Review

Diastereoselective Desymmetrization of Symmetric Dienes and its Synthetic Application

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Abstract: The desymmetrization of symmetric compounds is a useful approach to obtain chiral building blocks. Readily available precursors with a prochiral unit could be converted into complex molecules with multiple stereogenic centers in a single step. In this review, recent advances in the desymmetrization of symmetric dienes in the diastereotopic group differentiating reaction and its synthetic application are presented.

Keywords: desymmetrization; symmetric diene; chiral auxiliary; $C_2$-symmetric diol; acetal

1. Introduction

The desymmetrization of meso compounds has become one of the most powerful strategies in organic synthesis [1]. It allows the formation of multiple chiral centers in a single step and offers an entry to a wide range of stereochemically complex molecules including natural products. The main advantage of the desymmetrization reactions is that symmetric precursors are readily accessible and easily synthesized. Therefore, there are numerous reports on asymmetric synthesis through desymmetrization reactions. Among them, the desymmetrization of diene substrates has been stereoselectively achieved by cycloaddition, Michael addition, halocyclization, radical cyclization, ring-closing metathesis, etc. A remaining olefin unit in the reaction products could be used for further transformations. Substrate-based asymmetric inductions from the latent stereogenic centers, namely, diastereotopic group differentiating reactions during the asymmetric syntheses have been explored [2]. In particular, substituted 1,4-cyclohexadienes have a great potential for the desymmetrization reactions [3,4]. These compounds are easily prepared by the Birch reduction/alkylation sequence of aromatic
compounds. A broad range of reactions have been developed for the desymmetrization of cyclohexadienes, and synthetic applications to natural product synthesis have been reported. The reviews on the desymmetrization of dienes before 2005 have already been reported [1-4]. We will then highlight the recent reports for the desymmetrization of dienes by diastereotopic group differentiating reactions in a stereoselective manner and its applications (Figure 1).

**Figure 1.** Diastereoselective desymmetrization of symmetric dienes.

R*: chiral functional group
cycloaddition, Michael addition, halocyclization, radical cyclization, ring-closing metathesis, etc.

2. Desymmetrization of diene substrates by diastereotopic group differentiating reactions

2.1 Cycloaddition

Stockman *et al.* reported the tandem intramolecular cycloaddition/triazoline fragmentation reaction [5]. The treatment of the mesylate 1 with sodium azide in DMF at 50 °C produced the azide 2, and the subsequent [3+2] cycloaddition resulted in 3. Fragmentation of the cycloadduct 3 followed by the ring closing reaction afforded the quinolizidine derivative 4 in 52% (Scheme 1). This reaction features a novel self-desymmetrizing cascade process.

**Scheme 1.** Intramolecular cycloaddition/triazoline fragmentation.

Linclau *et al.* developed the formation method of a C9-substituted *trans*-hydrindene ring by the intramolecular Diels-Alder reaction (IMDA) [6]. The reaction was conducted under thermal conditions (150 °C in toluene) and the bis(1,3-diene) unit of 5 was desymmetrized leading to a 70:30 mixture of 6 and 7. The use of a Lewis acid (EtAlCl₂ in CH₂Cl₂ at -78 °C) as a catalyst afforded 6 and 7 with a higher selectivity (79:21) (Scheme 2).
Scheme 2. Diastereotopic group selective intramolecular Diels-Alder reaction.

2.2 Michael addition

The sulfoxide-directed desymmetrization of cyclohexadienes was studied by Elliott et al. [7]. When the sulfoxide 8 was treated with KOt-Bu, the bicyclic compounds 9 and 10 were obtained in different yields (Scheme 3).

Scheme 3. Sulfoxide-directed desymmetrization of cyclohexadiene.

Carreño et al. reported the diastereoselective Michael addition on the cyclohexadiene with the chiral sulfoxide [8]. The chiral sulfoxide 11 was reacted with aryl organoaluminum reagents, leading to the addition products 12 (up to 98% yield, up to 96:4 dr) (Scheme 4). They envisaged that the hydroxyl group has an essential role in the asymmetric induction. They also applied this strategy to synthesize the aryl cyclitol derivatives.

Scheme 4. Diastereoselective Michael addition on cyclohexadiene with chiral sulfoxide.

2.3 Iodocyclization

Elliott et al. employed the regio- and diastereoselective iodoetherification of 1,4-cyclohexadiene with a chiral tether [9]. Iodocyclization of the cyclohexadienes 13 having stereogenic centers adjacent to the oxygen atom with I₂ and NaHCO₃ or Na₂CO₃ smoothly proceeded to give 5-endo cyclization
products 14 with a high selectivity (up to >99:1 dr) and up to 91% yield (Scheme 5). They also studied the competition between the 6-exo and 7-endo cyclization.

**Scheme 5.** Iodocyclization of 1,4-cyclohexadiene with a chiral tether.

Crich *et al.* developed the desymmetrization of aryl cyclohexadienes [10]. Iodocyclization of the aryl cyclohexadiene 15 provided the lactone 16 in 71% yield (Scheme 6). Compound 16 is a key intermediate in the synthesis of (±)-pancratistatin reported by Danishefsky *et al.* [11].

**Scheme 6.** Iodocyclization of aryl cyclohexadiene.

2.4 Radical cyclization / Epoxidation-cyclization

Recently, Elliott *et al.* reported the synthetic studies of lycopodium alkaloids, lycoposerramine A and S, by the desymmetrization of cyclohexadienes under radical conditions [12,13]. The radical cyclization of the mono-TBS compound 17 gave 18 and 19 as a separable mixture. The major isomer 18 underwent further transformations to give the heterocycle compound 20, which is a model for the tetracyclic core of lycoposerramine A [12] (Scheme 7). They also carried out a synthesis towards lycoposerramine S by the same strategy [13].

**Scheme 7.** Synthesis of the tetracyclic core of lycoposerramine A.
They also described the stereoselective epoxidation and cyclization of 1,4-cyclohexadienes [14]. Epoxidation of the cyclohexadienes 21 with \( m \)-CPBA gave the cyclized products 22 (up to 75% yield) as single diastereoisomers, via the bis-epoxide intermediates (Scheme 8).

**Scheme 8.** Stereoselective epoxidation and cyclization of cyclohexadiene.

2.5 Ring-closing metathesis

Wallace *et al.* studied the double ring-closing metathesis reaction of the tetraenes 23 with the first generation Grubbs’ catalyst to stereoselectively form the spirocyclic rings 24 (up to 87% yield, up to 92:8 dr) [15]. They also applied this reaction to the enantioselective synthesis of the NK-1 receptor antagonist in 3 steps from 24 (\( R = \text{Ph} \)) [16] (Scheme 9). Recently, they revealed the reaction mechanism [17,18].

**Scheme 9.** Double ring-closing metathesis of tetraenes.

Lee *et al.* developed the dienylene ring-closing metathesis reaction of the alkynyl silaketals 25 with the second generation Grubbs’ catalyst to afford the bicyclic siloxanes 26 in up to 96% yield. Removal of the silicon tether was achieved with TBAF to give the corresponding 1,3-dienes 27 [19,20] (Scheme 10). This methodology is an efficient tool to synthesize the 1,4-disubstituted 1,3-dienes.

**Scheme 10.** Dienylene ring-closing metathesis of alkynyl silaketals.
The diastereoselective ring-closing metathesis of phosphorus-containing trienes was reported by Gouverneur et al. [21]. The prochiral trienes 28 reacted with the second generation Grubbs’ catalyst to give the P-stereogenic six-membered heterocycles 29 in up to 100% yield with a high diastereoselectivity (up to 94:6 dr) (Scheme 11).

**Scheme 11.** Ring-closing metathesis of P-containing trienes.

![Scheme 11](image)

Blechert et al. employed the diastereoselective ring-rearrangement metathesis (RRM) [22]. Treatment of the cyclodiene 30 with the second generation Grubbs’ catalyst gave the dihydropyran 31 in favor of the 2,6-cis product (>98% yield, 7:2 dr). They supposed that compound 30 reacted the precatalyst to produce the carbene complex and then RCM occurred to give the cyclopentene intermediate. This cyclopentene would rearrange to afford the isolated dihydropyran 31. They also conducted the reactions of the cyclooctadienes 32a,b under the same conditions, and obtained the dihydropyrrole 33a (83% yield, 6:1 dr) and the piperidine derivative 33b (95% yield, 14:1 dr), both of which are trans isomers (Scheme 12).

**Scheme 12.** Diastereoselective ring-rearrangement metathesis.

![Scheme 12](image)
Pickett et al. explored the concise synthesis of the sex pheromone of *Sitodiplosis mosellana* by the silicon tethered ring-closing metathesis [23]. The di-\(t\)-butyl silaketal 35, prepared from the chiral alcohol, prochiral 1,4-pentadien-3-ol and di-\(t\)-butylsilyl bis(trifluoromethanesulfonate) 34, was subjected to metathesis conditions to give 36 in 70% yield from 34 over 2 steps. Removal of the silyl group and further transformations furnished the desired product 37 in 22% overall yield with 97:3 dr (Scheme 13).

**Scheme 13.** Diastereoselective silicon-tethered ring-closing metathesis and synthesis of the sex pheromone of the orange wheat blossom midge.

![Scheme 13](image)

2.6 Miscellaneous reactions

Studer et al. found that the chiral cyclohexadienyl-Ti complex reacted with aldehydes to afford chiral 1,3-cyclohexadienyl compounds with a high stereoselectivity [24,25]. They recently reported the desymmetrization of the metallated cyclohexadienes 38 and 39 with chiral N-\(t\)-tert-butanesulfinyl imines 40 [26]. The cyclohexadienyl-MgCl compound 38 provided the 1,3-dienes 41 with a high diastereoselextivity (>99:1 dr). When the metal on the cyclohexadiene was changed from Mg to Zn, the 1,4-dienes 42 were obtained (up to 99:1 dr) (Scheme 14). The 1,4-dienes 42 were readily oxidized to the corresponding diarylmethylamine derivatives, which are found in biologically active compounds.

**Scheme 14.** Desymmetrization of metallated cyclohexadienes with N-\(t\)-tert-butanesulfinyl imines.

![Scheme 14](image)

Gromov and Mulzer et al. developed a desymmetrization approach to construct the functionalized cis-decaline core of branimycin [27]. The treatment of the diepoxynaphthalene 43 with Me₂PhSiC₃H₆MgCl/CuCl/Ph₃P resulted in an anti \(S_N^\prime\) opening one of the oxa-bridges to stereoselectively give 44 in 75% yield (82% based on the recovered starting material 43). Compound 44 underwent further transformations including the opening of the remaining oxa-bridge by hydride attack to synthesize the tricycle structure 45 (Scheme 15).
Scheme 15. Desymmetrization of diepoxynaphthalene and synthesis of cis-decaline core of branimycin.

Landais et al. reported that the highly regio- and stereoselective intramolecular hydroamination of the cyclohexadienes 46 bearing the chiral secondary amine moieties led to the bicyclic allylic amines 47 (up to 95% yield). This cascade reaction is a useful method to provide a key structure, the azabicyclo[4.3.0]nonane system, found in various alkaloids [28] (Scheme 16).

Scheme 16. Diastereoselective protonation-hydroamination cascade reaction.

The same group described two different approaches to the tetracyclic core of the aspidosperma alkaloids by a double oxidative amination and double conjugate addition process [29]. Treating the cyclohexadiene 48 with Pd(OAc)$_2$ and O$_2$ in DMSO provided the tetracyclic compound 49 as a single isomer in 75% yield. On the other hand, the allylic oxidation using Pd/C-$t$-BuOOH and subsequent double 1,4-addition in the presence of DBU led to 50 in 54% yield (Scheme 17).

Scheme 17. Two approaches to tetracyclic core of aspidosperma alkaloids.

Prins reaction was also used for the desymmetrization of the 1,8-diene [30]. Elliott et al. reported the Prins desymmetrization of 1,4-cyclohexadienes [31,32]. The cyclohexadienes 51 were treated with TiCl$_4$ or TfOH to form the benzo[c]furan carboxaldehyde derivatives 52 via the oxocarbenium ion (up
to 66% yield) (Scheme 18). TfOH is effective for this reaction due to its strong acidity with a non-nucleophilic counter-ion.

**Scheme 18.** Prins desymmetrization of 1,4-cyclohexadienes.

![Scheme 18](image)

Landais et al. studied the rearrangement of spirocyclohexadienyl oxindoles [33,34]. Upon treatment of the spirooxindole 53 with LDA at -40 °C, the dienes rearranged to deliver the lithium enolate intermediate. The intermediate was then trapped by alkyl halides at the C3 center to afford 54 (up to 67%). On the other hand, the aldehydes were reacted at the C5 center to give 55 (up to 63%) with a high stereoselectivity (up to >95:5 dr) (Scheme 19).

**Scheme 19.** Rearrangement of spirocyclohexadienyl oxindoles followed by addition of alkyl halides or aldehydes.

![Scheme 19](image)

Crich et al. reported the dihydroxylation of the aryl cyclohexadienes by the desymmetrization strategy [35]. Dihydroxylation of the cyclohexadiene 56 occurred exclusively with anti-selectivity to the substituted aromatic ring to minimize allylic strain to afford the triol 57 in 65% yield (Scheme 20).

**Scheme 20.** Dihydroxylation of aryl cyclohexadiene.

![Scheme 20](image)

2.7 Asymmetric desymmetrization using $C_2$-symmetric acetal or aminal

We have developed an asymmetric synthesis of the chiral 1,4- and 1,5-diols by the diastereoselective intramolecular haloetherification reaction of the ene acetals 58, easily prepared from the $C_2$-symmetric diols and ene aldehydes, involving the remote asymmetric induction [36,37]. This reaction stereoselectively proceeded via the chiral bicyclic cationic intermediates, and the subsequent nucleophilic addition of an alcohol to the oxonium ion intermediate afforded 59, which have two
newly formed chiral centers on the prochiral atom and the acetal center of the starting materials 58. The chiral auxiliary unit derived from the $C_2$-symmetric diol could be removed by various procedures, *i.e.*, Birch reduction, hydrogenolysis, and fragmentation promoted by CAN [38,39] (Scheme 21).

**Scheme 21.** Intramolecular haloetherification of ene acetals.

We then studied the intramolecular bromoetherification reaction of the substituted cyclohexadiene having the $C_2$-symmetric acetal 60 and found that the reaction successfully discriminated the two prochiral olefins in a stereoselective manner to provide 61 in 63% yield [40,41] (Scheme 22). This reaction was useful for constructing complex molecules because it could produce optically active cyclohexane derivatives bearing multiple chiral centers and the remaining olefin, which promised further transformations. The sterically hindered acetal moiety derived from the $C_2$-symmetric acetal could fix the cyclohexene ring conformation promising high regio- and stereoselective transformations. For example, the dihydroxylation of 62 with OsO$_4$ stereoselectively proceeded from the less hindered face to give the corresponding diol 63 in 85% yield as a single product [41] (Scheme 23).

**Scheme 22.** Intramolecular bromoetherification of cyclohexadiene acetal.

**Scheme 23.** Stereoselective dihydroxylation.

Enantioselective reactions with chiral catalysts are well-known as more powerful methods than diastereoselective approaches with chiral auxiliaries for asymmetric synthesis. The fatal drawback in diastereoselective reaction is that at least an equimolar amount of the auxiliary is necessary. However, for the synthesis of complex molecules including natural products, various reactions such as the regio-, stereo-, and chemoselective transformations must be considered. Recently, we have proposed a novel
concept, the chiral auxiliary multiple-use methodology [42]. This is a new perspective in asymmetric synthesis utilizing a chiral auxiliary several times, namely, asymmetric induction, regio-, stereoselective transformation and protective group of the functional group (Figure 2).

**Figure 2.** Chiral auxiliary multiple-use methodology.

We achieved the concise synthesis of (+)-Sch 642305 by this methodology starting from the bromoacetal 61, obtained by the bromoetherification of the cyclohexadiene acetal 60 [42]. First, the acetal 61 was subjected to the hydroboration-oxidation condition. The hydroboration reaction regioselectively proceeded and the subsequent oxidation gave the bromo ketone intermediate. This intermediate spontaneously converted to the enone 64 by elimination of HBr in 53% yield. The structure of 64 showed that the upper side of the cyclohexene ring was shielded by the axial C-C bond and methylene group of the acetal ring. Furthermore, the 8-membered acetal ring derived from chiral auxiliary fixed the conformation to prevent the cyclohexane ring inversion (Scheme 24).

**Scheme 24.** Hydroboration-oxidation procedure.

The aldol reaction of 64 with the chiral aldehyde proceeded from the sterically less hindered face to afford the alcohol 65 as a single diastereomer. Further transformations including the radical reduction and macrolactonization gave the macrolactone 66. The chiral auxiliary was finally removed under oxidative conditions to furnish (+)-Sch 642305 via the ester intermediate (Scheme 25).

**Scheme 25.** Total synthesis of (+)-Sch 642305.
We also achieved the asymmetric total synthesis of scyphostatin, a potent inhibitor of neutral sphingomyelinase [43]. The radical reduction of 61 and stereoselective introduction of the tertiary alcohol with SeO2 gave 68. Further transformations afforded the dimethylacetal 69. Deprotection of the acetal function by combination with silyl triflate/2,4,6-collidine under basic conditions gave 70 [44,45]. With 71 in hand, the deprotection of 2,4-dimethoxyphenylmethyl (2,4-DMPM) group with Ph3C+BF4 then completed the total synthesis of scyphostatin (Scheme 26).

Scheme 26. Total synthesis of scyphostatin.

We have found that the novel double iodoetherification reaction of acyclic σ-symmetric diene acetals from the C2-symmetric diol, i.e., the chiral hydrobenzoin, afforded tetrahydrofurans with multiple chiral centers in a single operation [46,47]. Although discrimination of the two olefins of the σ-symmetric dienes with chiral auxiliaries by asymmetric intramolecular halolactonization have been reported, they do not have auxiliaries in the reaction products [48-53]. Compared with other reports, our method features that the chiral auxiliary remained in the product. Therefore, we could utilize the product for further regio- and stereoselective transformations. The acyclic diene acetals 72 with NIS and H2O led to the optically active tetrahydrofuran derivatives 75 involving the newly installed four stereogenic centers (up to 78% yield, up to 11:1 dr). The reaction proceeded via the chiral hemiacetal intermediates 74 formed by iodoetherification of the acetal oxygen atoms and subsequent nucleophilic addition of H2O to 73, followed by a second iodoetherification to give 75 (Scheme 27). It is known that hemiacetal compounds could convert to hydroxyl aldehydes through a ring-opening reaction. Alternatively, the hemiacetal intermediates 74 have another double bond in the proper position and the second iodoetherification smoothly occurs.

Scheme 27. Double iodoetherification of diene acetals.
Since the acetals 75 have the iodomethyl functions, we tried to perform the regioselective nucleophilic substitution of iodine. The treatment of 75 with sodium cyanide or sodium malonate gave 76 (88\% yield) and 77 (73\% yield), the regioselective substitution products in the less hindered position (b) (Scheme 28). This result indicates that 75 could be a useful chiral synthon for the synthesis of optically active tetrahydrofurans or γ-lactones.

**Scheme 28. Regioselective substitution.**

We applied this method to the asymmetric synthesis of rubrenolide and rubrynolide, which have the remote asymmetric center and substituted the γ-lactone ring. The 8-membered acetal 78 was converted to the lactone 79. Removal of the chiral auxiliary with CAN, developed in our laboratory [38,39], followed by epoxidation of the resulting alcohol with Ag₂O afforded 80. The treatment of the epoxide 80 with the corresponding Grignard reagent, and further transformation to furnish the synthesis of rubrenolide and rubrynolide (Scheme 29).

**Scheme 29. Total synthesis of rubrenolide and rubrynolide.**

Our groups also employed the desymmetrization reaction using $C_2$-symmetric diene aminals in place of acetals to give compounds containing the nitrogen atom [54]. This reaction involves three steps, i.e., the formation of aminal (81$\rightarrow$82), stereoselective bromoamination (82$\rightarrow$83), and oxidation of the aminal (83$\rightarrow$84) in a cascade process (57\% yield) (Scheme 30).
Scheme 30. Desymmetrization of diene aminal.

Furthermore, we applied this reaction to the concise synthesis of \(-\)-\(\gamma\)-lycorane. We proposed that the chiral imidazoline 85 derived from 1,2-di(4-methoxyphenyl)-1,2-diamine was an useful chiral synthon for achievement of the total synthesis. The compound 85 was converted to 86 via lactam formation and condensation of the aromatic unit. Finally, Friedel-Crafts reaction of 86 and subsequent reduction furnished \(-\)-\(\gamma\)-lycorane (Scheme 31).

Scheme 31. Total synthesis of \(-\)-\(\gamma\)-lycorane.

3. Conclusions

The desymmetrization reaction have enjoyed much popularity in organic synthetic chemistry. Among the many desymmetrization reactions, we focused on the symmetric dienes as a precusor. Differentiation of the diastereotopic diene group could be attained by cycloaddition, Michael addition, halocyclization, radical cyclization, ring-closing metathesis, etc. The alkene moiety in the reaction products could be used for further transformation. Therefore, the cyclic and acyclic dienes are promising precursors to obtain complex molecules with several chiral centers including biologically active natural products.

References


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