Enantioselective Dihalogenation of Alkenes

Jonathan Bock, Sudip Guria, Vo Iker Wedek and Ulrich Hennecke*^[a]

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[a] J. Bock, S. Guria, Dr. V. Wedek, Prof. Dr. U. Hennecke
Organic Chemistry Research Group (ORGC)
Department of Chemistry and Department of Bioengineering Sciences
Vrije Universiteit Brussel (VUB)
Pleinlaan 2, 1050 Brussel, Belgium
Abstract: The dihalogenation of alkenes is one of the classic reactions in organic chemistry and a prime example for an electrophilic addition reaction. The often observed anti-selectivity in this addition reaction can be explained by the formation of a haliranium ion intermediate. Although dihalogenations have been studied for more than a century, the development of reagent-controlled, enantioselective dihalogenation has proved to be very difficult. Only recently, significant progress has been achieved. In this review, we provide an overview on current method development in enantioselective dihalogenation and discuss mechanistic aspects, which render this transformation challenging.

1. Introduction

The dihalogenation of alkenes is a very old reaction and was developed quickly after the discovery of the halogens. Already during the 1860s the dibromination was employed as a general synthetic transformation in organic chemistry.

![Scheme 1. Dibromination of fumaric acid (1) and maleic acid (3) by Kekulé in 1861/62.](image)

Remarkable examples were reported by Kekulé who studied the dibromination of fumaric and maleic acid. He recognized already in 1861/62 that bromination of fumaric acid 1 produced selectively meso-1,2-dibromosuccinic acid meso-2 (“Bibromberstein säure”), while bromination of isomeric maleic acid 3 provided rac-1,2-dibromosuccinic acid rac-2 (“Isobromberstein säure”). Kekulé carried out these experiments at a time when bonding theory was still in its infancy and without a clear idea about the structure of C-C double bonds and (E)/(Z)-diastereoisomerism. Today, these reactions are a good example of stereospecific reaction, which proceeds as an anti-addition. The explanation for this observation was only provided much later by Kimball, who suggested a cyclic halonium ion (more precisely according to IUPAC a haliranium ion) as a cationic intermediate. Haliranium ions can be found nowadays in Organic Chemistry textbooks as common intermediates in addition reactions to alkenes using electrophilic halogenating agents.

Alkene dihalogenations belong to the larger class of electrophilic halofunctionalizations, which play a significant role in modern synthetic chemistry. Like dihalogenations, these reactions are initiated by the addition of a halogen electrophile to a C-C-double bond forming supposedly in most cases a haliranium ion. Opening of the haliranium ion by a suitable nucleophile such as water (halohydrine formation), an intramolecular carboxyl group (halolactonization), an alcohol (haloetherification) or other nucleophilic groups leads to valuable synthetic transformations, which have found widespread application in synthesis. A reason for this is the high diastereoselectivity, that can be often observed on starting materials already containing a stereocenter (substrate control). However, it proved to be much more challenging to develop stoichiometric or catalytic reagents, capable of controlling the stereochemistry in case of starting materials without stereocenter (reagent control). A range of catalytic asymmetric halocyclization reactions was only reported over the last decade including enantioselective halolactonizations, cyloetherifications and intramolecular haloamidations. Intermolecular stereoselective halofunctionalization proved to be more challenging and only few examples have been described. This is especially true for dihalogenations, the classic example of these reactions. Nevertheless, this problem has been addressed recently and asymmetric dihalogenations are now emerging. In this review, we aim to summarize the current knowledge on reagent-controlled, asymmetric dihalogenation of alkenes. This includes a brief discussion of the reaction mechanism as far as it concerns the stereoselectivity of the reaction. For a more comprehensive, general overview on dihalogenation, the reader is referred to other recent reviews.

Jonathan Böck was born and raised in Staufenberg, Germany. He received his M.Sc. degree in Chemistry from the University of Münster (WWU), Germany in 2017. Subsequently, he started his PhD studies at the WWU and since April 2019 is undertaking his studies at the Vrije Universiteit Brussel, Belgium. His research interests are focused on stereoselective halogenation reactions.

Sudip Guria was born (1994) and grew up in West Bengal, India. He obtained his M.Sc. in Chemistry from Indian Institute of Technology, Kharagpur, India in 2018. In summer 2018 he joined the Hennecke group for his PhD studies in Organic Chemistry, first at the University of Münster (WWU), Germany, and since April 2019 at Vrije Universiteit Brussel (VUB), Belgium. He is studying enantioselective halocyclisation and Brønsted acid catalysis.
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Volker Wedek was born in Marl, Germany (1989). He studied chemistry at the University of Münster (WWU) and obtained his M.Sc. degree in 2015. Subsequently, he joined the Hennecke group for his graduate studies completing his PhD degree on asymmetric dihalogenation in 2019. His research interest are asymmetric dihalogenation, mixed alkene halogenations and terpene-derived fragrances.

Ulrich Hennecke studied chemistry at the University of Marburg (Germany) before joining the group of Thomas Carell for his PhD studies (PhD 2007, LMU Munch, Germany). After a postdoctoral stay with Jonathan Clayden (University of Manchester, UK), he moved to the Organic Chemistry Institute of the University of Münster as junior group leader. In 2018, he joined the Organic Chemistry Research Group (ORGC) at Vrije Universiteit of Brussels (VUB). His research interests involve synthetic organic as well as bioorganic chemistry with a special focus on new catalytic, enantioselective methods for halogenation.

2. Mechanistic Aspects

The mechanistic details of alkene dihalogenation can be more complex than the textbook, two-step mechanism with reaction via a haliranium ion suggests. There are significant differences between the halogens as only the heavier halogens chlorine, bromine and iodine are known to form haliranium ions, but not fluorine. Furthermore, dihalogenation can be carried out by other reagents than elemental halogens, which will involve certain other reaction pathways. Therefore, this section will provide only a brief summary of some mechanistic aspects relevant to the outcome of stereoselective dihalogenation.

The reaction of elemental fluorine with alkenes is highly exothermic and elemental fluorine can react “violently” with alkenes to form a complex product mixture resulting from radical chemistry. When the reaction of fluorine with cyclic alkenes was conducted at low temperature (-78 °C), vicinal difluorination products were obtained, but only in low yields and as stereosomeric mixtures. A more controlled reaction was possible when using diluted fluorine in combination with an ethanol-based solvent mixture at low temperature (Scheme 2). Under these conditions, selective syn-difluorination was observed.

The syn-selectivity can be explained by the formation of a tight ion pair of a β-fluorocarbeneium ion and its fluoride anion, which collapses to syn-difluoride before bond rotation or anion migration can occur. More detailed mechanistic studies are missing. Nevertheless, this method still requires handling of highly toxic and reactive fluorine gas and is therefore not commonly applied by synthetic chemists.

Dichlorination and dibromination of alkenes are possible using the respective elemental halogens as well as a range of other reagents. The mechanisms of the reactions of alkenes with both elemental chlorine and bromine have been studied in detail, especially for dibromination. These studies show that the mechanisms are rather complex and, to a significant extend, depend on reaction conditions, solvent(s) and the structure of the alkene. Many studies have been conducted in protic solvents such as methanol and acetic acid, however, incorporation of the solvent as a nucleophile cannot be prevented under these conditions leading to various amounts of haloetherification or haloesterification by-products, respectively. For preparative purposes, dihalogenation in non-protic solvents is preferred and, therefore, mechanistic studies in chlorinated solvents are more relevant for the current discussion.

\[
-\frac{d[Br_2]}{dt} = k \cdot [Br_2]^2 \cdot [alkene] \quad \text{Equation (1)}
\]

Kinetic studies on the dibromination of alkenes using elemental bromine in chlorinated solvents such as 1,2-dichloroethane (DCE) or 1,1,2,2-tetrachloroethane (TCE) showed that the reaction is second order in bromine and first order in alkene under these conditions (Equation 1).
In the first step of the reaction, bromine is forming a charge transfer complex 11 (CTC) with the alkene (Scheme 3). In non-protic solvents, the second step of the reaction, the formation of the charged intermediate, requires the participation of a second equivalent of bromine. The interaction with the second bromine allows heterolytic cleavage of the Br-Br bond to form a bromiranium ion 12 (or a β-bromocarbenium ion 13) with tribromide as counterion. Nucleophilic addition of a bromide and release of bromine leads to the vicinal dibromide 14. For each individual step of this mechanism, experimental evidence was found. Some sterically highly demanding alkenes form only CTCs with bromine without reacting any further and enabling characterization of these complexes. For the dibromination of cyclohexene, the kinetic relevance of the CTC for the reaction mechanism of dibromination was demonstrated. The cationic intermediate is generally a haliranium ion if the alkene is only substituted by alkyl groups. Haliranium ions were observed for the first time in solution by Olah, who prepared them under stable ion conditions. In the case of adamantyliden adamantan, solid bromiranium salts are stable, can be isolated, and their structures were determined by X-ray crystallography. Based on the observed diastereoselectivity and calculations, cyclic cations 12 are favored as long as the alkene is not substituted by an electron rich aromatic ring or another highly electron-donating substituent. In this case, open chain β-bromocarbenium ions 13 can be more stable than the cyclic form. Evidence for such carbocations is usually the observation of significant amounts of syn-diastereomer 14 in the reaction products.

For dichlorination, it is usually assumed that the reaction of alkenes with chlorine follows a very similar mechanism, however, investigations are less detailed. Furthermore, calculations and experimental evidence indicated that cyclic chloriranium ions are not as favorable for chlorine as for bromine in comparison to the open chain β-halocarbenium ions. This means that for dichlorination it is more common to observe the syn-diastereomer in higher amounts compared to dibromination.

The diiodination of alkenes is not a very common reaction. The problem is the limited thermodynamic stability of vicinal diiodides due to the much lower stability of the C-I bond compared to the other halogen-carbon bonds. This means that the reaction is to a certain extend reversible and vicinal diiodides tend to decompose back to the alkene and elemental iodine over time. Nevertheless, diiodination of alkenes is a well known reaction either under thermal or photochemical conditions. Like dichlorination or dibromination, the reaction is reported to be highly diastereoselective favoring anti-addition even in the case of photochemical reaction. Under thermal conditions, the reaction most likely proceeds via an iodiranium ion as shown for chlorine and bromine. For the photochemical reaction, the formation of cyclic radical intermediate has been suggested. However, due to the rather unstable products, the reaction is not of great synthetic value.

For reagent-controlled, asymmetric dihalogenation, additional aspects must be considered. If the alkene is symmetrically substituted, the (Z)-configured and reacting via a haliranium ion, the haliranium ion 16 would be a meso-comound and therefore achiral (Scheme 4A). The stereochemistry is only established during the opening of the haliranium to give the chiral product. If the alkene is symmetrical and (E)-configured, the haliranium ion 19 would be chiral, however, it would react to give only meso-product 20 (Scheme 4B). Lastly, if the alkene is not symmetrically substituted, the haliranium ion 22 is chiral, but the regiochemistry of its opening would determine, which product enantiomer is formed (Scheme 4C). This means that the reagent/catalyst would...
have to control the regiochemistry of the halide addition if none of the substituents is providing a bias.

For asymmetric halogenation of alkenes, one more aspect has to be considered. Haliranium ions can be transferred from one alkene to another by direct alkene-to-alkene as discovered by Brown (Scheme 5A). In principle, an enantio-enriched haliranium can racemize via this process if addition of the nucleophile is slower than alkene-to-alkene transfer. In the absence of alkenes, and therefore alkene-to-alkene transfer, haliranium ions are configurationally stable as shown by Braddock. However, in typical halogenation reactions the alkene will be at least initially present in large excess compared to the haliranium ion as the reactive intermediate. Denmark was able to demonstrate that enantio-enriched bromiranium ions generated by an elimination reaction from could racemize via alkene-to-alkene transfer (Scheme 5B). Racemization was dependent on alkene concentration as well as the properties of the nucleophile. If the nucleophile was reactive enough, racemization was suppressed. How relevant this process is under typical reaction conditions for asymmetric alkene halogenation is still open for debate.

The short discussion above suggests that asymmetric dihalogenations are far from trivial reactions. The geometry and substitution pattern of the alkene significantly influences the reaction. Depending on the alkene structure, the structure of the reaction intermediate can change and will influence regiochemistry and therefore also stereochemistry of the reaction product. Furthermore, racemization of haliranium ions via alkene-to-alkene transfer cannot be excluded. The development of a chiral electrophilic halogenation agent will usually not be sufficient as the absolute configuration of the product is in many cases only determined in the second step, the addition of the nucleophile, and depends onto which carbon of the haliranium ion the halide nucleophile is added.

3. Early Attempts

The first attempt of an asymmetric dihalogenation was carried out by Julià in 1979, studying dichlorination under phase transfer conditions (Scheme 6). Starting with conditions for racemic phase transfer-catalyzed dihalogenations published by Olah using quaternary ammonium salts such as or were employed as catalysts for dichlorination of simple alkenes. The electrophilic chlorinating agent was generated in situ by oxidation of calcium chloride using hydrogen peroxide. Under these conditions, Julià and co-workers were able to obtain the vicinal dichlorides of cyclohexene and other alkenes in moderate yields. The enantioselectivity of the reactions was only analyzed using optical rotation measurements and the non-zero values obtained were taken as a proof that the products were produced in enantioenriched form. However, the enantiomeric excess was not calculated and it is unclear if significant enantiomeric excess was achieved for the products.

The first example of a highly enantioselective dihalogenation was reported in 1983 by Tanaka and co-workers, who adopted Schmidt’s approach of a gas-solid reaction in the dibromination of chiral single-crystals. They prepared several, in some cases highly crystalline, inclusion complexes of alkene and cyclodextrins (CD) and, subsequently, treated them with a gas stream of chlorine or bromine. Based on optical rotation measurements, the dihalogenated compounds were formed inside the cyclodextrins with low to high enantioselectivity ranging from 15-100% ee, however, only four examples were investigated, and yields were only low to moderate. For example, the methacrylic acid inclusion complex in β-CD was chlorinated using chlorine gas to provide vicinal dichloride in moderate yield (53%) and high enantioselectivity (88% ee, Scheme 7). In a later experiment in 1999, the Tanaka group used a 2:1 inclusion complex of a (R,R)-TADDOL ligand and cyclohexene to enable an enantioselective dibromination. In this case, only a low enantioselectivity of 12% ee was observed for the formation of product 38. While these experiments certainly demonstrate enantioselective dihalogenation for the first time, gas-solid
reactions cannot be viewed as general synthetic approach to vicinal dihalides.

\[ \text{Scheme 7.} \quad \text{The use of inclusion complexes in dihalogenation as reported by Tanaka (1983/1999).} \]

In the year 2000, Adam and co-workers found the first example of a metal-mediated enantioselective dichlorination during their mechanistic studies of Jacobsen-Katsuki epoxidations.\(^{38}\) Oxidation of Mn(salen) complex 43 using iodosylbenzene in CH\(_2\)Cl\(_2\) provided a reactive compound that dichlorinated dihydronaphthalene 39 with moderate chemoselectivity (Scheme 8). A reaction mechanism involving the oxidation of the manganese complex 43 to a [OMn\(^{IV}\)(salen)]Cl species, which abstracted a Cl-atom from CH\(_2\)Cl\(_2\) to form [ClO Mn\(^{IV}\)(salen)]Cl as a chiral chlorinating agent was proposed. However, enantioselectivity for the formation of dichloride 40 was low and 40 was only obtained with 5\% ee, an enantioselectivity significantly lower than observed for the chlorohydrine 41 and the epoxide 42 formed during the same reaction.\(^{38}\)

\[ \text{Scheme 8. Dichlorination of dihydronaphthalene using a Mn(salen) complex (Adam, 2000).} \]

In 2003, Henry described highly enantioselective alkene dibrominations catalyzed by Palladium complexes such as 46 under modified Wacker conditions (Scheme 9).\(^{39}\) According to the publication, enantioselectivities as high as 97\% ee were obtained for terminal alkenes such as allyl ether 44. The publication has now been cited more than 100 times, however, only in a single case reproduction of the chemistry was attempted. Denmark reported that it proved to be difficult to repeat the experimental procedures and all of his groups efforts only led to the formation of racemic dibromination products.\(^{40}\)

\[ \text{Scheme 9. Palladium-catalyzed dibromination under Wacker-related conditions as reported by Henry (2003) and Denmark (2015).} \]

An intriguing example of a highly enantioselective dichlorination was described by Snyder and coworkers in 2009.\(^{41}\) In the framework of their synthesis of (-)-Napyradiomycin A1, they were able to dichlorinate alkene 47 with an enantioselectivity of 87\% ee (Scheme 10). To achieve this, the alkene was complexed with a stoichiometric amount of a BINOL-boric acid ester 50 creating a chiral environment around the alkene. The alkene was subsequently dichlorinated using elemental chlorine in very good enantioselectivity. While this method was certainly a very important achievement, the method is specific to alkene 47.
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Scheme 10. Dichlorination of a tricyclic (Z)-alkene 47 during the synthesis of napyradiomycin A1 by Snyder (2009).

4. Difluorination

Direct asymmetric difluorination of alkenes using electrophilic fluorinating agents has not been reported.\textsuperscript{[39]} Instead, mechanistically distinct methods based on hypervalent iodine-based reagents, often formed \textit{in situ} from suitable precursors, have been investigated.\textsuperscript{[42]} Difluoroiodo arenes can be used as fluorinating agents for the vicinal fluorination of alkenes.\textsuperscript{[42]} However, depending on reaction conditions and alkene structure, these reactions can be accompanied by skeletal rearrangement leading to the formation of geminal difluorides.\textsuperscript{[43]}

A first highly enantioselective difluorination of alkenes was an asymmetric geminal difluorination reported in 2016 by Jacobsen (Scheme 11).\textsuperscript{[44]} Using the chiral aryl iodide 56 as catalyst and \textit{m}-chloroperbenzoic acid (mCPBA) and hydrogen fluoride/pyridine as stoichiometric reagents, the geminal difluorination of cinnamic amide and ester derivatives 51 was achieved. The fluorination reaction was accompanied under the reaction conditions by aryl group migration leading to the geminal difluorination products 52. The amide containing reaction products such as 53 or 54 carrying a difluoromethyl substituent were obtained in good yields (up to 93%) and with good to excellent enantioselectivities (64-96% ee). Methyl cinnamates could be rearranged as well and in this case substituents in the $\alpha$-position were tolerated, leading to methyl propionates such as 55 with a difluoromethyl substituent at a quaternary stereocenter. Based on extensive DFT calculations a reaction mechanism was proposed involving an iodoarene difluoride as the key fluorinating agent and a phenonium ion-based rearrangement (Scheme 12).\textsuperscript{[45]} HF-mediated 1,2-difluoroiodination of the alkene by the difluoroiodo arene will result in iodonium cation 58 as the key intermediate. Depending on reaction conditions and substituents present, either a stereospecific rearrangement via phenonium ion 60 can occur resulting in the geminal difluoride 53. Or alternatively iodonium ion 58 can react with a nucleophile to a substitution product. In the case of unsubstituted cinnamic amides, the amide will participate as neighboring group followed by another substitution by fluoride leading to the vicinal difluoride 61 as the major product. The occurrence of the rearrangement of 58 versus nucleophilic substitution is very substrate-dependent and small structural variations can already lead to a change in reaction pathway. The presence of a rather nucleophilic carbonyl group and a sterically demanding substituent in 2-position, for example, favors nucleophilic substitution over rearrangement resulting in the vicinal difluoride 61.

Scheme 11. Enantioselective geminal difluorination of cinnamic acid derivatives according to Jacobsen (2016).

This means that catalytic vicinal difluorination of alkenes can be also carried out using hypervalent aryl iodides as a catalyst, when the substrate structure is not supporting rearrangement. The initial publication on catalytic diastereoselective difluorination by Jacobsen already reported a single example of an enantioselective reaction\textsuperscript{[46]}, however, more general methods were subsequently published by Gilmour and Jacobsen, respectively.\textsuperscript{[46,47]}

This scheme means that catalytic vicinal difluorination of alkenes can be also carried out using hypervalent aryl iodides as a catalyst, when the substrate structure is not supporting rearrangement.
In 2018, Gilmour reported the application of the aryl iodide catalyst for the 1,2-difluorination of a broad set of mono-substituted styrene derivatives (Scheme 13). Using Selectfluor as the oxidant and an amine/HF mixture as fluoride source, they were able to obtain vicinal difluoride products in moderate to very good yields and with good to very good enantioselectivities (50-88% ee). Interestingly, they observed that a change of amine:HF ratio strongly influenced the regioselectivity of geminal to vicinal difluorination. Whereas an amine:HF ratio of 1:4.5 led to high selectivity for the vicinal product (>20:1 vic. vs. gem.), higher amine:HF ratios induced a shift towards the geminal product reaching almost complete reversal of regioselectivity when using pure Pyr·(HF), (amine:HF ratio ~ 1:9.2; 1:20 vic. vs. gem.).

In 2019, Jacobsen described the vicinal difluorination of cinnamic amides using again aryl iodide as the catalyst (Scheme 14). They found that N-butyl cinnamic amides, when used instead of N-unsubstituted amides, preferentially underwent vicinal difluorination instead of rearrangement and geminal difluorination. Vicinal difluorination of these substrates occurred with high anti-diastereoselectivity, probably due to anichmeric assistance by the carbonyl group (Scheme 12). Using catalyst and reaction conditions similar to the geminal difluorination, the vicinal difluorides were obtained in moderate to very good yields and with excellent enantioselectivities (77-98% ee).
5. Dichlorination, Dibromination and mixed Dihalogenations

In pursuit of new halogenation agents for asymmetric dihalogenation, Snyder and coworkers developed in 2010 a chiral analogue of their electrophilic chlorinating agent CDSC (chloro diethylsulfonium hexachloroantimonate) using (R,R)-2,5-dimethylthiolane (Scheme 15). With stoichiometric amounts of isolated 73 at low temperature they were able to chlorinate dihydrornaphthalene 39 to give dichloride 40 in moderate yield, but with only low enantioselectivity (14% ee). They discovered that the solvent and method of reagent preparation had a significant influence on the reaction outcome. In a more polar solvent such as nitroethane and using in situ generation of 73 by treatment of 2,5-dimethylthiolane with elemental chlorine, they were able to increase the enantioselectivity up to 41% ee, however, this procedure resulted in a poor yield (10%). Bromochlorination and iodochlorination were also investigated under related conditions, but the observed enantioselectivities remained low to moderate.

They utilized (DHQ)2PHAL 79 as an organocatalyst for the 4-phenyl dichloriodobenzene 80 mediated dichlorination of allylic alcohols 74. The dichloride products 75 were obtained in moderate to good yields, and high enantioselectivities up to 81% ee were obtained on trans-cinnamyl alcohols. Allyl alcohols without aryl substituent or in cis-configuration provided lower enantioselectivities (25-54% ee). In their stereoinduction model they postulated the coordination of alcohol 74 via hydrogen bond formation to the phthalazine moiety of the catalyst. In a control experiment, they showed that the enantioselectivity vanishes (<10% ee), if the phthalazine moiety was exchanged to an anthraquinone (as in (DHQ)2AQN) or if the alcohol was silyl-protected. This indicates that the formation of a hydrogen bond between the alcohol and the phthalazine moiety of the catalyst is of decisive importance for selective catalysis.

In 2017, Borhan and co-workers showed a highly enantioselective dihalogenation of allylic amides 81 using the pseudoenantiomer (DHQD)2PHAL 83 as catalyst (Scheme 17). Instead of a hypervalent iodine-based halogenating agents, they used separate electrophilic (DCDMH or NBS) and nucleophilic halide sources (LiCl or LiBr). Preliminary studies showed that the use of polar solvents such as MeCN and TFE provides the best enantioselectivities, however, this required the use a large excess of lithium halides (100 equiv.) to prevent incorporation of the solvent into the product. Under these conditions, dichlorides 82 could be obtained in excellent yields and enantioselectivities of up to 99% ee. In addition, they also realized dibromination and bromochlorination with enantioselectivities ranging from 66-99% ee, whereby both (E)- and (Z)-alkenes were accepted as substrates by the catalyst.
Asymmetric dichlorination of allyl amides according to Borhan (2017).

Enantioselective dichlorinations of alkenes without directing hydroxyl or amide group were disclosed by Hennecke and co-workers in 2019 (Scheme 18). This required the use of unsymmetrical chinchona alkaloid-based organocatalyst carrying a sterically demanding secondary alcohol at the phthalazine moiety. Like in Borhan’s example, separate electrophilic (DCDMH) and nucleophilic halogen sources (TES-Cl) were used, but carrying out the reaction in non-polar solvent enabled the use of stoichiometric amounts of halide. Under these conditions, cyclic arylalkenes could be dichlorinated in high yields and with very good enantioselectivities up to 88% ee. Cyclic alkenes were clearly preferred substrates, and dichlorination of acyclic alkenes resulted in mixtures of syn- and anti-diastereomers with the anti-diastereomers being formed with enantioselectivities up to 58% ee. Based on these results and DFT-calculations the authors postulate that the reaction is not taking place via a symmetric haliranium ion. Instead, due to the electronic bias provided by the aryl group a non-symmetric reaction intermediate with β-chlorocarbenium ion structure is suggested.

The nucleophilic chloride source (TES-Cl) in the dichlorination reaction of Hennecke could also be replaced by KHFs in combination with a crown ether (18-crown-6). This resulted in the chlorofluorinated products and which were formed with similar enantioselectivity than the corresponding dichlorination products (62 and 86% ee, respectively, Scheme 19).

A different strategy to achieve asymmetric dihalogenation was pursued by Burns. Instead of organocatalysis, the Burns group investigated titanium-mediated dihalogenations on allylic alcohols. In 2013, Burns and co-workers demonstrated a new concept for enantioselective dibromination of allylic alcohols using dibromomalonate as bromenium source and a titanium bromide (BrTi(O(R)) species as bromide source (Scheme 20). When using tartaric acid-derived diol as chiral ligand on titanium and cinnamyl alcohols as substrates, very good yields and enantioselectivities were obtained. The hydroxyl group in...
allylic position was strictly required for high enantioselectivity. Allylic ethers, amides and sulfonamides were not effective as directing groups for this type of transformation and the products were racemic. The amount of chiral ligand could be lowered to 20 mol% without significant reduction in selectivity, however, lower ligand loading than 20 mol% resulted in only low enantioselectivity.

Scheme 20. Titanium-mediated enantioselective dibromination of cinnamyl alcohols as reported by Burns (2013).

In subsequent publications, the Bruns group demonstrated that under very related conditions highly enantioselective dichlorinations and bromochlorinations of alkenes were possible. For dichlorination, tert-butylylhydroxide was used as chlorenium source in combination with ClTi(OPr)₃ species as halide source. In combination with catalytic amounts of ligand 100 (10 - 30 mol%), dichlorination of (E)- and (Z)-configured allylic alcohols 101 was possible in good yields and very good enantioselectivities (Scheme 21).

Very remarkable results were also obtained for the bromochlorination conducted with the electrophilic brominating agent NBS and ClTi(OPr)₃ species (Scheme 21). While in general, electrophilic halogenation reactions of alkenes follow Markovnikov’s rule, in this case the regioselectivity was controlled by the titanium complex. The bromine atom was always placed at the more distal carbon atom of the alkene (viewed from the hydroxyl group) and the chlorine atom always at the more proximal position. As was the case for dibromination and dichlorination, yields and enantioselectivities for the bromochlorination products 103 were generally high on allylic alcohols. Furthermore, the reaction was highly chemoselective and only alkenes in allylic position were dihalogenated, while other alkenes were left untouched.


The Burns group applied their method to the synthesis of several halogenated natural products. Examples include (+)-bromochloromycene, which was prepared in only three steps, (+)-halomon, (-)-plocamenone, (-)-isoplocamenone and the antibacterial, polyhalogenated monoterpene (-)-anverene. As part of the last synthesis, the authors were able to extend the enantioselective dihalogenation method from allylic to a homoallylic alcohol with equal enantioselectivity. These syntheses highlight the value of efficient and highly selective dihalogenation methods for organic synthesis.

Another strategy for dihalogenation with the heavier halogens was investigated by the Gilmour group. Based on their previous results on enantioselective vicinal difluorination, they studied hypervalent iodine-catalyzed enantioselective vicinal dichlorination of terminal alkene (Scheme 22). For this work they choose 4-chlorostyrene 108 as model substrate. Alkene 108 was treated with cesium chloride as chlorine source and Selectfluor as oxidant in presence of aryl iodide 110 as catalyst to obtain the product 109 in 29% yield and 28% ee. This result is quite different in terms of yield and selectivity from the related difluorination and showed that the transfer of reaction conditions
from one type of halogen to another can be very difficult. For reactions via a cationic halogen-based intermediate such as a haliranium ion this seems logical, however, hypervalent iodine-catalyzed difluorinations and dichlorinations are supposed to follow a similar mechanism and the difference in enantioselectivity is not easily explained.

Their investigations demonstrated that enantioselective syn-dichlorinations are possible and under optimized conditions alkene \( 111 \) was transformed to syn-dichloride \( 112 \) in good yield and with an enantioselectivity of 48% ee. However, despite an extensive number of diselenides investigated by the authors, enantioselectivity could not be further improved.

6. Asymmetric synthesis of trihalides by kinetic resolution

With the number and scope of enantioselective dihalogenation methods being limited, other approaches for the synthesis of enantiopure vicinal dihalides have been investigated. One interesting method was reported by the Yan group in 2017. They found that \( \alpha,\beta \)-unsaturated arylketones can be converted into racemic \( \alpha,\beta,\gamma \)-tribromides \( 114 \) by a Wohl-Ziegler bromination followed by alkene dibromination with good diastereoselectivities. To obtain enantiopure compounds, a kinetic resolution of the racemates via \( \beta \)-elimination was developed. Using catalyst \( 119 \) and potassium fluoride as base, the resolution of a broad range of tribromides was possible leading to enantiocinriched tribromides in good yields and excellent enantioselectivities (Scheme 24).

For tribromides with an arylketone substituent, \( S \)-factors between 17 and more than 50 were observed. The isolation of the allylbromides \( 116 \) was also possible and according to the authors, also these compounds were obtained with good enantioselectivities. The method was also applicable to mixed
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bromides/chlorides and trichlorides such as 118, which could be resolved with similar yields and enantioselectivities.

7. Conclusions

The development of enantioselective dihalogenations of alkenes is currently an exciting research field and a range of new strategies for catalytic asymmetric dihalogenations are emerging. For dihaloamination, hypervalent iodine-catalyzed methods have proved to be very useful as they avoid the use of elemental fluorine and rather benign stoichiometric reagents such as Selectfluor and amine/HF complexes can be used as fluorinating agents. The enantioselectivities observed are very good on a range of substrates such as α,β-unsaturated amides and esters as well as styrenes. However, not all alkenes undergo smooth vicinal difluorination and, instead, depending on alkene structure, catonic rearrangements during hypervalent iodine-catalyzed alkene oxidation are quite common. As exemplified by Jacobson, this process can be employed to achieve useful geminal difluorination reactions, but it still limits the scope of vicinal difluorination.

For enantioselective dichlorinations and dibrominations the situation is different. Enantioselective dichlorination and dibromination of allyl alcohols and allylic amides is possible using methods developed by Nicolaou, Borhan and Burns. Burns' titanium-catalyzed method has a rather large scope similar to the Sharpless epoxidation enabling its application in a broad range of syntheses. For alkenes without directing group, dihalogenation is still very challenging. Hennecke has demonstrated highly enantioselective dichlorination on cyclic (Z)-alkenes, however, high enantioselectivities are only obtained if the alkene is cyclic and electronically-biased by an aryl substituent. The dihalogenation of alkenes without electronic bias, i.e. with only alkyl substituents is currently not known. The development of asymmetric dihalogenation methods is clearly hindered by the lack of mechanistic understanding of the catalytic chlorination and bromination. While it is generally assumed that many of these reactions proceed via haliranium ions, experimental evidence is meager and the mode-of-action of most catalysts is poorly understood. In the future, more detailed mechanistic investigations will be required. A better understanding of the key steps of the reaction mechanism should enable the design and development of a new generation of catalysts or novel catalytic concepts to finally create asymmetric dihalogenations for simple, alkyl-substituted alkenes.

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The dihalogenation is one of the most typical electrophilic addition reactions to alkenes. The iconic haliranium intermediate can be found in textbooks and is responsible for the high anti-selectivity of addition. Nevertheless, the development of reagent-controlled asymmetric versions of this reaction has proven to be a formidable challenge and general methods are not yet available. This review summarises the current state-of-the-art in this reaction and discusses relevant mechanistic features for future catalyst development.