Enantioselective Synthesis

International Edition: DOI: 10.1002/anie.201507152
German Edition: DOI: 10.1002/ange.201507152

Catalytic, Stereoselective Dihalogenation of Alkenes: Challenges and Opportunities

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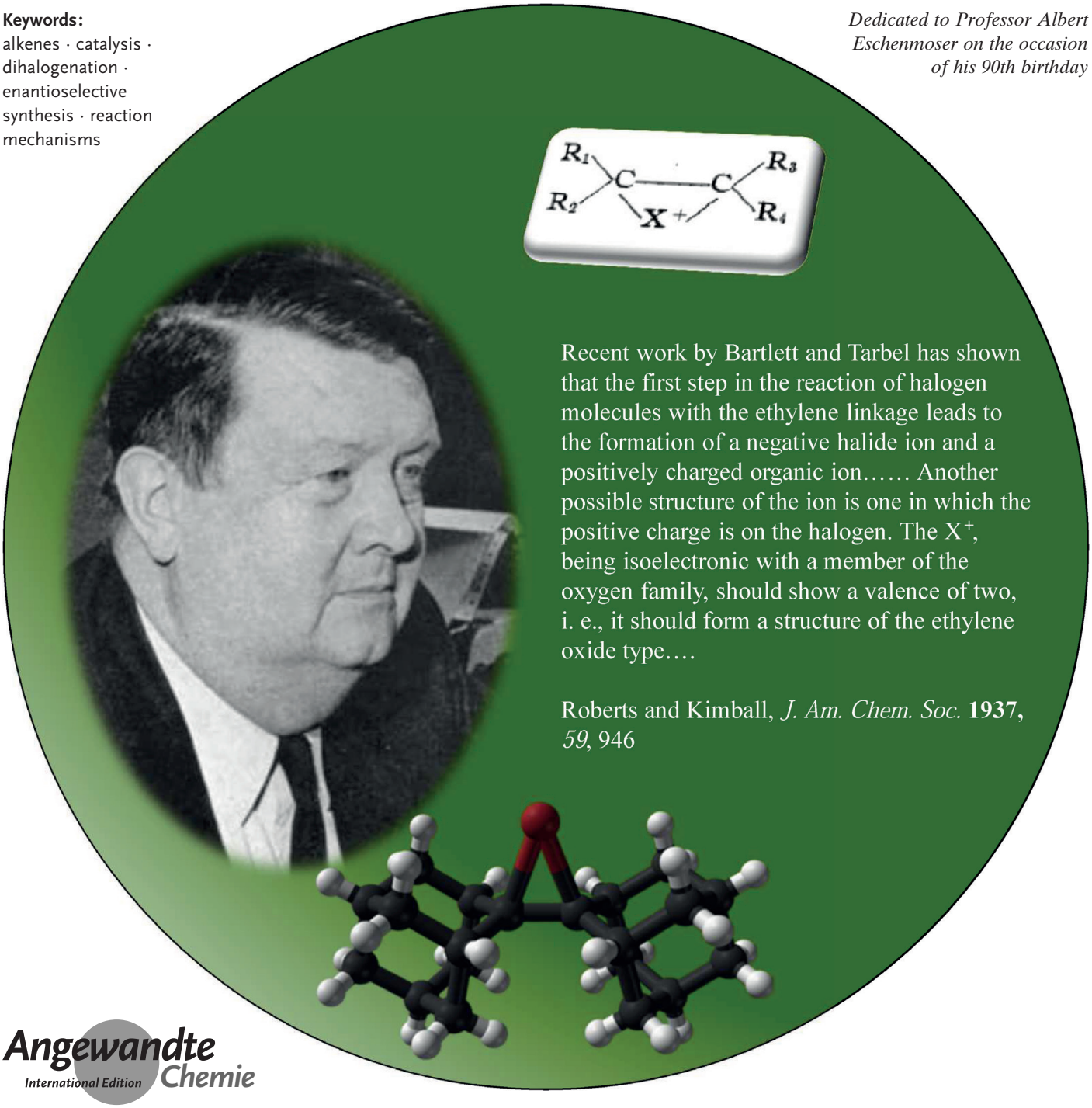
Keywords:
alkenes · catalysis · dihalogenation · enantioselective synthesis · reaction mechanisms

Dedicated to Professor Albert Eschenmoser on the occasion of his 90th birthday



Although recent years have witnessed significant advances in the development of catalytic, enantioselective halofunctionalizations of alkenes, the related dihalogenation of olefins to afford enantioenriched vicinal dihalide products remains comparatively underdeveloped. However, the growing number of complex natural products bearing halogen atoms at stereogenic centers has underscored this critical gap in the synthetic chemist's arsenal. This Review highlights the selectivity challenges inherent in the design of enantioselective dihalogenation processes, and formulates a mechanism-based classification of alkene dihalogenations, including those that may circumvent the "classical" haliranium (or alkene-dihalogen π-complex) intermediates. A variety of metal and main group halide reagents that have been used for the dichlorination or dibromination of alkenes are discussed, and the proposed mechanisms of these transformations are critically evaluated.

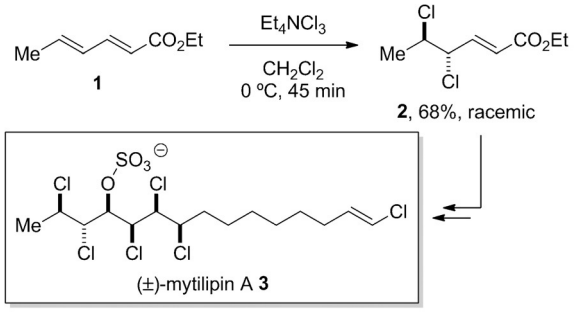
From the Contents

1. Introduction: State of the Art

The oxidative difunctionalization of alkenes with electrophilic halogen sources is among the most direct and versatile of strategies for the installation of vicinal, heteroatom-bearing, stereogenic centers with highly predictable diastereo- and constitutional selectivity.[1] However, despite spectacular successes in the development of highly enantioselective alkene dioxygenation protocols—principally epoxidation[2] and dihydroxylation[3]—the control of enantioselectivity in alkene halogenation has only recently begun to capture the imagination of the synthetic organic community. Whilst the field is undoubtedly still in its infancy, a variety of catalytic, enantioselective olefin difunctionalization reactions involving all four (common) halogens have now been realized, and these transformations fall under the broad umbrella of "alkene halofunctionalization" reactions.[4]

The majority of successful catalytic, enantioselective reactions in this class have involved the intramolecular capture of (putative) haliranium ion intermediates[5] by tethered nucleophiles, including carboxylic acids, alcohols, and (protected) amines, amongst others. However, much less attention has been paid to the development of catalytic, enantioselective variants of the prototypical alkene halogenation process—the addition of molecular dihalogens (X_2) to alkenes to afford vicinal dihalides. A particularly striking illustration of this gap in enantioselective synthetic methodology is evident in the landmark total synthesis of the chlorosulfolipid mytilipin A **3** by Carreira and co-workers, in which the very first step of the synthesis—the vicinal dichlorination of ethyl sorbate **1** to give dichloride **2**—is carried out in racemic fashion, necessarily leading to the racemic natural product **3** (Scheme 1).[6]

In fact, despite the ever growing number of halogenated natural products on record,[7] only two examples of *enantioselective* alkene dihalogenations in total synthesis have been reported, one of which—the synthesis of (+)-bromochloromyrcene[8]—was accomplished only recently (see below). The first instance of an enantioselective alkene dihalogenation in the preparation of a natural product was described by Snyder et al. during their synthesis of (−)-napyradiomycin **7**, although the dichlorination employed a stoichiometric amount of a chiral modifier. Thus, using the chiral, non-racemic dialkoxyborane **5** as a (super)stoichiometric additive to form a chiral 2:1 complex with alkene **4**, subsequent treatment with Cl_2 delivered the dichloride **6** in 93.5:6.5 er (Scheme 2).[9] The interaction of two equivalents of **5** with **4**



Scheme 1. A racemic alkene dichlorination as the first step of Carreira's landmark chlorosulfolipid total synthesis.

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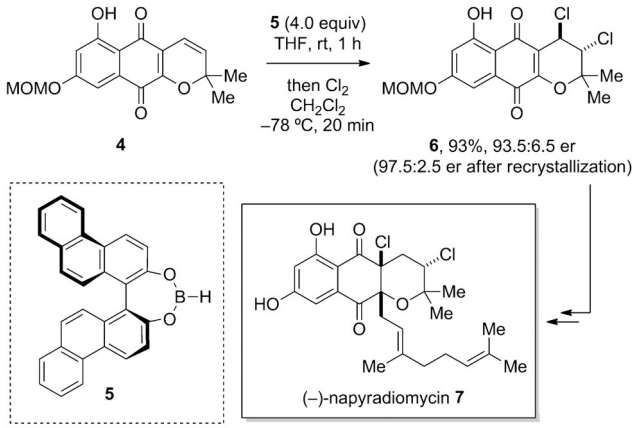


Scheme 2. Snyder's stoichiometric, enantioselective alkene dichlorination en route to (−)-napyradiomycin **7**. MOM = methoxymethyl.

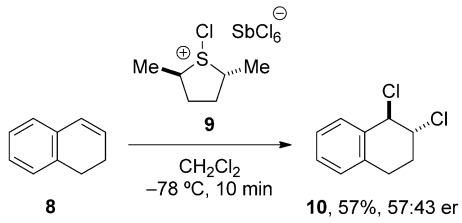
was proposed to shield one enantioface of the alkene, leading to the preferential formation of one enantiomer of the dichloride.

This strategy bears some resemblance to an earlier enantioselective dihalogenation based on host–guest inclusion complexes of unsaturated acids in crystalline α- or β-cyclodextrin, in which methacrylic acid in particular could be dichlorinated with high enantioselectivity upon treatment with Cl_2.[10]

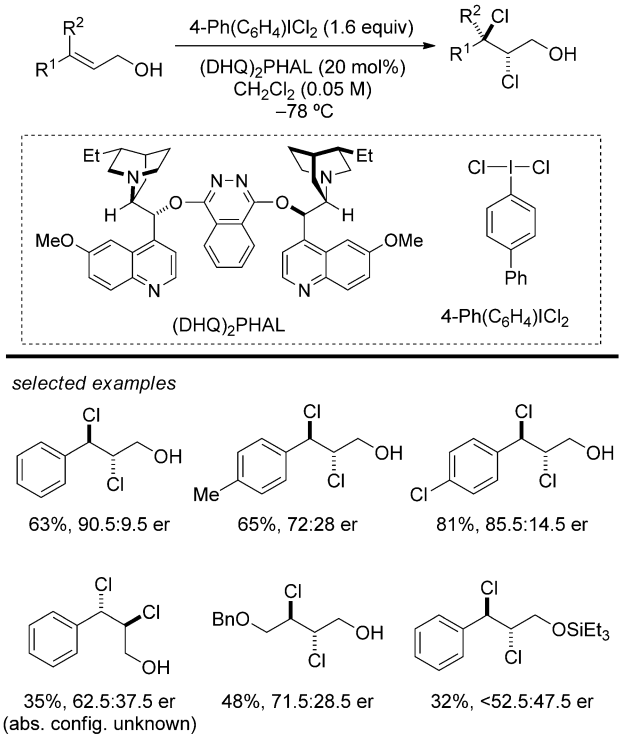
In another effort to effect enantioselective dichlorinations of olefins, Snyder and co-workers examined chiral *S*-Cl sulfonium salts as stoichiometric reagents for enantioselective chlorenium ion transfer. However, the treatment of 1,2-dihydronaphthalene **8** with *S*-Cl sulfonium salt **9** in CH_2Cl_2 delivered the vicinal dichloride **10** in 57 % yield but only 57:43 er (Scheme 3).[11]

The first practical, catalytic, enantioselective dichlorination of alkenes was reported by Nicolaou and co-workers in 2011. In this process, 4-Ph(C_6H_4)ICl_2 is employed as the chlorinating agent and $(DHQ)_2PHAL$ serves as the catalyst. A number of (*E*)-configured, 3-aryl 2-propenyl alcohols are dichlorinated in moderate to good er (71.5:28.5 to 90.5:9.5 er), although *O*-protected, (*Z*)-configured, or aliphatic allylic alcohols are generally less selective (< 52.5:47.5 to 81:19 er) (Scheme 4).[12]

Although detailed mechanistic investigations were not undertaken, the mode of catalysis was speculated to involve Lewis base activation[13] of the iodine(III) dichlorinating



Scheme 3. Stoichiometric, enantioselective alkene dichlorination employing a chiral, non-racemic, *S*-Cl sulfonium salt **9** as a chlorenium ion transfer reagent.



Scheme 4. Catalytic, enantioselective alkene dichlorination.

agent by one of the quinuclidine nitrogens of $(DHQ)_2PHAL$, with a potential hydrogen bonding interaction between a phthalazine nitrogen and the hydroxy group of the substrate as a stereocontrolling element (Figure 1).

Another landmark achievement in this area is the catalytic, enantioselective dibromination of alkenes recently

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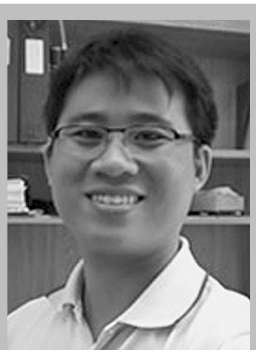

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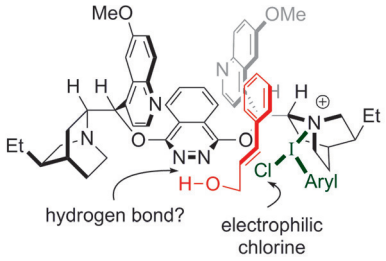
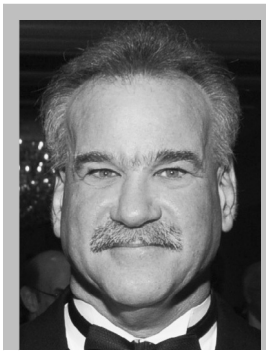


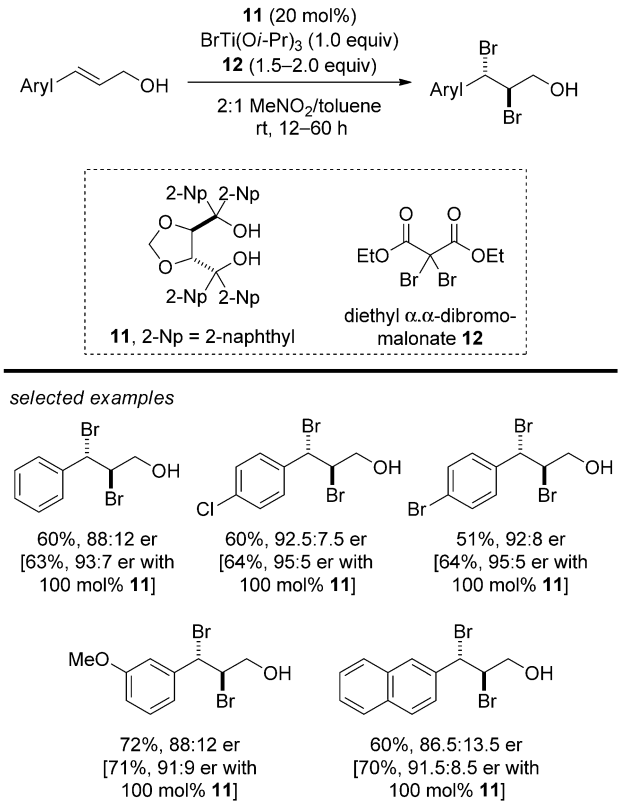
Figure 1. Proposed stereoinduction model.

developed by Burns and co-workers, employing diethyl α,α-dibromomalonate **12** as a Br^+ equivalent in conjunction with $BrTi(Oi\text{-}Pr)_3$ as a Lewis acid bound source of Br^-. The dibromination of a range of (*E*)-configured, 3-aryl 2-propenyl alcohols can be effected using 20 mol% of TADDOL[14] additive **11** to provide the corresponding dibromides with good enantioselectivities (85.5:14.5 to 92.5:7.5 er) (Scheme 5). Slightly higher enantioselectivities (5–10% *ee* increase) can be achieved when the diol **11** is used as a stoichiometric agent (100 mol%).[15]

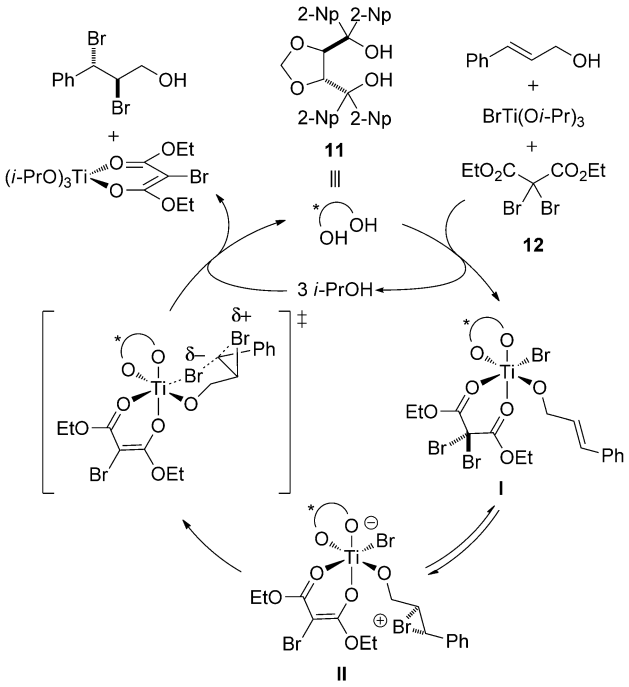
A proposed catalytic cycle for this reaction is outlined in Scheme 6. Ligand exchange at titanium may lead to the coordinatively saturated complex **I**, loaded with substrate, bromide ion, diethyl α,α-dibromomalonate **12**, and chiral diol **11**. Bromenium ion delivery to the alkene, assumed to be intramolecular and reversible, would then give the bromiranium ion species **II**. An enantioselectivity-determining attack of bromide ion at the benzylic carbon of the substrate may then ensue, setting the absolute configuration of the vicinal dibromide motif, and it was speculated that the bromide may be transferred intramolecularly from the coordination sphere of Ti. Ligand exchange at Ti by *i*-PrOH—presumably reversible—would then release the dibromide product and enable turnover of the diol **11**. Although this mechanistic scenario was described by the authors as a dynamic kinetic resolution of a reversibly formed, chiral bromiranium ion, the presence of the chiral diol ligand renders the two possible bromiranium ions diastereomeric rather than enantiomeric, and as such this mechanism would be classified as a Type 1 dynamic kinetic asymmetric transformation (DyKAT).[16] However, the authors did stress that an enantiodetermining, irreversible bromiranium ion formation, or even a concerted dibromination step, could not be ruled out with the evidence available. On the basis of an appreciable racemic background



Scott E. Denmark obtained an S.B. degree from MIT in 1975 and his D.Sc.Tech. (under the direction of Albert Eschenmoser) from the ETH Zürich in 1980. That same year he began his career at the University of Illinois and since 1991 he has been the Reynold C. Fuson Professor of Chemistry. His research interests include the invention of new synthetic reactions, exploratory organoelement chemistry, and the origin of stereocontrol in fundamental carbon–carbon bond-forming processes.



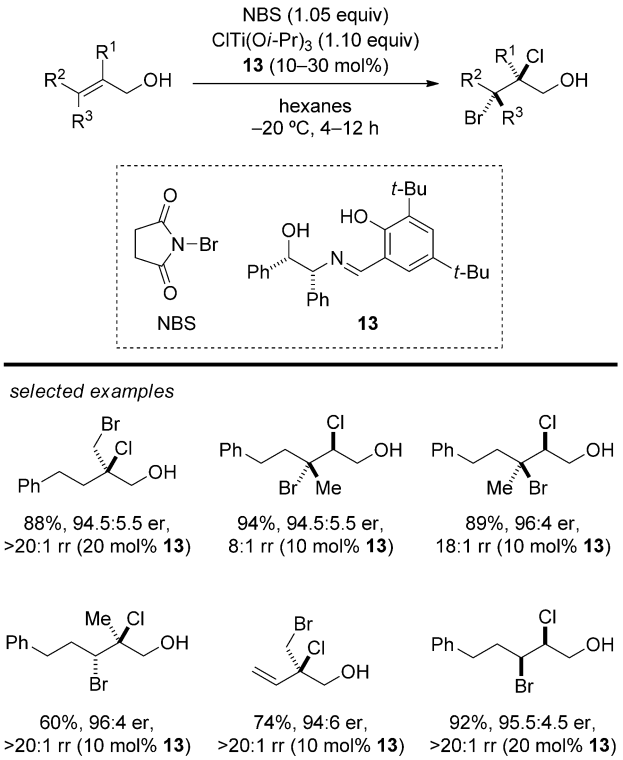
Scheme 5. Catalytic, enantioselective alkene dibromination.



Scheme 6. Proposed catalytic cycle. 2-Np = 2-naphthyl.

reaction in the absence of the chiral diol **11**, and on the fact that even substoichiometric amounts of **11** impart significant enantioselectivity, the authors suggest that this reaction constitutes an example of ligand-accelerated catalysis.[17] However, the origin of the acceleration is currently unclear.

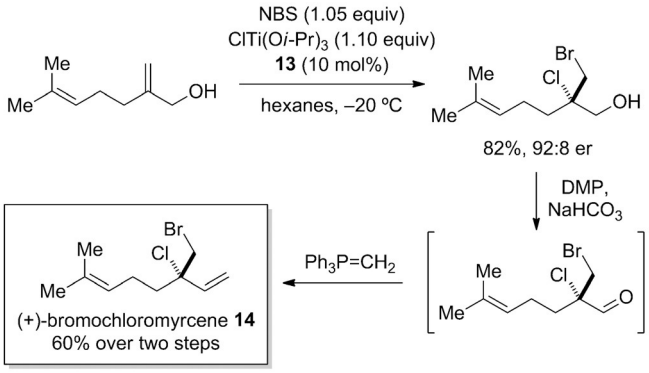
In a further development, Burns and co-workers have recently modified their enantioselective dihalogenation method to accomplish the first regio- and enantioselective chlorobromination reactions of alkenes.[8] In this study, *N*-bromosuccinimide (NBS) is employed as the Br^+ source, $ClTi(O\textit{i}\text{-}Pr)_3$ serves as a Lewis acid bound source of Cl^-, and tridentate Schiff base **13** is now used as a chiral, non-racemic catalyst (or possibly precatalyst). A variety of allylic alcohols are converted to the corresponding β-chlorobromides with generally high enantioselectivities (89:11 to 98.5:1.5 er) and site selectivities (6:1 to >20:1 rr) (Scheme 7). Perhaps the



Scheme 7. Catalytic, enantioselective alkene chlorobromination. NBS = *N*-bromosuccinimide.

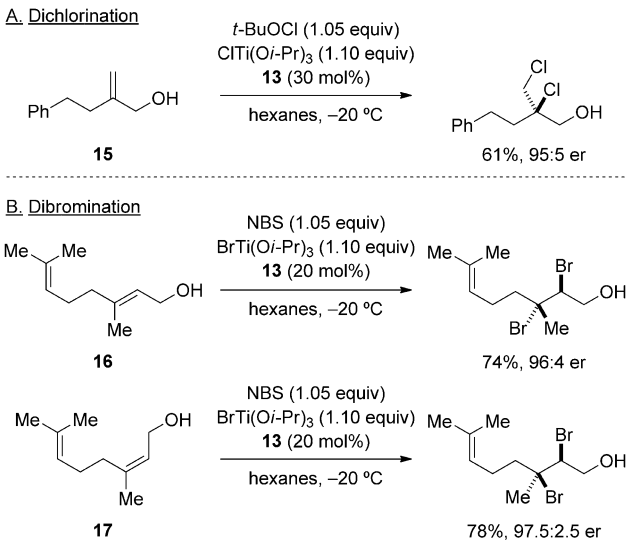
most remarkable aspect of this work is the fact that the catalyst is able to overturn the intrinsic (substrate-controlled) site selectivity of chloride ion addition to the putative bromiranium ion intermediates, as evidenced by control experiments conducted on a representative substrate. Although detailed mechanistic information is not yet available, the authors suggest that intramolecular chloride delivery to the bromiranium ion may occur from an alkoxy-ligated titanium center, with the enantioselectivity-determining step of the reaction yet to be established.

To showcase the power of this new method in the synthesis of halogenated natural products, the reaction was also applied to a concise, gram-scale synthesis of (+)-bromochloromyrcene **14** (Scheme 8). As well as providing the first example of a catalytic, enantioselective alkene dihalogenation in total synthesis, the halogenation step itself comprises an impressive case of catalyst-controlled chemo-, site- and enantioselectivity.



Scheme 8. Enantioselective synthesis of (+)-bromochloromyrcene **14**. DMP = Dess–Martin periodinane.

In the same report, Burns et al. also disclosed preliminary results for the catalytic, enantioselective dichlorination and dibromination of allylic alcohols bearing only alkyl substitution on the olefin.[8] This stands in contrast to their earlier dibromination reaction (Scheme 5), for which only cinnamyl alcohol derivatives delivered high enantioselectivities.[15] Thus, allylic alcohol **15** is dichlorinated in 95:5 er using *tert*-butyl hypochlorite (*t*-BuOCl) as the Cl^+ source (i.e., replacing NBS in their chlorobromination protocol), and diastereomeric alkenes **16** and **17** are dibrominated in 96:4 and 97.5:2.5 er, respectively, using $BrTi(O\textit{i}\text{-}Pr)_3$ in place of $ClTi(O\textit{i}\text{-}Pr)_3$ (Scheme 9).



Scheme 9. Preliminary examples of catalytic, enantioselective alkene dichlorination and dibromination.

Notably, these results constitute the first examples of highly enantioselective dihalogenation of non-conjugated (i.e., non-aryl-substituted) alkenes, although these substrates do still impose an electronic bias on the site selectivity of the nucleophilic halide addition by virtue of their alkene substitution patterns, and/or the inductive effect of the hydroxy group. Thus, at the time of writing, there are no examples of a catalytic, highly enantioselective dihalogenation of electronically-unbiased alkenes, or those that lack catalyst directing groups. In this Review, the selectivity issues underpinning this "grand challenge" of asymmetric synthesis are analyzed and potential solutions are offered to the problems identified.

In passing it should be mentioned that other reports of enantioselective dihalogenations can also be found in the literature. However, in several cases the enantioselectivities are not unambiguously determined, and only optical rotations for the dihalide products are provided, typically without comparison to the specific rotations of the enantiopure substances (which were unknown).[18,19] In another (highly cited) case, remarkable levels of enantioselectivity have been claimed (up to 98.5:1.5 er) for an enantioselective dibromination of alkenes catalyzed by palladium complexes.[20] However, this method has never been applied or reproduced,[21] and the Supporting Information is limited and incomplete (e.g., missing optical rotations for several products, ambiguity surrounding the palladium precatalysts employed). For these reasons, these particular contributions will not be discussed further.

In the remainder of this Review, various selectivity challenges will be examined that must be overcome to effect successful catalytic, enantioselective dihalogenations of alkenes, and several mechanistically distinct pathways by which such processes may occur are proposed. Additionally, a number of main group and transition metal halide reagents are presented that have been used to dihalogenate alkenes, and the available evidence regarding the mechanisms of these reactions is critically assessed. It is not the intention of this Review to provide a comprehensive overview of the dihalogenating agents currently available,[22] nor the additions of the molecular dihalogens themselves[23] (i.e., chlorine[24] or bromine),[25] but rather to focus on halogenating reagents that may provide opportunities for new catalytic (and potentially enantioselective) reactions. Because of the unique challenges specific to alkene difluorination reactions[26] and the thermodynamic disadvantage and reversibility of alkene diiodinations,[23] only dichlorinations and dibrominations will be considered. Halogenation reactions comprising the addition of two different halogen atoms across a C=C bond are also beyond the scope of this Review.

2. Challenges for Stereoselective Catalysis

2.1. Preamble: Dihalogenating Reagents

Much of the activity in (non-industrial) halogenation chemistry has comprised the development of new reagents which are easier to handle than the molecular dihalogens, as well as offering differential reactivity to the latter (i.e., being either more reactive or more selective). Moreover, such reagents often allow precise control of stoichiometry, which is a particular advantage for chlorination, given the difficulties in dispensing accurate quantities of chlorine gas on a laboratory scale. For example, ammonium polyhalide salts, of general formula $[R_4N]^+[(X_2)_nX]^-$, incorporate one or more equivalents of molecular dihalogen and are (typically) solid, crystalline compounds that have proven popular for alkene dihalogenation. For dibromination, pyridinium tribromide[27] and several other ammonium tribromide salts are commercially available and have enjoyed widespread use, although similar reagents for dichlorination—most notably Et_4NCl_3 (Mioskowski's reagent)[28]—are not available because of the slow release of Cl_2 on storage, and the laboratory synthesis of this compound requires the handling of elemental chlorine. Besides the use of "dihalogen carrier" reagents, another strategy is to generate molecular dihalogens (or their formal equivalent) in situ by the oxidation of halide sources with strong oxidants,[29] and this method is especially attractive for dichlorination. A large number of these protocols, summarized elsewhere,[29,30] have been developed for dibromination, although notably fewer are evident for dichlorination, including H_2O_2-HCl,[31] $KMnO_4$-Me_3SiCl-$BnEt_3NCl$,[32] and Oxone-NaCl.[33] As a complement to "halide oxidation" ($X^- \rightarrow X^+ + 2e^-$), the reverse process of "halenium reduction" ($X^+ + 2e^- \rightarrow X^-$) has also been employed, in which two equivalents of an X^+ reagent react with one equivalent of a suitable $2e^-$ reductant, generating X^- ions alongside the X^+ source (which may combine to give the molecular dihalogen).[34,35] Yoshimitsu's protocol for alkene dichlorination using a 2:1 NCS:PPh_3 reagent system (NCS = *N*-chlorosuccinimide), in which PPh_3 serves as the reducing agent, is a good example,[36] and several "organocatalytic" alkene dibrominations also fall into this category.[35]

However, none of the above reagents or reagent systems are well-suited for most *catalytic* dihalogenations (i.e., in which enantio- or diastereoselectivity is controlled), as all of these halogenating agents (e.g., dihalogens) exhibit a fast background rate of addition to alkenes.[37] An attractive alternative is to avoid molecular dihalogens altogether and employ either a combination of separate halenium (X^+) and halide (X^-) equivalents or a single dihalogen equivalent (SO_2Cl_2, $PhICl_2$, etc.) (Figure 2). Provided that these are sufficiently slow to react with the alkene substrate in the absence of a catalyst, then one has an ideal platform for catalytic dihalogenation. Alternative strategies to avoid background reactivity are outlined in Section 2.2.5, whereby only halide (X^-) ions or only halenium (X^+) sources are used as the source of halogen atoms, and the necessary X^+ or X^-

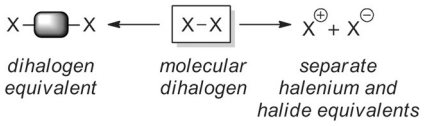
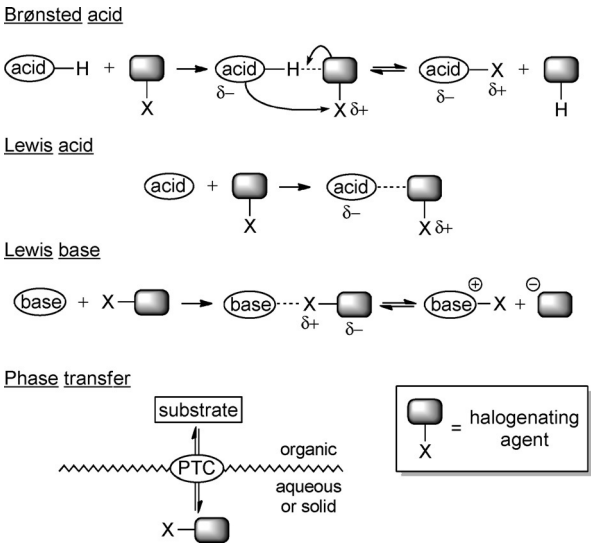


Figure 2. Strategies for avoiding the use of molecular dihalogens.

reaction partners are generated catalytically (by oxidation or reduction, respectively).

2.2. The Catalysis Problem

In our previous analysis of catalytic strategies to effect enantioselective halofunctionalizations of alkenes with oxygen-, nitrogen-, and carbon-centered nucleophiles, it was identified that most of the existing methods rely upon Brønsted acid, Lewis acid, or Lewis base catalysts to enhance the electrophilicity of an otherwise weakly reactive halenium ion (X^+) source.[4f] In this way, an uncatalyzed background reaction of the alkene with the halogenating agent can be minimized. Another distinct strategy is phase transfer catalysis, in which the alkene substrate and reactive halogenating agent are physically separated in different phases until brought into contact by the catalyst. All of these general catalysis strategies are summarized in Scheme 10.



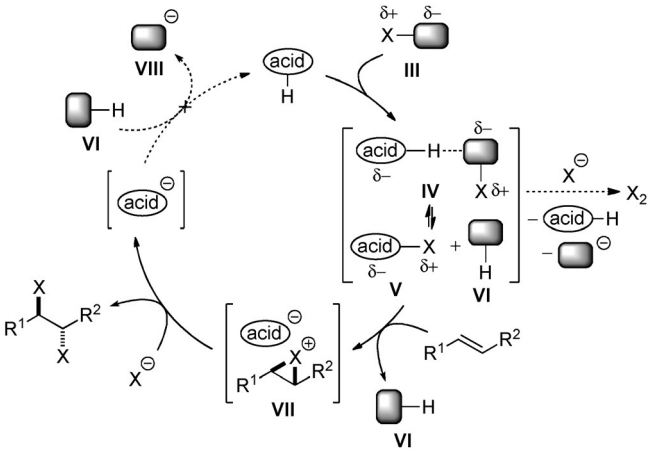
Scheme 10. General strategies for catalysis of halofunctionalization.

In this Review, these strategies will be reexamined in the context of alkene dihalogenation. An additional catalysis mode, termed "redox catalysis", will also be introduced, as this can offer conceptually and mechanistically distinct strategies for alkene dihalogenation (and perhaps halofunctionalization more broadly). It should be stressed that some of the catalytic cycles outlined in this section are currently only hypothetical for alkene dihalogenation, although known examples from the literature are highlighted where possible. The main objective is to provide the basic foundations on which to build new catalytic methods for alkene dihalogenation, and to preempt any obstacles that may arise in certain catalytic manifolds.

It should also be mentioned that several researchers report alkene dihalogenations in which the generation of X_2 (from X^+ equivalents), rather than the addition step to the alkene, is "catalyzed" (or perhaps just initiated).[35] Thus, any further reference to "catalytic" dihalogenations in this Review refers only to those reactions in which the alkene dihalogenation process itself is catalyzed, rather than the release of molecular dihalogen.

2.2.1. Brønsted Acid Catalysis

Brønsted acid catalysts may activate halenium ion (X^+) sources **III** either by protonation or by hydrogen-bonding (these being the limiting cases of a continuum), and this can be represented by the activated species **IV** (Scheme 11). Moreover, protonation of the X^+ equivalent (e.g., *N*-halo-

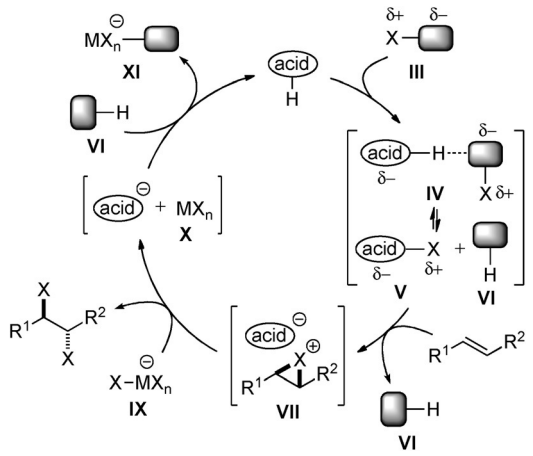


Scheme 11. A Brønsted acid-catalyzed alkene dihalogenation using separate X^+ and X^- sources.

imide) may lead to halenium ion transfer to the conjugate base of the Brønsted acid, generating an alternative reactive electrophile **V**. Electrophilic attack of either **IV** or **V** on the alkene substrate may generate a haliranium ion intermediate **VII**, that can be attacked by a halide ion to generate the vicinal dihalide product. However, haliranium ions need not necessarily be intermediates, and other possibilities include direct attack of halide ion on alkene-"halogen" π-complexes, or the intermediacy of species featuring covalent bonds to metal or main group elements (see Sections 4 and 5). An undesired side reaction, which must be avoided in this mechanistic manifold, is the reaction of species **IV** or **V** with halide ion to release the molecular dihalogen (X_2), which could contribute to an uncatalyzed background dihalogenation. However, the requirement for halide ion trapping of the haliranium ion presents a unique problem not encountered with neutral (protonated) trapping nucleophiles such as alcohols, carboxylic acids or amides. Specifically, the latter nucleophiles release a proton (H^+) following nucleophilic attack on the haliranium ion, and this H^+ ion serves to turnover the Brønsted acid catalyst. An anionic halide nucleophile (X^-) on the other hand carries no such acidic proton, and the only proton source available is the conjugate acid **VI** of the leaving group **VIII** from the X^+ reagent **III**. As the pK_a of **VI** will be significantly higher than that of the Brønsted acid catalyst, turnover will not proceed, and the

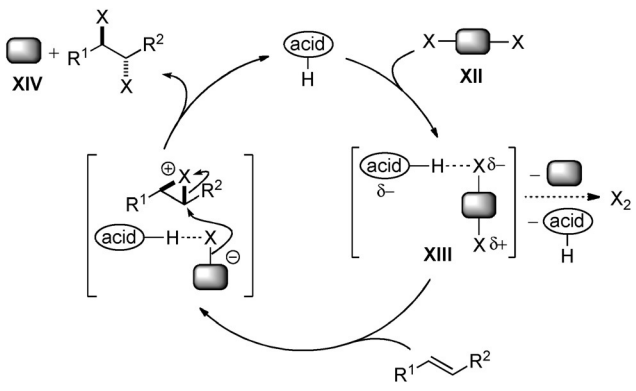
anionic leaving group **VIII** of the halenium source **III** will have deactivated the catalyst. Unfortunately, simply using the corresponding hydrohalic acid (HX) as a nucleophile is unlikely to resolve this issue, as the halogen atom is not nucleophilic in this form and the strongly acidic HX would promote a racemic Brønsted acid-catalyzed pathway.

A possible solution to this turnover problem may be to use a complex anion **IX** of the halide (e.g., BCl_4^-, $SbCl_6^-$) as the nucleophile source—one which is sufficiently nucleophilic to trap the haliranium ion intermediate **VII**[11,38] and then afterward release a Lewis acid **X** to sequester the reagent-derived anion as a complex **XI** (Scheme 12). A potential danger, however, is that the Lewis acid **X** may itself catalyze a racemic background reaction if it is not rapidly "quenched" by complexation with **VI**.



Scheme 12. A Brønsted acid-catalyzed alkene dihalogenation using an X^+ reagent **III** in combination with a complex anion of the halide as an X^- source.

Notably, the same turnover problem does not arise if one employs a dihalogen equivalent **XII**, because in this case only a neutral by-product **XIV** is generated that cannot sequester the proton of the Brønsted acid (Scheme 13). The mode of activation could involve hydrogen-bonding polarization of **XII** via a complex such as **XIII**, as exemplified by a (racemic)

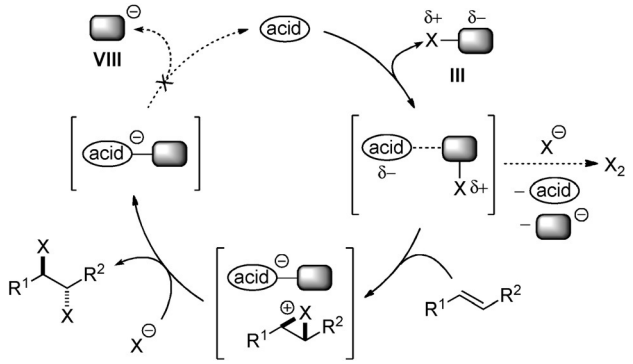


Scheme 13. A Brønsted acid-catalyzed alkene dihalogenation using a dihalogen equivalent **XII** as a single reagent.

Brønsted acid-catalyzed alkene dichlorination with $PhICl_2$ (see Section 4.5.1).[39] Note that in this case there is no longer an exogenous source of halide ions required (i.e., the halide is incorporated into the reagent **XII**), so that any undesired molecular dihalogen formation would result from the decomposition of complex **XIII**.

2.2.2. Lewis Acid Catalysis

Lewis acid catalysis, which has been invoked in several catalytic, enantioselective halocyclizations,[40] provides another means of activating halogenating agents that is conceptually very similar to Brønsted acid catalysts (see above). As was the case above, the use of separate halenium (X^+) and halide (X^-) equivalents leads to a problem with the catalytic turnover resulting from deactivation of the acidic catalyst by anionic leaving group **VIII** of the halenium ion source **III** (Scheme 14). As for Brønsted acid catalysis, this problem could potentially be solved through the use of a complex anion **IX** of the halide (e.g., BCl_4^-, $SbCl_6^-$) as the nucleophile source, releasing a stoichiometric amount of a Lewis acid by-product **X** to facilitate turnover (see above).

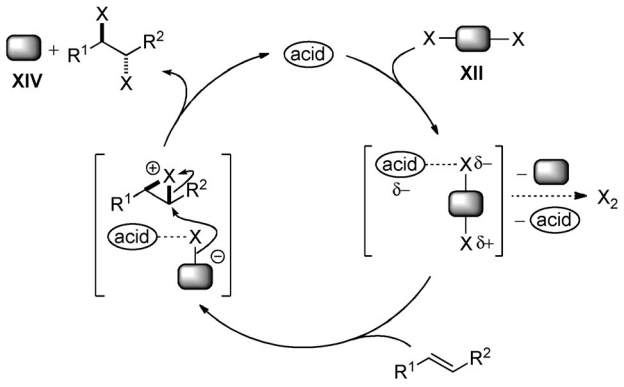


Scheme 14. A Lewis acid-catalyzed alkene dihalogenation using separate X^+ and X^- sources.

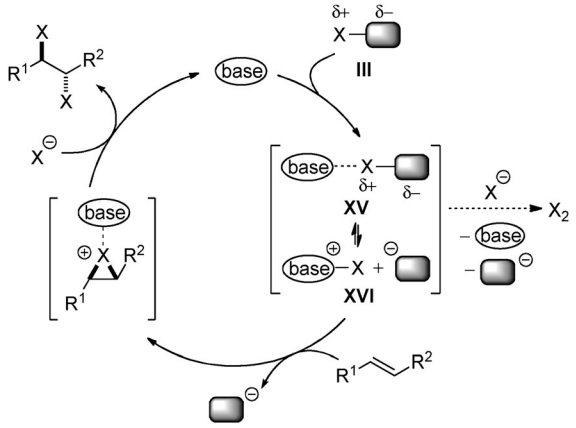
As for Brønsted acid catalysis (see above), no turnover problem exists if a dihalogen equivalent **XII** is employed, as the neutral by-product **XIV** does not strongly bind the Lewis acid catalyst (Scheme 15). Although no clear-cut examples are on record for alkene dihalogenation, Lewis acid catalysts have been used to effect the ionic chlorination of aromatics with SO_2Cl_2 via X–S–X bond polarization.[41]

2.2.3. Lewis Base Catalysis

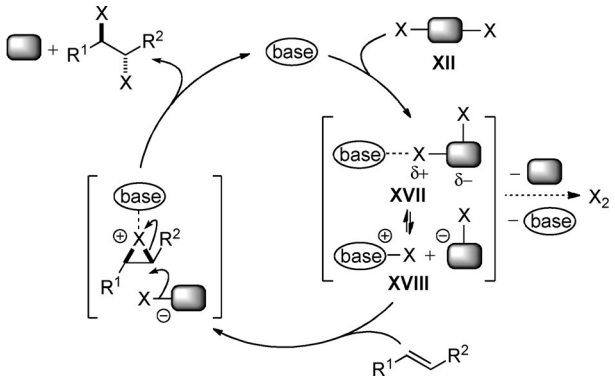
Following the general mechanism for Lewis base activation of Lewis acids,[13] a Lewis base catalyst may activate a halenium source **III** by forming a polarized complex **XV**, possibly in equilibrium with a highly reactive ion pair **XVI**, as the active halenium transfer agent. As always, an undesired reaction of **XV** or **XVI** with halide ion could potentially generate the molecular dihalogen (X_2) (Scheme 16).



Scheme 15. A Lewis acid-catalyzed alkene dihalogenation using a dihalogen equivalent **XII** as a single reagent.



Scheme 16. A Lewis base-catalyzed alkene dihalogenation using separate X^+ and X^- sources.



Scheme 17. A Lewis base-catalyzed alkene dihalogenation using a dihalogen equivalent **XII** as a single reagent.

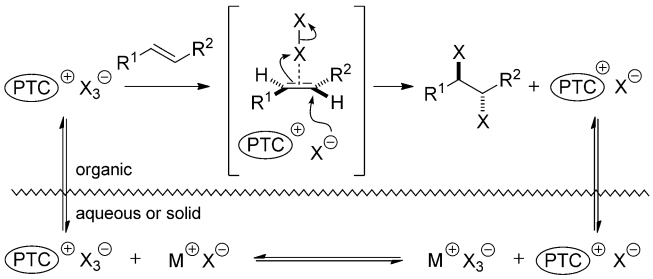
A similar catalytic cycle can be constructed for a Lewis base-catalyzed alkene dihalogenation process using a dihalogen equivalent **XII** (Scheme 17). Although complex **XVII** and ion pair **XVIII** are depicted as the activated species (by analogy to Scheme 16), it should be borne in mind that the Lewis base might also interact at an electrophilic site other than the halogen atom (e.g., a metal or main group element center, represented here by the shaded block).

An example of the latter type of Lewis base-catalyzed process is Nicolaou and co-worker's enantioselective dichlorination reaction, in which the dihalogen equivalent 4-Ph-(C_6H_4)ICl_2 is thought to be activated by substitution of a chloride ligand on the iodine(III) center with a neutral tertiary amine donor [i.e., a quinuclidine nitrogen on $(DHQ)_2PHAL$], conferring a positive charge to the reagent which increases its electrophilicity (Figure 1).[12] In contrast, Burns et al. have proposed a rather different role for the Lewis base (pre)catalyst (i.e., diol **11**) in their enantioselective alkene dibromination protocol, suggesting that it may serve to accelerate the nucleophilic trapping of the bromiranium ion intermediate with (Ti-bound) bromide ion, rather than the formation of the bromiranium ion itself (Scheme 5).[15] If this were true, it would constitute "nucleophile activation" as opposed to "electrophile activation" (as depicted in Scheme 6), which is another well-recognized facet of Lewis base catalysis.[13] However, this mechanistic proposal is somewhat speculative, and an "electrophile activation" mode of catalysis, involving interaction of the diol moiety **11** with the Ti center to enhance its Lewis acidity (which would indirectly activate the Ti-bound halogen electrophile), could not be discounted.

2.2.4. *Phase Transfer Catalysis*

Another potential means of catalyzing alkene dihalogenation reactions is phase transfer (PT) catalysis, whereby a catalyst serves to chaperone a charged reactant or intermediate across a phase boundary (usually liquid–liquid or solid–liquid).[42] If the catalyst-derived counterion present in the enantiodetermining step of the reaction is chiral and non-racemic, it may potentially impart enantioselectivity in this step by noncovalent interactions with one or both of the reacting partners.[42] One attractive strategy may be to capitalize on the ability of molecular dihalogens such as Br_2 and Cl_2 to reversibly form trihalide anions, X_3^-, with their corresponding halide salts.[43] In the presence of a PT catalyst featuring a chiral, lipophilic cation (e.g., NR_4^+, PR_4^+), an X_3^- anion could be transported from an aqueous (or solid) phase environment to the organic phase, at which point it could dihalogenate an alkene substrate and generate a halide ion as the by-product, which would return to the aqueous (or solid) phase along with the lipophilic cation. In non-polar reaction media, the dibromination of alkenes with Br_3^- anions (or Br_2 in the presence of at least an equimolar amount of Br^- ions) is thought to occur by rate- and product-determining attack of a Br^- ion on a 1:1 alkene-Br_2 π-complex.[44] As a counter cation must necessarily be closely associated with the Br^- ion during this step, the prospects for asymmetric induction with a chiral, non-racemic counter cation are promising, and similar considerations could apply to dichlorinations with Cl_3^- sources (Scheme 18).

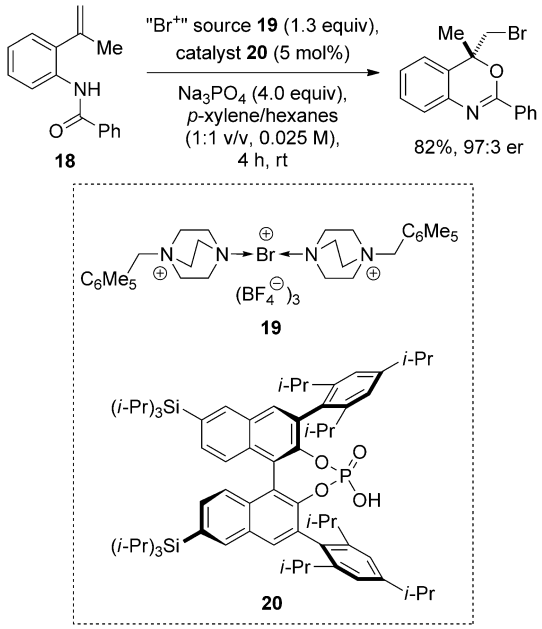
It should be noted that an enantioselective, phase transfer-catalyzed alkene dichlorination has already been claimed,[18] but as the product enantioselectivities were not actually



Scheme 18. Cationic phase transfer-catalyzed alkene dihalogenation.

measured (i.e., only optical rotations were provided), the feasibility of this approach for achieving meaningful levels of asymmetric induction has yet to be convincingly demonstrated.

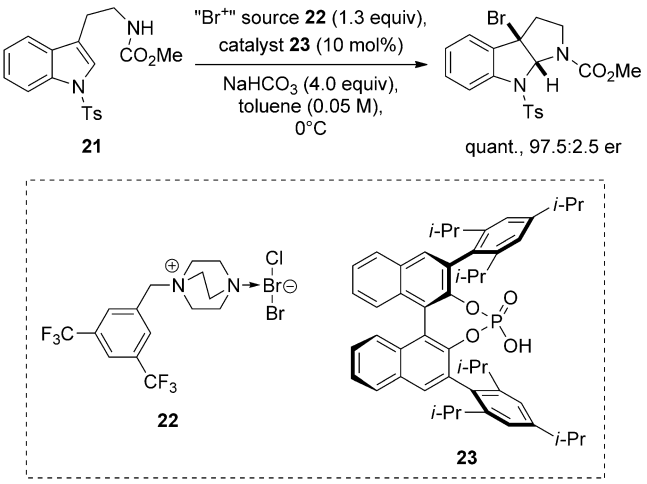
In recent years, catalytic, enantioselective halofunctionalizations based on the concept of anionic phase transfer catalysis have begun to appear,[45] and although initially applied solely to fluorination processes,[46] this concept has recently been extended to bromo- and iodocyclizations by Toste and co-workers.[47] By employing insoluble, DABCO-derived, tricationic "Br^+" salts of the form **19**, in combination with a chiral, lipophilic phosphoric acid **20** (as a precursor to



Scheme 19. Toste's enantioselective halocyclization via chiral anion phase transfer catalysis.

the chiral anion PT catalyst), highly enantioselective bromocyclizations of amido alkenes such as **18** could be achieved by solid-liquid phase transfer catalysis (Scheme 19). Similar results are obtained in iodocyclizations using an "I^+" salt analogous to **19**.

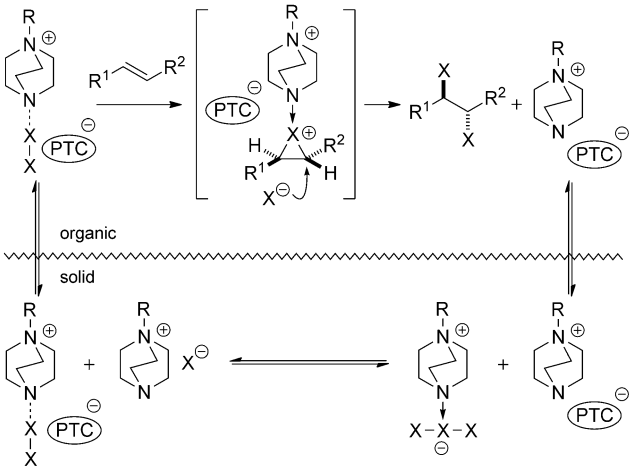
Subsequently, Ma and co-workers have shown that highly enantioselective bromocyclizations of tryptamine derivatives



Scheme 20. Ma's enantioselective bromocyclization via chiral anion phase transfer catalysis.

such as **21** could be achieved with the alternative "monocationic" "Br^+" salt **22** which, in this reaction at least, gives more reproducible results than the "tricationic" "Br^+" salts (e.g., **19**) developed by Toste (Scheme 20).[48] Later work by the same authors on a closely related bromocyclization reveals that mixtures of "monocationic" and "tricationic" DABCO-derived "Br^+" salts closely related to **22** and **19** gives optimal performance.[49]

Taking the "monocationic", DABCO-derived "Br^+" salts of type **22** for illustration, one could envisage a solid-liquid phase transfer catalysis process in which a chiral anion PT catalyst transports a monocationic, amine-bound X_2 complex into the organic phase, where it may undergo reaction with an alkene substrate (Scheme 21). If the Lewis basic nitrogen of the amine remains associated with the electrophilic bromine atom during the alkene addition step,[50] enantiotopic face selection might occur by virtue of the chiral counter anion. Such a process is speculative, however, and it remains to be seen whether an anionic phase transfer-catalyzed alkene

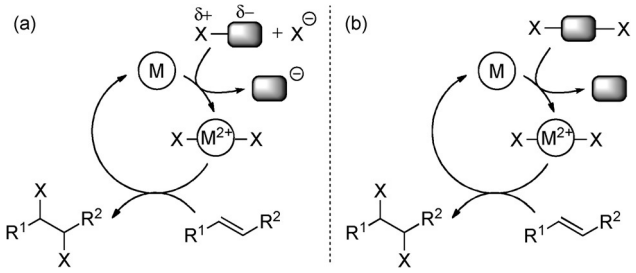


Scheme 21. Anionic phase transfer-catalyzed alkene dihalogenation.

dihalogenation (enantioselective or not) can be reduced to practice.

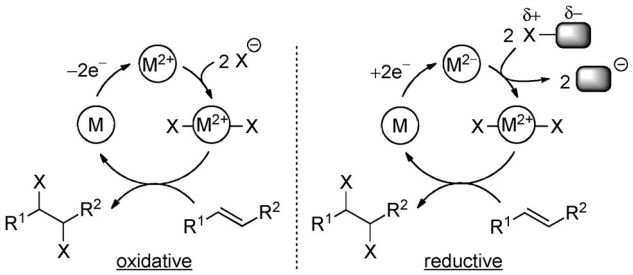
2.2.5. Redox Catalysis

So far, all of the catalytic activation modes discussed have featured catalysts which undergo no formal change in oxidation state during the catalytic cycle. However, catalytic cycles are also possible with redox-active catalysts, based on transition metal or main group element centers, in which catalyst oxidation state changes do occur. A popular analogy might be the cross-coupling of a carbon nucleophile with a carbon electrophile under the agency of a transition metal catalyst—a transformation which is isohypsic but nevertheless involves both oxidation and reduction events at the catalytic metal center. This type of catalysis, which has previously been classified under the rather broad banner of "group-transfer catalysis",[51] will be referred to as "redox catalysis" in this Review. Simple schematics of "isohypsic" alkene dihalogenations occurring under redox catalysis are shown in Scheme 22, both for: a) separate halenium (X^+) and halide (X^-) equivalents and for b) a single dihalogen equivalent. Although a two-electron oxidation state change at the "metal" is implied, a bimetallic mechanism involving one-electron changes at two "metals" could also be operative in principle. Moreover, this classification is silent regarding the mechanism of halogen transfer to the olefin from the "metal" halide, which could be polar, radical or concerted in nature. Clearly the involvement of metal or main group elements opens up new mechanistic possibilities beyond the typical haliranium ion (or alkene-"halogen" π-complex) intermediates, and this particular aspect is explored in detail in Sections 4 and 5.



Scheme 22. "Isohypsic" redox catalysis for alkene dihalogenation. M = transition metal or main group element.

Keeping the analogy with metal-catalyzed cross-coupling reactions, one can also envisage "oxidative" or "reductive" variants of redox-catalyzed alkene dihalogenation reactions (Scheme 23). In the "oxidative" case, two equivalents of a halide source (X^-) are employed in conjunction with a redox-active catalyst able to formally invert the reactivity of one X^- ion (i.e., generate a formal X^+ source) and an external (non-halogenating) oxidant to reoxidize the catalyst. An obvious requirement is that the reduced form of the catalyst is oxidized in preference to the stoichiometric halide source, in order to avoid the in situ generation of halogen electrophiles with high background reactivity (e.g., the molecular dihalogen). An example of an "oxidative" catalytic dihalogenation is Denmark and co-worker's *syn*-stereospecific dichlorination of alkenes, which relies upon an *N*-fluoropyridinium reagent as the stoichiometric re-oxidant (see Section 4.4.2).[52] The third strategy of "reductive" dihalogenation is the polar opposite of the "oxidative" approach: two equivalents of a halenium source (X^+) are employed in conjunction with a redox-active catalyst and an external reductant to regenerate the active catalyst. Similarly, the oxidized form of the catalyst must be reduced in preference to the X^+ source. At the time of writing, there are no examples of this strategy yet reported for catalytic dihalogenation, providing an exciting opportunity for reaction invention.

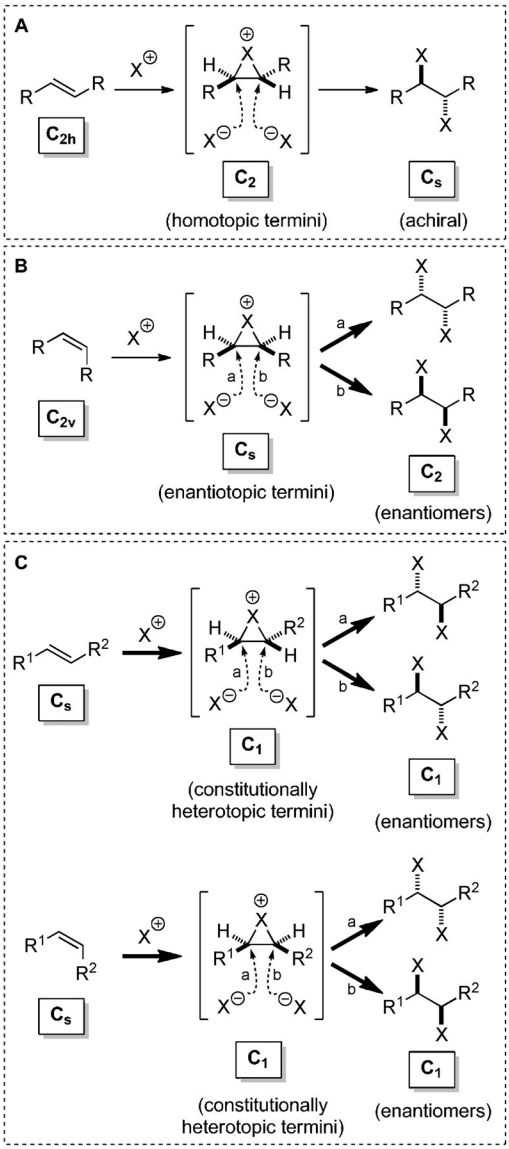


Scheme 23. "Oxidative" and "reductive" redox catalysis for alkene dihalogenation (note that all oxidation states are relative rather than absolute). M = transition metal or main group element.

2.3. The Enantioselectivity Problem

For alkene dihalogenation reactions proceeding by a two stage mechanism comprising haliranium ion (or alkene-dihalogen π-complex) intermediate formation and subsequent nucleophilic attack of halide ion, the absolute configuration of the vicinal dihalide product can potentially be decided at either, or both, of these stages. For the sake of simplicity, the following discussion will focus on haliranium ions as intermediates (setting aside the complication of "open" β-halo carbocations), although much of what follows is equally applicable to reactions involving direct nucleophilic attack on alkene-dihalogen π-complexes.[44]

The first line of analysis is to consider the symmetry properties of the alkene, which will in turn dictate the stereochemical features of the overall addition process (Scheme 24). For alkenes within the C_{2h} point group, such as symmetrical, (*E*)-configured olefins, the haliranium ion is chiral but the dihalide products, arising from attack of a halide ion at one of two homotopic carbon termini, are necessarily achiral (category **A**). However, for a symmetrical, (*Z*)-alkene (i.e., C_{2v} point group) the carbon termini within the (achiral) haliranium ion are enantiotopic, and so the enantiomer of the dihalide product formed depends solely on which of these two carbon atoms is attacked by the halide nucleophile (category **B**). In other words, nucleophilic trapping rather than haliranium ion formation is enantiodetermining for this class of alkene. In the case of unsymmetrical alkenes (C_s symmetry), of either (*E*)- or (*Z*)-configuration, the situation is more complicated: the haliranium ion intermediates are chiral and



Scheme 24. Symmetry-based analysis of alkene dihalogenations (*via* haliranium ions), with enantiodetermining steps highlighted by bold arrows. X = halogen atom.

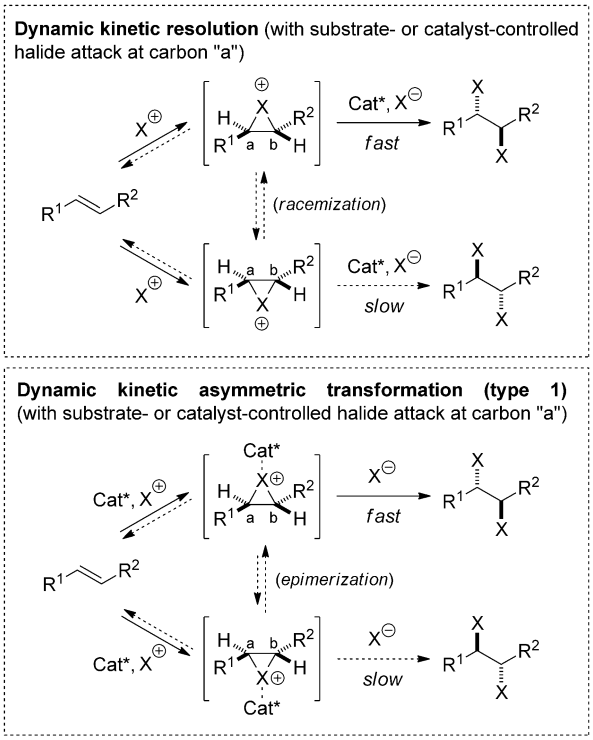
the two carbon termini are now constitutionally heterotopic (category **C**). In many alkene addition reactions via such chiral -iranium ions, the trapping nucleophile is different from the bridging group of the cyclic -onium species, and so the products of attack at the two different carbon termini are constitutional isomers. In such a scenario, the enantiomeric composition of both products is determined solely by the extent of enantiofacial discrimination in the -iranium ion formation step (assuming that no chiral catalyst-induced kinetic resolution occurs during trapping of the -iranium ions, which could lead to unequal enantiomeric ratios for the two constitutional isomers).[53] However, in the case of alkene dihalogenation the two halogen atoms are indistinguishable, and the products of attack at the two different carbon termini are now related as enantiomers. Consequently, if the formation of a haliranium ion is irreversible, both its formation and nucleophilic trapping will determine the enantiomeric composition of the products. Accordingly, both of these processes must be highly selective to ensure significant enantioenrichment in the vicinal dihalide product.

For alkenes falling into category **C**, situations may arise in which only one of the two stages, rather than both, is enantiodetermining, and this can significantly improve the prospects of achieving highly enantioselective reactions. These special cases are described in detail below, starting with enantiodetermining nucleophilic trapping (Section 2.3.1) and followed by enantiodetermining haliranium ion formation (Section 2.3.2).

2.3.1. *Enantiodetermining Nucleophilic Trapping*

If haliranium ion formation is fast and reversible,[54] or if the chiral haliranium ions are able to rapidly interconvert (e.g., via alkene-to-alkene transfer, see below), then the nucleophilic trapping event becomes enantiodetermining. To selectively form one enantiomer of the dihalide product, the chiral catalyst must kinetically resolve the chiral haliranium ions, such that one enantiomer undergoes nucleophilic trapping faster than the other. Additionally, the catalyst must also control which of the two carbon atoms of the haliranium ion undergoes nucleophilic attack by halide ion, unless a substrate-controlled bias for the site of attack is already present (e.g., at a benzylic carbon).

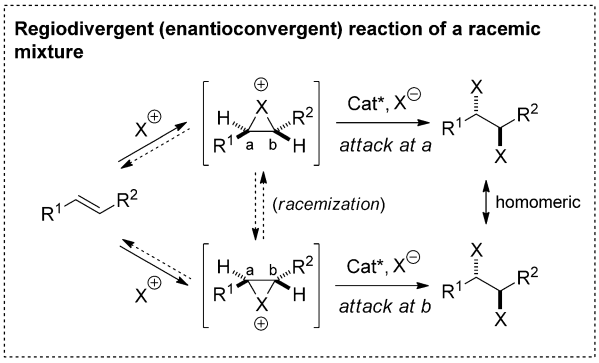
Depending on whether the chiral haliranium ion intermediates are associated with the chiral catalyst during their interconversion, the situation is either a dynamic kinetic resolution (DKR) or a (Type 1) dynamic kinetic asymmetric transformation (DyKAT) [Scheme 25, arbitrarily depicting an



Scheme 25. Enantiodetermining nucleophilic attack of halide ion by kinetic resolution of haliranium ions. Cat = catalyst, X = halogen atom.

(*E*)-alkene].[16] Although challenging to distinguish experimentally, the distinction is important because the relative rates of nucleophilic trapping (and hence the enantioselectivity) depend not only on the rate constant ratio (k_A/k_B), but also on the concentrations of the stereoisomeric haliranium ions ([I_A] and [I_B]). In a DKR manifold, the haliranium ions are enantiomeric and their concentrations are equal (assuming racemization is much faster than trapping), and so a high enantioselectivity rests solely on a high k_A/k_B ratio (ideally >20). For a Type 1 DyKAT however, the haliranium ions are diastereomeric by virtue of their association with the chiral catalyst, and their concentrations can be different. In principle, a relatively low k_A/k_B ratio can be augmented if $[I_A]>[I_B]$ (e.g., a k_A/k_B value of 5 in combination with $[I_A]/[I_B]=4$ would still give 20:1 er in favor of A). For these reasons, it can be beneficial to design chiral catalysts able to associate with (stereomutating) haliranium ion intermediates,[4f] encouraging a DyKAT as opposed to a DKR process. One such tactic is to employ alkene substrates bearing catalyst-coordinating functionality,[4f] as typified by Nicolaou's[12] and Burns's[8,15] use of allylic alcohols in their respective dihalogenation protocols (see Section 1). Another possible strategy, recently showcased for enantioselective selenocyclizations (*via* seleniranium ion intermediates) is to use a chiral anion-binding catalyst, which essentially partners the -iranium ion intermediate with a chiral counter anion.[55]

At least conceptually, an RRRM process (regiodivergent reaction of a racemic mixture) is possible if the catalyst can induce nucleophilic attack at opposite termini for each haliranium ion enantiomer, although such processes are difficult to rationally design [Scheme 26, arbitrarily depicting



Scheme 26. Enantiodetermining nucleophilic attack of halide ion by regiodivergent (enantioconvergent) reaction of a racemic mixture. Cat = catalyst, X = halogen atom.

an (*E*)-alkene].[56] Rather unusually, an RRRM process in the current context would generate the same enantiomer of dihalide product in both cases, as opposed to the constitutional isomers more typical of RRRM reactions. Consequently, such a process—if at all possible—would constitute a transformation that is mechanistically an RRRM but nominally an enantioconvergent reaction.

Although the above discussion has centered on haliranium ions as intermediates, a similar analysis may conceivably apply in dihalogenation reactions involving direct halide ion attack on (reversibly formed) alkene-dihalogen π-complexes.[44]

2.3.2. Enantiodetermining Haliranium Ion Formation

For haliranium ion formation to be enantiodetermining, two conditions must be met: 1) the halenium ion transfer to the olefin from the "X^+" source must be irreversible, and 2) the haliranium ion thus produced must be configurationally stable prior to its nucleophilic trapping (i.e., it must not racemize). If either one of these criteria are not fulfilled, then the decision as to which enantiomer of the dihalide product is formed will occur at the (subsequent) nucleophilic trapping stage (see Section 2.3.1).

From the earlier symmetry-based analysis (Scheme 25), it is also clear that *both* haliranium ion formation and nucleophilic trapping with halide ion can be enantiodetermining. Even if a single enantiomer of haliranium ion is formed, the enantioselectivity can be eroded if nucleophilic trapping occurs without high site selectivity. Thus, for haliranium ion formation *alone* to be enantiodetermining, the nucleophilic attack of the halide ion must be completely biased toward one of the two carbon centers of the haliranium ion intermediate. In practice, this is most easily achieved by substrate control rather than catalyst control, and electronically-biased olefins such as aryl-conjugated alkenes will inherently direct halide attack toward the benzylic carbon center, for example.

The following analysis will not be concerned with the factors that lead to highly enantioselective haliranium ion formation (as this is largely a question of catalyst design on a case-by-case basis), but rather the general factors that mitigate against obtaining high enantioselectivity (other than the operation of a racemic background reaction, see above). A clear difficulty in enantioselective halenium ion transfer to an alkene is the distance between the alkene substituents and the catalyst which is covalently associated with the halogen atom. This arrangement arises because of the stereoelectronic requirement for the alkene to approach the σ* orbital of the X^+–Cat* bond. A similar problem is encountered in gold catalysis because of the linear coordination geometry of Au^I complexes, although chiral counter anions or specially designed chiral ligands have begun to provide solutions.[57] By way of contrast, electrophilic species offering π* orbitals as a "docking" point for the catalyst (e.g., OsO_4) enable more diverse geometries and a better stereochemical communication between the catalyst and the alkene (Figure 3).

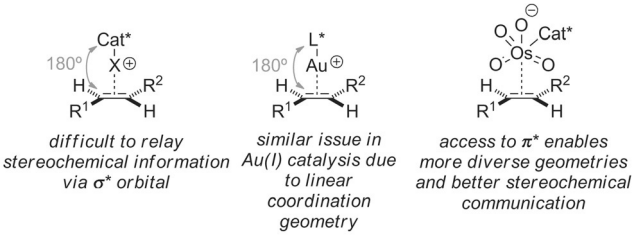
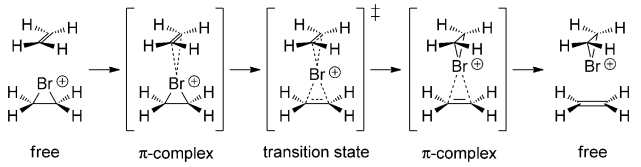


Figure 3. Challenges in stereochemical communication between the catalyst and the alkene substrate. Cat = catalyst, X = halogen atom.

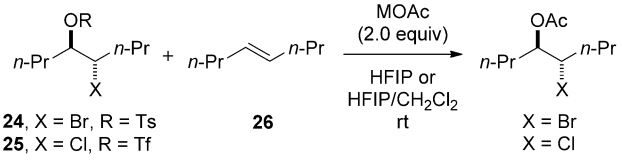
Even if the haliranium ion can be formed with high enantioselectivity, intermolecular halenium ion transfer from one alkene to another can lead to rapid racemization, unless the nucleophilic trapping event is kinetically more competitive (Scheme 27). The occurrence of rapid, degenerate



Scheme 27. Alkene-to-alkene transfer illustrated for ethylene and its corresponding bromiranium ion.

alkene-to-alkene halenium ion transfer processes was first demonstrated by Brown and co-workers, who studied adamantylidene adamantane and its corresponding (isolable) bromiranium or iodiranium ions.[25d,58] Computational studies support the notion that this process occurs via a low barrier, associative displacement at the halogen.[58a,59] Related alkene-to-alkene transfer processes have also been identified for thiiranium and seleniranium ions, similarly complicating the enantioselective additions of chalcogen electrophiles onto alkenes.[60]

The operation of alkene-to-alkene transfer as a racemization mechanism under catalytically relevant conditions has been probed by Denmark and co-workers.[61] Acetolysis experiments showed that the chiral bromiranium ion derived from enantioenriched bromo tosylate **24** can be captured with high enantiospecificity in the absence of alkenes.[62] However, the inclusion of (*E*)-4-octene **26** as an additive severely eroded the selectivity (Scheme 28). The extent of erosion



X	M	**26**, Equiv	es (%)
Br	Na	0.0	100
Br	Na	1.0	26
Br	*n*-Bu_4N	1.0	81
Cl	*n*-Bu_4N	1.0	100

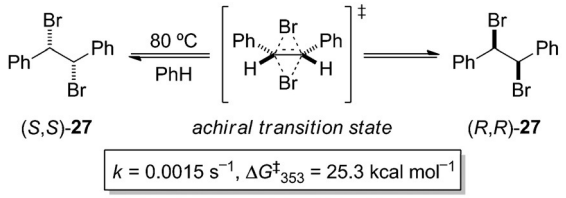
Scheme 28. Erosion of enantiospecificity in acetolysis from alkene-to-alkene transfer. HFIP = hexafluoroisopropanol, Tf = trifluoromethanesulfonyl, Ts = 4-toluenesulfonyl, $es = (ee_{product}/ee_{starting\ material}) \times 100\%$.

depends on the concentrations of the alkene and the nucleophile, as well as the identity of the counterion. Under similar reaction conditions, the analogous chloriranium ion from **25** is trapped with complete enantiospecificity, even in the presence of (*E*)-4-octene **26**, implying that alkene-to-alkene transfer is inherently less facile with chloriranium ions.

As alluded to in Section 2.3.1, fast racemization of chiral haliranium ions by alkene-to-alkene transfer is not necessarily an impediment to obtaining high enantioselectivities. In fact, it can actually be an advantage in cases for which the nucleophilic trapping step is enantiodetermining, as a concentration build up of the "undesired" (i.e., slower reacting) haliranium ion is avoided during the kinetic resolution process.

2.4. A Product Racemization Problem?

A less obvious source of imperfect enantioselectivity in alkene dihalogenation is that potentially arising from (partial) racemization of the vicinal dihalide products via a Type 1 dyotropic rearrangement.[63] This process, first observed as the mutarotation of 5α,6β-dibromocholestane (the dibromination product of cholest-5-ene) by Grob and Winstein in 1952,[64] is ascribed to a concerted pericyclic process in which the two halogen atoms migrate simultaneously and intramolecularly, with inversion of configuration at both carbon centers. In the first example of the racemization of an enantiopure, acyclic vicinal dibromide via a dyotropic rearrangement, Braddock, Schleyer and co-workers demonstrated that (*R*,*R*)- and (*S*,*S*)-1,2-dibromo-1,2-diphenylethane **27** racemize stereospecifically in refluxing benzene, without any crossover to the *meso*-diastereomer (Scheme 29).[65]



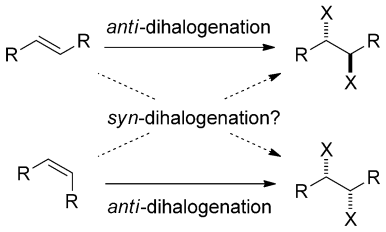
Scheme 29. Racemization of an enantioenriched, acyclic vicinal dibromide via a Type 1 dyotropic rearrangement.

Although the elevated temperatures required for such dyotropic racemizations are not likely to render this a cause for concern under the conditions of an enantioselective dihalogenation process, strong heating of an enantioenriched vicinal dihalide post reaction (as during a hot recrystallization or drying process) should be carried out with caution. Particularly troubling is an observation that the equilibration of 1,2-dibromo-3-*tert*-butylcyclohexane diastereomers has been found to occur at the temperature of the injection block of a gas chromatograph[66]—something that current practitioners should be aware of when relying upon chiral stationary phase GC methods to assess enantiomeric ratios!

2.5. The Diastereocontrol Problem

Unrelated to enantioselectivity, but nevertheless a challenging problem in stereoselective alkene dihalogenation, is the issue of control over the relative (or "simple") diastereoselectivity of vicinal dihalide formation. As reactions pro-

ceeding via halide ion attack upon haliranium ion or alkene-dihalogen π complexes are mechanistically constrained to be *anti*-diastereospecific processes, access to diastereomeric dihalide products typically necessitates inversion of the relative configuration of the alkene starting material. For example, an *anti*-dihalogenation of a (*Z*)-alkene would furnish the same diastereomer as a *syn*-dihalogenation of the (*E*)-alkene (Scheme 30). However, the option of diastereodivergent dihalogenation from a single alkene geometry is clearly preferable and, at any rate, the (*E*)-isomers of cyclic alkenes are inaccessible for ring sizes below eight. Although Denmark, Cresswell and Eey have recently achieved the first catalytic, *syn*-stereospecific dichlorination of alkenes (see Section 4.4.2),[52] an enantioselective variant of this reaction, as well as an analogous *syn*-dibromination process, remain elusive.[67]



Scheme 30. Correlation between alkene geometry and vicinal dihalide relative configuration for *anti*- and *syn*-selective dihalogenations.

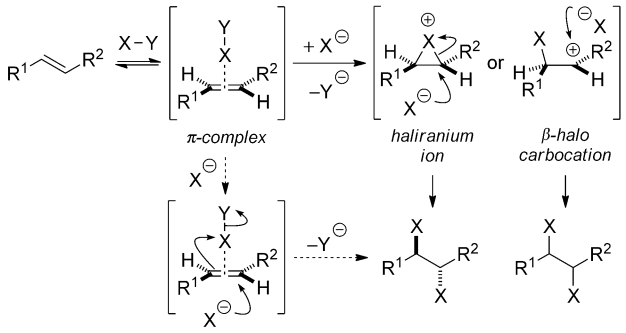
3. Mechanistic Classification of Alkene Dihalogenations

As should now be clear from the preceding discussion, dihalogenation reactions proceeding via halide ion attack upon haliranium ion or alkene-dihalogen π-complex intermediates present numerous challenges in terms of controlling the absolute configuration of the vicinal dihalide products. These include: 1) control of regioselectivity in the nucleophilic trapping with halide ion, 2) difficulties in transmitting stereochemical influence from a catalyst covalently bound to the halogen atom, and 3) potential for alkene-to-alkene halenium ion transfer processes causing racemization of enantioenriched haliranium ions. Though a separate issue, the control of relative configuration (i.e., relative diastereoselectivity) is also limited, as the reactions are stereoelectronically mandated to deliver *anti*-dihalogenated products, with no general means of overturning this selectivity.

In this Section, a variety of alternative mechanistic scenarios, previously suggested to be operative for main group element or metal-based halogenating reagents, are presented that may offer conceptually distinct strategies for stereoselective alkene dihalogenation. It must be emphasized, however, that a number of these mechanistic proposals are speculative, and some of them lack rigorous experimental or theoretical support. This is clearly an issue that needs to be addressed before one can rationally utilize these types of halogenating agents in enantioselective dihalogenation protocols.

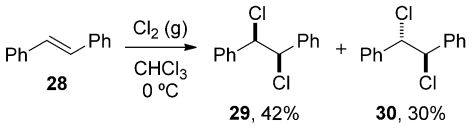
3.1. Type I Dihalogenation

Type I dihalogenations are defined as those reactions involving halide ion attack upon haliranium ions (or possibly alkene-"halogen" π-complexes)[44] as the only electrophilic intermediates [Scheme 31, arbitrarily depicting an (*E*)-alkene]. This is of course the prototypical mechanistic manifold for (ionic) dihalogenations of olefins with the molecular dihalogens, and is so far the only pathway which has been exploited/invoked in existing (highly) enantioselective dihalogenations (see Section 1). Of course, the simplistic depiction in Scheme 31 (with generalized halenium-transfer reagents of the form X–Y) belies the mechanistic complexity encountered in ionic additions of the molecular dihalogens themselves; the reactions of olefins with Br_2 in particular have been the subject of intense experimental and theoretical scrutiny since the late 1960s.[25] Although beyond the scope of this Review, the detailed mechanisms of such processes have received extensive coverage elsewhere,[23] including discussions of the role of the solvent and dihalogen/halide ion concentrations on the reaction pathway. The role of alkene-X_2 π-complexes as obligatory intermediates has also been recognized.[25c]



Scheme 31. A Type I dihalogenation process. Y = nucleofuge.

An additional complication in this type of dihalogenation is the extent of halogen atom bridging in the haliranium ion intermediate, and whether or not such intermediates are better formulated as β-halo carbocations.[68,69] As a generalization, cation-stabilizing substituents (e.g., *gem*-dialkyl substitution, aryl groups) at one end of the halonium ion, high dielectric solvents, or chlorine as the halogen are all factors which conspire to reduce the degree of halogen bridging.[70] This has obvious implications for both reaction stereoselectivity and -specificity, with weakly bridged haliranium ions typically resulting in non-stereospecific dihalogenations to give *anti*/*syn* dihalide mixtures.[23] In the dichlorinations of some conjugated alkene substrates, for example, imperfect *anti*-diastereoselectivity or even predominant *syn*-addition can occur,[71] as in the reaction of (*E*)-stilbene **28** with molecular Cl_2 (Scheme 32).[71d] However, the interpretation of such results as being the sole consequence of β-chloro carbocations should be made with caution, as the precise reaction conditions and concentrations have not always been specified, and the work of Poutsma has shown that certain



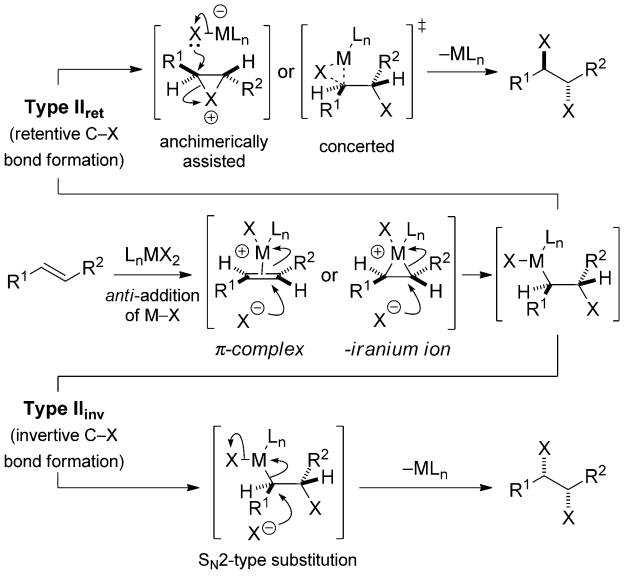
Scheme 32. Predominant *syn*-dichlorination in the reaction of (*E*)-stilbene **28** with molecular Cl_2.

alkenes at high concentrations can initiate radical chain additions of Cl_2.[24]

For the purposes of this Review, the generation of open β-halo carbocations as the first formed intermediates will also be referred to as a Type I dihalogenation reaction, regardless of the degree of *anti*-stereoselectivity or stereospecificity.

3.2. Type II Dihalogenation

In Type II dihalogenations, the alkene substrate is activated not by a halenium ion, X^+, but by either an electrophilic metal or main group electrophile, via a π-complex or -iranium ion (note that "M" shall be used to denote either a metal or main group element). Outer sphere attack of a halide ion, X^-, on such species results in *anti*-stereospecific addition of the elements of M–X across the alkene, this being the defining feature of a Type II dihalogenation. On the contrary, strained alkenes (e.g., norbornene) constitute potential exceptions to the *anti*-addition "rule", favoring *syn*-addition pathways with certain metal salts that otherwise prefer *anti*-addition [for example, mercury(II) or thallium(III) salts];[72] these special cases fall outside of the Type II classification (see Type III mechanism, see below). Following an *anti*-addition of M–X across the olefin, the final stage of a Type II dihalogenation involves reductive elimination (w.r.t. M) to expel the reduced M species and deliver the vicinal dihalide product—a process which may proceed via a number of different pathways and with either retention or inversion of configuration ("Type II_{ret}" or "Type II_{inv}", respectively) [Scheme 33, arbitrarily depicting an (*E*)-alkene]. If the M center is not already high-valent prior to M–X addition to the alkene, an oxidative activation of M may be necessary before reductive elimination can occur.[73] Crucially, the stereochemical course of the reductive elimination dictates the overall stereochemical course of the dihalogenation, with Type II_{ret} reactions resulting in *anti*-dihalogenation and Type II_{inv} reactions leading to *syn*-dihalogenation. Although a Type II_{ret} process may potentially involve a haliranium ion intermediate "downstream" in the mechanism (by anchimeric assistance from the β-halogen[74] to expel the M nucleofuge),[75,76] such halogenations would not be classified as Type I reactions because of the other electrophilic intermediates, featuring the metal or main group activator, which are actively involved. A third scenario (not depicted in Scheme 33) is also conceivable in which the final C–X bond formation occurs via a carbocation or carbon-centered radical—derived from C–M bond heterolysis or homolysis, respectively—which could potentially lead to non-stereospecific dihalogenation pathways.[77]



Scheme 33. A Type II dihalogenation mechanism.

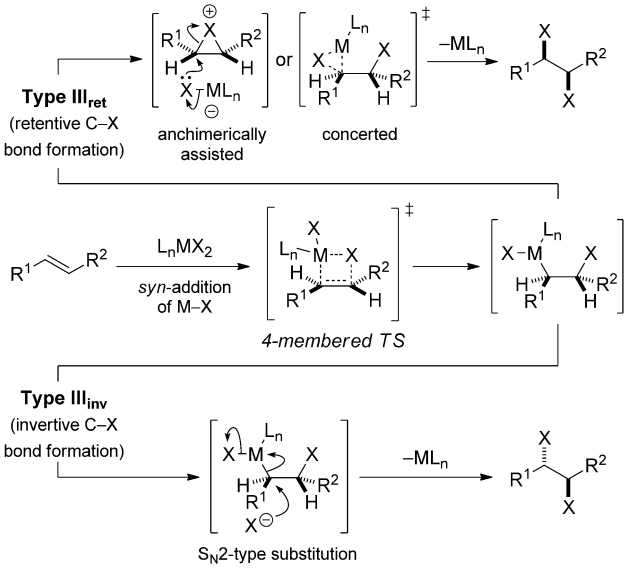
Examples of proposed Type II_{ret} mechanisms include the *anti*-selective dichlorination of alkenes with PCl_5[78] (Section 4.3.2) and the *anti*-selective dibrominations of alkenes with $CuBr_2$ (Section 5.7.1).[79] However, in neither of these processes is a Type II_{ret} mechanism substantiated by experimental evidence (e.g., detection or isolation of intermediates), and so to the best of our knowledge there are currently no unambiguous cases of Type II_{ret} alkene dihalogenation. There are however several other metal- or main group element-mediated alkene difunctionalization reactions,[80] including some halofunctionalizations,[81] which share similar elementary steps to a Type II dihalogenation, such as the *anti*-addition of a metal/main group electrophile (M) and nucleophile (Nu) across an olefinic double bond. Furthermore, although rare, *anti*-chlorometalation reactions of alkenes are on record,[82] and both stereoretentive[76,83] and invertive (S_N2-like)[76,84] oxidatively-induced reductive eliminations of alkylmetal halide intermediates to furnish $C(sp^3)$–halogen bonds are well precedented.[85]

A more clear-cut example of a Type II_{inv} process is the selenium-catalyzed, *syn*-dichlorination of olefins developed by Denmark et al.,[52] for which the proposed catalytic cycle is comprised of steps which are all known stoichiometrically and are of well established stereochemical course (see Section 4.4.2).

3.3. Type III Dihalogenation

Type III dihalogenation is broadly similar to Type II dihalogenation, with the exception being that the initial addition of the elements of M–X across the alkene double bond proceeds with *syn*-stereospecificity. Such *syn*-additions can be formulated as migratory insertions of the olefin into the M–X bond of the metal (or metalloid) halide, proceeding in a concerted fashion via a 4-center transition state. Just as

for Type II dihalogenations, the ensuing reductive elimination (w.r.t. M) may proceed via retentive or invertive pathways, leading to *syn*- or *anti*-dihalogenation, respectively [Scheme 34, arbitrarily depicting an (*E*)-alkene]. As before, a third type of reductive elimination may involve final C–X bond formation via a carbocation or carbon-centered radical, arising from C–M bond heterolysis or homolysis, respectively.[77]



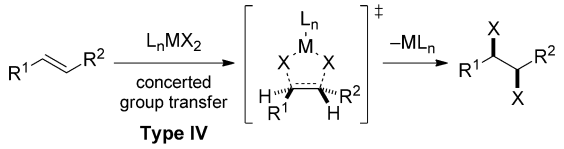
Scheme 34. A Type III dihalogenation mechanism. TS = transition state.

The proposal of *syn*-halometalation in Type III dihalogenations deserves further comment, particularly as migratory insertions of alkenes into M–X bonds are thermodynamically unfavorable for transition metals. It is in fact the microscopic reverse of this process—β-halide elimination—that is normally observed, accounting for the notorious instability of β-haloalkyl transition metal complexes.[86] The driving force for β-halide elimination has largely been attributed to the differences between metal–carbon and metal–halide bond strengths,[87] being most exothermic for "hard" early transition metals[88] and relatively less so for "softer" late metals.[89] Of course, endergonic elementary steps embedded in multistep sequences can still lead to productive reactions if they are offset by subsequent, exergonic steps, and halometalations of alkenes have been proposed in several catalytic cycles. For instance, the chloropalladation of π-unsaturates[90] is well precedented, primarily for alkynes[91] but also with olefins,[82,92] with the stereochemical course of the insertion (*syn* or *anti*) being dependent on the precise reaction conditions (e.g., halide ion concentration). In contrast to transition metals, β-halometalations of alkenes with main group halides are well known (e.g., PhSeCl), and although many of these additions are *anti*-stereospecific processes, the (ionic) β-chlorotelluration of alkenes has been shown to proceed in a *syn*-stereospecific fashion.[93]

As one might gather from the above discussion regarding the instability of many β-haloalkyl transition metal complexes, which often precludes their isolation,[86] direct experimental evidence for Type III dihalogenations is lacking, although such mechanisms have been invoked to account for both *anti*- and *syn*-selective dihalogenations of olefins mediated by high-valent metal or metalloid halides. For example, a Type III$_{ret}$ mechanism involving *syn*-chlorometalation of an alkene followed by stereoretentive reductive elimination has been suggested by Sharpless and co-workers to account for the formation of *syn*-dichlorination by-products from the oxidation of alkenes with chromyl chloride (CrO_2Cl_2) at low temperature.[94] Additionally, a Type III$_{inv}$ mechanism has been tentatively proposed for manganese(VII)-mediated alkene *anti*-dichlorinations, though it is not even clear in these cases that a manganese chloride species is the active chlorinating species (see Section 5.3.1).

3.4. Type IV Dihalogenation

Type IV dihalogenation involves a concerted delivery of two halogen atoms from a metal or main group element center to an alkene in a *syn*-stereospecific fashion, via a 5-membered transition state [Scheme 35, arbitrarily depicting an (*E*)-alkene].



Scheme 35. A Type IV dihalogenation mechanism.

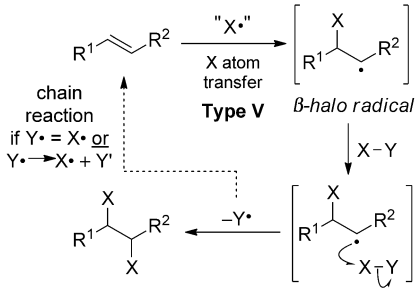
Originally invoked by Barton and Miller to account for the *syn*-selective dichlorination of cholesterol benzoate with $PhICl_2$ under anhydrous conditions,[95] this mechanism has since been discredited, despite receiving some theoretical support[96] (see Section 4.5.1). A Type IV mechanism has also been suggested to be operative for *syn*-stereospecific dichlorinations of olefins by high-valent antimony and molybdenum chlorides (see Sections 4.3.3 and 5.2.2, respectively). Sharpless has also pointed out that a Type IV dichlorination process cannot be excluded as an explanation for the formation of *syn*-dichlorination products in the oxidation of alkenes by CrO_2Cl_2, although he favored a Type III$_{ret}$ mechanism (see above).[94] However, Nelson and co-workers have concluded that a Type IV dichlorination is indeed more likely for the latter transformation, based on linear correlations between log k_{rel} and either alkene ionization potentials or HOMO energies (i.e., showing that only electronic and not steric effects are important).[97]

In terms of product stereostructure, the Type IV mechanism is indistinguishable from a Type II$_{inv}$ or Type III$_{ret}$ dihalogenation for which obvious parallels can be drawn to the *syn*-dihydroxylation of alkenes by OsO_4. In that case, both a [2+2] cycloaddition mechanism (analogous to the Type III$_{ret}$ pathway) and a [3+2] cycloaddition (analogous to the Type IV pathway) have been advocated.[98] However, compelling

support for the [3+2] pathway from $^{12}C/^{13}C$ kinetic isotope effects[99] and quantum chemical DFT and ab initio calculations[100] has now firmly established that the [3+2], and not the [2+2], cycloaddition mechanism is in operation with OsO_4.

3.5. Type V Dihalogenation

Type V dihalogenation involves halogen atom transfer to the alkene substrate to generate a β-halo radical, which can react further with a halogen atom donor (X–Y) to give a vicinal dihalide [Scheme 36, arbitrarily depicting an (*E*)-alkene]. If Y = X (or if Y can become X by extrusion of a neutral molecule), a radical chain reaction may ensue (e.g., as for Cl_2, SO_2Cl_2, $PhICl_2$, see below), although non-chain mechanisms may be operative in some metal-mediated or -catalyzed processes (e.g., for low-valent manganese, copper, and ruthenium halides, see below). The conditions under which molecular Cl_2 undergoes radical chain additions to alkenes have been thoroughly studied by Poutsma, with high concentrations of certain alkene substrates able to initiate radical processes even in the dark under a nitrogen atmosphere.[24] In terms of stereochemical course, the formation of vicinal dihalides by Type V mechanisms is generally non-stereospecific,[24,101] with the relative configurations of the products being determined by steric factors.



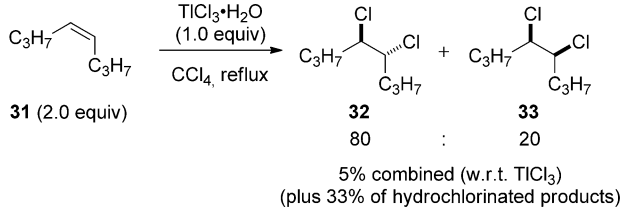
Scheme 36. A Type V dihalogenation mechanism.

4. Alkene Dihalogenations with Main Group Halides as Reagents or Catalysts

To fully realize the largely untapped potential of main group or metal halides as reagents or catalysts for catalytic alkene dihalogenation protocols, some knowledge of the *stoichiometric* reactivity of these compounds with alkenes is required, and particularly the mechanistic and stereochemical features of such reactions. This aspect shall be the focus of the remainder of this Review, with main group halides covered in this Section and transition metal halides discussed in Section 5. Although most main group or metal halides have been used in stoichiometric amounts, there are clearly opportunities to render this chemistry catalytic in such species.[52]

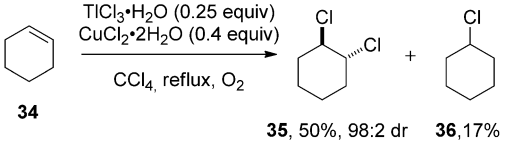
4.1. Group 13 Halides

Uemura and co-workers have reported that the reaction of alkenes with molten, heterogeneous $TlCl_3{\cdot}H_2O$ in refluxing CCl_4 gives vicinal dichlorides resulting from *anti*-addition in low yield, in addition to substantial amounts of hydrochlorinated products.[102] For example, the reaction of excess (*Z*)-4-octene **31** with $TlCl_3{\cdot}H_2O$ gave an 80:20 mixture of *anti*- and *syn*-dichlorination products **32** and **33**, respectively, in 5% combined yield (w.r.t. $TlCl_3$), in addition to several hydrochlorination products in 33% yield (Scheme 37).



Scheme 37. Low-yielding dichlorination reaction of (*Z*)-4-octene **31** with $TlCl_3{\cdot}H_2O$.

However, the reaction could be rendered catalytic in $TlCl_3{\cdot}H_2O$ using $CuCl_2{\cdot}2H_2O$ as a co-catalyst and O_2 as the terminal oxidant, with control experiments showing no reaction in the absence of $TlCl_3{\cdot}H_2O$. Under these conditions, cyclohexene **34** gave *anti*-dichloride **35** in 50% yield (w.r.t. **34**) and 98:2 dr, as well as cyclohexyl chloride **36** in 17% yield (Scheme 38). Although the catalyst loadings are very high—to such an extent that the reaction is not obviously catalytic based on the product yield—this process does constitute a very rare example of metal-catalyzed alkene dihalogenation.



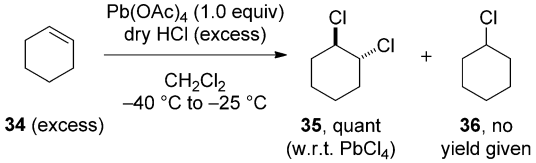
Scheme 38. A thallium-catalyzed alkene dichlorination?

Little is known regarding the mechanism of alkene dichlorinations with $TlCl_3{\cdot}H_2O$, although product distributions from norbornene[103] and norbornadiene[104] are suggestive of Type I processes involving chloriranium ion intermediates.

4.2. Group 14 Halides

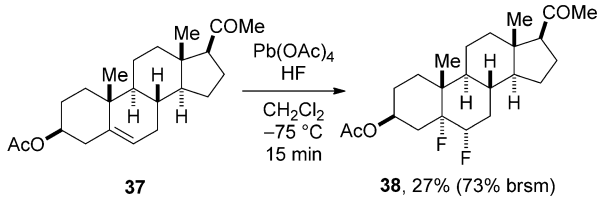
For Group 14 halides in the +4 oxidation state, only lead(IV) chloride ($PbCl_4$) possesses sufficient oxidizing power to dichlorinate alkenes,[105] although it's high oxidation potential and Lewis acidity, coupled with the severe cumulative toxicity of lead compounds, renders this a particularly unsavory reagent. A yellow, oily liquid in its pure form, $PbCl_4$

can be prepared in situ from $Pb(OAc)_4$ and excess dry HCl, although it thermally decomposes to $PbCl_2$ and Cl_2 above 0 °C. However, at cryogenic temperatures, in situ generated $PbCl_4$ reacts with an excess of several alkenes (cyclohexene, 4-*tert*-butylcyclohexene, cycloheptene, or Δ^2-cholestene) to afford the corresponding *anti*-dichlorides in quantitative yield with respect to $PbCl_4$ (Scheme 39).[106] Unfortunately, a Lewis acid-catalyzed hydrochlorination with the excess HCl is a major side reaction (hence the requirement for excess alkene), and this dominates with trisubstituted alkenes (e.g., 1-methyl-4-*tert*-butyl-cyclohexene) or alkenes which are slower to undergo 1,2-addition [e.g., (*Z*)-cyclooctene]. Little mechanistic information for this dichlorination is available, although product distributions for the reaction of $PbCl_4$ with norbornene,[103] norbornadiene,[104] and cyclooctadienes[107] as mechanistic probes are suggestive of an ionic mechanism that does not involve molecular Cl_2.



Scheme 39. The dichlorination of excess cyclohexene **34** with in situ generated $PbCl_4$, accompanied by extensive hydrochlorination.

Although difluorinations are beyond the scope of this Review, it is interesting to note in passing that the difluorination of alkenes with "PbF_4" has also been reported.[108] However, an early claim of the difluorination of stilbene with "PbF_4" [prepared in situ from $Pb(OAc)_4$ and HF],[109] was later found to be erroneous, with the purported vicinal difluoride product reassigned as a geminal difluoride.[110] Furthermore, the active fluorinating agent generated from $Pb(OAc)_4$ and HF has been proposed as $Pb(OAc)_2F_2$ and not PbF_4.[110] Bowers and co-workers have reported the *syn*-selective difluorination of pregnenolone acetate **37** using $Pb(OAc)_4$-HF to give the 5α,6α-difluoride **38** in 27% yield (Scheme 40).[111] To account for the stereochemical course, a concerted transfer of both fluorine atoms from PbF_4 to the alkene (i.e., a Type IV dihalogenation) was suggested, although a radical (or even carbocation) based mechanism might also be consistent with this outcome (see Section 4.5.1 for a similar *syn*-selective dichlorination of a steroidal alkene). A mechanistic study on the reaction of $Pb(OAc)_4$-HF with norbornene favored a *syn*-fluorometalation process (i.e., a Type III addition) followed by heterolytic cleavage of the C–Pb bond to furnish a carbocation intermediate (or homolytic cleavage and single electron transfer oxidation).[112]

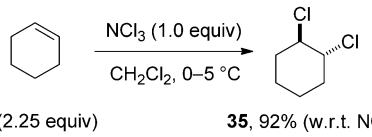


Scheme 40. Difluorination of pregnenolone acetate **37** using $Pb(OAc)_4$-HF.

4.3. Group 15 Halides

4.3.1. Nitrogen

Kovacic and co-workers have studied the use of nitrogen trichloride, (NCl_3) as a reagent for the dichlorination of alkenes in detail.[113] Although pure NCl_3 is an explosive yellow oil, it can be freshly prepared as a solution in chlorinated organic solvents via the reaction of NH_4Cl with $Ca(ClO)_2$, as described in an *Organic Syntheses* procedure.[114] When used in this form, it is stable for several days at 0–5 °C, and gives exceptionally clean dichlorinations of simple (unfunctionalized) alkenes such as cyclohexene **34**, albeit with the alkene used in excess (Scheme 41). The reaction probably proceeds via a radical mechanism,[113b,115] although a competing ionic pathway may be operative for certain alkene substrates,[116] much as for reactions with Cl_2.[24]



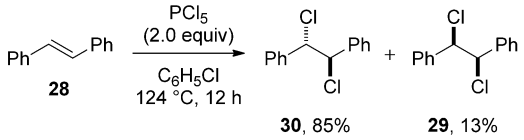
Scheme 41. The dichlorination of excess cyclohexene **34** with NCl_3.

Other alkene dihalogenations are reliant on more stable N–X reagents such as *N*-haloimides and related compounds, in which these X^+ equivalents are combined with a suitable source of nucleophilic halide ion. The halide can either be generated in situ by reduction of one equivalent of the N–X reagent with an added reductant (Section 2.1),[35,36] or it can be introduced via a different reagent entirely [e.g., R_4NBr,[34] LiBr,[117] $BrTi(O\textit{i}\text{-}Pr)_3$][15].

4.3.2. Phosphorus

Although the vicinal dichlorination of alkenes with PCl_5 has long been known,[118] this method has rarely been applied in synthesis and has been subjected to only limited mechanistic scrutiny.[78] In a representative example of this reaction, (*E*)-stilbene **28** reacts with an excess of PCl_5 in refluxing chlorobenzene to give *anti*-dichloride **30** in 85% yield and *syn*-dichloride **29** in 13% yield (Scheme 42).

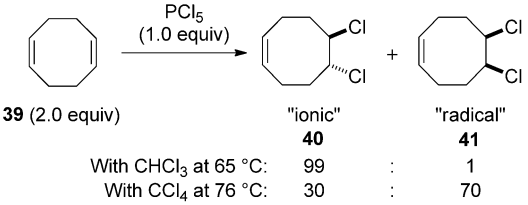
Based on the known reaction of PCl_5 with alkenes at low temperature to furnish β-chloro phosphinylated adducts,[119] it has been suggested that the dichlorination may proceed via initial addition of PCl_5 (in the form $[PCl_4]^+[PCl_6]^-$) to the alkene via a bridged phosphonium intermediate, followed by a stereoretentive S_Ni-type conversion of the C–PCl_3 bond to a C–Cl bond (i.e., a Type II_{ret} mechanism).[78] However, the intermediacy of β-chloro phosphinylated adducts at the elevated temperatures employed was not demonstrated, nor



Scheme 42. The dichlorination of (*E*)-stilbene **28** with PCl_5.

was the decomposition of such species to vicinal dichlorides. Although *anti*-selective dichlorination of cyclohexene was taken as support for the proposed (ionic) mechanism, this result could equally well be ascribed to a radical process.[120] It was however suggested that the stereochemical course of the reaction with (*E*)-stilbene **28** could be the result of parallel ionic and radical processes.

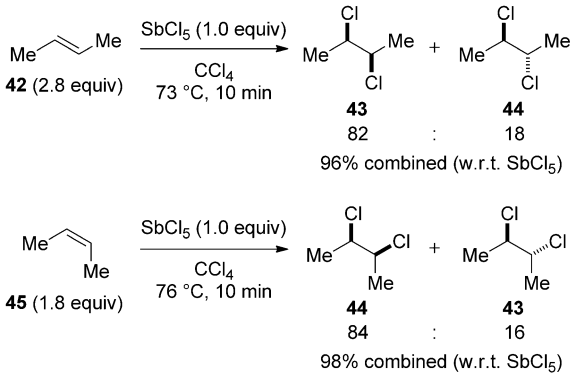
To gain further mechanistic insight, Uemura and co-workers examined the reactions of norbornene and 1,5-cyclooctadiene with PCl_5, as these substrates are known to give distinct product distributions in ionic versus radical dichlorinations.[121] With 1,5-cyclooctadiene **39**, for example, the reaction with PCl_5 in $CHCl_3$ ($\varepsilon = 4.70$) at 65 °C gives almost exclusively the "ionic" dichloride **40**, whereas the reaction in non-polar CCl_4 ($\varepsilon = 2.23$) at a slightly higher temperature (76 °C) delivers predominantly the "radical" dichloride **41** (Scheme 43). On the basis that PCl_5 is a covalent monomer in non-polar media such as benzene and CCl_4,[122] it was concluded that any "ionic" dichlorides produced in these solvents are unlikely to arise via a Type II_{ret} mechanism,[78] and that a Type I process may be in operation. As PCl_5 is known to decompose slightly to PCl_3 and Cl_2 near 100 °C, molecular Cl_2 could not be excluded as a contributor to the "ionic" pathway.



Scheme 43. The dichlorination of 1,5-cyclooctadiene **39** with PCl_5.

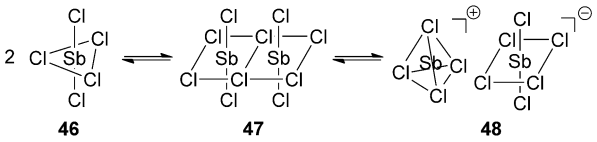
4.3.3. Antimony

On the basis of precedent for the use of $SbCl_5$ as a catalyst for the dichlorination of alkenes with Cl_2,[123] as well as an example of its use as a stoichiometric reagent with 1,2-dibromoethylene as the substrate,[124] Uemura and co-workers have performed a detailed study on the dichlorination of alkenes and dienes with $SbCl_5$ in chlorocarbon solvents.[125,126] Related studies have also been carried out by Heasley and co-workers,[127] in addition to other brief investigations on the use of liquid SO_2 as a solvent[128] and 1,3-butadiene as a substrate.[129] One of the most remarkable features of this reaction is the production of vicinal dichlorides resulting from a stereospecific[130] *syn*-dichlorination of the alkene. For example, addition of excess (*E*)-2-butene **42** (2.8 equiv) to a solution of $SbCl_5$ in CCl_4 at 73 °C gave an 82:18 mixture of dichlorides **43** and **44**, resulting from *syn*- and *anti*-selective addition respectively, in 96% combined yield (w.r.t. $SbCl_5$). The diastereomeric alkene (*Z*)-**45** behaved almost identically (i.e., 84:16 *syn*:*anti* addition), confirming the stereospecific nature of the process (Scheme 44). Control experiments verified that the *syn*-selectivity is the result of kinetic control. However, no reaction occurs with electron-deficient alkenes such as acrylonitrile, ethyl maleate, ethyl fumarate or tetrachloroethylene, and with styrene or ethyl vinyl ether, vigorous reactions ensued to give polymeric material.



Scheme 44. *Syn*-stereospecific dichlorination of alkenes using $SbCl_5$.

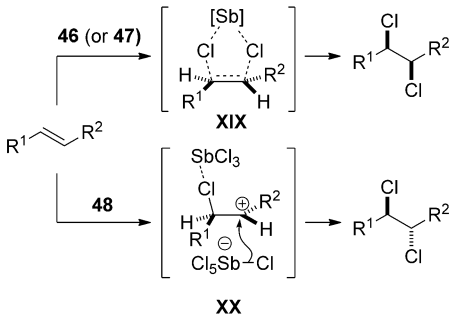
The *syn*-selectivity is sensitive to both the polarity of the chlorocarbon solvent and the reaction temperature, with higher *syn*-selectivities obtained in more polar media at elevated temperatures. Thus, the ratios of *syn*:*anti* addition for the dichlorination of cyclohexene in 1,2-dichloroethane ($\varepsilon = 10.37$) at 83 °C and in CCl_4 ($\varepsilon = 2.23$) at 30 °C are 89:11 and 60:40, respectively. The speciation of $SbCl_5$ in solution depends on the polarity of the solvent: in MeCN ($\varepsilon = 37.5$), conductivity data indicate that $SbCl_5$ is in equilibrium with $[SbCl_4]^+[SbCl_6]^-$ **48**,[131] whereas in CCl_4 ($\varepsilon = 2.23$) the conductivity data[132] and vibrational spectra[133] are consistent with molecular $SbCl_5$ **46** (of D_{3h} symmetry).[134] Uemura et al. have suggested that solutions of $SbCl_5$ in chlorocarbons may comprise an equilibrium mixture of $SbCl_5$ **46**, Sb_2Cl_{10} **47**,[135] and $[SbCl_4]^+[SbCl_6]^-$ **48** (Scheme 45).[125]



Scheme 45. Proposed equilibria in chlorocarbon solutions of $SbCl_5$.

To rationalize the *syn*-stereospecificity of the dichlorination, a Type IV mechanism involving concerted transfer of both chlorine atoms from $SbCl_5$ **46** (or possibly Sb_2Cl_{10} **47**) to the alkene via a 5-membered cyclic transition state **XIX** has been proposed.[125] A Type III_{ret} mechanism involving *syn*-

chlorometalation followed by stereoretentive reductive elimination (w.r.t. Sb) was seemingly not considered and should not be ruled out, especially as $TeCl_4$ (tellurium being the Group 16 neighbor of antimony) is known to β-chlorotellurate olefins in a *syn*-stereospecific fashion.[93] The formation of dichlorides resulting from *anti*-addition was ascribed to ion pair $[SbCl_4]^+[SbCl_6]^-$ **48** as the reactive chlorinating species,[136] which may promote an ionic mechanism via β-chloro carbenium ion intermediates **XX** (Scheme 46). An interaction of the chlorine atom in intermediates **XX** with antimony, which prevents bridging to give a chloriranium ion, is invoked to explain the formation of 1,1- and 1,3-dichloride products from cyclopentene (see below).[125,127] In support of the mechanistic proposal in Scheme 46, the *syn*:*anti* selectivity decreases considerably upon addition of a strong Lewis acid ($AlCl_3$ or SbF_3) to the $SbCl_5$, possibly due to the formation of $[SbCl_4]^+[MX_nCl]^-$ ion pair complexes. Additionally, as the ionization $SbCl_5 \rightarrow [SbCl_4]^+[SbCl_6]^-$ is likely to be exothermic (as for PCl_5),[122] the amount of $[SbCl_4]^+[SbCl_6]^-$ **48** would be expected to decrease as the temperature is raised, and this might account for the fact that *syn*-selectivity increases at higher temperatures. The effect of solvent—in which *syn*-selectivity *increases* in more polar solvents—is rationalized in terms of the different Ingold–Hughes charge-type classifications[137] of the *syn*- and *anti*-dichlorination pathways. Specifically, a more polar solvent should accelerate the *syn*-addition (a reaction between two uncharged species) because charge separation is greater in the transition state (TS) than the starting materials, and the former will be relatively more stabilized. Conversely, a polar solvent should retard the *anti*-addition (a reaction between an uncharged and a charged species) because the charge becomes more dispersed in the TS, relative to the starting species.



Scheme 46. Proposed parallel mechanisms for the formation of *syn*- and *anti*-dichlorides, respectively, arbitrarily illustrated for an (*E*)-configured alkene.

For certain alkenes, such as cyclopentene,[125,127] norbornene,[103,125] or norbornadiene,[104] rearrangement products consistent with carbocation intermediates of the form **XX** are produced. For instance, with cyclopentene, both 1,1- and 1,3-dichlorides (the products of 1,2-hydride shifts)[127] are obtained in addition to the 1,2-*anti*-dichloride product, with none of the 1,2-*syn*-dichloride detected.[125] This, and other unusual results,[103,127] have been explained in terms of carbocation stability (according to the Hammond postulate),[138] in which alkenes able to generate more stable carbocations are more prone to ionic reaction pathways. An alternative explanation for the anomalous reactivity of cyclopentene and norbornene with $SbCl_5$ is the unfavorable steric interaction expected between $SbCl_5$ and the proximal methylene group in a concerted *syn*-addition to the alkene substrate (Figure 4).[125,139]

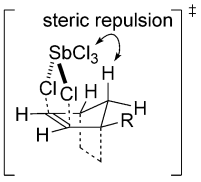


Figure 4. Anticipated destabilizing steric interaction in the concerted addition of $SbCl_5$ to either cyclopentene or norbornene.

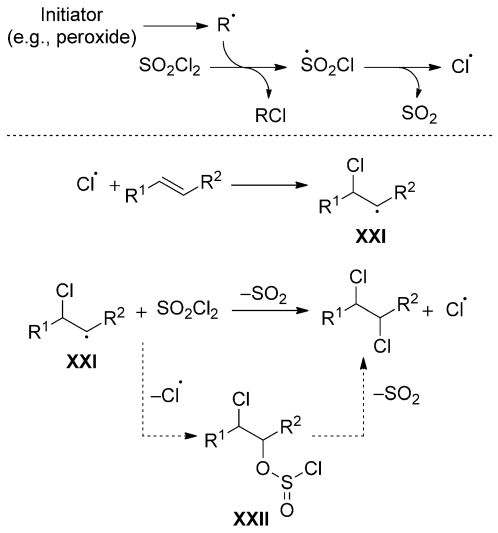
Uemura and co-workers have also extended the use of $SbCl_5$ to the *syn*-selective dichlorination of alkynes, albeit in low yields (20–30%).[140]

4.4. Group 16 Halides

4.4.1. Sulfur

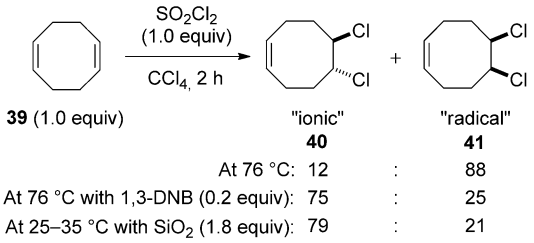
The reaction of sulfuryl chloride (SO_2Cl_2) with alkenes to afford vicinal dichlorides has long been known,[113a,118,141] and Kharasch and Brown have shown that these reactions can be initiated with organic peroxides.[142] On this basis, it was proposed that the dichlorinations proceed by a radical chain mechanism (i.e., Type V dichlorination), in which the initiation step involves the generation of chlorosulfuryl radicals ($^{\bullet}SO_2Cl$) from SO_2Cl_2. These radicals may lose SO_2 to release $Cl^{\bullet}$ atoms, which will add to olefins to generate β-chloro radical intermediates **XXI**, although $^{\bullet}SO_2Cl$ could potentially transfer chlorine to the olefin directly. With regard to the latter possibility, the $^{\bullet}SO_2Cl$ radical is thought to be at least partly responsible (along with $Cl^{\bullet}$) for hydrogen-abstraction in photoinitiated C–H chlorinations of hydrocarbons with SO_2Cl_2.[143] In either case, chlorine transfer from another molecule of SO_2Cl_2 to the β-chloro radical **XXI** could then furnish the vicinal dichloride directly and regenerate the $^{\bullet}SO_2Cl$ radical.[142] Alternatively **XXI** may react with SO_2Cl_2 to furnish chlorosulfite esters **XXII** as primary products (which are isolable at lower temperatures) and these may decompose on heating to give vicinal dichlorides (Scheme 47).[144] Typical side products of SO_2Cl_2 radical dichlorinations include higher chlorinated compounds from chlorine substitution along the alkyl chain,[142] as well as symmetrical β-chloro-*n*-alkyl sulfones arising from direct attack of $^{\bullet}SO_2Cl$ on the olefin.[144] The vicinal dichlorination of *alkynes* with SO_2Cl_2 is also possible and is thought to follow a similar radical chain pathway.[145]

Uemura and co-workers have also found that reactions of SO_2Cl_2 with alkenes by an ionic (possibly Type I) pathway are possible, as evidenced by the change in product distribution for the dichlorination of 1,5-cyclooctadiene **39** in the presence versus absence of 1,3-dinitrobenzene as a radical inhibitor.[121] Furthermore, under the assumption that silica gel promotes electrophilic aromatic chlorinations with SO_2Cl_2,[146] a similar effect was noted for alkene dichlorinations, and the addition of silica gel strongly promotes the ionic pathway (Scheme 48). Comparable results are also obtained with norbornene as a mechanistic probe for ionic versus radical dichlorination.



Scheme 47. Dichlorination of alkenes with SO_2Cl_2 via a radical chain mechanism (with $Cl^•$ depicted as the chain-carrier).

These particular results have interesting implications for the development of Brønsted/Lewis acid or Lewis base-catalyzed alkene dichlorinations with SO_2Cl_2 as a dihalogen equivalent, as opposed to the less stable and non-commercially available $PhICl_2$ (which has already been applied in Brønsted acid-catalyzed[39] and Lewis base-catalyzed[12] dichlorinations). Notably, Lewis acid catalysts have been used to promote the ionic chlorination of aromatic compounds with SO_2Cl_2 via X–S–X bond polarization.[41]

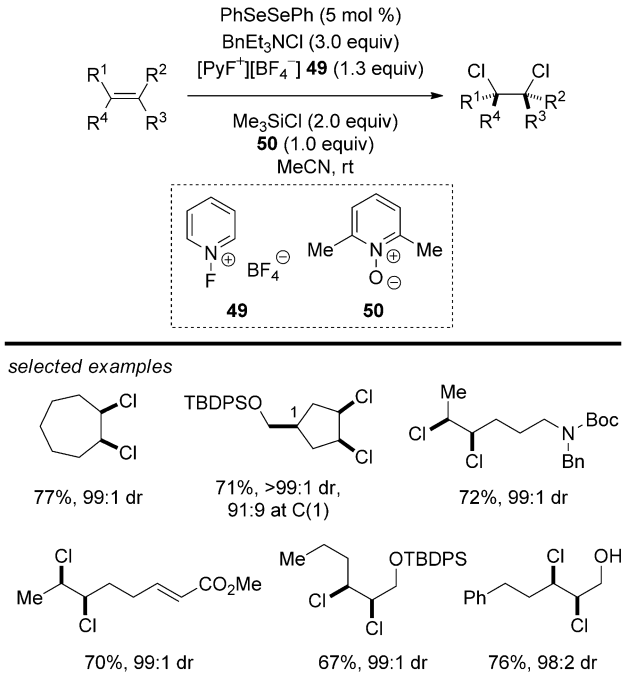


Scheme 48. The dichlorination of 1,5-cyclooctadiene **39** with SO_2Cl_2. 1,3-DNB = 1,3-dinitrobenzene.

4.4.2. *Selenium*

Although $SeCl_4$ is known to react with alkenes to produce bis(2-chloroalkyl)selenium dichlorides,[147] Uemura and co-workers have shown that this reagent is capable of dichlorinating various alkenes in CCl_4, including cyclohexene,[103] norbornene,[103] norbornadiene,[104] (*Z*)-cyclooctene,[126a] and cyclooctadienes.[107] Control experiments indicate that organoselenium compounds are not involved as intermediates, and product distributions from the aforementioned alkenes are most consistent with a Type I ionic mechanism, as opposed to a radical (Type V) dichlorination process.

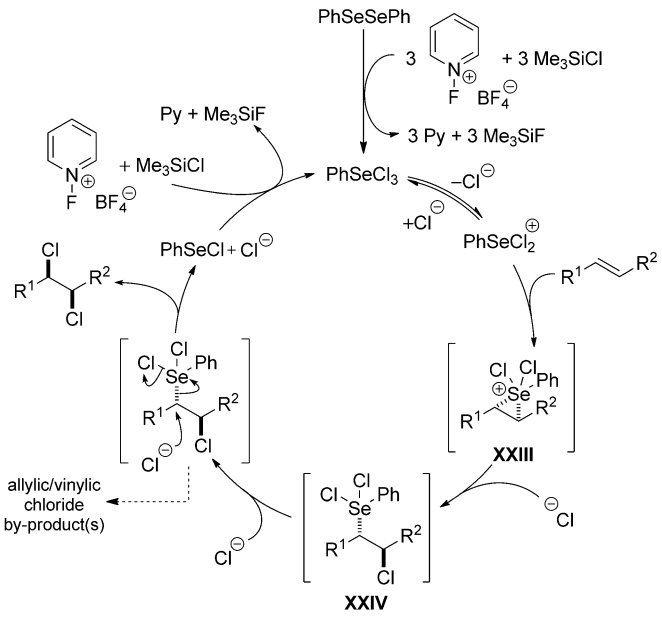
More recently, Denmark and co-workers reported a selenium-*catalyzed* alkene dichlorination reaction that also constitutes the first catalytic, *syn*-stereospecific dichlorination of alkenes.[52] On the basis of known *anti*-stereospecific β-chloroselenylation of alkenes with $PhSeCl_3$,[148] as well as the invertive nucleophilic displacement of the high-valent selenium(IV) moiety[149] by chloride ions in such adducts to afford *syn*-dichlorides,[150] it was surmised that a direct alkene *syn*-dichlorination that is *catalytic* in selenium may be possible. The key challenge in formulating such a catalytic cycle was the identification of a stoichiometric oxidant to selectively reoxidize Se^{II} to Se^{IV}, but which does not interfere with the alkene substrate, nor oxidize chloride ions to Cl_2. Thus, with diphenyl diselenide (PhSeSePh) as the precatalyst, benzyltriethylammonium chloride ($BnEt_3NCl$) as the chloride source, and an *N*-fluoropyridinium salt **49** as the oxidant, a wide variety of functionalized 1,2-disubstituted (*E*)- and (*Z*)-configured alkenes, including simple allylic alcohols, deliver *syn*-dichlorides with exquisite stereocontrol (Scheme 49).



Scheme 49. Selenium-catalyzed *syn*-dichlorination of alkenes.

Chlorotrimethylsilane (Me_3SiCl) is a crucial additive to facilitate turnover, presumably serving as a scavenger for fluoride ions generated from oxidant **49**. Additionally, the inclusion of 2,6-lutidine *N*-oxide **50** as an (optional) additive enhances the rate of the reactions (but not the yields or selectivities), although it actually is deleterious in some cases and was omitted (e.g., for allylic alcohol substrates).

A proposed catalytic cycle for these reactions—which are believed to follow a Type II_{inv} dihalogenation mechanism—is illustrated in Scheme 50 (without 2,6-lutidine *N*-oxide **50**). Following precatalyst activation under the oxidative conditions (i.e., $PhSeSePh \rightarrow PhSeCl_3$), the first step is thought to be addition of $PhSeCl_3$ to the alkene substrate to generate a seleniranium ion intermediate **XXIII**. Nucleophilic ring-



Scheme 50. Proposed catalytic cycle for the selenium-catalyzed *syn*-dichlorination of alkenes.

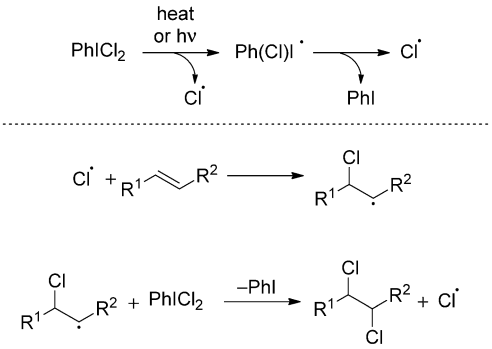
opening by Cl^- ion then gives a (β-chloroalkyl)phenylselenium dichloride **XXIV**,[148] following which stereoinvertive displacement of the Se^{IV} nucleofuge by Cl^- ion delivers the vicinal dichloride product, in an overall *syn*-stereospecific addition process. Oxidation of PhSeCl to $PhSeCl_3$ in the presence of oxidant **49** and Me_3SiCl completes the catalytic cycle.

4.5. Group 17 Halides (Except Dihalogens)

4.5.1. Iodine

Dichloroiodobenzene ($PhICl_2$)—a yellow, crystalline solid originally isolated in 1886 by Willgerodt,[151] and the first example of a hypervalent iodine(III) reagent[152]—is renowned for its ability to cleanly dichlorinate olefins under mild conditions. Although not commercially available due to its instability (being storable at −20 °C for about two weeks), it can be prepared by the treatment of iodobenzene with chlorine gas (via an *Organic Syntheses* procedure)[153] or, more conveniently, by the in situ generation of Cl_2 using strong oxidants with chloride sources.[154] However, $PhICl_2$ and other $ArylICl_2$ reagents undergo rapid and reversible dissociation to Cl_2 and the corresponding aryl iodide in polar solvents (e.g., AcOH, $MeNO_2$),[155] and even do so in non-polar solvents (e.g., CCl_4) if a strong acid catalyst is present (e.g., CF_3CO_2H).[156] Moreover, certain Lewis basic *ortho*-substituents on the aryl ring of $ArylICl_2$ reagents greatly accelerate this decomposition process (in AcOH), with 2-nitro and 2-carboxymethyl groups exerting the strongest effect.[157]

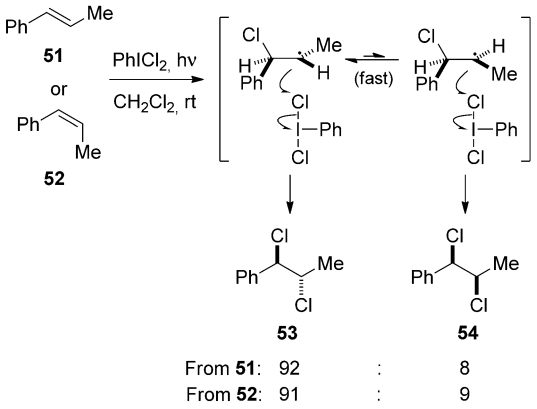
In general, dichlorinations of alkenes with $PhICl_2$ in chlorocarbon solvents follow either a radical chain mechanism (Type V) or an ionic mechanism (Type I or Type II), depending on the reaction conditions.[115,158,159] The radical chain mechanism (Scheme 51), originally proposed by Bloomfield,[160] can be initiated either thermally or photochemically (in the absence of radical inhibitors such as oxygen), and support for this mechanism comes from studies of certain alkenes as mechanistic probes for ionic versus radical dichlorination, including norbornene,[24b,121,158,159] cyclooctene,[126] cyclooctadienes,[107,121] cyclopentadiene and 1,3-cyclohexadiene,[115] vinylcyclopropanes,[116] and others.[159] By analogy to radical dichlorinations with SO_2Cl_2 (see above),[142] it has been proposed that $Cl^\bullet$ is the chain-carrying radical,[158,159] although $Ph(Cl)I^\bullet$ could also be the chain-carrier.[159,171,161] In possible support of the latter scenario, $Ph(Cl)I^\bullet$ (as opposed to $Cl^\bullet$) is thought to be a competent hydrogen-abstractor in photoinitiated C–H chlorinations of hydrocarbons with $PhICl_2$, based on comparison of product distributions to similar reactions with Cl_2.[162] A related question has arisen in ionic mechanisms with $PhICl_2$ as to whether Cl^- or $Ph(Cl)I^-$ is the active nucleophile (see above).[115,159,163]



Scheme 51. Dichlorination of alkenes with $PhICl_2$ via a radical chain mechanism (with $Cl^\bullet$ depicted as the chain-carrier).

Regarding the stereochemical course of these radical dichlorinations, mixtures of *anti*- and *syn*-dichlorination products are frequently obtained, which for cyclic alkenes typically (though not always) favor the *anti*-diastereomer.[121,126,158,164] High stereoselectivity can even be obtained with *acyclic* alkenes: β-methylstyrenes **51** and **52**, for example, give 92:8 and 91:9 ratios of *anti*-**53**/*syn*-**54** dichlorides, respectively, upon photoinitiated reaction with $PhICl_2$ (Scheme 52).[165] In all of these cases, the simple (relative) diastereoselectivity is explained on the basis of steric interactions between the β-chloro radical intermediate and $PhICl_2$ as a very bulky chlorine atom donor.[115,161,164,165]

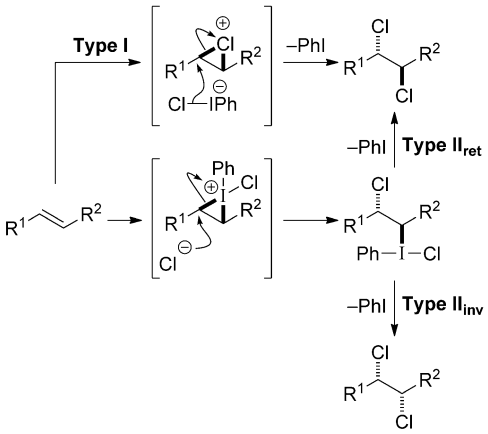
For some cyclic alkenes, however, including 1,5-cyclooctadiene[107,121] substituted norbornenes,[166] and various steroidal alkenes (e.g., cholesterol benzoate),[95,161,167] *syn*-selective dichlorination can occur with $PhICl_2$ under typical radical conditions. Barton and Miller originally rationalized this *syn*-addition pathway as being the result of a concerted, molecular addition mechanism involving synchronous transfer of both chlorine atoms from $PhICl_2$ onto the double bond (i.e., a Type IV dihalogenation)[95]—a process which has been calculated to be theoretically feasible.[96] However, this proposal has since been discredited on the basis that the "anomalous" *syn*-



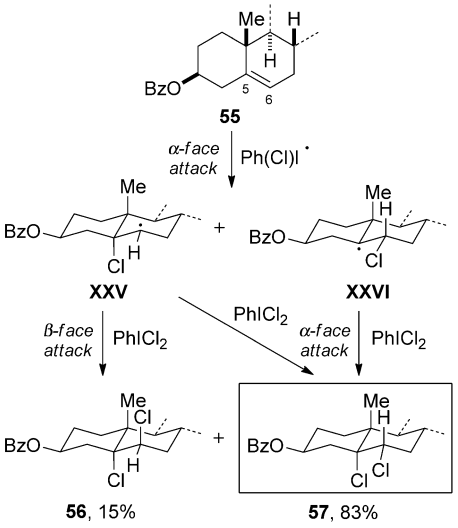
Scheme 52. The stereoconvergent dichlorination of β-methylstyrenes (*E*)-**51** and (*Z*)-**52** with $PhICl_2$.

selectivity is readily accommodated by a Type V radical process.[24b,158,159] Specifically, in the case of cholesterol benzoate **55**, attack of a Ph(Cl)I• radical may occur at the less hindered α-face of the alkene to afford two constitutionally isomeric β-chloro radical intermediates **XXV** and **XXVI**. As the axial methyl group in **XXVI** disfavors chlorine atom transfer by $PhICl_2$ to the β-face of the C(5) radical, attack should preferentially take place on the α-face, affording *syn*-dichloride **57** as the major product. Conversely, chlorine transfer to the C(6) radical of **XXV** might be expected to occur with similar facility from both the α- and β-faces, delivering a mixture of *syn*-**57** and *anti*-**56** dichlorides (Scheme 53).

The ionic pathway for alkene dichlorination with $PhICl_2$ proceeds when reactions are performed thermally in the presence of radical inhibitors (e.g., molecular oxygen), although these reactions tend to be very slow in (dry) chlorocarbon solvents in the absence of catalysts (see below), and can take several days to reach completion.[115,158,159,168] Typically these additions are highly *anti*-selective (at least in chlorocarbon media), and often more selective than Cl_2 when direct comparisons have been made.[115,169,170] Consequently, it has been suggested that $Ph(Cl)I^-$ rather than Cl^- may be the active nucleophile that traps a chloriranium ion (or β-chloro carbocation) intermediate (i.e., Type I mechanism).[115,159,163] However, a Type II_{ret} mechanism proceeding via an iodiranium ion intermediate could also be envisioned, and this would be consistent with the observed *anti*-selectivity (Scheme 54). A Type II_{inv} mechanism has even been suggested to be (at least partly) operative in Lewis basic solvents like THF, or in chlorocarbon solvents in the present of DMSO as an additive, to account for unusually high proportions of *syn*-dichlorination [particularly from (*Z*)-alkenes] under these conditions (Scheme 54).[171] It is conceivable that THF or DMSO may serve to catalyze the S_N2 displacement from the intermediate alkene–$PhICl_2$ adduct by generating a cationic iodine(III) nucleofuge and free chloride ion.

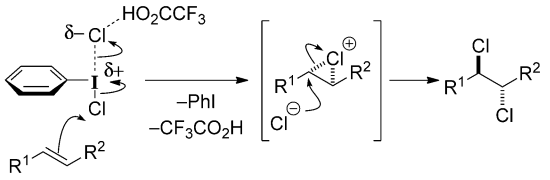


Scheme 54. Possible reaction pathways for the ionic dichlorination of alkenes with $PhICl_2$.



Scheme 53. Mechanistic rationale for the *syn*-selective dichlorination of cholesterol benzoate **55** via a Type V radical chain pathway.

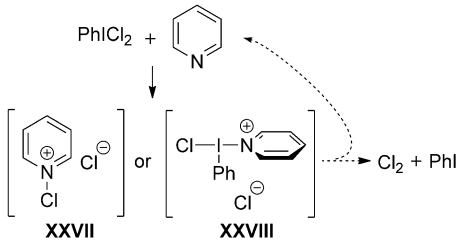
Of potential relevance to catalysis is the fact that various additives greatly accelerate *anti*-selective ionic dichlorinations of olefins with $PhICl_2$. For example, Cotter et al. have shown that trifluoroacetic acid (CF_3CO_2H) can catalyze the ionic dichlorination of alkenes by $PhICl_2$, probably via hydrogen-bond-induced polarization of the Cl–I–Cl unit (Scheme 55).[39,159] Provided that the alkene concentration is sufficiently high, this direct reaction of the olefin with the (activated) $PhICl_2$ outpaces the acid-catalyzed decomposition of $PhICl_2$ to molecular chlorine and iodobenzene.[156] A Type I mechanism has been suggested to be operative in this case, but an (ionic) Type II_{ret} process, in which the alkene attacks the activated $PhICl_2$ moiety at iodine to give an intermediate iodiranium ion species, should not be excluded. In a related phenomenon, the addition of up to 1.0 equivalent of H_2O promotes the ionic addition of $PhICl_2$ to cholesterol benzoate in refluxing $CHCl_3$, at the expense of the radical pathway.[95] Although this rate enhancement was originally ascribed to a H_2O-catalyzed dissociation of $PhICl_2$ into PhI and Cl_2, this was later disproved by other authors,[155b] and the generation



Scheme 55. Trifluoroacetic acid-catalyzed alkene dichlorination with $PhICl_2$ in CCl_4.

of trace HCl (perhaps from the hydrolysis of $PhICl_2$) has instead been suggested to catalyze the direct attack of the alkene onto $PhICl_2$ (activated by Cl–I–Cl polarization as in Scheme 55).[159]

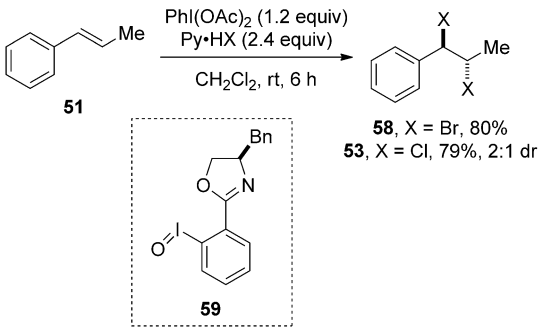
In a potential example of Lewis base catalysis,[13] the addition of pyridine is also found to greatly accelerate the ionic dichlorination of alkenes in chlorocarbon solvents such as CCl_4,[172] although the origin of the rate enhancement is unclear. Either *N*-chloropyridinium salt **XXVII** or $PhICl_2$·py complex **XXVIII** could plausibly be the active chlorinating species in these reactions, or the pyridine may even be serving to catalyze the formation of molecular Cl_2 (Scheme 56). An obvious parallel can be drawn to Nicolaou and co-worker's enantioselective dichlorination protocol, which uses 4-Ph-$(C_6H_4)ICl_2$ as the chlorinating agent and $(DHQ)_2PHAL$ as a chiral amine Lewis base catalyst (Section 1).[12] The fact that the enantioselectivity of their dichlorination shows a dependence on the nature of the aryl group of the iodoarene dichloride reagent supports the notion that $PhICl_2$·amine complexes such as **XXVIII** may be competent chlorinating species.



Scheme 56. Plausible active chlorinating agents in the pyridine-promoted dichlorination of alkenes with $PhICl_2$.

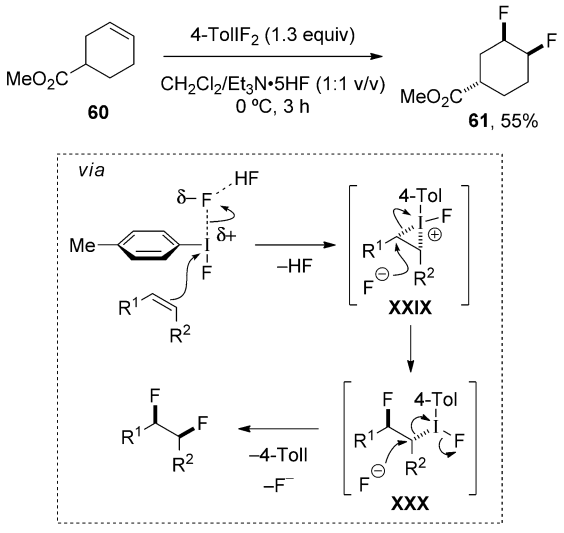
The in situ generation of iodine(III)-based halogenating agents derived from $PhI(OAc)_2$ and pyridinium halide salts has been reported by Lupton and co-workers, and alkene dichlorinations and dibrominations were briefly explored.[173] Whilst dibromination of (*E*)-β-methylstyrene **51** gives the *anti*-dibromide **58** exclusively, the analogous dichlorination affords the *anti*-dichloride **53** in only 2:1 dr. An enantioselective variant of the dibromination of (*E*)-**51** has also been attempted using the chiral, non-racemic iodoxyarene **59**, but only negligible enantioselectivity is obtained (51.5:48.5 er) (Scheme 57).

In contrast to alkene dichlorination reactions mediated by $PhICl_2$, the corresponding difluorination reactions with



Scheme 57. Dihalogenation of (*E*)-β-methylstyrene **51** with $PhI(OAc)_2$ and Py·HX (X = Br or Cl), and attempted enantioselective dibromination with chiral, non-racemic iodoxyarene **59**.

iodoarene difluorides ($ArIF_2$) are far less general. However, Hara, Yoneda and co-workers have reported that the combination of 4-iodotoluene difluoride (4-TolIF_2) in CH_2Cl_2 with Et_3N·5HF as a co-solvent enables the vicinal difluorination of (mostly terminal) alkenes in moderate to good yields.[174] As the sole example of an internal alkene, cyclohexene derivative **60** gave *syn*-difluoride **61** in 55% yield as a single diastereomer, providing some insight into the reaction mechanism. It is proposed that HF serves to activate the 4-TolIF_2 reagent via hydrogen-bonding (i.e., X–I–X polarization),[39] such that reaction with the alkene leads to iodiranium ion **XXIX**. Invertive ring-opening of **XXIX** by fluoride ion would give the *anti*-configured β-fluoroiodonium adduct **XXX** (examples of which have been isolated),[175] and then S_N2 displacement of the iodine(III) nucleofuge by a second fluoride ion would deliver the *syn*-difluorinated product (i.e., a Type II_{inv} dihalogenation pathway) (Scheme 58).



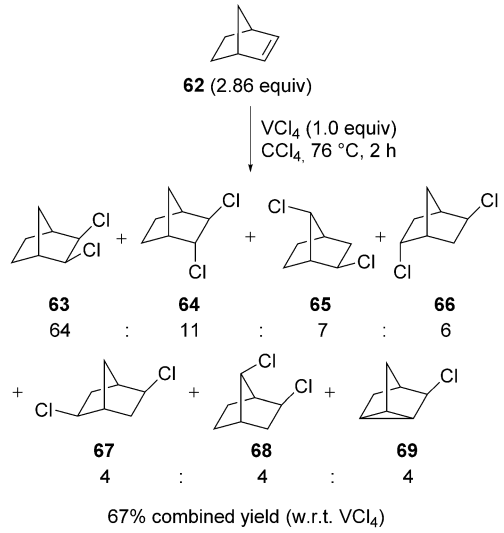
Scheme 58. Vicinal difluorination of alkene **60** with 4-TolIF_2 and Et_3N·5HF and the proposed Type II_{inv} mechanism.

5. Alkene Dihalogenations with Transition Metal Halides as Reagents or Catalysts

5.1. Group 5 Metal Halides

5.1.1. Vanadium

On the basis of a precedent for the use of vanadium(IV) chloride (VCl_4) as a chlorinating agent for arenes,[176] Uemura et al. have briefly investigated its competency as a dichlorinating agent for alkenes, reacting it with norbornene,[103] norbornadiene,[104] and (*Z*)-cyclooctene.[125,126] With norbornene **62**, a mixture of chlorinated products **63–69** is obtained, although *syn*-dichloride **63** predominates, and control experiments indicate that the product ratio is the result of kinetic control (Scheme 59). In contrast, almost no *syn*-dichloride is formed in similar reactions with cyclohexene and norbornadiene. Although a radical mechanism was excluded on the basis that no change in the isomer distribution occurs when the reactions are conducted in the presence of 1,3-dinitrobenzene or oxygen, the presence of **63** and **64** as major products is uncharacteristic of a purely ionic pathway. The results with norbornadiene are similarly inconclusive[104] and although some 1,4-dichlorination is observed with (*Z*)-cyclooctene (indicative of an ionic pathway), the yield and selectivity are low.[126]



Scheme 59. Dichlorination of norbornene **62** using VCl_4.

5.1.2. Niobium and Tantalum

Both niobium(V) chloride ($NbCl_5$) and tantalum(V) chloride ($TaCl_5$) are unreactive with cyclohexene and norbornene upon heating in CCl_4,[103] and there are no reports of their successful use as dichlorinating agents.

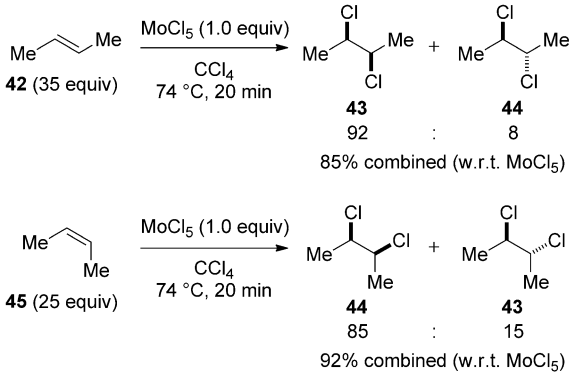
5.2. Group 6 Metal Halides

5.2.1. Chromium

Chromium halides have not been used preparatively for alkene dihalogenation, but Sharpless and co-workers have reported that *syn*-dichlorides are formed as minor products (in up to 13% yield) from the oxidation of alkenes with chromyl chloride (CrO_2Cl_2) at low temperature.[94] Although a Type III_{ret} mechanism was proposed by Sharpless et al., Nelson and co-workers suggest that a concerted Type IV dichlorination is in operation based on linear correlations between log k_{rel} and either alkene ionization potentials or HOMO energies.[97]

5.2.2. Molybdenum

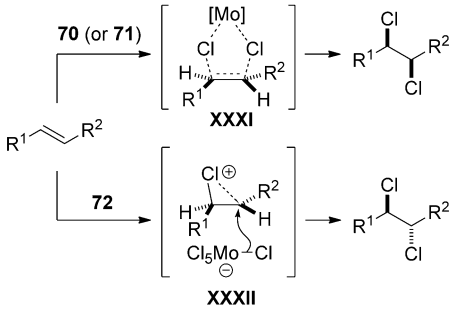
The dichlorination of alkenes with stoichiometric amounts of $MoCl_5$ shares many similarities with the corresponding reactions using $SbCl_5$ as the chlorinating agent (Section 4.3.3); *syn*-stereospecific dichlorination occurs, and typically with lower yields but higher diastereoselectivities than the $SbCl_5$-mediated processes. Following an early report on the dichlorination of tetrachloroethylene with $MoCl_5$ to give hexachloroethane,[177] the groups of Uemura[178] and San Filippo,[179] generalized the reaction and revealed its unusual *syn*-stereospecificity.[180] Thus, addition of excess (*E*)-2-butene **42** (35 equiv) to a pale red-brown solution of $MoCl_5$ in CCl_4 at 74 °C provides a 92:8 mixture of *syn*/*anti* dichlorination products **43**:**44** in 85% combined yield (w.r.t. $MoCl_5$). An analogous dichlorination of (*Z*)-2-butene **45** confirmed the stereospecific nature of the process (Scheme 60). As a large excess of the alkene component is generally required due to competing polymerization, all reported yields are based on $MoCl_5$ as the limiting reagent. 1,2-Disubstituted alkenes typically give reasonable quantities of *syn*-dichlorinated products (63–68%), but the use of terminal, tri- and tetrasubstituted alkenes did not lead to synthetically useful results (≤10% product).[179] Monochlorides were also formed as by-products in many cases which is ascribed to the in situ generation of HCl by hydride abstraction from the allylic position of the alkenes by $MoCl_5$.[178] No reaction occurs with electron-deficient alkenes such as ethyl fumarate and ethyl



Scheme 60. *Syn*-stereospecific dichlorination of alkenes using $MoCl_5$.

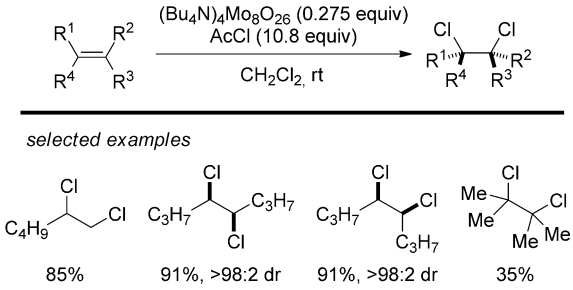
maleate, and only a trace (< 5 %) of dichloride is obtained from styrene.[178]

By analogy to their earlier proposal for $SbCl_5$-mediated *syn*-dichlorination,[125] Uemura and co-workers proposed that a concerted transfer of both chlorine atoms may occur from monomeric[181] $MoCl_5$ **70** (or possibly dimeric Mo_2Cl_{10} **71**)[182] to the alkene via a 5-membered cyclic transition state **XXXI** (i.e., a Type IV mechanism).[178] A Type III_{ret} mechanism involving *syn*-chlorometalation followed by stereoretentive reductive elimination (w.r.t. Mo) was seemingly not considered and should not be ruled out. The formation of dichlorides resulting from *anti*-addition, as well as certain rearranged products from norbornene and norbornadiene, is ascribed to ion pair $[MoCl_4]^+[MoCl_6]^-$ **72** as the reactive chlorinating species,[176] which may promote an ionic mechanism via β-chloro carbocation **XXXII** (or chloriranium ion) intermediates (Scheme 61). Comparison of the results with those for $SbCl_5$ as a chlorinating agent[125] indicates that $MoCl_5$ may exist primarily in neutral forms **70** or **71** in CCl_4, in contrast to $SbCl_5$ whereby an ion pair analogous to **72** (i.e., $[SbCl_4]^+[SbCl_6]^-$) appears to make a larger contribution, probably as a consequence of the higher Lewis acidity of $SbCl_5$.



Scheme 61. Proposed parallel mechanisms for the formation of *syn*- and *anti*-dichlorination products, respectively, arbitrarily illustrated for an (*E*)-configured alkene.

Considering the synthetic limitations of the aforementioned alkene dichlorinations with $MoCl_5$, Nugent has developed a milder and more selective variant of this reaction using tetrabutylammonium octamolybdate $[(Bu_4N)_4Mo_8O_{26}]$ in combination with acetyl chloride (AcCl) as the chloride source, in which a polychloromolybdenum(VI) chlorinating agent is thought to be generated in situ.[183] This method enables the clean *syn*-dichlorination of a range of alkenes in excellent yield (mostly 83–94 % based on alkene), and all with > 98:2 *syn*/*anti* addition selectivity, with the reactions being run at ambient temperature in CH_2Cl_2 (Scheme 62). In view of the isolation of Mo^V complexes $Bu_4NMoOCl_4$[184] and $MoOCl_3$ (as its $OPPh_3$ complex)[185] as by-products, the stoichiometry of the reaction is thought to be: alkene + $0.25\,Mo_8O_{26}^{4-}$ + 9 AcCl → dichloride + $MoOCl_4^-$ + $4\,MoOCl_3$ + $4.5\,Ac_2O$. In contrast to Uemura et al.,[178] Nugent suggests a Type III_{ret} mechanism to account for the *syn*-stereospecificity.



Scheme 62. Nugent's protocol for molybdenum-mediated *syn*-dichlorination of alkenes.

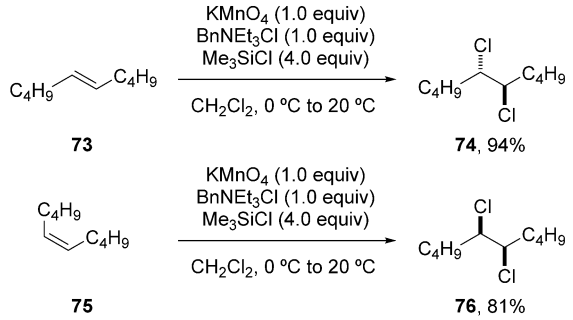
5.2.3. Tungsten

Tungsten hexachloride (WCl_6) is a competent chlorinating agent for (excess) cyclohexene, affording 41 % of the corresponding *syn*-dichloride and < 1 % of the *anti*-dichloride,[179] although it is unreactive with norbornene.[103] Moreover, in situ prepared tungsten hexabromide (WBr_6) reacts with an excess of cyclohexene to give a mixture of *syn*-dibromide (40–45 %) and *anti*-dibromide (5–10 %).[179]

5.3. Group 7 Metal Halides

5.3.1. Manganese(VII)

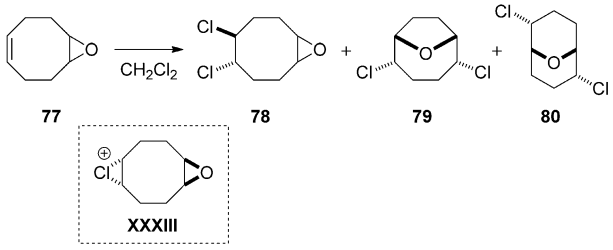
The combination of organic soluble benzyltriethylammonium permanganate ($BnNEt_3MnO_4$) with chloride-based promoters has been developed by Markó and co-workers as a reagent system for the highly *anti*-stereospecific dichlorination of alkenes.[32] Although the initial reports of this method employed oxalyl chloride [$(COCl)_2$] as the promoter and chloride source,[32b,c] the use of chlorotrimethylsilane (Me_3SiCl) was later found to be more practical,[32a] allowing the reactions to be run at ambient temperature as opposed to under cryogenic (−45 °C) conditions. Thus, the reaction of 5-decenes (*E*)-**73** or (*Z*)-**75** with a pre-formed mixture of $KMnO_4$/$BnNEt_3Cl$/Me_3SiCl (1:1:4) in CH_2Cl_2 affords dichlorides *anti*-**74** or *syn*-**76**, respectively, as single diastereomers in excellent yield (Scheme 63). A similar protocol has also been reported by Hazra and Pore, using tetradecyltrimethylammonium permanganate ($H_{29}C_{14}NMe_3MnO_4$) as a "safer" alter-



Scheme 63. *Anti*-stereospecific dichlorination of alkenes with Markó's reagent.

native to (isolated) $BnNEt_3MnO_4$ (the former does not detonate upon drying of the solid reagent at elevated temperatures).[186] With Me_3SiBr in place of Me_3SiCl, the latter reagent system has also been employed for the *anti*-selective dibromination of alkenes.[187] The use of $BnNEt_3MnO_4$ with $(COCl)_2$ or Me_3SiCl as promoters has also been extended to the vicinal dichlorination of allenes.[188]

Markó et al. have suggested that chloriranium ions (arising either from molecular Cl_2 or some other Cl^+ equivalent) are unlikely to be intermediates in these manganese(VII)-mediated dichlorinations. Specifically, different product distributions are observed for the dichlorination of cyclooctadiene monoepoxide **77** with either Cl_2 (in CH_2Cl_2 at 20 °C) or Markó's reagent [using either $(COCl)_2$ at −40 °C[32b] or Me_3SiCl at 0→20 °C.[32a] Whereas Cl_2 leads to extensive transannular participation by the oxirane oxygen to give dichlorinated bicyclic ethers **79** and **80** (via a putative chloriranium ion **XXXIII**), the manganese(VII)-mediated reactions give predominantly 1,2-dichloride **78**, and only traces of bicyclic products **79** and **80** (Scheme 64). Although this was cited as evidence for the lack of a chloriranium ion intermediate in the latter case, there are alternative explanations which are compatible with chloriranium ion (or alkene-Cl_2 π-complex) intermediacy in both cases.[189] Moreover, it is conceivable that the other components present in the manganese(VII)-mediated reactions may simply have suppressed the epoxide participation (e.g., Lewis acidic Mn salts complexing the oxirane), or that the chloride ion concentration is higher than in the reaction with Cl_2.[36] The difference in reaction temperatures also calls into question the validity of direct comparisons.

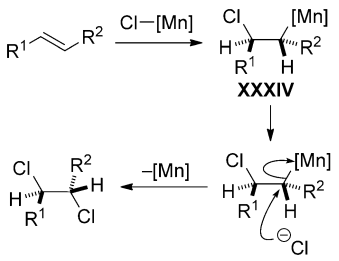


With Cl_2 at 20 °C:	18	:	33	:	49
With $BnNEt_3MnO_4$ + $(COCl)_2$ at −40 °C:	91	:	5	:	4
With $BnNEt_3MnO_4$ + Me_3SiCl at 0 °C to 20 °C:	60% (isolated)	:	~30% combined yield		

Scheme 64. Experiments to probe the intermediacy of chloriranium ions as intermediates.

Other observations, such as a lack of chlorination activity on pre-warming the active reagent to room temperature [with $(COCl)_2$ as promoter][32b,c] and the differing product distributions for dichlorinations of certain dienes with either "excess" Cl_2 or "excess" manganese-based reagent[186] have also been invoked as evidence that molecular Cl_2 is not the active chlorinating agent, although again the assumption that "all else is equal" may be invalid. Although further studies are needed to exclude chloriranium ions as intermediates (i.e., a Type I mechanism), both Markó[32] and Hazra[186] have proposed that the manganese(VII)-mediated reactions proceed via a Type III_{inv} mechanism, with an initial *syn*-chlorometalation of the alkene to give a β-chloro alkylmanganese species **XXXIV**, followed by an invertive S_N2-type reductive elimination of [Mn] by chloride ion (Scheme 65).

An argument against a Type III_{inv} process has been made by Vanderwal and co-workers, who noted that the Markó reagent is also capable of cleanly effecting the *anti*-dichlorination of *alkynes*, in which case a similar *syn*-chlorometalation would then necessitate an unlikely S_N2 invertive displacement by chloride ion at a $C(sp^2)$ center.[190]



Scheme 65. Mechanistic proposal for the *anti*-dichlorination of alkenes by Markó's reagent.

With Me_3SiCl as the promoter, Hazra and Pore have probed the in situ generated reagent by both EPR and UV-vis spectroscopy and have cautiously assigned the active species as manganese(V) oxide trichloride (Cl_3MnO).[186] Their assignment was based upon a UV-vis absorbance at 400 nm, which matched that reported for an independently prepared sample of Cl_3MnO.[191] An EPR spectrum was also obtained that consisted of "six sharp lines", and this was stated as being consistent with a "lower valent manganese species with unpaired electrons".[186] However, only transition metal complexes possessing an odd number of unpaired electrons (i.e., d^1, d^3, d^5, d^7, or d^9 configurations) are EPR active at the X-band frequencies which are typically employed,[192] so Cl_3MnO as a Mn^V (d^2) species cannot be responsible for the observed EPR signal. The signal would be consistent however with either Mn^{IV}[193] (d^3) or Mn^{II} (d^5).

The presence of lower valent manganese species in solution following the addition of Me_3SiCl, but prior to the addition of the alkene, proves that a redox reaction has occurred between Me_3SiCl and the MnO_4^- ion. By direct analogy to the oxidation of Cl^- by permanganate ions in acidic media, this reaction may be: $2[R_4N^+][MnO_4^-] + 16Me_3SiCl \rightarrow 2[R_4N^+][MnCl_3^-] + 5Cl_2 + 8(Me_3Si)_2O$. However, the stoichiometry required by this equation (i.e., 1:8 MnO_4^-/Me_3SiCl) implies that only half of the MnO_4^- employed in the Markó protocol (1:4 MnO_4^-/Me_3SiCl) should be consumed by this process (generating 1.25 equiv of Cl_2 w.r.t. the alkene). The excess MnO_4^- may react with the initial Mn^{II} product in a process such as $Mn^{VII} + Mn^{II} \rightarrow Mn^V + Mn^{IV}$, which could account for the EPR activity [that is, Mn^{IV}][193] and the assignment of the Mn^V species Cl_3MnO from UV-vis data (see above). A final complication arises

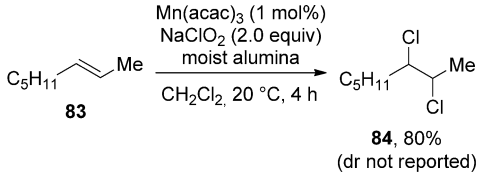
from the fact that M^V oxo compounds of the form O=Mn(salen)Cl are known to abstract chlorine atoms from CH_2Cl_2 to generate Mn^{IV} hypochlorite complexes [i.e., Mn(salen)(OCl)Cl] which are able to dichlorinate alkenes.[193a]

To conclude, if Cl_2 is indeed being generated in this redox process,[194] it is presumably responsible for dichlorinating the alkene, and there are even potential explanations for the loss of chlorination activity on warming.[195] Furthermore, Vanderwal and co-workers have reported that the diastereoselectivities of the dichlorination of chiral allylic alcohols with the Markó reagent and Mioskowski reagent (Et_4NCl_3)[28] are virtually identical, providing circumstantial evidence that the former reagent system may simply involve an in situ generation of an R_4NCl_3-type species, with Cl_3^- as the active chlorinating species.[190] Clearly, the overall picture for manganese(VII)-mediated alkene dichlorinations is complex, and further work is necessary to fully deconvolute the process.

5.3.2. *Manganese(III) and (IV)*

In addition to manganese(VII)-mediated alkene dichlorinations, a variety of other protocols employing lower valent manganese reagents (i.e., Mn^{III} or Mn^{IV}) have also been described. For example, isolated Mn^{III} chlorides such as $MnCl_3$·HOAc or salts of the form $M_2[MnCl_5]$ (e.g., $M^+ = NH_4^+$, NMe_4^+, PyH^+, $PhCH_2NMe_3^+$) are competent dichlorinating agents for alkenes, and $Mn(OAc)_3$ in AcOH combined with either $CaCl_2$ or AcCl can be used to generate "$MnCl_3$" in situ.[196] A related reagent system for alkene dichlorination is MnO_2-$MnCl_2$-AcCl (1.5:1:6) in DMF, which is thought to generate Mn^{III} chlorides by the comproportionation of Mn^{II} and Mn^{IV} (i.e., $Mn^{II} + Mn^{IV} \rightarrow 2\,Mn^{III}$).[197] Thus, the dichlorination of (*E*)-2-hexene **81** under the latter conditions affords a 64:36 mixture of *anti*/*syn* dichlorination products **82** in 95% combined yield. On the basis of the relatively low diastereoselectivity and the absence of ionic pathway-derived by-products from certain alkenes (e.g., *tert*-butylethylene, norbornene), as well as positive tests for radical cyclizations, a Type V dichlorination via a non-chain radical mechanism has been proposed for these Mn^{III}-mediated reactions (Scheme 66).[196,197]

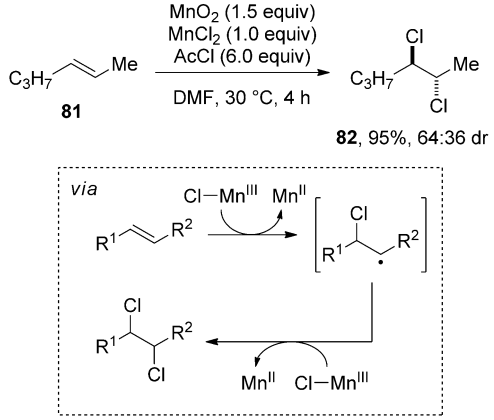
The vicinal dichlorination of alkenes has even been reported using a substoichiometric amount of $Mn(acac)_3$ (i.e., 1 mol%) with sodium chlorite ($NaClO_2$) as the reoxidant. For example, reaction of (*E*)-2-octene **83** under these conditions gives dichloride(s) **84** in 80% yield (Scheme 67).[198] However, the authors declined to report the relative configurations or diastereomeric compositions of the dichloride products, and they also did not report a control experiment in the absence of $Mn(acac)_3$. Furthermore, based on the reactivity of Mn^{III}(salen)Cl **87** with sodium hypochlorite (NaOCl) in CH_2Cl_2 (see below), the possibility that the CH_2Cl_2 solvent may be a source of chlorine atoms cannot be excluded.[193a]



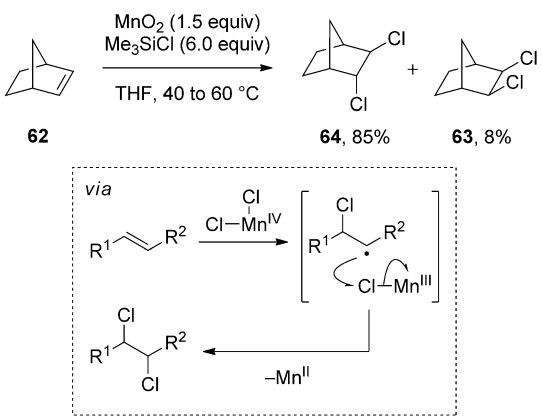
Scheme 67. Mn^{III}-catalyzed dichlorination of alkenes.

Manganese(IV) chlorides have also been implicated as dichlorinating agents for alkenes. Despite the fact that MnO_2 is well known to oxidize aqueous HCl to molecular chlorine,[194] the reagent combination of MnO_2-Me_3SiCl in THF reacts with alkenes at 40–60 °C to give vicinal dichlorides without the distinctive by-products characteristic of Cl_2 involvement.[199] For example, and similarly to the Mn^{III}-mediated dichlorinations above, no skeletal rearrangements take place with *tert*-butylethylene or norbornene, and no allylic chlorination occurs with trisubstituted alkenes. In the reaction with norbornene **62**, for example, clean conversion to vicinal dichlorides **64** and **63** is observed, and a Type V non-chain radical mechanism has been proposed for these reactions (Scheme 68).

Pecoraro and co-workers have reported Mn^{IV}(salpn)Cl_2 **85** as the first structurally well-characterized manganese chloride species capable of dichlorinating alkenes.[200] For

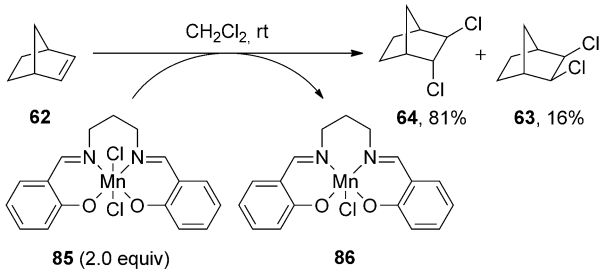


Scheme 66. Alkene dichlorination mediated by Mn^{III} chlorides.



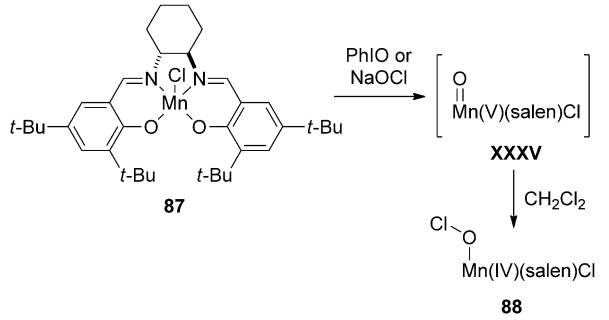
Scheme 68. Alkene dichlorination mediated by Mn^{IV} chlorides.

example, the treatment of norbornene **62** with 2.0 equiv of **85** gave dichlorides **64** and **63** in yields of 81% and 16%, respectively. The Mn product of the reaction was identified as Mn^{III}(salpn)Cl **86** (Scheme 69).



Scheme 69. Alkene dichlorination with a structurally well-characterized Mn^{IV} halide.

During a study on the possible involvement of Mn^{IV} species in the Jacobsen–Katsuki epoxidation, Mock-Knoblauch and co-workers showed that the treatment of Jacobsen's catalyst Mn^{III}(salen)Cl **87** with either PhIO or NaOCl in CH_2Cl_2 gave, inter alia, Mn^{IV} hypochlorite complex **88**.[193a] On the basis of EPR and mass spectrometry data, a mechanism for the formation of **88** involving chlorine abstraction from CH_2Cl_2 by a transient O=Mn^{V}(salen)Cl intermediate **XXXV** is proposed (Scheme 70).

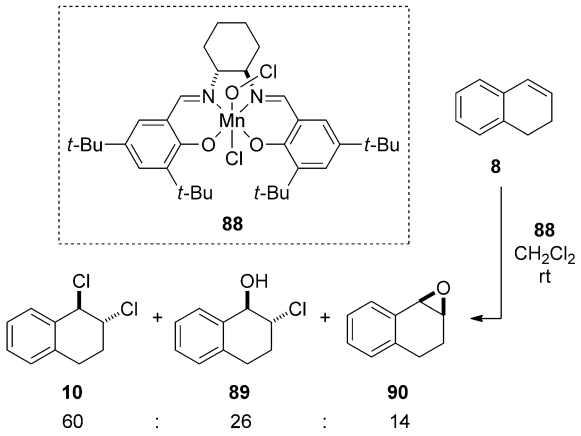


Scheme 70. Chlorine atom abstraction from CH_2Cl_2 to generate a Mn^{IV} hypochlorite complex **88**.

This Mn^{IV} hypochlorite complex **88** is capable of dichlorinating alkenes. For example, the reaction of **88** with 1,2-dihydronaphthalene **8** in CH_2Cl_2 affords *anti*-dichloride **10** as the major product, in addition to some chlorohydrin **89** and epoxide **90** (Scheme 71). Although the chlorinating agent **88** is chiral and non-racemic, **10** is formed with only negligible enantioenrichment (< 52.5:47.5 er).

5.3.3. Rhenium

Rhenium(V) chloride ($ReCl_5$) is known to react stoichiometrically with tetrachloroethylene to generate hexachloroethane, although the targeted compound in this particular reaction is actually the reduced metal salt, rhenium(IV) chloride ($ReCl_4$).[201]



Scheme 71. Ability of Mn^{IV} hypochlorite complex **88** to dichlorinate alkenes.

5.4. Group 8 Metal Halides

5.4.1. Iron

Although iron(III) chloride ($FeCl_3$) has been used as a stoichiometric reagent to effect the chlorination of arenes (i.e., $Ar{-}H + 2\,FeCl_3 \rightarrow Ar{-}Cl + 2\,FeCl_2 + HCl$),[202] it is unreactive toward norbornene,[103] and there are no examples of alkene dichlorination with this reagent.

5.4.2. Ruthenium

Sakai and co-workers have shown that the dichlorination of a variety of alkenes can be effected using hexachloroethane as the chlorinating agent in the presence of 1 mol% $RuCl_2(PPh_3)_2$ in refluxing toluene (Scheme 72).[203] This reaction is closely related to metal-catalyzed (or metal-initiated) variants of the Kharasch addition of polyhaloalkanes to alkenes,[204] with the exception here that the intermediate carbon radical derived from the polyhaloalkane undergoes β-scission to give a chlorine atom radical (and tetrachloroethylene) before it engages the olefin. Unfortunately the stereochemical course of the reaction, which might help to support or refute the proposed Type V mechanism, was not evaluated.

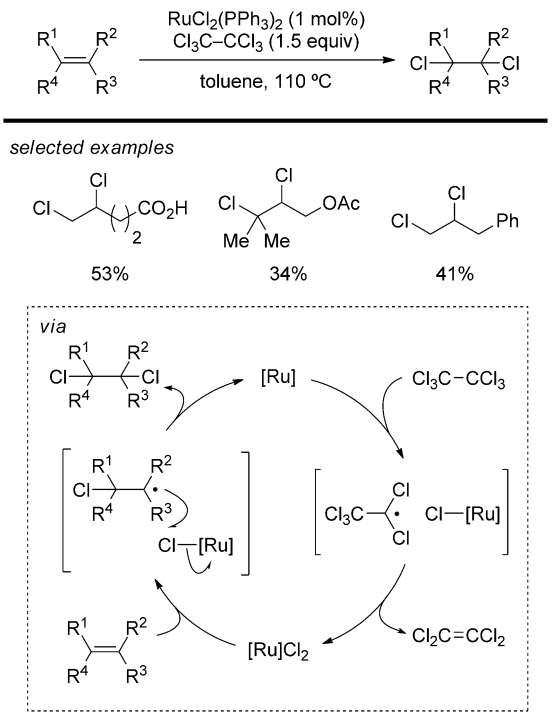
5.5. Group 9 Metal Halides

To the best of our knowledge, no reports of the use of cobalt, rhodium, or iridium halides as stoichiometric reagents for the dichlorination or dibromination of alkenes are extant, nor is the use of these elements as redox catalysts for such transformations. Cobalt(III) fluoride (CoF_3) has been used however to difluorinate simple halogenated olefins.[205]

5.6. Group 10 Metal Halides

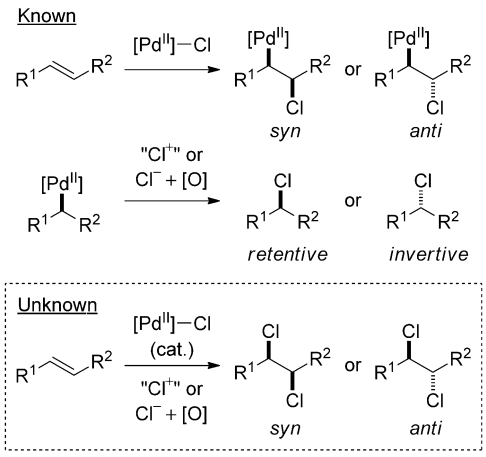
5.6.1. Palladium

Despite the fact that chloropalladations of alkenes with $Pd^{II}{-}Cl$ complexes are known,[82,92] as well as oxidatively-



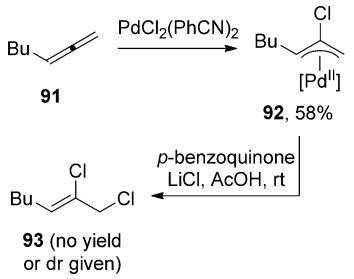
Scheme 72. Ruthenium-catalyzed alkene dichlorination by a Type V mechanism.

induced stereoretentive[76,83a–f,i] and invertive (S_N2-like)[76,84] reductive eliminations of alkyl–Pd^{II} intermediates to form $C(sp^3)$–Cl bonds, no Pd-catalyzed alkene dichlorinations combining these elementary steps are on record (Scheme 73).[206]



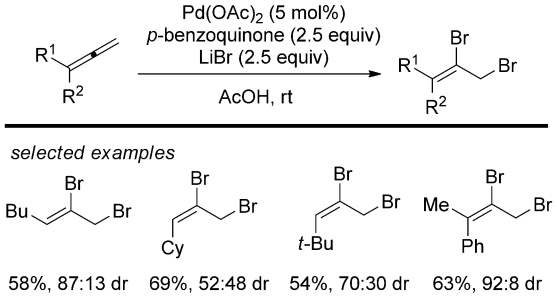
Scheme 73. A palladium-catalyzed dichlorination of alkenes?

However, the vicinal dichlorination of *allenes* with a stoichiometric amount of $PdCl_2(PhCN)_2$ has been achieved by Bäckvall and Jonasson, in which these two elementary steps are performed in a stepwise manner.[207] Thus, the reaction of 1,2-heptadiene **91** with stoichiometric $PdCl_2(PhCN)_2$ gave 2-chloro π-allyl complex **92** in 58% yield, and subsequent treatment with *p*-benzoquinone and LiCl in AcOH gave the corresponding vicinal dichloride **93** (of unspecified dr and in unspecified yield) (Scheme 74). Attempts to run the dichlorination under catalytic conditions were unsuccessful due to a competing reaction of the π-allyl complex **92** with unreacted allene **91**.



Scheme 74. Stepwise dichlorination of an allene using stoichiometric palladium.

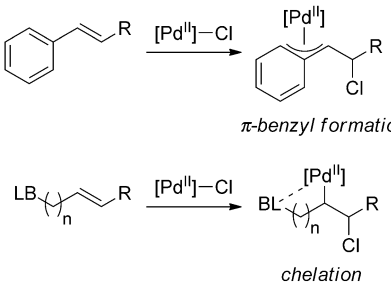
Interestingly, a catalytic *dibromination* of allenes could be achieved by replacing LiCl with LiBr, and this was applied to a range of allenes (Scheme 75).[207] The success may be ascribed to the greater nucleophilicity of the bromide ion (w.r.t. chloride ion), which enables the halide to outcompete the allene starting material in intercepting the π-allyl intermediate.



Scheme 75. Palladium-catalyzed dibrominations of allenes. Cy = cyclohexyl.

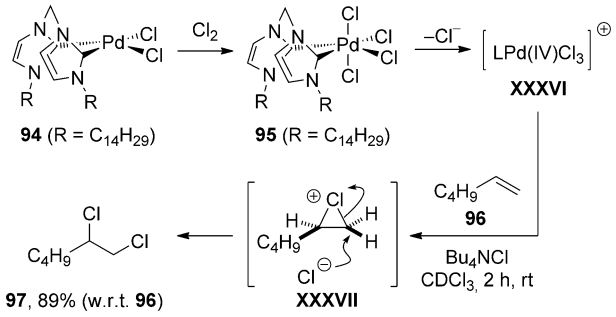
Of course the crucial difference between allenes versus alkenes as substrates for this transformation is the thermodynamic favorability of the halopalladation step in the former case—a consequence of the formation of a stable Pd^{II} π-allyl complex. On the other hand, halometalations of alkenes in general are endergonic, and the reverse process of β-halo elimination renders the β-halo metalated intermediates highly unstable.[86] This suggests that successful Pd-catalyzed alkene dihalogenations may benefit from stabilization of the alkyl–Pd^{II} intermediate, perhaps by π-benzyl formation (i.e., by employing aryl alkene substrates) or by chelation with a proximal functional group (Scheme 76).

Another strategy to avoid unproductive β-halo elimination from a chloropalladated intermediate might be to circumvent the alkyl–Pd^{II} species altogether, and design



Scheme 76. Potential strategies for stabilizing the alkyl–Pd^{II} intermediate against unproductive β-halo elimination. LB = Lewis base.

a catalytic system in which oxidation of $Pd^{II} \rightarrow Pd^{IV}$ precedes interaction with the alkene substrate. With this in mind, Kraft and co-workers have shown that the isolated $LPd^{IV}Cl_4$ complex **95** (prepared by oxidation of the corresponding $LPd^{II}Cl_2$ complex **94** with Cl_2) is capable of dichlorinating alkenes in an *anti*-selective fashion.[208] For example, the reaction of 1-hexene **96** with $LPd^{IV}Cl_4$ **95** and Bu_4NCl in $CDCl_3$ at rt affords dichloride **97** in 89% NMR yield (w.r.t. **96**). Mechanistic studies support a Type I mechanism involving the slow formation of cationic $LPd^{IV}Cl_3^+$ **XXXVI**, followed by chlorenium ion transfer to the alkene (in a ligand-mediated process devoid of π-coordination) to give a chloriranium ion species **XXXVII**, which is then trapped by chloride ion (Scheme 77). In subsequent work, Kraft et al. showed that pyridine significantly enhances the rate of the reaction of $LPd^{IV}Cl_4$ **95** with alkenes, and that a "catalytic" dichlorination of styrene is possible with $LPd^{IV}Cl_3(py)^+$ as an in situ generated catalyst and $LPd^{IV}Cl_4$ **95** as the stoichiometric oxidant.[209]

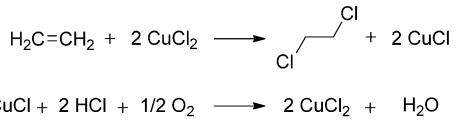


Scheme 77. Pd^{IV}-mediated dichlorination of alkenes.

5.7. Group 11 Metal Halides

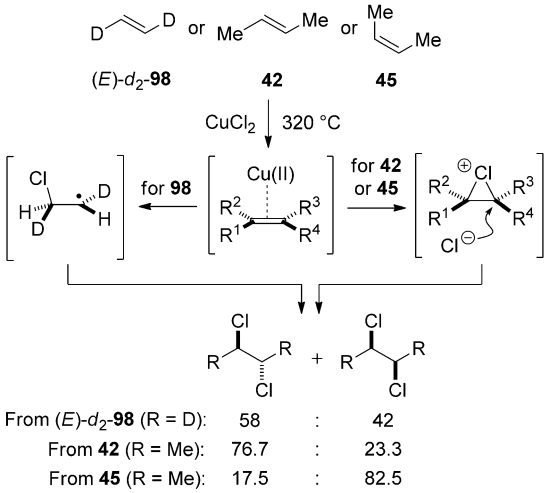
5.7.1. Copper

It has long been known that the gas-phase reaction of alkenes with solid-supported $CuCl_2$ at high temperatures (220–330 °C) results in the formation of vicinal dichlorides, along with reduction of $CuCl_2$ to CuCl. As the so-called "oxychlorination" process, this reaction is used on industrial scale for the synthesis of 1,2-dichloroethane, with the CuCl being reoxidized to $CuCl_2$ with HCl and O_2 (Scheme 78).[210]



Scheme 78. The "oxychlorination" process for the dichlorination of ethylene.

The mechanism of the (stoichiometric) reaction of alkenes with pumice-supported $CuCl_2$ has been studied,[211] as has the chemisorption of ethylene with $CuCl_2$ and CuCl,[212] and the initial step of the process is thought to involve π-complex formation between the olefin and surface Cu^{II} ions.[211a,212] The mechanistic course from this point depends on the nature of the olefin, with (*E*)-d_2-ethylene **98** giving poorly stereoselective dichlorination and 2-butenes **42** and **45** undergoing *anti*-dichlorination with moderately high stereospecificity (Scheme 79).[211a] Control experiments indicate that neither alkene nor dichloride isomerization is significant for the reaction of (*E*)-d_2-**98**, but both occur to some extent for **42** and **45**, eroding the stereospecificity. It was surmised that the reaction partitions between a radical and ionic pathway, depending on the substitution of the alkene. A similar phenomenon has been observed by Poutsma in the dark chlorination of several olefins using Cl_2 under nitrogen, with the ionic route being favored for more highly substituted alkenes at low alkene concentrations, and the radical addition being far less stereoselective than the former.[24] Control experiments indicate that Cl_2 is not the active chlorine source in these reactions,[213] although it is assumed that the rate of disproportionation of $CuCl_2$ is unaffected by [ethylene].

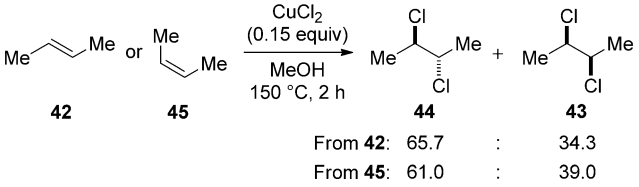


Scheme 79. Gas-phase dichlorination of alkenes on pumice-supported $CuCl_2$.

For solution-phase dichlorinations of olefins with $CuCl_2$, early work involving photochemical activation of $CuCl_2$ by Kochi[214] was followed by the development of a thermal reaction in aqueous solution by Miller and co-workers.[215] The dichlorination of alkenes with $CuCl_2$ in organic solvents (AcOH or alcohols) was later studied by Uemura et al.,

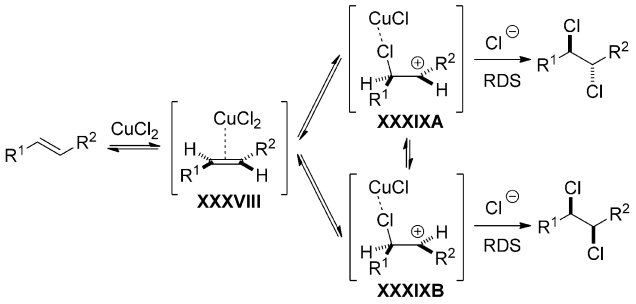
including the reaction scope,[216] kinetics,[217] effect of additives (NaOAc, NaCl),[218] and the use of butadiene as a substrate,[219] all of which are summarized in a subsequent overview article.[220] Further detailed investigations were performed by Koyano and co-workers,[221] including establishing the stereochemical course of the reaction,[222] the influence of additives (e.g., LiCl),[223] and the kinetics.[223]

In general, these dichlorination reactions are conducted using stoichiometric amounts of $CuCl_2$, typically in AcOH or alcohol solvents, at temperatures ranging from 70 to 150 °C (though often > 100 °C).[220,221] The use of somewhat lower temperatures (70–80 °C) is possible in MeCN as the solvent,[224] but LiCl is usually added in these cases to solubilize the $CuCl_2$ and to further enhance the rate.[220,225] Chlorine has been deemed unlikely to be the active chlorinating agent in these reactions[221] as $CuCl_2$ is known not to decompose to CuCl and Cl_2 at these temperatures in the solvents employed[226] (albeit in the absence of olefins). Dichlorinations conducted in alcohol solvents are often complicated by competing chloroalkoxylation processes,[220,221] although the addition of LiCl promotes the formation of dichloride products.[223] In contrast to the gas-phase chemistry,[211] the reactions of 2-butenes **42** and **45** in alcohols, AcOH or $MeNO_2$ as the solvent are not stereospecific, yielding a common ~60:40 mixture of *anti*/*syn* dichlorination products **44**:**43** (Scheme 80, data shown for MeOH). Control experiments probing isomerization of either the alkene substrates or dichloride products indicate that this ratio is the result of kinetic control.



Scheme 80. Non-stereospecific dichlorination of 2-butenes with $CuCl_2$ in MeOH.

The reaction kinetics in alcohol solvents have been studied by the groups of Uemura[220] (with styrene in *n*-PrOH) and Koyano (with 1-octene in MeOH),[223] with both sets of authors arriving at a similar (initial) rate law of the form: $\text{rate}_0 = k_{obs}[\text{alkene}]_0[CuCl_2]_0^n$ (where $n = 1.8$ for Uemura and $n = 1.6$ for Koyano). Additionally, a reactivity order (based on conversion of $CuCl_2$ in independent experiments) of ethylene > propylene > 1-butene > 2-butenes was also established. This behavior parallels the stability of Ag^I-olefin π-complexes,[227] and is taken as support for Cu^{II}-alkene π-complex intermediates. On the basis of all of the above findings, Koyano et al. have proposed the following mechanism (Scheme 81).[221] Initial formation of a Cu^{II}-alkene π-complex **XXXVIII** is followed by transfer of Cl^+ from the Cu to generate a β-chlorocarbenium ion intermediate **XXXIX**, in which association of the chlorine atom with the Cu prevents its efficient bridging to give a chloriranium ion species.[228] Rapid interconversion of these carbocations **XXXIXA** and



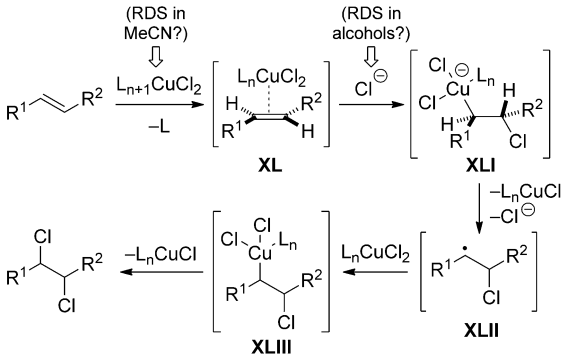
Scheme 81. Mechanistic proposal for the dichlorination of alkenes with stoichiometric amounts of $CuCl_2$ in alcohol solvents.

XXXIXB prior to nucleophilic trapping would account for the lack of stereospecificity. From the experimental rate law, the rate-determining step (RDS) is proposed to be the nucleophilic trapping of carbocations **XXXIX**. Considering an order in $CuCl_2$ of 1.8 (assumed to be 2 within error), Uemura and co-workers propose that $CuCl_2$ may be the active nucleophile in this process,[220] but Koyano et al. show that an order of 1.5 in $CuCl_2$ would be expected for ($CuCl_2$-derived) Cl^- ion as the active nucleophile—in good agreement with their order of 1.6.[223] Both the CuCl by-product and H_2O are potent inhibitors, probably due to the former sequestering free Cl^- ions[223] and the latter forming stable aqua complexes of $CuCl_2$. In contrast, the RDS in MeCN is believed to be formation of either the alkene-$CuCl_2$ π-complex **XXXVIII** or the β-chlorocarbenium ion **XXXIX**, based on a first-order dependence on both alkene and $CuCl_2$.[220]

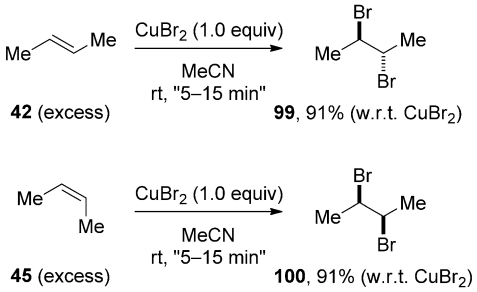
However, the proposed intermediacy of β-chlorocarbenium ions **XXXIX** in these reactions is difficult to reconcile with the results of other studies conducted with $CuCl_2$-LiCl in MeCN. Thus, a variety of alkenes (as mechanistic probes for ionic versus radical dichlorination) have been examined with $CuCl_2$-LiCl in MeCN, including norbornene,[103] norbornadiene,[104] cyclooctadienes,[107] and (*Z*)-cyclooctene.[126] In most cases the product distributions are more representative of radical rather than ionic processes, but the insensitivity of the reaction to radical inhibitors argues against a radical chain mechanism.

An alternative mechanism that is consistent with all of the experimental observations (i.e., kinetics, stereoconvergency, lack of carbocation-derived products) is outlined in Scheme 82. Thus, chloride ion attack on a Cu^{II}-alkene π-complex **XL** (i.e., a Type II addition), followed by homolysis of the C–Cu bond in **XLI** would furnish a β-chloroalkyl radical **XLII**. This carbon radical could then intercept another molecule of $CuCl_2$ to give a transient Cu^{III} alkyl species **XLIII**, which will reductively eliminate to give the dichloride product. Similar mechanisms involving nucleocupration of alkenes, C–Cu bond homolysis, and reductive elimination from Cu^{III} intermediates are well established for other copper-mediated alkene difunctionalizations.[229]

In contrast to alkene dichlorinations with $CuCl_2$, the analogous dibrominations with $CuBr_2$ proceed readily at ambient temperature,[79,224,226b,230] and are also highly *anti*-stereospecific in both alcohol[230] and MeCN solvents.[224] For example, the reactions of 2-butenes (*E*)-**42** and (*Z*)-**45** with



Scheme 82. A plausible mechanism for alkene dichlorinations with $CuCl_2$ that is consistent with all of the experimental observations.

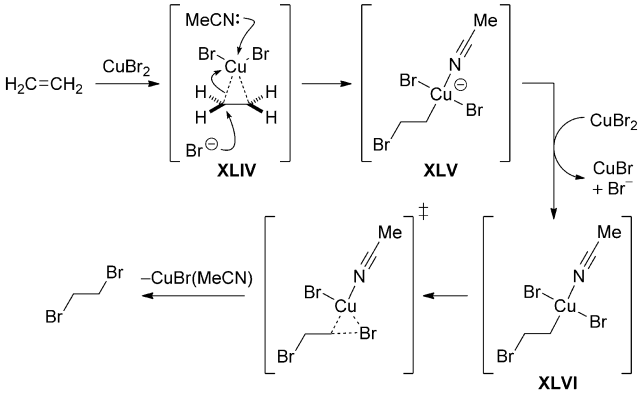


Scheme 83. Stereospecific dibromination of 2-butenes with $CuBr_2$.

$CuBr_2$ in MeCN at rt give dibromides *anti*-**99** and *syn*-**100**, respectively, in 91% yield (w.r.t. $CuBr_2$) (Scheme 83).

Baird and co-workers have found that certain "soft" or π-acidic ligands can substantially increase the chemical yield of alkene dibrominations with $CuBr_2$, and that in some cases these ligands are effective in only substoichiometric amounts [e.g., MeCN, Ph_3P, dppe [1,2-bis(diphenylphosphino)ethane], $(t\text{-BuO})_3P$].[224] In fact, the effectiveness of MeCN as a solvent for $CuBr_2$-mediated dibrominations is attributed to its π-acidic character as a ligand. These results are interpreted as being a consequence of the disproportionation of $CuBr_2$ to CuBr and molecular bromine (i.e., $CuBr_2 \rightarrow CuBr + {}^1/_2\,Br_2$), with "soft" or π-acidic ligands stabilizing the Cu^I product and driving the equilibrium to the right. An earlier kinetic study of these dibrominations by Castro et al., which found a second-order dependence on $CuBr_2$,[226b] was cited as support for this disproportionation as the rate-determining step, although other interpretations of this rate law are viable (c.f. mechanism of $CuCl_2$-mediated dichlorinations, see above). However, several other pieces of evidence, including the product distribution from the reaction of norbornadiene, the relative ordering of olefin reactivity ($R_2C{=}CR_2 > R_2C{=}CHR \gg RCH{=}CHR > RCH{=}CH_2$), and spectrophotometric evidence[231] for the generation of Br_2 and $CuBr_3^-$ in MeCN solutions of $CuBr_2$ are all supportive of Br_2 as the active brominating agent.[224]

However, for the dibromination of *n*-hexene with $CuBr_2$ in MeOH at 40 or 50 °C, a mechanism similar to that in Scheme 81 for $CuCl_2$ (albeit with fully bridged bromiranium ions) has been proposed by Koyano et al., on the basis of approximate third-order kinetics (approximately second-order in $CuBr_2$ and first-order in alkene).[230] A different mechanism altogether, supported by DFT calculations, has been advanced by Fraser-Reid, Snyder and co-workers for alkene dibrominations using a combination of $CuBr_2$ and LiBr in 3:1 MeCN/THF.[79] In what could be described as a Type II_{ret} mechanism (calculated for ethylene), attack of bromide ion on a Cu^{II}-alkene π-complex **XLIV** gives a square planar Cu^{II} anion **XLV**, followed by single electron transfer to $CuBr_2$ to generate a neutral Cu^{III} species **XLVI**. Reductive elimination then delivers the dibromide product and CuBr(MeCN) (Scheme 84). Ma and Wu propose a similar mechanism for CuX_2-mediated (X = Cl, Br) cyclization reactions of 2,3-allenoic acids.[232]



Scheme 84. Calculated Type II_{ret} mechanism for alkene dibromination with $CuBr_2$ and LiCl in MeCN/THF.

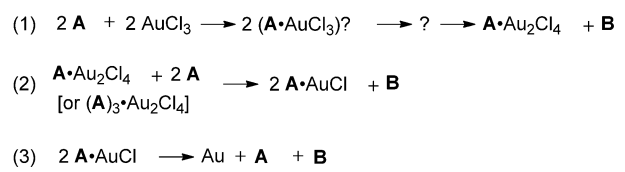
The dihalogenation of alkynes with $CuCl_2$[233] and $CuBr_2$[234] has also been reported, and is usually (though not always) *anti*-selective.

5.7.2. *Silver*

With the exception of silver(II) fluoride (AgF_2), which has been shown to difluorinate alkenes,[205] silver does not form halides in oxidation states higher than +1, and neither AgCl nor AgBr are sufficiently strong oxidants to effect halogenation reactions.

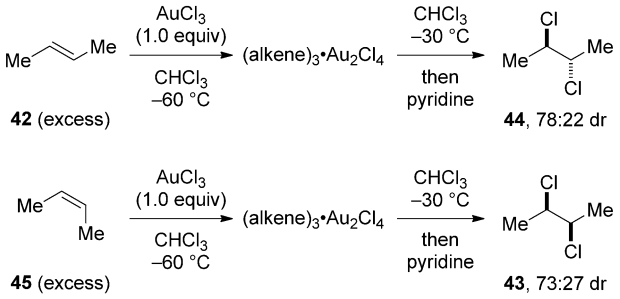
5.7.3. *Gold*

Unlike silver, gold is capable of forming halides in the +3 oxidation state, and gold(III) chloride ($AuCl_3$) is known to react with alkenes to afford the corresponding vicinal dichlorides.[235] Exposure of various alkenes (in excess) to $AuCl_3$ in cyclohexane at 20 °C over several hours provides vicinal dichlorides in excellent yields (w.r.t. $AuCl_3$) along with Au metal, but the reactions of 2-butenes **42** and **45** are non-stereospecific. Considering the isolation of intermediates, the net reactions are believed to be a composite of three sequential reactions (1)–(3), in which **A** is the alkene and **B** is the vicinal dichloride (Scheme 85).



Scheme 85. Sequential reactions in the dichlorination of alkenes with $AuCl_3$.

The $(alkene)_3{\cdot}Au_2Cl_4$ complexes implicated in this reaction manifold could actually be isolated at low temperature (−60 °C) in $CHCl_3$. The decomposition of these isolated $(alkene)_3{\cdot}Au_2Cl_4$ complexes in $CHCl_3$ at −30 °C (a model of reaction (2), Scheme 85), followed by sequestration of gold salts with added pyridine, affords the corresponding vicinal dichlorides. Curiously, under these conditions, the reactions of $(alkene)_3{\cdot}Au_2Cl_4$ complexes derived from 2-butenes (*E*)-**42** and (*Z*)-**45** are moderately stereospecific (Scheme 86). Furthermore, the decomposition of an authentic sample of alkene·AuCl [derived from (*Z*)-2-butene **45**] at 20 °C in $CHCl_3$ (a model of reaction (3), Scheme 85) is similarly stereospecific, giving **43** in 75:25 dr.



Scheme 86. Stereospecific dichlorination of 2-butenes with $AuCl_3$.

6. Closing Remarks

In the intervening years since the publication of our review on enantioselective halofunctionalization of alkenes,[4f] the pace of research activity in this burgeoning field has continued to increase. Impressive advances have been recorded for the functionalization of different types of alkenes engaging all of the common halogens in combination with a wide variety of nucleophilic heteroatoms. Although the vast majority of these halofunctionalization reactions are intramolecular and form small ring heterocycles, intermolecular process have also been described with increasingly better scope and stereoselectivity. Moreover, the development of novel reactivity concepts for the generation of electrophilic halenium sources has been parlayed with novel stereocontrol mechanisms as was presaged in our treatise.

Although this field is still in its infancy, by comparison the number of enantioselective dihalogenations hardly constitutes a field with fewer than a handful of reports to date. Yet, as is hopefully apparent from the foregoing disquisition, ample opportunities exist for a wide variety of reagents and reaction types. Moreover, given the remarkable range of mechanistic manifolds that are available for dihalogenation, opportunities for creative engineering of stereochemically robust and controllable processes abound. It is our hope that the possibilities revealed by this Review will stimulate inspired and intrepid incursions into the unexplored territories in the landscape of alkene difunctionalization.

Acknowledgements

We are grateful to the National Institutes of Health (GM R01-085235) for generous financial support. S.T.-C.E. thanks the Agency for Science, Technology, and Research of Singapore (A*STAR) for a postdoctoral fellowship. We thank Dr. Carl Poree and Dr. Dietrich Böse for their assistance with the translation of several papers.

How to cite: *Angew. Chem. Int. Ed.* **2015**, *54*, 15642–15682
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Received: July 31, 2015
Published online: December 2, 2015