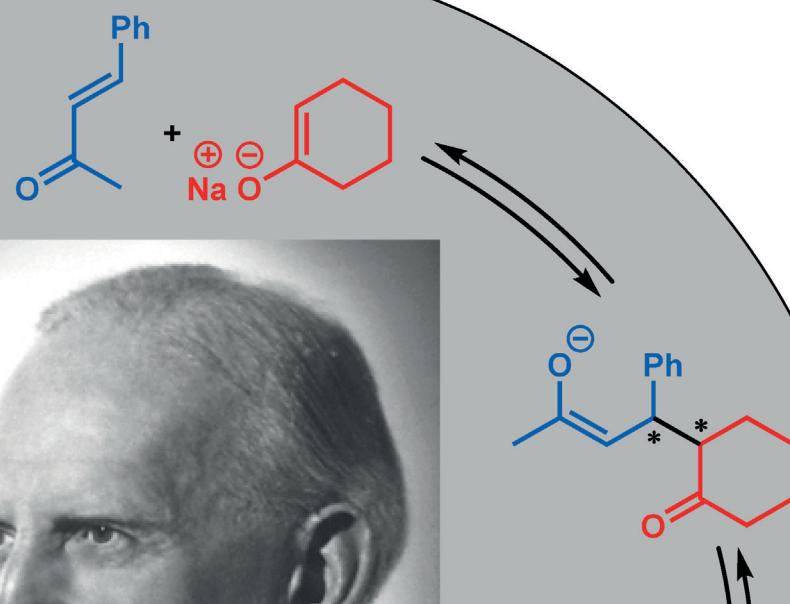


Enantioselective Access to Robinson Annulation Products and Michael Adducts as Precursors

Florian Gallier,* Arnaud Martel, and Gilles Dujardin

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Michael addition



The Robinson annulation is a reaction that has been useful for numerous syntheses since its discovery in 1935, especially in the field of steroid synthesis. The products are usually obtained after three consecutive steps: the formation of an enolate (or derivative), a conjugate addition, and an aldol reaction. Over the years, several methodological improvements have been made for each individual step or alternative routes have been devised to access the Robinson annulation products. The first part of this Review outlines the most relevant developments towards the formation of monocarbonyl-derived Robinson annulation products (MRA products, MRAPs) and activated monocarbonyl-derived Robinson annulation products (AMRA products, AMRAPs). The following sections are then devoted to the diastereoselective and enantioselective synthesis of these products, while the last section describes the enantiomeric resolution of racemic mixtures.

1. Introduction

The cyclohexenyl motif is common in numerous natural products (Figure 1), such as cyclic terpenes, steroids, statins, and even alkaloids.

Nowadays, chemists have developed a wide range of reactions to access cyclohex(en)yl frameworks in an efficient and stereocontrolled manner. Of these, the Robinson annulation has been successfully chosen for the synthesis of natural products, especially for steroids. In 1935, Sir Robert Robinson and William Sage Rapson published an original annulation procedure (Scheme 1).^[1] This reaction, one of the first tandem reactions described, involves a nucleophilic attack of the cyclohexanone sodium enolate **1a** on the styryl methyl ketone **2** though a Michael addition. Enolization of the 1,5-diketone **3**

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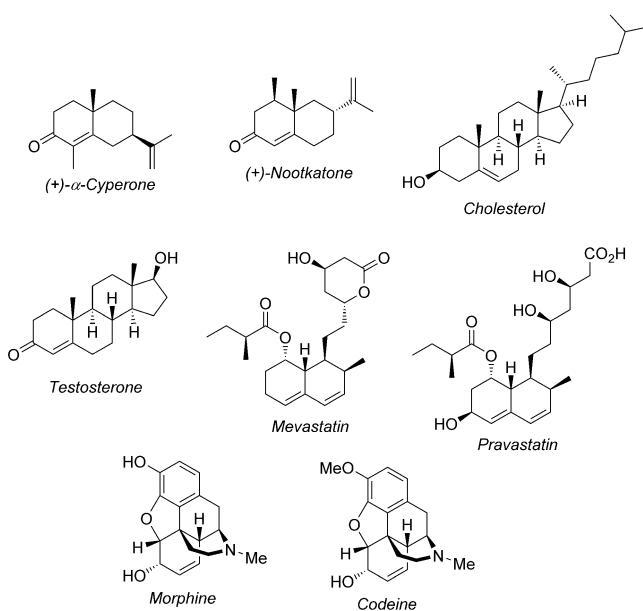


Figure 1. Structures of natural products containing a cyclohexenyl motif.

and intramolecular aldol condensation followed by a dehydration step produces the desired bicyclic enone **4**. Stereogenic centers are generated during the reaction, and the stereoselectivity (relative as well as absolute) may be controlled through different means, which will be discussed in this Review.

Interest in this reaction was initially tempered by the identification of several drawbacks, which have in turn stimulated tremendous efforts and the development of valuable strategies to improve the Robinson annulation procedures. Nowadays, the methodological improvements no longer focus on the reactivity pattern, but rather on the ability to promote an efficient diastereo- and enantiocontrol during the overall annelation of the ketone. Another challenge is regiocontrol of the initial enolization.

For a long time, the only known example of a Robinson annulation procedure that was able to fulfill these major criterions of reactivity as well as regio- and stereoselectivities was the transformation of cyclic 1,3-diketones to give steroid and terpene intermediates (Hajos-Parish-Eder-Sauer-Wiechert (HPESW) as well as Wieland-Miescher (WM) ketones).^[2–6] In addition to their specific reactivity, such

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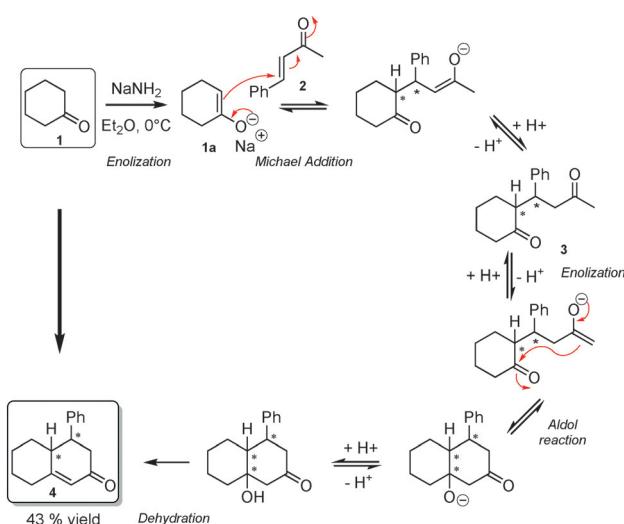
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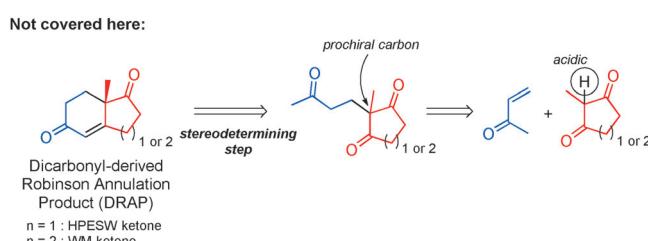


Scheme 1. Original annulation reaction developed by Rapson and Robinson.^[1]

annulation reactions involving a symmetrical 1,3-diketone yield an achiral adduct (isolated or not) in the first Michael addition step (Figure 2). Therefore, the stereodetermining step of this 1,3-diketone Robinson annulation (DRA) relies on the intramolecular cyclization process.

In contrast, the stereodetermining step in a more standard version of the Robinson annulation is the first Michael addition, an intermolecular process. This is the case for the formation of monocarbonyl-derived Robinson annulation products (MRA products, MRAPs), for which stereocontrol is often difficult. This is also the case for the formation of activated monocarbonyl-derived Robinson annulation products (AMRA products, AMRAPs), for which the reactivity and the stereocontrol can be significantly modified by the greater acidity of the ketone and by the presence of additional Lewis base site(s).

As a consequence of the remarkable expansion of stereocontrolled and asymmetric syntheses, several methods—including a number of recent ones—have been developed to synthesize enantioenriched MRAPs and AMRAPs, or at least to generate enantioenriched 1,5-diketones, which can be considered (and used) as precursors of the former.



Topic covered by this review:

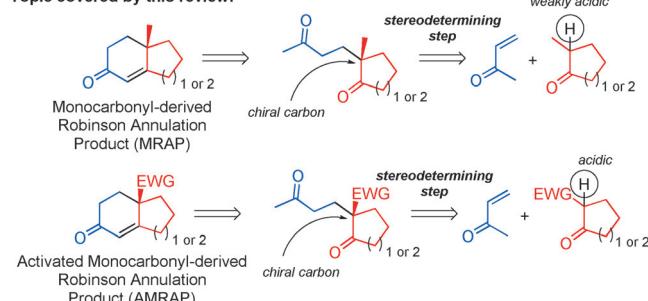


Figure 2. Retrosynthetic analysis of MRA and AMRA products. EWG = electron-withdrawing group.

Whereas the synthesis of DRAPs and their use have already been reviewed,^[7] the aim of this Review is to summarize these different approaches to MRA and AMRA products and intermediates published up to the end of 2016. Although different methods have been developed specifically for 1,5-ketoaldehydes, they are beyond the scope of this Review.

2. Methodological Improvements: Toolkit for Robinson Annulation

This section describes the synthetic efforts towards MRAPs, with an emphasis on the period since 1976, which corresponds to the publication of the last relevant reviews on the Robinson annulation.^[8,9]



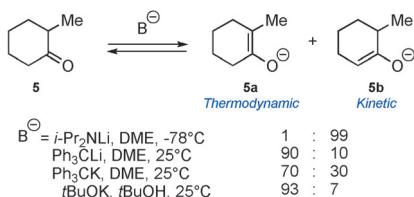
Florian Gallier was born in 1980 and raised in Normandy (France). He earned his PhD in chemistry (2007) from the Université du Maine (Le Mans, France) and the Leibniz University (Hanover, Germany) under the joint supervision of Dr. G. Dujardin and Prof. A. Kirschning. After postdoctoral research with Prof. J.-M. Beau at Université Paris-Sud (Orsay, France) and with Prof. P. Pale at Université de Strasbourg (Strasbourg, France), he became assistant professor at the Université de Cergy-Pontoise (France) in 2011. His research interests focus on the development of novel sustainable methods and their applications towards C-glycosides.



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2.1. Enolation

The initial Michael addition step requires the formation of an enolate or an enolate equivalent. Under basic conditions, unsymmetrical ketones can yield two regioisomeric enolates depending on the choice of the base and the nature of the starting ketone (Scheme 2).^[10,11] The thermodynamic enolate



Scheme 2. Regioselective formation of enolates.

5a is usually obtained at room temperature in protic solvents where equilibration between the enolates can occur. In contrast, slow addition of the ketone to a bulkier and stronger base in excess at low temperature in an aprotic solvent yields the kinetic enolate **5b** by the attack of the base at the less hindered position.

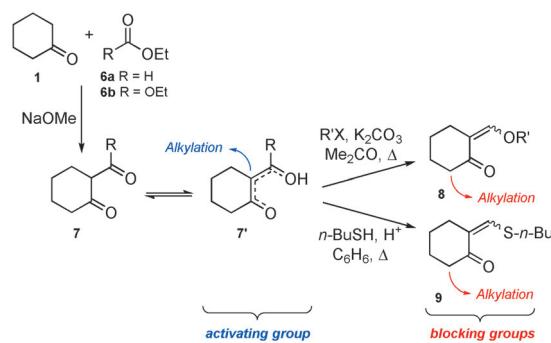
The weak acidity of the α -hydrogen atom of monoketones ($pK_a \approx 20-25$) necessitates the use of strong bases, which can lead to the formation of side products. Milder bases can be used with 1,3-dicarbonyl compounds **7** (prepared by enolate acylation), thus limiting the formation of side products or polyalkylation (Scheme 3).^[8] The 1,3-ketoaldehydes can also be easily transformed into alkoxymethylene or butylthiomethylene blocking groups (**8** or **9**). This was the initial method used for alkylating the least reactive position of a carbonyl compound.

Silyl enol ethers can also be used as nucleophiles for Michael addition. They are less basic than alkali enolates and can be isolated. The less substituted silyl enol ethers are usually obtained by trapping kinetic enolates, whereas the more substituted silyl enol ethers are obtained by silylation of thermodynamic enols or enolates.

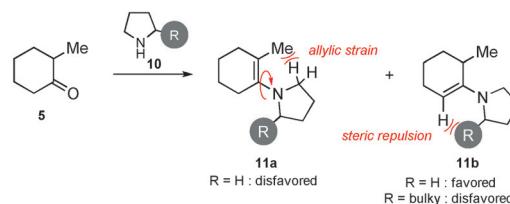
Probably the best alternative to the enolate chemistry was through the formation and reaction of enamines, as described by Stork et al. (Scheme 4).^[12] Indeed, enamines are reactive and far less basic than alkali enolates. In addition, the less



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Scheme 3. Introduction of activating or blocking groups for regio-specific alkylation.



Scheme 4. Regioselective formation of enamines.

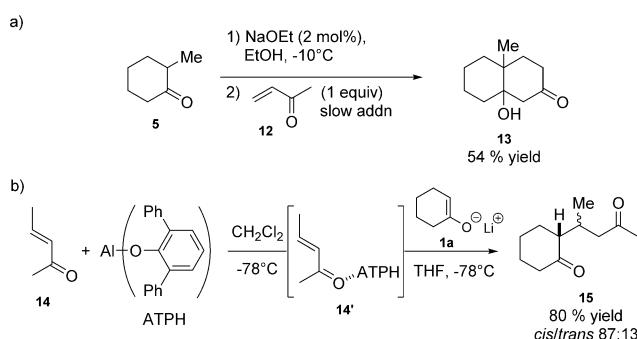
substituted enamine **11b** is usually thermodynamically the most stable and is generally also more reactive, as a result of a more effective overlap of the lone pair orbital of the nitrogen atom and the π orbital of the double bond. The more substituted enamine of pyrrolidine (**11a**) is disfavored due to steric repulsion (allylic strain). The structure of the starting amine is also crucial: pyrrolidine usually gives better ratios of the less substituted enamine compared to morpholine or piperidine.^[13,14] Finally, substitution at the α position to the nitrogen atom of the amine induces more steric constraints, thereby disfavoring both forms and, hence, selectivity becomes harder to predict.

Finally, α,β -unsaturated ketones can yield enolates regioselectively through either conjugate addition of an organocuprate or by specific reduction (Na or Li, liq. NH₃).^[15] Once the desired regioselective enolate/enamine is formed, the next step, namely, the Michael addition can be achieved.

2.2. Michael Addition

2.2.1. With the Free Enone

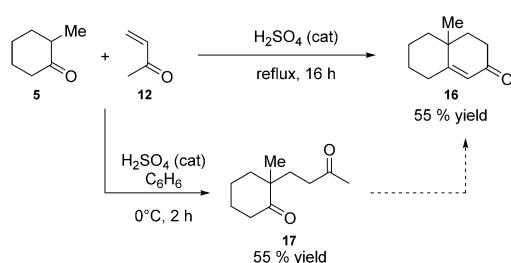
The original Robinson annulation procedure suffers from serious drawbacks which limit the yield of the desired products. Under the highly basic conditions usually required for annulation, the vinyl ketone has a high inclination to polymerize, especially under aprotic conditions. This problem can be addressed by the slow addition of the vinyl ketone to maintain its concentration as low as possible in the reaction media (Scheme 5a).^[16] Some vinyl ketones are also known to react at the carbonyl position rather than undergo 1,4-addition. Exclusive conjugate addition of the lithium enolate of cyclohexanone (**1a**) to (*E*)-3-penten-2-one (**14**) is observed in the presence of aluminum tris(2,6-diphenylphenoxyde)



Scheme 5. Improved procedures for the Michael addition under alkaline and Lewis acidic conditions.

(ATPH; Scheme 5 b). In this case, the 1,2-addition reaction is inhibited due to complexation of ATPH with the vinyl ketone ($\rightarrow 14'$).^[17]

Although classically performed under basic conditions, Michael addition can also take place in acidic media, which complements the above classical procedures. Heating 2-methylcyclohexanone (**5**) and MVK (**12**) at reflux with a catalytic amount of H_2SO_4 readily gives the bicyclic enone **16** in 55% yield.^[18] By decreasing both the reaction temperature and time, the 1,5-diketone **17** can also be isolated in 55% yield (Scheme 6).^[19]



Scheme 6. Annulation under protic conditions.

As briefly stated in Section 2.1, silyl enol ethers are fairly good alternatives to alkali enolates because of their low basicity and the ease of forming the thermodynamic or the kinetic enol ethers selectively. The Mukaiyama group first showed that $TiCl_4$ effectively promotes the Michael addition of silyl enol ethers with vinyl ketones to yield the corresponding 1,5-diketones.^[20,21] Later, Huffman et al. applied this method as an alternative to Robinson annulation.^[22] However, both groups found that the concomitant use of $Ti(OiPr)_4$ with $TiCl_4$ often afforded better yields and purities, especially with sensitive substrates. Even milder Lewis acids such as dibutyltin bis(triflate) are sufficiently acidic to promote alkylation but are also mild enough to avoid polymerization of the vinyl ketone as well as potential double alkylation.^[23,24]

Vinyl ketones, and MVK in particular, are highly reactive substrates. Therefore, milder reaction conditions were developed to increase the yield of the desired product (the 1,5-diketone, the corresponding ketol, or the octalone). Surrogates of vinyl ketones may also be used to achieve cleaner reactions and better yields (Figure 3).

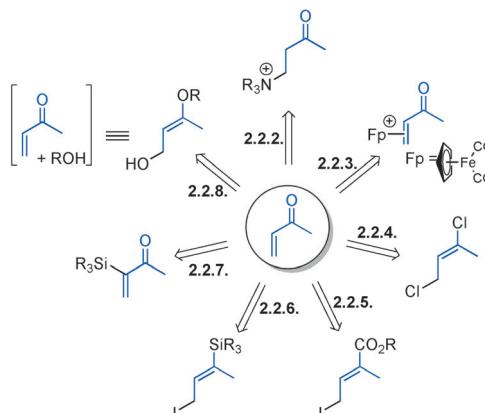
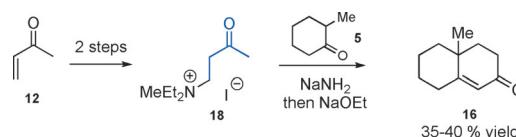


Figure 3. MVK surrogates.

2.2.2. Masked Enones: Mannich Bases

Shortly after their seminal publication, Robinson's group investigated the use of quaternarized Mannich bases to improve the yield and extend the scope of the reaction.^[25] They proposed that a progressive release of the vinyl ketone would be favorable because of the facile polymerization of vinyl ketones. Under the basic reaction conditions, the easily prepared Mannich base **18** undergoes Hofmann elimination and gradually affords the desired enone (Scheme 7).

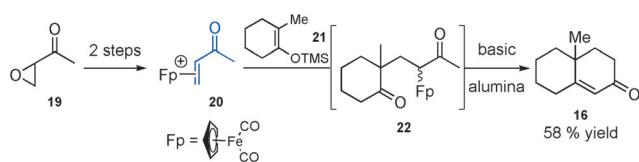


Scheme 7. Annulation using a Mannich base.

Similarly, other precursors such as β -ketoacids,^[26,27] 1,3-tosyloxyketones,^[28] and 1,3-benzoyloxyketones^[29] that are prone to *syn*-elimination have been successfully used as slow-releasing enone surrogates.

2.2.3. Masked Enones: Cyclopentadienyliron Dicarbonyl

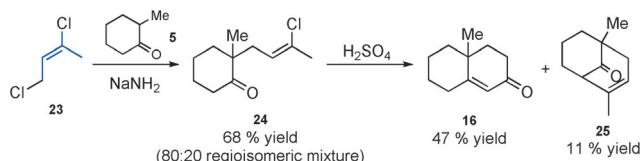
The coordination of an olefin to cyclopentadienyliron dicarbonyl (Fp) exerts a powerful activation on MVK, and the cation **20** is an effective acceptor of C-nucleophiles, such as lithium enolates or trimethylsilyl enol ethers of cycloalkanes **21** (Scheme 8).^[30] Removal of the organometallic group is achieved under very mild conditions during the cyclization of the 1,5-diketone.



Scheme 8. Annulation through olefin coordination. TMS = trimethylsilyl.

2.2.4. Alkylating Agent: Wichterle Reagent

One of the main limitations of the original Robinson annulation procedure is that enolates of sterically hindered cycloalkanones are totally ineffective at undergoing Michael addition to MVK.^[31] Highly electrophilic alkylating agents have, therefore, been designed to act as surrogates for MVK. To this end, (*Z*)-1,3-dichlorobut-2-ene (**23**; by-product from the manufacture of synthetic chloroprene rubber) was used early on by the Wichterle group, who showed that the resulting vinylic chloride **24** can be transformed into annulation product **16** in a harsh sulfuric acid medium (Scheme 9).^[32,33] Nevertheless, Caine and Tuller have devel-

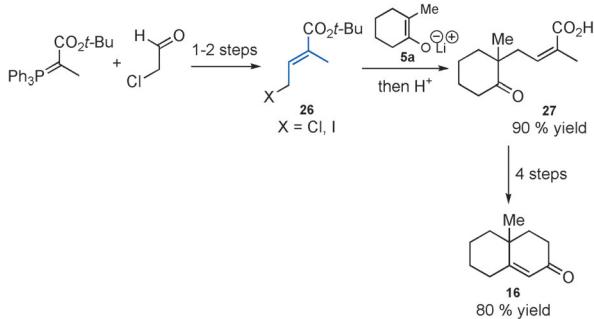


Scheme 9. Annulation using the Wichterle reagent (**23**).

oped a milder, although longer, method for hydrolysis that involves the formation of a terminal alkyne, through dehydrohalogenation and isomerization of the triple bond, which is subsequently hydrated to the corresponding methyl ketone.^[34] However, both methods afford the undesired bridged bicyclic [3.3.1] adduct **25** as a by-product.

2.2.5. Alkylating Agent: γ -Halotiglates

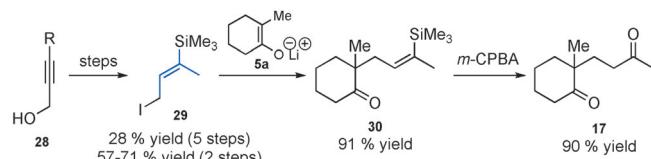
The bridged bicyclic [3.3.1] adduct (such as **25**) is usually obtained under the harsh acidic conditions required for unmasking the ketone functionality. Therefore, Stotter and Hill introduced the γ -halotiglates **26**, where the carboxy group can be transformed in four steps (through a Curtius degradation) into a methyl ketone which readily cyclizes under mild non-acidic conditions (Scheme 10).^[35,36] Although these γ -halotiglates are highly reactive, no polyalkylation was observed. In addition, the nature of the halogen has an important effect on the reactivity, as lithium enolates can be alkylated only by γ -iodotiglates, whereas enamines can react with both γ -chloro- and γ -iodotiglates.



Scheme 10. γ -Halotiglates in the annulation reaction.

2.2.6. Alkylating Agent: Vinylsilanes

Stork and Jung investigated the use of halomethyl vinylsilanes (Scheme 11).^[37] In this case, the ketone **17** is readily obtained after epoxidation of **30** and opening of the newly

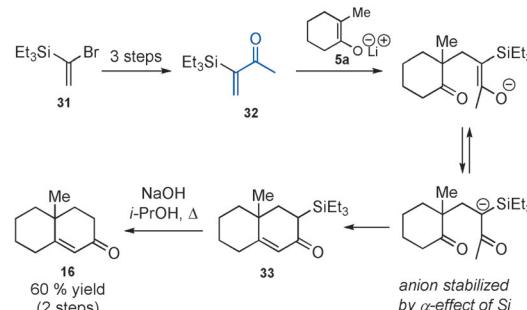


Scheme 11. Annulation using the Stork–Jung reagent **29**.

formed epoxysilane under mildly acidic conditions. The synthesis of these vinylsilanes **29** initially proved to be cumbersome.^[38] Nowadays, more convenient methods for the generation of the Stork–Jung vinylsilanes have been published.^[39,40]

2.2.7. Anion-Stabilizing Reagents: α -Silylated Vinyl Ketones

To avoid polyalkylation, Stork and Ganem introduced α -silylated vinyl ketones such as **32**, whose superior reactivity over MVK is explained by the ability of the silicon atom to stabilize an adjacent negative charge (Scheme 12).^[41]



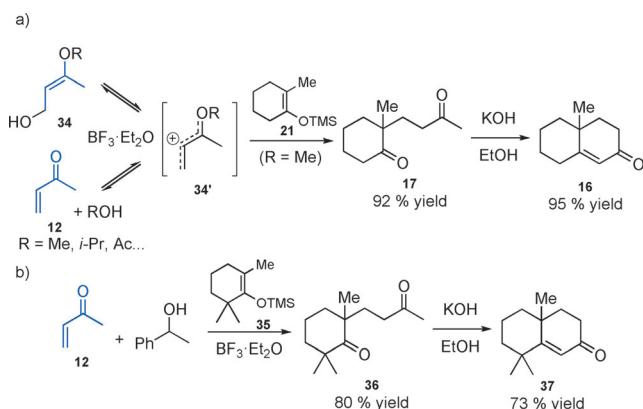
Scheme 12. α -Silylated vinyl ketones in the annulation reaction.

Although α -silylated vinyl ketones react efficiently with thermodynamically generated lithium enolates, their use with kinetic enolates is less convenient since they equilibrate faster than they undergo Michael addition. The trialkylsilyl group can be removed under basic conditions, either during the annulation or in a separate step. This method is probably one of the most often used because of its high regio- and stereoselectivity.

2.2.8. Hemiacetal Vinylogues or (Enone + ROH) Equivalents

All the alkylating reagents reviewed so far in this section were used under basic conditions with alkali enolates or enamines. Hemiacetal vinylogues **34**, prepared on a large scale in two steps from commercial sources, are among the latest MVK surrogates being developed and are special in the way that the alkylation is performed under Lewis acid

activation, through the transient formation of a stabilized carbocation **34'** (Scheme 13a).^[42–44] Moreover, hemiacetal vinyllogues (such as **34**) were found to be synthetically equivalent to a mixture of an enone (such as **12**) and an



Scheme 13. Annulation with hemiacetal vinyllogues or their synthetic equivalents.

hydroxylated compound (ROH or even acetic acid), thus allowing the direct use of the Michael acceptor, even MVK, as they are both able to react with the silyl enol ether **21** under mildly acidic conditions to afford the desired 1,5-diketone **17** directly.^[45] The regiodivergent annulation of 2-methylcycloalkanones has even become possible via the corresponding silyl enol ethers (more or less substituted), and proved to be diastereoselective both in the octalone and hydrindenone series.^[45] In addition, the efficient annulation of hindered ketone enol ethers such as **35**, which is difficult under classical conditions, was effective by this method (Scheme 13b).

2.3. Aldol Cyclization

Once the 1,5-diketone is formed, a second enolization step, necessarily regioselective, is required to ensure the formation of the desired lactol or octalone with a low amount of side products. Indeed, four different enolized systems (displaying similar acidity) are in equilibrium, and only one gives the desired product (Figure 4). The 1,5-diketone is not necessarily isolated when the classical basic conditions are used, as it usually undergoes cyclization under these conditions. If the conversion is not complete, treatment with alcoholic sodium or potassium hydroxide solution can afford the desired product cleanly.

To ensure the regiospecific formation of the enolate (as well as the selective functionalization of the octalone), a β -ketoester ($R = CO_2Me$; Figure 4) has been used for the synthesis of optically active constituents of some resin acids or for alkaloid structures (see Scheme 100).^[46,47] The annulation using pyrrolidine (through an enamine intermediate) has been found to be superior to other basic conditions, especially for hydrindenone systems.^[48]

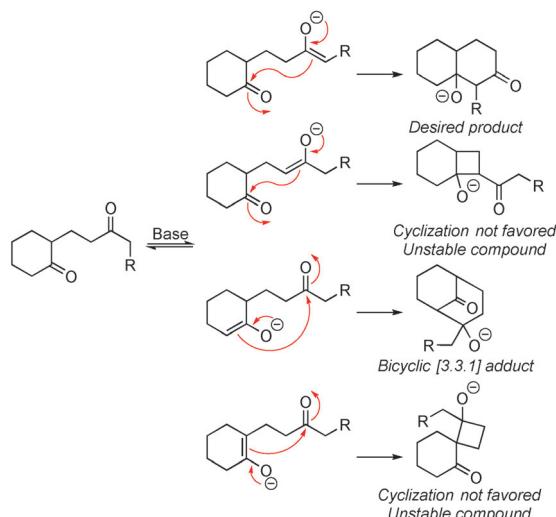


Figure 4. Possible aldol products.

2.4. Stereoselectivity Issues

Several stereogenic centers are (R^6 and R^7) created during the course of the octalone synthesis and these need to be controlled. Furthermore, epimerization can occur at the already existing stereocenters (R and R^4) and control of these configurations is important. The relative stereochemistry presented thereafter gives only a general trend under the kinetically or thermodynamically controlled conditions (Figure 5).

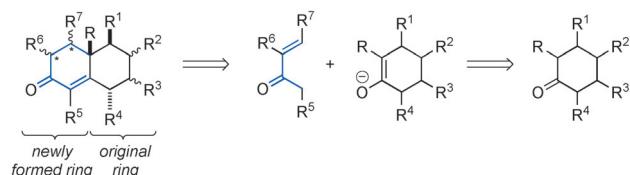
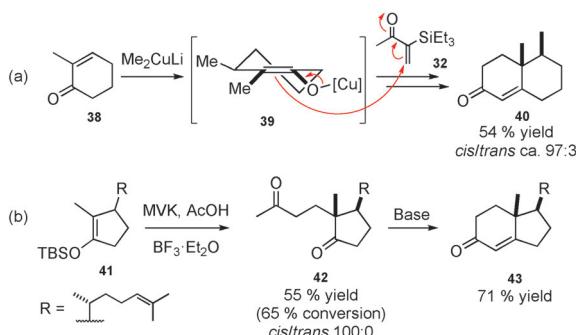


Figure 5. General stereochemical trends during the annulation of the octalone series.

- R : As a consequence of an enolization at the start of the synthesis, the configuration of the carbon atom of the starting cycloalkanone bearing the R group will be lost and will be controlled during the Michael reaction. This R group will usually lie in an axial position in the product.

- R^1 : The classical Robinson annulation of 2,3-dimethylcyclohexanone and MVK affords the octalone **40** in a non-selective manner (*cis/trans* 2:3) and in 15% yield. However, an acid-catalyzed annulation affords the *cis*-octalone selectively (>9:1) in a limited yield of 33%.^[49] The yield can be improved further by using the silyl enol ether and treating it with MVK and 2-propanol in nitromethane with a catalytic amount of $BF_3 \cdot Et_2O$ (with the same *cis* selectivity).^[45] Boeckman obtained the dimethyloctalone **40** with high stereocontrol during his study on the conjugate addition-annulation reaction.^[50–52] In the first step, conjugate addition occurs to yield a copper enolate **39**, which reacts with the Michael acceptor **32** on the less shielded face, thus yielding the *cis*-

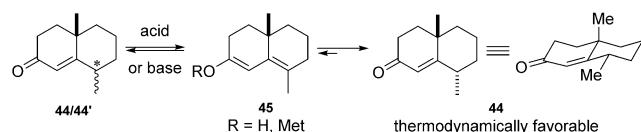
configured product (Scheme 14a). Importantly, total *cis*-diastereorecontrol were reached by the two above-mentioned methods for the hydrindenone series (**43**),^[45,53] thereby opening efficient pathways for the synthesis of the bicyclic CD unit of steroids and the bicyclic structure of vitamin D analogues (Scheme 14b).^[53,54]



Scheme 14. Stereocontrolled synthesis of dimethyloctalane and dialkyl hydrindenones.

- R² and R³: These two centers are usually not altered during the reaction, and this feature was exploited for the synthesis of enantiomerically pure products starting from optically active terpenes (see Section 3).

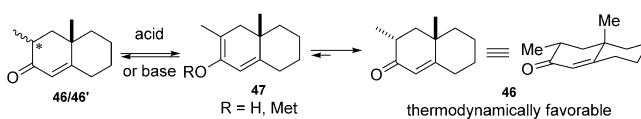
- R⁴: An annulation with MVK and 2,2-dimethylcyclohexanone yields an epimeric octalone (**44/44'**), which under enolization conditions (either acidic or basic) will equilibrate to the thermodynamically stable *trans* product **44** (Scheme 15). The formation of the transient dienolate **45** may also account for the over-alkylation occasionally encountered.



Scheme 15. Stabilization through dienolate formation.

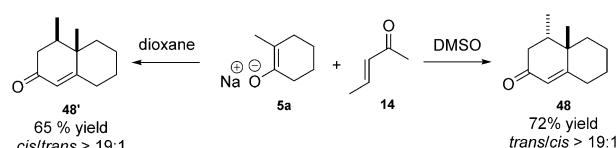
- R⁶: The octalone with a stereocenter in the α position to the carbonyl carbon atom (**46/46'**) is prone to enolization (Scheme 16). Unfavorable 1,3-*cis*-dixial interactions would lead mostly to the formation of the *trans* isomer **46** (with respect to the angular methyl group).

- R⁷: Substitution of this position requires the use of substituted vinyl ketones, such as 3-penten-2-one (**14**), which are notably less reactive than alkyl vinyl ketones. In addition,



Scheme 16. Stabilization through dienolate formation.

it is very difficult to achieve regiocontrol at this center, especially when 2-methylcyclohexanone is used, mainly because of high steric constraints of the transition state.^[55] The nature of the enolate or even the solvent is crucial for the outcome of the reaction. One striking example has been described by Scanio and Starrett during the annulation of 2-methylcyclohexanone with (*E*)-3-penten-2-one.^[56] Changing from dioxane to DMSO led to a complete inversion of the selectivity (**48/48'**), which in both cases reaches 95% (Scheme 17).



Scheme 17. Stereochemical influence of the solvent.

Many reactivity or selectivity issues may be encountered in the Robinson annulation that lower the yield of the targeted product. The following section describes the strategies used to synthesize Robinson annulation products in enantioenriched forms by using diastereoselective or enantioselective pathways and/or by resolution procedures.

3. Diastereoselective Pathways to Enantiopure (A)MRAPs

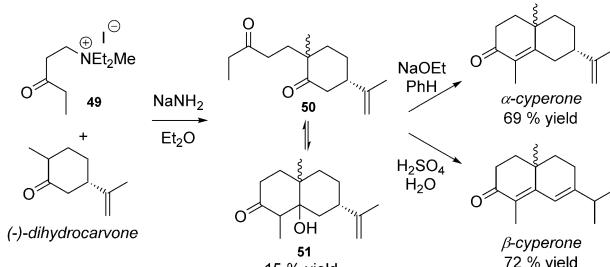
3.1. Annulation Precursor from the Chiral Pool

The first efficient method to prepare optically active MRAPs involved the use of natural chiral starting materials. Naturally occurring terpenic ketones were particularly useful in the Robinson annulation procedure.

3.1.1. Dihydrocarvone

The first and probably also the most used terpene in MRAP synthesis is dihydrocarvone. In 1937, the Robinson group devised the synthesis of cyperone sesquiterpenes,^[57] which possess interesting properties as insecticides (Scheme 18).^[58]

Annulation between the Mannich base **49** and (–)-dihydrocarvone affords a moderate yield of the Michael adduct **50** (which later proved to be the bicyclic ketol **51**).^[59] Treatment of this intermediate with either basic or protic media yields two different products, namely α- and β-cyperones. However, the authors reported uncertainties in the optical rotations for both compounds and, therefore, only claimed identical structures with the natural compounds and assumed at least partial racemization occurred. Several years later, one of the authors reinvestigated the synthesis of the natural product.^[50] He also described the synthesis of the epimer and enantiomer of α-cyperone starting from both enantiomers of dihydrocarvone (Figure 6).^[60]



Scheme 18. Robinson's synthesis of cyperones using dihydrocarvone.

However, these syntheses display a major drawback: the Michael reaction provides predominantly the *trans* isomer

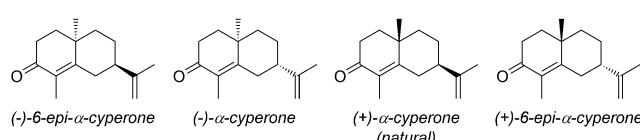
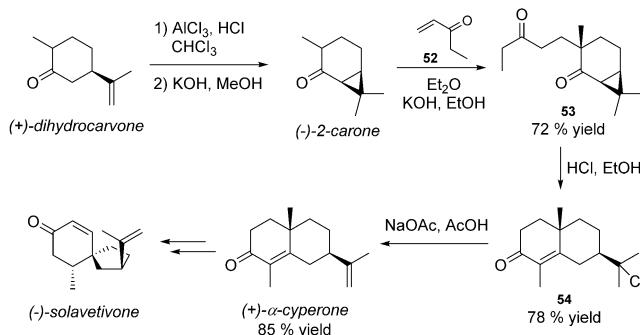


Figure 6. Structure of the cyperones.

(60 % yield, *trans/cis* = 85:15), which in turn will form the *epi*-cyperone, and isolation of the minor desired *cis* isomer is rather difficult. Therefore, Caine and Gupton transformed (+)-dihydrocarvone into (−)-2-carone (Scheme 19).^[61] The *cis*-configured Michael adduct **53** was obtained in high yield



Scheme 19. Synthesis of (+)-α-cyperone starting from (−)-2-carone.

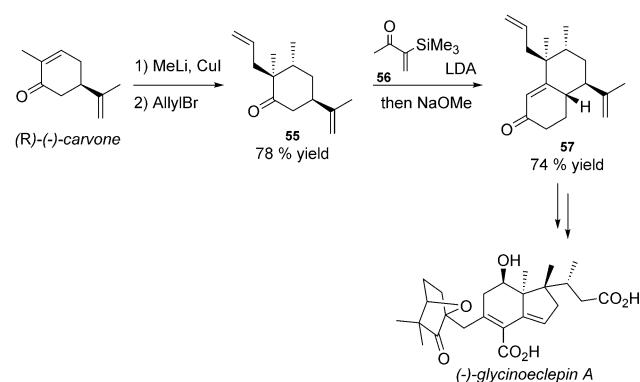
as the only isomer, presumably because of the dimethylcyclopropyl group efficiently shielding the top side of the enolate. Treatment of this 1,5-diketone with ethanolic hydrochloric acid readily opened the cyclopropane ring and annulation occurred without formation of the bridged [3.3.1] adduct. Completion of the synthesis required elimination of HCl under basic conditions. This efficient method enabled new targets such as (−)-solavetivone to be obtained from the (+)-α-cyperone intermediate.^[62]

The condensation of each enantiomer of dihydrocarvone allowed the synthesis of a chiral intermediate for the synthesis of polygodial, warburganal, and muzigadial,^[63] as well as several synthetic targets, such as (+)-7-hydroxycostal,^[64]

(+)-geosmin,^[65] and more recently (+)-decipienin A^[66] or (−)-valeranone.^[67] The last example can also be prepared from carvomenthone, the saturated analogue of dihydrocarvone.^[68,69]

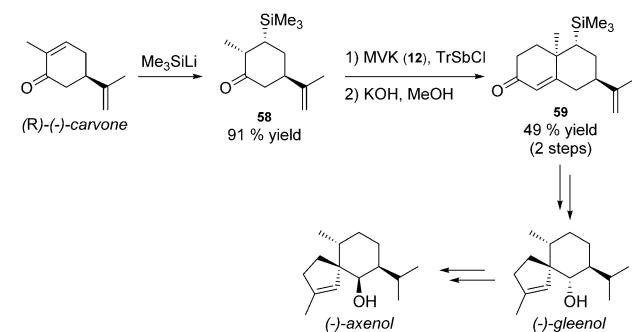
3.1.2. Carvone

Carvone is a valuable chiron for the introduction of virtually any nucleophilic group via its α,β -unsaturated ketone. For example, Murai et al. treated (−)-carvone with MeLi in the presence of CuI, and the enolate was subsequently trapped with allyl bromide (Scheme 20).^[70] This highly functionalized cyclohexanone **55** was then alkylated by the anion-stabilizing α -trimethylsilyl-MVK **56**, which yielded the desired enone **57** in 74 % after cyclization. Further synthetic transformations complete the synthesis of (−)-glycinoeclepin A.



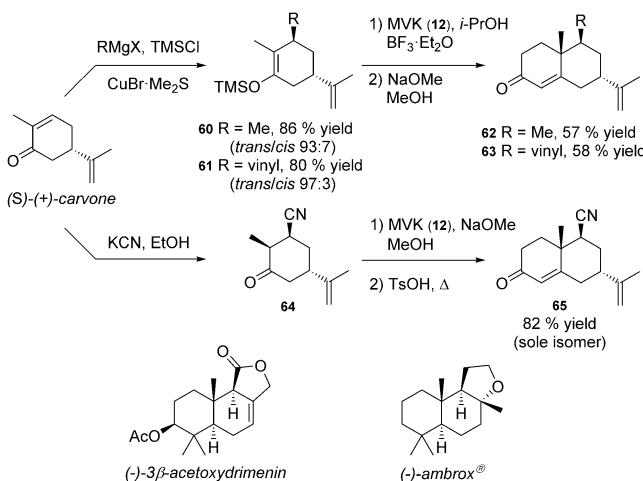
Scheme 20. Synthesis of (−)-glycinoeclepin A from (−)-carvone. LDA = lithium diisopropylamide.

This chiron was also used by Pedro and co-workers for their synthesis of both (−)-gleenol and (−)-axenol (Scheme 21).^[71] The regioselective 1,4-addition of Me₃SiLi without copper salts afforded the desired product **58**, whose stereochemistry was assigned according to preferential axial addition (and confirmed at a later stage). Lewis acid promoted alkylation by MVK yields a mixture, from which the desired 1,5-diketone could be isolated and annulated.



Scheme 21. Synthesis of (−)-gleenol and (−)-axenol from (−)-carvone. TrSbCl = tritylium hexachloroantimonate.

The de Groot group extensively studied the Robinson annulation of carvone derivatives and described the synthesis of drimane sesquiterpenes and the perfumery molecule Ambrox (Scheme 22).^[72–74] The conjugate addition of methyl

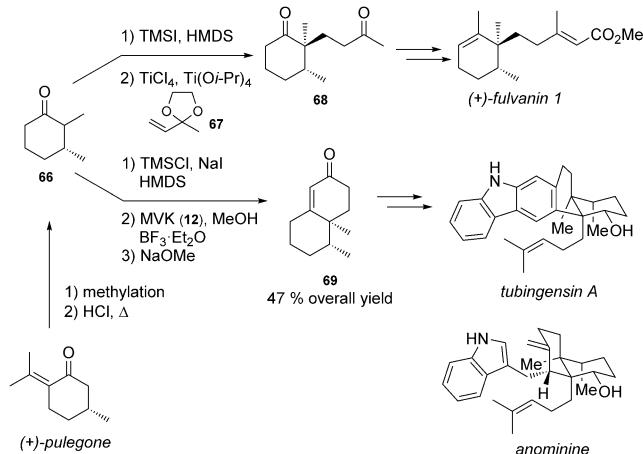


Scheme 22. Synthesis of drimane sesquiterpenes.

or vinyl magnesium halide to (*S*)-(+)-carvone and trapping of the enolate with TMSCl delivered the required silyl enol ethers **60** or **61**, respectively. Annulation of this sterically hindered cyclohexanone by Duhamel's hemiacetal vinylogues method yielded the octalones **62** and **63** in good overall yield and with good stereocontrol (99% of the desired diastereoisomer). The cyano derivative **64** affords the octalone **65** in high yield and very high stereoselectivity under standard conditions.

3.1.3. Pulegone

Pulegone has also been used indirectly as a chiron, after methylation followed by retro-aldolization (Scheme 23). Enolization, trapping of the chiral 2,3-dimethylcyclohexanone **66** as a silyl enol ether, and alkylation with the ethylene

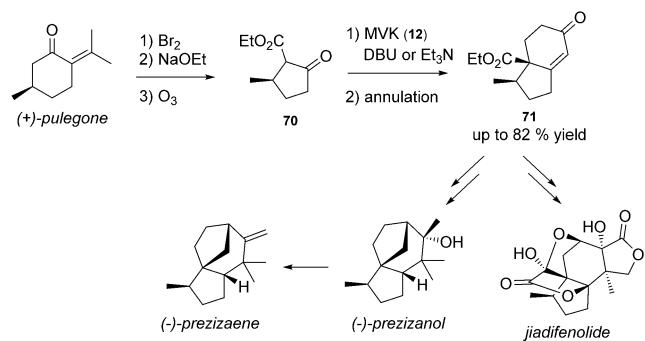


Scheme 23. Synthesis of natural products from (+)-pulegone.
HMDS = hexamethyldisilazane.

ketal of MVK **67** under Lewis acidic conditions yields predominantly the desired 1,5-diketone **68**, a precursor to (+)-fulvanin 1.^[75]

The same enol ether was used by the Nicolaou group for the synthesis of tubingensis A and anominine.^[76] Michael addition was achieved in this case by using the Lewis acid mediated enone-alcohol method,^[44,45] which yielded the chiral octalone **69** in a good overall yield of 47%.

(+)-Pulegone can also be transformed into the chiral cyclopentanone **70** through bromination of the double bond, a Favorskii rearrangement, and ozonolysis (Scheme 24). The

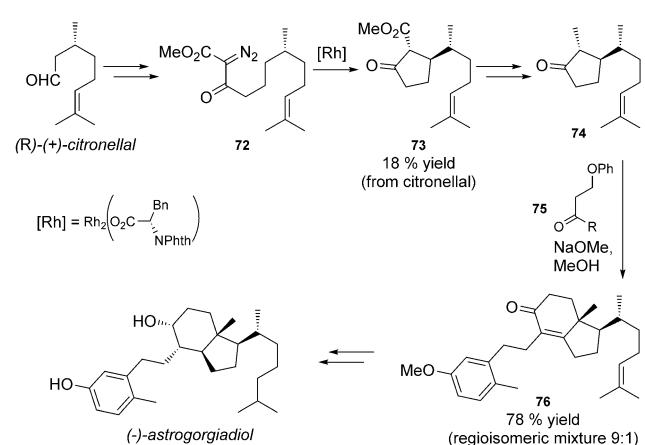


Scheme 24. (+)-Pulegone as a chiron for the synthesis of natural products. DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene.

addition of the stabilized enolate to MVK and annulation under either basic or acidic conditions yielded the chiral hydrindenone **71** in a yield ranging from 55 to 82%, depending on the conditions.^[77,78] This compound has been used as an intermediate for the synthesis of jiadifenolide and (−)-prezizaene, which is obtained upon dehydration of (−)-prezizanol.

3.1.4. Citronellal

A related chiral cyclopentanone **74** has been prepared from citronellal by Taber et al. for the synthesis of (−)-astrogorgiadiol (Scheme 25).^[29,79] After elongation of the side

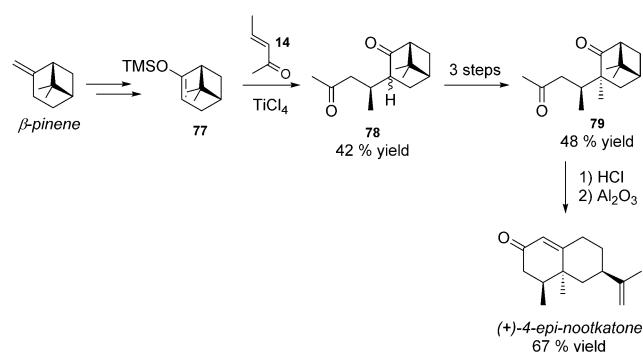


Scheme 25. Synthesis of astrogorgiadiol from (+)-citronellal.

chain, the cyclization of the diazo intermediate **72** was performed by using a $\text{Rh}_2(\text{S})\text{-[PTPA]}_4$ -mediated ((*S*)-[PTPA]₄=*N*-phthaloyl-(*S*)-phenylalaninate), C–H insertion to afford a diastereoisomeric mixture (70:30), from which the desired isomer **73** could be selectively crystallized. The Michael acceptor was prepared as the masked, slow-releasing, enone **75**, which also allowed easier purification from its by-products. The enone function could be recovered under the basic conditions required for the formation of the enolate, and the hydrindenone **76** then obtained in high yield. However, a partial equilibration of the enolate occurred during the process and separation of the by-products was only possible at a later stage.

3.1.5. β -Pinene

Oxidative cleavage of β -pinene yields (+)-nopolone, whose silyl enol ether **77** can react with (*E*)-3-penten-2-one

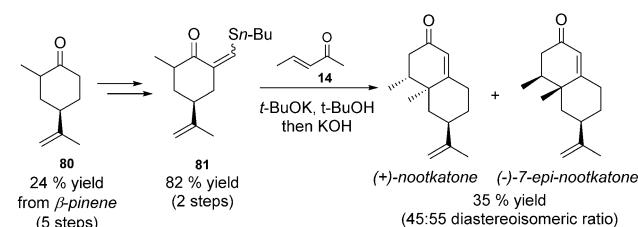


Scheme 26. Synthesis of (+)-4-epi-nootkatone from β -pinene.

(**14**) in the presence of TiCl_4 (Scheme 26).^[80] The selectivity of the Michael addition at this stage is inconsequential, since the adduct is in turn subjected to a diastereoselective methylation. Treatment of **79** with anhydrous HCl cleaves the cyclobutane ring concomitantly with annulation. The final dehydration occurred on treatment over activated alumina to afford the (+)-4-*epi*-nootkatone.

β -Pinene can be transformed into ketone **80** in five steps (Scheme 27). The most reactive methylene group can be blocked with the butylthiomethylene group (**81**) prior to alkylation with 3-penten-2-one (**14**). Removal of the blocking group is performed under basic conditions.^[81]

This example illustrates the problems arising from the use of 3-penten-2-one (**14**) as a Michael acceptor, as the yield of

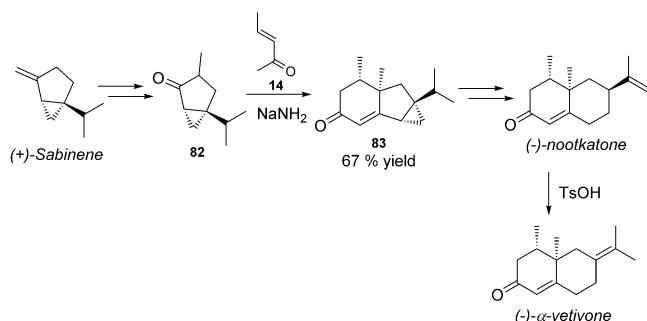


Scheme 27. Efforts toward the synthesis of nootkatone.

the reaction drops to 35 % and the stereoselectivity is low, due to the formation of (+)-nootkatone and (-)-7-*epi*-nootkatone in an almost equimolar mixture. Direct alkylation of the chiral cyclohexanone **80** with **14** only affords the (-)-7-*epi*-nootkatone in 29 % yield.^[82]

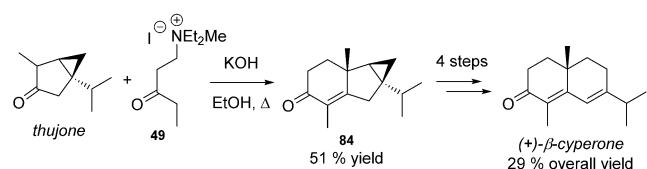
3.1.6. Other Terpene Derivatives

(–)-Nootkatone and (–)- α -vetivone have been prepared efficiently by the alkylation of the sabinene derivative **82** with **14** (Scheme 28).^[83] Regioselective formation of the enolate and stereospecific alkylation is ensured by the cyclopropane ring and affords the desired product **83** in 67 % yield.



Scheme 28. Synthesis of sesquiterpenoids from (+)-sabinene. $\text{TsOH} =$ toluenesulfonic acid.

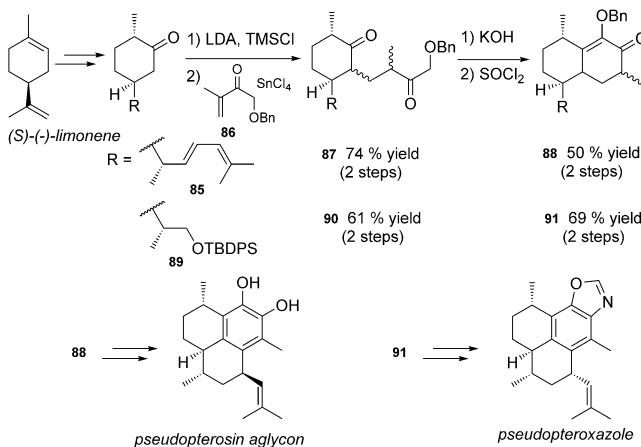
The tricyclic enone **84**, an intermediate for the highly stereoselective synthesis of (+)- β -cyperone (Scheme 29),^[84] has been directly isolated from the condensation of thujone with the quaternarized Mannich base **49**.



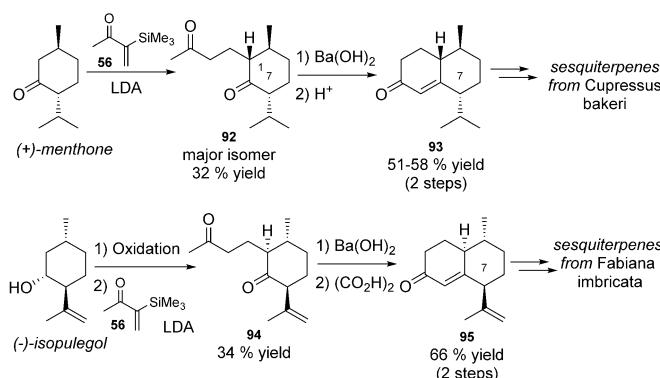
Scheme 29. Synthesis of β -cyperone from thujone.

(*S*)-(–)-Limonene can be transformed into the two chiral cyclohexanones **85** and **89** by using identical strategies (Scheme 30).^[85,86] Deprotonation, trapping of the enolate with chlorotrimethylsilane, and a subsequent Michael addition to vinyl ketone **86** under Lewis acid activation afford the desired enones **88** and **91** after annulation. The stereochemistry is not crucial in these cases, since aromatization of this ring will take place at a later stage.

During their studies towards sesquiterpenes derived from natural sources, Ngo and Brown used the same strategy starting either from (+)-menthone^[87] or from the ketone derived from (–)-isopulegol^[88] (Scheme 31). Alkylation with the anion-stabilizing reagent **56** gave predominantly the desired 1,5-diketones **92** and **94**, along with the corresponding epimers at the C-1 and C-7 positions (6 % yield for the three undesired isomers). The annulation was carried under mild conditions to avoid total epimerization at the C-7-position.

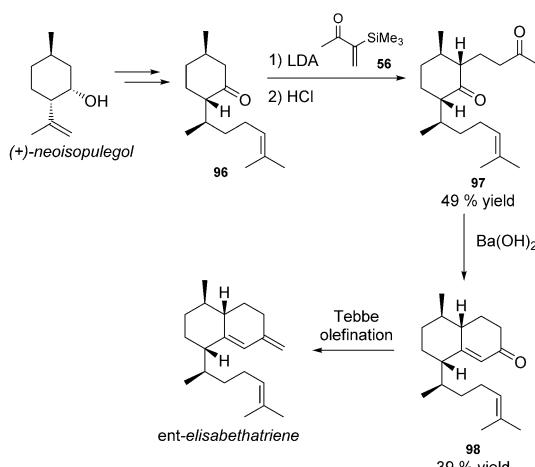


Scheme 30. Limonene as a chiral source for the synthesis of natural sesquiterpenes. Bn = benzyl, TBDPs = *tert*-butyldiphenylsilyl.



Scheme 31. Annulation of (+)-menthone and (-)-isopulegol towards sesquiterpenes.

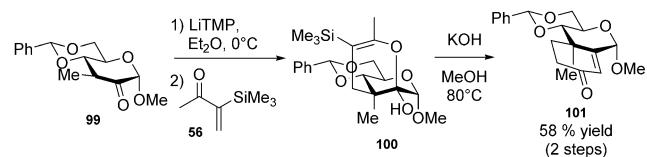
The same strategy was used for the alkylation of the chiral cyclohexanone **96** derived from (+)-neoisopulegol (Scheme 32).^[89] Treatment of the 1,5-diketone **97** with Ba(OH)₂ led to cyclization to the bicyclic enone **98** in moderate yield. A final Tebbe olefination yields the enantiomer of elisabethatriene.



Scheme 32. Synthesis of *ent*-elisabethatriene from (+)-neoisopulegol.

3.1.7. Glucose

Terpenes have been widely used for their inherent stereochemistry or functional groups. Interestingly, carbohydrates, another widespread source of chiral building blocks, have been used more rarely in Robinson annulations. The preparation of a chiral synthon for a taxoid synthesis by the Jenkins group is the only report to date (Scheme 33).^[90-92]



Scheme 33. Glucose derivative for MRAPs. TMP = 2,2,6,6-tetramethyl-piperidine.

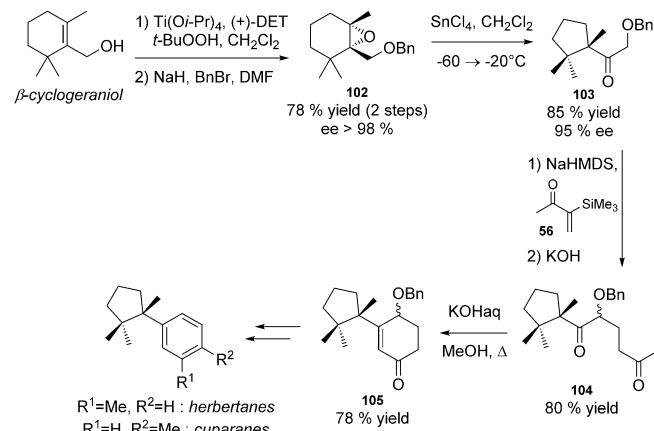
Deprotonation of the ketone **99** derived from D-glucose proceeds best with lithium tetramethylpiperidine (LiTMP) as the base. The α -trimethylsilylenone **56** then adds from the Si face, leaving the 3-Me group in the axial position (\rightarrow **100**), and the desired MRAP **101** is obtained after dehydration.

3.2. Asymmetric Synthesis of Starting Ketones

The diastereoselective formation of enantioenriched MRAPs has been reported in a number of cases from chiral starting ketones, which were prepared from achiral compounds using enantioselective reactions.

3.2.1. Sharpless Epoxidation/Pinacol Rearrangement

Abad et al. have performed a Sharpless–Katsuki asymmetric epoxydation of β -cyclogeraniol to set the desired stereocenters (Scheme 34).^[93-95] The chiral intermediate **102** was obtained in high yield and excellent optical purity and was then subjected to a pinacol rearrangement to yield the

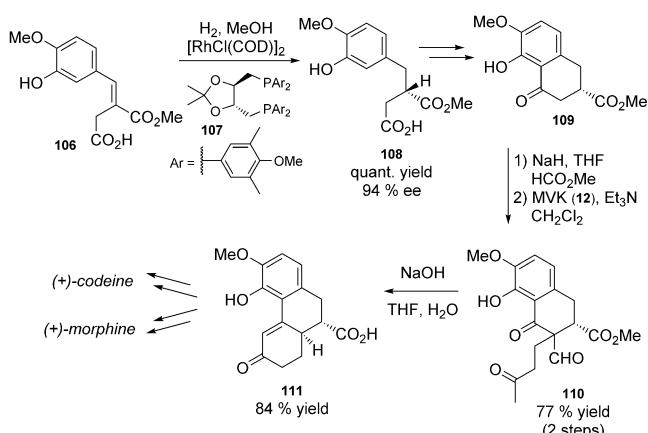


Scheme 34. β -Cyclogeraniol as a synthon for the synthesis of herberanes and cuparanes. (+)-DET = (+)-diethyltartrate, NaHMDS = sodium hexamethyldisilazide.

required chiral ketone **103** with a slight decrease in the enantiomeric excess. The enolate was then alkylated with the α -trimethylsilylenone **56** to furnish the desired 1,5-diketones **104** in good yield. It should be noted that, under similar conditions, MVK affords the product in only 5–10% yield. Cuparanes and herbertane sesquiterpenes can be synthesized by this method by using a different protecting group on the β -cyclogeraniol epoxide.

3.2.2. Catalytic Asymmetric Hydrogenation

The Stobbe condensation product of isovanillin (**106**) was submitted to a Rh-catalyzed asymmetric hydrogenation using a chiral DIOP ligand **107**, and the desired product **108** was isolated in quantitative yield with a good enantiomeric excess (Scheme 35).^[96,97] The required cyclohexanone **109** was

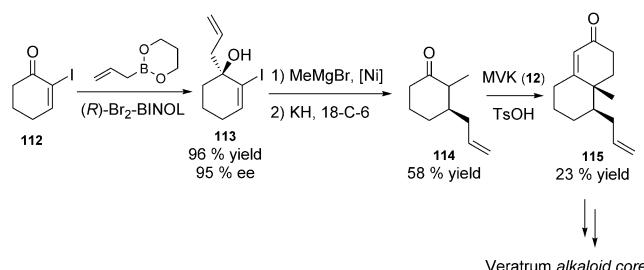


Scheme 35. Synthesis of (+)-morphine and (+)-codeine. COD = 1,5-cyclooctadiene.

obtained after Friedel–Crafts acylation and underwent formylation at the α position to facilitate the Michael addition of MVK. The 1,5-diketone **110** was then treated with aqueous NaOH and an annulation/deformylation/saponification sequence occurred to yield the desired carboxylic acid **111** as a single isomer. This intermediate paved the way to the synthesis of both (+)-morphine and (+)-codeine.

3.2.3. Enantioselective Allylation

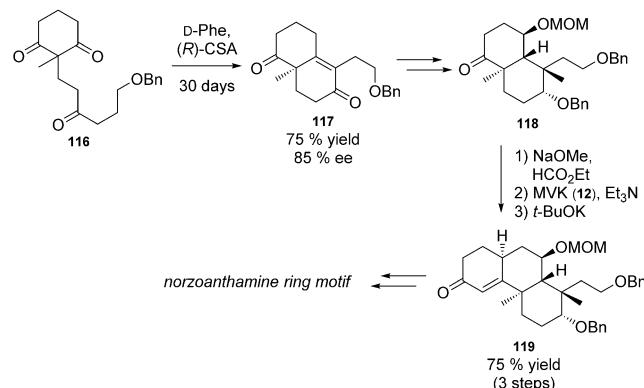
In 2013 Taber and Berry reported the synthesis of the 6-5 tricyclic core of the Veratrum alkaloids (Scheme 36).^[98] The α -iodocyclohexenone **112**, readily obtained from cyclohexenone, undergoes enantioselective allylboration in the presence of a chiral 1,1'-bi-2-naphthol (BINOL) ligand. A Kumada methylation followed by an anionic oxy-Cope rearrangement then delivers the cyclohexanone **114**. The Robinson annulation with MVK under acidic conditions occurs in a rather low yield as a result of incomplete conversion (ca. 35%) before decomposition.



Scheme 36. MRAPs as a synthon for the synthesis of Veratrum alkaloids.

3.2.4. Enantioselective 1,3-Diketone Robinson Annulation

The annulation of the prochiral triketone **116** with D-phenylalanine and (*R*)-camphorsulfonic acid yields slowly (in 30 days) the Wieland–Miescher ketone derivative **117** with 85% *ee* (Scheme 37).^[99] After functionalization, introduction of the formyl activating group, and alkylation with MVK, the final basic treatment affords the desired adduct **119**, the precursor of norzoanthamine, in 75% overall yield.

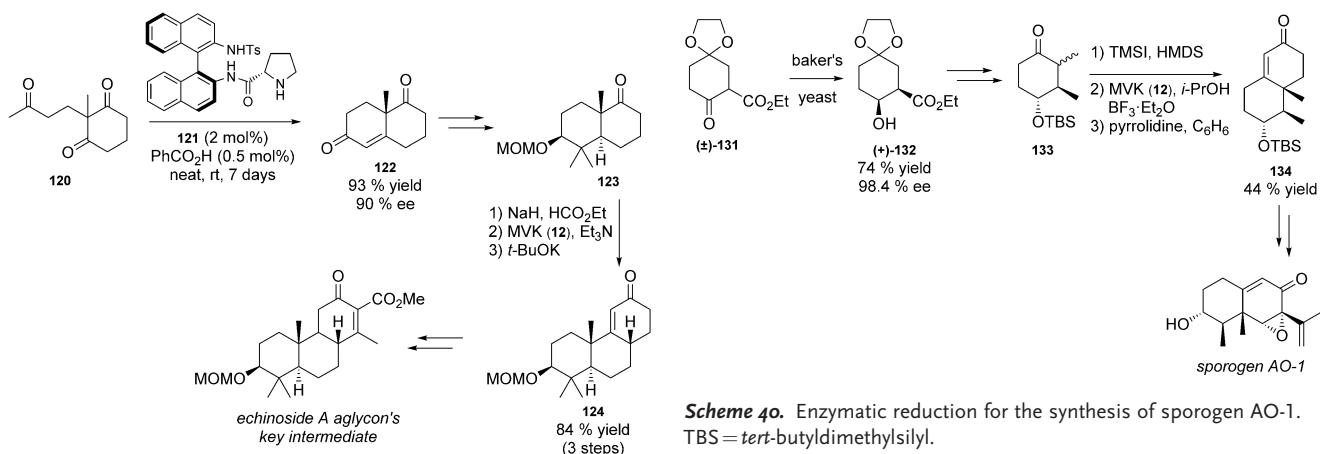


Scheme 37. Double Robinson annulation for accessing the norzoanthamine ring motif. MOM = methoxymethyl.

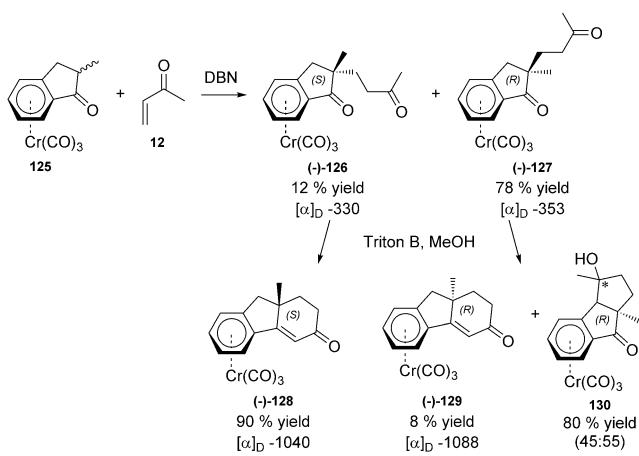
Similarly, the group of Yu has described the enantioselective cyclization of the prochiral triketone **120** using the atropisomeric prolinamide catalyst **121** (Scheme 38).^[100] These solvent-free conditions afford the Wieland–Miescher ketone **122** in 93% yield with 90% *ee*, which can be increased to 99.5% *ee* by recrystallization. Annulation of the follow-up product **123** with MVK ensures the formation of the ABC ring framework of an intermediate in the synthesis of echinose A aglycon.

3.2.5. Formation of Enantioenriched Keto-Arenetricarbonyl-Chromium Complexes

1-Indanone- and 1-tetralonetricarbonylchromium complexes have been prepared and isolated in enantioenriched forms.^[101] Epimeric complexes **125** can react with MVK (**12**) to afford (−)-**126** and (−)-**127** (Scheme 39). Cyclization of the minor product (−)-**126**, obtained from *endo* attack, proceeds smoothly to afford the enone (−)-**128**.^[102,103]



Scheme 40. Enzymatic reduction for the synthesis of sporogen AO-1.
TBS = *tert*-butyldimethylsilyl.



However, the same alkaline treatment of the *exo*-1,5-diketone (*-*)-127 yields only small amounts of the enone (*-*)-129. The Cr(CO)₃ group activates the methylene group next to the aromatic ring, thus making it more acidic, thereby directing the cyclization towards the formation of 130. Such cyclization of the *endo* product is hampered by the steric bulk of the metal center. Similar observations have been made in the tetralone series.

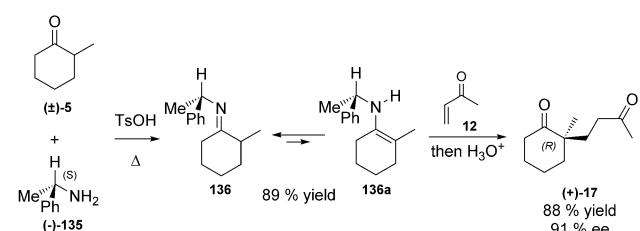
3.2.6. Ketones from Yeast Reduction

The enantioselective reduction of the β-ketoester (\pm)-131 with baker's yeast yields the corresponding alcohol (+)-132 with high efficiency (Scheme 40).^[104] After transformation of some functional groups, Robinson annulation takes place when the Lewis acid mediated enone–alcohol method is used.^[44,45] The bicyclic enone 134, whose enantiomeric purity has been assessed by the Mosher's ester method, is converted into sporogen AO-1 after six additional steps.

3.3. Annulation Precursor bearing a Chiral Auxiliary

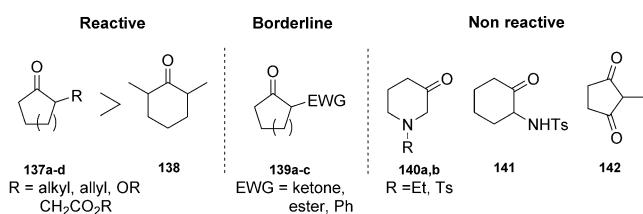
3.3.1. Chiral Imine: Pfau–d'Angelo Method

In 1985, a major breakthrough occurred in the field of enantioselective transformations when Pfau et al. first published the use of chiral enamines to achieve asymmetric Michael addition under neutral conditions.^[105] The condensation of a racemic cycloalkanone (\pm)-5 with (S)-1-phenylethylamine ((*-*)-135), which is readily available in both enantiomeric forms, yields a chiral imine/enamine mixture (**136/136a**) that is stable enough to be isolated. This compound reacts with 12 to afford the 1,5-diketone (+)-17 in high yield and enantiomeric excess (Scheme 41).



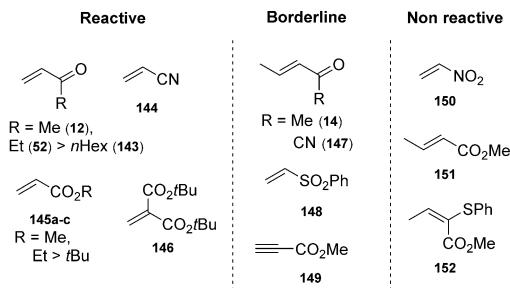
Scheme 41. Pfau–d'Angelo method for enantioselective conjugate addition.

Over the years, this reaction proved to be complementary to the Hajos–Parrish–Eder–Sauer–Wiechert (HPESW) reaction, and is arguably more versatile. The scope and limitations of this reaction have already been reviewed,^[106] so only a short survey will be presented here, with the most recent improvements highlighted. The nature of the chiral amine was investigated, and the presence of the aromatic ring at the α position to the amine was found to be crucial to ensure good enantioselectivity. Even if the scope is quite broad and usually gives very good results, the nature of the starting cyclic ketone has an effect on the outcome of the alkylation (Figure 7). Indeed, the presence of an electron-withdrawing group at the α position of the ketone (**139a–c**) facilitates the formation of the enamine (stabilized by conjugation), but on the other hand decreases its reactivity. Therefore, in such cases, the Michael addition could only be achieved with further activation (Lewis acid or hyperbaric conditions).^[107] Strik-

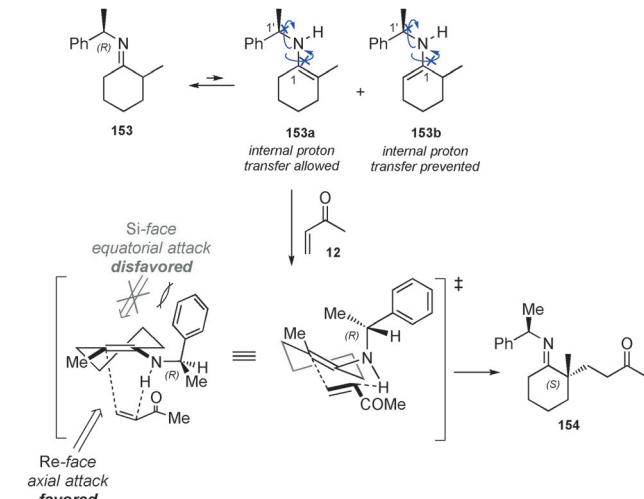
**Figure 7.** Reactivity of cyclic ketones.

ingly, 2-methylcyclopentan-1,3-dione (**142**), a convenient substrate in the HPESW reaction, does not undergo Michael addition under these neutral conditions. Compounds bearing a nitrogen atom at the α or β position of the ketone (**140a,b**, **141**) yield only very small amounts of the desired enamines.

The nature of the Michael acceptor was also examined (Figure 8). It appears that monosubstituted alkenes bearing an electron-withdrawing group such as α -ethylenic ketones, esters, or nitriles react readily (**12**, **52**, **144–145a–c**). However, substitution at the electrophilic center (**14**, **147**, **151**, and **152**) leads to a dramatic decrease in the reactivity.

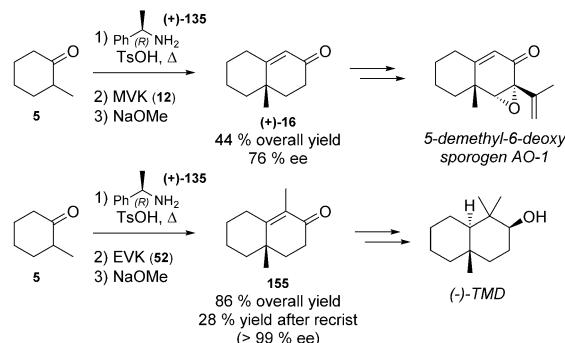
**Figure 8.** Reactivity of Michael acceptors.

The reaction conditions may also play an important role in the outcome of the reaction. Interestingly, increasing the reaction temperature does not affect the stereoselectivity, but substantially reduces the reaction time. Such an effect is also observed under high pressure, microwave irradiation, or in the presence of Lewis acids.^[107] However, a large change in the regio- and/or enantiocontrol is often observed in these cases. Aprotic solvents are the best suited for such transformations, but very polar media may lead to a loss of regiocontrol. This result, as well as computational models and labeling experiments, support a cyclic (chairlike) transition state with a concerted internal proton transfer.^[106,108–110] This proton transfer would then be possible only on the most substituted enamine tautomer **153a**, even though the less hindered enamine **153b** is preferentially predominant in the equilibrium when common secondary amines (such as pyrrolidine) are used (Figure 9). Furthermore, free rotation around the C₁–N bond as well as around the C₁–N bond is hampered by steric hindrance, and hence the remarkable regiocontrol only originates from the internal proton transfer. The enamine **153a** has two diastereotopic faces, but the *Si*-face is shielded by the phenyl ring and, therefore, the Michael acceptor **12** can only approach the double bond from the *Re*-face. The presence of an external proton source (such as

**Figure 9.** Proposed transition state.

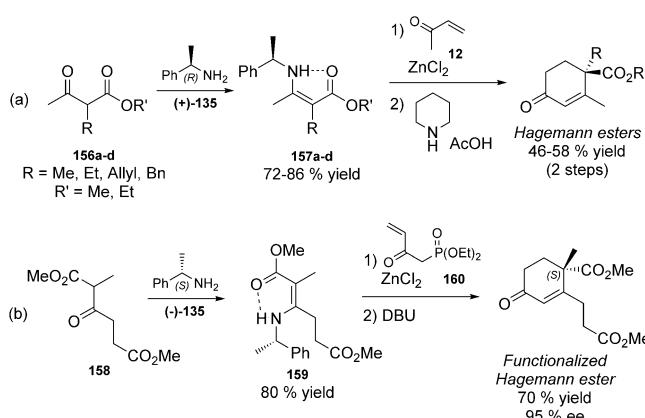
a protic solvent) will lead to the regioisomeric product, since the cyclic transition state will no longer be favored and attack will preferentially occur on the less substituted enamine.

The robustness of this method is illustrated well by numerous syntheses (Scheme 42). Starting from 2-methylcy-

**Scheme 42.** Synthesis of natural products by using the Pfau-d'Angelo method.

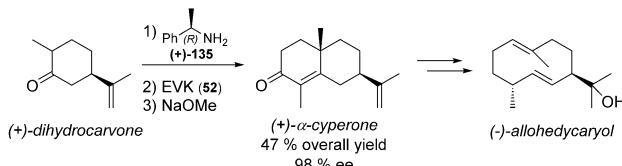
clohexanone (**5**), the corresponding imine is quantitatively obtained and condensation with **12**, followed by cyclization gives the octalone **(+)-16** in 44% yield with an enantiomeric excess of 76%.^[111] This octalone could then be transformed into a sporogen analogue. Similarly, alkylation with ethyl vinyl ketone (EVK, **52**) yields the corresponding octalone **155** in 86% yield along with 8% of the regioisomeric product.^[112] Successive recrystallizations can increase the enantiopurity to >99% ee, and three additional steps are required to yield **(-)-(2S,4aS,8aR)-1,1,4a-trimethyldecahydronaphthalen-2-ol** ((**-**TMD)).

The condensation of (*R*)-1-phenylethylamine ((*+/-*)-**135**) with the ketoesters **156a–d** gives the stabilized conjugated enamines **157a–d**, which can further react with **12** in the presence of ZnCl_2 (Scheme 43a).^[113] The 1,5-diketone intermediate that is obtained in very high enantioselectivity (93–96% ee) is further cyclized to the chiral Hagemann ester

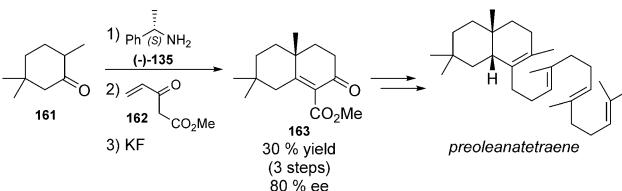
**Scheme 43.** Synthesis of Hagemann esters.

under classical conditions. A similar strategy has been used to access functionalized analogues by using the vinyl phosphonate **160** (Scheme 43 b).^[114] Simpler vinyl ketones or the Nazarov reagent failed to give this key intermediate for the synthesis of natural compounds.

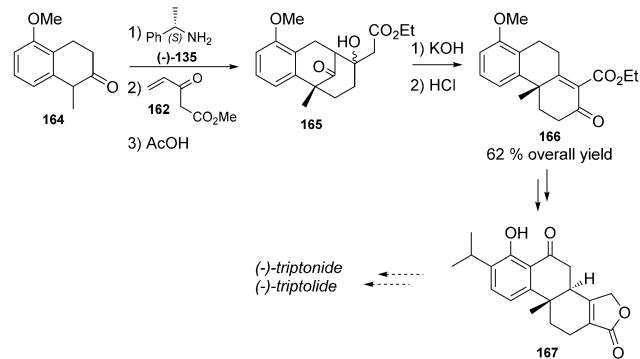
Chiral cyclohexanones such as (+)-dihydrocarvone have been used for the synthesis of (−)-allohedycaryol through the intermediate formation of (+)- α -cyperone (Scheme 44).^[115] Azeotropic imination followed by Michael alkylation with **52** and cyclization readily gives (+)- α -cyperone in excellent enantiopurity and with a good overall yield even though the epimeric lactol is formed (in 11% yield).

**Scheme 44.** Synthesis of (+)- α -cyperone and (−)-allohedycaryol.

The 2,5,5-trimethylcyclohexanone (**161**; obtained from dimethyl dimedone) reacts with (S)-1-phenylethylamine (−)**135** to afford the corresponding imine, which was then treated with the Nazarov reagent **162** (Scheme 45).^[116] Partial cyclization readily occurs, but the remaining 1,5-diketone can be converted into the desired product **163** with KF. The farnesyl side chain is then incorporated to finally give preoleanatetraene.

**Scheme 45.** Synthesis of preoleanatetraene.

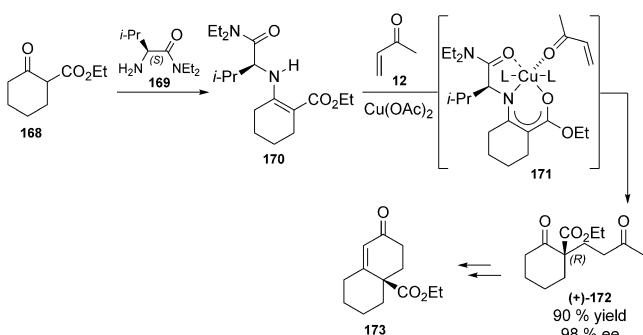
Recently, Zhang et al. used the Pfau–d’Angelo method for the stereoselective alkylation of 5-methoxytetralone **164** with the Nazarov reagent **162** (Scheme 46).^[117] Acidic treatment results in the bridged [3.3.1] product **165**, but alkaline

**Scheme 46.** Synthesis of a key intermediate of (−)-triptonide and (−)-triptolide.

conditions yields the desired enone **166** (with a good 90% ee) in a 10:1 mixture along with the tautomeric dienol. Subsequent functionalization yields the known intermediate **167** in the synthesis of both (−)-triptonide and (−)-triptolide.

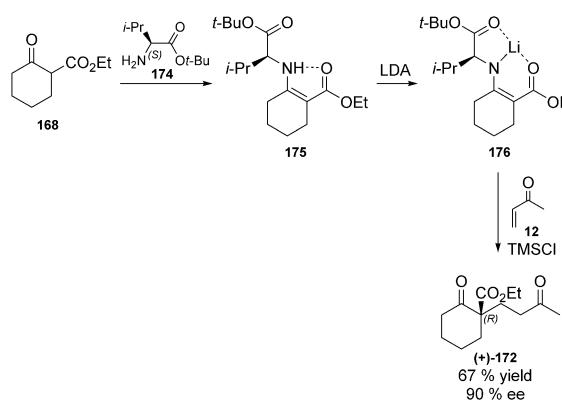
3.3.2. Chiral Enamine: Christoffers Method

To overcome the limitations of the Pfau–d’Angelo method with α -activated ketones, the Christoffers group has reported an alternative method which relies on the formation of an enamine of a chiral α -amino ester or amide (**170**) and subsequent reaction with MVK (**12**) catalyzed by copper salts to yield the desired 1,5-diketone **172** (Scheme 47).^[118–121]

**Scheme 47.** Christoffers method for the annulation of β -ketoesters.

Several amino acid derivatives were screened and the best results were obtained with L-valine diethylamide (**169**). In this reaction, the stereoselectivity seems to arise from a favored coordination between the enamine, the MVK, and the copper salt (\rightarrow **171**) rather than the internal proton delivery observed in the Pfau–d’Angelo method. The 1,5-diketone (+)-**172** can be isolated in high yield and optical purity, and the chiral auxiliary can be recovered in 96% yield.

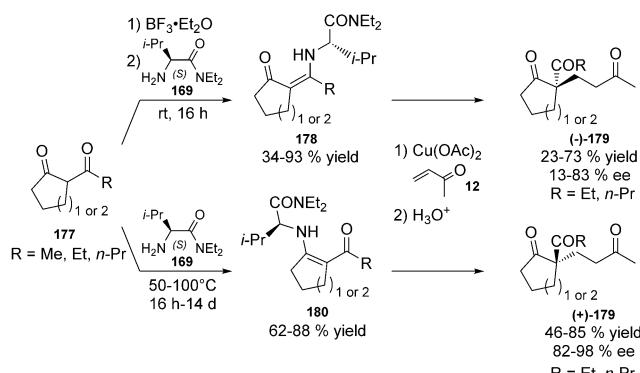
A similar reaction was described earlier by Koga and co-workers, who used L-valine *tert*-butyl ester (**174**;



Scheme 48. A chiral lithium enamide for accessing 1,5-diketones.

Scheme 48).^[122,123] However, the enantioselectivities are somewhat lower and more importantly require LDA deprotonation and activation of **12** with 5 equiv of chlorotrimethylsilane at -100°C .

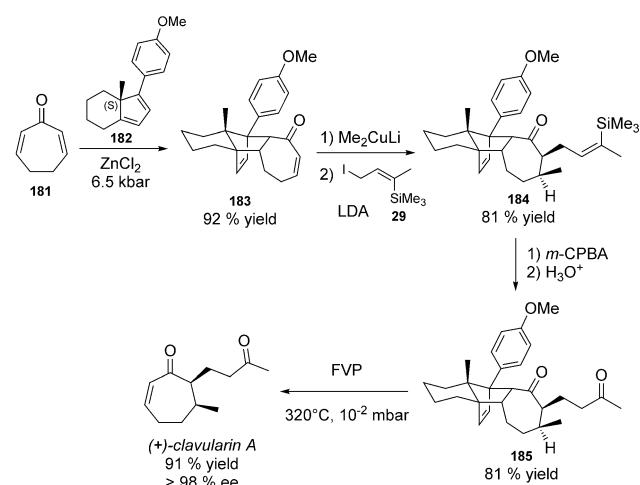
When the cyclohexanone is activated by a second ketone function (**177**), the two regiosomeric enamines **178** and **180** (exo- and endocyclic, respectively) can be obtained, which subsequently lead to the formation of the enantiomeric 1,5-diketones **179** (Scheme 49). The Christoffers group has developed a method to control the formation of either the kinetic exocyclic enamine **178** or the thermodynamic endocyclic enamine **180**, whose regiochemical ratio relies mainly on the ring size.^[124]



Scheme 49. Configurationally switching the asymmetric Michael addition through the enamine regiochemistry.

3.3.3. Winterfeldt's Chiral Diene

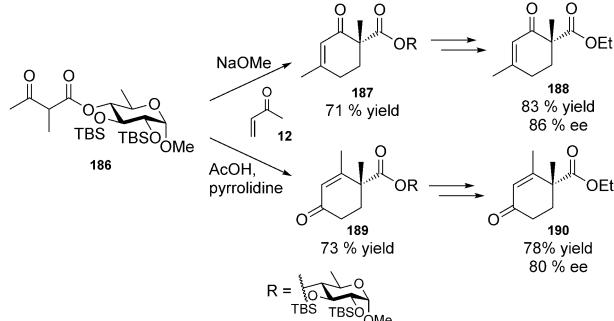
The cycloaddition of cycloheptadienone **181** with the chiral diene **182** proceeds under high pressure and Lewis acid catalysis (Scheme 50).^[125] This adduct then undergoes conjugate addition followed by reaction with the Stork–Jung vinylsilane **29** under complete stereoselectivity and in high overall yield. (+)-Clavularin A is finally obtained in high yield and with excellent enantiopurity after regeneration of the ketone and flash-vacuum pyrolysis.



Scheme 50. Diels–Alder/Retro-Diels–Alder approach towards 1,5-diketones. *m*-CPBA = *meta*-chloroperbenzoic acid, FVP = flash vacuum pyrolysis.

3.3.4. Tadano's Carbohydrate Method

Cyclization of the glucose-derived β -ketoester **186** can be performed either under strongly basic conditions or using the pyrrolidine/acetic acid method to obtain the two different cyclohexenones **187** and **189** (Scheme 51).^[126] Ethanolysis of the carbohydrate moiety affords the corresponding esters **188** and **190** in a good yield over two steps and with reasonable enantiomeric excess.



Scheme 51. Use of a carbohydrate as a chiral auxiliary in the Robinson annulation.

Of the different diastereoselective methods described, terpenes offer the possibility to control the stereochemistry and to introduce a specific side chain. The chiral imine (Pfau–d'Angleo) or enamine (Christoffers) methods are the most general and robust with achiral substrates.

4. Enantioselective Pathways to (A)MRAPs

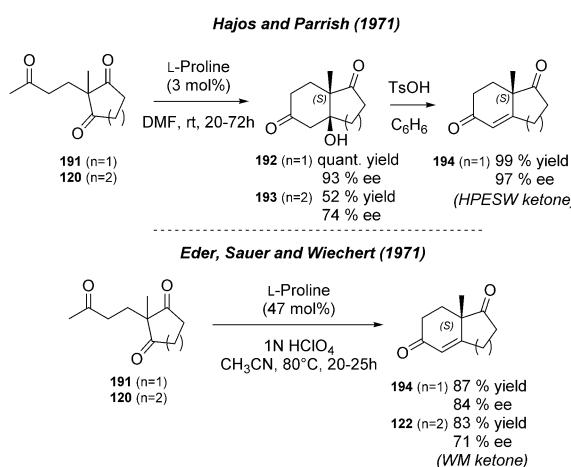
4.1. Asymmetric Organocatalysis

Organocatalysis is a pillar of modern organic chemistry and can be defined as the use of a small organic molecule

without help of metal salts to achieve a transformation. The mode of activation between the substrate and the organocatalyst can be divided into two subgroups depending on whether the interaction is covalent or not.

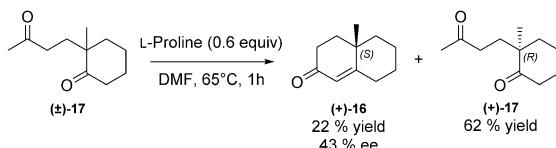
4.1.1. Covalent Interaction: Enamine/Iminium Catalysis

Of all the organocatalysts, L-proline is probably the most widely used, particularly since 2000. However, it had already been used simultaneously in the early 1970s by Hajos and Parrish at Hoffmann La Roche^[2-4] and by Eder, Sauer, and Wiechert at Schering^[5,6] for the synthesis of bicyclic enones (**122** and **194**) from prochiral diones (Scheme 52).



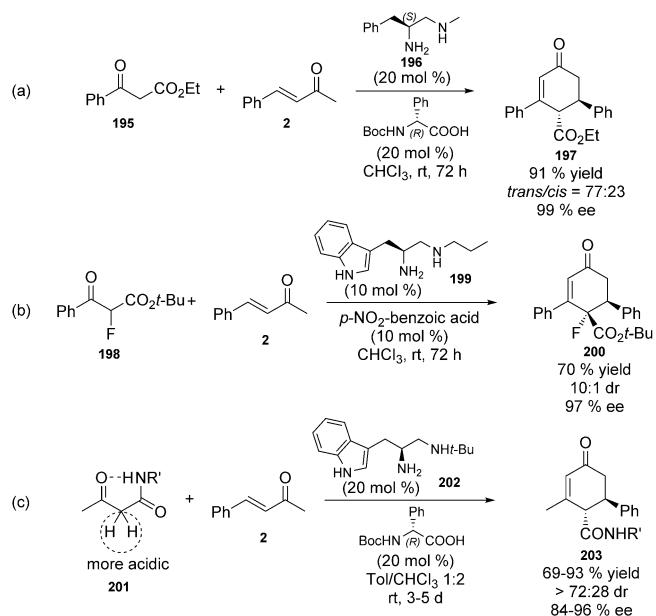
Scheme 52. Hajos–Parrish and Eder–Sauer–Wiechert reactions for DRAPs.

Similarly, Agami et al. used fairly high amounts of L-proline for the annulation of racemic 1,5-diketones (Scheme 53).^[127] The desired *S* enone (+)-**16** was isolated in moderate yield and optical purity, with the major product being the enantioenriched 1,5-diketone (+)-**17**.



Scheme 53. Agami's procedure for the synthesis of MRAPs.

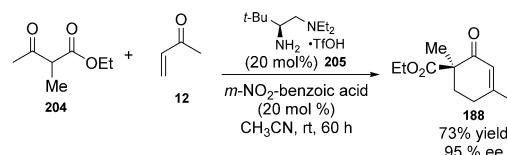
Chiral primary-secondary diamines have also been found to catalyze Robinson annulations of activated β -ketoesters in the presence of an acidic additive (Scheme 54 a).^[128,129] Further modification of the catalyst can even allow the formation of a quaternary stereogenic center containing a fluorine atom in **200** (Scheme 54 b). Under these conditions, aliphatic ketoesters generally give low yields, whereas β -ketoamides can be good alternatives.^[130] The secondary amide (**201**) can adopt a conformation that allows internal hydrogen



Scheme 54. Chiral primary-secondary diamine catalysts for AMRA. Boc = *tert*-butoxycarbonyl.

bonding and, therefore, increases the acidity of the methylenic protons and enables formation of the desired product **203** (Scheme 54 c). The mechanism for this transformation involves the formation of the iminium species derived from the stryryl methyl ketone (**2**). The secondary amine group forms a hydrogen bond with the enol form of the ketoester (or amide), thus bringing it close to the reactive center. After intermolecular Michael addition, cyclization can occur either through an aldol mechanism or a Mannich-type reaction.

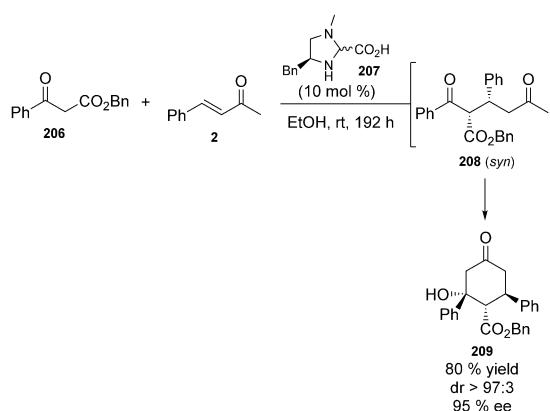
The cyclohexanone **188** is obtained when **12** is used as the Michael acceptor in combination with the chiral primary-tertiary diamine **205** (Scheme 55).^[131] In this case, the initial



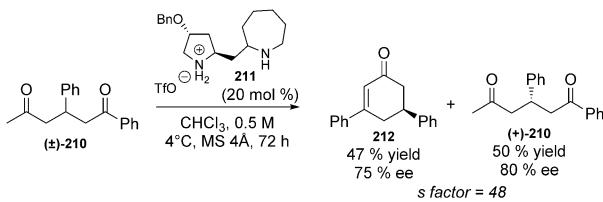
Scheme 55. Formation of a cyclohexanone bearing a quaternary center through chiral diamine catalysis. TfOH = trifluoromethanesulfonic acid.

activation of the enone through formation of an iminium species does not prevail. Instead, the β -ketoester reacts with the primary amine of the catalyst to give an enamine which is further alkylated by **12** and cyclized to the product.

Styryl methyl ketone (**2**) and β -ketoester **206** can react with imidazolidine catalyst **207** derived from phenylalanine, although in this case dehydration is not observed (Scheme 56).^[132] The Michael adduct **208** is formed as a *syn/anti* mixture in equilibrium; however, only the *syn* product gives the cyclized product **209**, thus explaining the good diastereoselectivity observed.

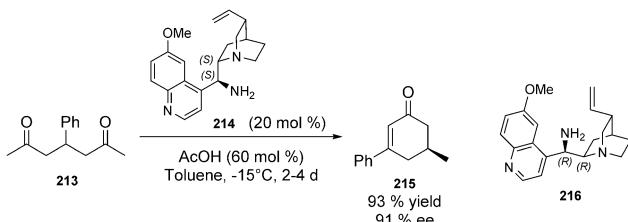
**Scheme 56.** A chiral cyclohexanone through imidazoline catalysis.

The organocatalyst **211** derived from 4-hydroxyproline is able to perform a kinetic resolution of the 1,5-diketone (\pm)-**210** through an asymmetric aldol reaction (Scheme 57).^[135]

**Scheme 57.** Kinetic resolution of 1,5-diketones to afford MRAPs.

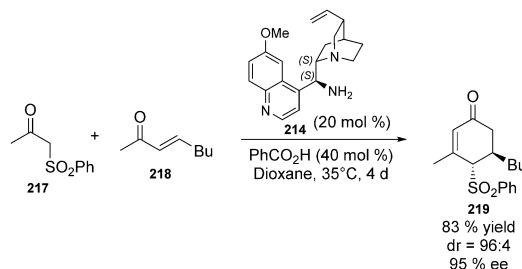
Optimized conditions (concentration, temperature, and presence of molecular sieves) allow the isolation of the enone **212** and the unreacted enantiomer of the substrate (**(+)**-**210**, both in good enantioselective excess. The *s* factor (relative rate of reaction of the two enantiomers) was calculated to be up to 48 in this case (in practice, *s* factors > 20 are considered to be effective for kinetic resolution). This preference is explained by deleterious steric interactions of the cycloheptylamine ring in the transition states.

Similarly, desymmetrization of the prochiral dione **213** can be achieved with the 9-amino-9-deoxyepiquinine catalyst **214** in the presence of acetic acid.^[134] Good yields and enantioselective excess of the MRAP **215** are obtained (Scheme 58). The pseudoenantiomer 9-amino-9-deoxyquinidine **216** yields the enantiomeric product with equal selectivity. This selectivity is

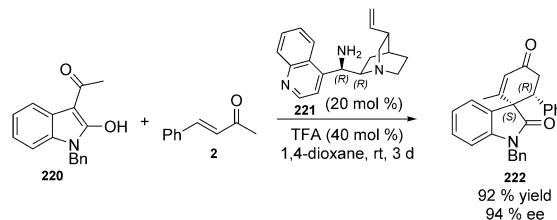
**Scheme 58.** Epiquinine and epiquinidine catalysts for the desymmetrization of a prochiral dione.

believed to be the result of a dual catalysis, where the protonated quinine moiety might activate and direct the electrophilic carbonyl group to the reactive center. In addition to the synthesis of (*R*)- or (*S*)-celery ketones starting from the same prochiral substrate (by changing the chiral catalyst), this method has also been applied for the preparation of a chiral intermediate in the synthesis of the norzoanthamine core.^[135]

The same epiquinine catalyst **214** later proved to efficiently perform the Michael addition of β -ketosulfones **217** to aliphatic vinyl ketones **218** (Scheme 59).^[136] Aminoquinine- or quinidine-derived catalysts were also used under similar conditions for the preparation of spirocyclic benzofuranones.^[137,138]

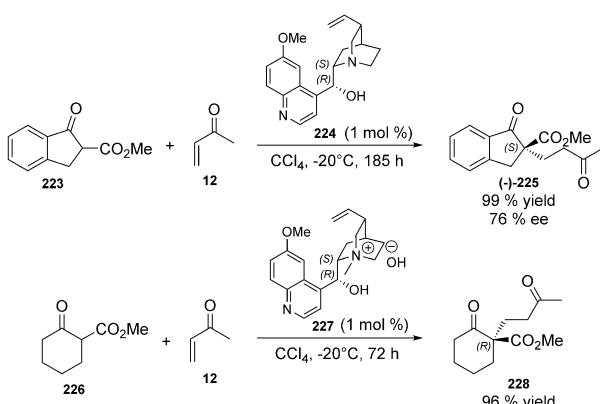
**Scheme 59.** A β -ketosulfone as a substrate for the formation of MRAPs.

Likewise, cinchona-based alkaloids (e.g. **221**) were found to promote the efficient creation of quaternary chiral centers with highly controlled selectivity to afford spirooxindole motifs **222** (Scheme 60).^[139]

**Scheme 60.** A cinchona alkaloid as a catalyst for the formation of MRAPs.

4.1.2. Noncovalent Interaction: Brønsted Base

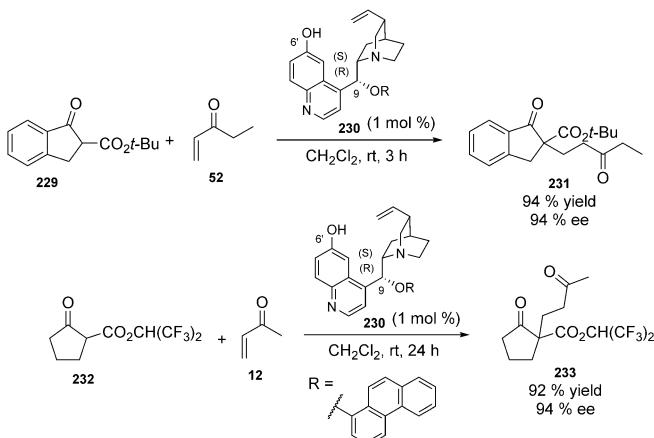
Alkaloids were already used in the 1970s as chiral bases for the Michael addition of the acidic indanone **223** to vinyl ketones (e.g. **12**; Scheme 61).^[140,141] Only a catalytic amount of alkaloid **224** (ca. 1 mol %) is required to achieve good asymmetric induction and reasonable yields. With less activated substrates, such as **226**, the quininium hydroxide salt **227** must be used to ensure reactivity, although a dramatic decrease in the asymmetric induction is observed.



Scheme 61. Michael addition using quinine as a chiral inducer.

The reaction is assumed to proceed through the formation of the enolate followed by irreversible alkylation. The difference in the selectivity observed here is attributed to the higher acidity of the indanone system and the higher reactivity of five-membered enolates compared to six-membered ones.^[142] In addition, the spatial arrangement of the tertiary amine and the hydroxy group are reported to be responsible for the selectivity, with a special emphasis on the hydroxy group since its acetylation causes a strong decrease in the reactivity and selectivity. The immobilization of quinine alkaloids on polymers (styrene-divinylbenzene or acrylonitrile) allows asymmetric conjugate addition of **12** to indanone derivatives, although the selectivity is dramatically diminished.^[143,144]

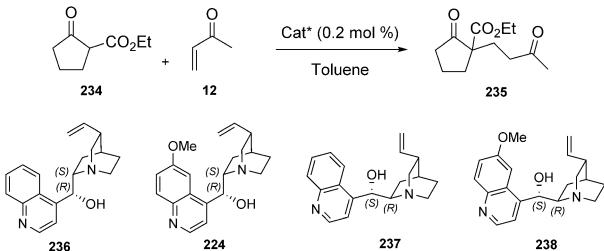
More recently, Wu et al. reported the use of cinchona alkaloids **230** for the Michael addition of several vinyl ketones to ketoesters with good yields and enantioselectivities at room temperature (however, the configuration of the stereogenic center was not reported; Scheme 62).^[145] The phenanthryl group allows an increase in selectivity. Therefore, different interactions between the catalyst and the substrate may be involved (see above). Changing from the most acidic indanone **229** to a cyclopentanone derivative causes



Scheme 62. Michael addition using phenanthryl-protected quinine as the catalyst.

a decrease in the reactivity unless a strong electron-withdrawing ester group is present (such as in **232**) or the catalyst loading is increased.

A systematic study of the influence of the nature of the cinchona alkaloid on the conjugate addition has been conducted (Scheme 63).^[146] The reaction of ketoester **234**

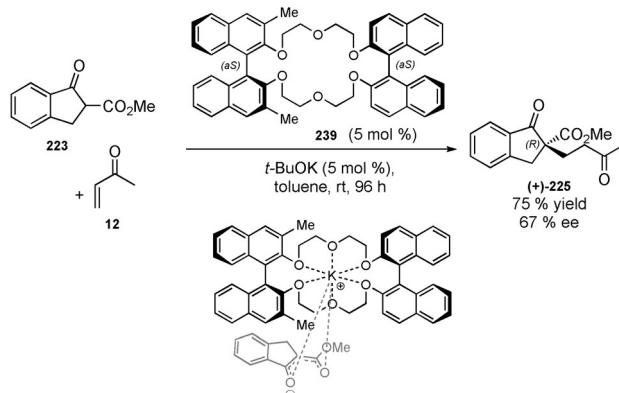


Scheme 63. Influence of the alkaloid on the enantioselectivity of the Michael addition.

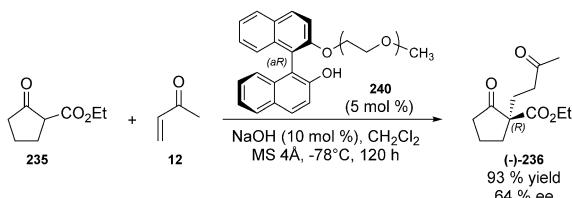
catalyzed by quinine **224** is slower than with cinchonidine **236**, although the enantioselectivity is higher. Cinchonidine **237** and quinidine **238** give the opposite enantiomeric adduct, although with a diminished enantiomeric excess. As already noticed by Hermann and Wynberg, the presence of the free hydroxy group is essential for ensuring good enantiomeric excess.^[141] The exact nature of the interactions is not well understood, since opposite selectivity is observed with the same catalyst **224** on changing from the cyclopentyl to the cyclohexyl derivative.

Enantioselectivity can also be obtained by means of a chiral counterion. One of the earliest examples is given by the use of the chiral crown ether **239** derived from BINOL (Scheme 64).^[147] A chiral supramolecular cationic complex is formed in the presence of potassium *tert*-butoxide, which can chelate the enolate of the β -keto ester substrate **223**. The product (+)-**225** is formed in good yield with 67% ee at room temperature and can be enhanced by lowering the temperature to 48% yield.

Chiral BINOL derivative **240** can be deprotonated by NaOH to afford a chiral base (Scheme 65).^[148] The length of the oligoethyleneglycol moiety has an influence on the selectivity, thus indicating the possible formation of a supra-



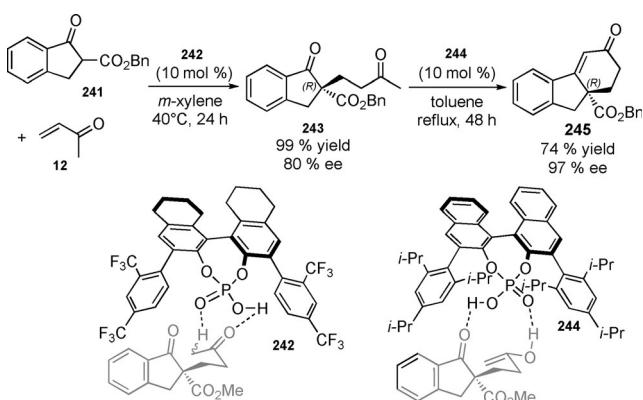
Scheme 64. Catalysis by a chiral counteranion in conjugate addition.

**Scheme 65.** A chiral BINOL catalyst for Michael addition.

molecular scaffold similar to the one described above. The yields obtained are good, but the enantioselectivities are moderate.

4.1.3. Noncovalent Interaction: Brønsted Acid

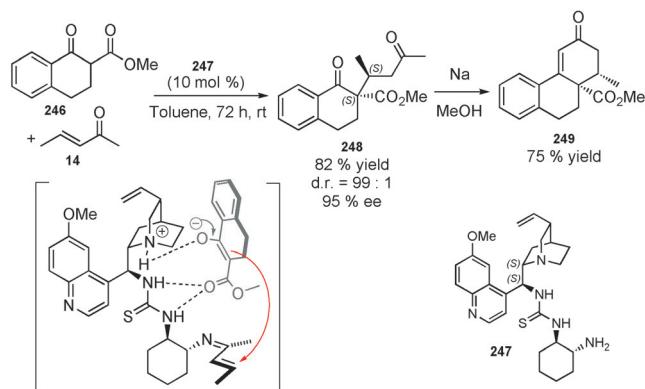
In 2009, a Robinson annulation catalyzed by two different chiral phosphoric acids was published (Scheme 66).^[149] The Michael addition was performed efficiently with catalyst **242**

**Scheme 66.** Synthesis of MRAPs mediated by axially chiral phosphoric acids.

and the subsequent annulation was achieved by catalyst **244**. This catalyst proved to be able to induce a kinetic resolution at high temperature (as observed on a racemic substrate), thus explaining the enhanced enantioselectivity. The authors hypothesized a double activation leading to a preferential enol, which then cyclizes to the desired product. This proposition was confirmed shortly after through computational studies.^[150] The phosphoric acid acts both as a Brønsted acid to activate the carbonyl group of **12** through hydrogen bonding as well as a Lewis base via its phosphoryl oxygen atom to deprotonate the substrate **241**. The 1,5-diketone **243** is further activated through a similar dual mode and allows the aldol condensation to proceed selectively.

4.1.4. Noncovalent Interaction: Hydrogen Bonding

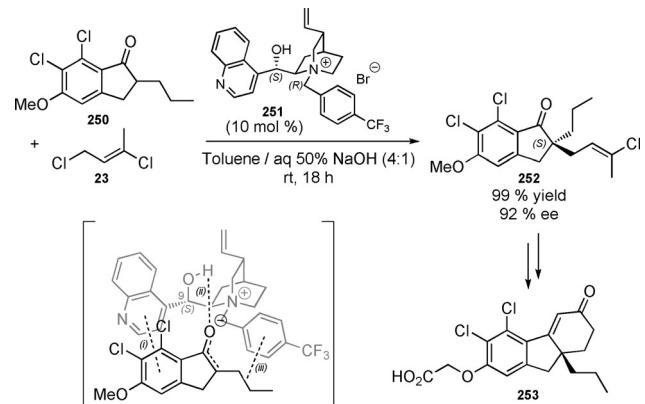
The Ye group described the epiquinidine-based organocatalyst **247**, which was able to perform efficient conjugate addition between 3-penten-2-one (**14**) and a tetralone derivative **246** (Scheme 67).^[151] The desired alkylated product **248** was obtained in good yield and very high selectivity (both

**Scheme 67.** Dual activation organocatalysis for the synthesis of MRAPs.

relative and absolute) and could subsequently be transformed to the octalone **249**. The authors have postulated that the primary amine is involved in the formation of the enamine of 3-penten-2-one, whereas the thiourea binds to the carbonyl group of the ester whose deprotonation is ensured by the epiquinidine base. The enolate can then readily attack the enamine in a stereospecific manner.

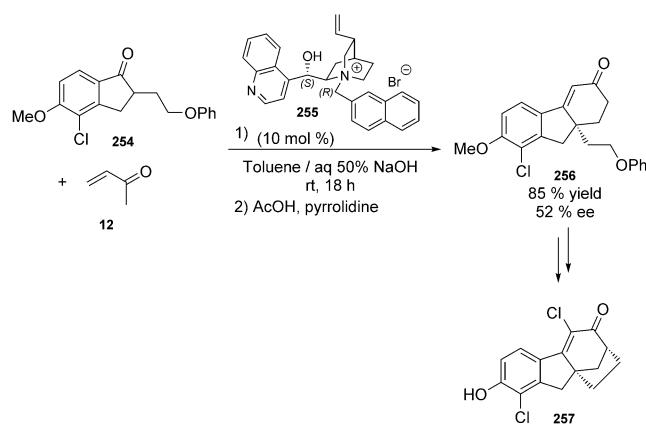
4.1.5. Noncovalent Interaction: Phase-Transfer Catalysis

One of the first efficient and practical methods for asymmetric phase-transfer catalysis (PTC) was developed by Merck, Sharp & Dohme. During the synthesis of the drug candidate **253**, the authors demonstrated the power of using a cinchoninium catalyst **251** to perform the asymmetric alkylation of the indanone derivative **250** with the Wichterle reagent **23** in a biphasic system (Scheme 68).^[152] The product **252** was obtained in quantitative yield with high enantiomeric excess (92%). This was explained by three major noncovalent interactions between the catalyst and the enolate which efficiently shield one face of the latter: i) $\pi-\pi$ interaction between the quinoline and the dichloromethoxyphenyl rings, ii) hydrogen bonding between the C₉-hydroxy group and the enolate, and iii) alkyl- π interaction between the propyl chain and the trifluoromethylbenzyl group. Interestingly, the use of

**Scheme 68.** Synthesis of MRAPs under phase-transfer catalysis with the Wichterle reagent.

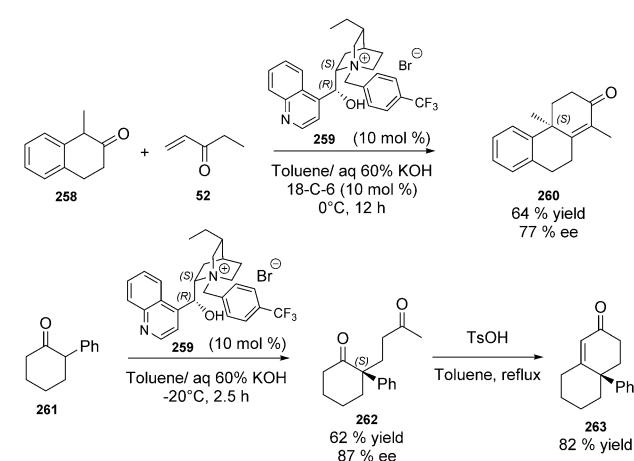
the pseudoenantiomeric catalyst (cinchonidinium) leads to a decrease in the enantioselectivity (78% *ee*), presumably because of increased steric congestion caused by the vinyl group.

Shortly after, they devised the direct use of MVK (**12**) instead of the Wichterle reagent to shorten the synthesis of this drug candidate.^[153] Almost 25 years after their seminal paper, Merck, Sharp & Dohme recently published a new development of PTC for the preparation of pharmaceutical compounds. A robust asymmetric synthesis without HPLC resolution was required to produce multikilogram quantities of an estrogen receptor- β selective agonist (**257**) for preclinical and clinical studies.^[154] After an extensive survey of different chiral phase-transfer catalysts, the key Robinson annulation was developed and the enone **256** could be recovered in 85% yield with a moderate enantioselectivity, optimized to 97% after recrystallization (Scheme 69).



Scheme 69. Synthesis of MRAPs under phase-transfer catalysis with MVK.

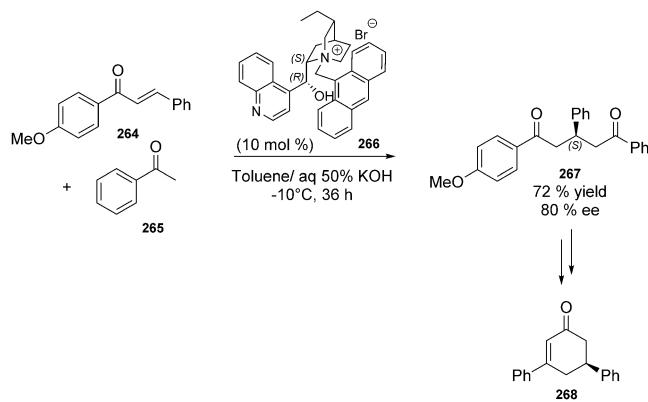
Nerinckx and Vandewalle, authors of a pioneering study in the field of asymmetric phase-transfer catalysis, have found that tetralones such as **258** undergo fast 1,4-addition, but the subsequent aldol reaction and dehydration can take several hours or days unless a crown ether is added (Scheme 70).^[156]



Scheme 70. Synthesis of MRAPs under phase-transfer catalysis.

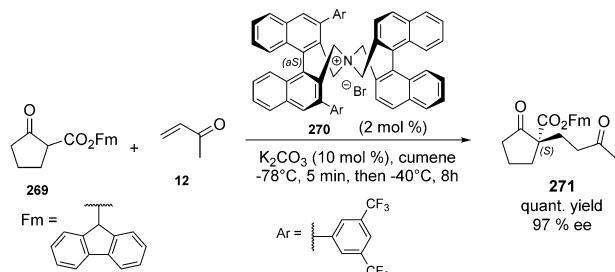
They also observed that cinchonidinium catalysts such as **259** are consistently superior to cinchonium catalysts. Moderately reactive substrates such as 2-phenylcyclohexanone (**261**) react more sluggishly; however, the 1,5-diketone **262** can be isolated in good yield and high enantioselectivity. Further cyclization can be performed under classical conditions. This method has been efficiently applied to the synthesis of a potent analgesic agent and a podocarpene terpene derivative^[156] as well as of (+)-triptoquinone A.^[157]

Cinchonidinium catalysts such as **266** are also able to promote the Michael addition between mildly reactive chalcone derivatives **264** and acetophenone (**265**; Scheme 71).^[158]



Scheme 71. Michael addition to chalcones to obtain MRAPs.

The Maruoka group has developed chiral, BINOL-derived phase-transfer catalysts **270** which were able to alkylate β -ketoesters.^[159] They also found that **269** was reactive towards **12** and that the desired product **271** could be recovered quantitatively (Scheme 72). The fluorenyl ester group enables very high optical purity, probably through privileged interactions with the catalyst.



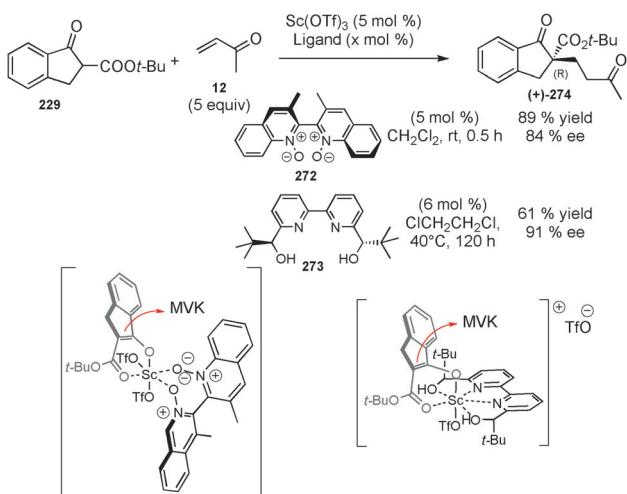
Scheme 72. Phase-transfer catalysis with a BINOL derivative.

4.2. Chiral Transition-Metal Catalysis

Transition-metal catalysts coordinated to chiral ligands constitute an important keystone of asymmetric synthesis. These are highly reactive species and only small amounts are required to perform highly efficient catalysis.

4.2.1. Scandium

Nakajima et al. have shown that the axially chiral *N*-oxide ligand **272** efficiently complexes metal centers, especially scandium, as a result of the strong electron-donating effect of the *N*-oxide group.^[160,161] This reaction requires a large excess of the Michael acceptor (5 equiv), and more importantly is limited to indanone systems such as **229** (Scheme 73). A few

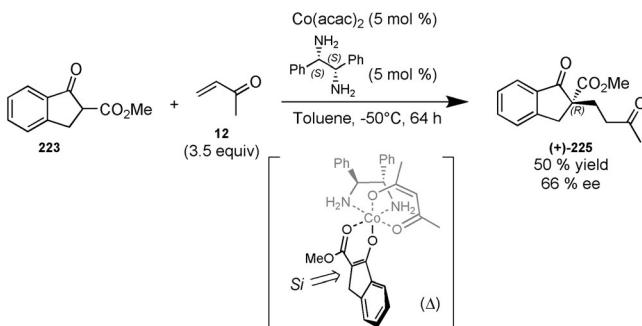


Scheme 73. Chiral scandium catalysts for Michael addition to MVK (12).

years later, a chiral bipyridine ligand **273** was found to exhibit high activity and selectivity in this reaction.^[162] The reaction to afford (+)-**274** requires a higher temperature and a longer time. However, the scope of the substrate is larger and can be extended to tetralone or cyclopentanones esters, which can give moderate yield (54 %) but good enantioselectivity (92 %) or reasonable yield (69 %) with moderate selectivity (61 %), respectively.

4.2.2. Cobalt

Similar indanone substrates have been used with a cobalt catalyst (Scheme 74).^[163] In the presence of (*S,S*)-1,2-diphenyl-1,2-ethanediamine and the β -ketoester **223**, the Co(acac)₂ is transformed to an octahedral complex that



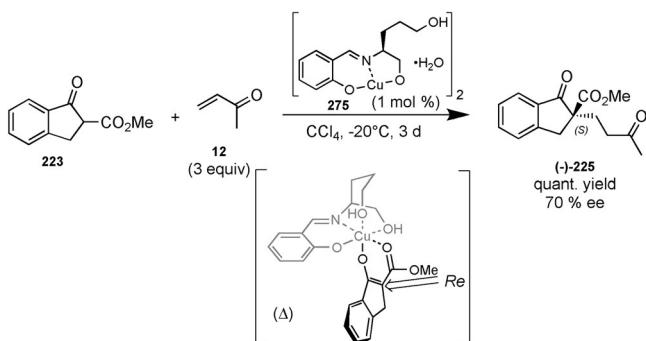
Scheme 74. Chiral conjugate addition catalyzed by cobalt complexes. acac = acetylacetanoate.

adopts a Δ configuration at the metal center. In this complex, **12** is presumed to form a hydrogen bond with one of the nitrogen atoms and, thus, Michael addition occurs at the *Si*-face of the indanone cobalt enolate.

Later, Botteghi et al. studied this conjugate addition reaction using the same substrates but in the presence of Co^{II} or Ni^{II} catalysts with chiral diamine ligands.^[164] The yields and *ee* values obtained were slightly lower than those discussed above; however, they presumed that this reaction is an enantiomer-discriminating process in which epimerization occurs through a planar metal enolate.

4.2.3. Copper

The Desimoni group developed a salicylaldehyde imine dinuclear complex **275** for the enantioselective Michael reaction.^[165] Even at 1 mol %, this catalyst can achieve a quantitative transformation with very high enantioselectivity (Scheme 75). In the presence of the β -ketoester, the

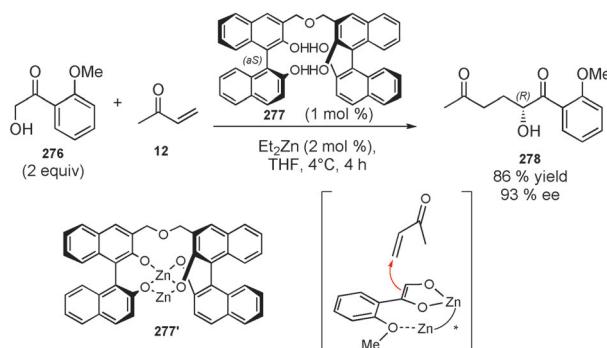


Scheme 75. Salicylaldehyde-derived copper complexes for Michael addition to indanones.

dinuclear catalyst dissociates to the octahedral Δ -configured complex, in which the hydroxy group of the side chain becomes an apical ligand. Conjugate addition then occurs on the *Re*-face of the β -ketoester. Further tuning of the catalyst, such as the length of the side chain, nature of the functional group at the end of the side chain, or steric hindrance of the equatorial belt, was explored with limited success.^[166]

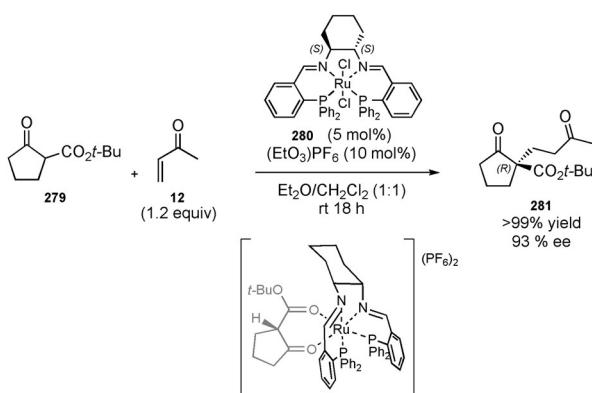
4.2.4. Zinc

In the presence of Et₂Zn as a Lewis base in THF, (*aS,aS*)-linked-BINOL **277** generates the bimetallic Zn-Zn-linked-BINOL complex **277'**, which has been shown to catalyze the Michael reaction of **12** or **52** and an α -hydroxyketone in high yield and with very good enantioselectivity (Scheme 76).^[167] By increasing the catalyst loading as well as the Et₂Zn/ligand ratio up to 4:1, the authors were later able to use other Michael acceptors such as indenones, cyclopentenone, or chalcones.^[168] However, in this study, the donor remains limited to the ketone **276**, as the selectivity is presumed to arise from the formation of a chiral zinc enolate at the hydroxy ketone moiety, whereas the other zinc center is complexed to the aromatic methoxy group.



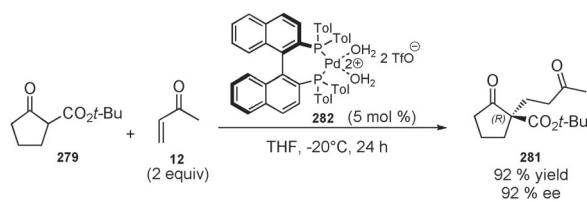
4.2.5. Ruthenium

Double chloride abstraction from the $\text{RuCl}_2(\text{PNNP})$ complex **280** gives a highly oxophilic complex that can bind to 1,3-dicarbonyl compounds (such as the cyclopentanone derivative **279**; Scheme 77).^[169] This complex can react with **12** in a $\text{CH}_2\text{Cl}_2/\text{Et}_2\text{O}$ solvent mixture to yield the desired 1,5-diketone **281** in very high yield and enantioselectivity (Et_2O allows higher selectivity).



4.2.6. Palladium

Palladium is also efficient for the enantioselective Michael addition of β -ketoesters and affords the desired 1,5-diketones in very high yield and enantioselectivity (Scheme 78).^[170,171] Interestingly, the complex **282** proved to be quite versatile, with several acyclic and cyclic β -ketoesters and enones found to be compatible. The selectivity was rationalized by the formation of a palladium enolate (observed in the ^1H NMR and ESI-MS spectra), whose *Si*-face is blocked by the bulky *tert*-butyl ester group. The μ -hydroxo bimetallic complex **282''** and the diaquo palladium(II) complex **282** are both in equilibrium with the hydroxo complex **282'**, which exhibits amphoteric properties. It acts as a Lewis acid, activating the carbonyl group of the ketone, and at the same time it also acts as a Brønsted base, to deprotonate the acidic hydrogen atom, thereby furnishing the chiral Pd-enolate **283**. The use of an ionic liquid as the



solvent allows the formation of the expected products with almost the same efficiency (**281** is obtained in 98 % yield and 83 % *ee* in [bmim][OTf] after only 8 h at 0 °C), but, interestingly, the catalyst can be readily recovered and reused for up to five consecutive runs.^[172]

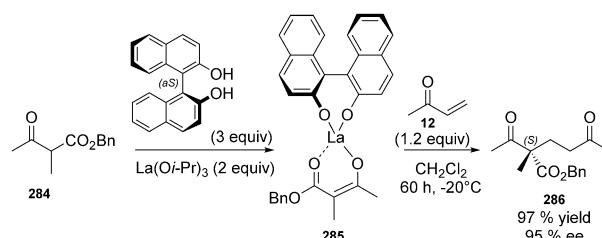
4.2.7. Silver

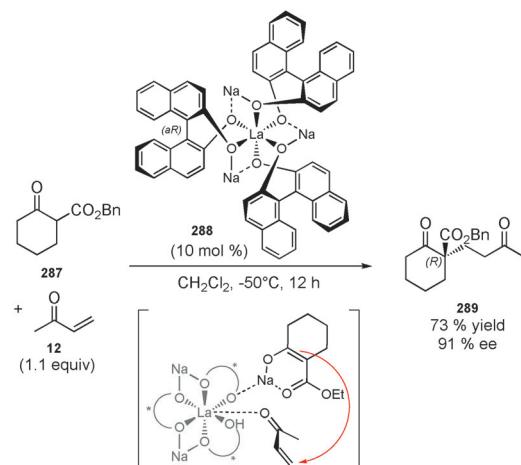
Water was efficiently used as the solvent with (*R*)-Tol-BINAP (15 mol %) and silver triflate (10 mol %) for the enantioselective conjugate addition of MVK (or EVK) with β -ketoesters of cyclic ketones.^[173] The yields obtained were very good (> 77 %) and the *ee* values were around to be 80 %.

4.2.8. Lanthanum

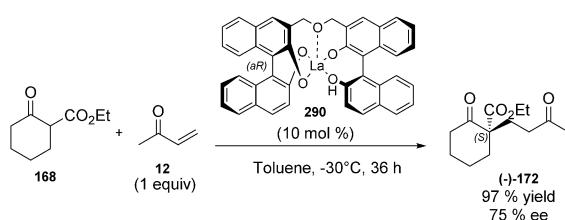
The Shibasaki group has developed numerous asymmetric transformations using chiral lanthanide-based catalysts. For example, the catalyst formed by simply mixing (*as*)-BINOL and lanthanum isopropoxide (3:2 ratio) allows the formation of the desired adduct **285** in high yield and enantioselectivity from the simple ketoester **284** and **12** (Scheme 79).^[174]

The heterobimetallic complex LSB (La-Na-BINOL, **288**) has Lewis acid character (from the La atom) and also acts as a Brønsted base at the same time.^[175] Conjugate addition of the β -ketoester **287** to **12** is efficiently performed in CH_2Cl_2 at -50 °C (Scheme 80).



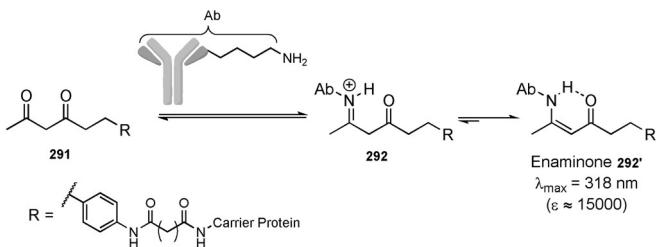


The third generation catalyst **290** was then developed to increase the sustainability.^[176] Indeed, this complex shows activities similar to the previous ones, and can be reused up to four times without loss of enantioselectivity (Scheme 81). In addition, this catalyst keeps its activity when stored for several weeks under air.

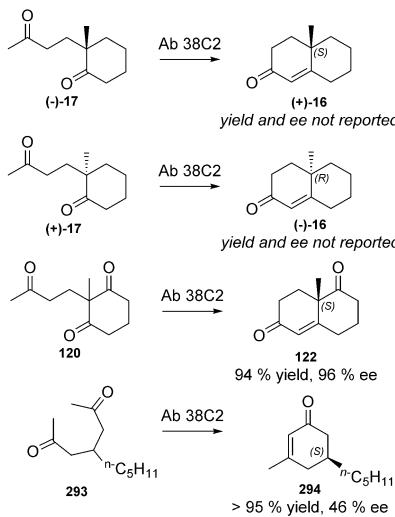


4.3. Biocatalysis

At the end of the 1990s, Lerner, Barbas, and co-workers described the development and use of abzymes as catalysts for the aldol condensation through a covalent enamine mechanism similar to the natural class I aldolases.^[177] Abzymes are antibodies with catalytic activity. It is well-known that the immune system is able to produce almost unlimited different antibodies, which in turn have different highly specific binding sites. These sites would then act as catalytic active sites for different chemical reactions. The process to detect efficient abzymes for a desired chemical transformation is called “reactive immunization”. A small molecule bearing a 1,3-dicarbonyl moiety (hapten, **291**) is used to select antibodies through the antibody–antigen specificity. The suitable antibody would form a stable enaminone **292'**, which could be detected by UV-absorption measurements (Scheme 82).



It was found that 2 abzymes (38C2 and 33F12), both bearing a lysine residue, out of 20 were able to promote aldol reactions^[178,179] and Robinson annulations^[180] with a wide substrate scope (at least 200 aldol reactions were performed; Scheme 83). The enantioselectivities observed were usually



moderate to very good, and often higher than with L-proline. However, this comparison prompted the authors to further investigate the use of proline, which is easier to use, and this study is considered to form the roots of modern organocatalysis (see Section 4.1.1).

Different enantioselective Robinson annulation procedures have been reported, but they mainly rely on the use of easily enolized substrates (β -ketoesters). The use of organocatalysts has often been limited to the synthesis of 1,5-diketones without studying the cyclization step. The same can be said for metal complexes, with perhaps the exception of palladium complex **282**, which seems to be rather versatile.

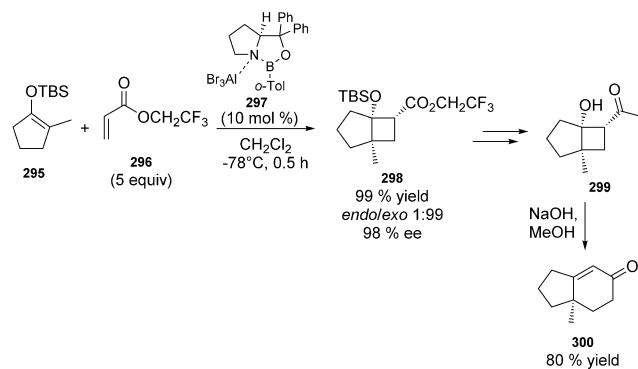
5. Indirect Alternative Pathways to Enantioenriched (A)MRAPs

In this section, the miscellaneous methods which can lead to chiral nonracemic 1,5-diketones or Robinson adducts will be presented.

5.1. Cycloadditions

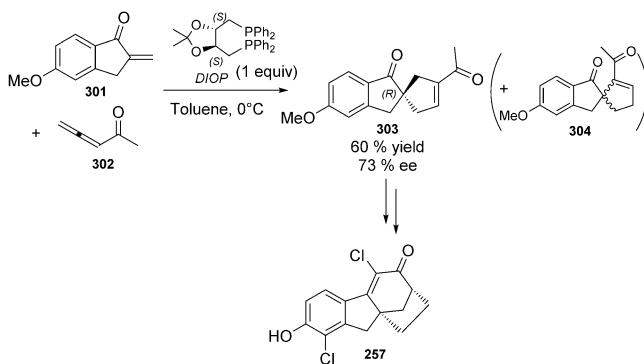
The high selectivity and efficiency of different types of cycloaddition reactions have been used on several occasions to afford MRAPs.

The oxazaborolidine aluminum bromide complex **297** has been reported to be highly efficient for the [2+2] cycloaddition of the enol ether **295** and trifluoroethyl acrylate (**296**; Scheme 84).^[181] The bicyclic adducts **298** were obtained in yields of >87% and very high enantioselectivity (>92%). The trifluoroethyl ester can be easily transformed to a methyl ketone **299**, which upon alkaline treatment affords the known enone **300**.



Scheme 84. Synthesis of MRAPs using [2+2] cycloaddition. *o*-Tol = *ortho*-tolyl.

Merck has devoted much effort in finding the best synthetic route for the agonist **257** for the treatment of menopausal vasomotor instability. The previous route required the use of hazardous chemicals such as *N,N*-dimethylhydrazine or MVK on a large scale. An alternative asymmetric [3+2] cycloaddition between the enone **301** and allenyl methyl ketone **302** was reported (Scheme 85).^[182] Among the diphosphine ligands tested, DIOP gave the best results, and after careful optimization the desired spirocyclic adduct **303** could be isolated in 60% yield with 73% *ee* and minimum formation of the regioisomeric product **304** (93:7



Scheme 85. Phosphine-catalyzed [3+2] cycloaddition to generate a chiral enone.

ratio). The enone **257** was generated by hydrogenation of the double bond under harsh conditions and cyclization.

Robinson annulation and Diels–Alder cycloaddition share common structural features, such as a similar pattern of bond formation (Figure 10). However, the stereochemical course of the reactions is usually different.

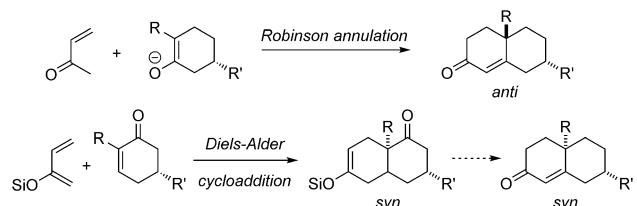
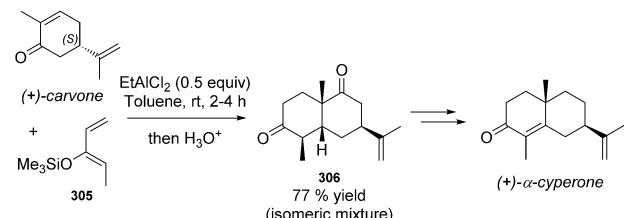


Figure 10. Configuration of the products from Diels–Alder cycloaddition and Robinson annulation.

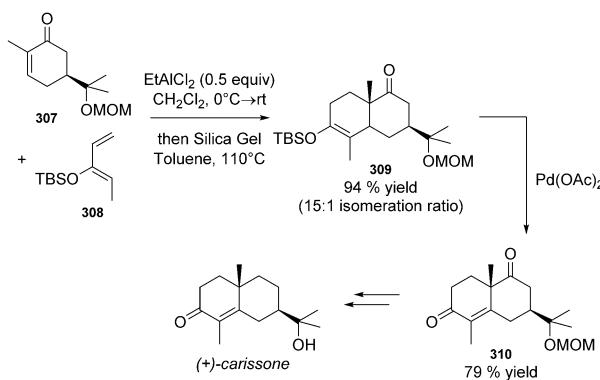
This specificity has been emphasized by the synthesis of (+)- α -cyperone (Scheme 86).^[183] The EtAlCl₂-catalyzed Diels–Alder cycloaddition of (+)-carvone with the silyloxy diene **305** yields the adduct **306** from the *anti*-addition (*anti/syn* 91:9 ratio). The acidic hydrolysis required for the deprotection results in a variable mixture of isomers from epimerization at the α position of both ketones, with the major isomer being the desired product.



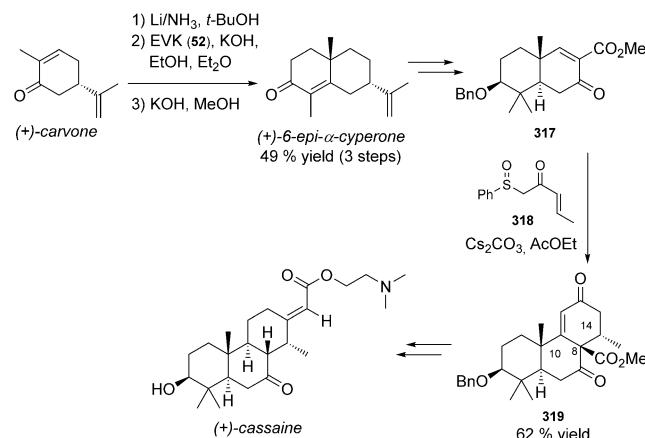
Scheme 86. Synthesis of (+)-cyperone by a Diels–Alder method.

Danishefsky and co-workers have further improved this reaction, including isomerization of the silyl enol ether **309** by treatment with silica gel at high temperature followed by a Saegusa–Ito oxidation to afford the enone **310** (Scheme 87).^[184] The total synthesis of (+)-carissone and cosmostic acid was achieved by using this method.

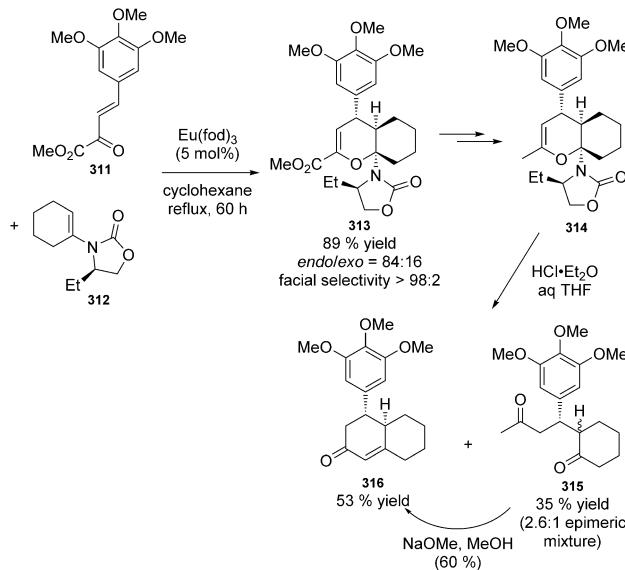
As part of a study concerning the reactivity of various chiral enamides in the inverse electronic demand hetero-Diels–Alder reaction (IED-HDA), our group disclosed the formation of the enone **316** from the Diels–Alder adduct **313** (Scheme 88).^[185] The acid-catalyzed reaction of the chiral oxazolidinone with a cyclic ketone furnishes the desired dienophile **312**, which can react with an alkyl arylidene pyruvate (**311**) under Eu(fod)₃ catalysis (fod = 1,1,2,2,3,3-heptafluoro-7,7-dimethyl-4,6-octanedionate) to yield the desired adduct **313** in high yields (>82%) with a good *endo/exo* selectivity (usually >90:10) and with almost complete facial selectivity. After complete reduction of the methyl



Scheme 87. Improved Diels–Alder method for the synthesis of (+)-carisssone.



Scheme 89. Double MRAP formation for the synthesis of (+)-cassaine.



Scheme 88. Hetero-Diels–Alder alternative for the synthesis of MRAPs.

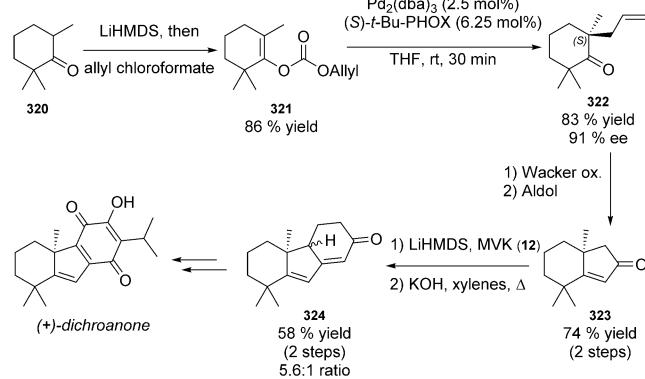
ester group (\rightarrow 314), acidic treatment leads to the formation of octalone 316 and 1,5-diketone 315 (which can further be cyclized under the classical conditions).

5.2. Nazarov Reagents

The synthesis of (+)-cassaine is interesting as it features two different annulation strategies (Scheme 89).^[186] First, the reaction of (+)-carvone with EVK (52) under the usual conditions furnishes the known 6-*epi*- α -cyperone. A series of functional-group transformations yields the β -keto ester 317, which reacts readily with the Nazarov reagent 318 under slightly basic conditions. This particular method allows the formation of a single diastereoisomer of the requisite stereochemistry (axial C14 methyl group), as implied by the configuration of the angular methyl group at C10.

5.3. Tsuji–Trost Allylation

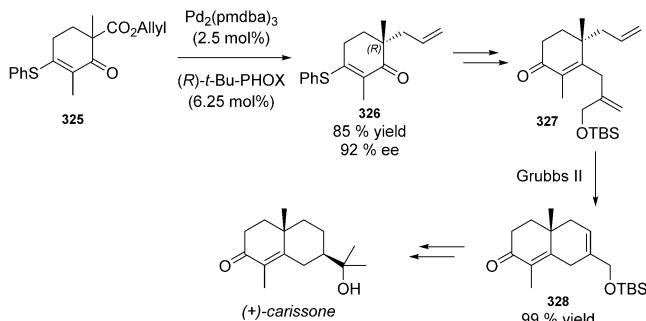
The enolate of 2,2,6-trimethylcyclohexanone (320) can be trapped with allyl chloroformate, and internal delivery of the allylic moiety can occur on treatment with a chiral palladium source (Scheme 90).^[187,188] The desired product 322 is



Scheme 90. Tsuji–Trost allylation as the key step for chiral cyclohexanone formation. dba = dibenzylidene, LiHMDS = lithium hexamethyldisilazide.

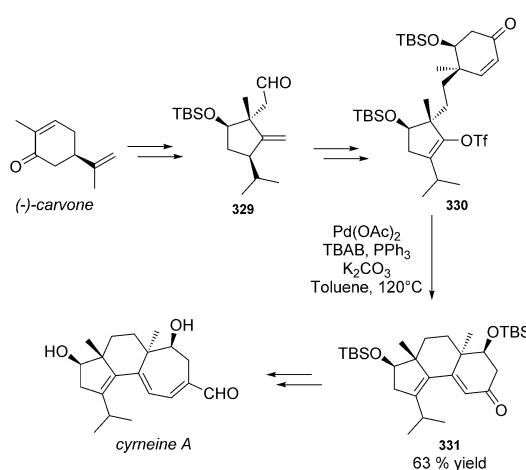
obtained in high yield with high optical purity. Wacker oxidation generates the methyl ketone and further enolization leads to the formation of the enone 323. A traditional Robinson annulation can then take place on reaction of the enolate of this enone with 12. The total synthesis of (+)-dichroanone is completed by modification of several functional groups.

The intramolecular asymmetric Tsuji allylation has been improved through the use of allyl β -keto esters 325 (Scheme 91).^[189] Under similar conditions, the desired allylic product 326 is obtained in high yield and enantiopurity. The formation of the bicyclic enone 328 is ensured by a ring-closing metathesis and it serves as a key intermediate in the synthesis of eudesmane sesquiterpenes such as (+)-carisssone and (−) α -eudesmol.



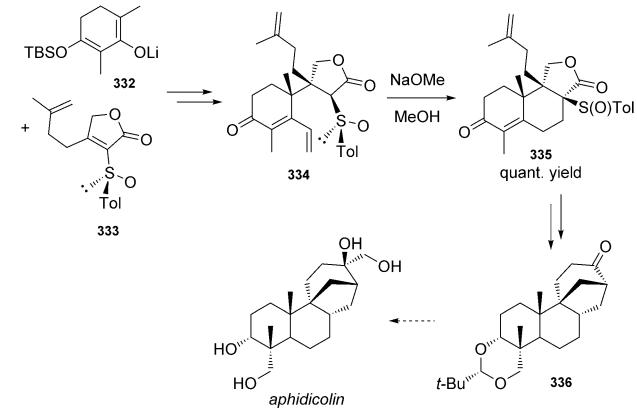
5.4. Heck Reaction

In the total synthesis of cyreneine A, (*-*)-carvone is used as the chiral starting material and serves for the synthesis of the five-membered ring in **330** (Scheme 92).^[190] An intramolecular Heck coupling is used for the formation of the Robinson adduct **331**. Despite rather harsh conditions (120 °C), the yield of this complex molecule is pretty good.



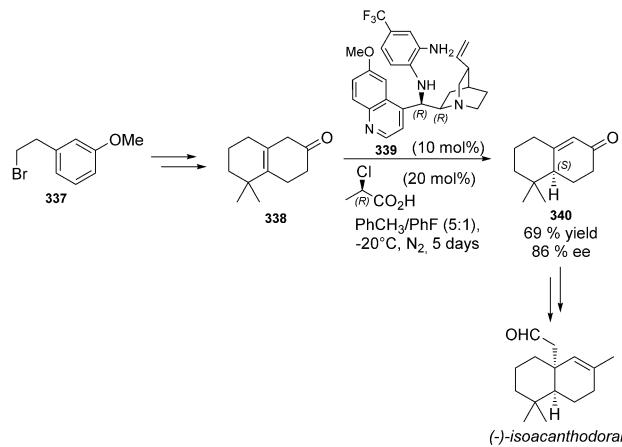
5.5. Sulfinyl-Mediated Formation of the Octalone B Ring

The formation of the B ring of the MRAP **335** through C–C bond formation has also been performed by conjugate addition (Scheme 93).^[191] The addition of the lithium dienolate **332** to the S_S(+)-sulfinyl butenolide **333** creates two contiguous quaternary stereogenic centers with high control. After vinylation, cyclization to **335** is achieved by conjugate 1,6-addition under alkaline conditions. Further functional-group modification allows the synthesis of an advanced intermediate **336** as well as a formal synthesis of aphidicolin.



5.6. Asymmetric Isomerization of β,γ -Enones

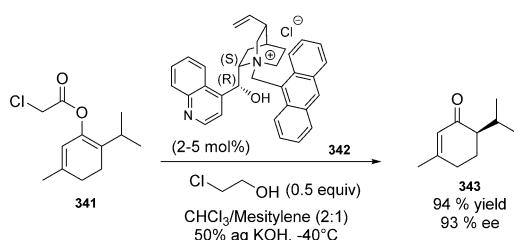
Cinchona alkaloids have recently become very attractive for promoting the enantioselective isomerization of β,γ -cyclohexenones, for example, **338** (Scheme 94).^[192] Various



substrates have been tested and the results are consistently good in terms of yields (75–94 %) and enantioselectivity (84–90 %). Although bicyclic systems are somewhat less reactive, the authors have applied this method to the synthesis of (*-*)-isoacanthodoral starting from an aromatic substrate **337**.

5.7. Asymmetric Protonation of Dienyl Acetates

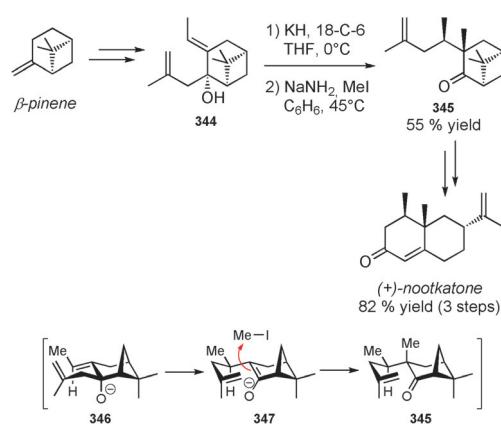
The asymmetric protonation of dienyl esters has been reported under phase-transfer catalysis (Scheme 95).^[193] The formation of a chiral dienolate from the hydrolysis of the ester **341** is presumed to occur, and this is supported by DFT calculations. The authors have also reported the generation of this enolate from a retro-Claisen reaction. The overall yields and enantiomeric ratios were very good.



Scheme 95. Phase-transfer asymmetric protonation

5.8. Oxy-Cope Rearrangement

As mentioned in Section 3.1.5, the *cis* configuration of the vicinal methyl groups of (+)-nootkatone is problematic for an efficient synthesis by a classical Robinson annulation, but can be circumvented by an anionic oxy-Cope rearrangement (Scheme 96).^[194] The substrate for the rearrangement is prepared efficiently from β -pinene.



Scheme 96. Synthesis of a chiral cyclohexanone by an oxy-Cope rearrangement.

Under highly basic conditions, the quaternary alcoholate **346** evolves stereospecifically to an enolate **347**, which is then trapped by MeI to afford the desired *cis* selectivity in **345**. Oxidation of the double bond, followed by the opening of the cyclobutane ring and annulation under basic conditions affords the (+)-nootkatone.

No general trend can be drawn from this section, as these methods were devoted to solve particular problems such as the reactivity of non-activated ketones.

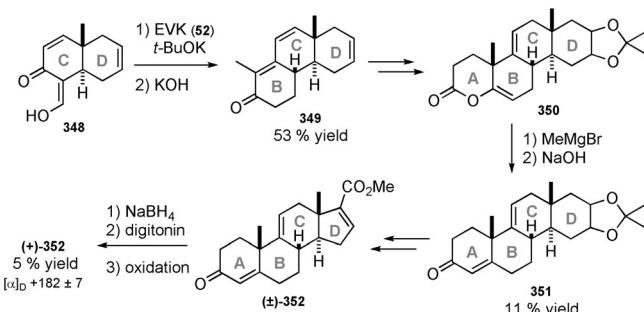
6. Enantiomeric Resolution of (A)MRAPs

Despite the tremendous progress made in the field of asymmetric synthesis of MRAPs (see Sections 3–5), enantioselective resolution may serve as an ultimate way to afford or to improve the level of the enantiopurity of the MRAPs obtained through the methods described in the preceding sections. However, this method suffers from an important drawback, since only half of the product could be recovered as

the desired compound. The methods fall into two distinctive groups, depending on whether a new covalent bond is formed or not. The following examples often lack a clear description of the enantiomeric excess. The specific optical rotation is reported with or without a reference to an enantiopure reference.

6.1. Digitonin Precipitation

One of the most elegant studies in total synthesis was the flexible synthesis of cholesterol-related steroids by Woodward et al. (Scheme 97).^[195] The rings A and B of the key

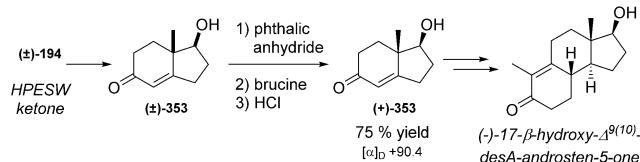


Scheme 97. Asymmetric steroid synthesis according to Woodward et al.

intermediate **352** were obtained through standard Robinson annulation reactions. After reduction of the ketone function of the key intermediate (\pm)-**352**, treatment with a digitonin solution induced a preferential precipitation of one enantiomer. Repeated precipitation and crystallization afforded only a small amount of the desired product (+)-**352**, although in good optical purity.

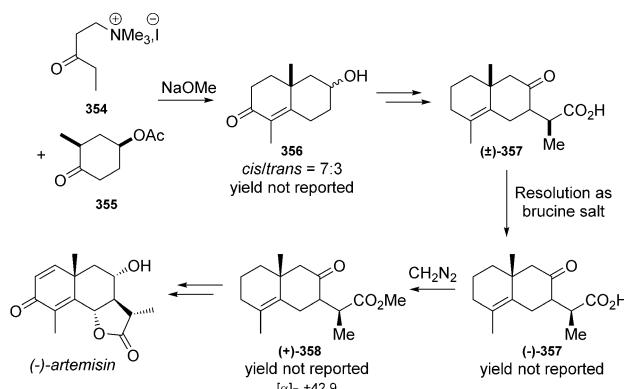
6.2. Carboxylic Acid Resolution: Brucine Salt

Resolution was performed at an early stage during the synthesis of an androstenone derivative (Scheme 98).^[196] The alcohol (\pm)-**353** derived from the reduction of the racemic HPESW ketone (\pm)-**194** is firstly transformed into a phthalic acid monoester and exposed to brucine (alkaloid from the strychnine family). The dextrorotatory salt crystallized, whereas the levorotatory salt remained in solution. Acidic cleavage of the phthalate monoester gives back the alcohol (+)-**353**.



Scheme 98. Enantiomeric resolution of an intermediate in the synthesis of an androstenone derivative.

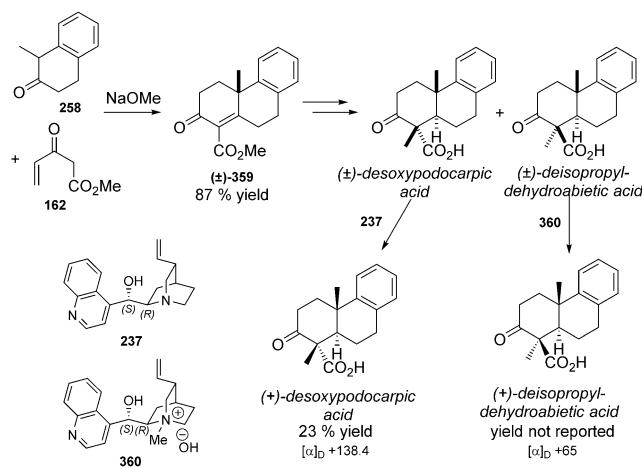
The bicyclic core of (–)-artemisin was obtained under standard Robinson conditions with the Mannich base **354** (Scheme 99).^[197] Functional-group manipulation leads to the racemic acid (±)-**357**, which can be resolved by a similar treatment with brucine.



Scheme 99. Synthesis of (–)-artemisinin.

6.3. Carboxylic Acid Resolution: Cinchonine Salt

Annulation of the Nazarov reagent **162** and the tetralone **258** yields a common intermediate (±)-**359** for the synthesis of various constituents of some conifer resins, such as abietic or podocarpic acids (Scheme 100).^[46] Resolution of (±)-desoxypodocarpic acid can be achieved by treatment with cinchonine alkaloid **237**, whereas the epimeric (±)-deisopropyl-dehydroabietic acid is best resolved with the *N*-methyl-cinchonine hydroxide salt (**360**).

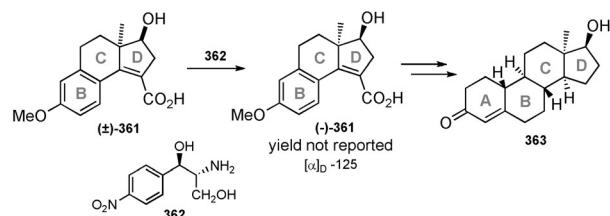


Scheme 100. Synthesis of abietic and podocarpic acid derivatives by resolution with alkaloids.

6.4. Carboxylic Acid Resolution: Chloramphenicol Derivative Salt

During the 1960s, the tremendous demand for steroids (especially for the birth-control pill) led organic chemists to develop new efficient routes towards both natural and

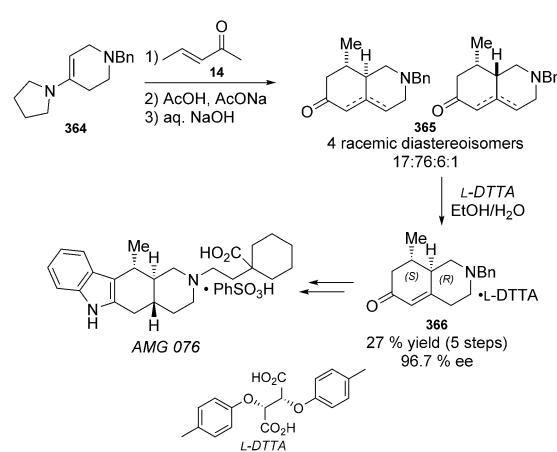
synthetic targets. In a series of publications, Velluz et al. described the use of the chloramphenicol base L-(+)-*threo*-1-(*p*-nitrophenyl)-2-aminopropan-1,3-diol (**362**) for the resolution of an early intermediate (±)-**361** of the synthesis of the 19-nortestosterone **363** (Scheme 101).^[198] This method has been applied to the synthesis of other derivatives of the nortestosterones as well as for oestradiol and its homologue 13-propynolnoroeastradiol.^[199–201] In these cases, formation of the A ring is achieved by using the Wichterle reagent **23**.



Scheme 101. A chloramphenicol derivative for the resolution of steroid intermediates.

6.5. Amine Resolution: Tartaric Acid Salt

A chiral carboxylic acid can be used to resolve a racemic mixture of amines. This method was used for the stereoselective synthesis of AMG 076, a melanin-concentrating hormone antagonist for the treatment of obesity (Scheme 102).^[202] The Robinson annulation of the enamine **364** and (*E*)-3-penten-2-one (**14**) yielded the desired adduct in a mixture of four racemic diastereoisomers **365**. The crude mixture was then treated with the L-tartaric acid derivative L-DTTA to yield the desired 8*S*,8*aR* enantiomer **366** in a good overall yield (25–28 % from piperidone) and with high optical purity (96.7 % ee which could be increased to 98.5 % by a second crystallization).



Scheme 102. Resolution of octahydroquinolone with a chiral acid.

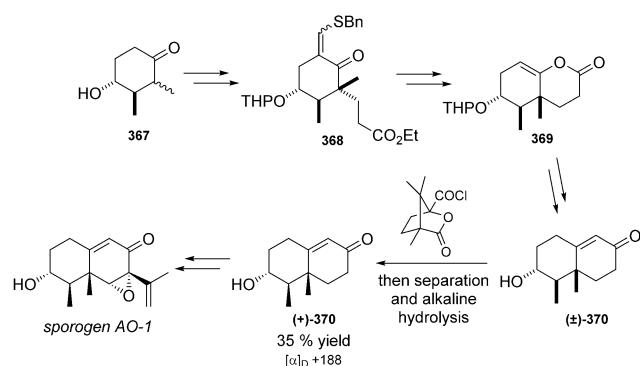
6.6. Imine Resolution: Camphorsulfonic Acid Salt

Camphorsulfonic acid has also been used to resolve, at least partially, ketones through the formation of the corresponding imine.^[203] When no acidic or basic groups are

present for generating the diastereoisomeric salts, a covalent bond must be generated, but regeneration of the desired function may be more difficult.

6.7. Camphanic Ester

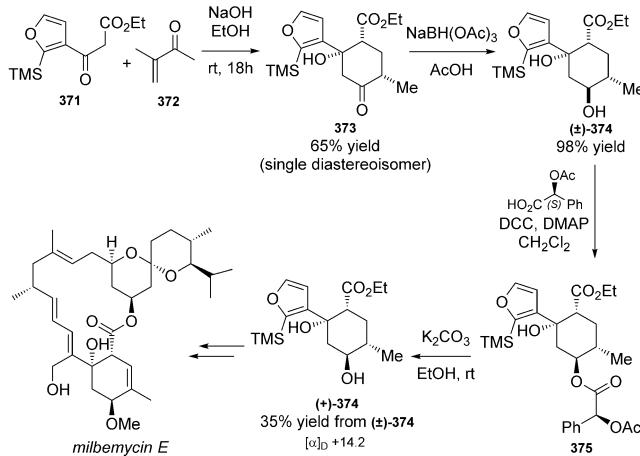
During their synthesis of sporogen AO-1, Mori and Tamura attempted enzymatic resolution of the racemic hydroxycyclohexanone **367**, but the enantioselectivity remained low.^[204] The octalone (\pm)-**370** obtained from the enol lactone **369** also failed in the enzymatic resolution. Of the chiral reagents tested, camphanic chloride allowed a good separation and the alcohol (+)-**370** could be recovered by simple alkaline hydrolysis (Scheme 103).



Scheme 103. Synthesis of sporogen AO-1 by the formation of a chiral octalone ester. THP = tetrahydropyran.

6.8. Mandelic Ester

The annulation of ketoester **371** with 3-methyl-3-buten-2-one (**372**) yielded the racemic ketol **373** in 65% yield after recrystallization (Scheme 104).^[205] After reduction of the ketone, the resulting alcohol (\pm)-**374** was converted into the

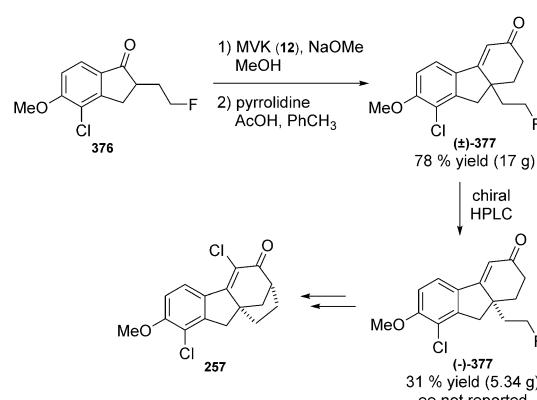


Scheme 104. Synthesis of milbemycin E by resolution through mandelate formation. DCC = dicyclohexylcarbodiimide, DMAP = 4-(dimethylamino)pyridine.

corresponding acetoxymandelates **375**, which could be separated by crystallization. An additional amount of product could be recovered from the mother liquor. After saponification, the overall process resulted in a 35% yield of the desired enantiomer (+)-**374** starting from the corresponding racemic mixture.

6.9. Chiral Preparative HPLC

Instead of the formation of a diastereoisomeric pair, resolution can also be achieved by eluting a solution of the racemate over a chiral stationary phase. The two enantiomers interact differently with the chiral stationary phase and, therefore, display different retention times. This HPLC method, which is commonly used to measure enantiomeric ratios, can also be applied on a larger scale. In fact, this efficient but expensive method was used for the synthesis of gibbatetraen-6-one derivatives **257** (Scheme 105).^[154] After performing the Robinson annulation on the indanone derivative **376** under classical conditions, the racemic enone (\pm)-**377** was subjected to chiral separation on a multigram scale to afford the desired tetrahydrofluorenone (-)-**377**.



Scheme 105. Enantiomeric separation of MRAPs by HPLC.

When the above-mentioned methods fail to give good diastereo- or enantioselectivity, resolution can be employed, even though the loss of valuable material is unavoidable.

7. Summary and Outlook

In conclusion, the Robinson annulation has proved to be a very powerful synthetic reaction for over almost 80 years, as shown by its numerous applications (many more examples performed in the racemic series were not covered here). To answer the question: “Where do we stand now?”, one must look at the different features of the reaction. From a reactivity point of view, the limitations of the original procedure have progressively been overcome, at least partially. The intrinsic tendency of the Michael acceptor to polymerize under acidic or alkaline conditions has been addressed by using surrogates or by limiting its presence by slow release in the reaction

medium. On the other hand, asymmetric access to Robinson annulation products is more problematic. Indeed, stereoselective intermolecular Michael addition using catalysts has been studied extensively in cases involving activated ketones (both organic and metallic) and this may lead to high asymmetric stereocontrol in a range of valuable synthetic applications. In contrast, in the important case of simple ketones, the state of art of asymmetric Robinson annulation remains limited by the slow progress in intermolecular Michael addition in this area, with the best methods being the use of a chiral auxiliary (Pfau-d'Angelo method) or a phase-transfer catalyst. Therefore, alternative routes to asymmetric monocarbonyl Robinson annulation products have been devised (e.g. cycloaddition) and the development of new reactions is still of synthetic interest. Even though no asymmetric version has been reported so far, homologous Pauson-Khand reactions seem to be valuable transformations.^[206–208] Sustainability is also a great challenge for chemists nowadays and has scarcely been addressed in the field of the Robinson annulation. Thanks to higher heat and mass transfer, continuous flow chemistry should also constitute an alternative in the future and could allow higher reactivity or shorter reaction times. An organocatalytic monocarbonyl Robinson annulation under continuous flow has been published recently,^[209] and there is no doubt that more examples will follow in the near future, especially from chemical companies.

Conflict of interest

The authors declare no conflict of interest.

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- [1] W. S. Rapson, R. Robinson, *J. Chem. Soc.* **1935**, 1285–1288.
- [2] Z. G. Hajos, D. R. Parrish, *Asymmetrische Synthese Polycyclischer Organischer Verbindungen*, 2102623, **1971**.
- [3] Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1612–1615.
- [4] Z. G. Hajos, D. R. Parrish, *J. Org. Chem.* **1974**, *39*, 1615–1621.
- [5] U. Eder, R. Wiechert, G. Sauer, *Verfahren Zur Herstellung Optisch Aktiver Bicycloalkan-Derivate*, 2014757, **1971**.
- [6] U. Eder, G. Sauer, R. Wiechert, *Angew. Chem. Int. Ed. Engl.* **1971**, *10*, 496–497; *Angew. Chem.* **1971**, *83*, 492–493.
- [7] B. Bradshaw, J. Bonjoch, *Synlett* **2012**, 337–356.
- [8] R. E. Gawley, *Synthesis* **1976**, 777–794.
- [9] M. E. Jung, *Tetrahedron* **1976**, *32*, 3–31.
- [10] D. Stoltz, U. Kazmaier, in *Chem. Met. Enolates (Pt. 1)*, Wiley, Hoboken, **2009**, pp. 355–409.
- [11] J. D'Angelo, *Tetrahedron* **1976**, *32*, 2979–2990.
- [12] G. Stork, A. Brizzolara, H. Landesman, J. Szmulskovicz, R. Terrell, *J. Am. Chem. Soc.* **1963**, *85*, 207–222.
- [13] W. D. Guowitz, M. A. Joseph, *Tetrahedron Lett.* **1965**, *6*, 4433–4439.
- [14] W. D. Guowitz, M. A. Joseph, *J. Org. Chem.* **1967**, *32*, 3289–3292.
- [15] R. A. Kretchmer, E. D. Mihelich, J. J. Waldron, *J. Org. Chem.* **1972**, *37*, 4483–4485.
- [16] J. A. Marshall, W. I. Fanta, *J. Org. Chem.* **1964**, *29*, 2501–2505.
- [17] S. Saito, I. Shimada, Y. Takamori, M. Tanaka, K. Maruoka, H. Yamamoto, *Bull. Chem. Soc. Jpn.* **1997**, *70*, 1671–1681.
- [18] C. H. Heathcock, J. E. Ellis, J. E. McMurry, A. Coppolino, *Tetrahedron Lett.* **1971**, *12*, 4995–4996.
- [19] W. C. Still, F. L. VanMiddlesworth, *J. Org. Chem.* **1977**, *42*, 1258–1259.
- [20] K. Narasaka, K. Soai, T. Mukaiyama, *Chem. Lett.* **1974**, *3*, 1223–1224.
- [21] K. Narasaka, K. Soai, Y. Aikawa, T. Mukaiyama, *Bull. Chem. Soc. Jpn.* **1976**, *49*, 779–783.
- [22] J. W. Huffman, S. M. Potnis, A. V. Satish, *J. Org. Chem.* **1985**, *50*, 4266–4270.
- [23] T. Sato, Y. Wakahara, J. Otera, H. Nozaki, *Tetrahedron Lett.* **1990**, *31*, 1581–1584.
- [24] T. Sato, Y. Wakahara, J. Otera, H. Nozaki, *Tetrahedron* **1991**, *47*, 9773–9782.
- [25] E. C. Du Feu, F. J. McQuillin, R. Robinson, *J. Chem. Soc.* **1937**, 53–60.
- [26] R. A. Micheli, Z. G. Hajos, N. Cohen, D. R. Parrish, L. A. Portland, W. Sciamanna, M. A. Scott, P. A. Wehrli, *J. Am. Chem. Soc.* **1975**, *40*, 675–681.
- [27] S. D. Rychnovsky, D. E. Mickus, *J. Org. Chem.* **1992**, *57*, 2732–2736.
- [28] D. F. Taber, W. Zhang, C. L. Campbell, A. L. Rheingold, C. D. Incarvito, *J. Am. Chem. Soc.* **2000**, *122*, 4813–4814.
- [29] D. F. Taber, S. C. Malcolm, *J. Org. Chem.* **2001**, *66*, 944–953.
- [30] A. Rosan, M. Rosenblum, *J. Org. Chem.* **1975**, *40*, 3621–3622.
- [31] J. A. Marshall, D. J. Schaeffer, *J. Org. Chem.* **1965**, *30*, 3642–3646.
- [32] O. Wichterle, *Collect. Czechoslov. Chem. Commun.* **1947**, *12*, 93–100.
- [33] M. Hudlický, *Collect. Czechoslov. Chem. Commun.* **1993**, *58*, 2229–2244.
- [34] D. Caine, F. N. Tuller, *J. Org. Chem.* **1969**, *34*, 222–224.
- [35] P. L. Stotter, K. A. Hill, *J. Am. Chem. Soc.* **1974**, *96*, 6524–6526.
- [36] P. L. Stotter, K. A. Hill, *Tetrahedron Lett.* **1975**, *16*, 1679–1682.
- [37] G. Stork, M. E. Jung, *J. Am. Chem. Soc.* **1974**, *96*, 3682–3684.
- [38] G. Stork, M. E. Jung, E. Colvin, Y. Noel, *J. Am. Chem. Soc.* **1974**, *96*, 3684–3686.
- [39] J. A. Singletary, H. Lam, G. B. Dudley, *J. Org. Chem.* **2005**, *70*, 739–741.
- [40] B. B. Snider, B. Shi, *Tetrahedron Lett.* **2001**, *42*, 9123–9126.
- [41] G. Stork, B. Ganem, *J. Am. Chem. Soc.* **1973**, *95*, 6152–6153.
- [42] P. Duhamel, J.-M. Poirier, G. Tavel, *Tetrahedron Lett.* **1984**, *25*, 43–46.
- [43] P. Duhamel, L. Hennequin, N. Poirier, J.-M. Poirier, *Tetrahedron Lett.* **1985**, *26*, 6201–6204.
- [44] P. Duhamel, L. Hennequin, J.-M. Poirier, G. Tavel, C. Vottero, *Tetrahedron* **1986**, *42*, 4777–4786.
- [45] P. Duhamel, G. Dujardin, L. Hennequin, J.-M. Poirier, *J. Chem. Soc. Perkin Trans. 1* **1992**, 387–396.
- [46] E. Wenkert, A. Afonso, J. B. Bredenberg, C. Kaneko, A. Tahara, *J. Am. Chem. Soc.* **1964**, *86*, 2038–2043.
- [47] B. M. Trost, R. A. Kunz, *J. Am. Chem. Soc.* **1975**, *97*, 7152–7157.
- [48] C. J. V. Scanio, L. P. Hill, *Synlett* **1970**, 651–652.
- [49] P. A. Zoretic, J. A. Golen, M. D. Saltzman, *J. Org. Chem.* **1981**, *46*, 3554–3555.
- [50] R. K. Boeckman, Jr., *Tetrahedron* **1983**, *39*, 925–934.
- [51] R. K. Boeckman, Jr., *J. Am. Chem. Soc.* **1973**, *95*, 6867–6869.
- [52] R. K. Boeckman, Jr., *J. Am. Chem. Soc.* **1974**, *96*, 6179–6181.
- [53] D. Desmaële, J. Ficini, A. Guingant, A. M. Touzin, *Tetrahedron Lett.* **1983**, *24*, 3083–3086.
- [54] J. Ficini, *Pure Appl. Chem.* **1989**, *61*, 381–384.
- [55] J. A. Marshall, T. M. Warne, Jr., *J. Org. Chem.* **1971**, *36*, 178–183.
- [56] C. J. V. Scanio, R. M. Starrett, *J. Am. Chem. Soc.* **1971**, *93*, 1539–1540.

- [57] P. S. Adamson, F. J. McQuillin, R. Robinson, J. L. Simonsen, *J. Chem. Soc.* **1937**, 1576–1581.
- [58] J. Alarcon, C. Lamilla, C. L. Cespedes, *Ind. Crops Prod.* **2013**, 42, 268–272.
- [59] F. J. McQuillin, *J. Chem. Soc.* **1955**, 528–534.
- [60] R. Howe, F. J. McQuillin, *J. Chem. Soc.* **1955**, 2423–2428.
- [61] D. Caine, J. T. Gupton III, *J. Org. Chem.* **1974**, 39, 2654–2656.
- [62] J. R. Hwu, J. M. Wetzel, *J. Org. Chem.* **1992**, 57, 922–928.
- [63] B. J. M. Jansen, J. A. Kreuger, A. de Groot, *Tetrahedron* **1989**, 45, 1447–1452.
- [64] A. Tanaka, H. Kamata, K. Yamashita, *Agric. Biol. Chem.* **1988**, 52, 2043–2048.
- [65] H. J. Swarts, A. A. Haaksma, B. J. M. Jansen, A. De Groot, *Tetrahedron* **1992**, 48, 5497–5508.
- [66] F. A. Macías, J. M. Aguilar, J. M. G. Molinillo, F. Rodríguez-Luís, I. G. Collado, G. M. Massanet, F. R. Fronczek, *Tetrahedron* **2000**, 56, 3409–3414.
- [67] J. A. Marshall, G. L. Bundy, W. I. Fanta, *J. Org. Chem.* **1968**, 33, 3913–3922.
- [68] J. A. Marshall, W. I. Fanta, G. L. Bundy, *Tetrahedron Lett.* **1965**, 6, 4807–4815.
- [69] E. Wenkert, D. A. Berges, *J. Am. Chem. Soc.* **1967**, 89, 2507–2509.
- [70] A. Murai, N. Tanimoto, N. Sakamoto, T. Masamune, *J. Am. Chem. Soc.* **1988**, 110, 1985–1986.
- [71] G. Blay, A. M. Collado, B. García, J. R. Pedro, *Tetrahedron* **2005**, 61, 10853–10860.
- [72] A. A. Verstegen-Haaksma, H. J. Swarts, B. J. M. Jansen, A. de Groot, *Tetrahedron* **1994**, 50, 10073–10082.
- [73] H. J. Swarts, A. A. Verstegen-Haaksma, A. de Groot, *Tetrahedron* **1994**, 50, 10083–10094.
- [74] A. A. Verstegen-Haaksma, H. J. Swarts, B. J. M. Jansen, A. de Groot, *Tetrahedron* **1994**, 50, 10095–10106.
- [75] P. Dagneau, P. Canonne, *Tetrahedron: Asymmetry* **1996**, 7, 2817–2820.
- [76] M. Bian, Z. Wang, X. Xiong, Y. Sun, C. Matera, K. C. Nicolaou, A. Li, *J. Am. Chem. Soc.* **2012**, 134, 8078–8081.
- [77] D. A. Siler, J. D. Mighion, E. J. Sorensen, *Angew. Chem. Int. Ed.* **2014**, 53, 5332–5335; *Angew. Chem.* **2014**, 126, 5436–5439.
- [78] P. R. Vettel, R. M. Coates, *J. Org. Chem.* **1980**, 45, 5430–5432.
- [79] D. F. Taber, D. M. Raciti, *Tetrahedron* **2011**, 67, 10229–10233.
- [80] T. Yanami, M. Miyashita, A. Yoshikoshi, *J. Org. Chem.* **1980**, 45, 607–612.
- [81] Y. Takagi, Y. Nakahara, M. Matsui, *Tetrahedron* **1978**, 34, 517–521.
- [82] A. Van der Gen, L. M. Van der Linde, J. G. Witteveen, H. Boelens, *Recl. des Trav. Chim. des Pays-Bas* **1971**, 90, 1034–1044.
- [83] A. Van der Gen, L. M. Van der Linde, J. G. Witteveen, H. Boelens, *Recl. des Trav. Chim. des Pays-Bas* **1971**, 90, 1045–1054.
- [84] J. P. Kutney, J. Balsevich, P. Grice, *Can. J. Chem.* **1980**, 58, 2641–2644.
- [85] J. P. Davidson, E. J. Corey, *J. Am. Chem. Soc.* **2003**, 125, 13486–13489.
- [86] E. J. Corey, S. E. Lazerwith, *J. Am. Chem. Soc.* **1998**, 120, 12777–12782.
- [87] K. Ngo, G. D. Brown, *J. Chem. Soc. Perkin Trans. 1* **2000**, 189–194.
- [88] K.-S. Ngo, G. D. Brown, *Tetrahedron* **1999**, 55, 15099–15108.
- [89] M. Nasuda, M. Ohmori, K. Ohyama, Y. Fujimoto, *Chem. Pharm. Bull.* **2012**, 60, 681–685.
- [90] R. V. Bonnert, P. R. Jenkins, *J. Chem. Soc. Chem. Commun.* **1987**, 6–7.
- [91] R. V. Bonnert, J. Howarth, P. R. Jenkins, N. J. Lawrence, *J. Chem. Soc. Perkin Trans. 1* **1991**, 1225–1229.
- [92] P. R. Jenkins, *Pure Appl. Chem.* **1996**, 68, 771–774.
- [93] A. Abad, C. Agulló, M. Arnó, A. C. Cuñat, M. T. García, R. J. Zaragozá, *Synthesis* **1996**, 3263, 5916–5919.
- [94] A. Abad, C. Agulló, A. C. Cuñat, R. H. Perni, *J. Org. Chem.* **1999**, 64, 1741–1744.
- [95] A. Abad, C. Agulló, A. C. Cuñat, R. H. Perni, *Tetrahedron: Asymmetry* **2000**, 11, 1607–1615.
- [96] J. D. White, P. Hrnciar, F. Stappenbeck, *J. Org. Chem.* **1997**, 62, 5250–5251.
- [97] J. D. White, P. Hrnciar, F. Stappenbeck, *J. Org. Chem.* **1999**, 64, 7871–7884.
- [98] D. F. Taber, J. F. Berry, *J. Org. Chem.* **2013**, 78, 8437–8441.
- [99] T. X. Nguyen, M. Dakanali, L. Trzoss, E. A. Theodorakis, *Org. Lett.* **2011**, 13, 3308–3311.
- [100] J. Yu, B. Yu, *Chin. Chem. Lett.* **2015**, 26, 1331–1335.
- [101] G. Jaouen, A. Meyer, *J. Am. Chem. Soc.* **1975**, 97, 4667–4672.
- [102] G. Jaouen, A. Meyer, *Tetrahedron Lett.* **1976**, 17, 3547–3550.
- [103] A. Meyer, O. Hofer, *J. Am. Chem. Soc.* **1980**, 102, 4410–4414.
- [104] T. Kitahara, H. Kurata, K. Mori, *Tetrahedron* **1988**, 44, 4339–4349.
- [105] M. Pfau, G. Revial, A. Guingant, J. D'Angelo, *J. Am. Chem. Soc.* **1985**, 107, 273–274.
- [106] J. D'Angelo, D. Desmaële, F. Dumas, A. Guingant, *Tetrahedron: Asymmetry* **1992**, 3, 459–505.
- [107] C. Camara, L. Keller, K. Jean-Charles, D. Joseph, F. Dumas, *High Pressure Res.* **2004**, 24, 149–162.
- [108] M.-E. Tran Huu Dau, C. Riche, F. Dumas, J. D'Angelo, *Tetrahedron: Asymmetry* **1998**, 9, 1059–1064.
- [109] M. J. Lucero, K. N. Houk, *J. Am. Chem. Soc.* **1997**, 119, 826–827.
- [110] L. G. da Silveira, D. Sacheto, P. A. Netz, E. R. de Oliveira, *J. Mol. Struct. THEOCHEM* **2007**, 814, 75–84.
- [111] S. Tamogami, M. Katayama, S. Marumo, M. Isobe, *Biosci. Biotechnol. Biochem.* **1996**, 60, 1372–1374.
- [112] I. Jabin, G. Revial, K. Melloul, M. Pfau, *Tetrahedron: Asymmetry* **1997**, 8, 1101–1109.
- [113] M. Nour, *Tetrahedron: Asymmetry* **2001**, 12, 765–769.
- [114] A. Gassama, J. D'Angelo, C. Cavé, J. Mahuteau, C. Riche, *Eur. J. Org. Chem.* **2000**, 3165–3169.
- [115] V. N. Zhabinskii, A. J. Minnaard, J. B. P. A. Wijnberg, A. de Groot, *J. Org. Chem.* **1996**, 61, 4022–4027.
- [116] A. F. Barrero, S. Arseniyadis, J. F. Moral, M. M. Herrador, A. Rosellón, *Synlett* **2005**, 0789–0792.
- [117] H. Zhang, H. Li, J. Xue, R. Chen, Y. Li, Y. Tang, C. Li, *Org. Biomol. Chem.* **2014**, 12, 732–736.
- [118] J. Christoffers, A. Mann, *Angew. Chem. Int. Ed.* **2000**, 39, 2752–2754; *Angew. Chem.* **2000**, 112, 2871–2874.
- [119] J. Christoffers, H. Scharl, *Eur. J. Org. Chem.* **2002**, 1505–1508.
- [120] J. Christoffers, *Chem. Eur. J.* **2003**, 9, 4862–4867.
- [121] J. Christoffers, J. Sluiter, J. Schmidt, *Synthesis* **2011**, 895–900.
- [122] K. Tomioka, W. Seo, K. Ando, K. Koga, *Tetrahedron Lett.* **1987**, 28, 6637–6640.
- [123] K. Ando, W. Seo, K. Tomioka, K. Koga, *Tetrahedron* **1994**, 50, 13081–13088.
- [124] B. Kreidler, A. Baro, W. Frey, J. Christoffers, *Chem. Eur. J.* **2005**, 11, 2660–2667.
- [125] H. Weinmann, E. Winterfeldt, *Synthesis* **1995**, 1097–1101.
- [126] H. Kubo, I. Kozawa, K. Takao, K. Tadano, *Tetrahedron Lett.* **2008**, 49, 1203–1207.
- [127] C. Agami, J. Levisalles, H. Sevestre, *J. Chem. Soc. Chem. Commun.* **1984**, 418–420.
- [128] Y.-Q. Yang, Z. Chai, H.-F. Wang, X.-K. Chen, H.-F. Cui, C.-W. Zheng, H. Xiao, P. Li, G. Zhao, *Chem. Eur. J.* **2009**, 15, 13295–13298.
- [129] H.-F. Cui, Y.-Q. Yang, Z. Chai, P. Li, C.-W. Zheng, S.-Z. Zhu, G. Zhao, *J. Org. Chem.* **2010**, 75, 117–122.
- [130] Y. Huang, C. Zheng, G. Zhao, *J. Org. Chem.* **2015**, 80, 3798–3805.

- [131] C. Xu, L. Zhang, S. Luo, *J. Org. Chem.* **2014**, *79*, 11517–11526.
- [132] N. Halland, P. S. Aburel, K. A. Jørgensen, *Angew. Chem. Int. Ed.* **2004**, *43*, 1272–1277; *Angew. Chem.* **2004**, *116*, 1292–1297.
- [133] L. Chen, S. Luo, J. Li, X. Li, J.-P. Cheng, *Org. Biomol. Chem.* **2010**, *8*, 2627–2632.
- [134] J. Zhou, V. Wakchaure, P. Kraft, B. List, *Angew. Chem. Int. Ed.* **2008**, *47*, 7656–7658; *Angew. Chem.* **2008**, *120*, 7768–7771.
- [135] H. Xue, J. Yang, P. Gopal, *Org. Lett.* **2011**, *13*, 5696–5699.
- [136] X. Sun, F. Yu, T. Ye, X. Liang, J. Ye, *Chem. Eur. J.* **2011**, *17*, 430–434.
- [137] N. Dong, X. Li, F. Wang, J.-P. Cheng, *Org. Lett.* **2013**, *15*, 4896–4899.
- [138] L.-W. Qi, L.-L. Wang, L. Peng, L.-N. Jia, F. Tian, X.-Y. Xu, L.-X. Wang, *Tetrahedron* **2013**, *69*, 9303–9308.
- [139] L.-L. Wang, L. Peng, J.-F. Bai, Q.-C. Huang, X.-Y. Xu, L.-X. Wang, *Chem. Commun.* **2010**, *46*, 8064–8066.
- [140] H. Wynberg, R. Helder, *Tetrahedron Lett.* **1975**, *16*, 4057–4060.
- [141] K. Hermann, H. Wynberg, *J. Org. Chem.* **1979**, *44*, 2238–2244.
- [142] S. J. Rhoads, A. W. Decora, *Tetrahedron* **1963**, *19*, 1645–1659.
- [143] K. Hermann, H. Wynberg, *Helv. Chim. Acta* **1977**, *60*, 2208–2212.
- [144] N. Kobayashi, K. Iwai, *J. Am. Chem. Soc.* **1978**, *100*, 7071–7072.
- [145] F. Wu, H. Li, R. Hong, L. Deng, *Angew. Chem. Int. Ed.* **2006**, *45*, 947–950; *Angew. Chem.* **2006**, *118*, 961–964.
- [146] G. Szöllösi, M. Bartók, *Chirality* **2001**, *13*, 614–618.
- [147] D. J. Cram, G. D. Sogah, *J. Chem. Soc. Chem. Commun.* **1981**, 625–628.
- [148] Y. Tamai, A. Kamifuku, E. Koshiishi, S. Miyano, *Chem. Lett.* **1995**, *24*, 957–958.
- [149] K. Mori, T. Katoh, T. Suzuki, T. Noji, M. Yamanaka, T. Akiyama, *Angew. Chem. Int. Ed.* **2009**, *48*, 9652–9654; *Angew. Chem.* **2009**, *121*, 9832–9834.
- [150] M. Yamanaka, M. Hoshino, T. Katoh, K. Mori, T. Akiyama, *Eur. J. Org. Chem.* **2012**, 4508–4514.
- [151] J. Yang, W. Li, Z. Jin, X. Liang, J. Ye, *Org. Lett.* **2010**, *12*, 5218–5221.
- [152] A. Bhattacharya, U.-H. Dolling, E. J. J. Grabowski, S. Karady, K. M. Ryan, L. M. Weinstock, *Angew. Chem. Int. Ed. Engl.* **1986**, *25*, 476–477; *Angew. Chem.* **1986**, *98*, 442–443.
- [153] R. S. E. Conn, A. V. Lovell, S. Karady, L. M. Weinstock, *J. Org. Chem.* **1986**, *51*, 4710–4711.
- [154] R. R. Wilkening, A. Fried, D. L. Parker, Jr., *Synthesis of 1,5-Disubstituted-2-Hydroxy-Gibbatetraen-6-Ones*, WO 2006/050399 A2, **2006**.
- [155] J. P. Scott, M. S. Ashwood, K. M. J. Brands, S. E. Brewer, C. J. Cowden, U.-H. Dolling, K. M. Emerson, A. D. Gibb, A. Goodyear, S. F. Oliver, et al., *Org. Process Res. Dev.* **2008**, *12*, 723–730.
- [156] W. Nerinckx, M. Vandewalle, *Tetrahedron: Asymmetry* **1990**, *1*, 265–276.
- [157] K. Shishido, K. Goto, S. Miyoshi, Y. Takaishi, M. Shibuya, *J. Org. Chem.* **1994**, *59*, 406–414.
- [158] F.-Y. Zhang, E. J. Corey, *Org. Lett.* **2000**, *2*, 1097–1100.
- [159] T. Ooi, T. Miki, M. Taniguchi, M. Shiraishi, M. Takeuchi, K. Maruoka, *Angew. Chem. Int. Ed.* **2003**, *42*, 3796–3798; *Angew. Chem.* **2003**, *115*, 3926–3928.
- [160] M. Nakajima, Y. Yamaguchi, S. Hashimoto, *Chem. Commun.* **2001**, 1596–1597.
- [161] M. Nakajima, S. Yamamoto, Y. Yamaguchi, S. Nakamura, S. Hashimoto, *Tetrahedron* **2003**, *59*, 7307–7313.
- [162] C. Ogawa, K. Kizu, H. Shimizu, M. Takeuchi, S. Kobayashi, *Chem. Asian J.* **2006**, *1*, 121–124.
- [163] H. Brunner, B. Hammer, *Angew. Chem. Int. Ed. Engl.* **1984**, *23*, 312–313; *Angew. Chem.* **1984**, *96*, 305–306.
- [164] C. Botteghi, S. Paganelli, A. Schionato, C. Boga, A. Fava, *J. Mol. Catal.* **1991**, *66*, 7–21.
- [165] G. Desimoni, P. Quadrelli, P. Righetti, *Tetrahedron* **1990**, *46*, 2927–2934.
- [166] G. Desimoni, G. Dusi, G. Faita, P. Quadrelli, P. Righetti, *Tetrahedron* **1995**, *51*, 4131–4144.
- [167] N. Kumagai, S. Matsunaga, M. Shibasaki, *Org. Lett.* **2001**, *3*, 4251–4254.
- [168] S. Harada, N. Kumagai, T. Kinoshita, S. Matsunaga, M. Shibasaki, *J. Am. Chem. Soc.* **2003**, *125*, 2582–2590.
- [169] F. Santoro, M. Althaus, C. Bonaccorsi, S. Gischig, A. Mezzetti, *Organometallics* **2008**, *27*, 3866–3878.
- [170] Y. Hamashima, D. Hotta, M. Sodeoka, *J. Am. Chem. Soc.* **2002**, *124*, 11240–11241.
- [171] Y. Hamashima, D. Hotta, N. Umebayashi, Y. Tsuchiya, T. Suzuki, M. Sodeoka, *Adv. Synth. Catal.* **2005**, *347*, 1576–1586.
- [172] Y. Hamashima, H. Takano, D. Hotta, M. Sodeoka, *Org. Lett.* **2003**, *5*, 3225–3228.
- [173] S. Kobayashi, K. Kakumoto, Y. Mori, K. Manabe, *Isr. J. Chem.* **2001**, *41*, 247–249.
- [174] H. Sasai, T. Arai, M. Shibasaki, *J. Am. Chem. Soc.* **1994**, *116*, 1571–1572.
- [175] H. Sasai, E. Emori, T. Arai, M. Shibasaki, *Tetrahedron Lett.* **1996**, *37*, 5561–5564.
- [176] Y. S. Kim, S. Matsunaga, J. Das, A. Sekine, T. Ohshima, M. Shibasaki, *J. Am. Chem. Soc.* **2000**, *122*, 6506–6507.
- [177] C. F. Barbas III et al., *Science* **1997**, *278*, 2085–2092.
- [178] T. Hoffmann, G. Zhong, B. List, D. Shabat, J. C. Anderson, S. Gramatikova, R. A. Lerner, C. F. Barbas III, *J. Am. Chem. Soc.* **1998**, *120*, 2768–2779.
- [179] B. List, R. A. Lerner, C. F. Barbas III, *Org. Lett.* **1999**, *1*, 59–61.
- [180] G. Zhong, T. Hoffmann, R. A. Lerner, S. J. Danishefsky, C. F. Barbas III, *J. Am. Chem. Soc.* **1997**, *119*, 8131–8132.
- [181] E. Canales, E. J. Corey, *J. Am. Chem. Soc.* **2007**, *129*, 12686–12687.
- [182] D. J. Wallace, R. A. Reamer, *Tetrahedron Lett.* **2013**, *54*, 4425–4428.
- [183] A. A. Haaksma, B. J. M. Jansen, A. De Groot, *Tetrahedron* **1992**, *48*, 3121–3130.
- [184] F. Peng, M. Dai, A. R. Angeles, S. J. Danishefsky, *Chem. Sci.* **2012**, *3*, 3076–3080.
- [185] F. Gallier, H. Hussain, A. Martel, A. Kirschning, G. Dujardin, *Org. Lett.* **2009**, *11*, 3060–3063.
- [186] K. Ravindar, P.-Y. Caron, P. Deslongchamps, *Org. Lett.* **2013**, *15*, 6270–6273.
- [187] A. Y. Hong, B. M. Stoltz, *Eur. J. Org. Chem.* **2013**, 2745–2759.
- [188] R. M. McFadden, B. M. Stoltz, *J. Am. Chem. Soc.* **2006**, *128*, 7738–7739.
- [189] S. R. Levine, M. R. Krout, B. M. Stoltz, *Org. Lett.* **2009**, *11*, 289–292.
- [190] E. Elamparuthi, C. Fellay, M. Neuburger, K. Gademann, *Angew. Chem. Int. Ed.* **2012**, *51*, 4071–4073; *Angew. Chem.* **2012**, *124*, 4147–4149.
- [191] R. A. Holton, R. M. Kennedy, H. Kim, M. E. Krafft, *J. Am. Chem. Soc.* **1987**, *109*, 1597–1600.
- [192] J. H. Lee, L. Deng, *J. Am. Chem. Soc.* **2012**, *134*, 18209–18212.
- [193] E. Yamamoto, D. Gokuden, A. Nagai, T. Kamachi, K. Yoshizawa, A. Hamasaki, T. Ishida, M. Tokunaga, *Org. Lett.* **2012**, *14*, 6178–6181.
- [194] A. M. Sauer, W. E. Crowe, G. Henderson, R. A. Laine, *Org. Lett.* **2009**, *11*, 3530–3533.
- [195] R. B. Woodward, F. Sondheimer, D. Taub, K. Heusler, W. M. McLamore, *J. Am. Chem. Soc.* **1952**, *74*, 4223–4251.
- [196] Z. G. Hajos, D. R. Parrish, E. P. Oliveto, *Tetrahedron* **1968**, *24*, 2039–2046.
- [197] M. Nakazaki, K. Naemura, *Bull. Chem. Soc. Jpn.* **1969**, *42*, 3366.
- [198] L. Velluz, G. Nominé, J. Mathieu, E. Toromanoff, D. Bertin, J. Tessier, A. Pierdet, *C. R. Hebd. Séances Acad. Sci.* **1960**, *250*, 1084–1085.

- [199] L. Velluz, G. Nominé, R. Bucourt, A. Pierdet, J. Tessier, *C. R. Hebd. Seances Acad. Sci.* **1961**, *252*, 3903–3905.
- [200] L. Velluz, G. Nominé, J. Mathieu, E. Toromanoff, D. Bertin, M. Vignau, J. Tessier, *C. R. Hebd. Seances Acad. Sci.* **1960**, *250*, 1510–1511.
- [201] L. Velluz, G. Nominé, R. Bucourt, A. Pierdet, P. Dufay, *Tetrahedron Lett.* **1961**, *2*, 127–130.
- [202] D. Andersen et al., *J. Org. Chem.* **2007**, *72*, 9648–9655.
- [203] W. R. Adams, O. L. Chapman, J. B. Sieja, W. J. Welstead, Jr, *J. Am. Chem. Soc.* **1966**, *88*, 162–164.
- [204] K. Mori, H. Tamura, *Liebigs Ann. Chem.* **1988**, 97–105.
- [205] E. R. Parmee, P. G. Steel, E. J. Thomas, *J. Chem. Soc. Chem. Commun.* **1989**, 1250–1253.
- [206] Y. Koga, K. Narasaka, *Chem. Lett.* **1999**, *28*, 705–706.
- [207] L. Jiao, M. Lin, L.-G. Zhuo, Z.-X. Yu, *Org. Lett.* **2010**, *12*, 2528–2531.
- [208] M. H. Shaw, E. Y. Melikhova, D. P. Kloer, W. G. Whittingham, J. F. Bower, *J. Am. Chem. Soc.* **2013**, *135*, 4992–4995.
- [209] C. Zhi, J. Wang, B. Luo, X. Li, X. Cao, Y. Pan, H. Gu, *RSC Adv.* **2014**, *4*, 15036–15039.

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