CHEMICAL REVIEWS

REVIEW

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Asymmetric Organocatalytic Cyclization and Cycloaddition Reactions

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1. INTRODUCTION

The stereocontrolled construction of chiral carbo- and heterocycles is a topic of paramount importance in modern organic synthesis, driven by the predominance of chiral mono- and polycyclic systems in natural products and in chiral pharmaceuticals.[1] The historical development of enantioselective versions of the Diels−Alder reaction can serve as a paradigm for the evolution experienced by other well-established cycloaddition and cyclization methods: the first practical enantioselective versions were achieved in the decade of the 1980s by using chiral auxiliaries covalently bonded to the diene[2] or, more commonly, to the dienophile;[3] the decade of the 1990s witnessed the development of asymmetric metal-catalyzed Diels−Alder reactions;[4] and in the past 10 years, asymmetric organocatalyzed Diels−Alder cycloadditions have attained excellent degrees of efficiency and stereoselectivity.[5]

The use of small chiral organic molecules as enantioselective catalysts, with the associated advantages of their easy availability and of carrying out asymmetric transformations in a metal free-environment and under mild and simple reaction conditions, has lately experienced an impressive growth;[6,7] therefore, asymmetric organocatalysis is now considered the "third pillar" of enantioselective catalysis, together with biocatalysis and metal catalysis, and is being increasingly used in the key steps in the total synthesis of complex natural products.[8,9] Among the great variety of organic transformations that are amenable to asymmetric organocatalysis, cycloaddition and cyclization reactions occupy a preeminent position, and in fact, two of the widely recognized milestones in its historical development, the Hajos−Parrish−Eder−Wiechert−Sauer reaction (1971, discussed in section 3.1) and the chiral imidazolidinone-catalyzed Diels−Alder cycloaddition (2000, dealt with in section 5.1), belong to this cathegory.[10]

The aim of this review is to cover asymmetric organocatalytic methods leading to the enantioselective synthesis of carbocyclic and heterocyclic compounds, focusing on synthetically useful protocols. Wherever possible, working mechanistic models are presented. Reactions requiring a stoichiometric amount of an organic promoter are not discussed in detail, except when they bear a direct relationship with truly catalytic methods or when there is no other alternative (cf. section 3.4). It must be born in mind, however, that in many instances, especially so for amino-catalyzed processes, relatively large amounts of the organocatalyst (20−30 mol % or even more) are required.

This review is organized according to the different types of synthetic procedures affording cyclic frameworks: After an overview of organocatalytic modes of activation (section 2), we discuss in the first place organocatalytic desymmetrizing cyclizations of prochiral substrates, in which at least one of the newly created stereogenic centers arises as a result of the desymmetrization (section 3). Organocatalytic asymmetric ring-closing reactions of acyclic and monocyclic achiral substrates, in which the stereogenic centers are the result of the newly created carbon−carbon or carbon−heteroatom bonds, are dealt with in section 4. Asymmetric organocatalytic reactions corresponding (at least formally) to classical cycloaddition processes are discussed in section 5, irrespectively of the concerted or multistep nature of their mechanism. Finally, two-component and multicomponent cyclization reactions (including organocatalytic cascade processes), taking place through well-defined intermediates, are considered in sections 6 and 7, respectively.

Several reviews dealing with specific aspects (processes, reaction conditions, catalyst and reagent types, and mechanisms) of organocatalysis have been published in the past few years,[11] but with very scarce exceptions,[5,12] none of them is devoted to asymmetric organocatalytic cycloadditions and cyclizations. The coverage of the present review extends generally until July 2010, although selected more recent references have been included.

2. ORGANOCATALYTIC MODES OF ACTIVATION

2.1. Introduction

Asymmetric organocatalysis stands out both for the variety of its modes of activation and for the structural simplicity of most organocatalysts, a feature that has often allowed the generation of mechanistic working models that can rationalize or even predict the stereochemical outcome of organocatalyzed reactions.[11v]

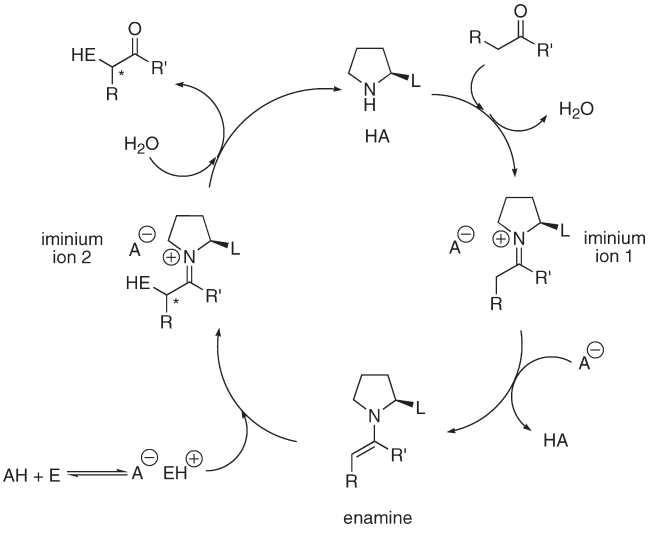
From a mechanistic point of view, organocatalytic modes of activation can be classified according to the covalent or noncovalent character of the substrate−catalyst interaction and to the chemical nature (Lewis base, Lewis acid, Brønsted base, Brønsted acid) of the catalyst.[7b] It is important to bear in mind, however, that many organocatalysts (cf. amino acids, phosphoric acids) act through both covalent and noncovalent interactions and/or display a dual acid/base character ("bifunctional catalysts").

All of the known organocatalytic modes of activation are operative in the reactions covered in this review. We will presently discuss the basic features of each activation mode and present the structures of the most representative catalysts, whose numbering (in Roman numerals) follows their order of appearance in the main body of the review (sections 3−8).

2.2. Covalent Catalysis

2.2.1. Enamine Activation Catalysis. After the initial reports on proline-catalyzed intermolecular aldol[13] and Mannich[14]

Scheme 1. General Mechanism for the Amine-Catalyzed α-Functionalization of Carbonyls



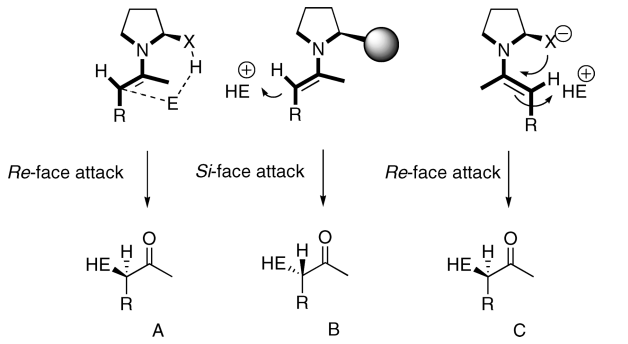


Figure 1. Stereochemical models for enamine reactivity: (A) List−Houk model, (B) steric model, and (C) Seebach model.

reactions, enamine activation catalysis has become one of the most intensively used organocatalytic modes of activation,[15] allowing the enantioselective α-functionalization of enolizable aldehydes and ketones with a huge variety of electrophiles.

The catalytic cycle for a chiral pyrrolidine-catalyzed α-functionalization of a carbonyl compound is depicted in Scheme 1 and involves the initial acid-promoted condensation of the carbonyl with the amine to form an iminium ion. One of the α-acidic protons of the iminium ion is then removed by the basic counterion and the key nucleophilic enamine intermediate is formed. Reaction with the electrophile E (generally in its protonated form EH^+; the protonation can take place before or after this step) regenerates an iminium ion, whose hydrolysis liberates the product, the acid, and the amine catalyst, which can re-enter the catalytic cycle. The acid cocatalyst can be a protic solvent (water, alcohols), an added external acid, or an acidic moiety of the chiral amine catalyst.

The enantioselective step, the reaction of the enamine with the electrophile, can take place via two different pathways. If the chiral amine substituent contains a hydrogen-bond-directing group (a carboxylic acid, an amide or thioamide, a protonated amine), the attack of the electrophile takes place in an intramolecular fashion, via a cyclic transition state (List−Houk model; Figure 1A); on the other hand, if the amine substituent is bulky and devoid of acidic protons, it directs the attack of the electrophile with purely steric effects, leading to the opposite facial stereoselectivity (Figure 1B). Seebach et al. have proposed an alternative mechanism for the first case, in which the electrophilic attack is directed by anchimeric assistance of the deprotonated amine substituent X (Figure 1C).[16] Although the mechanistic debate opened by this proposal is still lively, it is worth noting that some features of the catalytic cycle proposed by Seebach et al. for the proline-catalyzed aldol reaction, especially in aprotic solvents, have recently received strong experimental support.[17]

Intramolecular aldol reactions discussed in sections 3.1 and 4.1 are representative examples of this mode of activation, and their stereochemical outcome can be generally rationalized by an intramolecular version of the Houk−List model.[18]

Representative chiral amines with hydrogen-bond-directing groups used in enamine catalysis and appearing in this review are depicted in Figure 2, and examples of chiral secondary amines with nonacidic substituents can be found in Figure 3. It must be born in mind, however, that compounds shown in Figure 3 having both a primary or secondary amine and a tertiary amine (cf. **VII**, **IX**, **X**, **XI**...), when used in conjunction with an acid cocatalyst, can act from the mechanistic point of view like those with hydrogen-bond-directing groups by means of the tertiary ammonium cation; on the other hand, achiral amines like **CXXXVI** can act as chiral catalysts when used in conjunction with a chiral acid such as **VIII** (asymmetric counterion-directed catalysis, discussed in section 6.2.2).

2.2.2. Iminium Activation Catalysis. Iminium activation catalysis is another key catalytic concept in organocatalysis.[8,19] Initial work was centered on cycloadditions,[20] but it was rapidly extended to Michael additions[21] and is now established as a general strategy for the asymmetric conjugate addition of nucleophiles to α,β-unsaturated carbonyl compounds. The catalytic cycle for a chiral pyrrolidine-catalyzed β-functionalization of an α,β-unsaturated carbonyl compound is shown in Scheme 2 and begins with the acid-promoted condensation of the carbonyl with the amine to form an unsaturated iminium ion. This reactive intermediate suffers then the addition of the nucleophile at the β-position, leading to a β-functionalized enamine that upon protonation gives a saturated iminium ion. Hydrolysis of this intermediate releases both the product and the catalyst.

Although chiral amines with hydrogen-bond-directing groups like those shown in Figure 2 can be used in iminium activation catalysis, usually best results are obtained with amines substituted with bulky nonacidic groups. In this case, the stereochemical outcome of the addition to enals can be usually predicted by the transition state depicted in Figure 4, which implies the attack of the electrophile by the face opposite to the bulky amine substituent in the energetically favored *s*-trans conformer of the (*E*)-configured unsaturated iminium ion.[22] An alternative mechanistic explanation, based on stereoelectronic effects, has been recently proposed by Seebach and co-workers.[23]

Representative examples of iminium activation catalysis are found for instance in asymmetric organocatalytic Diels−Alder cycloadditions (discussed in section 5.1), in intramolecular Michael additions to unsaturated carbonyl compounds (section 4.2), and in the epoxidation of enals (section 6.2). The most common chiral amines used in iminium activation catalysis are those shown in Figure 3 and MacMillan's imidazolidinones (See Figure 5 for examples).

2.2.3. Dienamine Activation Catalysis. Initially discovered in 2006,[24] dienamine activation catalysis is finding increasing applications in asymmetric organocatalysis. Examples of its use

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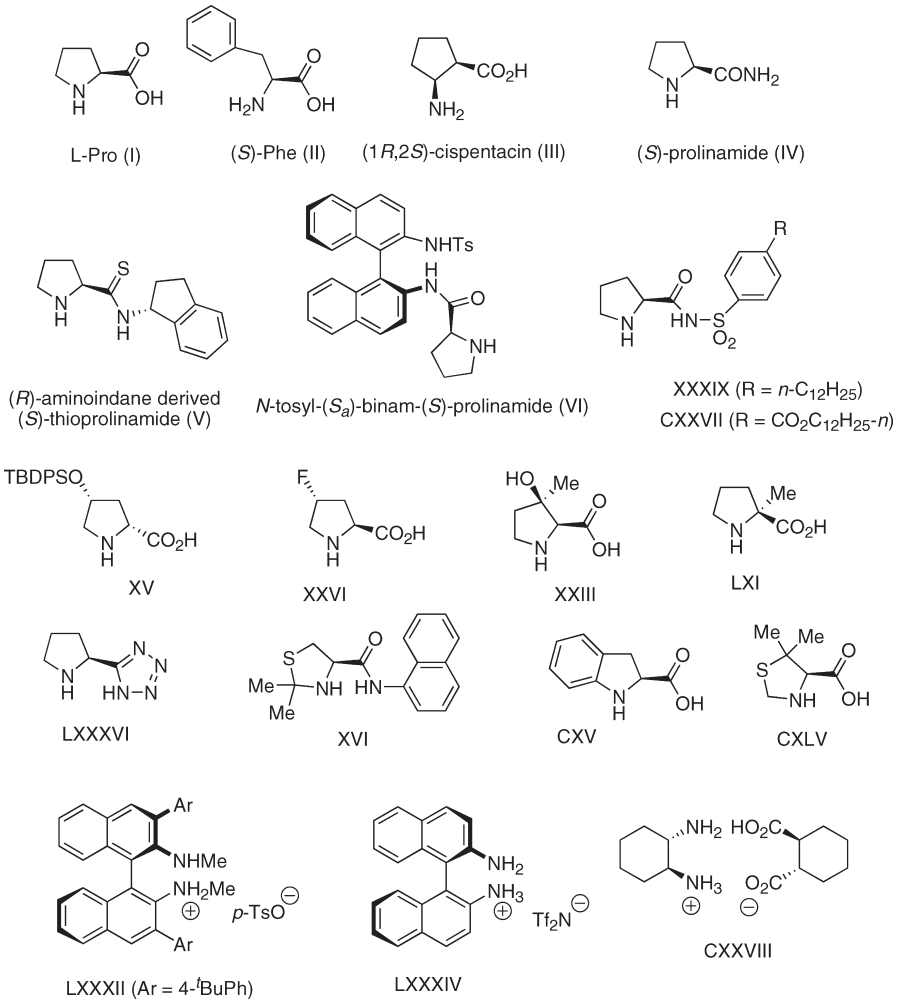

Figure 2. Chiral amines with hydrogen-bond-directing groups used in asymmetric enamine and iminium activation catalysis.

within the scope of this review are found in intramolecular Rauhut−Currier reactions (section 4.3) and in [4 + 2]-cycloadditions (section 5.1). The mechanistic cycle is very similar to that depicted in Scheme 2, but the presence of acidic γ-hydrogens in the initially formed iminium intermediate leads to the formation of an electron-rich dienamine intermediate whose *s-cis* conformer undergoes a highly stereoselective [4 + 2]-cycloaddition. Release of the catalyst is then achieved by hydrolysis (giving γ-functionalized carbonyls) or by E1cb-elimination, affording cyclic compounds (Scheme 3). Prolinol derivatives such as **XLVIII** (Figure 3) are typical catalysts for these transformations.

2.2.4. SOMO Activation Catalysis. Organo-SOMO activation catalysis is an alternative pathway for the asymmetric organocatalytic α-functionalization of carbonyls that was uncovered by MacMillan and co-workers in 2007.[25] The mechanistic cycle is outlined in Scheme 4. Condensation between the secondary amine catalyst (up to now only chiral imidazolidinones have been employed successfully in this process; see Figure 5) leads first to an iminium ion and then to the enamine. In the presence of a mild oxidant (usually a transition metal ion), the enamine is converted into a cation radical, which then reacts with a radicophile to form a new cation radical intermediate. Oxidation of this intermediate followed by hydrolysis liberates the α-functionalized carbonyl and the catalyst. Two equivalents of a one-electron oxidant and 2 equiv of base are consumed in the process. A variant of this cycle relying on the combination of an imidazolidinone with a photoredox catalyst in which a photochemically generated radical reagent couples with the classical enamine intermediate has been also reported by MacMillan.[26] Examples of organo-SOMO activation catalysis of asymmetric cyclizations are discussed in sections 4.6 and 4.8.

2.2.5. Carbene Activation Catalysis. Chiral *N*-heterocyclic carbenes (NHC's) are a particular class of Lewis basic (nucleophilic) catalysts that are playing an important role in the discovery of new asymmetric organocatalytic processes.[27] The two fundamental reaction types catalyzed by these compounds are the ipso-functionalization of saturated carbonyls and the enantioselective α-functionalization of unsaturated carbonyls (Scheme 5).

Examples of the use of chiral NHC's in this review are found in sections 3.1, 3.3, 4.4, and 5.1. These catalysts are usually generated in situ by treatment of chiral triazolium (see Figure 6) or imidazolium salts by a suitable base.

2.2.6. Lewis Base Activation Catalysis. Lewis base or nucleophilic catalysis by chiral amines and phosphines has been intensively exploited in asymmetric organocatalysis.[28] Among its numerous applications, several reactions leading to cyclic products are covered in this review (cf., sections 3.4, 4.1, and 4.3). Representative catalysts are shown in Figure 7. Note that some of these compounds (cf. **XLVI** and **XLVII**, used in intramolecular Morita−Baylis−Hillman cyclizations) are in fact bifunctional

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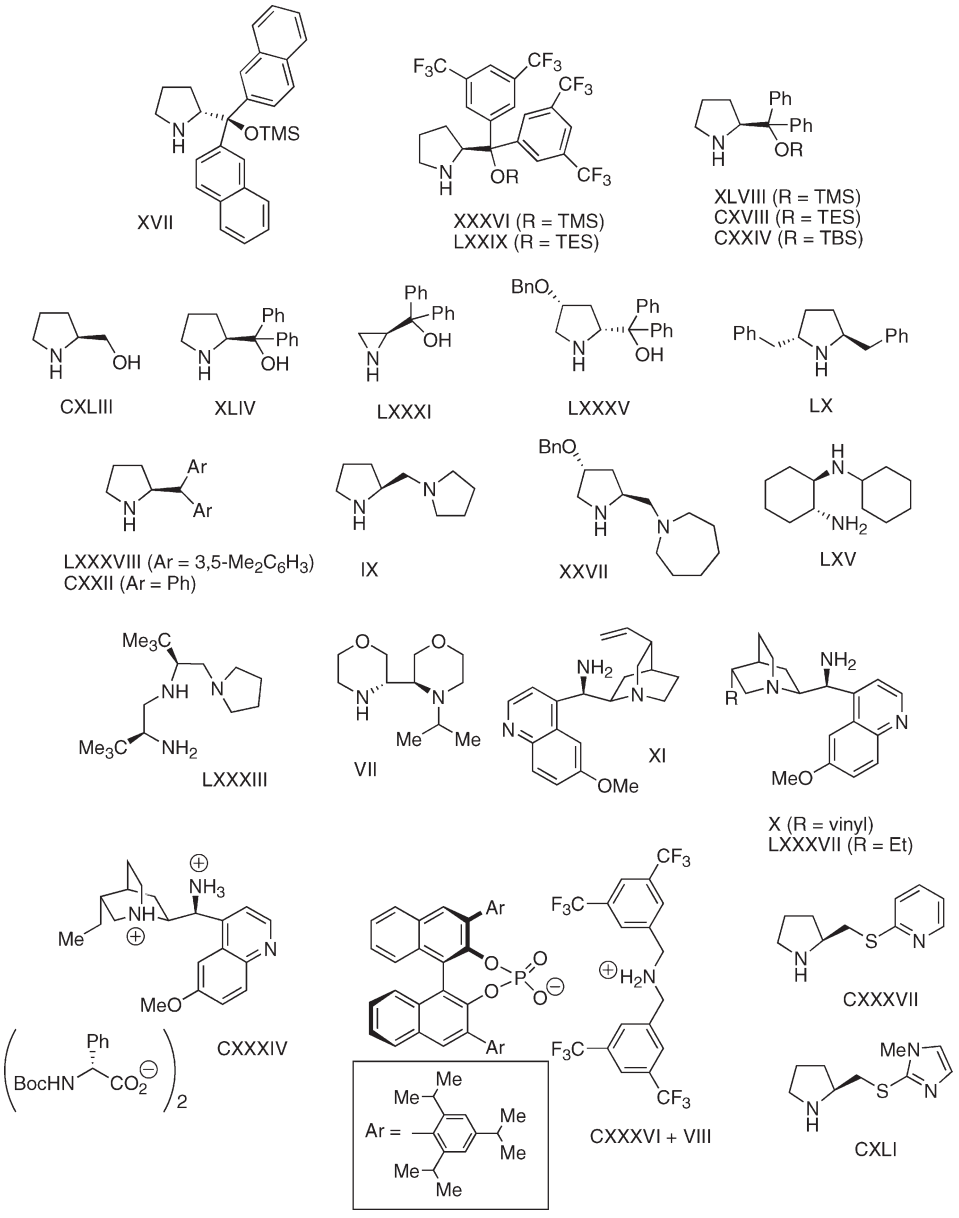

Figure 3. Chiral amines with nonacidic substituents used in enamine and iminium catalysis.

(Lewis base/hydrogen-bond donor) catalysts and that those having tertiary amino groups (cf. **LXXI**, **LXXII**, **XC**, **CXXXII**...) can also act as Brønsted base catalysts.

2.3. Noncovalent Catalysis

2.3.1. Hydrogen-Bonding and Brønsted Acid Activation Catalysis. Chiral organic compounds with acidic hydrogens that interact with substrates contaning basic functional groups are able to catalyze a great variety of processes and have become extremely useful tools in asymmetric organocatalysis.[29] Depending on the degree of proton transfer in the transition state, one may distinguish between hydrogen-bonding activation catalysis (when the hydrogen is still bound to the catalyst) and Brønsted acid activation catalysis (complete proton transfer from the catalyst to the substrate), but obviously several intermediate situations are possible. Chiral thioureas, chiral amidinium ions, chiral squaramides, and chiral diols are the most widely used catalysts of this type (see Figure 8 for chiral hydrogen-bonding catalysts appearing in this review).[30]

On the other hand, the field of Brønsted acid activation organocatalysis[31] is clearly dominated by chiral BINOL-derived phosphoric acids, which after the seminal reports of Akiyama et al.[32] and of Uraguchi and Terada[33] have become one of the most powerful types of organic catalysts.[34] Figure 9 shows several BINOL-derived phosphoric acids and amides that efficiently catalyze cyclization or cycloaddition reactions covered in this review (cf. sections 3.1, 3.2, 4.2, 4.5, and 5.1). The relationship between hydrogen-bonding and Brønsted acid catalysis has lately been emphasized by Jacobsen through the principle of hydrogen-bond-donor catalysis by anion-binding.[35] Figure 10 summarizes the main types of catalysis by organic molecules containing acidic hydrogens. In Brønsted acid activation catalysis (Figure 10a,b) the catalyst (exemplified by a chiral phosphoric acid) transfers a proton to a basic center in the substrate, making it more

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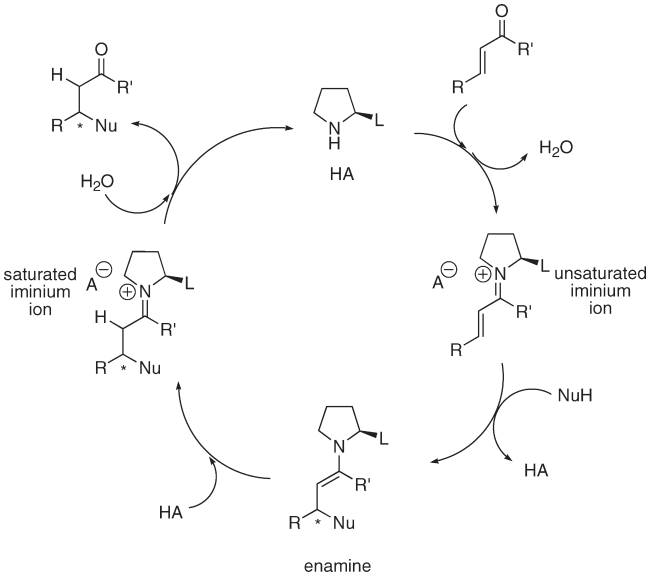
Scheme 2. General Mechanism for the Amine-Catalyzed *β*-Functionalization of α,*β*-Unsaturated Carbonyls



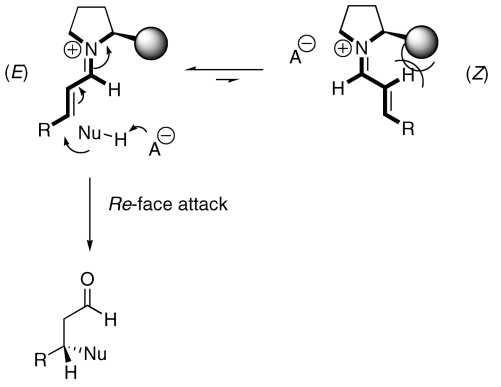


Figure 4. Stereochemical outcome of the amine-catalyzed Michael addition to enals.

electrophilic. In hydrogen-bonding activation catalysis (Figure 10c), the catalyst (exemplified by a chiral thiourea) also enhances the electrophilicity of the substrate, in this case by hydrogen-bonding to an heteroatom. Finally, in hydrogen-bond-donor activation catalysis by anion-binding, the chiral catalyst enhances the acidity of an achiral Brønsted acid (Figure 10d) or makes the substrate more prone to a nucleophilic substitution process (Figure 10e).

2.3.2. Brønsted Base and Bifunctional Activation Catalysis. With a few exceptions, most them involving the *Cinchona* alkaloid compounds shown in Figure 7 and related compounds,[36] catalysts acting solely as Brønsted bases are not highly enantioselective, probably due to the rather loose nature of nonbonded interactions between extended organic anions and quaternary ammonium salts.

On the other hand, the concept of bifunctional asymmetric catalysis, involving the synergistic activation of both acidic and basic sites in the substrate,[37] has received considerable attention. Asymmetric activation organocatalysis by bifunctional species containing a hydrogen-bond donor in addition to a Brønsted basic moiety (Figure 11), foreshadowed by the seminal paper of Riant and Kagan[38] on quinidine-catalyzed Diels–Alder reactions (see section 5.1) and first developed by Takemoto and co-workers,[39] has evolved into a general and reliable strategy.[11p,29a,30e] Although initially applied to intermolecular Michael reactions,[40] bifunctional activation organocatalysis has been shown to be useful in intramolecular Michael additions (section 4.2), in Nazarov cyclizations (section 4.7), in halolactonization reactions (section 4.9), as well as in a variety of cycloaddition (section 5) and multicomponent cyclizations (sections 6 and 7).

Some bifunctional hydrogen-bond-donor/Brønsted base catalysts appearing in this review (including Takemoto's thiourea **XLI**)[39] are shown in Figure 12.

2.3.3. Phase-Transfer Catalysis. Since the successful application of *Cinchona*-alkaloid-based quaternary amonium salts as chiral phase-transfer catalysts in 1984,[41] the use of chiral quaternary ammonium salts in asymmetric catalysis has experienced a notable growth.[11p,42] In particular, the asymmetric alkylation of glycine-derived Schiff bases by means of phase-transfer organocatalysis, pioneered by O'Donnell et al.[43] and further improved by Lygo and co-workers[44] and Maruoka and co-workers,[45] among others, has become one of the most reliable procedures for the enantioselective preparation of α-amino acids.[46]

The generally accepted (but simplified) mechanism for asymmetric phase-transfer catalysis, depicted in Figure 13, assumes that the quaternary ammonium cation forms a tight ionic complex with the nucleophile anion, generated by deprotonation of the neutral pronucleophile at the interphase of the organic and aqueous phases by an alkaline hydroxide. This ionic complex reacts with the electrophile, liberating the product and the quaternary ammonium salt, which returns to the interphase for catalyst recycling. The asymmetric induction originates on the chiral environment of the complexed nucleophile anion provided by the chiral tetrahedral ammonium cation.[47]

Asymmetric phase-transfer catalysis has been employed, within the scope of this review, for 6π electrocyclizations (section 4.7), for the synthesis of planar chiral heterocycles (section 4.9.6), and for the synthesis of some cyclic α-alkyl-α-amino acid derivatives and of epoxides (section 6.2). Structures of the corresponding catalysts can be found in Figure 14.

3. ORGANOCATALYTIC DESYMMETRIZING CYCLIZATIONS OF PROCHIRAL SUBSTRATES

3.1. Desymmetrizing Aldol Cyclizations: The Hajos–Parrish–Eder–Sauer–Wiechert Reaction and Related Processes

As mentioned in the Introduction, the simultaneous discovery in 1971 by Hajos and Parrish at Hoffmann-La Roche[48] and by Eder, Sauer, and Wiechert at Schering[49] of the proline-catalyzed intramolecular aldol reaction of 2,2-disubstituted cyclic 1,3-diketones, which afforded synthetically useful bicyclic diketones in good yield and enantioselectivities, can be regarded as the first practical asymmetric organocatalytic cyclization.[50]

Hajos and Parrish[48] found that, using *N*,*N*-dimethylformamide (DMF) as the solvent in the presence of 3 mol % of (*S*)-proline (**I**), the intramolecular enol/endo-aldolization of 2-methyl-2-(3-oxobutyl)-1,3-cyclopentanedione (**1**) afforded the bicyclic diketone **2** in 99% yield and with 93% ee. Acid-promoted dehydration of **2** provided the unsaturated diketone (*S*)-**3** (the Hajos–Parrish diketone), a very useful building-block in steroid synthesis. As shown by Eder et al.,[49] **3** can be obtained

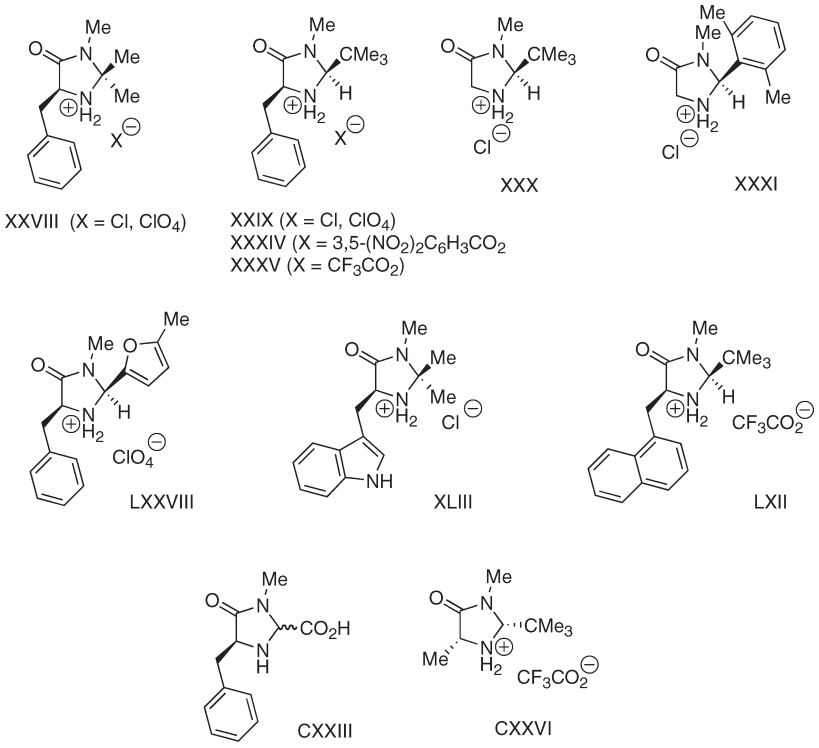
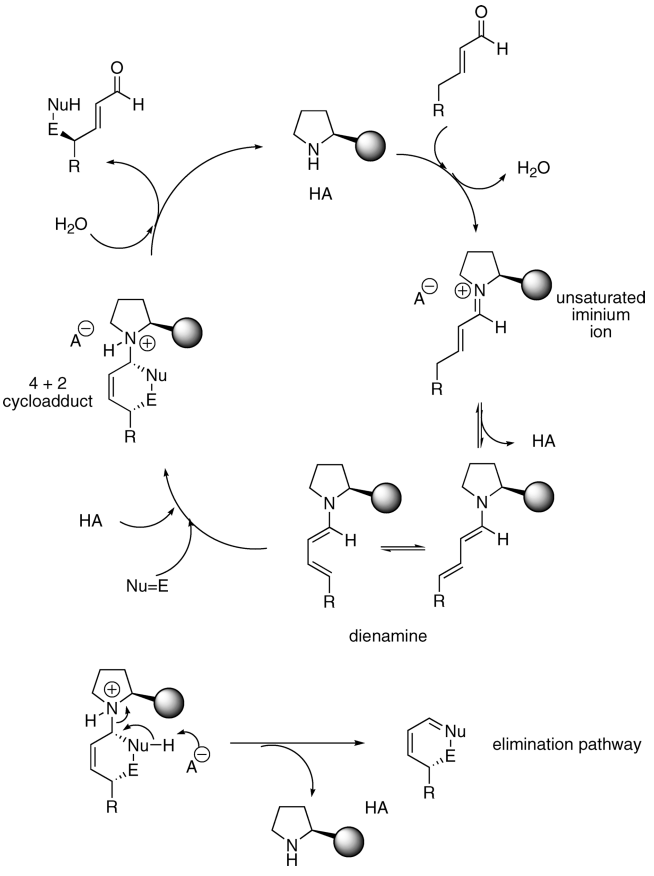


Figure 5. MacMillan's imidazolidinonium salt catalysts.

Scheme 3. Generalized Mechanism for the Amine-Catalized γ-Functionalization of α,β-Unsaturated Aldehydes



directly from **1**, albeit with somewhat lower yield and enantiomeric purity, by using perchloric acid as a cocatalyst in refluxing acetonitrile (Scheme 6).[51]

The proline-catalyzed reactions of substrates related to **1** generally take place with useful yields and enantioselectivities (Figure 15).[48,49,52−54]

It is worth noting here that the use of primary amino acids as catalysts can be sometimes advantageous, especially so for sterically hindered substrates. Thus, in the case of compound **7**, both the yield (up to 82%) and the enantioselectivity (up to 86% ee) could be improved by using (*S*)-phenylalanine (**II**) instead of (*S*)-proline (**I**).[53]

The (*S*)-proline-catalyzed cyclization of 2-methyl-2-(3-oxobutyl)-1,3-cyclohexanedione (**9**), under the conditions reported by Hajos and Parrish,[48] takes place both with moderate yield (52%) and enantioselectivity (74% ee), and after dehydration of the intermediate ketol **10**, a recrystallization step is necessary to obtain highly enantiopure Wieland−Miescher ketone (*S*)-**11**.[55] The direct cyclization−dehydration conditions of Eder et al.[49] do not give much better results (Scheme 7). While the synthesis of **9** is conveniently effected by heating 2-methylcyclohexane-1,3-dione (**12**) with methyl vinyl ketone (**13**) in aqueous acetic acid at 75 °C for 1 h,[51b] in 2000 Bui and Barbas found that the entire Robinson annulation sequence can be performed by reaction of **12** and **13** (slow addition, 1.5 mol equiv) in DMSO at 35 °C in the presence of (*S*)-proline (**I**) (35 mol %). After purification, (*S*)-**11** was obtained in 49% yield and 76% ee (Scheme 8).[56]

Given the importance of optically active Wieland−Miescher ketone (and of the Hajos−Parrish ketone **3**) in natural product synthesis,[53−57] it is not surprising that much effort has been devoted to improving the organocatalytic aldol cyclization of **9** and of related compounds. As we have already seen, in the case of

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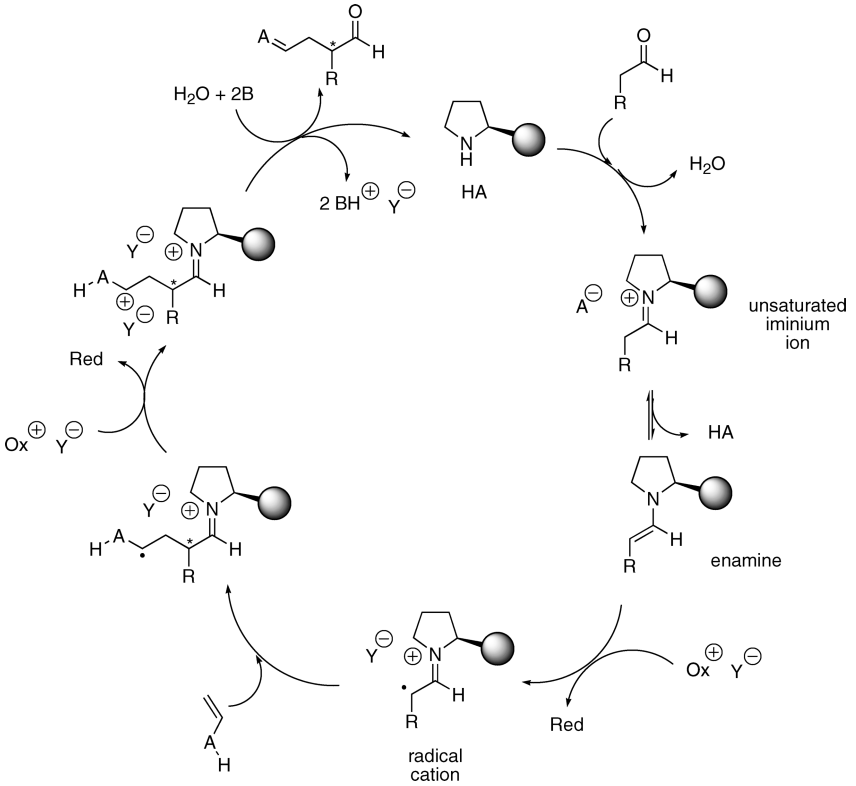
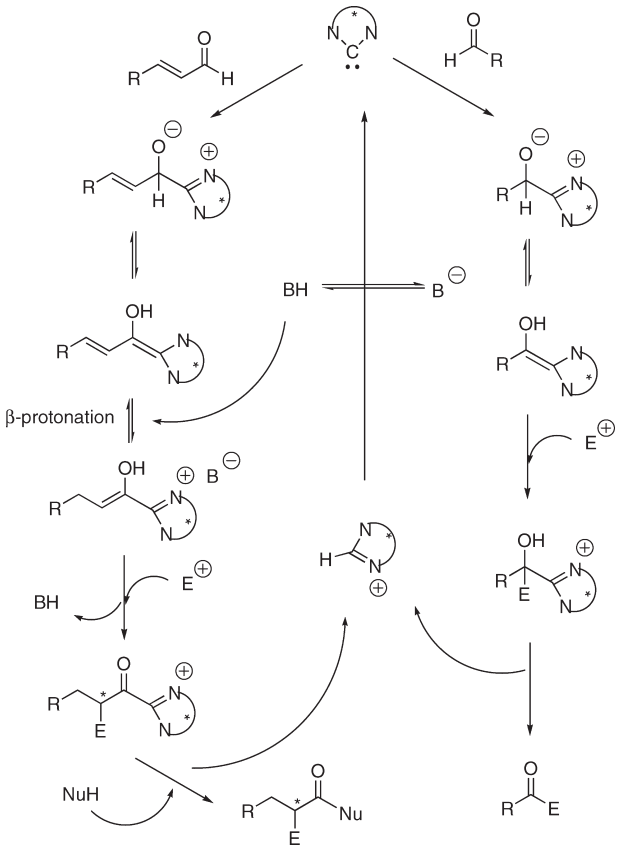
Scheme 4. Representative Mechanistic Cycle for Asymmetric Organo-SOMO Activation Catalysis



Scheme 5. Basic Processes in Carbene Activation Catalysis



hindered ketones, the use of primary amino acids can lead to good enantioselectivities. Thus, Agami[58] has described that the cyclization of the ethyl ketone **14** takes place with 95% ee under catalysis by (*S*)-phenylalanine (**II**) (Scheme 9). The use of (*S*)-proline (**I**) in DMSO gave the same compound **15** in only 32% ee.

In a similar way, Davies and Smith[59] have found that the primary *β*-amino acid (1*R*,2*S*)-cispentacin (**III**) (30 mol %, DMF, rt, 108 h) catalyzes the cyclization of **9**, affording (after dehydration of **10** with *p*TsOH in refluxing toluene) the Wieland−Miescher ketone (*R*)-**11** in 75% overal yield and with 86% ee. A very similar enantiomeric purity (87% ee) for (*S*)-**11** can be achieved by using (*S*)-prolinamide (**IV**) as the catalyst,[60] while slightly better results [88% yield and 92% ee for (*S*)-**11**] have been described by Reiser[61] by catalysis with proline-containing tripeptides. On the other hand, Nájera and coworkers have reported on the use of the (*R*)-1-aminoindane-derived prolinethioamide (**V**)[62] and of the *N*-tosyl-(S_a)-binam-(*S*)-prolinamide (**VI**)[63] as efficient catalysts for the cyclization of **9** (Figure 16).

Recently, Bradshaw et al. have reported that the use of **VI** results in a highly efficient (93% overall yield) and enantioselective (94% ee) synthesis of the (*S*)-Wieland−Miescher ketone **11** (10 g scale) through a single-step, solvent-free aldol cyclization−dehydration of **9**.[64] The process involves only 2 mol % of the catalyst **VI** and benzoic acid (0.5 mol %) and can be applied to the preparation of a wide range of analogues of **11** (Figure 17).

The allyl derivative **16** (obtained in a 20 g scale in 94% ee under slightly different reaction conditions from those of ref 64, 1 mol % of **VI** and 2.5 mol % of benzoic acid) has been employed by Bradshaw et al. as the starting material in a very elegant total synthesis of the structurally challenging diterpenoid (−)-anominine.[57g]

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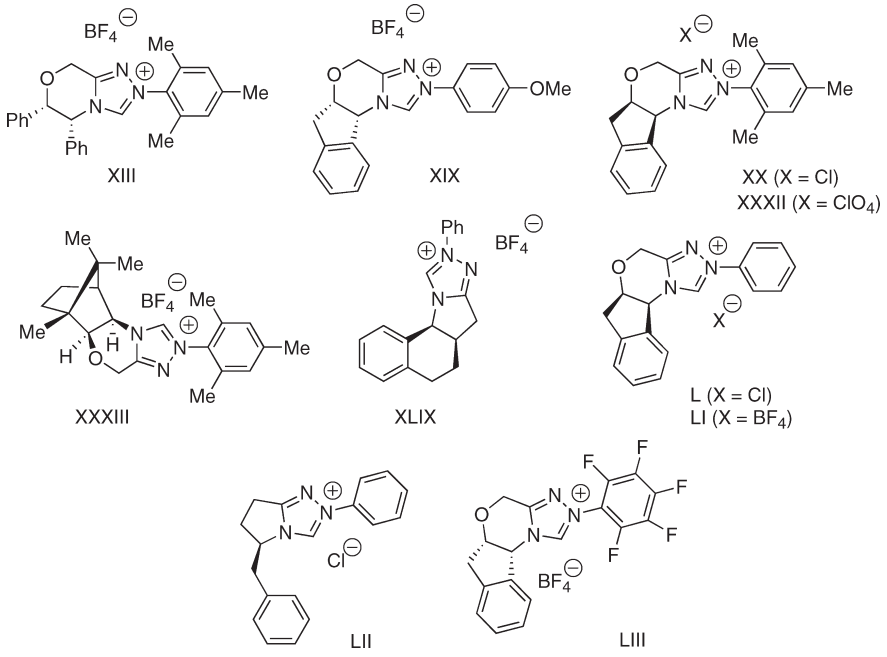

Figure 6. Chiral triazolium salts used as precursors of NHC's.

The performance of the Hajos−Parrish−Eder−Sauer−Wiechert reaction with immobilized catalysts was examined several years ago by Takemoto et al.[65] by means of a polystyrene-grafted proline catalyst. Surprisingly enough, in spite of the fast development of the field of supported asymmetric organocatalysts,[66] no further attention has been paid to this topic.

Agami and co-workers have studied the application of the proline-catalyzed cyclization of prochiral triketones to the kinetic resolution of chiral racemic diketones.[67] Interestingly enough, they found that the enantiodifferentiation depends on the presence or the absence of an angular methyl group. Thus, cyclization of the methyl-substituted cyclohexanone *rac*-**26** afforded the bicyclic ketone (*S*)-**27** in 43% ee, leaving optically active ketone (*R*)-**26** (ee not determined) unreacted; on the other hand, cyclization of the unsubstituted compound *rac*-**28** gave the cyclization product (*R*)-**29** in 46% ee, together with unreacted ketone (*S*)-**28** (ee not determined; Scheme 10).

The domino Michael−aldol reaction of symmetrical 1,3-diaryl-1,3-propanediones **30** with methyl vinyl ketone (**13**) in the presence of (*S*)-proline (**I**) was examined by Gryko in 2005.[68] When the reaction was run in 1-methyl-2-pyrrolidinone (NMP), high yields (up to 93%) and moderate to good enantioselectivities (43−80% ee) of the cyclohexanones **32** were obtained, together with variable amounts of the intermediate triketones **31**. It is noteworthy that this procedure can also be applied to unsymmetrical diketones. Thus, diketone **33** gave the cyclohexanone derivative **34** (resulting from the intramolecular enolate addition to the more electron-defficient carbonyl group) as the sole product in 93% yield and 50% ee (Scheme 11).

Proline has also been found to promote, although rather inefficiently, the asymmetric Robinson annulation of 2-formylcyclohexanone **35** with **13** (Scheme 12).[69] More recent examples of domino Michael−aldol cyclizations will be discussed in section 6.1.

Catalysts other than amino acids can also be used for the Hajos−Parrish−Eder−Sauer−Wiechert process. Kanger et al. have reported on the use of the trifluoromethanesulfonate salt of a chiral bimorpholine (**VII**) (5 mol %) for the asymmetric cyclization of both **1** and **9**. In this way, both the Hajos−Parrish diketone (*S*)-**3** and the Wieland−Miescher ketone (*S*)-**11** were obtained in yields and enantiomeric purities comparable to those obtained with proline (Scheme 13).[70]

In 2009, Akiyama and co-workers disclosed the first useful asymmetric synthesis of chiral cyclohexenones through the desymmetrization of prochiral 2,2-disubstituted-1,3-dicarbonyl compounds induced by a chiral phosphoric acid.[71] Under the optimal reaction conditions, treatment of the prochiral indanediones **37a**−**e** with 5 mol % of the (*R*)-BINOL-derived phosphoric acid **VIII** in refluxing hexane gave access to the cyclized compounds **38a**−**e** in excellent yield and enantioselectivity (Scheme 14). It is worth noting that for these substrates the use of proline gave much inferior results (cf. 57% yield and 60% ee for **38a**). Under these conditions, the cyclization of **1** afforded (*R*)-**3** in 86% yield and 70% ee and that of **9** produced (*R*)-**11** in 64% yield and 82% ee. The stereochemical sense of induction provided by **VIII** is therefore opposite to that of (*S*)-proline.

The origin of the enantioselectivity could be clarified by means of ONIOM hybrid DFT-HF calculations. In the transition state, the chiral phosphoric acid simultaneously activates the carbonyl and enol moieties, with preferred nucleophilic attack to the *pro*-(*S*) carbonyl of the indanone (1.3 kcal mol^{-1} energy difference for **37a**, in agreement with the experimental results).[71]

The desymmetrization of 2-substituted-2-(3-formylpropyl)-1,3-cyclohexanediones **39a**−**c** by means of an organocatalytic exo aldol cyclization was reported in 2007 by Hayashi et al.[72] After testing several chiral secondary amines, the trifluoroacetic salt of 2-(pirrolidinylmethyl)pyrrolidine (**IX**) was found to be the catalyst of choice, affording the bicyclo[4.3.0]nonane derivatives **40a**−**c** with a high enantioselectivity (Scheme 15). The absolute configuration of **40a**, ascertained by chemical correlation with the Wieland−Miescher ketone (*S*)-**11**, could be accounted for by a model transition state in which a proton coordinated to the nitrogen of the pyrrolidine ring in the key enamine intermediate derived from **39a** preferentially activates the *pro*-(*R*) carbonyl group.[72]

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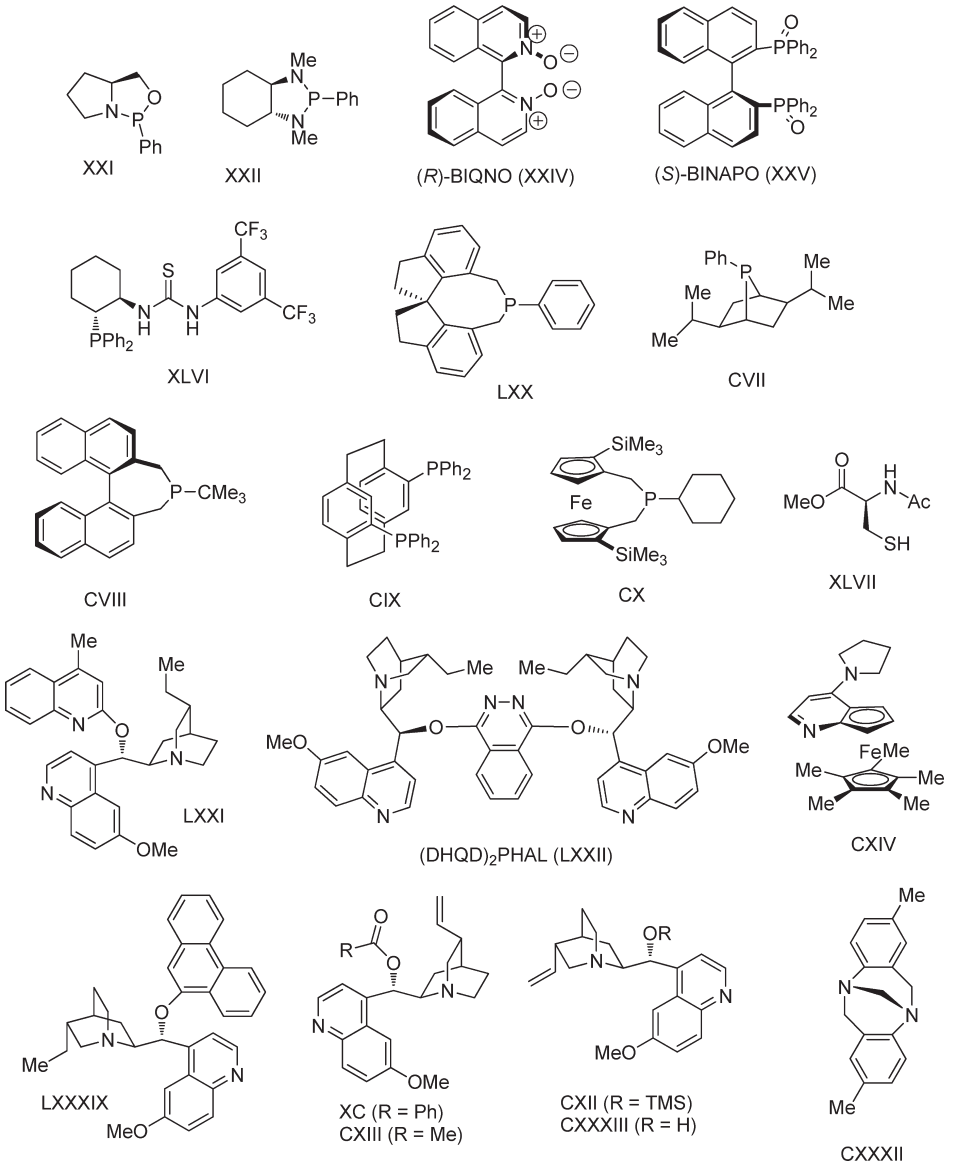

Figure 7. Representative Lewis base organocatalysts.

The desymmetrizing aldol cyclodehydration of 4-substituted-2,6-heptanediones (**41**) to the chiral 5-substituted 3-methyl-2-cyclohexenones (**42**) was initially studied by Agami and Sevestre.[73] In their pioneering investigation, these authors found that (*S*)-proline (**I**) was able to catalyze this process. Thus, treatment of a DMF solution of 4-methylheptane-2,6-dione (**41a**) with (*S*)-proline afforded the (*R*)-enone **42a** (arising from nucleophilic attack onto the *pro*-(*S*) carbonyl group of **41a**) in 75% yield and 43% ee (Scheme 16). Catalysis of the same reaction with (*S*)-phenylalanine (**II**) gave a much lower enantiomeric purity (7% ee).[73a] The stereochemical outcome of the reaction fits with the Houk mechanism for the Hajos−Parrish−Eder−Sauer−Wiechert reaction.[74]

Catalytic antibody 38C2, developed in 1999 by Lerner et al., gave a somewhat higher but still moderate enantiomeric excess.[75] A substantial improvement could be achieved only in 2008 by the research group of List.[76] The acetate salt of 9-amino-9-deoxye-piquinine (**X**), in which the protonated quinuclidine nitrogen probably acts as a hydrogen-bond-directing group, proved to be particularly powerful in this desymmetrization, and a variety of chiral cyclohexenones **42a**−**l** were obtained in excellent yields and enantioselectivities (Scheme 17).

As expected, the quinidine-derived catalyst **XI** gave the opposite enantiomers, also with high enantioselectivity. This is illustrated in Scheme 18, which shows how the (*R*)-enantiomer of **42c** (the so-called celery ketone) can be obtained in 91% ee. However, the authors did not provide a mechanistic model that could account for the stereochemical outcome of this reaction.

A related transformation, based on the intramolecular aldol cyclodehydration of the macrocyclic diketone **43**, had been previously disclosed by Knopff et al.[77] The use of 8 mol equiv of the sodium alkoxide derived from (+)-*N*-methylephedrine (**XII**) was necessary to achieve a 76% ee of the bicycic enone (*S*)-**44**, by a process that apparently involves the dinamic kinetic resolution of the racemic aldol intermediate. The final enone was subsequently transformed into the musk odorants (*R*)-muscone (**45**) and (*R*,*Z*)-5-muscenone (**46**) without loss of enantiomeric purity (Scheme 19).

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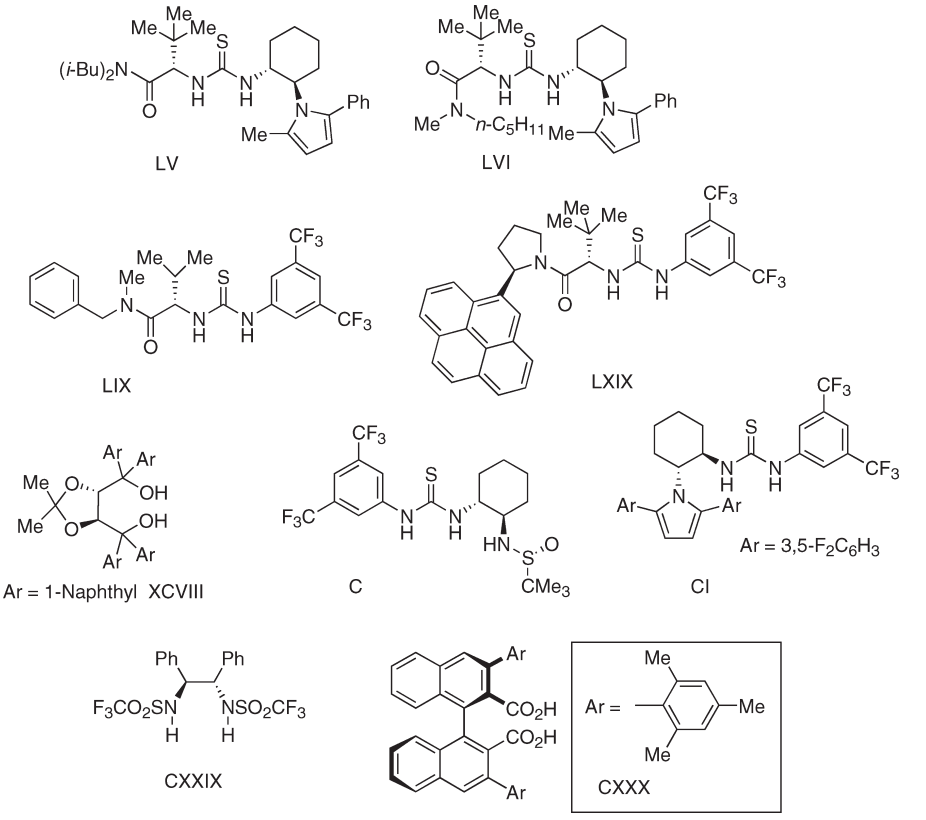

Figure 8. Chiral hydrogen-bond-donor catalysts.

An *N*-heterocyclic carbene-catalyzed (NHC) desymmetrization of prochiral 2,2-disubstituted-1,3-diketones, also relying on an intramolecular aldol reaction, was reported in 2007 by Scheidt and co-workers.[78] Building on the previous work of Nair, who had demonstrated that NHC's catalyzed the formation of cyclopentenes from enals and chalcones,[79] these authors found that the treatment of a series of 2-substituted-2-(3-formyl-2-propenyl)-1,3-diaryldiones **47a**−**h** with a catalytic amount of the chiral triazolium salt **XIII** in the presence of Hünig's base (that generates the NHC by proton abstraction from **XIII**) afforded the chiral α,α-disubstituted cyclopentenes **48a**−**h** with high enantioselectivity (Scheme 20).

The mechanism of this interesting transformation, summarized in Scheme 21, involves the initial addition of the NHC to the aldehyde, whose protonation generates an enol intermediate that undergoes an intramolecular aldol addition. The enantioselectivity of the reaction relies on the discrimination at this stage between the two enantiotopic ketone carbonyls. The resulting β-hydroxy ketone intermediate is intramolecularly acylated, producing an intermediate β-lactone (together with releasing of the NHC catalyst) that undergoes loss of carbon dioxide to generate the final product **48**.

It is worth noting that in the case of aliphatic diketones **47i,j** the β-lactone products **49i,j** (both with a 20:1 dr) are obtained instead of the cyclopentenes (Scheme 22), showing that in this case the chelotropic elimination of carbon dioxide requires higher reaction temperatures. The easy chelotropic elimination of carbon dioxide in the cyclization of aromatic diketones **47a**−**h** is probably due to the conjugation of the double bond in **48** with the aromatic substituent. Most recently, Scheidt has described the use of lactone **49j** (prepared on a 5 g scale in 69% yield and with 98% ee) as a key intermediate in the enantioselective total syntheses of bakkenolides I, J, and S.[80] The absolute configuration of the cyclized compounds (ascertained by X-ray diffraction analysis of **48a**) was rationalized by the authors through the model transition state depicted in Figure 18.

Iwabuchi developed in 2005 the desymmetrizing aldol cyclization of 3-(4-oxocyclohexyl)propionaldehyde (**50**).[81] A high enantioselectivity and a high catalytic activity was exhibited by the tetrabutylammonium salt of (4*R*,2*S*)-4-(*tert*-butyldiphenylsilyloxy)prolinate (**XIV**), which furnished (1*S*,5*R*,8*R*)-8-hydroxybicyclo[3.3.1]nonan-2-one (**51**) with 94% ee. The enantiomer of **51** could be obtained by using (4*R*,2*R*)-4-(*tert*-butyldiphenylsilyloxy)proline (**XV**) as the catalyst. This last compound, prepared in enantiomerically pure form (>99% ee) after recrystallization, was used in an efficient synthesis of the cannabinoid receptor agonist (−)-CP 55940 (Scheme 23).[81a] Iwabuchi later reported an asymmetric synthesis of (+)-jubavione starting from **51**.[81c] The stereochemical outcome of this cyclization can be rationalized within the framework of the Houk mechanism[74] for the Hajos−Parrish−Eder−Sauer−Wiechert reaction. This process has nevertheless a narrow substrate scope: 2-(4-oxocyclohexyl)acetaldehyde underwent the intramolecular aldolization with very low enantioselectivity.[81b] The replacement of the C3 methylene by a NCO_2Me unit in the propionaldehyde chain of **50** also leads to diminished yields and enantioselectivities in the aldol cyclization reaction catalyzed by proline derivatives.[81d]

The application of the intramolecular aldol reaction to the desymmetrization of *meso*-dialdehydes will be discussed in section 4.1, and the use of aldehydes as the nucleophilic component in Hajos−Parrish-type reactions will be dealt with in section 6.1.

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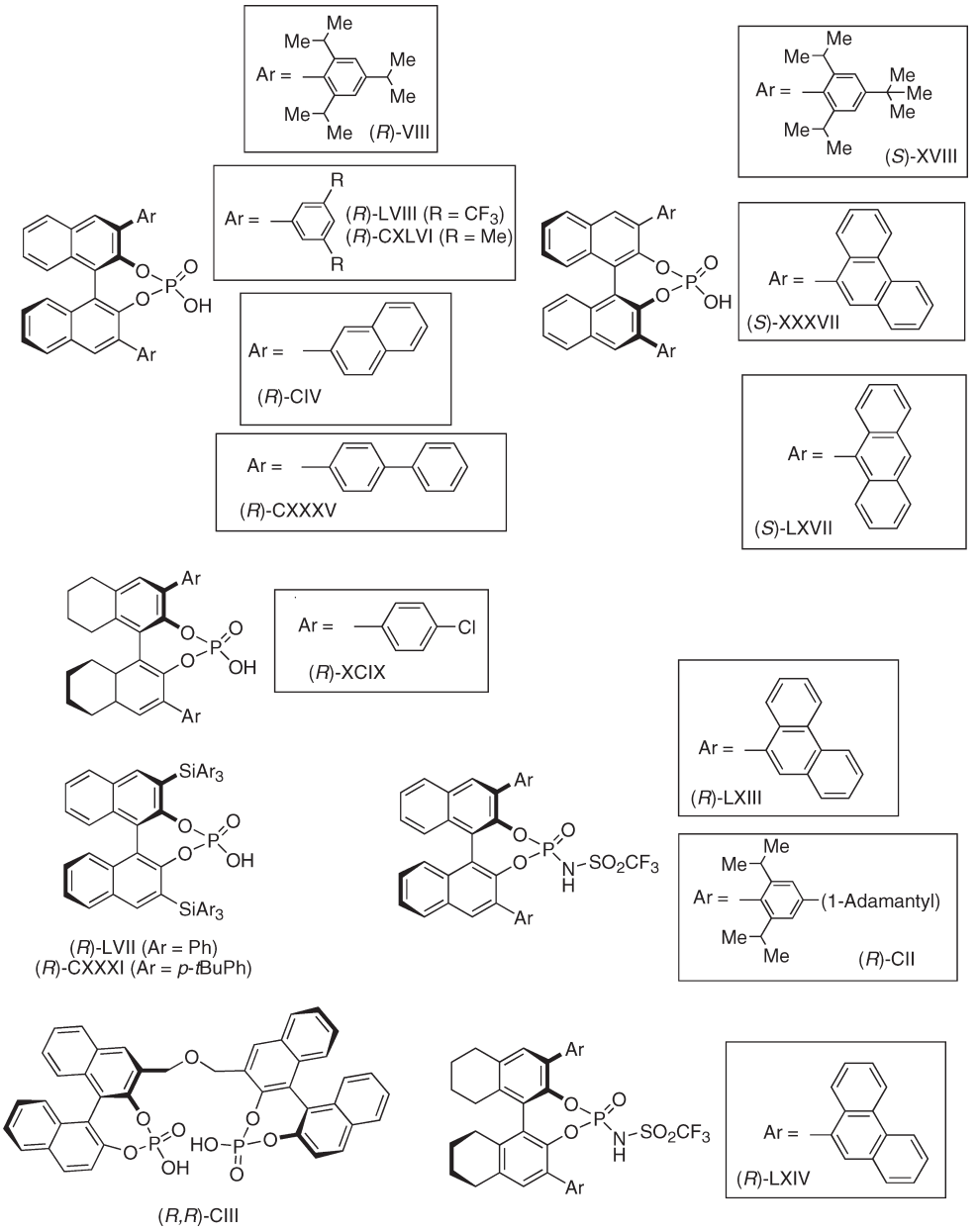

Figure 9. Chiral BINOL-derived phosphoric acids and amides.

3.2. Desymmetrizing Michael Cyclizations

The first organocatalytic desymmetrization of 4,4-disubstituted cyclohexenones was described in 2005 by Hayashi et al.[82] Hayashi hypothesized that the bicyclo[4.3.0]nonene skeleton, found in a variety of natural products, could be accessed from an achiral precursor, a 4-substituted-4-(3-formylpropyl)cyclohexa-2,5-dien-1-one (**52**), via asymmetric intramolecular Michael reaction, in a process that involves the creation of three contiguous stereogenic centers in a single step. In the experimental implementation of this concept, the catalyst of choice was found to be trifluoroacetic salt of the cysteine-derived thiazolidine **XVI**, which allowed the preparation of the bicyclic enones **53a**−**d** in good yield and with high diastereo- and enantioselectivity (Scheme 24). As we will see later in section 4.2, this process can be applied to the asymmetric cyclization of acyclic formyl enones.

In 2008, Gaunt and co-workers disclosed an extremely elegant catalytic enantioselective conversion of phenols into complex chiral polycyclic compounds.[83] The process involved the oxidative dearomatization of 4-substituted phenols **54** to the 4,4-disubstituted cyclohexenones **55**, which were in situ desymmetrized by a chiral amine-catalyzed intramolecular Michael addition. With the (*R*)-diarylprolinol-derived catalyst **XVII**, the bicyclized enones **56a**−**h** were obtained with high stereoselectivity (Scheme 25).

In the oxidative dearomatization step, nucleophiles other than methanol (water, acetonitrile, fluoride ion) can be used with equally good yields and stereoselectivities. The absolute configuration of the products, deduced from the crystal structure of a derivative of **56c**, can be accounted for by the model transition state (depicted in Figure 19) in which a 2-naphthyl group shields the top face of the intermediate enamine.

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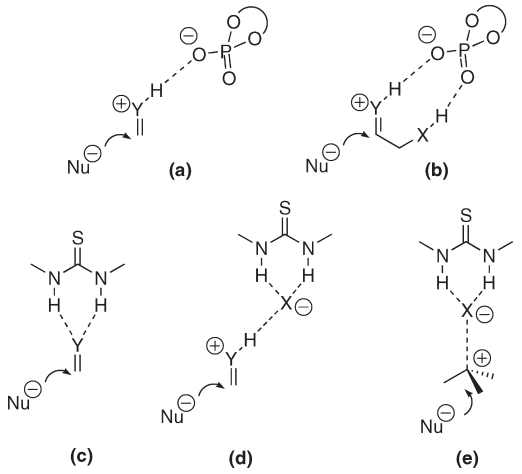

Figure 10. Different types of catalysis by organic molecules containing acidic hydrogens: (a, b) Brønsted acid activation catalysis, (c) hydrogen-bonding activation catalysis; and (d, e) hydrogen-bond-donor activation catalysis by anion-binding.

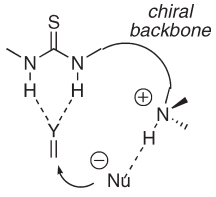

Figure 11. Dual activation of electrophile and nucleophile by a bifunctional amine thiourea catalyst.

In a related approach, You et al. have recently reported a dearomatization−desymmetrization of 4-substituted phenols via an oxa-Michael reaction.[84] A series of 4-substituted-4-(3-hydroxy-2-oxopropyl)cyclohexadienones **57**, readily obtained from the corresponding 4-substituted phenols by oxidation with $PhI(OAc)_2$ in the presence of ethylene glycol, was treated with a chiral BINOL-derived phosphoric acid that induced their oxa-Michael cyclization, giving access to enantioenriched bicyclic enones **58**. The most efficient catalyst was compound **XVIII**, although the BINOL-derived phosphoric acid (*S*)-**VIII** gave very similar results (Scheme 26). Interestingly enough, in many instances the enantiomeric access of the products could be upgraded to 99% after one recrystallization. The authors proposed a catalytic working model for the desymmetrization process. The chiral phosphoric acid acts as a bifunctional catalyst, in which the acidic proton and the P═O moiety form hydrogen bonds with the carbonyl and the hydroxy groups, respectively (Figure 20).[84]

As a further demonstration of the usefulness of the dearomatization−desymmetrization process, the authors developed concise total syntheses of cleroindicins C, D, and F,[85] natural products isolated from a chinese plant employed for the treatment of malaria and rhumatism (Scheme 27). Cyclohexanedione **59** was readily prepared through the oxidative dearomatization of commercial 4-(2-hydroxyethyl)phenol with oxone. Under catalysis by (*S*)-**XVIII**, **59** underwent the intramolecular oxa-Michael reaction, affording the key intermediate **60** in 80% ee. This compound afforded cleroindicin D after successive epoxidation and reduction with aluminum amalgam (27% overall yield from **59**). On the other hand, reduction of **60** with triphenylphosphite furnished cleroindicin F (57% yield from **59**). Further hydrogenation of this last compound afforded cleroindicin C in 94% yield, without loss of enantiomeric purity.

3.3. Desymmetrizing Cyclizations via Stetter and Benzoin Reactions

The Stetter reaction, the nucleophile-catalyzed addition of an aldehyde to a Michael acceptor,[27c,86] was applied in 2006 by Liu and Rovis to the first asymmetric organocatalytic dearomatization−desymmetrization sequence of 4-substituted phenols.[87] The (1-substituted-4-oxocyclohexa-2,5-dienyloxy)acetaldehydes (**61a**−**i**), obtained from the alcohol precursors **57** by oxidation with the Dess−Martin periodinane (DMP), afforded the diastereomerically pure (>95:5 dr) products **62a**−**i** by treatment with a 10 mol % amount of the aminoindanol-derived triazolium salt **XIX** in the presence of potassium hexamethyldisilazane (base used to generate in situ the chiral NHC catalyst). As seen in Scheme 28, both the yields and enantioselectivities of the cyclized adducts were good or excellent. The reaction conditions were very mild and the reaction was extremely fast, although highly diluted solutions (0.008 M in toluene) had to be used. The authors were able to ascertain both the absolute and relative configuration of several products, but they did not propose any working model to explain the stereochemical outcome of the process.

The process tolerates the presence of additional substituents in the cyclohexadienone moiety, as evinced by the examples shown in Figure 21.

Although the bulk of the work of Liu and Rovis focused on oxygen-tethered substrates, the process can also be applied to the synthesis of carbocycles. Thus, the cyclization of **54b** afforded the hydrindanedione **65** in moderate yield and 90% ee (Scheme 29).

Ema et al. have examined the NHC-catalyzed intramolecular crossed benzoin reactions of cyclic 1,3-diketones such as **39a** or **66**.[88] Even if the racemic version of the reaction took place with satisfactory yields and diastereoselectivities, the development of an asymmetric version proved to be much more challenging. Thus, after extensive experimentation, the best conditions found for the desymmetrization of **66** involved the use of the chiral triazolium salt **XX**, cesium carbonate as the base, and dichloromethane as the solvent (Scheme 30). In this way, the cyclized product **67** was obtained in 50% yield and with 78% ee.

3.4. Desymmetrizing Cyclizations via Aza−Wittig Reactions

Progress in this area has been achieved through the efforts of Marsden's research group. Marsden envisaged the possibility that cyclic ketoimines could be prepared enantioselectively from simple prochiral dicarbonyl precursors bearing an amine equivalent by a desymmetrizing imine cyclization. A diastereoselective variant of this strategy had been previously developed by Solé and Bonjoch[89] and successfully applied to total synthesis.[90] Marsden decided to study the applicability of the aza-Wittig reaction of iminophosphoranes with carbonyl compounds,[91] induced by a chiral phosphine. The experimental actualization of this concept[92] revealed that the desymmetrization of acyclic (**68a**,**b**) or cyclic (**69a**,**b**) diketo azides could be achieved with moderate enantioselectivities by using the chiral phosphanes **XXI** or **XXII**, respectively (Scheme 31).

In 2007, Headley and Marsden disclosed that the enantioselectivity in the cyclization of **69a**,**b** could be somewhat improved (up to 83% ee for **71b**) by using *P*-stereogenic phosphines.[93] It must be born in mind, however, that the phosphines in these

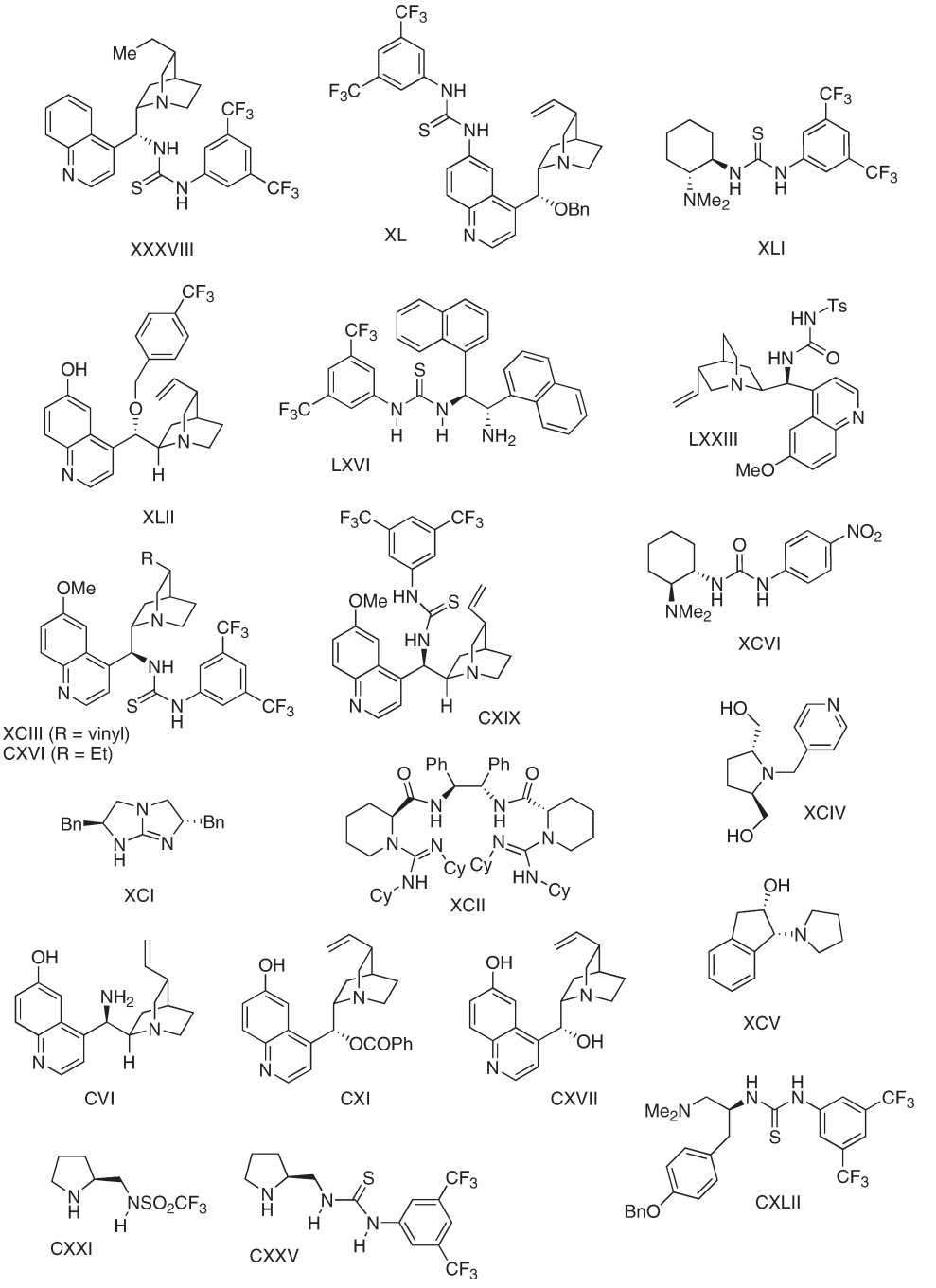

Figure 12. Bifunctional hydrogen-bond-donor/Brønsted base catalysts.

reactions are oxidized to the corresponding *P*-oxides, so that these aza-Wittig desymmetrizations are not catalytic processes. The development of a truly organocatalytic desymmetrization of 1,3-dicarbonyls by formation of a keto imine is still a challenge.

4. ORGANOCATALYTIC ASYMMETRIC RING-CLOSING REACTIONS OF ACYCLIC AND MONOCYCLIC ACHIRAL SUBSTRATES

4.1. Intramolecular Aldol Additions

The first intramolecular asymmetric organocatalytic aldol reaction of a ketoaldehyde was described in 1981 by Woodward et al., in the course of their total synthesis of erythromycin A.[8] Although this reaction is in fact a kinetic resolution of a chiral racemic substrate and the enantiomeric excess of the aldol was only moderate (36% ee), this is a seminal report in organocatalysis that includes several noteworthy features (Scheme 32). It constitutes the first example of asymmetric iminium activation, as well as that of a domino thia−intramolecular aldol reaction and dynamic kinetic resolution.

In 2003, List and co-workers uncovered the first asymmetric organocatalytic enol/exo intramolecular aldol addition of an achiral dialdehyde.[94] Using (*S*)-proline (**I**) as the catalyst, the cyclization of a series of heptanedials **72** took place with excellent diastereo- and enantioselectivity (Scheme 33). The resulting cyclic aldols **73** were majoritarily trans. In a similar way, the cyclization of

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the ketoaldehyde **74** afforded a 2:1 mixture of the two possible tertiary aldols **75**. The major anti diastereomer was practically enantiopure (99% ee), and the minor syn diastereomer of **75** was obtained in 95% ee. On the other hand, the aldolization of hexanedial **76** took place with markedly lower stereoselectivity.

The absolute configuration of the major products was rationalized by List[94] by the transition state depicted in Figure 22. This mechanistic hypothesis has been subsequently validated by DFT calculations.[95]

The proline-catalyzed aldol cyclization has been applied with variable success to prochiral dialdehydes. Thus, the aldolization of 4-methylheptanedial **78**[94] gave a mixture of the four possible diastereomers **79a**−**e**, with variable enantioselectivities (Scheme 34). The DFT calculations of Santos et al. were able to reproduce qualitatively the experimental values.[95b]

On the other hand, the intramolecular aldol addition of the *meso*-dialdehyde **80** gave a 1:1 mixture of the two possible anti diastereomers **81a** and **81b**, with 99% and 75% ee, respectively.[94] The cyclic *meso*-dialdehyde **82** also afforded a 1:1 mixture, in this case of the cis and trans isomers. The cis isomer of **83**, separated at a later stage, provided (+)-cocaine of 86% ee after a five-step synthetic sequence (Scheme 35).[96] A direct intramolecular asymmetric catalytic aldol cyclodehydration of *meso*-3,4-disubstituted-1,6-dialdehydes that takes place with variable conversion and with low stereocontrol has been described by Kurteva and Afonso.[97]

Besides compound **74**, other achiral ketoaldehydes have been submitted to intramolecular aldol additions. Thus, Enders et al.[98] reported the (*S*)-proline-catalyzed cyclization of ortho-substi-

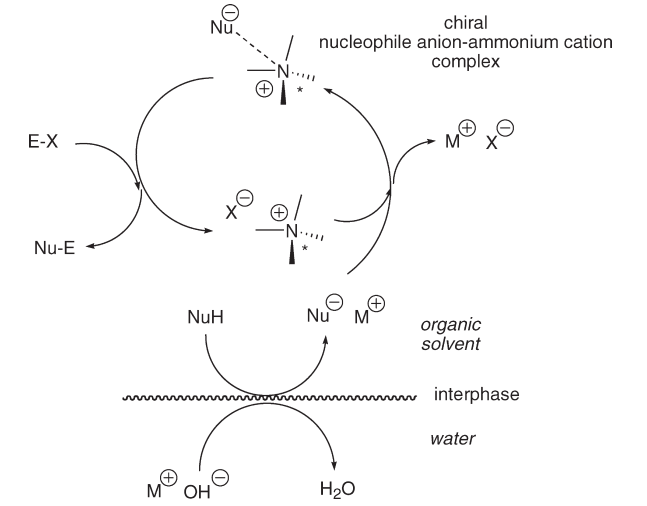
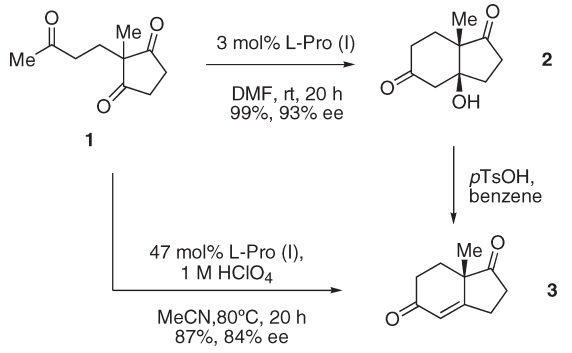


Figure 13. Interphase mechanism for phase-transfer catalysis by a chiral quaternary ammonium salt.

Scheme 6. Proline-Catalyzed Synthesis of the Bicyclic Diketone 3



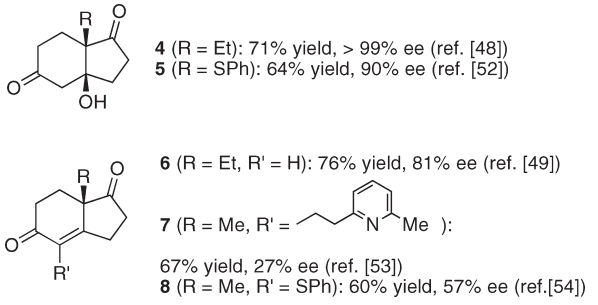


Figure 15. Products from proline-catalyzed aldol cyclizations of compounds related to **1**.

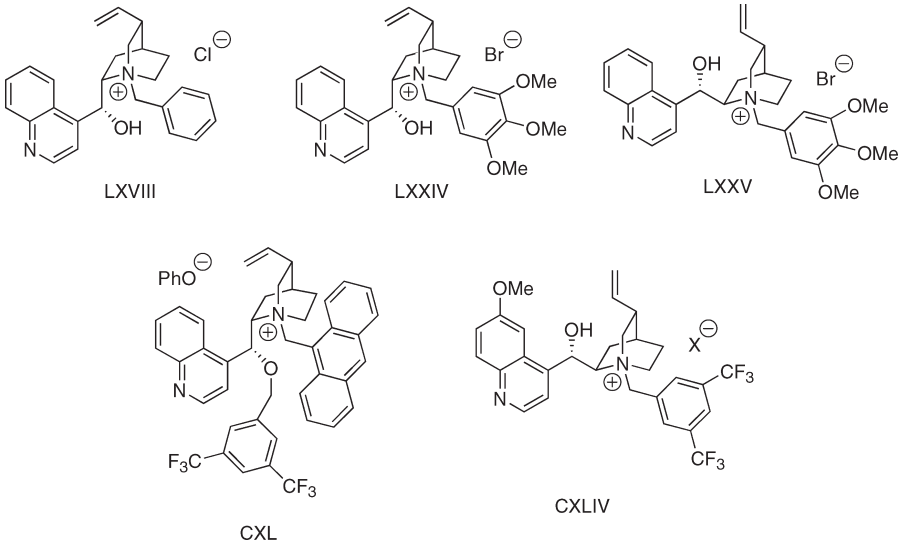


Figure 14. Chiral phase-transfer organocatalysts.

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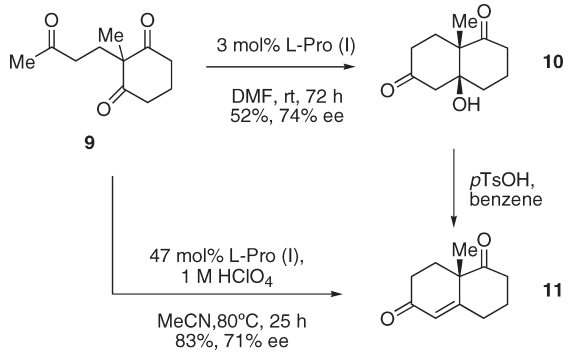
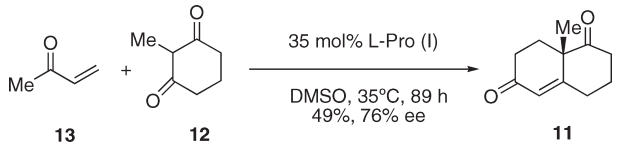
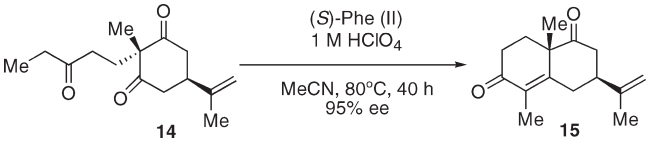
Scheme 7. Proline-Catalyzed Synthesis of the Wieland−Miescher Ketone 11



Scheme 8. Proline-Catalyzed Single-Step Synthesis of the Wieland−Miescher Ketone 11



Scheme 9. Phenylalanine-Catalyzed Aldol Cyclization of the Prochiral Triketone 14



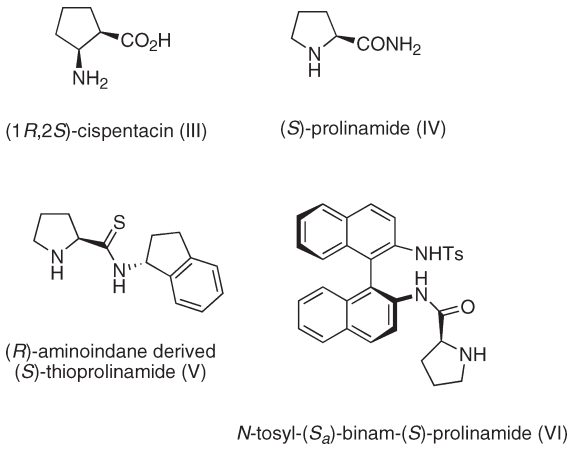
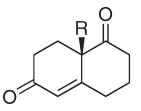


Figure 16. Chiral amino acid and amino acid derivatives that catalyze the Hajos−Parrish−Eder−Sauer−Wiechert reaction.

tuted aromatic aldehydes and ketones **84**. This reaction exhibited a high syn-diastereoselectivity (from 93:7 to >99:1 dr) and good enantioselectivity (from 76% to 87% ee). Enantiomerically pure 2,3-dihydro-3-hydroxybenzofurans **85** were isolated by recrystallization of the reaction products from hexane−ethyl acetate;



16 (R = allyl): 93% yield, 97% ee
17 (R = 3,3-dimethylallyl): 88% yield, 96% ee
18 (R = benzyl): 70% yield, 94% ee
19 (R = propargyl): 78% yield, 90% ee
20 (R = 2-bromoallyl): 70% yield, 96% ee
21 (R = 3-butenyl): 54% yield, 95% ee
22 (R = 4-methyl-3-pentenyl): 59% yield, 84% ee
23 (R = 4-methylpentyl): 53% yield, 84% ee
24 (R = $(CH_2)_2CO_2Me$): 71% yield, 95% ee
25 (R = $(CH_2)_3OBn$): 78% yield, 94% ee

Figure 17. Wieland−Miescher ketone analogues obtained by using binam-prolinamide **VI** (5 mol %) and benzoic acid (1 mol %).

the absolute configurations can be rationalized by an enol/exo transition state working model (Scheme 36).

Subsequently, Hamada and co-workers disclosed an efficient synthesis of (2*S*,3*R*)-3-hydroxy-3-methylproline **88**, a component of polyoxypeptins, in which an intramolecular asymmetric aldol reaction of the ketoaldehyde **86a** constituted a key step.[99] Interestingly enough, (*S*)-proline (**I**) furnished (after reduction of the intermediate aldol) the cyclic compound **87a** with moderate diastereoselectivity (78:22 syn/anti) and with low enantiomeric purity (49% ee), and the catalyst of choice was in fact the acid **88** (= **XXIII**, previously obtained in the author's laboratory by other methods).[100] The reaction was then applied to ketoaldehydes **86b**−**f** (Scheme 37). In all instances the syn isomer is the major (or even the exclusive) product, suggesting a TS similar to that proposed by Enders in the case of the aldol cyclization of compounds **84**.[98]

Sugiura et al. first reported in 2008 that phosphorus oxides function as Lewis base organocatalysts, promoting both the conjugate reduction of enones with trichlorosilane and the reductive aldol reaction of enones with aldehydes (Scheme 38).[101]

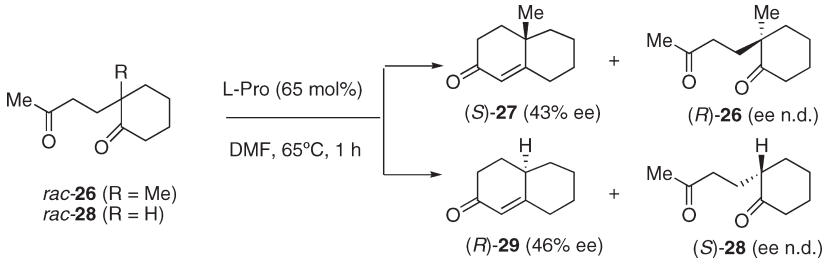
Recently, the same research group has found that enantioselective catalysis of this tandem reaction can be achieved with chiral Lewis bases such as the bis(isoquinoline) *N*,*N*′-dioxide (*R*)-BIQNO (**XXIV**) or the bis(naphthalene) phosphine oxide (*S*)-BINAPO (**XXV**).[102] For intermolecular reactions, catalyst **XXV** leads to good diastereo- and enantioselectivities. In the cyclization of ketoenone **89**, however, **XXV** produced the cyclic ketol **90** in good yield but in very low enantiomeric purity, and the use of **XXIV** gave *ent*-**90** with 55% ee (Scheme 39).

In 2007, Zhou and List developed a highly efficient asymmetric organocatalytic approach to *cis*-3-substituted-cyclohexylamines that takes place through an intramolecular aza-aldol condensation of an achiral 1,5-diketone, followed by a Brønsted acid-catalyzed transfer hydrogenation with a Hantzsch ester (Scheme 40).[103] It should be noted, however, that in this process the asymmetric induction takes place in the hydrogenation and not in the cyclization step.

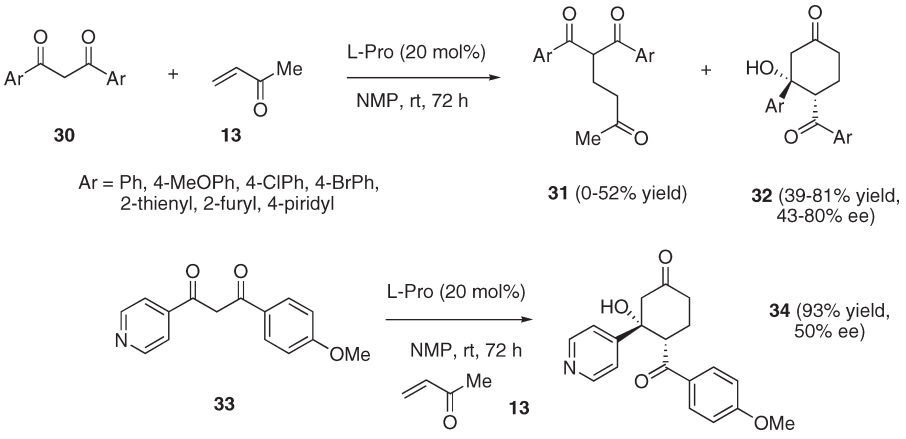
After screening a number of chiral Brønsted acid catalysts, the authors found that the (*R*)-binol-derived phosphoric acid **VIII** (10 mol %; see Figure 9) with Hantzsch ester **91** (2.2 equiv), *p*-alkoxyanilines **92a**,**b** (1.5 equiv) at 50 °C in cyclohexane, and in the presence of molecular sieves afforded the *cis*-3-substituted-cyclohexylamines **94** from the corresponding diketones **93** in good yields, variable diastereoselectivities, and in good to excellent enantioselectivities (Scheme 41).

The organocatalytic asymmetric transannular aldolization of achiral mono- and bicyclic diketones was also developed in List's laboratory.[104] After testing several proline derivatives, Chandler and List found that *trans*-4-fluoroproline **XXVI** (20 mol %) was able to catalyze the transannular aldol reaction of several monocyclic diketones (Scheme 42). The conversions were generally

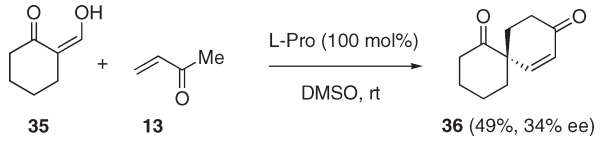
Scheme 10. Proline-Catalyzed Asymmetric Annelation of Chiral Diketones



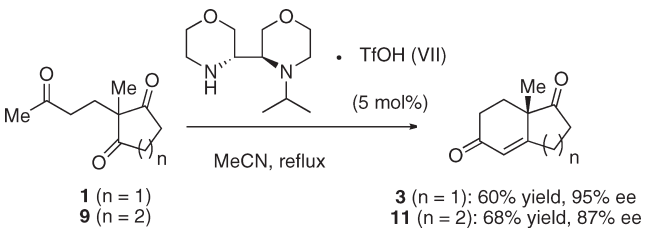
Scheme 11. Proline-Catalyzed Transformation of 1,3-Diketones into Optically Active Cyclohexanones



Scheme 12. Proline-Catalyzed Asymmetric Robinson Annulation of 2-Formylcyclohexanone



Scheme 13. Bimorpholine-Mediated Enantioselective Intramolecular Aldol Condensation



moderate, but the selectivities were uniformly high, and the enantioselectivity of the process was highly dependent on the aldol ring size. In general, the absolute configurations of the transannular aldol products can be accounted for by a transition state based on the Houk−List model.[74c]

The case of cycloocta-1,4-dione (**95**) is especially interesting, since the introduction of a fused aromatic or aliphatic ring did not diminish the enantioselectivity of the process, and a series of tricyclic compounds, shown in Figure 23, was obtained with high diastereo- and enantioselectivity (90−96% ee).

Compound **105** was subsequently transformed into (+)-hirsutene, a popular synthetic target,[105] by means of a high-yielding three-step sequence.

Chen et al. have recently devoted their efforts to the kinetic resolution of racemic 6-aryl-2,6-hexanediones (**106**) via intramolecular aldol condensation.[106] After the usual screening of several primary and secondary chiral amines, the triflate salt of the *trans*-4-hydroxyproline derivative **XXVII**[107] (20 mol %) in chloroform solution and in the presence of molecular sieves was found to catalyze preferentially the cyclization of the (*R*)-isomers of the starting diketones with selectivity factors >20, giving rise to enantioenriched (*S*)-diketones **106** and to (*S*)-3,5-diaryl-2-cyclohexenones (**107**) (Scheme 43). The transition states depicted in Figure 24 can account for the observed stereoselectivity.

4.2. Intramolecular Michael and Related Additions

The first intramolecular catalytic asymmetric Michael reaction of aldehydes was reported in 2004 by Hechavarria Fonseca and List.[108] These authors initially studied as a model reaction the amine-catalyzed Michael cyclization of (*E*)-8-oxo-8-phenyl-6-octenal **108a** to give ketoaldehyde **109a**. This reaction was indeed catalyzed by (*S*)-proline (**I**), but with low diastereo- (2:1 trans/cis) and enantioselectivity [15% ee for the trans (anti) isomer]. Fortunately, MacMillan's chiral imidazolidinone **XXVIII**[109] gave much better results that could be extended to other structurally related aldehydes **108b**−**f** (Scheme 44). The absolute configuration of the cyclized products could be established (chemical correlation of **109c**), but the actual mechanism of the

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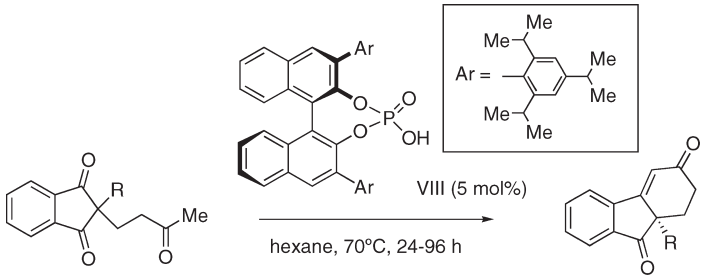
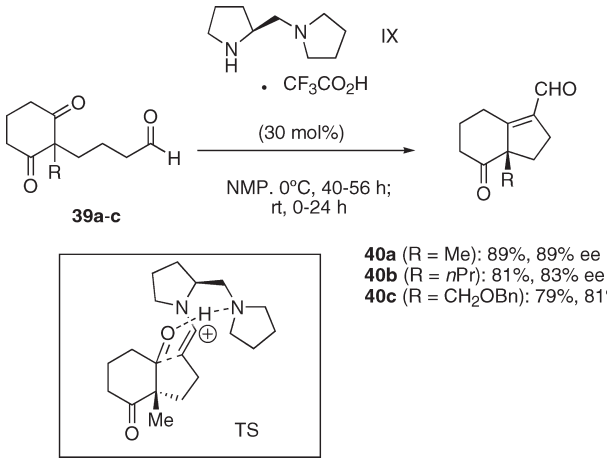
Scheme 14. Chiral Phosphoric Acid Catalyzed Desymmetrization of 1,3-Diketones



37a-e

38a (R = Me): 95%, 90% ee
38b (R = Et): 89%, 92% ee
38c (R = propargyl): 82%, 94% ee
38d (R = Bn): 94%, 87% ee
38e (R = Ph): 72%, 90% ee

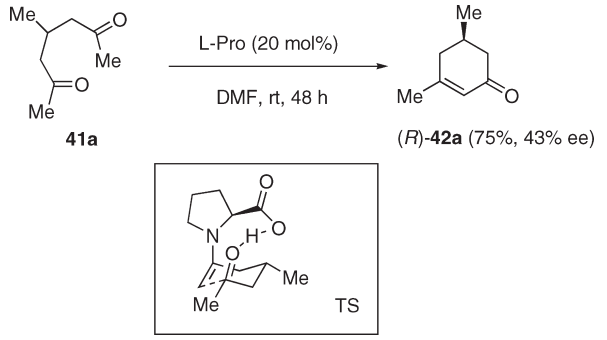
Scheme 15. Chiral Secondary Amine-Catalyzed Desymmetrization of 1,3-Diketones



39a-c

40a (R = Me): 89%, 89% ee
40b (R = *n*Pr): 81%, 83% ee
40c (R = CH_2OBn): 79%, 81% ee

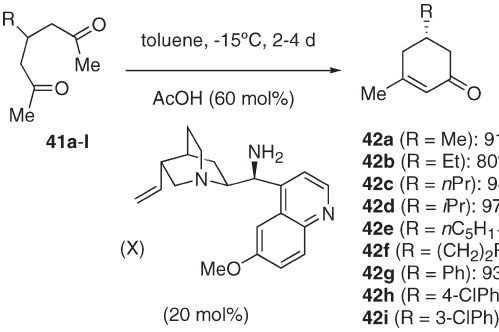
Scheme 16. Proline Catalyzed Desymmetrization of 2,6-Heptanediones



41a

(*R*)-**42a** (75%, 43% ee)

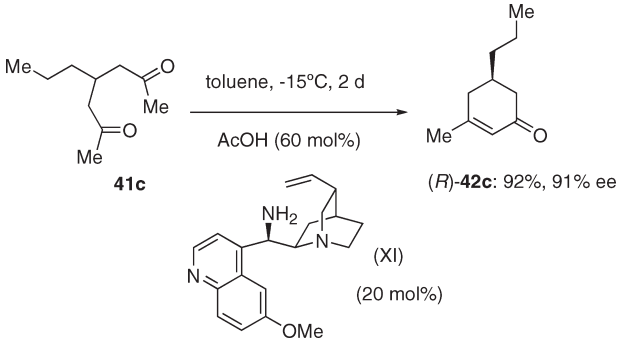
Scheme 17. Primary Amine Catalyzed Desymmetrization of 2,6-Heptanediones



41a-l

42a (R = Me): 91%, 92% ee
42b (R = Et): 80%, 90% ee
42c (R = *n*Pr): 94%, 90% ee
42d (R = *i*Pr): 97%, 86% ee
42e (R = nC_5H_{11}): 96%, 93% ee
42f (R = $(CH_2)_2Ph$): 98%, 90% ee
42g (R = Ph): 93%, 91% ee
42h (R = 4-ClPh): 94%, 91% ee
42i (R = 3-ClPh): 92%, 92% ee
42j (R = *p*Tol): 94%, 91% ee
42k (R = 2-thienyl): 92%, 92% ee
42l (R = 2-furyl): 95%, 94% ee

Scheme 18. Organocatalytic Enantioselective Synthesis of (*R*)-Celery Ketone



41c

(*R*)-**42c**: 92%, 91% ee

reaction (enamine, enamine−iminium, intramolecular hetero-Diels−Alder) is still unknown.

The enantioselective Michael cyclization of formyl enones **108** was also examined by Hayashi et al.[82] When treated with a 10 mol % of the cysteine-derived organocatalyst **XVI** in acetone at 0 °C, the reaction proceeded smoothly to the cyclopentene products **109**. With this catalyst, however, the major diastereomers were the cis (syn) isomers. (Scheme 45) Careful examination of the cis/trans ratio at different reaction times revealed that the cis-isomer is the kinetic product, while the trans-isomer is thermodynamically more stable. Both isomers are formed with excellent enantioselectivity [cf. 99% ee for **109a′** (cis), 94% ee for **109a** (trans)].

Building on the iminium ion-catalyzed transfer hydrogenation of enals with Hantzsch esters,[110] List and co-workers subsequently developed a reductive version of the asymmetric Michael cyclizations of formyl enones.[111] The preferred

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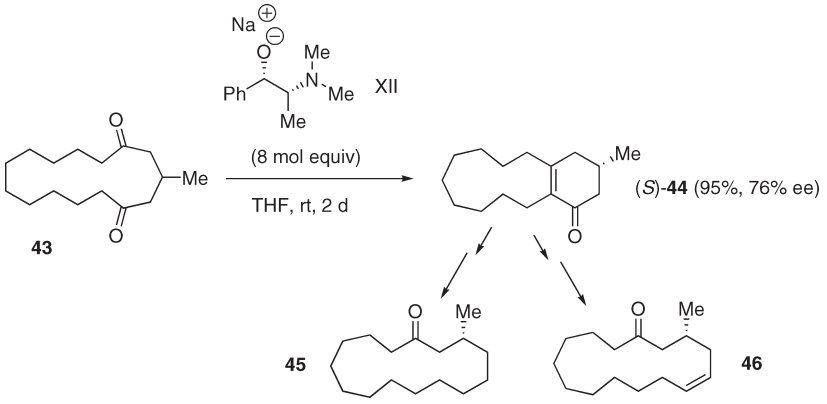
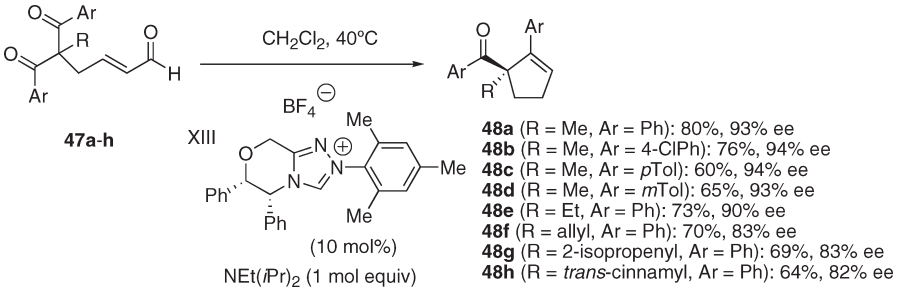
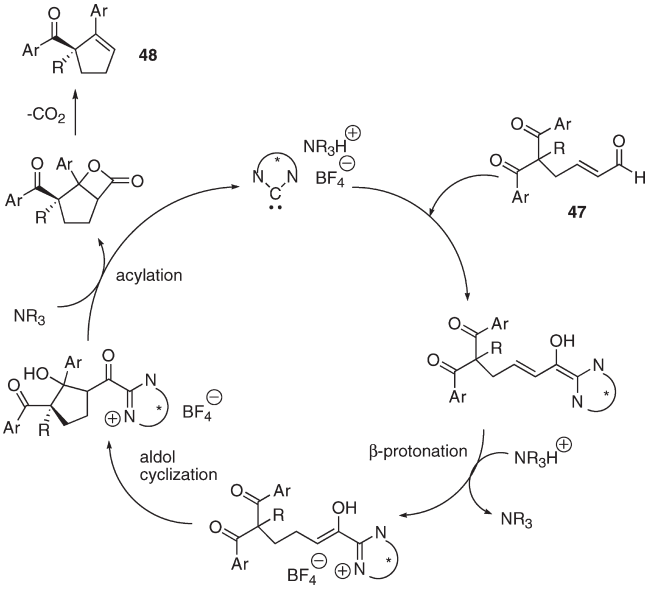
Scheme 19. Enantioselective Intramolecular Aldol Addition−Dehydration Reaction of a Prochiral Macrocyclic Diketone



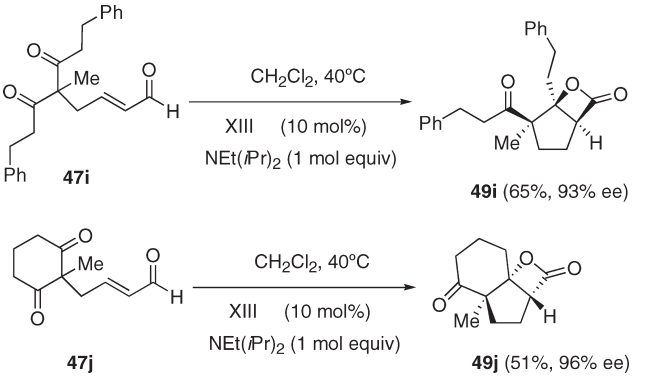
Scheme 20. NHC-Catalyzed Desymmetrization of 1,3-Diketones



Scheme 21. Proposed Reaction Pathway for the NHC-Catalyzed Desymmetrization of 1,3-Diketones



Scheme 22. Enantioselective β-Lactone Synthesis



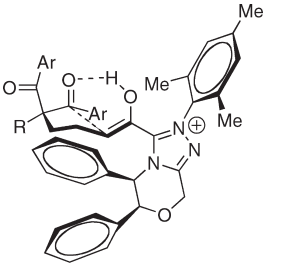


Figure 18. Proposed transition state for the NHC-catalyzed desymmetrization of 1,3-diketones.

substrates for this reaction are the aromatic enals **110** that cyclize in the presence of Hantzsch ester **91** (1.1 equiv) in dioxane at room temperature under catalysis by imidazolidinone hydrochloride **XXIX** (20 mol %; Scheme 46). The Michael acceptor moiety tolerates both aromatic and aliphatic enones, giving the major

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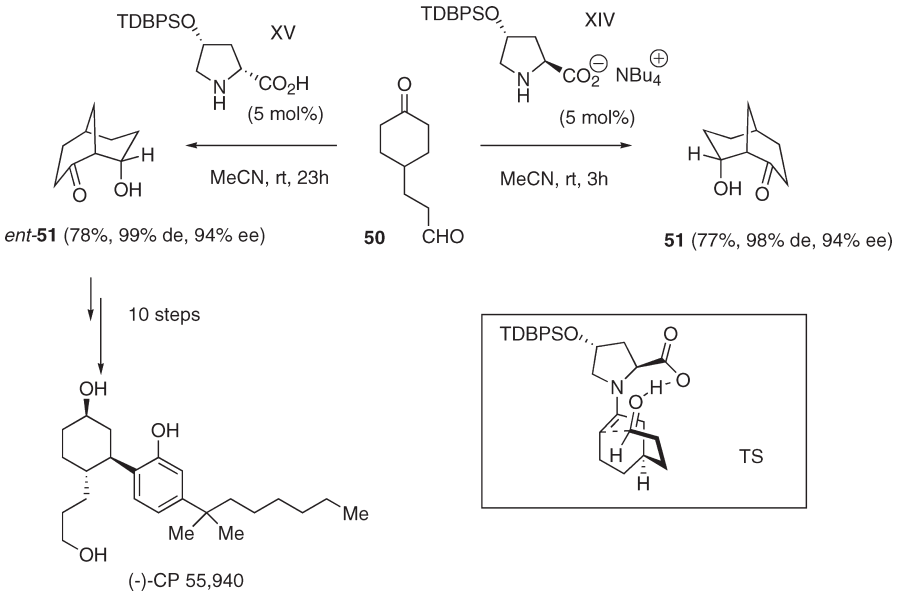
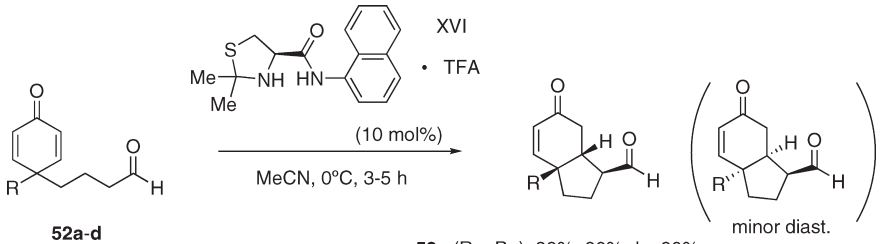
Scheme 23. Desymmetrizing Aldol Cyclization of 3-(4-Oxocyclohexyl)propionaldehyde



Scheme 24. Asymmetric Ontramolecular Michael Reaction of 4-Substituted-4-(3-formylpropyl)cyclohexa-2,5-dien-1-ones



53a (R = Bn): 89%, 90% de, 90% ee
53b (R = Me): 93%, 92% de, 91% ee
53c (R = *n*-Bu): 100%, 82% de, 90% ee
53d (R = allyl): 96%, 84% de, 95% ee

trans (anti) diastereomers **111** with uniformly high enantioselectivity. Interestingly enough, imidazolidinone hydrochloride **XVIII** was not catalytically active in this process. For some substrates, other imidazolidinones (**XXX**, **XXXI**) were the optimal catalysts.

Furthermore, the spacer between the enal and the Michael acceptor moiety is not necessarily a phenyl ring, as evinced by the reductive cyclization of enals **112** and **114** (Scheme 47). The authors assume that the reaction proceeds via a (racemic) iminium conjugate reduction, followed by an in situ catalytic (asymmetric) Michael cyclization. No mechanistic working model was proposed, however, to account for the stereochemical outcome.

Subsequently, an alternative Michael cyclization of aromatic enals **110**, catalyzed by chiral NHC's, was developed by Scheidt and co-workers.[112] The NHC derived from the chiral triazolium salt **XXXII** (differing from **XX** only in the nature of the anion) by treatment with Hünig's base gave satisfactory yields and excellent enantiomeric purities. The intermediate cyclization products **117** were treated in situ with methyl alcohol to provide the methyl esters **118** with excellent diastereoselectivities (>20:1 cis/trans ratio; Scheme 48). The procedure was applied to the aliphatic enals **119** and **121** with variable stereoselectivities.

The proposed pathway to this process, related to that previously discussed in Scheme 21 (section 3.1), involves the addition of the NHC to the unsaturated aldehyde to afford a transient diene intermediate that upon protonation at the β-position by the ammonium salt generates the key enol intermediate that undergoes the asymmetric intramolecular Michael addition. An intramolecular acylation of this Michael adduct **116** regenerates the NHC catalyst and gives the enol lactone **117** (Scheme 49).

More recently, You et al. have found that chiral NHC's generated from the camphor-derived triazolium salt **XXXIII** are also highly efficient in the asymmetric intramolecular Michael addition.[113] With 1−5 mol % of the catalyst, aromatic enals **110** afforded the cyclized methyl esters *ent*-**118** with very good yields and enantiomeric purities (Scheme 50). The authors proposed a model for the transition state that is able to rationalize the high enantioselectivity of the process.[113]

An imidazolidinone salt very similar to **XXIX** (**XXXIV**, with 3,5-dinitrobenzoate instead of chloride) was found by Xiao and co-workers to be the optimal catalyst for the Michael cyclization of indolyl α,β-unsaturated aldehydes **123**.[114] This reaction, which can also be viewed as an intramolecular ring-closing Friedel−Crafts-type alkylation,[115] furnished the tricyclic indoles **124** with good yields and enantioselectivities, although the reaction times were very long (Scheme 51). The stereochemical

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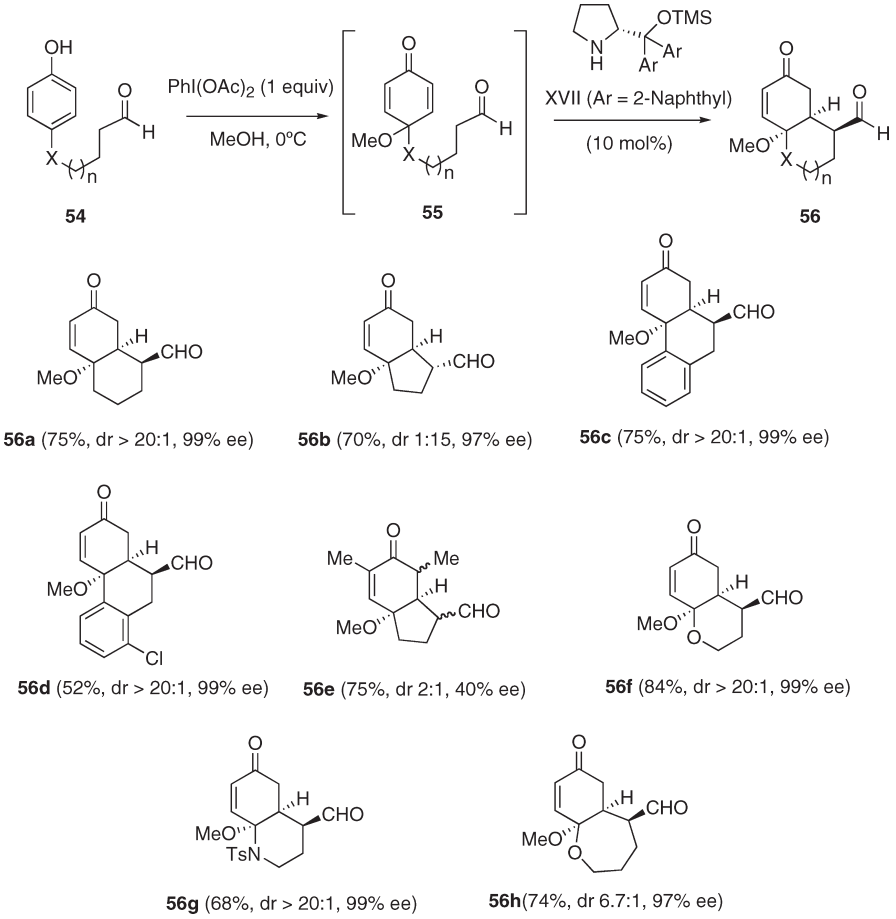
Scheme 25. Catalytic Enantioselective Dearomatization of 4-Substituted Phenols



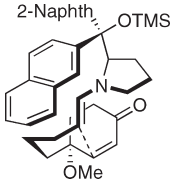


Figure 19. Model transition state for the intramolecular Michael addition.

outcome of the cyclization was determined by X-ray diffraction analysis of the alcohol derived from **124g**.

A precedent for this reaction had been previously described by the group of Banwell, who had performed the intramolecular Friedel−Crafts reaction of the pyrrolyl α,β-unsaturated aldehyde **125** (Scheme 52) for the syntheses of the alkaloids (−)-rhazinal, (−)-rhazinilam, (−)-leuconolam, and (+)-epileuconolam.[116]

Subsequently, Xiao's group have extended their approach to the intramolecular hydroarylation of phenol- and aniline-derived enals **127**.[117] Although MacMillan's imidazolidinone salt **XXXIV** was a suitable catalyst for this reaction, somewhat better stereoselectivities were achieved with the TMS-protected (*S*)-diarylprolinol **XXXVI**.[118] In this way, several functionalized chromans and tetrahydroquinolines **128** could be prepared in high enantiopurity (Scheme 53). The stereochemical outcome of the process is consistent with that observed for intermolecular conjugate additions to enals catalyzed by diaryl pyrrolinol ethers.

Recently, You et al. have addressed the more challenging problem of intramolecular Friedel−Crafts-type reaction of indolyl enones **129**.[119] These authors explored the use of chiral Brønsted acid catalysis for this transformation. The (*S*)-BINOL-derived phosphoric acid **XXXVII**, bearing 9-phenanthryl groups, afforded high yields and enantioselectivities in the intramolecular Friedel−Crafts alkylation of several substrates (Scheme 54). The absolute configuration of the products was determined by an anomalous X-ray diffraction analysis of compound **130d**. From the practical point of view, it is worth noting that the substrates **129** are easily prepared by olefin cross-metathesis between the corresponding indolyl allyl ethers and aryl vinyl ketones and that the cascade cross-metathesis−cyclization process can be run in a one-pot fashion with almost no erosion in enantioselectivity.

Cobb and co-workers have developed a highly stereocontrolled route to cyclic γ-amino acids that uses in its key step the asymmetric organocatalytic intramolecular Michael addition of a nitronate to a a conjugated ester.[120] On the basis of previous studies using nitronates as nucleophiles,[121] Cobb and co-workers screened a range of tertiary amine−thiourea catalysts in this process. Finally, the bifunctional catalyst **XXXVIII**, derived from 9-amino-9-deoxydihydrocinchonidine, gave satisfactory results in the cyclization of the (*E*)-configured nitro esters **131** (Scheme 55).

Most recently, and in the context of a total synthesis of the alkaloid lycopodine, Yang and Carter have been studying the organocatalytic asymmetric intramolecular Michael additions of

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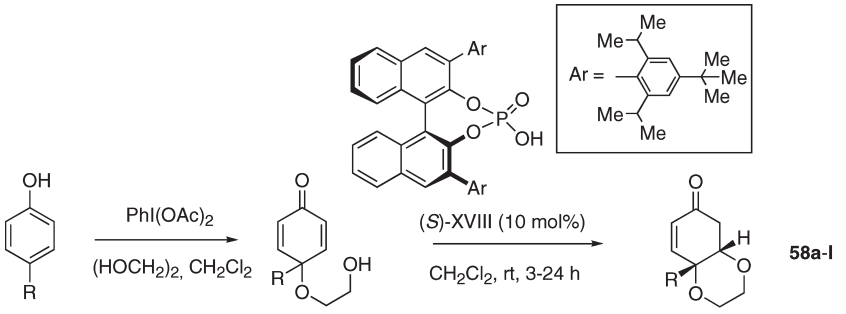
Scheme 26. Enantioselective Organocatalytic Intramolecular Oxa-Michael Reaction



58a (R = Me): 91%, 94% ee
58b (R = Et): 91%, 78% ee
58c (R = ^{i}Pr): 71%, 61% ee
58d (R = Ph): 92%, 91% ee
58e (R = 4-F-Ph): 91%, 90% ee
58f (R = 4-Cl-Ph): 90%, 91% ee
58g (R = 4-Br-Ph): 84%, 90% ee
58h (R = *p*-Tol): 91%, 92% ee
58i (R = *m*-Tol): 91%, 91% ee
58j (R = *o*-Tol): 92%, 95% ee
58k (R = 3,5-Me_2Ph): 81%, 90% ee
58l (R = 3,5-$(CF_3)_2$Ph): 93%, 88% ee

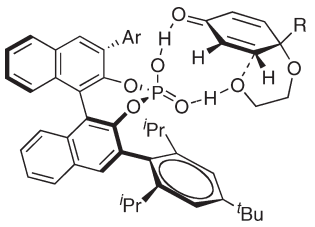


Figure 20. Transition state model for the phosphoric acid-catalyzed oxa-Michael desymmetrization.

keto sulfones to enones.[122,123] To that end, they have developed the previously unknown (*S*)-prolinamide derivative **XXXIX**, which due to its good solubility at low temperatures gives good yields and enantioselectivities in the cyclization of compounds **133a**−**e** (Scheme 56). The resulting cyclic enones **134a**−**e** were obtained with almost complete diastereoselectivity (20:1 dr in all instances). The absolute configuration of **134a** was conclusively established by X-ray crystallographic analysis and can be rationalized by the working transition state model depicted in Scheme 56.

A *Cinchona*-alkaloid-derived thiourea catalyst (the quinine derivative **XL**, originally described by Hiemstra et al.,[121b] was employed by Scheidt and co-workers in a catalytic enantioselective synthesis of flavanones and chromanones[124] based on the intramolecular oxa-Michael addition of α-substituted chalcones **135** (Scheme 57). Without further purification, the initially formed flavanones **136** were treated with tosic acid to remove the 3-*tert*-butoxycarbonyl group, a step that was required in order to render irreversible the cyclization of the starting substrates. The final chromanones **137** were obtained with good yields and enantioselectivities.

Substrates with R = alkyl were challenging due to competing nonselective cyclization. In this case, a domino Knoevenagel−conjugate addition sequence gave superior results. Thus, the combination of the phenol ketone **138**, hydrocinnamaldehyde **139**, and Takemoto's thiourea catalyst **XLI**[39,125] in toluene at room temperature afforded the natural product flindersiachromanone **137k** in 77% overall yield and 80% ee after decarboxylation (Scheme 58).

Subsequently, Zhao and co-workers have achieved the asymmetric synthesis of fluorinated flavanone derivatives by an organocatalytic domino intramolecular oxa-Michael addition−electrophilic fluorination reaction by using bifunctional *Cinchona* alkaloids as catalysts.[126] The fluorination reagent was *N*-fluorobenzenesulfonimide (NFSI), and the best catalyst identified by Zhao's group was the cupreidine derivative **XLII** (Scheme 59). In this way, the cyclization−fluorination of several substrates afforded the fluorinated flavanones **141** with total diastereoselectivity and with high enantiomeric purities.

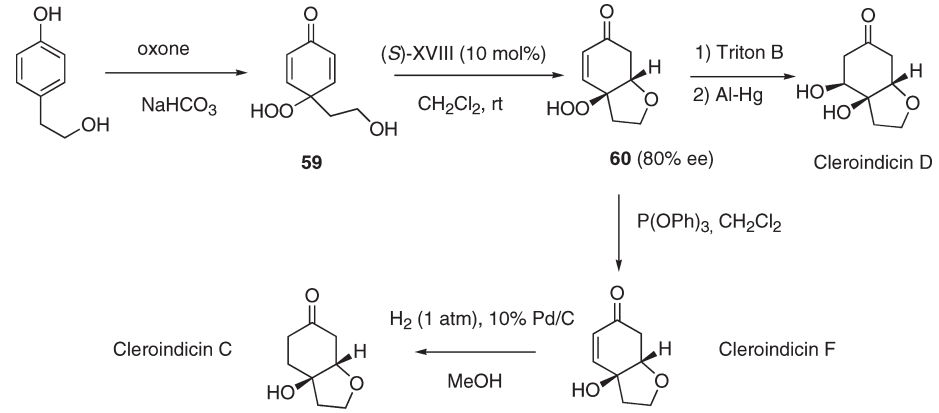
The absolute configuration of the final products was inferred from the (2*R*,3*R*) configuration determined for **141d** by anomalous X-ray diffraction analysis. The authors assumed that the oxa-Michael cyclization was the enantiodiscriminating step and that the stereocenter generated governed the stereochemical outcome of the fluorination step (i.e., fluorine trans to the R group). The transition state model depicted in Scheme 59 shows how hydrogen bonding activates both the nucleophile and the electrophile, directing the phenolic oxygen to attack the *re* face of the double bond to form the (3*R*)-configured product.

Most recently, Kurth et al. have disclosed a highly diastereoselective synthesis of medicinally relevant substituted chromanones that takes place via an organocatalytic aldol−oxa-Michael domino reaction sequence.[127] Pyrrolidine has been shown to be a suitable catalyst for both steps, but the use of chiral secondary amines has not been reported.

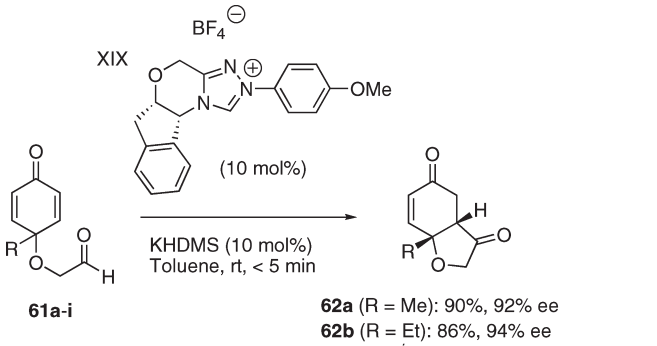
The first asymmetric organocatalytic aza-Michael cyclization[128] was described by Ihara et al. in 2003.[129] These authors developed a synthesis of 1,2,3,4-tetrahydroisoquinolines **143** from the amido enals **141** under catalysis from the tryptophan-derived imidazolidinone salt **XLIII** (Scheme 60). This addition took place with

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

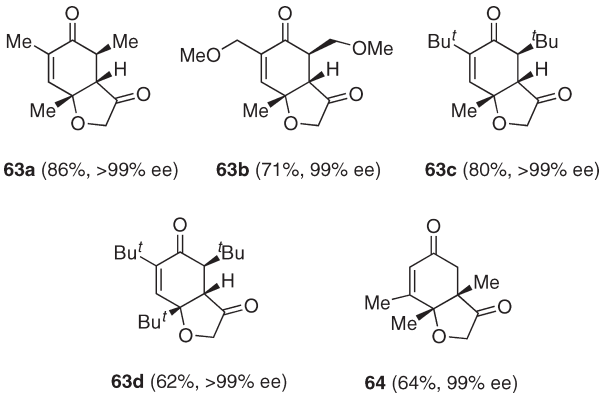
Scheme 27. Asymmetric Synthesis of Cleroindicins



Scheme 28. Asymmetric NHC-Catalyzed Intramolecular Stetter Reaction



62a (R = Me): 90%, 92% ee
62b (R = Et): 86%, 94% ee
62c (R = ^{i}Pr): 87%, 94% ee
62d (R = ^{t}Bu): 86%, 94% ee
62e (R = Ph): 87%, 88% ee
62f (R = 4-Br-Ph): 78%, 85% ee
62g (R = CH_2OAc): 86%, 83% ee
62h (R = $(CH_2)_2OMe$): 86%, 82% ee
62i (R = $(CH_2)_2CO_2Me$): 94%, 97% ee



63a (86%, >99% ee) **63b** (71%, 99% ee) **63c** (80%, >99% ee)

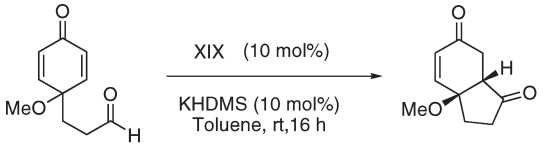
63d (62%, >99% ee) **64** (64%, 99% ee)

Figure 21. Asymmetric NHC-catalyzed Stetter cyclization products.

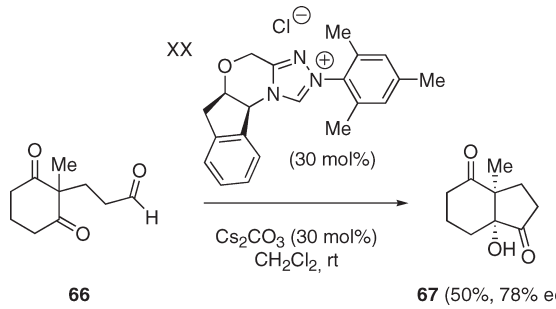
good yields (70−90%) but with low enantioselectivity (less than 54% ee).

Some time later, Hsung et al. described a formal aza-[3 + 3]-cycloaddition that involves an aza-Michael cyclization as the initial

Scheme 29. Asymmetric Synthesis of Hydrindane 65



Scheme 30. NHC-Catalyzed Asymmetric Benzoin Cyclization of a 2,2-Disubstituted-1,3-cyclohexanedione



step.[130] The best catalyst in this case was the (*S*)-diphenylprolinol (**XLIV**) acetate salt (Scheme 61). The stereogenic center in the final products **145** is created in the iminium ion triggered Michael addition step, and protonation of the resulting intermediate enamine facilitates the subsequent intramolecular Mannich cyclization. Elimination of the catalyst (protonated) gives the final products in moderate yields, but again with low enantioselectivities. The turnover of the process is very low, and high quantities of **XLIV** (up to 50 mol %) were required. The preferential formation of the (*R*)-products was rationalized by means of PM3 calculations, which gave a differential stability of 1.4 kcal mol^{-1} for the lowest energy transition state (Scheme 62).

It was not until 2007 that highly stereocontrolled intramolecular organocatalytic aza-Michael reactions were developed. Fustero and co-workers[131] found that the cyclization of carbamates bearing remote α,β-unsaturated aldehydes took place with moderate to good yields (30−80%) and with good to excellent enantioselectivities (85−99% ee) when the TMS-protected

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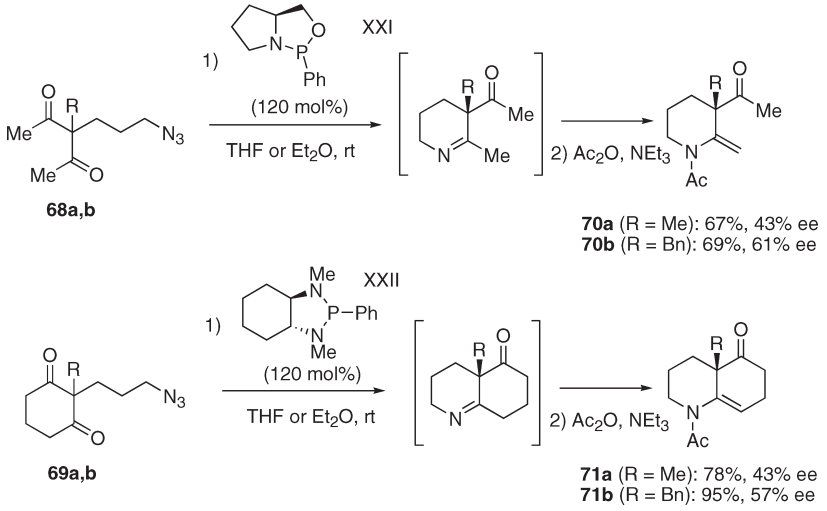
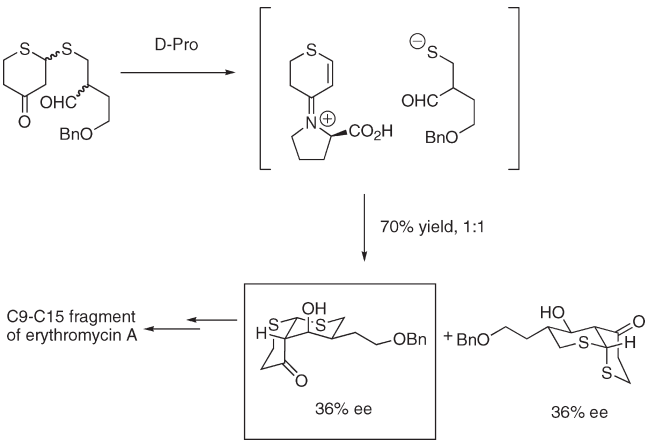
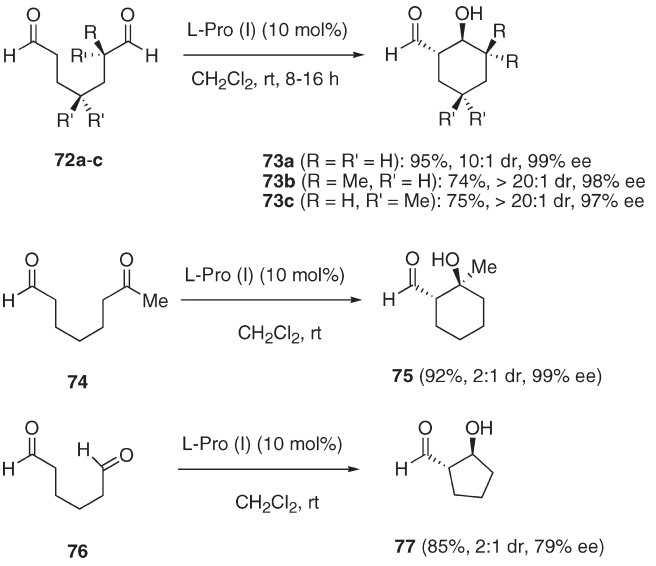
Scheme 31. Chiral Phosphine-Mediated Enantioselective Desymmetrization of Keto Azides



Scheme 32. Proline-Catalyzed Intramolecular Aldol Reaction of a Ketoaldehyde with Dynamic Kinetic Resolution in the Synthesis of Erythromycin A



Scheme 33. Proline-Catalyzed Intramolecular Aldol Reaction of Alkanedials and Ketoaldehydes



(*S*)-diarylprolinol-derived catalyst **XXXVI** was used in the process. The starting materials **146** were easily accessed by a cross-metathesis reaction of the corresponding unsaturated amines with acrolein, and the intermediate aldehydes **147** were reduced in situ with sodium borohydride to the more stable alcohols **148**. In this way, several five- and six-membered monosubstituted heterocycles could be obtained. Optimal conditions required low temperatures (typically starting at −50 °C), warming the solution to −30, −20, or −10 °C over a period of 48 h, and the use of benzoic acid as a cocatalyst (Scheme 63).

The absolute configuration of the cyclized products was determined to be (*R*) by comparison of the spectroscopic and polarimetric data of compound **148a** with those described in the literature and can be easily rationalized by the general stereochemical course of Michael additions to enals catalyzed by **XXXVI**[118] and by related compounds (Scheme 63). The usefulness of the method was nicely demonstrated by Fustero et al. by synthesizing the alkaloids (+)-sedamine, (+)-allosedamine, and (+)-coniine (Scheme 64).

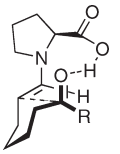


Figure 22. Proposed transition state for the proline-catalyzed enol/exo aldol cyclization of heptanedials and of 7-oxoalkanals.

A closely related approach was developed independently by Carter and co-workers.[132] They used the same catalyst as Fustero (**XXXVI**, 20 mol %), but working in CH_2Cl_2/MeOH mixtures (1:1) at −25 °C, they found that no acidic cocatalyst was necessary. According to this protocol, compound **148b** was obtained in 67% yield and with 90% ee; aldehyde **147g**, prepared in 69% yield and 95% ee, was converted into (−)-homopipecolic acid and into the

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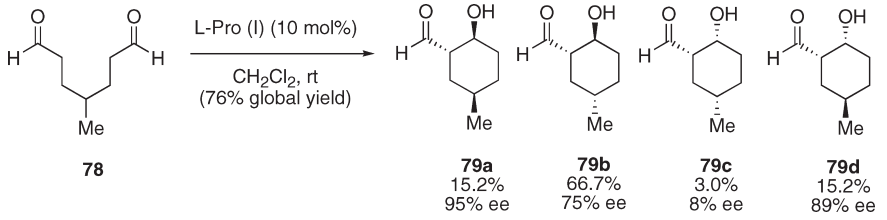
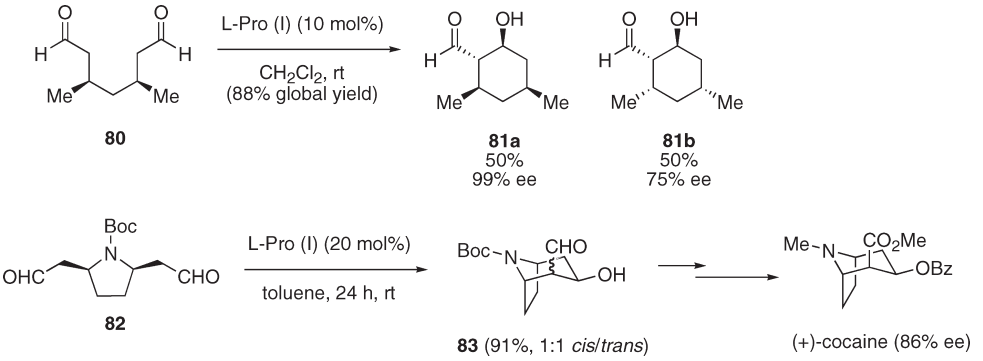
alkaloid (−)-pelletierine. Other substrates successfully cyclized by Carter et al. (including **149**, which led to the indoline **150**) are shown in Scheme 65.

Subsequently, Fustero et al.[133] extended their protocol, not only for the synthesis of indoline **150** (obtained in 70% yield and 93% ee) but for that of other bicyclic heterocycles

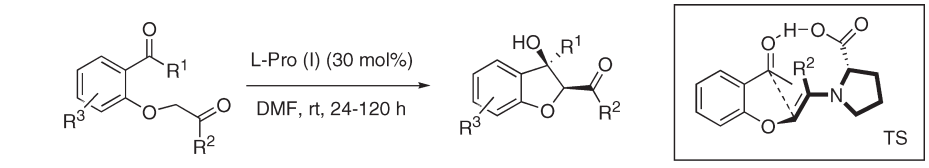
Scheme 34. Proline-Catalyzed Intramolecular Aldol Reaction of 4-Methylheptanedial



Scheme 35. Proline-Catalyzed Aldol Cyclization of *meso*-Dialdehydes



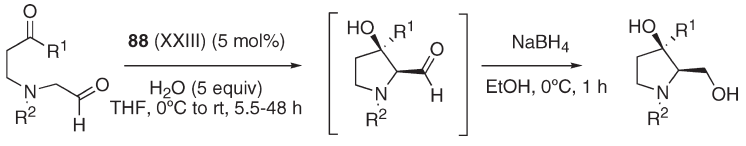
Scheme 36. Proline-Catalyzed Aldol Cyclization of Aromatic Ketoaldehydes



84
(R^1 = H, Me; R^2 = Me, Et; R^3 = H, Me)

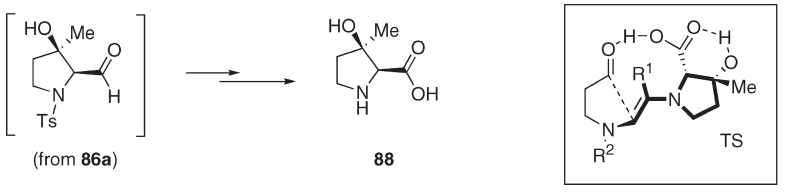
85
(74-96% yield, > 93:7 dr, 76% - 87% ee)

Scheme 37. Aldol Cyclization of Ketoaldehydes 86



86a-f

87a (R^1 = Me, R^2 = Ts): 73%,95:5 dr, 88% ee
87b (R^1 = Me, R^2 = Cbz): 49%,89:11 dr, 80% ee
87c (R^1 = Me, R^2 = SO_2Bn): 90%,91:9 dr, 73% ee
87d (R^1 = Et, R^2 = Ts): 74%,90:10 dr, 80% ee
87e (R^1 = $(CH_2)_2CHMe_2$, R^2 = Ts): 67%, > 99:1 dr, 76% ee
87f (R^1 = Ph, R^2 = Ts): 30%, dr not determined, 30% ee



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such as isoindolines (**151**, >99% ee), tetrahydroquinolines (**152**, 92% ee), and tetrahydroisoquinolines (**153**, 99% ee). Aldehyde **155**, the precursor of **152**, was used in a short, enantioselective synthesis of the alkaloid (+)-angustureine (Scheme 66).

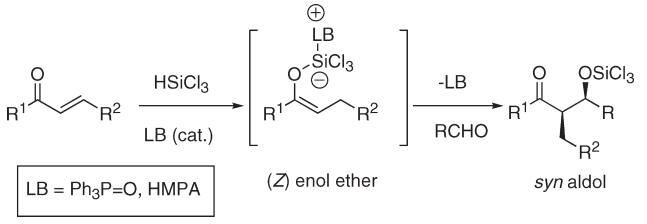
4.3. Intramolecular Morita–Baylis–Hillman and Rauhut–Currier Reactions

The Morita–Baylis–Hillman (MBH) reaction[134,135] and its vinylogous counterpart, the Rauhut–Currier (RC) reaction,[136,137] are two useful C–C bond-forming processes that rely on the latent enolate generation from a Michael acceptor by the conjugate addition of a nucleophilic catalyst. The enolate then undergoes an aldol (in the MBH reaction) or a Michael addition (in the RC reaction), followed by a prototropic rearrangement and regeneration of the nucleophilic catalyst to give the final compound in which a new C–C bond at the α-position of the starting activated alkene has been created (Scheme 67).

Until 2005, the only asymmetric intramolecular MBH reaction was that reported by Fráter's group in 1992 that afforded the product in 14% ee with 40% yield after a reaction time of 10 days.[138] Thirteen years later, Miller et al.[139] and Hong et al.[140] independently disclosed the first highly enantioselective (ee >80%) version of this process, by using very similar catalytic systems.

The approach of Miller's group relies on the use of a combination of (*S*)-pipecolic acid (**XLV**) and *N*-methylimidazole (NMI). In aqueous tetrahydrofuran, the cyclization of a series of 7-aryl-7-oxo-5-heptenal derivatives **156** took place with satisfactory conversions and with moderate to good enantioselectivities (Scheme 68).[139] The use of (*S*)-proline (**I**) instead of **XLV** gave lower enantiomeric purities (60% ee for **157a**). The enantiomeric purity of the this last product could be increased to >98% ee by subsequent kinetic resolution of the reaction mixture (80% ee **157a**) by a peptide-catalyzed[141] asymmetric acylation.

Scheme 38. Lewis Base-Catalyzed Reductive Aldol Reaction with Trichlorosilane

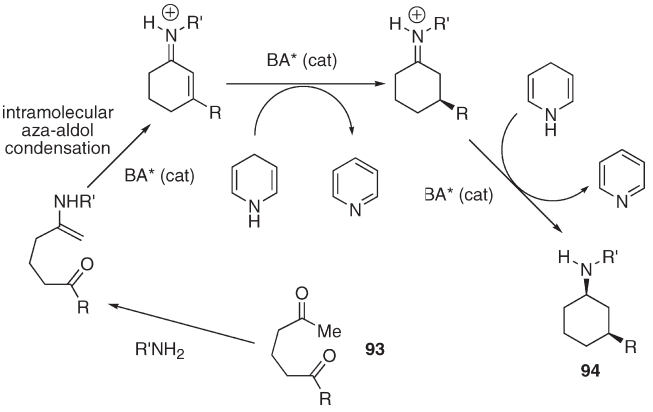


On the other hand, Hong and co-workers studied the intramolecular MBH reaction of hept-2-enedial **158**.[140] In accordance with the results of Miller,[139] (*S*)-proline (10 mol %) was a rather inefficient catalyst for this reaction, and product (*S*)-**159** was obtained in 73% yield and with 45% ee after 5 h in DMF at rt. The addition of 10 mol % of imidazole increased the enantioselectivity of the process, but the major enantiomer of **159** had the opposite (*R*)-configuration, also in accordance with the reactions studied by Miller (Scheme 69). A mechanistic rationale for this inversion of the enantioselectivity was provided by the authors.

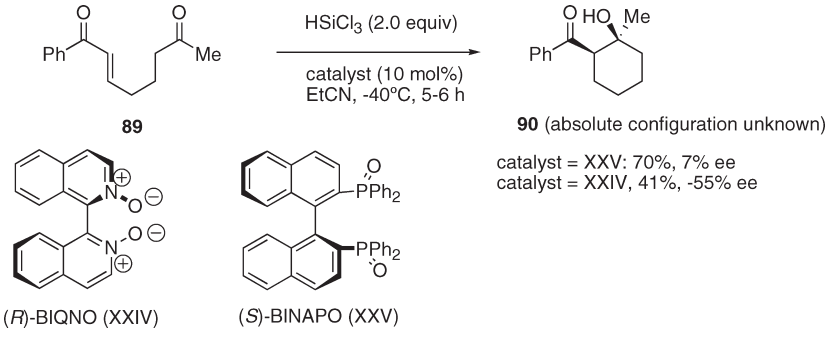
Recently, Wu and co-workers have explored the use of chiral amine-derived phosphinothioureas in the asymmetric MBH cyclization of the substrates **156**.[142] The best catalyst was the cyclohexane-based phosphinothiourea **XLVI**, which provides enantioselectivities superior to those obtained by Miller (Scheme 70). The stereochemical outcome of the reaction [(*R*)-configured products *ent*-**157**] was explained by the authors through the transition state working model depicted in Scheme 70.

In 2007, Aroyan and Miller[143] uncovered the first asymmetric organocatalytic intramolecular RC reaction.[144] These authors found that, upon exposure to *N*-acetyl-(*R*)-cysteine methyl ester **XLVII** and potassium *tert*-butoxide (1.5 equiv), several bis(enones) **160** were clearly converted into the cyclized products **161**. Best yields and enantioselectivities were achieved by using equimolar amounts of **XLVII** in aqueous acetonitrile (Scheme 71). The enantiomeric purities of the cyclohexenones **161a–f**, derived from the symmetric precursors **160a–f**, were very high (ee >84%). The cyclization of the keto ester **160g** gave a single product, **161g**, but with diminished enantioselectivity.

Scheme 40. Aza-Aldol Condensation–Transfer Hydrogenation Route to 3-Substituted-Cyclohexylamines

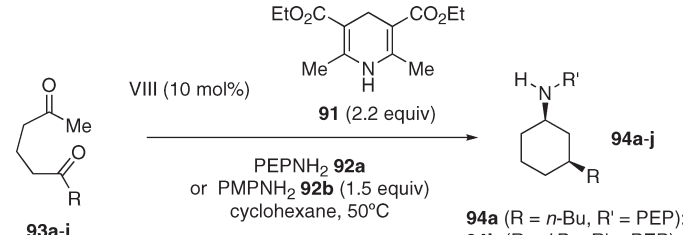


Scheme 39. Chiral Lewis Base-Catalyzed Asymmetric Reductive Aldol Cyclization



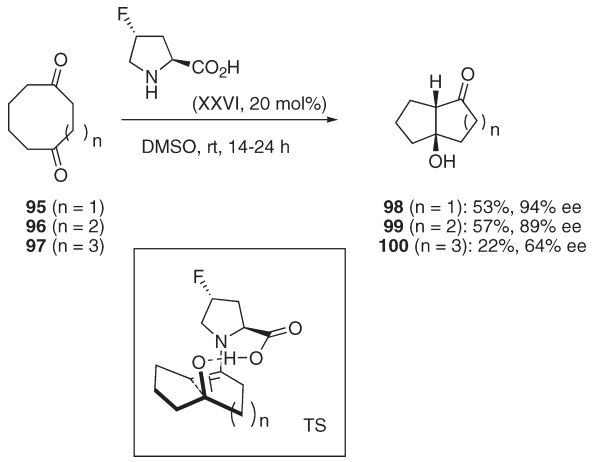
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 41. Scope of the Aza-Aldol Condensation−Transfer Hydrogenation Route to 3-Substituted-Cyclohexylamines



94a (R = *n*-Bu, R' = PEP): 75%, 10:1 dr, 90% ee
94b (R = *i*-Bu, R' = PEP): 79%, 12:1 dr, 96% ee
94c (R = Bn, R' = PEP): 77%, 6:1 dr, 86% ee
94d (R = $Ph(CH_2)_2$, R' = PEP): 82%, 24:1 dr, 96% ee
94e (R = Me, R' = PEP): 88%, 6:1 dr, 84% ee
94f (R = *c*-$PentCH_2$, R' = PEP): 72%, 24:1 dr, 96% ee
94g (R = *c*-$HexCH_2$, R' = PMP): 89%, 19:1 dr, 96% ee
94h (R = *c*-$Hex(CH_2)_2$, R' = PEP): 78%, 4:1 dr, 92% ee
94i (R = *i*-Pr, R' = PMP): 76%, 3:1 dr, 92% ee
94j (R = 2-Naphthyl, R' = PEP): 73%, 2:1 dr, 82% ee

Scheme 42. Asymmetric Transannular Aldol Reaction of Monocyclic Diketones



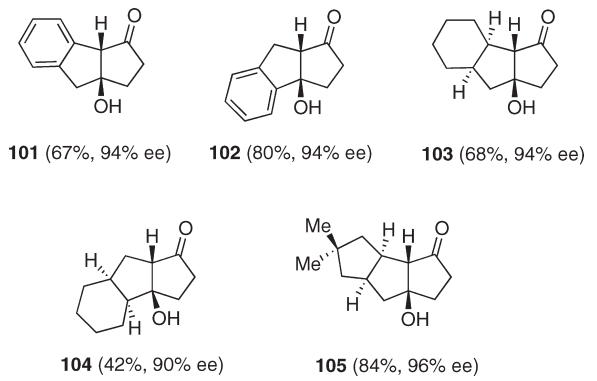
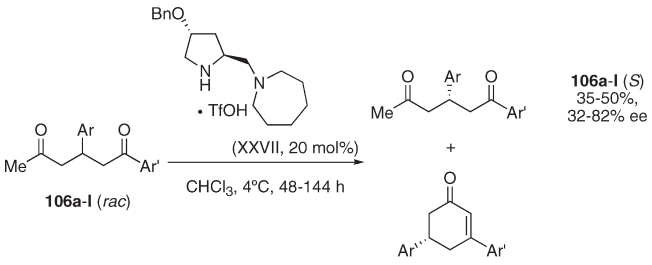


Figure 23. Bicyclic 1,4-cyclooctanedones in transannular aldolizations.

The preferent formation of the observed enantiomers can be explained by a transition-state working model in which the potassium salt of **XLVII** is the true catalyst.

A crossed intramolecular asymmetric organocatalytic RC-type reaction has been developed by Christmann and co-workers.[145] A variety of dienals **162** were cyclized under catalysis by the

Scheme 43. Organocatalytic Kinetic Resolution of 1.5-Diketones via Intramolecular Aldol Condensation



107a (Ar = Ar' = Ph): 47%, 80% ee
107b (Ar = *m*-ClPh, Ar' = *p*-BrPh): 54%, 90% ee
107c (Ar = Ph, Ar' = 2,4-$(MeO)_2$Ph): 59%, 80% ee
107d (Ar = *m*-ClPh, Ar' = Ph): 50%, 70% ee
107e (Ar = *p*-PhPh, Ar' = Ph): 39%, 90% ee
107f(Ar = Ph, Ar' = *p*-BrPh): 53%, 90% ee
107g (Ar = *o*-BrPh, Ar' = Ph): 43%, 91% ee
107h (Ar = *p*-ClPh, Ar' = Ph): 39%, 76% ee
107i (Ar = *p*-MeOPh, Ar' = Ph): 59%, 96% ee
107j (Ar = *o*-ClPh, Ar' = Ph): 50%, 85% ee
107k (Ar = Ph, Ar' = *p*-ClPh): 50%, 75% ee
107l (Ar = *p*-ClPh, Ar' = *p*-ClPh): 36%, 56% ee

Jørgensen−Hayashi (*S*)-diphenylprolynol derivative **XLVIII** (20 mol %). The use of acetic acid as a cocatalyst greatly increased the reaction rate, and moderate to good (up to 96% ee) enantioselectivities were achieved in dichloromethane at room temperature in the formation of the cyclopentenecarbaldehydes **163a**−**h**. The absolute configuration of the adducts was determined both by anomalous X-ray diffraction analysis of compound **163e** and by the identification of **163h** with the natural product (+)-rotundial (Scheme 72).

The mechanism of this process implies a dienamine activation of the aldehyde by the chiral secondary amine followed by intramolecular Michel addition to the activated olefin, as depicted in Scheme 73, and is therefore only formally a RC cyclization. The presence of a methyl group in the β-position of the enal is crucial for the success of the cyclization, probably by securing the required (*E*,*Z*) configuration of the dienamine. It is worth noting that a dienamine activation−Michael addition mechanism had been previously proposed by Hong et al. in order to explain the results obtained in the proline-catalyzed cyclization of hept-2-enedial **158** (see Scheme 69).[140]

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

4.4. Cyclizations via Stetter and Benzoin Reactions

Asymmetric intramolecular crossed-benzoin reactions catalyzed by chiral NHC's were ushered in by the independent efforts of Enders[146] and of Suzuki.[147] The first results to be published, in 2006, were those of Enders et al. After a careful optimization of the catalyst structure, the cyclization of ketoaldehydes **164a**−**e** was found to be efficiently catalyzed by the chiral NHC derived from the triazolium salt **XLIX** to give the α-alkyl-α-hydroxytetralones **165a**−**e** in up to 98% ee (Scheme 74). The stereochemical outcome of the process was explained by the authors with the aid of the working transition state model depicted in Figure 25.[146] Other substrates explored gave inferior enantioselectivities (cf. product **167** in Figure 26 below that was obtained by Enders in 95% yield and 74% ee).

The approach of Suzuki et al.[147] is very similar, but these authors propose the chiral NHC derived from the triazolium salt **L** (closely related to **XIX**, **XX**, and **XXXII**) as the optimal catalyst. Under the conditions developed by Suzuki, the cyclization of **164a** takes place in 70% yield and with 96% ee (Scheme 75). Other cyclic benzoins prepared in this way are shown in Figure 26. Note that the absolute stereochemistry of the products is consistent with a transition state based on that depicted in Figure 25. Subsequently, Suzuki has reported that the yields and enantiomeric purities of some of these compounds (cf. **168a**,**b**, **169**) can be improved by using a precursor triazolium salt differing from **L** in that the *N*-Ph group has been replaced by a *N*-[3,5-$(CF_3)_2C_6H_3$] moiety and has applied this modified methodology to the synthesis of the natural isoflavanone (+)-sappanone B.[148]

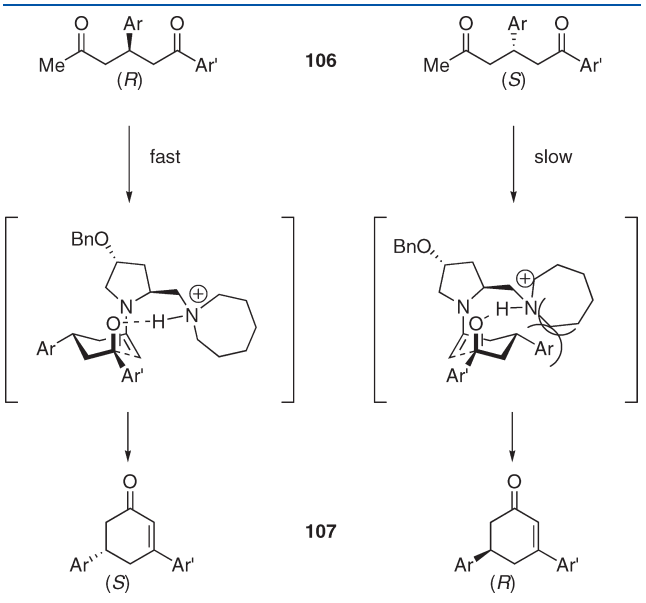


Figure 24. Proposed transition state for the organocatalytic kinetic resolution by intramolecular aldol condensation.

Research on the enantioselective catalytic intramolecular Stetter reaction has been carried out in the past few years at Rovis' laboratory. The first results were reported in 2002.[149] It was shown that the chiral NHC generated by treatment with potassium (hexamethyl)disilazide from the aminoindanol-derived triazolium salt **XIX** provided high yields and enantioselectivities in the cyclization of the salicylaldehyde-derived unsaturated esters **171** (Scheme 76).[149a] The unsaturated ketone **173** and the unsaturated nitrile **175** were also enantioselectively cyclized under very similar conditions (Scheme 77).[149b]

The cyclization of the aliphatic substrate **177** was best performed with the NHC derived from **LII** (Scheme 78). The same catalyst gave better yields than **XIX** in the intramolecular Stetter reaction of **172h**.[149]

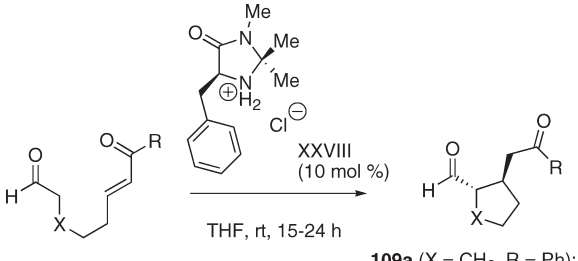
Subsequently, the Rovis' group has further explored the scope of this transformation. The introduction of an additional substituent at the β-position of the Michael acceptor in the substrate, leading to cyclized products containing a quaternary stereocenter, is compatible with the intramolecular Stetter reaction.[150] The *N*-(pentafluorophenyl) triazolium salt **LIII** gives good yields and excellent enantioselectivities both for aromatic (Scheme 79) and for aliphatic (Scheme 80) substrates. No explanation was provided for the reversal of stereoinduction between aromatic (**179**, **181**) and aliphatic (**183**) substrates.

A convenient method for the generation of the free NHC catalyst **LIV** allowed the use of α,α-disubstituted Michael acceptors in the asymmetric intramolecular Michael addition.[151] Again, both aromatic (**185**, Scheme 81) and aliphatic (**187**, Scheme 82) substrates can be used in this reaction.

This remarkable process, in which two contiguous stereogenic centers are generated, takes place with exquisite degrees of stereocontrol (up to 50:1 dr, up to 99% ee). The mechanism shown in Scheme 83 was proposed by the authors to account for the stereochemical outcome of the reaction.[151]

More recently, Cullen and Rovis[152] have demonstrated that the chiral NHC derived from **LIII** can be applied to the intramolecular Stetter reaction of aromatic or aliphatic aldehyde substrates containing vinylphosphine oxide or vinylphosphonate moieties (Schemes 84 and 85).

Scheme 44. Catalytic Asymmetric Intramolecular Michael Reaction of Aldehydes



108a-f

109a (X = CH_2, R = Ph): 99%, 24:1 dr; 97% ee
109b (X = CH_2, R = 2-Naphthyl): 99%, 17:1 dr; 97% ee
109c (X = CH_2, R = Me): 99%, 20:1 dr; 93% ee
109d (X = CH_2, R = Et): 99%, 21:1 dr; 94% ee
109e (X = CH_2, R = H): 85%, 49:1 dr; 80% ee
109f (X = NTs, R = Me): 90%, 8:1 dr; 93% ee

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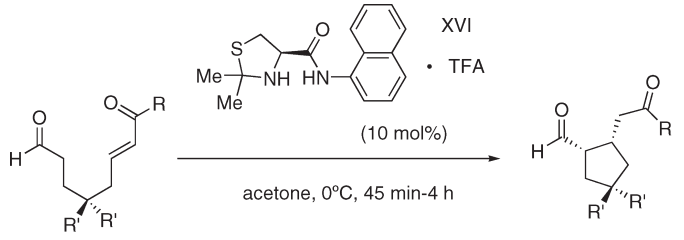
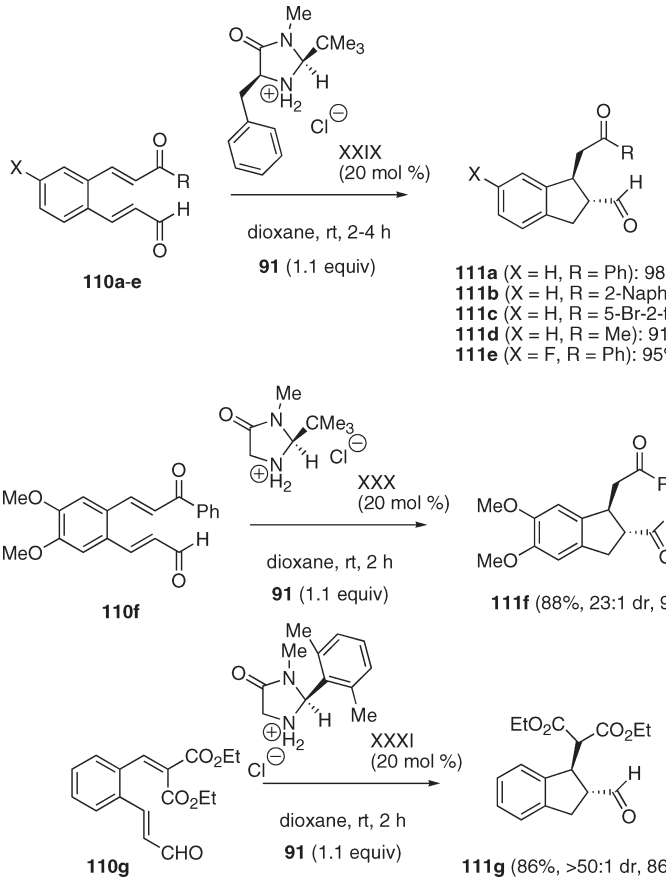
Scheme 45. Asymmetric Intramolecular Michael Reaction of Formyl Enones



108a,g-i

109a' (R = Ph, R' = H): 100%, 89:11 dr, 99% ee
109g' (R = Ph, R' = CO_2Me): 95%,91:9 dr, 97% ee
109h' (R = Ph, R',R' = $S(CH_2)_3S$): 93%, > 95:5 dr, 99% ee
109i' (R = Me, R',R' = $S(CH_2)_3S$): 93%, > 95:5 dr, > 99% ee

Scheme 46. Organocatalytic Asymmetric Reductive Michael Cyclization



4.5. Pictet–Spengler Reactions and Related Cyclizations

The Pictet–Spengler (PS) reaction is an important transformation, both from the biosynthetic point of view and as a laboratory method, for the construction of the biologically important tetrahydroisoquinoline and tetrahydro-β-carboline skeletons.[153,154] From the mechanistic point of view, it implies the acid-catalyzed cyclization of an aromatic aldimine, which is usually formed in situ from an aromatic amine (2-phenylethylamines, tryptamines) and an aldehyde. Whereas several useful substrate- or auxiliary-controlled diastereoselective versions of this reaction have been known since the last quarter of the past century,[155] the development of truly catalytic enantioselective versions was only possible with the advent of asymmetric organocatalysis. This approach was heralded by Taylor and Jacobsen, who in 2004[156] reported an extremely elegant organocatalytic acyl-Pictet–Spengler reaction. These authors recognized that the challenge of developing a catalytic asymmetric PS reaction was mainly due to the lack of reactivity of the imine substrate and that, on the other hand, the use of strong Brønsted acids was likely to promote the racemic pathway; they decided, therefore, to use both a more active *N*-acyl iminium ion as a substrate[157] and a chiral hydrogen-bond-donor catalyst. Thus, they found that when a mixture of the tryptamine **195**, an aliphatic aldehyde **196**, 2,6-lutidine, and acetyl chloride was treated with 5–10% molar

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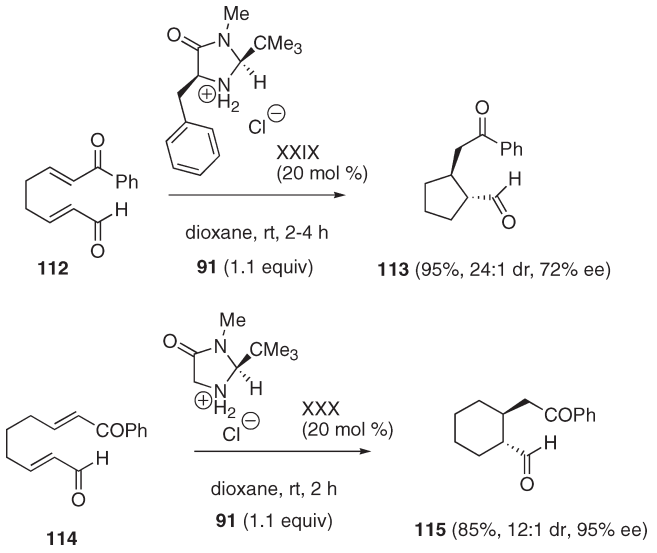
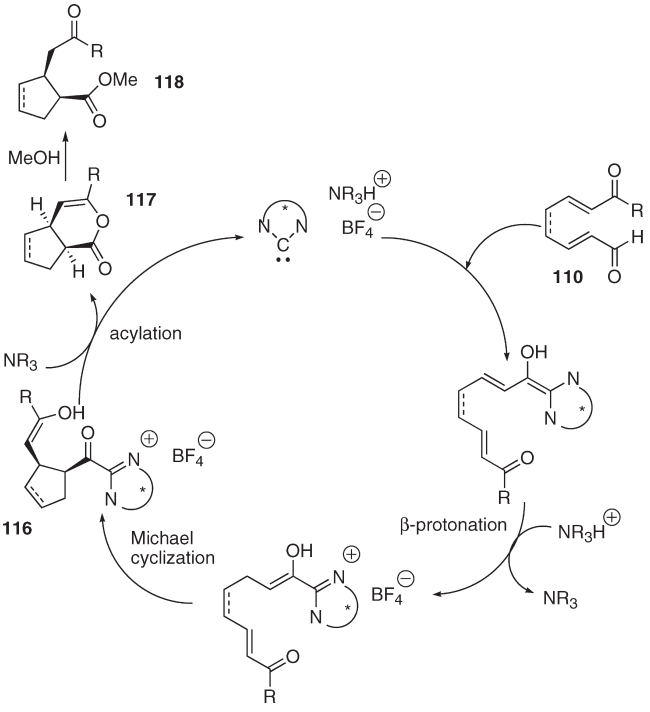
amounts of the thiourea **LV** in diethyl ether in the presence of molecular sieves or of sodium sulfate, the N_β-acetyltetrahydro-β-carbolines **197a**−**g** were obtained in moderate to good yields and with good enantiomeric purities (Scheme 86). The absolute configuration of compounds **197b** and **197d** was determined by deacylation to the previously known tetrahydro-β-carbolines. The authors initially assumed that catalysis by **LV** probably involved activation of the weakly basic *N*-acyliminium ion by hydrogen bonding, but no mechanistic model was proposed.

Later on, Jacobsen's group extended this approach to the enantioselective Pictet−Spengler-type cyclizations of the tryptamine-derived hydroxylactams **198**. The presence of an acidic additive such as trimethylsilyl chloride is necessary in order to generate the intermediate acyl iminium **199**. Key experimental observations, supported by DFT calculations, suggest an S_N1-type pathway for the cyclization and, more importantly, that the catalytic effect of the thiourea **LVI** (a slightly modified version

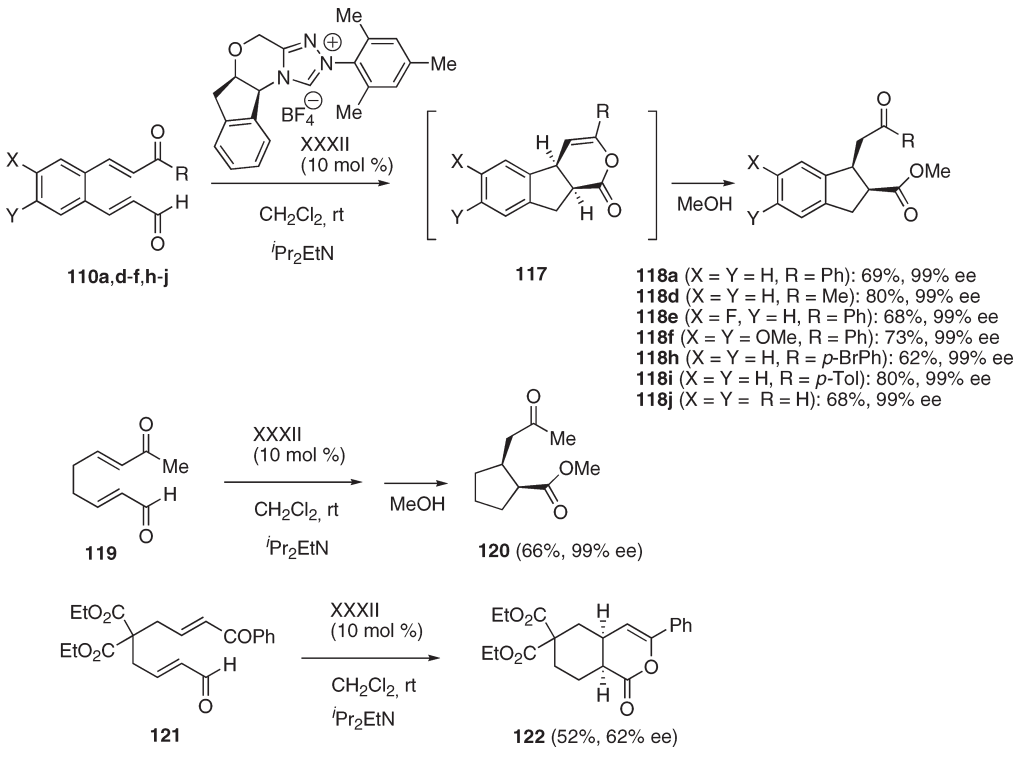
Scheme 47. Reductive Cyclization of Aliphatic Enals



Scheme 49. Proposed Catalytic Pathway for the NHC-Catalyzed Asymmetric Michael Cyclization of Enals



Scheme 48. Chiral NHC-Catalyzed Asymmetric Michael Cyclization of Enals



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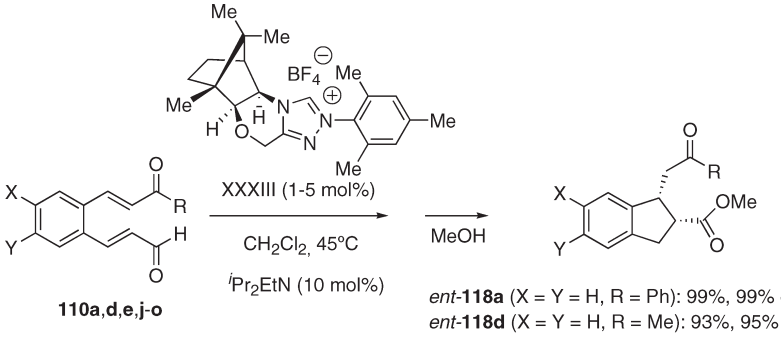
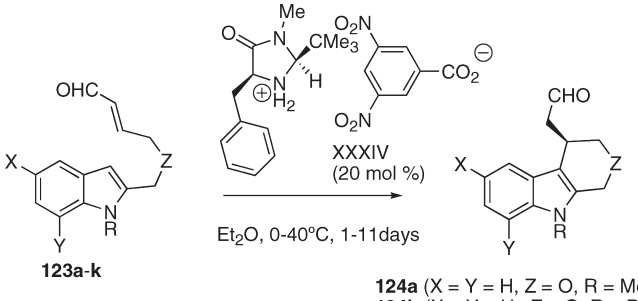
Scheme 50. Enantioselective Intramolecular Michael Reactions by D-Camphor-Derived Triazolium Salts



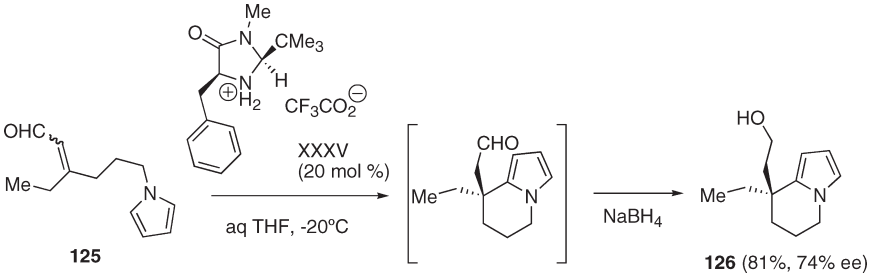
ent-**118a** (X = Y = H, R = Ph): 99%, 99% ee
ent-**118d** (X = Y = H, R = Me): 93%, 95% ee
ent-**118e** (X = F, Y = H, R = Ph): 71%, 98% ee
ent-**118j** (X = Y = R = H): 80%, 98% ee
ent-**118k** (X = Y = H, R = ^{t}Bu): 85%, 99% ee
ent-**118l** (X = Y = H, R = *p*-ClPh): 85%, 99% ee
ent-**118m** (X = Y = H, R = *p*-MeOPh): 96%, 99% ee
ent-**118n** (X = Y = H, R = *p*-NO_2Ph): 52%, 98% ee
ent-**118o** (X,Y = CH_2OCH_2, R = Ph): 80%, 99% ee

Scheme 51. Organocatalyzed Intramolecular Friedel−Crafts Reaction of Indolyl Unsaturated Aldehydes



124a (X = Y = H, Z = O, R = Me): 85%, 90% ee
124b (X = Y = H, Z = O, R = Bn): 75%, 92% ee
124c (X = F, Y = H, Z = O, R = Me): 86%, 84% ee
124d (X = F, Y = H, Z = O, R = Bn): 89%, 85% ee
124e (X = Cl, Y = H, Z = O, R = Me): 73%, 90% ee
124f (X = H, Y = Cl, Z = O, R = Me): 77%, 90% ee
124g (X = Br, Y = H, Z = O, R = Me): 95%, 93% ee
124h (X = MeO, Y = H, Z = O, R = Me): 57%, 80% ee
124i (X = MeO, Y = H, Z = O, R = Bn): 58%, 92% ee
124j (X = Me, Y = H, Z = O, R = Bn): 75%, 92% ee
124k (X = Y = H, Z = NTs, R = Bn): 78%, 90% ee

Scheme 52. Organocatalyzed Intramolecular Michael Addition of a Pirrolyl Unsaturated Aldehyde



of **LV**) is due to hydrogen-binding of the chloride anion in **199**. Both the yields and enantioselectivities were very good (Scheme 87), and the applicability of the methodology was nicely demonstrated by the lithium alumninum hydride reduction of compound **200a** to the alkaloid (+)-harmicine.[158]

More recently, Dixon and co-workers have found that chiral Brønsted acids such as BINOL-derived phosphoric acids are indeed able to catalyze enantioselectively a cyclization cascade between tryptamine derivatives **195** and enol lactones **202** that involves the intermediate formation of acyl iminium ions similar

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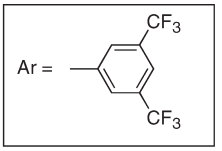
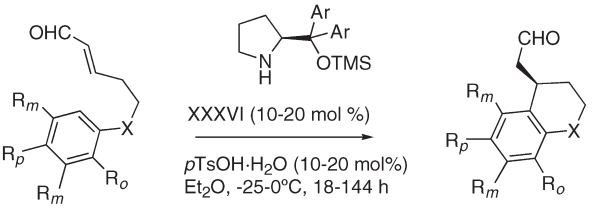
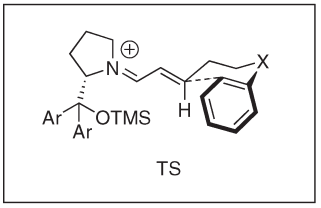
Scheme 53. Organocatalyzed Intramolecular Hydroarylation of Phenol- and Aniline-Derived Enals



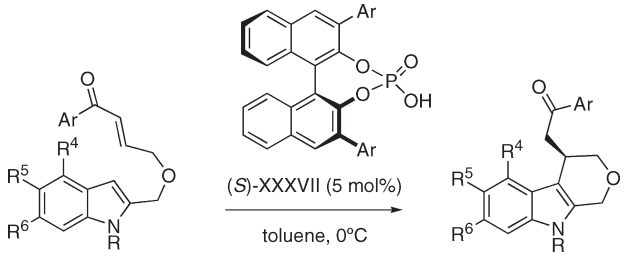


127a-k

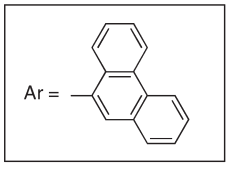


128a (R_o = R_p = H, R_m = H, NMe_2, X = O): 78%, 96% ee
128b (R_o = Me, R_p = H, R_m = H, NMe_2, X = O): 72%, 96% ee
128c (R_o = H, R_p = Me, R_m = H, NMe_2, X = O): 50%, 89% ee
128d (R_o = R_p = H, R_m = H, NMe_2, X = NBoc): 70%, 87% ee
128e (R_o = R_p = H, R_m = H, NMe_2, X = NCbz): 68%, 87% ee
128f (R_o = R_p = R_m = H, X = NMe): 61%, 70% ee
128g (R_o = R_p = R_m = H, X = NBn): 65%, 76% ee
128h (R_o = R_m = H, R_p = OEt, X = NBn): 80%, 74% ee
128i (R_o = R_p = R_m = H, X = NTs): 64%, 90% ee
128j (R_o = R_p = R_m = H, X = $N(CH_2)_5$): 65%, 90% ee
128k (R_o = R_p = H, R_m = Me, Me, X = NBn): 99%, 86% ee
128l (R_o = R_p = H, R_m = H, NMe_2, X = NCbz): 80%, 79% ee
128a (R_o = R_p = H, R_m = H, NMe_2, X = NBoc): 71%, 71% ee

Scheme 54. Asymmetric Intramolecular Friedel−Crafts Alkylation of Indolyl Enones



129a-k



130a (R^4 = R^5 = R^6 = H, Ar = Ph, R = Me): 99%, 98% ee
130b (R^4 = R^5 = H, R^6 = OMe, Ar = Ph, R = Me): 99%, 97% ee
130c (R^4 = R^6 = H, R^5 = Me, Ar = Ph, R = Me): 98%, 96% ee
130d (R^4 = R^5 = H, R^6 = Br, Ar = Ph, R = Me): 99%, 97% ee
130e (R^4 = R^6 = H, R^5 = F, Ar = Ph, R = Me): 99%, 96% ee
130f (R^4 = R^6 = H, R^5 = Br, Ar = Ph, R = Me): 98%, 90% ee
130g (R^4 = R^5 = R^6 = H, Ar = Ph, R = Bn): 97%, 95% ee
130h (R^4 = R^5 = R^6 = H, Ar = *m*-MeOPh, R = Me): 97%, 97% ee
130i (R^4 = R^5 = R^6 = H, Ar = *p*-ClPh, R = Me): 98%, 97% ee
130j (R^4 = R^5 = R^6 = H, Ar = *p*-BrPh, R = Me): 97%, 96% ee
130k (R^4 = R^5 = R^6 = H, Ar = *p*-Tol, R = Me): 99%, 98% ee

to **199** (except that the chloride anion is replaced by a chiral phosphate anion) and the subsequent Pictet−Spengler-type enantioselective cyclization, leading to an alternative entry to the tetracyclic compounds **200**.[159] The (*R*)-BINOL-derived phosphoric acid **LVII** was found to be the most convenient catalyst. Interestingly enough, the requisite enol lactones **202** can be formed in situ by Au(I)-catalyzed cycloisomerization of the 3-alkynoic acids **201**. Some representative examples are shown in Scheme 88.

The first Brønsted acid-catalyzed asymmetric Pictet−Spengler reaction had been in fact reported in 2006 by List and co-workers.[160] Key to the success of their approach was the use of easily accessible geminally disubstituted tryptamines **203**, which were deemed to be promising substrates both for electronic reasons and for the existence of Thorpe−Ingold effects favoring the PS cyclization in front of the competitive enamine formation. The (*R*)-BINOL-derived phosphoric acid **VIII** was indeed an excellent catalyst for the reaction between the tryptamine diesters **203** and aldehydes **196**, leading to the formation of the tetrahydro-*β*-carbolines **204** with good yields and enantioselectivities (see Scheme 89 for some selected examples).

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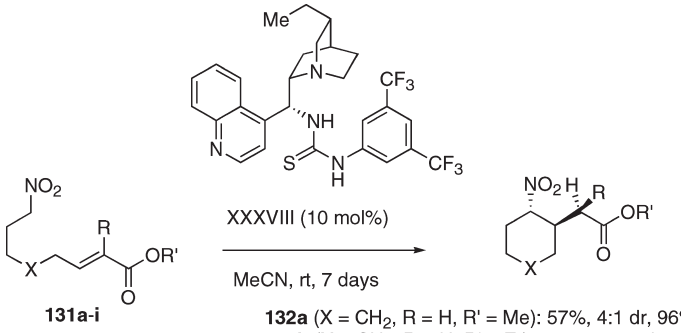
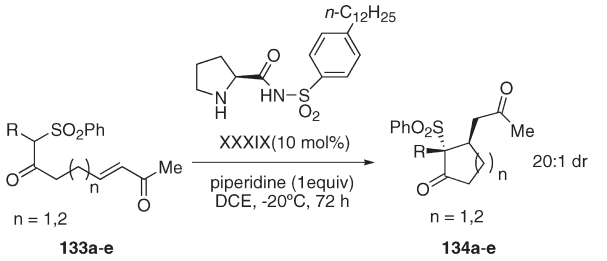
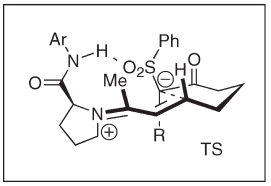
Scheme 55. Enantioselective Intramolecular Michael Addition of Nitronates onto Conjugated Esters



132a (X = CH_2, R = H, R' = Me): 57%, 4:1 dr, 96% ee
132b (X = CH_2, R = H, R' = Et): 87%, >19:1 dr, 96% ee
132c (X = CH_2, R = Bn, R' = Et): 52%, >19:4:1 dr, >99% ee
132d (X =O, R = H, R' = Et): 69%, >19:1 dr, 92% ee
132e (X = CH_2, R = NHBoc, R' = Me): 11%, 3:1:<1 dr, >99% ee
133f (X = CH_2, R = H, R' = Bn): 66%, 4:1 dr, 98% ee
134g (X = CH_2, R = Me, R' = Et): 50%, >19:6:1 dr, 94% ee
135h (X = CH_2, R = NHZ, R' = Me): 65%, 2:1:<1 dr, 95% ee
136i (X = $C(Me)_2$, R = H, R' = Et): 76%, >19:1 dr, 96% ee

Scheme 56. Enantioselective Organocatalyzed Intramolecular Michael Addition of Keto Sulfones





134a (n = 2, R = $(CH_2)_3N_3$): 75%, 88% ee
134b (n = 2, R = Me): 80%, 83% ee
134c (n = 2, R = $(CH_2)_2$OTBS): 76%, 83% ee
134d (n = 2, R = Bn): 89%, 81% ee
134e (n = 1, R = Me): 58%, 84% ee

The structural limitation imposed by the presence of the geminal bis(ethoxycarbonyl) substituent at **203** (and at **204**) was later removed by Hiemstra and co-workers.[161,162] In their first approach, *N*-(tritylsulfenyl)tryptamine (**205**) (readily obtained from tryptamine and tritylsulfenyl chloride) was used as a substrate for the acid-catalyzed PS reaction with aldehydes **196**. Careful optimization of the reaction conditions was necessary, since the resulting *N*-(tritylsulfenyl)tetrahydro-β-carbolines appeared to be unstable due to the lability of the trityl−sulfur bond. The addition of 3,5-di(*tert*-butyl)-4-hydroxytoluene (BHT) solved this problem, and after screening of a number of BINOL-derived phosphoric acids, **LVIII** was found to be the best catalyst. Without isolation, the PS products were treated with thiophenol and hydrogen chloride to afford the unprotected tetrahydro-β-carbolines **206** with useful yields (77−90%) and enantioselectivities (up to 87% ee, Scheme 90). Comparison of the sign of the specific rotation of **206a** with reported data[155d] established an (*S*) configuration for the major enantiomer of the product obtained when (*R*)-**LVIII** was used as the catalyst.

Subsequently, Hiemstra's group examined the PS reaction of *N*-benzyltryptamine (**207**).[162] The (*R*)-BINOL-derived phosphoric acid **LVII** catalyzed the reaction of **207** with a range of aldehydes **196** to give the desired *N*-benzyltetrahydro-β-carbolines (**208**) with very good yields and with variable enantiomeric purities (from 0 to 87% ee; see selected examples in Scheme 91). The absolute configuration was ascertained by the X-ray crystallographic structure of **208a**. These compounds are interesting since their Winterfeldt oxidation[163] affords pharmaceutically relevant pyrroloquinolones.

The counteranion-binding concept for the catalysis of the iminium cyclization[158] has been recently exploited by Klausen and Jacobsen for the development of the first catalytic asymmetric direct PS reaction of unsubstituted tryptamine precursors **195a**−**c**.[164] The chiral thiourea **LIX**, more acidic than their analogs **XLII** and **XLIII**, appears to form a stable hydrogen-bond complex with acetate or benzoate anion, favoring the protonation of aldimines derived from **195** and the subsequent enantioselective cyclization of the resulting iminium cation. In this way, unprotected tetrahydro-β-carbolines *ent*-**206** are formed directly and with remarkable enantioselectivity (85−95% ee) by the reaction between tryptamines **195a**−**c** and aldehydes **196**, typically (but not always, for instance in the case of aliphatic aldehydes) in the presence of benzoic acid (usually 20 mol %). Some representative examples of this procedure are shown in Scheme 92.

Up to now, there are no reports on the application of asymmetric organocatalytic PS reactions to the synthesis of tetrahydroisoquinolines from 2-phenylethylamines and aldehydes. However, in 2005 Jørgensen and co-workers reported an organocatalytic diastereo- and enantioselective approach to the synthesis of 1,2-dihydroisoquinolines, based on the amine-promoted cyclization of 2-(5-oxopentyl)isoquinolinium salts (Scheme 93).[165] After screening several chiral secondary amines, the C_2-symmetric 2,5-dibenzylpyrrolidine (**LX**) was found to catalyze the cyclization of several 2-(5-oxopentyl)isoquinolinium iodide derivatives such as **209** with moderate yields (18−73%) and with high enantioselectivities (ee >85%, except in one instance). A representative example is shown in Scheme 94. The intermediate tricyclic aldehyde **210** was very unstable and was first treated in situ with trifluoroacetic anhydride and then

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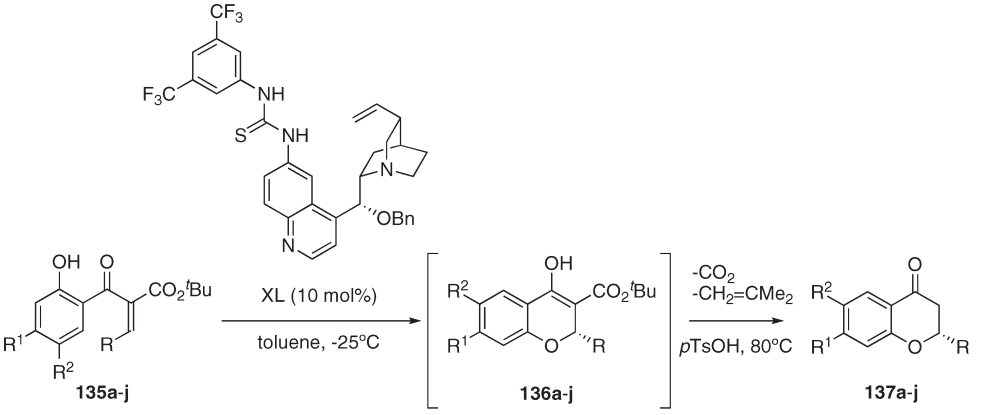
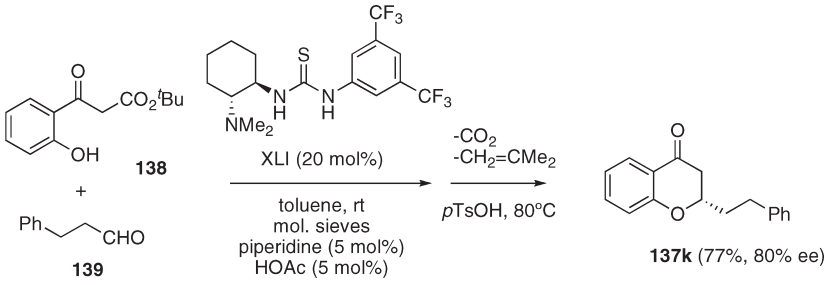
Scheme 57. Catalytic Enantioselective Synthesis of Chromanones by Oxa-Michael Cyclization−Decarboxylation



137a (R = Ph, $R^1 = R^2 = H$): 92%, 94% ee
137b (R = *p*-BrPh, $R^1 = R^2 = H$): 65%, 92% ee
137c (R = 2-Naphthyl, $R^1 = R^2 = H$): 89%, 91% ee
137d (R = *p*Tol, $R^1 = R^2 = H$): 83%, 90% ee
137e (R = *o*-ClPh, $R^1 = R^2 = H$): 67%, 88% ee
137f (R = *p*-MeOPh, $R^1 = R^2 = H$): 94%, 91% ee
137g (R = Ph, R^1 = OMe, $R^2 = H$): 71%, 89% ee
137h (R = Ph, R^1 = Me, $R^2 = H$): 97%, 90% ee
137i (R = Ph, R^1, $R^2 = -(CH_2)_4-$): 78%, 89% ee
137j (R = *c*-C_6H_{11}, $R^1 = R^2 = H$): 65%, 80% ee

Scheme 58. Catalytic Asymmetric Synthesis of Flindersiachromanone



137k (77%, 80% ee)

with sodium borohydride to afford the tricyclic 4-trifluoroacetyl-1,2-dihydroisoquinoline **212** in 24:1 dr and 92% ee. An anomalous X-ray diffraction analysis of the major product established its absolute configuration (*S*,*S*) and was used by the authors to propose a mechanistic working model for the transition state of the cyclization.[165]

4.6. Organocatalytic Intramolecular α-Alkylation and α-Arylation of Aldehydes

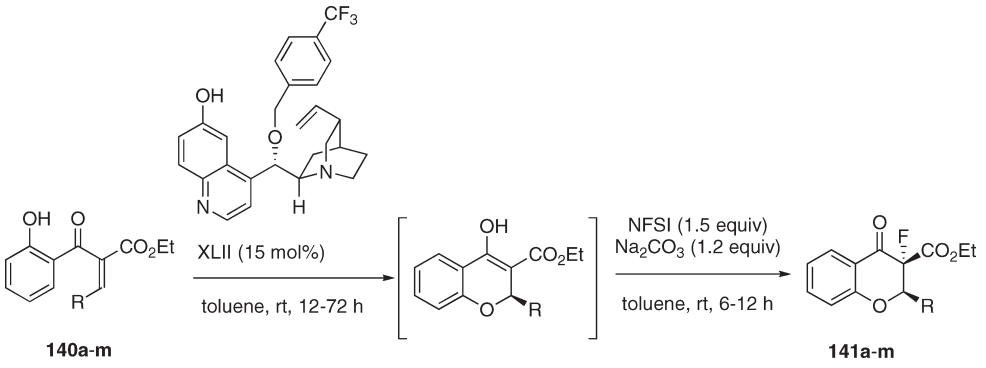
The catalytic asymmetric intramolecular α-alkylation of aldehydes was achieved in 2003 by Vignola and List.[166] (*S*)-Proline (**I**) catalyzed the reaction, but optimal results were achieved with (*S*)-α-methylproline (**LXI**). The results of this method were excellent in terms of yield and of enantioselectivity, and it allowed the enantioselective synthesis of several five-membered ring-systems (Scheme 95) and of a cyclopropane derivative (Scheme 96). The addition of 1 equiv of a tertiary amine was required, probably in order to trap the hydrogen halide produced in the reaction. It is remarkable how the presence of the α-methyl group in **LXI** increased the enantioselectivity of the reaction, either by increasing the population of the anticonformer of the *trans*-enamine intermediate or by minimizing the enamine formation from the cyclized product.

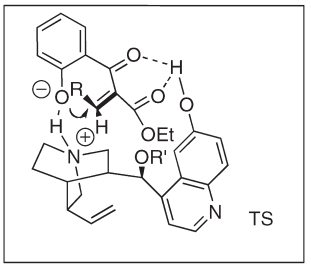
The absolute configuration of **214f** was determined to be (*S*) by measuring the optical rotation of its known alcohol reduction product (sodium borohydride, methanol) obtained in 52% yield and 91% ee. The much more challenging intermolecular organocatalytic asymmetric α-alkylation of aldehydes was not developed until 2008, thanks to the efforts of Melchiorre, Petrini, and co-workers[167] and of Cozzi and co-workers.[168]

Saicic and co-workers have demonstrated that enamine activation of aldehydes by secondary amines can be used in synergistic combination with palladium catalysis for the intramolecular Tsuji−Trost reaction, leading to a new method for the construction of five- and six-membered carbocycles.[169] Attempts to use chiral secondary amines in enantioselective versions of this process (MacMillan's imidazolidinones, proline, prolinol derivatives) were unsuccessful, either for lack of catalytic activity or of asymmetric induction. Better results were obtained when the role of the asymmetric inductor was transferred to the metal complex (see Scheme 97 for an example).

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

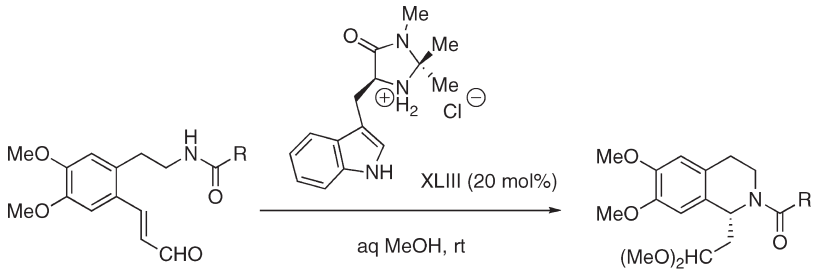
Scheme 59. Organocatalytic Asymmetric Synthesis of Chiral Fluorinated Flavanones





141a (R = Ph): 99%, 93% ee
141b (R = *p*-FPh): 99%, 92% ee
141c (R = *p*-ClPh): 99%, 92% ee
141d (R = *p*-BrPh): 100%, 90% ee
141e (R = *p*-NO_2Ph): 99%, 90% ee
141f (R = *p*-CNPh): 99%, 92% ee
141g (R = *p*-CF_3Ph): 97%, 92% ee
141h (R = *o*-BrPh): 99%, 89% ee
141i (R = *m*-BrPh): 99%, 93% ee
141j (R = 2-Naphthyl): 96%, 92% ee
141k (R = *p*-Tol): 95%, 91% ee
141l (R = *p*-MeOPh): 96%, 90% ee
141m (R = 2-Furyl): 56%, 73% ee

Scheme 60. Asymmetric Intramolecular Aza-Michael Addition of Amides to Enals



Asymmetric intramolecular α-arylation of aldehydes was reported in 2009 first by Nicolaou et al.[170] and shortly afterward by MacMillan and co-workers,[171] using organo-SOMO catalysis. The conditions developed by Nicolaou involved the use of imidazolidinone salt *ent*-**XXXV** as the catalyst, cerium ammonium nitrate (CAN) as the oxidant, and water in 1,2-dimethoxyethane (DME).[170] The reaction was applied to several (5-oxopentyl)benzene, naphthalene, or indole derivatives, furnishing the cyclized products in good yields and >85% ee (Scheme 98).

Compound **220g** was used as the starting material in a short and efficient total synthesis of the antitumor natural product demethylcalamenene.

MacMillan's procedure[171] is essentially the same, except that the imidazolinone salt **LXII** was found to give somewhat better results than its analog **XXXV**, that an iron(III) complex ($[Fe(phen)_3]\cdot(PF_6)_3$) was used in some instances as the oxidant, and that the presence of a base ($NaHCO_3$ or Na_2HPO_4) was necessary. Some of the cyclization products obtained by MacMillan are shown in Scheme 99.

The synthetic applicability of the method was nicely demonstrated by the two-step transformation of **225** into the natural product (−)-tashiromine.

Very recently, the intramolecular α-arylation of aldehydes via organo-SOMO catalysis has been studied theoretically by Houk, MacMillan, and co-workers using density functional theory.[172] These studies have helped to understand the electronic structure of the intermediate radical cations. In agreement with the experimental results, the calculated 1,3-disubstituted aromatic systems cyclize preferently at the ortho position of the two aromatic substituents (cf. the formation of **220c** from **219c**), while the 1,3,4-trisubstituted systems show para selectivity with respect to the most electron-donating aromatic substituent (cf. the formation of **220g** from **219g**). The proposed catalytic cycle for this oxidative cyclization is depicted in Scheme 100, where it can be noted that the unpaired electron in the intermediate radical cations resides mainly at the carbon atom.

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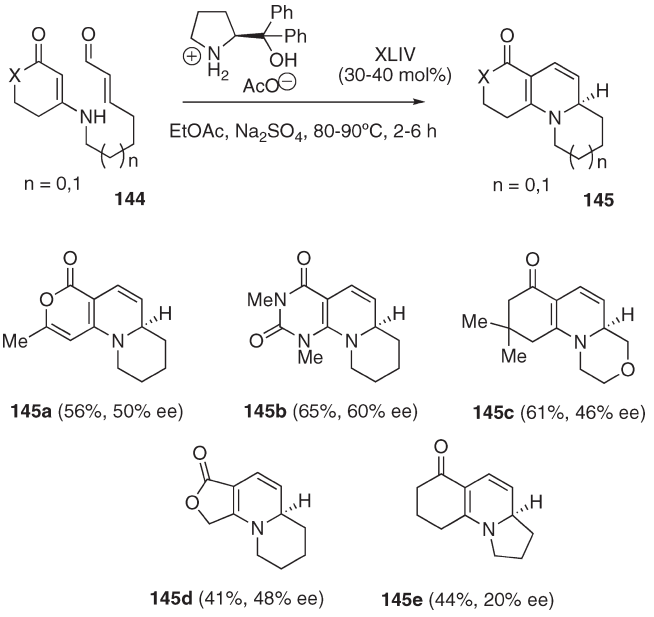
4.7. Organocatalytic Asymmetric Nazarov and Other Electrocyclic Reactions

The acid-promoted conversion of divinyl ketones into 2-cyclopentenones, known as the Nazarov cyclization,[173] is a useful procedure that has been applied to the total synthesis of natural products.[174] From a mechanistic point of view, its key step involves the conrotatory ring-closure of a pentadienyl carbocation to a five-membered oxyallyl cation, and the 2007 report of Rueping et al. on the chiral Brønsted acid-catalyzed asymmetric Nazarov cyclization[175] constitutes in fact the first enantioselective organocatalytic electrocyclic reaction. Dienones of general structure **229** were chosen as suitable substrates on the basis of their favored *s*-trans/*s*-trans conformation and the stabilization by the exocyclic oxygen of the intermediate cyclic oxyallyl cation, and a screening of several BINOL-based phosphoric acids and amides signaled **LXIII** as the most efficient catalyst. The resulting cyclopentenones **230** were formed with total regioselectivity, when applicable with good cis-diastereoselectivity, and with ee higher than 85% (Scheme 101).

Scheme 61. Enantioselective Organocatalytic Intramolecular Formal Aza-[3 + 3]-Cycloaddition



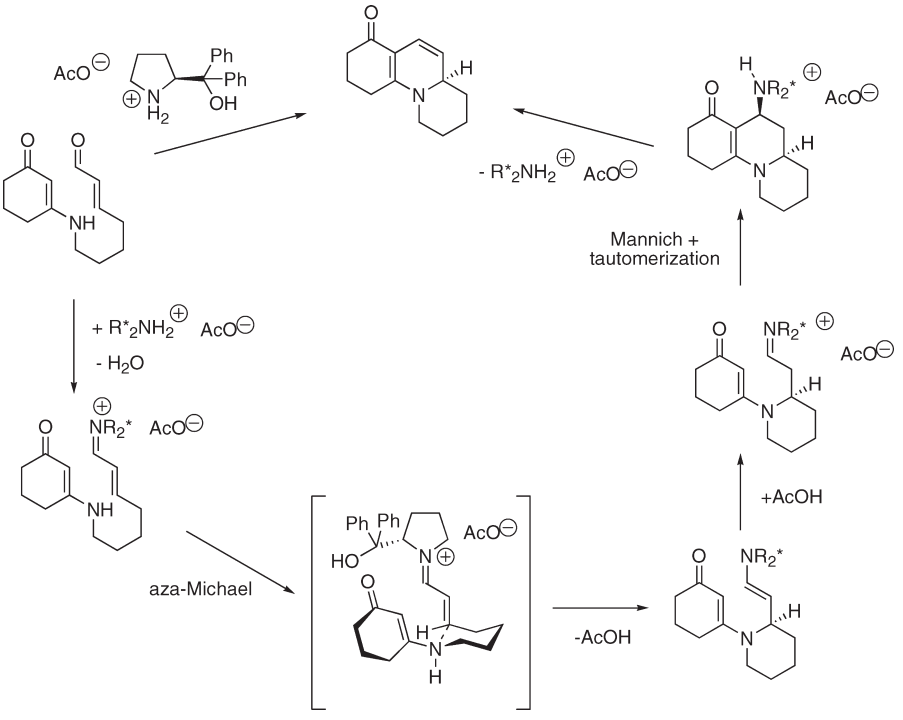
The absolute configuration of the products was deduced from an anomalous X-ray diffraction analysis of the major isomer of compound **230g**. The preferential formation of the cis-diastereomers was assumed to arise from a kinetic diastereoselective protonation of the cyclic dienol intermediate by the chiral acid catalyst (see Scheme 102). In fact, treatment of *cis*-**230a** with basic alumina (dichloromethane, room temperature, 24 h) resulted in its quantitative conversion to *trans*-**230a** without loss of enantiomeric purity.

Subsequently, Rueping and Ieawsuwan extended this methodology to the cyclization of the monosubstituted dienones **231**.[176] This is in fact a more difficult transformation since with R^2 = H, the mechanism depicted in Scheme 102 is modified in that the enantiodifferentiating step must now be that of the final protonation instead of the electrocyclization that leads to an achiral cyclic dienol (Scheme 103).

The most suitable catalyst for this reaction was compound **LXIV**, a hydrogenated analog of **LXIII**, that furnished the final cyclopentenones **232a**−**i** in moderate to good yields and with moderate enantioselectivities (67−78% ee; Scheme 104).

Other organocatalytic modes of activation for enantioselective Nazarov cyclizations are surfacing from the work carried out at Tius' laboratory in Hawaii. An enamine−iminium ion Nazarov cyclization of diketones **233**, promoted by the chiral diamine monotriflate salt **LXV**, was achieved after catalysis with several

Scheme 62. Intramolecular Aza-Michael−Mannich Mechanism for the Formal Aza-[3 + 3]-Cycloaddition



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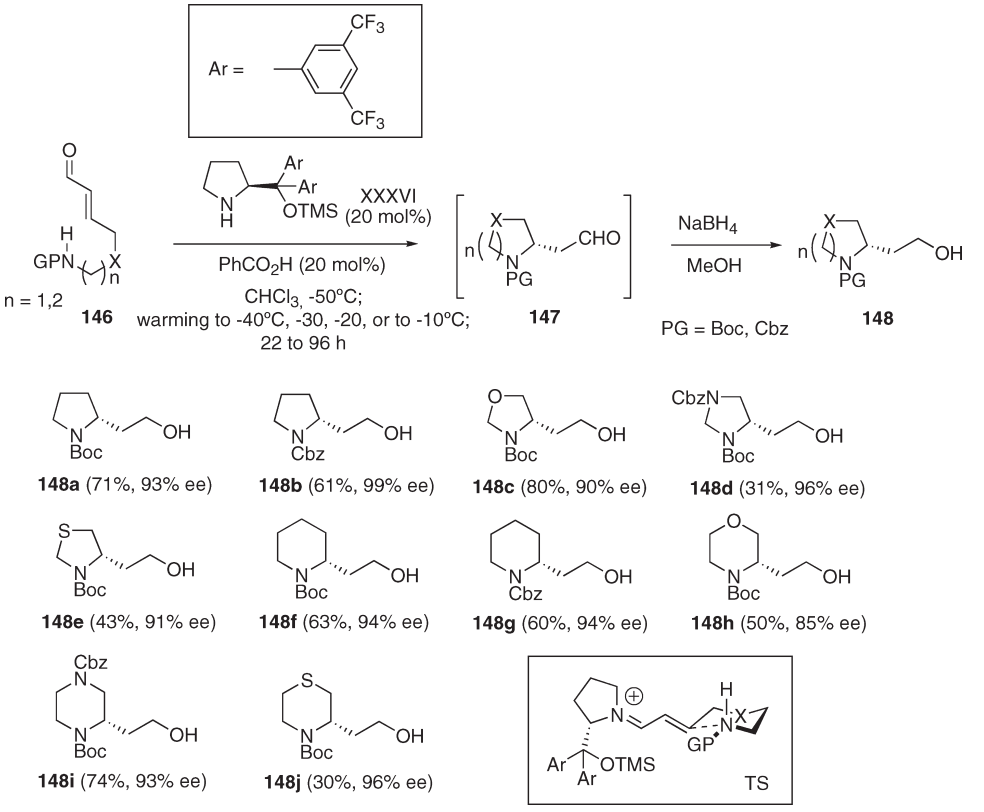
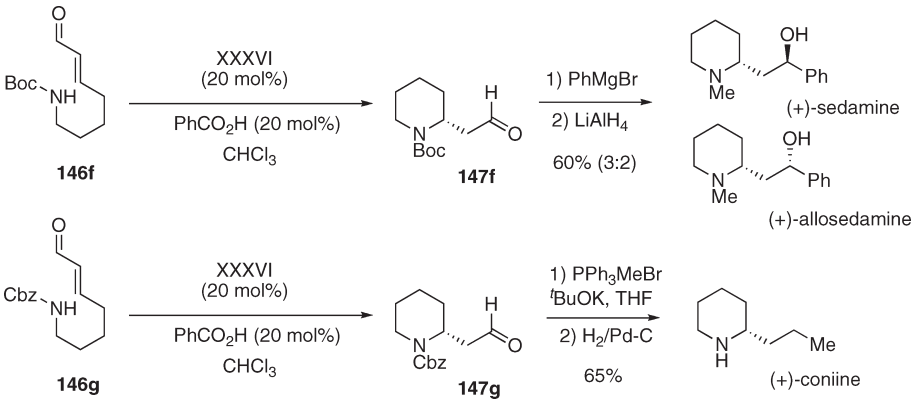
Scheme 63. Organocatalytic Intramolecular Aza-Michael Reaction of Carbamates



Scheme 64. Organocatalytic Asymmetric Synthesis of (+)-Sedamine, (+)-Allosedamine, and (+)-Coniine



chiral monoamines gave disappointing results.[177] A cooperative mechanism triggered by a diamine was then devised, in which the Nazarov cyclization would take place on an iminium−enamine intermediate (Scheme 105). The experimental implementation of this concept proved successful, and chiral α-hydroxycyclopentenones **234** could be obtained in up to 99% ee, although the required reaction times were very long (5−8 days, yields from 11 to 66%), and stoichiometric amounts of **LXV** were required (Scheme 106). The absolute configuration of **234a** was determined crystallographically from its enol ester of (1*S*)-camphanic acid.

Recently, Tius et al. have reported an unusual organocatalytic asymmetric cyclization of the racemic ketoazirine **235** that is accompanied by a kinetic resolution and leads to the formation of the 4-hydroxy-3-oxotetrahydropyridine **236** in more than 98% ee.[178] The proposed mechanism for the formation of **236** involves an aza-Nazarov cyclization of the iminium ion derived from **235** and **LXV**; the resulting bicyclic intermediate that is then trapped with water undergoes a ring expansion. Finally, hydrolysis of the protonated monocyclic enamine affords **236** and releases the catalyst **LXV** (Scheme 107).

Another strategy developed by Tius et al. relies on the use of a bifunctional organocatalyst combining Brønsted acidic and Lewis basic functional groups.[179] Suitable substrates for this approach are the unsaturated diketo esters **237** that are cyclized in the presence of the chiral aminothiourea **LXVI** in good

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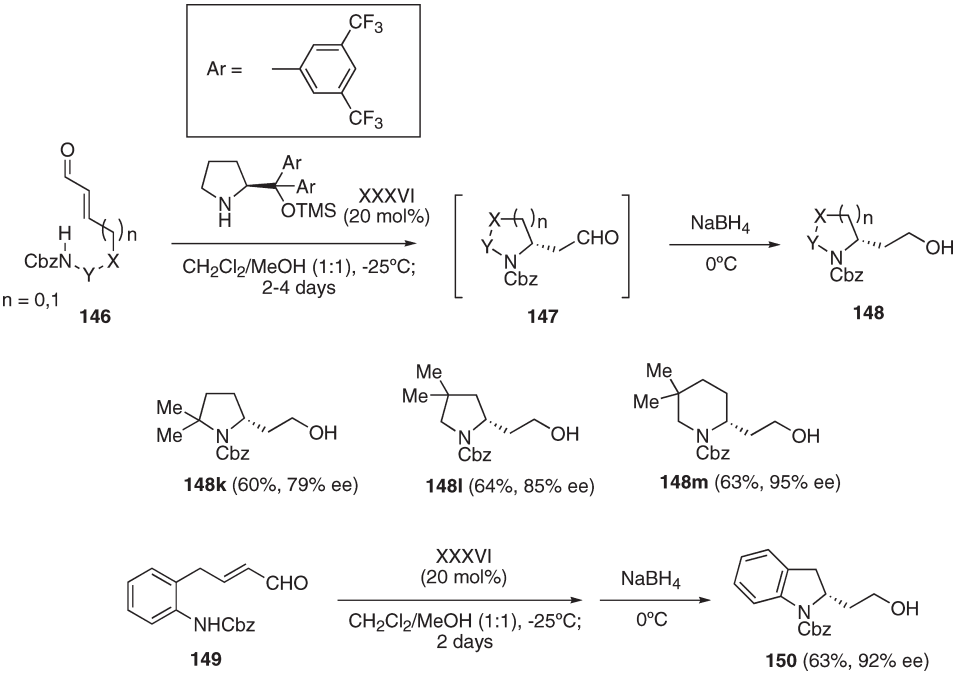
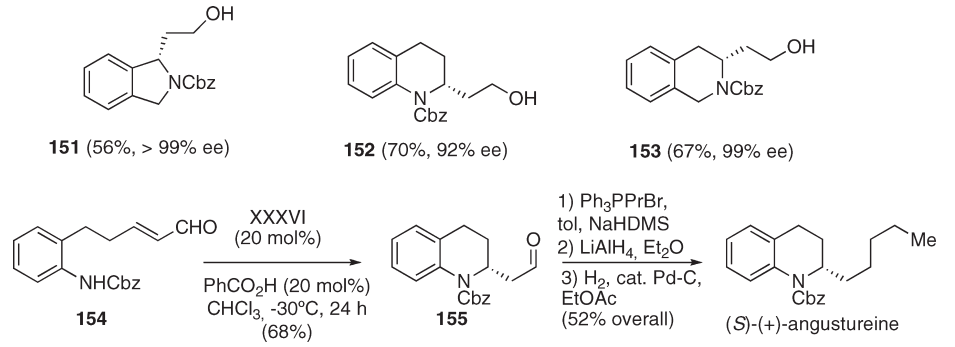
Scheme 65. Alternative Protocol for Organocatalytic Asymmetric Aza-Michael Cyclizations



Scheme 66. Asymmetric Organocatalytic Synthesis of Isoindolines, Tetrahydroquinolines, and Tetrahydroisoquinolines by Aza-Michael Cyclization



yields (58−95%) and good to excellent enantiomeric purities (Scheme 108). The catalysis probably implies complementary polarization at the two terminal carbon atoms to favor the cyclization. It is also worth noting that two adjacent stereogenic carbon atoms (one of them quaternary) are generated diastereoselectively, the relative stereochemistry of the major diastereomer being in accordance with a conrotatory electrocyclization taking place from the (*E*)-enol form of **237**. The absolute stereochemistry of the α-hydroxycyclopentenones **238** was assigned on the basis of X-ray crystallographic analysis.

The 6π electrocyclization of pentadienyl anion takes place thermally via a disrotatory pathway,[180] and two reports dealing with the asymmetric organocatalysis of aza-variants of this transformation were published simultaneously in 2009.[181] The first of these two approaches, due to Müller and List,[182] deals with the asymmetric catalysis of the cyclization of α,β-unsaturated hydrazones, an acid-mediated transformation leading to pyrazolines that was discovered by Fischer more than 100 years ago[183] and whose isolectronic relationship with the 6π electrocyclization of pentadienyl anion was later recognized by Huisgen.[184] After testing several chiral phosphoric acids, the (*S*)-BINOL derivative **LXVII** was found to catalyze efficiently the cyclization of α,β-unsaturated aryl hydrazones **239a**−**n** to the biologically relevant pyrazolines **240a**−**n** (Scheme 109). From a preparative point of view, it is worth noting that the in situ preparation of the substrates **239** by condensation of the corresponding α,β-unsaturated-β-aryl ketones and phenylhydrazine in the presence of molecular sieves can be coupled in a one-pot fashion with the acid-catalyzed cyclization without loss of enantioselectivity.

The attempted cyclization of α,β-unsaturated alkyl hydrazones (one-pot procedure) took place with low yields and enantioselectivities. The authors propose a mechanism (Scheme 110) in which the phosphoric acid catalyzes both the *E*/*Z* isomerization of the hydrazone double bond and the enantioselective electrocyclization step.[182]

On the other hand, Martin and co-workers have used a 2-azapentadienyl anion to explore the possibility that a chiral organic ammonium cation could induce asymmetry in the 6π

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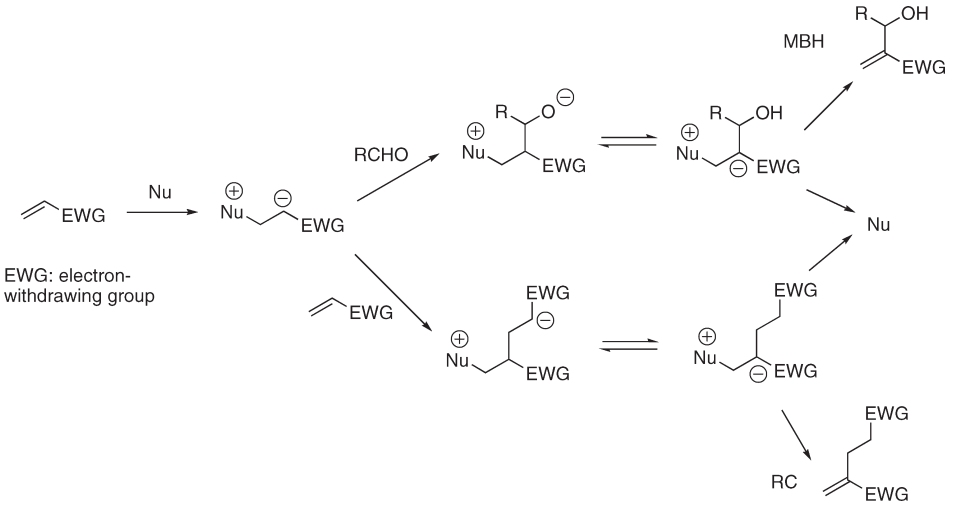
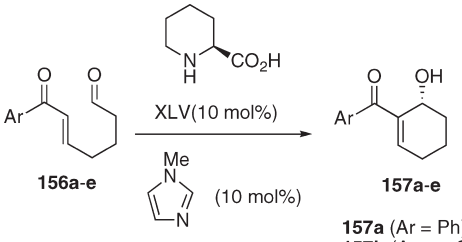
Scheme 67. Intermolecular Morita–Baylis–Hillman (MBH) and Rauhut–Currier (RC) Reactions



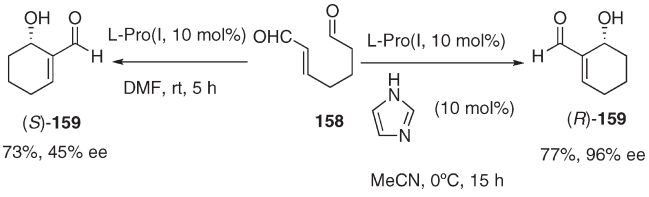
Scheme 68. Asymmetric Organocatalytic Intramolecular MBH Reaction



156a-e **157a-e**

157a (Ar = Ph): 82%, 80% ee
157b (Ar = *p*-ClPh): 92%, 79% ee
157c (Ar = *p*-BrPh): 88%, 79% ee
157d (Ar = *o*-Tol): 94%, 51% ee
157e (Ar = 2-Thienyl): 83%, 74% ee

Scheme 69. Inversion of Enantioselectivity in the Proline-Catalyzed Intramolecular MBH Reaction



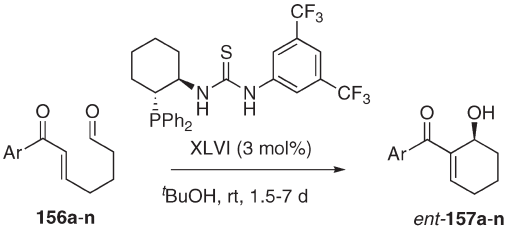
(*S*)-**159** **158** (*R*)-**159**

73%, 45% ee

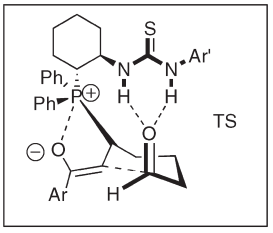
MeCN, 0°C, 15 h

77%, 96% ee

Scheme 70. Enantioselective Intramolecular MBH Reaction Catalyzed by Amino Acid-Derived Phosphinothiourea



156a-n *ent*-**157a-n**



ent-**157a** (Ar = Ph): 92%, 85% ee
ent-**157b** (Ar = *p*-ClPh): 90%, 79% ee
ent-**157c** (Ar = *p*-BrPh): 90%, 75% ee
ent-**157d** (Ar = *o*-Tol): 63%, 66% ee
ent-**157e**(Ar = 2-Thienyl): 73%, 76% ee
ent-**157f** (Ar = *p*-MeOPh): 92%, 97% ee
ent-**157g** (Ar = *p*-Tol): 90%, 93% ee
ent-**157h** (Ar = *m*-Tol): 96%, 90% ee
ent-**157i** (Ar = *p*-FPh): 93%, 83% ee
ent-**157j** (Ar = *m*-BrPh): 92%, 63% ee
ent-**157k** (Ar = *o*-BrPh):97%, 16% ee
ent-**157l** (Ar = 2-Naphthyl): 92%, 83% ee
ent-**157m** (Ar = *p*-Me_2NPh): 86%, 98% ee
ent-**157n** (Ar = *p*-NO_2Ph): 98%, 39% ee

electrocyclization.[185] The optimized process developed by these authors consists of the generation of the aldimines **242** by condensation of the anilines **241** with the aldehydes **196**. Without purification, the crude aldimines are treated with 0.1 equiv of the cinchonidine-derived ammonium salt **LXVIII** under phase-transfer conditions (toluene/aqueous potassium carbonate), to afford the chiral indolines **243** in good yields and enantioselectivities (Scheme 111).

Although the exact mechanistic pathway of this reaction remains unclear, the authors propose a catalytic cycle in which the anion derived from **242** undergoes an electrocyclic ring-closure and suggest that the sense of stereoinduction can be rationalized by using a modification of the tight ion pair model for asymmetric phase transfer mediated alkylation proposed some years ago by Corey et al.,[186] in which the enolate oxygen is closely associated with the bridgehead ammonium cation. This mechanism is also compatible with the observation that the cyclization of the nonsymmetrical malonate *rac*-**244** takes pace with a good diastereoselectivity and that both diastereoisomers of the product **245** are obtained with sizable ee (Scheme 112).

4.8. Organocatalytic Asymmetric Polycyclizations

Biomimetic polyene cyclizations, inspired by mechanistic considerations on the biosynthetic pathways leading to terpenoidal natural products,[187] are a classical tool for the synthesis of steroids and other polycyclic skeletons.[188] Some success has been achieved in rendering these polycyclizations enantioselective either by using substrate or chiral auxiliary control or by metal catalysis,[189] and enantioselective iodobicyclization and iodotricyclization of polyprenoids, which require the use of stoichiometric amounts of

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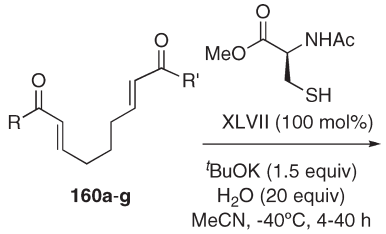
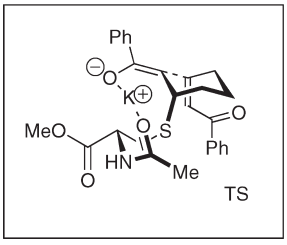
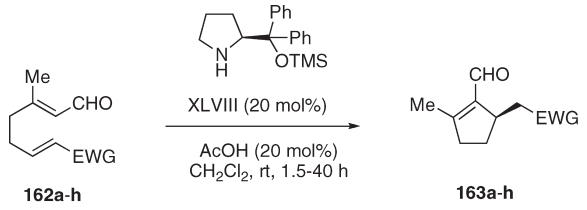
Scheme 71. Enantioselective Intramolecular Rauhut−Currier Reaction Promoted by Protected Cysteine



161a (R = R' = Ph): 70%, 95% ee
161b (R = R' = *p*-MeOPh): 73%, 90% ee
161c (R = R' = *p*-BrPh): 70%, 93% ee
161d (R = R' = *p*-NO_2Ph): 71%, 84% ee
161e (R = R' = Me): 55%, 90% ee
161f (R = R' = 2-Furyl): 54%, 92% ee
161g (R = Ph, R' = OEt): 66%, 67% ee



Scheme 72. Asymmetric Intramolecular Crossed Rauhut−Currier-type Reaction



163a (EWG = CO-Me): 63% , 91% ee
163b (EWG = CO-Ph): 68%, 89%ee
163c (EWG = CO-(*p*-NO_2Ph)): 73%, 96% ee
163d (EWG = CO-(2-Naphthyl)): 71%, 88%ee
163e (EWG = CO-(*p*-ClPh)): 53%, 91%ee
163f (EWG = CO-(*p*-MeOPh)): 45%, 90%ee
163g (EWG = NO_2): 51%, 68%ee
163h (EWG = CHO): 36%, 86%ee

chiral phosphoramidites as nucleophilic promoters, have been reported by Ishihara and co-workers.[190] Only very recently two independent approaches dealing with asymmetric organocatalytic polycyclizations have been simultaneously published. Rendler and MacMillan have applied organo-SOMO catalysis to develop an organocatalytic enantioselective cyclization strategy for accessing steroidal and terpenoidal skeletons.[191] In this work, which can be regarded as an extension of the asymmetric cyclization of aryl aldehydes,[171] they have used the imidazolidinone salt *ent*-**LXII**, with the aid of cupric triflate as the stoichiometric oxidant, to catalyze the bi-, tri-, tetra-, penta- and hexacyclization of ω-aryl-substituted polyunsaturated aldehydes (Scheme 113).

The experimental procedure calls for a slow addition (7 h) of a solution of the oxidant, sodium trifluoroacetate, and trifluoroacetic acid to a solution of the aldehyde **246** and the catalyst, followed by stirring at room temperature for 17 h. Products arising from bicyclization (**247a**−**f**), tricyclization (**248a**−**c**), tetracyclization (**249**), pentacyclization (**250**), and even hexacyclization (**251**; six new carbon−carbon bonds and eleven contiguous stereocenters, five of them quaternary, are created in a single step!) are achieved in good yields (ca. 90% yield per carbon−carbon bond) and enantioselectivities (85−93% ee). The cyclization is completely diastereoselective, giving the trans−antitrans arrangement of contiguous stereogenic centers arising from a 6-endo-trig radical addition to trisubstituted olefins. The presence of the nitrile groups as olefin substituents is a key design element for favoring 6-endo regiocontrol in the cyclization.[192] It is also remarkable that both electron-rich or electron-poor aromatic rings can be used as terminators in this cyclization. In the case of the *m*-substituted substrates **246b** and **246e**, regioisomer mixtures are obtained (4:1 and 2:1, respectively), the major ones being **247b** and **247e**. A mechanism derived from that depicted in Scheme 100,[171] but involving a radical polyene cyclization, is presumably operative in this transformation (Scheme 114).

The enantioselective cationic polycyclization developed by Jacobsen and co-workers[193] proceeds through an *N*-acyliminium intermediate and takes advantage of the anion binding thiourea catalysis and therefore can be regarded as an extension of the work carried out in the same laboratory on Pictet−Spengler cyclization.[158,164] Extensive catalyst and reaction condition optimization was necessary, but the authors were finally able to find a suitable protocol for the enantioselective bicyclization of the unsaturated hydroxylactams **252**, leading to the polycyclic lactams **254** with moderate to good yields and with excellent enantioselectivities (Scheme 115). The absolute configuration of **254g** was established by X-ray crystallography, and the stereochemistry of all other products was assigned by analogy. Hydroxylactams **252** are not the actual substrates of the reaction but upon treatment with hydrochloric acid in *tert*-butyl methyl ether (TBME) are converted into the corresponding chlorolactams **253**. Ionization of these compounds by the chiral thiourea **LXIX** generates the cation, that is cyclized enantioselectively under the influence of the chiral thiourea−chloride anion complex. The authors provide compelling evidence, based on Eyring analysis of enantioselectivity of cyclizations performed with **LXIX** and with other structurally related thiourea catalysts, for a mechanism in which a cation π-interaction with the large aromatic substituent of the pyrrolidine ring in **LXIX** determines the enantioselectivity of the reaction (Scheme 116).

4.9. Synthesis of Heterocycles via Asymmetric Organocatalytic Cyclizations

We deal in this section with miscellaneous asymmetric syntheses of heterocycles by organocatalytic cyclizations that involve

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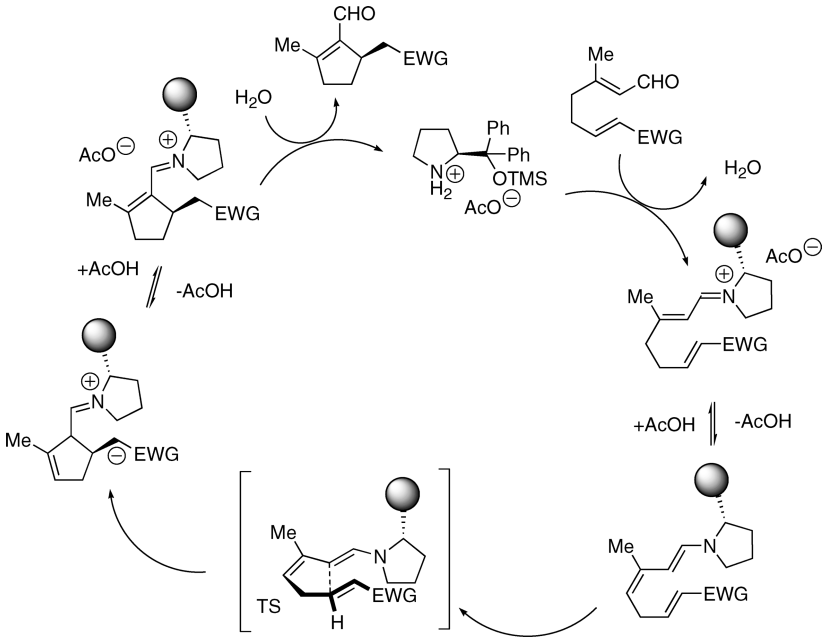
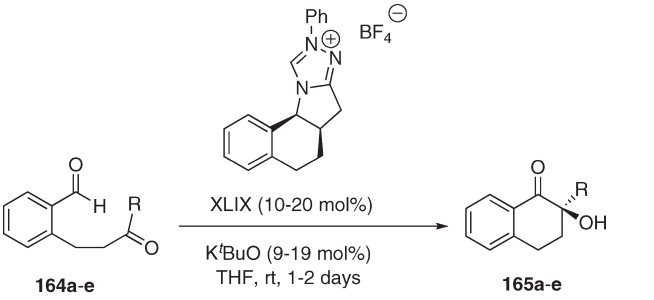
Scheme 73. Dienamine Mechanism for the Intramolecular Crossed Rauhut−Currier-type Reaction



Scheme 74. Asymmetric Intramolecular Crossed-Benzoin Reactions by NHC Catalysis



164a-e → **165a-e**

165a (R = Me): 93%, 94% ee
165b (R = Et): 90%, 95% ee
165c (R = *n*-Bu): 85%, 98% ee
165d (R = *t*Bu): 91%, 98% ee
165e (R = Bn): 43%, 93% ee

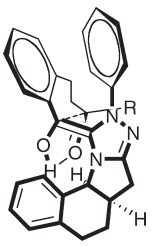
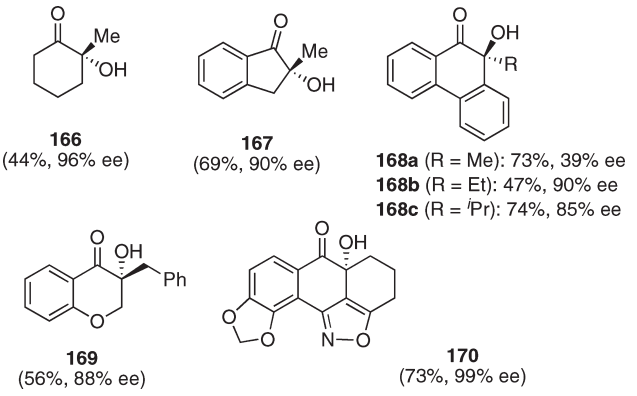


Figure 25. Proposed transition state for the chiral NHC-catalyzed benzoin cyclization.



166 (44%, 96% ee)

167 (69%, 90% ee)

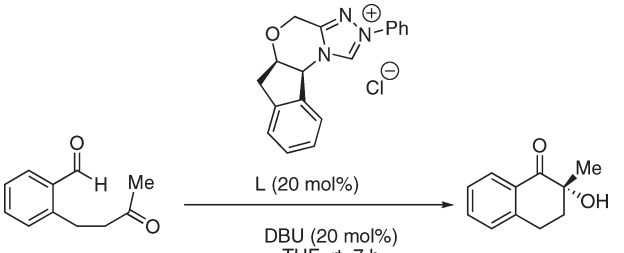
168a (R = Me): 73%, 39% ee
168b (R = Et): 47%, 90% ee
168c (R = *i*Pr): 74%, 85% ee

169 (56%, 88% ee)

170 (73%, 99% ee)

Figure 26. Other compounds obtained by chiral NHC-catalyzed intramolecular crossed benzoin reaction.

Scheme 75. Alternative Method for the Chiral NHC-Catalyzed Intramolecular Crossed Benzoin Reaction



164a → ***ent*-165a** (70%, 96% ee)

the enantiocontrolled formation of stereogenic centers with endocyclic carbon−heteroatom bonds. Several reactions falling into this cathegory have been already discussed:

(a) intramolecular β-lactone synthesis (section 3.1),[78,80]
(b) dearomatization−desymmetrization of 4-substituted phenols via intramolecular oxa-Michael addition (section 3.2),[84]
(c) dearomatization−desymmetrization of 4-substituted phenols via intramolecular Stetter reaction (section 3.3),[87]

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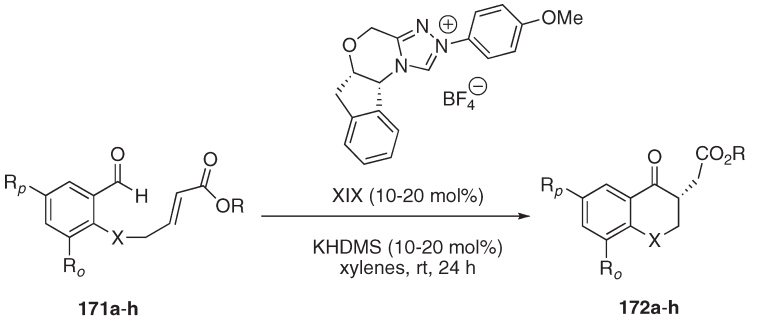
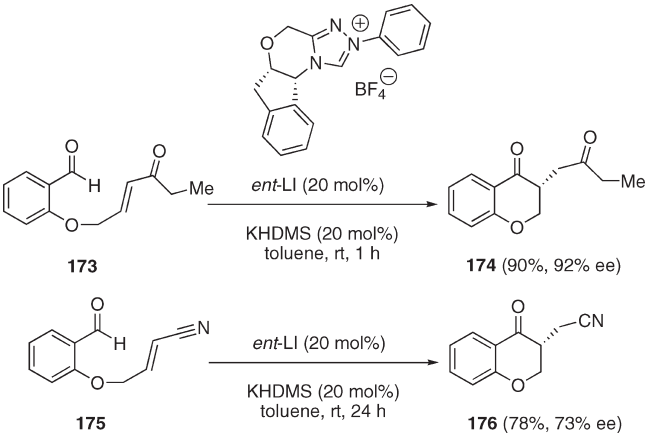
Scheme 76. Enantioselective Organocatalytic Intramolecular Stetter Reaction of Salicyaldehyde-Derived Unsaturated Esters

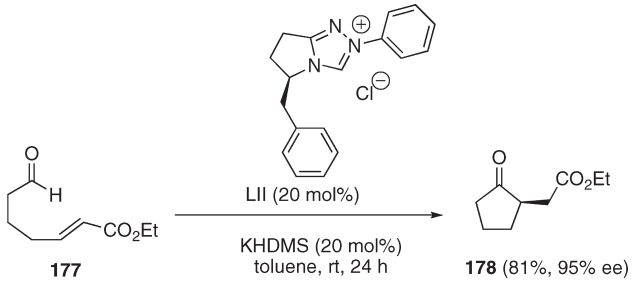


172a (R_o = R_p = H, X = O, R = Et): 94%, 94% ee
172b (R_o = H, R_p = Me, X = O, R = Et): 80%, 97% ee
172c (R_o = Me, R_p = H, X = O, R = Et): 90%, 84% ee
172d (R_o = OMe, R_p = H, X = O, R = Et): 95%, 87% ee
172e (R_o = R_p = H, X = S, R = Me): 63%, 96% ee
172f (R_o = R_p = H, X = NMe, R = Me): 64%, 82% ee
172g (R_o = R_p = H, X = N(CH_2CH=$CHCO_2Me$), R = Me): 72%, 84% ee
172h (R_o = R_p = H, X = CH_2, R = Et): 35%, 94% ee

Scheme 77. Enantioselective Organocatalytic Intramolecular Stetter Reaction of Other Salicyaldehyde-Derived Unsaturated Substrates



Scheme 78. Enantioselective Organocatalytic Intramolecular Stetter Reaction of an Aliphatic Substrate



(d) aldol cyclization of α-heterosubstituted carbonyls (section 4.1),[98,99]
(e) intramolecular oxa-Michael[124,126] and aza-Michael[128,130−133] additions (section 4.2),
(f) intramolecular Stetter reactions of α-heterosubstituted aldehydes (section 4.4),[150]
(g) Pictet−Spengler and related cyclizations (section 4.5;[156,158−162,164,165] see also section 4.8),[192]
(h) aza-Nazarov cyclization−rearrangement of ketoazirines (section 4.7),[178] and
(i) synthesis of pyrazolines[182] and of indolines[185] by 6π-electrocyclization (section 4.7).

4.9.1. Phosphine-Catalyzed Cyclization of Hydroxyl-2-alkynoates. In 1994, Trost and Li disclosed a phosphine-catalyzed cyclization of ω-hydroxy-2-alkynoates, leading to saturated oxygen heterocycles, for which the mechanism outlined in Scheme 117 was proposed.[194]

At the beginning of 2009, Chung and Fu disclosed an asymmetric approach to this cyclization.[195] After testing several chiral mono- and bisphosphines, they found that the spirocyclic phosphepine **LXX** efficiently catalyzed the cyclization of the hydroxyalkynoates **255**, leading to substituted tetrahydrofurans and tetrahydropyrans in excellent enantioselectivity (Scheme 118).

Chung and Fu were also able to extend their methodology to the asymmetric synthesis of dihydrobenzopyrans **258** by the cyclization of 2-alkynoates bearing pendant phenols **257**, with cyclopentyl methyl ether (CPME) as the solvent and using 2-bromobenzoic acid as a cocatalyst (Scheme 119). The absolute configurations of the heterocycles obtained do not appear to have been established.

It is worth noting that an enantioselective synthesis of 2-alkenyltetrahydrofurans had been previously reported by Toste and co-workers by gold catalysis.[196]

4.9.2. Reductive Cyclization of *N*-Acyl β-Amino Enones. Also in 2009, Sugiura et al. reported an asymmetric synthesis of 4*H*-1,3-oxazines **260** by the enantioselective reductive cyclization of *N*-acylated β-amino enones **259** with trichlorosilane,[197] a process catalyzed by several chiral Lewis bases among which the most enantioselective was (*S*)-BINAPO (**XXV**; see Scheme 120). The saturated amino ketones **261** were obtained as side products with low enantioselectivities. The presence of an electron-donating R^2 group enhanced the formation

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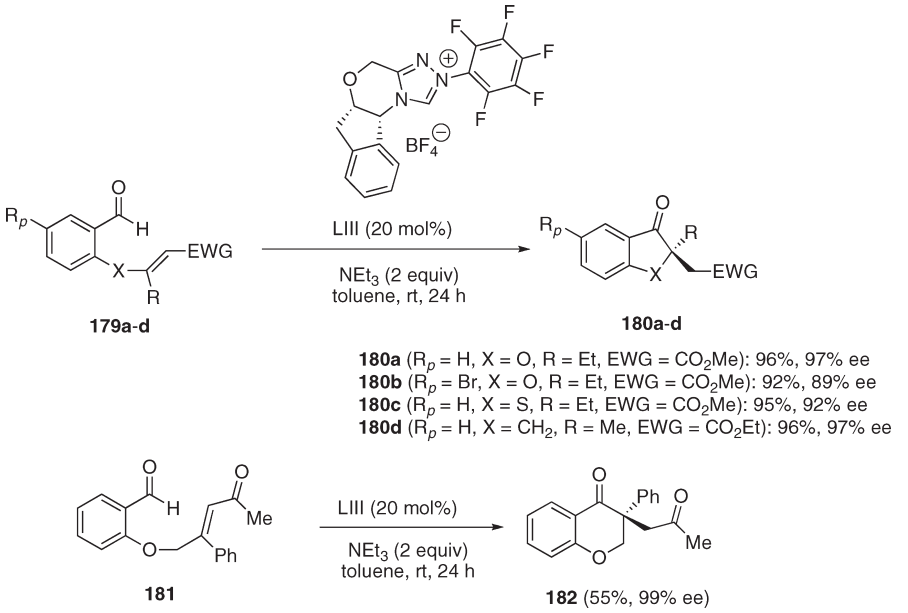
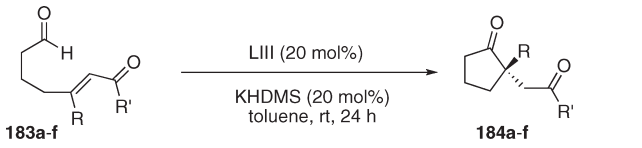
Scheme 79. Intramolecular Asymmetric Stetter Reaction of Aromatic Substrates Leading to the Formation of Quaternary Stereocenters

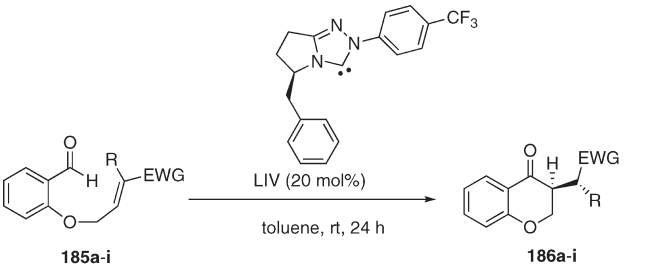


Scheme 80. Intramolecular Asymmetric Stetter Reaction of Aliphatic Substrates Leading to the Formation of Quaternary Stereocenters



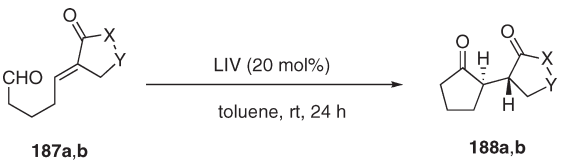
184a (R = Me, R' = Ph): 85%, 96% ee
184b (R = Me, R' = 4-Pyr): 85%, 96% ee
184c (R = Me, R' = *p*-NO_2Ph): 90%, 84% ee
184d (R = Me, R' = Me): 81%, 95% ee
184e (R = Me, R' = $(CH_2)_2$Ph): 63%, 99% ee
184f (R = *n*-Bu, R' = Ph): 71%, 98% ee

Scheme 81. Enantio- and Diastereoselective Intramolecular Stetter Reaction of Aromatic Substrates



186a (R = Me, EWG = CO_2Et): 94%, 30:1 dr, 95% ee
186b (R = Et, EWG = CO_2Et): 95%, 35:1 dr, 92% ee
186c (R = *n*-Bu, EWG = CO_2Et): 53%, 12:1 dr, 94% ee
186d (R = Bn, EWG = CO_2Et): 80%, 20:1 dr, 84% ee
186e (R = allyl, EWG = CO_2Me): 95%, 13:1 dr, 83% ee
186f (R = CH_2CO_2Me, EWG = CO_2Me): 80%, 42:1 dr, 92% ee
186g (R = Me, EWG = COMe): 85%, 10:1 dr, 55% ee
186h (R, EWG = $(CH_2)_2$OCO): 95%, 10:1 dr, 94% ee
186i (R, EWG = $(CH_2)_3$CO): 80%, 18:1 dr, 95% ee

Scheme 82. Enantio- and Diastereoselective Intramolecular Stetter Reaction of Aliphatic Substrates



188a (X = O, Y = CH_2): 94%, 50:1 dr, 99% ee
188b (X = NPh, Y = CO: 80%, 15:1 dr, 88% ee

rate of oxazines **260**, as well as the enantioselectivity (cf. **260e** vs **260d**).

In this reaction, trichlorosilane acts not only as a reductant[102] but also as a dehydrating agent. The fact that in most instances both the enantiomeric purity and the absolute configuration of the ketones **261** differed from that of the corresponding oxazines **260** suggests that the latter are not formed from simple dehydration of the former but that the oxazines are generated via the conjugate reduction of **259**, followed by cyclization of the resulting enolate and elimination of trichlorosilanol, whereas keto amides **261** originate from the 1,2-reduction of the *N*-acyl imine generated from equilibration of the enamide moiety in **259**. The synthetic utility of 4*H*-1,3-oxazines was exemplified by the hydrolysis of **260e** to the keto amide (*R*)-**261e**, by its reduction to the saturated amide (*R*)-**262**, and by its oxidation to the 4,5-dihydrooxazole (*R*)-**263** (Scheme 121). All of these transformations take place without loss of enantiomeric purity, and the hydrolysis of (*R*)-**262** to the known (*R*)-4-phenyl-2-butanamine allowed the determination of its absolute configuration.

4.9.3. Intramolecular Allylic Substitution of Morita–Baylis–Hillman Acetates. An organocatalytic asymmetric intramolecular allylic substitution of Morita–Baylis–Hillman

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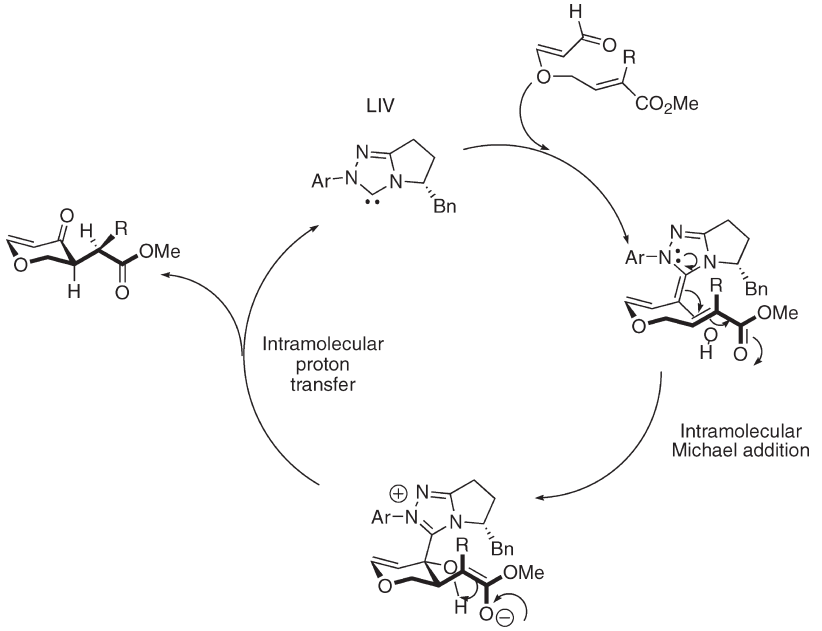
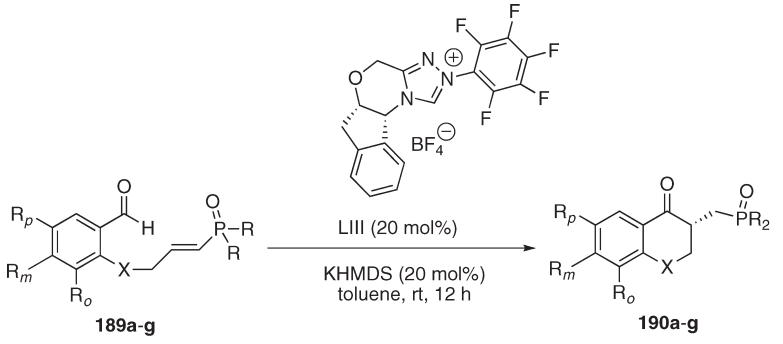
Scheme 83. Proposed Mechanistic Cycle for the Enantio- and Diastereoselective Intramolecular Stetter Reaction



Scheme 84. Catalytic Asymmetric Intramolecular Stetter Reaction of Aromatic Phosphorus-Containing Substrates



190a ($R_o = R_m = R_p$ = H, X = O, R = Ph): 90%, 86% ee
190b ($R_o = R_m$ = H, R_p = Br, X = O, R = Ph): 88%, 96% ee
190c ($R_o = R_m$ = H, R_p = Cl, X = O, R = Ph): 90%, 94% ee
190d (R_o = MeO, $R_m = R_p$ = H, X = O, R = Ph): 75%, 87% ee
190e ($R_o = R_p$ = H, R_m = MeO, X = O, R = Ph): 86%, 93% ee
190c (R_p = H, X = S, R = Et, EWG = CO_2Me): 95%, 92% ee
190d (R_p = H, X = CH_2, R = Me, EWG = CO_2Et): 96%, 97% ee

acetates **264a,b**, leading to 2-(α-methylene)pyrrolidines **265a,b**, has been reported by Cho and co-workers.[198] Optimization of the reaction conditions established that the best catalyst was the dihydroquinidine-4-methyl-2-quinolyl ether **LXXI**, although both the yields and enantioselectivities achieved with this compound in 1,2-dichloroethane (DCE) at room temperature were only moderate, even after prolonged reaction times, and the absolute configurations of the products were not determined (Scheme 122).

4.9.4. Organocatalytic Asymmetyric Halolactonization. Organocatalytic asymmetric halolactonization reactions have been the object of some very recent reports. Borhan and co-workers[199] have established that Lewis base catalysis with Sharpless' $(DHQD)_2PHAL$ ligand **LXXII**, in the presence of benzoic acid and of *N,N′*-dichloro-5,5-diphenylhydantoin as the source of positive halogen, gives good yields and useful enantioselectivities in the asymmetric chlorolactonization of several 4-substituted-4-pentenoic acids (Scheme 123).

The absolute configuration of **267a** was determined by reductive dehalogenation (tributyltin hydride) to the previously known (*R*)-5-methyl-5-phenyldihydro-2-furanone. The ligand $(DHQ)_2PHAL$, quasienantiomeric to **LXXII**, afforded as expected the lactone *ent*-**267a**, but in a reduced 75% yield and 77% ee. Lactone **267b** was obtained in essentially racemic form, a fact that can be attributed to the intermediacy of a planar carbocation intermediate instead of a chloronium ion. Consistent with this explanation are the high enantioselectivities obtained for lactones **267a,d,f** and the modest enantiomeric excess obtained for the alkyl-substituted lactone **267i**. Interestingly enough, the catalyst loading can be reduced to 1 mol % without erosion either of yield

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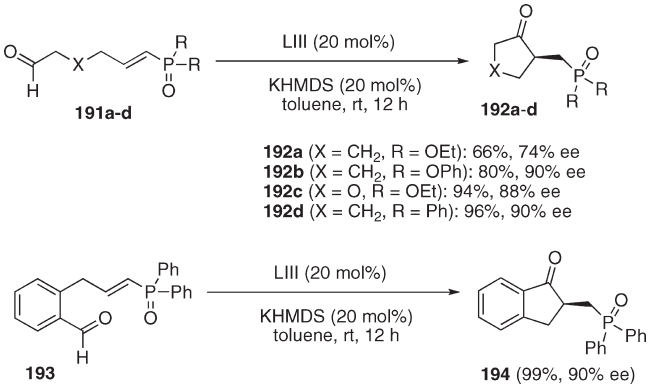
or of enantiomeric purity for **267a,c,e,h**. NMR experiments suggest the formation of an associative complex between the chlorohydantoin and the catalyst and indicate an intriguing synergistic role of two chlorine atoms; it appears that the more electrophilic N_3-chlorine atom, flanked by two carbonyls, is transferred to the chlorolactone, while the N_1-chlorine inductively activates this transfer. The synthetic usefulness of chlorolactones **267** was showcased by the lithium borohydride reduction of **267e** followed by base-induced cyclization of the resulting chlorohydrin to the epoxy alcohol **268**, without appreciable loss of enantiomeric purity (Scheme 124).

Tang and co-workers have developed a similar approach to the enantioselective bromolactonization of conjugated (*Z*)-enynes.[200] A screening of several *Cinchona* alkaloid derivatives showed that a suitable catalyst for this transformation was the *N*-tosyl urea **LXXIII**, derived from 9-amino-9-deoxyepiquinine, in 1,2-dichloroethane solution and with *N*-bromosuccinimide (NBS) as the halogen source. The scope of the catalytic bromolactonization was rather broad, and both aliphatic (**269**) and aromatic (**271**) *cis*-enynes could be cyclized with good yields and excellent enantioselectivities (Schemes 125 and 126). The relative stereochemistry of the products and the absolute stereochemistry of the bromoallene moieties were determined on the basis of previous work from the same laboratory on the diastereoselective bromolactonization of enynes[201] and of Lowe's rule for allenes,[202] respectively. An X-ray structure of lactone **272b** further confirmed this assignment. Experimental results suggest that both the quinuclidine and the urea groups in **LXXIII** are essential for its catalytic activity, and the authors propose that this compound acts as a bifunctional catalyst, activating the system via the deprotonation of the carboxylic acid and formation of hydrogen bonds with NBS.

Scheme 85. Catalytic Asymmetric Intramolecular Stetter Reaction of Aliphatic and Aromatic Phosphorus-Containing Substrates Leading to Five-Membered Rings

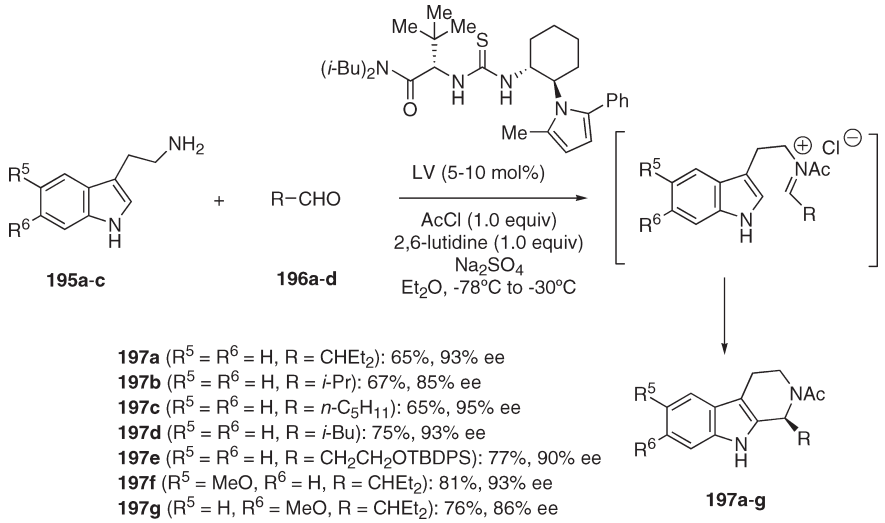


4.9.5. Asymmetric Organocatalytic Intramolecular Transacetalization. A remarkable asymmetric organocatalytic intramolecular transacetalization, leading to 2-ethoxytetrahydrofurans, has been lately disclosed by List and co-workers.[203] This reaction is catalyzed by several BINOL-derived phosphoric acids, but the best enantioselectivities were achieved with the (*S*)-BINOL derivative *ent*-**VIII**. In benzene as the solvent at room temperature and in the presence of molecular sieves (necessary to remove the ethanol formed during the transacetalization), a variety of 4,4-disubstituted-4-hydroxybutanal diethyl acetals **273** were cyclized to the tetrahydrofurans **274**, with the acetal carbon as the only stereogenic center, in generally high yields and enantioselectivities (see Scheme 127 for selected examples). Both a reduced catalyst loading (1 mol %) and low substrate concentration (0.025 M) have beneficial effects in the process.

Aliphatic and aromatic substituents on the alcohol are equally well-tolerated, and their absence has a detrimental effect on the enantioselectivity of the cyclization (cf. **274a**). No appreciable effect on the electronic character of the aromatic substituents is observed, while for aliphatic substituents increased bulkyness leads to higher enantioselectivity (cf. **274d** and **274e**). The 3,3-disubstituted regioisomer of **273k** was cyclized in 94% yield and 65% ee. A single example for the transacetalization of a hydroxypentanal diethyl acetal was examined: the cyclization of 5-hydroxy-5,5-bis(4-fluorophenyl)pentanal diethyl acetal gave 2-ethoxy-6,6-bis(4-fluorophenyl)tetrahydropyran in excellent yield (96%) but with reduced enantioselectivity (64% ee). The absolute configuration of the cyclic acetal **274j** was established by single-crystal anomalous X-ray diffraction analysis, and configurations of other products were assigned by analogy.

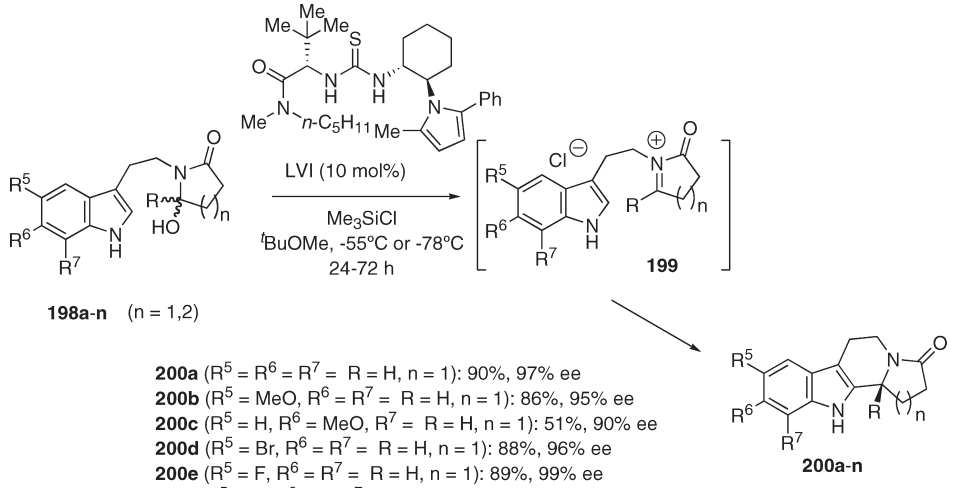
In order to account for the high degree of asymmetric induction exhibited by the chiral Brønsted acid catalyst on the cyclization, the

Scheme 86. Catalytic Enantioselective Acyl-Pictet–Spengler Reaction



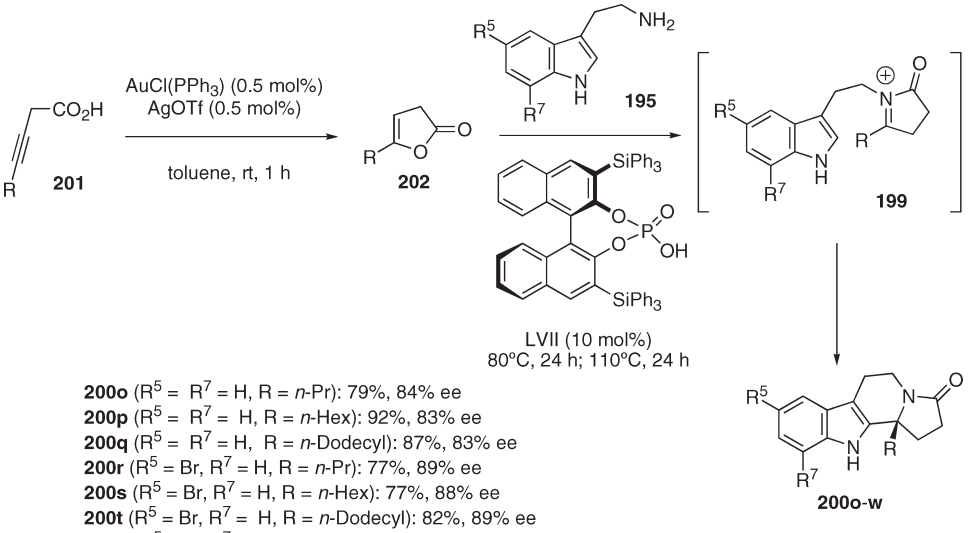
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 87. Asymmetric Pictet−Spengler Cyclization of Hydroxylactams



200a ($R^5 = R^6 = R^7 =$ R = H, n = 1): 90%, 97% ee
200b (R^5 = MeO, $R^6 = R^7 =$ R = H, n = 1): 86%, 95% ee
200c (R^5 = H, R^6 = MeO, $R^7 =$ R = H, n = 1): 51%, 90% ee
200d (R^5 = Br, $R^6 = R^7 =$ R = H, n = 1): 88%, 96% ee
200e (R^5 = F, $R^6 = R^7 =$ R = H, n = 1): 89%, 99% ee
200f (R^5 = H, R^6 = F, $R^7 =$ R = H, n = 1): 94%, 97% ee
200g ($R^5 = R^6$ = H, $R^7 =$ Me, R = H, n = 1): 91%, 93% ee
200h ($R^5 = R^6 = R^7 =$ H, R = Me, n = 1): 92%, 96% ee
200i ($R^5 = R^6 = R^7 =$ H, R = *n*-Bu, n = 1): 74%, 98% ee
200j ($R^5 = R^6 = R^7 =$ H, R = Ph, n = 1): 68%, 85% ee
200k (R^5 = MeO, $R^6 = R^7 =$ H, R = Me, n = 1): 84%, 91% ee
200l ($R^5 = R^6 = R^7 =$ R = H, n = 2): 95%, 81% ee
200m ($R^5 = R^6 = R^7 =$ H, R = Me, n = 2): 63%, 92% ee
200n ($R^5 = R^6 = R^7 =$ H, R = *n*-Bu, n = 2): 65%, 96% ee

Scheme 88. Enantioselective Brønsted Acid-Catalyzed *N*-Acyliminium Cyclization Cascade



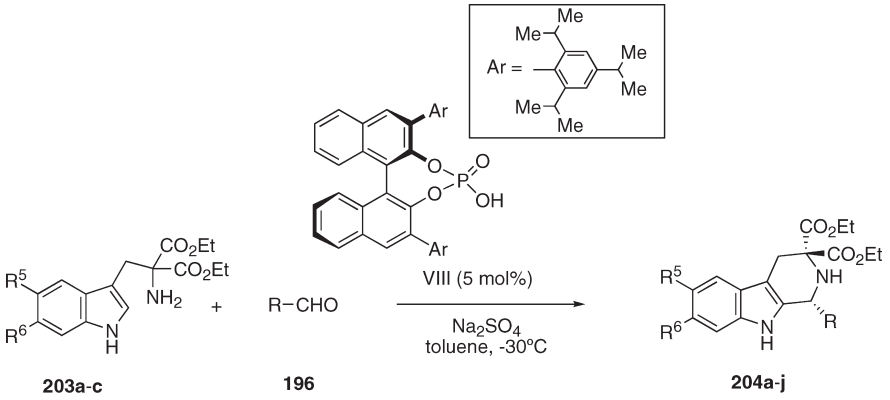
200o ($R^5 = R^7$ = H, R = *n*-Pr): 79%, 84% ee
200p ($R^5 = R^7 =$ H, R = *n*-Hex): 92%, 83% ee
200q ($R^5 = R^7$ = H, R = *n*-Dodecyl): 87%, 83% ee
200r (R^5 = Br, R^7 = H, R = *n*-Pr): 77%, 89% ee
200s (R^5 = Br, R^7 = H, R = *n*-Hex): 77%, 88% ee
200t (R^5 = Br, $R^7 =$ H, R = *n*-Dodecyl): 82%, 89% ee
200u (R^5 = H, $R^7 =$ Me, R = *n*-Pr): 96%, 95% ee
200v (R^5 = H, $R^7 =$ Me, R = *n*-Hex): 84%, 95% ee
200w (R^5 = H, $R^7 =$ Me, R = *n*-Dodecyl): 81%, 95% ee

authors suggest that both the bifunctional character of the phosphoric acid **VIII** and the presence of the hydroxyl group on the substrate that serves as a directing group and increases the acidity of the phosphoric acid are crucial for the observed reactivity and selectivity. List et al. speculate on a mechanism like that depicted in Scheme 128, where the initially formed hydrogen-bonded assembly **A** could account for the simultaneous activation of the hydroxyl and of the acetal groups. The enantioselective cyclization would then proceed either by a hydrogen-bonded oxocarbenium intermediate (**B**; S_N1-like pathway) or by intramolecular nucleophilic substitution of a hydrogen-bonded alkoxy group of the acetal (**C**; S_N2-like pathway).

4.9.6. Organocatalytic Asymmetric Synthesis of Planar Chiral Heterocycles. An organocatalytic asymmetric synthesis of planar chiral heterocycles has been reported very recently by Tomooka et al.[204] Both enantiomers of *N*-tosyl-1-aza-3,7-dimethyl-3,7-nonadiene **276**, which exhibit planar chirality due to topological constraints and that interconvert very

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

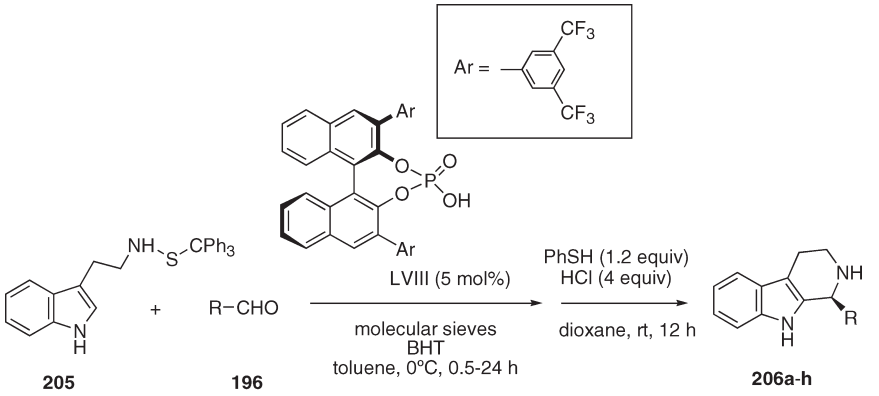
Scheme 89. Organocatalytic Asymmetric Pictet–Spengler Reaction



203a-c **196** **204a-j**

204a (R^5 = R^6 = H, R = Et): 76%, 88% ee
204b (R^5 = MeO, R^6 = H, R = Et): 96%, 90% ee
204c (R^5 = H, R^6 = MeO, R = Et): 94%, 86% ee
204d (R^5 = R^6 = H, R = *n*-Bu): 91%, 87% ee
204e (R^5 = MeO, R^6 = H, R = *n*-Bu): 90%, 87% ee
204f (R^5 = R^6 = H, R = Bn): 58%, 76% ee
204g (R^5 = MeO, R^6 = H, R = Bn): 85%, 72% ee
204h (R^5 = R^6 = H, R = *p*-NO_2Ph): 60%, 88% ee
204i (R^5 = MeO, R^6 = H, R = *p*-NO_2Ph): 98%, 96% ee
204j (R^5 = MeO, R^6 = H, R = Ph): 82%, 62% ee

Scheme 90. Catalytic Asymmetric PS Reactions via Sulfenyliminium Ions



205 **196** **206a-h**

206a (R = *n*-Pent): 87%, 84% ee
206b (R = *i*-Pr): 77%, 78% ee
206c (R = Me): 88%, 30% ee
206d (R = *c*-Hex): 81%, 72% ee
206e (R = CH_2CH_2Ph): 88%, 76% ee
206f (R = Bn): 90%, 87% ee
206g (R = Ph): 77%, 82% ee
206h (R = *p*-NO_2Ph): 78%, 82% ee

slowly at room temperature, can be accessed by base-induced cyclization of **275**. While the truly catalytic cyclization of **275**, mediated by the *Cinchona*-alkaloid-derived phase-transfer catalysts **LXXIV** and **LXXV**, takes place with low enantioselectivity [37% ee for (*S*)-**276** and 23% ee for (*R*)-**276**, respectively], much better results, in terms of stereoselectivity, were obtained with 2 equiv of the carbohydrate-derived lithium alkoxides **LXXVI** and **LXXVII** [80% ee for (*S*)-**276** and 93% ee for (*R*)-**276**, respectively; see Scheme 129]. The stereochemical outcome of this cyclization was rationalized by means of theoretical calculations, at the HF/3-21G level, of model transition states.[204]

5. ORGANOCATALYTIC ASYMMETRIC CYCLOADDITIONS

5.1. Diels–Alder and Related [4 + 2]-Cycloadditions

5.1.1. Introduction. Since the seminal report by Otto H. Diels and Kurt Alder in 1928,[205] the reaction that bears their name has become one of the most interesting and used

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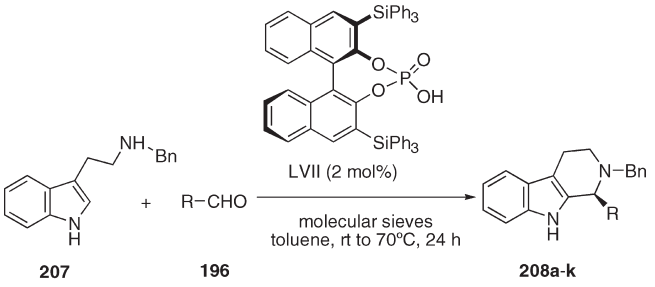
transformations in organic chemistry. The Diels−Alder reaction is formally a [4 + 2]-cycloaddition that gives access to a broad range of six-membered rings in a highly regio- and stereocontrolled fashion. Several research groups focused their research efforts in developing new and improved versions of the Diels−Alder reaction. They uncovered a wide variety of dienes and dienophiles, achieving important modifications such as hetero-Diels−Alder reactions, which allow the synthesis of heteroatom-substituted six-membered rings.[206] These more than 70 years of research have provided detailed information about the mechanism as well as on different factors that have an considerable importance in the final output of the reaction.[207] During this time, the Diels−Alder reaction evolved from achiral reactions to the use of chiral auxiliaries to obtain enantiopure compounds,[3] until the discovery of enantioselective Diels−Alder reactions promoted by chiral catalysts. Summarizing the magnificient history of the Diels−Alder reaction, the major achievements were the first asymmetric Diels−Alder reaction reported by Korolev and Mur in 1948,[209] the discovery that Lewis acids can catalyze efficiently the reaction, or the development of new enantio- and catalytic methods using metal-free catalysts like those reported by MacMillan in 2000.[20]

In this chapter, we will describe the most important advances in the organocatalytic Diels−Alder reaction reported as a function of the type of catalyst used.

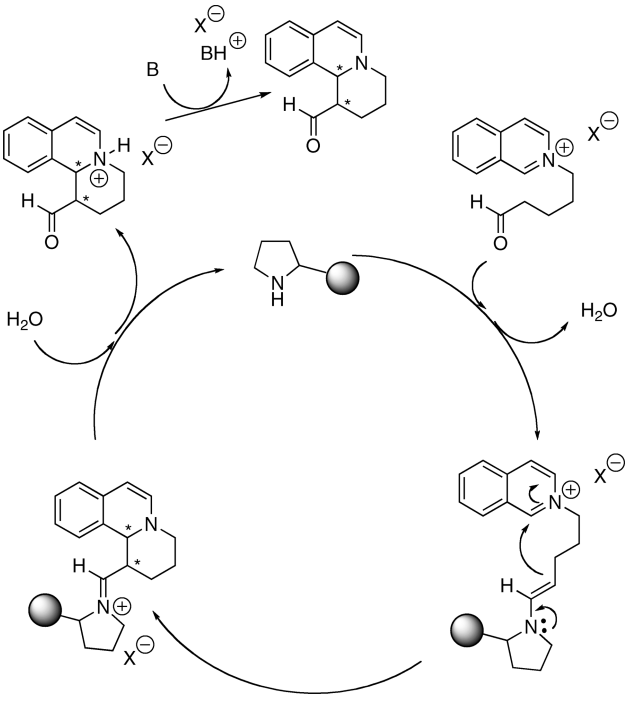
Scheme 91. Catalytic Asymmetric PS Reactions of *N*-Benzyltryptamine



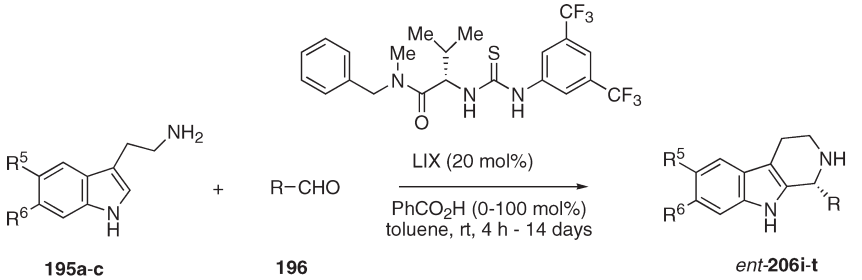
207 196 208a-k

208a (R = *p*-BrPh): 92%, 85% ee
208b (R = *p*-NO_2Ph): 95%, 87% ee
208c (R = *p*-CF_3Ph): 93%, 83% ee
208d (R = *m*-ClPh): 92%, 20% ee
208e (R = *m,m*-$(CF_3)_2$Ph): 82%, 0% ee
208f (R = *i*-Pr): 90%, 81% ee
208g (R = *n*-Pent): 77%, 68% ee
208h (R = CH_2CH_2Ph): 93%, 8% ee
208i (R = Bn): 0%, –% ee
208j (R = Ph): 83%, 61% ee
208k (R = *p*-MeOPh): 84%, 80% ee

Scheme 93. Mechanistic Proposal for the Chiral Secondary Amine-Catalyzed Synthesis of 1,2-Dihydroisoquinolines from 2-(5-Oxopentyl)isoquinolinium Salts



Scheme 92. Catalytic Enantioselective Protio-PS Reactions

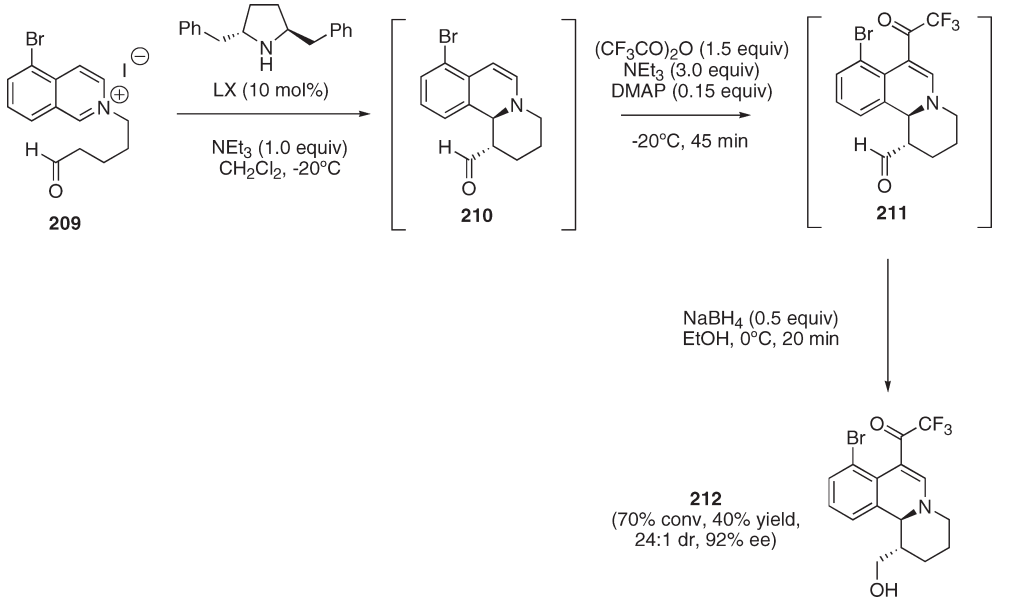


195a-c 196 *ent*-206i-t

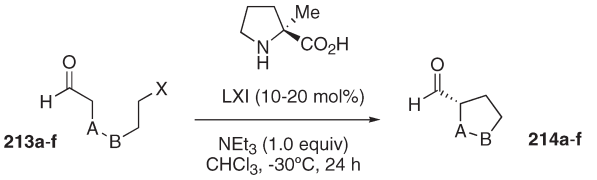
ent-**206i** (R^5 = H, R^6 = OMe, R = *n*-Pent): 74%, 86% ee
ent-**206j** (R^5 = H, R^6 = OMe, R = *i*-Pr): 90%,94% ee
ent-**206k** (R^5 = H, R^6 = OMe, R = Ph): 94%, 86% ee
ent-**206l** (R^5 = H, R^6 = OMe, R = *p*-ClPh): 78%, 94% ee
ent-**206m** (R^5 = H, R^6 = OMe, R = *p*-FPh): 81%, 92% ee
ent-**206n** (R^5 = H, R^6 = OMe, R = *p*-BrPh): 79%, 94% ee
ent-**206o** (R^5 = H, R^6 = OMe, R = *m*-BrPh): 87%, 94% ee
ent-**206p** (R^5 = H, R^6 = OMe, R = *o*-BrPh): 74%, 95% ee
ent-**206q** (R^5 = H, R^6 = OMe, R = *p*-MeOPh): 78%, 85% ee
ent-**206r** (R^5 = OMe, R^6 = H, R = *p*-ClPh): 73%, 89% ee
ent-**206s** (R^5 = OMe, R^6 = H, R = *o*-BrPh): 82%, 99% ee
ent-**206t** (R^5 = R^6 = H, R = *o*-BrPh): 45%, 95% ee

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 94. Organocatalytic Asymmetric Synthesis of a 1,2-Dihydroisoquinoline Derivative

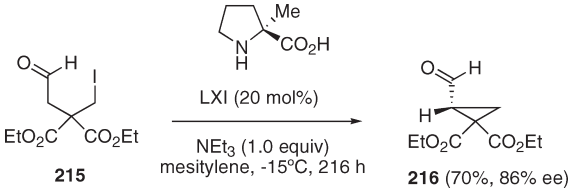


Scheme 95. Catalytic Asymmetric Intramolecular α-Alkylation of Aldehydes Leading to Five-Membered Rings



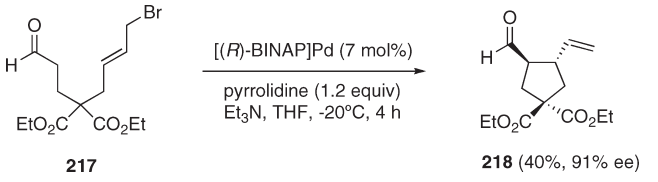
214a (A = $C(CO_2Et)_2$, B = CH_2, X = I): 92%, 95% ee
214b (A = $C(CO_2Et)_2$, B = CH_2, X = Br): 90%, 94% ee
214c (A = $C(CO_2Et)_2$, B = CH_2, X = OTs): 20%, 91% ee
214d (A = $C(CO_2Bn)_2$, B = CH_2, X = I): 94%, 95% ee
214e (A = CH_2, B = $C(CO_2Et)_2$, X = Br): 92%, 96% ee
214f (A = NTs, B = CH_2, X = I): 52%, 91% ee (after reduction)

Scheme 96. Enantioselective Synthesis of a Cyclopropane by Intermolecular Alkylation of an Aldehyde



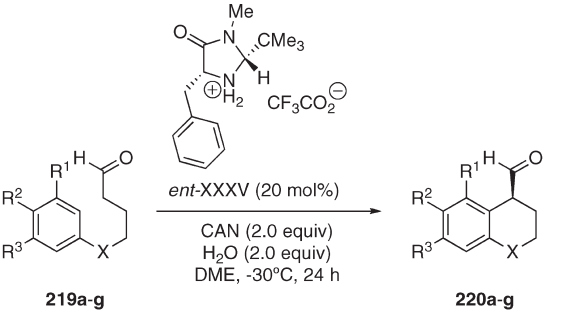
216 (70%, 86% ee)

Scheme 97. Catalytic Asymmetric Intramolecular Tsuji–Trost Allylation

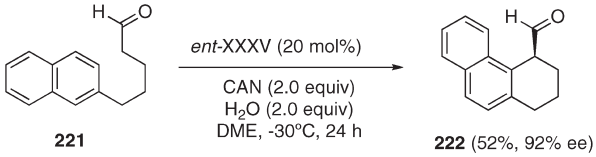


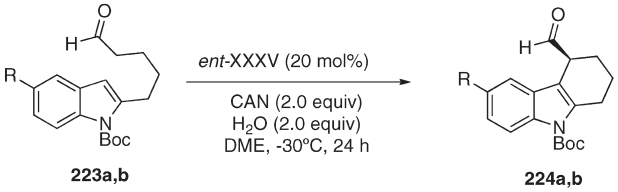
218 (40%, 91% ee)

Scheme 98. Intramolecular α-Arylation of Aldehydes via Organo-SOMO Catalysis, According to Nicolaou et al.[121]



220a (R^1 = R^3 = OMe, R^2 = H, X = CH_2): 80%, 94% ee
220b (R^1 = R^3 = OMe, R^2 = H, X = O): 76%, 86% ee
220c (R^1 = OMe, R^2 = R^3 = H, X = CH_2): 77%, 97% ee
220d (R^1 = R^3 = OMe, R^2 = H, X = NTs): 76%, 87% ee
220e (R^1 = H, R^2 = R^3 = OMe, X = CH_2): 58%, 94% ee
220f (R^1 = H, R^2 ,R^3 = OCH_2O, X = CH_2): 54%, 84% ee
220g (R^1 = H, R^2 = Me, R^3 = OMe, X = CH_2): 56%, 90% ee

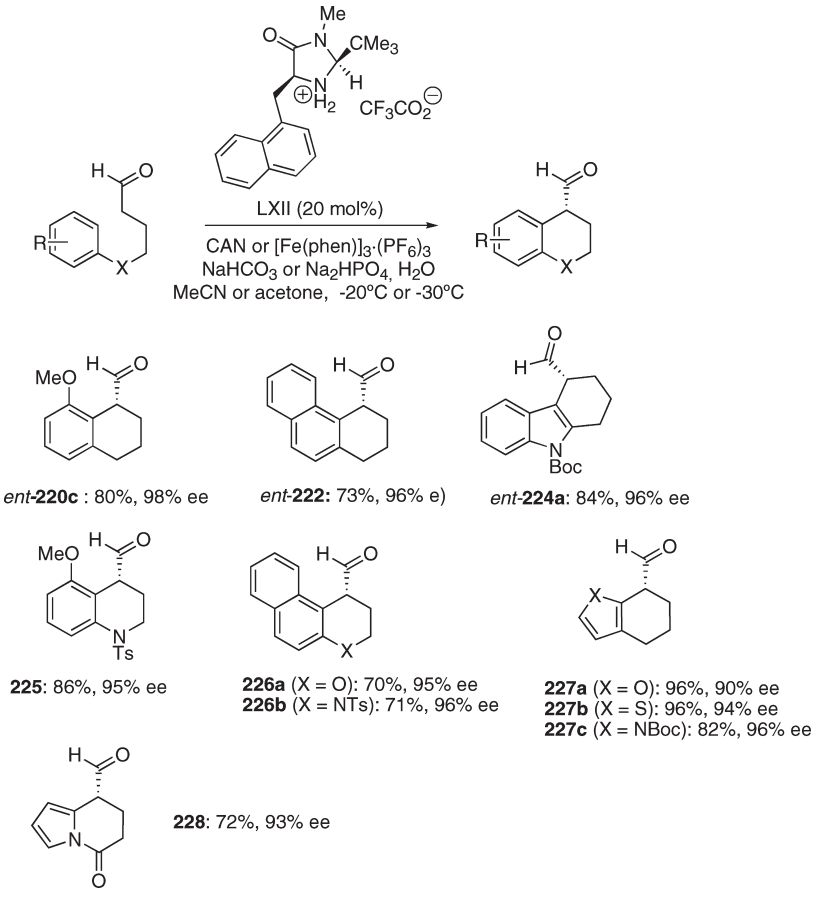




224a (R = H): 64%, 98% ee
224b (R = OMe): 55%, 94% ee

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 99. Alternative Procedure for the Organo-SOMO Intramolecular α-Arylation of Aldehydes



5.1.2. Organocatalytic Lewis Base-Catalyzed Diels–Alder Reaction. *5.1.2.1. Iminium Activation.* The use of amines as chiral catalysts in organocatalysis has been extensively employed since the seminal paper of MacMillan in 2000.[20] In this work, MacMillan and co-workers use as a catalytic system iminium ions formed by the reversible reaction of α,β-unsaturated aldehydes with secondary amines. The use of chiral amines could transfer this enantioinformation to the process rendering chiral cyclohexanes.

MacMillan and co-workers used as chiral catalysts different salts of imidazolidinones. In particular, the imidazolidinone hydrochloride **XXVIII** is able to catalyze the reaction between different α,β-unsaturated aldehydes (**277**) and cyclopentadiene (**278**), affording the cycloadducts **279** in good yields and with excellent stereoselectivities, as it is shown in Scheme 130.

Importantly, the reaction allows for the use of different β-substituted α,β-unsaturated aldehydes and is also general with respect to the diene structure; however, α-substituted aldehydes were not tested.

The mechanism proposed by the authors is described in Scheme 131. It was reasoned that LUMO-lowering activation of the enal dienophile could be effected by the formation of the unsaturated iminium ion **B**. This iminium ion is activated enough to react with the diene to furnish the saturated iminium ion **A**, which after hydrolysis provides the enantioenriched Diels–Alder product **279** and regenerates the imidazolidinone salt for a new catalytic cycle.[210]

An important improvement of the reaction was made by the same authors when they extended the scope of the reaction to α,β-unsaturated ketones (**284**) using the imidazolidinone salt **LXXVIII** as the catalyst (Scheme 132).[211]

In this report, the final products were obtained with good enantiocontrol, with the exception of methyl ketones (that gave low enantioselectivities) and of isopropyl ketones that did not show any enantioinduction and rendered the product in poor yields, probably for steric reasons. The scope of the reaction regarding the diene structure was broad, allowing the enantioselective access to a range of alkyl-, alkoxy-, amino-, or aryl-substituted cyclohexenyl ketones.

On the basis of these results, MacMillan and co-workers applied this methodology to the synthesis of solanapyrone D (**289**, a phytotoxic polyketide isolated from the fungus *Alternaria solani*), using as a key step an asymmetric intramolecular Diels–Alder reaction (Scheme 133).[212]

Moreover, in this report they showed that this methodology could be generally applied to intramolecular Diels–Alder reactions, as shown in Scheme 134.

Some other groups applied the same intramolecular Diels–Alder methodology for the synthesis of natural products. For example, Koskinen[213] and Christmann[214] reported the synthesis of amanimol A and B, respectively, using as a key step the intramolecular Diels–Alder reaction developed by MacMillan (Scheme 135).

Several other research groups have applied the intramolecular Diels–Alder strategy developed by MacMillan in total synthesis,

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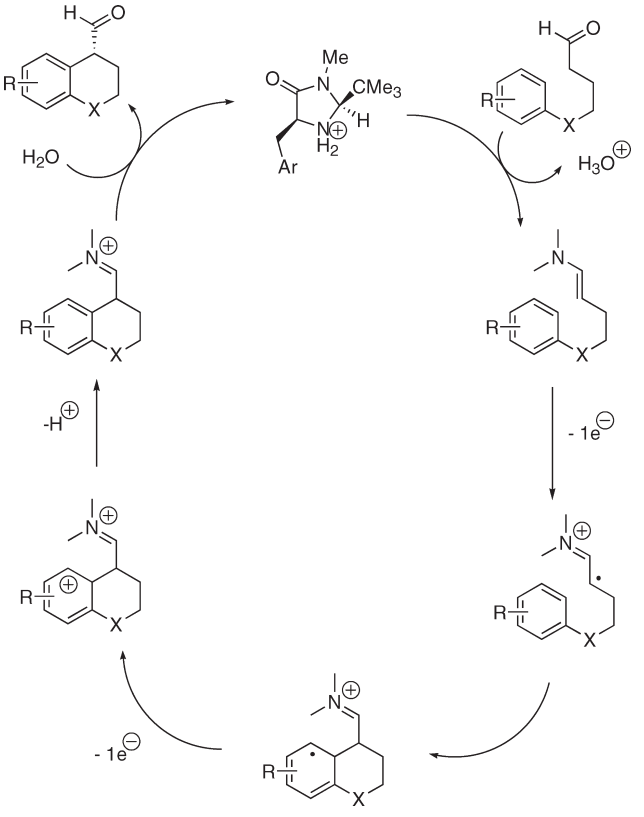
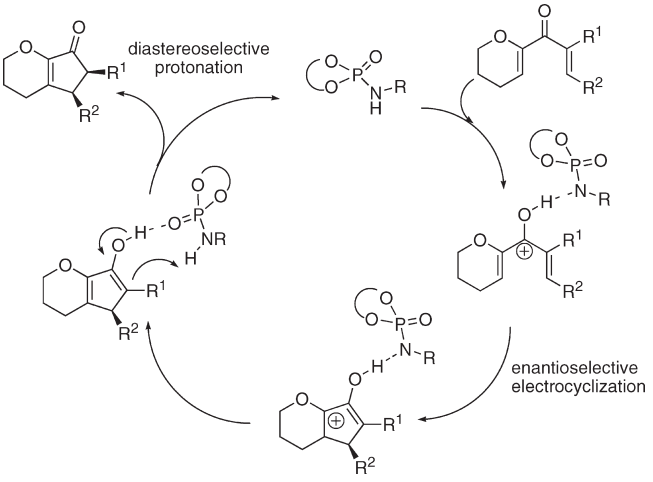
and some excellent results were reported by Hong[215] in the synthesis of aromatic benzaldehydes via [4 + 2]- or [3 + 3]-cycloadditions depending on the substitution of the α,β-unsaturated aldehydes and subsequent oxidation of the Diels–Alder adduct with DDQ.

More importantly, the organocatalytic intramolecular Diels–Alder strategy was applied by Holmes et al. to the synthesis of the eunicellin core, a common structural motif in many natural

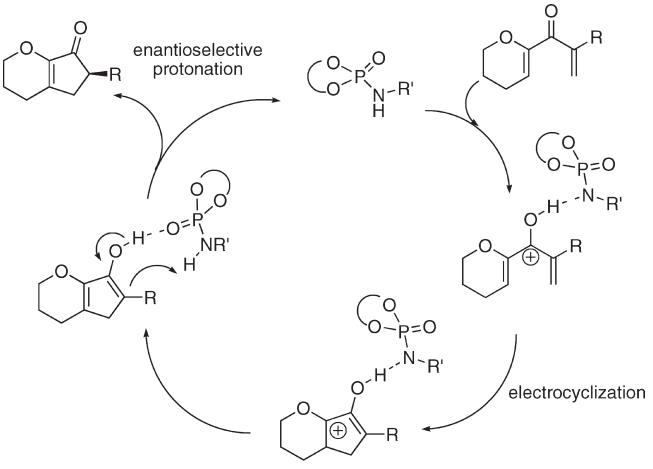
Scheme 100. Proposed Catalytic Cycle for the Intramolecular α-Arylation of Aldehydes via Organo-SOMO Catalysis



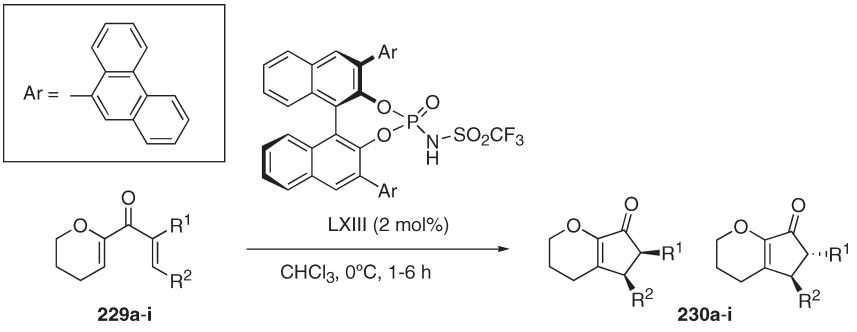
Scheme 102. Proposed Mechanism for the Enantioselective Brønsted Acid-Catalyzed Nazarov Cyclization



Scheme 103. Mechanism for the Enantioselective Brønsted Acid-Catalyzed Nazarov Cyclization of Dienones 231



Scheme 101. Enantioselective Brønsted Acid-Catalyzed Nazarov Cyclization



229a-i **230a-i**

230a (R^1 = Me, R^2 = Ph): 88%, 6:1 *cis/trans*, 87% ee (*cis*), 95% ee (*trans*)
230b (R^1 = *n*-Pent, R^2 = Ph): 78%, 3.2:1 *cis/trans*, 91% ee (*cis*), 91% ee (*trans*)
230c (R^1 = Me, R^2 = 2-Naphthyl): 92%, 9.3:1 *cis/trans*, 88% ee (*cis*), 98% ee (*trans*)
230d (R^1 = Et, R^2 = Ph): 61%, 4.3:1 *cis/trans*, 92% ee (*cis*), 96% ee (*trans*)
230e (R^1 = *n*-Pr, R^2 = Ph): 85%, 3.2:1 *cis/trans*, 93% ee (*cis*), 91% ee (*trans*)
230f (R^1 = *n*-Pr, R^2 = *p*-Tol): 77%, 2.6:1 *cis/trans*, 91% ee (*cis*), 90% ee (*trans*)
230g (R^1 = *n*-Pr, R^2 = *p*-BrPh): 87%, 4.6:1 *cis/trans*, 92% ee (*cis*), 92% ee (*trans*)
230h (R^1 = *n*-Pr, R^2 = *m*-BrPh): 72%, 3.7:1 *cis/trans*, 90% ee (*cis*), 91% ee (*trans*)
230i (R^1, R^2 = $(CH_2)_4$): 68%, 86% ee (*cis*)

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

products.[216] The use of imidazolidinone hydrochloride **XXVIII** as a catalyst gave the exo-selective intramolecular Diels–Alder reaction that furnished the tricyclic core of eunicellin in excellent yields and enantioselectivities (Scheme 136).

Kerr and co-workers used a similar strategy for the preparation of a key intermediate in the synthesis of (+)-hapalindole Q.[217] In this example, the enantioselectivity is good, but on the other hand, a substoichiometric amount of the catalyst (40 mol %) is needed for a low chemical yield and a moderate diastereomeric ratio in favor of the endo isomer.

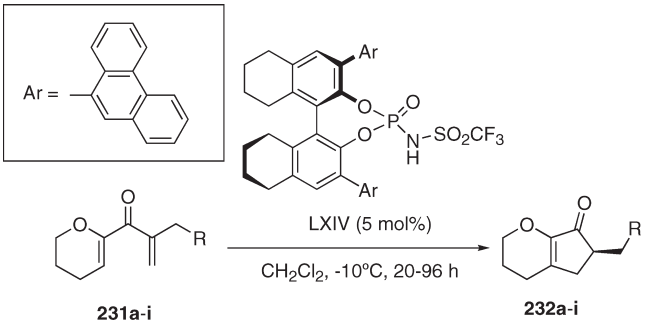
In 2007, Hayashi and Gotoh developed an exo-selective Diels–Alder reaction of α,β-unsaturated aldehydes catalyzed by the diarylprolinol silyl ether **LXXIX** in acidic conditions, obtaining the cycloadducts in good yields and excellent diastereoselectivities, as shown in Scheme 137.[218] Remarkably, the diastereoselectivities are better than those reported by MacMillan, and the catalyst loading could be reduced to 2 mol % without loss of stereoselectivity. The scope of the reaction was rather good, allowing for the use of aliphatic, aromatic, and heteroaromatic substituted enals with good enantioselectivity. However, no α-substituted unsaturated aldehydes were employed. The same research group reported a year later the same reaction using water as a solvent.[219]

In 2005, Ogilvie[220] and co-workers reported the same reaction in water catalyzed this time by a camphor-derived hydrazine (**LXXX**). The products were obtained in high yields and with high enantioselectivities. However, the diastereoselectivity was rather low, affording a slight excess of exo product, as depicted in Scheme 138.

Bonini and co-workers synthesized a new set of catalysts based on aziridin-2-yl-diphenylmethanol (**LXXXI**). They tested these catalysts in the Diels–Alder cycloaddition between α,β-unsaturated aldehydes and cyclopentadiene.[221] However, as shown in Scheme 139, the reaction rendered the cycloadducts in low enantioselectivities.

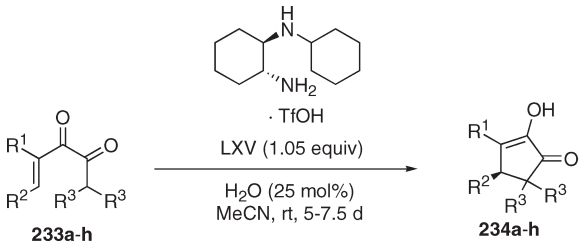
Lee and co-workers developed later on a sulfonylhydrazine derived from camphorsulfonic acid. They tested it as a catalyst in the Diels–Alder reaction of unsaturated aldehydes and cyclopentadiene, obtaining the final compounds with good yields and enantioselectivities but with almost no diastereoselectivity.[222]

Scheme 104. A Catalytic Asymmetric Electrocyclization–Protonation Reaction



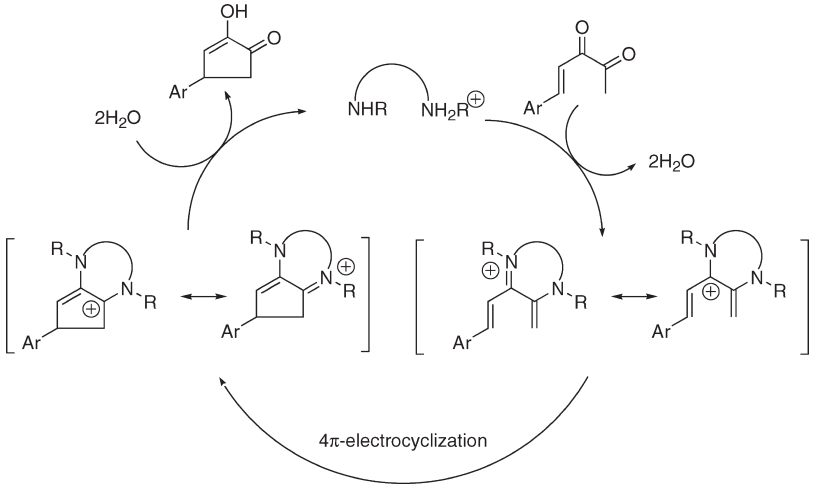
232a (R = *n*-Bu): 83%, 78% ee
232b (R = H): 44%, 70% ee
232c (R = Me): 72%, 70% ee
232d (R = Et): 71%, 76% ee
232e (R = *n*-Pent): 79%, 78% ee
232f (R = Ph): 81%, 71% ee
232g (R = *p*-ClPh): 93%, 67% ee
232h (R = *p*-MeOPh): 87%, 71% ee
232i (R = *m*,*p*-$(MeO)_2$Ph): 49%, 67% ee

Scheme 106. Chiral Diamine-Promoted Enantioselective Nazarov Cyclization of α-Ketoenones



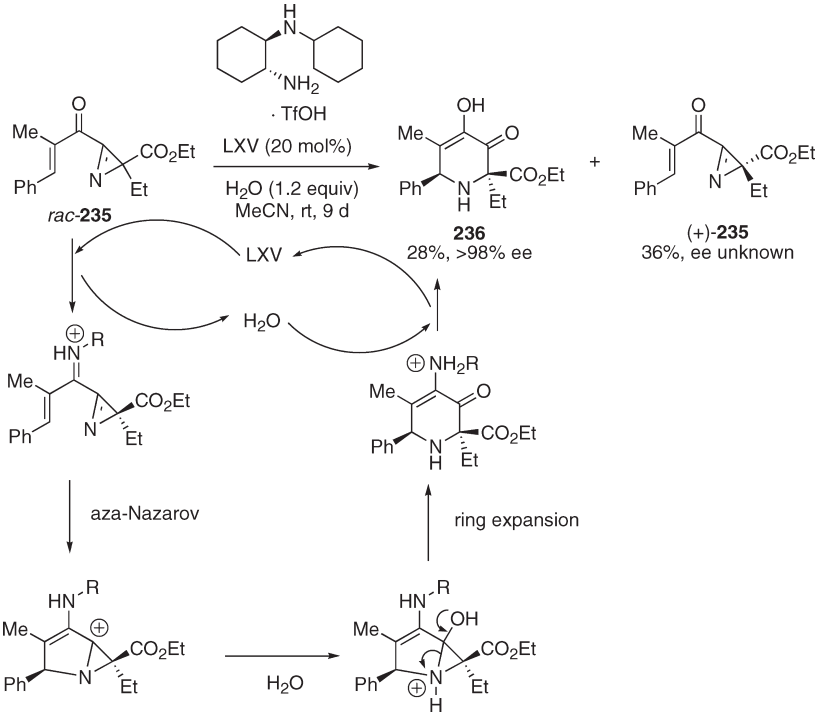
234a (R^1 = Me, R^2 = Ph, R^3 = H): 60%, 94% ee
234b (R^1 = Me, R^2 = Ph, R^3 = Me): 66%, >98% ee
234c (R^1 = Me, R^2 = Me, R^3 = Me): 49%, >98% ee
234d (R^1 = Me, R^2 = Et, R^3 = Me): 65%, >98% ee
234e (R^1,R^2 = $(CH_2)_4$, R^3 = Me): 62%, >98% ee
231f (R^1 = Ph, R^2 = Ph, R^3 = H): 11%, 80% ee
234g (R^1 = Me, R^2 = *p*-MeOPh, R^3 = H): 20%, 82% ee
234h (R^1 = *p*-MeOPh, R^2 = Ph, R^3 = H): 24%, 62% ee

Scheme 105. Enamine–Iminium Ion Mechanism for the Nazarov Reaction

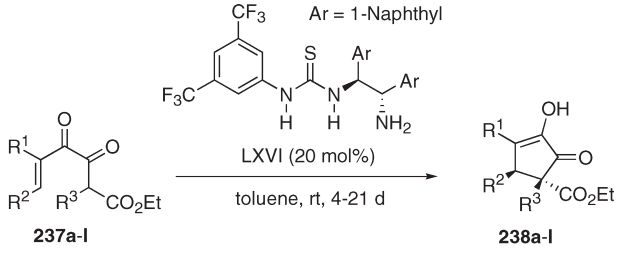


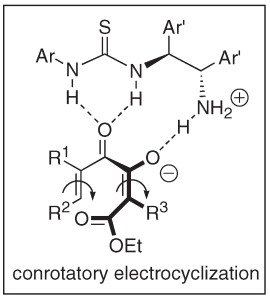
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 107. Organocatalytic Asymmetric Kinetic Resolution and Aza-Nazarov Cyclization-Rearrangement of a Ketoazirine



Scheme 108. Organocatalytic Asymmetric Nazarov Cyclization Mediated by a Chiral Aminothiourea





238a (R^1 = Me, R^2 = Ph, R^3 = Me): 67%, 81% ee
238b (R^1 = Me, R^2 = Ph, R^3 = Et): 65%, 90% ee
238c (R^1 = Me, R^2 = *p*-MeOPh, R^3 = Et): 60%, 91% ee
238d (R^1 = Me, R^2 = *p*-ClPh, R^3 = Et): 42%, 84% ee
238e (R^1 = Me, R^2 = 3,4-(OCH_2O)Ph, R^3 = Et): 58%, 89% ee
238f (R^1 = Ph, R^2 = Ph, R^3 = Et): 70%, 82% ee
238g (R^1 = Me, R^2 = Ph, R^3 = Ph): 70%, 87% ee
238h (R^1 = Me, R^2 = *p*-Tol, R^3 = Ph): 87%, 96% ee
238i (R^1 = Me, R^2 = *p*-ClPh, R^3 = Ph): 75%,85% ee
238j (R^1 = Me, R^2 = 3,4-(OCH_2O)Ph, R^3 = Ph): 95%, 85% ee
238k (R^1 = Me, R^2 = 2-Furyl, R^3 = Ph): 60%,91% ee
238l (R^1 = Et, R^2 = *p*-Tol, R^3 = Ph): 85%, 82% ee
238m (R^1 = OEt, R^2 = Ph, R^3 = Ph): 60%, 80% ee

In 2010, Zhang and co-workers reported the same reaction catalyzed by C_2-symmetric bipyrrolidines and using water as a solvent, with excellent results.[223]

Maruoka and co-workers reported the use of binaphthyl-based diamines that afford exo selectivity in the Diels−Alder reaction between unsaturated aldehydes and cyclopentadiene.[224] The reaction was carried out in trifluoromethylbenzene as a solvent and in the presence of 10% molar amount of *p*-toluenesulfonic acid (Scheme 140).

In order to explain the unusual diastereoselectivity, the authors proposed the mechanism depicted in Scheme 141. According to their proposal, the methylamino group in the diamine-TsOH catalyst would react with the α,β-unsaturated aldehyde in first instance to form the iminium intermediate **C** by dehydration of the protonated aminal **B**. This iminium would react with cyclopentadiene to give the exo adduct **D** under the influence of the sterically hindered binaphthyl moiety. The resulting iminium intermediate upon hydrolysis renders the exo cycloadduct

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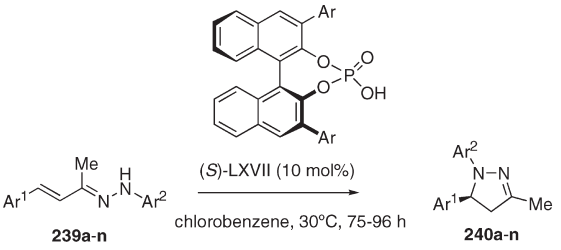
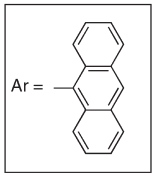
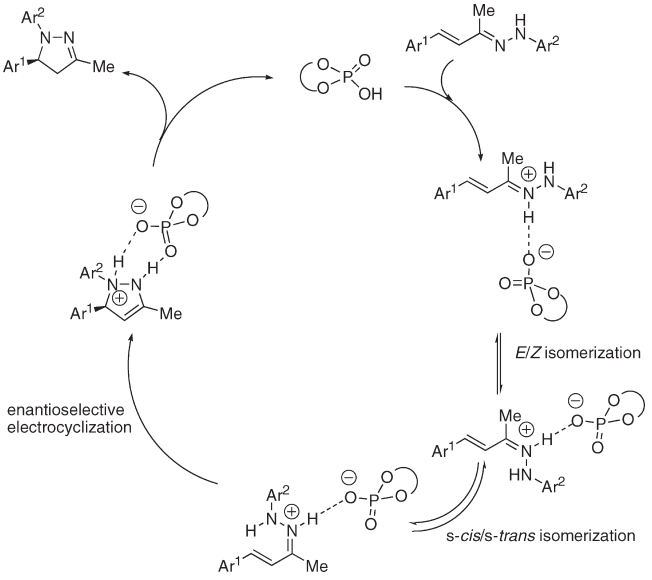
Scheme 109. Enantioselective Synthesis of Pyrazolines by Asymmetric Organocatalytic 6π Electrocyclization





240a (Ar^1 = Ar^2 = Ph): 92%, 76% ee
240b (Ar^1 = *p*-FPh, Ar^2 = Ph): 94%, 88% ee
240c (Ar^1 = *p*-ClPh, Ar^2 = Ph): 96%, 90% ee
240d (Ar^1 = *p*-BrPh, Ar^2 = Ph): 95%, 90% ee
240e (Ar^1 = *p*-NO_2Ph, Ar^2 = Ph): 93%,92% ee
240f (Ar^1 = *p*-CF_3Ph, Ar^2 = Ph): 88%, 92% ee
240g (Ar^1 = *m*-FPh, Ar^2 = Ph): 91%, 92% ee
240h (Ar^1 = *m*-ClPh, Ar^2 = Ph): 96%, 92% ee
240i (Ar^1 = *m*-BrPh, Ar^2 = Ph): 95%, 92% ee
240j (Ar^1 = *m*-NO_2Ph, Ar^2 = Ph): 99%,96% ee
240k (Ar^1 = *m*-BrPh, Ar^2 = *p*-MeOPh): 91%, 84% ee
240l (Ar^1 = *m*-Br-*p*-MeOPh, Ar^2 = Ph): 93%, 90% ee
240m (Ar^1 = 3,4-(OCH_2O)Ph, Ar^2 = Ph): 85%, 86% ee
240n (Ar^1 = *p*-$MeSO_2$Ph, Ar^2 = *p*-FPh): 88%, 76% ee

Scheme 110. Proposed Catalytic Cycle for the Cyclization of α,β-Unsaturated Aryl Hydrazones



and regenerates the catalyst. A strong limitation of this methodology is as we cited before, the impossibility of using α-substituted α,β-unsaturated aldehydes.

In order to overcome this limitation, several research groups have applied chiral primary amines that have emerged as a new and powerful family of organocatalysts.

Using this type of catalyst, Ishihara and Nakano developed a Diels–Alder reaction of α-acyloxyacroleins **305**. As a catalyst they use compound **LXXXIII**, which bears primary, secondary, and tertiary amino groups, in the presence of a Brønsted acid.[225] The scope of the rection was demonstrated by extending the process to different dienes, such as cyclohexadiene and isoprene. The expected cycloadducts **307** were obtained in excellent yields and with good enantioselectivities (Scheme 142).

In 2006, the same authors reported the use of BINAM (**LXXXIV**) as a catalyst for the Diels–Alder reaction between cyclopentadiene and α-(cyclohexylcarbonyloxy)acrolein.[226] The reaction was carried out in the presence of trifluoromethanesulfonimide and was extended to other dienes such as 1,3-cyclohexadiene (Scheme 143).

In order to explain the enantioselectivity of the reaction and based both on ^{1}H NMR studies and the X-ray structural analysis of α-(cyclohexylcarbonyloxy)acrolein, a transition state was proposed (Figure 27) in which both the aldimine and the acyloxy group are activated by the ammonium protons although through a weak nonlinear hydrogen bond. In these trifluoromethanesulfonimide-activated **TSI**, the diene should approach the *si* face of the dienophile from the less hindered face to give the (2*S*)-exo adduct.

Triamine **LXXXIII** was also used by Ishihara et al. in the Diels–Alder reaction of cyclic and acyclic dienes with α-(phthalimido)-acrolein, providing cyclic α-quaternary α-amino acid derivatives.[227] When the triamine catalyst was used with pentafluorobenzenesulfonic acid, good yields, very high endo selectivity, and very good enantioselectivities were obtained (Scheme 144).

The authors used this methodology for the preparation of norbornane 2-amino-2-methanol derivatives and (−)-altemicidin.

In 2010, Zhao and co-workers reported the Diels–Alder reaction between 2-vinylindoles (**312**) and α,β-unsaturated aldehydes, catalyzed by secondary amines.[228] In this case, the authors run the reaction in toluene using as additive CF_3SO_2H; as catalyst the best secondary amine was a 4-hydroxydiphenylprolinol derivative (**LXXXV**) that gives good yields and diastereoselectivities and excellent enantioselectivities for the major endo adduct. The scope of the reaction is broad in terms of vinylindoles and in terms of unsaturated aldehydes, using aliphatic and aromatic aldehydes without loss of stereoselectivity (Scheme 145). However, some limitations can still be found, such as the impossibility of using α-substituted or β,β-disubstituted unsaturated aldehydes.

Moreover, Zhao and co-workers applied this methodology to the synthesis of the core structure of vinvorine.

In 2010, Nakano et al. reported a similar Diels–Alder reaction leading to the synthesis of isoquinuclidines; in the same report they show the applicability of this methodology, synthesizing an important intermediate for the synthesis of oseltamivir.[229] The reaction between 1,2-dihydropyridines and enals is simply catalyzed by secondary amine catalysts, affording the final compounds in good yields, excellent enantioselectivities, and in highly endo fashion.

5.1.2.2. Enamine Activation. In this section, we will disclose the different examples of organocatalytic Diels–Alder reactions where the activation of the diene is done via the formation of an enamine between a carbonyl group and an amine. The organocatalytic Diels–Alder reaction via enamine activation is normally based on the reaction between an α,β-unsaturated ketone and a reactive alkene. The first step of this reaction, as shown in Scheme 146, consists of the formation of the enamine of the enone, affording the diene. Two possible pathways are commonly accepted for the subsequent Diels–Alder reaction: (a) the concerted mechanism between the formed diene and the dienophile and then hydrolysis to afford the final product (pathway A) or (b) the two-step mechanism consisting first of the enamine attack to the dienophile via a Michael reaction followed by again an intramolecular Michel attack of the formed anion to the enone (pathway B).

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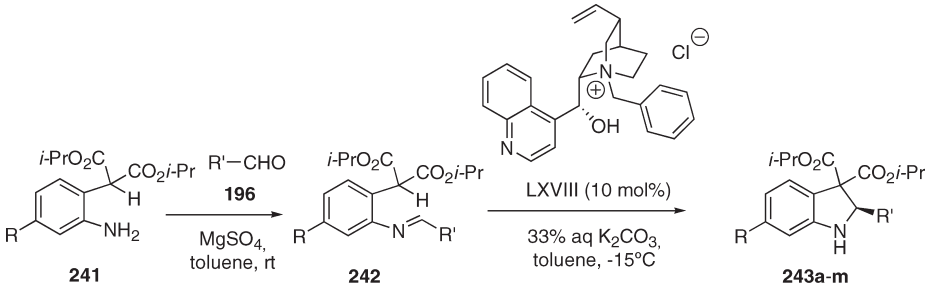
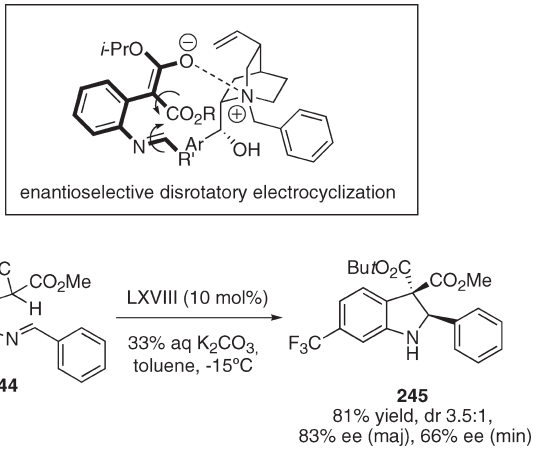
Scheme 111. Enantioselective Synthesis of Functionalized Indolines by Organocatalytic Asymmetric 6π Electrocyclization



243a (R = CF_3, R' = Ph): 87%, 94% ee
243b (R = CF_3, R' = *m*-ClPh): 84%, 86% ee
243c (R = CF_3, R' = *p*-ClPh): 69%, 93% ee
243d (R = CF_3, R' = *m*-NO_2Ph): 75%, 98% ee
243e (R = CF_3, R' = *m*-MeOPh): 76%, 92% ee
243f (R = CF_3, R' = *p*-BrPh): 80%, 93% ee
243g (R = CF_3, R' = 2-Naphthyl): 90%, 85% ee
243h (R = CF_3, R' = *o*-ClPh): 78%, 91% ee
243i (R = CF_3, R' = *o*-NO_2Ph): 89%, 76% ee
243j (R = H, R' = *p*-BrPh): 70%, 90% ee
243k (R = H, R' = 2-Furyl): 68%, 86% ee
243m (R = H, R' = *i*-Pr): 52%, 73% ee
243n (R = H, R' = Cyclohexyl): 94%, 90% ee
243o (R = F, R' = *p*-BrPh): 67%, 91% ee
243p (R = F, R' = Ph): 72%, 89% ee

Scheme 112. Mechanistic Hypothesis and Diastereo- and Enantioselective Cyclization



In 2003, Ohsawa and co-workers reported the first catalytic asymmetric addition reaction of 3,4-dihydro-β-carboline (**314**) using L-proline (**I**) as the chiral catalyst.[230] When 3-buten-2-one (**284a**) was used as the ketone, an asymmetric aza-Diels−Alder reaction was observed (Scheme 147):

The same authors in 2006 applied this methodology to the total synthesis of *ent*-dihydrocorynantheol (**320**) with excellent results, as illustrated in Scheme 148.[231]

Yamamoto and co-workers described in 2004 a nitroso Diels−Alder adduct obtained in uniformly high enantioselectivity via a tandem nitroso aldol−Michael reaction using a proline-derived catalyst (**LXXXVI**).[232] The regiochemical outcome of this construction was documented to be the opposite of that of the normal nitroso aldol reaction (Scheme 149).

Córdova and co-workers performed the first complete study of the enantioselective organocatalytic aza-Diels−Alder reaction.[233] The reaction proceeds through a tandem one-pot, three-component Mannich−Michael reaction pathway and is catalyzed by L-proline (**I**) or by one of its derivatives with excellent chemo-, regio- and stereoselectivity (Scheme 150).

In 2007, Córdova and co-workers described the direct amine-catalyzed enantioselective synthesis of bicyclic Diels−Alder products, starting from α,β-unsaturated cyclic ketones (**321**) and nitroolefins (**327**).[234] Bicyclic molecules (**328**) containing four stereocenters were formed with excellent diastereoselectivities and good to high enantioselectivities (Scheme 151). One of the limitations of the reaction was the need to use cyclic enones, given that when acyclic enones were used no reaction was observed. Two years later, Xu and co-workers reported the same reaction in seawater and in brine.[235]

In 2009, Melchiorre and co-workers developed a similar Diels−Alder reaction overcoming the limitations explained above, via an organocascade addition between acyclic enones and nitroalkenes catalyzed by chiral primary amines such as 9-amino-9-deoxyepidihydroquinine **LXXXVII**.[236] The reaction furnishes, via a double Michael addition, the 4-nitrocyclohexanones **329** in very good yields and with excellent stereoselectivities (Scheme 152).

A related approach was reported by Melchiorre and co-workers in 2009, for the synthesis of spiro compounds.[237] Unsaturated oxindoles **330** react with unsaturated ketones under catalysis by primary amines via a (formally) Diels−Alder reaction to furnish the spirocyclic compounds **331** in good yields and excellent enantioselectivities. The use of 2-fluorobenzoic acid as a cocatalyst is of paramount importance for the high stereoselectivity of the reaction (Scheme 153).

A different pathway takes place in an inverse-electron-demand hetero-Diels−Alder (IEDHDA) reaction between an aldehyde and an enone. The reaction begins with the enamine formation from the enolizable aldehyde, followed by a Michael addition of

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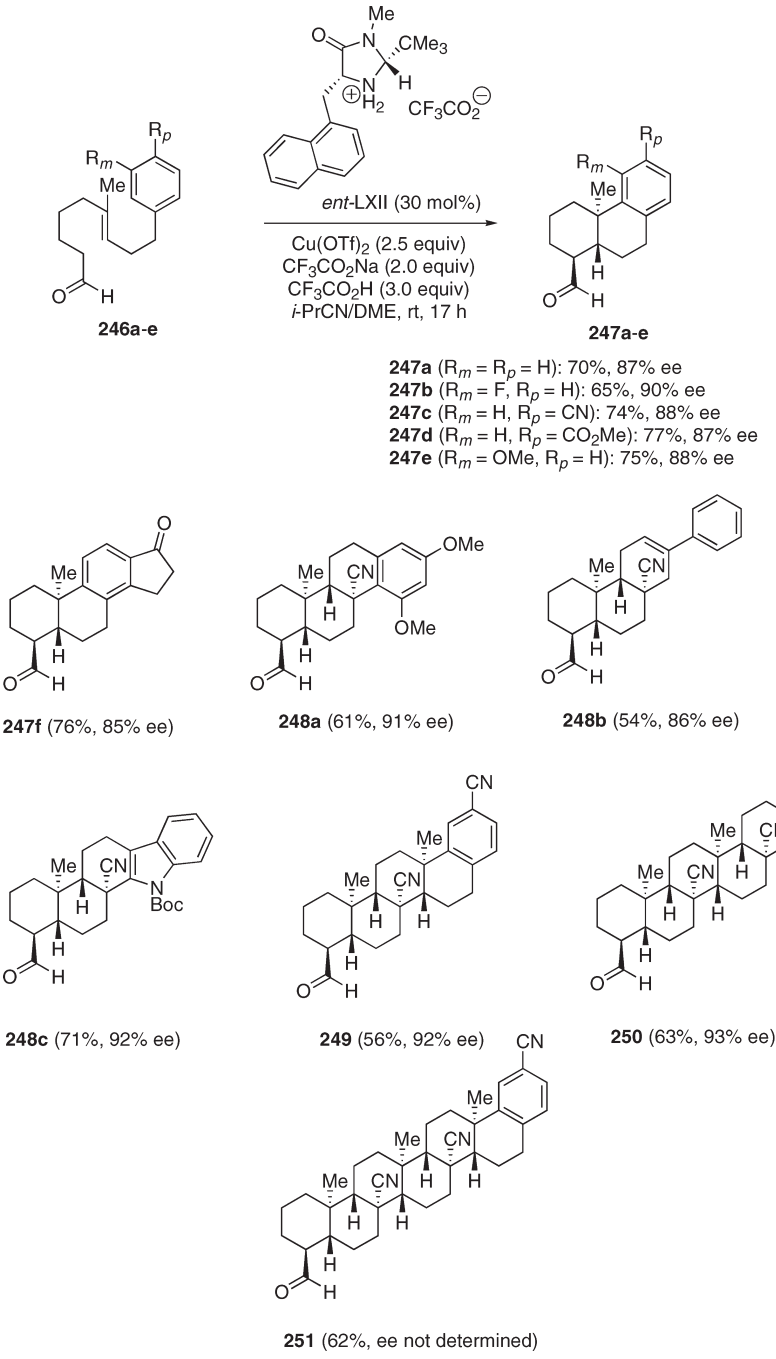
Scheme 113. Stereoselective Polycyclization by Organo-SOMO Catalysis



the preformed enamine to the enone. Subsequently, an intramolecular hemiacetalization takes place, rendering the final adduct as it is shown in Scheme 154.

In 2008, Liu and co-workers published an asymmetric IEDHDA reaction of α,β-unsaturated trifluoromethylketones **333** with aldehydes, which takes place via a Michael−aldol process.[238] The reaction was simply catalyzed by the chiral secondary amine **XLVIII**, and adducts **334** were obtained in high yields with excellent diastereo- and enantioselectivities, after oxidation and dehydration, as shown in Scheme 155. One of the limitations of this methodology seems to be the nature of the aldehyde, so that when some aldehydes such as 3-phenylpropanaldehyde **332f** were used the enantioselectivities decreased drastically.

Jørgensen and Juhl reported in 2003 the first organocatalytic IEDHDA reaction between β,γ-unsaturated-α-keto esters **335** and aldehydes, obtaining, after oxidation, the cyclic lactone in good yields and enantioselectivities.[239] The reaction was efficiently catalyzed by chiral secondary amines such as **LXXXVIII** (Scheme 156). The authors observed that the use of bulky C2-substituted pyrrolidines, such as the diphenylprolinol derivative **XLVIII**, led to low yields.

Following the work of Jørgensen, Zhao, and co-workers reported a novel prolinal dithioacetal derivative as a catalyst

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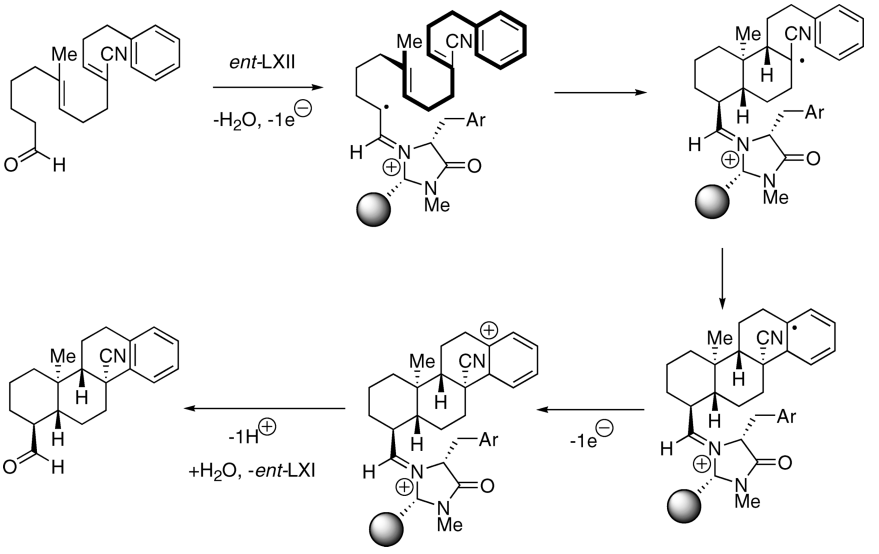
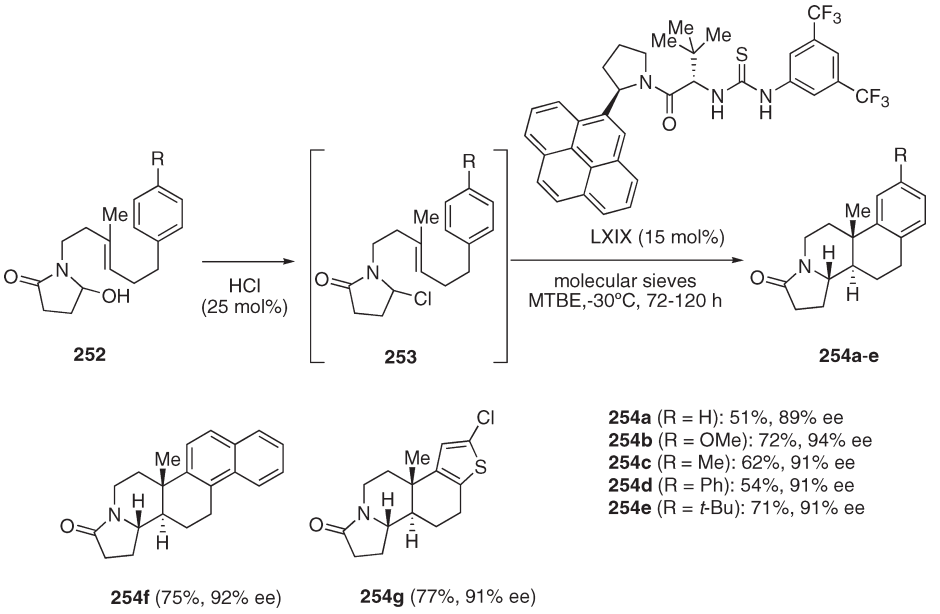
Scheme 114. Organo-SOMO Catalysis Mechanism for Polycyclization



Scheme 115. Enantioselective Thiourea-Catalyzed Cationic Polycyclization



for the hetero-Diels–Alder reaction between enolizable aldehydes and β,γ-unsaturated-α-ketophosphonates.[240] The final pyranones were obtained in good yields and enantioselectivities.

A similar reaction was reported by Ma and co-workers in 2010; the main difference with the works of Jørgensen and Zhao was the use of diphenylprolinol derivatives as catalysts.[241] The reaction afforded the final tetrahydropyran-2-ones in good yields and enantioselectivies.

In 2008, Christmann and co-workers developed an organocatalytic intramolecular Diels–Alder reaction based on the concept of dienamine catalysis.[242] The reaction was efficiently catalyzed by prolinol derivatives such as diphenylprolinol trimethylsilyl ether **XLVIII**, rendering the final cycloadducts with excellent yields and enantioselectivities (Scheme 157). One of the keys for the success of this reaction was the elimination step of the catalyst, probably promoted by the benzoic acid cocatalyst. One of the strongest limitations of this methodology was its exclusive application to intramolecular reactions.

A similar approach was explored by Chen in 2010.[243] In this work, an IEDHDA between electron-deficient dienes and crotonaldehyde was reported. The reaction was simply catalyzed by diphenylprolinol derivatives, rendering the final cycloadducts in good yields and excellent stereoselectivities.

5.1.3. Organocatalytic Asymmetric Diels–Alder Reactions Catalyzed by Brønsted Bases. Brønsted bases have been extensively used in organic chemistry. However, the use of substoichiometric amounts of a chiral base in organocatalysis

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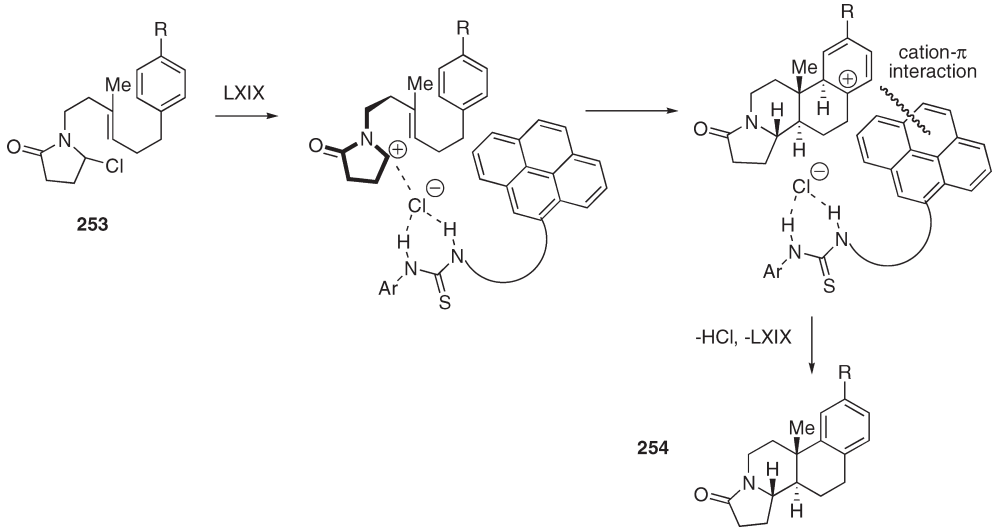
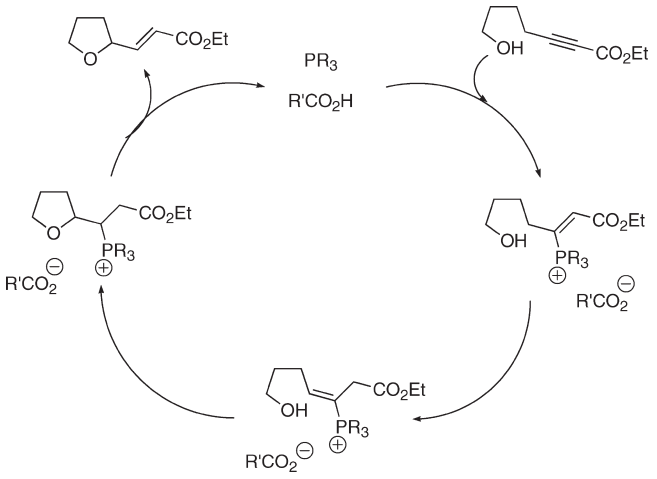
Scheme 116. Mechanistic Proposal for the Enantioselective Thiourea-Catalyzed Cationic Polycyclization



Scheme 117. Possible Mechanism for the Phosphine-Catalyzed Heterocyclization of ω-Hydroxy-2-alkynoates



was not disclosed until the seminal work of Kagan in 1989 on the Diels–Alder reaction between anthrones and maleimides.[38] In this work Riant and Kagan reported on the use of *Cinchona* alkaloids as suitable chiral catalysts for this reaction. The authors used a 10% molar amount of quinidine as a base and they proposed that it acts in a dual manner by activating the maleimide through a hydrogen bond between the hydroxyl group of the quinidine and the carbonyl group of the maleimide and by forming an ionic pair with the deprotonated form of anthrone.

In 2000, Okamura et al. reported the Diels–Alder cycloaddition between 3-hydroxy-2-pyrone **340a** and *N*-benzylmaleimide, also promoted by quinidine.[244] The cycloadduct was obtained in good yields and moderate enantioselectivities and it is a key intermediate in the synthesis of RPR 107880, a P-38 antagonist.

In 2008, Deng and co-workers reported that in the Diels–Alder reaction between 3-hydroxy-2-pyrones **340** and α,β-unsaturated carbonyls, 6′-OH *Cinchona* alkaloid derivatives such as the dihydrocupreine derivative **LXXXIX** afforded much better results in terms of activity and diastereoselectivity than the natural ones. They tested the scope of the reaction with a wide range of α,β-unsaturated ketones **339**, obtaining excellent yields and diastereo- and enantioselectivities (Scheme 158).[245]

Lectka and co-workers developed an organocatalytic Diels–Alder reaction between ketenes (generated in situ from the corresponding acyl chlorides **343** and ethyl(diisopropyl)amine) and *o*-quinones.[246] The reaction was catalyzed by benzoylquinidine **XC** and rendered the corresponding cycloadducts with excellent enantioselectivities in the case of *o*-chloranil (**342**). The same catalytic system was applied to the cyclization of the ketene enolates with *o*-benzoquinone imides[247] and with *o*-benzoquinone diimides,[248] affording the corresponding 1,4-benzoxazinones and quinoxalinones, respectively, in excellent enantioselectivities (Scheme 159).

Lately, the use of guanidines as chiral bases in organocatalysis has grown exponentially.[11s,249] For example, several research groups have developed Strecker reactions, Henry reactions,[250] epoxidations, Michael additions,[251] Mannich reactions,[252] etc.

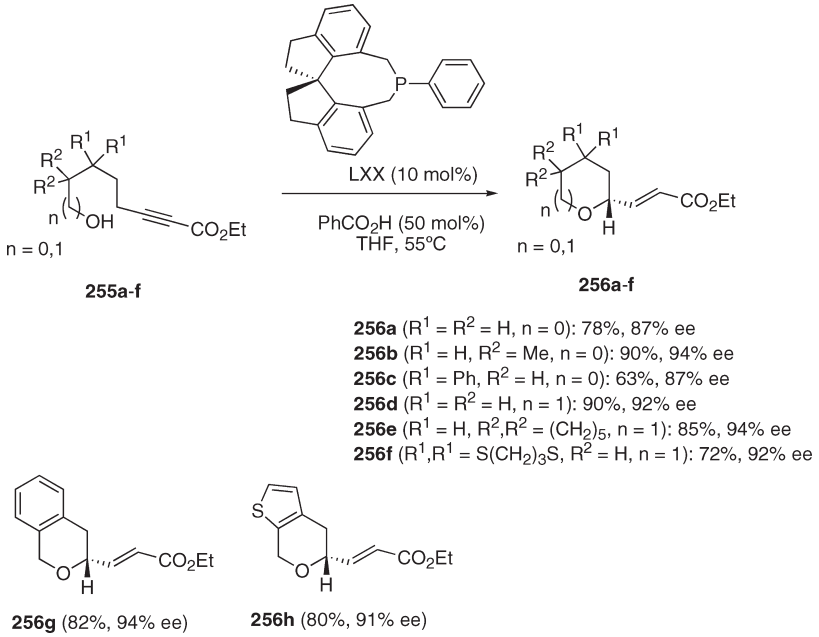
In the Diels–Alder reaction, Tan and co-workers reported the use of chiral bicyclic guanidines as efficient catalysts for the reaction between anthrones (**345**) and maleimides (**346**).[253] The cycloadducts **347** were obtained both in excellent yields and enantioselectivities. Remarkably, the reaction was also extended to *N*-acetoxymaleimide (**346d**), and the corresponding cycloadduct **347d** was easily converted into the *N*-hydroxy derivative (Scheme 160).

In 2008, Göbel and co-workers developed an addition of anthrones to maleimides catalyzed by metal-free bis(oxazolines), with moderate enantioselectivities (39–70% ee).[254]

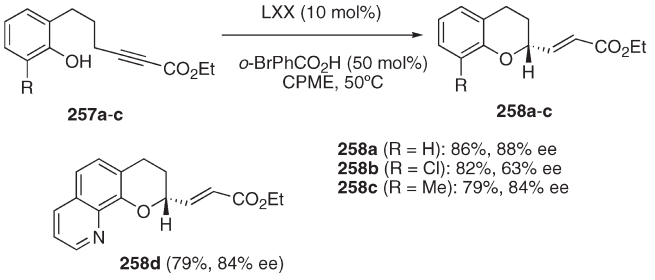
In 2010, a reaction of chalcones **284** with azlactones **348** was reported by Feng and co-workers.[255] This process was catalyzed by a new type of C_2-symmetric chiral bisguanidines (**XCII**), and a wide variety of γ,δ-unsaturated δ-lactone derivatives **349** with α-quaternary-β-tertiary stereocenters was obtained, as shown in Scheme 161. Both electron-deficient and electron-rich chalcones (**284**) underwent the reaction smoothly, giving the corresponding adducts **349** in good yields and with excellent

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 118. Catalytic Enantioselective Synthesis of Tetrahydrofurans and Tetrahydropyrans



Scheme 119. Catalytic Enantioselective Synthesis of Dihydrobenzopyrans



enantio- and diastereoselectivities. The tested oxazolones had an aromatic substituent at C2 and were derived from different amino acids. The reaction could be performed on a multigram scale.

In order to prove that the pathway leading to the lactones was an IEDHDA reaction and not a Michael addition followed by an intramolecular nucleophilic addition (see Scheme 162), Michael byproducts were resubmitted to the reaction system and none of them could perform the intramolecular nucleophilic addition, which suggested that the cyclic adducts were obtained via the IEDHDA reaction at the C4 and C5 positions of the azlactone.

5.1.4. Asymmetric Diels–Alder Reactions Catalyzed by Organic Bifunctional Catalysts. After the pioonering work of Riant and Kagan in the Diels–Alder reaction[38] and the discovery of the importance of the hydroxyl group to activate the maleimide, several research groups devoted their efforts to the synthesis and evaluation of different bifunctional catalysts that could act as a Brønsted base and hydrogen-bond donor at the same time, in order to improve the outcome of the process. For example, Yamamoto and co-workers described the asymmetric cycloaddition of anthrone (**345a**) to maleimides catalyzed by C_2-chiral 2,5-bis(hydroxymethyl)pyrrolidines such as **XCIII** that can establish a hydrogen bond between a maleimide carbonyl and one hydroxyl group in the transition state (Figure 28), obtaining moderate enantioselectivities in some instances (up to 74% ee; Scheme 163).[256]

Deng and co-workers demonstrated that the use bifunctional catalysts can control the endo/exo selectivity.[257] Thus, the Diels–Alder cycloaddition between 3-hydroxy-2-pyrone (**350**) and α-chloroacrylonitrile (**351**) was carried out in the presence of the catalysts **LXXXIX** and **XCIII** (Scheme 164). The first catalyst was found to be endo selective, while the second one (a bifunctional catalyst) afforded preferentially the exo adduct in good yields and good enantioselectivities.

More recently, Bernardi, Ricci and co-workers have reported a catalytic asymmetric Diels–Alder reaction between 3-vinylindoles and maleimides, obtaining optically active tetrahydrocarbazole derivatives with excellent yields and enantioselectivities.[258] The reaction could also be carried out with quinones as dienophiles, with excellent enantioselectivities.

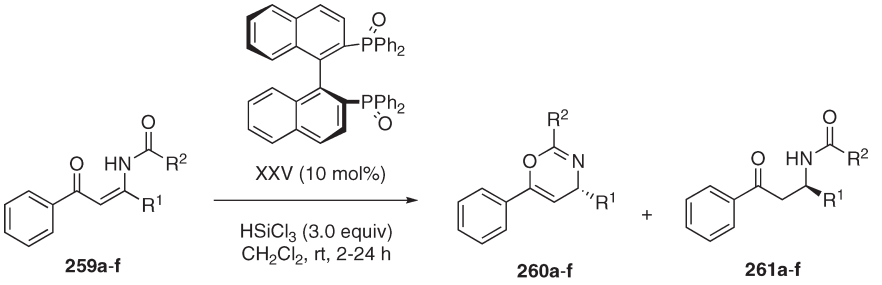
In 2009, Tan and Soh developed a Diels–Alder reaction between *N*-sulfonyl-3-hydroxy-2-pyridones (**354**) and maleimides catalyzed by aminoindanol derivatives, obtaining the cycloadducts **355** in excellent yields and stereoselectivities (Scheme 165). However, when unsaturated ketones were used as dienophiles instead of maleimides, the diastereoselectivities decreased drastically. Another important limitation of this methodology is the narrow scope of the reaction in terms of the diene; for example, when 3-hydroxy-2-pyrones (**340**) were used the enantioselectivities decreased down to a 30% ee.[259]

In 2010, Moyano, Rios and co-workers developed a Diels–Alder reaction between anthrones and maleimides catalyzed by Takemoto's thiourea catalyst **XLI** that afforded the cycloadducts **347** in good yields and enantioselectivities (Scheme 166).[260]

Gong and Wei have recently reported the synthesis of spirooxindoles via a [4 + 2]-cycloaddition.[261] The reaction between α-methyleneindolinones and Nazarov reagents **356**

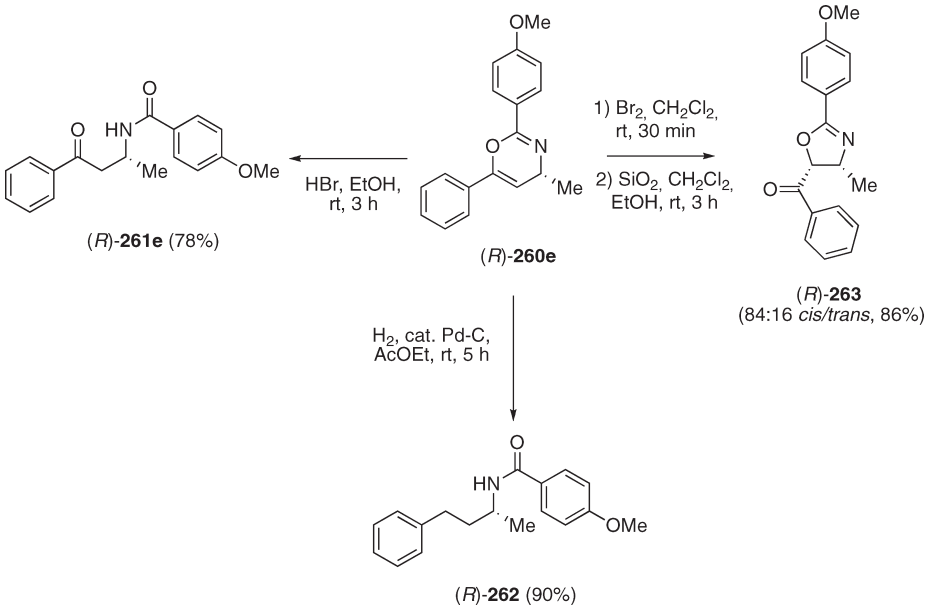
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 120. Enantioselective Reductive Cyclization of *N*-Acylated *β*-Amino Enones

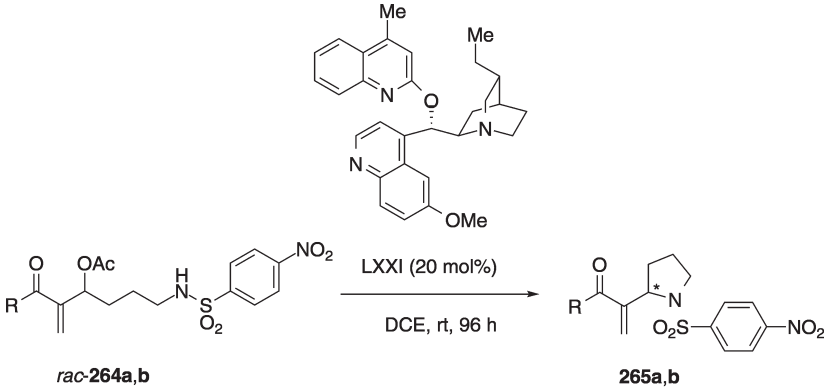


260a (R^1 = Me, R^2 = Ph): 68%, 74% ee
260b (R^1 = *i*-Pr, R^2 = Ph): 72%, 47% ee
260c (R^1 = R^2 = Ph): 75%, 53% ee
260d (R^1 = Me, R^2 = *p*-NO_2Ph): 38%, 50% ee
260e (R^1 = Me, R^2 = *p*-MeOPh): 68%, 81% ee
260f (R^1 = R^2 = Me): 58%, 26% ee

Scheme 121. Synthetic Utility of 4*H*-1,3-Oxazines



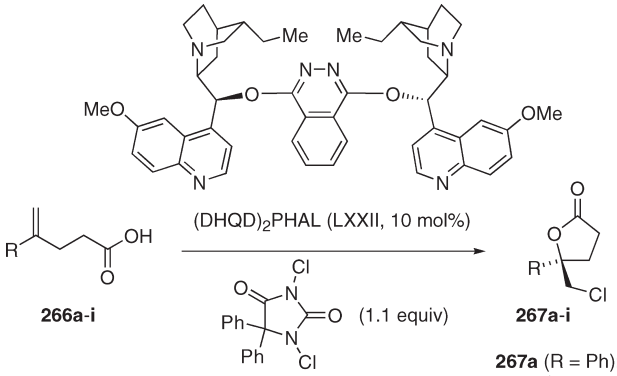
Scheme 122. Organocatalytic Asymmetric Intramolecular Allylic Substitutions of MBH Acetates



265a (R = EtO): 43%, 70% ee
265b (R = Me): 77%, 73% ee

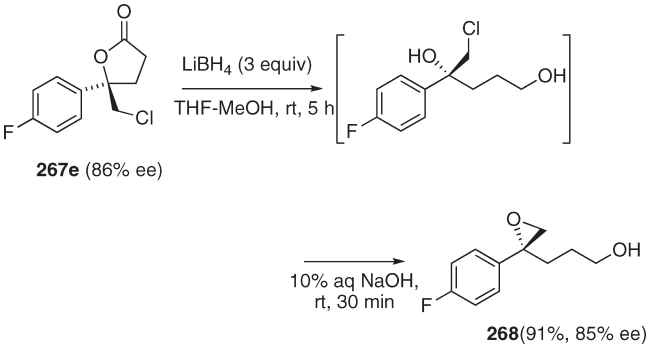
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 123. Organocatalytic Asymmetric Chlorolactonization

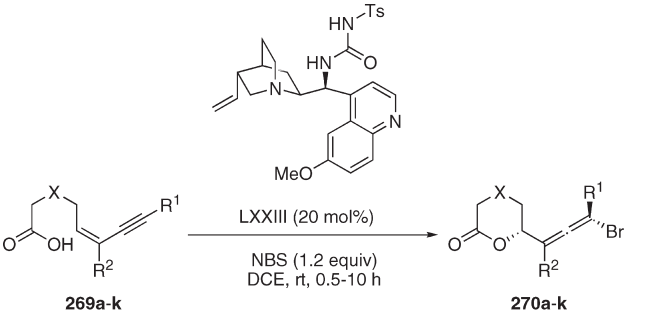


267a (R = Ph): 86%, 89% ee
267b (R = *p*-MeOPh): 99%, <5% ee
267c (R = *p*-Tol): 86%, 80% ee
267d (R = *p*-ClPh): 80%, 88% ee
267e (R = *p*-FPh): 81%, 89% ee
267f (R = *p*-CF_3Ph): 61%, 90% ee
267g (R = *p*-Ph-Ph): 75%, 83% ee
267h (R = 2-Naphthyl): 84%, 74% ee
267i (R = Cyclohexyl): 55%, 43% ee

Scheme 124. One-Pot Conversion a Chlorolactone to a Chiral Epoxy Alcohol



Scheme 125. Enantioselective Organocatalytic Bromolactonization of Aliphatic *cis*-Enynes



270a (X = O, R^1 = R^2 = H): 71%, 90% ee
270b (X = O, R^1 = *n*-Pr, R^2 = H): 77%, 90% ee
270c (X = O, R^1 = *i*-Pr, R^2 = H): 72%, 90% ee
270d (X = O, R^1 = *t*-Bu, R^2 = H): 76%, 90% ee
270e (X = O, R^1 = TES, R^2 = H): 87%, 88% ee
270f (X = O, R^1 = CH_2OPh, R^2 = H): 70%, 90% ee
270g (X = O, R^1 = CH_2OPMB, R^2 = H): 70%, 92% ee
270h (X = NTs, R^1 = R^2 = H): 62%, 93% ee
270i (X = CH_2, R^1 = CH_2OPh, R^2 = H): 82%, 80% ee
270k (X = O, R^1 = TES, R^2 = Me): 86%, 81% ee

is efficiently promoted by the amino urea catalyst **XCVI** and renders the corresponding spirocyclohexanes **357** with very good yields and excellent stereoselectivities, as depicted in Scheme 167. The reaction starts with a Michael addition of the β-keto ester to the unsaturated oxindole, followed by an intramolecular Michael addition of the resulting carbanion to the enone moiety.

5.1.5. Asymmetric Diels–Alder Reactions Catalyzed by Organic Brønsted Acids. In recent years, the use of Brønsted acids as catalysts has attracted much attention. Since the pioneering works of Terada[33,262] and Akiyama[32] with chiral phosphoric acids, several research groups have devoted their efforts in the development of enantioselective Diels–Alder reactions promoted by Brønsted acids.

One of the first examples of the use of chiral Brønsted acids as promoters for the Diels–Alder reaction was reported by Göbel and co-workers in 2000.[263] They disclosed that the amidinium ion **XCVII** promoted the cycloaddition reaction between cyclopentene-1,2-dione **358** and the diene **359**, leading to a complex mixture of diastereomers. The reaction presents some limitations, such as the use of stoichiometric amounts of the chiral amidinium ion and the low enantioselectivities achieved (Scheme 168).

In 2003, Rawal and co-workers made a significant advance in the use of Brønsted acids as catalysts, when they reported that TADDOL (**XCVIII**) was able to catalyze the hetero-Diels–Alder reaction between aminodiene **361** and aldehydes.[264] The reaction took place with moderate to high yields and with high enantiomeric ratios (Scheme 169). The TADDOL activates the aldehyde by a single hydrogen bond interaction that is stabilized by another intramolecular hydrogen bond in the catalyst.

Some years later, the same research group reported an improved catalyst with a BINOL backbone.[265]

The first chiral phosphoric acid catalyzed asymmetric direct aza-hetero-Diels–Alder reaction was reported by Gong and co-workers.[266] Cyclohexenone (**321e**) reacts with imines (**363**) formed in situ from the corresponding aldehydes and

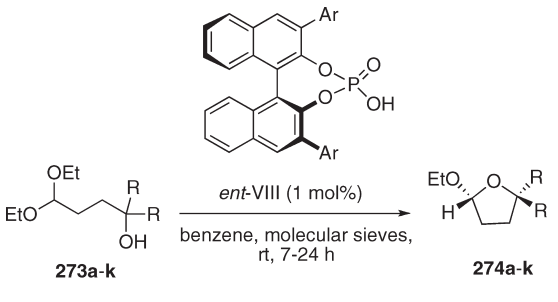
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 126. Enantioselective Organocatalytic Bromolactonization of Aromatic *cis*-Enynes

271a-h **272a-h**

272a ($R^1 = R^2 = R^3 = H$): 44%, 97% ee
272b ($R^1 = R^3 = H$, $R^2 = Cl$): 72%, 98% ee
272c ($R^1 = R^3 = H$, $R^2 = CF_3$): 74%, 99% ee
272d ($R^1 = R^2 = H$, $R^3 = CH_3CO$): 68%, 97% ee
272e ($R^1 = R^3 = Br$, $R^2 = H$): 85%, 94% ee
272f ($R^1 = R^2 = H$, $R^3 = NO_2$): 80%, 97% ee
272g ($R^2 = R^3 = H$, $R^1 = NO_2$): 88%, 95% ee
272h ($R^1 = R^3 = H$, $R^2 = NO_2$): 76%, 98% ee

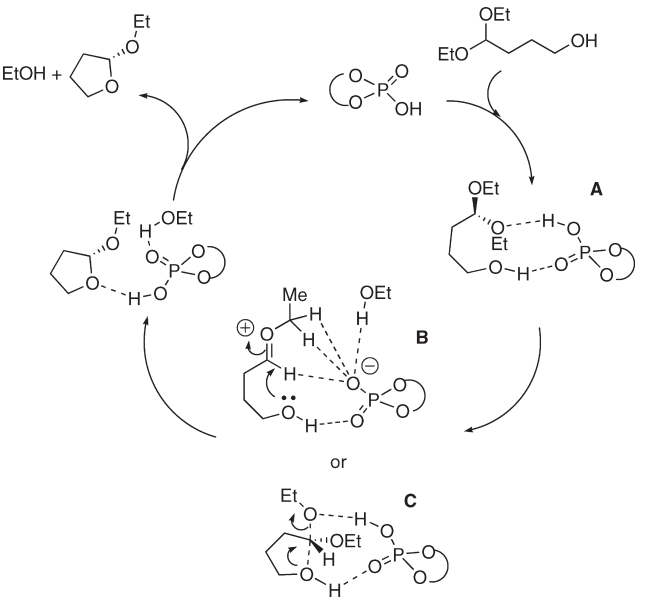
Scheme 127. Asymmetric Organocatalytic Intramolecular Transacetalization



273a-k **274a-k**

274a (R = H): 76%, 58% ee
274b (R = Me): 84%, 89% ee
274c (R = Et): 92%, 94% ee
274d (R = *i*-Pr): 93%, 96% ee
274e (R = *t*-Bu): 90%, 96% ee
274f (R = Bn): 98%, 94% ee
274g (R = Ph): 95%, 89% ee
274h (R = *p*-MeOPh): 96%, 89% ee
274i (R = *p*-FPh): 98%,94% ee
274j (R = *p*-BrPh): 99%, 94% ee
274k (R,R = $(CH_2)_5$): 94%, 94% ee

Scheme 128. Mechanistic Hypothesis for the Asymmetric Organocatalytic Intramolecular Transacetalization



4-methoxyphenylamine, under catalysis by chiral phosphoric acids such as **XCIX**. The reaction only works with aromatic aldimines, with good yields and moderate diastereo- and enantioselectivities (Scheme 170). The authors hypothesized that the activation of the imine occurs through protonation by the phosphoric acid. The reactive ion pair reacts then with the enone, rendering the final cycloadducts **364**.

Almost at the same time, Akiyama and co-workers reported the same reaction using Brassard's diene (**365**) instead of cyclohexenone to afford the piperidinone derivatives **367**.[267] The reaction was limited to the use of aromatic or heteroaromatic aldimines (**366**) derived from 2-hydroxy-*m*-toluidine and gave the corresponding cycloadducts with good yields and excellent enantioselectivities (Scheme 171). The best catalyst was the anthryl-derived BINOL phosphoric acid **LXVII**.

In this case, the authors postulate that the presence of the hydroxyl group on the *N*-aryl moiety of the imine was essential for achieving high enantioselectivity (the absence of this hydroxyl group results in the formation of the final cycloadducts with low ee). On the basis of these data, the authors propose a nine-membered cyclic transition state in which the phosphoryl oxygen atom forms a hydrogen bond with the hydrogen atom of the hydroxy group. Under these conditions, the nucleophile should preferentially attack the less-hindered *re* face of the aldimine (Figure 29).

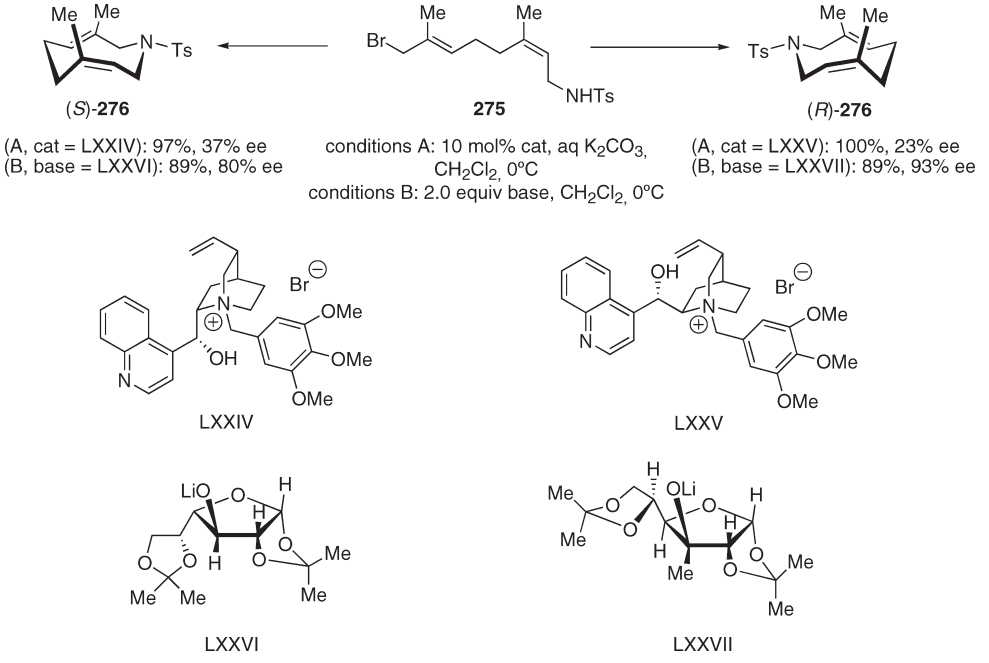
In the same report, Akiyama and co-workers used Danishefsky's diene instead of Brassard's diene, achieving the cycloadducts in good yield but with worse enantiomeric purities than those previously obtained with Brassard's diene.

The same research group published also an inverse-electron-demand aza-Diels–Alder reaction of aldimines derived from 2-hydroxyaniline (**363a–d**) with vinyl ethers (**368**, electron-rich alkenes), also using **LXVII** as a catalyst.[268] The process gave access to tetrahydroquinoline derivatives (**369**) with high to excellent enantioselectivities (Scheme 172).

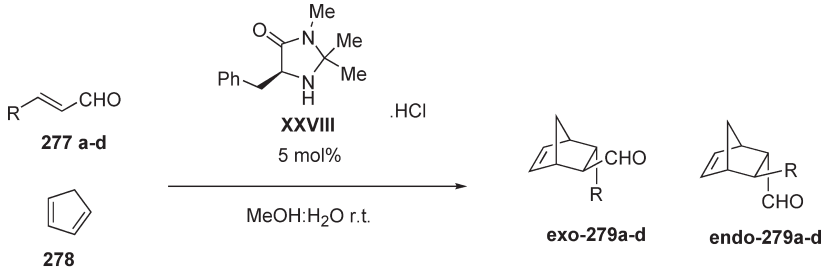
Very recently, Jacobsen and co-workers reported a [4 + 2]-cycloaddition between *N*-aryl imines and electron-rich alkenes (Povarov reaction).[269] The reaction was efficiently catalyzed

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

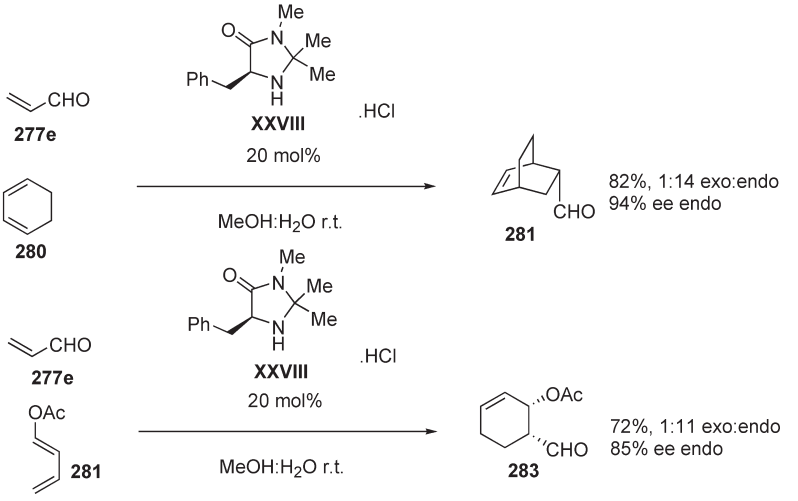
Scheme 129. Enantioselective Synthesis of Planar Chiral Nitrogen Heterocycles



Scheme 130. Diels−Alder Reaction Reported by MacMillan

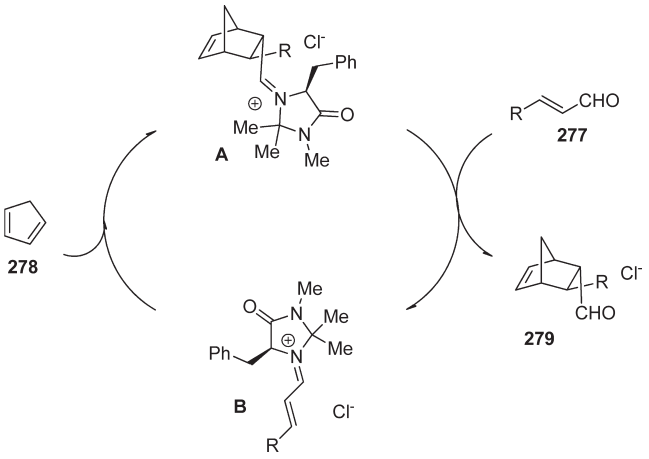


279a R=Me 75% 1:1 exo:endo 86%ee exo 90%; ee endo
279b R=Pr 92% 1:1 exo:endo 86%ee exo 90%; ee endo
279c R=Ph 99% 1.3:1 exo:endo 93%ee exo 93%; ee endo
279d R=2-furyl 89% 1:1 exo:endo 91%ee exo 93%; ee endo

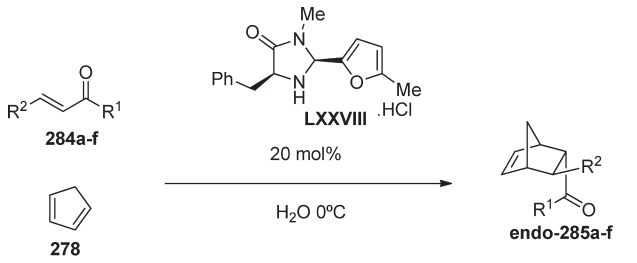


dx.doi.org/10.1021/cr100348t |Chem. Rev. 2011, 111, 4703–4832

Scheme 131. Mechanism of the Diels–Alder Reaction Reported by MacMillan



Scheme 132. Organocatalytic Diels–Alder Reaction of Unsaturated Ketones Reported by MacMillan



285a R^1=Me R^2= Me 85%; 1:14 exo:endo; 61% ee endo
285b R^1=Et R^2= Me 89%; 1:25 exo:endo; 90% ee endo
285c R^1=n-Bu R^2= Me 83%; 1:22 exo:endo; 92%; ee endo
285d R^1=Et R^2= *n*-Pr 84%; 1:15 exo:endo; 92%; ee endo
285e R^1=Et R^2= *i*-Pr 78%; 1:6 exo:endo 90% ee endo
285f R^1=*i*-Pr R^2= Me 24%; 1:8 exo:endo 0%; ee endo

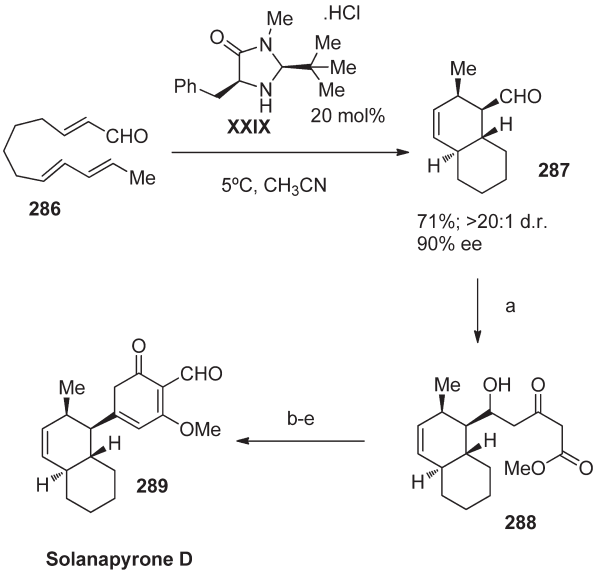
by a dual catalyst containing both a strong Brønsted acid and a chiral urea (**C**). Both groups have a cooperative effect in the transition state through a noncovalent interaction network, as depicted in Figure 30. This interaction leads to an attenuation of the reactivity of the iminium ion and allows high enantioselectivity in cycloadditions with electron-rich alkenes (the Povarov reaction).

The reaction furnishes the corresponding cycloadducts in good yields and excellent enantioselectivities (Scheme 173). A detailed experimental and computational analysis of this catalyst system has revealed the precise nature of the catalyst–substrate interactions and the likely basis for enantioinduction.

5.2. [3 + 2]-Cycloadditions[12a,270]

5.2.1. Introduction. 1,3-Dipolar cycloadditions, also known as Huisgen cycloadditions,[271] consist of the reaction between 1,3-dipoles and a dipolarophile. These important reactions, in general, furnish five-membered heterocycles in high yields. Another important feature of these reactions is their versatility, allowing the presence of several functional groups in the

Scheme 133. Synthesis of Solanapyrone D via an Organocatalytic Intramolecular Diels–Alder Reaction



(a) Methyl acetoacetate bis (trimethylsilyl) enol ether, $TiCl_4$, CH_2Cl_2, -78ºC. (b) Dess-Martin periodinane, CH_2Cl_2, 71%. (c) DBU, benzene, 60ºC, 87%. (d) Methyl *p*-toluenesulfonate, K_2CO_3, DMF, r.t., 81%. (e) LDA, THF, -78ºC to 0ºC; methyl formate, -78ºC, 57%.

reactants, such as alkenes, alkynes, and molecules possessing related heteroatom functional groups like carbonyls and nitriles.

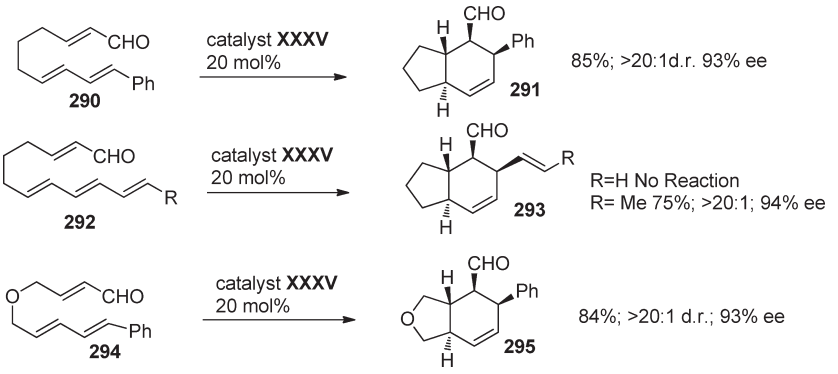
Most dipolarophiles are alkenes, alkynes, and molecules possessing related heteroatom functional groups (such as carbonyls and nitriles). The 1,3-dipoles can be basically divided into two different types: (a) the allyl anion type such as nitrones, azomethine ylides, nitro compounds bearing a nitrogen atom in the middle of the dipole, and carbonyl ylides or carbonyl imines bearing an oxygen atom in the middle of the dipole and (b) the linear propargyl/allenyl anion type such as nitrile oxides, nitrilimines, nitrile ylides, diazoalkenes, or azides. Two π-electrons of the dipolarophile and four π-electrons of the dipolar compound participate in a concerted [3 + 2]-cycloaddition (with some exceptions). The addition is stereoconservative (suprafacial), and the reaction is therefore a $[2\pi s + 4\pi s]$-cycloaddition (Schemes 174 and 175).

5.2.2. Organocatalytic Asymmetric Dipolar Cycloadditions of Nitrones. The first asymmetric organocatalytic 1,3-dipolar cycloaddition reaction was reported by MacMillan and co-workers in 2000.[272] They disclosed that chiral imidazolidinone catalysts promote the reaction between enals and nitrones, by activating the double bond of enal via iminium activation, affording the corresponding adducts in good yields and with moderate to good diastereo- and enantioselectivities. It should be noticed that the endo adduct was the major isomer obtained and that the scope of the reaction in terms of the enal was quite narrow, since only acroleine or crotonaldehyde was used as a suitable dipolarophile (Scheme 176).

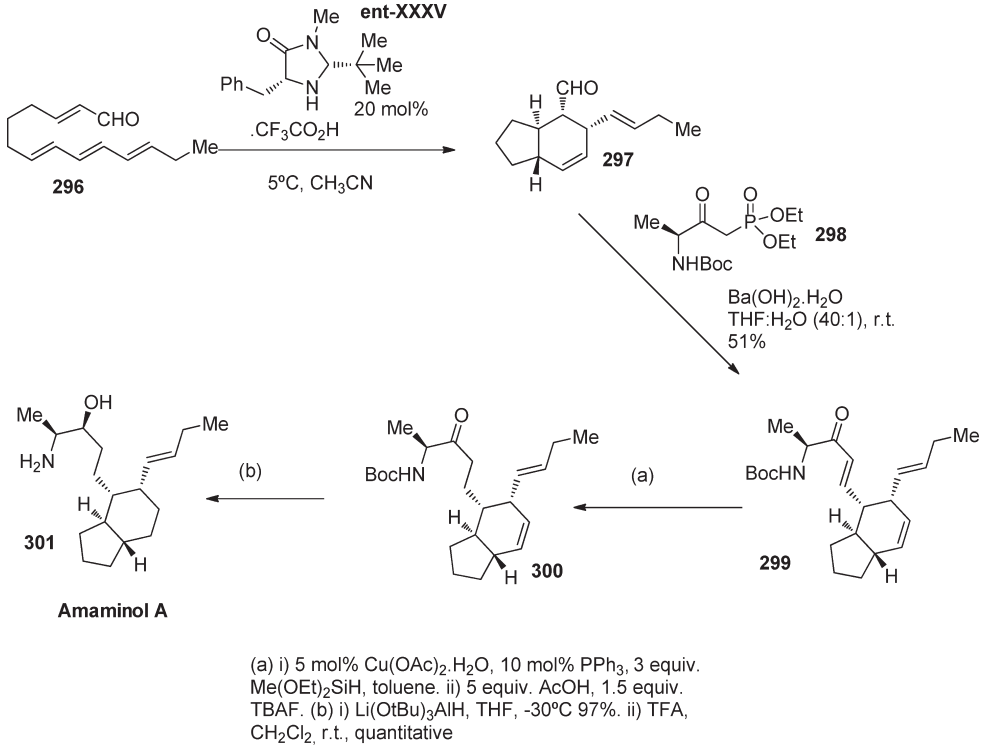
A few years later, Karlsson and Högberg reported the enantioselective 1,3-dipolar cycloaddition of nitrones to 1-cycloalkene-1-carbaldehydes by using chiral pyrrolidinium salts as catalysts.[273] In this work, they obtained as predominant isomer

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

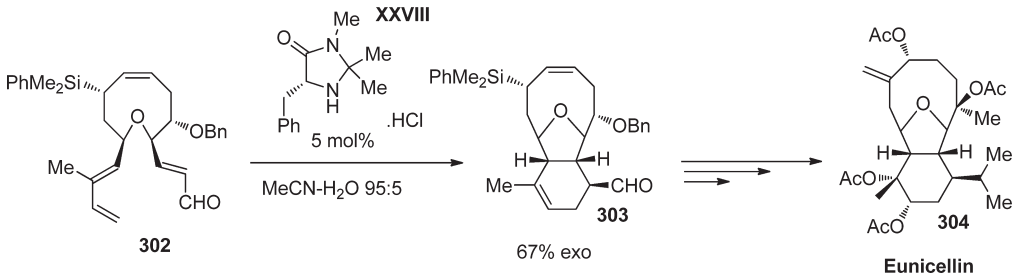
Scheme 134. Intramolecular Diels–Alder Cycloaddition Developed by MacMillan



Scheme 135. Synthesis of Amaminol A Reported by Koskinen



Scheme 136. Synthesis of Eunicellin Reported by Holmes

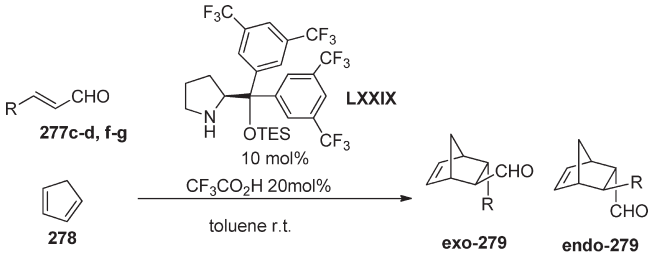


the exo-bicyclic isoxazolidinone in good yields and diastereoselectivities but with moderate to low enantioselectivities.

In 2004, Benaglia and co-workers developed a poly(ethylene glycol)-supported imidazolidinone catalyst that

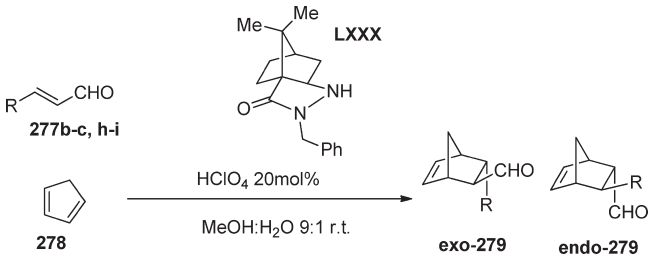
dx.doi.org/10.1021/cr100348t |Chem. Rev. 2011, 111, 4703–4832

Scheme 137. Organocatalytic Diels−Alder Reaction Reported by Hayashi



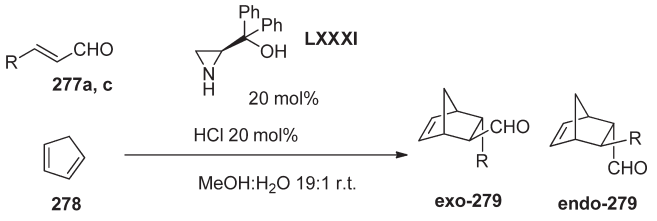
279c R=Ph 99% 85:15 exo:endo; 97% ee exo; 88% ee endo
279d R=2-furyl 89% 80:20 exo:endo; 94% ee exo; 78% ee endo
279f R=n-Bu 75% 78:22 exo:endo; 94% ee exo; 91% ee endo
279g R=CO_2Et 92% 70:30 exo:endo; 84% ee exo; 64% ee endo

Scheme 138. Organocatalytic Diels−Alder Reaction Reported by Ogilvie



279b R=Pr 83% 1.6:1 exo:endo; 81% ee exo
279c R=Ph 96% 1.9:1 exo:endo; 90% ee exo
279h R=p$NO_2C_6H_4$ 93% 2.2:1 exo:endo; 92% ee exo
279i R=pClC_6H_4 92% 2:1 exo:endo; 90% ee exo

Scheme 139. Diels−Alder Reaction Catalyzed by Chiral Aziridines

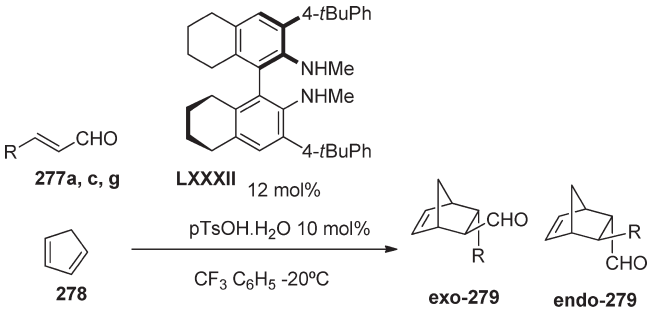


279a R=Me 85% 1:1 exo:endo; 24% ee exo; 22% ee endo
279c R=Ph 33% 1:1.8 exo:endo; 36% ee exo; 37% ee endo

promotes the enantioselective dipolar cycloaddition between nitrones and enals in good yields and stereoselectivities.[274] As in MacMillan's work, the major isomer was the endo one.

Córdova and co-workers in 2007 developed a similar reaction promoted by diphenylprolinol derivatives.[275] In this work, the nitrones were prepared in situ by reaction of *N*-arylhydroxylamines (**375**) with aldehydes. The resulting nitrones were trapped with α,β-unsaturated aldehydes (**277**) to give, after reduction of the formyl group with sodium borohydride, the isoxazolidines **376** in good yields and stereoselectivities (Scheme 177).

Scheme 140. Diels−Alder Reaction Reported by Maruoka



279a R=Me 72% >20:1 exo:endo; 88% ee exo
279c R=Ph 80% 13:1 exo:endo; 92% ee exo; 91% ee endo
279g R=CO_2Et 90% 5:1 exo:endo; 83% ee exo; 56% ee endo

Soon after, the same research group reported a synthesis of cycloheptene derivatives **377** involving two consecutive 1,3-dipolar cycloadditions that afforded the final products in moderate yields and high stereoselectivities, as shown in Scheme 178.[276]

In 2007, Ogilvie and co-workers reported the use of chiral hydrazides in the 1,3-dipolar nitrone cycloaddition.[277] The results, however, were less satisfactory than those previously reported by MacMillan's[272] or Córdova's[275,276] groups.

Also in 2007, Nevalainen and co-workers reported the triflate salt of diphenylprolinol trimethylsilyl ether (**XLVIII**) as a suitable catalyst for the dipolar cycloaddition of enals and nitrones.[278] Remarkably, the authors used for the first time α-substituted enals, obtaining the corresponding endo cycloadducts **379** in excellent yields and good to moderate enantioselectivities, as depicted in Scheme 179.

Chen and co-workers, in 2008, reported the 1,3-dipolar cycloaddition of nitrones and β-alkyl nitroolefins catalyzed by the thiourea derivative **CI**.[279] Using 10 mol % of catalyst in MTBE as a solvent, at 0 °C for 6 days, gave rise to chiral isoxazolidines in good chemical yields, high enantioselectivities, and excellent exo-diastereoselectivities (Scheme 180).

Almost at the same time, Yamamoto and co-workers reported the enantioselective 1,3-dipolar cycloaddition of nitrones and ethyl vinyl ether promoted by the *N*-triflylphosphoramide **CII**.[280] With only 5 mol % catalyst loading, the reaction was completed in 1 h, affording the endo adducts **381** in quantitative yields and excellent enantioselectivities (Scheme 181). The proposed mechanism that explaines the elevated degree of stereocontrol is based on dominant secondary π-orbital interactions deduced by computational calculations.

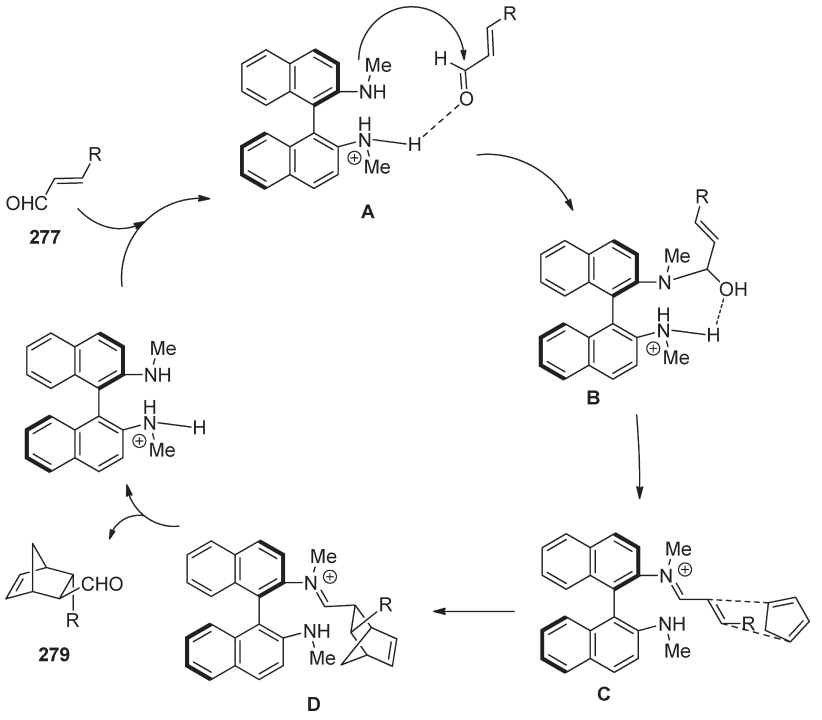
In 2009, Bernardi, Fini, and co-workers reported the first organocatalytic [3 + 2]-cycloaddition between in situ generated *N*-carbamoyl nitrones and unsaturated esters.[281] The reaction is efficiently catalyzed by *Cinchona*-alkaloid-derived salts, rendering the final cycloadducts in good yields and stereoselectivities.

5.2.3. Organocatalytic Asymmetric Dipolar Cycloadditions of Azomethyne Ylides. The use of azomethyne ylides in organocatalysis has lately received much attention. Azomethyne ylides are planar 1,3-dipoles composed of a central nitrogen atom and two terminal sp^2 carbon atoms. Their cycloaddition to olefinic dipolarophiles provides a direct and general method for the synthesis of pyrrolidine derivatives. Normally the azomethine ylides are generated in situ and trapped by a multiple C−C or C−X bond.

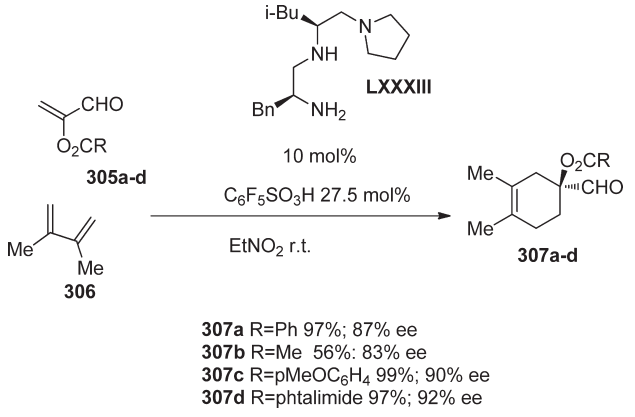
The first organocatalytic 1,3-dipolar cycloaddition of azomethyne ylides was reported by Arai et al.[282] In this work they

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

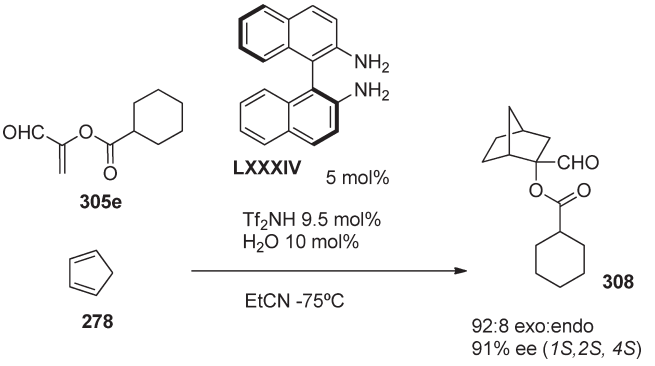
Scheme 141. Mechanism of the Diels–Alder Reaction Reported by Maruoka



Scheme 142. Diels–Alder Reaction of 2-Acetoxyacroleins Reported by Ishihara



Scheme 143. Diels–Alder Reaction Catalyzed by BINAM



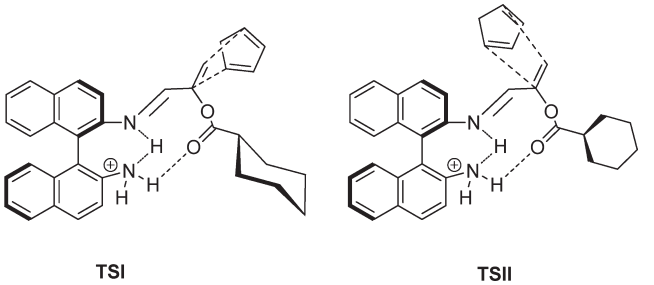


Figure 27. Proposed transition state for the BINAM-catalyzed Diels–Alder reaction.

used a D_2-symmetrical ammonium salt as a phase-transfer catalyst to promote the reaction. The reaction between *tert*-butyl alaninate and methyl acrilate rendered the expecte cycloadduct but in low yields and enantioselectivities.

The first highly enantioselective organocatalytic 1,3-dipolar cycloaddition with azomethyne ylides was described in 2007 by Vicario and co-workers.[283] In this report, diphenylprolinol (**XLIV**) promoted the reaction of (arylidene)iminomalonates **382** with α,β-unsaturated aldehydes with good yields and stereoselectivities. The reaction needed long reaction times to proceed in the presence of 4 equiv of water in THF at 4 °C. On the basis of previous studies and taking into account that the activation of the aldehyde occurs via its chiral pyrrolidinium ion, the authors proposed a mechanism involving a Michael addition of the dipole **A** that is supported by the stereochemical outcome of the reaction (Scheme 182). One of the disavantatges of this work is the use of preformed (arylidene)iminomalonates and the

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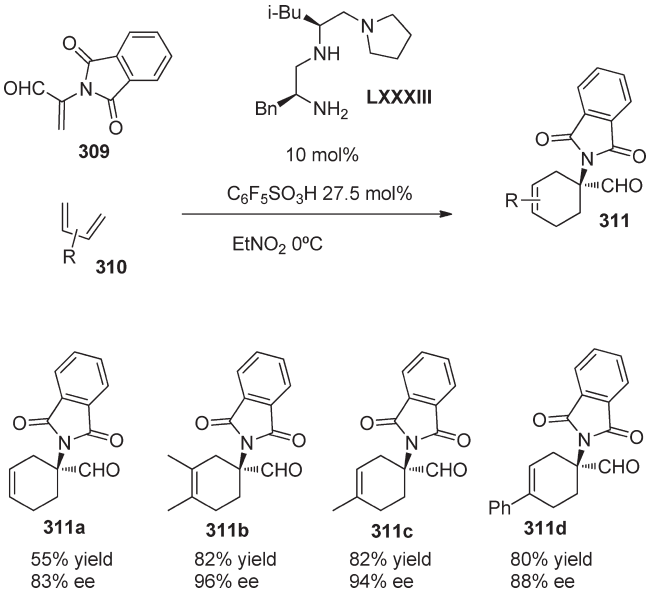
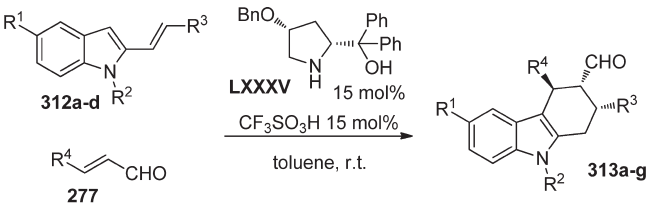
Scheme 144. Diels−Alder Reaction of α-Phthalimidoacrolein Developed by Ishihara



Scheme 145. Diels−Alder Reaction between 2-Vinylindoles and α,β-Unsaturated Aldehydes



313a R^1=H R^2=Me R^3=Ph R^4=Ph 83%; 12:1 d.r.; 97% ee
313b R^1=H R^2=Me R^3=*p*BrC_6H_4 R^4=Ph 79%; 19:1 d.r.; 99% ee
313c R^1=H R^2=Me R^3=Ph R^4=CO_2Et 72%; 12:1 d.r.; 98% ee
313d R^1=H R^2=H R^3=Ph R^4=Ph 62%; 8:1 d.r.; 96% ee
313e R^1=H R^2=allyl R^3=Ph R^4=Ph 66%; 6:1 d.r.; 68% ee
313f R^1=OMe R^2=Me R^3=Ph R^4=Ph 76%; 12:1 d.r.; 98% ee
313g R^1=OMe R^2=Me R^3=Ph R^4=Et 74%; 12:1 d.r.; 99% ee

necessity of a multistep sequence to furnish the corresponding proline derivatives **383**.

Independently, Córdova and co-workers overcame the necessity of using preformed (arylidene)iminomalonates by means of a multicomponent reaction.[284] In this way, an aldehyde and diethyl 2-aminomalonate (**384**) furnish in situ the arylideniminomalonate that is immediately trapped by an α,β-unsaturated aldehyde. The reaction was promoted by the trimethylsilyl ether of diphenylprolinol (**XLVIII**), affording the final cycloadducts **383** in excellent yields and enantioselectivities and with good diastereoselectivities (Scheme 183). The major diastereomer was, as in the Vicario's reaction,[283] the endo adduct, a fact that could be explained by an efficient blocking of one face in the chiral iminium intermediate by the two bulky phenyl groups.

More recently, Gong and co-workers developed a three-component reaction of diethyl 2-aminomalonate, an aldehyde, and dialkyl maleate.[285] The reaction was efficiently promoted by catalyst **CIII**, rendering the endo cycloadducts **386** as the only diastereoisomers in good yields and with excellent enantioselectivities (Scheme 184).

In 2010, the same research group extended the scope of the reaction by using unsaturated esters as dipolarophiles, giving access to multiply substituted hexahydrochromeno[4,3-*b*]pyrrolidine derivatives in high enantiomeric purity (Scheme 185). Probably the excellent outcome of the cycloaddition is caused by the intramolecular nature of the reaction. The optimal catalyst was the BINOL-derived phosphoric acid **CIV**.[286]

In 2008, Gong and co-workers reported the first 1,3-dipolar cycloaddition between azomethyne ylides and nitroalkenes, using the bifunctional quinine-derived catalyst **XCIII** as an effective promoter of the reaction.[287] This transformation was rather limited because it was only applied to the reaction of the benzophenone imine derivative **389** and different nitroalkenes. The final cycloadducts **390** were isolated with good yields and diastereoselectivities, although with low enantioselectivities (Scheme 186).

Soon after, Chen[288] and Takemoto[289] disclosed, almost simultaneously, the first asymmetric three-component 1,3-dipolar cycloaddition of aldehydes (**196**), α-aminomalonate (**384**), and nitroalkenes (**327**), catalyzed by chiral thioureas (**XLI**, **CV**). The reaction begins with the formation of the imine (**A**) from the α-aminomalonate and the aldehyde. This compound then reacts with the nitrostyrene (**327**) via a Michael addition and a subsequent aza-Henry reaction (formally a [3 + 2]-cycloaddition), affording the highly substituted pyrrolidine (**391**), as shown in Scheme 187.

The reaction works well with aromatic aldehydes and aromatic nitroalkenes, affording the corresponding pyrrolidine derivatives in high yields, diastereoselectivities, and enantioselectivities (Scheme 188). However, when aliphatic nitroalkenes were used, the enantioselectivity of the reaction dropped dramatically.

On the basis of this methodology, Xie and co-workers developed in 2010 a powerful kinetic resolution of racemic 3-nitro-2*H*-chromene derivatives by a [3 + 2]-cycloaddition with preformed iminomalonates.[290] The reaction is promoted by Takemoto's catalyst (**XLI**), rendering the final compounds and the starting 3-nitro-2*H*-chromene in moderate enantioselectivities.

In 2009, Gong and co-workers reported a 1,3-dipolar cycloaddition involving 2,3-allenoate dipolarophiles.[291] The reaction between 2,3-allenoates **392** and in situ formed azomethyne ylides is efficiently catalyzed by biphosphoric acids such as **CIII**, rendering the corresponding 3-methylene pyrrolidine derivatives **393** in good yields and excellent enantioselectivities (Scheme 189). One of the limitations of this methodology is the decrease of enantioselectivity when aliphatic aldehydes were used.

Azomethyne imines have also been used in organocatalytic 1,3-dipolar cycloaddition with notorious success. For example, Chen and co-workers, in 2006, developed a very elegant 1,3-dipolar cycloaddition between enals and azomethyne imines.[292] The reaction was efficiently catalyzed by Jørgensen's catalyst (**XXXVI**), affording the corresponding adducts in good yields and enantioselectivities and with moderate diastereoselectivities, with the exo adduct as the major diastereoisomer. The use of acid additives (TFA 10 mol %) and water became crucial in order to obtain good stereoselectivities. The reaction has some limitations in the scope of enals, only allowing the use of aliphatic enals (Scheme 190).

One year later, Chen's research group reported the same reaction using cyclic enones instead of enals.[293] This time, the

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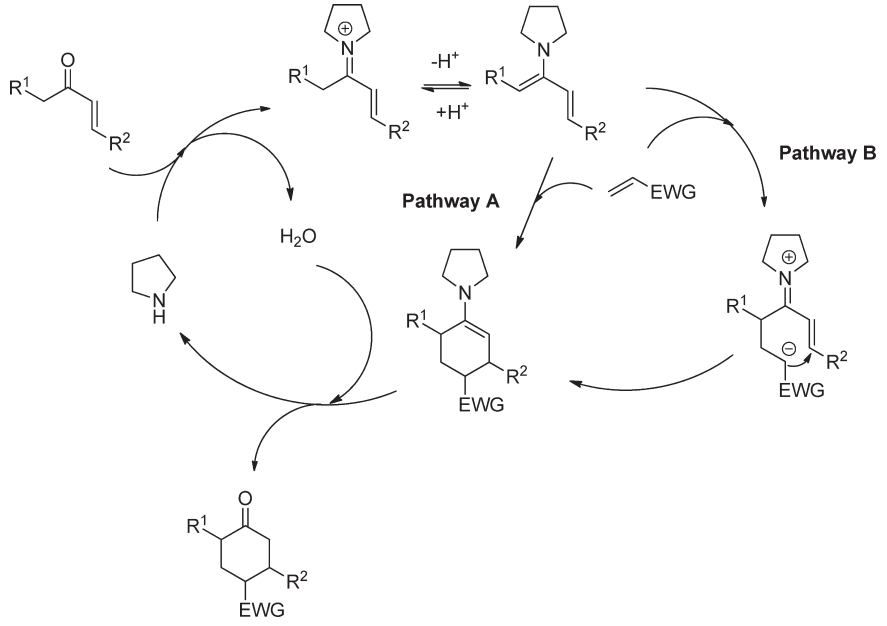
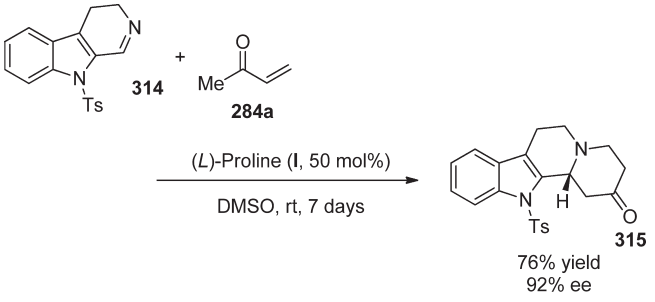
Scheme 146. Diels−Alder Reaction via Enamine Activation



Scheme 147. Asymmetric Tandem Mannich−Michael Reaction Observed by Ohsawa



reaction was promoted by multifunctional primary amines derived from *Cinchona* alkaloids, in the presence of arylsulfonic acids. The authors stressed the importance of the presence of other functionality in the catalysts in order to form a hydrogen-bonding interaction with the dipole. This interaction allows for furnishing the desired cycloadducts **396** in good yields and excellent enantioselectivities (Scheme 191). The only limitation of this methodology was the need to use cyclic enones. When acyclic enones were used, no reaction was observed.

In 2010, Gong and co-workers developed a [3 + 2]-cycloaddition between quinones, amines, and 2-aminomalonates or 2-amino esters catalyzed by chiral phosphoric acids.[294] The reaction constitutes a formal double arylation of azomethynes. The reaction renders the corresponding isoindolines in good yields and excellent enantioselectivities.

5.2.4. Miscellaneous Organocatalytic Asymmetric Dipolar Cycloadditions. In 1997, Zhang and co-workers developed the first asymmetric [3 + 2]-cycloaddition of 2,3-butadienoates with electron-deficient olefins, catalyzed by novel chiral phosphabicyclo-[2.2.1]heptanes.[295] The cycloaddition is normally triggered by the phosphane attack to the β-carbon of the alkyl allenoate, generating a 1,3-dipole, which is an inner salt containing a phosphonium cation (Scheme 192).

It was confirmed that the generation of the 1,3-dipole is the rate-determining step. These zwitterionic species are ready to undergo 1,3-dipolar cycloaddition with the electrophilic alkene, generating an intermediate betaine, which is transformed into the stabilized 1,3-dipole after an internal prototropic shift. The final β-elimination regenerates the catalyst and liberates the enantioenriched carbocycle. In the case where an imine is used as the dipolarophile, a pyrrolidine is formed.

The reaction renders the final carbacycles with excellent yields and enantioselectivities, as depicted in Scheme 193.

In 2006, Fu and Wilson developed a new phosphine catalyst derived from BINOL. This catalyst (**CVIII**) was successfully employed in [3 + 2]-cycloaddition reactions between allenoates and a wide array of enones, affording the final compounds in very good yields and enantioselectivities (Scheme 194).[296]

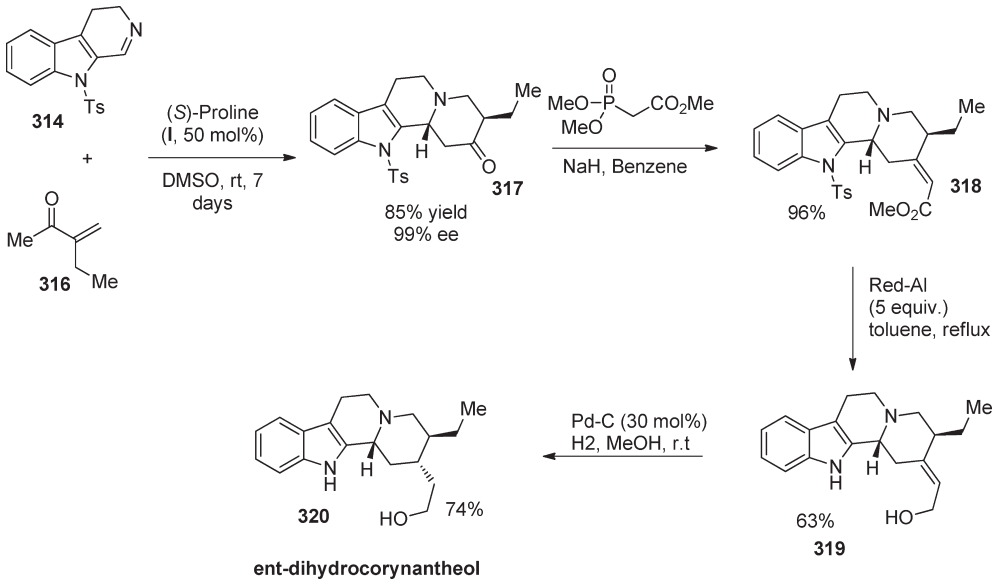
In 2006, Marinetti and Jean reported a phosphine-catalyzed [3 + 2]-cycloaddition between 2,3-butanodienoates and *N*-tosyl imines, and later on the same research group reported better results when *N*-DPP imines were used.[297] The reaction was promoted by tertiary chiral phosphines such as **CVIII** or **CIX** affording the desired cycloadducts **402** in moderate yields and moderate enantioselectivities, as it is shown in Scheme 195.

In 2008, Jacobsen reported a similar reaction between allenes and phosphinoyl imines catalyzed by chiral phosphinothioureas. The final cyclopentenes were obtained in good yields and excellent stereoselectivities.[298]

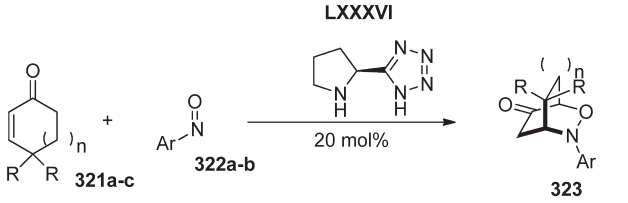
In 2008, Marinetti and co-workers reported the use of chiral 2-phospha[3]ferrocenophanes such as **CX** in the [3 + 2]-cycloaddition between allenoates and α,β-unsaturated ketones.[299] The corresponding adducts were obtained in good yields and excellent enantioselectivities, as shown in Scheme 196. One of the limitations of the work is the use of terminal allenic esters.

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 148. Synthesis of *ent*-Dihydrocorynantheol by Ohsawa



Scheme 149. Tandem Nitroso Aldol−Michael Reaction Described by Yamamoto



A similar reaction was reported by Miller in 2007 and in 2009, using as a catalyst a phosphine containing α-amino acid[300a] or pyridil alanine peptide.[300b] The final cyclopentenes were obtained in excellent yields and stereoselectivities.

In 2010, both Marinetti[301] and Zhao[302] disclosed a [3 + 2]-cycloaddition between allenes and malononitriles catalyzed by phosphines. In both cases, the results in terms of yield and stereoselectivity were excellent.

In 2009, Marinetti's group applied chiral 2-phospha[3]-ferrocenophanes as catalysts to the reaction between allenes and enones, achieving good yields and enantioselectivities.[303]

In 2009, Krische and Jones applied a similar methodology for the synthesis of (+)-geniposide; the [3 + 2]-cycloaddition catalyzed by phosphines was the key step of the synthesis, yielding the final compound with good diastereoselectivities.[304]

Gong and co-workers reported an asymmetric [3 + 2]-cycloaddition reaction of isocyanoesters (**403**) to nitroolefins (**327**) catalyzed by a chiral *Cinchona* alkaloid derivative (cupreine benzoate, **CXI**).[305] In this approach, isocyanoesters undergo a Michael addition to the nitroalkene, and a subsequent intramolecular alkylation affords the dihydropyrrole (**404**) after protonation (Scheme 197).

5.3. [3 + 3]-Cycloadditions

In 2006, Hong et al.[306] published a very interesting example of iminium and enamine activation performed on the same substrate. Concretely, they described the synthesis of *cis*- and *trans*-4-methyl-6-hydroxycyclohexenecarbaldehyde (**405a,b**) starting from crotonaldehyde (**277a**). L-Proline (**I**) catalyzed the process, which constituted a formal [3 + 3]-cycloaddition of crotonaldehyde (Scheme 198).

While the diastereoselectivity of the present reaction is low (1.14:1 dr), the two C6-epimers are obtained in high optical purity (80% and 95% ee, respectively) when it is performed in DMF at −10 °C with a 50 mol % of catalyst **I**. The mechanism proposed by the authors is summarized in Scheme 199.

As shown in Scheme 199, the authors proposed a Michael/Morita−Baylis−Hillman sequence. First of all, proline (**I**) activates a molecule of crotonaldehyde by iminium formation, with the other molecule of crotonaldehyde forming a dienamine. Then, the dienamine promotes a conjugate-type addition over the iminium-activated crotonaldehyde, forming the intermediate **A**. Subsequently, this intermediate undergoes an intramolecular Morita−Baylis−Hillman-like reaction promoted by free proline, furnishing the six-membered enal ring.

However, the aldehyde scope of this transformation is rather limited. Unlike crotonaldehyde, all other enals tested under the same reaction conditions gave the diene product, via an indirect Mannich reaction pathway, a formal [4 + 2]-cycloaddition.

5.4. [2 + 2]-Cycloadditions

One of the earliest examples of organocatalysis was the asymmetric synthesis of β-lactones via [2 + 2]-cycloaddition catalyzed by *Cinchona* alkaloid derivatives. The seminal studies by Wynberg and Staring on the quinidine-catalyzed ketene−chloral [2 + 2]-cycloaddition disclosed in 1982 provided the first examples of chiral organocatalysis in a [2 + 2]-cycloaddition.[307] Some years later, Calter and co-workers developed an efficient *Cinchona*-alkaloid-catalyzed methodology for the asymmetric dimerization of pyrolitically generated methylketene and employed the resulting highly enantioenriched β-lactone in the

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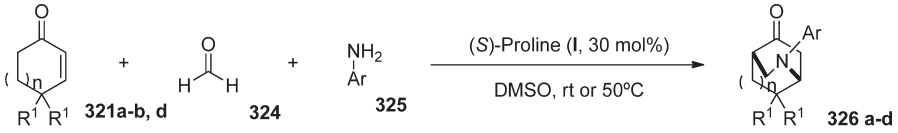
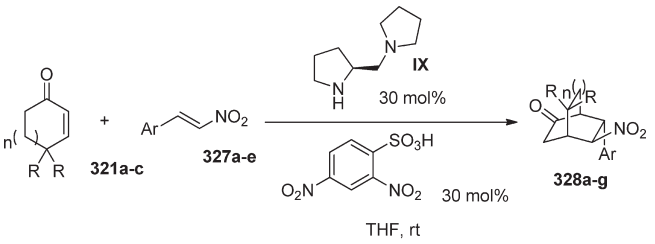
Scheme 150. Enantioselective Organocatalytic Aza-Diels–Alder Reaction Developed by Córdova



326a n=1 R^1=H Ar=PMP 82%; 99% ee
326b n=1 R^1=Me Ar=PMP 72%; >99% ee
326c n=2 R^1=H Ar=PMP 90%; 98% ee
326d n=1 R^1=Me Ar=Ph 54%; 96% ee

Scheme 151. Enantioselective Organocatalytic Diels–Alder Reaction Described by Córdova



328a n=1 R=Me Ar=Ph 93%: >25:1 d.r.; 78% ee
328b n=1 R=Me Ar=*p*$OMeC_6H_4$; 57%; >25:1 d.r.; 75% ee
328c n=1 R=Me Ar=*p*BrC_6H_4; 92%; >25:1 d.r.; 77% ee
328d n=1 R=Me Ar=*m*ClC_6H_4; 66%; >25:1 d.r.; 80% ee
328e n=1 R=H Ar=Ph 61%; >25:1 d.r.; 67% ee
328f n=2 R=H Ar=Ph 80%; >25:1 d.r.; 71% ee
328g n=0 R=H Ar=Ph 66%;>25:1 d.r.; 32% ee

synthesis of a variety of biologically relevant polypropionates.[308] Later on, the scope of this reaction was extended to a variety of ketenes, generated in situ from acid chlorides (Scheme 200).[309] In order to obtain more easily isolable products, the authors prepared in situ the corresponding Weinreb amides, affording the final compounds **406** in moderate to good yields and excellent enantiomeric excesses (91–97% ee).

In 2010, Pini, Mandoli, and co-workers reported the same reaction using as catalysts dimeric *Cinchona* alkaloid derivatives on a polystyrene support.[310] The reaction afforded the corresponding compounds **406** in good yields and excellent enantioselectivities.

Armstrong and co-workers reported the synthesis of *trans*-β-lactone carboxylates starting from ethyl glyoxylate and substituted ketenes. The reaction is efficiently ctatalyzed by dihydroquinidine esters at low temperatures, rendering the final lactones in very good enantioselectivities.[311]

In 2001, Romo and co-workers developed an intramolecular ketene–aldehyde formal [2 + 2]-cycloaddition leading to bicyclic *cis*-lactones, catalyzed by quinidine derivatives.[312] In this approach, the ketene was generated starting from a carboxylic acid using Mukaiyama's reagent (**A**). Catalyst **CXIII** turned out to be highly stereoselective for this reaction, yielding the cycloadducts **408** in excellent enantiomeric excesses (Scheme 201). Interestingly, changing the catalyst to β-isocupreidine resulted in a complete reversal of enantioselectivity with identical levels of asymmetric induction.

Arguably, the most important [2 + 2]-cycloaddition is the so-called Staudinger cycloaddition reaction. The Staudinger reaction, an overall [2 + 2]-cycloaddition of a ketene with an imine, provides an efficient, convergent route to β-lactams. Although a number of chiral auxiliary-based asymmetric Staudinger processes have been described, there are some organocatalytic and enantioselective examples in the literature. Lectka and co-workers demonstrated that, using a quinine derivative as the catalyst, the highly stereoselective coupling of a range of monosubstituted ketenes, as well as a symmetrically disubstituted ketene, with imines could be achieved; one important limitation of this methodology is that only one imine, derived from glyoxylate, was shown to be a suitable reaction partner.[313] Several years later, Fu and co-workers reported a highly enantioselective Staudinger cycloaddition catalyzed by planar-chiral PPY derivatives such as **CXIV**.[314] The lactams **410** were obtained in excellent yields and enantioselectivities, as depicted in Scheme 202.

Very recently, Zajac and Peters uncovered a procedure for the asymmetric synthesis of β-sultams starting from *N*-sulfonyl imines and alkyl sulfonyl chlorides.[315] When activated imines were used in this reaction, quinine afforded the cyclic products with good enantio- and diastereoselectivities (10:1 to 20:1 dr, 78–94% ee). On the other hand, the reaction of aryl imines required the use of a Lewis acid cocatalyst and an ether additive (15:1 to 51:1 dr, 73–85% ee).

In 2008, Smith and co-workers reported the first chiral *N*-heterocyclic carbene-catalyzed β-lactam synthesis between ketenes and *N*-tosyl imines.[316] The reaction affords the corresponding β-lactams in good yields, but with moderate enantioselectivities (80–96% yield, 55–75% ee).

In 2007, Ishihara and Nakano reported the first cycloaddition of unactivated alkenes with α-acylacroleins, catalyzed by chiral organoammonium salts.[317] The reaction afforded the corresponding cyclobutanes **412** in good stereoselectivities, albeit with moderate yields, as shown in Scheme 203. The resulting cyclobutenes rearrange under basic or acid conditions to cyclopentenones in good yields without losing enantiomeric purity.

6. ORGANOCATALYTIC TWO-COMPONENT CYCLIZATION REACTIONS

6.1. Synthesis of Carbocycles

The synthesis of carbocycles by annulation reactions in an asymmetric fashion has attracted much attention from the chemical community. In particular, the syntheses of cyclopropanes, cyclopentanes, and cyclohexanes have been one of the common goals for organocatalytic chemists. The high level of

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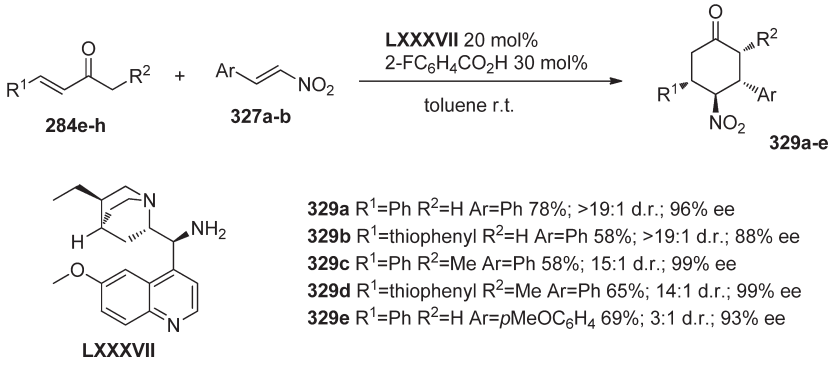
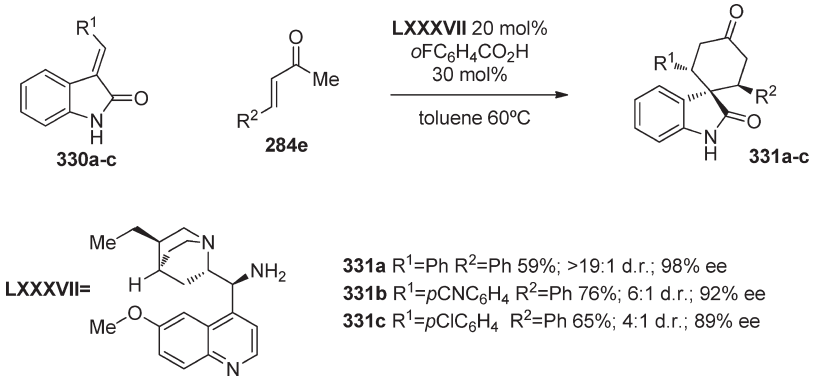
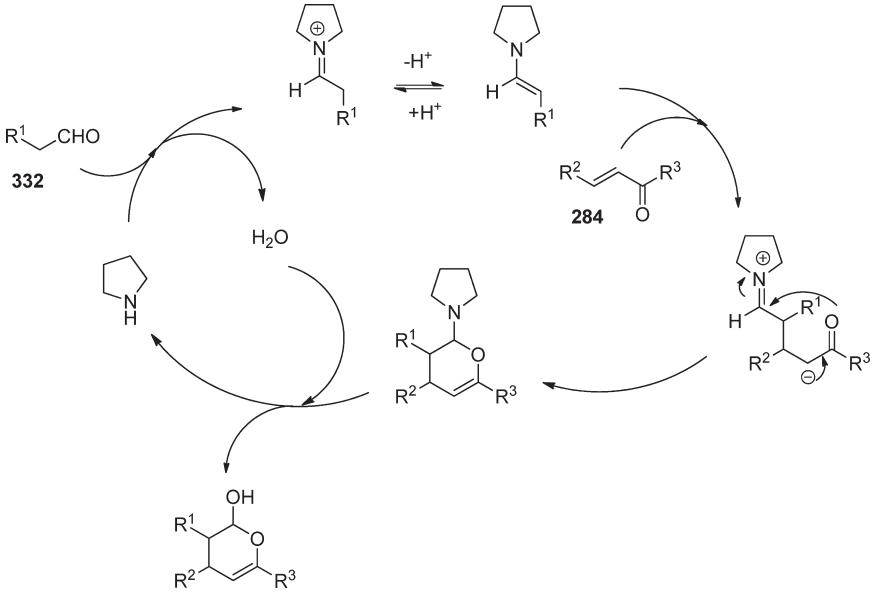
Scheme 152. Enantioselective Organocatalytic Diels–Alder Reaction Described by Melchiorre



Scheme 153. Diels–Alder Reaction Developed by Melchiorre



Scheme 154. Inverse-Electron-Demand Hetero-Diels–Alder Reaction via Enamine Activation



stereoselectivity achieved makes this organocatalytic aproximation one of the most effective methodologies to build complex cyclic scaffolds.

6.1.1. Organocatalytic Asymmetric Synthesis of Cyclopropanes[318]. The first example of enantioselective organocatalytic synthesis of cyclopropanes was developed by

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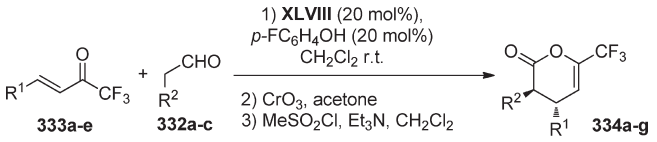
MacMillan and Kunz in 2005.[319] Their methodology deals with the reaction between enals (**277**) and benzoylmethyl sulfonium ylides (**413**) to afford the final cyclopropanes (Scheme 204).

In the catalyst screening, MacMillan realized that, in the transition state, the iminium ion and the ylide might engage in an electrostatic association via the pendant carboxylate and the thionium substituents, respectively. In this scenario, MacMillan's imidazolidinones were electronically averse to this association and were revealed to be inert in this reaction (0% conversion). The use of proline (**I**) provided good levels of reaction efficiency (72% conversion) but moderate enantiocontrol (46% ee). They assumed that the zwitterion iminium ion derived from proline (Scheme 205a) could readily populate both (*E*) and (*Z*) iminium isomers. This equilibrium led to a diminished enantiocontrol.

In order overcome this limitation, MacMillan used dihydroindole 2-carboxylic acid (**CXV**) as the catalyst. In order to minimize the repulsive steric interaction between the olefinic substrate and the arylic hydrogen, the iminium ion predominantly adopts a (*Z*)-configuration (Scheme 205b), raising the enantiocontrol up to 96% ee.

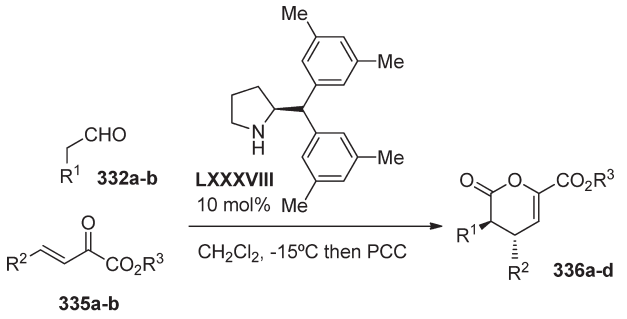
This activation mode was called directed electrostatic activation (DEA). To validate the proposed DEA mechanism, they proved that the reaction only worked with enals but not with other electron-deficient olefins, such as unsaturated nitriles, nitroalkenes or alkylidene malonate systems, supporting an iminium-mediated pathway. Moreover, *N*- or *O*-methylation of the catalyst suppressed completely their catalytic activity, also consistent with the need for a zwitterionic iminium intermediate.

Scheme 155. Inverse-Electron-Demand Hetero-Diels–Alder Reaction Developed by Liu



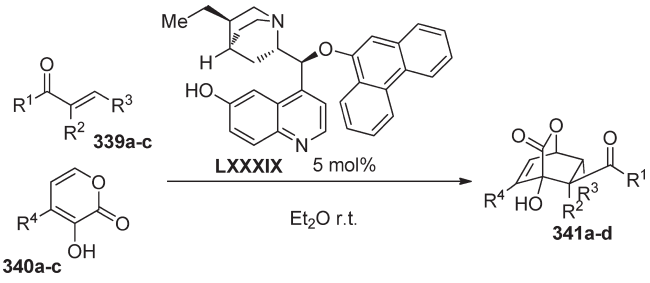
334a R^1=Ph R^2=Me 63%; >95:5 d.r.; 97% ee
334b R^1=*p*ClC_6H_4 R^2=Me 62%; >95:5 d.r.; 97% ee
334c R^1=*p*BrC_6H_4 R^2=Me 63%; >95:5 d.r.; 95% ee
334d R^1=*p*MeOC_6H_4 Ph R^2=Me 57%; >95:5 d.r.; 93% ee
334e R^1=1-Naphtyl R^2=Me 50%; >95:5 d.r.; 92% ee
334f R^1=Ph R^2=Bn 51%; 94:6 d.r.; 46% ee
334g R^1=Ph R^2=iPr 71%; 95:5 d.r.; 93% ee

Scheme 156. Enantioselective Inverse-Electron-Demand Diels–Alder Reaction Developed by Jørgensen



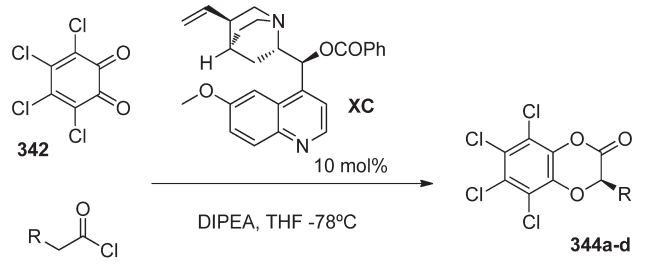
336a R^1=Et R^2=Ph R^3=Me 69%; 84% ee
336b R^1=Bn R^2=Ph R^3=Me 65%; 86% ee
336c R^1=Et R^2=Me R^3=Et 81%; 86% ee
336d R^1=Bn R^2=Me R^3=Et 72%; 89% ee

Scheme 158. Diels–Alder Reaction Reported by Deng



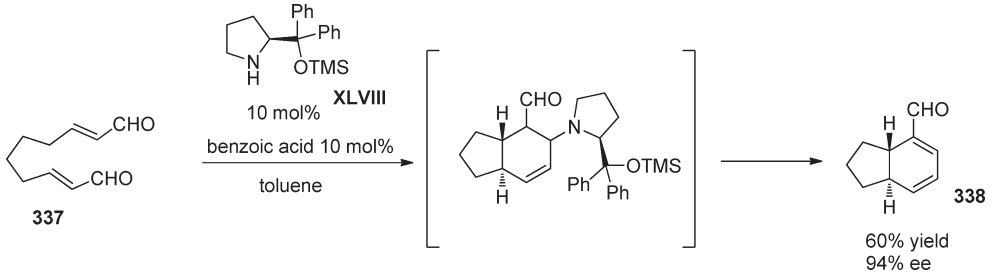
341a R^1=Ph R^2=H R^3=CO_2Et R^4=H 87%; 93:7 exo:endo; 94% ee exo
341b R^1=Me R^2=Me R^3=H R^4=H 65%; 24:76 exo:endo; 91% ee endo
341c R^1=Ph R^2=H R^3=CO_2Et R^4=Me 77%; 88:12 exo:endo; 82% ee exo
341d R^1=Ph R^2=H R^3=CO_2Et R^4=Cl 75%; 86:14 exo:endo; 84% ee exo

Scheme 159. Diels–Alder Reaction Reported by Lectka



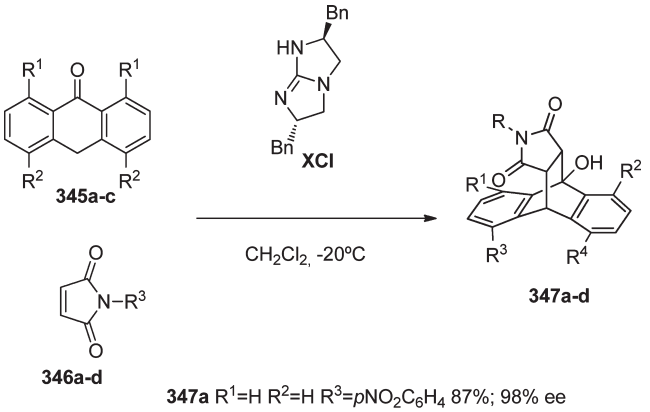
344a R=Et 91%, 99% ee
344b R=Ph 90%; 90% ee
344c R=Bn 72%; 99% ee
344d R=*p*MeOC_6H_4 58%; 99% ee

Scheme 157. Enantioselective Organocatalytic Diels–Alder Reaction Developed by Christmann



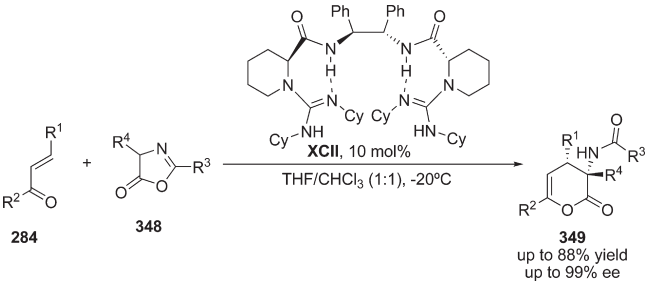
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 160. Diels−Alder Reaction Reported by Tan, Catalyzed by Chiral Guanidines



347a R^1=H R^2=H R^3=*p*$NO_2C_6H_4$ 87%; 98% ee
347b R^1=Cl R^2=H R^3=Bn 92%; 95% ee
347c R^1=H R^2=Cl R^3=Ph 92%; 99% ee
347d R^1=Cl R^2=H R^3=$MeCO_2$ 83%; 64% ee

Scheme 161. Inverse-Electron-Demand Hetero-Diels−Alder Reaction of Chalcones with Oxazolones



The next examples of enantioselective cyclopropanation of enals were reported in 2007. Córdova and co-workers[320] and several month later Wang and co-workers[321] developed a simple and highly diastereo- and enantioselective cyclopropanation via

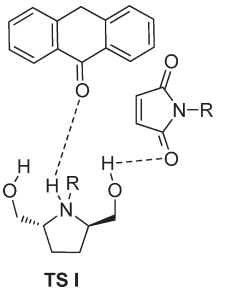
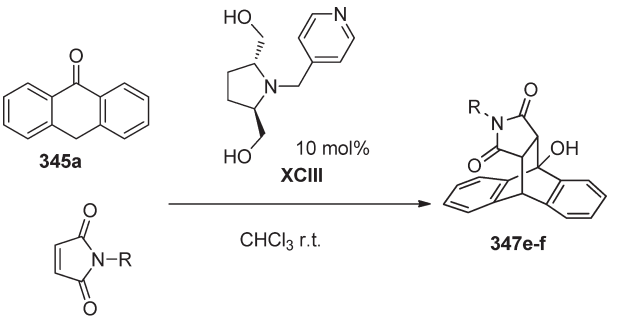


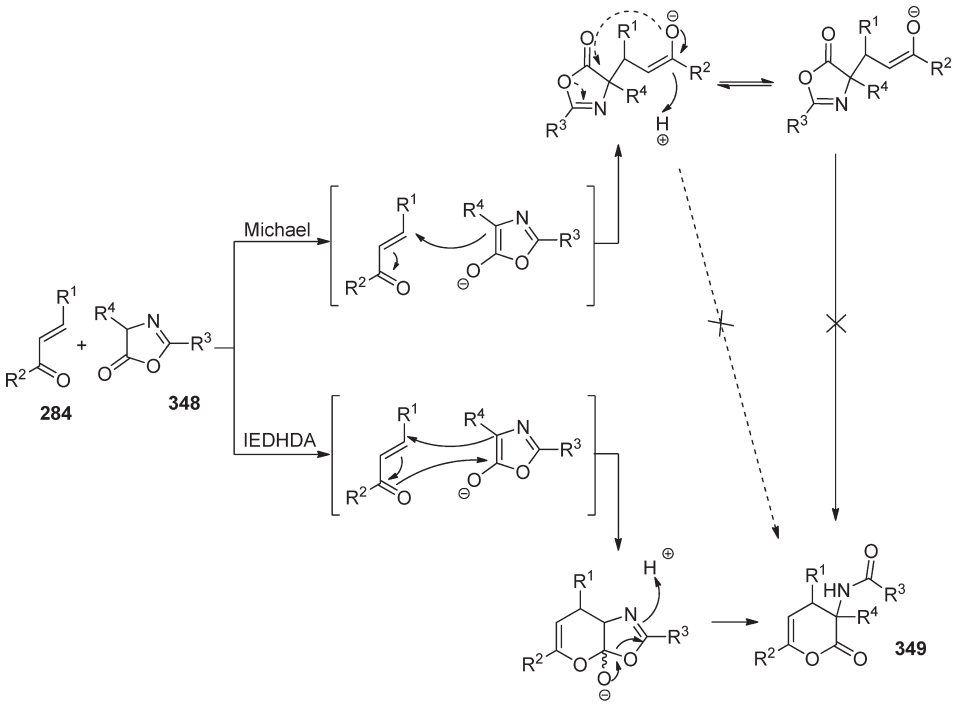
Figure 28. Transition state model for the reaction depicted in Scheme 163.

Scheme 163. Anthrone Addition to Maleimides Reported by Yamamoto



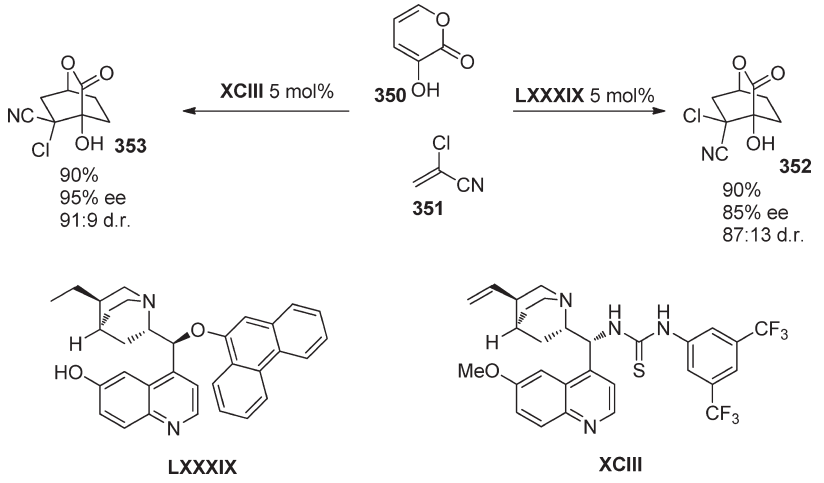
347e R=Me 99%; 74% ee
347f R=Bn 82%; 70% ee

Scheme 162. Possible Reaction Pathways of Chalcones (284) with Oxazolones (348)

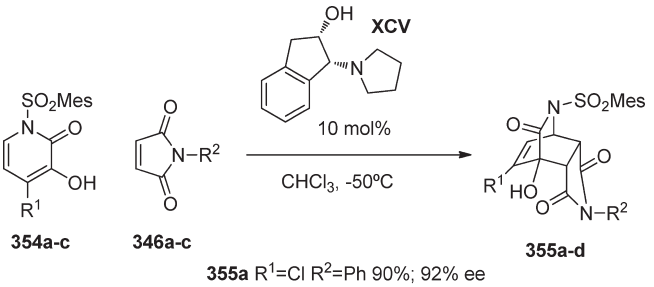


dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 164. Diels−Alder Reaction Reported by Deng

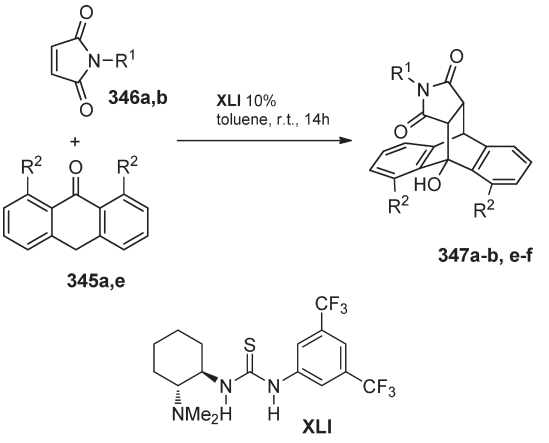


Scheme 165. Diels−Alder Reaction Reported by Tan



355a R^1=Cl R^2=Ph 90%; 92% ee
355b R^1=Br R^2=Bn 92%; 90% ee
355c R^1=Allyl R^2=Ph 89%; 87% ee
355d R^1=Cl R^2=Et 88%; 94% ee

Scheme 166. Diels−Alder Reaction Reported by Moyano and Rios



347a R^1=Ph R^2=H 91%; 90% ee
347b R^1=Bn R^2=H 92%; 83% ee
347e R1=Ph R^2=OH 93%; 99% ee
347f R^1=Bn R^2=OH 92%; 86% ee

the reaction of enals (**277**) and 2-bromomalonates (**415**) in the presence of diphenylprolinol-derived catalyst **XLVIII**, based on the Michael addition and subsequent intramolecular α-alkylation (i.e., a Bingel−Hirsch reaction) of the enamine intermediate to furnish the cyclopropane motif (Scheme 206).

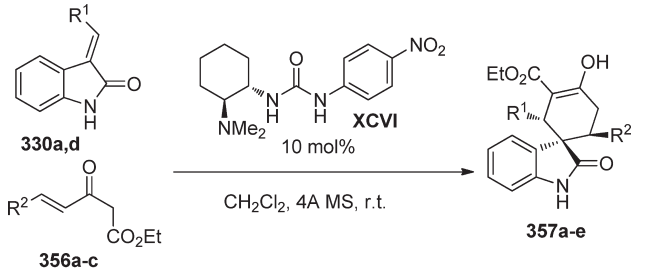
Among the enals (**277**) cyclopropanated, the best results were obtained with aromatic unsaturated aldehydes, achieving a total trans diastereoselectivity and excellent enantioselectivities. When aliphatic aldehydes were used, the trans/cis ratio diminished up to 9:1−15:1, maintaining the high enantiocontrol.

The only difference between Córdova's work and Wang's work was the use of 2,6-lutidine as a base instead of triethylamine in the case of the cyclopropanation reported by Wang.

In 2010, Vicario and co-workers expanded the scope of the reaction by using water as the solvent, achieving similar results to those reported by Córdova.[322]

Recently, Moyano, Rios, and co-workers[323] have developed an improvement of the previous results reported by Cordova[320] and Wang,[321] employing 2-bromo keto esters (**416**). The formation of only two diastereomers, both of them having a trans relationship between the formyl group and the R^1 substituent and differing only in the configuration to the new quaternary stereocenter, was observed. The relative configuration of the substituents of the cyclopropane ring was ascertained by NMR studies (Scheme 207).

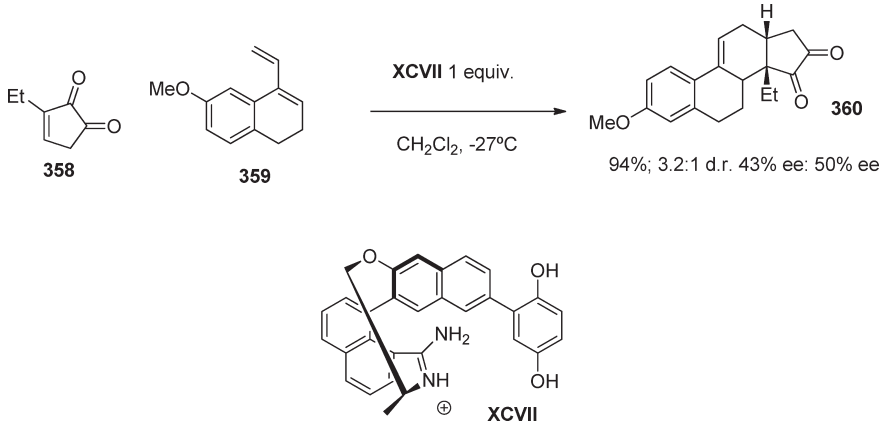
Scheme 167. [4 + 2]-Cycloaddition Reported by Gong



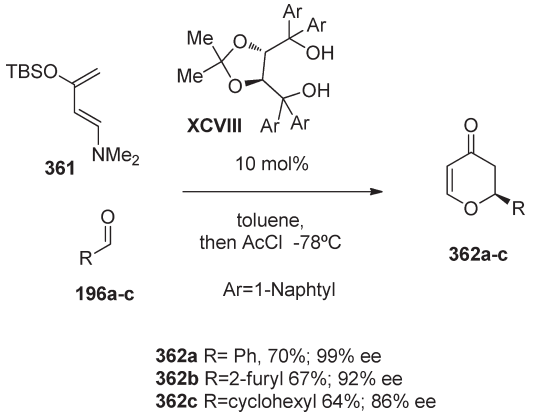
357a R^1=Ph R^2=Ph 86%; 96:4 d.r.; 95% ee
357b R^1=Pr R^2=Ph 91%; 99:1 d.r.; 90% ee
357c R^1=Ph R^2=Pr 89%; 97:3 d.r.; 90% ee
357d R^1=CO_2Et R^2=OMe 29%; 99:1 d.r.; 93% ee
357e R^1=CO2Et R^2=Ph 80%; 94:6 d.r.; 96% ee

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

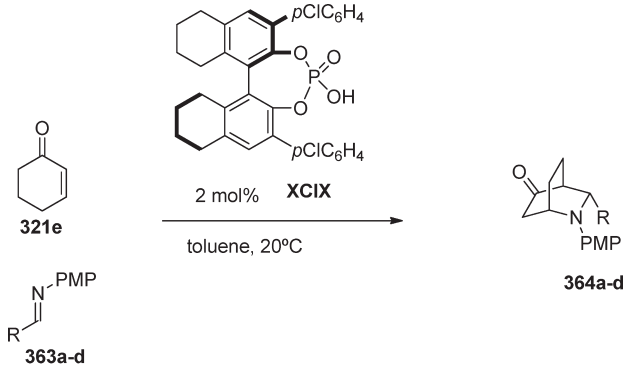
Scheme 168. Diels−Alder Reaction Catalyzed by Amidinium Ion



Scheme 169. Diels−Alder Reaction Catalyzed by TADDOL

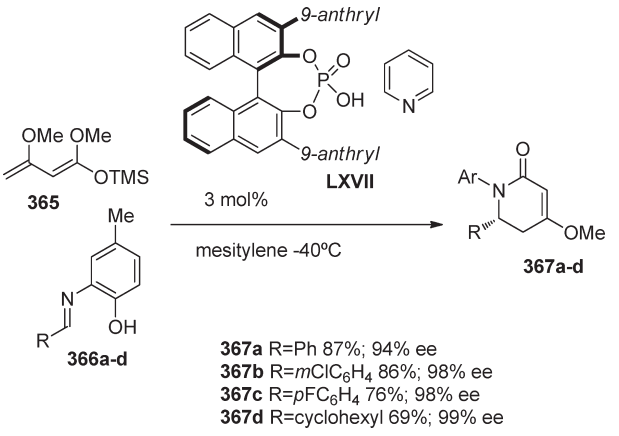


Scheme 170. Hetero-Diels−Alder Reaction Reported by Gong



This modification allows for the synthesis of chiral cyclopropanes (**417**) containing a quaternary carbon with high diastereo- and enantiocontrol. To determine the relative configuration of the quaternary carbon formed, the authors

Scheme 171. Hetero-Diels−Alder reaction reported by Akiyama



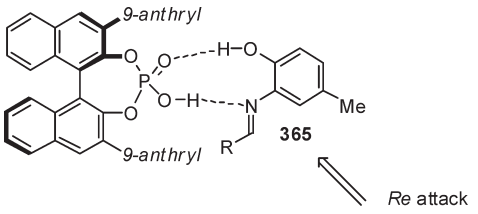


Figure 29. Activation of imine proposed by Akiyama.

performed NOE experiments on the major diastereomers, observing in all cases a cis relationship between the keto group and the R^1 moiety and a trans relationship between this substituent and the formyl group. The absolute configuration of adducts **417** was assumed to be that expected by the general stereochemical outcome of enantioselective Michael additions catalyzed by **XLVIII**.

In 2010, Campagne and co-workers reported the cyclopropanation of α-substituted-α,β-unsaturated aldehydes with bromomalonates, catalyzed by diphenylprolinol derivatives, obtaining the corresponding cyclopropanes in good yields and enantioselectivities.[324] The reaction was limited to

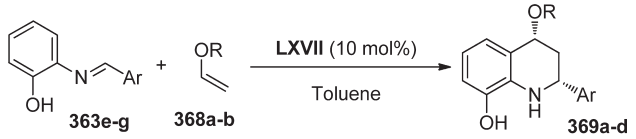
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

β-unsubstituted unsaturated aldehydes, probably due their low reactivity.

In 2008, Córdova and co-workers reported a novel nitrocyclopropanation of α,β-unsaturated aldehydes employing bromonitromethane (**418**).[325] The reaction was efficiently catalyzed by Jørgensen's diphenylprolinol derivative (**XLVIII**) and afforded the corresponding cyclopropanes **419** in good yields and excellent enantioselectivities, albeit with low diastereoselectivities (Scheme 208).

In 2009, Takemoto and co-workers reported a similar approach using α,β-unsaturated-α-cyanoimides and bromonitromethane.[326] The reaction was efficiently promoted by bifunctional thiourea catalysts such as **XLI** (Takemoto's catalyst). The corresponding cyclopropanes **421** were isolated in excellent yields and enantioselectivities. One of the limitations of this methodology was the need to use 2-fluorobenzylamide derivatives as starting materials in order to obtain good enantioselectivities, and another one was the poor diastereoselectivities obtained (Scheme 209).

Scheme 172. Inverse-Electron-Demand Aza-Diels−Alder Reaction



369a Ar=Ph R=Et 89%; 99:1 d.r.; 94% ee
369b Ar=*p*BrC$_6$H$_4$ R=Et; 77%; 99:1 d.r.; 90% ee
369c Ar=Ph R=Bn 76%; 99:1 d.r.; 91% ee
369d Ar=2-Naphtyl R=Et 74%; 99:1 d.r.; 95% ee

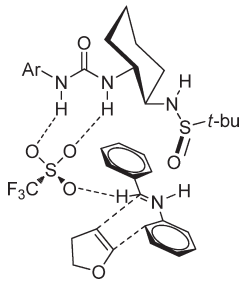
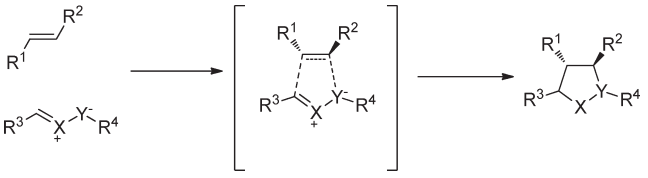


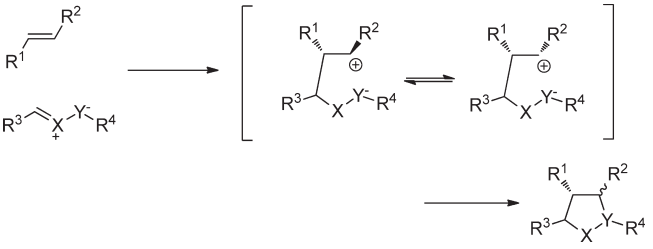
Figure 30. Proposed transition state for the Povarov reaction catalyzed by **C**.

In 2006, Ley and co-workers reported an asymmetric organocatalytic intermolecular cyclopropanation reaction between enones and bromonitromethane,[327] which used (*R*)-5-(pyrrolidin-2-yl)-1*H*-tetrazole (*ent*-**LXXXVI**) as the catalyst. The nitrocyclopropanation

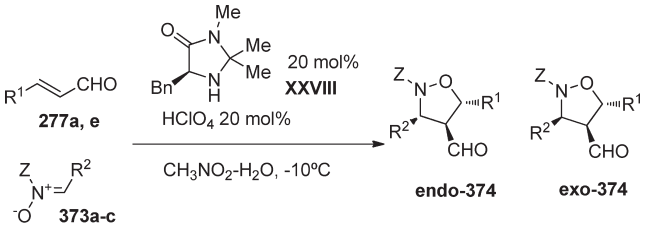
Scheme 174. General Concerted 1,3-Dipolar Cycloaddition



Scheme 175. General Non-Concerted 1,3-Dipolar Cycloaddition

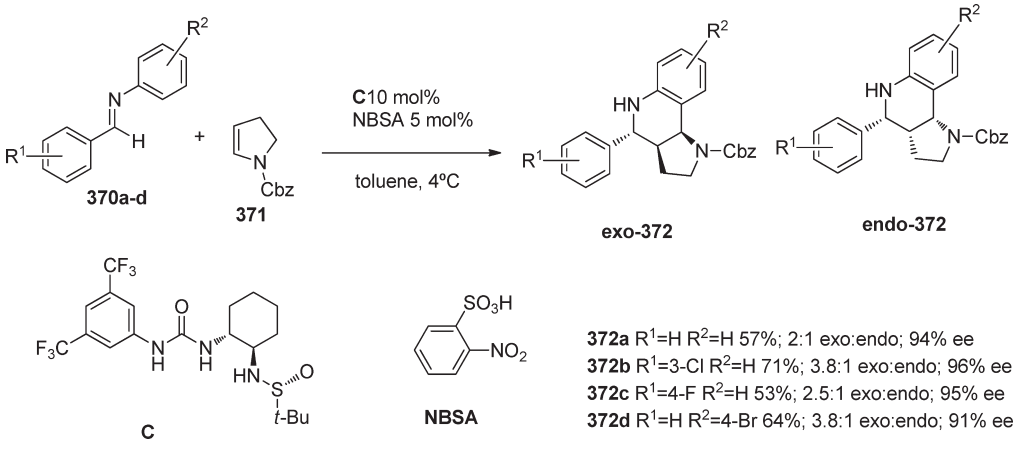


Scheme 176. Enantioselective 1,3-Dipolar Cycloaddition of Nitrones Developed by MacMillan



374a Z=Bn R^1=Me R^2=Ph 98%; 94:6 endo:exo; 94% ee endo
374b Z=Allyl R^1=Me R^2=Ph 73%; 93:7 endo:exo; 98% ee endo
374c Z=Me R^1=Me R^2=Ph 66%; 95:5 endo:exo; 99% ee endo
374d Z=Bn R^1=Me R^2=cyclohexyl 70%; 99:1 endo:exo; 99% ee endo
374e Z=Bn R^1=H R^2=Ph 72%; 81:19 endo:exo; 90% ee endo

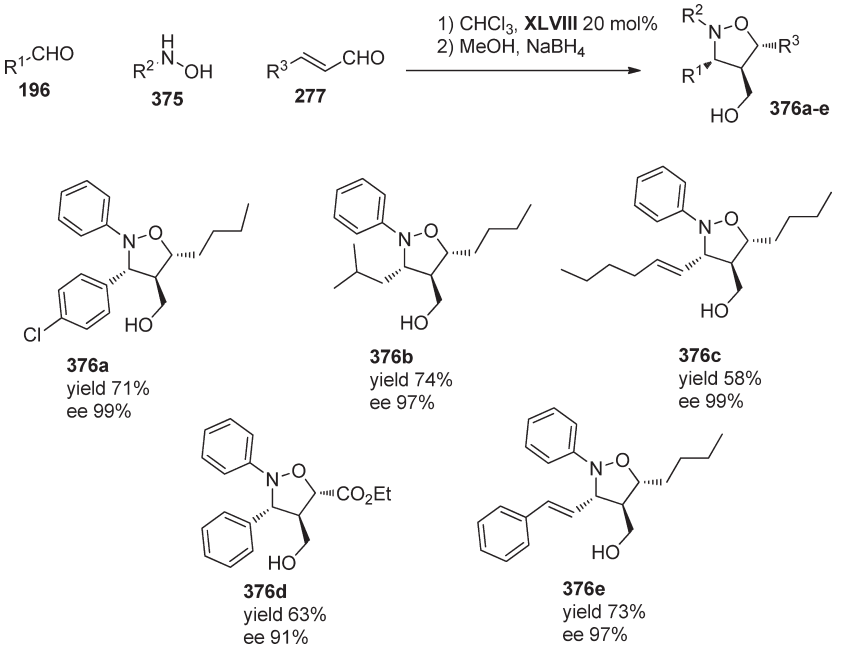
Scheme 173. Asymmetric Organocatalytic Povarov Reaction Reported by Jacobsen



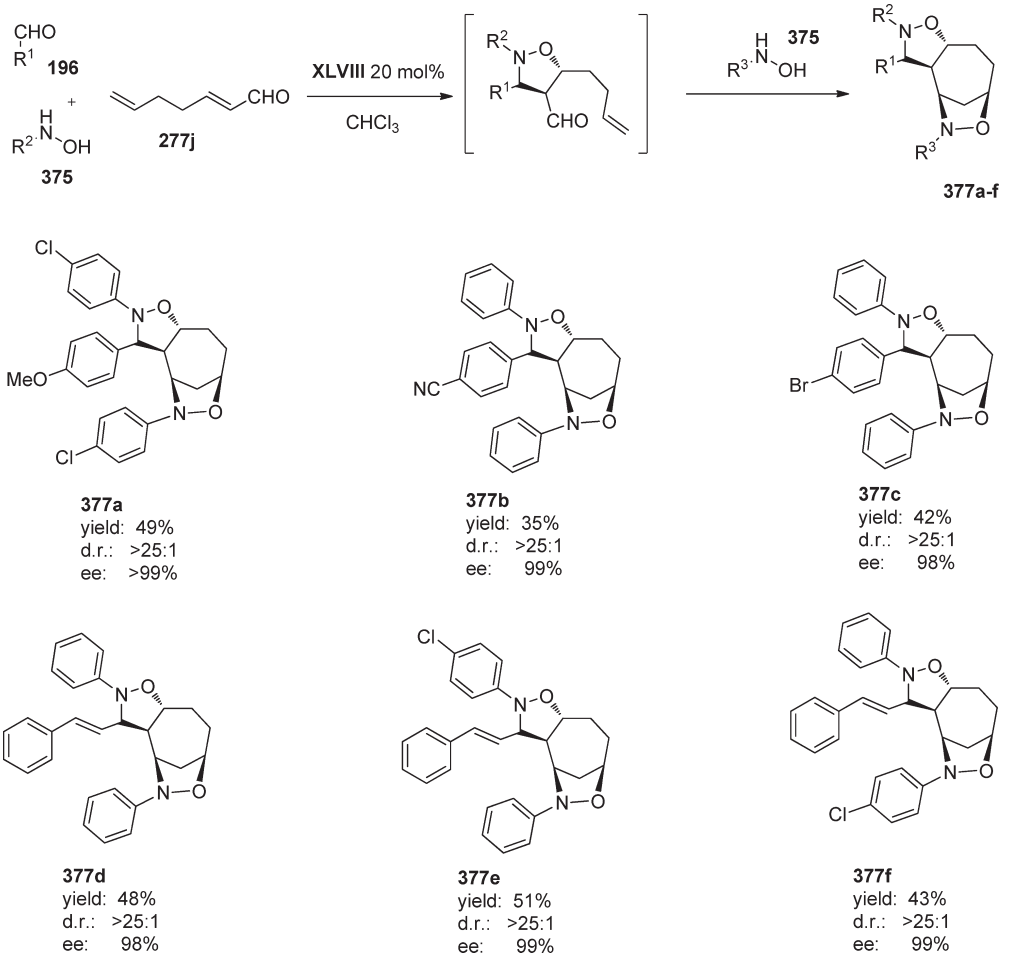
372a R^1=H R^2=H 57%; 2:1 exo:endo; 94% ee
372b R^1=3-Cl R^2=H 71%; 3.8:1 exo:endo; 96% ee
372c R^1=4-F R^2=H 53%; 2.5:1 exo:endo; 95% ee
372d R^1=H R^2=4-Br 64%; 3.8:1 exo:endo; 91% ee

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 177. Three-Component 1,3-Dipolar Cycloaddition of Nitrones Developed by Córdova



Scheme 178. Synthesis of Cycloheptanes Reported by Córdova



dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

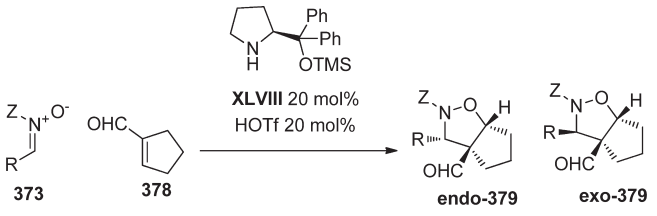
of 2-cyclohexen-1-one (**321b**) was achieved, setting up three new stereogenic centers in a single operation and proceeding in high yield (80%) and with good enantioselective control (up to 77% ee). An important point for the success of the reaction is the need of an excess of base, which is needed probably to trap the hydrobromic acid generated in the process (Scheme 210).

Very recently, Yan and co-workers have reported the same reaction under bifunctional catalysis by primary amines bearing a thiourea moiety. The final compounds were obtained in good yields and excellent enantioselectivities. However, the scope of the reaction was very narrow, only allowing the use of cyclic enones.[328]

In 2008, Ley and co-workers expanded the scope of the reaction by using a variety of cyclic and acyclic enones (Scheme 211). Unfortunately, the reaction seems to be very dependent on the structure of the enone, so that when enones other than cyclohexenone were used the stetereoselectivities decreased dramatically.[329]

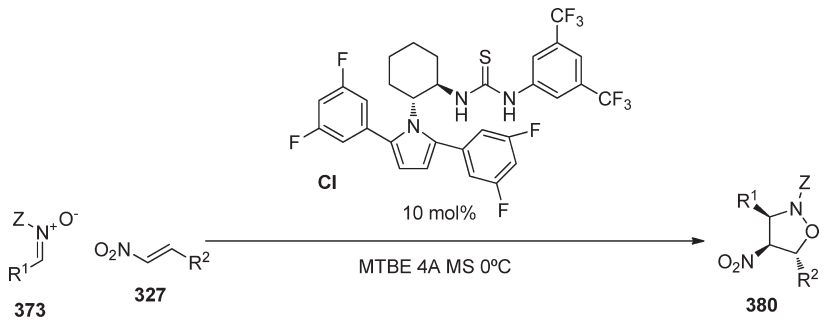
In 2006, Connon and co-workers developed an elegant and convenient cyclopropanation reaction of β-nitrostyrenes (**327**) with 2-chloromalonates (**425**).[330] The reaction was efficiently catalyzed by chiral thioureas (**CXVI**) and needed 1 equiv of base for the final cyclization. The reaction works with aromatic and aliphatic nitroalkenes, rendering the final cyclopropanes (**426**) in good yields and excellent diastereoselectivities (>99:1 dr). Mechanistically, the chloromalonate addition to nitroalkenes takes place first and a consequent intramolecular alkylation activated by base furnishes the corresponding cyclopropanes. However, the enantioselectivity was only poor to moderate in all of the examples (Scheme 212).

Scheme 179. Asymmetric 1,3-Dipolar Cycloaddition of Nytrones Developed by Nevalainen



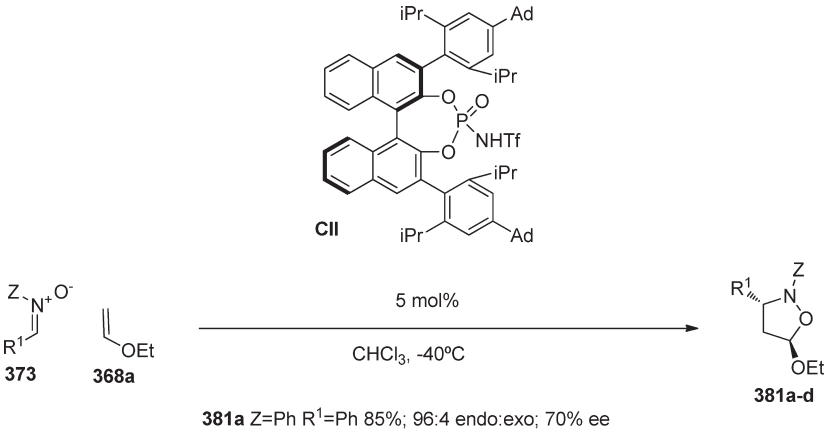
379a Z=Bn R=Ph 66%; 80:20 endo:exo 46% ee
379b Z=Me R=Ph 75%; 79:21 endo:exo 83% ee
379c Z=Bn R=Naph 75%; 90:10 endo:exo 37% ee

Scheme 180. Exo-Selective Asymmetric 1,3-Dipolar Cycloaddition of Nitrones Developed by Chen



380a Z=Ph R^1=Ph R^2=iPr 79%; 82% ee
380b Z=Ph R^1=Ph R^2=Cyclohexyl 85%; 83% ee
380c Z=Ph R^1=Tol R^2=Et 71%; 86% ee
380d Z=*p*FC_6H_4 R^1=Ph R^2=Et 65%; 84% ee

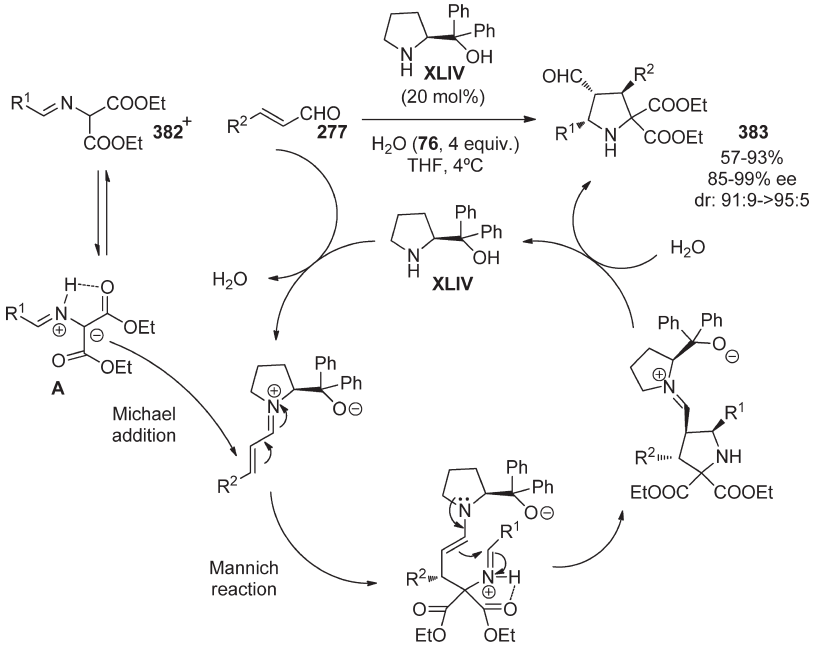
Scheme 181. Asymmetric 1,3-Dipolar Cycloaddition of Vinyl Ethers Reported by Yamamoto



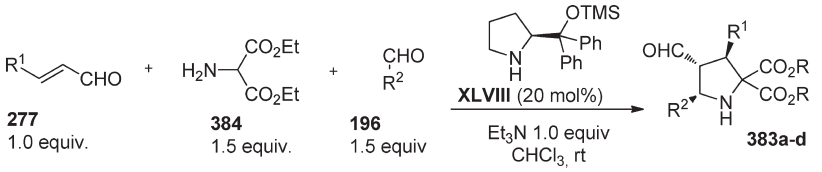
381a Z=Ph R^1=Ph 85%; 96:4 endo:exo; 70% ee
381b Z=*p*FPh R^1=*p*FPh 76%; 87:13 endo:exo 85% ee
381c Z=*p*FPh R^1=2-furyl 90%; 88:12 endo:exo 87% ee
381d Z=*p*FC_6H_4 R^1=2-thienyl 97%; 93:7 endo:exo 87% ee

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 182. Asymmetric 1,3-Dipolar Cycloaddition of Azomethyne Ylides Reported by Vicario et al.

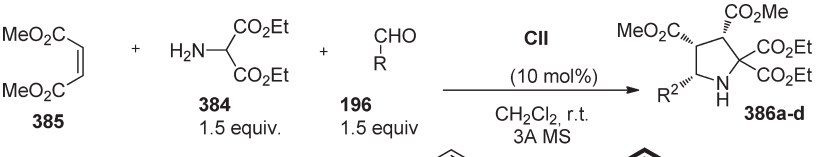


Scheme 183. Enantioselective 1,3-Dipolar Cycloaddition of Azomethyne Ylides Reported by Córdova et al.

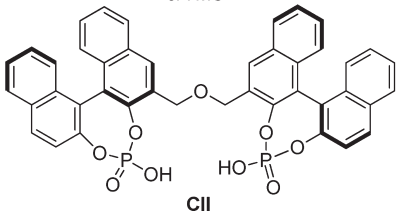


383a R^1=Ph R^2=Ph 63% 10: d.r.; 95% ee
383b R^1=*n*-Bu R^2=Ph 51% 10: d.r.; 95% ee
383c R^1=n-Pr R^2=*p*BrC_6H_4 57% 5: d.r.; 98% ee
383d R^1=Et R^2=*p*ClC_6H_4 55% 5: d.r.; 92% ee

Scheme 184. Asymmetric 1,3-Dipolar Cycloaddition of Azomethyne Ylides Reported by Gong et al.



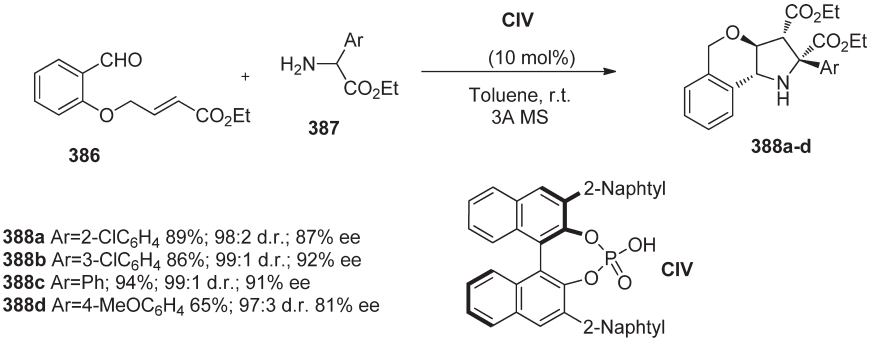
386a R=Ph 93%; 91% ee
386b R=*p*BrC_6H_4 89%; 99% ee
386c R=*p*MeOC_6H_4 87%; 90% ee
386d R=cyclohexyl 74%; 76% ee



Very recently, Yan and co-workers uncovered an improved methodology for the cyclopropanation of nitroalkenes, based on the addition of 2-bromomalonates (**415**) to nitroalkenes (**327**), catalyzed by *Cinchona* alkaloids (cupreine, **CXVII**).[331] The reaction proceeds with excellent yields and diastereo- and enantioselectivities. In this improved protocol, Yan and co-workers use DABCO as a cocatalyst in order to facilitate the final intramolecular alkylation after the first Michael addition (Scheme 213).

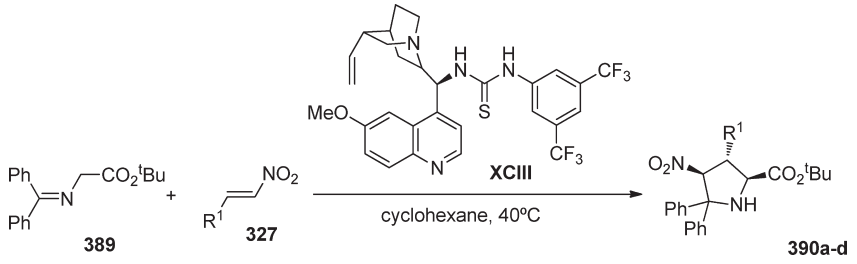
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 185. Intramolecular 1,3-Dipolar Cycloaddition of Azomethyne Ylides Reported by Gong et al.



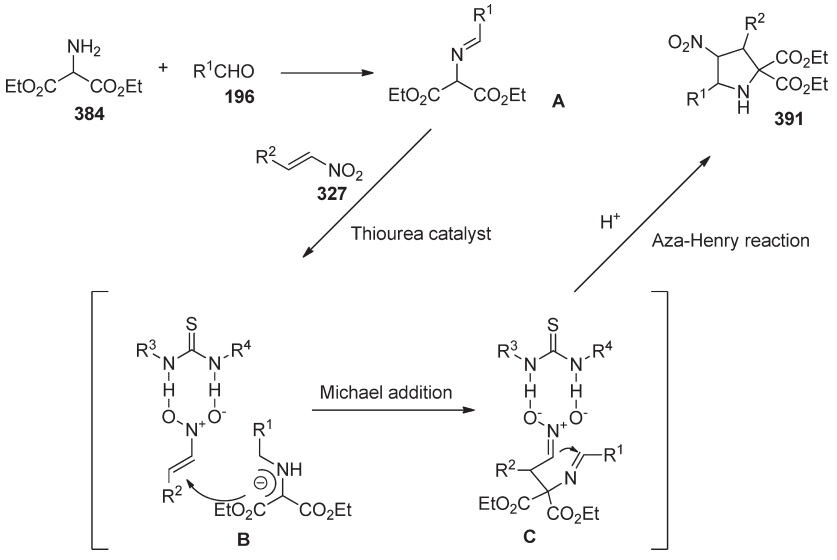
388a Ar=2-ClC$_6$H$_4$ 89%; 98:2 d.r.; 87% ee
388b Ar=3-ClC$_6$H$_4$ 86%; 99:1 d.r.; 92% ee
388c Ar=Ph; 94%; 99:1 d.r.; 91% ee
388d Ar=4-MeOC$_6$H$_4$ 65%; 97:3 d.r. 81% ee

Scheme 186. First 1,3-Dipolar Cycloaddition of Azomethyne Ylides with Nitroalkenes Reported by Gong et al.



390a R^1=Ph 77%; 93:7 d.r.; 63% ee
390b R^1=Tol 56%; 95:5 d.r.; 62% ee
390c R^1=*m*MeC$_6$H$_4$ 68%; 88:12 d.r.; 62% ee
390d R^1=*p*FC$_6$H$_4$ 49%; 87:13 d.r.; 50% ee

Scheme 187. Proposed Mechanism for the formal [3 + 2] Cycloaddition

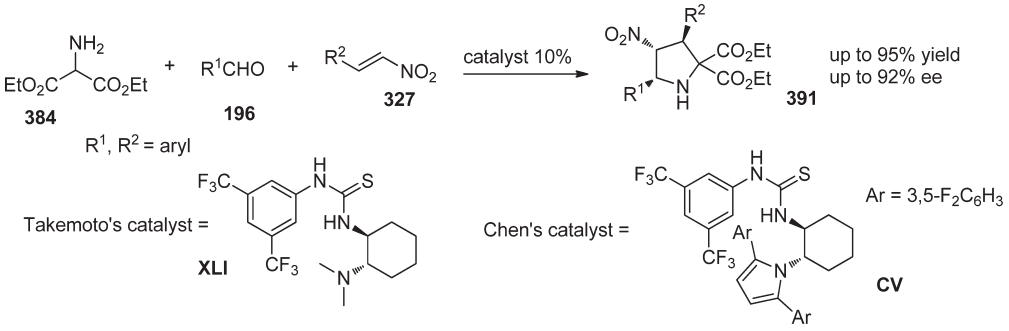


6.1.2. Synthesis of Five-Membered Carbocycles. In 2007, employing a tandem Michael−α-alkylation sequence similar to that previously reported in their cyclopropanation, Córdova and co-workers developed an enantioselective synthesis of cyclopentanones (**428**) and cyclopentanols (**429**) starting from enals (**277**) (Scheme 214).[320b,332]

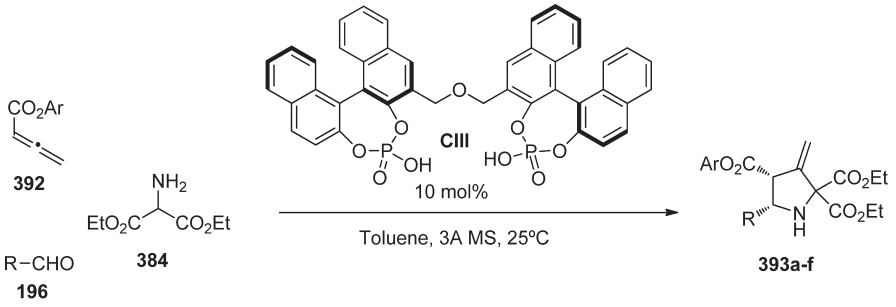
Using 4-bromo-acetoacetate **427**, under the effect of 20 mol % of catalyst **XLVIII** and 1 equiv of potassium carbonate, formed

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 188. Formal [3 + 2]-Cycloaddition Reported by Takemoto and Chen

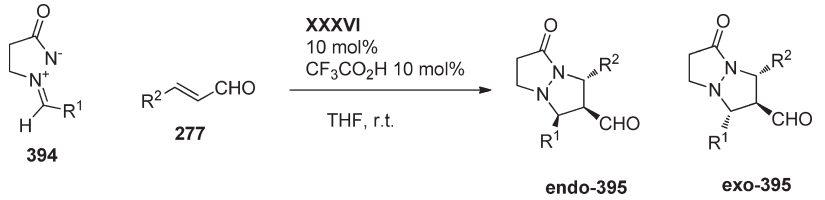


Scheme 189. Asymmetric [3 + 2]-Cycloaddition Reported by Gong



393a Ar=Bn R=pNO$_2$C$_6$H$_4$ 85%; 50% ee
393b Ar=9-AnCH$_2$ R=pNO$_2$C$_6$H$_4$ 98%; 90% ee
393c Ar=1-NaphCH$_2$ R=pNO$_2$C$_6$H$_4$ 68%; 88% ee
393d Ar=9-AnCH$_2$ R=Ph 84%; 92% ee
393e Ar=9-AnCH$_2$ R=2-furan 98%; 75% ee
393f Ar=9-AnCH$_2$ R=Pr 90%; 69% ee

Scheme 190. Formal [3 + 2]-Cycloaddition of Azomethyne Imines Reported by Chen



395a R^1=Ph R^2=Me 85%; 84:16 exo:endo; 96% ee
395b R^1=Ph R^2=n-Pr 95%; 95:5 exo:endo; 95% ee
395c R^1=pClC$_6$H$_4$ R^2=Me 80%; 81:19 exo:endo; 96% ee
395d R^1=n-Pr R^2=Me 40%; 95:5 exo:endo; 77% ee
395e R^1=Ph R^2=Ph No Reaction

cyclopentanones with three new stereocenters (**428**) in good to high yields, 6:1−12:1 dr, and 93−99% ee.

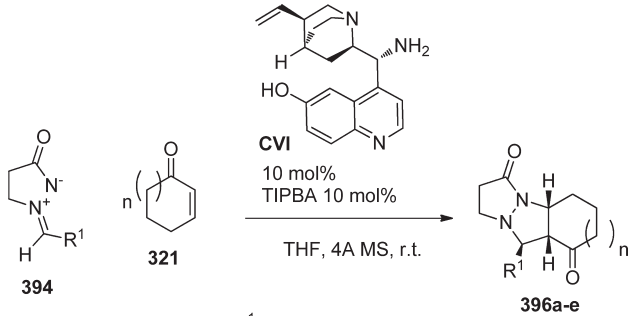
Moreover, the chemoselective reduction of **428** with $NaBH_3CN$, furnished the corresponding cyclopentanols (**429**) containing four stereocenters with excellent diastereoselectivity, without affecting the enantiomeric excess (R = Et, 63% yield, >25:1 dr, 98% ee; Scheme 215). One of the limitations of this methodology is the need to use aliphatic enals due the poor reactivity of aromatic enals in the optimized reaction conditions.

Soon after, Wang and co-workers made two contributions to the synthesis of highly functionalized chiral five-membered carbocycles, both initiated with a carboconjugated addition of malonate derivatives (Scheme 216). The first one, an asymmetric double Michael addition between enals (**277**) and γ-malonate-α,β-unsaturated esters (**430**),[333] was catalyzed by **XLVIII** in ethanol to afford cyclopentanes (**432**) with three stereogenic centers. The final products were isolated with high yields (87−92%) as well as excellent diastereo- (9:1→20:1 dr) and enantioselectivities (84−99% ee).

The second contribution of Wang et al. was focused on the synthesis of cyclopentenes (**433**).[334] On the basis of a Michael−aldol sequence followed by dehydration between

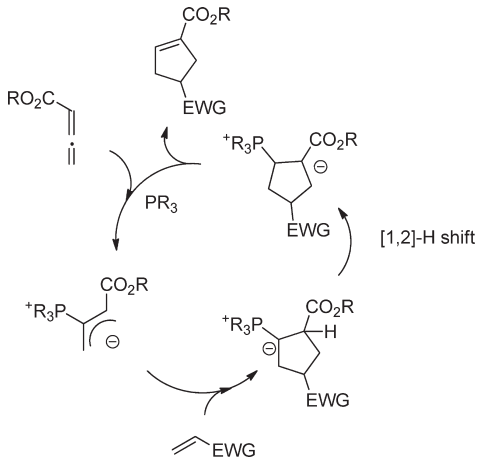
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 191. Formal [3 + 2]-Cycloaddition of Azomethyne Imines with Enones Reported by Chen

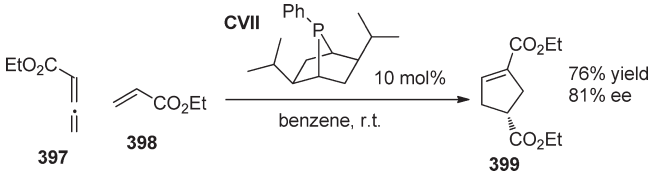


396a n=1 R^1=Ph 89%; 90% ee
396b n=1 R^1=*p*ClC_6H_4 73%; 92% ee
396c n=1 R^1=*n*-Pr 76%; 91% ee
396d n=0 R^1=Ph 78%; 90% ee
396e n=2 R^1=*p*$MeOC_6H_4$ 76%; 93% ee

Scheme 192. General Mechanism for the [3 + 2]-Cycloaddition of Allenoates Catalyzed by Phosphines



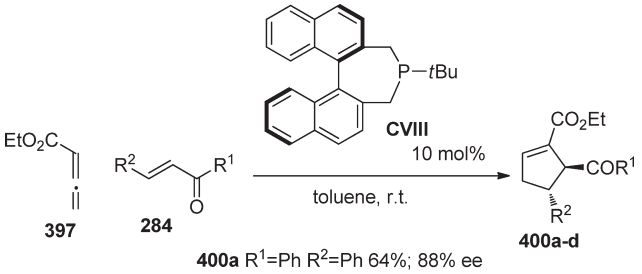
Scheme 193. Asymmetric 1,3-Dipolar Cycloaddition of Allenoates Reported by Zhang



aromatic enals (**277**) and dimethyl 2-oxoethylmalonate (**431**), a set of densely functionalized chiral cyclopentenes **433** were synthesized in high yields (63−89%) and excellent enantioselectivities (91−97% ee).

Later on, Córdova and co-workers presented a related process that constructs cyclopentanes through a nitro-Michael−Michael sequence.[335] Instead of malonate derivatives, they used γ-nitro-α,β-unsaturated esters as nucleophiles for the initial Michael addition, obtaining nitrogen-, formyl-, and ester-functionalized cyclopentane derivatives with four

Scheme 194. Asymmetric 1,3-Dipolar Cycloaddition of Allenoates Reported by Fu



400a R^1=Ph R^2=Ph 64%; 88% ee
400b R^1=Ph R^2=2-furyl 69%; 88% ee
400c R^1=Ph R^2=C_5H_{11} 39%; 75% ee
400d R^1=2-thienyl R^2=Ph 74%; 90% ee

stereocenters with excellent results (70−88%, 97−99% ee, and dr 7:1:1:1−12:0:1:2).

In 2008, Zhong and co-workers developed a pair of powerful domino reactions to synthesize highly substituted cyclopentanes.[336] In the first approach, Zhong developed a double Michael reaction between nitrostyrenes (**327**) and diethyl 5-acetylhex-2-enedionate (**434**), catalyzed by *Cinchona* alkaloid derivatives (**XI**). The reaction consists of the keto ester Michael addition to a nitrostyrene and a subsequent intramolecular cyclization via a Michael reaction of nitro compound and α,β-unsaturated ester. This reaction is possible due the low reactivity as Michael acceptors of unsaturated esters in comparison with nitrostyrenes. The reaction furnishes the tetrasubstituted cyclopentanes (**435**) with very good yields and in almost diastereo- and enantiopure form, as shown in Scheme 217. However, the reaction appears to be limited to aromatic nitroalkenes, since no examples of aliphatic nitroalkenes were reported.

Soon after, the same research group developed a similar aproximation to the synthesis of cyclopentanes. This time they built the cyclopentanes via a domino Michael−Henry reaction.[337] Once again, the reaction furnished the cyclopentanes (**437**) in excellent yields and in almost diastereo- and enantiopure form (Scheme 218). The limitations of this methodology seem to be the same that the previous one, given that only aromatic nitroalkenes was used.

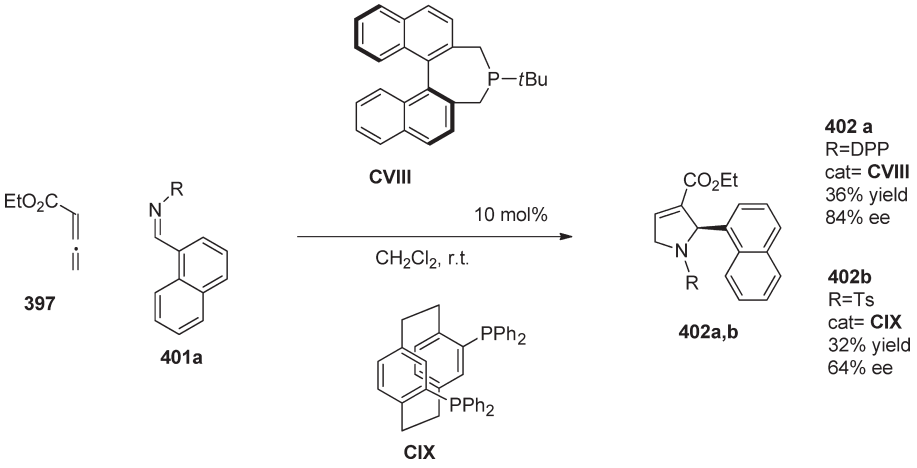
Zhong and co-workers, in 2010, reported a similar reaction beween nitrostyrenes and cyclic diketo esters via a Michael−Henry cascade reaction.[338] The reaction was efficiently catalyzed by bifunctional thiourea catalysts derived from *Cinchona* alkaloids (**CXIX**). As it is shown in Scheme 219, the reaction furnished the desired bicyclic products **439** in good yields and excellent stereoselectivities.

Soon after, both Zhao and co-workers[339] and Rueping and co-workers[340] reported a similar reaction using cyclic 1,2-diones. The final bicyclo[3.2.1]octan-8-ones were obtained in good yields and stereoselectivities.

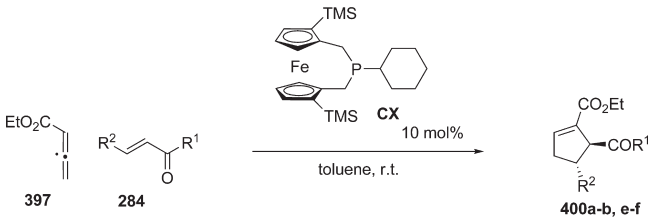
In 2008, Enders reported a powerful cascade reaction between aldehydes and halonitroalkenes **440**; in this aproximation the aldehyde reacts with a secondary amine catalyst to form the enamine, which undergoes a Michael addition to the nitroalkene.[341] The intermediate enamine reacts via an intramolecular α-alkylation to afford the desired carbocycles **441** (Scheme 220). However, the scope of the reaction is very narrow, because only unhindered substituents could be placed in the aldehyde, and the final products **441** were obtained in moderate yields and diastereoselectivities.

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 195. Enantioselective 1,3-Dipolar Cycloaddition of Allenoates with *N*-DPP Imines Reported by Marinetti

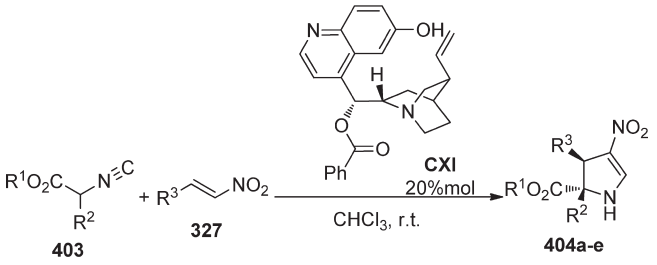


Scheme 196. Asymmetric 1,3-Dipolar Cycloaddition of Allenoates with Enones Reported by Marinetti



400a R^1=Ph R^2=Ph 65%; 92% ee
400b R^1=Ph R^2=2-furyl 71%; 93% ee
400e R^1=OEt R^2=CO_2Et 68%; 90% ee
400f R^1=*p*MeOC_6H_4 R^2=Ph 85%; 95% ee

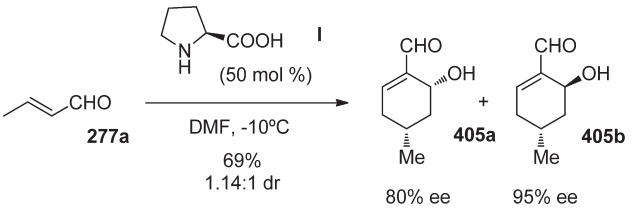
Scheme 197. Enantioselective Synthesis of Dihydropyrroles



404a R^1=Me R^2=Ph R^3=*p*BrC_6H_4 74%; >20:1 d.r.; 96% ee
404b R^1=Me R^2=Ph R^3=*p*CNC_6H_4 82%; 10:1 d.r.; 95% ee
404c R^1=Me R^2=Ph R^3=*p*$CF_3C_6H_4$ 68%; 10:1 d.r.; 98% ee
404d R^1=Bn R^2=Ph R^3=$\alpha C_{10}H_7$ 73%; 20:1 d.r.; 97% ee
404e R^1=Me R^2=Bn R^3=$\alpha C_{10}H_7$ 64%; 5:1 d.r.; 90% ee

Bode and co-workers reported in 2007 the asymmetric synthesis of *cis*-1,3,4-trisubstituted cyclopentenes (**443**).[342] Chiral NHC-catalysts generated from triazolium salts (**XX**) promote the cyclopentene-forming annulation of α,β-unsaturated aldehydes (**277**) by 4-oxoenoates (**442**), with excellent levels of enantioinduction (Scheme 221). Mechanistic and stereochemical investigations performed by the authors strongly supported a novel reaction manifold featuring an intermolecular

Scheme 198. Formal [3 + 3]-Cycloaddition Reported by Hong



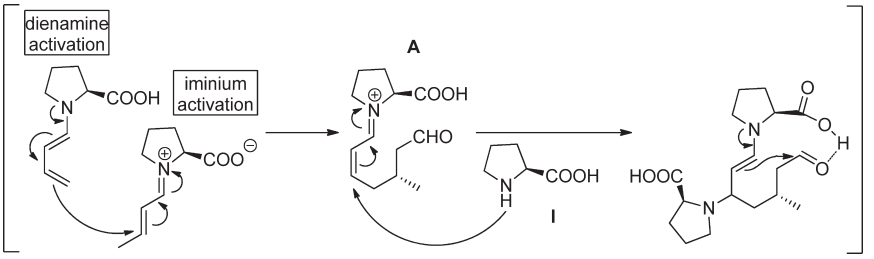
crossed-benzoin reaction and an NHC-catalyzed oxy-Cope rearrangement, followed by tautomerization and intramolecular aldol and, finally, acyl addition and decarboxylation (Scheme 222).

The same research group reported in 2009 the synthesis of cyclopentanes employing a closely related strategy.[343] This time, α,β-unsaturated aldehydes reacted with α-hydroxy enones to furnish cyclopentane-fused lactones, as shown in Scheme 223. The reaction was efficiently catalyzed by chiral NHC's, rendering the final compounds in good to moderate yields and excellent stereoselectivities. One important feature of this work is the different outcome observed when chiral imidazolium- or chiral triazolium-derived NHC catalysts were used. When imidazolium salts such as **CXX** were used, cyclopentane fused γ-lactones (**445**) were obtained. On the other hand, when triazolium-derived NHC catalysts promoted the reaction, the products of the reaction were cyclopentane-fused β-lactones (**446**).

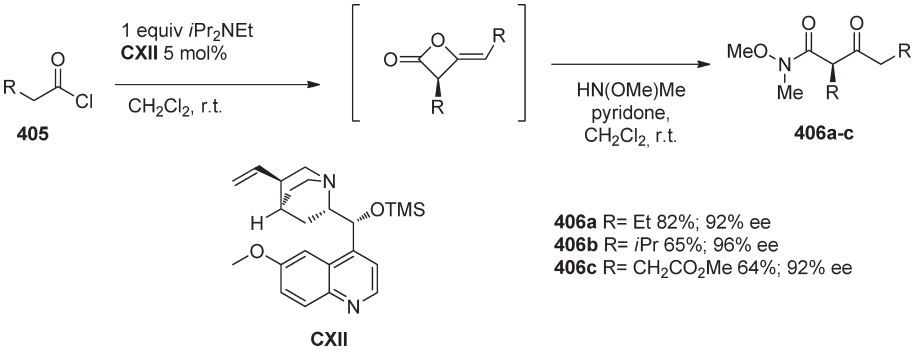
6.1.3. Synthesis of Six-Membered Carbocycles. The first example of an enantioselective organocatalytic domino reaction with nitroalkenes was disclosed by Takemoto in 2004.[344] Takemoto and co-workers reported the domino Michael addition of γ,δ-unsaturated-β-keto esters (**447**) to nitroalkenes (**327**) catalyzed by a bifunctional amino-thiourea (Takemoto's catalyst, **XLI**) and 1,1,3,3-tetramethylguanidine (TMG). Interestingly, the keto ester 1,4-addition to nitroalkenes took place first and then an intramolecular Michael addition catalyzed by base furnished the corresponding cyclohexane derivatives. The reaction afforded the corresponding highly functionalized cyclohexanones (**448**) in high yields and enantioselectivities, as shown in Scheme 224.

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

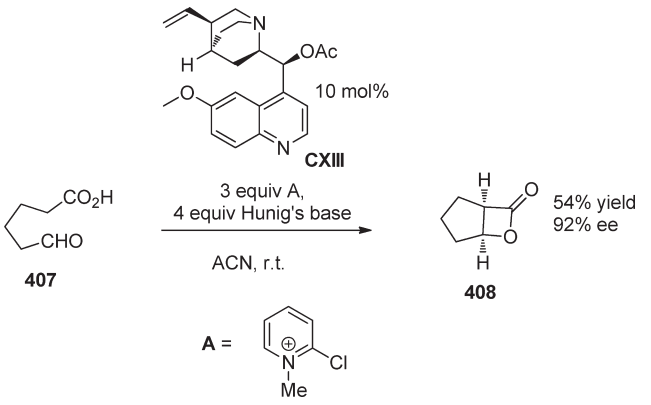
Scheme 199. Proposed Morita−Baylis−Hillman Pathway for the Reaction Depicted in Scheme [198]



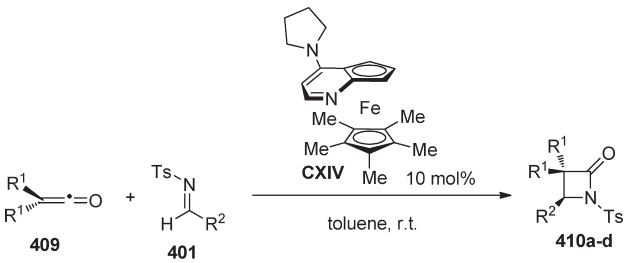
Scheme 200. Asymmetric Dimerization of Ketenes Reported by Calter



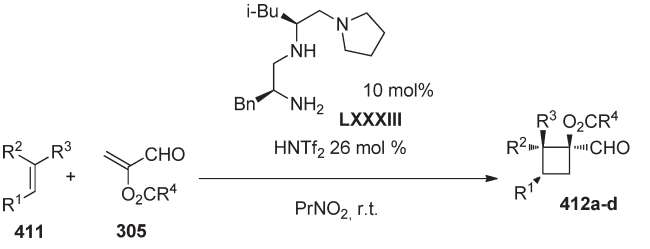
Scheme 201. Asymmetric Intramolecular Ketene−Aldehyde Cycloaddition Reported by Calter



Scheme 202. Asymmetric Staudinger Cycloaddition Reported by Fu



Scheme 203. Asymmetric [2 + 2]-Cycloaddition Reported by Ishihara

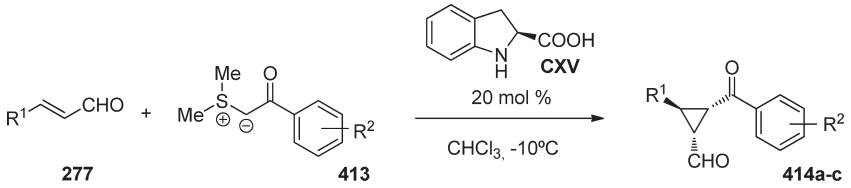


Takemoto applied this methodology to the synthesis of (−)-epibatidine (**449**), an alkaloid isolated from the skin of an equatorean frog. This compound presents analgesic properties (Scheme 225).

The first example of an asymmetric domino reaction catalyzed by chiral primary amines was reported in 2007 by Chen, Deng, and co-workers.[345] The chiral primary amino catalyst **X**, derived from quinine, catalyzed a Michael−Michael−retro-Michael cascade, where the two reagents act alternatively and selectively as the Michael donor and acceptor under readily controllable conditions. The corresponding cyclohexenones **454** were obtained in good yields and excellent stereoselectivities (Scheme 226). However, an extra step was necessary sometimes in order to push the reaction to afford the cyclic

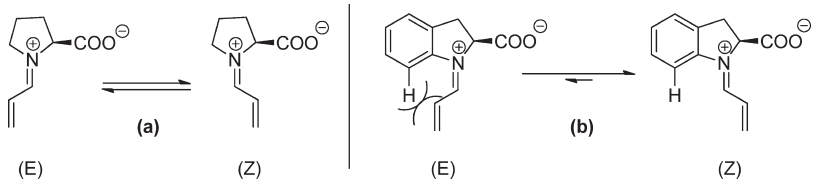
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 204. Enantioselective Cyclopropanation between Enals and Benzoylmethyl Sulfonium Ylides

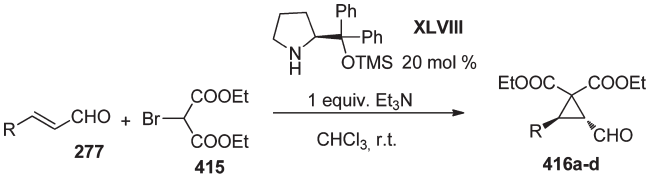


414a R^1=Me R^2=H 67%; >19:1 d.r.; 90% ee
414b R^1=Ph R^2=H 73%; 33:1 d.r.; 89% ee
414c R^1=Propyl R^2=*p*-MeOH 64%; >11:1 d.r.; 93% ee

Scheme 205. (a) Configurational Equilibrium of Iminium Ion Derived from Proline (I) and (b) Configurational Equilibrium of Iminium Ion Derived from Catalyst CXV

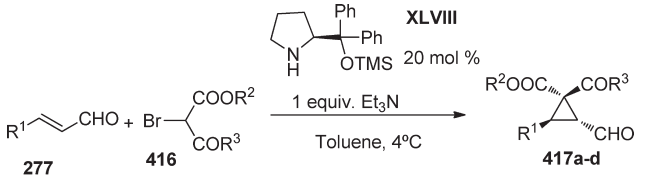


Scheme 206. Enantioselective Cyclopropanation Reported by Córdova



416a R=Ph 83%; >25:1 d.r.; 94% ee
416b R=Me 88%; 9:1 d.r.; 94% ee
416c R=CO_2Et 50%; >25:1 d.r.; 93% ee
416d R=*p*ClC_6H_4 60%; >25:1 d.r.; 96% ee

Scheme 207. Cyclopropanation Reported by Moyano, Rios, and Co-Workers

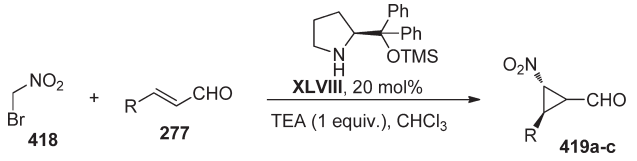


417a R^1=Ph R^2=Et R^3=Me 90%; 9.5:1 d.r.; 94% ee
417b R^1=Ph R^2=Me R^3=Me 90%; 7.5:1 d.r.; 99% ee
417c R^1=*p*$NO_2C_6H_4$ R^2=Et R^3=Me 88%; 12:1 d.r.; 96% ee
417d R^1=Et R^2=Et R^3=Me 91%; 3:1 d.r.; 85% ee

products. In this case, the initial Michael adducts was treated with benzylamine and TFA to render the cycloadduct.

The first example of an asymmetric formal [3 + 3]-annulation of cyclic ketones (**457**) with enones (**455**) was reported in

Scheme 208. Asymmetric Organocatalytic Nitrocyclopropanation Reported by Córdova



419a R=Ph, 63%; 1:1 d.r. 95% ee; 95% ee
419b R=Pr, 42%; 1:1 d.r. 91% ee; 92% ee
419c R=Naphtyl, 56%; 3:2 d.r.; 98% ee; 99% ee

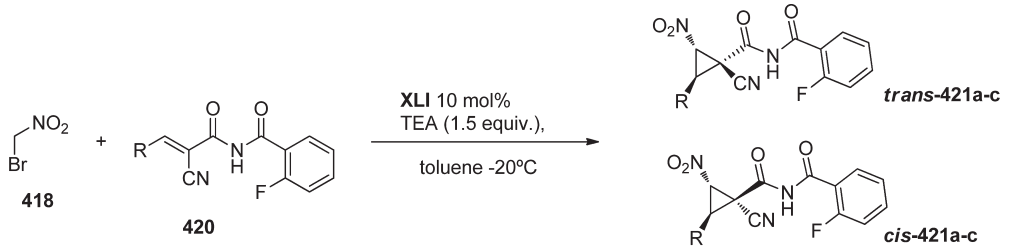
2007.[346] Tang and co-workers obtained compounds with a bicyclo[3.3.1] skeleton (**456**) via a Michael−aldol reaction, resulting in the formation of two new C−C bonds and four stereogenic centers with high enantioselectivities under mild conditions (Scheme 227). However, when other types of ketones such as acyclic ketones or cyclopentenones were used, the enantioselectivities decreased dramatically.

In 2008, Liu and co-workers disclosed the formation of β-hydroxy-β-trifluoromethylcyclohexanones, which also involved a Michael−aldol process.[238,347] In this case, the authors only described one enantioselective example between an α,β-unsaturated trifluoromethyl ketone (**459**) and acetone (**460**). The 3-hydroxy ketone **458** was obtained as a single diastereoisomer in high yields and with moderate enantioselectivity (Scheme 228).

In 2004, Jørgensen and co-workers assembled optically active cyclohexanones (**461**) as single diastereomers with three to four contiguous stereogenic centers.[348] This constituted the first organocatalytic asymmetric domino Michael−aldol reaction of acyclic β-keto esters (**462**) and unsaturated ketones (**284**), and took place with excellent enantioselectivities (Scheme 229). The same research group later on broadened the scope of this reaction

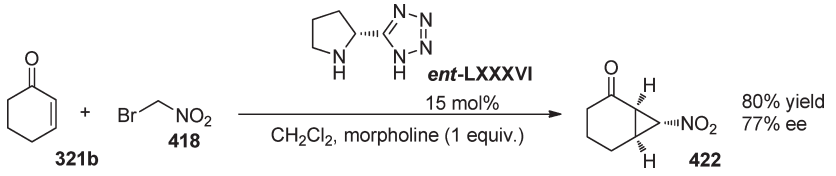
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 209. Asymmetric Organocatalytic Nitrocyclopropanation Reported by Takemoto

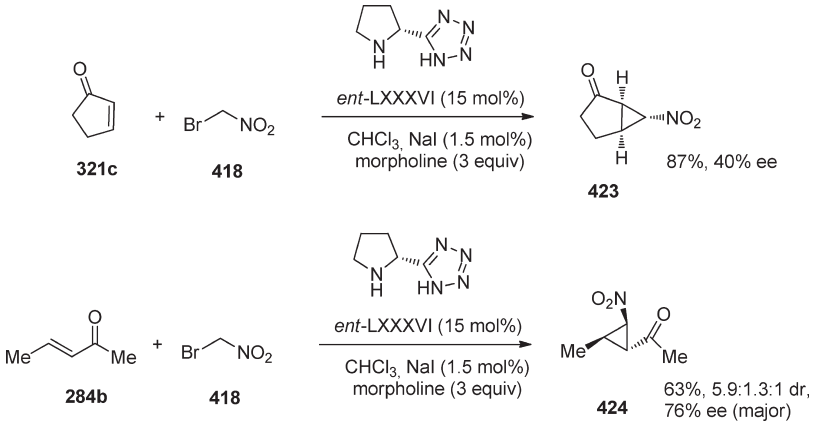


421a R=Tol, 81%; 3:2 d.r. trans:cis; 99% ee
421b R=Pr, 75%; 3:2 d.r. trans:cis; 98% ee
421c R=1-Naphtyl, 81%; 7:3 d.r.trans:cis; 98% ee

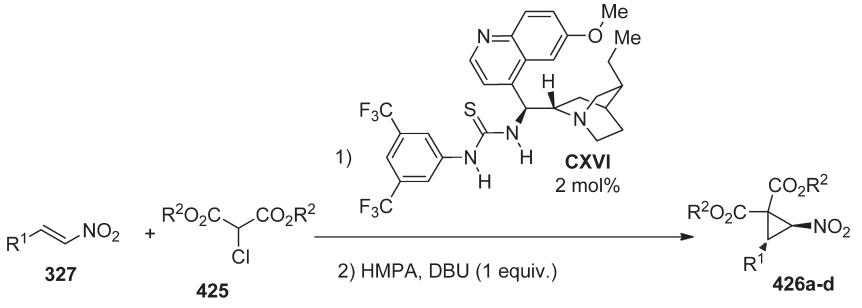
Scheme 210. Asymmetric Organocatalytic Cyclopropanation Reported by Ley



Scheme 211. Scope of the Cyclopropanation Reaction Performed by Ley



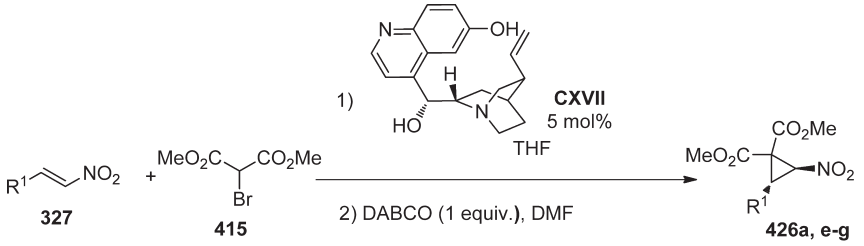
Scheme 212. Connon's Asymmetric Organocatalytic Cyclopropanation



426a R^1 = Ph, R^2 = Me, 75%; 38% ee
426b R^1 = *p*-BrC_6H_4, R^2 = Me, 73%; 47% ee
426c R^1 = *p*-$CF_3C_6H_4$, R^2 = Me, 74%; 14% ee
426d R^1 = *n*-C_6H_{11}, R^2 = Me, 70%; 17% ee

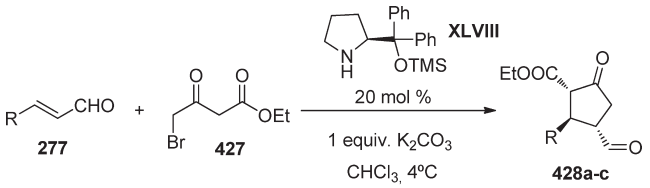
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 213. Asymmetric Organocatalytic Cyclopropanation Reported by Yan



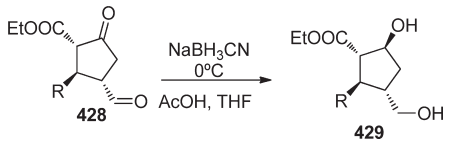
426a R^1=Ph 78%; 99% ee
426e R^1=Tol 63%; 97% ee
426f R^1=2-thienyl 69%; 98% ee
426g R^1=2-furyl 47%; 99% ee

Scheme 214. Cyclopentane Synthesis Reported by Córdova



428a R=Me 76% 6:1 d.r.; 93% ee
428b R=Et 70%; 9:1 d.r.; 98% ee
428c R=Pr 83%; 10:1 d.r.; >99% ee

Scheme 215. Synthesis of Cyclopentanols (429)



by using phenylsulfonylacetophenone instead of β-keto esters, obtaining similar results.[349]

In 2007, Hayashi and co-workers developed a very elegant tandem Michael−Henry reaction that gives rise to chiral cyclohexanes (**463**) with total control of four stereocenters.[350] The reaction between 2,5-dihydroxy-3,4-dihydrofuran, an equivalent of pentanodial (**464**), and a different set of nitrostyrenes (**327**) was efficiently catalyzed by the diphenylprolinol derivative **XLVIII**, rendering the chiral cyclohexanes (**463**) in high yields and enantioselectivities (Scheme 230). In 2009, Córdova and co-workers reported a similar reaction using alkylidene malonates and 2,5-dihydroxy-3,4-dihydrofuran, obtaining the corresponding cyclohexanes with good yields and stereoselectivities.[351]

In 2006, Jørgensen developed a nice asymmetric synthesis of cyclohexenones (**465**).[352] The reaction is based on an organocatalytic asymmetric conjugated addition of β-keto esters (**466**) to α,β-unsaturated aldehydes (**277**) and proceeds in aqueous solution or under solvent-free conditions. The reaction is efficiently catalyzed by diphenylprolinol derivatives (**XXXVI**), rendering the final cyclohexenones (**465**) in excellent yields and enantioselectivities (Scheme 231). Soon after, Jørgensen developed a similar reaction starting from 4-chloro keto esters. This process furnished highly functionalized epoxycyclohexanone derivatives with excellent yields and enantioselectivities.[353]

A similar reaction was reported by Zhao in 2009,[354] using enones instead of α,β-unsaturated aldehydes. The reaction was catalyzed by primary/secondary amines, affording the final cyclohexenes in good yields and stereoselectivities.

Jørgensen and co-workers reported in 2008 an organocatalytic tandem Michael/Morita−Baylis−Hillman reaction catalyzed by the simple diphenylprolinol derivative **XLVIII**.[355] α,β-Unsaturated aldehydes (**277**) reacted with Nazarov reagent (**447**), furnishing highly substituted cyclohexanones (**467**) in high yields and diastereo- and enantioselectivities, as illustrated in Scheme 232.

Also in 2008, Jørgensen and co-workers reported the synthesis of bridged cyclohexanones (**468**) by reaction of α,β-unsaturated aldehydes (**277**) with dimethyl 3-oxoglutarate (**469**) via an initial domino reaction involving Michael addition−Knoevenagel condensation between the enal and the keto diester; the intermediate obtained reacts with another molecule of **469** to afford the final compound.[356] The reaction exhibits high levels of diastereo- and enantioselectivities, furnishing only one diastereomer out of the possible 32. The reaction is efficiently catalyzed by diphenylprolinol trimethylsilyl ether (**XLVIII**) and can be performed at the gram scale, leading to highly enantioenriched bicyclic products, as depicted in Scheme 233.

In 2009, Hayashi and co-workers developed a highly enantioselective formal carbo-[3 + 3]-cycloaddition reaction of α,β-unsaturated aldehydes (**277**) and dimethyl 3-oxopentanedioate (**469**), catalyzed by a diphenylprolinol silyl ether (**CXXIV**) via a domino reaction involving Michael addition−Knoevenagel condensation. Contrary to what happened in the last example, the Knoevenagel adduct did not react with a new molecule of **469**, due the absence of base (Scheme 234). The reaction proceeds with high yields and constitutes a clean process, affording substituted cyclohexenone derivatives (**470**) with excellent enantioselectivities (up to 99% ee).[357]

A similar approach was developed by Jørgensen and co-workers in 2007.[358] They reported the addition of dinitroalkanes (**472**) to α,β-unsaturated aldehydes (**277**) followed by an intramolecular

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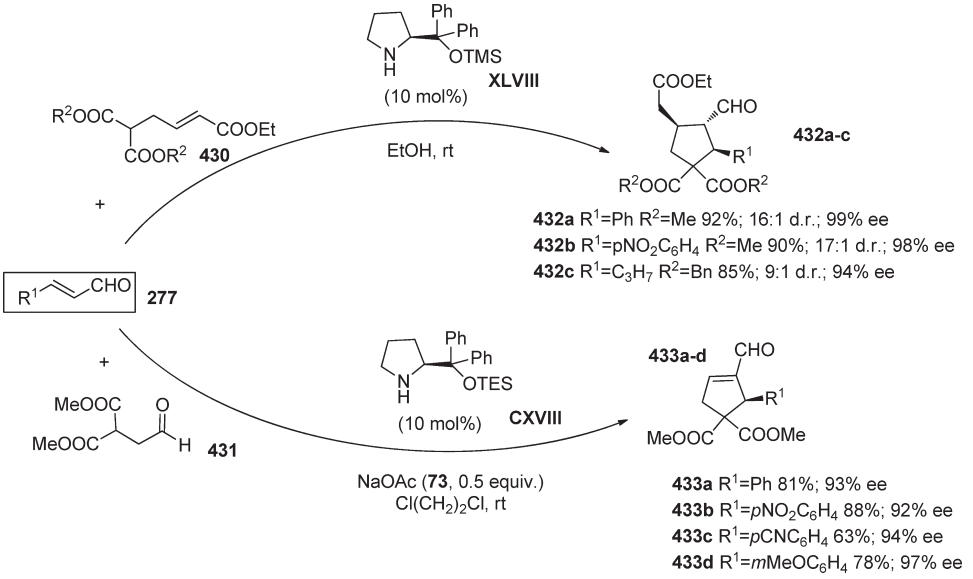
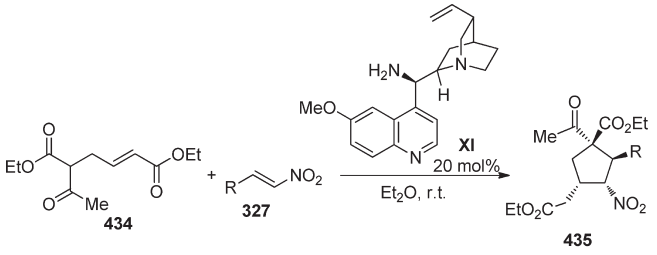
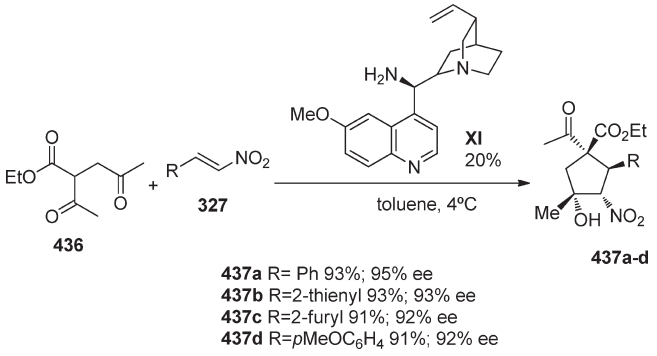
Scheme 216. Synthesis of Cyclopentanes Developed by Wang



Scheme 217. Synthesis of Cyclopentanones via a Double Michael Reaction



Scheme 218. Synthesis of Cyclopentanones via a Domino Michael−Henry Reaction



Henry reaction, which led to the formation of highly substituted cyclohexanols (**471**) with control over five contiguous stereocenters. The reaction is catalyzed by the commercially available diarylprolinol trimethylsilyl ether (**XXXVI**) and proceeds with moderate to low yields and with moderate diastereoselectivity and good enantioselectivity, as illustrated in Scheme 235. One of the limitations of this methodology is the need to use aliphatic α,β-unsaturated aldehydes, due the poor reactivity showed by cinnamyl aldehyde derivatives.

In 2009, Brenner and McGarraugh reported a highly enantioselective synthesis of fused cyclohexanes catalyzed by chiral secondary amines.[359] The reaction consists of an initial Michael reaction between the dicarbonylic compound **474** and the enal and a subsequent intramolecular cyclization via a second Michael reaction. The cyclohexane derivatives **473** were obtained with good yields, with good diastereoselectivities, and with excellent enantioselectivities (Scheme 236). One of the limitations of this methodology is that only 5−6-fused ring systems can be obtained, since no other examples were described.

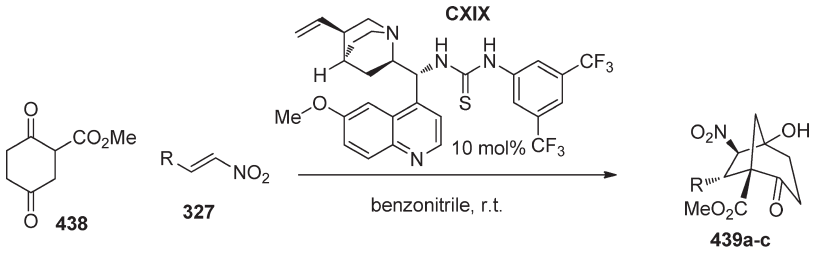
In 2007, Enders and co-workers reported an asymmetric organocatalytic domino reaction of γ-nitroketones **476** and enals.[360] The reaction was efficiently catalyzed by the Jørgensen−Hayashi catalyst **XLVIII**, rendering the final cyclohexene carbaldehydes **475** in good yields and stereoselectivities (Scheme 237). The reaction began with a Michael reaction between the nitroalkane and the enal, followed by an intramolecular aldol reaction that after dehydration furnished the cyclohexenecarbaldehyde **475**.

Two years later, the same research group reported a related reaction starting from 2-(nitromethyl)benzaldehyde.[361] The reaction proceeds via a domino nitroalkane−Michael−aldol condensation reaction that leads to the final 3,4-dihydronaphthalenes in excellent yields and enantioselectivities.

Tang, Li, and co-workers have recently developed an elegant synthesis of fused cyclohexanes by using Seebach's nitroallylic acetate reagent **478**.[362] The Seebach reagent[363] reacts with cyclohexanones via a double Michael addition, affording the final fused bicyclic ketones **477** in excellent yields and stereoselectivities (Scheme 238). The reaction is

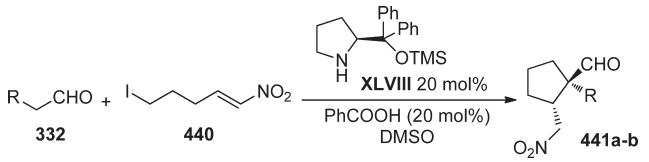
dx.doi.org/10.1021/cr100348t |Chem. Rev. 2011, 111, 4703–4832

Scheme 219. Synthesis of Bicyclo[3.2.1]octanes via a Domino Michael−Henry Reaction



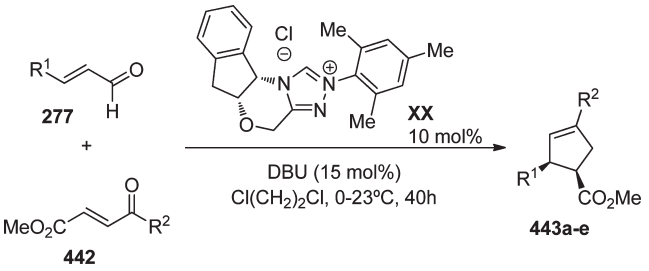
439a R = Ph, 93%; >99:1 d.r.; 94% ee
439b R = 2-Thienyl, 80%; >99:1; 92% ee
439c R = 2-Furyl, 84%; >99:1; 92% ee

Scheme 220. Synthesis of Cyclopentanecarbaldehydes Reported by Enders



441a R=Me 62%; 66:34 d.r.; 94% ee
441b R=Et 59%; 13:87 d.r.; 97% ee

Scheme 221. NHC-Catalyzed *cis*-Cyclopentannulation of Enals and Chalcones Described by Bode



443a R^1=Ph R^2=Ph 78%; 11:1 *cis:trans*; 99% ee
443b R^1=Ph R^2=*p*MeOC_6H_4 58%; 5:1 *cis:trans*; 99% ee
443c R^1=Ph R^2=2-furyl 93%; >20:1 *cis:trans*; 98% ee
443d R^1=2-furyl R^2=Ph 53%; 5:1 *cis:trans*; 99% ee
443e R^1=*n-Pr* R^2=Ph 25%; 14:1 *cis:trans*; 96% ee

efficiently catalyzed by a proline−thiourea derivative (**CXXV**). One of the limitations of this methodology is the need to use cyclic ketones; when acyclic ketones such as acetone were used, the reaction did not furnish the expected products.

Very recently, MacMillan and co-workers, taking advantage of the SOMO activation, reported the synthesis of chiral cyclohexanes from enolizable aldehydes bearing a nucleophile such as a thiophene or an alkene.[364] The reaction was simply catalyzed by an imidazolidinone catalyst (**CXXVI**, MacMillan's second generation) and renders the final cyclohexanes **480** in good yields and excellent enantioselectivities. The reaction seems to be quite sensitive to the steric hindrance of the aldehyde, due to the requirement of using only α-unsubstituted aldehydes and terminal alkenes (Scheme 239).

In 2010, almost at the same time, Carter[365] and Kotsuki[366] reported the highly enantioselective synthesis of cyclohexenones from α,α-disubstituted aldehydes and enones. In both cases, the results were excellent. The main difference between both works was the choice of the catalyst. In Kotsuki's paper,[368] the catalyst was a primary ammonium carboxylate, concretely that derived from (*S*,*S*)-1,2-cyclohexyldiamine and (*S*,*S*)-1,2-cyclohexanedicarboxylic acid (**CXXVIII**); on the other hand, Carter and co-workers[367] used a prolinol derivative (**CXXVII**). In both cases, the reaction seems to be very dependent on the substitution at the β-position of the enone, and only H or Me are allowed. The reaction affords the corresponding cyclohexenes **482** in moderate yields, excellent diastereoselectivities, and good enantioselectivities, as shown in Scheme 240.

In 2010, Xiao and co-workers reported the formal Diels−Alder reaction between 2-vinylindoles **312** and nitroalkenes **327**, catalyzed by hydrogen-bond-donating catalysts such as **CXXIX**.[367] The scope of the reaction is quite narrow in terms both of the vinylindoles and the nitroalkenes, since only aromatic nitroalkenes were used and R^2 and R^3 are always methyl groups. The final cyclohexane derivatives **484** were isolated in good yiels and good stereoselectivities, as shown in Scheme 241.

6.2. Synthesis of Heterocycles

6.2.1. Organocatalytic Asymmetric Synthesis of Azacycles. *6.2.1.1. Organocatalytic Asymmetric Synthesis of Aziridines via Aza-Darzens Reaction.* Aziridines are among the most important types of nitrogenated heterocycles. A widely used methodology to perform their synthesis is the aza-Darzens reaction. The development of an enantioselective organocatalytic aza-Darzens reaction with diazo compounds was not achieved until 2008, when Maruoka and co-workers developed the first enantioselective *trans*-aziridination of diazoacetamides with *N*-Boc imines, catalyzed by chiral dicarboxylic acids such as **CXXX**.[368] In this work, aryl *N*-Boc imines (**401**) react with α-diazoacetamides (**485**) to furnish the desired *trans*-aziridines (**486**) with excellent yields and diastereo- and enantioselectivities, as shown in Scheme 242. One of the limitations of this methodology is the need to use aromatic imines, and examples concerning aliphatic imines were not reported by the authors.

The authors speculate that the trans selectivity arises from the preference of a rotamer wherein the carboxamide group and the

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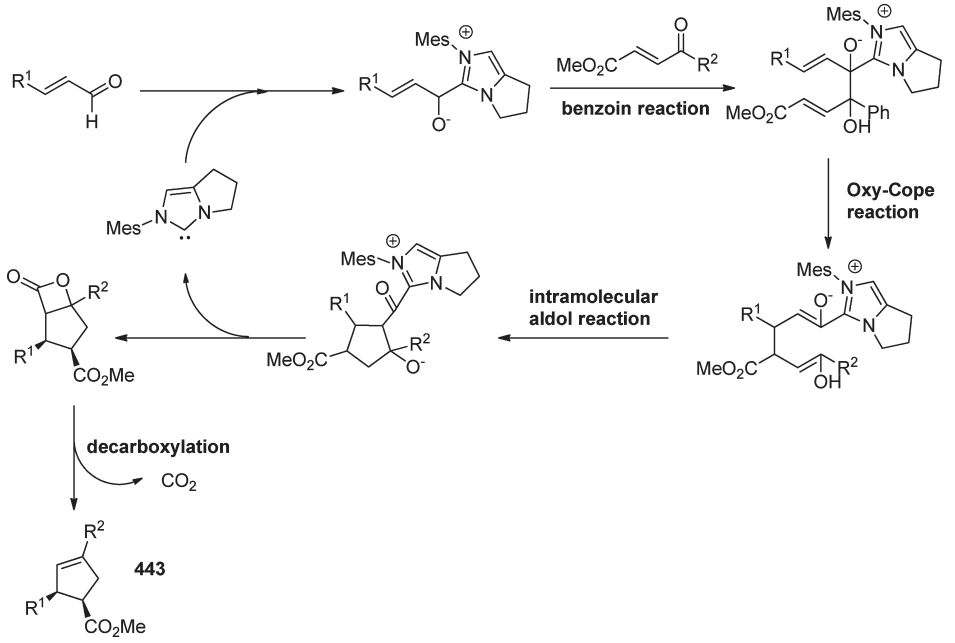
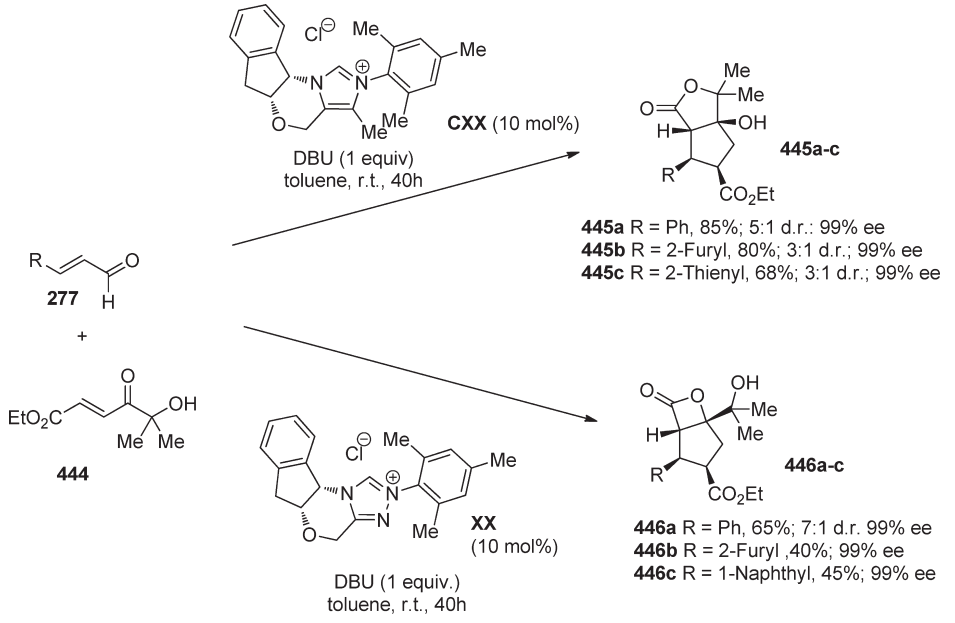
Scheme 222. Proposed Mechanism



Scheme 223. Synthesis of Fused Cyclopentanes Reported by Bode



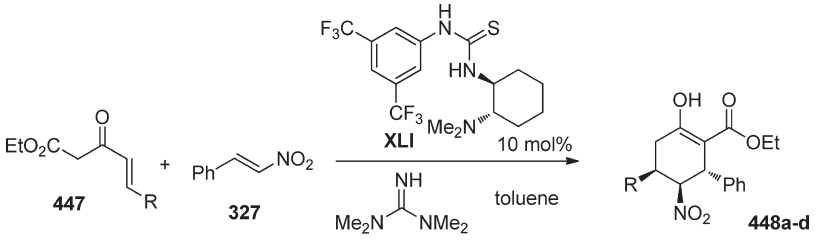
aryl group of *N*-Boc imine adopt an antiperiplanar orientation. A synclinal orientation would be disfavored by steric repulsion. The possible hydrogen bonding between the amide N−H bond and the Boc group might act as a secondary interaction, further stabilizing the antiperiplanar tyransition state, as depicted in Figure 31.

In 2009, Zhong and co-workers reported the same reaction using chiral phosphoric acid derivatives instead of dicarboxylic acids, obtaining the chiral *trans*-aziridines **486** in excellent yields and stereoselectivities (Scheme 243).[369] As in Maruoka's work, only aromatic imines were reported.

Almost at the same time, Akiyama and co-workers developed a similar aza-Darzens reaction using aldimines derived from aryl glyoxals (**487**) and ethyl diazoacetate **488**, also promoted by chiral BINOL-derived phosphoric acid catalysts such as **CXXXI**.[370] The reaction renders exclusevily the *cis*-aziridine carboxylates **489** in excellent yields and enantioselectivities (Scheme 244). However, the scope of the method

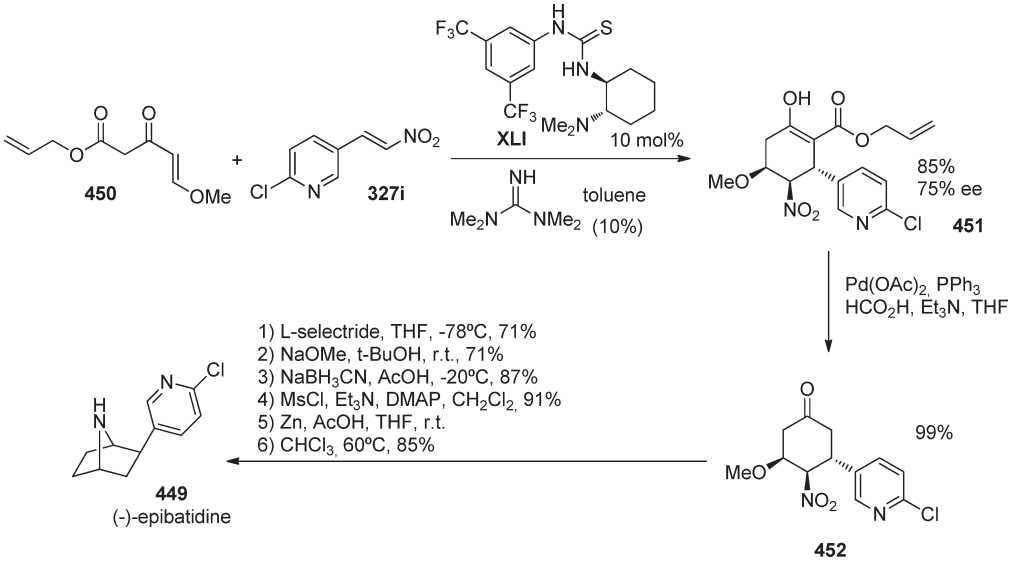
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 224. Synthesis of Cyclohexanones Reported by Takemoto

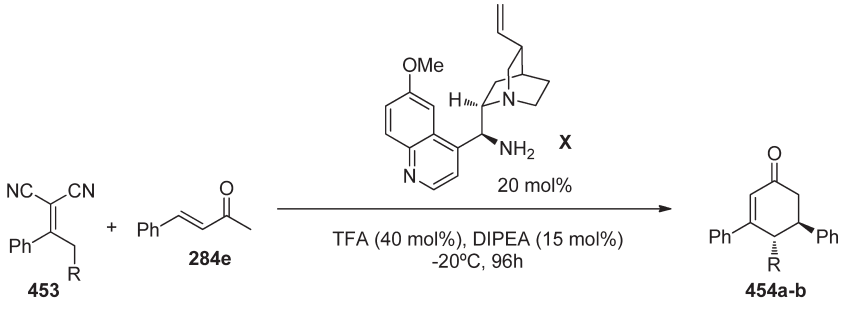


448a R = Me, 65%; >99% d.e.; 86% ee
448b R = Ph, 71%; 90% d.e.; 89% ee
448c R = OMe, 63%; 64% d.e.; 85% ee
448d R = *i*-Pr, 71%; >99% d.e.; 88% ee

Scheme 225. Enantioselective Synthesis of (−)-Epibatidine (449)



Scheme 226. Michael−Michael−Retro-Michael Cascade Reported by Chen and Deng



454a R=H 46%; 98% ee
454b R=Me 54%; 99% ee

seems to be quite narrow; only aromatic glyoxals were used in this report.

6.2.1.2. Organocatalytic Asymmetric Aziridination of Activated Alkenes. The first organocatalytic aziridination of activated

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alkenes was reported in 2006. Shi and co-workers reported the aziridination of chalcones promoted by amines.[371] In this paper, the authors developed a one-pot process that involved the in situ generation of a hydrazinium salt, deprotonation of the hydrazinium cation to form an aminimide, and subsequent aziridination. *O*-(Mesitylenesulfonyl)hydroxylamine (MSH) can readily aminate various tertiary amines to give the corresponding hydrazinium salts in high yield. The best conditions for the reaction were obtained using 1 equiv of *N*-methylmorpholine, obtaining the final aziridines **490** in good yields.

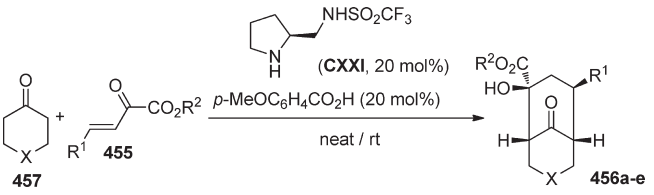
Remarkably, the authors used (+)-Tröger's base (**CXXXII**) in order to induce chirality in the reaction, achieving moderate enantioselectivities (Scheme 245).

In 2007, Armstrong and co-workers reported an aziridination of enones catalyzed by amines, using *O*-(diphenylphosphinyl)-hydroxylamine.[372] The reaction renders the racemic trans-products in good yields when 1.05 equiv of *N*-methylmorpholine were used as a base. The use of a readily available chiral amine like quinine (**CXXXIII**) renders the *trans*-aziridines **490** in low yields and moderate enantioselectivities, as shown in Scheme 246.

In 2007, Córdova et al. developed the first asymmetric organocatalytic synthesis of aziridines from aliphatic enals (**277**) and acylated hydroxycarbamates (**491**), catalyzed by commercially available diphenylprolinol trimethylsilyl ether (**XLVIII**) in chloroform (Scheme 247).[373]

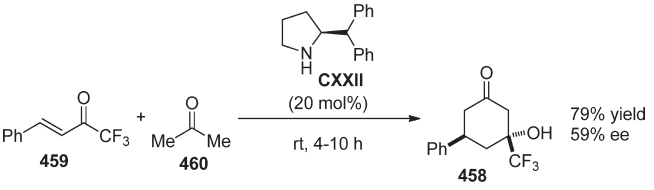
The choice of the nitrogen source is crucial for the success of the process. It was necessary to find a nitrogen-atom-containig compound that would first act as a nucleophile and that at a later stage became electrophilic. Acylated hydroxycarbamates (**491**) were demonstrated to be the best substrates, affording 2-formylaziridines (**492**) with moderate yields (54−78%, maybe due their high reactivity), good diastereoselectivities (4:1−10:1 dr), and excellent enantioselectivities (84−99% ee).

Scheme 227. Formal [3 + 3]-Annulation of Cyclic Ketones with Enones Described by Tang

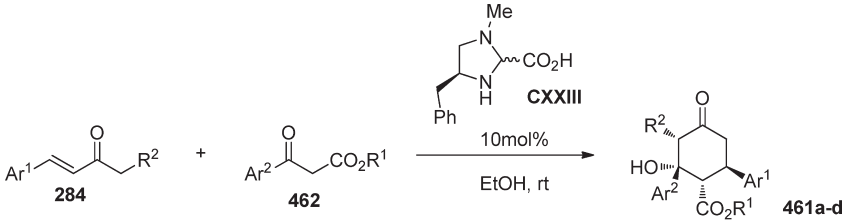


456a X = CH_2, R^1 = Ph, R^2 = Me, 80%; 90% ee
456b X= CH_2, R^1 = Ph, R^2 = Et, 74%; 91% ee
456c X = CH_2, R^1 = *p*-$MeOC_6H_4$, R^2 = Me, 77%; 87% ee
456d X = O, R^1 = Ph, R^2 = Me, 66%; 90% ee
456e X = NMe, R^1 = Ph, R^2 = Me, 92%; 80% ee

Scheme 228. Formation of β-Hydroxy-β-trifluoromethylcyclohexanones (458) Published by Liu

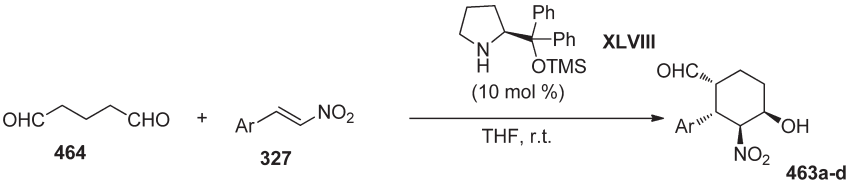


Scheme 229. Domino Michael−Aldol Reaction Reported by Jørgensen



461a Ar^1=Ph R^2=H Ar^2=Ph R^2=Bn 80%; >97:3 d.r.; 95% ee
461b Ar^1=2-Np R^2=H Ar^2=Ph R^2=Bn 85%; >97:3 d.r.; 91% ee
461c Ar^1=Ph R^2=Me Ar^2=Ph R^2=Bn 50%; >97:3 d.r.; 95% ee
461d Ar^1=Ph R^2=H Ar^2=*p*F-C_6H_4 R^2=Me 44%; >97:3 d.r.; 92% ee

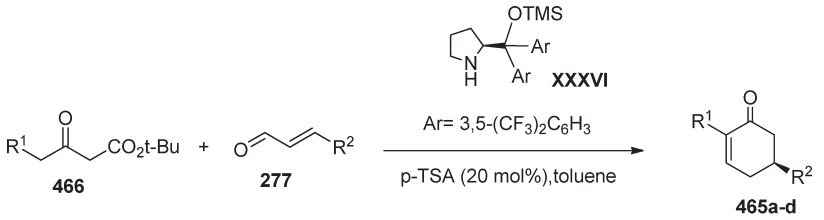
Scheme 230. Synthesis of Cyclohexanes (463) Reported by Hayashi



463a Ar= Ph 66%; 99% ee
463b Ar=*p*$NO_2C_6H_4$ 71%; 97% ee
463c Ar=2-Naphtyl 66%; 99% ee
463d Ar=furyl 68%; 99% ee

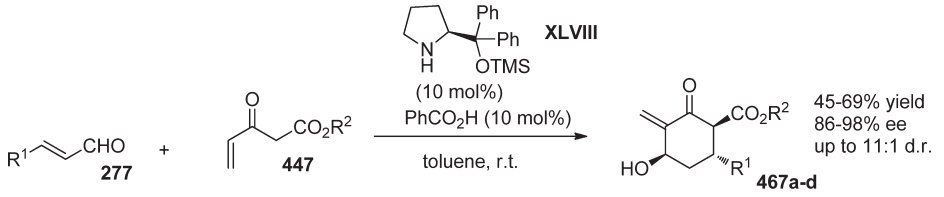
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 231. Cyclohexenone (465) Synthesis Reported by Jørgensen



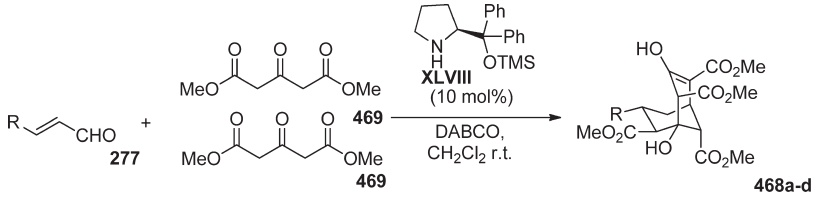
465a R^1=H R^2=Me 93%; 80% ee
465b R^1=H R^2=Ph 63%; 94% ee
465c R^1=Me R^2=Et 82%; 91% ee
465d R^1=Et R^2=Et 74%; 89% ee

Scheme 232. Tandem Michael/Morita−Baylis−Hillman Reported by Jørgensen



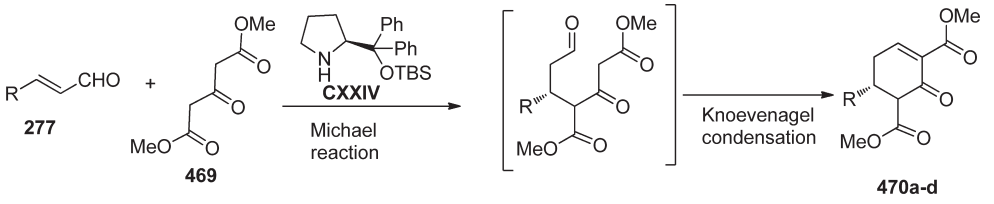
467a R^1=Ph R^2=Et 55%; 7:1 d.r.;94% ee
467b R^1=2-thienyl R^2=Et 57%; 6:1 d.r.; 95% ee
467c R^1=2-furyll R^2=Et 66%; 4:1 d.r.; 92% ee
467d R^1=Et R^2=Et 64%; 6:1 d.r.; 86% ee

Scheme 233. Synthesis of Bicyclic Products Reported by Jørgensen



468a R=Et, 48%; >99;1 d.r.; 94% ee
468b R=Ph 70%; >99:1 d.r.; 93% ee
468c R=CO2Et 38%; >99:1 d.r.; 89% ee
468d R=2-furyl 86%; 94:6 d.r.; 90% ee

Scheme 234. Enantioselective Domino Michael−Knoevenagel Reaction between α,β-Unsaturated Aldehydes and Dimethyl 3-Oxopentanedioate



470a R = Ph, 75%; 95% ee
470b R = 2-Naphthyl, 68%; >99% ee
470c R= *p*-$NO_2C_6H_4$, 74%; 99% ee
470d R= 2-Furyl, 63%; 97% ee

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Recently, Hamada et al. have reported an interesting variation on the enantioselective aziridination of α,β-unsaturated aldehydes (**277**) previously reported by Córdova, employing *N*-arenesulfonylcarbamates as the nitrogen source (**493**) and 3 equiv of base (Scheme 248).[374]

Thus, this new protocol improves both the chemical yields (51−99%) and the diastereoselectivity (9:1−99:1 dr), maintaining the excellent enantiocontrol (91−99% ee) in comparison with the previous methodology reported by Córdova. It is also noteworthy that this methodology expands the aldehyde scope, allowing the aziridination of aromatic enals with total diastereoselectivity.

Melchiorre and co-workers developed in 2008 the aziridination of α,β-unsaturated ketones.[375] This reaction was catalyzed by a primary ammonium salt (**CXXXIV**) derived from 9-amino-9-deoxy-9-epidihydroquinine and D-*N*-Boc-phenylglycine and worked efficiently with both linear and cyclic substrates, leading to chiral aziridines (**494**, **495**) in high yield, with complete diastereoselectivity and very high enantioselectivity (Scheme 249).

6.2.1.3. Organocatalytic Asymmetric Synthesis of Other Azacycles. In 2007, Córdova and co-workers[376] developed the first organocatalytic aza-Michael−aldol sequence for the synthesis of 1,2-dihydroquinolines **497** (Scheme 250).

The development of the asymmetric conjugate addition of an amine to an electron-deficient α,β-unsaturated system (**277**) represented an unprecedented organocatalytic process since, generally, an amine is a much weaker nucleophile than a thiol or an alcohol. In fact, this methodology exemplifies the first asymmetric organocatalytic aza-Michael reaction of primary amines with α,β-unsaturated aldehydes. Thus, the aza-Michael−aldol sequence reaction between 2-aminobenzaldehydes (**496**) and enals (**277**) was reported with excellent results in terms of chemical yield (31−90%) and enantioselectivities (94−99%), employing as catalyst diphenylprolinol trimethylsilyl ether (**XLVIII**) and benzoic acid in DMF at −25 °C.

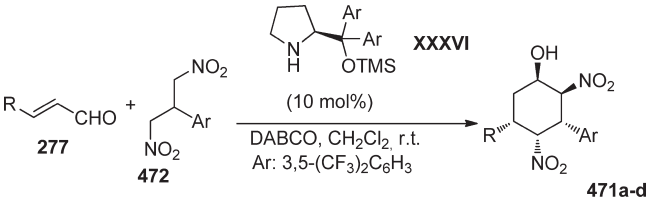
Some months later, Wang and co-workers reported the same sequence employing *N*-protected-2-aminobenzaldehydes in a basic medium, also obtaining good results.[377] In 2009, Xu and co-workers developed a similar reaction using nitroalkenes instead of enals.[378] The reaction was catalyzed by bifunctional thiourea catalysts, affording the corresponding dihydroquinolines in excellent yields and enantioselectivities.

One common strategy for the synthesis of azacycles consists in first a Michael addition to an activated alkene followed by hemiaminal formation that furnishes the final heterocycle. In 2008, Chen and co-workers reported the first organocatalytic inverse-electron demand aza-Diels−Alder reaction of *N*-sulfonyl-1-aza-1,3-butadienes (**498**) and aldehydes (**332**) based on this strategy.[379] The reaction is efficiently catalyzed by simple diphenylprolinol derivatives (**XLVIII**) as illustrated in Scheme 251. The yields and enantioselectivities were excellent, and remarkably, only one diastereomer of the tetrahydropyridines **499** was detected. However, the reaction seems to be dependent on the nature of the unsaturated ketone. Only when R^1 = aromatic, the reaction renders the final product; when R^1 = alkyl, no reaction was observed.

In 2009, Chen's research group reported a similar reaction using as starting material α,β-unsaturated aldehydes instead of enolizable aldehydes.[380] The reaction takes place via dienamine activation with good yields and excellent stereoselectivities.

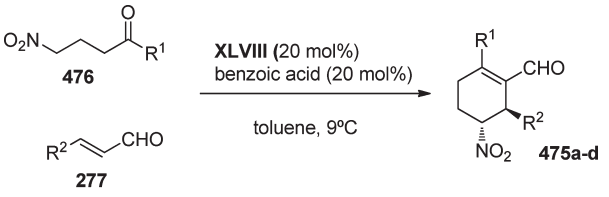
Rios and Córdova developed, in 2007, an enantioselective synthesis of chiral pyrrolidines (**501**). In this approach, 2-aminomalonates (**500**) reacted with α,β-unsaturated aldehydes (**277**) by a Michael malonate addition followed by hemiaminal formation between the corresponding amide and the formyl group, as shown in Scheme 252.[381] This

Scheme 235. Enantioselective Synthesis of Cyclohexanols (471) Reported by Jørgensen



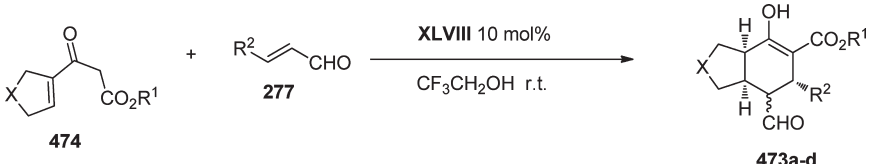
471a R=Et Ar=Ph 45%; 4:2:1 d.r. 90% ee
471b R=Me Ar=Ph 43% 4:1:1 d.r. 75% ee
471c R=*i*Pr Ar=Ph 38% 3:1:1 d.r. 90% ee
471d R=Et Ar=tiophen-2-yl 43% 5:1:1 d.r.; 90% ee

Scheme 237. Enantioselective Synthesis of Cyclohexenes Reported by Enders



475a R^1=Me R^2=Ph 43%; 85:15 d.r.; 93% ee
475b R^1=Me R^2=furan-2-yl 46%; 71:29 d.r.; 96% ee
475c R^1=Me R^2=thien-2-yl 45%; 82:18 d.r.; 96% ee
475d R^1=Et R^2=Ph 37%; 78:22 d.r.; 93% ee

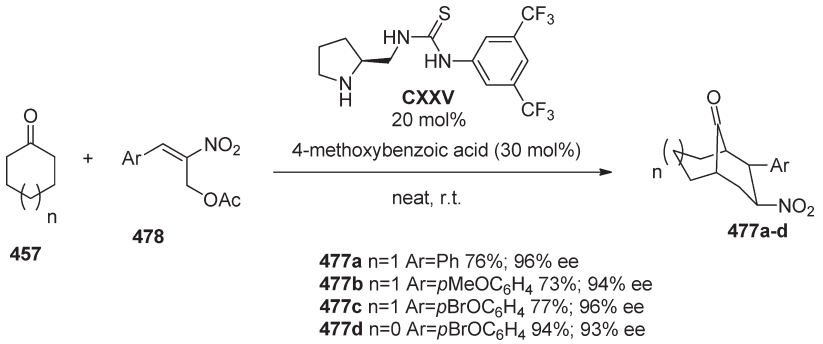
Scheme 236. Enantioselective Synthesis of Bicyclo[4.3.0]carbaldehydes Reported by Brenner



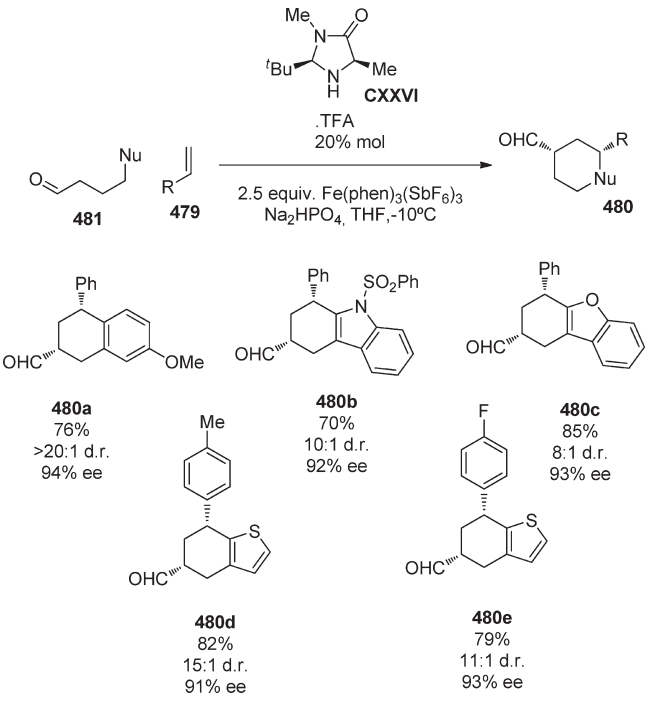
473a R^1=Et R^2=Ph X=CH_2 87%; 92:8 d.r.; 99% ee
473b R^1=Et R^2=pClC_6H_4 X=CH_2 82%; 92:8 d.r.; 99% ee
473c R^1=Me R^2=p$NO_2C_6H_4$ X=CH_2 76%; 91:9 d.r.; 97% ee
473d R^1=Ph R^2=p$NO_2C_6H_4$ X=S 80%; 93:7 d.r.; 98% ee

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 238. Enantioselective Synthesis of Cyclohexenes Reported by Tang and Li



Scheme 239. Synthesis of Cyclohexanes Reported by MacMillan



reaction sequence furnished chiral pyrrolidines from aromatic α,β-unsaturated aldehydes in a single step, with excellent yields and diastereo- and enantioselectivities; however, only aromatic enals could be used, since aliphatic unsaturated aldehydes decomposed under the reaction conditions.

Franzén et al. reported a similar reaction that leads to chiral quinazolidines (**503**, **504**) in a one-pot procedure starting with malonic acid monoamide derivatives (**502**) and α,β-unsaturated aldehydes (**277**).[382] The reaction is efficiently catalyzed by chiral secondary amines (**XLVIII**), affording the desired indolo[2,3-*a*]quinolizidines (**503**) and benzo[*a*]quinolizidines (**504**) with excellent yields and enantioselectivities and with moderate diastereoselectivities, as illustrated in Scheme 253. In the first step, an asymmetric Michael reaction takes place between the enal and the imidomalonate and then the internal hemiaminal is formed. The hemiaminal eliminates in acidic conditions, forming the corresponding imine that reacts with the heteroaromatic moiety, rendering the final product. The scope of the reaction is quite narrow, since again only aromatic enals could be used.

Soon later, Vesely, Moyano, and Rios reported an easy entry to the synthesis of piperidinones (**506**) based on the reaction of 2-carboxamidoacetates (**505**) and α,β-unsaturated aldehydes (**277**) (Scheme 254).[383]

As in previous works, the driving force of the reaction consists of the formation of a cyclic hemiaminal after the initial Michael malonate addition. Piperidinones are obtained with excellent yields and diastereo- and enantioselectivities. The absolute configuration of the products was determined by the synthesis of the blockbuster drug (−)-paroxetine from adduct **506c** in three steps.

In 2009, Enders and co-workers reported an organocatalytic synthesis of 3*H*-pyrrolo[1,2-*a*]indole-2-carbaldehydes (**508**) via a domino aza-Michael addition−aldol condensation reaction sequence.[384] The reaction between 1*H*-indole-2-carbaldehyde (**507**) and different enals was efficiently catalyzed by secondary amine catalysts such **XLVIII**, affording the corresponding tricyclic indoles in good yields and enantioselectivities, as it is shown in Scheme 255. This methodology presents important limitations like the need to use aromatic enals.

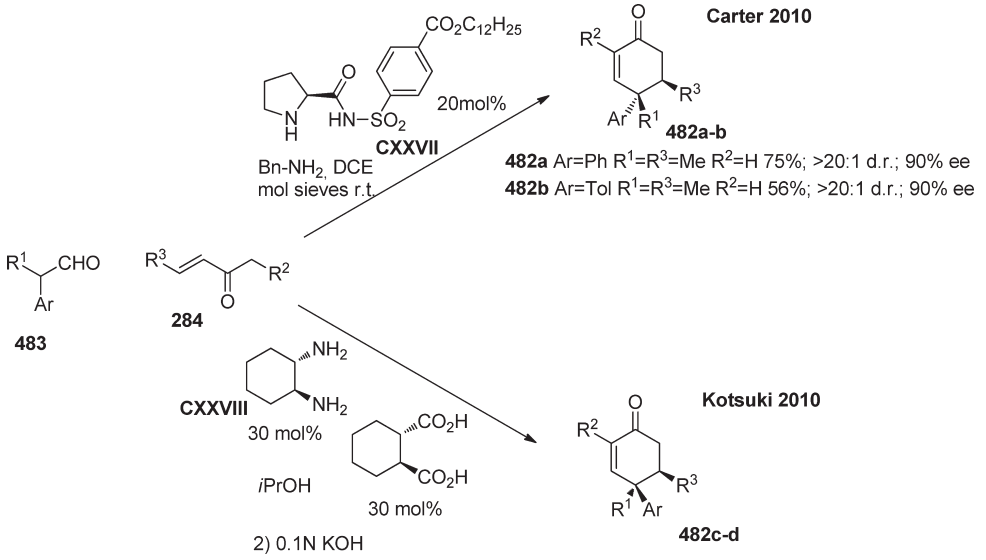
In 2010, Wang and co-workers reported the same reaction, only changing the solvent (toluene instead of MTBE).[385]

In 2007, a tandem aza−ene-type reaction−cyclization cascade catalyzed by chiral BINOL-derived phosphoric acids (**CXXXV**) was described by Terada and co-workers.[386] It enabled the rapid construction of enantioenriched piperidine derivatives (**511**). The potential of such cascade transformations was highlighted through their ability to achieve a rapid increase in molecular complexity from simple enecarbamates (**510**) and a broad range of aldimines (**509**) while also controlling the formation of three stereogenic centers in a highly diastereo- and enantioselective manner (Scheme 256).

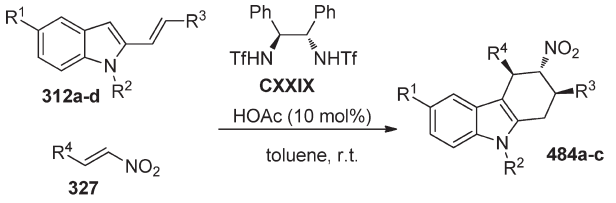
Rueping and Antonchick performed in 2008 a highly enantioselective reaction between an enamine (**512**), a vinyl ketone (**284**), and a Hantzsch ester (**91**).[387] In this process, each of the six reaction steps was catalyzed by the same chiral Brønsted acid (**LXVII**). This reaction offered efficient access to tetrahydropyridines (**513**) from simple and readily available starting materials (Scheme 257).

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

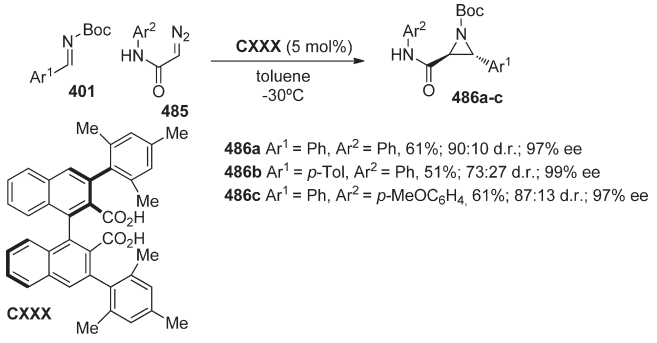
Scheme 240. Synthesis of Cyclohexenes Reported by Kotsuki and Carter



Scheme 241. Formal Diels–Alder Reaction Reported by Xiao



Scheme 242. Aziridination Reported by Maruoka



In 2006, Bode and co-workers performed the first chiral NHC-catalyzed aza-Diels–Alder reaction.[388] This process was performed in the presence of a novel chiral triazolium salt (**XX**) based on the *cis*-1,2-aminoindanol platform, which served as

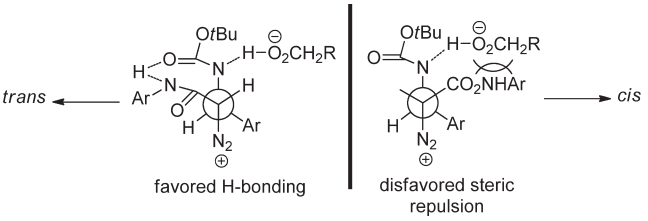
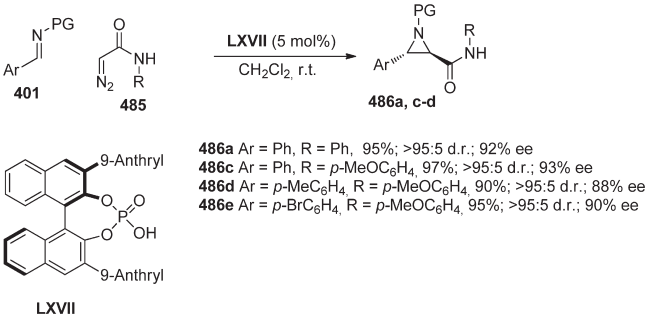


Figure 31. Possible mechanism for the reaction described by Maruoka.

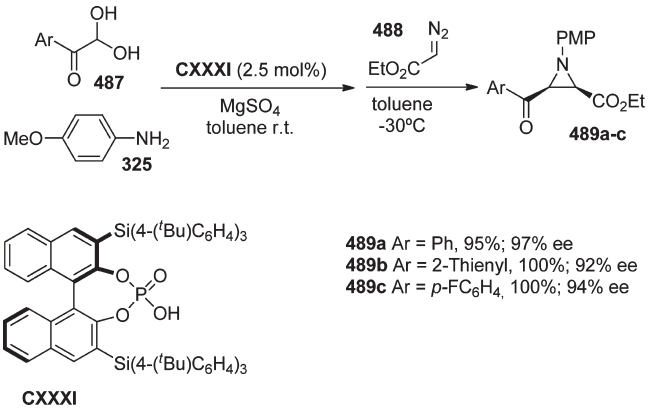
Scheme 243. Aza-Darzens Reaction Developed by Zhong



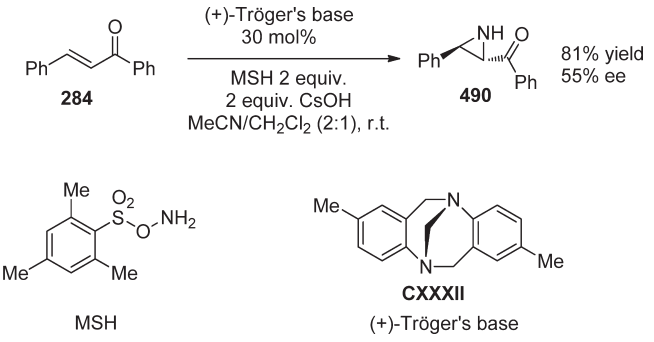
an efficient precatalyst for the NHC-catalyzed redox generation of enolate dienophiles, which were exceptionally reactive. These species underwent $LUMO_{diene}$-controlled Diels–Alder reactions with *N*-sulfonyl-α,β-unsaturated imines (**496**) in good yields and with exceptional diastereo- and enantioselectivities, affording *cis*-3,4-disubstituted dihydropyridinone products (**515**). Additionally, it proceeded at room temperature without stoichiometric reagents, in contrast to uncatalyzed variants, and constitutes a rare example of a highly enantioselective intermolecular Diels–Alder-type reaction catalyzed by an NHC-organocatalyst (Scheme 258).

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

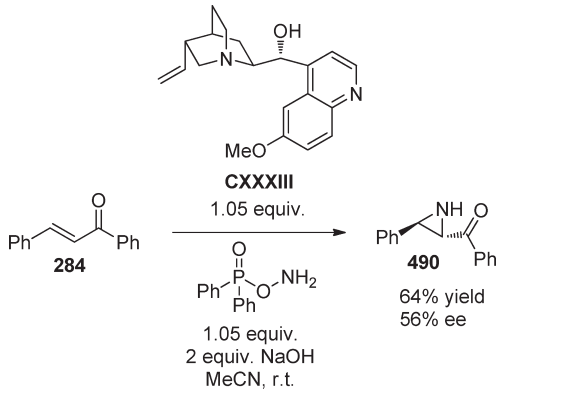
Scheme 244. Aza-Darzens Reaction Developed by Akiyama



Scheme 245. Aziridination of Calchones Reported by Shi

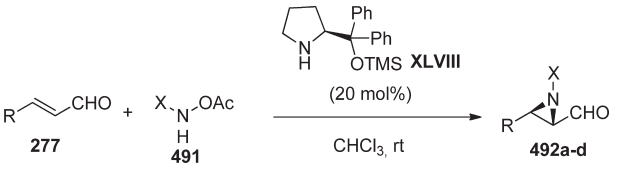


Scheme 246. Aziridination Reported by Armstrong



As shown in Scheme 259, the enal (**514**) undergoes the nucleophilic addition of the carbene catalyst, forming the Breslow intermediate **516** (with its homoenolate resonance structure **517**). Then, intramolecular protonation of **517** affords the catalyst-bound enolate **518**, an exceptionally reactive dienophile that undergoes $LUMO_{diene}$-controlled Diels–Alder with the imine partner **496**, furnishing the dihydropyridinone derivatives **515** in excellent diastereo- and enantioselectivities.

Scheme 247. Aziridination Developed by Córdova



492a X=Boc R=Me 54%; 5:1 d.r.; 90% ee
492b X=Boc R=Ch_2Ch_2Ph 68%; 5:1 d.r.; 96% ee
492c X=Cbz R=Pr 78%; 4:1 d.r.; 96% ee
492d X=Cbz R=Et 60%; 5:1 d.r.; 97% ee

The exceptional diastereoselectivity of the process can be rationalized by the high preference for an endo transition state in the NHC-catalyzed pathway. This reaction mode is reinforced by the presence of the bulky triazolium moiety in the active dienophile **518** (Scheme 260). In addition, the cis-stereoselectivity would arise from a (*Z*)-enolate **518** reacting as the dienophile.

In 2010, Takemoto and co-workers developed a highly enantioselective synthesis of 1,4-dihydropyridines from β-enamino esters and enals.[389] The reaction is simply catalyzed by a mixture of a Brønsted acid (difluoroacetic acid, DFA) and a chiral thiourea catalyst. The reaction affords the corresponding 1,4-dihydropyridines in good yields and moderate enantioselectivities.

6.2.2. Organocatalytic Asymmetric Synthesis of Oxacycles. Epoxides are extremely usuful synthetic intermediates. Over the years, huge research efforts have been made toward the development of asymmetric methodologies for their synthesis. In this section, we will deal with the asymmetric aminocatalytic epoxidation of enals and related reactions. However, due the extension of the previous works and the presence of some recent exhaustive reviews in the literature, we will not discuss other previously developed organocatalytic approaches like the Shi epoxidation[390] or the Julià–Colonna epoxidation.[391]

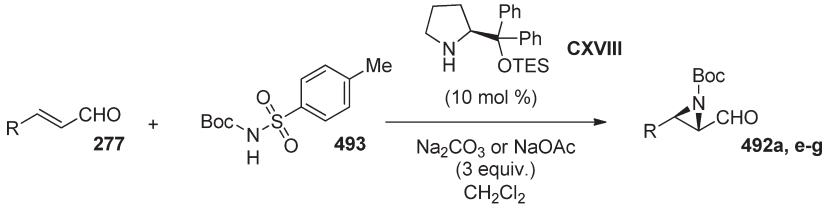
In the realm of aminocatalysis, Jørgensen and co-workers published in 2005 the first asymmetric aminocatalytic epoxidation of α,β-unsaturated aldehydes (**277**),[392] employing as oxygen source simple peroxides such as H_2O_2 (Scheme 261). The reaction mechanism is as follows: first, an electrophilic attack from the peroxide to the activated enal takes place, followed by an intramolecular attack from the enamine previously formed to the peroxide, rendering after hydrolysis the desired epoxide (Scheme 261).

This reaction proceeds through an iminium–enamine mechanism. First of all, the chiral iminium ion formed from the enal and amine **XXXVI** is attacked by the nucleophilic peroxide oxygen at the electrophilic β-carbon, forming the first carbon–oxygen bond and leading to an enamine intermediate. Next, the nucleophilic enamine carbon attacks the electrophilic peroxygen atom, forming after hydrolysis of the resulting iminium ion the α,β-epoxy aldehyde **519** and regenerating the catalyst.

It is noteworthy that the reaction worked well in a wide range of solvents at room temperature, obtaining the best results when dichloromethane was used with 10 mol % of catalyst (**XXXVI**). The reaction tolerates a broad range of β-substituents in the enal moiety, such as differently substituted aromatic rings, alkylic substituents, and functionalized carbons, for example, esters or protected alcohols.

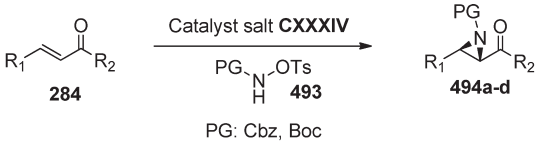
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 248. Aziridination Developed by Hamada



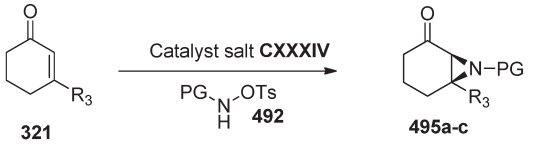
492a R = Me, 73%; 91:9 d.r.; 96% ee
492e R = CO_2Me, 61%; >99:1 d.r.; 98% ee
492f R = Ph, 41%; >99:1 d.r.; 97% ee
492g R = 3-Pyridyl, 77%; >99:1 d.r.; 99% ee

Scheme 249. Enantioselective Aziridination of Enones Developed by Melchiorre

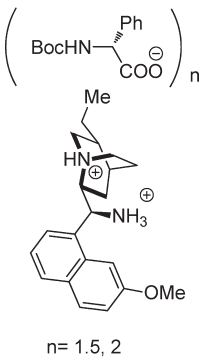


PG: Cbz, Boc

494a R^1 =n-Pentyl, R^2 = Me, PG = Cbz, 93%; 19:1 d.r. 96% ee
494b R^1 = n-Pentyl, R^2 = Me, PG = Boc, 82%; >19:1 d.r. 99% ee
494c R^1= Ph, R^2 = Me, PG = Cbz, 85%; >19:1 d.r. 73% ee
494d R^1 = CO_2Et, R^2 = Me, PG = Cbz, 74%; >19:1 d.r. 95% ee



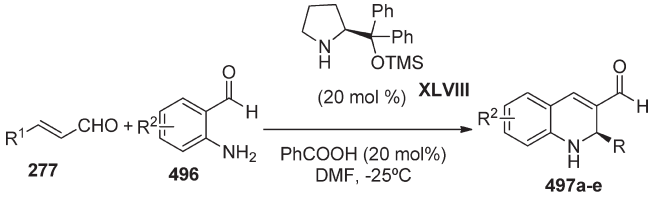
Catalyst salt CXXXIV



n= 1.5, 2

495a R^3 = H, PG = Boc. 73%; 99% ee
495b R^3 = Me, PG = Boc, 75%; 92% ee
495c R^3 = Bn, PG = Boc, 93%; 95% ee

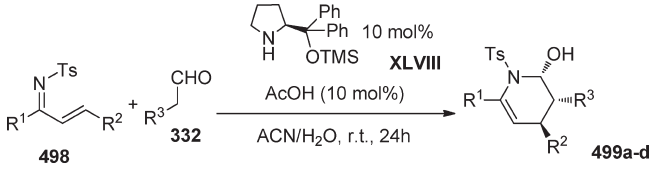
Scheme 250. Synthesis of 1,2-Dihydroquinolidines Reported by Córdova



497a R^1=Ph R^2=H 71%; 94% ee
497b R^1=*p*CNC_6H_4 R^2=H 83%; 98% ee
497c R^1=CO_2Et R^2=H 76%; 97% ee
497d R^1=Pr R^2=H 78%; 96% ee
497e R^1=Ph R^2=5-F 83%; 90% ee

Soon after, Córdova and co-workers performed a similar reaction using diphenylprolinol trimethylsilyl ether (**XLVIII**) as the catalyst, with excellent results in terms of conversion and diastereo- and enantioselectivities.[393]

Scheme 251. Organocatalytic Aza-Diels−Alder Reported by Chen



499a R^1=Ph R^2=Ph R^3=Et 88%; 97% ee
499b R^1=Ph R^2=2-furyl R^3=Et 83%; 98% ee
499c R^1=Ph R^2=Me R^3=Et 83%; 93% ee
499d R^1=Ph R^2=CO_2Et R^3=Et 95%; 99% ee

In 2008, Wang and List published a nice epoxidation of α,*β*-unsaturated aldehydes (**277**) by asymmetric counteranion-directed catalysis (ACDC) (Scheme 262).[394]

This asymmetric induction mode works as follows: the achiral secondary amine (**CXXXVI**) forms a cationic achiral iminium

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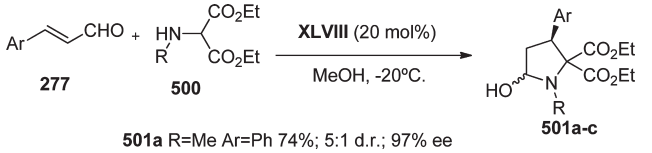
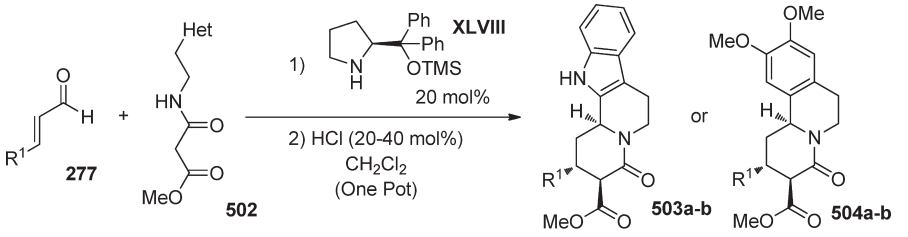
Scheme 252. Synthesis of Pyrrolidines Reported by Rios and Córdova



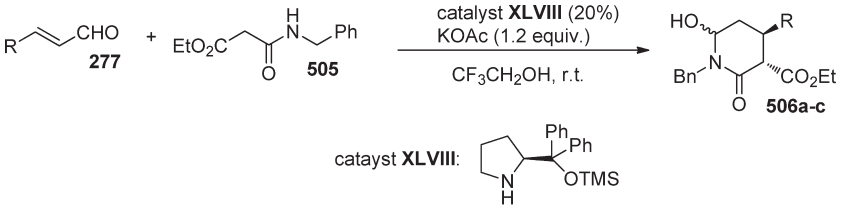
501a R=Me Ar=Ph 74%; 5:1 d.r.; 97% ee
501b R=Me Ar=2-Naphtyl 76% 5:1 d.r.; 90% ee
501c R=Ph Ar=Ph 71%; >10:1 d.r.; 99% ee

Scheme 253. Synthesis of Quinolizidine Derivatives Developed by Franzén et al.



503a R^1=Ph 69%; 85:15 d.r.; 94% ee
503b R^1=*p*$MeOC_6H_4$ 71%; 83:17 d.r.; 87% ee
504a R^1=Ph 69%; 62:38 d.r.; 90% ee
504b R^1=*p*BrC_6H_4 56%; 72:38 d.r.; 98% ee

Scheme 254. Synthesis of Piperidines Described by Vesely, Moyano, and Rios

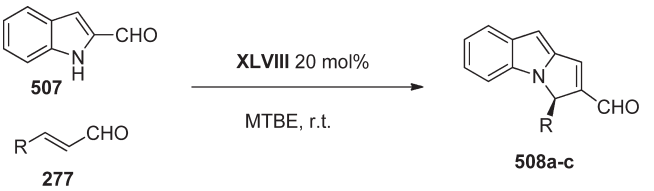


506a R=Ph 90%; 3:1 d.r.; 98% ee
506b R=*p*CNC_6H_4 94%; 5:1 d.r.; 94% ee
506c R=*p*FC_6H_4 84%; 5:1; 90% ee

ion with the enal. The interaction of this cation with the anion of the chiral phosphoric acid **VIII** (the chiral counteranion) creates a chiral environment. Then, the *tert*-butyl hydroperoxide performs an asymmetric epoxidation through an iminium−enamine mechanism, in the same way as in the Jørgensen's epoxidation reaction discussed above.

Aromatic enals were epoxidated with excellent results (62−84% yield, 97:3→99:1 dr, 94−96% ee), improving the diastereoselectivities in comparison with Jørgensen's method and maintaining the high enantiocontrol. However, the reaction of aliphatic enals such as *trans*-2-nonenal gave the epoxyaldehyde with a high dr value (94:6) but moderated enantioselectivity (70% ee) as the major diastereoisomer. Moreover, the epoxidation of β,β-disubstituted-α,β-unsaturated aldehydes (**279**) employing TBME (*tert*-butyl methyl ether) as a solvent afforded the desired epoxyaldehydes (**519**) with excellent enantioselectivities (90−94% ee).

Scheme 255. Synthesis of Tricyclic Indoles Developed by Enders



508a R=Ph 55%; >99% ee
508b R=tolyl 60%; 87% ee
508c R=piperonyl 58%; >99% ee

In 2010, List and co-workers expanded the scope of the reaction by using a similar catalytic system consisting of a chiral

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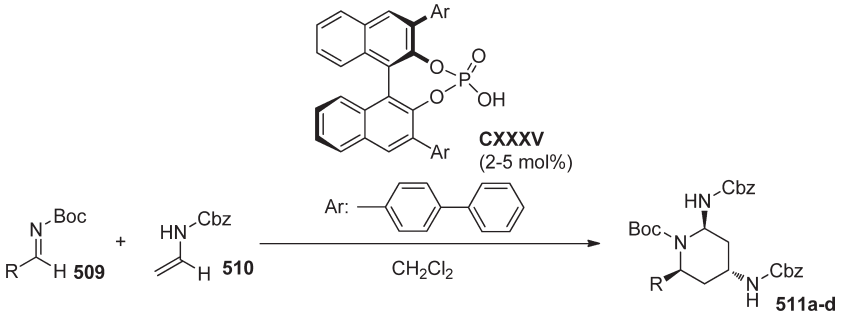
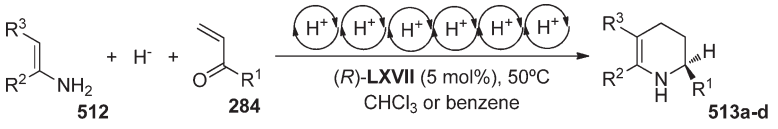
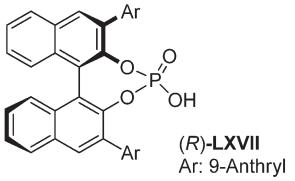
Scheme 256. Tandem Aza−Ene-type Reaction−Cyclization Cascade Described by Terada



511a R = Ph, 99%; 95:5 d.r.; >99% ee
511b R = 2-Furyl, 76%: 88:12 d.r.; 99% ee
511c R = Cyclohexyl, 68%; 94:6 d.r.; 97% ee
511d R = CO_2Me, 84%; 88:12 d.r.; 98% ee

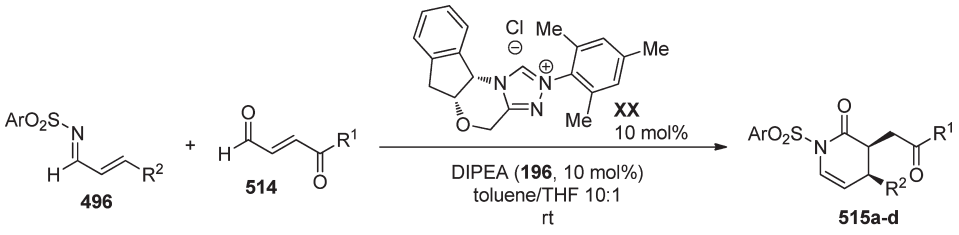
Scheme 257. Highly Enantioselective Cascade Reported by Rueping





513a R^1= *p*-$MeOC_6H_4$, R^2 = Me, R^3 = CN, 89%; 96% ee
513b R^1= *p*-BrC_6H_4, R^2 = Me, R^3 = CN, 77%; 97% ee
513c R^1= *p*-$MeOC_6H_4$, R^2 = Me, R^3 = Ac, 56%; 97% ee
513d R^1= *p*-$MeOC_6H_4$, R^2 = M,e R^3 = CO_2Me, 42%; 97% ee

Scheme 258. NHC-Catalyzed Aza-Diels−Alder Reaction Performed by Bode



515a R^1=OEt R^2=Ph 90%; 99% ee
515b R^1=OEt R^2=2-furyl 71%; 99% ee
515c R^1=OEt R^2=n-Pr 58%; 99% ee
515d R^1=Me R^2=Ph 51%; 99% ee

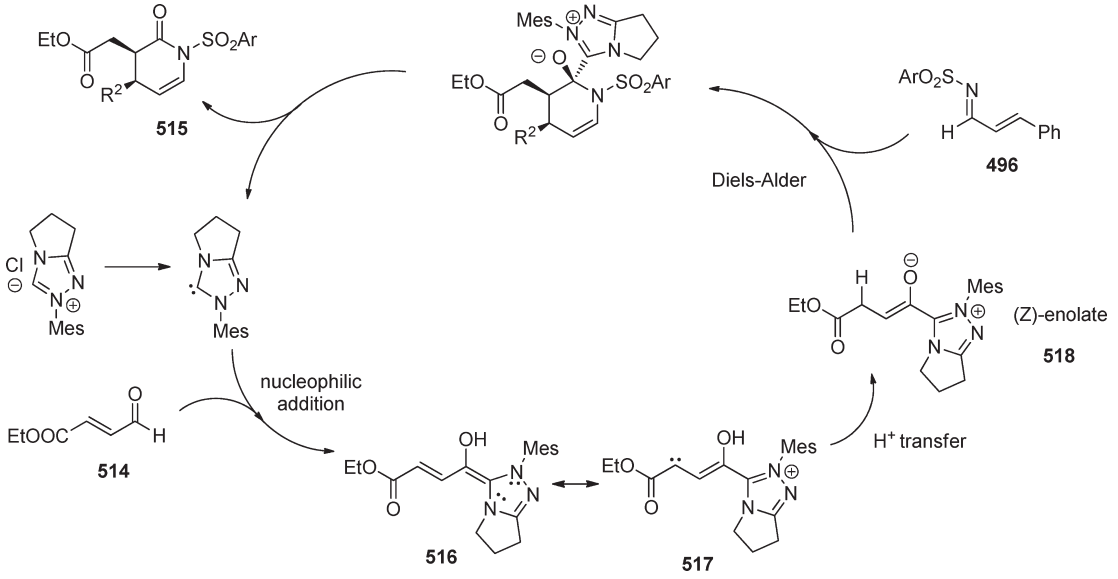
primary amine (**X**) and a phosphoric acid (**VIII**). With this new catalyst on hand, they were able to epoxidize α-branched enals (**520**)[395a] and enones[395b] with excellent yields and stereoselectivities (Scheme 263). However, this methodology does not allow for the epoxidation of aromatic enals.

In 2007, both Córdova et al.[396] and Wang et al.[397] described two closely related processes that gave access to chromanes (**522**). Oxygenated analogous compounds were synthesized using the same approach: an oxa-Michael−aldol condensation reaction sequence between enals (**277**) and 2-hydroxybenzaldehydes (**523**). Under similar reaction conditions, the outcome of the process was excellent (53−98% yield, 75−99% ee and 31−90% yield, 94−99% ee, respectively) (Scheme 264). In 2010, Xu and co-workers presented a similar work, using as a counterion a Mosher acid. As in the cases previously cited, the results were excellent.[398]

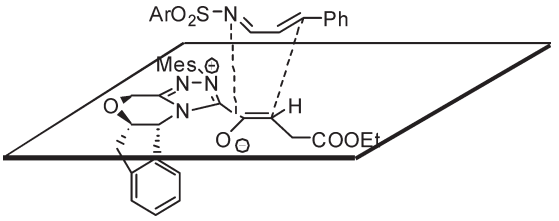
On the basis of these seminal papers, Córdova and co-workers developed a simple catalytic synthesis of tetrahydroxanthenones (**524**).[399] The catalytic domino Michael−aldol reaction

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

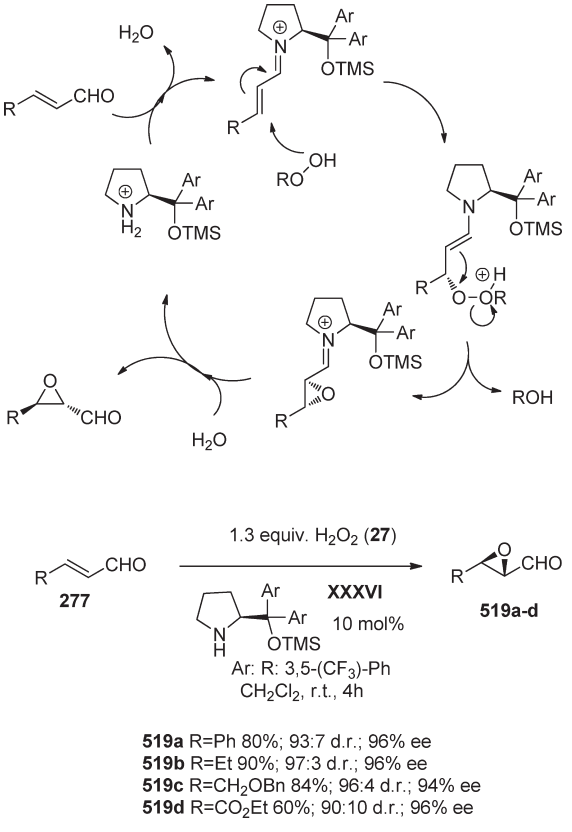
Scheme 259. Postulated Catalytic Cycle for the NHC-Promoted Aza-Diels–Alder Reaction



Scheme 260. Stereochemical Model for Endo-Diels–Alder Cycloaddition



Scheme 261. Asymmetric Organocatalytic Epoxidation of Enals Developed by Jørgensen



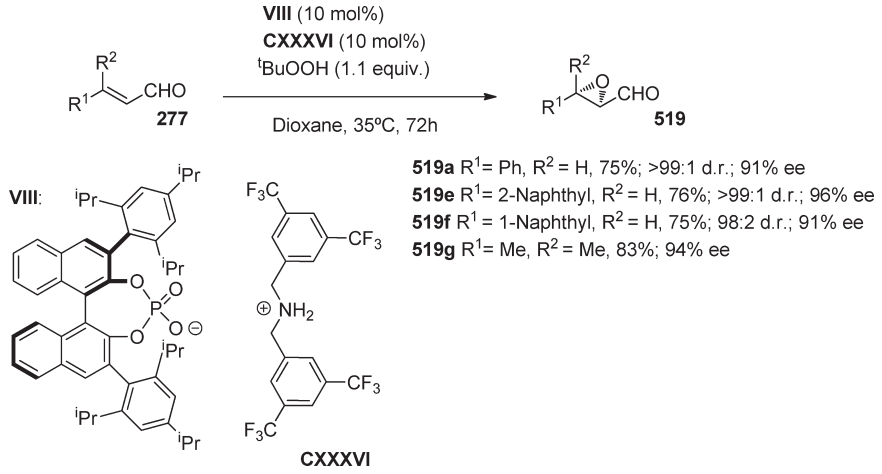
of salicylic aldehyde derivatives (**523**) with cyclic enones (**321**) proceeded in a highly chemoselective fashion, furnishing the corresponding products in high yields and with moderate to good enantioselectivities (Scheme 265). The mechanism proposed involves the iminium activation of the α,β-unsaturated cyclic enone by the chiral pyrrolidine derivative **IX**. Stereoselective nucleophilic conjugate attack on the β-carbon by the alcohol results in a chiral enamine intermediate, which performs an intramolecular 6-exo-trig aldol addition from the same face as the incoming alcohol. Hydrolysis of the resulting iminium intermediate gives the aldol **525**. Elimination of water affords the tetrahydroxanthenone (**524**).

Very recently, Xu, Xu, and co-workers reported an improved protocol for the same reaction.[400] They used as a catalytic system a chiral pyrrolidine bearing a 2-mercaptopyridine moiety (**CXXXVII**) and simple α-amino acids such as *tert*-leucine (**CXXXVIII**). As it is shown in Scheme 266, the reaction afforded the corresponding tetrahydroxanthenones **524** in excellent yields and enantioselectivities.

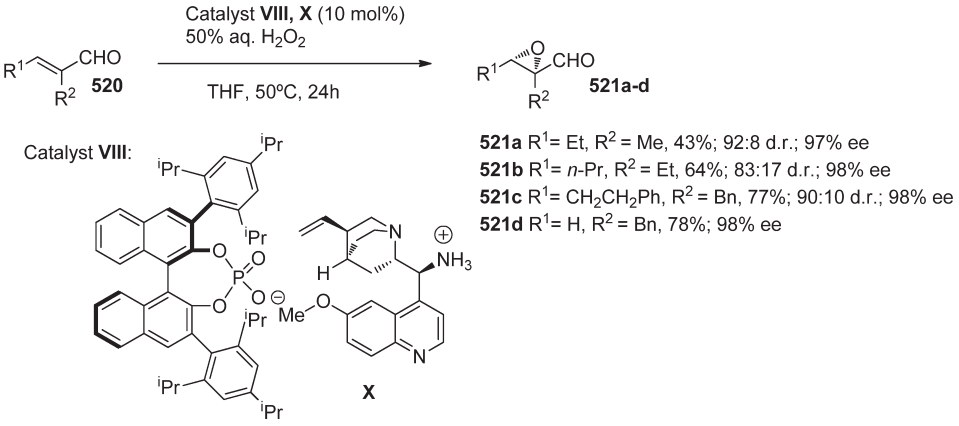
In 2009, Xie and co-workers reported a similar reaction which led to the obtention of chiral 2-amino-2-chromenes.[401] 2-Hydroxybenzalacetone derivatives (**526**) reacted with malonodinitrile (**384**) to furnish 2-amino-2-chromenes **527** via a Michael addition–intramolecular cyclization. The reaction is efficiently catalyzed by primary amines derived from *Cinchona* alkaloids in combination with chiral phosphoric acids, rendering the corresponding chromenes in good yields and good enantioselectivities, as it is shown in Scheme 267.

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

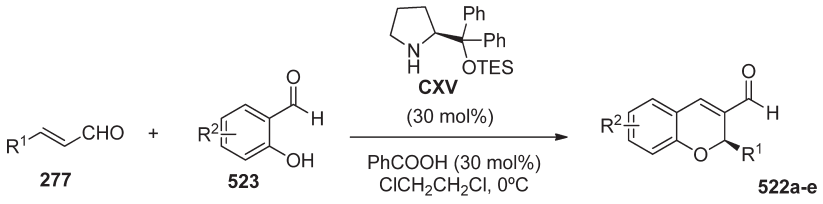
Scheme 262. Epoxidation through ACDC Developed by List



Scheme 263. Asymmetric Epoxidation of α-Branched Enals through ACDC Developed by List



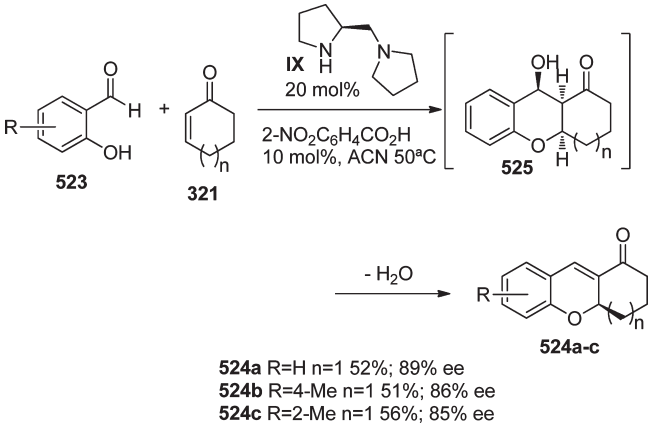
Scheme 264. Chromane Synthesis Reported by Wang



In 2007, Mukaiyama and co-workers described chiral quaternary ammonium phenoxides readily prepared from commercially available *Cinchona* alkaloids and demonstrated their utility as asymmetric organocatalysts.[402] A cinchonidine-derived catalyst bearing both a sterically hindered 9-anthracenylmethyl group and a strongly electron withdrawing 9-*O*-3,5-bis(trifluoromethyl)benzyl group (**CXL**) was found to be highly effective for the Michael addition of ketene silyl acetals (**528**, derived from phenyl carboxylates) to α,β-unsaturated ketones (**284**) followed by lactonization. Optically active

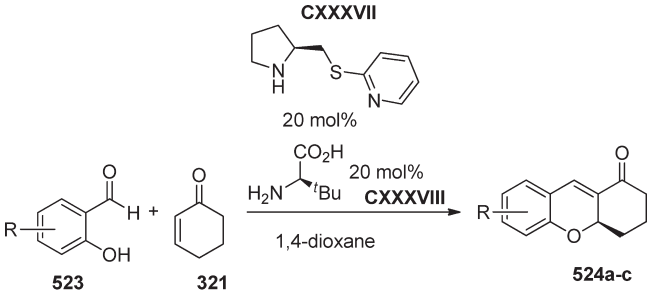
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 265. Catalytic Synthesis of Tetrahydroxanthenones Disclosed by Córdova



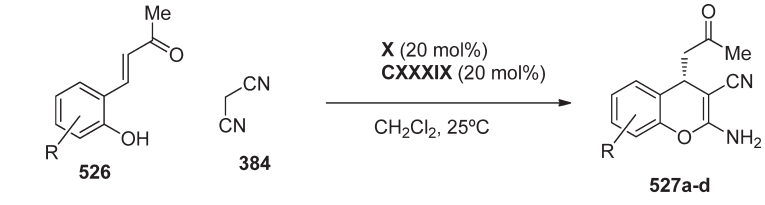
524a R=H n=1 52%; 89% ee
524b R=4-Me n=1 51%; 86% ee
524c R=2-Me n=1 56%; 85% ee

Scheme 266. Catalytic Synthesis of Tetrahydroxanthenones Developed by Xu and Xu



524a R = H, 89%; 92% ee
524b R = 3-MeO, 90%; 95% ee
524c R = 3-F, 95%; 91% ee

Scheme 267. Catalytic Synthesis of 2-Amino-2-chromenes Developed by Xie



527a R^1= H, R^2 = Et, 66%; 85% ee
527b R^1= H, R^2 = Ph, 63%; 91% ee
527c R^1= 5-Cl, R^2 = Ph, 69%; 91% ee
527d R^1= 5-Cl, R^2 = *p*-$MeOC_6H_4$, 67%; 95% ee

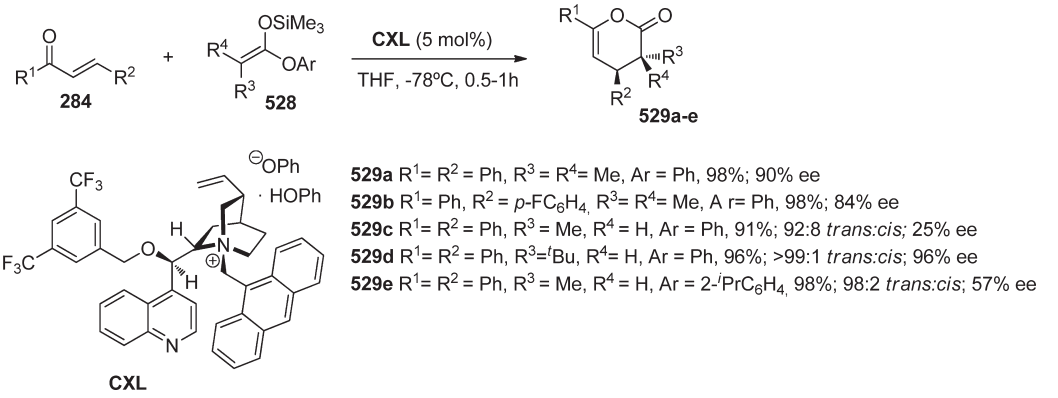
3,4-dihydropyran-2-one derivatives (**529**) were obtained in high yields with excellent control of enantio- and diastereoselectivity (Scheme 268).

In 2008, Xu and co-workers developed a novel catalytic tandem oxa-Michael−Henry reaction between salicyl aldehydes (**523**) and nitrostyrenes (**327**), catalyzed by the chiral pyrrolidine derivative **CXLI**.[403] This reaction furnished 3-nitro-2*H*-chromenes (**530**) in high yields and good enantioselectivities (Scheme 269). One of the limitations of this technology was the need to use aromatic nitroalkenes.

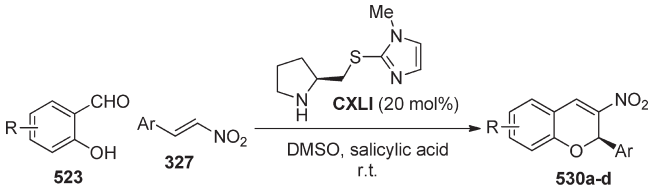
In the first step, the alcohol effects a nucleophilic attack to the *β*-position of the nitrostyrene, and a subsequent cyclization

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 268. Domino Michael Addition and Lactonization Described by Mukaiyama



Scheme 269. Synthesis of 3-Nitro-2*H*-chromenes Reported by Xu



(Henry reaction), followed by dehydration, furnishes the corresponding adducts as shown in Scheme 270.

In 2008, Rueping and co-workers developed an organocatalytic synthesis of pyranonaphthoquinones (**532**) from 2-hydroxy-1,4-naphtoquinone (lawsone, **531**) and enals.[404] The reaction is efficiently catalyzed by Jørgensen's catalyst (**XXXVI**). The reaction takes place via a Michael addition of the 2-hydroxy-1,4-naphtoquinone to the enal and subsequent hemiacetal formation between the aldehyde and the enolic form of the naphthoquinone. The final compounds were obtained in good yields and enantioselectivities (Scheme 271). Soon after, the same research group reported a similar reaction with cyclic diketones.[405]

In 2009, Wang and co-workers reported a synthesis of chromanes and of dihydrobenzopyrans from α,β-unsaturated aldehydes and 1-naphthol (**533**) via a Friedel–Crafts alkylation (or Michael addition) and subsequent intramolecular cyclization by hemiacetal formation.[406] The reaction is simply catalyzed by diphenylprolinol derivatives affording the cyclic products in good yields and stereoselectivities, as shown in Scheme 272. However, this methodology seems to be limited to the use of 1-naphthols, and when other aromatic alcohols such as phenols were used no reaction was observed.

In 2008 and 2009, Hayashi and co-workers reported two closely related approaches for the synthesis of tetrahydropyrans. In the first of them, a highly enantioselective synthesis of tetrahydropyrans **535** was achieved via a domino proline-mediated aldol reaction–intramolecular acetal formation.[407] The second report deals with the addition of 2-nitroethanol (**536**) to α,β-unsaturated aldehydes catalyzed by diphenylprolinol derivatives, furnishing chiral tetrahydropyrans **537** via a domino Michael reaction–intramolecular acetal formation and subsequent isomerization in basic media. In both cases, the corresponding tetrahydropyrans were produced in good yields and with excellent enantioselectivities (Scheme 273).[408]

In 2010, Wang and co-workers reported the highly enantioselective synthesis of chiral 4*H*-chromenes through iminium allenamide catalysis.[409] The reaction consists of a Michael–Michael sequence between propargylic aldehydes **539** and 2-(*E*)-(2-nitrovinyl)phenols **538**. The reaction is catalyzed by diphenylprolinol derivatives (**CXXIV**), affording the corresponding chromenes **540** in good yields and with excellent enantioselectivities (Scheme 274).

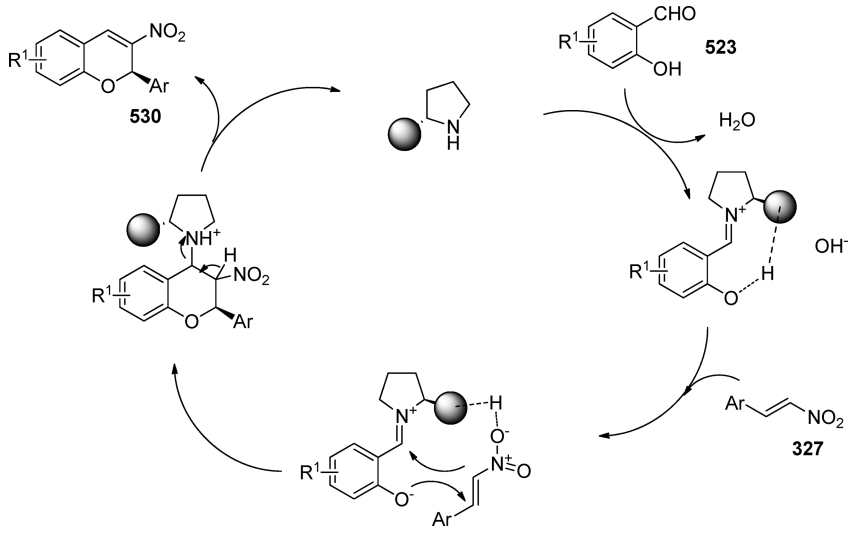
In 2009, Vicario and co-workers reported the synthesis of polysubstituted furofuranones via a domino oxa-Michael–aldol–hemiacetal formation sequence.[410] The reaction between enals and dihydroxyacetone dimer **541** is simply catalyzed by readily available chiral secondary amines such as the diphenylprolinol derivative **XLVIII**. The sequence reaction begins with an oxo attack to the β-position of the enal by the hydroxyl of the ketone, followed by an intramolecular aldol reaction between the resultant enamine and the carbonyl of the ketone. Next, the other hydroxyl group of the ketone forms an hemiacetal with the carbonyl of the aldehyde to furnish the corresponding hexahydrofuro[3,4-*c*]furanes **542** with good yields and with excellent stereoselectivities (Scheme 275). Remarkably, the use of an acid additive such as benzoic acid is crucial for enhancing the rate of the reaction. Without the use of an acid additive, no reaction was observed after 16 h.

An enantioselective synthesis of pyranones catalyzed by chiral NHC's was reported by Bode et al. in 2008.[411] In this report Bode describes that α-chloroaldehyde bisulfite adducts **543** react with unsaturated carbonyls **284** under biphasic reaction conditions, affording the pyranones **544**. The reaction, which is formally a hetero-Diels–Alder reaction of ketenes and enones, was efficiently promoted by the NHC catalyst derived from the triazolium salt **XX** (1 mol % was enough for an efficient rate), affording the corresponding products in excellent to good yields and with superb diastereo- and enantioselectivities (Scheme 276).

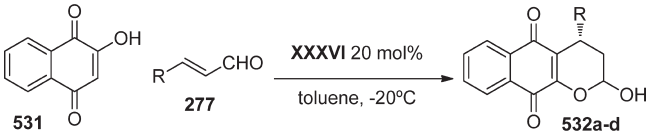
Very recently, Bode and co-workers reported an enantioselective Claisen rearrangement promoted by a NHC catalyst leading also to the synthesis of pyranones.[412] In this approximation,

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 270. Proposed Mechanism for the Amine-Catalyzed Synthesis of 3-Nitro-2*H*-chromenes

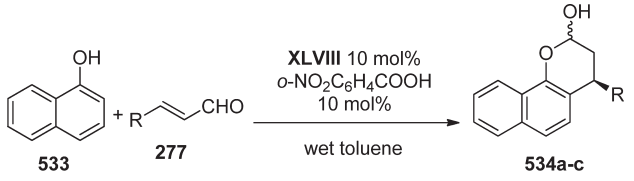


Scheme 271. Synthesis of Pyranonaphthoquinones Developed by Rueping



532a R=Ph 56%; 91% ee
532b R=Et 55%; 98% ee
532c R=*m*ClC$_6$H$_4$; 50%; 99% ee
532d R=*m*BrC$_6$H$_4$; 84%; 99% ee

Scheme 272. Friedel–Crafts Alkylation–Intramolecular Cyclization Reported by Wang

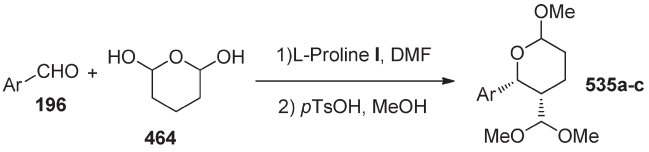


534a R=Ph 81%; 7:2 d.r.; 84% ee
534b R=2-furyl 63%; 7:2 d.r.; 74% ee
534c R=Me 70%; 2:1 d.r.; 72% ee

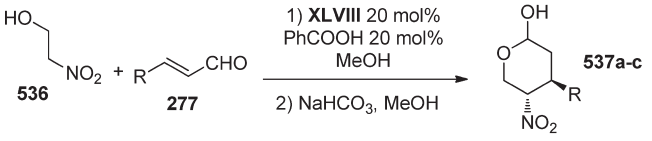
propargylic aldehydes react with pyruvic esters, kojic acids, or naphthols to afford the corresponding pyranones in good yields and moderate to good stereoselectivities (Scheme 277).

In 2005, Calter and co-workers reported the synthesis of furans through an interrupted Feist–Bénary reaction.[413] α-Bromopyruvates react with 1,3-dicarbonyl compounds under catalysis by *Cinchona* alkaloids (quinine, **CXXXIII**). The reaction begins with a dicarbonyl attack to the pyruvate followed by an intramolecular cyclization, rendering the final furanes such as **548** in good yields and enantioselectivities (Scheme 278).

Scheme 273. Synthesis of Tetrahydropyrans Reported by Hayashi



535a Ar=Ph 42%; 4:1 d.r.; 97% ee
535b Ar=*p*NO$_2$C$_6$H$_4$ 78%; 7:1 d.r.; 94% ee
535c Ar=*p*BrC$_6$H$_4$ 59%; 4:1 d.r.; 95% ee



537a R=Ph 86%; 89:11 d.r.; 95% ee
537b R=2-furyl 80%; 4:1 d.r.; 91% ee
537c R=Cyclohexyl 79%; 3:1 d.r.; 96% ee

In 2009, Zhao and co-workers reported the synthesis of chiral dihydropyrans via a Michael addition of α-substituted cyano ketones to β,γ-unsaturated esters.[414] The reaction is efficiently catalyzed by bifunctional thiourea–tertiary amine catalysts such as **CXLII**, affording the final compounds **550** in good yields and enantioselectivities (Scheme 279).

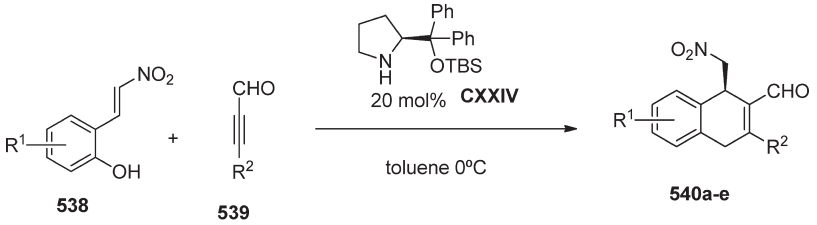
In 2010, Zhao and Cao expanded the scope of the reaction by using cyclic 1,3-dicarbonyl compounds instead of α-substituted cyano ketones.[415]

In 2010, Rueping and co-workers reported an asymmetric synthesis of aminobenzopyrans via a Mannich–ketalization reaction.[416] The reaction is catalyzed by chiral Brønsted acids such as **LXIII**, affording the final benzopyrans **553** in good yields and excellent enantioselectivities (Scheme 280).

6.2.3. Organocatalytic Asymmetric Synthesis of Thiacycles. In 2006, Wang et al.[417] and Córdova et al.[418] developed almost at the same time the organocatalytic asymmetric synthesis

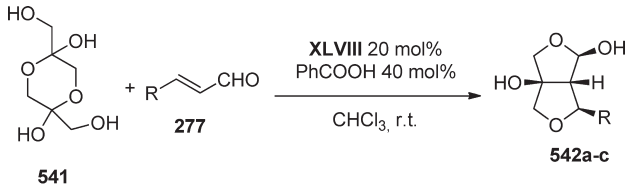
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 274. Synthesis of 4*H*-Chromenes Reported by Wang



540a R^1= H, R^2 = Ph, 97%; 99% ee
540b R^1 = H, R^2= 2-Thienyl, 92%; 99% ee
540c R^1 = H, R^2 = ^{t}Bu, 93%; 98% ee
540d R^1= 4-Cl, R^2 = Ph, 92%; 99% ee
540e R^1= 6-MeO, R^2= Ph, 95%; 98% ee

Scheme 275. Synthesis of Hexahydrofuro[3,4-c]furanes Reported by Vicario



542a R=Ph 76%; >10:1 d.r.; 98% ee
542b R=Me 89%; 7:1 d.r.; 92% ee
542c R=Bu 89%; >10:1 d.r.; 97% ee

of chiral thiochromenes (**554**) via a sulfa-Michael−aldol tandem reaction (Scheme 281).

This one-pot procedure from α,β-unsaturated aldehydes (**277**) and 2-mercaptobenzaldehyde (**555**) is catalyzed by commercially available prolinol derivatives (**XLVIII**) in the presence of benzoic acid as additive. Carrying the reaction out in choroform at room temperature yields thiochromenes (**554**) derived both from aromatic and from alkylic enals, in good to excellent levels of enantioselectivity (91−98% ee) and in high yields (55−93%). In addition, the presence of substituents in the benzene ring of the mercaptobenzaldeyde (**555**) does not significantly reduce the excellent outcome of the reaction.

More recently, Córdova and co-workers[419] reported also this tandem sequence upon mercaptobenzophenone. Avoiding the dehydration step, it is possible to obtain thiochromanes bearing three contiguous stereocenters with excellent enantioselectivities (96−99% ee) and yields (71−98%) and with good diastereocontrol (10:1−15:1 dr).

The concept of hetero-Michael−aldol domino reactions was also put into practice by Jørgensen and co-workers[420] for the formation of optically active highly functionalized tetrahydrothiophenes (**556**, **557**), a family of compounds very useful in biochemistry, pharmaceutical science, and nanoscience (Scheme 282). Moreover, Jørgensen demonstrated that an appropriate choice of the additive (bicarbonate or benzoic acid) allowed the control of the regioselectivity of the reaction (aldol step).

When aliphatic α,β-unsaturated aldehydes (**277**) and α-mercaptoacetophenone (**558**) react under the effect of 10 mol % of catalyst (**XLVIII**) and in the presence of benzoic acid, tetrahydrothiophene carbaldehydes (**556**) are obtained with moderate yields, excellent enantioselectivities (90−96% ee), and total diastereocontrol (only one diastereomer is formed). This outcome involves the usual pathway in this kind of domino reactions (sulfa-Michael addition over the iminium ion and a subsequent intramolecular aldol reaction between the intermediate enamine and the ketone moiety). On the other hand, when the reaction is carried out under basic conditions ($NaHCO_3$), the aldol cyclization step is thermodynamically controlled by the substrate, without catalyst induction, affording (tetrahydrothiophen-2-yl)phenyl methanones (**557**) with similar yields but with lower enantioselectivities. One limitation of these methodologies is the need to use aliphatic enals, so that when aromatic enals or α-branched enals were used no reaction was observed.

Pursuing a similar target, a different approach was disclosed by Wang and co-workers.[421] In particular, they developed a double Michael addition between enals (**277**) and 4-mercapto-2-butenoate (**559**) to obtain chiral tetrahydrothiophenes (**560**) under catalysis by diphenylprolinol trimethylsilyl ether **XLVIII** (Scheme 283).

After the first thio-Michael addition, the enamine intermediate undergoes a conjugate addition to the α,β-unsaturated ester, furnishing the thiophene ring. The reaction allows for the use of different aromatic, heteroaromatic, and aliphatic enals (**277**), affording the thiophenes **560** in good yields (62−96%), good diastereoselectivities (6:1−15:1 dr), and excellent enantioselectivities (94→99% ee) in all cases.

Córdova and co-workers presented a simple catalytic synthesis of tetrahydrothioxanthenones (**561**).[422] The catalytic domino reaction of 2-mercaptobenzaldehyde (**555**) and cyclic enones (**321**) proceeded in a highly chemoselective fashion, furnishing the corresponding products in high yields and with poor

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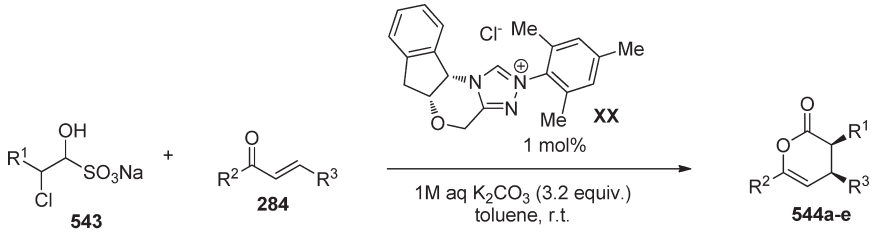
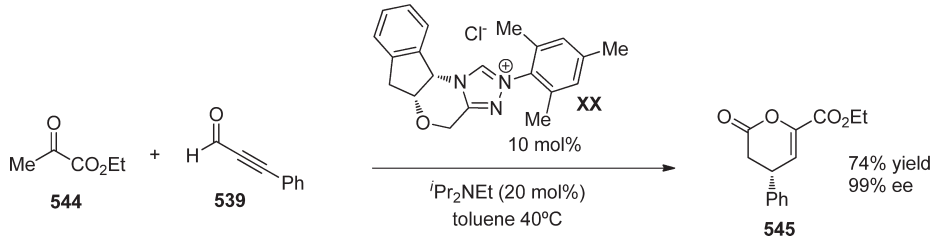
Scheme 276. Synthesis of Pyranones Reported by Bode

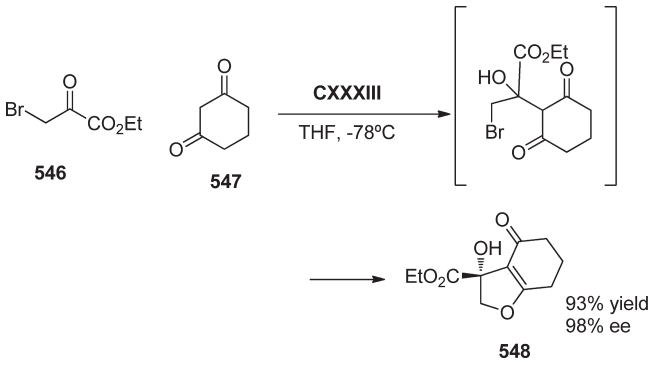


544a R^1=H R^2=Ph R^3=CO_2Et 84%; 90% ee
544b R^1=H R^2=cyclohexyl R^3=CO_2Et 52%; 91% ee
544c R^1=H R^2=CO_2Et R^3=Pr 80%; >99% ee
544d R^1=Bn R^2=Me R^3=CO_2Et 65%; 99% ee
544e R^1=Bn R^2=Ph R^3=CO_2Et 98%; 99% ee

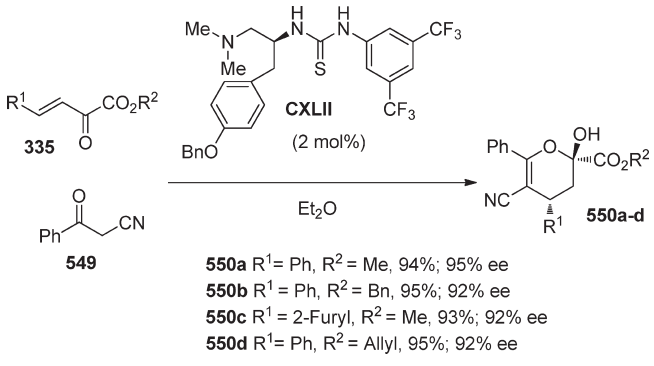
Scheme 277. Synthesis of Pyranones from Propargylic Aldehydes Reported by Bode



Scheme 278. Synthesis of Furans Reported by Calter



Scheme 279. Synthesis of Dihydropyranes Reported by Zhao



550a R^1= Ph, R^2 = Me, 94%; 95% ee
550b R^1 = Ph, R^2 = Bn, 95%; 92% ee
550c R^1 = 2-Furyl, R^2 = Me, 93%; 92% ee
550d R^1= Ph, R^2 = Allyl, 95%; 92% ee

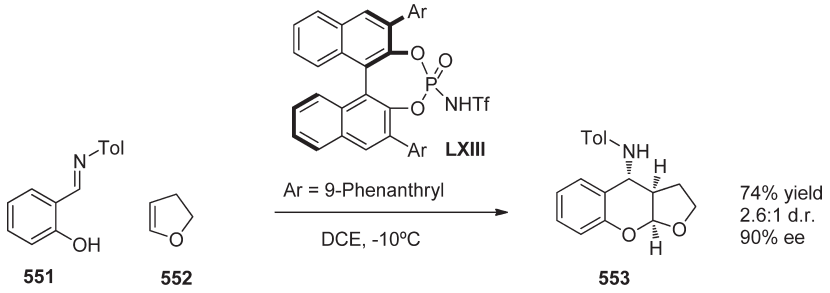
enantioselectivities. Aldols (**562**) could be isolated as single diastereomers when a rapid column chromatography eluent system was used. The mechanism proposed involves the iminium activation of the α,β-unsaturated cyclic enone by the chiral pyrrolidine derivatives (**IX**, **CXLIII**). Stereoselective nucleophilic conjugate attack on the β-carbon by the thiol results in a chiral enamine intermediate, which experiences an intramolecular 6-exo-trig aldol addition from the same face as the incoming thiol. Hydrolysis of the resulting iminium intermediate gives aldol **562**. Elimination of water affords the tetrahydrothioxanthenone (**561**) (Scheme 284).

In 2007, Zhao and co-workers developed a similar reaction for the synthesis of thiochromanes (**563**) via a tandem Michael−Henry reaction of 2-mercaptobenzaldehydes (**555**) and nitrostyrenes (**327**), simply catalyzed by cupreine (**CXVII**).[423] Chiral 2-aryl-3-nitrothiochroman-4-ols **563** were synthesized with enantioselectivities up to 86% ee and diastereomeric ratios up to 78:22, as shown in Scheme 285.

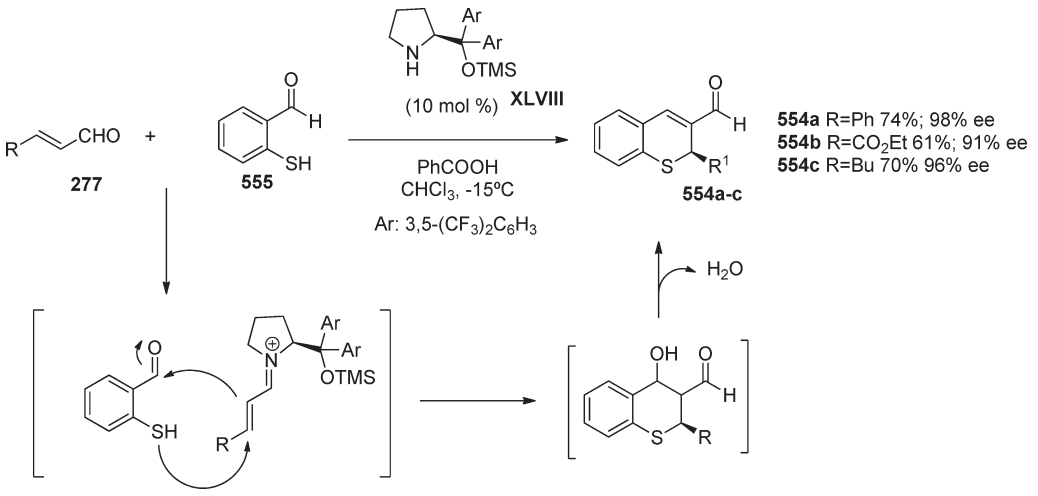
Another similar approach to the synthesis of thiochromenes was reported by Wang and co-workers.[424] They developed a Michael−Michael cascade reaction catalyzed by a quinine-derived thiourea (**XCIII**). This process involves a dynamic kinetic resolution that allows for building substituted thiochromenes (**565**) in high yields and with excellent diastereomeric and enantiomeric excesses, as shown in Scheme 286.

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

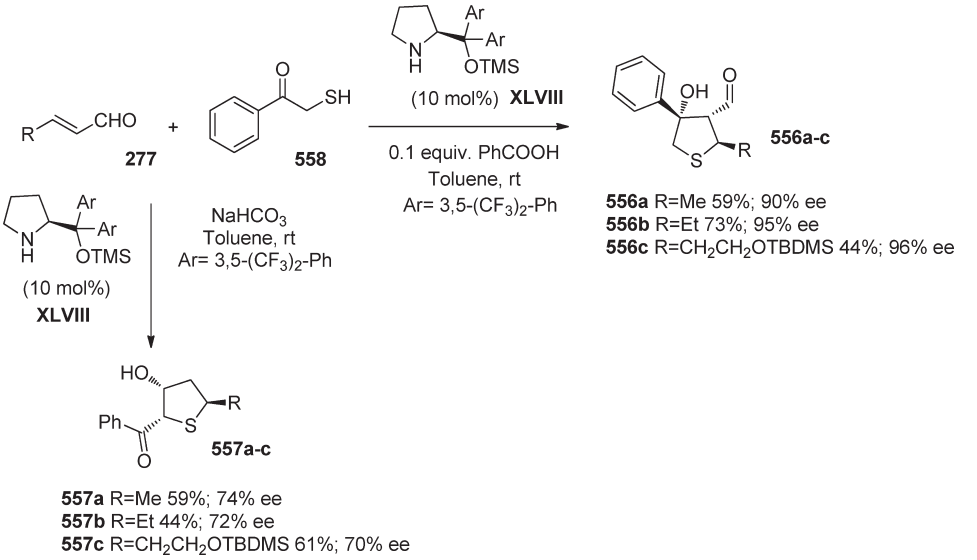
Scheme 280. Synthesis of Aminobenzopyrans Reported by Rueping



Scheme 281. Asymmetric Organocatalytic Synthesis of Thiochromenes



Scheme 282. Synthesis of Tetrahydrothiophenes Developed by Jørgensen



Hydrogen-bonding-mediated catalysis was used by Wang and co-workers in 2007 in order to perform highly enantio- and diastereoselective tandem Michael−aldol reactions.[425] These were also efficiently catalyzed by a quinine-derived thiourea

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

(**XCIII**), using as few as 1 mol % of catalyst loading, via synergistic noncovalent hydrogen-bonding activation of both the Michael donor and of the acceptor. This strategy mimics closely the action mode of enzyme catalysis. Chiral thiochromanes (**567**) were obtained by means of this procedure, with the formation of three stereogenic centers with total diastereoselectivity and with excellent yields and enantioselectivities (Scheme 287).

Soon after, the same group published another organocatalytic, enantioselective domino Michael−aldol reaction, this time between 2-mercaptobenzaldehydes (**555**) and maleimides (**346**), these last being much less explored substrates.[426] They managed to incorporate succinimides into complex benzothiopyrans (**568**) generating again three stereogenic centers in a single operation. The process was catalyzed by the bifunctional chiral amine thiourea (**XLI**) described by Takemoto and co-workers, via a hydrogen-bonding-mediated activation mechanism (Scheme 288). One of the limitations of this methodology is the need to use aromatic maleimides, since when *N*-aliphatic substituents were used, such as *N*-benzylmaleimide, the diastereoselectivities decreased dramatically.

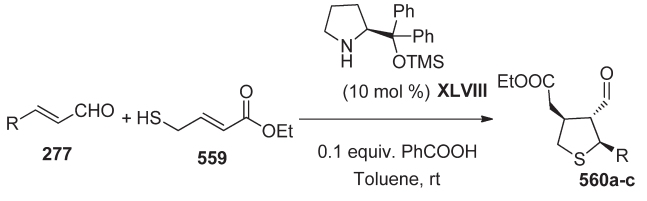
In 2009, Wang and co-workers reported the synthesis of thiophenes **570** via a Michael−aldol reaction between enals and ethyl 3-mercapto-2-oxopropanoate (**569**).[427] The reaction was catalyzed by diphenylprolinol derivatives, rendering the corresponding thiophenes bearing three contiguous stereocenters (one of them quaternary) in moderate yields and with good to excellent diastereo- and enantioselectivities (Scheme 289). However, there were no examples of the use of aliphatic enals or of α-branched enals, this being an important limitation for this methodology.

6.2.4. Organocatalytic Asymmetric Synthesis of Other Heterocycles. In 2008, Zhong and co-workers developed a novel, practical, and highly enantio- and diastereoselective domino reaction for the synthesis of functionalized tetrahydro-1,2-oxazines (**571**) by using simple L-proline (**I**) as the organocatalyst. The authors reported the reaction between aldehyde **572**, which bore a nitroalkene moiety, and nitrosobenzene (**322**).[428] In the first step, *O*-alkylation took place at the α-position of the aldehyde, and then an intramolecular aza-Michael reaction took place, closing the ring and furnishing tetrahydro-1,2-oxazines (**571**) with excellent yields and enantioselectivities (Scheme 290).

In 2007, Córdova and co-workers developed a very elegant synthesis of 5-hydroxyisoxazolidine compounds (**573**), based on the addition of *N*-protected hydroxyamines (**574**) to α,β-unsaturated aldehydes (**277**), catalyzed by **XLVIII**.[429] The authors disclosed that, in a first step, the amine attacked the β-position of the iminium ion, this reaction being at equilibrium. This equilibrium was displaced toward the final products due to cyclic hemiacetal formation between the hydroxyl moiety at the nitrogen atom and the aldehyde. The reaction worked well with any unsaturated aldehyde (aromatic and aliphatic), affording the final compounds in high yields and enantioselectivities. Moreover, the usefulness of this reaction is clearly shown by the synthesis of chiral β-amino acids **576** from α,β-unsaturated aldehydes in only two steps, as shown in Scheme 291.

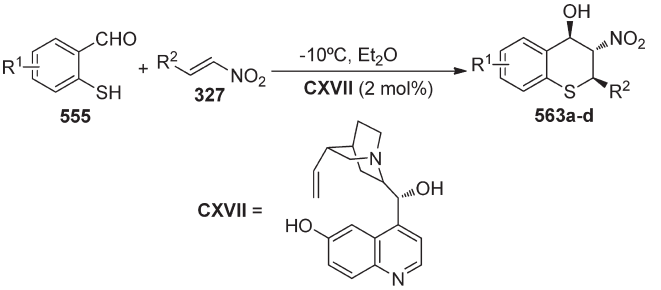
In 2010, Shibata and co-workers reported a similar reaction using as starting materials β-trifluoromethyl enones (**577**) and hydroxylamine (**578**).[430] They synthesized chiral trifluoromethyl-substituted 2-isoxazolines (**579**) in one step. Trifluoromethyl-substituted 2-isoxazolines are an important class of heterocyclic

Scheme 283. Synthesis of Tetrahydrothiophenes (559) Developed by Wang



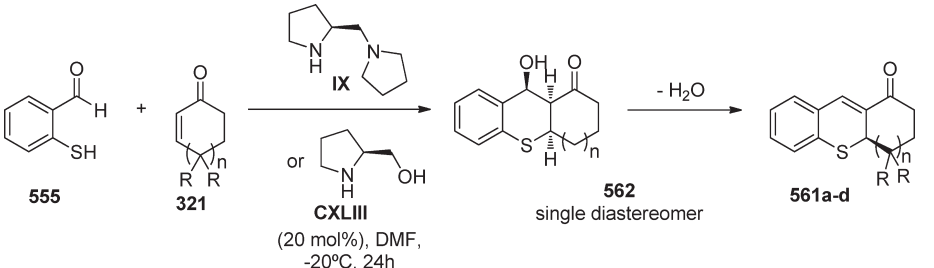
560a R=Ph 76%; 15:1 d.r.; >99% ee
560b R=2-furanyl 88%; 6:1 d.r.; 98% ee
560c R=BnOCH2 62%; 7:1 d.r.; 94% ee

Scheme 285. Zhang's Synthesis of 3-Nitro-2*H*-thiochromenes



563a R^1= H, R^2 = Ph, 95%; 7:3 d.r.; 86% ee
563b R^1= H, R^2 = *p*-BrC_6H_4, 95%; 74:26 d.r.; 76% ee
563c R^1= H, R^2 = *m*-ClC_6H_4, 96%; 65:35 d.r.; 78% ee
563d R^1= 4-MeO, R^2 = Ph ,95%; 7:3 d.r.; 82% ee

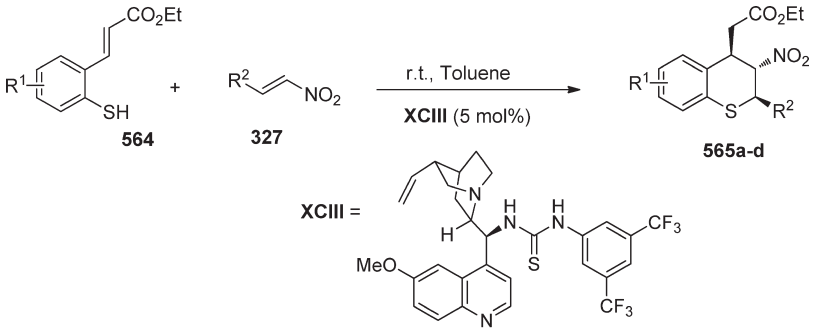
Scheme 284. Catalytic Enantioselective Synthesis of Tetrahydrothioxanthenones Developed by Córdova



561a (n=1) R = H, 74%; 62% ee
561b (n=1) R = Me, 77%; 48% ee
561c (n=0) R = H, 78%; 38% ee
561d (n=2) R = H, 70%; 60% ee

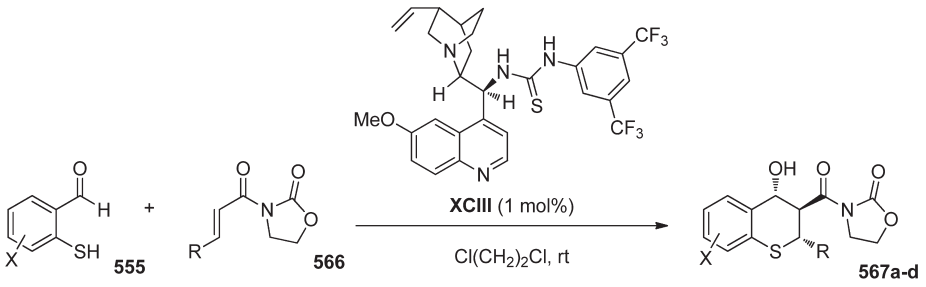
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 286. Wang's Synthesis of 3-Nitrothiochromenes



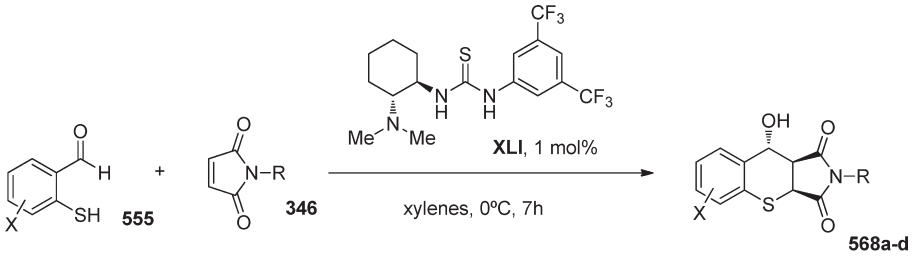
565a R^1= H, R^2 = Ph, 90%; >30:1 d.r.; 97% ee
565b R^1= H, R^2 = *p*-BrC_6H_4, 97%; >30:1 d.r.; 97% ee
565c R^1 = H, R^2 = *m*-BrC_6H_4, 83%; >30:1 d.r.; 97% ee
565d R^1= 5-MeO, R^2 = Ph, 42%; >30:1; 97% ee

Scheme 287. Tandem Michael−Aldol Reactions Performed by Hydrogen-Bonding-Mediated Catalysis by Wang



567a X = H, R = Ph, 90%; 99% ee
567b X = H ,R = *p*-ClC_6H_4, 92%; 99% ee
567c X= H, R = *m*-ClC_6H_4, 95%; 97% ee
567d X= 5-Cl, R = Ph, 97; 97% ee

Scheme 288. Domino Michael−Aldol Reaction Reported by Wang



568a X = H, R = Ph ,90%; 10:1 d.r.; 84% ee
568b X = 4-Me, R = Ph, 95%; 8:1 d.r.; 83% ee
568c X = 5-Me, R = Ph, 92%; 7:1 d.r.; 83% ee
568d X = H, R = Bn, 92%; 3:1 d.r.; 80% ee

compounds with remarkable biological activities. The reaction is simply catalyzed by quaternary ammonium salts such as quaternized *Cinchona* alkaloids. The authors disclosed that, in a first step, the hydroxyl attacked the β-position of the trifluoromethyl enone, this reaction being at equilibrium. This equilibrium was pushed to the final products due to imine formation between the amine moiety and carbonyl of the enone. The reaction worked well with any aromatic (R^1 = aryl) enone, affording the final compounds in high yields and enantioselectivities (Scheme 292).

In 2010, Pitacco and co-workers reported the symthesis of chiral 1,4-dihydropyridazines (**581**) starting from enolizable aldehydes and 1,2-diaza 1,3-dienes (**580**).[431] The reaction was simply catalyzed by proline, affording the corresponding cycloadducts in low yields with moderate enantioselectivities (Scheme 293).

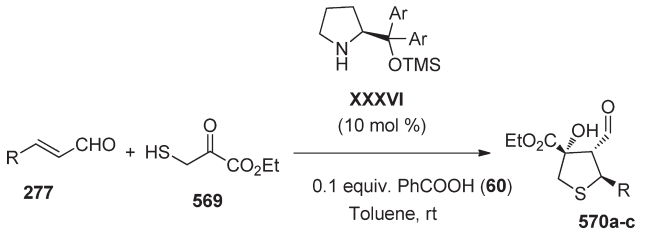
dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

7. ORGANOCATALYTIC ASYMMETRIC MULTICOMPONENT CYCLIZATIONS

One of the present challenges in asymmetric organocatalysis is to implement various reaction strategies in a multicomponent domino reaction to achieve multibond formation in one operation. This strategy is atom-economical and avoids the necessity of protecting groups and isolation of intermediates. Its goal is the resembling of nature in its highly selective sequential transformations.

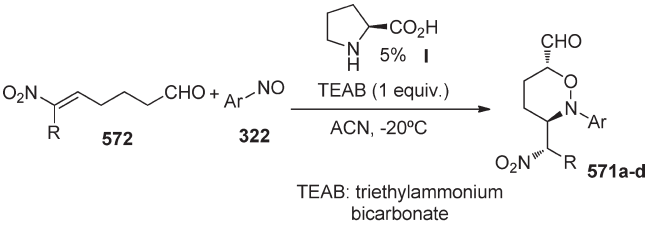
The combination of enamine−iminium ion activations in asymmetric organocatalytic domino and multicomponent reactions has been developed to achieve the enantioselective consecutive formation of two or more bonds in a stereoselective fashion.

Scheme 289. Domino Thia-Michael−Aldol Reaction Reported by Wang



Ar=3,5-$(CH_3)_2C_6H_3$
570a R=Ph 42%; 10:1 d.r.; 95% ee
570b R=2-furanyl 59%; >20:1 d.r.; 93% ee
570c R=*p*-BrC_6H_4 34%; 12:1 d.r.; 93% ee

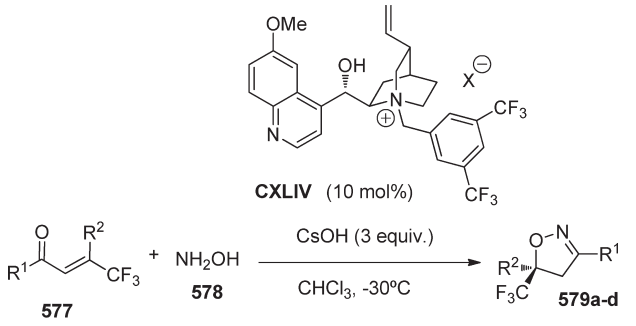
Scheme 290. Synthesis of Tetrahydro-1,2-oxazines (570) Reported by Zhong



571a R=H Ar=Ph 90%; >99% ee
571b R=Me Ar=2-MeC_6H_4 75%; 99% ee
571c R=Ph Ar=Tolyl 73%; >99% ee
571d R=Bn Ar=4-BrC_6H_4 66%; 99% ee

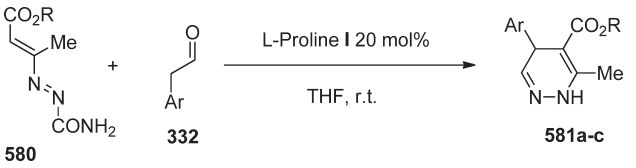
In 2003, Barbas and co-workers reported the first organocatalytic diastereospecific and enantioselective direct asymmetric domino Knoevenagel/Diels−Alder reaction.[432] This methodology produced highly substituted spiro[5,5]undecane-1,5,9-triones (**583**) from commercially available 4-substituted-3-buten-2-ones (**284**), aldehydes (**196**), and 2,2-dimethyl-1,3-dioxane (Meldrum's acid, **582**). An amino acid derivative (**CXLV**) catalyzed the domino Knoevenagel condensation of aldehyde **196** with Meldrum's acid (**582**) to provide the alkylidene derivative of Meldrum's acid, which underwent a concerted [4 + 2]-cycloaddition with a 2-amino-1,3-butadiene generated in situ from the enone **284** and the amino acid catalyst. The resulting

Scheme 292. Synthesis of Trifluoromethylisoxazolines Described by Shibata



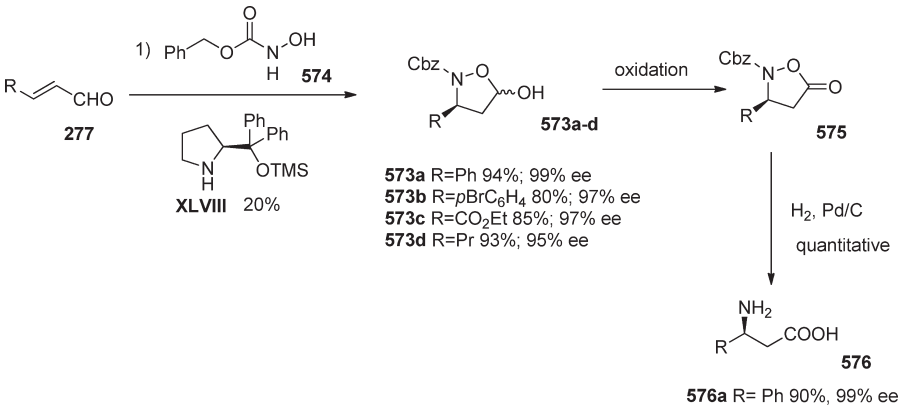
579a $R^1 = R^2$ = Ph, 88%; 92% ee
579b R^1= Ph, R^2= *p*-Tolyl, 99%; 93% ee
579c R^1= *p*-Tolyl, R^2 = Ph, 83%; 94% ee
579d R^1= Ph, R^2 = Cyclohexyl, 80%; 91% ee

Scheme 293. Synthesis of 1,4-Dihydropyridazines Described by Pitacco



581a R=Et Ar=Ph 35%; 39% ee
581b R=Me Ar=Ph 25%; 59% ee
581c R=Me Ar=*p*-BrC_6H_4 23%; 62% ee

Scheme 291. Synthesis of *β*-Amino Acids Described by Córdova

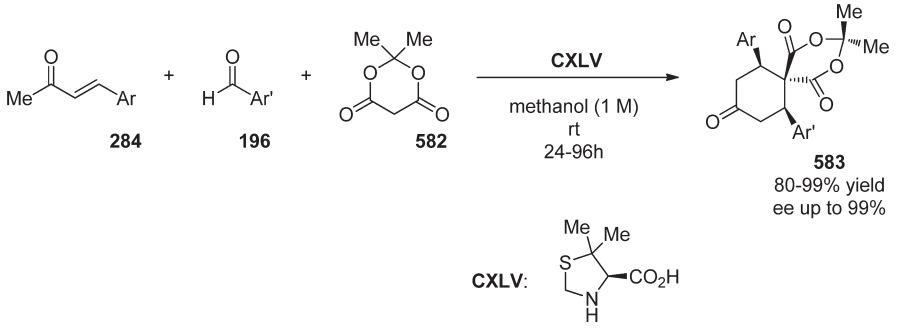


573a R=Ph 94%; 99% ee
573b R=*p*-BrC_6H_4 80%; 97% ee
573c R=CO_2Et 85%; 97% ee
573d R=Pr 93%; 95% ee

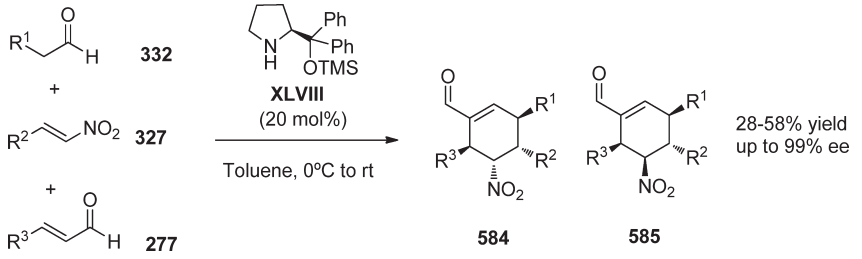
576a R= Ph 90%, 99% ee

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

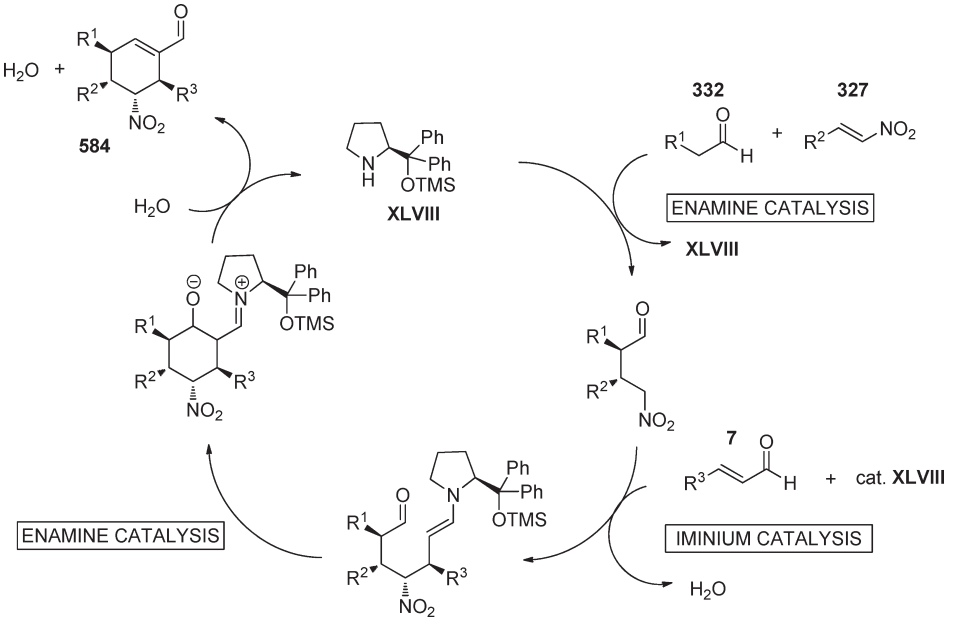
Scheme 294. Domino Knoevenagel/Diels–Alder Reaction Reported by Barbas



Scheme 295. Asymmetric Organocatalytic Triple Cascade Reaction



Scheme 296. Proposed Catalytic Cycle for the Asymmetric Organocatalytic Triple Cascade Reaction Developed by Enders



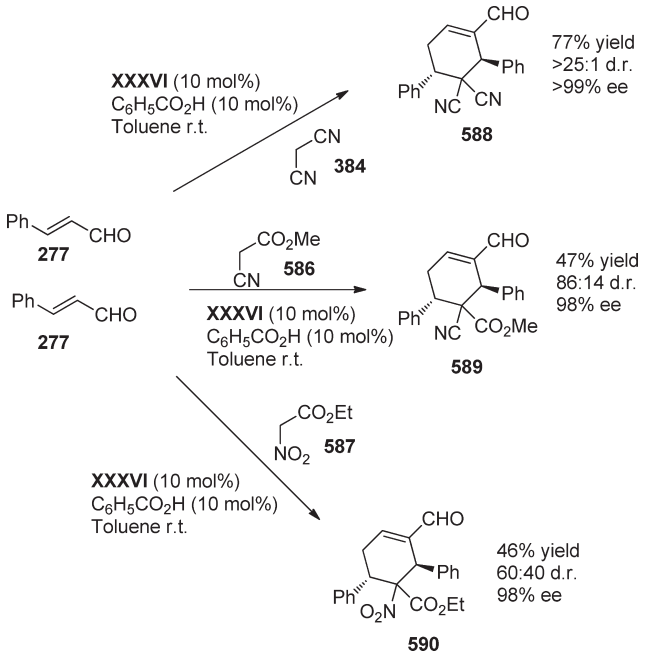
spirocyclic ketones (**583**) are attractive intermediates in the synthesis of natural products and in medicinal chemistry (Scheme 294).

Enders and co-workers developed in 2006 an asymmetric organocatalytic triple cascade reaction for the construction of tetrasubstituted cyclohexenecarbaldehydes (**584**) from enals (**277**), nitroalkenes (**327**), and enolizable aldehydes (**332**) (Scheme 295).[433] In this work, they paved the way for the sequential creation of three bonds by a high enantioselective combination of enamine–iminium–enamine catalysis for a triple cascade reaction.

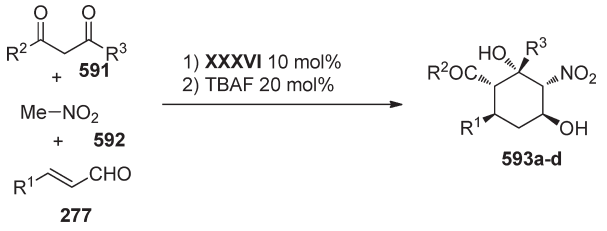
This catalytic cascade is a three-component reaction comprising a linear aldehyde (**332**), a nitroalkene (**327**), an α, β-unsaturated aldehyde (**277**), and a simple chiral secondary amine (**XLVIII**), which is capable of catalyzing each step of this triple cascade. This multicomponent reaction proceeds through a

dx.doi.org/10.1021/cr100348t |*Chem. Rev.* 2011, 111, 4703–4832

Scheme 297. Cyclohexene Synthesis Reported by Jørgensen



Scheme 298. Synthesis of Cyclohexane Derivatives Developed by Ruano and Alemán



593a R^1=Me R^2=Ph R^3=Ph 55%; >98:2 d.r.; 99% ee
593b R^1=Me R^2=PMP R^3=PMP 35%; >98:2 d.r.; 98% ee
593c R^1=Me R^2=Ph R^3=Me 44%; >98:2 d.r.; 94% ee
593d R^1=Et R^2=Ph R^3=Me 47%; >98:2 d.r.; 98% ee

Michael−Michael−aldol condensation sequence, leading to four stereogenic centers generated in three consecutive carbon−carbon bond formations with high diastereoselectivities and with essentially complete enantioselectivities (Scheme 296). Thus, from the eight possible diastereomeric pairs of **584**, only two epimers located in the α-position of the nitro group are formed in a ratio ranking from 2:1 to 99:1, the minor isomer being easily separated by chromatography. Besides, varying the starting materials, diverse polyfunctional cyclohexene derivatives can be obtained by employing roughly a 1:1:1 ratio of the three substrates.

In the first step, the catalyst activates the linear aldehyde (**332**) by enamine formation to achieve the first Michael-type addition to the nitroolefin (**327**). Then, the catalyst is liberated by hydrolysis, being able to form the iminium ion with the enal (**277**) to catalyze the second conjugate addition of the nitroalkane. During this addition, a new enamine intermediate is formed; it cyclizes through an intramolecular aldol condensation to afford cyclohexenes (**584, 585**) with moderate to good yields (30−58%) and complete enantioselectivity (≥99% ee; Scheme 296).

In 2008, Gong reported the highly enantioselective synthesis of dihydropiperidines via an asymmetric three-component cyclization reaction between cinnamaldehyde, an aromatic primary amine, and a 1,3-dicarbonyl compound.[434] The reaction is efficiently catalyzed by chiral phosphoric acid derivatives, furnishing the corresponding dihydropyridines in high yields and enantioselectivities.

In 2007, Jørgensen and co-workers developed a new organocatalytic multicomponent domino reaction that leads to the obtention of cyclohexenes from malononitriles or related compounds and enals.[435] The reaction occurs via a Michael−Michael−aldol reaction sequence and it is promoted by chiral secondary amine catalysts such as the diphenylprolinol derivative **XXXVI**. The reaction works perfectly with malonodinitrile (**384**), affording the final cyclohexenes **588** in good yields and excellent stereoselectivities. When α-cyano esters (**586**) or α-nitro esters (**587**) were used the corresponding cyclohexenes (**589** and **590**, respectively) were also obtained in good yields and excellent enantioselectivities, albeit with low diastereoselectivities due the poor stereocontrol in the newly formed quaternary carbon (Scheme 297).

In 2009, Ruano, Alemán, and co-workers reported the synthesis of pentasubstituted cyclohexanes via a multicomponent reaction via a Michael reaction followed by a domino interintramolecular double Henry reaction between an unsaturated enal, a 1,3-dicarbonyl compound, and nitromethane.[436] First, the 1,3-dicarbonyl **591** compound reacts with the unsaturated enal **277** via a Michael reaction catalyzed by the chiral secondary amine (**XXXVI**), and the resulting compound reacts with nitromethane via an intermolecular Henry reaction with the aldehyde, followed by an intramolecular Henry reaction, rendering the final cyclohexane **593**. As shown in Scheme 298, the reaction affords the cyclohexanes in good yields, as well as with excellent diastereo- and enantioselectivities. However, the scope of the reaction is limited to the use of nitromethane and of aliphatic enals. When aromatic enals were used, no reaction was detected.

In 2009, Dixon and co-workers developed a nice cascade reaction for the synthesis of cyclohexanes from malonates (**594**), nitroalkenes **327**, and α,β-unsaturated enals **277**.[437] The cascade needs the use of two different catalysts, and begins with the malonate addition to nitroalkenes promoted by a bifunctional amine−thiourea catalyst (**CXIX**). Next, the resulting nitroalkane reacts via an iminium-promoted Michael reaction with the α,β-unsaturated enal. This time, the reaction is catalyzed by a diphenylprolinol derivative (**CXVIII**). Finally, a base-promoted cyclization takes place between the malonate and the resulting aldehyde, affording the final cyclohexane **595** as it is depicted in Scheme 299.

The reaction affords the corresponding cyclohexanes with moderate yields and with excellent stereoselectivities (Scheme 300). Remarkably, individual changes in the stereochemistry of either catalyst give access to different stereoisomers of the final compound, enriching the versatility of this methodology.

In 2010, the same research group developed a related reaction for the synthesis of piperidines **596**.[438] This time, the reaction begins with an aldehyde addition to a nitroalkene, followed by an aza-Henry reaction between the resulting nitroalkane and a *N*-tosylimine; next, an intramolecular hemiaminal formation

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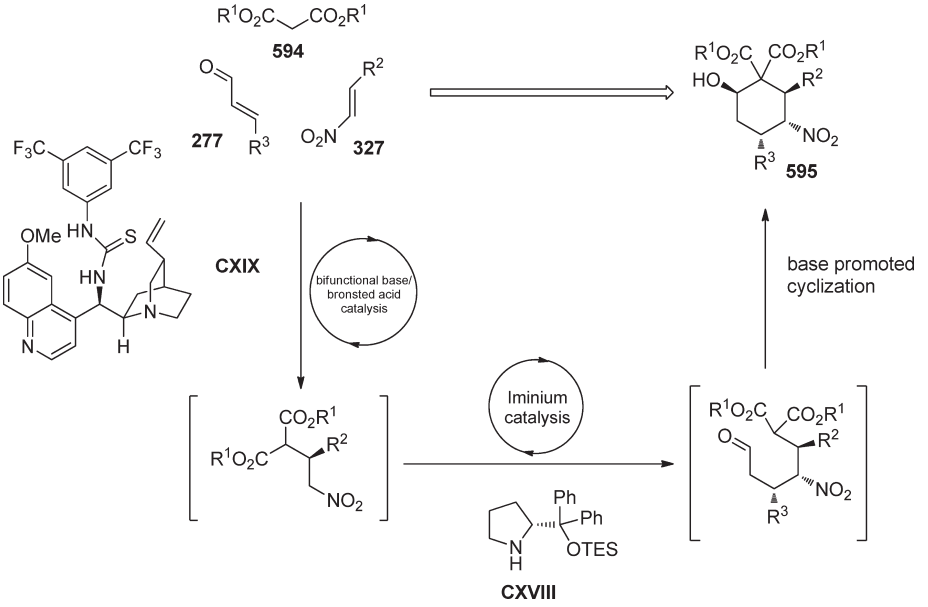
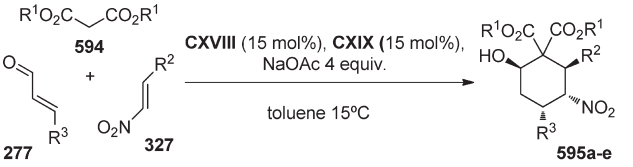
Scheme 299. Reaction Pathway for the Synthesis of Cyclohexanes Reported by Dixon

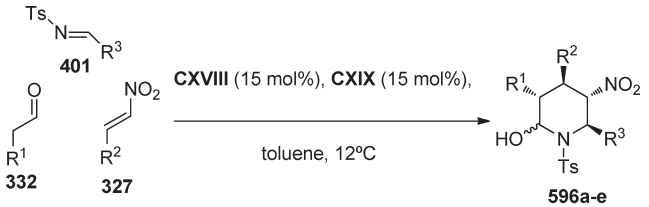


Scheme 300. Synthesis of Cyclohexanes Reported by Dixon



595a R^1= Me, R^2= *o*-BrC_6H_4, R^3 = Ph, 63%; 4.1:1.3:1 d.r.; 98% ee
595b R^1= Me, R^2 = R^3 = Ph, 52%; 7.1:1.8:1 d.r.; 96% ee
595c R^1= Me, R^2 = *n*-C_6H_{13}, R^3 = Ph, 26%; 6.7:1:0 d.r.; n.d.
595d R^1= Me, R^2 = 2-Furyl, R^3 = *p*-CNC_6H_4, 74%; 9.3:1.8:1 d.r.; >99% ee
595e R^1= Me, R^2= 2-Furyl R^3 = Me, 69%; 3.1:1:1 d.r.; >99% ee

Scheme 301. Synthesis of Piperidines Reported by Dixon

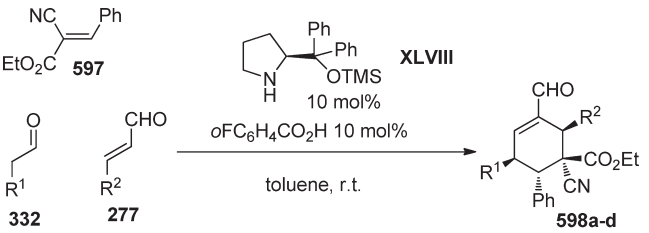


596a R^1= Me, R^2 = *o*-BrC_6H_4, R^3 = Ph, 54%; 99% ee
596b R^1= Me, R^2 = R^3 = Ph, 56%; 99% ee
596c R^1= Bn, R^2 = R^3 = Ph, 48%; 98% ee.
596d R^1= Me, R^2 = Ph, R^3 = *p*-CNC_6H_4, 47%; >99% ee
596e R^1= Me, R^2 = 2-Furyl, R^3 = Ph, 65%; >99% ee

takes place to furnish the piperidine. The reaction is efficiently catalyzed by the same mixture of a diphenylprolinol catalyst (**CXVIII**) and a bifunctional catalyst (**CXIX**), rendering the final compounds in good yields and stereoselectivities (Scheme 301).

In 2008, Melchiorre and co-workers developed a triple cascade reation that led to the synthesis of cyclohexanes.[439]

Scheme 302. Asymmetric Organocatalytic Cyclohexane Synthesis Reported by Melchiorre



598a R^1=Me R^2=Ph 52%; 2.6:1 d.r.; >99% ee
598b R^1=Et R^2=Ph 40%; 2.3:1 d.r.; >99% ee
598c R^1=allyl R^2=Me 40%; >20:1 d.r.; 99% ee.
598d R^1=Me R^2=Me 48%; >20:1 d.r.; 99% ee

The reaction consists of first the aldehyde addition to a 2-cyanoacrylate derivative (**597**), promoted by a diphenylprolinol derivative (**XLVIII**); next, the resulting adduct reacts via a Michael addition with an enal again promoted by the same catalyst. Finally, an intramolecular aldol reaction takes place between the formed enamine and the aldehyde, leading to the cyclohexane. It should be noticed that the use of an acid as a cocatalyst is crucial to obtain high levels of stereoselectivity. The scope of the reaction is broad, allowing the use of either aromatic or aliphatic enals, rendering in both cases the final cyclohexanes **598** in good yields and excellent stereoselectivities (Scheme 302).

One year later, the same group reported the synthesis of spirocyclic compounds derived from oxindoles via a triple cascade reaction.[237] As shown in Scheme 303, the reaction between α-methyleneoxindoles (**330**), aldehydes (**332**), and enals (**277**) catalyzed by a diphenylprolinol derivative (**XLVIII**) renders the corresponding spirocyclohexenes **599** in good yields and with excellent stereoselectivities. The cascade reaction

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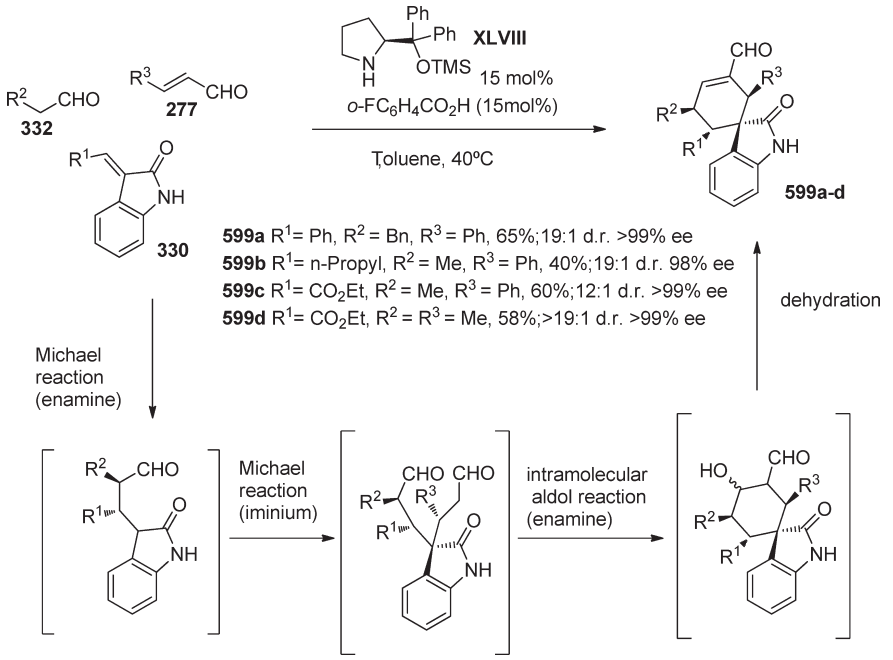
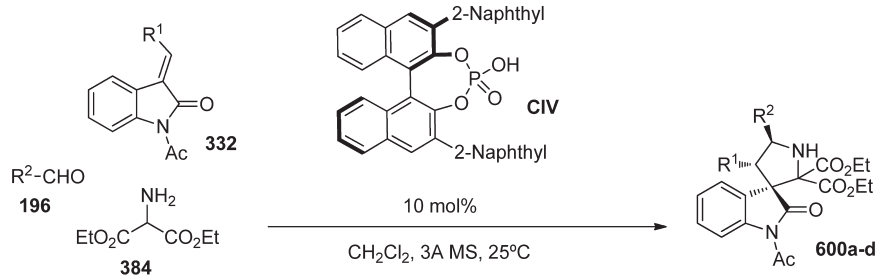
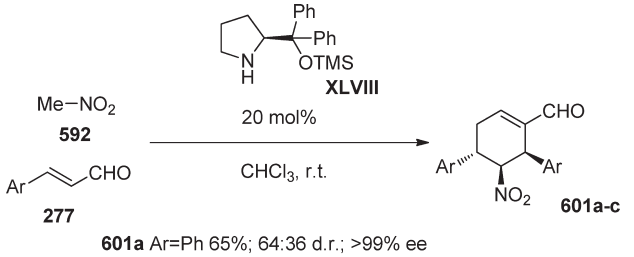
Scheme 303. Synthesis of Spiro Compounds Reported by Melchiorre



Scheme 304. Synthesis of Spirocyclic Compounds Reported by Gong



Scheme 305. Triple Cascade Reaction Reported by Enders



begins with a Michael addition of the aliphatic aldehyde to the unsaturated oxindole, followed by a second Michael addition to the enal, and finally the intermediate enamine reacts with the aldehyde via an intramolecular aldol reaction; dehydration of the aldol gives the final product.

In 2010, Chen and co-workers, building on this idea, reported the synthesis of spiro compouds with nitroalkenes, imines, or maleimides instead of enals.[440] In all of the examples, the final compounds were obtained in excellent yields and stereoselectivities.

In the same year, Gong and co-workers reported an organocatalytic synthesis of spiro oxindoles via a [3 + 3]-cycloaddition.[441] The reaction between *N*-acetyl methylideneindolines and azomethyne ylides (formed in situ from aldehydes and aminomalonate) was simply catalyzed by a phosphoric acid derivative (**CIV**), affording the final spiropyrrolidines **600** in excellent yields and stereoselectivities (Scheme 304).

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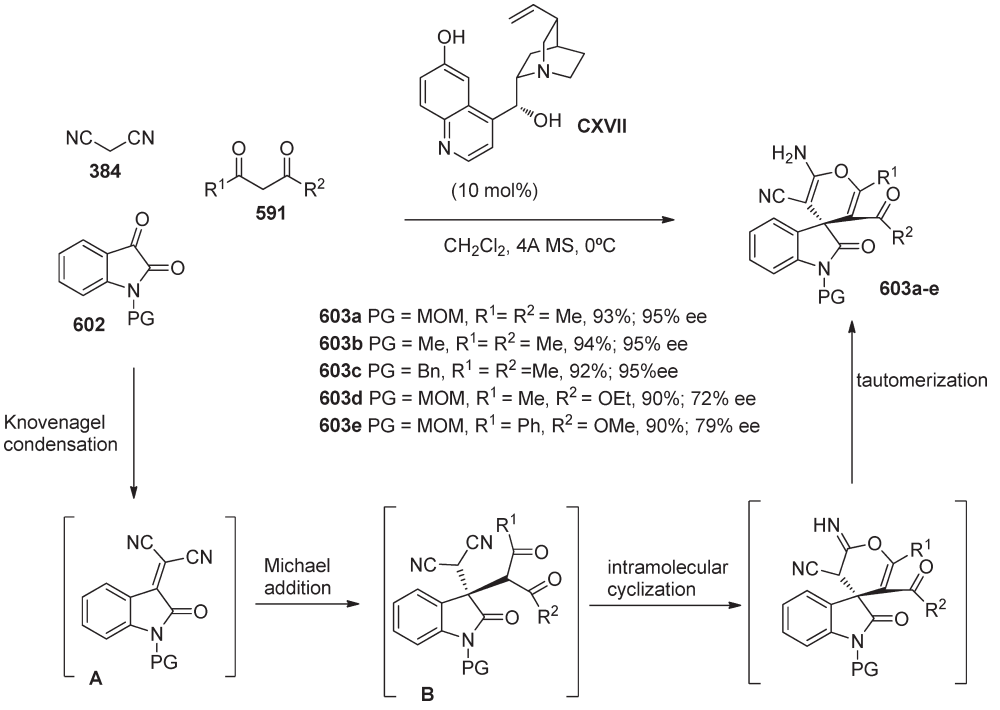
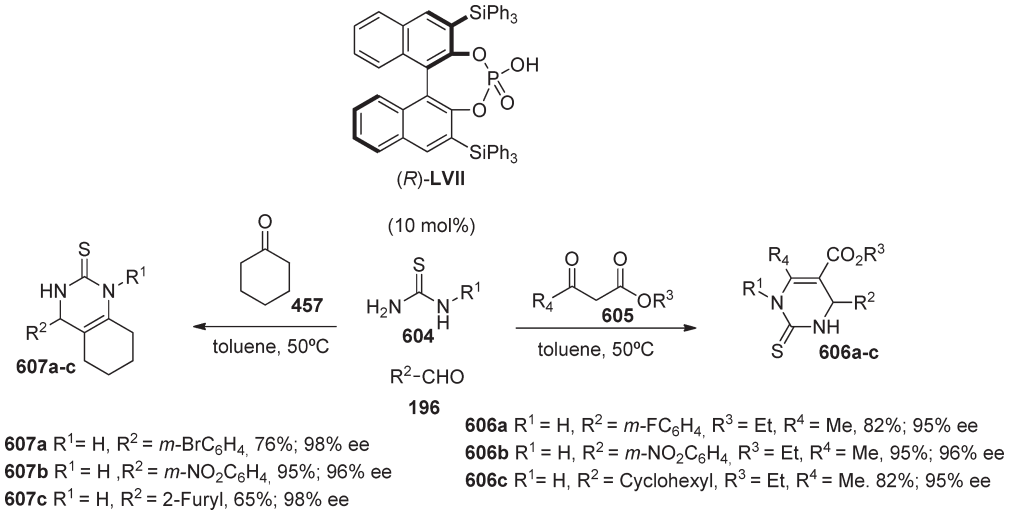
Scheme 306. Triple Cascade Reaction Reported by Yuan



Scheme 307. Enantioselective Biginelli Condensation Developed by Gong



In 2009, Enders and co-workers reported the asymmetric synthesis of cyclohexenes via a triple cascade reaction using nitromethane **592** and enals (**277**) as substrates.[442] This triple cascade sequence is based on two consecutive Michael additions followed by an intramolecular aldol condensation. The reaction is catalyzed by commercially available diphenylprolinol derivatives such as **XLVIII** and renders the corresponding 5-nitrocyclohexene-1-carbaldehydes **601** in good yields and excellent enantioselectivities, albeit with poor diastereoselectivities (Scheme 305). Another limitation of this methodology is the need to use aromatic enals, given that when aliphatic enals were used no domino product was isolated.

Soon after, the same research group reported a closely related reaction, using acetaldehyde instead of nitromethane and nitroalkenes instead of enals; this time the reaction needed the use of microwaves in order to achieve the final cyclohexenes.[443] The reaction was again catalyzed by simple diphenylprolinol derivatives, affording the final cyclohexenes with low yields and excellent stereoselectvities.

In 2010, Yuan and co-workers reported the first enantioselective organocatalytic three-component reactions via a domino Knoevenagel−Michael−cyclization sequence with cupreine (**CXVII**) as the catalyst.[444] A wide range of optically active spiro[4*H*-pyran-3,3-oxindoles] were obtained in excellent yields

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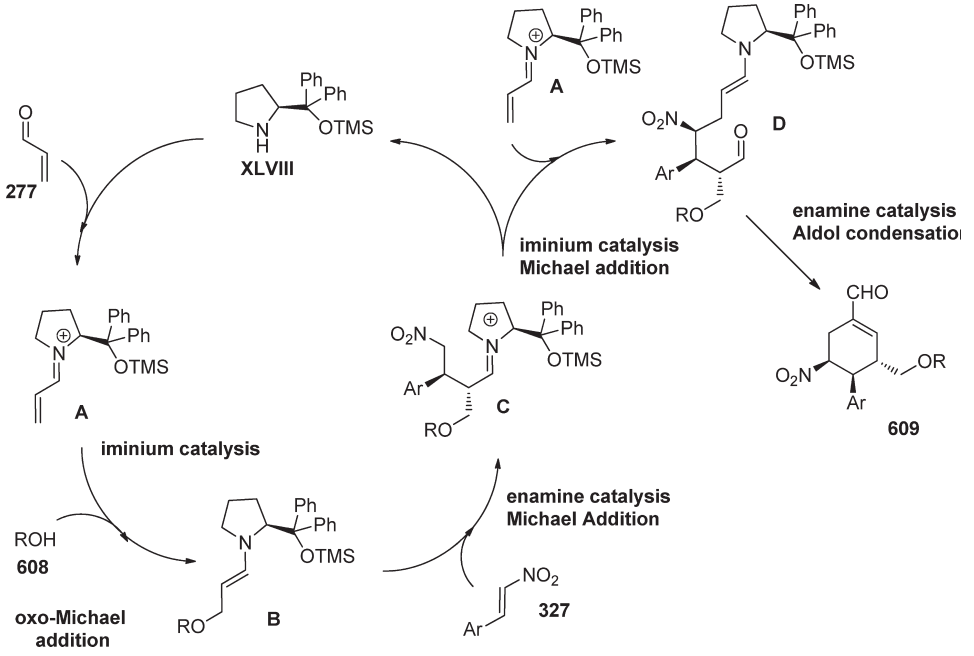
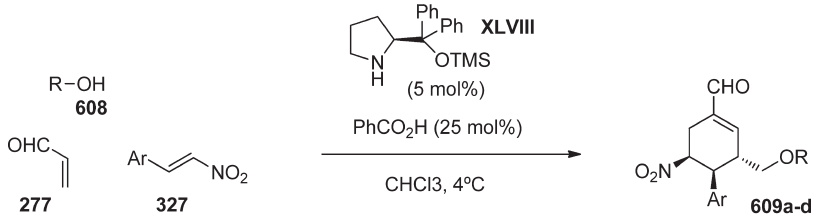
Scheme 308. Mechanism of the Quadruple Domino Reaction Developed by Gong



Scheme 309. Quadruple Domino Reaction Developed by Gong



609a R=Me Ar=Ph 54%; >20:1 d.r.; >99% ee
609b R=*i*Pr Ar=Ph 57%; >20:1 d.r.; >99% ee
609c R=Propargyl Ar=Ph 41%; >20:1 d.r.; >99% ee
609d R=Me Ar=2-furanyl 54%; >20:1 d.r.; >99% ee

(up to 99%) with good to excellent enantioselectivities (up to 97% ee) from simple and readily available starting materials under mild reaction conditions. The *N*-protected isatin **602** first condenses with malonodinitrile (**384**) to afford the intermediate compound **A** through a fast Knoevenagel condensation. Subsequently, the Michael addition of the 1,3-dicarbonyl compound **591** to **A** catalyzed by cupreine takes place, followed by an intramolecular cycloaddition involving the CN group activated by the phenolic OH as the electrophile. Finally, molecular tautomerization leads to the formation of the desired spiro[4*H*-pyran-3,3-oxindole] derivatives **603** (Scheme 306). The stereochemical outcome of this asymmetric cascade reaction catalyzed by cupreine results from a network of hydrogen-bonding interactions among the sequence Michael addition, keto−enol tautomerization, cyclization, and tautomerization sequence steps.

In 2009, Gong and co-workers developed the first highly enantioselective Biginelli reaction catalyzed by chiral phosphoric acid derivatives.[445] They reported the condensation between an aldehyde, a thiourea (**604**), and a ketone or a β-keto ester (**605**), rendering the cycloadducts (**606**, **607**) in good yields and with excellent enantioselectivities (Scheme 307).

In the same year, Chen and co-workers developed a similar reaction using this time ureas as starting materials.[446] The reaction is catalyzed by bifunctional primary amine−thiourea catalysts, affording the corresponding dihydropyrimidines in excellent yields and enantioselectivities. In 2010, Zhao and Ding reported the same reaction as Chen but catalyzed by primary amines, obtaining worse stereoselectivities.[447]

A different quadruple domino reaction was developed by Gong and co-workers in 2009.[448] This time an alcohol (**608**), two molecules of acrolein (**277**), and a nitroalkene (**327**) react in an enantioselective fashion, leading to a highly functionalized cyclohexene. As outlined in Scheme 308, in the first step the catalyst **XLVIII** reacts with acrolein to give the iminium ion intermediate **A**. Alcohol **608**, as a hard oxygen nucleophile, selectively reacts with **A** to give the enamine intermediate **B**, which then

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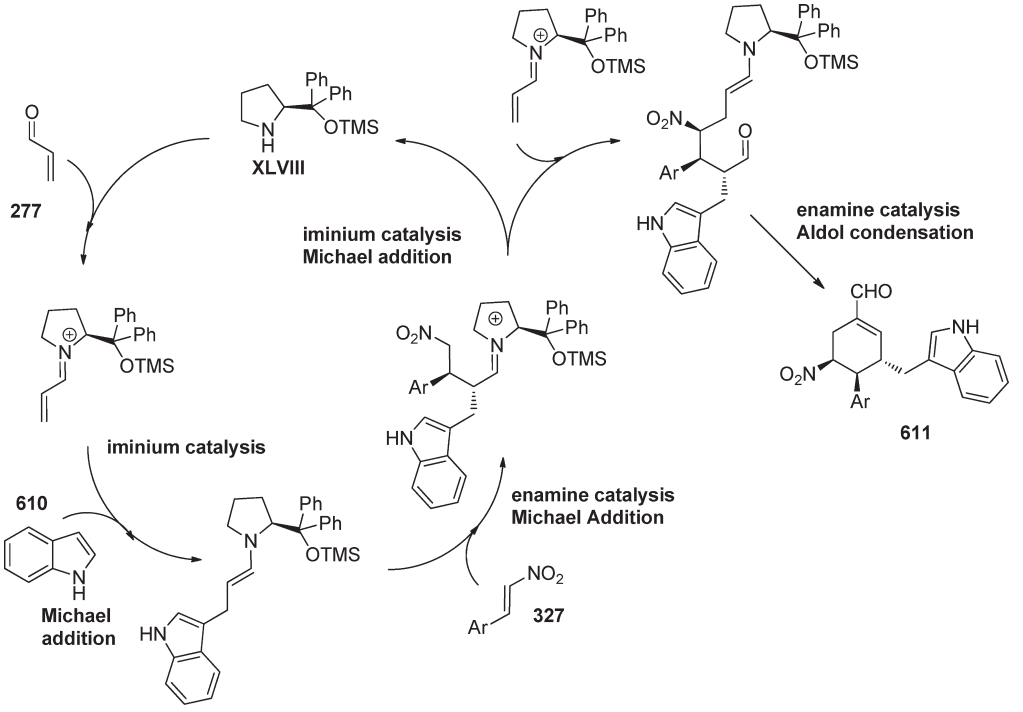
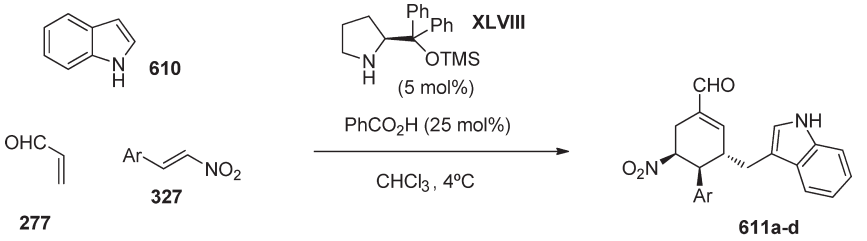
Scheme 310. Mechanism of the Reaction Developed by Enders



Scheme 311. Quadruple Domino Reaction Reported by Enders



611a Ar=Ph 55%; >95:5 d.r.; 94% ee
611b Ar=Piperonyl 82%; >95:5 d.r.; >99% ee
611c Ar=2-furyl 30%; >95:5 d.r.; >99% ee
611d Ar=*m*BrC_6H_4 48%; >95:5 d.r.; >99% ee

prefers to react with nitroalkene **327** to give Michael product **C**. In the third step, the nitroalkane **C** subsequently reacts with **A** to generate another enamine intermediate **D**, which is unstable and easily reacts through an intramolecular aldol condensation under the reaction conditions, providing the desired trisubstituted cyclohexenecarbaldehyde **609** and regenerating the catalyst.

The reaction is efficiently catalyzed by the diphenylprolinol derivative **XLVIII**, affording the final compounds in good yields and excellent enantioselectivities (Scheme 309). The only limitation of this methodology is the need to use acrolein due to its high reactivity; when more substituted enals were used, no reaction was observed.

In 2010, Enders and co-workers reported an almost identical organocatalytic synthesis of polyfunctionalized 3-(cyclohexenylmethyl)indoles **611** via a quadruple domino Friedel−Crafts-type/Michael/Michael/aldol condensation reaction.[449] The only difference with the precedent reaction is the use of indoles instead of alcohols. This cascade is initiated by a Friedel−Crafts reaction of indole (**610**) by an iminium activation mode, followed sequentially by an enamine- and an iminium-mediated Michael addition. After an intramolecular aldol condensation, four C−C bonds are formed, and the domino product is constructed bearing three contiguous stereogenic centers, as shown in Scheme 310.

The reaction, as in the methodology of Gong, is simply catalyzed by commercially available catalyst **XLVIII** and affords the polysubstituted cyclohexenes **611** in good yields and enantioselectivities (Scheme 311).

In 2009, Gestwicki and co-workers reported the organocatalytic synthesis of Hantzsch esters via a quadruple domino reaction.[450] The reaction is catalyzed by BINOL-phosphoric acid derivatives such as **CXLVI**, affording the final compounds **613** in good yields and excellent enantioselectivities

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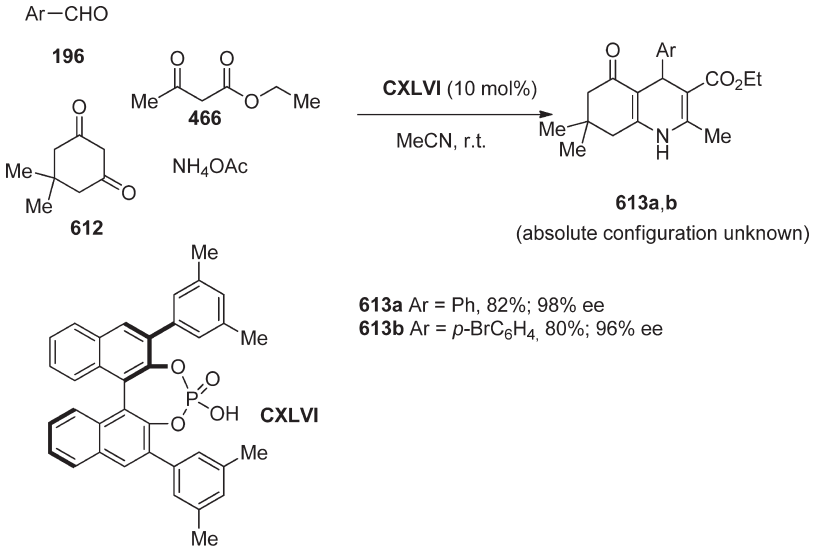
Scheme 312. Quadruple Domino Reaction Reported by Gestwicki



(Scheme 312). However, the scope of the reaction does not seem to be very broad: the need to use cyclic 1,3-dicarbonylic compounds and 2-oxobutanoates is a clear limitation of this methodology.

8. CONCLUSIONS

Since the seminal reports of Hajos and Parrish,[48] Eder, Wiecher, and Sauer,[49] and Woodward et al.,[8] asymmetric organocatalysis has been providing, especially so in the past decade, powerful and practical methods for the highly stereocontrolled construction of a huge variety of carbo- and heterocyclic compounds. In the case of polycyclic systems, either fused, bridged, or spiranic ring arrangements can be accessed. As we have shown in this review, desymmetrization, ring-closing, cycloaddition, annulation, and multicomponent reactions are amenable to organocatalytic methods, and all of the major activation modes in asymmetric organocatalysis (enamine and dienamine activation catalysis, iminium activation catalysis, SOMO activation catalysis, carbene activation catalysis, Lewis base activation catalysis, hydrogen-bonding and Brønsted acid activation catalysis, Brønsted base and bifunctional activation catalysis, and phase-transfer catalysis) have been efficiently used for this purpose. Around 150 different small chiral organic molecules have been proven to be useful catalysts in asymmetric cyclization, annulation, and cycloaddition processes. Some of these processes (cf. intramolecular aldol reactions, intramolecular aza-Michael reactions, or Diels—Alder cycloadditions) have reached impressive levels of stereoselective control and are increasingly being used in enantioselective total syntheses.[9c] Other organocatalytic asymmetric cyclizations of great synthetic potential (cf. intramolecular Michael additions leading to carbocyclic compounds, Pictet—Spengler reactions of phenethylamine derivatives) are on the other hand clearly underdeveloped, so that many exciting challenges still lie ahead. Moreover, the vitality of asymmetric organocatalysis is far from declining, and new and exciting developments (polyene cyclizations, domino processes,[9b] combination of organocatalysis with transition metal-based catalysis and/or biocatalysis,[11u,451] polymer-supported and supramolecular-gel-supported catalysts,[66,452] self-assembled organocatalysts,[453] and multiphase homogeneous catalysis and flow chemistry[454]) are either experiencing a fast growth or are sure to surface in the near future.

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BIOGRAPHIES

Albert Moyano was born in 1955 and educated in Barcelona. He graduated with a degree in chemistry from the University of Barcelona (1978), where he also obtained a Ph.D. in organic chemistry, under the guidance of Prof. Félix Serratosa. After a postdoctoral position at the "Joseph Fourier" University in Grenoble (1985—1986) in the laboratory of Prof. Andrew E. Greene, working on asymmetric cycloadditions, he came back to the University of Barcelona, where he has been a Professor of Organic Chemistry since 2003. His scientific activity over the years has involved work in theoretical organic chemistry (localized molecular orbitals, theory of aromaticity), in the

application of organometallic chemistry to organic synthesis (development of enantioselective versions of the Pauson−K-hand reaction), and in the asymmetric synthesis of biologically active compounds. His present research interests are centered on the enantioselective synthesis of metallocenes, the development of new methods of catalytic asymmetric organic synthesis, and the study of asymmetric autocatalysis and of spontaneous symmetry-breaking processes.

Ramon Rios was born in 1974 in Barcelona. In 1996 he got his Bachelor Degree from the University of Barcelona. In 2000, he got his Ph.D. degree from the same university by studying the Pauson−Khand reaction with electron-deficient enynes. He has enjoyed several postdoctoral and research positions with Prof. Greg C. Fu (MIT, Boston, MA, 1999), Prof. Patrick Walsh (University of Pennsylvania, Philadelphia, PA, 2001), Prof. Benjamin List (Max Plank, Muelheim an der Ruhr, Germany, 2004−2006), Armando Córdova (University of Stockholm, Stockholm, Sweden, 2006−2007) and Prof. Jose M[a] Alvarez-Pez (University of Granada, Granada, Spain, 2007) as well as industrial experience (J.C. Uriach S. A., Barcelona, Spain, 2002−2004). He was given an ICREA Junior Academia award in 2008. He began his independent career as ICREA Researcher in 2008 at the University of Barcelona. He is author of more than 80 papers and several chapters in chemical books. His research interests are the development of new asymmetric methodologies based on organocatalysis and/or organometallic chemistry and their application in total synthesis.

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ABBREVIATIONS

ACDC	asymmetric counterion-directed catalysis
BINAM	1,1′-bi-2,2′-naphthaleneamine
BINOL	1,1′-bi-2,2′-naphthol
Bn	benzyl
CAN	cerium(IV) ammonium nitrate
CPME	cyclopentyl methyl ether
DABCO	1,4-diazabicyclo[2.2.2]octane
DBU	1,8-diazabicyclo[5.4.0]undec-7-ene
DCE	1,2-dichloroethane
DDQ	2,3-dichloro-5,6-dicyano-1,4-benzoquinone
DEA	directed electrostatic activation
DFA	difluoroacetic acid
DIPEA	diisopropylethylamine
DMAP	4-(dimethylamino)pyridine
DME	1,2-dimethoxyethane
DMF	*N*,*N*-dimethylformamide
DMSO	dimethyl sulfoxide
HMPA	hexamethylphosphoric acid triamide
IEDHDA	inverse-electron-demand hetero-Diels−Alder reaction
LDA	lithium diisopropylamide
MBH	Morita−Baylis−Hillman
MOM	methoxymethyl
MSH	(*O*-mesitylenesulfonyl)hydroxylamine
MTBE	methyl *tert*-butyl ether
NBS	*N*-bromosuccinimide
NBSA	2-nitrobenzenesulfonic acid
NFSI	*N*-fluorobenzenesulfonimide
NHC	*N*-heterocyclic carbene
NMI	*N*-methylimidazole
NMP	*N*-methyl-2-pyrrolidinone
OTBDPS	*tert*-butyldiphenylsilyloxy
OTBS	*tert*-butyldimethylsilyloxy
OTES	triethylsilyloxy
PEP	*p*-ethoxyphenyl
PMP	*p*-methoxyphenyl
PPY	4-(pyrrolidino)pyridine
PS	Pictet−Spengler
RC	Rauhut−Currier
SOMO	singly occupied molecular orbital
TADDOL	2,2-dimethyl-α,α,α′,α′-tetraaryl-1,3-dioxolane-4,5-dimethanol
TBAF	tetrabutylammonium fluoride
TEA	triethylamine
TEAB	triethylammonium bicarbonate
TFA	trifluoroacetic acid
THF	tetrahydrofuran
TIPBA	2,4,6-triisopropylbenzenesulfonic acid
TMG	1,1,3,3-tetramethylguanidine

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