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Recent progress on asymmetric organocatalytic construction of chiral cyclohexenone skeletons

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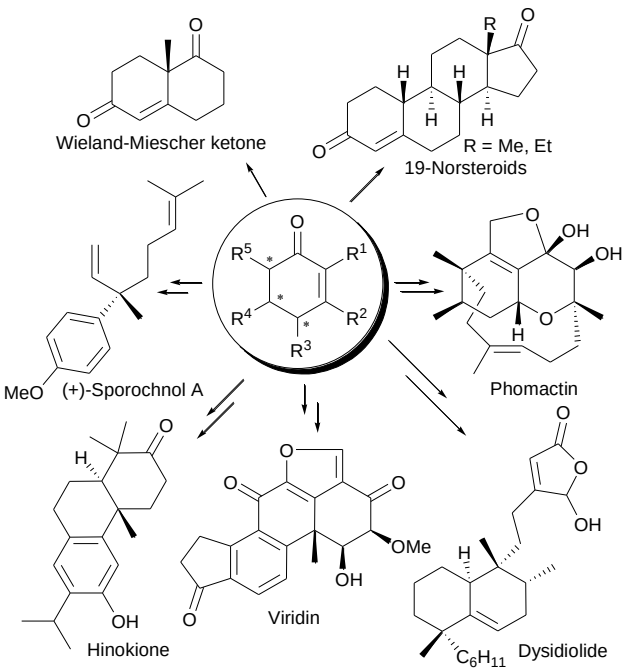
Chiral cyclohex-2-enones are so important building blocks in synthetic chemistry and life science industry that much attention has been drawn to the development of efficient and practical methodologies for accessing these enantio-enriched cyclohex-2-enone skeletons. This review described impressive progresses in terms of employing new methodology, suitable reactants as well as more efficient catalyst systems for this important enantioselective transformation. Also, the reaction mechanisms are briefly discussed.

Introduction

Chiral cyclohex-2-enones has been well-known building blocks for the synthesis of a large number of versatile natural products and other important bioactive compounds (Scheme 1).[1] In this context, much attention has been drawn to the development of efficient and practical methods for accessing these enantio-enriched cyclohex-2-enones. For example, chiral cyclohex-2-enones can be prepared by a kinetic resolution procedure,[2] or by a more articulated multistep synthesis.[3] Alternatively, a well exploited approach is based on the functionalization of readily available compounds from the chiral pool, such as carvone, pulegone or piperitone. High optical purity and low cost starting materials are advantages of the latter strategy. However, obvious limitation still exists as the lack of flexibility of choosing appropriate starting materials for specialized products.

Aldol cyclization/dehydration cascade has been employed to construct chiral cyclohex-2-enone skeletons, which involves intramolecular asymmetric aldol reaction followed by dehydration. Another method is the enantioselective Robinson annulation, which consists of three consecutive processes: I) asymmetric Michael addition of a carbonyl compound to an α,β-unsaturated ketone / aldehyde, II) an intramolecular aldol reaction, and III) dehydration.

Over the last decade, asymmetric organocatalysis has recieved an impressive growth and is now considered the "third pillar" of enantioselective catalysis together with biocatalysis and metal catalysis.[4] Significant progress has been made in the past several years towards the accomplishment of organocatalytic asymmetric construction of chiral cyclohex-2-enone skeletons. Many new substrates have been applied accordingly in this transformation, together with the new approaches developed for the purpose of target- and diversity-oriented asymmetric synthesis. In this review the recent progress is overviewed to provide the first complete picture of these exciting developments in this important field. This review is organized according to reaction types as well as the substrate structures.



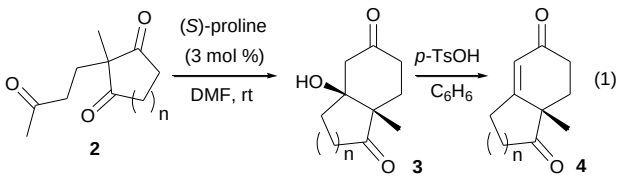
Scheme 1 Synthetic applications of chiral cyclohex-2-enones

Intramolecular annulation to chiral cyclohex-2-enone skeletons

Aldol-type reaction: triketones as substrate

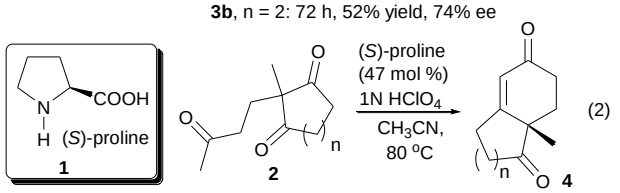
The first example of an organocatalytic intramolecular aldol cyclization/dehydration cascade to construct chiral cyclohex-2-enone skeletons was the Hajos-Parrish-Eder-Sauer-Wiechert cyclization. In the early 1970s, Hajos and Parrish discovered that (*S*)-proline (**1**) could catalyse intramolecular aldol reaction of

triketones **2**, affording aldols **3** in good yields, yet only one example was found to have more than 90% ee (Scheme 2).[5] Furthermore, acid-catalyzed dehydration of aldol adducts furnished condensation products **4** (eqs 1). In the same year, Eder et al. independently found that the condensation products **4** could be directly obtained from the (*S*)-proline-catalyzed intramolecular cyclizations (eqs 2).[6]



3a, n = 1: 20 h, 100% yield, 93% ee

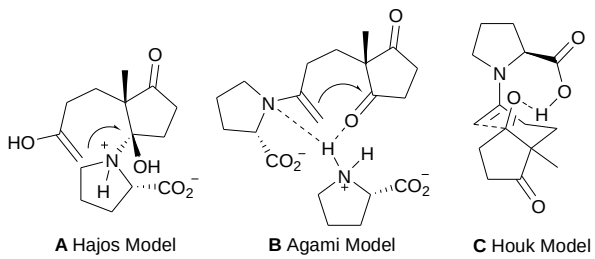
3b, n = 2: 72 h, 52% yield, 74% ee



4a, n = 1: 20 h, 87% yield, 84% ee

4b, n = 2: 25 h, 83% yield, 71% ee

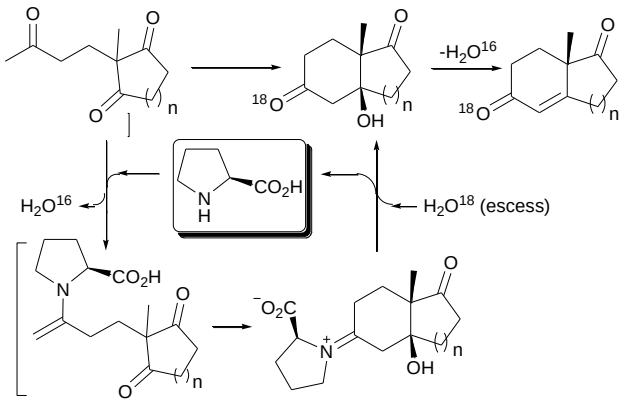
Scheme 2 Hajos-Parrish-Eder-Sauer-Wiechert reactions



Scheme 3 Mechanistic models for Hajos-Parrish-Eder-Sauer-Wiechert reactions

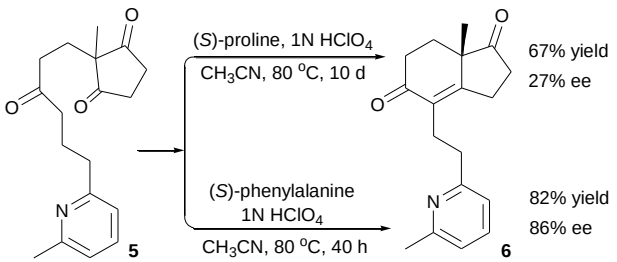
When the Hajos-Parrish-Eder-Sauer-Wiechert reaction was carried out in the presence of ^{18}O-enriched water, no ^{18}O was apparently incorporated into the annulation products.[5b] With respect to this finding, Hajos et al. proposed that proline activates one of the two enantiotopic acceptor carbonyl groups as a carbinol amine (Model **A**, Scheme 3). According to the observed small negative nonlinear effect in enantioselective reaction, Agami et al. suggested a side-chain enamine mechanism (Model **B**, Scheme 3).[7] They proposed two proline molecules joining in the C-C bond-forming transition state: one proline molecule is involved in the enamine formation, and the second one acts as a proton-transfer mediator. However, List's study indicated that a nonlinear effect could not be confirmed.[8] Moreover, the investigation by the Houk's group supported a one-proline mechanism.[9] They suggested that the side-chain enamine reacts with the ring acceptor carbonyl group, under concomitant activation via hydrogen bonding to proline's carboxylic acid group (Model **C**, Scheme 3). Swaminathan et al. reported a heterogeneous mechanism on the surface of the crystalline proline.[10] Yet, most proline-catalyzed reactions are completely homogeneous.

On the basis of experiments under carefully controlled conditions, List and co-workers found high ^{18}O incorporation (ca. 90%) in the aldol product, consistent with the proposed enamine mechanism.[11] Enamine was formed between proline and triketone, and then intramolecular aldolizaiton furnished the imine salt, followed by a hydrolysis to afford ^{18}O-labelled aldol product (Scheme 4). This enamine mechanism is also supported by parallel theoretical calculations.[12]



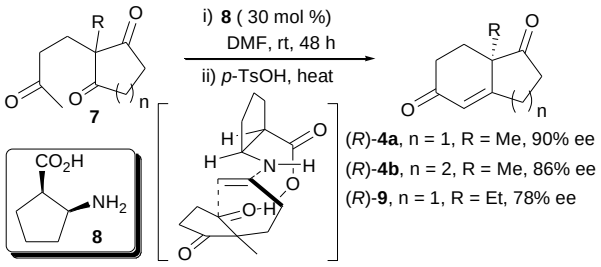
Scheme 4 ^{18}O-incorporation in the enamine catalysis cycle

Although proline remains a relatively more efficient catalyst for such aldol reactions, primary amino acid has also been found to be another highly efficient catalyst for this intramolecular aldol cyclization/dehydration cascade. It should be noted that better results could be obtained in the (*S*)-phenylalanine-catalyzed reactions when non-methyl ketones are employed as substrates (Scheme 5).[13]



Scheme 5 Proline / phenlalanine catalyzed intramolecular annulations

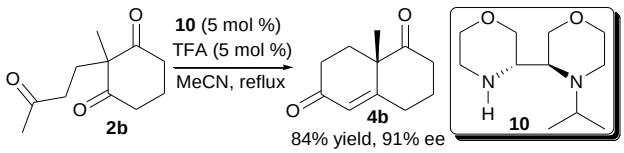
About 20 years later, Davies et al. reported a β-amino acid (1R,2S)-cispentacin **8** catalyzed Hajos-Parrish-Eder-Sauer-Wiechert reaction (Scheme 6).[14] With a catalyst loading of 30 mol% in DMF at room temperature, annulation products **4** and **9** were afforded with enantioselectivity comparable to or even higher than those obtained from proline-catalyzed reactions. The reaction mechanism was also discussed in which the cis-relative orientation of the carboxylic acid and amine functionalities within cispentacin was predicted to provide a defined asymmetric environment, with the reaction proceeding preferentially via the *S*-cis enamine geometry and hydrogen bonding activation of the carbonyl. Later, they gave a systemic study of the effect of substitution within β-amino acid framework on the asymmetric induction of Hajos-Parrish-Eder-Sauer-Wiechert reaction. The conformational constraints offered by the homochiral β-amino acids **8** were considered to be responsible for conferring high efficiency and enantioselectivity in this transformation.[15]



Scheme 6 8-Catalyzed Hajos-Parrish-Eder-Sauer-Wiechert Reaction

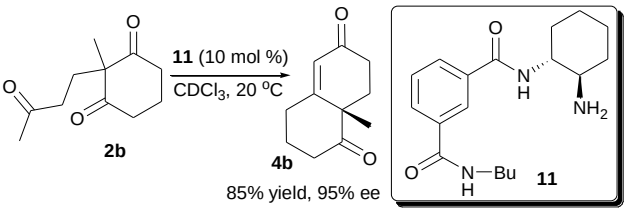
In 2007, Inomata, Paquette and co-workers gave a detailed study of an α-amino acid-mediate d intramolecular asymmetric aldol cyclization/dehydration cascade for construction of chiral cyclohex-2-enone skeletons.[16] Different α-amino acid and acidic co-catalysts were investigated and a modest level of asymmetric induction was obtained. The enantioselectivity was affected obviously by the ring size of the substrate.

Kanger et al. used the trifluoroacetic acid salt of bimorpholine derivative **10** as catalyst in the intramolecular annulation of triketone **2b** to afford product **4b** in high yield and enantioselectivity (Scheme 7).[17] Later, they improved ee value to 95% by using the trifluoromethanesulfonic acid salt of **10** as the catalyst.[18]

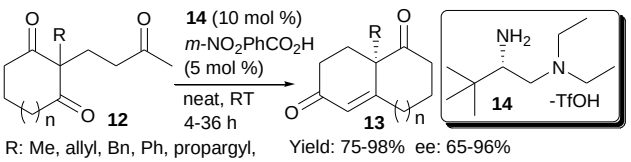


Scheme 7 Salt of **10** catalyzed Hajos-Parrish-Eder-Sauer-Wiechert Reaction

Morán et al. reported that monofunctionalized (*R,R*)-1,2-cyclohexanediamines could be employed as catalysts in the intramolecular aldol condensation of triketones **2b** for the synthesis of Wieland-Miescher ketone **4b** (Scheme 8).[19] The best result of 85% yield with up to 95% ee was obtained.



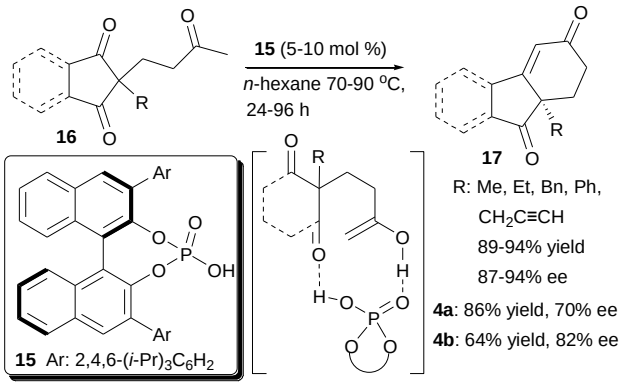
Scheme 8 11-Catalyzed Hajos-Parrish-Eder-Sauer-Wiechert Reaction



Scheme 9 Salt of **14** catalyzed Hajos-Parrish-Eder-Sauer-Wiechert Reaction

Recently, Luo et al. presented a highly enantioselective and efficient protocol for the synthesis chiral cyclohex-2-enones **4** as well as their analogues **13** catalyzed by a simple chiral primary amine **14** (Scheme 9).[20] Notably, the reaction could be conducted in gram scale with 1 mol % catalyst loading. Up to 95% yield and 96% ee were afforded.

An entirely different catalyst type for intramolecular annulation to construct chiral cyclohex-2-enones skeletons was established by Akiyama et al. (Scheme 10).[21] This represents the first example of chiral phosphoric acid **15** catalyzed desymmetrization of meso-1,3-dicarbonyl compounds **16**. The substrate was activated via hydrogen bond formed with chiral phosphoric acid. Chiral cyclohex-2-enones **4** could be obtained via this method. A wide variety of substrates could be applied in this system to furnish chiral cyclohex-2-enones **17** in high yields and with excellent enantioselectivities.

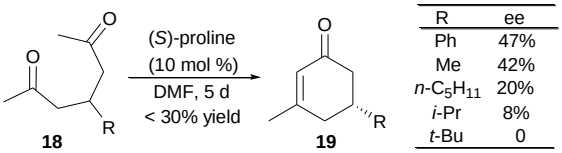


Scheme 10 Chiral phosphoric acid **15** catalyzed intramolecular annulation

Aldol-type reaction: diones as substrate

Chemists have been actively to expand the current scope of the Hajos-Parrish-Eder-Sauer-Wiechert reaction for constructing chiral cyclohex-2-enone skeletons.

Agami et al. described an aldol cyclization/dehydration cascade of acyclic 4-substituted 2,6-heptandiones **18** to construct chiral cyclohex-2-enone skeletons (Scheme 11).[22] This asymmetric transformation was catalyzed by proline. Products **19** were furnished in moderate yields and ee values. Barbas et al. employed aldolase antibody 38C2 as the catalyst to catalyse this reaction.[23] With a catalyst loading of 2 mol %, products (*S*)-**19** with more than 95% yield could be obtained after two days. However, the asymmetric induction was still in moderate level.

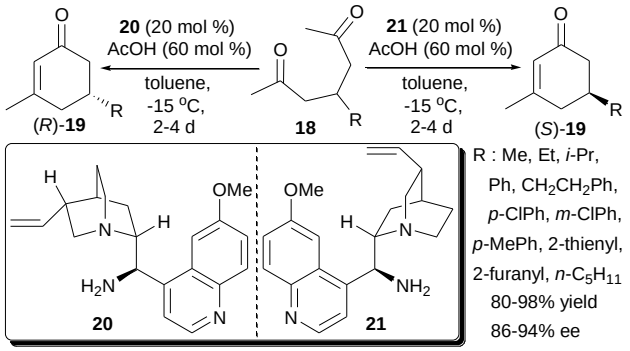


R	ee
Ph	47%
Me	42%
n-C_5H_{11}	20%
i-Pr	8%
t-Bu	0

Scheme 11 Intramolecular annulation of 4-substituted 2,6-heptandiones

An important breakthrough in the field of organocatalytic enantioselective intramolecular annulation of diones was reported by List in 2008.[24] In the presence of cinchona alkaloid-derived primary amine (**20** or **21**) associated with acid, excellent yields (80-98%) and enantioselectivities (86-94%) were afforded (Scheme 12). Notably, this methodology could constitute an access to both enantiomers of **19**, taking advantage of the pseudoenantiomeric effect of the primary amine derived from cinchona alkaloid. It was found that the acid co-catalyst

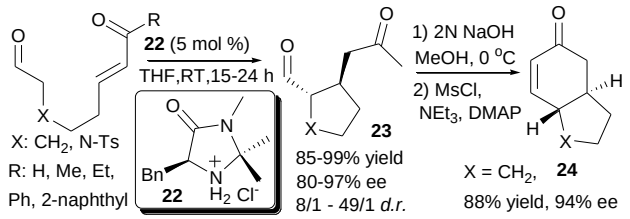
significantly influenced both reactivity and enantioselectivity. A double-activation model was suggested that the primary amine activated carbonyl group via enamine pathway and the protonated quinine moiety acted as synergistic Brønsted acid for the direction and activation of the electrophilic carbonyl group by hydrogen bonding.



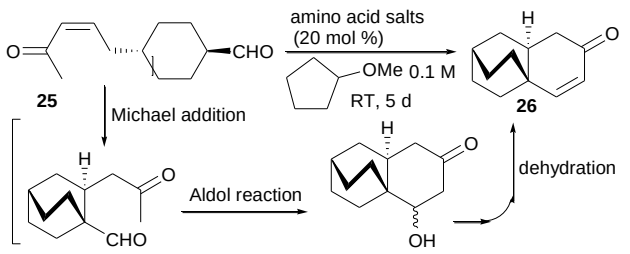
Scheme 12 Primary amine **20**/**21**-catalyzed intramolecular annulation

Robinson-type reaction: functionalized enone as substrate

Using MacMillan's catalyst **22**, List et al. disclosed the first asymmetric intramolecular Michael reaction of formyl enone to furnish cyclic ketoaldehydes **23** in excellent enantioselectivities and yields.[25] The intramolecular Aldol-type annulation of these cyclic ketoaldehydes **23** afforded optically active cyclohex-2-enone **24** in high yield and enantiomeric purity (Scheme 13).



Scheme 13 Michael-intramolecular Aldol reaction for chiral cyclohexenones

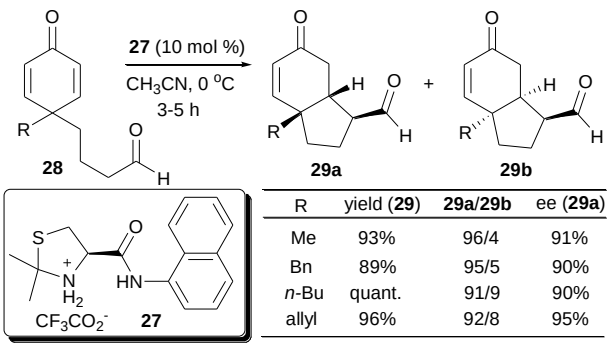


Scheme 14 Salts of amino acid catalyzed Robinson annulation

Independently, Yamamoto et al. accomplished the key Robinson annulation event in the synthesis of platensimycin with 95% yield.[26] *L*-proline was used as the chiral control element to mediate the initial intramolecular Michael addition, followed by sodium hydroxide treatment to complete the aldol dehydration. Two years later, the authors re-examined this intramolecular Robinson annulation for the construction of chiral cyclohex-2-enones (Scheme 14).[27] Many types of amino acid salts were employed as catalysts in this transformation and most of the probed catalysts could furnish the desired products **26** with more than 90% ee. However, yields of the desired products, ranging from 0 to 84%, were affected obviously by the catalyst employed.

Michael-type reaction: 4-functionalized cyclohexa-2,5-dienone as substrate

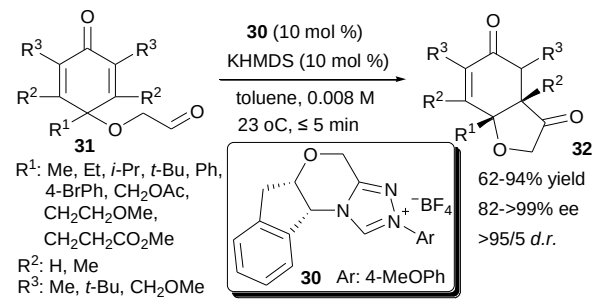
In 2005, Hayashi et al. presented a successful application of the cysteine-derived organocatalyst in a highly enantioselective intramolecular Michael reaction to construct chiral cyclohex-2-enones (Scheme 15).[28] In the presence of organocatalyst **27**, the bicycle[4,3,0]nonene carbon skeletons **29** were formed smoothly with high yields and asymmetric induction.



R	yield (**29**)	**29a**/**29b**	ee (**29a**)
Me	93%	96/4	91%
Bn	89%	95/5	90%
n-Bu	quant.	91/9	90%
allyl	96%	92/8	95%

Scheme 15 27-Catalyzed intramolecular Michael reaction

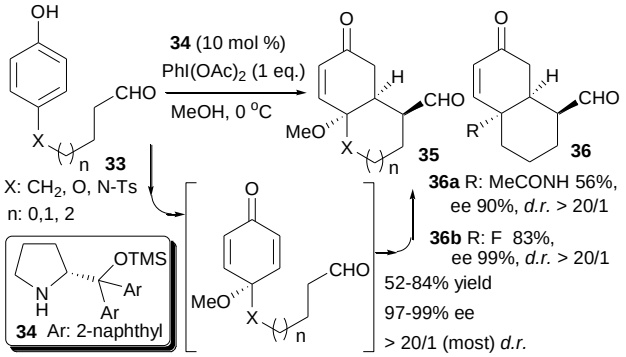
Using aminoindanol-derived triazolium salt **30** bearing an anisyl substituent as organocatalyst, Rovis et al. documented an intramolecular Stetter reaction for the asymmetric synthesis of hydrobenzofuranones **32** through desymmetrization of cyclohexa-2,5-dienones **31** (Scheme 16).[29] With a catalyst loading of 10 mol%, the annulation proceeded promptly and products **32** were obtained in good-to-excellent yields with enantioselectivities of ranging from 82% to 99% and more than 95/5 of diastereoselectivities. Remarkably, quaternary stereocenters and up to three contiguous stereocenters could be generated in excellent enantioselectivities and diastereoselectivities.



Scheme 16 30-Catalyzed intramolecular Stetter reaction

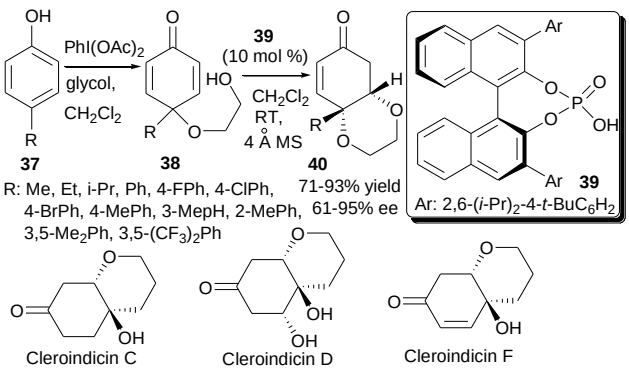
An elegant process for directly converting a para-substituted phenol to a highly functionalized chiral cyclohex-2-enone skeleton **35** was reported by Gaunt's group.[30] The process involved oxidative dearomatization of substituted phenols **33** followed by a desymmetrizing secondary amine **34** catalyzed asymmetric intramolecular Michael addition (Scheme 17). This one-step transformation revealed a complex structure formation with exquisite control of three new stereogenic centers and an array of exploitable orthogonal functionality directly from a flat molecule that is devoid of architectural complexity. Interestingly, authors found that non-oxygen nucleophiles could also participate

in this reaction. When the reaction was carried out in a mixture of $(CF_3)_2CHOH$ and MeCN, -CN could act as a nucleophile through a Ritter-type reaction to furnish amide **36a**. Furthermore, oxidation in the presence of HF-pyridine complex resulted in product **36b**. This method provided a simple route to form a tertiary C-F bond within a complex chiral molecule using enantioselective catalysis.



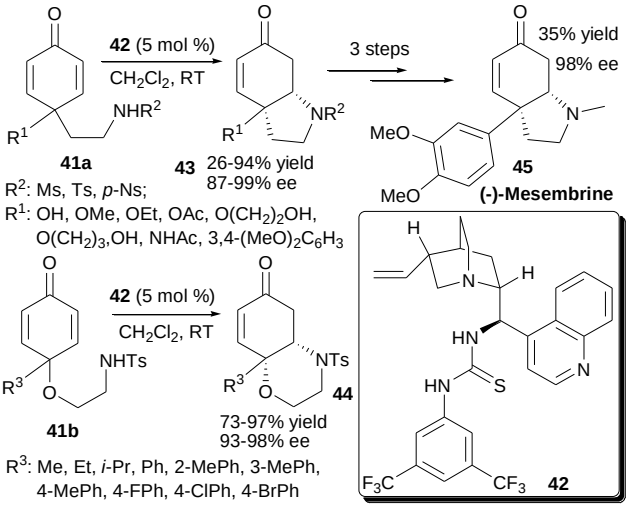
Scheme 17 Organocatalytic oxidative dearomatization

You et al. used a similar process in the desymmetrization of cyclohexadienones via Brønsted acid-catalyzed enantioselective oxo-Michael reaction, affording chiral 1,4-dioxane derivatives in high yields (Scheme 18).[31] 4-Substituted phenols **37** were initially treated with $PhI(OAc)_2$ in a mixture of dichloromethane and glycol to furnish cyclohexadienones **38**. Then in the presence of chiral phosphoric acid **39**, asymmetric intramolecular oxo-Michael addition of **38** afforded enantioenriched cyclohex-2-enones **40**. With this synthetic method, enantioselective synthesis of cleroindicins (C, D, F) could be realized in a highly efficient and concise manner, which were natural products isolated from Clerodendum indicum, a plant used in China for treatment of malaria and rheumatism.



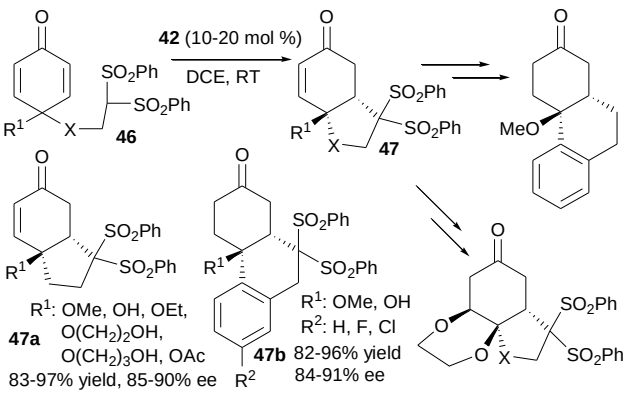
Scheme 18 39-Catalyzed desymmetrization of cyclohexadienones

Continuing their investigations, You et al. elegantly realized the intramolecular aza-Michael addition of cyclohexadienones **41** for constructing chiral cyclohex-2-enones by using cinchonine derived thiourea **42** as organocatalyst (Scheme 19).[32] With this established methodology, a series of highly enantioenriched pyrrolidine **43** and morpholine **44** derivatives were obtained in excellent yields and ee values. In particular, the total synthesis of (-)-Mesembrine **45** was yielded 35% with up to 98% ee. This is the major alkaloid component of Sceletium tortuosum with potent serotonin reuptake inhibitor activity.

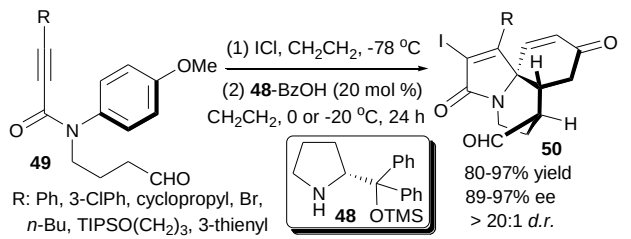


Scheme 19 42-Catalyzed intramolecular aza-Michael reaction

With the aid of the same organocatalyst **42**, You et al. successfully explored the substrate scope to cyclohexadienones **46** bearing a bisphenylsulfonyl methylene group for the construction of chiral cyclohex-2-enone skeletons via asymmetric intramolecular Michael addition (Scheme 20).[33] Highly enantioenriched cyclohex-2-enone derivatives **47** were obtained in good-to-excellent yields. The transformations of multifunctionalized products **47** have also been demonstrated.



Scheme 20 42-Catalyzed intramolecular Michael reaction

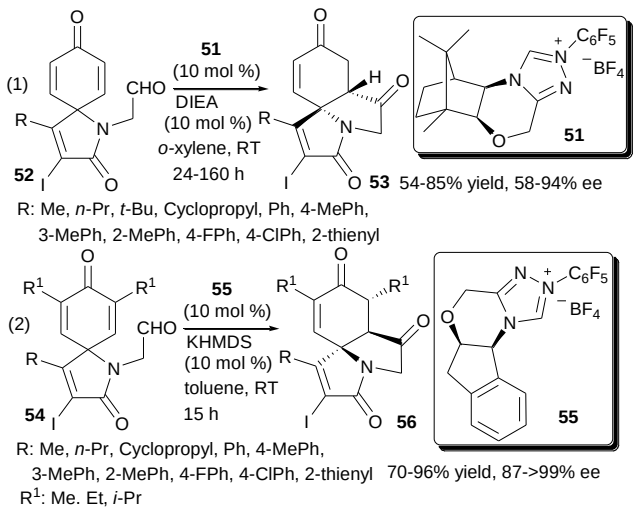


Scheme 21 48-Catalyzed desymmetrization of cyclohexadienones

A straightforward enantioselective synthesis of chiral cyclohex-2-enone skeletons was established by Gaunt et al. using anisidine derivatives as the precursor for a stepwise Larock's I-Cl dearomatization and intramolecular Stetter reaction (Scheme 21).[34] This electrophile-triggered, secondary amine **48** catalyzed enantioselective dearomatizaztion transformation converts simple

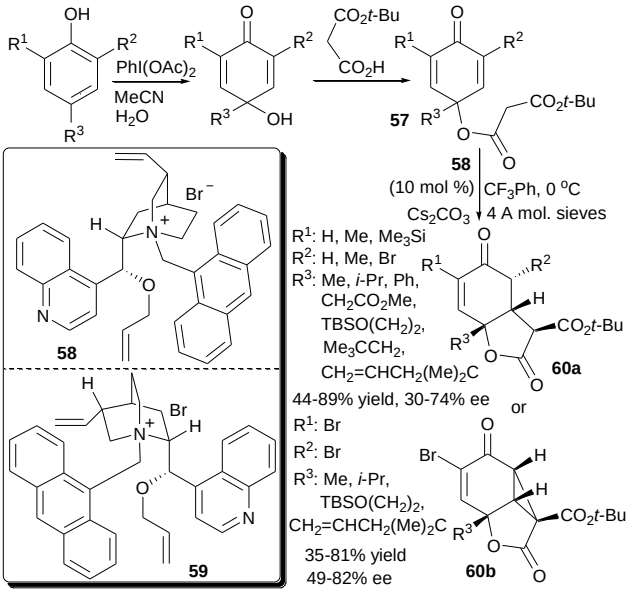
anisidine derivatives **49** into complex tricyclic structures **50** containing a quaternary stereogenic centre embedded in a densely functionalized molecule. Importantly, these architecturally complex molecules display multiple stereochemical features and orthogonal functional groups that can be utilised in downstream diversification of drug discovery and synthesis of nature products called the cyclindricines.

Intrigued by Gaunt's report, You et al. successfully used a desymmetrization process via an NHC-catalyzed intramolecular Stetter reaction to construct this interesting backbone (eq 1, Scheme 22).[35] With *D*-camphor-derived triazolium salt **51** as catalyst, desymmetrization of cyclohexadienones **52**, derived from Larock's *ipso*-iodocyclization reaction, furnished highly functionalized tricyclic structures **53** in moderate-to-good yields and ee values. They also found that the dialkyl substituted cyclohexadienones **54** (R^1 = Me) could be used as the precursor to afford excellent enantioselectivity (99%) yet in low yield (9%). After extensive efforts in catalyst survey, amino-indanol derived NHC **55** was found to be the most efficient system for this type of substrate **54** (eq 2, Scheme 22).[36] Under the standard conditions, functionalized tricyclic structures **56** were obtained in 70-96% yields with a range of enantioselectivities from 87% to more than 99% ee.



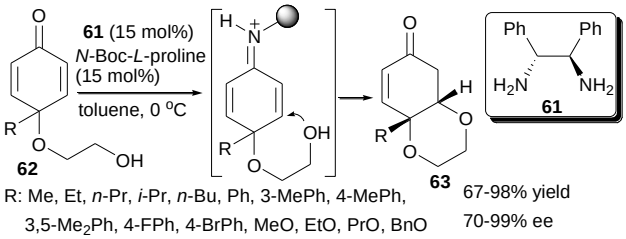
Scheme 22 NHC-Catalyzed desymmetrization of cyclohexadienones

Independently, Harned et al. published a desymmetrization of cyclohexadienones to construct chiral cyclohex-2-enones using *Cinchona* alkaloid-based phase-transfer catalyst (Scheme 23).[37] The cyclization of 2,5-cyclohexadienones **57**, which prepared in two steps from the corresponding phenols, was firstly investigated with Cs_2CO_3 as basic catalyst and the reaction proceeded well to yield cyclic products with good regioselectivity. For the cyclization of brominated substrates, tricyclic cyclopropanes were obtained. In the presence of *Cinchona* alkaloid-based phase-transfer catalyst **58** combined with Cs_2CO_3, chiral cyclohex-2-enone skeletons **60** were obtained in moderate-to-good yields and asymmetric induction. By employing catalyst **59**, the pseudo-enantiomer of catalyst **58**, led to opposite enantiomer with similar levels of enantioselectivities.



Scheme 23 58 / **59**-Catalyzed desymmetrization of cyclohexadienones

Recently, Ye et al. realized the desymmetrization of cyclohexadienones via iminium-based activation using a primary amine salt as catalyst (Scheme 24).[38] In the presence of commercially available chiral diphenylethylenediamine **61** and *N*-Boc-*L*-proline, intramolecular oxa-Michael reaction afforded the enantioenriched cyclohex-2-enone derivatives in 67-98% yields with 70-99% ee values.

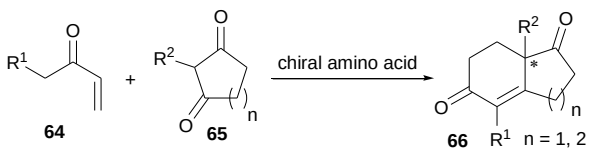


Scheme 24 61-Catalyzed desymmetrization of cyclohexadienones

Intermolecular annulation to chiral cyclohex-2-enone skeletons

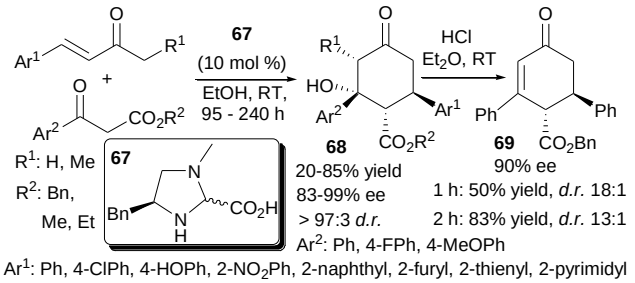
Robinson-type reaction: 1,3-dicarbonyl compound and enone as substrates

Enantiopure Wieland-Miescher ketone **4b** has been proven to be a particularly useful building block in the synthesis of a variety of biologically active compounds.[1] Consequently, much attention has been paid to the preparation of chiral **4b** and its analogues. For this purpose, asymmetric Robinson annulations between vinyl ketone **64** and cyclic 1,3-diones **65** have been investigated with chiral amino acid as catalyst leading to moderate product enantioselectivities and yields (Scheme 25).[39]



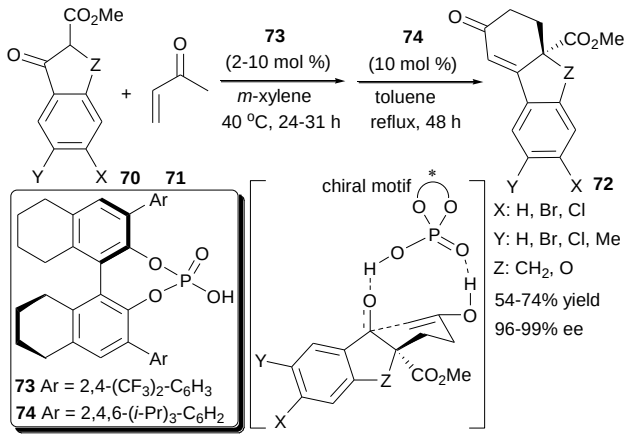
Scheme 25 Amino acid catalyzed Robinson annulation

In 2004, Jørgensen et al. remarkably reported the first highly enantio- and diastereoselective domino Michael-Aldol reaction of acyclic β-keto ester and enone in the presence of an imidazolidine organocatalyst **67**.[40] Domino Michael-Aldol products **68** were obtained in 20-85% yield with 83-99% ee and > 97/3 diastereoselectivity. These products could be easily transformed into the corresponding chiral cyclohex-2-enones **69** in one step (Scheme 26). Notably, no chromatography was required as the optically active Michael-Aldol products precipitated from the reaction mixture and were simply obtained by filtration, washing with Et_2O, and drying under vacuum.



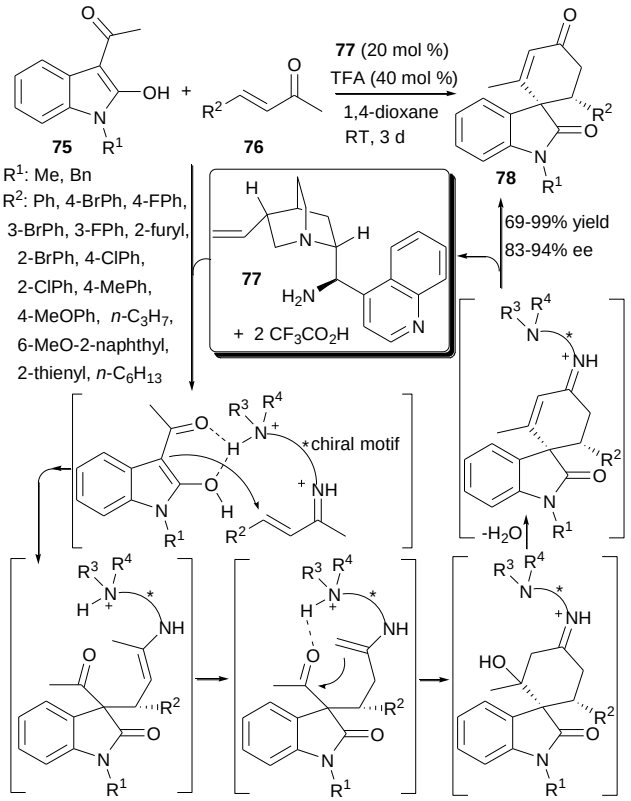
Scheme 26 67-Catalyzed Michael-Aldol reaction for chiral cyclohexenones

The landmark study reported by Akiyama and co-workers presented chiral phosphoric acids that were efficient catalysts for the intermolecular Robinson annulation between β-keto ester **70** and methyl vinyl ketone **71** to construct chiral cyclohex-2-enone skeletons **72** (Scheme 27).[41] Catalyzed by chiral phosphoric acid **73**, β-keto ester **70** reacted with methyl vinyl ketone **71** smoothly to afford 1,4-adducts, which was treated with chiral phosphoric acid **74** in toluene at reflux conditions and furnished Robinson-type annulation products **72** with excellent enantioselectivities. In the annulation process, the phosphoric acid was supposed to work as a multifunctional catalyst: the phosphoric acid hydrogen atom activated the ketone group via a Brønsted acid pathway and thus promoted the formation of an enol from the ketone unit. Besides, the phosphoryl oxygen atom formed a hydrogen bond with the enol hydrogen atom, acting as a Lewis base.

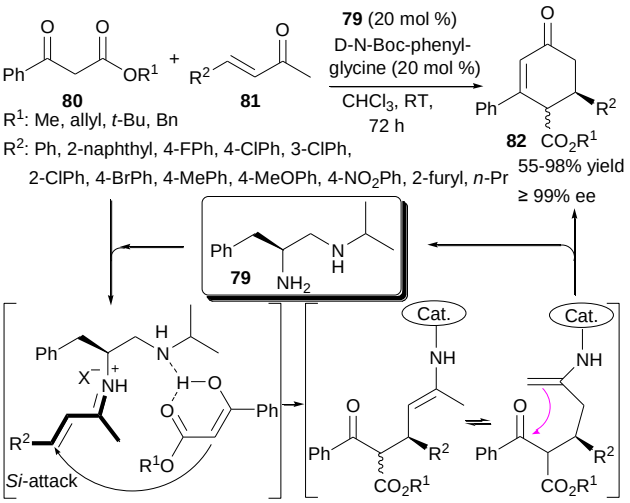


Scheme 27 Chiral phosphoric acid **73**/**74** catalyzed Robinson annulation

Similar to Akiyama's work, Xu and Wang et al. demonstrated asymmetric Robinson annulation between ketone **75** and enone **76** catalyzed by the primary amine **77** associating with trifluoroacetic acid (TFA). This transformation led to the formation of six-membered spirocyclic oxindoles **78** with contiguous stereogenic centers in good-to-excellent yields and asymmetric induction (Scheme 28).[42] The enamine-iminium activation model was supposed. In the presence of 9-amino(9-deoxy)-epicinchonine and TFA, enone **76** was activated via the formation of iminium salt and ketone **75** was activated via hydrogen bond, which resulted in asymmetric intermolecular Michael addition. The annucation product **78** was obtained through the intramolecular aldol reaction and dehydration of enamine intermediate.



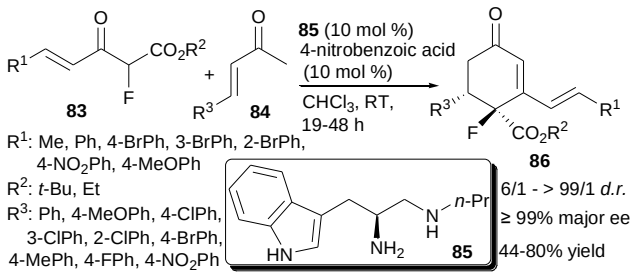
Scheme 28 Chiral primary amine **77** catalyzed Robinson annulation



Scheme 29 Chiral amine **79** catalyzed Robinson annulation

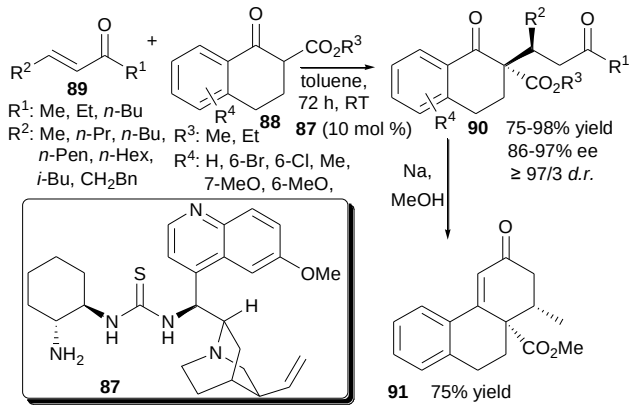
Remarkably, chiral primary-secondary diamines **79** catalyzed Robinson annulation between benzoylacetates **80** and enone **81** was established by Zhao et al. to access functionalized chiral cyclohex-2-enones.[43] In the presence of **79** and *D*-N-Boc-phenylglycine, the asymmetric Robinson annulation proceeded smoothly via imiinium-enamine mechanism to afford functional cyclohex-2-enones **82** in good yields with excellent ee values (Scheme 29). However, the diastereoselectivities remained to be further improved.

Zhao et al. continued to report that both excellent diastereoselectivities and excellent enantioselectivities could be obtained in asymmetric Robinson annulations between α-fluoro-β-keto esters **83** and enones **84**.[44] This transformation was promoted by the primary-secondary diamines **85** to furnish multiply substituted fluorinated chiral cyclohex-2-enones **86** with two contiguous stereogenic centers in moderate-to-good yields with essentially complete asymmetric induction (Scheme 30). This primary-secondary catalyzed reaction also proceeded via imiinium-enamine mechanism, which is similar with the mechanism shown in Scheme 29.



Scheme 30 Chiral amine **85** catalyzed Robinson annulation

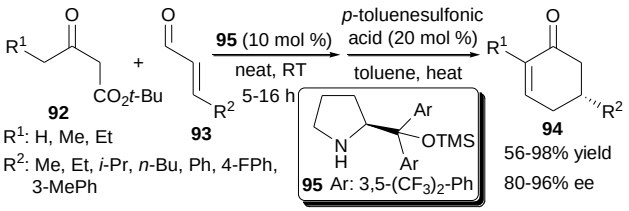
Based on their previous progress in the field of primary amine-thiourea catalyzed Michael additions of enones,[45] Ye et al. successfully employed the primary amine-thiourea **87** as catalyst in the Michael addition of β-alkyl-β-keto esters **88** to β-substituted α,β-unsaturated ketones **89** to afford adducts **90** in good to excellent yields with excellent diastereoselectivities and enantioselectivities.[46] The Michael adducts could be easily transformed into a synthetically useful hexahydrophenanthrene structure **91** under mild conditions in good yield (Scheme 31).



Scheme 31 87-Catalyzed Michael reaction for chiral cyclohexenones

Robinson-type reaction: β-keto ester and enal as substrates

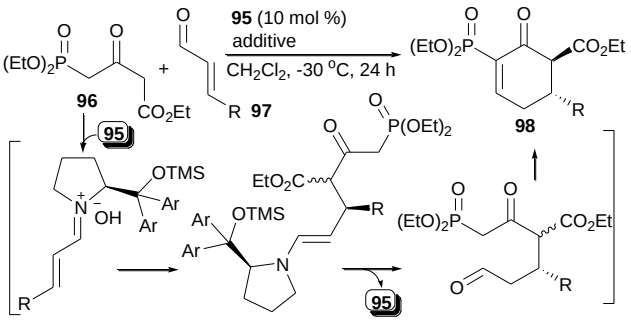
Jørgensen and co-workers developed an asymmetric organocatalytic Robinson annulation between β-keto ester **92** and α,β-unsaturated aldehyde (**93** enal) leading to optically active cyclohex-2-enones **94**.[47] They employed chiral diarylprolinol silyl ether **95** as the organocatalyst, and this catalyst was able to achieve a series of substituted chiral cyclohex-2-enones in good-to-excellent yields and ee values (Scheme 32). Michael adducts were firstly obtained via iminium-enamine mechanism, which was then treated with *p*-toluenesulfonic acid to afford chiral cyclohex-2-enones. With the same catalyst **95**, Jørgensen et al. established a simple organocatalytic approach to highly attractive chiral building blocks from functionalized β-keto ester and enal.[48] Notably, enantioenriched 5-(trialkylsilyl)cyclohex-2-enones were formed in good yields and with 98-99% ee. This method could be easily applied in the target- and diversity-oriented asymmetric synthesis.



Scheme 32 Chiral amine **95** catalyzed Robinson annulation

Michael-Knoevenagel condensation reaction: functionalized β-keto ester and enal as substrates

Domino reactions in which more than one chemical bond is formed in a multistep one-pot reaction sequence, give an access to molecules with complex structure without isolation and purification of the intermediates, which are of great importance in synthetic organic chemistry.[49]

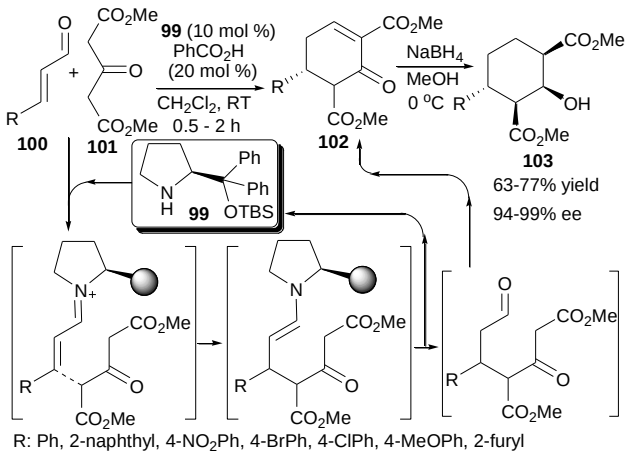


Scheme 33 95-Catalyzed Michael-Knoevenagel condensation

Jørgensen et al. disclosed their special organocatalyst **95** in the domino Michael-Knoevenagel condensation reaction for the synthesis of optically active 3-diethoxyphosphoryl-2-oxocyclohex-3-enecarboxylates **98** from enal **97** and ethyl 4-diethoxyphosphoryl-3-oxobutanoate **96** (Scheme 33).[50] The Michael addition proceeded via the standard catalytic cycle: enal **97** was firstly activated by the formation of iminium with catalyst **95** and then chemo- and region-selective nucleophilic attack by the C-2 methylene atom of **96** at the β-carbon of iminium salt, followed by the hydrolysis to yield 1,4-adducts. Finally, intramolecular Knoevenagel condensation took place to afford

annulation products **98**. The cyclohexecarboxylates **98** were obtained in yields of 71-94% with 94-98% of enantioselectivities and diastereoselectivities of a range from 75:25 to > 95:5, which are particularly well suited for the preparation of densely functionalized cyclohexene and cyclohexane derivatives. Up to four chiral centers and high levels of stereocontrol could be achieved.

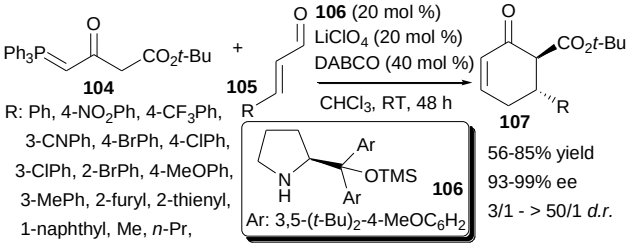
Under a similar context, Hayashi et al. published a highly enantioselective formal carbo [3+3] cycloaddition reaction of enal **100** and dimethyl 3-oxopentanedioate **101** catalyzed by diphenylprolinol silyl ether **99** catalyst (Scheme 34).[51] The amine catalyst **99** reacted with enal **100** to generate an iminium ion, which would then reacted with **101** to give enamine intermediate via asymmetric Michael addition. Hydration of the enamine intermediate furnished 1,4-adduct, and an intramolecular Knoevenagel condensation would proceed to afford the functionalized cyclohex-2-enones **102**. The **102** were reduced in situ to yield alcohol **103** in 63-77% yields with 94-99% ee. However, the aliphatic enals were found not compatible in this catalytic system.



Scheme 34 99-Catalyzed Michael-Knoevenagel condensation

Michael-Wittig reaction: functionalized β-keto ester and enal as substrates

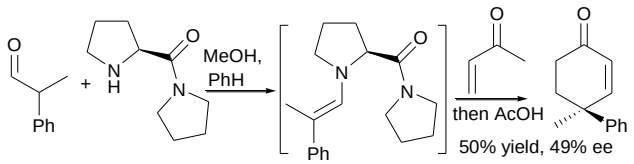
A similar work reported by Chen's group demonstrated that by employing chiral secondary amine **106** catalyst, (3-carboxy-2-oxopropylidene)triphenylphosphorane **104** could be transformed to multifunctional 6-carboxycyclohex-2-enones **107** via the formal [3+3] cycloaddition of enal **105** (Scheme 35).[52] In the presence of **106** combined with $LiClO_4$ and DABCO, a broad spectrum of enal substrates could be used in this transformation to yield desired products **107** in good yield and excellent diastereo- and enantioselectivities.



Scheme 35 Chiral amine **106** catalyzed Michael-Wittig reaction

Robinson-type reaction: aldehyde and enone as substrates

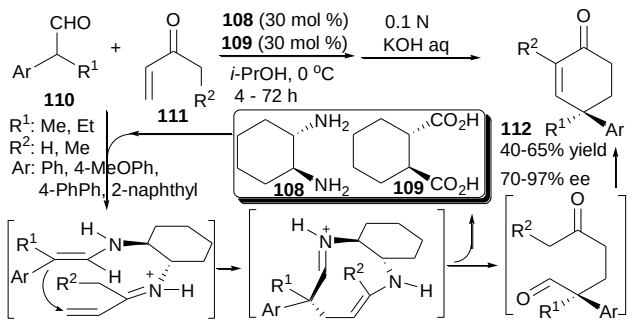
In 1970s, Yamada and Otani reported an asymmetric synthesis of optically active 4,4-disubstituted cyclohexenone derivatives via a stepwise strategy in which enamines prepared from *L*-proline derivatives and 2-phenylpropanal were used as the nucleophiles (Scheme 36).[53] However, both yield and asymmetric induction remained moderate.



Scheme 36 Yamada and Otani reported Robinson-type reaction

In 2008, Kurth et al. described the application of resin-bound hydroxyprolylthreonine derivatives in the enamine-mediated reactions.[54] Only one example was given to construct chiral cyclohex-2-enone from the asymmetric Robinson annulation between acetaldehyde and (*E*)-pent-3-en-2-one. (*R*)-5-Methylcyclohex-2-enone was obtained in 69% yield and 91% ee.

The preliminary studies of Kotsuki's group revealed that the direct treatment of 2-phenylpropanal with methyl vinyl ketone in the presence of a catalytic amount of *L*-proline was unsuccessful. Using (*1S,2S*)-cyclohexane-1,2-diamine **108** as catalyst and (*1S,2S*)-cyclohexane-1,2-dicarboxylic acid **109** as co-catalyst, they showed an efficient method for the construction of cyclohex-2-enone derivatives bearing a quaternary carbon stereogenic center at the 4-position based on a novel chiral diamine-catalyzed Robinson-type annulation (Scheme 37).[55] They suggested that aldehyde **110** and enone **111** were simultaneously activated by **108** through the formation of an enamine-iminium double-activation intermediate, leading to an intramolecular Michael addition to afford the cyclic enamine-iminium ion intermediate. Spontaneous hydrolysis of the cyclic enamine-iminium ion intermediate furnished the keto-aldehyde precursor. Following by intramolecular Aldol reaction and dehydration, the desired chiral cyclohex-2-enone derivatives **112** were afforded in 40-65% yields and 70-97% ee.

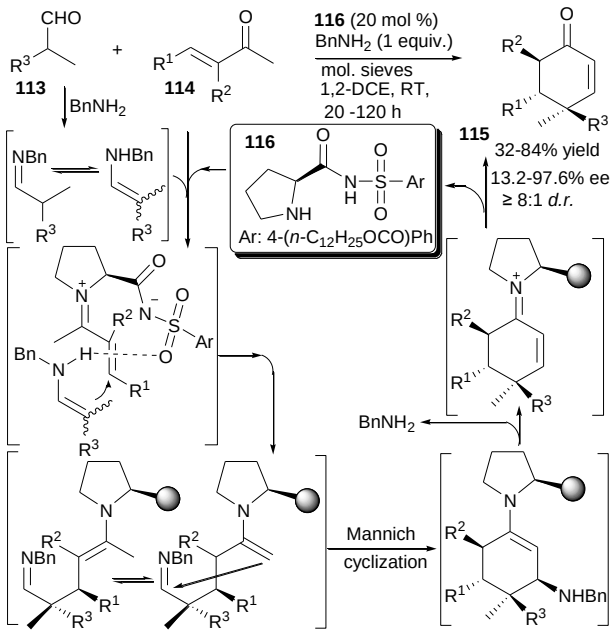


Scheme 37 Chiral amine **108** catalyzed Robinson-type reaction

Acyclic enone substrates bring a challenge of controlling rotational freedom around the σ bond in connecting the alkene and ketone moieties. Furthermore, this rotational freedom also affects stereochemical outcome with β-substituted acyclic enones.

Shortly after the publication of Kotsuki's group, a facile and efficient enantioselective Robinson annulation between aldehyde

113 and β-substituted acyclic enone **114**, that gives access to chiral cyclohex-2-enone skeletons **115**, was developed by Carter et al. (Scheme 38).[56] When (*2S*)-*N*-(*p*-dodecylphenylsulfonyl)-2-pyrrolidine-carboxamide **116** was employed as the organocatalyst, annulation products **115** were formed in 32-84% yields and with 13.2-97.6% ee and more than 8:1 of diastereoselectivities. It was found that molecular sieves displayed a beneficial effect on the reaction profile, thus the chemical yield and enantioselectivity were increased. Benzylamine was also found to be a potentially useful additive in this transformation, in which was critical to the success of this reaction as no product was formed in its absence. In particular, using of less than 1 equiv benzylamine led to appreciably slower rates. The experimental procedure premixed the aldehyde and benzylamine prior to addition of the enone or catalyst, resulting in the formation of imine-enamine mixture. A dual-catalyzed Michael addition mechanism was proposed to afford the key quaternary stereogenic centre and the vicinal stereocenter. An intramolecular Mannich cyclization followed by elimination of benzylamine and hydrolyzation furnished these enantioenriched cyclohex-2-enone frameworks. This plausible catalytic cycle was proposed by an in-depth computational study.[57]



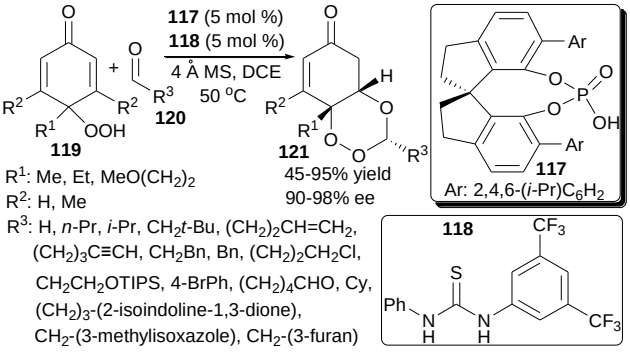
R^1: Me, Bu, Ph, $Br(CH_2)_3$, $I(CH_2)_3$, $TsO(CH_2)_3$, $CH_2{=}CH(CH_2)_3$, $BnO(CH_2)_4$, $TBSO(CH_2)_4$, $N_3(CH_2)_4$, $I(CH_2)_4$, $I(CH_2)_5$, $PhSO_2(CH_2)_4$, $PhthN(CH_2)_5$

R_2: H, Me R_3: Ph, 4-MePh, 4-BrPh, 4-ClPh

Scheme 38 Chiral amine **116** catalyzed Robinson-type reaction

Michael-type reaction: aldehyde and functionalized enone as substrates

In continuing their previous research study,[29] Rovis et al. reported the first catalytic enantioselective synthesis of trioxanes using a desymmetrization of *p*-peroxyquinols via an acetalization/oxa-Michael cascade.[58] With chiral phosphoric acid **117** as the catalyst and thiourea **118** as the co-catalyst, *p*-peroxyquinols **119** reacted with a variety of aliphatic and aryl aldehydes **120** smoothly to afford 1,2,4-trioxane products **121** in moderate-to-good yields and more than 90% ee values (Scheme 39). The authors proposed that the reaction proceeds via a dynamic kinetic resolution of peroxy hemiacetal intermediate and the enantio-determining step is the oxa-Michael event. The resulting 1,2,4-trioxane products were easily derivatized and showed promising cancer cell-growth inhibition.



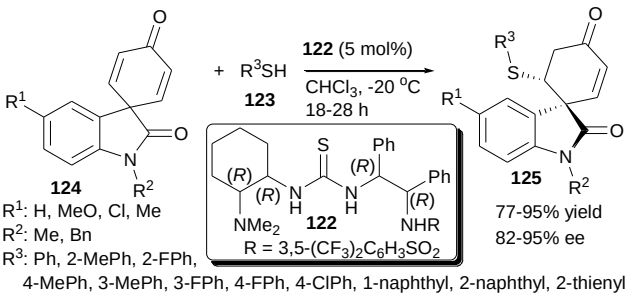
R^1: Me, Et, $MeO(CH_2)_2$

R^2: H, Me

R^3: H, *n*-Pr, *i*-Pr, CH_2*t*-Bu, $(CH_2)_2CH{=}CH_2$, $(CH_2)_3C{\equiv}CH$, CH_2Bn, Bn, $(CH_2)_2CH_2Cl$, CH_2CH_2OTIPS, 4-BrPh, $(CH_2)_4CHO$, Cy, $(CH_2)_3$-(2-isoindoline-1,3-dione), CH_2-(3-methylisoxazole), CH_2-(3-furan)

Scheme 39 Chiral phosphoric acid **117**-catalyzed Michael-type reaction

Wang et al. successfully developed an enantioselective desymmetrization of spiro cyclohexadienone oxindoles via sulfa-Michael addition (Scheme 40).[59] When bifunctional amine–thiourea catalyst **122** was employed, the sulfa-Michael addition of sulfa-nucleophile **123** to spiro[cyclohexadienone-oxindole] **124** furnished the chiral spirocyclic oxindole derivatives **125** with excellent diastereo-selectivity, good enantioselectivity. Notably, this broad substrate scope protocol provided a facile access to spirocyclic oxindoles bearing a unique all-carbon quaternary stereogenic center with excellent levels of asymmetric induction.



R^1: H, MeO, Cl, Me

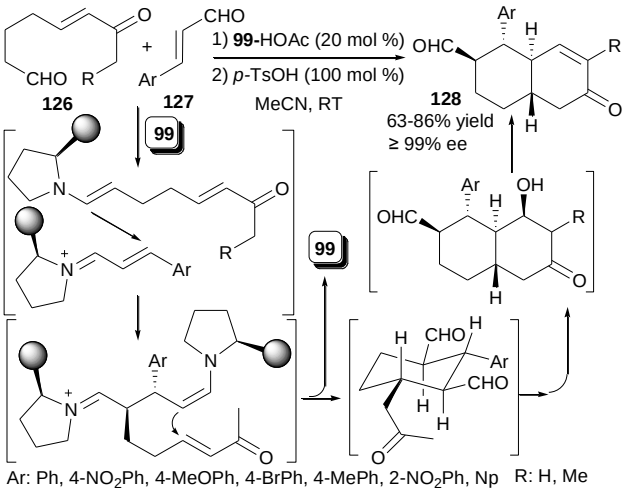
R^2: Me, Bn

R^3: Ph, 2-MePh, 2-FPh, 4-MePh, 3-MePh, 3-FPh, 4-FPh, 4-ClPh, 1-naphthyl, 2-naphthyl, 2-thienyl

Scheme 40 Amine-thiourea **122** catalyzed Michael-type reaction

Michael-Robinson-type reaction: functionalized enone and enal as substrates

Using Jørgensen's and Hayashi's catalyst **99**, Hong et al. established an organocatalytic domino Michael-Robinson-type process of (*E*)-7-oxooct-5-enal **126** and arylacrylaldehyde **127**.[60] This method allowed to furnish the highly functionalized decalins, hexahydronaphthalen-2(1H)-ones **128**, with complete control of four stereocenters in a one-step, three-bond-formation reaction sequence (Scheme 41). The first Michael addition of **126** to **127** proceeded with high diastereo- and enantioselectivity, and the resulting product presumably dictated the stereochemistry of the subsequent Robinson reaction. In this regard, only one enantiomer was isolated in this Michael-Robinson-type reaction, in which it could theoretically generate 16 stereoisomers.

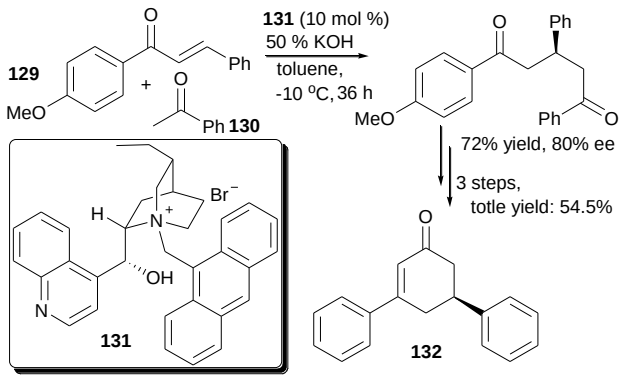


Scheme 41 Chiral amine **99**-catalyzed Michael-Robinson-type reaction

Miscellaneous methodologies to chiral cyclohex-2-enone skeletons

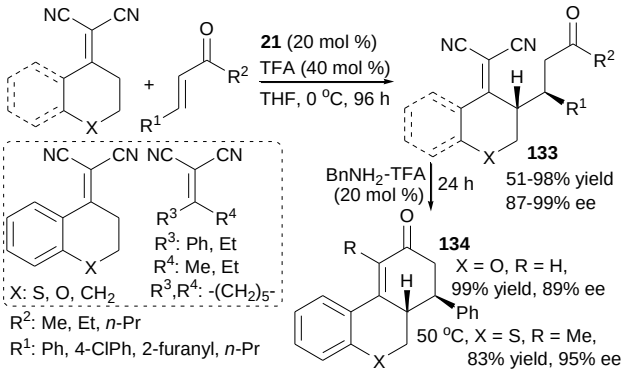
Due to the versatile usefulness of chiral cyclohex-2-enones, many indirect methodologies have also been developed for the construction of enantioenriched cyclohexenone motif.

In 2000, Corey et al. discovered that the use of the chiral quaternary ammonium salts **131** allowed enantioselective Michael addition for the asymmetric synthesis of the chiral cyclohex-2-enone **132** (Scheme 42).[61] Catalyzed by **131**, enone **129** could reacted with acetophenone **130** to afford the Michael adduct in 72% yield and 80% ee. This versatile process afforded annulation product **132** in three steps with 54.5% yield.



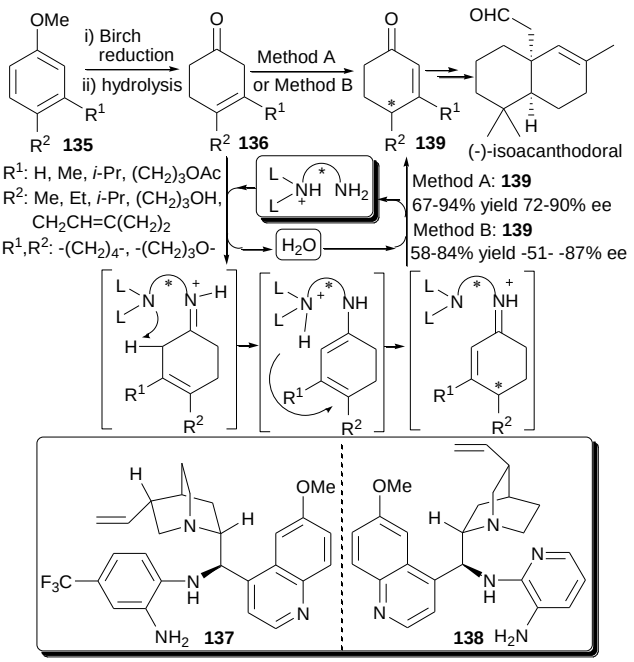
Scheme 42 131-Catalyzed Michael addition for chiral cyclohexenones

Chen and Deng et al. published a highly asymmetric Michael addition of α,α-dicyanoalkenes to enone catalyzed by 9-amino (9-deoxy)-epiquinine **21** (Scheme 43).[62] The straightforward intramolecular Michael addition of the vinylogous products **133** was found not successful in the presence of bulky chiral primary amine **21**, but such reactions could be promoted in a separate step. Products **133** could be converted cleanly into the annulated compound **134** by catalysis with achiral benzylamine without compromising the ee value. Enantiomerically pure polysubstituted cyclohex-2-enones could be conveniently prepared through the novel organocatalytic Michael-Michael-retro-Michael reaction cascade, which provided an alternative protocol for the construction of chiral cyclohex-2-enone skeletons.



Scheme 43 Michael-Michael-retro-Michael reaction for chiral cyclohexenones

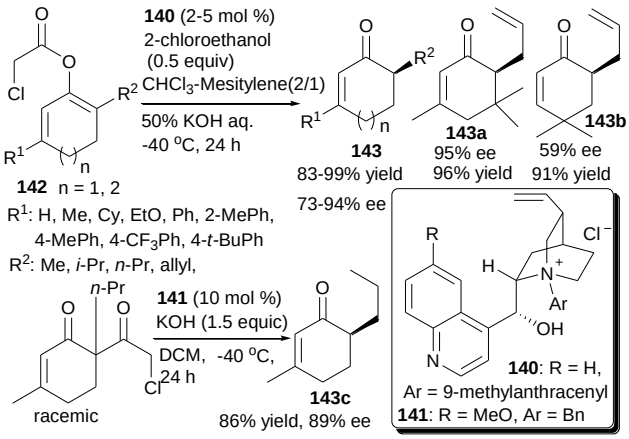
A three-step asymmetric approach toward the enantioenriched cyclohex-2-enones from anisoles via an enantioselective isomerization was realized by Deng et al.[63] Anisoles **135** were transformed to β,γ-unsaturated ketones **136** via Birch reduction followed by hydrolysis. Isomerization of enone **136** was catalyzed by chiral diamine **137** or **138** to furnish enantioenriched cyclohex-2-enone skeletons **139** (Scheme 44). The chiral diamine catalyst was supposed to mediate the enantioselective isomerization of enone **136** via the enamine pathway with cooperative iminium-base catalysis. Notably, both enantioisomers of **139** could be accessed, taking advantage of the pseudoenantiomeric effect of the chiral diamine catalyst. The synthetic utility of this methodology was highlighted by the enantioselective total synthesis of (-)-isoacanthodoral, featuring a new strategy for the construction of the *cis*-fused bicyclo[4.4.0]dec-1-ene ring.



Scheme 44 137/**138**-Catalyzed isomerization for chiral cyclohexenones

The first example of an enantio-convergent retro-Claisen condensation for the construction of chiral cyclohex-2-enones

was developed by Tokunaga et al. using phase-transfer catalyst to catalyse hydrolytic enantioselective protonation of dienyl esters and a β-diketone (Scheme 45).[64] In the presence of chiral phase-transfer catalyst (**140** or **141**), the corresponding optically active cyclohex-2-enones **143** having tertiary chiral centers adjacent to carbonyl groups were obtained in good-to-excellent yields and asymmetric induction.



Scheme 45 140/141-Catalyzed protonation for chiral cyclohexenones

Conclusions and outlook

Asymmetric organocatalytic reactions have emerged as a versatile protocol for access a number of optically active compounds. These stereocontrolled methods offer a practical pathway for the construction of a variety of enantioenriched cyclohex-2-enones. However, this target-oriented asymmetric synthesis is still far from demand. Prospective studies into organocatalytic synthesis of optically active cyclohex-2-enone system would include the development of new organocatalysts and new asymmetric transformations. In view of environmental and industrial awareness, using highly attractive and inexpensive acetone is one of the most ideal approaches for this synthetic aim. In particular, two-component or multi-component domino reactions with excellent atom economy are of high challenge and significance. Genuine industrial application of these methodologies is anticipated to be attainable in the near future.

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Notes and references

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