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Recent Halocyclization Reactions of Alkenes - A Review

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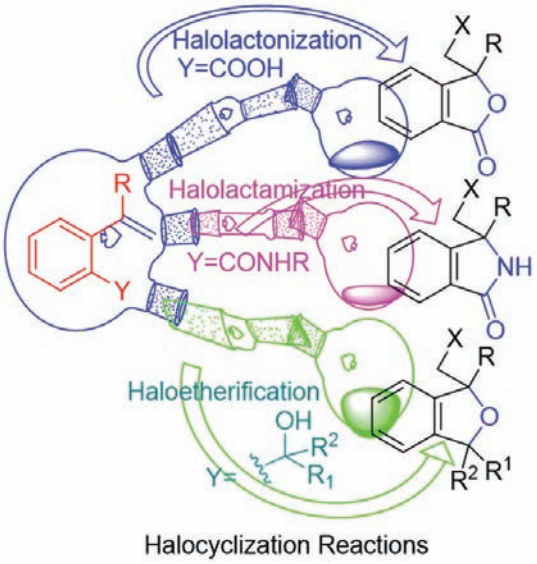
ABSTRACT This review highlights recent advances in catalytic enantioselective halofunctionalization of alkenes and explains the various planning to bring about regio- or stereoselective transformations. Halocyclization of olefinic substrates is an encouraging organization in creating *O*- and *N*-heterocyclic compounds, which additionally connotes the advancement of their asymmetric variations. The initiation of alkenes and their ensuing functionalization is an as often as possible utilized system in synthetic chemistry. The degree and difficulties of intra- and inter-molecular reaction variations have well talked about. The point is to give an outline of different reports, featuring the new reaction composes and techniques created amid the previous 5 years.



Halocyclization Reactions

KEY WORDS Functionalization, Halocyclization, Halolactonization, Heterocyclic compounds, Regioselective, Asymmetry.

INTRODUCTION

Halofunctionalization of alkenes is essential inversion for the rapid construction of complex organic molecules.[1] Electrophilic halocyclization of olefinic substrates is a favorable methodology in the development of heterocyclic compounds.[2] In this procedure, a general mechanism includes an alkene that communicates with an electrophilic halogen to frame a halonium ion first. The halonium ion is then assaulted by a nucleophile in anti-fashion to form intra- or inter-molecularly. The obtaining product contains a novel functional halogen group, which can be effectively control the further reaction.[3] Whereby heterocyclic rings are the result of halocyclization reactions,

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a sub-class of halofunctionalization reactions. For example, lactones can be synthesized through the halocyclization of olefinic acids; cyclic lactams can be synthesized through the halocyclization of olefinic amides; and cyclic ethers can be synthesized through the halocyclization of olefinic alcohols.[4,5] These reactions typically occur through the intramolecular addition of a heteronucleophile to a carbon-carbon double bond in the presence of an electrophilic halogen source. One of the long-standing difficulties in building up an asymmetric variation of the alkene halofunctionalization reaction is the racemization of the enantioenriched halonium ion through the decline olefin-to-olefin trade.[6] Over the most recent couple of years, be that as it may, there has been fast advancement in the making of novel procedures for the enantioselective halofunctionalization of alkenes utilizing sub-stoichiometric quantity of catalyst. The majority of these systems concentrated on the intramolecular reaction, i.e., halocyclization and has been broadly examined in different surveys. Chiral radiance functionalized compounds, which have one of the individual properties, are utilized for different purposes in material and pharmaceutical science.[7] Stereoselective halocyclization is a powerful synthetic tool for construction of halofunctionalized cyclic products, and this has been broadly applied utilizing chiral substrates and in the total synthesis of natural products. As a result of their significance, the evolution of catalytic asymmetric halocyclization reactions has awarded more consideration in the last years.[8]

This review paper will give a detailed analysis of the evolution of enantioselective halocyclization reactions and highlight the critical challenges faced in developing useful methodologies for this class of reactions in past 5 years, and if necessary, some of the previous work in the field of halofunctionalization reactions.

Halolactonization reactions

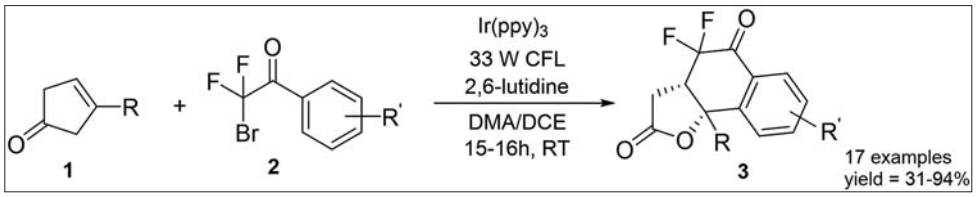
The halolactonization reaction becomes strong by the introduction of electrophilic halocyclization. The first halolactonization reactions were discovered by Frost in the Fittig School in Strassbourg in 1884,[9] followed by more detailed studies by Stobbe followed by more detailed studies in the 19th.[10] Over the time, it has been widely, and essential synthetic tool used for the development of synthetic lactones. This section describes some examples of halolactonization processes over the past years, the catalysts and new methods used to carry out these reactions.

In 2012, Qu *et al*.[11] described a mild and novel approach toward lactone synthesis through visible light radical cyclization of enol lactone **(Scheme 1)**. The reaction is value by its wide substrate range, and simple protocol under mild conditions for the synthesis of difluoroalkylated heterocyclic compounds. The suggested mechanism proceeds through the generation of difluoroacetophenone radical intermediate **2** under visible light photoredox catalyst cycle, followed by reaction with the carbon-carbon double bond of the α-angelica lactone **1**, which can undergo the tautomerism with the base producing the desired products **3** with moderate to excellent yields.

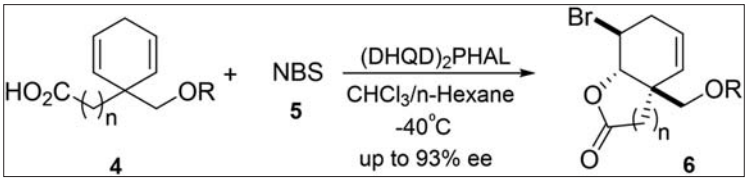
While Ikeuchi *et al*. group[12] described an efficient protocol for the desymmetrization of cyclohexadienes through bromolactonization reaction process in presence of *N*-bromosuccinimide 5 and $(DHQD)_2$ PHAL as a catalyst (**Scheme 2**). Desymmetrization of various cyclic dienes **4** was compatible with the reaction conditions and providing the corresponding products **6** up to 93% ee. This reaction is predictable to be worthy route towered total synthesis of (-)-sphingofungin E.

In 2013, Meng *et al*.[13] have reported the effective usage of iodolactonization in the one-step transformation of γ, δ-unsaturated carboxylic acids **7** and **11** to the corresponding five or six-membered lactone products **9**, **10,** and **12** under neutral conditions at room temperature **(Scheme 3)**. A range of simple carboxylic acid substrates was subjected to the cyclization conditions, and it was observed that using DMAP as a unique catalyst and dichloromethane as a solvent were the preferred protocol for this reaction.

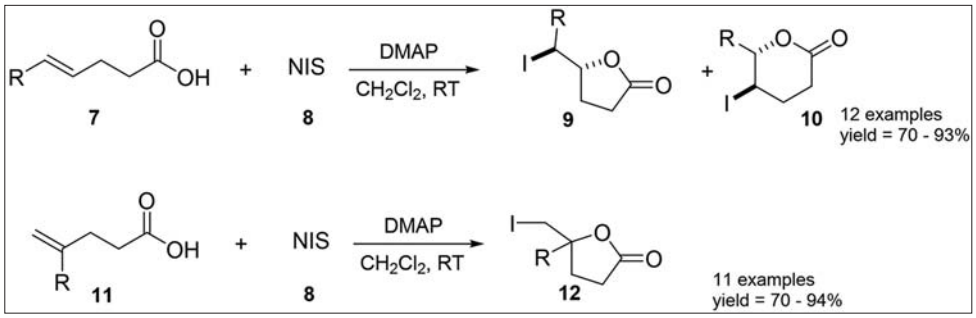
Han *et al*.[14] have reported the effective transformation of styrene-type carboxylic acids to the relating isochroman-1-ones **16** in up to 99% ee, employing asymmetric chlorolactonization process **(Scheme 4)**. Here, the reaction is depended on using styrene-type carboxylic acids **13** with 1,3-dichloro-5,5-dimethylhydnation in the presence of C_3-symmetric



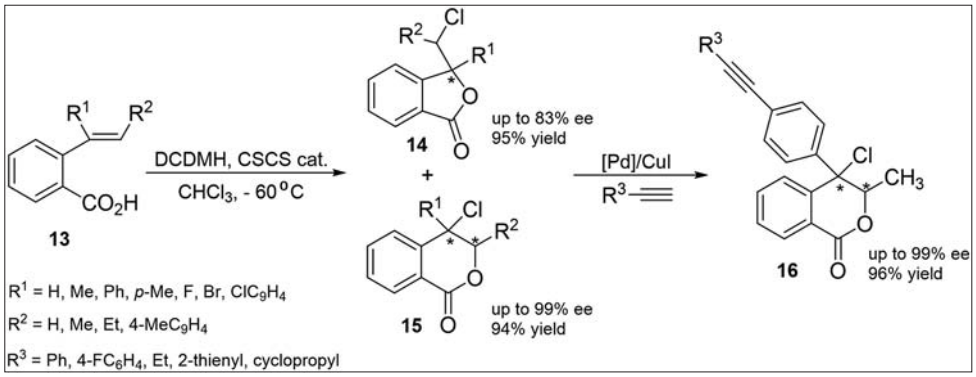
Scheme 1: Radical cyclization of enol lactone



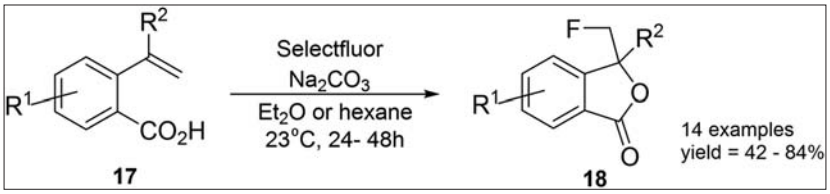
Scheme 2: Catalytic desymmetrization of cyclohexadienes through bromolactonization reactions



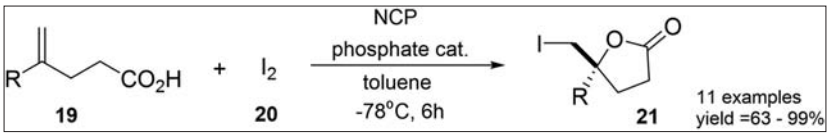
Scheme 3: Lodolactonization of γ, δ-unsaturated carboxylic acids in the presence of DMAP



Scheme 4: Synthesis of chiral isochroman-1-ones through chlorolactonization process



Scheme 5: Fluorolactonization of aromatic carboxylic acids



Scheme 6: Enantioselective lodolactonization of 4-arylmethyl-4-pentenonic acids

cinchonine squaramide as an organocatalyst. Wide variety of useful carboxylic acids derivatives were tolerated under the mild conditions and shown an excellent transformation to the corresponding products and up to 99% ee.

In parallel, Parmar *et al*. group[15] focused on fluorolactonization process of aromatic carboxylic acids **17** mediated by anion phase transfer reagent **(Scheme 5)**. A variety of substituents on both aromatic backbone (R^1) and alkene (R^2), including electron - withdrawing and - donating groups show a broad amplitude toward the reaction conditions and affording the expected products **18** with good yields.

In 2014, a successful iodolactones synthesis has been developed by Nakatsuji *et al*. group[16] using *N*-chlorophthalimide as a Lewis acid and oxidant I_2 **20** in toluene at −40°C **(Scheme 6)**. The catalyzed reaction of 4-benzylpent-4-enoic acids **19** bearing electron withdrawing (chloro and fluoro) and electron donating substituents (methyl and methoxy) on phenyl group gave the product **121** with excellent enantiomeric excesses, while the phenyl- and aryl-substituted afforded poor enantioselectivity and good reactivity.

In 2015, other enantioselective fluorolactonization protocol was developed by Egami *et al*. group[17] using the fluorinating agent (Selectfluor) in the presence of phosphoric acid as a novel bifunctional pre-catalyst **(Scheme 7)**. Here, the catalyst, possessing both carboxylate anion and benzyl alcohol sites, acts as a phase-transfer agent and unit, respectively, to coordinate with the substrate **22** through

hydrogen bonding. *O*-vinyl benzoic acids produce the corresponding isobenzofuranone **23** products in good yield up to 94% ee.

More recent, Huang *et al*.[18] developed the enantioselective 6-*endo* bromoaminocyclization of 2,4-dienyl *N*-tosylcarbamates using chiral phosphine oxide-$Sc(OTf)_3$ catalysts to activate milder bromination reagent **(Scheme 8)**. A wide range of 5-bromo-1,3-oxazinan-2-ones **24** was compatible with reaction conditions with excellent yields of products **25**, obtained.

Furthermore, Arai *et al*. group[19] developed the asymmetric iodolactonization of alkene carboxylic acids **26** using poly-$Zn_3(OAc)_4$-3,3-Bis(aminoimino)binaphthoxide complex catalyst **(Scheme 9)**. It is noteworthy that Poly-zinc complex found to be a stable, active catalyst for this type of the reaction and reused after recovering it by filtration through five cycles.

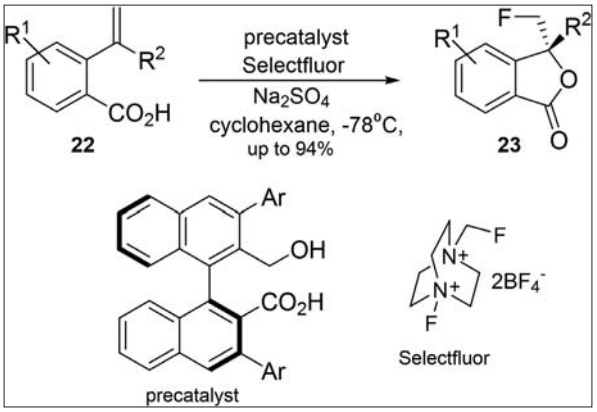
In 2016, Gelat *et al*.[20] reported a flexible route toward the construction of 3-substituted isobenzofuranones through regioselective asymmetric bromolactonization of aryl acrylate-type carboxylic acids **28 (Scheme 10)**. In this case, addition of a small amount of benzoic acid as an organocatalyzed was employed as bifunctional catalyst cavity might potentially demonstrate its efficiency through the cyclization process in the presence of NBS reagent and forming the corresponding products **29** with promising enantioselectivities (up to 53%).

Asymmetric bromolactonization later was carried out using Aursnes *et al*. conditions[21] using chiral squaramide hydrogen-bonding as an organocatalyst **(Scheme 11)**. This method reported a flexible cyclization manner of 5-arylhex-5-enoic acid derivatives **30** to the corresponding products **31** in high to excellent yields with up to 96% enantiomer excess. The feature of the advanced strategy afforded highly enantioselective syntheses of the sesquiterpenoids (−)-gossoronol and (−)-boivinianin B.

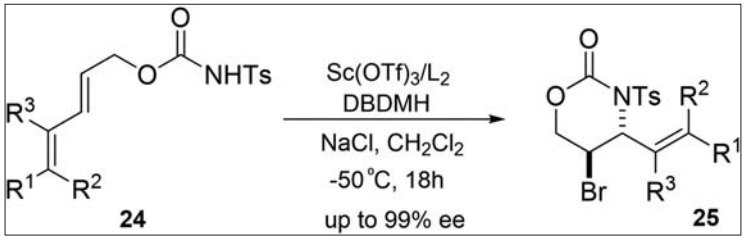
Next, Woerly *et al*.[22] developed the synthesis of 4-fluoro isochromanones through an enantio- and diastereoselective fluorolactonization protocol of aryl alkene substrates **32**, giving the 6-membered lactones including fluorine with stereogenic centers **(Scheme 12)**. Stoichiometric amounts of pyridine (nucleophilic fluoride source), peracid (oxidant), and resorcinol derivative (catalyst) were employed and furnished the final products **33** with new C-F bond formation.

In the same year, Wilking *et al*. group[23] have reported a new synthetic method for direct enantioselective bromolactonization of alkenoic and alkynoic acids **34** in the presence of a new class of phthalazine-substituted cinchona alkaloid as a monomeric catalyst **(Scheme 13)**. Remarkably, this catalyst (DHQD) PHAL acts as a bifunctional nucleophile as well as more applicable for such asymmetric electrophilic halogenation reactions.

More recently, Pan *et al*. group[24] have reported a mild and novel synthesis of difluoro γ-Butyrolactone heterocycles through cascade visible-light photocatalytic radical cyclization reaction **(Scheme 14)**. In general, the reaction proceeded smoothly under mild conditions with several types of bromofluoroalkane substrates **36** bearing amido, keto, ester, and phosphate functional groups, affording the expected difluoralkylated oxygen products with yield up to 97%. Mechanistic studies revealed that the lactonization proceeds through formation of difluoroalkyl radical intermediate **37** from the photocatalyst cycle process, followed by addition to the unsaturated carboxylic acids and give the radical intermediate. Subsequently, the later can



Scheme 7: Asymmetric fluorolactonization with selecfluor and bifunctional catalyst

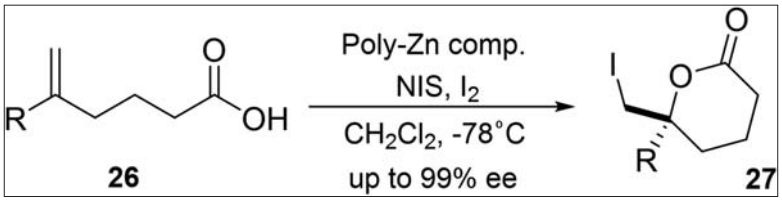


Scheme 8: Enantioselective bromolaminocyclization of 2,4-dienyl *N*-tosylcarbmates

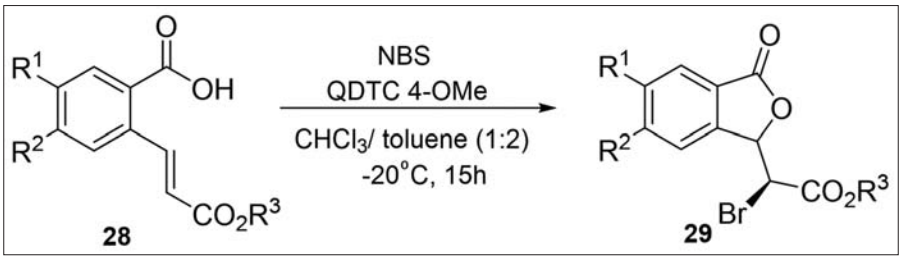
undergo deprotonation in the presence of a base and provide the expected final products **38**.

Next, Weung *et al*. group[25] illustrated the utility of electrophilic bromocyclization of olefinic substrates **39** encouraged by Lewis base catalysts and bromine source **(Scheme 15)**. In the report, the incorporation of thiocarbamate with amino group activate the electrophilic Br and acidic pro-nucleophile, respectively, and be the optimal catalyst to give γ-bromolactone. The reaction forward in higher yields **(40-44)** with the both of electron deficient group (has a deteriorating effect on enantiomer excess) and electron-rich (increase the enantioselectivity of the product dramatically).

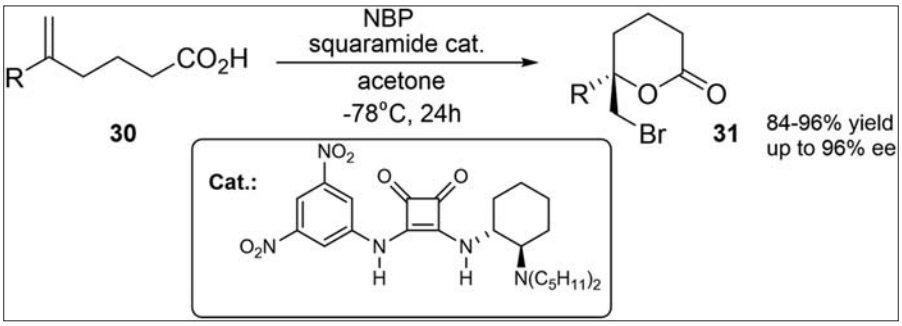
Recently, photoredox process has been employed for the regioselectivity of halofunctionalization of unsaturated carboxylic acids. In this context, Nicewicz *et al*. group[26] reported straightforward copper catalyst mediated intra- and inter-molecular preparation of series of halolactone derivatives **46** and **47** through novel functionalization **(Scheme 16)**. The mechanism strategy of this reaction begins with the formation of the single electron oxidation alkene **45** through anti-Markovnikov reactionfollowed by producing cation radical. Alternatively, the latter captures by nucleophile, then the reaction with the halide which is transferred by a copper catalyst, produces the products **46** and **47** in 41% to 94% yields.



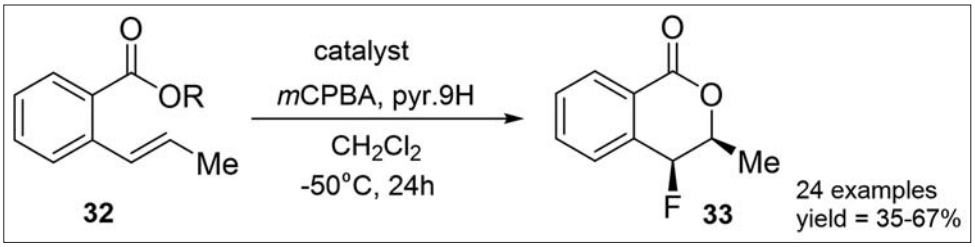
Scheme 9: Asymmetric lodolactonization using catalyst poly-Zn complex



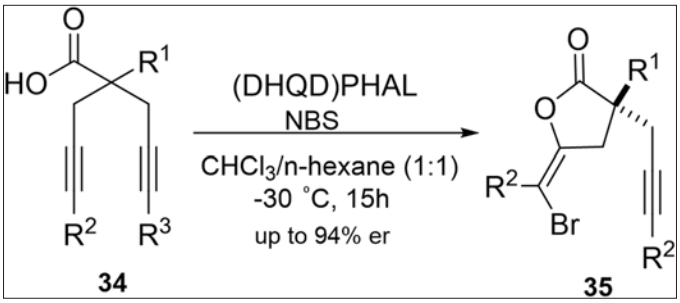
Scheme 10: Enantioselective bromolactonization of aryl acrylate-type carboxylic acids



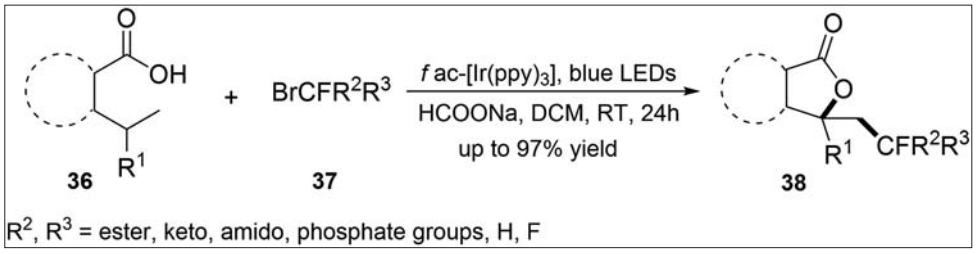
Scheme 11: Asymmetric bromolactonization reaction using chiral squaramide catalyt



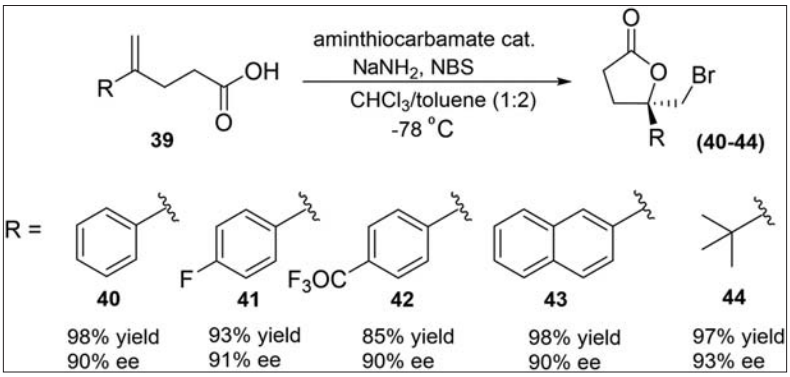
Scheme 12: Enantio- and diasteroseletive, catalytic synthesis of 4-fluoroisochromanones



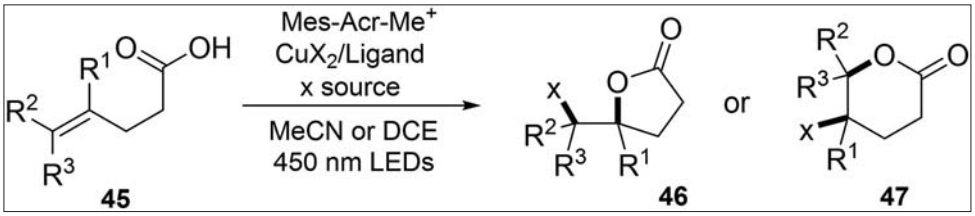
Scheme 13: Monomeric cinchona alkaloid-based catalyst for bromolactonization of alkynes



Scheme 14: Photoredox-catalyzed cascade difluoroalkylation cyclization reaction



Scheme 15: Asymmetric bromolactonization of 1,1-disubstituted olefinic acid



Scheme 16: Alkenes halofunctionalization photoredox reactions

In parallel with successful enantioselective halolactonization reaction processes, Daniel *et al*.[27] developed bromo- and iodolactonization reaction of unsaturated carboxylic acids using BINOL-derived as a bifunctional catalyst **(Scheme 17)**. The protocol here depends on the reaction of 5-alkyl-4(*Z*)- **48** and 6-substituted-5-(*Z*)-olefinic acids **51** with NIS through 5- and 6-exo cyclization, respectively, to produce the lactones **49**, **50**, **52,** and **53** with new carbon-halogen bond containing stereogenic center with high enantio- and diasteroselectivities.

Halolactamization reactions

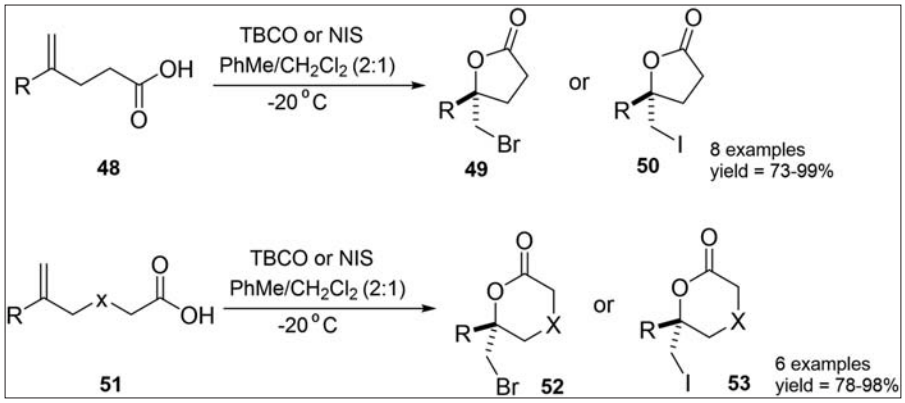
This reaction was not until 2004 that the first enantioselective halolactamization reaction was illustrated by Shen and Li.[28] A major obstacle lies in the direction of olefinic amides to subject O-cyclization, rather than N-cyclization to produce the lactam: Due to the higher electronegativity of oxygen contrast to that of nitrogen.[29] Hence, enormous efforts have been applied to improve an effective catalytic enantioselective halolactamization style which proposed a helpful level of enantioselectivity for the lactam products.

In 2015, Cheng *et al*. group[30] described a flexible strategy toward bromolactams framework including two stereogenic centers **(Scheme 18)**. This took place through enantioselective bromolactamization of the amide, using a carbamate catalyst and promoted by

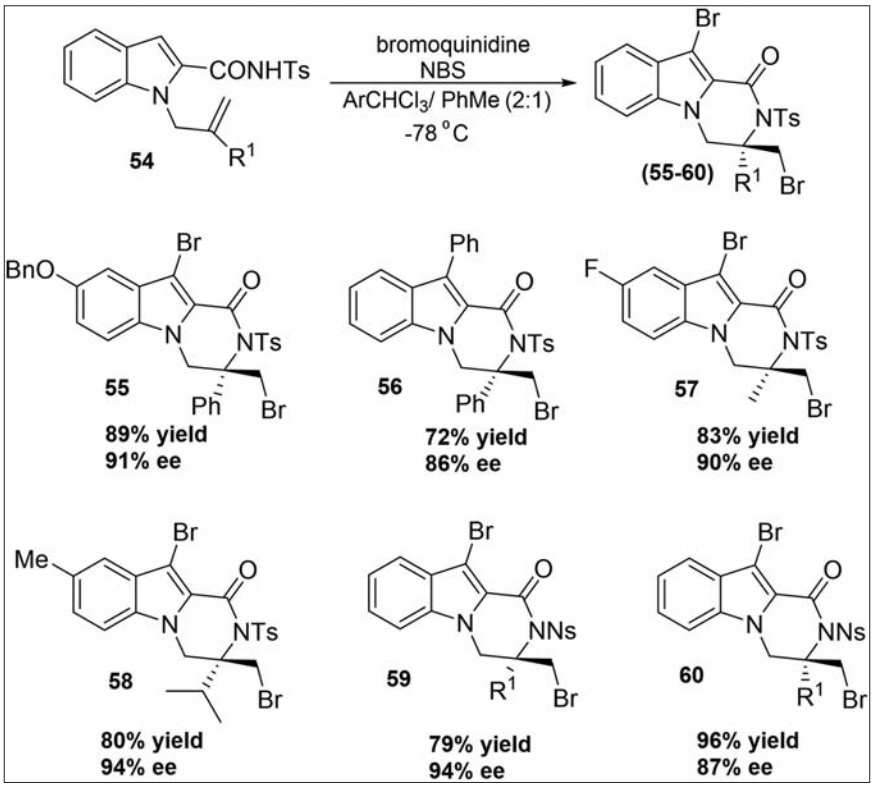
ethanol additive. Mechanistic studies showed the formation of chiral brominating species through halogen exchange between bromo quinidine and NBS followed by reaction with an acidic proton of the amide substrate **54** and give the intermediate. The hydrogen bonding between the OH of amidic acid (tautomer of amide) and the base quinuclidine, afford imidic nitrogen base to grab the bromonium and produce the desired bromolactam products **(55-60)**.

Furthermore, Xu *et al*. group[31] described trifluoromethylthio lactonization/lactamization of gem-disubstitued alkenes in presence of Me3SiCl as a Lewis acid catalyst[31] **(Scheme 19)**. The sequence of exo-cyclization is based first on the generation of thiiranium ion species **63i**, which attacked by the carboxylic acid **61** or amide **62**, furnishing the expected trifluoromeththiolated -lactone and -lactam products **(64 and 65),** respectively. Wide variety of substituted 2-(1-phenylvinyl)benzoic acids and 4-arylpent-4-enoic acids are tolerated under mild conditions, qualify a flexible cyclization method.

Next, Shi *et al*.[32] disclosed a straightforward application of enantioselective 6-exo-bromoaminocyclization process, giving the (*E*)-homoallylic *N*-tosylcarbamates as the single product with up to 99% ee **(Scheme 20)**. The protocol here depends on the direct use of *N*-bromoacetamide as the bromonium ion origin and monophosphine-Sc $(OTf)_3$ complex as unfamiliar Chiral catalyst. The reaction mechanism proceeds through that catalyst has rigid structural demands for the ligand for the aforesaid bromocyclization. The transformation of the optically active 1,3-oxazinan-2-one products **67** can undergo further functionalization reactions without losing their optical purity.



Scheme 17: Halolactonization of 5-alky-4(Z) and 6-substituted-5-(Z)-olefinic acids



Scheme 18: Enantioselective bromolactamization process using carbamate catalyst

In parallel with success to construct a variety of significant (*E*)-cinnamyl tosylcarbamates framework **68**, Shi *et al*.[33] developed a high regio- and enantioselective bromoamino cyclization reactions in the presence of chiral phosphine oxide-$Sc(OTf)_3$ complex utilized as the catalyst and 1,3-dibromo-5,5-dimethylhydantion (DBDMH) as the bromine source **(Scheme 21)**. The advantage of such reaction that can proceed smoothly with maximum regioselectivity and particularly single 6-endo products were obtained and be applied on a comparatively larger scale.

Haloetherification reactions

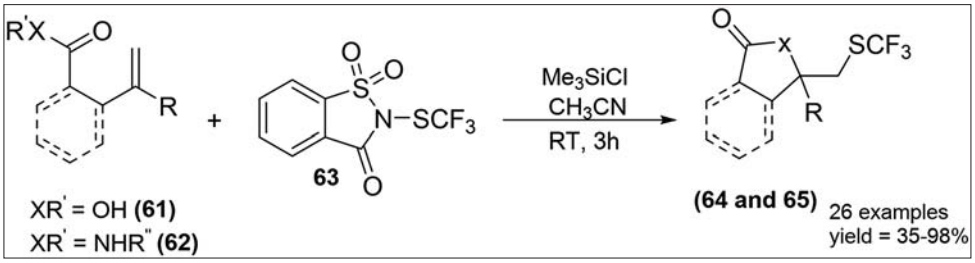
Asymmetric alkene halogenation is a impact synthetic transformation that awards for an explicit functionalization of readily available compounds into worthy chiral, halogenated building blocks. Regardless of the isolated reports of enantioselective evidence in the literature in the 1990s. Ever after, Thies Research field has attended spectacular progress with an estimate to the range of conversions and mechanical perception. Newly, converge has moved to the more affront intra- and inter-molecular halo functionalization of alkenes. The development of such transformations is especially take on as an effective way for asymmetric haloetherification rest in meliorative the rate of nucleophilic take as opposite to the olefin-to-olefin halogen interchange which purpose racemization.[34]

Xie *et al*.[35] reported an enantioselective 3-*exo* iodo-cycloetherification of allyl alcohols. In general, this reaction forward through generation of chiral ion-pair from the interaction of chiral phosphate and DABCO-derived quaternary ammonium followed by activation of NIS to produce iodine reagent **(Scheme 22)**. Based on the active role of this catalyst, a wide range of 2-iodomethyl-2-aryl epoxide derivatives was prepared in a good to excellent enantioselectivities. Furthermore, straightforward access to 2-iodomethyl-2-aryl cycloalkanones **70** syntheses was recorded by employing the asymmetric 3-exo iodocycloetherification/ Wagner-Meerwein rearrangement on the 2-aryl-2-propen-3-ol substrate **69**.

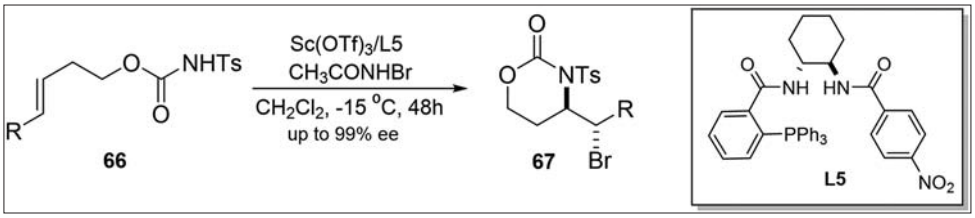
In 2014, Scott *et al*. group[36] progressed ^{19}F-NMR kinetic study to improve an enantioselective bromolacycloetherification of 5-aryl-4-pentenols by employing mutual catalysis of chiral Bronsted acid and an achiral Lewis base **(Scheme 23)**. Here, the reaction outlines high post selectivity through good compatibility between the substrate and catalyst directing. On the other hand, they observed that a 5-alkyl-4-pentenols **71** can undergo cyclization, but with lower enantioselectivity in the absence of achiral Lewis base.

While Yeung *et al*. group[37] have been reported a flexible, efficient and quite enantio- and diastereoselective desymmetrizing bromoetherification of diolefinic diols promoted by amino-thiocarbamate catalyst **(Scheme 24)**. A sensible mechanism for such reaction proceeds through three serious components: First, formation of the intramolecular hydrogen bonding between the acidic diol proton and quinuclidine nitrogen atom of the amino-thiocarbamate catalyst, which help to enclose the 1,3-diol **73** in a chair six-membered ring transition intermediate, then all the bulky groups possess in equatorial status, and finally, the role of amino-thiocarbamate as a bifunctional pocket restricts the geometry of the intermediate. Subsequently, this protocol performed to produce a system of chiral hetero-spiro systems.

In parallel, the Wilking *et al*. group[38] choose noteworthy 1,1'-bi-2-naphthol (BINOL) phosphates catalyst incorporation with *N*-haloamides, such as *N*-iodopyrrolidinone or *N*-bromosuccinimide to elevate the asymmetric enantioselective haloetherifications of diol derivatives, such as (*Z*)-Dec-4-en-1-ol **75** and (*E*)-Alk-4-ene-1,8-diols **77 (Scheme 25)**. The reaction mechanism is slightly *pseudo*. The key incorporation between the catalyst and substrate could proceed by activating the hydroxyl group generation of hydrogen bonding with (BINOL) phosphate in the transition state inclusive the *N*-haloamide halogenating agents, worthy of encouraging high selectivity on all substrates.



Scheme 19: Lewis acid mediated trifluoromethylthio lactonization/lactamization prosesses



Scheme 20: Enantioselective bromoaminocyclization of homoallylic *N*-tosylcarbamates

While, Asymmetric bromoetherification and desymmetrization of alkenoic and trisubstituted alkenoic diols was described by Tay *et al*. group **(Scheme 26)**.[39] This methodology disclosed the efficient role of C_2-symmetric sulfide as a catalyst in the synthesis route of tetrahydrofuran derivatives, contains three stereogenic centers with two tetra-substituted carbons. The authors suggested that the mechanism starts with the formation of the active species Br through activation step of NBS with chiral cyclic sulfide catalyst, followed by transfer the Br to the olefin substrate **79** and **81**, furnished the desired products **80** and **82**.

Later on, the regio-, diastereo-, and enantioselective intermolecular haloetherification and haloesterification of allyl amides were demonstrated by Soltanzadeh *et al*. **(Scheme 27)**.[40] Under catalytic conditions, the bromination and chlorination reactions proceeded easily with various nucleophiles. A wide variety of alkene substrates is tolerated under the mild conditions, qualify a flexible method towered this chemistry in some the face selectivity in chlorenium delivery for the intramolecular process is the same for both *E*- and *Z*-olefin substrates **83**, while in others are opposite. These outcomes lead to say that the mechanism of such reactions is controlled by the catalyst and proceed either through cyclization process **85** and **87** or through intermolecular addition reactions **84** and **86**.

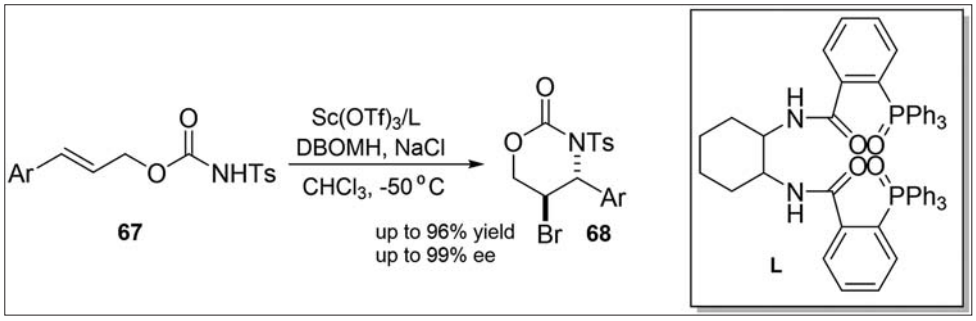
In 2016, Zhou *et al*. group[41] proposed asymmetric intra- and inter-molecular haloetherification of alkenes containing electron withdrawing groups such as (I, B r, and Cl), in the presence of chiral metal complexes of *N*, *N*'-dioxides **(Scheme 28)**. The mild reaction conditions with the presence of Fe (III) complex, tetrahydropyran derivatives **89** were achieved in excellent yields up to 99% with high enantioselectivities, while using chiral Ce (III) complex, the oxepane products **91** were given in a good yield. Meanwhile, the intermolecular haloetherification catalyzed by Sc (III) complex and demonstrated by methanol as a nucleophile, afforded the corresponding chalcone derivatives **93**. Enantioselective synthesis route of (-)-Centrolobine was employed through six-membered bromocyclization methodology step, and the yield was 89% with 99% ee.

In 2017, Böse *et al*. group[42] described the development of catalytic and enantioselective halofunctionalization of unactivated alkenes **94 (Scheme 29)**. In this context, the bromiranium ion fashioning is most supposedly the enantio-determining step in the Lewis base catalyzed the enantioselective bromocycloetherification reaction. Furthermore, the presence of water and fast nucleophilic reaction on bromiranium ion was the key for high enantiomeric ratios in such reactions.

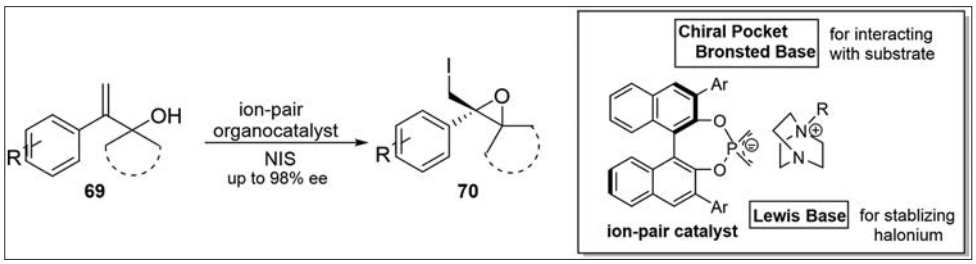
Other halocyclization reactions

Alkene halofunctionalization reactions have newly been become as huge tools for the building of varied polycyclic framework compounds from readily available substrates. Conventionally, halofunctionalization reactions proceed dependably through the formation of halonium ions, which lead to the regioselective production of the halofunctionalized adducts.[43]

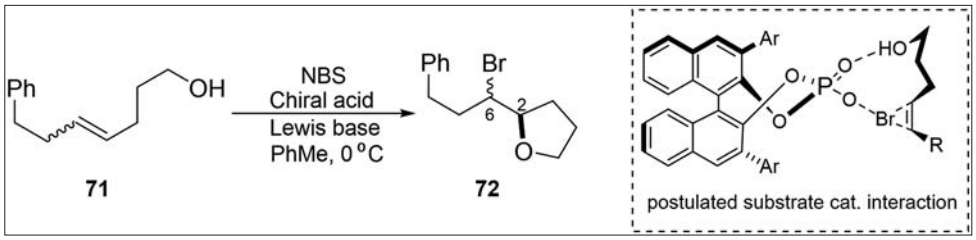
In 2013, Wang *et al*. group[44] described a mild and efficient route to an intermolecular halocyclization of simple N-vinyl-tethered methylenecyclopropanes in the presence of Fe (III) as a Lewis acid catalyst, producing a range of halogenate 1,2-dihydroquinoline derivatives **(Scheme 30)**. A possible deuterium labeling mechanism proposed, started with the formation of iminium ion intermediate **96i** through protonation step reaction between the enamine **96** and H_2O, which catalyzed by Lewis acid (FeX_3 or I_2).[45] Subsequently, the enamine intermediate subjected to the intramolecular



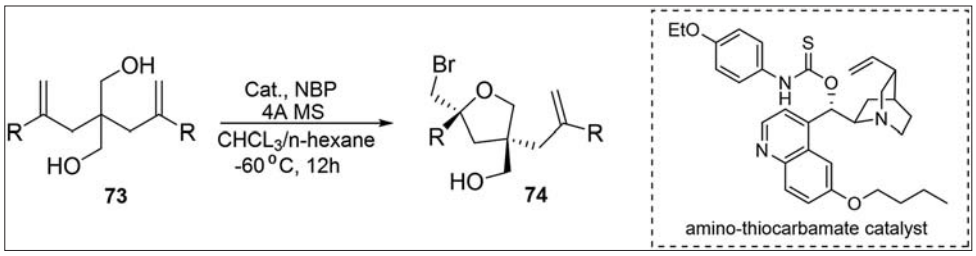
Scheme 21: Enantioselective bromoaminocyclization of (*E*)-cinnamyl tosylcarbamates



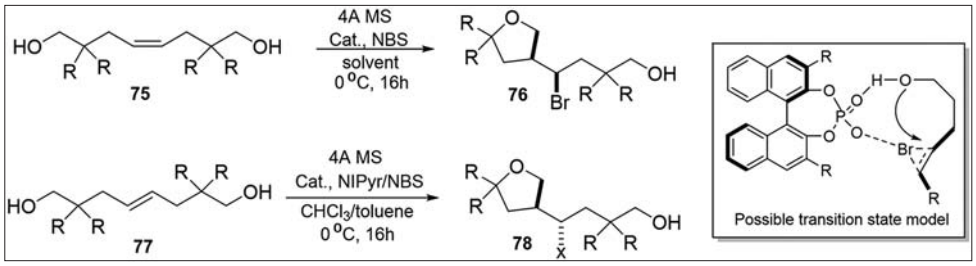
Scheme 22: Enantioselecive 3-exo iodo-cycloetherification



Scheme 23: Scope of bromocycloetherification



Scheme 24: Desymmetrizing bromocycloetherification of diols



Scheme 25: Enantioselective haloetherification of (*Z*)- and (*E*)-alkenediols

aza-Prins cyclization.[46] Finally, the halogenation and rearrangement reactions of cyclopropylcarbinyl cation furnished the corresponding 1,2-dihydroquinoline products **97** and **98**.

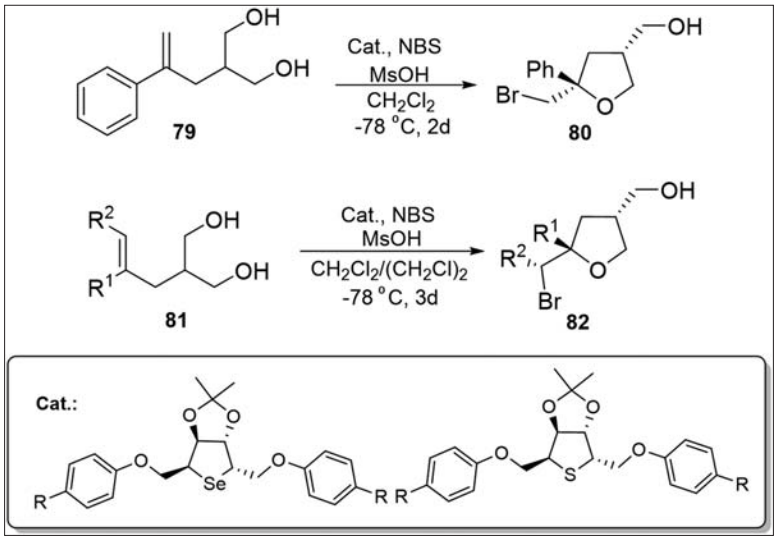
In the same year, Xua and Tong[47] have reported a simple route (KX/oxone) route towered the oxidative halocyclization of tryptamine and tryptophol derivatives **(Scheme 31)**. Here, the successful key to effective investigation of this system is employing a suitable inorganic oxidant that is can oxidize the halide and not indole such as oxone (potassium peroxymonosulfate, $2KHSO_5.KHSO_4.K_2SO_4$), which was able to couple with alkali metal halide to progress the halocyclization of Tryptamine/Tryptophol derivatives **99** through generation of halogenated agent.

Furthermore, Sawamura *et al*.[48] designed a chiral phosphite-urea bifunctional catalyst for the enantioselective bromocyclization of 2-geranylphenols **101** promoted by N-bromophthalimide as a generating agent of bromophosphonium ion **(Scheme 32)**. The mechanism of the reaction supposed hydrogen bond formation between the urea and 2-hydroxyl group of the substrate that effectively accelerates the enantioselective bromocyclization process and resulting in the brominated products **102** and **103** in good yields.

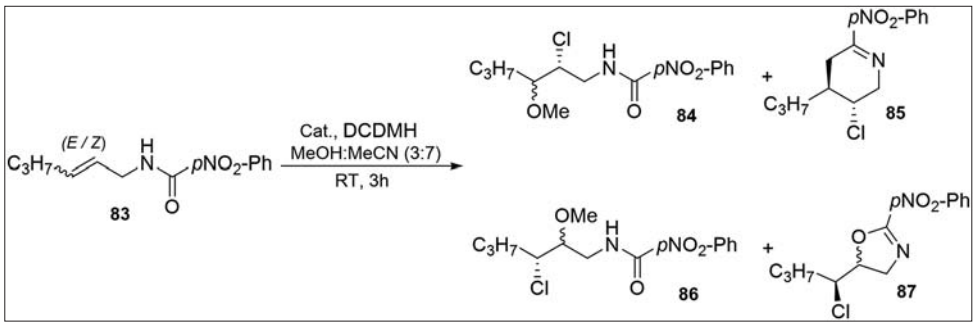
While Toda *et al*. group [49] described a convenient approach towered synthesis of C- and P-chiral phosphoramidate derivatives, catalyzed by a chiral Bronsted acid **(Scheme 33)**. Normally, the reaction confirmed by treatment of unactivated alkene substrates **104** with NIS (electrophilic iodine source) and phosphoramidic acid under diastereo- and enantioselective halocyclization conditions, to afford the corresponding cyclic phosporamidic products **105** with two new stereogenic centers at carbon and phosphorus atoms.

Egart and Czekelius group[50] then reported a new protocol for the synthesis of bromo-5,6-dihydro-4H-1,3-oxazines **(Scheme 34)**. In general, this reaction forward with intramolecular bromoamination of allylated aldoxime ethers **106**. The proposed mechanism based on the generation of isoxazolidinium salts containing protons in the 3- or 5-position that can undergo ring-opening elimination reactions to produce the oxazine products **107**.

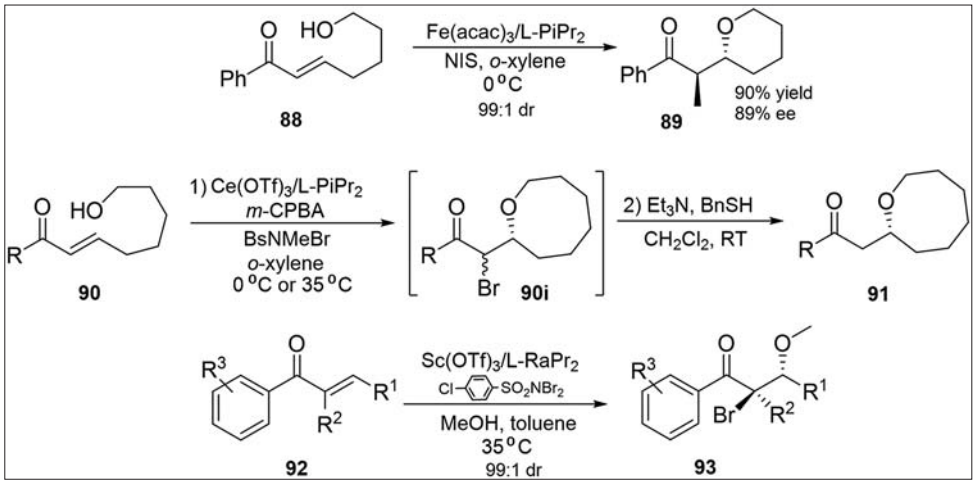
Later, a variety of bioactive fused indoles that contain quaternary carbon center have been prepared through asymmetric chlorocyclization process by You group **(Scheme 35)**.[51] Under optimization conditions, using 1 mol% of $(DHQD)_2PHAL$ as catalyst in trifluoroethanol solvent in open flask, various substituents on the indole framework **108**, including electron withdrawing group at the meta or para position of benzamide (R^1), electron-donating group, 2-naphthamid, and heteroaryamide were tolerated and shown highly efficient substrates, leading to the enantiopure products **109**.



Scheme 26: Asymmetric bromoetherification and desymmetrization of alkenoic and trisubstituted alkenoic diols



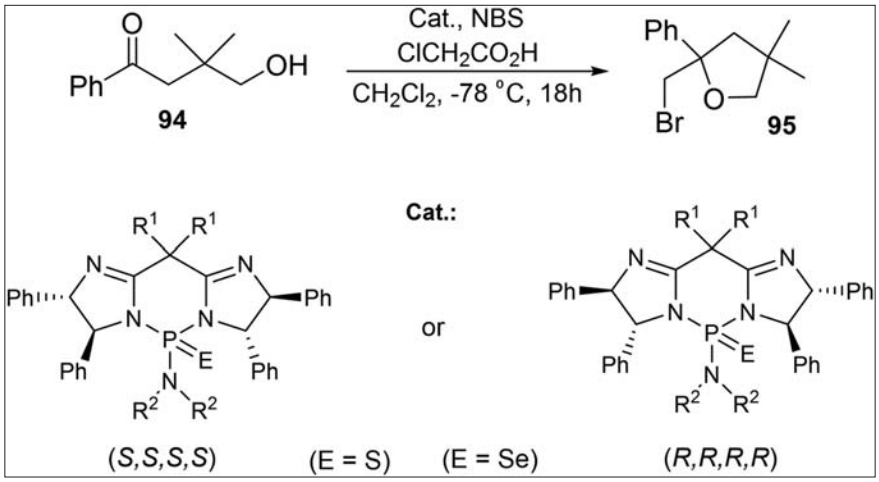
Scheme 27: Demonstration of catalyst control in the intermolecular chloroetherification of allyl amides



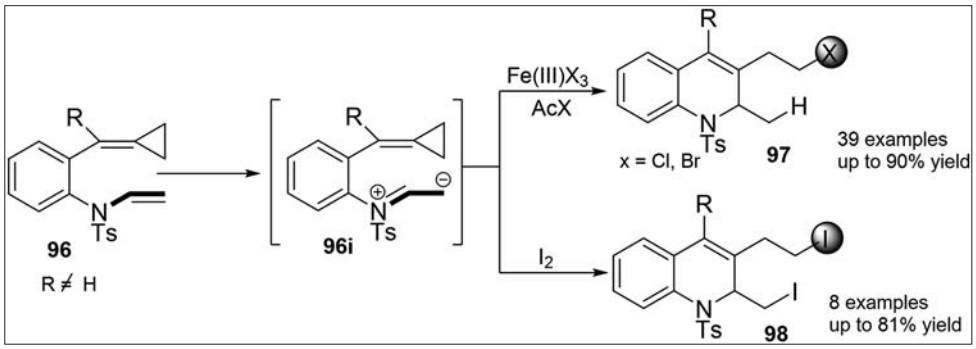
Scheme 28: Synthesis of tetrahydropyran, oxepane, and chalcone derivatives

In subsequent publications, Liu *et al*.[52] demonstrated that the chiral anionic phase-transfer DABCO-derived bromine complex catalyst system is also useful for the quite asymmetric bromocyclization of tryptophol core **(Scheme 36)**. Under optimal reaction conditions, it was noted that using (R)-TRIP **L1**, bromine complex (**B3** and **B4**) as brominating agents and Na_2CO_3 base, were the best catalyst for the enantioselective bromocyclization of different tryptophol substrates **110**, furnished various chiral 3-bromofuroindoline products **111**.

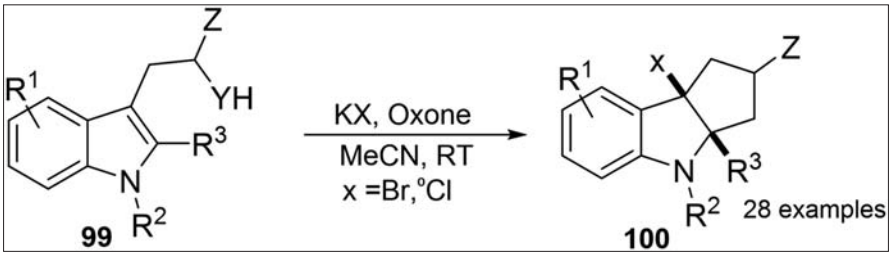
Compared to the fast improvement in the field of organocatalytic asymmetric halocyclization, Jaganathan and Borhan[53] have used chlorosulfonamide salts as a swift available and inexpensive pioneer of chlorenium ion in the chlorocyclization of unsaturated amides **(Scheme 37)**. Under mechanism conditions in HFIP solvent at ambient temperature, the protonation of chloramine-T.$3H_2O$, produce the TsNHCl intermediate, which is fatly disproportionate into $TsNCl_2$ in aqueous solution[54]



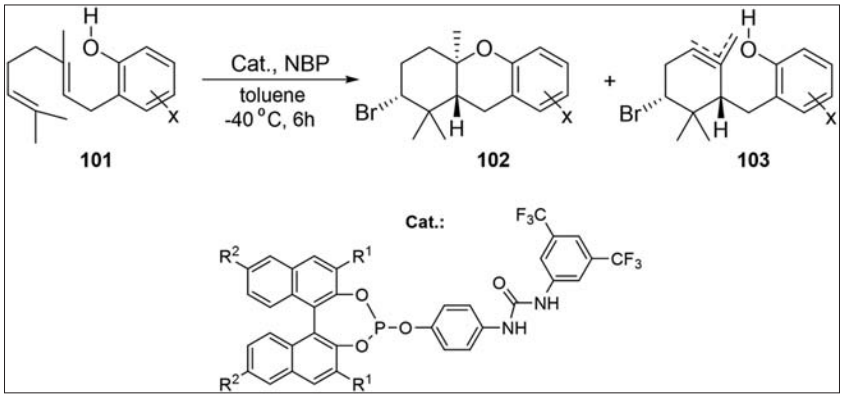
Scheme 29: Enantioselective bromocycloetherification of unactivate alkenes



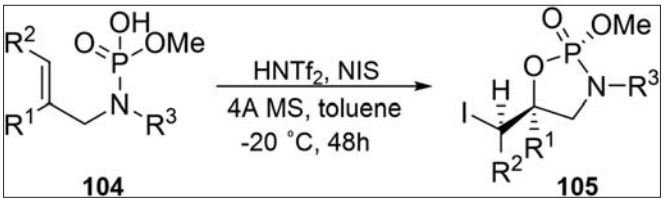
Scheme 30: A facile synthetic methods to access halogenated 1,2-dihydroquinolines



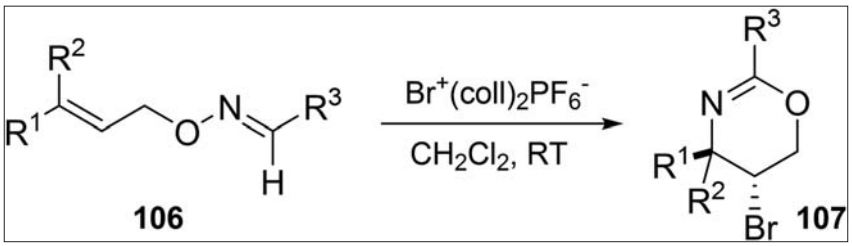
Scheme 31: Oxidative halocyclization of tryptamine and tryptophol derivatives



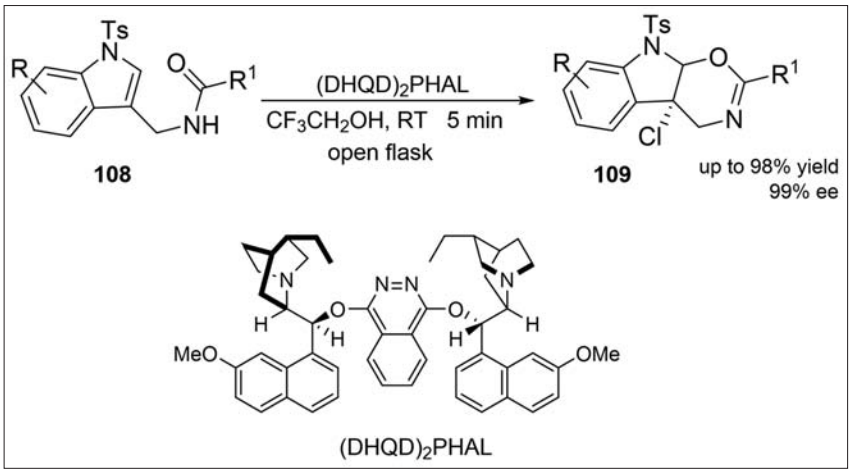
Scheme 32: Enantioselective bromocyclization of 2-geranylphenols



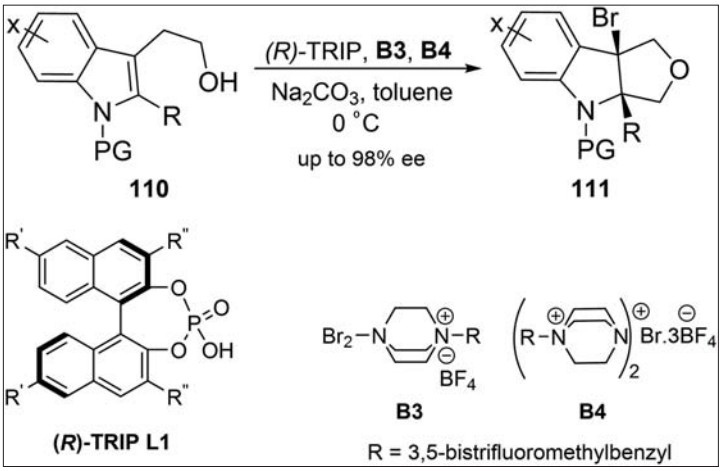
Scheme 33: Chiral bronsted acids catalysed distereo- and enantioselective lodocyclization



Scheme 34: Bromocyclization of allylated aldoxime ethers



Scheme 35: Asymmetric clorocyclization of indole-3-yl-benzamides



Scheme 36: Asymmetric bromocyclization of tryptopholes

followed by transport of Cl^+ to the olefin substrates **112** and **113**, to yield the expected products **114** and **115** with a high level of stereoselectivity.

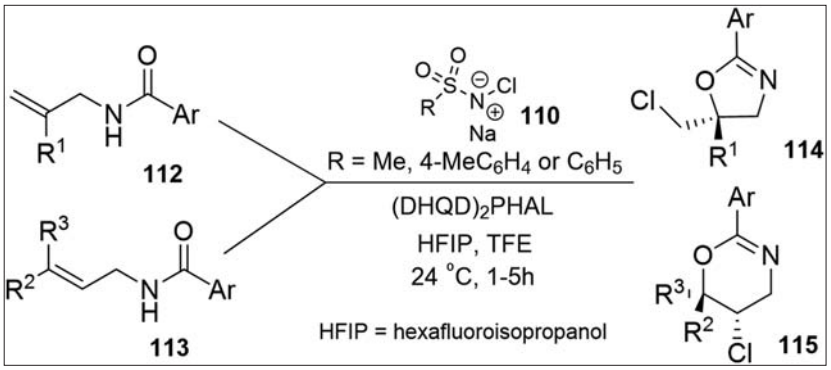
Independently, Tripathi and Mukherjee group[55] recorded Δ^2-pyrazoline derivatives **118** containing a quaternary stereogenic center, using trans-1,2-diaminocyclohexane as a bifunctional thiourea catalyst for the first enantioselective iodoaminocyclization of *β, γ*-unsaturated hydrazone derivatives **116 (Scheme 38)**. Here, the role of the bifunctional catalyst is not only to activate the iodine source

and accelerate the transfer it to the olefin and yield the product but also to activate the nucleophilic functional group through initially iodonium intermediate formation **117i.** Furthermore, this reaction demonstrated a first using of hydrazones as nucleophilic in olefin halofunctionalization reactions.[56]

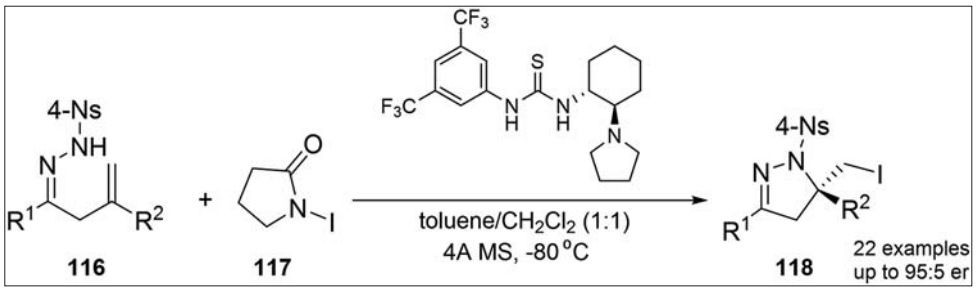
After 1 year, the same group[57] has been reported an efficient role of tertiary aminothiourea catalyst in the synthesis of Δ^2-isoxazoline and Δ^2-pyrazoline derivatives core **(Scheme 39)**. Under catalytic and mild conditions with *N*-iodosuccinimide **117** as the electrophilic iodine source, the *β,γ,δ,ε*-unsaturated oxime derivatives **119** and 4-Ns-hydrazones undergo cyclization reaction in 1,4-design to yield the corresponding products **120**, containing a quaternary stereogenic center in high yields with excellent enantioselectivities.

In the same year Liu *et al*.[58] have been reported a straightforward route towered the highly enantioselective carbonate synthesis,[59] promoted by a dual Bronsted acid/base catalyst **(Scheme 40)**. The authors suggested that the activation and the enantioselective reaction of the substrates **121** proceeds through the donor and acceptor hydrogen-bond formation. This metal-free process utilizes comparatively weak nucleophiles (homoallylic alcohols) in the carbon monoxide **122**, generating transient acid that can undergo addition reaction to the alkene substrate incorporation with NIS and cyclic carbonate products **123** are yield enantioselectively.

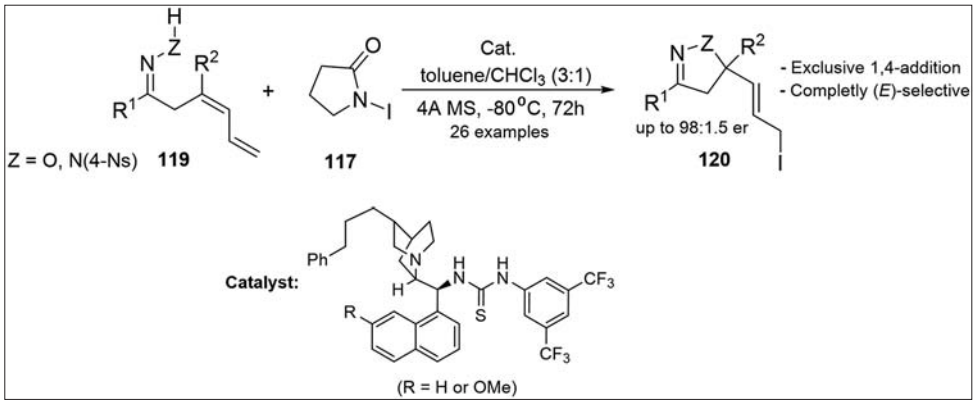
Later, the oxazolines and oxazines cores synthesis have been disclosed by Wong *et al*. group **(Scheme 41)**,[60] employing the electrophilic bromocyclization of cyclopropylmethylamides, through Lewis base sulfide catalyst. 1,2-Dichloromethane solvent and various amide substrates **124,** for example, 1,2-cyclopropylmethyl amide and 1,1-cyclopropylmethyl amide, and carbamate, were tolerated and found to be appropriate in this type of cyclization. A plausible reaction mechanism proceeds



Scheme 37: Organocatalytic asymmetric halocyclization of unsaturated amides using chloramine-T.3 H_2O salt



Scheme 38: Iodoaminocyclization of *β, γ*,-unsaturated hydrazones



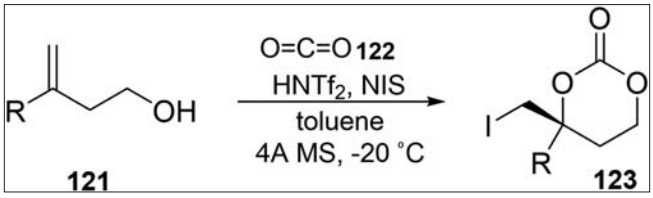
Scheme 39: Catalytic enantioselective 1,4-Iodofunctionalization of unsaturated oximes (dienes)

through a successful interaction between the Lewis basic sulfide and Br, followed by addition and cyclization reactions of the intermediate species and affording the 1,2-trans-substituted cyclopropane products **125** and **126** with excellent diastereoselectivity.

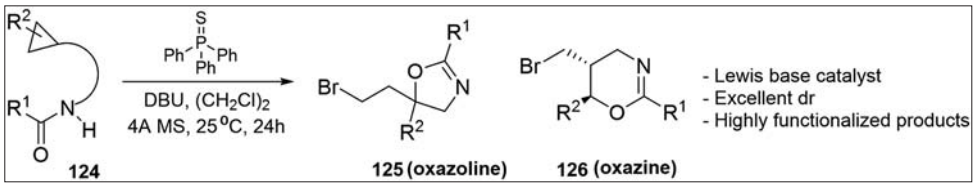
Furthermore, Kawato *et al*.[61] group reported the enantioselective bromocyclization of allylic amides **127**, using DTBM-BINAP as a catalyst **(Scheme 42)**.The reaction was conducted in CH_2Cl_2 with chiral phosphine DTBM-BINAP catalyst incorporation with *N*-bromosuccinimides as the electrophilic halogen source. This method afforded chiral oxazolines products **128** containing tetrasubstituted carbon center with excellent in both yield and enantioselectivity. Interestingly, the reaction was compatible with both electron-rich and electron withdrawing - alkyl substituents. Moreover, the reaction forward in significant with heteroaromatic substrates containing pyridyl and thienyl groups.

In subsequent publications, Arai *et al*.[62] disclosed a flexible route towered synthesis and biological importance of chiral 8-Oxa-6-azabicyclo [3.2.1] octane skeleton[63] promoted by aminoiminiophenoxy copper (II) acetate complex in powder form as a catalyst **(Scheme 43)**. The authors suggested that this catalyst utilize the iodocyclization of *N*-Tosylamide substrates **129** through hydrogen bond connection to form the corresponding products **130** through *O*-selective cyclization style with high yields. Various aromatic substituents on the R group of alkeneamide substrate were successfully tested and shown highly enantioselective iodocyclization reactions.

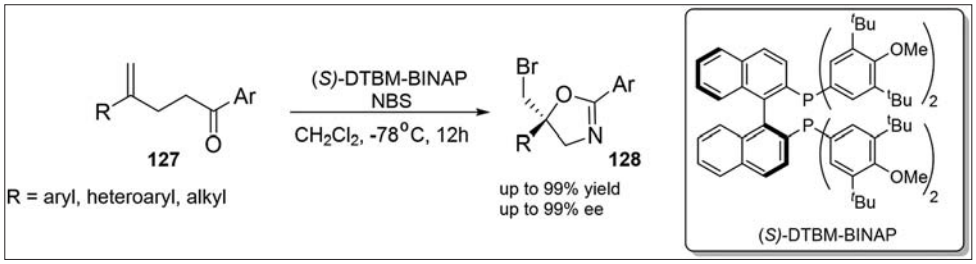
Regarding to the nucleophilicity of silanol in the development of silcon-combined scaffold containing stereogenic center, Xia *et al*.[64] have been reported asymmetric enantioselective bromo-oxycyclization of olefinic silanoles **131**, promoted by individual reactivity of bromine/*N*-benzyl-DABCO complex **(Scheme 44)**. Actually, different non-polar solvents and chiral phosphoric catalysts were employed and disclose that toluene and (8H-*R*-TRIP **L1**) were the best candidates in this type of reaction. On the other hand, the reaction was examined with substrates containing electron-donating and electron drawing groups on phenyl, finishing the benzoxasilole products **132** in excellent enantioselectivities. Furthermore, the bromine complexs were applied here and surprising that the bromonium ion was ineffective for this reaction.



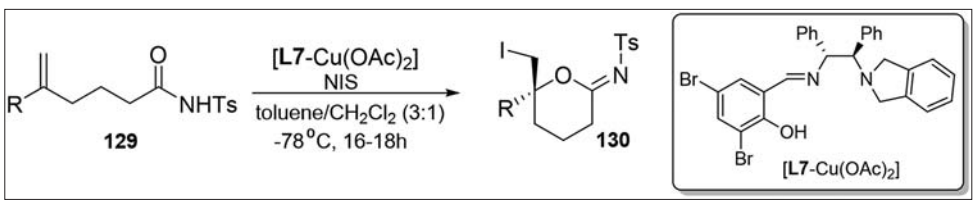
Scheme 40: Enantioselective CO_2 capture reaction using a homoallylic alcohols



Scheme 41: Lewis basic sulfide catalyzed electrophilic bromocyclization of cyclopropylmethyl amids



Scheme 42: BINAP catalyzed the enantioselective bromocyclization of allylic amides



Scheme 43: [L7-Cu(OAc)$_2$] catalyzed the enantioselective lodocyclization of N-tosyl alkenamides

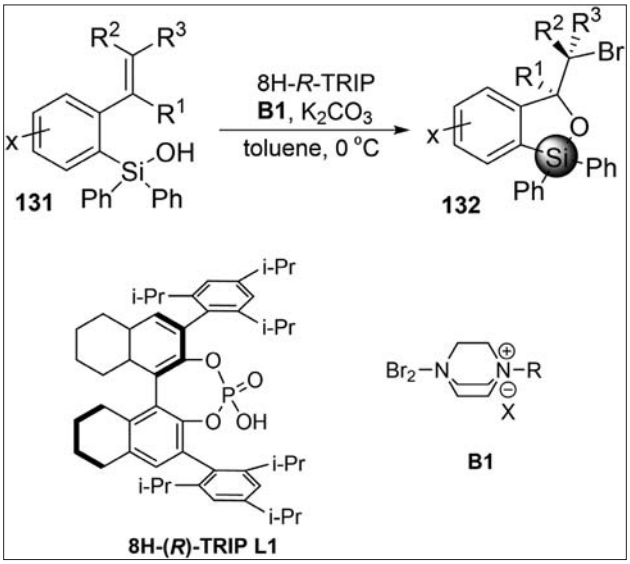
Later, Kawato *et al*.[65] recorded a novel phosphorus Lewis bases catalyzed the enantioselective bromocyclization of allylic amides **133 (Scheme 45)**. Under ideal reaction conditions, anhydrous solvent and an inert atmosphere, the NMR and detailed mechanistic study can proceed through generation *in situ* of DTBM-BINP monoxide as an actual catalyst. Coordination of this catalyst with NBS, produce the intermediate species. This intermediate then undergoes the electrophilic attack on the olefin to afford chiral bromonium intermediate. Capture of the later with an amide oxygen atom furnished the desired chiral oxazoline products **134**.

Furthermore, Samanta and Yamamoto group[66] detailed the efficient role of chiral BINOL-derived thiophosphoramide as a catalyst in the asymmetric bromocyclization of Polyenes **(Scheme 46)**. Using optimal reaction conditions, various geranyl benzene and geranylphenol derivatives **135** and **137** were cyclized with high enantioselectivities, using BINOL as catalyst and DBDMH as an electrophilic bromine source. More ever, it is surprisingly that the bromocyclization reaction was assumed with the scale-up and the products were obtained with corresponding enantioselectivities **136** and **138**.

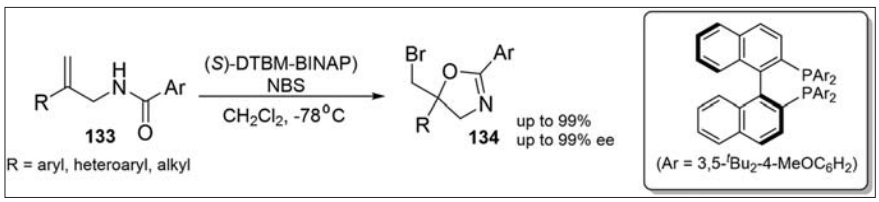
Furthermore, Yu *et al*.[67] designed an efficient protocol for the enantioselective synthesis of 2-bromomethyl Indolines, catalyzed by BINAP(S) **(Scheme 47)**. Applying different conditions including solvents, catalysts, and brominating reagents, led to speculate that the combination of toluene/CH_2Cl_2 solvents, BINAP monosulfide, and NBS was the best candidates for the transformation of N-tosyl-2-allylaniline substrates **139**, furnishing the series of chiral indoline derivatives products **140** bearing various functional groups in high yields.

In 2018, Liu *et al*.[68] developed an effective process towered the enantioselective bromocyclization of protected Tryptamines, promoted by bifunctional catalyst under an air atmosphere **(Scheme 48)**. The mechanism of the reaction is based on their previous work[69] and Marsden *et al*. finding.[70] The reaction started with the generation of the unstable CO_2Br species ([Co*]-Br) through the exchange reaction between the Bronsted acid and readily available *N*-bromosuccinimide in toluene, followed by conversion to chiral brominating reagent ([Co*]-Br^+) soluble in the non-polar solvent. Subsequently, the later undergo enantioselective bromocyclization with tryptamine **141** through the transition state **TS-I** to form 3-bromohexahydropyrrolo[2,3-*b*] indoles **142** with up to 95% yield.

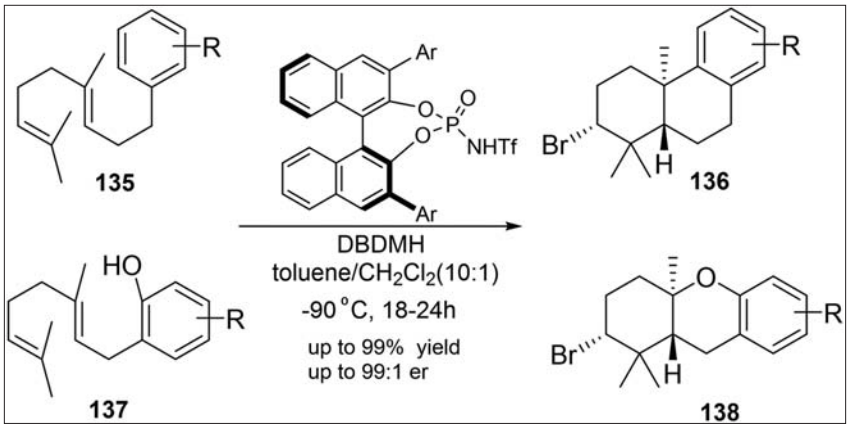
More ever, Lu *et al*.[71] described the same protocol for the construction of chromans and pyrrolidines **144** frameworks from 2-alkenylphenol and unsaturated amide substrates, utilized by chiral amidophosphate catalysts and halo-Lewis acids **(Scheme 49)**. Based on the outcomes of an NMR study, they promoted that the dual activation of iodine with NBS/DBU, generated in situ NIS with nucleophilic phosphoric acid and IBr in non-polar at ambient temperature which provided the iodonium ion species **i**. The immediately transformation of the later to electrophilic species **ii**, efficiently promoted



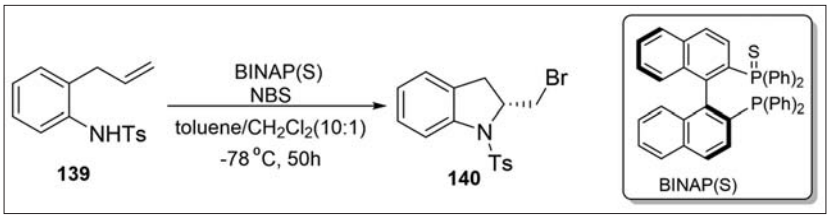
Scheme 44: Enantioselective bromo-oxycyclization of olefinic silanols



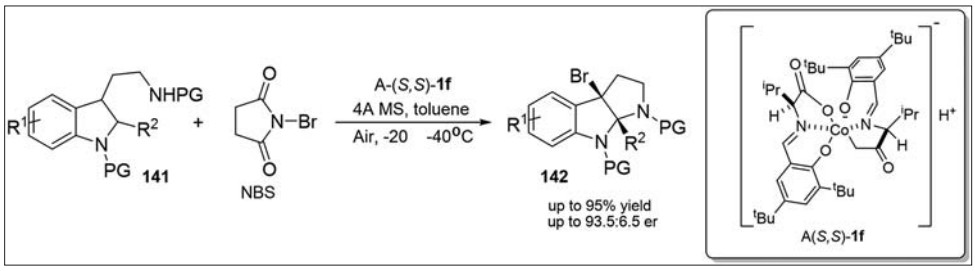
Scheme 45: Enantioselective bromocyclization of allylic amides in the presence of Lewis base catalyst



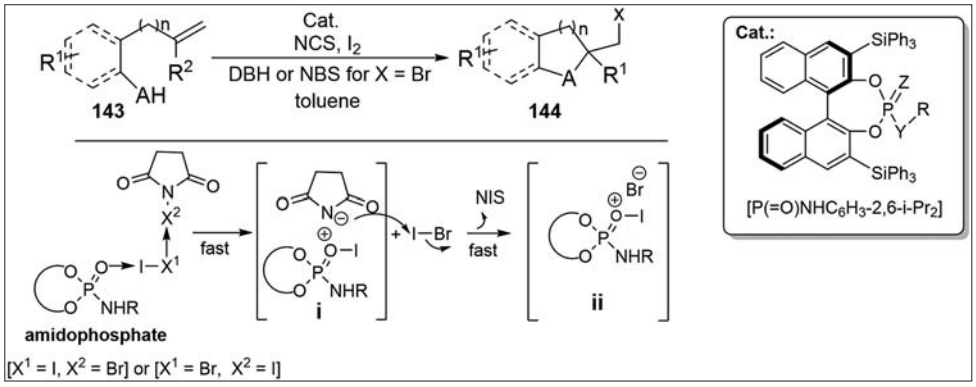
Scheme 46: Catalytic asymmetric bromocyclization of polyenest



Scheme 47: Enantioselective synthesis of 2-bromomethyl indolines



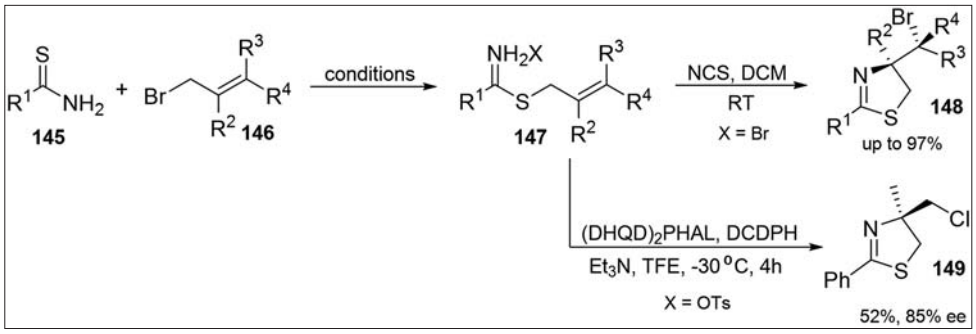
Scheme 48: Enantioselective bromocyclization of tryptamines indeuced by Co(III)-complex



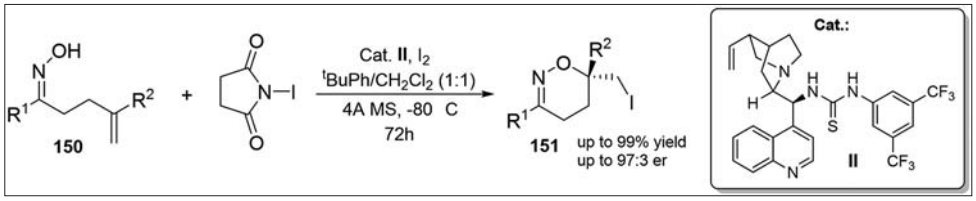
Scheme 49: Enantioselective Halo-oxy- and Halo-azacyclization induced by the chiral amidophosphate catalyst and halo-Lewis acid

the iodocyclization reaction of 2-alkenylphenol or unsaturated amide substrates **143** in high yields with high enetioselectivities. Furthermore, the chiral halogen chroman products can switch to the corresponding α-tocopherol and α-tocotrienol as well as the halocyclic products considered as a key intermediate in the synthesis Vitamin E [72,73] and englitazone.[74]

Later, Parker *et al*. group[75] reported novel coupling for the synthesis of *S*-allyl thioimidate salts through incorporation between thioamides and allyl bromide derivatives **(Scheme 50)**. First, the reaction proceeds forward with the bromothioimidate salt intermediate compounds **147** synthesis, through reaction of thiobenzamide **145** with bromo-2-methylpropene **146** in refluxing THF. Subsequently,



Scheme 50: Synthesis of *S*-allyl thioimidate salts through incorporation between thioamides and bromide derivatives



Scheme 51: A catalytic enantioselective Iodocyclization route to dihydrooxazines

treatment of bromothioimedate substrate as well as various olefins, including different substituted with NBS in CH_2Cl_2 at room temperature provided the corresponding alkyl- and arylthiazoline products **148** in high yield. Furthermore, their results demonstrated that the efficient diastereoselective haloyclization of bromothiazoline salts, promoted by the quinine-based catalyst $(DHQD)_2$PHAL and hydantoin-based halogen electrophiles (DCDPH), affords tetra-substituted chlorinated thiazoline products **149**.

Finally, Suresh *et al.*[76] disclosed a flexible route towered synthesis of 5,6-dihydro-4*H*-1,2-oxazines **151** with quaternary stereogenic center though iodocyclization of *γ,δ*-unsaturated oximes **150 (Scheme 51)**. In Thies context, starting with 1,4-diphenyl-*γ,δ*-usaturated (*E*)-oxime as a model and NIS as the electrophilic iodine source, variety of thioureas derived from Cinchona alkaloids were examined as catalysts and **II** was found to be equally effective in this type of reaction and furnished the products in high yields and high enantioselectivities. Furthermore, improvement of this protocol led to the successful synthesis of nitrogenous heterocycle 4,5,6,7-tetrahydro-1,2-oxazepine with seven-membered rings under similar conditions.[77]

CONCLUSION

After a large-scale survey of reports about enantioselective halo-functionalization reactions of alkenes that were published in the past 5 years, it was noted that it is possible to develop a general framework for the strategies that were used. In general, halofunctionalization reactions with their calcifications as halocyclization, haloetherification, and halolactonization reactions can be catalyzed by Lewis acids, Brønsted acids, Lewis bases, and phase transfer catalysts. Lewis acids and Brønsted acids increase the electrophilicity and consequently the reactivity of halogen sources by bonding to the compounds containing halogen intermolecularly, Lewis bases can activate halogen compounds by contribution its lone pair of electrons to the electrophilic halogen. The Phase transfer catalysts played as an effective roles in the reactions above, regardless what ever the halogen sources.Halocyclization of olefinic substrates is supporting strategy in creating *O*- and *N*-heterocyclic compounds, which supplementary imports the promotion of their asymmetric modifications. The most challenging project in this field is the catalytic asymmetric halogenation of unfunctionalized alkenes; novel catalysts and catalytic style are demanded to tackle the weak cooperation and interaction between the alkenes and catalysts, the use of a metal or synergistic catalytic system might help.

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