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Review Article

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Recent Advances in Asymmetric Intra- and Intermolecular Halofunctionalizations of Alkenes

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This review seeks to provide coverage on the recent advances in catalytic enantioselective halofunctionalization of alkenes. The aim is to give an overview on various reports, highlighting the new reaction types and strategies developed during the past two years. The scope and challenges in intra- and intermolecular reaction variants will be discussed as well.

1. Introduction

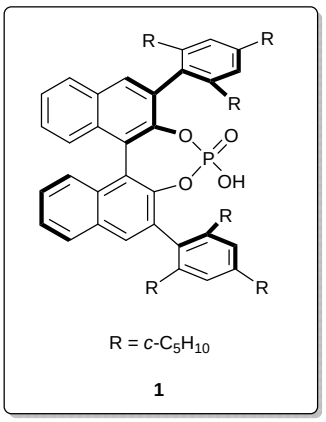
Halofunctionalization of alkenes is a fundamental organic transformation. In this process, a widely accepted mechanism involves an alkene that interacts with an electrophilic halogen to form a halonium ion first.[1-8] The halonium ion is then attacked by a nucleophile in an *anti*-fashion intra- or intermolecularly. The resultant product contains two new functional groups, including a halogen handle which can be easily manipulated further.

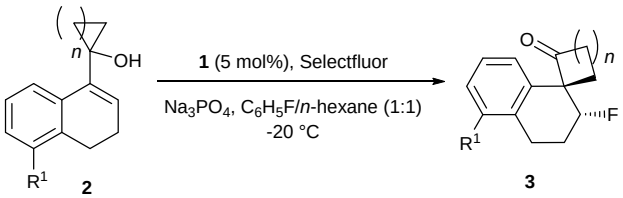
One of the longstanding challenges in developing an asymmetric variant of the alkene halofunctionalization reaction is the racemization of the enantioenriched halonium ion through the degenerate olefin-to-olefin exchange.[9-12] In the last few years, however, there has been rapid progress in the creation of novel strategies for the enantioselective halofunctionalization of alkenes using sub-stoichiometric amount of catalysts. Most of these strategies focused on the intramolecular reactions, *i.e.* halocyclization, and have been extensively discussed in various reviews.[13-22] The scope of this review will cover the most recent advancements in asymmetric halofunctionalization, with an emphasis on literature published in 2012 and 2013. In these two years, the diversity of catalysts and halofunctionalization reaction types have greatly expanded. In particular, enantioselective intermolecular halofunctionalization is an emerging area of research with a number of articles on the subject appearing very recently. In view of these new developments, selected examples of both intramolecular and intermolecular enantioselective halofunctionalizations using sub-stoichiometric amount of catalysts will be reviewed.

2. Enantioselective Intramolecular Halofunctionalization of Alkenes

Enantioselective Fluorocyclizations

An enantioselective alkene fluorination was reported by Alexakis and co-workers (Scheme 1).[23] In contrast to many other catalytic asymmetric halocyclizations, ring closure was not achieved by direct attack by an intramolecular nucleophile in this case. Instead, a Wagner-Meerwein rearrangement is involved. With a combination of BINOL-based phosphoric acid **1** as the catalyst and Selectfluor, allylic cyclobutanols and cyclopropanols **2** underwent ring expansion during the reaction resulting in the formation of enantioentriched *β*-fluorospiroketones **3**. Organocatalytic Wagner-Meerwein rearrangements mediated by chlorine or bromine electrophiles have also been previously documented in the literature as well.[24,25]



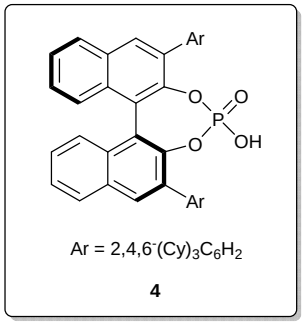


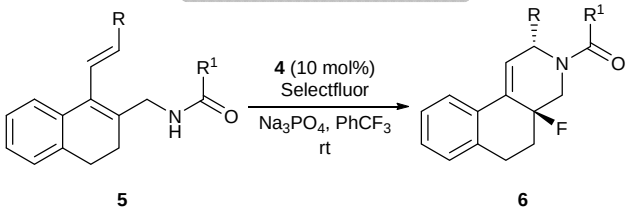
R^1 = Me, n = 1, 96% yield, 94% ee
R^1 = H, n = 2, 85% yield, 92% ee
R^1 = F, n = 2, 92% yield, 92% ee

Scheme 1. Enantioselective Wagner-Meerwein rearrangement catalyzed by phosphoric acid **1**.

An enantioselective fluorocyclization was reported by Toste and co-workers (Scheme 2).[26] BINOL-derived phosphoric acid **4** was developed as an anionic phase-transfer catalyst to effect 1,4-aminofluorocyclization of 1,3-dienes with Selectfluor as a

fluorinating reagent. The 1,3-diene substrates **5** underwent 6-*endo*-trig cyclization to give benz[*f*]isoquinoline derivatives **6** as the products. In the process, the authors also developed a new fluorinated amine reagent to replace Selectfluor for use on the cyclization of less reactive dienes, with somewhat lower yields and enantioselectives being achieved for the corresponding octahydroisoquinoline products.



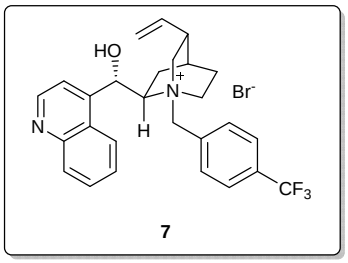


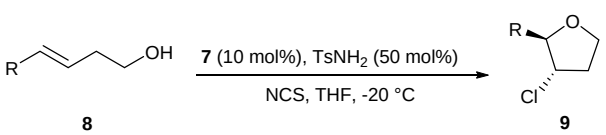
R = 3-Me-Ph, R^1 = 4-*t*Bu-Ph, 92% yield, 5.9:1 d.r., 92% ee
R = Ph, R^1 = 4-Br-Ph, 96% yield, 8.7:1 d.r., 92% ee

Scheme 2. Enantioselective 1,4-aminofluorocyclization of 1,3-dienes **5** using phosphoric acid **4**.

Enantioselective Chlorocyclizations

A recent example of chlorocyclization was illustrated by the work of Sun and co-workers (Scheme 3).[27] Using a quaternary ammonium salt **7** derived from cinchonine as a catalyst together with *N*-chlorosuccinmide (NCS) as the electrophilic chlorine source, 5-*endo* chloroetherification of homoallylic alcohols **8** to give chiral chlorotetrahydrofurans **9** was demonstrated.

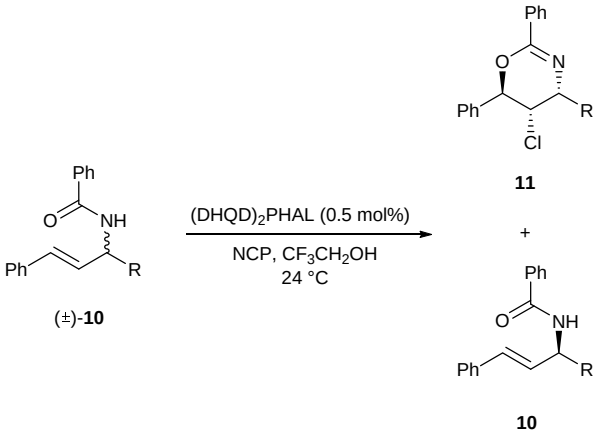




R = 3-Me-Ph, 81% yield, 92% ee
R = 4-CF_3-Ph, 85% yield, 92% ee

Scheme 3. Enantioselective chloroetherification of homoallylic alcohols **8**.

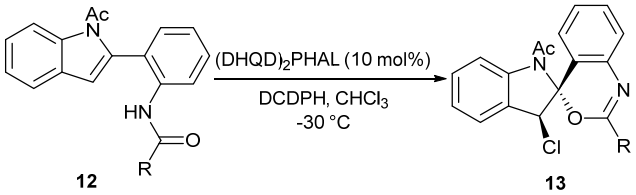
An interesting kinetic resolution of unsaturated amides utilizing an asymmetric chlorocyclization reaction was reported by Borhan and co-workers (Scheme 4).[28] The same group demonstrated $(DHQD)_2PHAL$-catalyzed enantioselective chlorocyclizations of alkenoic acids in 2010,[29] and unsaturated amides in 2011.[30] In the current case, racemic unsaturated amides **10** were subjected to the same catalytic process with *N*-chlorophthalimide (NCP) as the chlorine source, resulting in the simultaneous formation of both enantioenriched oxazines **11** and unreacted substrates **10**. Based on NMR studies, the authors postulated that the quinuclidine nitrogen atoms of $(DHQD)_2PHAL$ were protonated and as a result, might act as hydrogen-bonding catalysts.



R	**11**: dr, yield, ee (%)	**10**: yield, ee (%)
Me	95:5, 55, 94	43, 97
n-C_5H_{11}	97:3, 49, 88	46, 85

Scheme 4. Kinetic resolution of unsaturated amides **10** using chlorocyclization.

A final example of chlorocyclization relates to the work of You and co-workers (Scheme 5).[31] Catalytic amount of $(DHQD)_2PHAL$ was used in the enantioselective chlorocyclization of indole derived benzamides **12** to give enantioenriched spiro-indolines **13**, with 1,3-dichloro-5,5-diphenylhyantoin (DCDPH) as the electrophilic chlorine source.



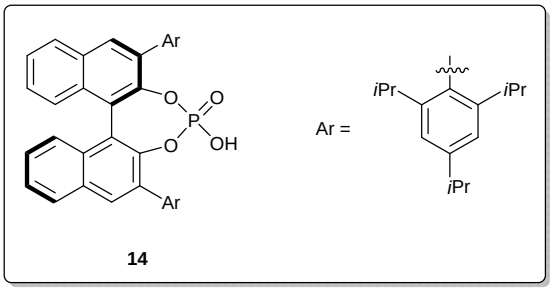
R = Ph, 85% yield, 95% ee
R = *t*Bu, 76% yield, 80% ee

Scheme 5. Enantioselective chlorocyclization of indole derived benzamides **12**.

Enantioselective Bromocyclizations

Denmark and co-workers reported a catalyst system consisting of a 1:1 combination ratio of achiral Lewis base Ph_3PS and chiral

Brønsted acid catalyst BINOL-derived phosphoric acid **14** for enantioselective bromocycloetherification (Scheme 6).[32] (*Z*)-5-arylpentenols **15** reacted smoothly in the presence of *N*-bromosuccinimide (NBS) as the halogen source to afford the *exo*-cyclized bromomethyltetrahydrofurans **16** products with high constitutional selectivity. Relatively lower ees were obtained for the cyclization of (*E*)-5-arylpentenols **15**. Recently, the same group reported a mechanistic investigation demonstrating the importance of Ph_3PS in obtaining high yields.[33] Similar strategies of haloetherification without the use of Ph_3PS as co-catalyst have also been reported by different groups preceding Denmark's work. Hennecke and co-workers offered a desymmetrizing approach to enantioselective haloetherifications using the sodium salts of chiral phosphoric acids as catalysts,[34] while Shi and co-workers used catalytic chiral phosphoric acid to achieve enantioselective *O*- and *N*-bromocyclizations, affording enantioenriched heterocyclic products.[35]



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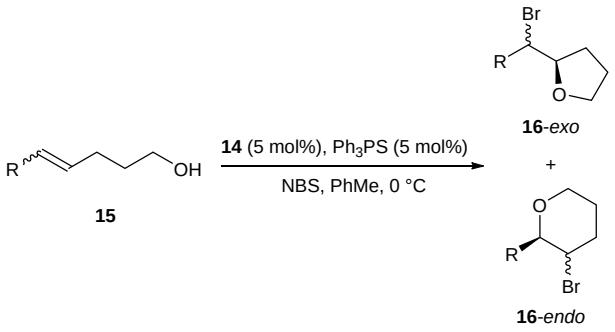
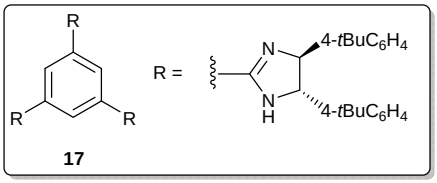


15

R	**16**-***exo***: yield, ee (%)	**16**-***endo***: yield, ee (%)
(*E*)-4-Me-Ph	28, 94	67, 30
(*Z*)-4-Me-Ph	64, 88	9, 30

Scheme 6. Enantioselective bromoetherification of (*Z*)-5-arylpentenols **15**.

Fujioka and co-workers reported the kinetic resolution of racemic *β*-substituted carboxylic acids **18** using the C_3-symmetric trisimidazoline catalyst **17** (Scheme 7). 1,3-Dibromo-2,2-dimethylhydantoin (DBDMH) was used as the halogen source.[36] The enantioselectivity of the enantioenriched lactones **19** and the recovered **18**, and the *s* factor of reaction were found to be highly dependent on the position and nature of R^1 substituent. It is noted that the same group also utilized a structurally similar C_3-symmetric catalyst for asymmetric bromolactonization in 2010.[37]



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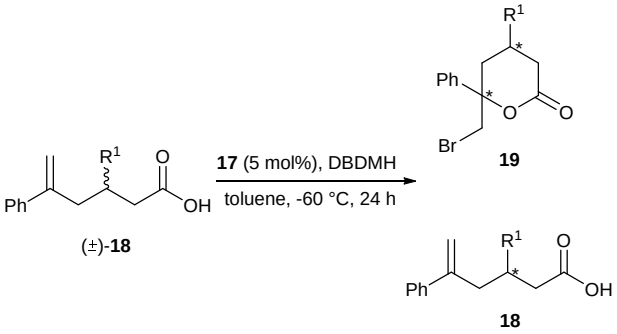
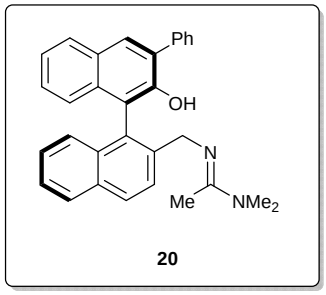


(±)-**18**

R^1	**19**: yield, ee (%)	**18**: yield, ee (%)
Me	56, 65	34, 94
Ph	43, 84	50, 62

Scheme 7. Kinetic resolution of *β*-substituted carboxylic acids **18**.

The use of a BINOL-derived bifunctional catalyst **20** in enantioselective bromolactonization was reported by Martin and co-workers (Scheme 8).[38] 2,4,4,6-Tetrabromo-2,5-cyclohexadienone (TBCO) was used as the brominating agent. The substrate scope is broad as various 4- and 5-aryl-4-pentenoic acids **21** and **23** could undergo cyclization to give enantioenriched 5- and 6-membered bromolactones **22** and **24**. Most notably, the catalyst also promoted the cyclization of different 5-alkyl-4-(*Z*)-pentenoic acids via 5-*exo* mode cyclizations. The same selectivity was obtained by our research group previously using amino-thiocarbamate as the catalyst.[39] Another interesting point worth noting is that the same catalyst can be applied on desymmetrization of a prochiral dienoic acid to give promising enantioselectivity of 46% ee. By using this strategy, the same group also successfully developed an enantioselective iodolactonization protocol using a structurally similar catalyst.[40]



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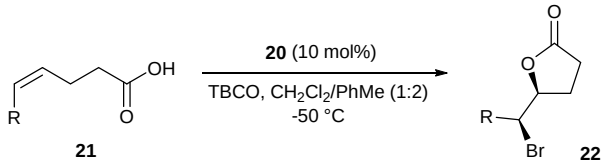
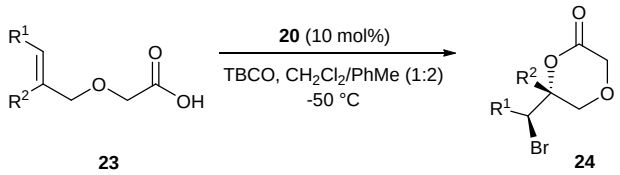


21 **22**

R = Et, 90% yield, 70% ee
R = *t*-Bu, 97% yield, 94% ee

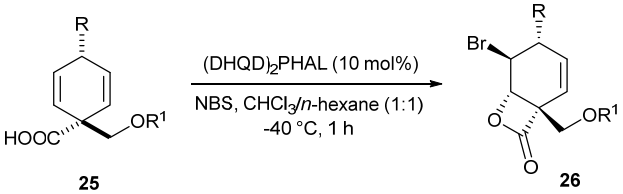


23 **24**

R^1 = H, R^2 = Ph, 98% yield, 72% ee
R^1 = Me, R^2 = Me, 93% yield, 70% ee

Scheme 8. Enantioselective bromolactonizaton with BINOL-derived catalyst **20**.

The concept of desymmetrization using bromolactonization was also reported by Kan and co-workers (Scheme 9).[41] Using $(DHQD)_2PHAL$ as the catalyst and NBS as the brominating agent, desymmetrization was performed on prochiral cyclic dienes **25** to give enantioenriched bromolactones **26**. The reaction could be completed in one hour. The protocol could also be applied to the kinetic resolution of a racemic cyclic ene-carboxylic acid.

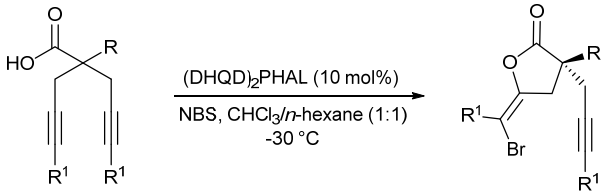


25 **26**

R = H, R^1 = TIPS, 87% yield, 91% ee
R = Me, R^1 = TBDPS, 89% yield, 81% ee

Scheme 9. Desymmetrization of prochiral cyclic dienes **25** by asymmetric bromolactonization.

Hennecke and co-workers reported another desymmetrization approach where enantioselective bromolactonization of di-alkynes **27** to give bromoenol lactone products **28** was catalyzed by $(DHQD)_2PHAL$ (Scheme 3).[42] Following a series of mechanistic investigations, the authors believe that the interaction between the pyridazine nitrogen in the catalyst and the carboxylic acid group in **27** is important for the high enantioselectivity.

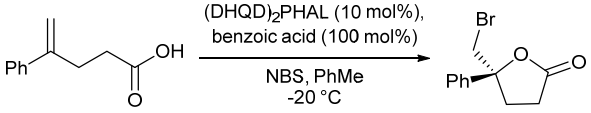


27 **28**

R = CO_2Me, R^1 = H, 79% yield, 72% ee
R = Ph, R^1 = Me, 98% yield, 92% ee
R = H, R^1 = Me, 95% yield, 86% ee

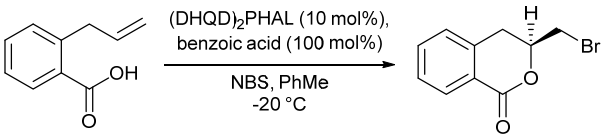
Scheme 10. Enantioselective and desymmetrizing bromolactonization of di-alkynes **27**.

In addition to desymmetrization reactions, catalytic $(DHQD)_2PHAL$ was also employed in enantioselective bromolactonizations of various alkenoic acids such as **29** and **31** with benzoic acid as an additive, as described by Braddock and co-workers (Scheme 11).[43] The enantioselectivity was highly dependent on the structure of the substrate, with generally moderate to good enantioselectivities achieved for the bromolactone products.



29 **30**

95% yield, 82% ee

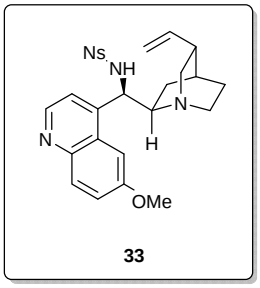


31 **32**

94% yield, 60% ee

Scheme 11. Enantioselective bromolactonization with $(DHQD)_2PHAL$ and benzoic acid additive.

Ma and co-workers described the use of quinine-derived catalyst **33** in the enantioselective bromohydroxylation of 2-aryl-2-propen-1-ols **34** to give bromohydrins **35** (Scheme 12).[44] The strategy involves a reaction between **34** and phenylboronic acid to give the corresponding boronic acid hemiester, which then underwent a 5-*exo* bromocyclization. Oxidative cleavage of the cyclized product with H_2O_2 furnished enantioenriched bromohydrins **35**.



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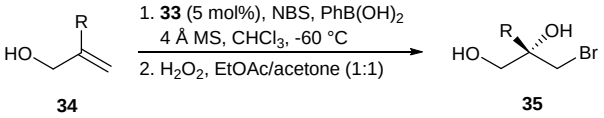


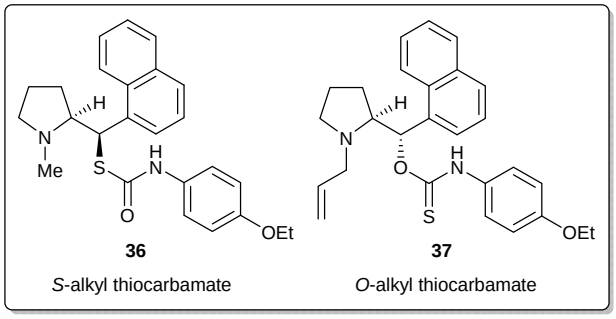
34 **35**

R = Ph, 86% yield, -95% ee
R = 3-MeO-Ph, 82% yield, 89% ee

Scheme 12. Enantioselective bromohydroxylation of 2-aryl-2-propen-1-ols **34**.

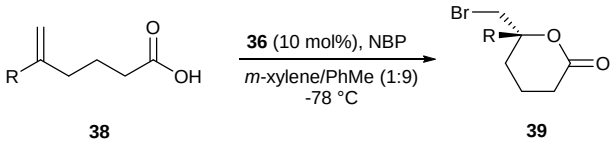
Our laboratory has developed several asymmetric bromocyclization reactions in recent years. These include cinchona alkaloid-derived amino-thiocarbamate catalyzed bromolactonizations[45-47] and bromoaminocyclizations.[48-50] The use of prolinol-derived amino-thiocarbamates in asymmetric bromolactonization has also been studied.[51] In this piece of work, it is noteworthy that both *S*-alkyl and *O*-alkyl thiocarbamates **36** and **37** could be utilized in the asymmetric bromolactonization reactions (Scheme 13) using *N*-bromophthalimide (NBP) as the brominating agent. Interestingly, it was found that **36** was suitable for the cyclization of **38** that resulted in *δ*-lactone **39**. On the other hand, effective asymmetric cyclization of **40** in the formation of *γ*-lactone **41** required the use of catalyst **37**. The interested reader can refer to the various reviews mentioned in the *Introduction section* which provide well-rounded coverage on our earlier work on amino-thiocarbamates.

Lately, our studies revealed that in addition to bromolactonization and bromoaminocyclization, the amino-thiocarbamate could also be employed as a catalyst in the enantioselective bromocyclization of olefinic 1,3-dicarbonyl compounds **43** (Scheme 14).[52] Amino-thiocarbamate **42** was first benchmarked against several common Lewis basic catalysts and it was found to be able to effect highly chemoselective bromination at the desired alkene position of the substrate and cyclization, instead of bromination at the α-position of the carbonyl functionalities. The bromocyclization gave highly substituted furans **44** in high enantioselectivities.



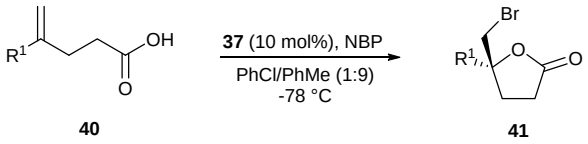
36 **37**

S-alkyl thiocarbamate *O*-alkyl thiocarbamate



38 **39**

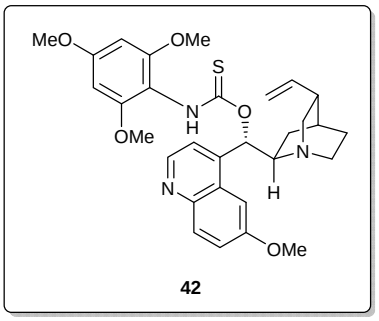
R = Ph, 97%, 92% ee



40 **41**

R^1 = 1-naphthyl, 99%, 91% ee

Scheme 13. *S*-Alkyl and *O*-alkyl thiocarbamates catalyzed asymmetric bromolactionization.



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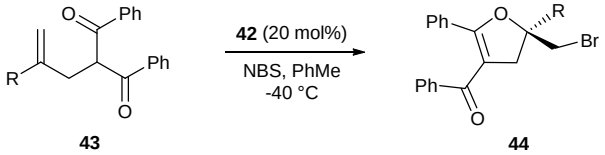


43 **44**

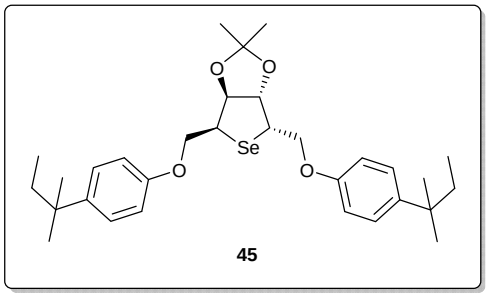
R = Ph, 89% yield, 96% ee
R = 2-naphthyl, 87% yield, 81% ee
R = *i*Pr, 87% yield, 90% ee

Scheme 14. Enantioselective bromocyclization of olefinic 1,3-dicarbonyl compounds **43**.

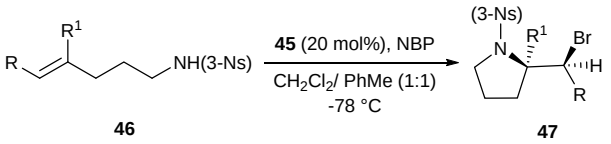
Similar to our previous proposals, the amino-thiocarbamate is believed to act as a bifunctional catalyst: the Lewis basic sulfur may activate the Br in NBS and the quinuclidine base moiety in the catalyst may remove the acidic proton at the α-position of the carbonyl functionalities.

In addition, we have discovered that the C_2-symmetric monofunctional cyclic selenium **45** could function as a Lewis basic catalyst in the bromoaminocyclization of trisubstituted

olefinic amides **46** (Scheme 15).[53] NBP was found to be the superior electrophilic brominating source. The pyrrolidine products **47** contain two sterogenic centers and were able to undergo a silver salt-mediated rearrangement to form 2,3-disubstituted piperidines with excellent stereospecificity.



45

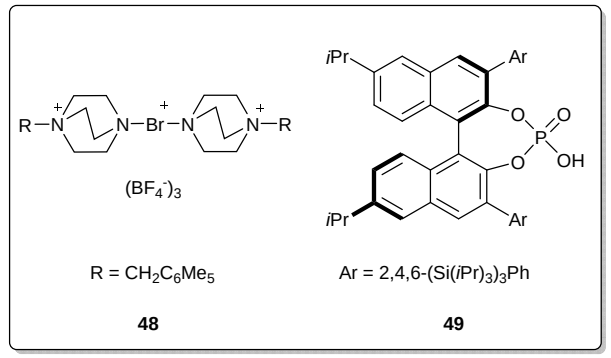


46 **47**

R = Et, R^1 = Ph, 93% yield, 91% ee
R= Me, R^1 = 3-Cl-Ph, 85% yield, 83% ee

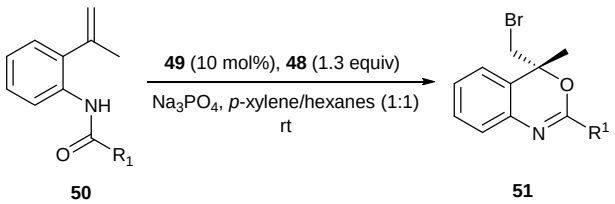
Scheme 15. Enantioselective bromoaminocyclization with C_2-symmetric cyclic selenium catalyst **46**.

Another strategy in enantioselective halocyclization is the design and use of novel halogenating reagents as reported by Toste and co-workers (Scheme 16).[54] Based on their earlier work on the enantioselective fluorocyclization using chiral anion



R = $CH_2C_6Me_5$ Ar = 2,4,6-$(Si(iPr)_3)_3Ph$

48 **49**



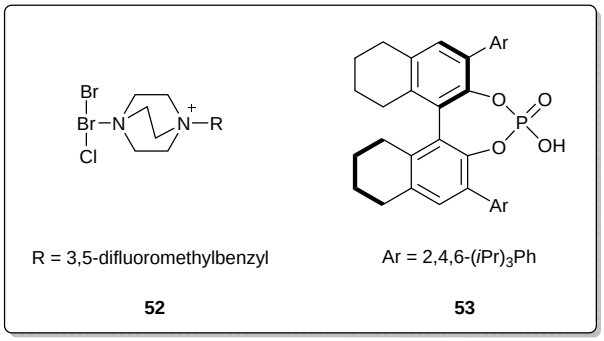
50 **51**

R^1 = Ph, 82% yield, 94% ee
R^1 = *t*Bu, 72% yield, 87% ee

Scheme 16. Enantioselective halocyclization with halogen-containing ionic reagent **48**.

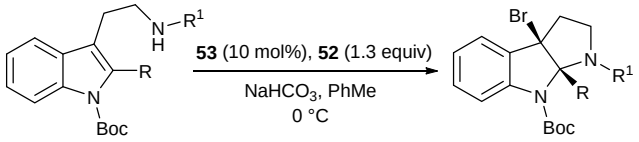
phase-transfer catalysis,[55] a similar concept was used for developing analogous bromine and iodine-containing ionic reagents such as **48** as the electrophilic halogen sources. As such kinds of reagents are insoluble in organic media, the racemic background reaction could be suppressed. With these reagents and catalytic amount of chiral phosphoric acid **49**, an enantioselective protocol for 6-*exo*-trig bromo- and iodocyclization of styrenyl amides to afford 4*H*-3,1-benzoxazines was developed. Mechanistic experiments suggest that the chiral phosphate anion functioned as the catalytically active species.

A related strategy was also used successfully by Ma and co-workers to achieve enantioselective bromocyclization of tryptamines (Scheme 17).[56] Using the ionic brominating reagent **52** and chiral phosphoric acid **53** as a phase-transfer catalyst, tryptamines **54** underwent cyclization to give enantioenriched 3-bromopyrroloindoles **55**. The authors further demonstrated the application of their methodology in the synthesis of the natural product (-)-chimonanthine.



R = 3,5-difluoromethylbenzyl Ar = 2,4,6-$(iPr)_3Ph$

52 **53**

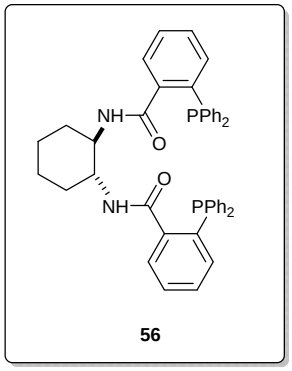


54 **55**

R = H, R^1 = Ts, 95% yield, 92% ee
R = $CH_2CH_2CO_2Et$, R^1 = CO_2Me, 99% yield, 89% ee

Scheme 17. Enantioselective bromocyclization of tryptamines.

Apart from organocatalysts, metallic catalyst could also be employed in the enantioselective bromocyclization reaction. An enantioselective bromoaminocyclization of allyl *N*-tosylcarbamates catalyzed by $Sc(OTf)_3$ and chiral phosphine ligand **56** was presented by Shi and co-workers (Scheme 18).[57] A number of substituted *cis*-olefinic carbamate **57** could be cyclized to yield oxazolidinone **58** with high enantioselectivity. The reaction was tolerant of various functional groups in the substrates such as NHBoc and α,β-unsaturated ester.



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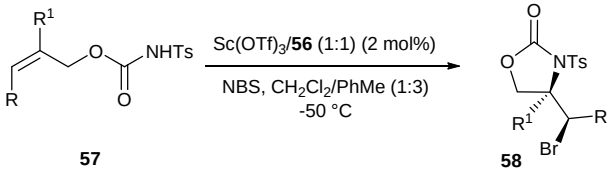


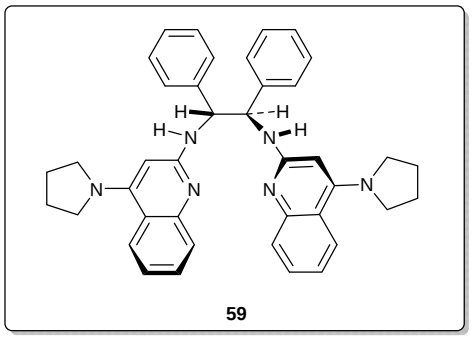
57 **58**

R = *n*-Bu, R^1 = H, 80% yield, 96% ee
R= Cy, R^1 = H, 71% yield, 96% ee
R= Me, R^1 = Me, 81% yield, 93% ee

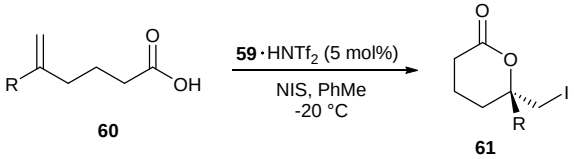
Scheme 18. Enantioselective bromoaminocyclization with $Sc(OTf)_3$ and chiral ligand **56**.

Enantioselective Iodocyclizations

An example of catalytic asymmetric iodocyclization relates to the bis(amidine) (BAM) **59**-triflimidic acid ($HNTf_2$) catalyst system developed by Johnston and co-workers (Scheme 19).[58] The catalyst system was used on the iodolactonization of **60** to produce δ-lactones **61** using *N*-iodosuccinimide (NIS) as the iodinating agent. BAM **59** is believed to undergo proton exchange with $HNTf_2$, forming a polar ionic hydrogen bonded BAM-H^+ and the corresponding achiral counter-anion. The enantioselectivity was found to be dependent on the type of achiral counter-anion used.



59

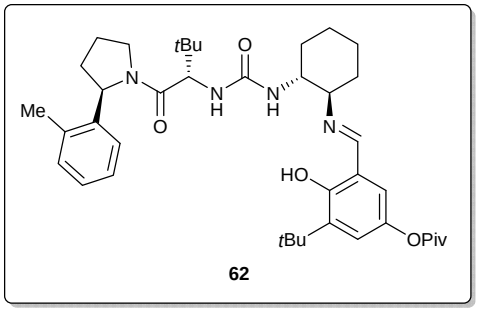


60 **61**

R = 2-napthyl, 96% yield, 96% ee
R = 3-Cl-Ph, 51% yield, 97% ee

Scheme 19. Enantioselective iodolactonization with BAM-$HNTf_2$ catalyst system.

The next enantioselective iodocyclization was published by Jacobsen and co-workers (Scheme 20).[59] In 2010, the same group demonstrated the use of chiral tertiary aminoureas in the asymmetric iodolactonization.[60] In the most recent work, they designed a new type of Schiff-base derived catalyst **62** while retaining the urea functionality. **62** was used to catalyze the iodocyclization of alkenyl trichloroacetimidates **63**, resulting in the enantioselective vicinal iodoamination of the olefins to yield **64**. Based on solubility and NMR studies, they reasoned that the catalyst reversibly complexes with the iodinating agent, NIS. Combined with some preliminary computational studies, they proposed that the urea Schiff-base catalysts may act as a neutral phase transfer agent in the cyclization reaction.



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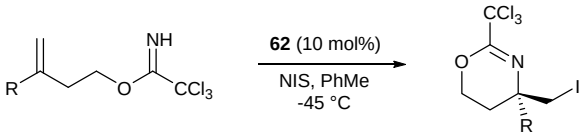
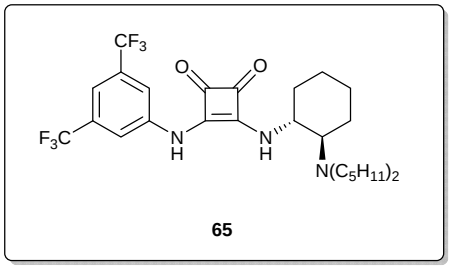


63 **64**

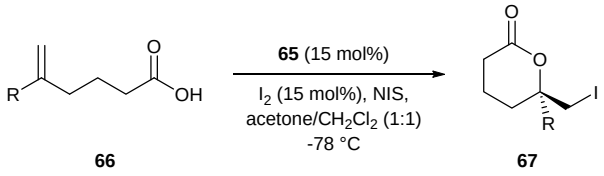
R =4-F-Ph, 86% yield, 90% ee
R = 3,5-$(MeO)_2$-Ph, 86% yield, 90% ee

Scheme 20. Enantioselective iodocyclization of alkenyl trichloroacetimidates **63**.

Another catalytic iodocyclization related to the tertiary aminourea developed by Jacobsen and co-workers[60] is the use of a chiral squaramide **65** in enantioselective iodolactonization of hexenoic acids **66** as reported by Hansen and co-workers (Scheme 21).[61] While δ-lactones **67** were produced in high enantioselectivities, the ee appeared greatly diminished when the authors applied the same conditions to synthesize γ-lactones through the cyclization of pentenoic acids.



65

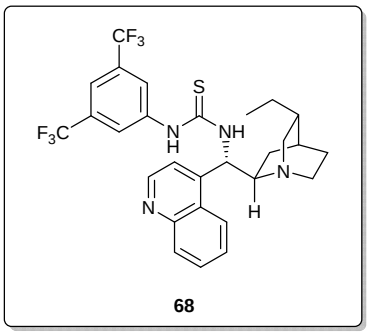


66 67

R = Ph, 83% yield, 87% ee
R = 4-Cl-Ph, 78% yield, 96% ee

Scheme 21. Enantioselective iodolactonization with chiral squaramide **65**.

Following their previous work on *N*-bromosuccinimide (NBS)-mediated alcohol oxidation based on thiourea catalysts,[62] Mukherjee and co-workers reported an enantioselective iodoetherification using dihydrocinchonidine-derived thiourea catalyst **68** (Scheme 22).[63] *β*,*γ*-Unsaturated oximes **69** were converted to Δ^2-isoazolines **70** containing a quaternary sterogenic center. Through a study of related sulfur-based catalyst analogues, the authors demonstrated that both the Lewis-basic sulfur and a Brønsted basic functionality in the catalyst scaffold are required for the high catalytic activity. The reaction did not proceed when an amino-thiocarbamate was used as the catalyst, which the authors ascribe to the importance of dual hydrogen bonding from thiourea.



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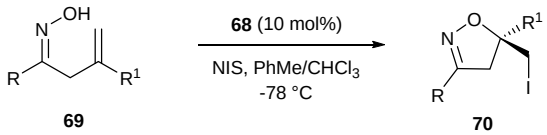


69 70

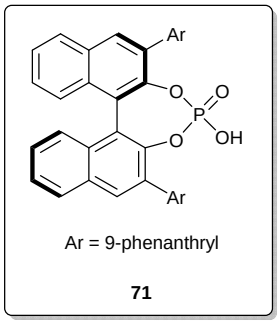
R = Ph, R_1 = Ph, 88% yield, 90% ee
R = 4-Cl-Ph, R_1 = 4-F-Ph 82% yield, 92% ee
R = Ph, R_1 = Me, 98%, 84% ee

Scheme 22. Enantioselective iodoetherification of *β*,*γ*-unsaturated oximes **69**.

3. Enantioselective Intermolecular Halofunctionalization of Alkenes

In contrast to the intramolecular counterpart, enantioselective intermolecular halofunctionalizations of alkenes are less commonly reported in the literature. Generally, this class of reaction suffers from low enantioselectivity and/or low catalytic activity.[64,65] Attempts at enantioselective intermolecular halogenation using stoichiometric amounts of chiral promoter or reagent have also been reported. The use of a chiral diol to mediate asymmetric alkene dichlorination as part of the the total synthesis of the natural product (-)-napyradiomycin A1,[66] as well as the use of chiral sulfonium reagents in enantioselective dihalogenation and halohydroxylation of alkenes,[67] were both detailed in the work of Snyder and co-workers. In recent years, considerable efforts have been devoted to the exploration of chiral phosphoric acids and cinchona alkaloid-derived molecules as potential catalysts for enantioselective intermolecular halofunctionalizations. This section will provide an overview of these reactions in the literature where promising enantioselectivities had been achieved.

In 2012, Tang and co-workers reported an enantioselective intermolecular bromoesterification catalyzed by BINOL-based phosphoric acid catalyst **71** (Scheme 23).[68] Enantioselectivities of up to 70% could be attained by varying the carboxylic acid partner in the reaction. It was noted that the product yields were generally low. The authors attributed this to the competitive nucleophilic attack by the chiral phosphoric acid catalyst on the cyclic bromonium ion, which resulted in the consumption of catalyst **71**.



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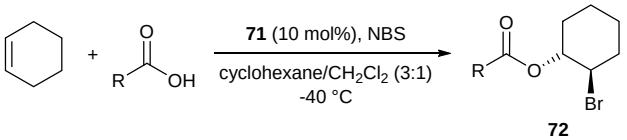


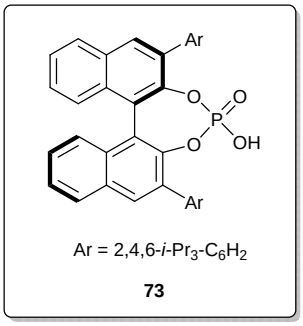
72

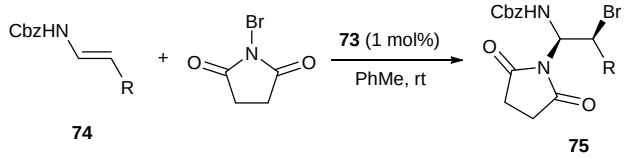
R = 4-OMe-PhCH$_2$, 20% yield, 69% ee
R=2-OMe-PhCH$_2$, 18% yield, 70% ee
R=4-F-PhCH$_2$, 23% yield, 53% ee

Scheme 23. Enantioselective intermolecular bromoesterification using chiral phosphoric acid **71**.

Masson and co-workers reported an enantioselective *α*-bromination of ene-carbamates **74** catalyzed by BINOL-derived phosphoric acid **73** (Scheme 24).[69] It is worth noting that NBS plays a dual role in this reaction; the Br in NBS acts as the electrophilic brominating agent while the succinimide anion acts

as the nucleophile. The opposite enantiomeric product could be obtained by simply using the lithium or calcium salt of the phosphoric acid **73** as catalyst. After performing some mechanistic experiments, the authors proposed that **73** may behave as a bifunctional catalyst which activate the ene-carbamate substrate and NBS via hydrogen bonding. On the other hand, the calcium salt of **73** is believed to interact with NBS and the ene-carbamate via metal chelation instead.



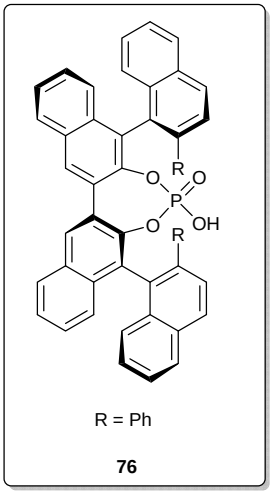


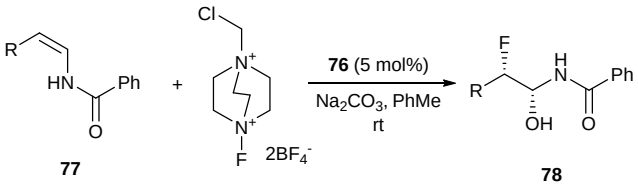
R = $(CH_2)_3CHCH_2$, 90% yield, 97% ee
R = $(CH_2)_3$OTBDPS, 94% yield, 98% ee

Scheme 24. Enantioselective α-bromination of ene-carbamates **74**.

In another approach of utilizing chiral phosphoric acid as catalyst, Toste and co-workers reported an enantioselective oxyfluorination of enamides **77** based on a chiral anion phase-transfer strategy (Scheme 25).[70] Using the novel phenyl-substituted doubly axial chiral phosphoric acid 7**6** as the catalyst, fluorofunctionalization of **77** was achieved, affording enantioenriched α-fluoro-*N*,*O*-aminal products **78**.

Cinchona alkaloid-based $(DHQD)_2PHAL$ was used by Tang and co-workers as the catalyst in the enantioselective intermolecular bromoesterification of allylic sulfonamide **79** with (+)-camphor sulfonic acid (CSA) as an additive (Scheme 26).[71] Based on NMR studies, the authors believe that the (+)-CSA acid additive may protonate the highly basic quinuclidine nitrogen of $(DHQD)_2PHAL$ which minimized the quinuclidine-Br adduct formation. This in turn favoured the hydrogen bonding interaction between phthalazine nitrogen of the catalyst and sulfonamide N-H group in the substrate.





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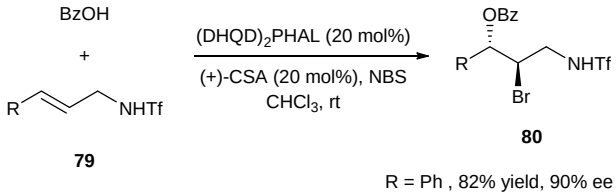
R = Ph, 86% yield, 98% ee
R = -$(CH_2)_5$-, 80% yield, 90% ee

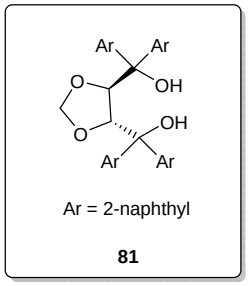
Scheme 25. Enantioselective oxyfluorination of enamides **77**.

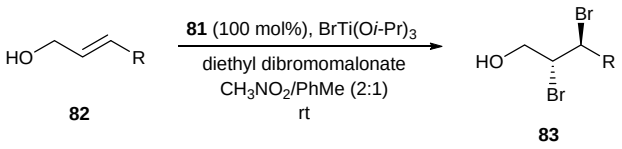


R = Ph , 82% yield, 90% ee
R = 4-CN-Ph, 79% yield, 93% ee
R = 2-Naphthyl, 80% yield, 90% ee

Scheme 26. Enantioselective intermolecular bromoesterification with $(DHQD)_2PHAL$.

A final example of intermolecular alkene halofunctionalization presented in this review was performed by Burns and co-workers (Scheme 27).[72] Using a combination of diethyl dibromomalonate as the cationic Br source and bromotitanium triisopropoxide as the bromide source, a protocol for enantioselective dibromination of allylic alcohols **82** was developed. The authors proposed that the tartaric acid-derived diol **81**, which was used as the chiral ligand in the reaction, may function as a catalyst although there was some decrease in enantioselectivity when the ligand was used in sub-stoichiometric quantities. Further studies revealed that bromide anion delivery is involved in the selectivity-determining step. Interestingly, when diethyl dibromomalonate was replaced with other common and stronger electrophilic brominating sources like NBS, there was significant erosion of enantioselectivity.





R = Ph, 63% yield, 86% ee
R = 3-OMe-Ph, 71% yield, 82% ee

Scheme 27. Enantioselective dibromination of allylic alcohols **82**.

4. Conclusion

A considerable number of catalytic enantioselective halofunctionalization reactions published in 2012-2013 has been covered in this review. This exemplifies the heightened interest and also successes achieved in this area of research. A major part of the efforts were devoted to the development of novel strategies in intramolecular halocyclization processes. Concurrently, attention has also been given to the intermolecular variant with a few reports obtaining high catalytic activity and enantioselectivity. One limitation in halofunctionalization is the subtle mechanistic understanding. In view of this, expectations are high that, newer reaction types, novel strategies and publications focusing on elucidating the mechanistic details will continue to appear in the near future.[73]

Acknowledgements

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