosulfones **252** in moderate to excellent yield and high diastereoselectivity. The approach was extended to acrylate-tethered alkynolsulfones (not shown here), which gave access to various spirocyclic β-ketosulfones. Mechanistically (Scheme 54b), sulfone-tethered alkynol **253** generates allene intermediate **I** by isomerization of the alkyne moiety upon treatment with a base. Intermediate **I** undergoes intramolecular hydroalkoxylation forming vinyl ether **II**. The deprotonation/retro-*oxa*-Michael reaction of sulfone **II** then leads to vinyl sulfone intermediate



SCHEME 53 | (a) Serendipitous synthesis of 1,4-oxazepine dienes **250**. (b) Proposed mechanism.

III (which could be isolated) which by an intramolecular Michael addition yields cyclic β-ketosulfone **254**.

In a recent paper, Jiang et al. [83] reported one of the few examples of retro-*oxa*-Michael undergone by a suitable enamine as the precursor to generate an electrophilic species in a new example of organocatalytic domino reaction to construct optically pure polyfunctionalized cyclohexene-carbaldehydes **257** in good yield and excellent enantio- and diastereoselectivity (Scheme 55a). The reaction sequence consists of two intermolecular Michael reactions, one retro-*oxa*-Michael reaction and one intramolecular aldol condensation through the double use of the starting aldehyde (**255**) as both the Michael donor and precursor of acrolein (i.e., intermediate **II** in Scheme 55b). The authors suggest that enamine **I** forms first from the condensation of 3-(benzyloxy) propanal **255** and (*S*)-diphenylprolinol silyl ether **149**. Next,



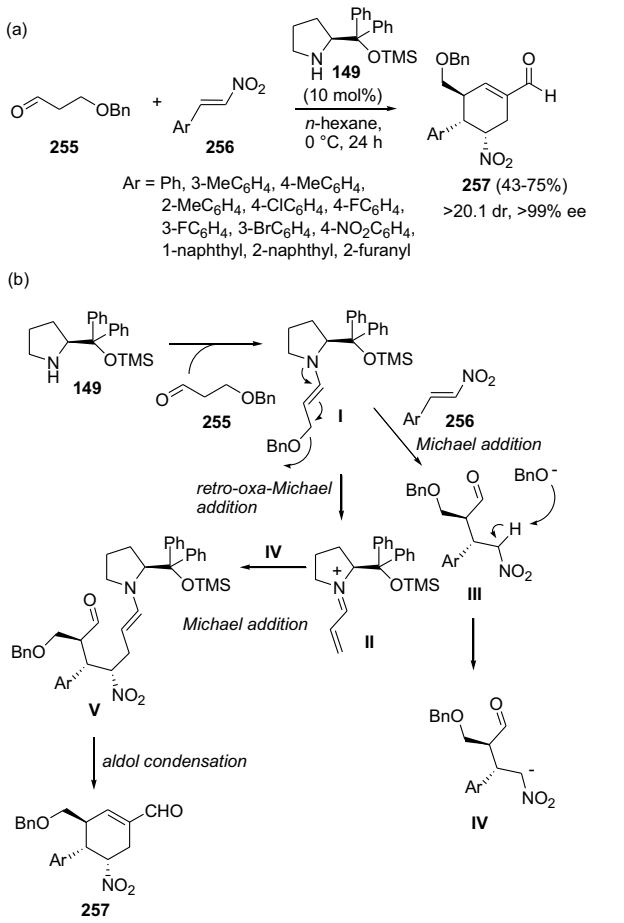
SCHEME 54 | (a) Serendipitous synthesis of heterocyclic β-ketosulfones **252**. (b) Proposed mechanism.

the Michael addition of intermediate **I** with β-nitroalkenes **256** affords Michael adduct **III**. Along this, through a retro-*oxa*-Michael addition, intermediate **I** decomposes into iminium ion **II** and the benzyloxy anion which deprotonated the carbon atom bearing the nitro group in **III** to form anion **IV**. The latter thus attacks iminium ion **II** and generates enamine intermediate **V**, which provides the desired trisubstituted cyclohexene-carbaldehyde **257** and regenerated the organocatalyst through an intramolecular aldol condensation.

The same metal-free approach to the synthesis of substituted indoles **57** with high double bond geometry control reported by Mandal et al. (Scheme 13), and which was based on a formal vinyl shift from a N to a C atom in the TfOH promoted cyclization of vinylogous amides **56** [37], was extended by the same authors to vinylogous esters **258** in pursuit of the expansion of the scope of the methodology (Scheme 56). The cyclization of vinylogous esters derived from *o*-alkynyl phenols provided the corresponding 3-alkenyl benzofurans **259** in excellent yields (87%–90%). Interestingly, the double bond geometry of these products was mostly *cis* (the lowest dr was 9:1) unlike the nitrogen analogs where the exclusive *trans* geometry of olefin was observed, as the high electronegativity of oxygen and the consequent less electron density at the C3 of benzofuran does not promote the *cis* to *trans* isomerism in the benzofuran products under acidic conditions.

3.2 | Synthesis of Natural Products

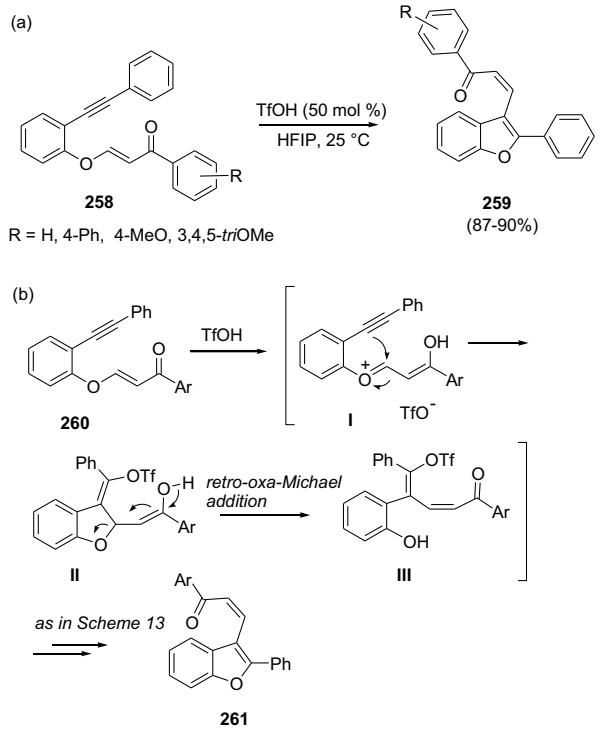
The ring opening/reconstruction strategy based on the retro-*oxa*-Michael addition was used by Han et al. to correct the



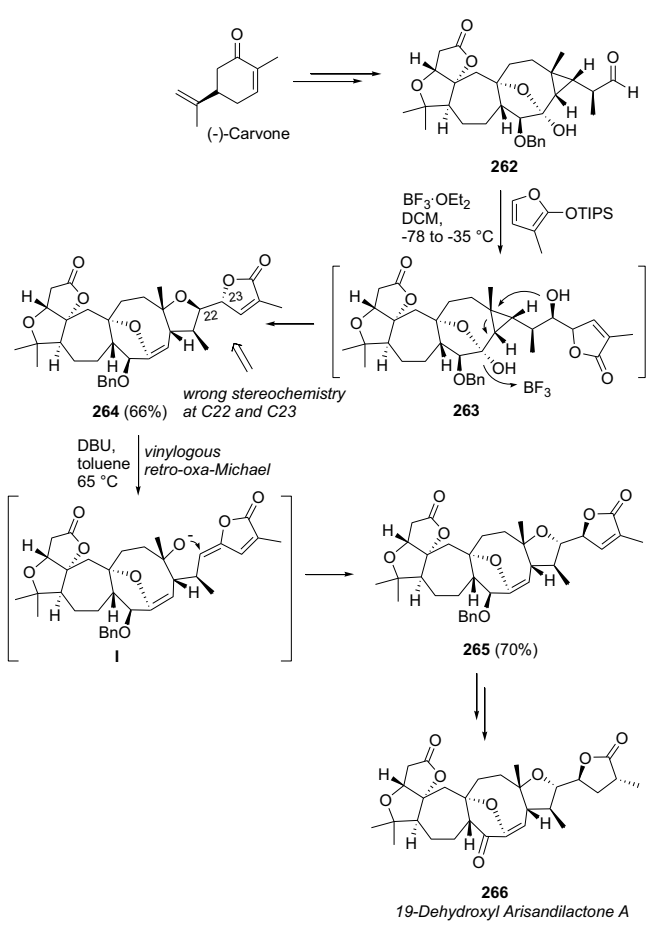
SCHEME 55 | (a) The retro-*oxa*-Michael of an enamine in the synthesis of trisubstituted cyclohexene-carbaldehyde **257**. (b) Proposed mechanism.

absolute stereochemistry at positions 22 and 23 of key intermediate **264** (Scheme 57) during their total synthesis of 19-dehydroxyl arisandilactone A **266**, a derivative of arisandilactone A isolated from *Schisandra chinensis* [84]. In the key step of the asymmetric synthesis, which started from (−)-carvone, coupling of intermediate **262** with triisopropyl-(3-methylfuran-2-yloxy)silane in the presence of a Lewis acid generated lactone **264** as a single diastereomer via a homo-Michael reaction undergone by intermediate **263**. Unfortunately, the latter process generated the wrong stereoisomer and for this reason **264** was treated with DBU in toluene at 65 °C, and, as a result, product **265** was obtained in 70% yield with inversion of the stereogenic centers at C22 and C23.

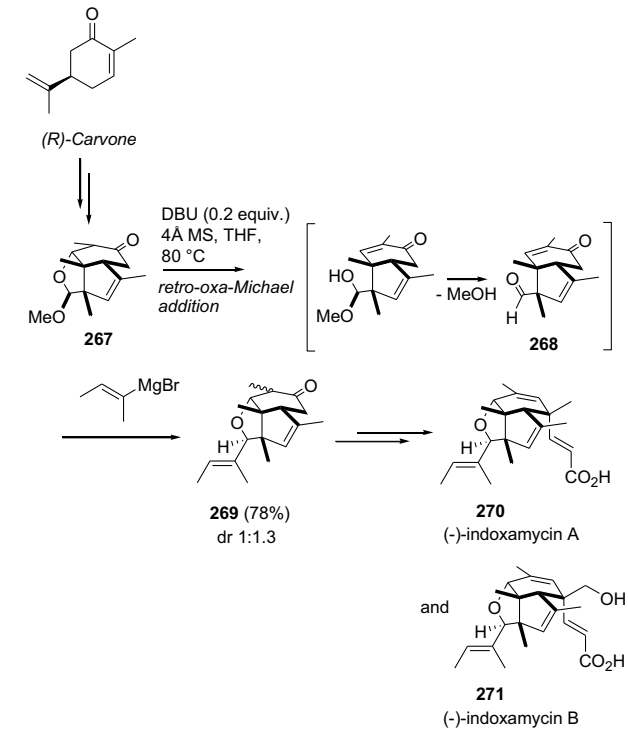
Indoxamycins A and B (Scheme 58), isolated from a saline culture group of marine-derived actinomyces, are a novel class of polyketide natural products, containing a highly congested [5.5.6] tricyclic cage-like carbon skeleton featuring six contiguous stereogenic centers [85]. The synthesis by Hu et al. started from (*R*)-carvone and through a Pauson–Khand reaction for the rapid construction of a basic scaffold bearing a quaternary carbon and a copper-catalyzed Michael addition for the introduction of another adjacent all-carbon quaternary stereocenter reached ketone intermediate **267** with a masked carbonyl group. To carry out the next nucleophilic addition step on the latter with (*E*)-2-butenyl-2-magnesium bromide, a retro-*oxa*-Michael addition was



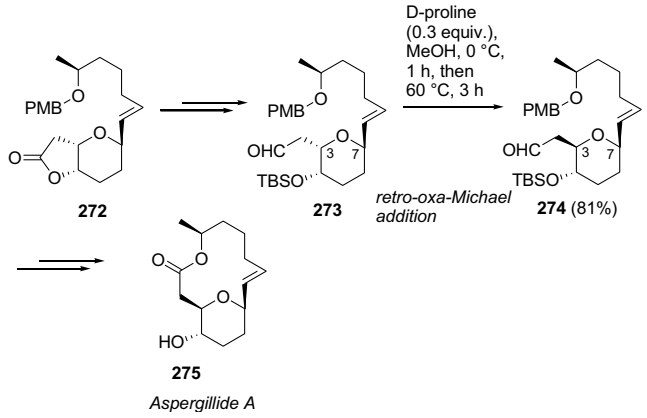
SCHEME 56 | (a) Synthesis of substituted indoles **259**. (b) Proposed mechanism.



SCHEME 57 | Synthesis of 19-dehydroxyl arisandilactone A.



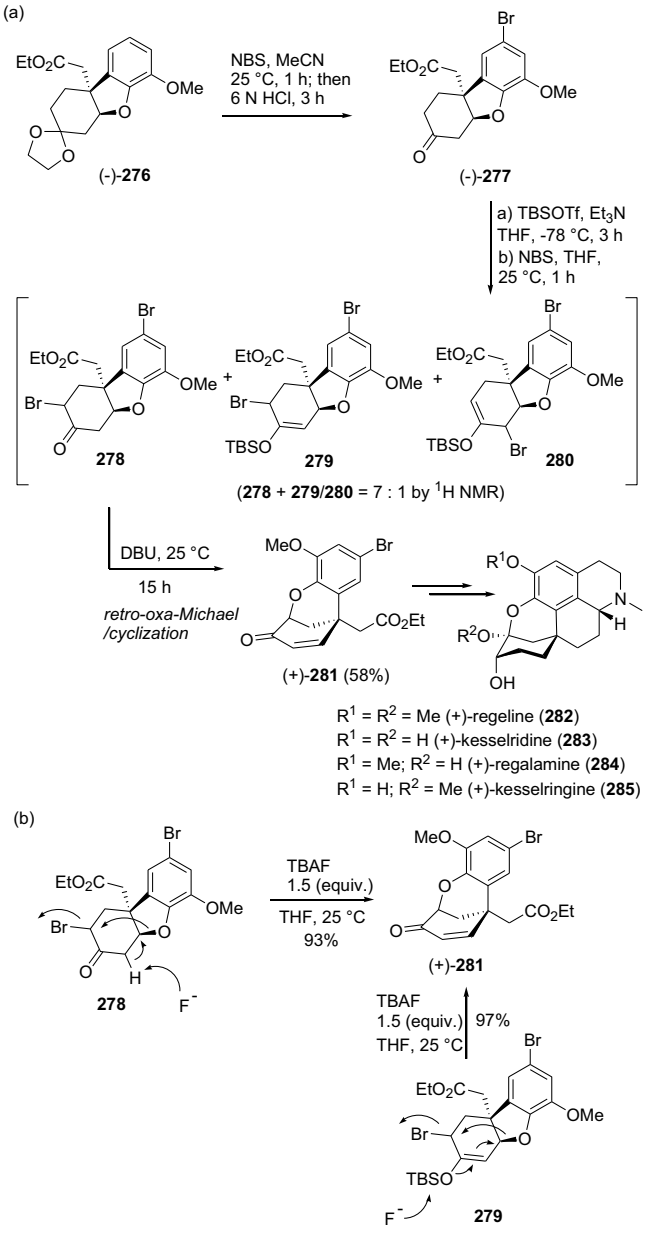
SCHEME 58 | Synthesis of (−)-indoxamycins A and B.



SCHEME 59 | Synthesis of aspergillide A.

exploited to generate aldehyde intermediate **268**. After extensive screening of bases (t-BuOK, NaOMe, LDA, Et_3N, DABCO, DBU), the authors found that **267** underwent retro-*oxa*-Michael reaction when exposed to DBU in the presence of 4 Å MS to afford an unstable aldehyde **268**. Fortunately, the treatment in situ of **268** with (*E*)-2-butenyl-2-magnesium bromide generated desired tricyclic product **269**, via a nucleophilic addition/*oxa*-Michael addition sequence, as a 1:1.3 diasteromeric mixture in 87% yield which was then used as the common intermediate for the synthesis of both (−)-indoxamycins A and B.

The ring opening/reconstruction protocol by a retro-*oxa*-Michael was used by Nagasawa and Kuwahara during the synthesis of aspergillide A, a 14-membered macrolide isolated from a bromine-modified 1/2PD (potato-dextrose) culture medium of



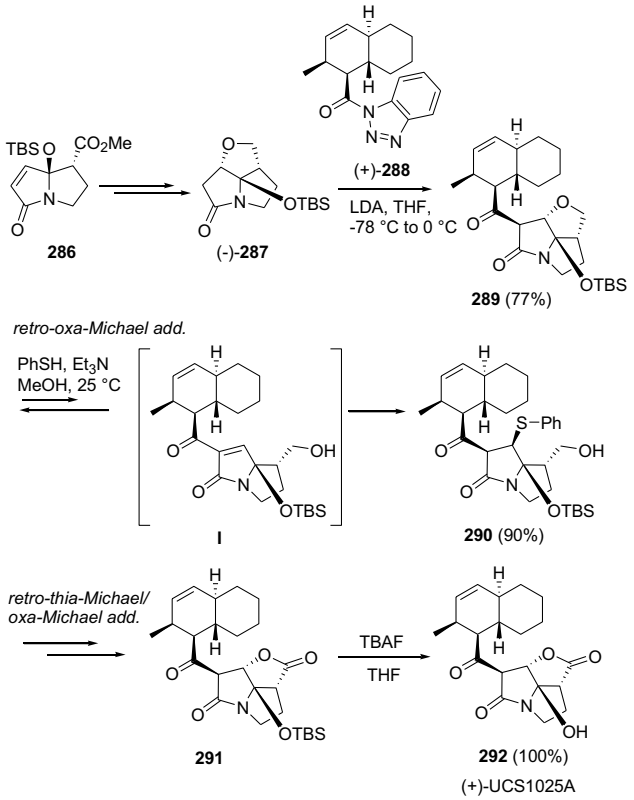
SCHEME 60 | (a) Syntheses of pentacyclic homoproaporphine alkaloids **282**-**285**. (b) The two retro-*oxa*-Michael pathways to **281**.

Aspergillus ostianus strain 01F313 [86]. Starting from a known precursor (**272**) (Scheme 59), the aldehyde **273** was synthesized, which set the stage for the key transformation in this synthesis, i.e., the epimerization at the C3 position of the 3,7-*trans*-substituted **273** to the corresponding 3,7-*cis* isomer **274**. This conversion was realized very efficiently by the Massi–Dondoni protocol using D-proline as the epimerization catalyst. Treatment of **273** with D-proline for 1 h at 0 °C and then for an additional 3 h at 60 °C gave a 95:5 epimeric mixture of **274** and **273** in 81% yield, favoring the desired 3,7-*cis* isomer which was then converted into aspergillide A **275**.

In the unified strategy for the enantioselective total syntheses of pentacyclic homoproaporphine alkaloids **282**-**285** (Scheme 60), isolated from the Eurasian species *Colchicum kesselringii*, a tandem process including a ring opening/reconstruction process based on a retro-*oxa*-Michael addition and an intramolecular nucleophilic substitution was the key step to generate the chiral oxabenzobicyclo[3.3.1]nonane core structure of these alkaloids [87]. In these syntheses, tricyclic benzofuran (−)-**276** was converted into aryl bromide **277** which was then subjected to treatment with *tert*-butyldimethylsilyl triflate to obtain a crude mixture directly reacted with NBS to obtain bromide ketone **278** along with allylic bromides **279** and **280**. Given the difficulty the authors encountered in separating the mixed products, and the instability of bromide **278**, as well, they directly added a base into the reaction mixture to convert the bromide mixture to the desired product (+)-**281**. Best base was DBU, which promoted the tandem reaction of retro-*oxa*-Michael addition/nucleophilic substitution to afford (+)-**281** in 58% yield. To improve the yield, allylic bromide **279** was converted into ketone **281** by desilylation with tetrabutylammonium fluoride (TBAF) which triggered the retro-*oxa*-Michael/nucleophilic substitution sequence (Scheme 60b) providing (+)-**281** in 97% yield. Interestingly, treatment of **278** with TBAF yielded (+)-**281** in high yield (93%), too. In this case, the fluoride anion acts as a base in extracting an α-proton from **278** to generate the oxy anion by a retro-*oxa*-Michael which ultimately forms **281** by the nucleophilic substitution of the bromide. With (+)-**281** prepared on a multigram scale, the authors concluded their synthesis of four different homoproaporphine alkaloids (**282**-**285**) plus (+)-regelinine (not shown) by inversion of configuration of the carbinolic carbon atom.

UCS1025A **292**, isolated from the fermentation broth of the *Acremonium* sp. KY4917 fungus, has been shown to possess antiproliferative activity against human cancer cell lines by inhibition of the telomerase enzyme [88]. In the course of their total synthesis of **292** (Scheme 61), which started from pyrrolizidinone **286**, Sano et al. [89] had the necessity to oxidize the alcohol functionality to a carboxylate group in intermediate **I** in order to obtain the right nucleophile for the subsequent *oxa*-Michael addition which would provide their target compound. Unfortunately, the retro-*oxa*-Michael/*oxa*-Michael equilibrium involving **287** and intermediate **I** was shifted toward the former and for this reason the retro-*oxa*-Michael intermediate produced by treating **287** with Et_3N as the base was trapped by thiophenol to form **290** in 95% yield. After elaboration of the alcohol functionality, a retro-*thia*-Michael addition set the stage for the *oxa*-Michael reaction which, after removal of the OH protecting group, afforded the target compound.

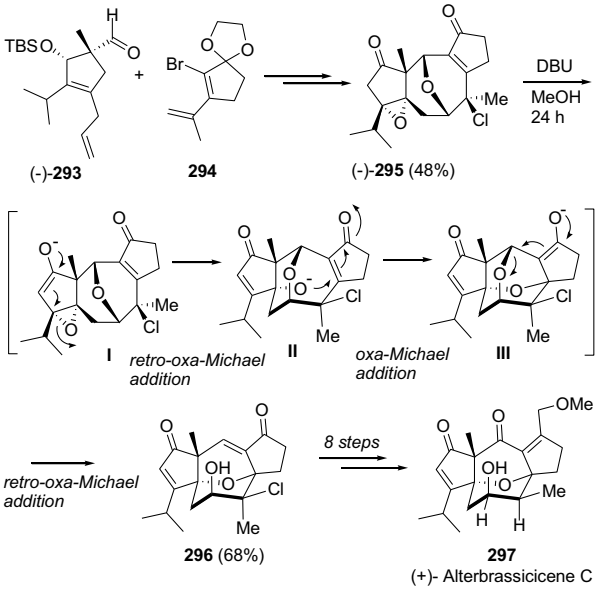
The ring opening/reconstruction by a retro-*oxa*-Michael/*oxa*-Michael strategy was fundamental in the total synthesis of (+)-alterbrassicicene C **297**, a novel fusicoccane diterpenoid from the fungal plant pathogen *Alternaria brassicicola* [90]. The (+)-alterbrassicicene C structural core **296** was in fact synthesized by Sims et al. (Scheme 62) through a DBU promoted retro-*oxa*-Michael undergone by key intermediate **295**, in turn prepared from precursors **293** and **294** in several steps. Treatment of epoxide **295** with DBU in methanol initiated a cascade that involved β-eliminative epoxide opening (the first retro-*oxa*-Michael) to form intermediate **II** which, by a trans-annular *oxa*-Michael addition, formed intermediate **III**. Completion of the process occurred via a β-eliminative opening of bis-oxa-adamantane intermediate **III** (the second retro-*oxa*-Michael) to furnish **296**, which possesses the core 5/6/6/5 ring system of **297** and was eight steps away from



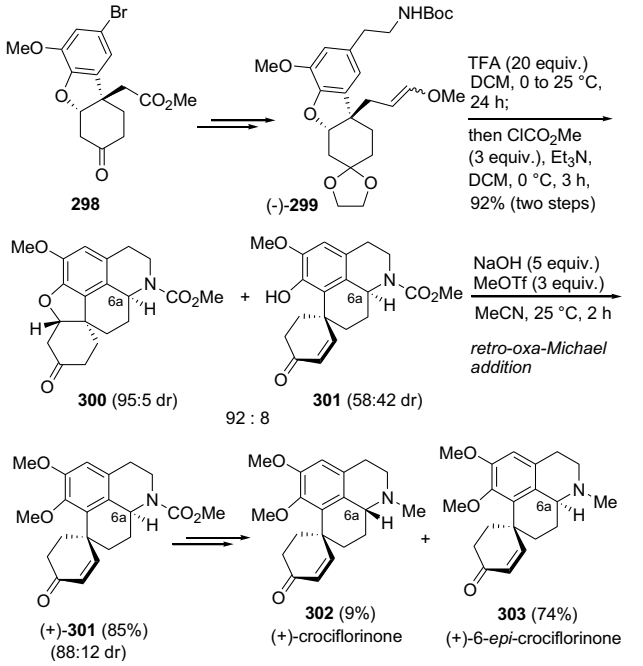
SCHEME 61 | Synthesis of UCS1025A **292**.

the latter. In total, six C—C and C—O bonds were either broken or formed during this *oxa*-Michael/retro-*oxa*-Michael cascade.

Tetracyclic homoproaporphine alkaloids are a subset of isoquinoline alkaloids bearing a tetrahydroisoquinoline fused spiro skeleton. The first asymmetric total synthesis of tetracyclic homoproaporphine alkaloid (+)-crociflorinone **302**, alongside its C6a epimer (+)-6a-*epi*-crociflorinone **303** (Scheme 63) was achieved by Yang et al. [91] starting from chiral tricyclic



SCHEME 62 | Synthesis of (+)-alterbrassicicene C.



SCHEME 63 | Synthesis of tetracyclic homoproaporphine alkaloid (+)-crociflorinone.

cyclohexanone **298** containing a quaternary carbon center as the starting material and by a strategy involving Wittig reaction and Pictet–Spengler cyclization as the key steps to construct the chiral pentacyclic skeleton **300** in mixture with a small amount of tetracyclic compound **301** possessing the spiro skeleton of the natural compounds. The conversion of pentacyclic compound **300** into (+)-**301** was performed via a tandem retro-*oxa*-Michael reaction/methylation process in the presence of NaOH as a base, which led to the pure spiro compound in 85% yield as an 88:12 epimeric mixture at C6a. Late elaboration of this mixture provided the two natural compounds (+)-crociflorinone **302** and (+)-6a-*epi*-crociflorinone **303** in 9% and 74% yield respectively, which allowed the authors to definitely demonstrate the absolute configuration of the two products.

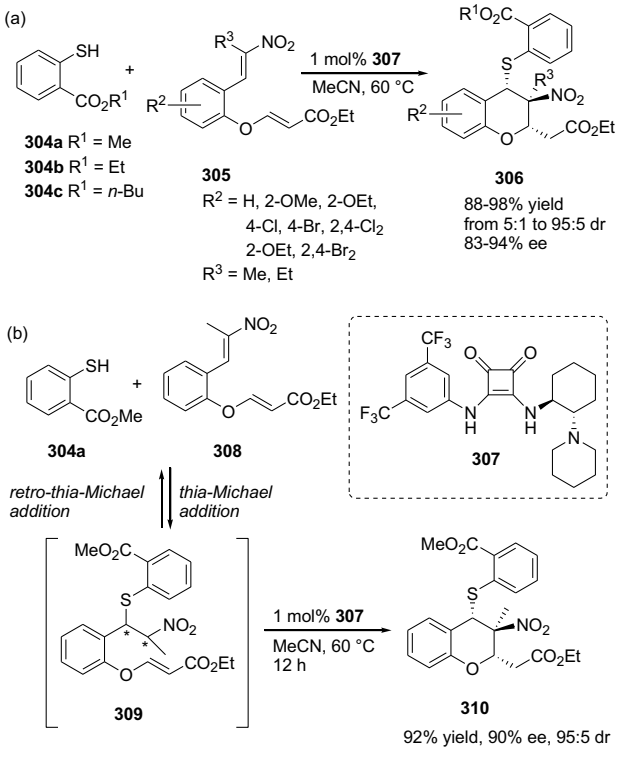
4 | Retro-Thia-Michael Addition Reaction

The reversibility of the *thia*-Michael reaction has been demonstrated for small molecules and is generally promoted by base and/or elevated temperatures. From a series of studies, nicely summarized by Berne et al. [8], it resulted that the *thia*-Michael equilibrium is controlled by the α-EWG group, the "stimulus" used to activate the retro-*thia*-Michael (i.e., temperature or pH), and to a lesser extent a β−carbon substituents if present. So, the increase of the pH value or the presence of a base in the reaction medium favors the retro-*thia*-Michael addition, even if heating is the most common way to promote the reaction. The occurrence of the *thia*-Michael equilibrium allows for the possibility to use this reaction in dynamic exchange chemistry, by which, under appropriate conditions, the *thia*-Michael adduct dissociates and the free thiol so generated can react with another acceptor present in the system [8]. This tactic has been widely employed in material chemistry for, e.g., covalent adaptable networks (CAN) [8], in bioconjugation and cargo release

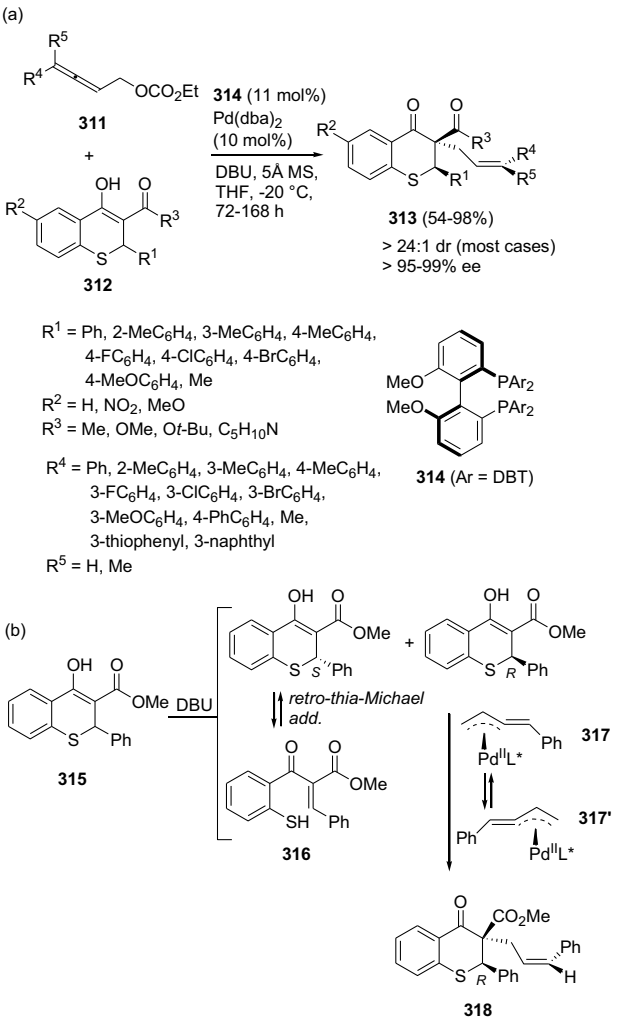
[14–17], but it has found applications in classical organic chemistry, too. In the period covered by this review, the *thia*-Michael addition/retro-*thia*-Michael addition strategy has been used in the synthesis and/or transformation of carbo- and heterocycles, as well as for dynamic kinetic resolutions. A strategy based on the base-induced retro-Michael-type dehydrosulfinylation of β-sulfonyl carbonyl compounds to produce the corresponding α,β-unsaturated carbonyls has been used for the same purpose.

4.1 | Synthesis and Transformation of Carbo- and Heterocycles

Chroman is a heterocyclic skeleton found in a wide variety of natural products and synthetic bioactive compounds [92]. Yang et al. developed an efficient squaramide-catalyzed asymmetric cascade *thia*-Michael/Michael addition of thiosalicylates with nitroalkene enoates for the synthesis of chiral chromans **306** (Scheme 64a) with three contiguous stereocenters, including one quaternary center, with high diastereoselectivity and enantioselectivity (up to 95:5 dr, 94% ee) [92]. This organocatalytic cascade reaction was best carried out on substrates **304** and **305** with 1 mol% of squaramide **307**, providing the products in high yield. In the course of their investigations, the authors discovered that the high diastereomeric and enantiomeric ratios were due to a DKR involving a *thia*-Michael/retro-*thia*-Michael equilibrium as the racemization step of intermediate **309** before the final intramolecular Michael addition as the irreversible, final step. The authors prepared and isolated intermediate **309** as both *syn* and *anti* diastereomer in 93% and 49% ee, respectively, and as racemate as well, and found that subjecting these four *thia*-Michael adducts to the reaction conditions (MeCN, 60 °C, catalyst) the very same results were obtained in terms of both yield (92%–96%), dr (94:6-95:5) and ee (90%–91%) (Scheme 64b). The practical usefulness of this approach was demonstrated by a gram-scale preparation of product **310** (2.08 g) in high yield, dr, and ee. Also, the scope was evaluated for this cascade process as summarized in Scheme 64a.

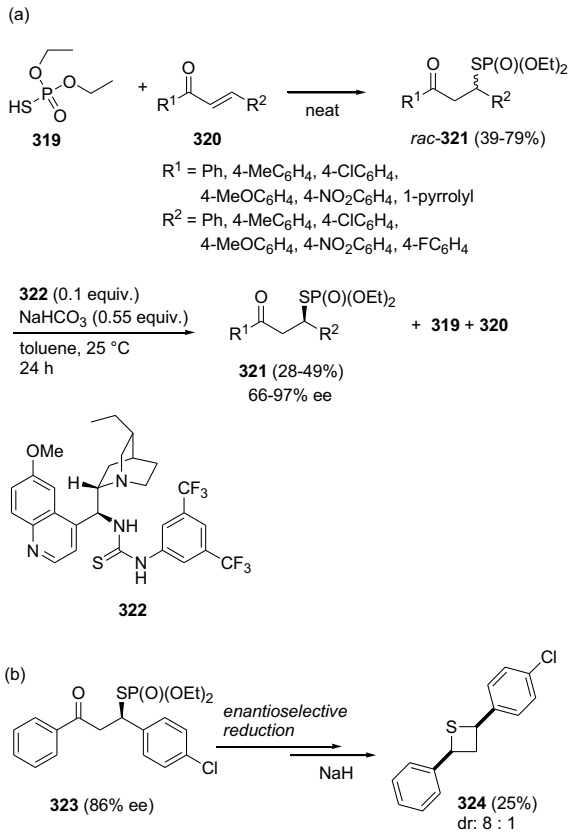


SCHEME 64 | (a) Cascade reaction for the synthesis of chiral chromans **306**. (b) Proposed mechanism.



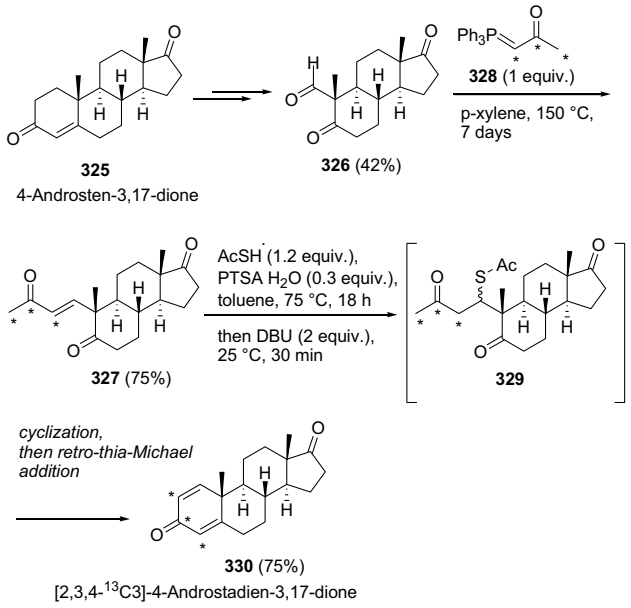
SCHEME 65 | (a) Synthesis of enantioenriched, multiple-substituted thiochromanone derivatives **313**. (b) Proposed mechanism.

The reversibility of the intramolecular *thia*-Michael addition in 4-thio-chromanone derivatives **312** (Scheme 65a) in the presence of a base was exploited by Liu et al. for a DKR carried out by reacting **312** with allenes in the presence of a chiral palladium complex [93]. This was possible as the rate of the racemization process via retro-*thia*-Michael addition was faster than the rate of the next allenylic alkylation (Scheme 65b). Thus, through the combination of the retro-*thia*-Michael addition under basic conditions and the palladium-catalyzed allenylic alkylation, the synthesis of enantioenriched multiple substituted thiochromanone derivatives **313**, containing two stereogenic centers and a stereogenic axis was realized, obtaining products in generally high yields, with up to 49:1 dr and >99% ee. The reaction was best carried out with axially chiral bisphosphine ligand **314**, in the presence of DBU as the base, and THF as the solvent. With this ligand, the *R* enantiomer generated during the racemization



SCHEME 66 | (a) Preparation of enantioenriched *O*,*O*'-diethyl *S*-(3-oxo-1,3-diphenylpropyl) phosphorothioates **321** and (b) chiral 2,4-diarylthietanes **324**.

process reacted faster with the π-allylpalladium complex **317**, which underwent nucleophilic attack from the back side of the terminal carbon atom to give the chiral products. The reaction showed great functional group tolerance, as shown in Scheme 65a.

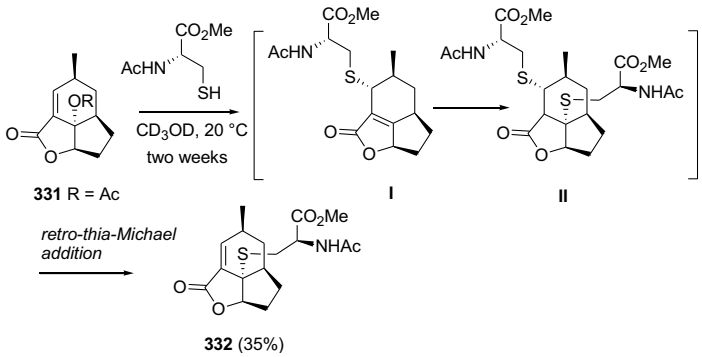


SCHEME 67 | Synthesis of [2,3,4-^{13}C3]-1,4-androstadien-3,17-dione **330**.

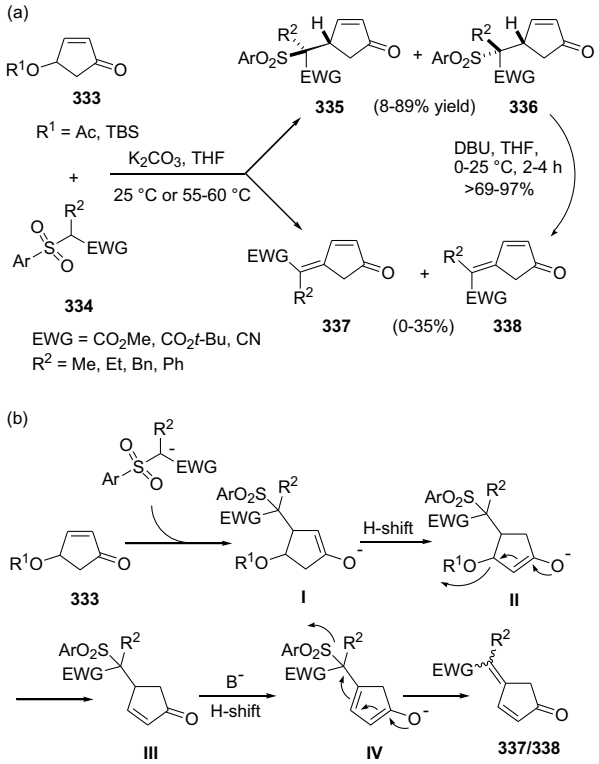
The enantioselective retro-*thia*-Michael addition of racemic Michael adducts **321** in the presence of a catalytic amount of bifunctional thiourea catalyst in aqueous biphasic system allowed Bacsó et al. [94] to achieve the kinetic resolution of such substrates and thus the preparation of enantioenriched *O*,*O*'-diethyl *S*-(3-oxo-1,3-diphenylpropyl) phosphorothioates **321** in 28%–49% yield and 66%–97% ee (Scheme 66a). Dialkylphosphorothioic acids such as **319** are unique sulfur nucleophiles that can be used as safer alternatives of H_2S in organic synthesis. In this work, the authors reacted diethylphosphorothioic acid **319** with chalcone derivatives **320** without any solvent, which spontaneously and rapidly gave racemic Michael adducts (±)-**321** at room temperature. The subsequent kinetic resolution provided products with enantiomeric excesses proportional to the catalyst loading. The authors assumed that Michael adducts **321** underwent a stoichiometric retro-*thia*-Michael reaction by the bifunctional thiourea and the released phosphorothioic acid **319** formed a catalytically inactive salt with **322**. To turn the reaction into catalytic, the authors envisioned a biphasic reaction system in which the retro-Michael reaction occurred in the organic phase, and the catalyst was regenerated from its salt in the aqueous phase by an inorganic base, thus liberating the catalyst from its phosphorothioic salt without impairing the retro-Michael procedure. The enantioenriched products obtained were then used for the synthesis of chiral 2,4-diarylthietanes **324** (both enantiomers of the 1,3-*cis* and 1,3-*trans* isomers), an example of which is reported in Scheme 66b.

For the detection and quantification of steroidal residues in various biological materials, the synthesis of [2,3,4-^{13}C3]-1,4-androstadien-3,17-dione **330** was carried out by Berthonneau et al. by a route from 4-androsten-3,17-dione **325** (Scheme 67) which included the conversion of the latter into key aldehyde intermediate **326** using a six-step sequence optimized to produce 40 mmol batches in 42% overall yield [95]. The final stage of the synthesis was the reconstruction of the A ring. This was realized through a Wittig reaction with the 1-triphenylphosphoranylidene-^{13}C3-2-propanone **328** to generate ^{13}C-labeled intermediate **327** in 75% yield. The challenge was now to develop a ring closing ketolization of the (*E*)-enone **327** under reaction conditions enabling the isomerization of the (*E*)-carbon−carbon double bond into the (*Z*)-isomer to furnish the target ^{13}C3-labeled product in a single step. As a solution, the authors found that intramolecular condensation assisted by thioacetic acid via a *thia*-Michael addition/retro-*thia*-Michael reaction sequence provided the target, ^{13}C-labeled, 1,4-androstadien-3,17-dione **330**. The *thia*-Michael adduct **329** underwent cyclization and the resulting intermediate (not shown) was then treated with an excess of DBU to promote the retro-*thia*-Michael reaction. Following this one-pot, three-step process, the targeted compound **330** was obtained in a good yield (75%).

In their effort to expand the chemical diversity of the galiellalactonoids, in particular of galiellalactone **331** (Scheme 68), a fungal secondary metabolite that has been shown to inhibit the STAT3 pathway [96], Escobar et al. discovered that by treating **331** with *N*-acetyl cysteine methyl ester in deuteromethanol at 20 °C an initial allylic substitution took place to form in a few hours, a new Michael acceptor (**I**). This underwent conjugate addition of a second equivalent of the cysteine nucleophile to restore, after a retro-*thia*-Michael reaction, the original galiellalactone system with a double bond between C-2a and C-3, but with a new substituent at C-7b (compound **332**). This second process was quite



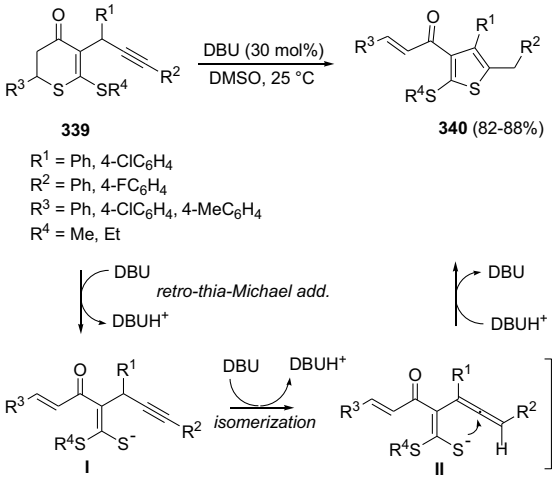
SCHEME 68 | Expanding the chemical diversity of galiellalactonoids.



SCHEME 69 | (a) Synthesis of terminally disubstituted alkylidene cyclopent-2-en-4-ones **337** and **338**. (b) Proposed mechanism.

slow, lasting 2 weeks, and not high-yielding. This process was successfully extended by the authors to other nucleophiles different from thiols (N and O nucleophiles).

The base-induced retro-Michael-type dehydrosulfinylation of β-sulfonyl carbonyl compounds strategy to produce the corresponding α,β-unsaturated carbonyls, was used by Trifonov et al. for the synthesis of terminally disubstituted electron-poor alkylidene cyclopent-2-en-4-ones **337** and **338** (Scheme 69), in view of the potential value of 11-*cis*-locked 5-membered cyclic retinals for chemotherapy of retinal degenerative disorders [97]. Secondary sulfones **334**, activated by electron-withdrawing groups at the adjacent carbon atom, after deprotonation by K_2CO_3 gave conjugate addition to 4-acyloxy- and 4-*tert*-butyldimethylsilyloxycyclopent-2-en-1-ones **333** providing—directly (albeit in low yield) or after a separate dehydrosulfinylation step undergone by diastereomeric intermediates **335** and **336**—



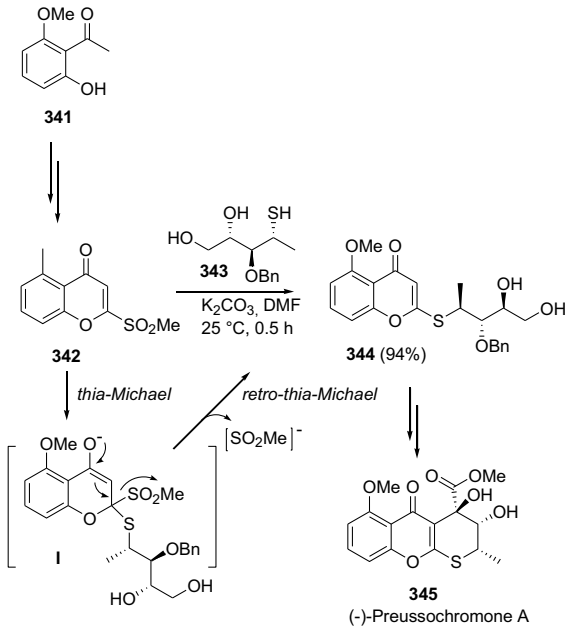
SCHEME 70 | Unexpected rearrangement of 5-propargyl-2*H*-thiopyran-4(3*H*)-ones **339**.

mixtures of alkylidene cyclopent-2-en-4-ones **337** and **338** which could be separated by chromatography. The reaction carried out in THF provided mainly intermediates **335** and **336** as variable diastereomeric mixtures in up to 89% yield, mixtures which were then treated with DBU in THF to trigger the Zaitsev-type retro-Michael vinylogous dehydrosulfinylation which yielded the target products in yields higher than 69%. Thermal exposure to silica gel worked equally well.

Tang et al. developed a route to densely functionalized thiophenes **340** based on the unexpected rearrangement of 5-propargyl-2H-thiopyran-4(3H)-ones **339** when exposed to a base such as DBU in either DMF or DMSO as the best conditions (Scheme 70) [98]. The reaction proceeded via base-catalyzed retro-*thia*-Michael addition undergone by the substrate **339** followed by propargyl isomerization to 1,1-dithiovinyl allene **II** and eventual intramolecular 5-exo-dig *thia*-Michael addition to the allene moiety, providing thiophenes **340** in excellent yields.

4.2 | Synthesis of Natural Products

The enantioselective total synthesis of the natural product (−)-preussochromone A **345**, isolated from solid cultures of an endolichenic fungus, *Preussia africana* [99], was based on a *thia*-Michael/retro-*thia*-Michael addition sequence (Scheme 71)

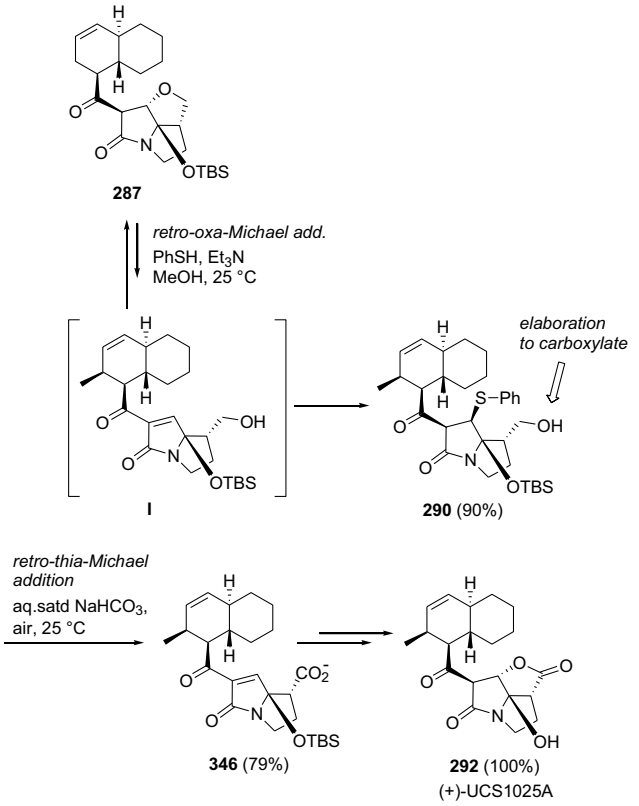


SCHEME 71 | Enantioselective total synthesis of (−)-preussochromone A.

undergone by 2-sulfonylchromenone **342** following the retro-Michael-type dehydrosulfinylation of β-sulfonyl carbonyl compounds strategy [100]. Compound **342** was the key intermediate for the attachment of the C5a-sulfur side chain to the chromenone core, and it was prepared in three steps from acetophenone derivative **341**. The *thia*-Michael/retro-*thia*-Michael addition sequence of **342** with unprotected diol **343** was carried out in DMF in the presence of potassium carbonate as the base and worked remarkably at room temperature to provide (−)-preussochromone A diol intermediate **344** in 94% yield.

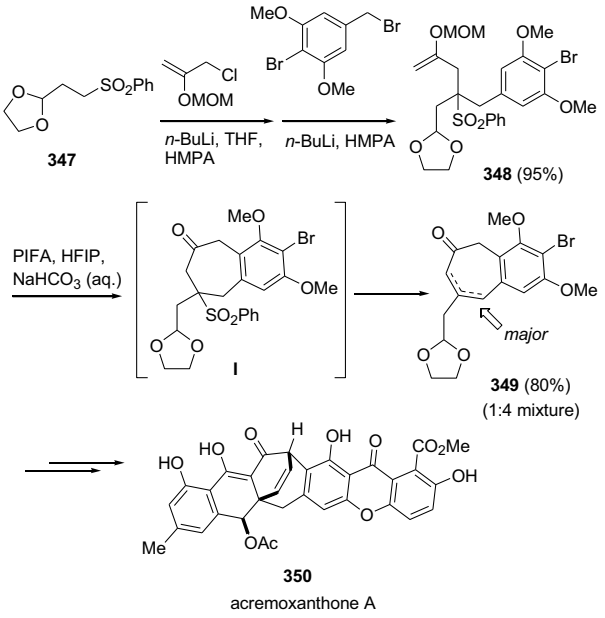
In the synthesis of UCS1025A **292** (see Scheme 61 in the retro-*oxa*-Michael chapter) [89], the reversibility of the *thia*-Michael addition was exploited to overcome the problem generated by the fact that the retro-*oxa*-Michael/*oxa*-Michael equilibrium involving **287** and intermediate **I** catalyzed by Et_3N was shifted toward the former (Scheme 72). To cope with this, α,β-unsaturated ketone **I** was trapped by thiophenol to produce **290** in 95% yield thus allowing for the elaboration of the alcohol functionality. Afterward, a retro-*thia*-Michael addition carried out by exposure to aqueous sat. $NaHCO_3$, under air at room temperature, set the stage for the final *oxa*-Michael reaction which, after removal of the OH protecting group, afforded the target compound.

The dehydrosulfinylation of β-sulfonyl carbonyl compounds strategy was used by Holmbo and Pronin to prepare a key intermediate (**349**) in the synthesis of acremoxanthone A (**350**) (Scheme 73), a natural compound belonging to the anthraquinone–xanthone heterodimers family of fungal metabolites derived from aromatic polyketides which exhibit a diverse set of biological activities [101]. The route to the pentacyclic core included an efficient assembly via a new intramolecular oxidative arylation of enol ether **348** prepared by sequential alkylation of sulfone **347** with the requisite allyl chloride and benzyl bromide. Treatment of enol ether **348** with [bis-(trifluoroacetoxy)iodo]benzene (PIFA) in



SCHEME 72 | Synthesis of UCS1025A.

1,1,1,3,3,3-hexafluoroisopropanol (HFIP) followed by mild basic workup resulted in direct formation of a 1:4 mixture of unsaturated ketones **349**, with the β,γ-regioisomer being the major product. After cyclization, the reaction proceeds through the retro-*thia*-Michael reaction. In fact, omission of the basic workup prevented elimination of phenylsulfinate and allowed for the isolation of oxidative arylation intermediate **I**. Overall, the synthesis of racemic acremoxanthone A **350** was completed in 10 steps.



SCHEME 73 | Synthesis of acremoxanthone A.

5 | Summary and Outlook

In this review, the authors have collected and discussed the synthetic approaches to carbo- and heterocyclic compounds, including natural products, published in the last fifteen years (2011–2025) which have either relied upon or included a retro-*hetero*-Michael addition step at some stage. The review covers the applications of retro-*aza*-, retro-*oxa*-, and retro-*thia*-Michael addition reactions, which together account for most, if not all, the examples appeared in the literature. Despite being at times considered a problem to cope with, the reversibility of the *hetero*-Michael reactions under the appropriate conditions has nevertheless become an established tool to manipulate and transform molecules and materials. The analysis of the literature revealed that retro-*hetero*-Michael addition reactions, often included in complex cascade processes, were exploited for a wide range of synthetic transformations which have led to complex bioactive and natural compounds. The simplest strategies based on the retro-*hetero*-Michael addition include the regeneration or the proper installation of a double bond inside a ring in the final stages of a synthesis, as well as the generation of reactive electrophiles undergoing intramolecular conjugate addition to attain ring closure. In a few cases, the retro-*hetero*-Michael addition was also used in functional group protection/deprotection procedures. However, where the retro-*hetero*-Michael addition really plays a key role, is in those processes reshaping the stereochemistry and the molecular skeleton of polycyclic compounds. Through a ring opening/ring reconstruction approach, the reversibility of the retro-*hetero*-Michael addition allows one to achieve isomerization to the wanted stereoisomer, isomeric amplification, skeletal editing, and, especially, racemization for very elegant metal- and enzyme-mediated DKR. Often, complex and sophisticated intramolecular rearrangements preceding the ring reconstruction step determine deep changes in the molecular architecture. While in most synthesis and methodologies discussed herein the involvement of a retro-Michael addition was planned from the beginning, it is also true that in a few cases it was a fortuitous finding, leading to unexpected and interesting rearrangement products. This means that not all the cards have been played yet, and further discoveries could amplify the importance of the retro-*hetero*-Michael addition as a tool in synthetic organic chemistry.

Acknowledgments

The authors thank MUR and European Union – "Next Generation EU" for financial support (PRIN2022 "Achieving Molecular Diversity by Metal-Catalyzed Tandem Reactions – AMODIVE", project no. 2022R2FYE3; CUP: B53D2301-5620006) and the MUR-Department of Excellence 2023-2027. 58503_DIPECC_23_27.

Funding

This work was supported by the Ministero dell'Università e della Ricerca (grant 2022R2FYE3).

Conflicts of Interest

The authors declare no conflicts of interest.

Data Availability Statement

All data are contained in the original papers discussed in this review.

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Biographies

Dina Scarpi received her Ph.D. in Chemical Sciences in 1999 at the University of Florence (Italy) under the supervision of Prof. Antonio Guarna. She was then appointed Research Associate at the Imperial College of Science Technology and Medicine (London, UK) where she worked at the Department of Chemistry in Prof. Robin J. Leatherbarrow's research group. In 2005, she became Assistant Professor at the Department of Chemistry "U. Schiff" of the University of Florence. Her research interests concern the transition metal-catalyzed synthesis of heterocyclic bioactive compounds and natural products.

Ernesto G. Occhiato obtained his Ph.D. in Chemical Sciences in 1994 at the University of Florence (Italy) under the supervision of Prof. Antonio Guarna, spending 1 year in the laboratories of Prof. J. Bryan Jones in Toronto (Canada). He became Assistant Professor in 2001 and then Associate Professor in Organic Chemistry in 2011 at the University of Florence. He is interested in new methodologies for the synthesis of chiral hetero- and carbocyclic compounds by transition metal catalysis (Pd, Au), as well as enzyme catalysis. In 2006 he was recipient of the CINMPIS award for "Innovation in Organic Synthesis."