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Asymmetric transformations of achiral 2,5-cyclohexadienones

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Abstract

Cyclohexadienones are versatile platforms for performing asymmetric synthesis as evidenced by the numerous natural product syntheses that exploit their diverse reactivity profile. However, there are few general methods available for the direct asymmetric synthesis of chiral cyclohexadienones. To circumvent this problem, several researchers have developed catalytic asymmetric methods that employ readily available achiral 2,5-cyclohexadienones as substrates. Many of these reactions are desymmetrizations in which one of the enantiotopic alkenes of an achiral dienone is transformed. Others involve selective reaction at one alkene of an unsymmetrically substituted, achiral dienone. This review will cover advances in this area over the last 20 years and the application of these strategies in complex molecule synthesis.

Keywords

asymmetric catalysis; desymmetrization; organocatalysis; transition metal catalysis; cyclohexadienones

1. Introduction

Cyclohexadienones are a versatile class of building blocks derived from phenols.¹ Two varieties of these compounds are possible: 2,5-cyclohexadienones (**1**) and 2,4-cyclohexadienones (**2**). The greatest practical difference between the two varieties relates to stability. 2,4-Cyclohexadienones have a propensity to dimerize via [4+2] cycloaddition; in many cases, this dimerization is so rapid that the monomeric products cannot be isolated. In contrast, 2,5-cyclohexadienones are usually isolable and generally stable over the time periods required for use as a synthetic intermediate. Both motifs can undergo a large array of transformations, as summarized in Figure 1. Additionally, the products of these transformations often retain a synthetic handle, such as an enone, that is useful for further elaboration. As a result of this versatility, both 2,4- and 2,5-cyclohexadienones have become attractive intermediates for natural product synthesis.^{1,2}

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The most direct synthetic route to a cyclohexadienone is through the oxidative dearomatization of a phenol (**3**). There are many notable procedures for accomplishing this transformation;^{3,4,5} however, the use of hypervalent iodine reagents like PhI(OAc)₂ (PIDA), PhI(O₂CCF₃)₂ (PIFA), and 2-iodoxybenzoic acid (IBX) has become popular in recent years (Scheme 1).⁶ Although there is still some debate regarding the exact mechanism through which these reactions proceed,⁷ the product distribution is generally well understood. Iodine (III) reagents (e.g., PIDA) can generate products of nucleophilic attack at either the ortho or para position (producing **4** or **5**, respectively), whereas iodine(V) reagents (e.g., IBX) generally produce *ortho*-quinols (**6**).

In many cases, the product of an oxidative dearomatization reaction is chiral. This means that enantioenriched dienones **4**, **5**, or **6** could, in principle, be produced by the action of a suitable chiral oxidant on phenol **3**. Indeed, recent years have seen great progress in the development of chiral catalysts and reagents for asymmetric dearomatization reactions, both oxidative and non-oxidative.^{7,9} When coupled with their synthetic versatility, it is easy to see how such technology would make cyclohexadienones attractive platforms for asymmetric synthesis.

Another way in which cyclohexadienones can be used in asymmetric synthesis is through the desymmetrization of symmetrically substituted substrates. Enantioselective desymmetrization¹⁰ involves the differentiation of two enantiotopic functional groups (in this case, the two enones) through selective reactivity, thus breaking the symmetry of the molecule and setting the configuration of one or more stereocenters. This strategy is extremely versatile, as many of the transformations available to cyclohexadienones have the potential to be rendered asymmetric under the appropriate conditions. Importantly, desymmetrization of achiral cyclohexadienones is complementary to the asymmetric dearomatization reactions mentioned above. In certain scenarios a desymmetrization approach will be the most efficient strategy, while in other cases an asymmetric dearomatization may be a better solution.

Although each transformation will have its own specific challenges, the general stereochemical considerations leading to substrate desymmetrization are the same. Any reaction that engages the alkene of an achiral 2,5-cyclohexadienone has four possible stereochemical outcomes. This is illustrated in Scheme 2 with the conjugate addition of a nucleophile (NucH) into cyclohexadienone **7** to give cyclohexenone **8**. The distribution of the resulting stereoisomers depends on both selective approach to one face of the dienone (i.e., facial selectivity, **9**) and preferential reaction with one of the two olefins (i.e., group selectivity, **10**).

Designing a catalyst or ligand capable of controlling both facial and group selectivity can be quite challenging. Fortunately, there are strategies available to simplify the problem to one of enantioselectivity. A common approach is to utilize a reaction with an inherent diastereoselective bias, such as a cyclization reaction that preferentially forms a cis-fused bicyclic system (**11**→**12**, Scheme 3A). The issue of diastereoselectivity can also be avoided with transformations that ultimately retain the double bond (e.g., the intramolecular Heck reaction of compound **13** to provide bicyclic cyclohexadienone **14**, Scheme 3B). Another

strategy that has seen only limited application is the so-called *syn* oxygen phenomenon. Paquette and co-workers advanced this model¹¹ in order to explain the diastereoselectivity observed during Diels–Alder reactions between oxygen-substituted cyclohexadienones (**15**) and various dienes (Scheme 3C). In all cases, the major diastereomer (**16**) was the one arising through approach of the diene from the same side as the oxygen in the 4-position of the cyclohexadienone. This facial selectivity was rationalized, in part, by hyperconjugation effects involving the antibonding orbital of the developing C–C bond and the σ -orbital of the 4-*anti*-C–C bond. Wipf and Kim made a similar proposal in order to explain the diastereoselectivity observed during 1,2-addition of organometallics to the ketone of oxygen-substituted cyclohexadienones.¹²

It is also possible to construct achiral 2,5-cyclohexadienones that are not symmetrically substituted (e.g., **17**, Scheme 4). In these cases, the alkenes are usually substituted in such a way that they will display reactivity differences that can be exploited by different reagents. For example, addition of a nucleophile to **17** might occur on the less substituted, and less electron-rich, alkene. The chiral environment provided by the catalyst would then allow for the formation of either **18** or *ent*-**18**. Reactions of this type are not desymmetrizations in the strictest sense, and the problem of asymmetric induction can be simplified to just discrimination of the two enantiotopic faces of the reacting alkene.

In this article we will provide a comprehensive review¹³ of asymmetric transformations involving achiral cyclohexadienones as substrates. Sections 2–4 will cover, primarily, desymmetrization reactions involving enantiotopic alkenes of symmetric cyclohexadienones (i.e., **10**). In Section 5, we will cover asymmetric transformations that are not desymmetrizations, but still involve achiral cyclohexadienones as substrates. The coverage of the review is through roughly the first half of 2014.

2. Transition Metal-Catalyzed Desymmetrizations

2.1. Heck reactions

The first example of enantioselective cyclohexadienone desymmetrization was reported by Shibasaki and co-workers in 1993.¹⁴ The authors' primary interest was in the development of an intramolecular Heck reaction of bisallylic alcohol **19** to provide cyclohexenone **20** in the presence of (*R*)-BINAP (Scheme 5). Interestingly, cyclohexadienone **21** was observed as a side product in significant amounts, but its formation could be suppressed by the addition of *tert*-butanol. The authors postulated that this product might arise from oxidized intermediate **22**. To further investigate this observation, **22** was subjected to the cyclization conditions. The reaction proceeded efficiently, providing the desymmetrized product **21** in 66% yield and an enantiomeric ratio of 92:8.

Despite Shibasaki's work being limited to this single example, it would be nearly a decade before the Heck reaction was examined again in the context of cyclohexadienone desymmetrization. This would come in 2002 with Feringa's report on the asymmetric Heck cyclization of cyclohexadienone-tethered aryl iodides **23** to provide bicyclic dienones **24** (Scheme 6).¹⁵ A variety of TADDOL-derived monodentate phosphoramidite ligands were screened, with **25** providing the highest level of enantioselectivity. Variation of substitution

on the substrate had a slight negative effect on both conversion and selectivity, as the parent substrate ($R^1 = \text{Me}$, $R^2, R^3, R^4 = \text{H}$) provided the best results (100% conversion, 98:2 er). Additionally, carbon-tethered substrate **26** successfully underwent cyclization to provide product **27** with an enantiomeric ratio of 90:10.

2.2. Conjugate addition of organometallic reagents

In addition to the Heck cyclization example above, Feringa also performed a series of studies on the conjugate addition of alkylzinc reagents to cyclohexadienones (Scheme 7). A preliminary report in 1997¹⁶ showed the successful Cu-catalyzed addition of Et_2Zn to dienone **28** in the presence of phosphoramidite ligand **30**, providing enone **29** in very good yield and enantiomeric ratio of 97:3. This specific example is not a desymmetrization as defined above: because the two substituents at the 4 position of the cyclohexadienone are identical, the two enones are homotopic, not enantiotopic. However, Feringa and co-workers later expanded on this result, performing conjugate additions into substrates **31** to provide desymmetrized enones **32** with high levels of enantioselectivity.¹⁷ Notably, spirocyclic substrate **33** exhibited a reduced level of selectivity during formation of **34**. The authors also found that the diastereoselectivity of the reaction was dictated by a directing effect of alkoxy substituents in the 4 position, as monoalkoxides **31** exhibited excellent stereocontrol, whereas mixed dialkoxide **35** was converted to product **36** as a 1:1 mixture of diastereomers. The authors speculated that the observed diastereoselectivity might be due to either steric effects or coordination of the alkoxy group to the metal catalyst. However, the aforementioned *syn* oxygen phenomenon may also be at play here. In an additional report,¹⁸ products **37** were subjected to a second conjugate addition, providing 3,5-disubstituted cyclohexenones **38** and **39**. Interestingly, the authors were able to control the diastereoselectivity of this second addition by utilizing either enantiomer of the phosphoramidite ligand **30**, indicating that the selectivity of this addition is completely under catalyst control.

In a clever application of Feringa's methodology, Thomson and co-workers have used the desymmetrized products as a means to impart chirality during an oxidative dimerization/aromatization sequence (**40**→**41**, Scheme 8).¹⁹ In their initial report, a rhodium-catalyzed conjugation addition of aryl zinc species was used to produce cyclohexenone **40** from benzoquinone monoketal **28**. Oxidative dimerization of **40** produced a compound similar to **43**, which then aromatized in the presence of $\text{BF}_3 \cdot \text{OEt}_2$. These conditions resulted in high central-to-axial chirality transfer and produced biaryl compound **41** as essentially one atropisomer. The utility of this methodology was demonstrated with their synthesis of (+)-bismurayaquinone A.²⁰ In this case, Feringa's conditions were used for the production of cyclohexenone **42**, which was advanced to biaryl intermediate **44**. Only two more transformations were required to convert **44** into (+)-bismurayaquinone A (**45**) with little loss in enantiopurity.

More recently, Bräse has shown that the functionality contained in these desymmetrized products can be used to form functionalized enantioenriched cyclohexenone building blocks (Scheme 9).²¹ For example, asymmetric conjugate addition of benzoquinone monoketal **28** in the presence of either enantiomer of ligand **30** produced both enantiomers of **42**. These

were then reduced with both antipodes of the CBS ligand to give ketone **46** after ketal hydrolysis. By using the appropriate reagents, this three-step sequence provides access to all four stereoisomers of **46** in good yield and with high enantiopurity. Previously reported synthetic routes to ketones like **46** have required at least six steps.

2.3. Enyne cyclizations

Recently, a variety of enyne cyclizations of cyclohexadienones have been reported. Harned and co-workers reported a regioselective Pd-catalyzed cyclization in 2009,²² and an enantioselective variant was published in 2013.²³ Alkynetethered cyclohexadienones **47** underwent an acetoxylationcyclization sequence, providing bicyclic enones **48** with moderate selectivity in the presence of pinene-derived bipyridine ligand **49** (Scheme 10). Selectivity was found to be largely insensitive to substitution at the quaternary carbon of the cyclohexadienone, but highly sensitive to substitution on the tethered alkyne. It is thought that the Pd-promoted acetoxylation reaction proceeds to form enolate **50** after migratory insertion of the vinyl Pd intermediate. Protonation of this enolate would form the product and regenerate the Pd(II) catalyst.

Sasai recently reported promising preliminary results in an extension of this reaction utilizing SPRIX ligand **53**²⁴ developed by their group (Scheme 11).²⁵ In this case, alkyne-tethered substrates **51** underwent a tandem cyclization/oxidation process to afford products **52** in an enantiomeric ratio of up to 91:9, albeit with significant structural dependence. Under these conditions, the initially formed Pd enolate **54** appears to be long-lived enough to undergo a subsequent oxidation reaction, which leads to the installation of the second acetate moiety.

In 2013, Lautens and co-workers reported a Rh-catalyzed cyclization of alkyne-tethered cyclohexadienones.²⁶ Subjecting substrates **55** and aryl boronic acids to catalytic $[\text{Rh}(\text{coe})_2\text{Cl}]_2$ in the presence of chiral diene ligand **57** provided bicyclic enones **56** in moderate yields and with good stereocontrol (Scheme 12). The authors found that the stereoselectivity of the reaction was generally insensitive to both the nature of the aryl boronic acid and to variations of the alkyne tether (products **58–61**). The enantioselectivity of the reaction decreased significantly only when a sterically crowded tether was utilized (e.g., product **58**). Product **60** is particularly notable, as it demonstrates that this methodology is also applicable to internal alkynes. The choice of ligand was found to play a large role in both the efficiency and the selectivity of the reaction. Diene ligands were found to be necessary, as phosphine ligands generally lead to decomposition of the starting material. The substitution pattern on the ligand was also found to be very important in suppressing the formation of dimeric side products (e.g., **62**).

Around the same time as the Lautens report, Tian and Lin published a similar Rh-catalyzed arylation cyclization.²⁷ In this case, catalytic $[\text{Rh}(\text{C}_2\text{H}_4)_2\text{Cl}]_2$ was utilized with (*R*)-BINAP as the chiral ligand to provide products **64** from internal alkynes **63** in excellent yields and with high levels of stereocontrol (Scheme 13). Once again, the efficiency and selectivity of the reaction were found to be largely insensitive to both substrate substitution and aryl boronic acid identity.

Tian and Lin have reported a Cu-catalyzed borylative cyclization that provides similar bicyclic enone products (**66**) with up to 99:1 enantioselectivity (Scheme 14).²⁸ The authors rationalized the regioselectivity of the cis-borylation by invoking coordination of the copper to the propargylic oxygen atom in substrate **65**, as represented in structure **67**. Migratory insertion of vinyl copper intermediate **68** would then serve as the symmetry-breaking step.

Ding and co-workers utilized a Pd-catalyzed reductive enyne cyclization in their synthesis of indoxamycins A, C, and F (**72–74**, Scheme 15).²⁹ Racemic cyclohexadienone **69** was treated with a cationic Pd catalyst in the presence of (*R*)-SEPHOS to provide epimeric products **70** and **71** with enantiomeric ratios of 97:3 and 90:10, respectively. Although this reaction would typically be viewed in terms of diastereoselectivity (and is technically not a desymmetrization reaction as defined above), the stereocenter already present in substrate **69** appears to have little to no influence on selectivity. As a result, the overall transformation is essentially an enantioselective desymmetrization of the cyclohexadienone core.

2.4. Silver-catalyzed cycloadditions

Wang and co-workers found that a Ag-catalyzed [3+2] cycloaddition can be used to provide tricyclic products **77** from spirocyclic cyclohexadienones **75** and imino esters **76** (Scheme 16).³⁰ These products contain five contiguous stereocenters and are formed with impressive stereocontrol (>20:1 dr, up to 99:1 er) in the presence of TF-Biphosphos ligand **78**. Modifications to the ligand largely resulted in lower efficiency or selectivity, especially for examples with increased steric bulk near the phosphorus atom. Additional complexity could be incorporated by the use of substituted dienones **79**, which yielded products **81** with additional points of diversification. The use of α -substituted imino esters **76b** had little adverse influence on yield and enantioselectivity and furnished products containing two fully substituted stereogenic carbon atoms.

3. Organocatalytic Desymmetrizations

3.1. Michael reactions

Organocatalytic Michael additions have provided the basis for a large number of desymmetrization methodologies. The earliest example of cyclohexadienone desymmetrization through an asymmetric Michael addition was reported by Hayashi in 2005.³¹ After a brief catalyst screening, it was found that cysteine-derived catalyst **84** promoted the cyclization of aldehydes **82**, providing bicyclic products **83** with an enantiomeric ratio of up to 98:2 (Scheme 17). The alkyl substituent at the 4 position of the cyclohexadienone could be varied with little effect on yield or selectivity. Excellent diastereocontrol was also observed: only cis-ring fusion was observed and the epimer of the aldehyde-bearing stereocenter was observed in only minor amounts.

In 2007, Gaunt and co-workers demonstrated a one-pot dearomatization/Michael addition sequence (Scheme 18).³² By subjecting aldehyde-tethered phenol **85** to PIDA and proline-derived catalyst **87**, bicyclic product **86** was obtained in moderate yield and good selectivity. The steric bulk of catalyst **87** was required to obtain high levels of enantioselectivity and served to protect the amine functional group in the catalyst from oxidation by excess PIDA.

To further investigate the diastereoselectivity of the reaction, the authors subjected isolated quinol **88** to the Michael addition conditions. The organocatalytic reaction demonstrated a strong solvent dependence on selectivity. Methanol was found to be particularly effective, providing **86** in 91% yield and >20:1 dr. This discovery was then applied to the one-pot reaction, in which enones **90** were produced via intermediate methyl quinols using methanol as the solvent. The cyclization of a variety of aldehyde tethers (**89**) was examined. All furnished products in consistently high yields and enantiomeric ratios. However, the diastereoselectivity was highly substrate dependent, both in the level of selectivity and the identity of the major diastereomer. Finally, α,α' -disubstituted substrate **91** was cyclized, affording the product **92** with poor selectivity, indicating that α substitution is not well tolerated by this reaction.

Gaunt continued to work in the area of dearomatization and desymmetrization, publishing a report of a second conjugate addition methodology in 2011.³³ In this work, alkynamidetethered cyclohexadienones **93** were dearomatized³⁴ using ICl to provide spirocycles **94** (Scheme 19). These intermediates were used without purification in the next step, in which the benzoic acid salt of pyrrolidine catalyst **96** promotes the Michael addition of the aldehyde side chain into the dienone core. This reaction provides tricyclic products **95**, which contain three contiguous stereocenters and a variety of synthetically useful functional groups. The reaction generally proceeds with high yields and selectivity – the only notable exception is the cyclization of substrate **97**, containing a shortened carbon chain between the amide and aldehyde. In this case, tricyclic lactone **98** was obtained as a single diastereomer, but low levels of enantioselectivity were observed. The authors were able to extend the scope to include substrate **99**, in which the electrophile for the dearomatization (alkyne) and the nucleophile for the desymmetrization (aldehyde) are on the same component of the amide. This cyclization also proceeded with high enantioselectivity and afforded tricycle **100** as a single diastereomer.

More recently, Johnson³⁵ reported an interesting extension of the desymmetrization reported by Hayashi and Gaunt. In this case, the chiral enamine responsible for the desymmetrization was generated by an initial asymmetric oxa-Michael addition of quinols **101** into α,β -unsaturated aldehydes (Scheme 20). The reaction between the aldehyde component and catalyst *ent*-**96** presumably generates an iminium ion, which promotes the initial oxa-Michael addition. This would generate an enamine intermediate, which is responsible for performing the conjugate addition. This transformation is quite remarkable in that the cascade process is capable of forming a product (**102**) with four contiguous stereocenters with excellent enantioselectivity and generally high diastereoselectivity. Furthermore, the simplicity of the starting materials allows this reaction to be run on multigram scale, as demonstrated by the synthesis of product **103**.

In 2011, Harned and co-workers reported the cyclization of cyclohexadienones tethered to active methylene groups (Scheme 21).³⁶ *Cinchona* alkaloid-derived phase transfer catalyst **107** promoted the cyclization of malonate-containing substrates **104** to afford bicyclic lactones **105** with varying levels of stereocontrol. Notably, the use of α,α' -dibrominated substrates resulted in unique tricyclic cyclopropane products **106**. Substrates in which the

nucleophile identity had been changed to either an amide or a sulfones cyclized with high efficiency, but diminished enantioselectivity.

Also in 2011, You and co-workers reported an asymmetric bifunctional-urea catalyzed Michael addition (Scheme 22).³⁷ Substrates **108** contain a bis(phenylsulfonyl) methylene group, which is highly activated for use as a Michael donor. Treatment with the *Cinchona* alkaloid-derived catalyst **110** provided bicyclic enones **109** in high yields with good enantioselectivity. Substrates with an aryl group as the tether between the dienone and bis(phenylsulfonyl) nucleophile were also viable (**111**→**112**). A key feature of these products is the potential to remove the phenylsulfonyl groups. This was demonstrated by the conversion of bis(phenylsulfonyl) product **113** to unsubstituted tricycle **114** using a three step procedure.

3.2. Stetter reactions

In 2006, Rovis and co-workers demonstrated the desymmetrization of cyclohexadienones using an intramolecular Stetter reaction (Scheme 23).³⁸ Aminoindanol-derived triazolium catalyst **117** promoted the cyclization of aldehyde substrates **115**, providing bicyclic diketones **116** in good yield with excellent stereocontrol. Substitution around the cyclohexadienone ring was well tolerated: α,α' -disubstituted substrates **118** provided products **119** as a single diastereomer and β,β' -disubstituted substrates **120** cyclized efficiently to give products **121** containing an additional quaternary stereocenter. Substrate **122** with an all-carbon aldehyde tether also successfully underwent cyclization, providing bicyclic enone **123**, although the use of free carbene catalyst **124** was required in this case. Interestingly, the efficiency and selectivity of this reaction were highly dependent on concentration, with dilute conditions (0.008 M) being optimal. The authors suggest that this effect is caused by the increased potential for hydrogen bonding at higher concentrations. In addition to the preliminary report, a detailed account of the development of the methodology, including conditions for gram-scale reactions, has been published.³⁹

In 2012, You and co-workers reported the asymmetric intramolecular Stetter reaction of spirocyclic cyclohexadienones (Scheme 24).⁴⁰ Aldehydes **125**, reminiscent of the starting materials used by Gaunt described above, were treated with camphor-derived triazolium catalyst **127** to induce cyclization. Tricyclic products **126** were obtained as a single diastereomer in moderate yields with good stereocontrol. In a separate study, the authors extended this methodology to α,α' -disubstituted cyclohexadienones **128**.⁴¹ The cyclization of these substrates required altered conditions, including the use of aminoindanol-derived triazolium catalyst **129**.

Continuing their investigation of desymmetrizations via Stetter reactions, You and co-workers also developed the cyclization of aryl-substituted cyclohexadienones **130** (eqn 1).⁴² Using the camphor-derived catalyst **127** from their previous study, products **131** were obtained in very good yield with high enantioselectivity.

(1)

3.3. Heteroatom conjugate additions

You and co-workers also investigated desymmetrizations involving other conjugate addition reactions. In 2010, they reported the Brønsted acid-catalyzed intramolecular oxo-Michael addition of cyclohexadienones **132** (Scheme 25).⁴³ Cyclization in the presence of chiral phosphoric acid **134** afforded bicyclic products **133** in good yields with high levels of stereocontrol. Aryl-substitution at the 4 position of the cyclohexadienone was well tolerated; however, the use of alkyl groups larger than methyl resulted in decreased enantioselectivity. The scope of the desymmetrization was also extended to include hydroperoxide **135**. This substrate cyclized efficiently to afford enone **136** with good enantioselectivity. This product served as a common intermediate for the synthesis of cleroidins C, D, and F (**137–139**).

In a separate study, You also described an aza-Michael addition catalyzed by *Cinchona* alkaloid-derived thioureas (Scheme 26).⁴⁴ Catalyst **110** promoted the cyclization of sulfonamide-tethered cyclohexadienones **140**, providing bicyclic enones **141** in good yields with high levels of enantioselectivity. Interestingly, substrates capable of undergoing oxo-Michael addition (**140**, R = O(CH₂)_nOH) preferentially cyclize through sulfonamide addition. The cyclization of oxygen-tethered substrates **142** to afford morpholine derivatives **143** was also investigated. The efficiency of this reaction followed the same trend as the oxo-Michael addition: high yields and enantiomeric ratios were obtained for most 4-substituted substrates, but isopropyl substitution caused a drop in yield and *t*-butyl substitution shut down the reaction completely. Finally, the authors applied this methodology in the total synthesis of (–)-mesembrine (**146**), obtaining key intermediate **145** from the cyclization of cyclohexadienone **144**.

Doyle and co-workers reported a one-pot tandem dearomatization/conjugate addition procedure (Scheme 27).⁴⁵ While the desired reaction did occur with excellent diastereocontrol, an efficient enantioselective version was elusive. As a part of their investigation, the authors attempted the asymmetric cyclization of cyclohexadienones **147** using chiral phosphoric acid catalysts **149**. Bicyclic ethers and carbamates **148** were produced in good yields, but with low enantioselectivity.

Rovis and co-workers reported an interesting variant of a desymmetrizing oxa-Michael reaction involving a peroxyquinol (**150a** or **150b**) and an aldehyde (Scheme 28).⁴⁶ Trioxane products **151a** and **151b** were obtained with high enantioenrichment by using spirobiindane

phosphoric acid catalyst **152**. In all cases, the products were formed as a single diastereomer. Achiral thiourea **153** functioned as an effective co-catalyst at low loadings of the chiral phosphoric acid, but was an ineffective catalyst by itself. To probe the mechanism of this transformation, peroxyquinol **150a** was heated with isobutyraldehyde in order to form racemic peroxyhemiacetal **154**. Catalyst **152** was then used to convert the unpurified peroxyhemiacetal into trioxane **155** in good yield as a single diastereomer with high enantioenrichment. Based on this result, the authors concluded that the desymmetrization reaction involves a dynamic kinetic resolution of the initially formed peroxyhemiacetal. Importantly, a crossover experiment involving the reaction of **155** and *n*-butyraldehyde revealed that the oxa-Michael step is not reversible under the reaction conditions.

Ye and co-workers developed a chiral diamine-catalyzed variant of an oxo-Michael addition (Scheme 29).⁴⁷ (*R,R*)-DPEN (**158**) mediated cyclization of cyclohexadienones **156** provided bicyclic ethers **157** in good yields with very good stereocontrol. The authors were also able to access the enantiomeric series of products (*ent*-**157**) through the use of diamine catalyst **159**. In both cases, an amino acid additive was required for the reaction to proceed. Substitution at the 4 position of the cyclohexadienone was well tolerated, as a variety of alkyl-, aryl-, and oxo-substituted substrates cyclized efficiently. However, variation of the alcohol tether length was not tolerated: both increasing and decreasing the chain length resulted in nearly racemic products.

Later, Wang and co-workers reported the desymmetrization of cyclohexadienones via an asymmetric sulfa-Michael addition.⁴⁸ Spirocyclic oxindole substrates **160** were treated with aryl sulfides in the presence of bifunctional thiourea catalyst **162** (Scheme 30). Products **161** were obtained in high yields and with high levels of enantiocontrol. The reaction was found to be very tolerant of substitution on both the aryl sulfide as well as the arene ring of the oxindole.

The potential utility of desymmetrizing conjugate additions was demonstrated by Fan and co-workers in their formal synthesis of ($\pm$)-morphine (**167**).⁴⁹ Although the overall synthesis accesses racemic material, the authors did investigate a potential asymmetric desymmetrization reaction for the formation of the morphine E ring. Specifically, spiro lactone **163** was treated with various alcohols in the presence of bifunctional thiourea catalyst **166** to induce a tandem alcoholysis/oxa-Michael addition (Scheme 31). Although the reaction did proceed in good yield, the authors were unable to attain high levels of enantioselectivity despite extensive optimization. The best conditions, shown in Scheme 31, provided **165** through intermediate **164** with an enantiomeric ratio of 74:26.

3.4. Rauhut-Currier reactions

Sasai and co-workers reported the asymmetric Rauhut–Currier reaction⁵⁰ of cyclohexadienones bearing unsaturated esters.⁵¹ Substrates **168** were efficiently converted to bicyclic lactones **169** in good yields and high levels of enantioselectivity (Scheme 32). Lewis basic catalysts (e.g., PPh_3) could be employed in the reaction, but only with an accompanying Brønsted acid catalyst (e.g., phenol). The authors identified bifunctional catalyst **170**, which satisfied both catalytic requirements and provided excellent

stereocontrol. The cyclization of β,β' -disubstituted substrate **171** was also investigated. In this case, the reaction provided lactone **172** with a low level of stereoselectivity. The use of a Brønsted acid co-catalyst provided higher levels of selectivity, but also lower yields. This inverse relationship was observed with a variety of phenolic Brønsted acids, with the extreme example being the use of phenol to afford **172** in 5% yield and an enantiomeric ratio of 98:2. Unfortunately, the authors were unable to find conditions that provided both high yields and high levels of selectivity.

4. Desymmetrization Using Internal Asymmetric Induction

There have been several examples of internal asymmetric induction being used to achieve formal enantioselective transformations of cyclohexadienones. These sequences allow the relevant stereocenters to be installed in a diastereoselective manner, greatly simplifying the challenges associated with cyclohexadienone desymmetrization.

In 1995, Winterfeldt and co-workers reported the formal enantioselective epoxidation of spiro lactone **75** through the use of a chiral Diels–Alder adduct (Scheme 33).⁵² The cycloaddition of **75** and cyclopentadiene **173** provided adduct **174**, which underwent diastereoselective epoxidation when treated with H_2O_2 and K_2CO_3 to afford epoxide **175**. Release of the enone core was accomplished by flash vacuum pyrolysis, affording the formal desymmetrization product **176** after a three step sequence. In a later report, the Winterfeldt group described an in depth investigation of the Diels–Alder reaction.⁵³ This study also included a cycloaddition/reduction sequence (**177**→**178**) that, upon release of enone **179**, would correspond to a formal enantioselective hydrogenation of a cyclohexadienone; however, the authors did not perform the cycloreversion on this particular substrate.

In 1995, Carreño and co-workers reported the synthesis of chiral sulfoxide **180** and its reactivity with cyclopentadiene.⁵⁴ Shortly thereafter, the group described the diastereoselective addition of organoalanes (AlR_3) into the cyclohexadienone core of enantiopure sulfoxide **182** (Scheme 34).⁵⁵ In all cases, product **183** was isolated as a single diastereomer. A highly organized transition state similar to **182** was proposed in order to explain the observed diastereoselectivity. The Carreño group has used this methodology numerous times in natural product synthesis.⁵⁶

In an interesting extension of this strategy, Carreño and co-workers⁵⁷ reported that amino-substituted sulfoxide **183** could participate in an aza-Michael/Michael cascade reaction with different enone partners (Scheme 35). The resulting hydroindole products **184** were formed as a single stereoisomer in moderate to good yields. A transition state similar to **185** was used to explain how the chirality of the sulfoxide was transferred to the new stereocenters formed by the cascade reaction.

In a very limited study, Elliott and co-workers were able to show that sulfoxides can impose modest stereocontrol during intramolecular Michael reactions (Scheme 36).⁵⁸ Thus, cyclization of racemic sulfoxide **186** led to the formation of three new products. The first two, **187a** and **187b**, were found to be diastereomeric and result from addition to different

diastereotopic alkenes. The authors comment that **187a** and **187b** were present in the crude reaction product in a 2:1 mixture and that the reported yields were a consequence of losses during column chromatography. The formation of sulfone **187c** was attributed to oxidation of the sulfoxide during chromatography. Although the diastereoselectivity is modest, compounds **187a** and **187b** are separable and could therefore be used to access products in opposite enantiomeric series (assuming (+)- or (-)-**186** could be prepared).

5. Other Asymmetric Transformations of Achiral 2,5-Cyclohexadienones

In 1996, Iwata and co-workers reported a limited study of asymmetric copper-catalyzed conjugate additions into unsymmetric cyclohexadienones (Scheme 37).⁵⁹ Dienone **188** was the only substrate investigated in these studies. After an extensive screen of chiral ligands, solvent, additives, and Cu sources; it was determined that oxazoline ligand **190** afforded the highest level of enantioinduction under the conditions shown. The identity of the major enantiomer of the product was determined by comparing HPLC retention times with authentic samples of the enantiopure product, obtained by HPLC resolution of the racemate and assigned by X-ray analysis of a 1:1 complex with TADDOL.

The authors proposed model **191** in order to explain the production of the major enantiomer of **189**. In this model, the ligand-bound MeCu species preferentially binds to the less-substituted alkene of the starting material. The binding of the dienone to the metal occurs in such a way as to minimize interactions between the substrate and the isopropyl group of the oxazoline ligand. The observation that TBDMSOTf was required for reaction led to the proposal that this additive activates the enone for 1,4-addition and results in the generation of a initial silyl enol ether product. It was not clear if the silicon was facilitating transfer of triflate to the metal in an organized manner, as shown in **191**, but this would certainly lead to a more organized and rigid transition state. Unfortunately, the authors did not report the applicability of these conditions to other substituted dienones.

In 2001, Corey and Choi reported asymmetric Diels–Alder cycloadditions between several different dienes and substituted benzoquinone monoketals (Scheme 38).⁶⁰ For this work the authors employed a chiral, titanium-based catalyst prepared in situ from (*S*)-BINOL and Cl₂Ti(Oi-Pr)₂. Spirocyclic 1,4-quinone monoketals **192a** and **192b** were excellent dienophiles for asymmetric cycloaddition reactions with (*E*)-1,3-pentadiene, and Diels–Alder adduct **193** was isolated in high yield and enantiopurity. The endo product was produced exclusively. Also, in cases where an unsymmetric dienone was used (R¹ and/or R² H), the cycloaddition occurred with the less substituted, and presumably more electron deficient, enone. Similar results were obtained for the production of **195**, in which other dienes were used for the cycloaddition. White and Choi have reported a similar asymmetric Diels–Alder reaction using benzoquinone as the dienophile.⁶¹

Nicolaou and co-workers have reported two synthetic routes toward esperamicinone (**204**), both of which use a substituted benzoquinone monoketal as a substrate for a Sharpless asymmetric epoxidation (Scheme 39).⁶² In the first route, triol **196** was converted into ketal **197** in three steps. Sharpless' catalytic conditions were then used to epoxidize allylic alcohol **197** in high yield with enantioselectivity. This reaction proved to be quite robust and

proceeded well on a 10 gram scale. Eventually, epoxide **198** was converted into advanced intermediates **199** and **200**. During this work they experienced some difficulty in installing the nitrogen atom present in **200**. This caused them to investigate a second route in which the requisite nitrogen atom is introduced at an earlier stage. To this end, triol was converted into modified ketal **201** over eight steps. The subsequent epoxidation proceeded well and provided gram quantities of **202** with good enantiocontrol. This material was then advanced to provide intermediate **203**.

As part of a program aimed at synthesizing the epoxyquinoid natural products, Porco and co-workers accomplished the asymmetric epoxidation of achiral dienones by modifying conditions originally reported by Jackson.⁶³ In these nucleophilic epoxidation reactions, DIPT serves as a relatively inexpensive source of chirality. Porco's first results in this area were revealed as part of their synthesis of (–)-cycloepoxydon (**207**, Scheme 40).⁶⁴ When NaHMDS was used to generate the peroxyanion nucleophile, monoepoxide **206** was formed in high yield and enantiopurity. Interestingly, using *n*-BuLi as the base resulted in the monoepoxide having the *opposite* absolute configuration (*ent*-**206**), albeit with diminished enantioselectivity. The authors proposed that the reason for this reversal in enantioselectivity is the difference in coordination environment between the lithium and sodium counterions. Thus, the smaller size of the lithium ion allows for the selective formation of a DIPT-peroxide complex with five-membered metal chelates (e.g., **208**). In contrast, the larger sodium ion would prefer to form a six-membered chelate, as shown by **209**. These two complexes are expected to have different conformations, which would then give rise to different interactions with substrate **205**.

Following their initial report, the Porco group was able to extend the use of their asymmetric epoxidation to other natural products (Scheme 41). For example, epoxide **206** also proved useful for synthesizing the dimeric natural product (+)-epoxyquinol (**210**).⁶⁵ Meanwhile, the related epoxide **211** could be accessed with similarly high enantioselectivity.⁶⁶ This was then advanced, over four steps, to quinone monoepoxide **212**. This compound served as a common intermediate for two natural products. Oxidative conditions were used to convert **212** into (+)-torreyanic acid (**213**); another dimeric epoxyquinoid. Alternatively, the monomeric epoxyquinoid (+)-ambuic acid (**214**) was formed from **212** using reductive conditions.

The Porco–Jackson epoxidation was further challenged with brominated dienone **215** (Scheme 42). In this case, epoxide **216** was formed in good yield and high enantioenrichment.⁶⁷ This result is interesting in that the nucleophilic oxidant preferentially attacks the seemingly more electron-rich, but less sterically crowded alkene. The epoxide product was then advanced through several more steps to arrive at diene **217a**, which dimerized to give (+)-paneophenanthrin (**220**) upon standing. Using slightly modified conditions, epoxide **216** was also used to generate dienyl ether **217b**.⁶⁸ This intermediate proved invaluable for synthesizing Rychnovsky's proposed,⁶⁹ and in the end, correct, structure of hexacyclinol (**218**) from the dimeric intermediate **219**.

6. Conclusion

Over the past 20 years, there have been numerous advances in techniques for the enantioselective desymmetrization of cyclohexadienones. The examples described in this review demonstrate that, in the right context, these desymmetrization reactions can be an effective approach to rapidly introduce molecular complexity from relatively simple starting materials. A notable feature of many of these reactions is their ability to set the configuration of multiple stereocenters in a single transformation. Given the rapidly growing interest in this field, we anticipate exciting new developments in the coming years. It would be especially interesting to see the development of new asymmetric methodologies that do not involve intramolecular reactions (e.g., Scheme 7).

Perhaps one obstacle hindering the development of new dienone desymmetrization reactions is a lack of predictive models for rationalizing the observed stereochemical outcomes of the known transformations. To a certain extent, the reactions reported here involve catalysts and intermediates whose reactivity is well understood in other contexts (e.g., chiral enamines, asymmetric Stetter reactions). Consequently, the relevant models used to predict the stereoselectivity of other reactions may very well extend to these desymmetrization reactions. However, a number of other dienone desymmetrizations involve reactive intermediates whose presence may be inferred from other contexts, but for which a predictable model for stereoselectivity in these systems may be less clear. This is especially true for the metal catalyzed reactions discussed in Section 2. Establishing these models is important, as it will allow for both the design of new ligands and catalysts with improved stereoselectivity in dienone desymmetrizations, and the invention of new reactions for dienone desymmetrization.

Another area that needs more growth is the use of these desymmetrization strategies in the context of complex molecule synthesis. A few of these techniques have been applied in natural product total synthesis, but many targets have been relatively simple. Some notable exceptions to this are Ding's synthesis of the indoxamycins (Scheme 15) and Porco's work on the epoxyquinols (Schemes 40–42). Thomson's use of a desymmetrized product as an entry into chiral biaryl natural products is also notable and shows that these products can also be useful for non-obvious applications.

We are of the opinion that the full scope of cyclohexadienone desymmetrization has yet to be realized. It is our hope that this review can inspire the development of new desymmetrization catalysts and reactions that can be applied to more complex molecules.

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Biographies

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Kyle Kalstabakken was born in Burnsville, MN in 1986. He received his B.S. in Chemistry in 2008 from The University of Tulsa (2008), where he worked on various synthetic chemistry projects under Profs. Paul Baures and John DiCesare. In 2014, he earned his Ph.D. from the University of Minnesota under the guidance of Prof. Andrew Harned. His graduate research focused on the development of methodologies for the catalytic

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Figure 1. Structure and reactivity of cyclohexadienones.⁸ Bonds formed using a cyclohexadienone indicated in red.

Scheme 1.

Hypervalent iodine-mediated oxidative dearomatization and asymmetric oxidative dearomatization.

Scheme 2.

Stereochemical outcomes of cyclohexadienone desymmetrization. Stereochemical descriptors are arbitrary.

Scheme 3.

Strategies for controlling diastereoselectivity during the desymmetrization of cyclohexadienones.

Scheme 4.

A potential stereochemical outcome of a conjugate addition to an unsymmetric, achiral cyclohexadienone.

Scheme 5.
Shibasaki's asymmetric Heck cyclization.

Scheme 6.
Feringa's asymmetric Heck cyclization.

Scheme 7.

Feringa's Cu-catalyzed asymmetric conjugate addition.

Scheme 8.

Thomson's oxidative dimerization/aromatization of desymmetrized cyclohexenones.

Scheme 9.

Bräse's synthesis of enantioenriched building blocks.

Scheme 10.
Harned's Pd-catalyzed asymmetric cyclization.

Scheme 11.
Sasai's enantioselective diacetoxylation reaction.

Variation of the alkyne tether (Ar = 4-MeOC₆H₄)

Scheme 12.

Lautens' Rh-catalyzed asymmetric arylation cyclization. coe = cyclooctene.

Scheme 13.
 Tian and Lin's Rh-catalyzed asymmetric arylation cyclization.

Scheme 14.

Tian and Lin's Cu-catalyzed asymmetric borylative cyclization

Scheme 15.

Ding's asymmetric Pd-catalyzed cyclization in the synthesis of indoxamycins A, C, and F.

Scheme 16.
Wang's Ag-catalyzed [3+2] cyclization.

Scheme 17.
Hiyashi's organocatalytic Michael addition.

Scheme 18.
Gaunt's one-pot dearomatization/Michael addition sequence.

Scheme 19.
Gaunt's ICl dearomatization/Michael addition.

Scheme 20.

Johnson's oxa-Michael/Michael desymmetrization cascade. PNBA = 4-nitrobenzoic acid.

Scheme 21.
Harned's Pd-catalyzed asymmetric cyclization.

Scheme 22.
You's bifunctional-urea catalyzed Michael addition.

Scheme 23.
Rovis' asymmetric intramolecular Stetter reaction.

Scheme 24.

You's asymmetric intramolecular Stetter reaction.

Scheme 25.
You's asymmetric oxo-Michael addition.

Scheme 26.
You's asymmetric aza-Michael addition.

Scheme 27.
 Doyle's intramolecular conjugate additions.

Scheme 29.
Ye's intramolecular oxo-Michael addition.

Scheme 30.

Wang's intramolecular sulfa-Michael addition.

Scheme 31.

Asymmetric alcoholysis/oxo-Michael addition in Fan's synthetic investigations of morphine.

BHT = 2,6-di-*tert*-butyl-4-methylphenol.

Scheme 32.
Sasai's asymmetric Rauhut–Currier reaction.

Scheme 33.
Winterfeldt's use of a Diels–Alder adduct as a chiral auxiliary.

Scheme 34.

Carreño's use of a chiral sulfoxide for internal asymmetric induction with organoalanes.

Scheme 35.

Carreño's use of a chiral sulfoxide in a cascade reaction.

Scheme 36.

Elliott's use of a chiral sulfoxide for internal asymmetric induction.

Scheme 37.
Iwata's asymmetric Cu-catalyzed conjugate addition.

Scheme 38.
Corey's Ti-catalyzed Diels–Alder reaction.

Scheme 39.

Nicolaou's application of a Sharpless asymmetric epoxidation en route to esperamicinone.

DIPT = diisopropyl tartrate

Scheme 40.

Porco's initial report on the asymmetric epoxidation of cyclohexadienones and its application in the synthesis of (-)-cycloepoxydon.

Scheme 41.

Porco's asymmetric synthesis of (+)-epoxyquinol A, (+)-torreyanic acid and (+)-ambuic acid

Scheme 42.

Porco's asymmetric synthesis of hexacyclinol and (+)-paneophenanthrin.