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## RECENT PROGRESS IN ORGANOCATALYTIC ASYMMETRIC HALOCYCLIZATION

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**Abstract** – In this review, recent progress made in the development of organocatalytic asymmetric halocyclization reactions that form heterocyclic compounds is described. New reactions and their mechanistic features are discussed in the context of an outline based on catalyst types, including bispinchona alkaloids, amino ureas, amino thioureas, amino thiocarbamates, chiral phosphoric acids, and trisimidazolines.

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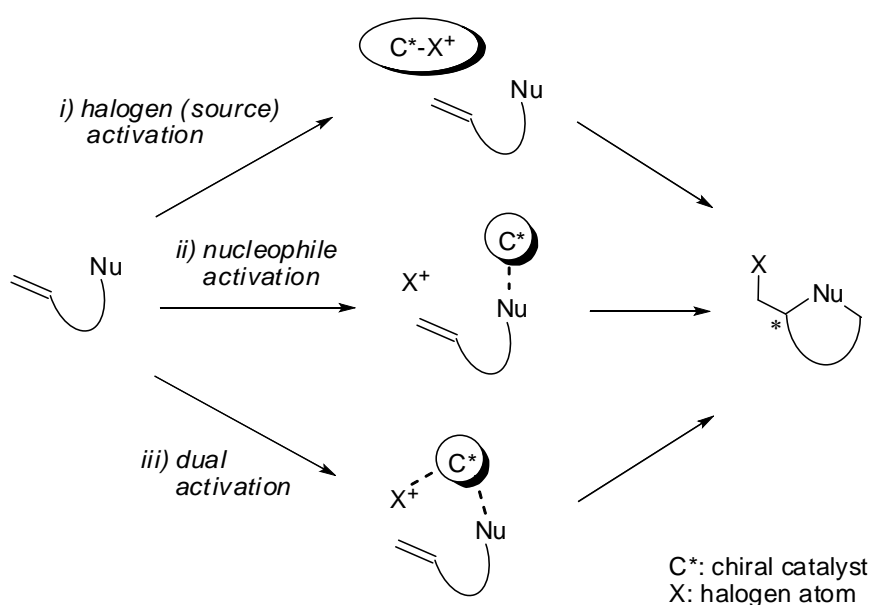
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### 1. INTRODUCTION

Halocyclization reactions of olefinic substrates, containing a pendant nucleophilic groups, serve as powerful methods in the synthesis of organic compounds.<sup>1</sup> In particular, these processes can be employed to synthesize various simple and even complex heterocyclic compounds, including lactones, cyclic ethers, and cyclic amines. As well as their applicability to constructing heterocyclic ring systems, halocyclization

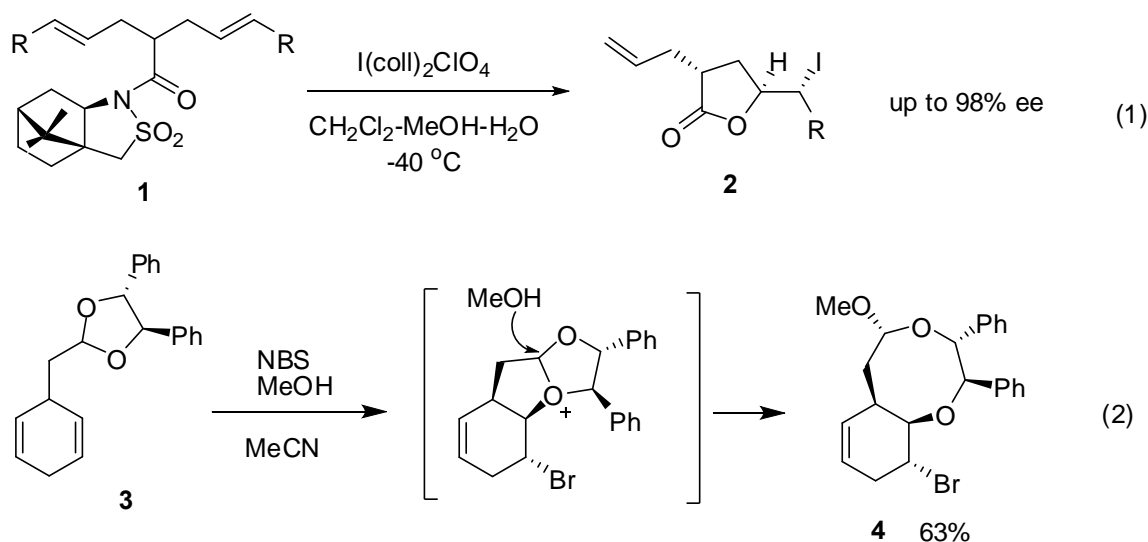
reactions introduce halogen atoms into products, which is important because many halogen containing biologically active compounds are found in nature.<sup>2</sup> In addition, from the viewpoint of synthetic utility, the halogen containing compounds generated in this manner are highly desirable as well-functionalized building blocks that can be utilized in further transformation. Another advantageous feature of halocyclization reactions is that they generally generate products with high degrees of diastereoselectivity and in a highly predictable manner. Therefore, these processes have been widely used in routes for the synthesis of various natural products. In contrast, the development of enantioselective versions of halocyclization reactions has been taken place more slowly with advances being made only very recently.<sup>3</sup>

The mechanistic pathway for halocyclization reactions generally consists of an initial electrophilic addition of the halogen to olefin, forming a halonium ion intermediate, and subsequent anti-selective intramolecular cyclization through substitution by an internal nucleophile on carbon of the halonium ion. Based on this pathway, two approaches to the design of asymmetric halocyclization reactions have been considered. One involves the use of a halogen source that enables creation of a chiral environment for formation of the halonium ion intermediate from the olefin (Figure 1, (i)). In the development of this strategy, the most challenging and, in most cases, prohibiting task is to devise a method to generate the chiral halogenating agent in a catalytic manner. In addition, as recognized independently by Brown<sup>4</sup> and Denmark,<sup>5</sup> in the case of bromonium and iodonium ions, the propensity for degenerate halogen exchange reactions with olefins leads to undesirable racemization of the chiral halonium ion intermediates. The intervention of this process limits the degree of asymmetric induction in the halocyclization reaction.



**Figure 1.** Possible approaches for asymmetric halocyclization reactions

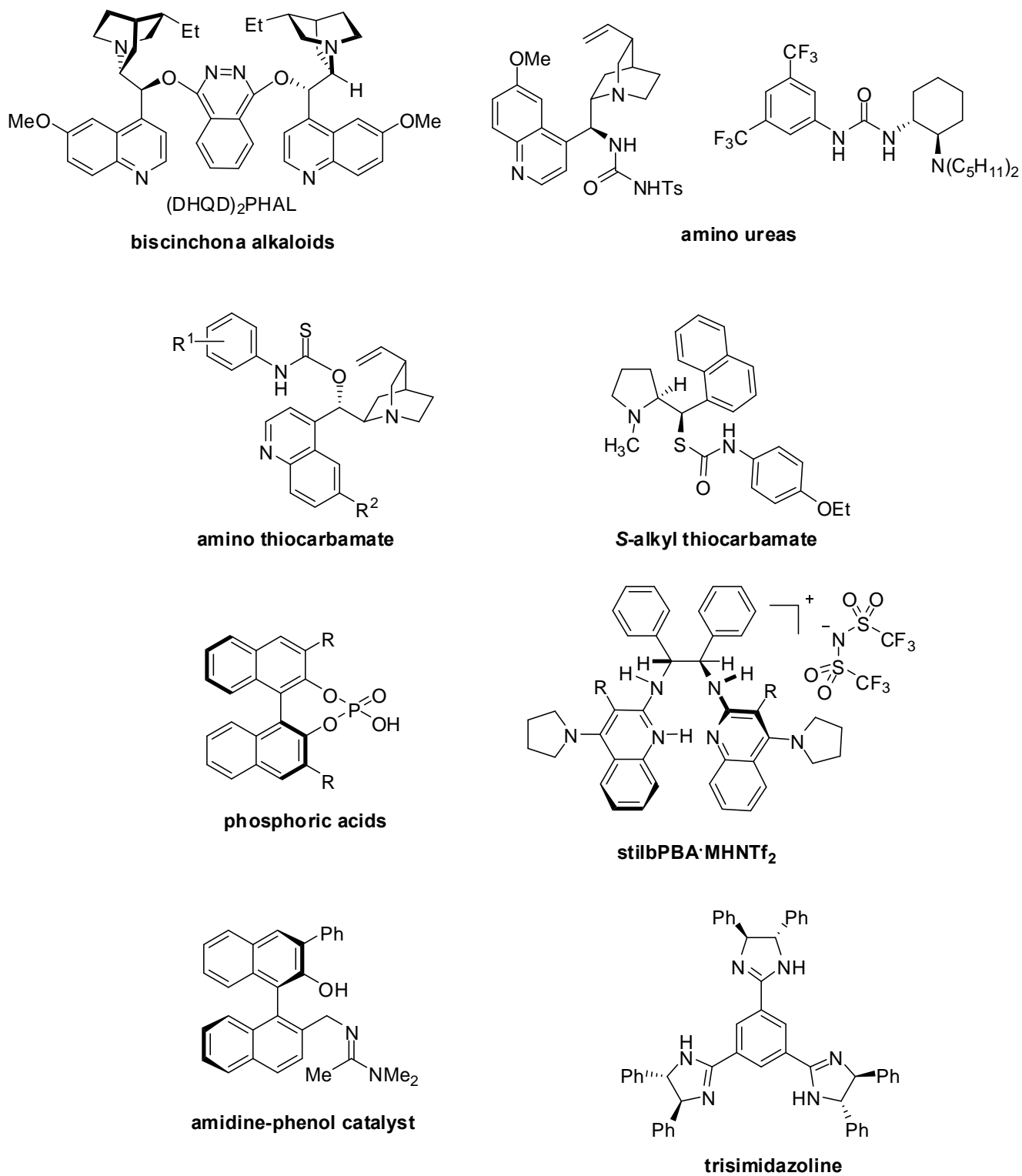
A second approach involves creation of chiral environment for the nucleophilic substitution step in the pathway (Figure 1, (ii)). The guiding principle here is that a chiral nucleophile is expected to react selectively with one enantiomer of the halonium ion intermediate. The prospect of controlling the stereochemistry of the cyclization process by using chiral nucleophiles is supported by many successful examples of chiral auxiliary induced halocyclizations. Several examples of this phenomenon are found in halolactonization reactions using chiral amides (Scheme 1, (1)),<sup>6</sup> as well as haloetherification reactions of chiral acetals (Scheme 1, (2)).<sup>7</sup> Consequently, a great effort has been given recently to the development of the proper methods to bring about catalytic asymmetric nucleophile activation in asymmetric halocyclization reactions. In addition, dual activation approaches that include methods to activate both the halogen source and nucleophile are promising (Figure 1, (iii)), and some organocatalysts developed for promoting enantioselective halocyclization reactions are believed to behave in this manner.



**Scheme 1.** Examples of chiral auxiliary induced halocyclization reactions

In this review, recent investigations aimed at the development of organocatalytic asymmetric halocyclization reactions are described. In these efforts, various types of organocatalysts, including bisquinona alkaloids, amino ureas, amino thiocarbamates, *S*-alkyl thiocarbamates, chiral phosphoric acids, bifunctional and a trisimidazoline catalyst, have been shown to induce highly enantioselective processes (Figure 2). These processes along with their mechanistic features are discussed using a format, which classifies methods by catalyst type. Except for trisimidazoline catalysts, which have been developed recently in our laboratory, background information and characteristics of the organocatalysts are not presented because discussions of these topics can be found in earlier reviews.<sup>3</sup> Electrophilic fluorination reactions of olefins likely are mechanistically different from other halogenations from the

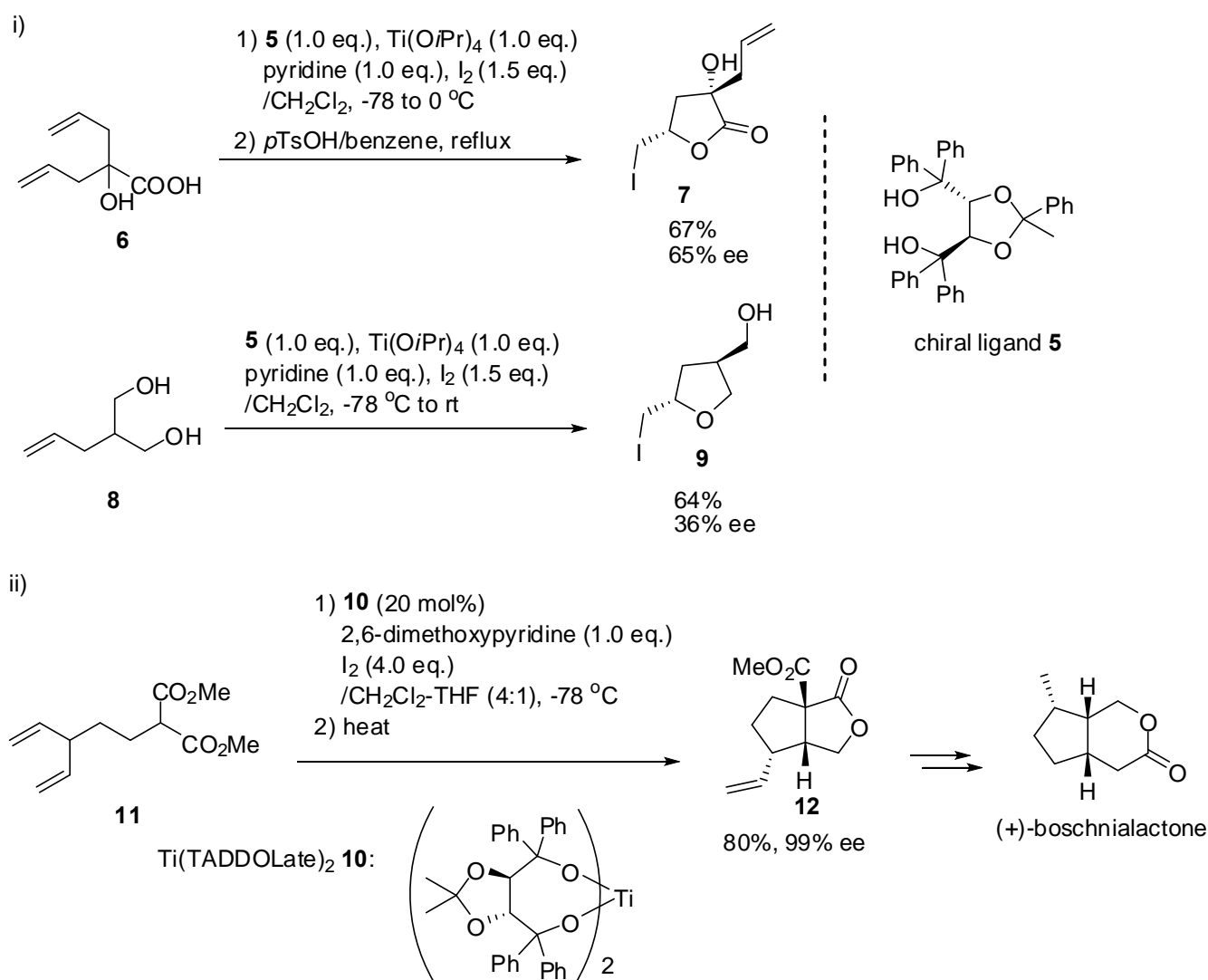
perspective of the intermediacy of halonium ion intermediates.<sup>8</sup> Despite this potential difference, asymmetric versions of fluorocyclization reactions are covered in this review.



**Figure 2.** Organocatalysts for asymmetric halocyclization reactions

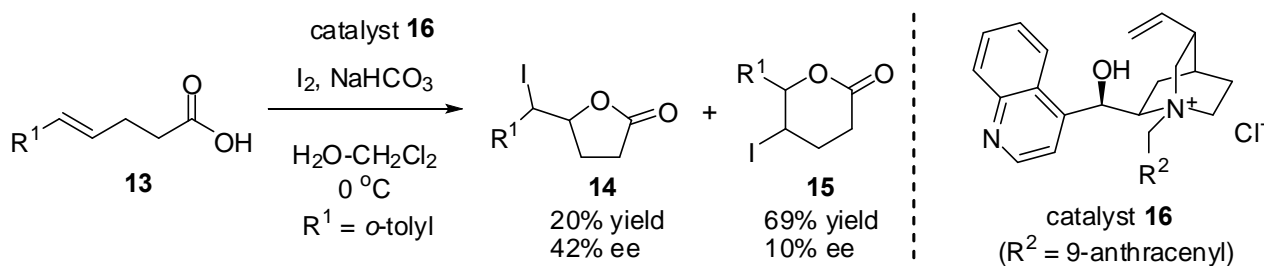
## 2. BACKGROUND

Before describing recent discoveries made in the field of catalytic asymmetric halocyclization reactions, we felt that it would be appropriate to summarize the results of important earlier work in this field. In 1992, Taguchi's group described some appropriate bidentate ligands for carrying out asymmetric halocyclizations (Scheme 2, (i)).<sup>9</sup> These workers found that in the presence of I<sub>2</sub> and the chiral titanium complex generated from TADDOL derivative **5** and Ti(O*i*Pr)<sub>4</sub> diallyl-2-hydroxyacetic acid (**6**) as well as 2-hydroxymethylpent-4-en-1-ol (**8**) undergo respective desymmetrization type iodolactonization and iodoetherification reactions with moderate enantioselectivities (65% and 36% ee, respectively). Although a stoichiometric amount of the chiral ligand was necessary for these processes, the results of subsequent studies showed that only a catalytic amount of Ti(TADDOLate)<sub>2</sub> (**10**) promotes iodocarbocyclization reaction of the 4-alkenylmalonate derivative **11** with excellent enantioselectivity (>95% ee) (Scheme 1, (ii)).<sup>10</sup> This process was applied to a concise synthesis of the natural product, boschnialactone.



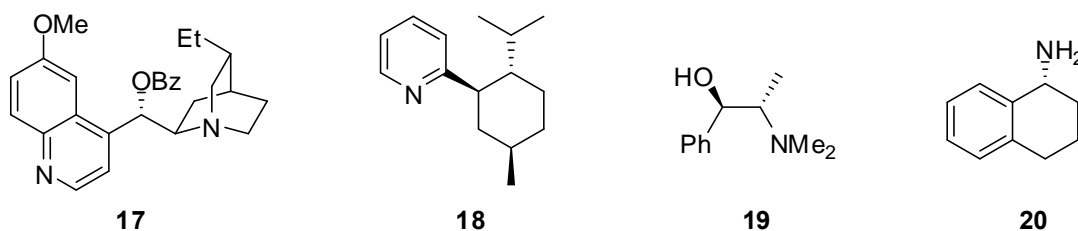
**Scheme 2.** Iodocyclization reactions described by Taguchi's group

The observations summarized above show that a chiral environment for the nucleophile does indeed promote enantioselective halocyclization reactions. Although this technique is applicable to substrates that contain select types of functional groups like malonates, it is challenging to design catalysts that create chiral environments in halocyclization reactions of substrates containing more simple functional groups such as carboxylic acids and alcohols. For example, Gao's group examined iodolactonization reactions of 5-aryl-4-pentanoic acids **13** using cinchona alkaloids as catalysts. These workers anticipated that chiral ion pairs would form between the carboxylic acid and catalyst and that the pairing would lead to stereochemical control. Although treatment of **13** with a stoichiometric amount of the catalyst led to formation of the cyclized products **14** and **15**, the levels of enantioselectivity were not high (<35% ee).<sup>11</sup> A two phase enantioselective iodolactonization reaction, using the chiral quaternary ammonium salts **16** derived from cinchonidine, was also described by the same group (Scheme 3).<sup>12</sup> In this process, a chiral ammonium carboxylate ion pair with phase transfer capability might be formed in this reaction system. Although the first example of asymmetric iodolactonization using a catalytic amount (30 mol%) of a chiral catalyst was uncovered in this effort, the level of enantioselectivity control was not high (up to 42% ee).

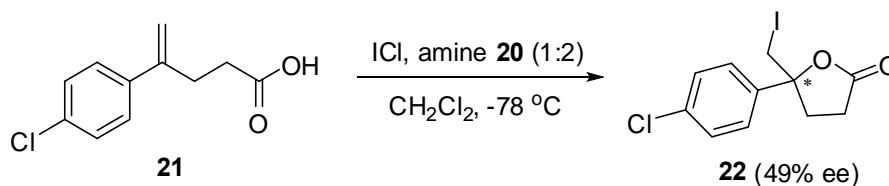


**Scheme 3.** Iodolactonization reaction using a phase transfer catalyst

In addition to employing chiral nucleophiles, chiral halogenating agents have been utilized to induce enantioselective halocyclization reactions. Stoichiometric amounts of various chiral amines have been used to prepare the chiral amine-halogen complexes. For example, *O*-benzoyl dihydroquinidine derivatives **17**, 2-menthylpyridine (**18**), and *N*-methylephedrine (**19**) were employed to generate (amine)<sub>2</sub>X<sup>+</sup>Y<sup>-</sup> species (X = Br, I; Y = SbF<sub>6</sub>, BF<sub>4</sub>), and primary amines, such as 1-aminotetralin (**20**), were employed for preparation of ICl-amine complexes (Figure 3).<sup>13-15</sup> Unfortunately, many studies aimed at using these chiral amine-halogen complexes for the halolactonization or haloetherification reactions failed to uncover acceptable levels of enantioselectivity. In only one case reported by Wirth's group, involving iodolactonization reaction promoted by the chiral primary amine **20**, was moderate selectivity achieved (up to 49% ee) (Scheme 4).<sup>15</sup> These observations demonstrate the difficulty associated with the design of a proper chiral halogenation agent that brings about asymmetric halocyclization reactions.

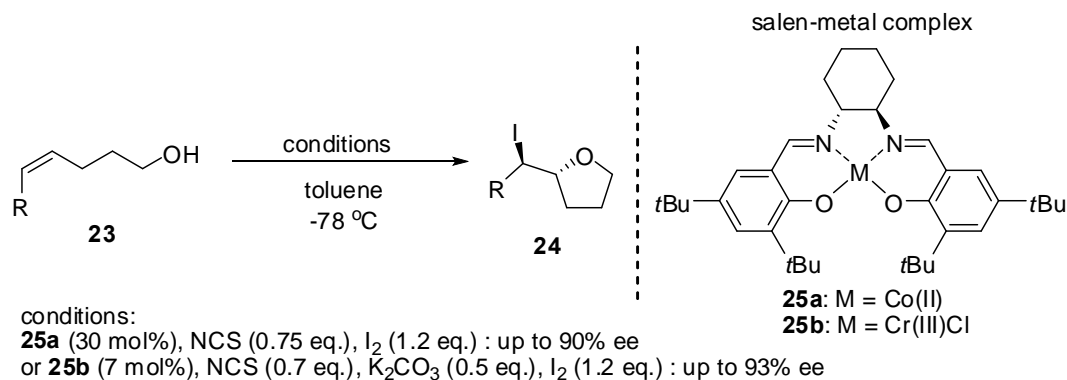


**Figure 3.** Tested amines for preparing amine-halogen complexes

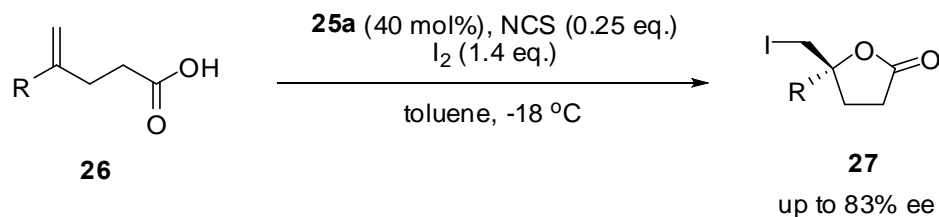


**Scheme 4.** Iodolactonization reaction with the primary amine **20**

In contrast, more success has been achieved with using metal catalysts to induce formation of chiral halogen species in enantioselective halocyclization reactions. For example, the first highly enantioselective iodoetherification reaction of  $\gamma$ -hydroxy-*cis*-alkenes **23** was developed by Kang's groups in 2003.<sup>17</sup> The process, promoted by using  $I_2$  in the presence of an unprecedented catalytic system generated from salen-Co(II) complex and *N*-chlorosuccinimide (NCS), produces 2-monosubstituted tetrahydrofurans **24** with high enantioselectivities (up to 90% ee). Although the first reactions explored required a relatively high loading of the salen-Co(II) complex **25a** (30 mol%), improved conditions were found in which a lower loading of the salen-Cr(III)Cl complex **25b** (7 mol%) promoted efficient and highly enantioselective reactions (Scheme 5). In 2009, Gao's group demonstrated the utility of the reaction system comprised of salen-Co(II) **25a**, NCS and  $I_2$  by its application to asymmetric iodolactonization reactions of various 4-pentenoic acid derivatives **26** that generate cyclized products **27** with high enantioselectivities (up to 83% ee) (Scheme 6).<sup>18</sup>

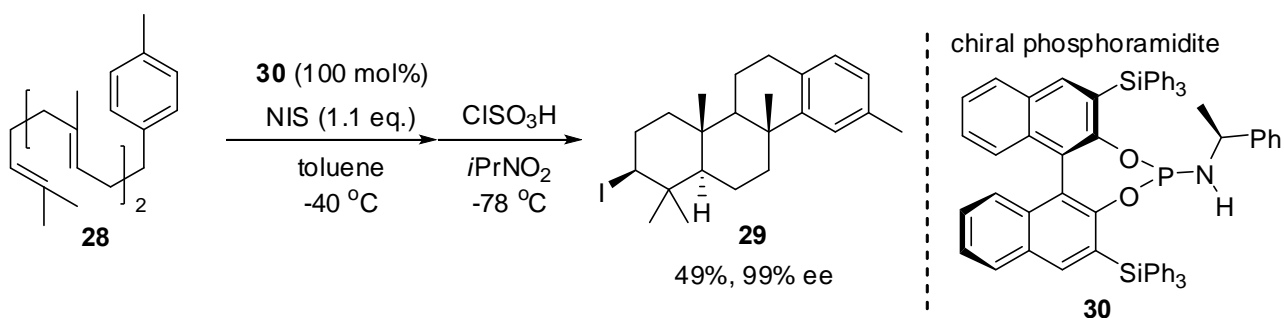


**Scheme 5.** Iodoetherification reaction with salen metal complex **25**



**Scheme 6.** Iodolactonization with **25a**

Along with metal catalysts, since 2007 organocatalysts have been used to generate chiral halogenating species and to induce high levels of enantioselectivity in halocyclization reactions. One example comes from studies by Ishihara's group, which uncovered an enantioselective halopolycyclization of polyprenoid **28** (Scheme 7).<sup>19</sup> In this process, the nucleophilic chiral phosphoramidite **30** and *N*-iodosuccinimide (NIS) are believed to form a tight ion pair. Unfortunately, a stoichiometric amount of **30** as the chiral promoter is required in this reaction system because the use of a catalytic amount (20 mol%) gave a poor enantioselectivity.



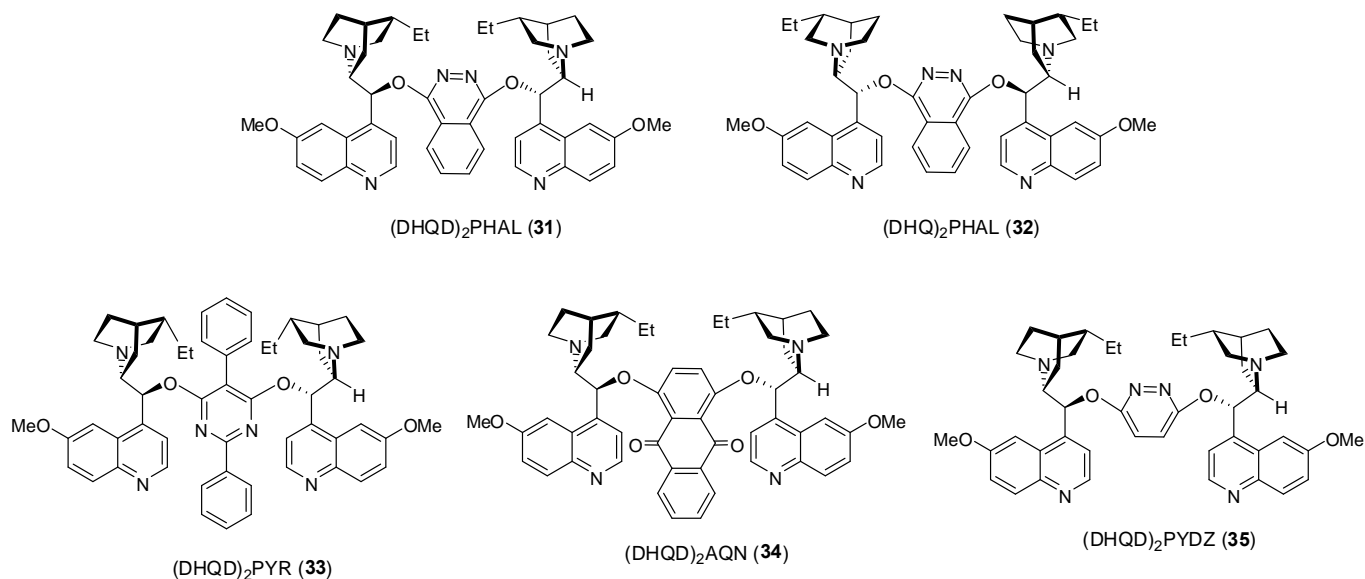
**Scheme 7.** Iodopolycyclization reaction using the chiral phosphoramidite **30**

### 3. BISCINCHONA ALKALOID CATALYSTS

Beginning in 2010, intense research efforts led to the development of enantioselective halocyclization reactions that rely on the use of organocatalysts. Although earlier studies using cinchona alkaloid derivatives did not lead to the discovery of asymmetric halocyclization reactions that take place with sufficiently high levels of enantioselectivity, many efforts demonstrated that these alkaloids serve as privileged catalysts for a number of processes. The high efficiencies of reactions promoted by bisquinchona alkaloids, such as (DHQD)<sub>2</sub>PHAL (**31**), (DHQ)<sub>2</sub>PHAL (**32**), (DHQD)<sub>2</sub>PYR (**33**), (DHQD)<sub>2</sub>AQN (**34**) and (DHQD)<sub>2</sub>PYDZ (**35**) (Figure 4), in contrast to those induced by their monomeric counterparts, has been shown in many investigations. The quinuclidine amine moiety in these catalysts is considered to play a significant role in governing catalytic activity. Because the DHQD and DHQ groups



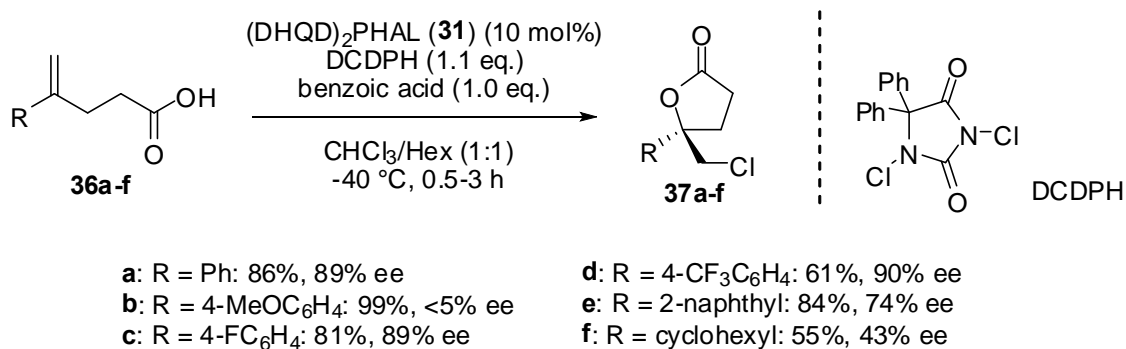
in the catalysts have a pseudo-enantiomeric relationship, reactions producing both enantiomers of products are possible, as shown (although not discussed) below.



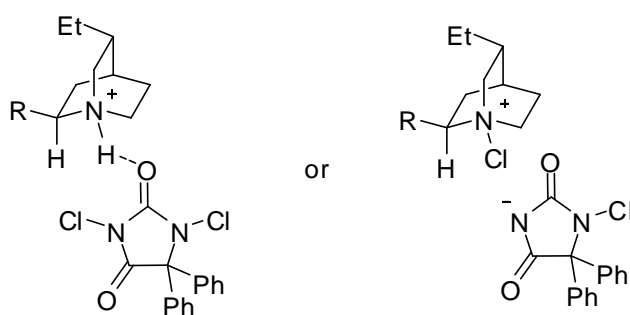
**Figure 4.** Biscinchona alkaloid catalysts

Borhan's group reported the first examples of catalytic enantioselective halolactonization reactions that take place with synthetically useful levels of enantioselectivity.<sup>20</sup> For example, (DHQD)<sub>2</sub>PHAL (31) was shown to catalyze asymmetric chlorolactonization reactions of 4-substituted-4-pentenoic acids (36) that produce  $\gamma$ -lactones 37 (Scheme 8). The system in which 1,3-dichloro-5,5-diphenylhydantoin (DCDPH) is employed as the chlorine source and benzoic acid as a co-additive was found to promote the most efficient reactions using this catalyst. In addition, DCDPH, instead of the more common 1,3-dichloro-5,5-dimethylhydantoin (DCDMH), was utilized in this process because better results were obtained in scale-up reactions. Finally, a facile method for the preparation of DCDPH had been developed earlier by the same group.

Borhan and his coworkers utilized <sup>1</sup>H NMR studies to elucidate the role played by two possible complexes formed between (DHQD)<sub>2</sub>PHAL (31) and DCDPH in governing asymmetric delivery of chlorine to the olefin in this reaction. The authors proposed that two types of association complexes can be formed in this process (Figure 5), one in which hydrogen bonding mediates association between the protonated catalyst and DCDPH, and another in which a tight ion pair is generated between the chlorinated catalyst and the anion of hydantoin. These complexes are suggested not only to control enantioselectivity but also to enhance the rate of the reaction.

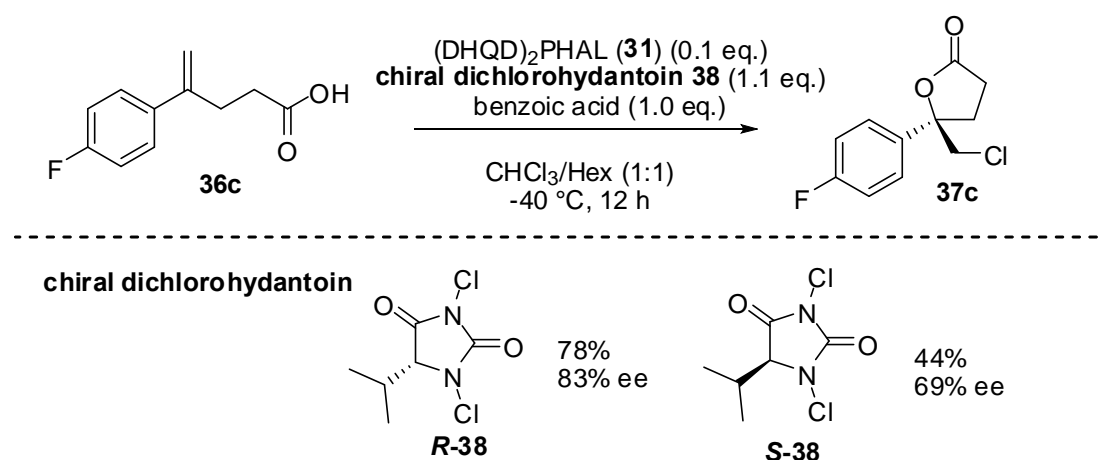


**Scheme 8.** Chlorolactonization reactions of 4-substituted-4-pentenoic acids (**36**) catalyzed by (DHQD)<sub>2</sub>PHAL (**31**)



**Figure 5.** Proposed complexes formed between (DHQD)<sub>2</sub>PHAL (**31**) and DCDPH

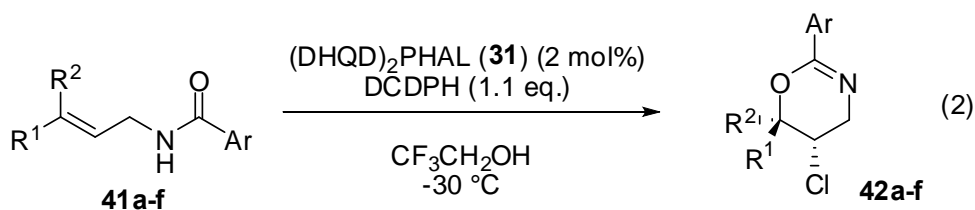
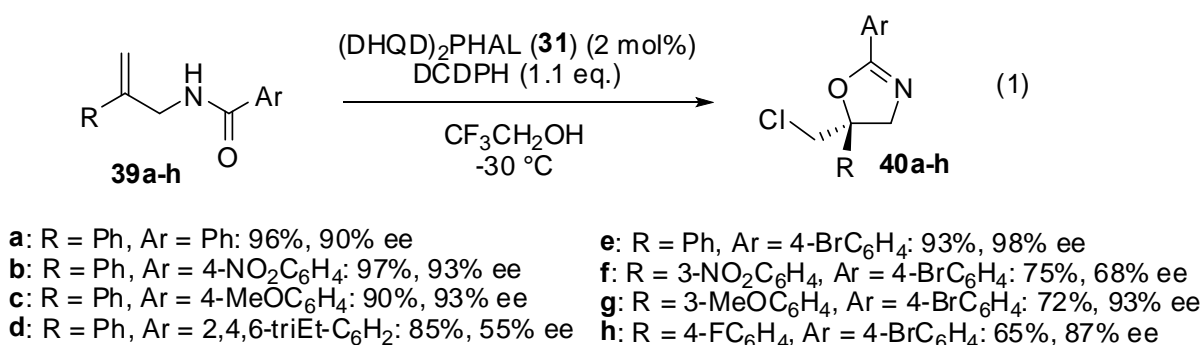
The effect of the combinations of (DHQD)<sub>2</sub>PHAL (**31**) and chiral *N*-chlorohydantoin, such as the *R* and *S* enantiomers of 5-isopropyl-1,3-dichlorohydantoin (*R*-**38** and *S*-**38**), was also probed in a subsequent study by Borhan's group (Scheme 9).<sup>21</sup> Interestingly, a clear matched/mismatched behavior was



**Scheme 9.** Studies with chiral dichlorohydantoin

observed in the chlorolactonization of **36c** with (DHQD)<sub>2</sub>PHAL, where lactone **37c** is produced in 78% yield with 83% ee when (*R*)-**38** is employed while (*S*)-**38** promotes a lower yielding and less enantioselective (44%, 69% ee) reaction. These results provide experimental support for the role played by a complex between the catalyst and the chlorine source.

The same group also reported that use of a combination of (DHQD)<sub>2</sub>PHAL (**31**) and DCDPH also promotes efficient, asymmetric chlorocyclization reactions of unsaturated amides **39** and **41**.<sup>22</sup> The respective oxazolines **40** and dihydrooxazines **42** are produced selectively in these processes in a manner that depends on the substitution pattern in the olefin. For example, 1,1-disubstituted olefin substrates **39** react to produce oxazolines **40** (Scheme 10, (1)) whereas *trans*-disubstituted and trisubstituted olefins **41** react to form dihydrooxazines **42** (Scheme 10, (2)). Olefins containing both aromatic and aliphatic olefin substituents participate in highly enantioselective reactions, whose products can be transformed to chiral 1,2- and 1,3-amino alcohols by utilizing simple procedures. It is interesting that, rather than the less polar CHCl<sub>3</sub> and MeCN/CCl<sub>4</sub>, both polar and protic 2,2,2-trifluoroethanol is an optimal solvent for this process.

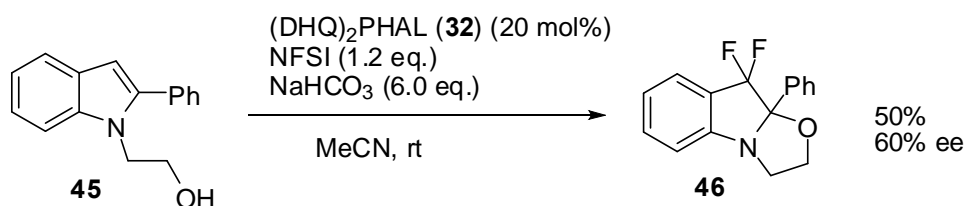
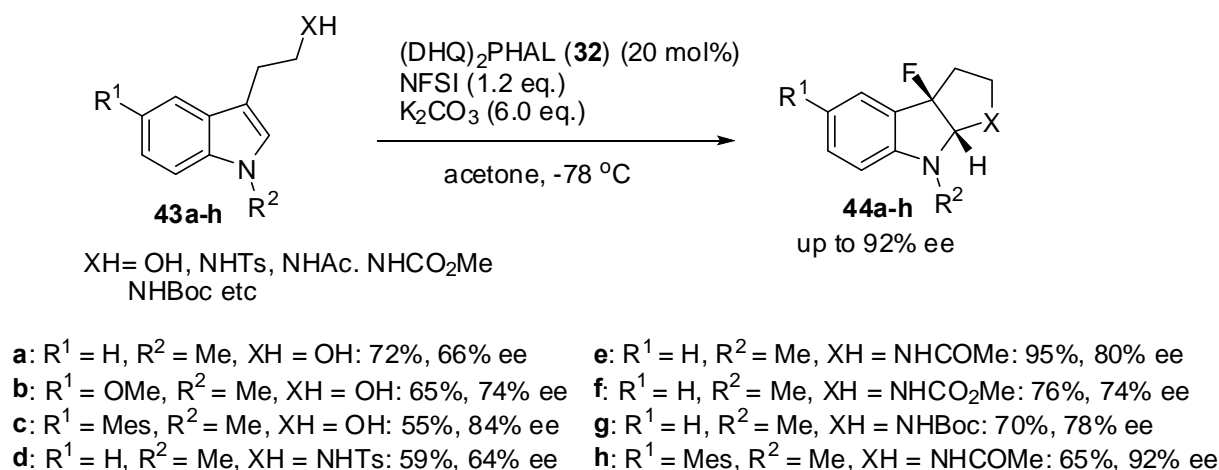


- a:** R<sup>1</sup> = Ph, R<sup>2</sup> = H, Ar = 4-BrC<sub>6</sub>H<sub>4</sub>: 91%, 99% ee  
**b:** R<sup>1</sup> = Ph, R<sup>2</sup> = H, Ar = 4-MeOC<sub>6</sub>H<sub>4</sub>: 93%, >99% ee  
**c:** R<sup>1</sup> = Ph, R<sup>2</sup> = Ph, Ar = 4-BrC<sub>6</sub>H<sub>4</sub>: 92%, 86% ee  
**d:** R<sup>1</sup> = Ph, R<sup>2</sup> = Me, Ar = 4-BrC<sub>6</sub>H<sub>4</sub>: 52%, 91% ee  
**e:** R<sup>1</sup> = cyclohexyl, R<sup>2</sup> = H, Ar = 4-BrC<sub>6</sub>H<sub>4</sub>: 77%, 99% ee  
**f:** R<sup>1</sup> = *n*-C<sub>5</sub>H<sub>11</sub>, R<sup>2</sup> = H, Ar = 4-BrC<sub>6</sub>H<sub>4</sub>: 90%, 99% ee

**Scheme 10.** Chlorocyclization of unsaturated amides with (DHQD)<sub>2</sub>PHAL (**31**)

The first examples of asymmetric fluorocyclization reactions that employ (DHQ)<sub>2</sub>PHAL (**32**) as an organocatalyst were reported by Gouverneur's group (Scheme 11).<sup>23</sup> The results of this effort show that various indole derivatives **43**, possessing nucleophilic tethers at the C3 position, undergo fluorocyclization reactions enantioselectively (up to 92% ee). To obtain high yields and high levels of enantioselectivity, *N*-fluorobenzenesulfonimide (NFSI) rather than Selectfluor is the best fluorinating agent for this process. Additionally, the presence of excess K<sub>2</sub>CO<sub>3</sub> is critical to the success of the reaction, an observation that matches one made earlier by Shibata's group, who showed the beneficial effects of using inorganic carbonate bases for catalytic enantioselective fluorination reactions of ally silanes, silyl enol ethers, and oxindoles promoted by cinchona alkaloids.<sup>24</sup>

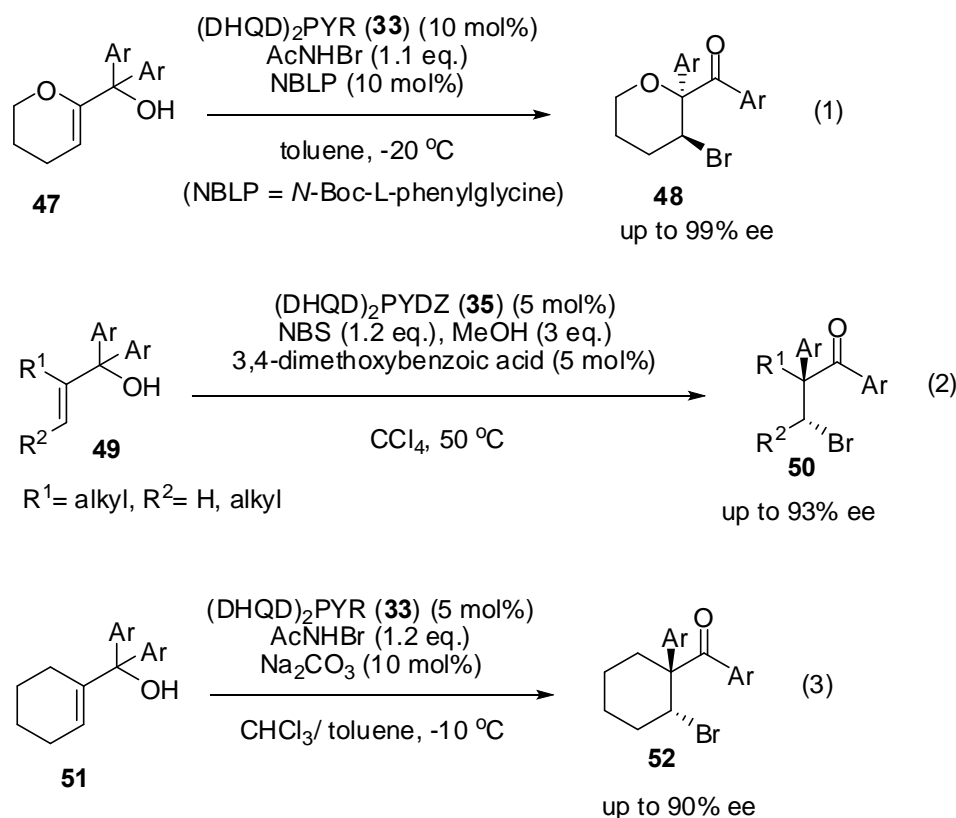
Gouverneur's group provided interesting mechanistic insight into the reaction. Although it was previously observed that chiral *N*-fluoroammonium salts are formed by transfer fluorination reactions between cinchona alkaloids and NFSI, the results of <sup>19</sup>F NMR studies performed by the authors revealed that fluorine transfer from NFSI to (DHQ)<sub>2</sub>PHAL **32** does not occur at the low temperature (-78 °C) used for the asymmetric fluorocyclization reaction. Gouverneur suggested that F(DHQ)<sub>2</sub>PHAL<sup>+</sup><sup>25</sup> might not be involved in the reaction pathway but, instead, that the process is initiated by generation of complex between the cinchona alkaloids and substrate induced by hydrogen bonding interactions. This proposal



**Scheme 11.** Enantioselective fluorocyclization reactions of indoles catalyzed by (DHQ)<sub>2</sub>PHAL (**32**)

gains some support from the observation that the enantioselectivity of the reaction is dependent on the nature of the nucleophile. Indole **45**, which has an *O*-nucleophilic tether on nitrogen, also reacts to produce the difluorocyclization product **46** with moderate enantioselectivity under the modified reaction conditions.

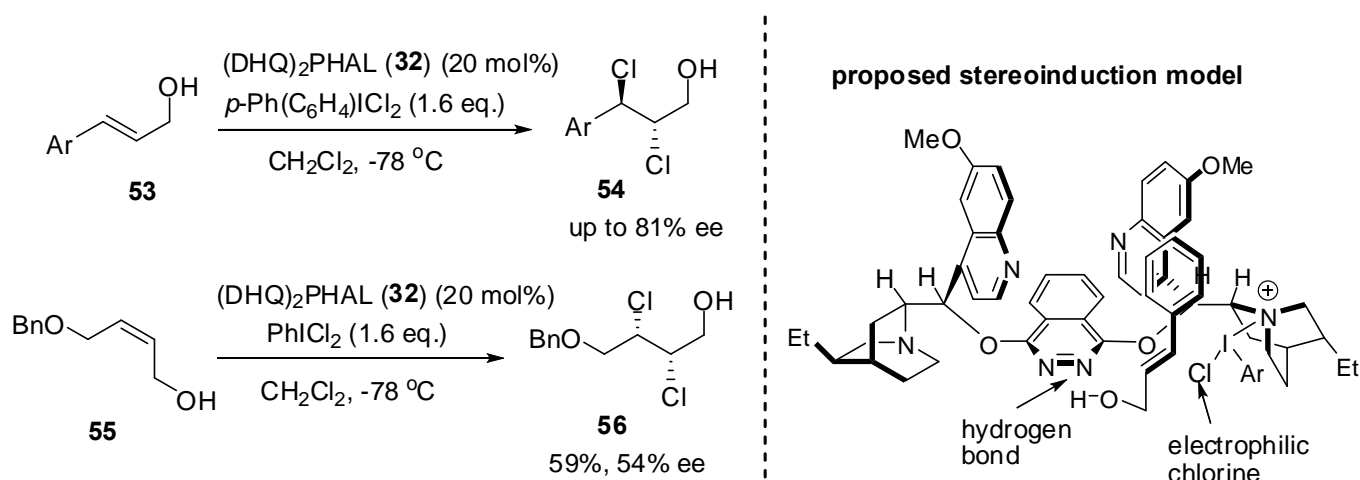
Biscinchona alkaloids not only promote cyclization reactions, they also serve as catalysts for related asymmetric halogenation reactions. For example, enantioselective halogenation/semipinacol rearrangement reactions of allylic tertiary alcohols **47**, **49**, and **51** catalyzed by biscinchona alkaloids **33** and **35** were independently developed by Tu's group (Scheme 12, (1) and (2))<sup>26</sup> and Hennecke's group (Scheme 12, (3)).<sup>27</sup> As well as dihydropyran derivatives **47**, unactivated olefin substrates **49** and **51** were employed in these generally highly enantioselective transformations to give  $\beta$ -haloketo compounds **48**, **50**, and **52**, which contains chiral all carbon substituted, quaternary centers. The processes are thought to proceed via face selective halogenation followed by stereospecific 1,2-carbon migration pathways. Concerning the reaction mechanism, one of the interesting and potentially mechanistically relevant observation made by Tu is that the enantioselectivities of these reactions are positively effected by carboxylic acid additives such as *N*-Boc-L-phenylglycine (NBLP) and 3,4-dimethoxybenzoic acid. In contrast, Hennecke demonstrated showed that inorganic bases, such as  $\text{Na}_2\text{CO}_3$ , are effective and



**Scheme 12.** Halogenation/semipinacol rearrangement reactions of allylic tertiary alcohols

carboxylic acids are ineffective in enhancing enantioselectivity. In spite of these observations, no asymmetric induction model has been proposed thus far.

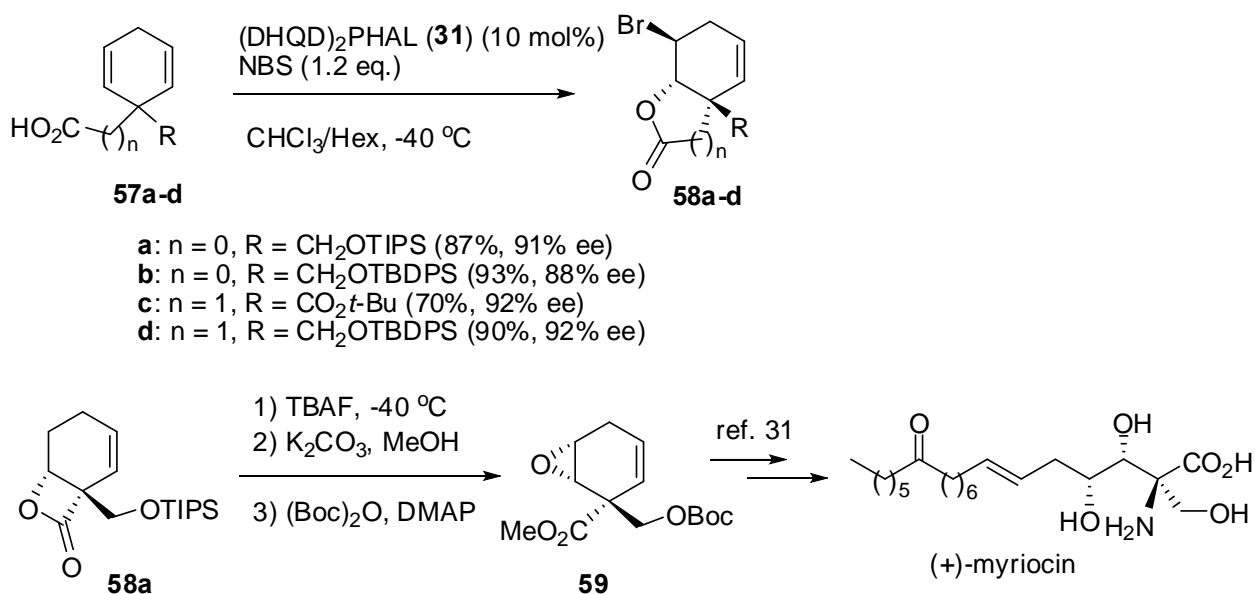
Carrying out olefin dichlorination reactions in an enantioselective manner is challenging because both face-selectivity in the initial chlorination step and regioselectivity in the subsequent nucleophilic chloronium ion ring opening needs to be controlled.<sup>28</sup> Nicolaou's group carried out a study of aryl iododichloride promoted enantioselective dichlorination reactions of allylic alcohols catalyzed by (DHQ)<sub>2</sub>PHAL (**32**) (Scheme 13).<sup>29</sup> Moderate to high levels of enantioselectivity (up to 81%) were observed for reactions of *trans*-3-aryl allylic alcohols **53** and even with the monobenzylated *cis*-butenediol **55** a 54% ee was obtained. A stereoinduction model, in which a hydrogen bonding interaction between the alcohol and one of the phthalazine nitrogens of **32** results in generation of an intermediate with chlorine bonded to one of the quinuclidine nitrogens of **32**, has been proposed. The importance of the hydrogen bonding interaction was supported by the observation that reaction of the TES protected cinnamyl alcohol takes place with low enantioselectivity and that (DHQ)<sub>2</sub>AQN (**34**), lacking the phthalazine nitrogen, is not an effective catalyst.



**Scheme 13.** Dichlorination reactions with (DHQ)<sub>2</sub>PHAL (**32**)

Although optically active lactones are recognized to be useful chiral building blocks in organic synthesis, the optically active ones obtained by enantioselective lactonization using chiral organocatalysts are limited to apply natural product synthesis. However the first catalytic desymmetrization of cyclohexadiene by enantioselective bromolactonization was reported by Martin's group as we discuss later, their enantio-excess for desymmetrization was insufficient and the level of enantioselectivity was low. Hamashima, Kan, and co-workers recently reported a highly enantioselective desymmetrization reaction of cyclohexadienes that relies on asymmetric bromolactonization.<sup>30</sup> An examination of several

organocatalysts resulted in the observation that (DHQD)<sub>2</sub>PHAL (**31**) was ideal for this purpose. In addition, these workers found that the substrate on the prochiral center of cyclohexadiene is very important to get high enantioselectivity, and achieved efficient desymmetrization of cyclohexadiene acids. Specifically, efficient desymmetrization reactions occur when cyclohexadiene acids having TIPSOCH<sub>2</sub>-, TBDPSOCH<sub>2</sub>-, or *t*-BuOCO-group are employed as substrates. The processes form β-lactone **58a,b** as well as γ-lactone **58c,d**. DCDMH did not serve as a good halogen source in reactions of **57a,b**, a finding that should be contrasted with the results obtained by Borhan's group which showed that (DHQD)<sub>2</sub>PHAL (**31**) in combination with DCDMH was effective in promoting chlorolactonization reactions of 4-phenyl-4-pentanoic acids (Scheme 8). The asymmetric bromolactonization reaction developed by Hamashima, Kan, and co-workers also can be applied to desymmetrization of various cyclic dienes. Interestingly, the desymmetrized, optically active bromolactone **58a** was utilized to produce epoxide **59**, which served as a key intermediate in the authors earlier synthesis of (+)-myriocin (Scheme 14).<sup>31</sup>

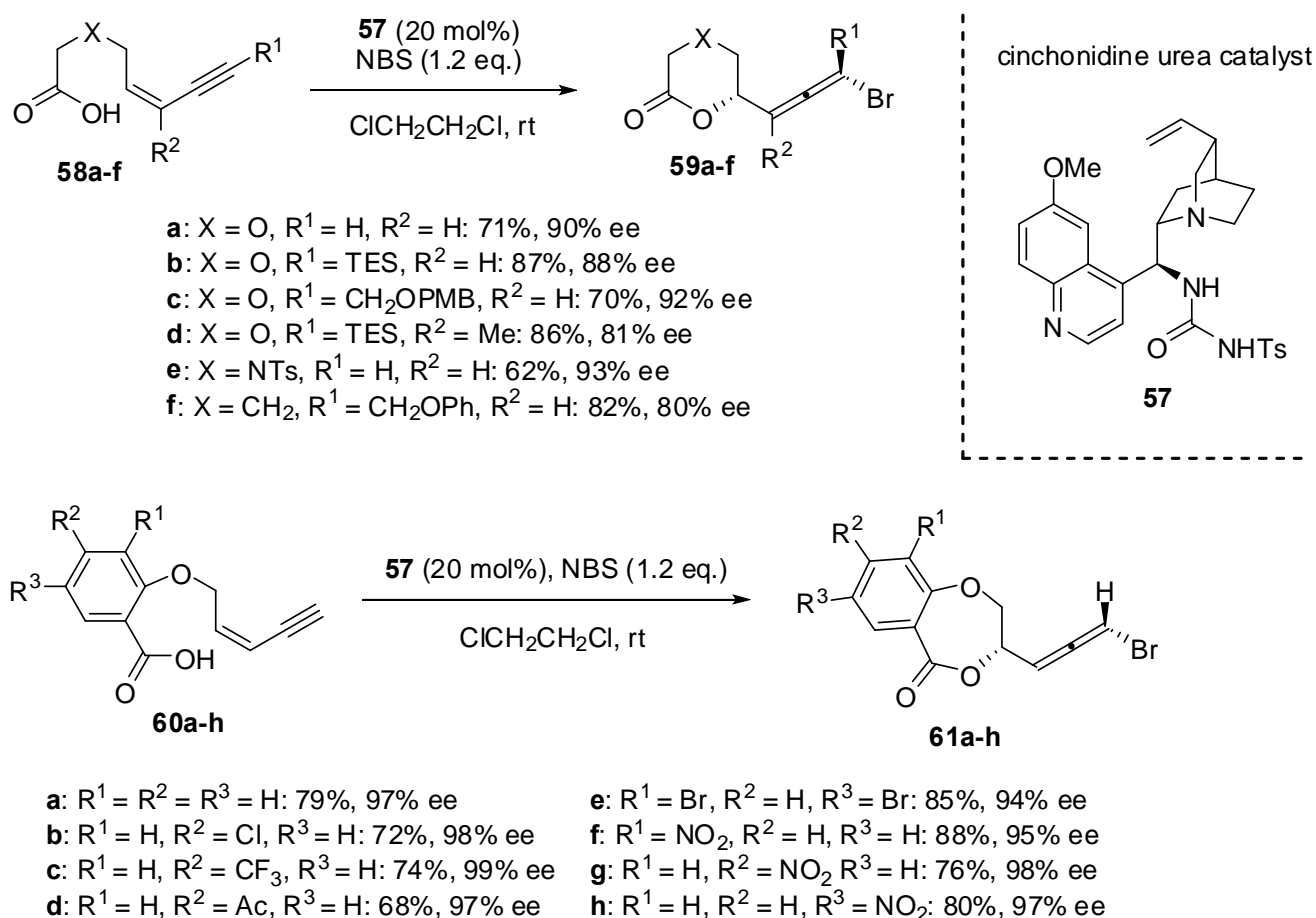


**Scheme 14.** Desymmetrization reactions of various 1,4-cyclohexadienes by using asymmetric bromolactonization reactions

#### 4. AMINO UREA CATALYSTS

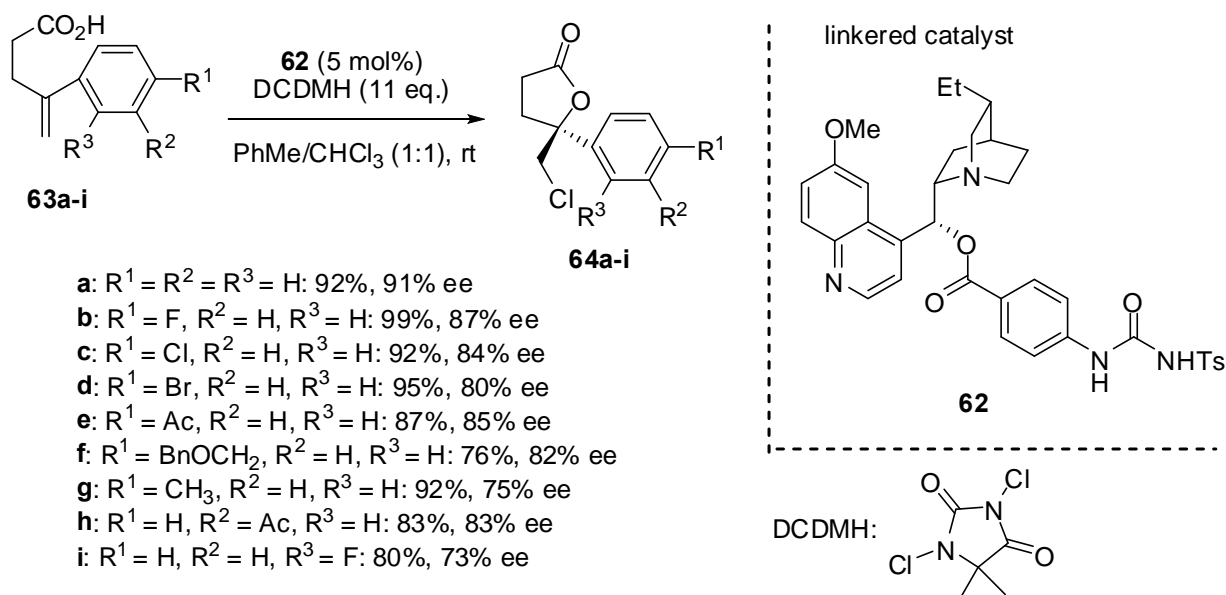
As well as amine catalysts like the bis-cinchona alkaloids, amines containing urea moieties that can participate in hydrogen bonding interactions (eg., **57**) are effective catalysts for asymmetric halocyclization reactions. In a continuation of an earlier study of 1,4-diazabicyclo[2.2.2]octane (DABCO) catalyzed, highly diastereoselective *syn*-1,4-bromolactonization reactions of conjugated enynes, Tang's group observed that NBS promoted catalytic enantioselective bromolactonization reactions of

conjugated (*Z*)-enyne **57** and **60** (Scheme 15).<sup>32,33</sup> Cinchonidine urea catalyst **57**, which has a bridgehead nitrogen similar to that in DABCO, effectively promotes these processes that occur with high levels of diastereo- and enantioselectivity (up to >20:1 dr and 99% ee) to yield the respective lactones **59** and **61** bearing di-, tri-, and tetra-substituted bromoallene moieties. Mechanistic insight into this process has come from the observation that both the quinuclidine and urea moieties are critical components of the catalyst. Specifically, catalysts lacking either the quinuclidine unit or urea moieties (BnNHC(O)NHTs or DABCO or a combination of both) do not effectively promote cyclization reactions of conjugated (*Z*)-enyne. This result is consistent with the possible operation of an activation mode that involves formation of hydrogen bonds between the catalyst and NBS. Although **57** was not effective as a catalyst for enantioselective lactonization reactions of alkenes, use of the related catalyst **62**, containing an appropriate linker between the quinuclidine and urea groups, and different reaction conditions (DCDMH as a choline source and PhMe/CHCl<sub>3</sub> (1:1) as a reaction solvent) led to highly enantioselective lactonization reactions of alkenes **63** (Scheme 16).



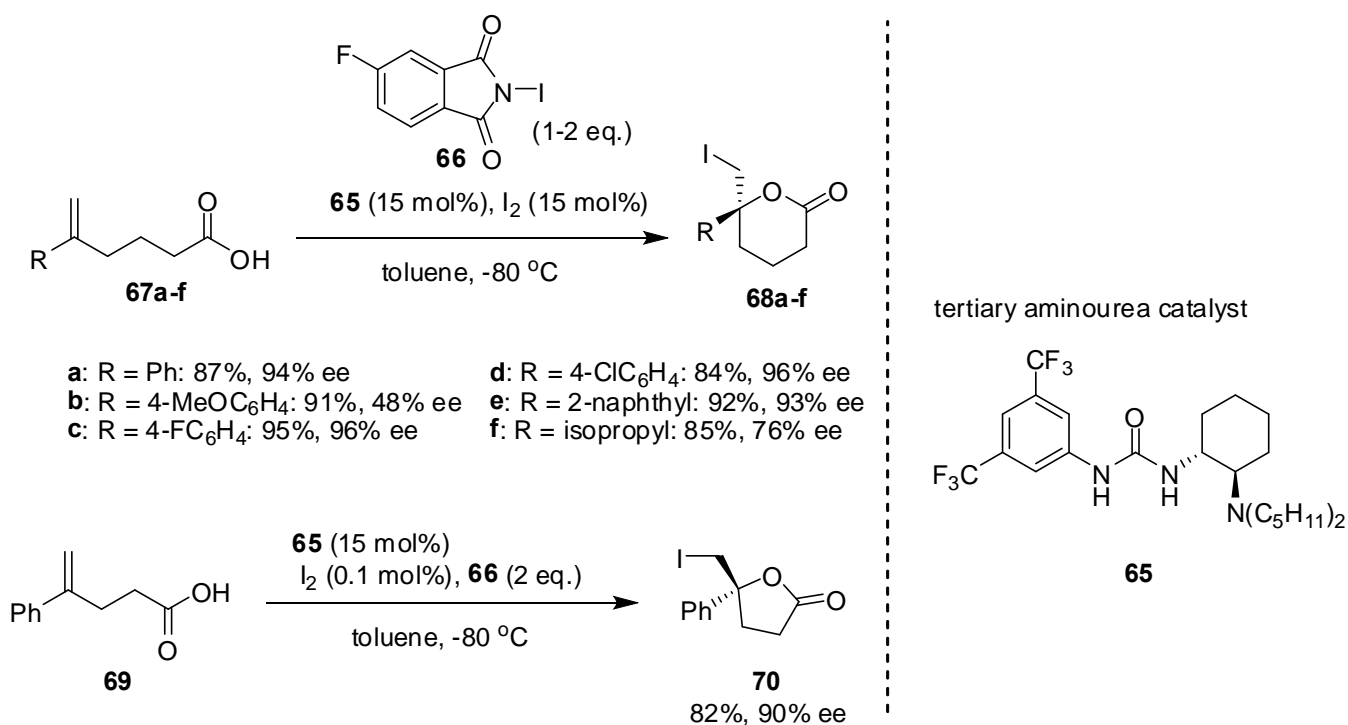
**Scheme 15.** Bromolactonization reactions of conjugated (*Z*)-enyne using the cinchonidine urea catalyst





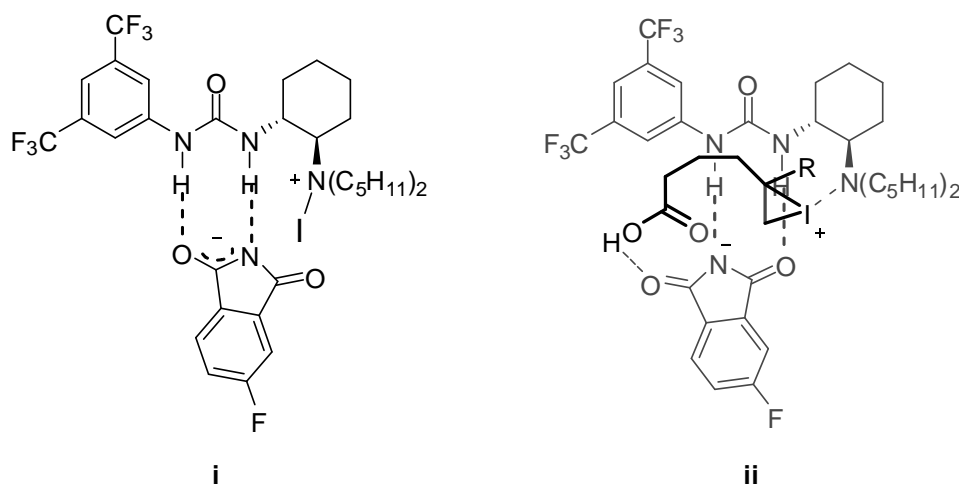
**Scheme 16.** Chlorolactonization reactions of alkenes using the linker catalyst **62**

As part of their continuing studies of H-bonding catalysts,<sup>34</sup> Jacobsen's group devised a highly enantioselective iodolactonization reaction that uses the cyclohexane diamine derived tertiary aminourea **65** (Scheme 17).<sup>35</sup> Various substituted 5-hexenoic acids **67** were observed to react with *N*-iodo-4-fluorobenzosuccinimide (**66**) in the presence of catalytic amounts of **65** and  $\text{I}_2$  to afford 6-membered



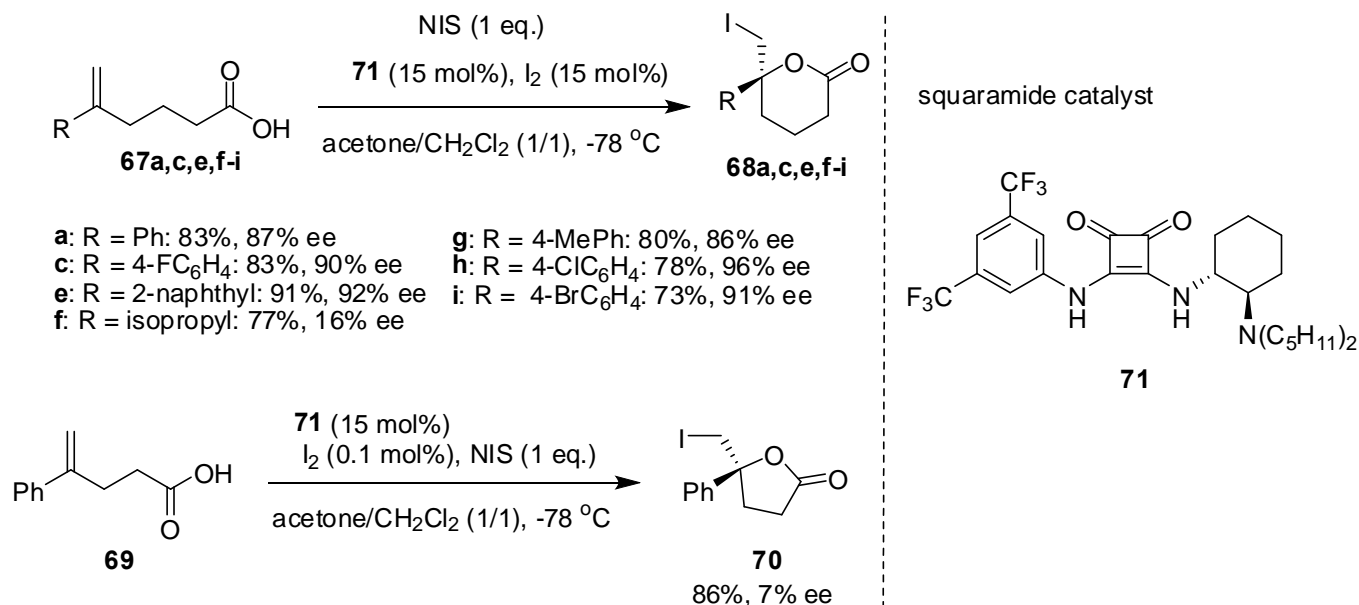
**Scheme 17.** Iodolactonization reactions using the tertiary aminourea catalysts **65**

iodolactones **68** in high yields with excellent enantioselectivities. Formation of 5-membered lactone **70**, whose absolute configuration is opposite that of the 6-membered lactones **68**, also occurred in reaction of pentenoic acid **69**. In these cases, use of the non-commercial halogen source **66** was effective. Jacobsens' group suggested that the reaction proceeds via the pathway shown in Figure 6, in which formation of *N*-iodo complex **i** takes place initially by rapid reaction of the catalyst **65** with **66** and iodine followed by conversion to the complexed iodonium ion **ii** to product via rate- and enantio-determining cyclization. Evidence for this proposal came from low temperature  $^1\text{H}$  NMR and computational studies and the reactivity profile expected for **ii**. The synergistic effect of **66** and catalytic iodine is interesting because it leads to high-yielding and highly enantioselective reactions, while **66** or iodine alone displayed both low reactivity and enantioselectivity. The authors suggested that this beneficial effect of these reagents combination can be explained by a recent report on a formation of triiodide cation from *N*-iodoimides by treatment with iodine and a protic acid.<sup>36</sup>



**Figure 6.** Proposed mechanistic pathway for iodolactonization reactions promoted by the tertiary aminourea catalyst **65**

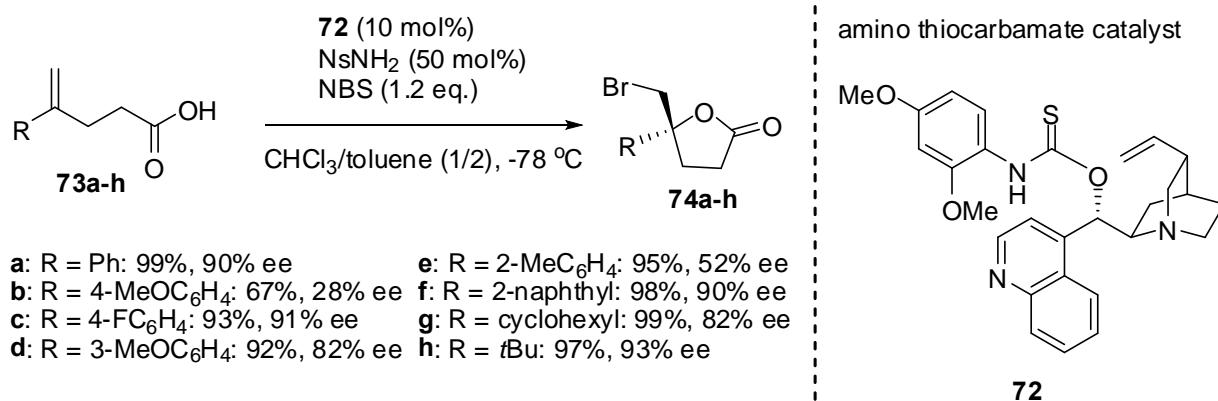
Quite recently, Hansen and his coworkers described an asymmetric halolactonization reaction that takes place using the squaramide catalyst **71** under conditions that are similar to those developed by the Jacobsen's group using the aminourea catalyst **65**. However, the catalytic propensity of **71** was found to be lower than that of **65**, especially in reactions of the alkyl substituted acid **67f** and  $\gamma,\delta$ -unsaturated acid **69**. A benefit of **71** is that NIS can be used in place of **66** as the iodination agent (Scheme 18).<sup>37</sup>



**Scheme 18.** Iodolactonization reactions using the squaramide catalyst **71**.

## 5. AMINO THIOCARBAMATE CATALYSTS

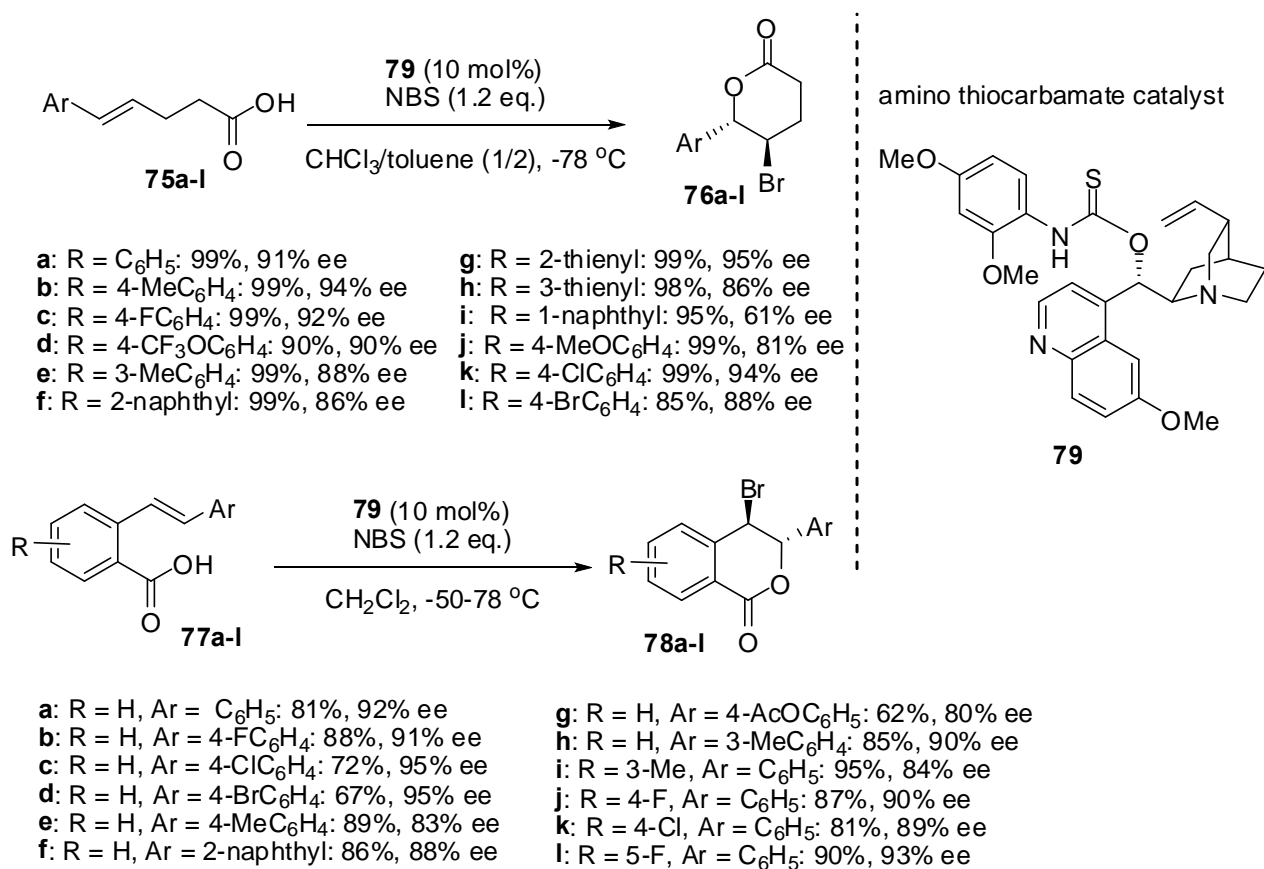
The use of amino thiocarbamate catalysts **72** in asymmetric bromocyclization reactions was introduced by Yeung's group.<sup>38</sup> Importantly, they revealed that thiocarbamate function can activate NBS efficiently based on Lewis base activation of Lewis acid concept as previously demonstrated in selenolactonization reactions.<sup>39</sup> By using the amino thiocarbamate **72**, possessing a cinchona alkaloid moiety, 4-substituted-4-pentenoic acids **73** are transformed to the corresponding  $\gamma$ -lactones **74** in high yields with high enantioselectivities (up to 93% ee) (Scheme 19).



**Scheme 19.** Bromolactonization reactions using the amino thiocarbamate catalyst **72**

This study also demonstrated that 1,2-disubstituted olefinic acids, *E*-5-aryl-4-pentenoic acids **75** and styrene containing carboxylic acids **77** also undergo asymmetric bromolactonization reactions, catalyzed

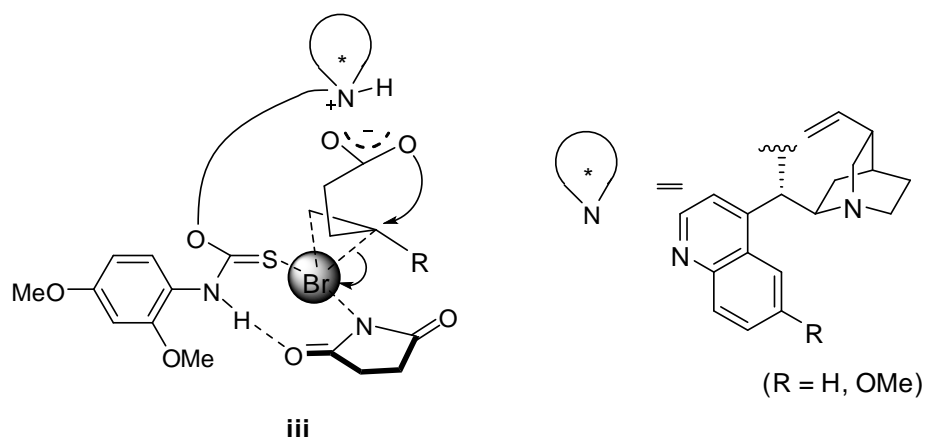
by thiocarbamate **79**, to produce  $\delta$ -lactones **76** and 3,4-dihydroisocoumarin derivatives **78**, respectively, in high yields and with high enantioselectivities (Scheme 20).<sup>40</sup>



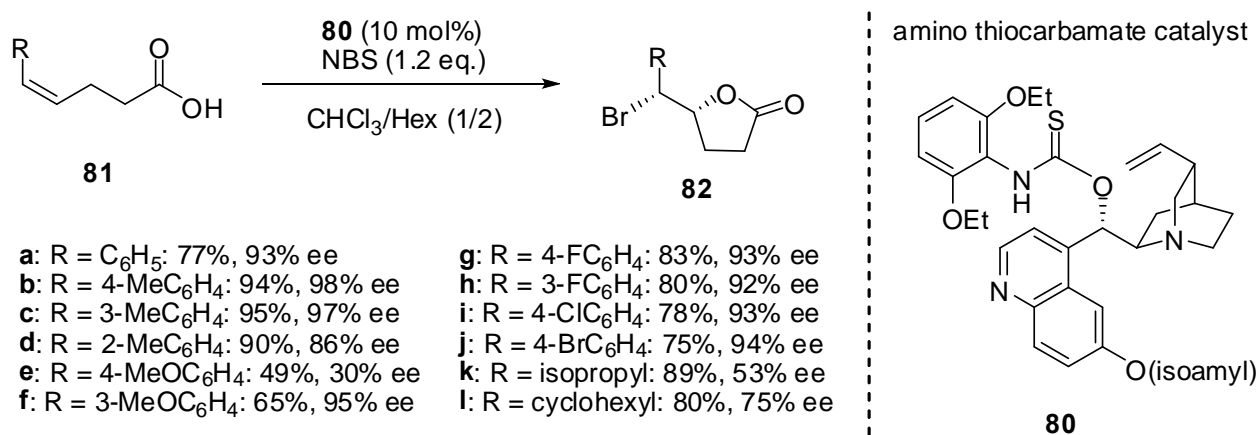
**Scheme 20.** Versatility of bromolactonization reactions promoted by amino thiocarbamate catalyst **79**

A plausible transition state, involving dual activation of NBS and the carboxylic acid, which enables asymmetric delivery of bromine, is believed to intervene in this process (Figure 7). The key feature of transition state is the interaction between the thiocarbamate and NBS that promotes activation of bromine by the Lewis basic sulfur and NH hydrogen bonding to the succinimide carbonyl oxygen, along with complexation of the carboxylic acid to the quinuclidine unit. The results of related studies, in which N-H of the catalyst is changed to N-Me, S of the catalyst is changed to O, and thiocarbamate is changed to thiourea, support the proposed function of the thiocarbamate.

Amino thiocarbamate **79** was only effective in catalyzing highly enantioselective reactions of *trans*-1,2-disubstituted unsaturated acids (see Scheme 20). In the case of the *cis*-1,2-disubstituted analog **81a**, reaction catalyzed by **79** gave **82a** in only 40% yield with 64% ee. Owing to this limitation, another amino thiocarbamate catalyst **80** was developed. This catalyst is effective in reactions of *cis*-1,2-disubstituted unsaturated acids. Although the structure of **80** is similar to that of **79**, its use leads to highly improved yields and enantioselectivities (Scheme 21).<sup>41</sup>

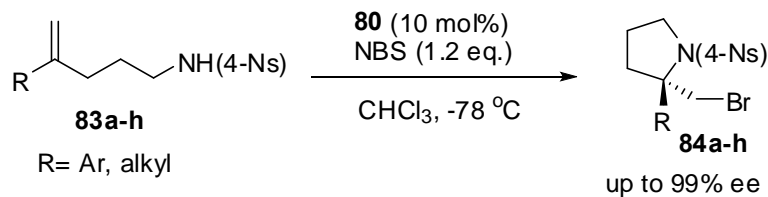


**Figure 7.** Proposed transition state of the bromolactonization reaction promoted by amino thiocarbamate catalysts **72** and **79**

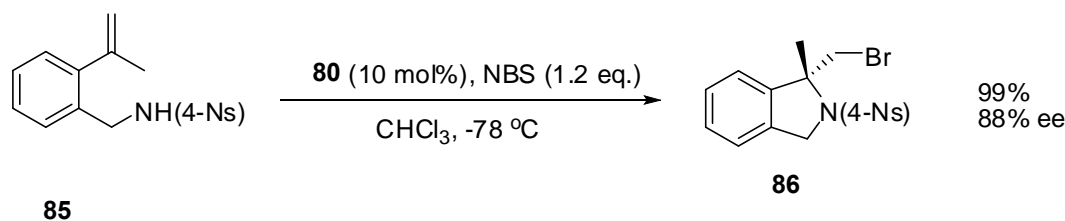


**Scheme 21.** Bromolactonization reactions using the amino thiocarbamate catalyst **80**

Yeung and his coworkers also found that the amino thiocarbamate catalyst **80** is effective in promoting enantioselective bromoaminocyclization reactions, the first catalytic asymmetric halo-*N*-cyclization reactions that take place with synthetically useful levels of enantioselectivity (Scheme 22).<sup>42</sup> Studies probing the effect of changes in substituents on the ortho position of the aniline ring and the 6-alkoxy group of the quinoline moiety revealed that amino thiourea **80** is the optimum catalyst for reactions that generate a range of enantio-enriched pyrrolidines **84** from olefinic sulfonamides **83**. The acidic nature of the N-H group in the substrates is proposed to be important in providing stabilization of the transition state for the bromolactonization reaction (Figure 7). This reaction system is also applicable to the preparation of chiral isoindolinone **86**.

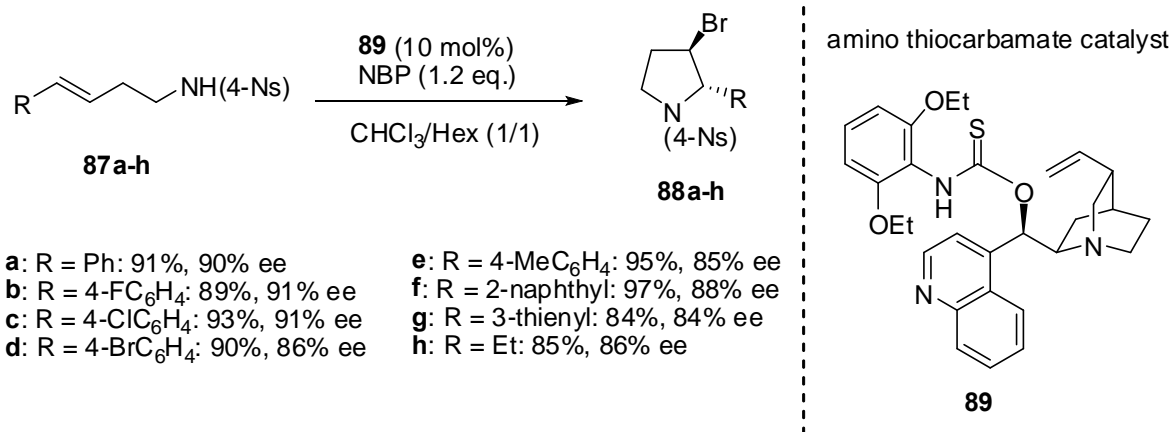


- |  |   |
|--|---|
| <b>a:</b> R = Ph: 98%, 95% ee                                  | <b>e:</b> R = 2-MeC <sub>6</sub> H <sub>4</sub> : 82%, 94% ee |
| <b>b:</b> R = 4-MeOC <sub>6</sub> H <sub>4</sub> : 61%, 19% ee | <b>f:</b> R = 2-naphthyl: 93%, 96% ee                         |
| <b>c:</b> R = 4-FC <sub>6</sub> H <sub>4</sub> : 99%, 95% ee   | <b>g:</b> R = H: 99%, 46% ee                                  |
| <b>d:</b> R = 3-MeOC <sub>6</sub> H <sub>4</sub> : 85%, 95% ee | <b>h:</b> R = Me: 96%, 40% ee                                 |



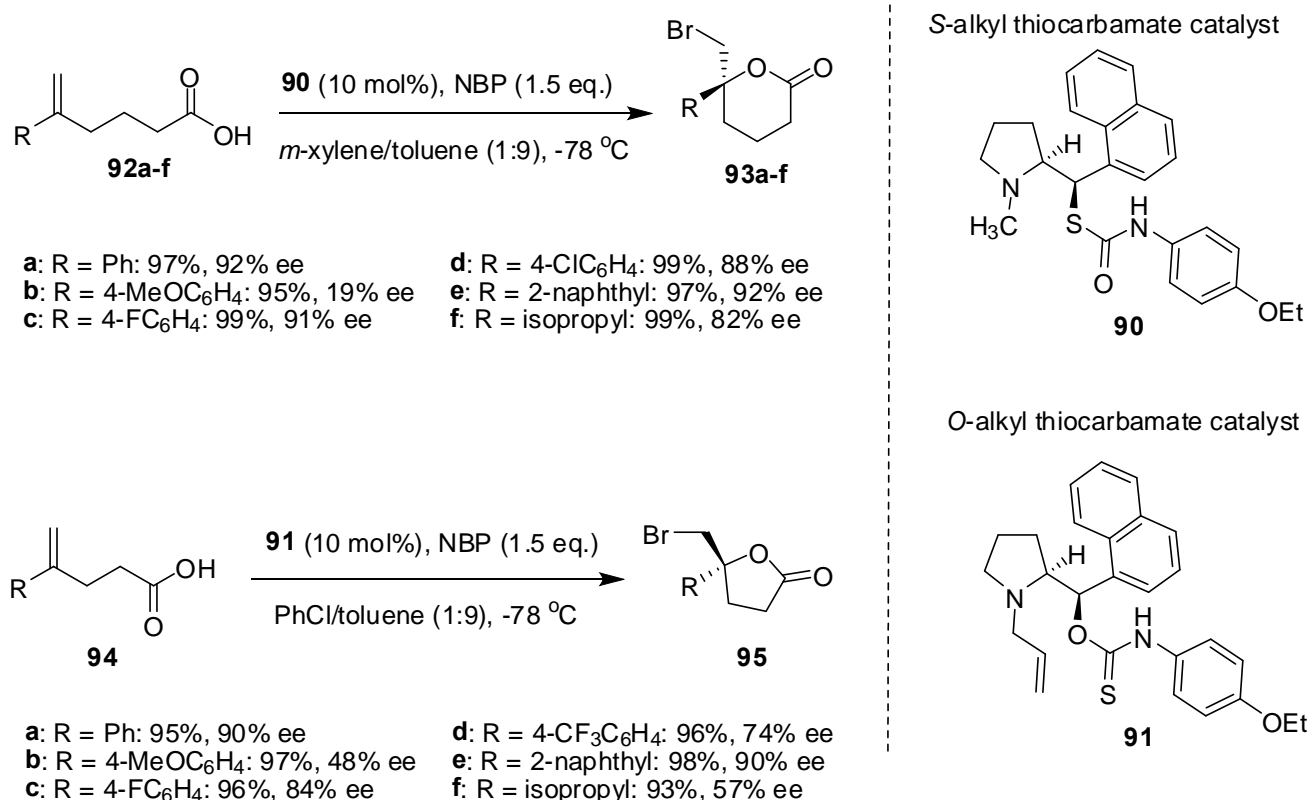
**Scheme 22.** Bromoaminocyclization reaction using the amino thiocarbamate catalyst **80**

Although reactions of 1,1-disubstituted olefinic amides **83** and **85** proceeded in a highly enantioselective manners giving 1,1-disubstituted pyrrolidines **84** and **86** with high enantiomeric purities, the corresponding endocyclization process does not occur smoothly owing to the fact that the complexed halogen occupies an exocyclic positions. Further studies uncovered the first bromoaminocyclization reaction of *trans*-1,2-disubstituted olefinic amides **87** that generate 2-substituted 3-bromopyrrolidines **88**.<sup>43</sup> The combination of catalyst **89**, *N*-bromophthalimide (NBP) and *n*-hexane-chloroform as a co-solvent system were found to be optimized conditions for these reactions. Most substrates containing substituted aryl R groups react to give products with moderate to high ee. In addition, alkyl substrate also react smoothly (Scheme 23).



**Scheme 23.** Bromoaminocyclization reactions catalyzed by amino thiocarbamate **89**

Further investigations carried out by Yeung's group led to the development of two new thiocarbamate catalysts **90** and **91** derived from L-proline, which promote bromocyclization reactions of ene-carboxylic acids (Scheme 24). *S*-Alkyl thiocarbamate **90** was observed to be a superior catalyst for bromocyclization reactions of 5-substituted-5-hexenoic acids **92**, which in each case displayed a high ee. It is noteworthy that substrates containing aliphatic substituents on the alkene moiety also react to form the corresponding products with high ee. In contrast, reactions of 4-substituted-4-pentenoic acids **94**, which yield  $\gamma$ -lactones **95**, are promoted better by using the *O*-alkyl thiocarbamate catalyst **91**.<sup>44</sup>



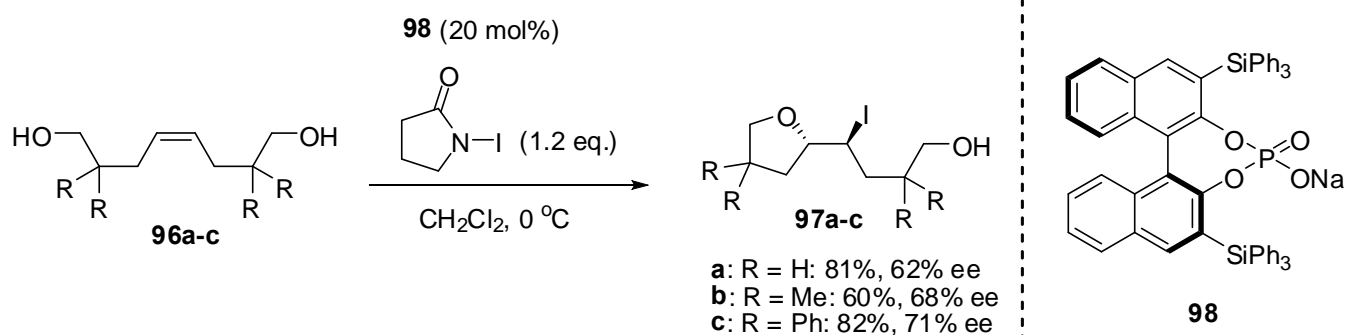
**Scheme 24.** Enantioselective bromolactonization reactions promoted by *S*-alkyl or *O*-alkyl thiocarbamates **90** and **91**

## 6. PHOSPHORIC ACID CATALYSTS

Chiral phosphoric acids have also been shown to promote efficient in asymmetric halocyclization reactions. In particular, the highly efficient nature of these reactions has been demonstrated using haloetherifications, which had not been explored yet using the amine containing organocatalysts described in Sections 2, 3 and 4.

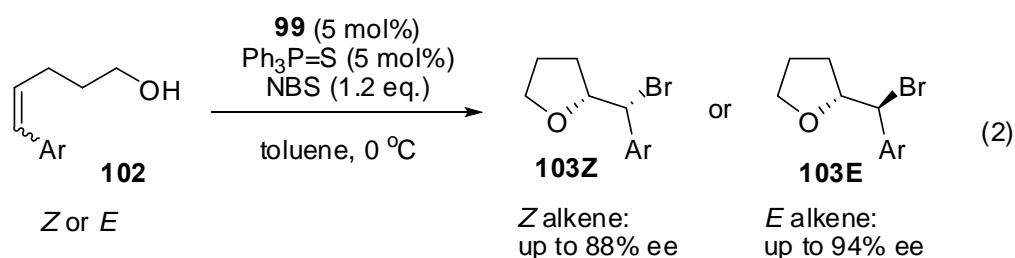
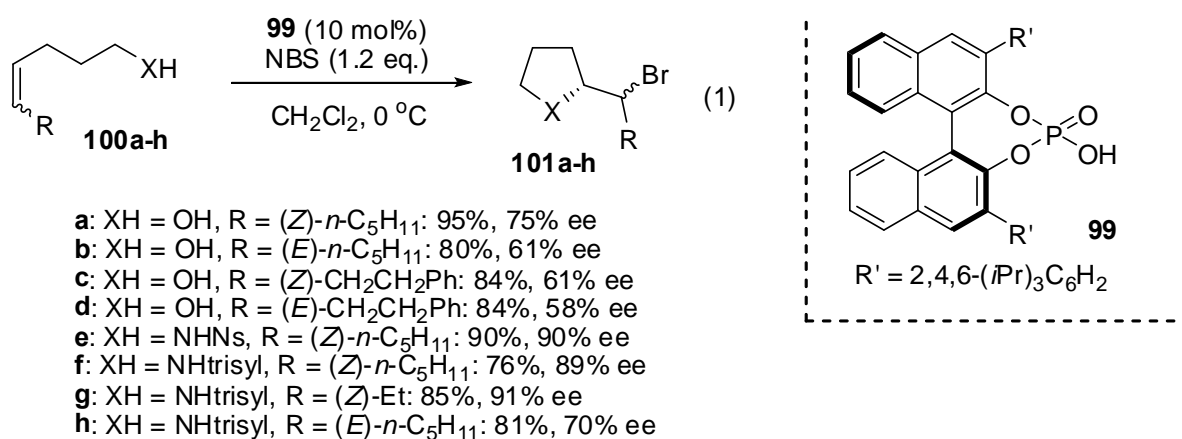
The first example came from Hennecke's group, who reported that symmetric diols **96** in the presence of the sodium salt of phosphoric acid **98** undergo enantioselective iodo- and bromoetherification reactions to

yield desymmetrized products **97**.<sup>45</sup> Generally, higher degrees of enantioselectivity were observed for the iodocyclization reactions, which utilized *N*-iodopyrrolidinone (NIPyr) as the iodine source (Scheme 25).



**Scheme 25.** Enantioselective desymmetrization reactions of *meso*-diols **96** by haloetherification using catalyst **98**

The second examples, reported by Shi's group, are bromoetherification reactions of  $\gamma$ -hydroxy alkenes **100a-d**, which are catalyzed by phosphoric acids **99** (TRIP) and promoted using NBS.<sup>46</sup> The sulfonyl-protected  $\gamma$ -amino alkenes **100e-h** also participate in this process and, as a result, both 2-substituted tetrahydrofurans **101a-d** and tetrahydropyrroles **101e-h** can be prepared with generally high

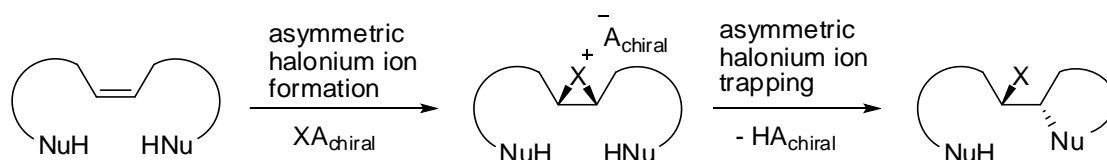


**Scheme 26.** Bromoetherification and bromoamination reactions catalyzed by chiral phosphoric acids **99**



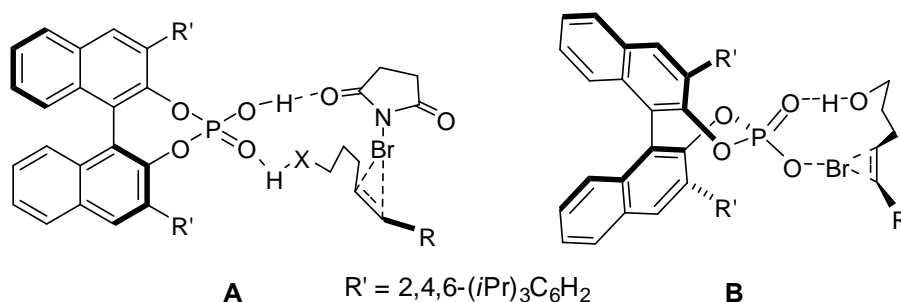
enantioselectivities (Scheme 26, (1)). Furthermore, Denmark's group also described enantioselective bromoetherification reactions of 5-aryl-4-pentenols **102** (Scheme 26, (2))<sup>47</sup> that are induced using a combination of phosphoric acids **99** and the achiral Lewis base,  $\text{Ph}_3\text{P}=\text{S}$ .

Although the exact manner in which chiral phosphoric acids promote these enantioselective processes has not been established, mechanistic possibilities can be suggested. In the reaction developed by Hennecke,<sup>45</sup> the sodium salt of phosphoric acid **98** might act as a Lewis base in a reaction with the halogenating agent, which forms a phosphate NIPyr complex ( $\text{XA}_{\text{chiral}}$ ) that serves as the activated iodination agent. Iodonium ion formation is then quickly followed by asymmetric ring opening via a selective, chiral counter anion cyclization. This is an interesting explanation of the desymmetrization process because in its ring opening of a *meso*-iodonium ion is the stereochemical determining step. Thus, enantioselective formation of a halonium ion is not required (Scheme 27).



**Scheme 27.** Possible mechanism of desymmetrization reactions of *meso*-diols involving asymmetric halonium ion trapping

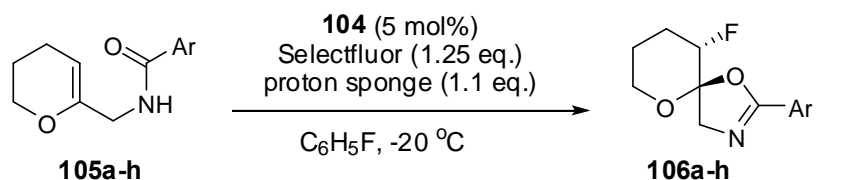
In bromoetherification reactions, different bifunctional activation models have been independently proposed by Shi<sup>46</sup> (Figure 8, **A**) and Denmark<sup>47</sup> (Figure 8, **B**). As illustrated in Figure 8, the chiral phosphoric acids **99** have been proposed to interact with both the nucleophile (XH) and NBS or bromonium ion via hydrogen bonding interactions.



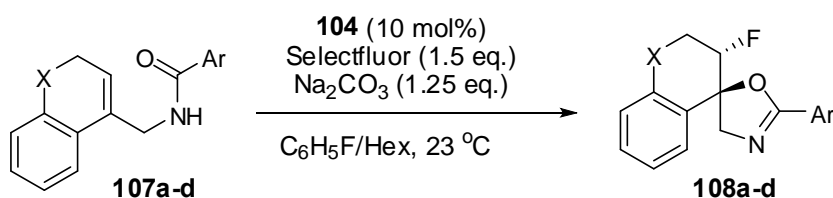
**Figure 8.** Proposed mechanism bromoetherification reactions promoted by chiral phosphoric acids **99**

An asymmetric fluorocyclization process, using chiral phosphoric acid **104** as an anionic chiral phase-transfer catalyst, was developed by Toste's group.<sup>48</sup> Dihydropyran-derived substrates **105** as well

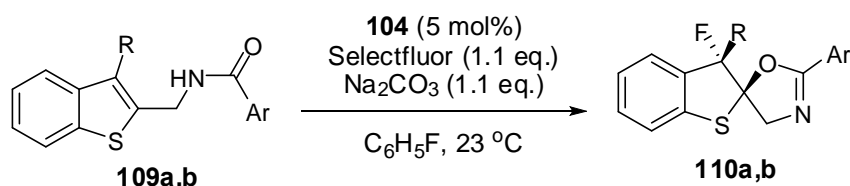
as unactivated alkene **107** and benzothiophene **109**, all containing amide tethers, were observed to undergo cyclization reactions to give the respective spiro-oxazoles **106**, **108**, and **110**, possessing two stereogenic centers, with one being fluorine substituted, with generally excellent levels of enantioselectivity and anti-diastereoselectivity (Scheme 28). To explain the outcomes of these reactions,



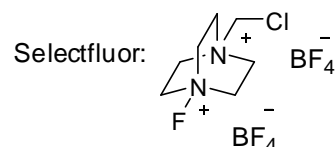
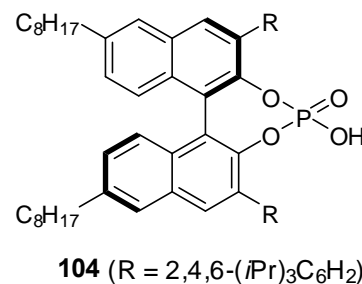
- a:** R = Ph: 86%, 92% ee      **e:** R = 4-NO<sub>2</sub>C<sub>6</sub>H<sub>4</sub>: 67%, 97% ee  
**b:** R = 4-ClC<sub>6</sub>H<sub>4</sub>: 95%, 97% ee      **f:** R = 2-naphthyl: 96%, 96% ee  
**c:** R = 4-BrC<sub>6</sub>H<sub>4</sub>: 84%, 95% ee      **g:** R = 4-*t*-BuC<sub>6</sub>H<sub>4</sub>: 95%, 95% ee  
**d:** R = 4-IC<sub>6</sub>H<sub>4</sub>: 95%, 97% ee      **h:** R = 2-IC<sub>6</sub>H<sub>4</sub>: 66%, 87% ee



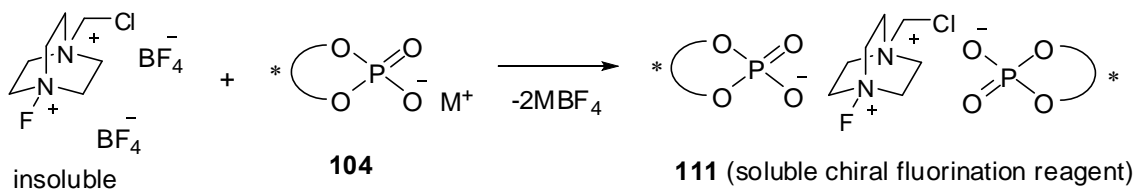
- a:** R = 4-BrC<sub>6</sub>H<sub>4</sub>, X = CH<sub>2</sub>: 87%, 93% ee  
**b:** R = 4-IC<sub>6</sub>H<sub>4</sub>, X = CH<sub>2</sub>: 71%, 93% ee  
**c:** R = 2-naphthyl, X = CH<sub>2</sub>: 80%, 96% ee  
**d:** R = 2-naphthyl, X = O: 70%, 92% ee



- a:** R = Me, X = Br: 69%, 90% ee  
**b:** R = CH<sub>2</sub>CH<sub>2</sub>OTBS, X = Cl: 55%, 89% ee



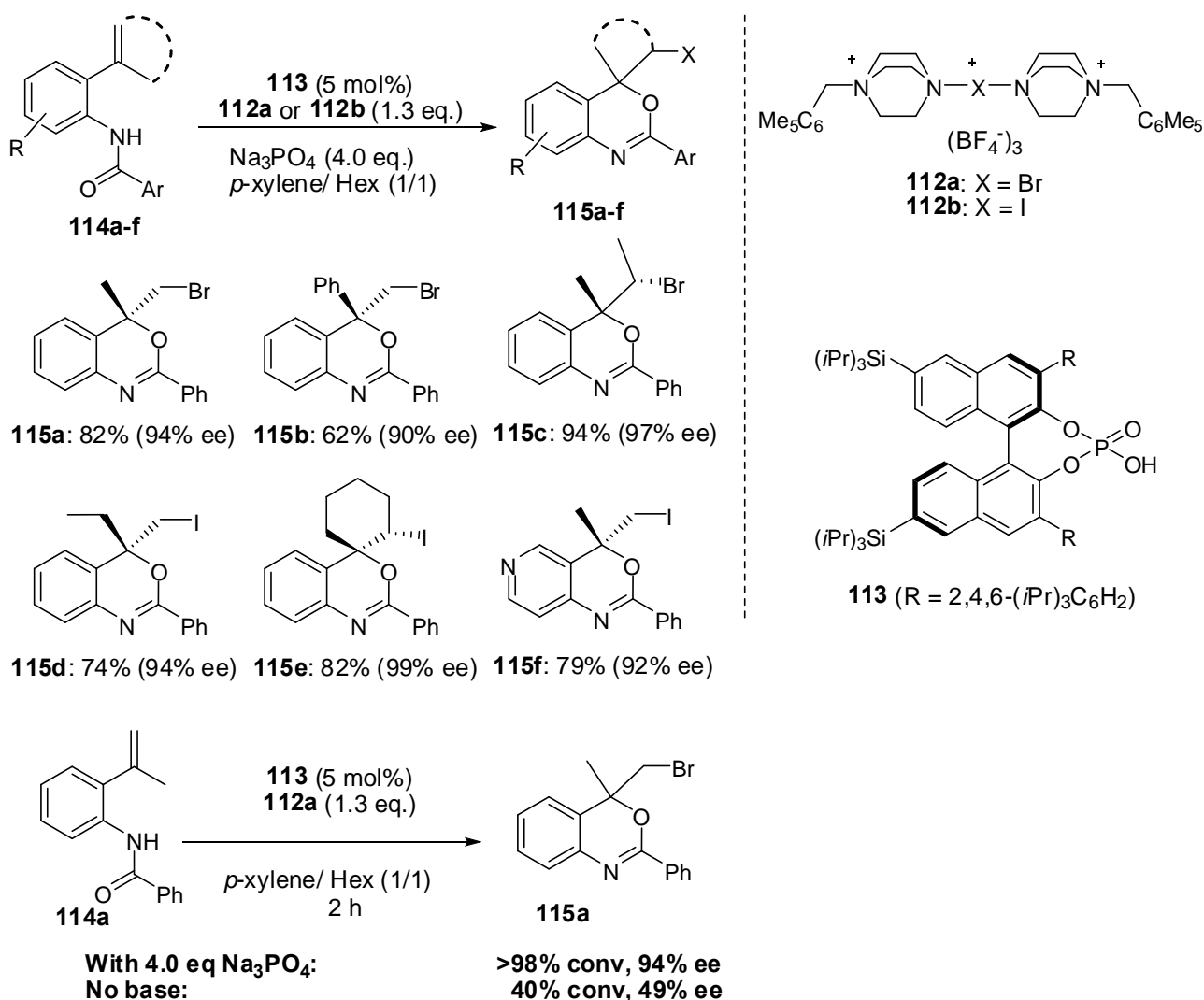
**Scheme 28.** Fluorocyclization reactions using chiral phosphoric acid **104** and Selectfluor



**Scheme 29.** Formation of the chiral fluorination reagent **111**

the authors proposed a mechanism involving formation of the chiral fluorination reagent **111** via exchange of both tetrafluoroborate anions associated with Selectfluor in the presence of the proton sponges, 1,8-bis(dimethylamino)naphthalene or  $\text{Na}_2\text{CO}_3$  (Scheme 29).

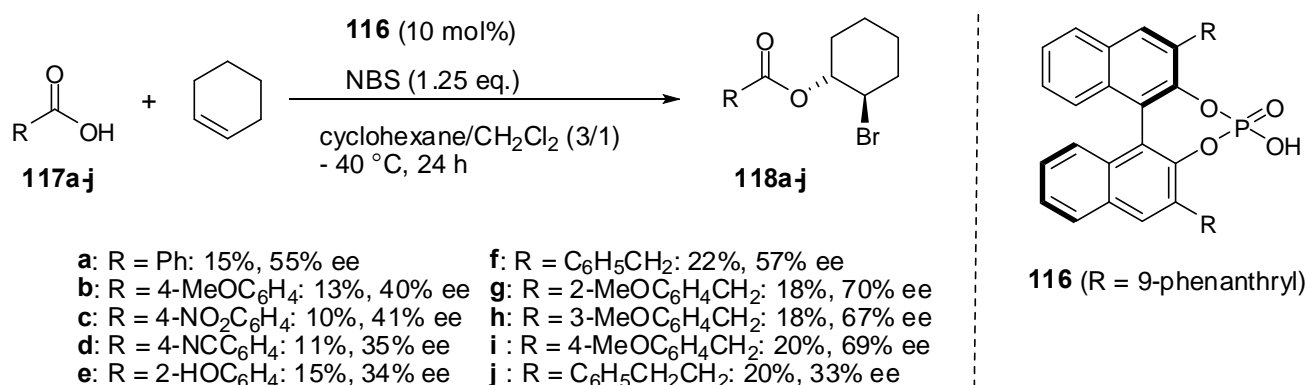
In an extension of the study described above, Toste and his coworkers also successfully developed highly enantioselective bromo- and iodo-cyclization reactions that rely on chiral anion phase-transfer catalysis (Scheme 30)<sup>49</sup> and in which monoalkyl DABCO tetrafluoroborates **112a** serve as tricationic brominating reagents. 6,6'-TIPS substituted binaphthylphosphoric acid **113** and  $\text{Na}_3\text{PO}_4$  were used in this process. It is noteworthy that substrates with substituents at both the  $\alpha$  and  $\beta$  positions of the styrene moiety react to afford products with high levels of enantioselectivity (**114a-c** to **115a-c**). By using the same procedure with **112b** in place of **112a** as the iodonium source highly enantioselective electrophilic iodocyclization reactions were achieved (**114d-f** to **115d-f**). The authors suggested that these processes involve anionic



**Scheme 30.** Bromo- and iodo-cyclization reactions promoted by the chiral anion phase-transfer catalysis

phase-transfer catalysis, because of the observation that enantioselectivity was diminished when a base, required for the formation and regeneration of the chiral phosphate anion, was not present.

Tang et al. recently described the first examples of intermolecular bromoesterification reactions.<sup>50</sup> Following an examination of several organocatalysts, these workers found that the chiral phosphoric Brønsted acid catalyst **116**, is effective in promoting these processes. The results of this study showed that reactions of various acids **117** and cyclohexene led to products with 70% ees. An ion-pair mechanism was proposed to explain the results (Scheme 31). In addition, studies of the reactions of cyclopentene or cyclooctene take place under these catalytic conditions with low ees (10-20% ee).



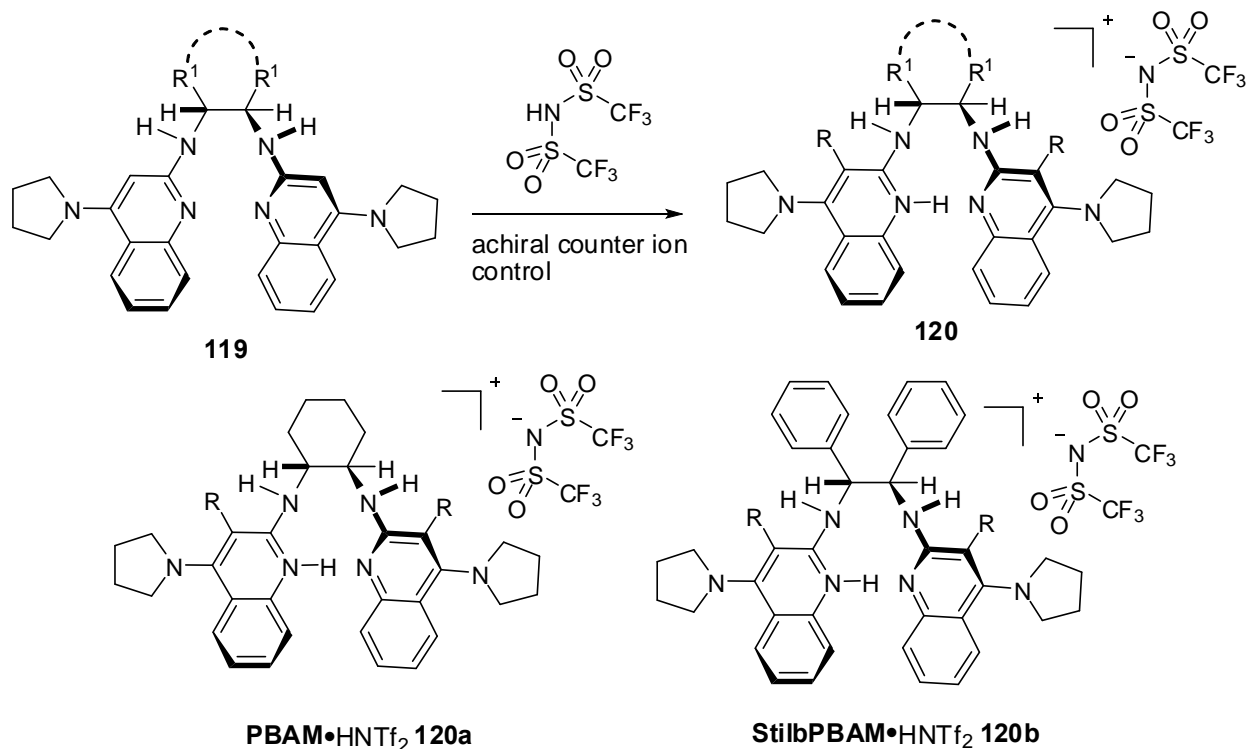
**Scheme 31.** Intermolecular bromoesterification reactions using the chiral phosphoric Brønsted acid catalyst **116**

## 7. MISCELLANEOUS CATALYSTS

### 7.1 StilbPBAM•HNTf<sub>2</sub> CATALYSTS

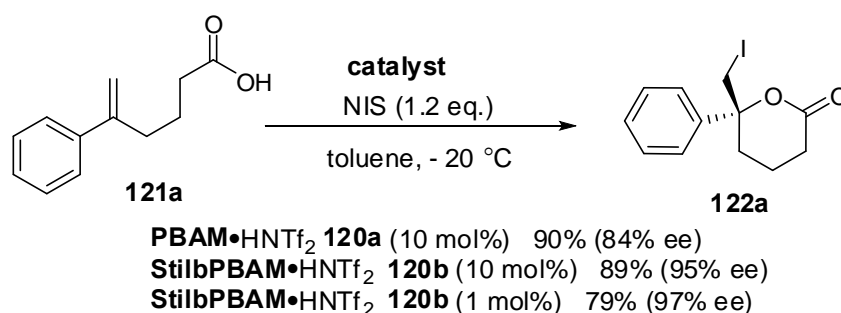
Above, we described a large number of enantioselective halolactonization reactions that rely on the use of organocatalysts. However, only a few enantioselective iodolactonization processes have been reported. Although a modest to high level of enantioselection has been reported for iodolactonizations by Jacobsen's group, the process requires low temperature reaction conditions (-80 °C) and a noncommercial halogen source (Scheme 17). Hansen and his coworkers also described an enantioselective iodolactonization process that uses commercially available NIS, which process, however, also requires low temperatures (-78 °C) and the reported substrate scope are limited to aryl substituted olefinic acids (Scheme 18).

Johnston *et al.* developed a more practical enantioselective iodolactonization method that uses the commercial halogen source, NIS, reactions run at -20 °C, and bis(amidine) (BAM)-based protic acid complexes **119**, which had already been demonstrated to act as bifunctional catalysts for nitroalkane



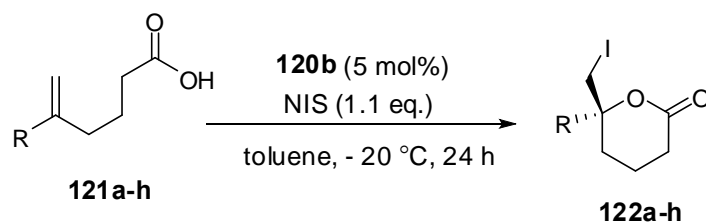
**Figure 9.** Formation of the acid-base complex with catalyst **119**

addition reactions (ref. 26).<sup>51</sup> The conjugate base of the acid appears to play a major role in governing levels of enantioselectivity, as reflected by the fact that triflimidic acid is the best acid promoter among those examined. Studies probing a range of catalysts revealed that substances containing the stilbendiamine backbone (StilbPBAM•HNTf<sub>2</sub> **120b**) are more effective from the perspective of reactivity and stereoselectivity than those possessing the cyclohexanediamine backbone (PBAM•HNTf<sub>2</sub> **120a**). Even the use of 1 mol% **120b** affords high enantioselectivities (Figure 9, Scheme 32), and this catalyst can be used to convert many 5-substituted 5-hexenoic acids **121** to their corresponding  $\delta$ -lactones **122** with high enantiomeric excesses. Perhaps most noteworthy is the observation that this catalyst is able to promote



**Scheme 32.** Optimization of the chiral proton-catalyzed iodolactonization reaction

iodolactonization reactions of 5-aliphatic substituted acids **121f,g**. It should be noted that 5-hexenoic acid **121h** is a reluctant substrate (Scheme 33).

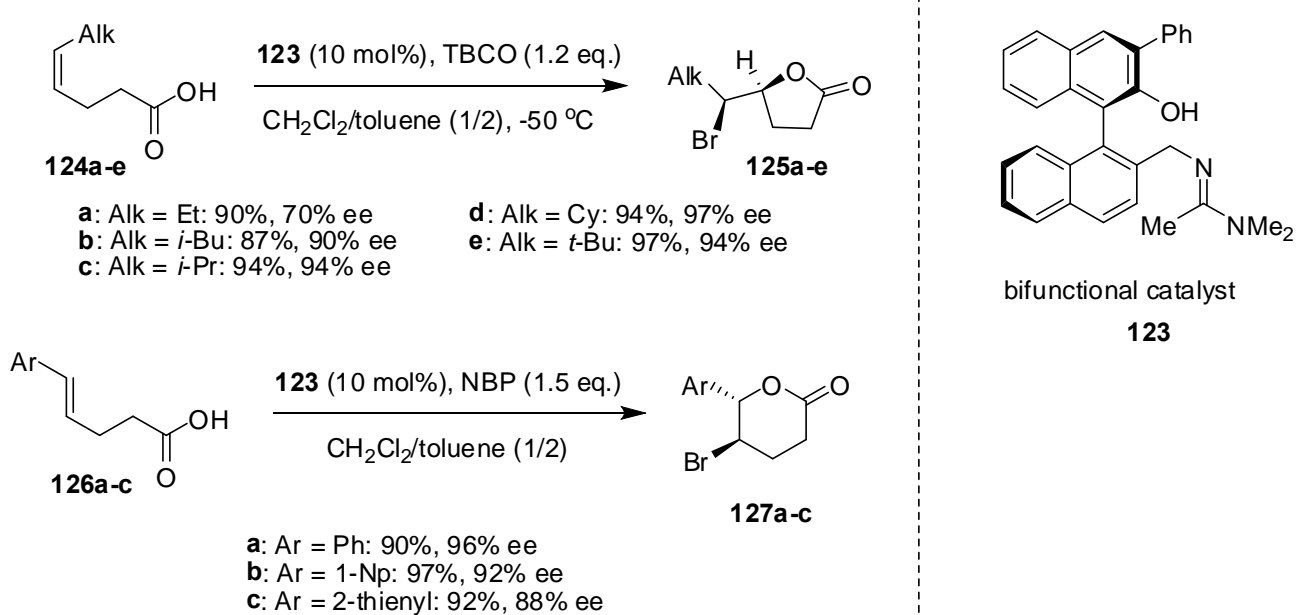


|   |  |
|---|--|
| <b>a:</b> R = Ph: 95%, 97% ee   | <b>e:</b> R = 4-MeOC <sub>6</sub> H <sub>4</sub> : 84%, 85% ee |
| <b>b:</b> R = 4-MeC <sub>6</sub> H <sub>4</sub> : 97%, 96%                  | <b>f:</b> R = <i>n</i> -butyl: 95%, 89% ee                     |
| <b>c:</b> R = 4-FC <sub>6</sub> H <sub>4</sub> : 96%, 98% ee                | <b>g:</b> R = isopropyl: 86%, 81% ee                           |
| <b>d:</b> R = 4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> : 26%, 96% ee | <b>h:</b> R = H: 25%, 33% ee                                   |

**Scheme 33.** Enantioselective iodolactonization reactions using the chiral proton catalyst **120b**

## 7.2. AMIDINE-PHENOL CATALYSTS

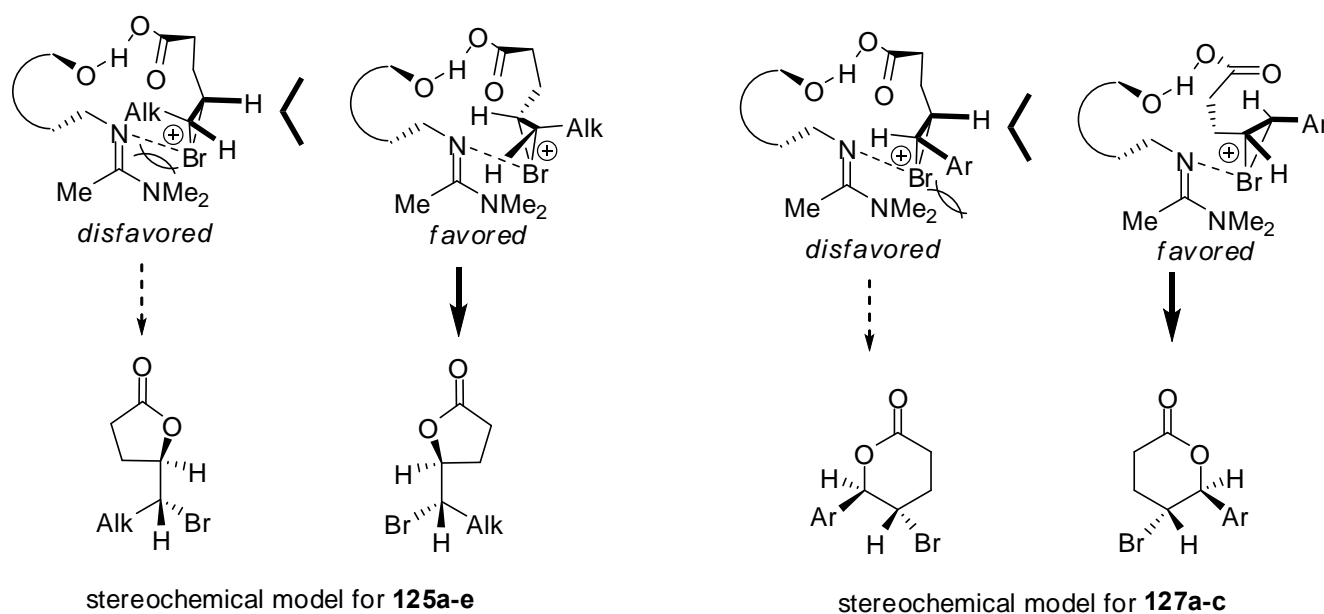
Martin's group developed the new bifunctional amidine-phenol catalyst **123**, which possesses Lewis base and Brønsted acid components positioned on a binaphthyl backbone. This catalyst promotes highly enantioselective bromolactonization reactions of a number of structurally different unsaturated acids using 2,4,4,6-tetrabromocyclohexadienone (TBCO) as the bromine source.<sup>52</sup> It is especially noteworthy that **123** catalyzes highly enantioselective bromolactonization reactions of 5-alkyl-4(*Z*)-pentenoic acids, as well as 4- and 5-aryl-4-pentenoic acids. It appears that **123** is the most effective catalyst that has been



**Scheme 34.** Scope of enantioselective bromolactonization reactions catalyzed by **123**

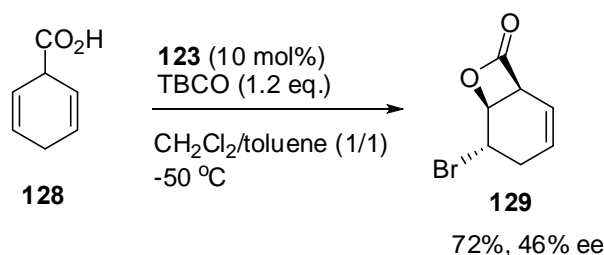
developed until now for highly enantioselective 5-*exo* mode bromolactonization reactions of alkyl substituted olefinic acids **124**. In this process, 5-aryl-4(*E*)-pentenoic acids **126** also afford  $\delta$ -lactones **127** with high levels of enantioselectivity (Scheme 34).

The catalyst **123** contains relatively acidic phenolic and highly basic amidine functions. As a consequence of these properties, it participates in strong hydrogen bonding with unsaturated acids, which orients the substituent on the carbon-carbon double bond away from the face of the binaphthyl scaffold. In addition, the bromonium ion is stabilized by interaction with the amidine moiety in the catalyst. Finally, based on the observation that the norphenyl analog of **123** promotes reactions that take place with somewhat lower enantioselectivities it appears that the 3-phenyl group in **123** assists by compressing the substrate toward the amidine moiety (Figure 10).



**Figure 10.** Stereochemical model for enantioselective bromolactonization reactions catalyzed by **123**

The first catalytic desymmetrization reaction of a prochiral dienolic acid was also achieved by using this

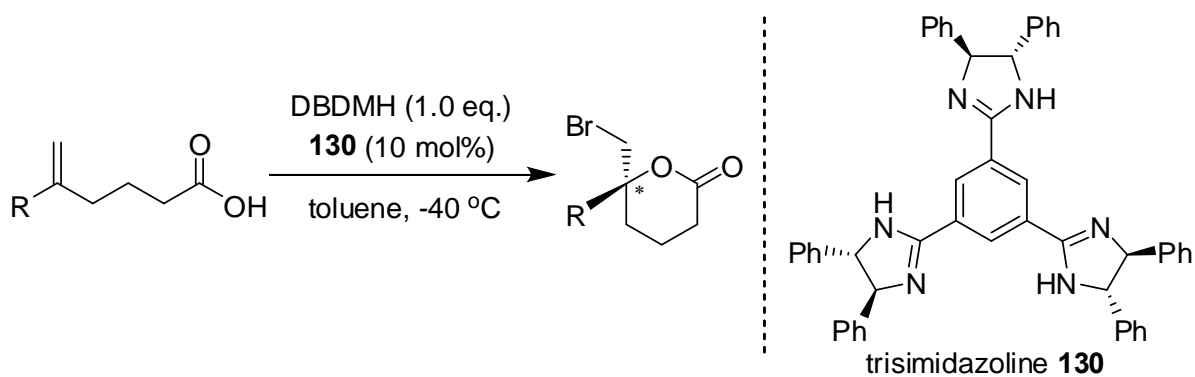


**Scheme 35.** Desymmetrization reaction of prochiral dienolic acid **128** promoted by **123**

catalyst (Scheme 35). Specifically, the cyclohexadiene carboxylic acid **128** was transformed to the fused bromo-lactone **129** in a process promoted by **123**. It should be noted that Hamashima and Kan *et al.* described a more efficient desymmetrization reaction of the cyclohexadiene acid derivatives in a later effort (Scheme 14).

## 8. TRISIMIDAZOLINE CATALYSTS

In studies carried out in the author's laboratory, an enantioselective bromolactonization reaction promoted by using the structurally unique  $C_3$ -symmetric trisimidazoline **130**, was developed (Scheme 36). Because **130** compared with others described in this review is not a common organocatalyst, a brief introduction to its preparation and properties will be given before summarizing its use in promoting halocyclization reactions.



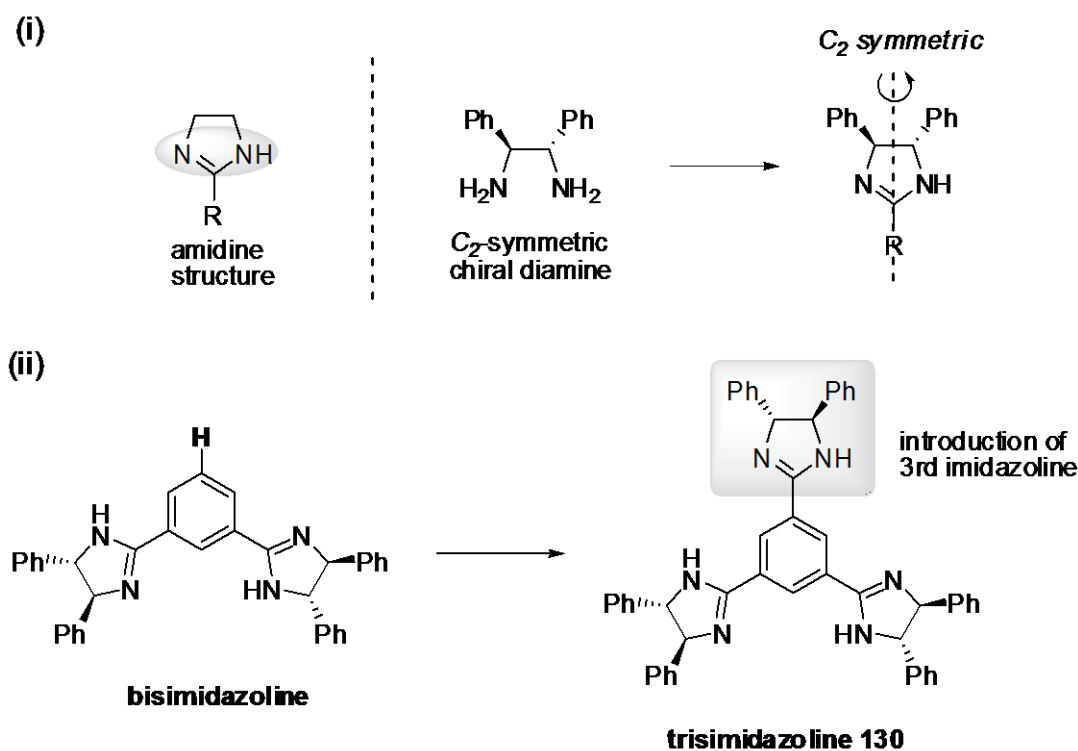
**Scheme 36.** Enantioselective bromolactonization reactions using trisimidazoline **130**

### 8.1 DEVELOPMENT OF TRISIMIDAZOLINE CATALYSTS

In recent studies, we developed a novel synthetic method for the preparation of imidazolines that begins with aldehydes and diamines and involves a one-pot process. In addition, we demonstrated the utility of the method in the context of natural product synthesis.<sup>53</sup> More recently, we became interested in the utility of the imidazolines as organocatalysts. We believed that the catalytic propensity of these substances would be fostered by the basicity, nucleophilicity and the Brønsted acidity of their salts. Before beginning work in this area in 2009, the use of imidazolines as organocatalysts had not been significantly explored. Only a few asymmetric reactions occurring with low levels of enantioselectivity had been described in which, for example, these substances served as acid catalysts for Diels-Alder reactions,<sup>54</sup> and as nucleophilic base catalysts for Morita Baylis-Hillman reactions.<sup>55</sup> It is only recently that the use of  $C_3$ -symmetric molecules as chiral ligands has been developed and, in some case, applied to highly enantioselective reactions.<sup>56</sup>

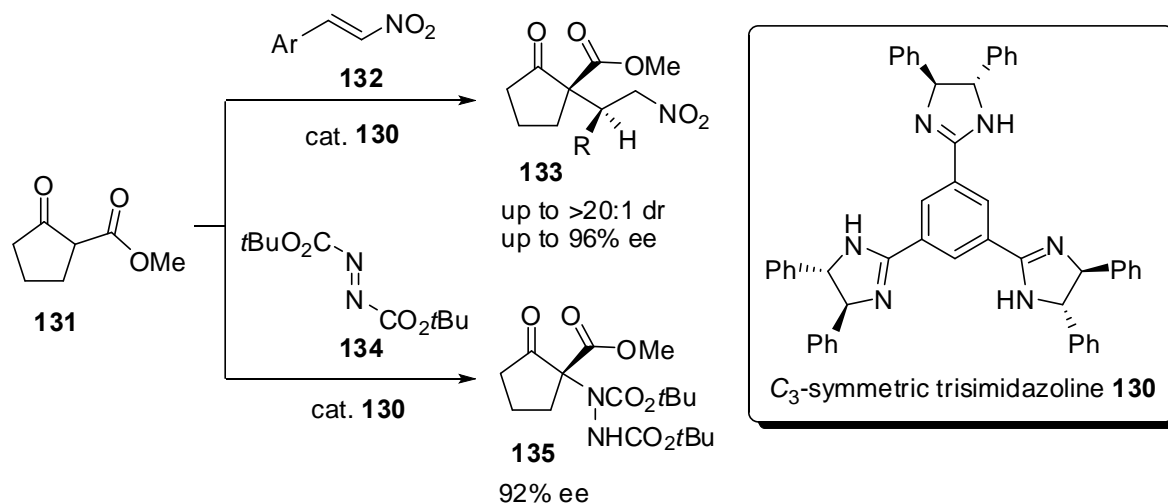


In designing new imidazoline organocatalysts, we took into account of the fact that these substances are analogous to oxazolines and that bisoxazolines are among the most widely used chiral ligands.<sup>57</sup> These observations suggested that analogous bisimidazolines structures could serve as chiral ligands<sup>54</sup> as well as organocatalyst. We also took into consideration the symmetric nature of imidazolines and, in particular, the fact that, owing to the presence of an amidine (N-C=N) moiety, imidazolines derived from  $C_2$ -symmetric diamines such as chiral 1,2-diphenyl-1,2-ethylenediamine would have symmetric structures (Figure 11, (i)). Although bisimidazoline catalyst derived from 1,2-diphenyl-1,2-ethylenediamine had already been described by another group,<sup>54</sup> trisimidazoline **130** formed by introduction of a third imidazoline moiety into the bisimidazoline structure would be an interesting  $C_3$ -symmetric compounds. These substances would have three imidazoline groups, derived from the 1,2-diphenyl-1,2-ethylenediamine moiety, at the 1-, 3-, and 5-positions of a benzene ring (Figure 11, (ii)).



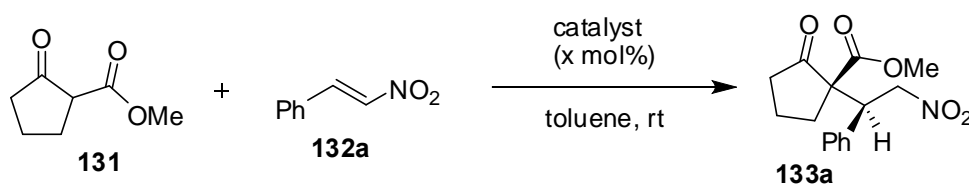
**Figure 11.** Design of  $C_3$ -symmetric trisimidazoline catalyst **130**

The trisimidazoline **130** was initially applied as a Brønsted base catalyst to highly enantioselective conjugate addition reactions of  $\alpha$ -substituted  $\beta$ -ketoesters **131** to nitroolefins **132**. In addition, asymmetric  $\alpha$ -amination reactions of  $\beta$ -ketoesters **131** with di-*tert*-butyl azodicarboxylate **134** were found also to be promoted by **130**. These were the first examples of highly enantioselective reactions using imidazolines as organocatalysts (Scheme 37).<sup>58</sup>



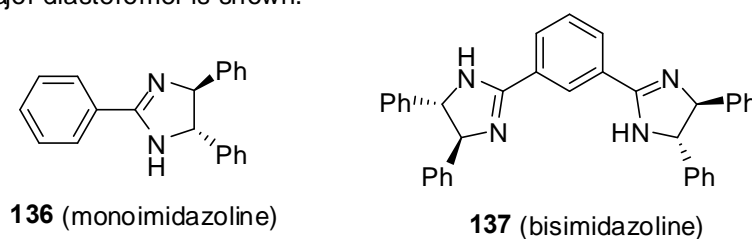
**Scheme 37.** Reaction of  $\beta$ -ketoester **131** catalyzed by trisimidazole **130**

**Table 1.** Comparison of reactions catalyzed by tris-, bis-, and monoimidazoles



| entry | catalyst                   | x   | yield (%) | dr     | ee (%) <sup>a</sup> |
|-------|----------------------------|-----|-----------|--------|---------------------|
| 1     | <b>136</b> (monoimidazole) | 5   | 29        | 5 : 1  | 1                   |
| 2     | <b>137</b> (bisimidazole)  | 5   | 91        | 18 : 1 | 61                  |
| 3     | <b>130</b> (trisimidazole) | 5   | 94        | 18 : 1 | 89                  |
| 4     | <b>137</b> (bisimidazole)  | 7.5 | 90        | 16 : 1 | 67                  |
| 5     | <b>130</b> (trisimidazole) | 2.5 | 97        | 18 : 1 | 90                  |

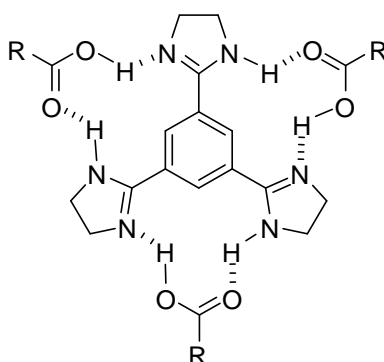
<sup>a</sup> Ee of major diastereomer is shown.



Importantly, the superior features of catalysts with  $C_3$ -symmetric structures were demonstrated by the high levels of asymmetric induction seen in conjugate addition reactions of the methyl 2-oxocyclopentanecarboxylate **131a** with  $\beta$ -nitrostyrene (**132a**) promoted by the bisimidazole **137** as well as monoimidazole **136** (Table 1).

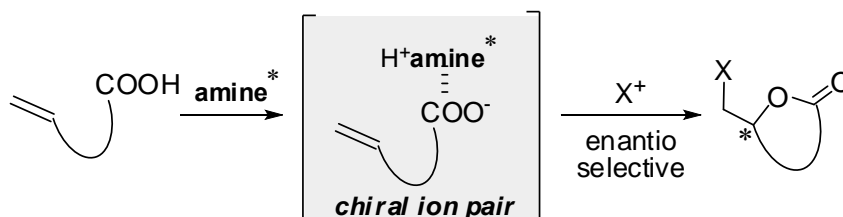
## 8.2 ASYMMETRIC BROMOLACTONIZATION REACTIONS<sup>59</sup>

Before applying imidazolines in a new method for catalyzing asymmetric halolactonization reactions, we recognized the interesting molecular recognition properties of trisimidazoline, which had been shown by Kraft's material science studies to form 1:3 complexes with carboxylic acids (Figure 12).<sup>60</sup> This finding suggested that trisimidazolines have a high potential to form tight ion pairs with carboxylic acids. As a consequence, we envisioned that the trisimidazoline **130** might serve as a chiral amine catalyst for enantioselective halolactonizations reactions (Scheme 38). In these processes, **130** and ene-carboxylic acids were expected to form a chiral ion pair, thus, creating a chiral environment around carboxylic acids. At the same time, the carboxylic acids should be activated in the form of carboxylate anion nucleophiles. The resulting complexes should then undergo highly enantioselective cyclizations.



**Figure 12.** 1:3 Complex of trisimidazoline and carboxylic acids

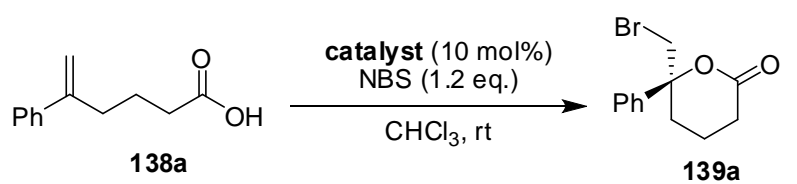
We therefore envisioned that the trisimidazoline **130** could be employed as the chiral amine catalyst for enantioselective halolactonizations (Scheme 38). The chiral trisimidazoline **130** and the substrates, ene-carboxylic acids, were expected to form a chiral ion pair and a chiral environment around carboxylic acids could be created. At the same time, carboxylic acids should be activated as a carboxylate anion. The activated carboxylic acid, which was surrounded by the chiral environment, should cyclize enantioselectively.



**Scheme 38.** Chiral ion pair approach for halolactonization

The plausibility of this idea was examined using reaction of 5-phenylhex-5-enoic acid (**138a**) in the presence of **130** with *N*-bromosuccinimide (NBS) as a bromine source (Table 2). Even at room temperature, the lactone **139a** was produced in 69% ee (entry 1), whereas the reactions catalyzed by other chiral amines, such as quinidine or (DHQD)<sub>2</sub>PHAL, proceeded with lower degrees of selectivity at this temperature (entries 2 and 3). The lower enantioselectivities associated with reactions promoted by bisimidazoline **137** and monoimidazoline **136** demonstrated the significance of utilizing C<sub>3</sub>-symmetric catalysts (entries 4 and 5).

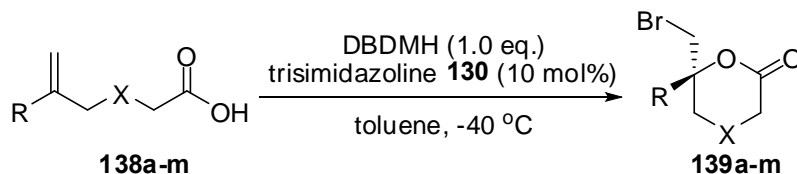
**Table 2.** Evaluation of the chiral amine

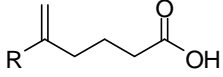
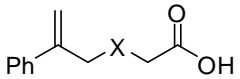


| entry | catalyst                   | yield (%) | ee (%) |
|-------|----------------------------|-----------|--------|
| 1     | trisimidazoline <b>130</b> | 95        | 69     |
| 2     | quinidine                  | 86        | -5     |
| 3     | (DHQD) <sub>2</sub> PHAL   | 89        | 47     |
| 4     | bisimidazoline <b>137</b>  | 99        | 28     |
| 5     | monoimidazoline <b>136</b> | 92        | 6      |

The results of further studies showed that toluene is much better solvent than CHCl<sub>3</sub> for this process and that 1,3-dibromo-5,5-dimethylhydantoin (DBDMH) is superior over NBS as a bromine source. After the optimization studies, various 1,1-disubstituted olefinic acids **138** were subjected to asymmetric bromolactonization reactions promoted by trisimidazoline **130** that were found to produce chiral  $\delta$ -lactones **139** with high enantioselectivities even with catalyst loadings as low as 2.5 mol% (entry 1, Table 3). Olefinic acids containing electron-withdrawing and electron-donating substituted aryl substituents participate in this reaction, and high levels of enantioselectivity are obtained in each case (entries 1-9, 11). Even a substrate having cyclohexyl substituent reacted with a moderate selectivity (entry 10). Finally, substrates containing O and N heteroatom linkers in the chain connecting the acid and olefin moieties were observed to undergo the cyclization reaction to give the respective chiral dioxanone **139l** and morpholinone **139m** (entries 12 and 13) with moderate selectivity.

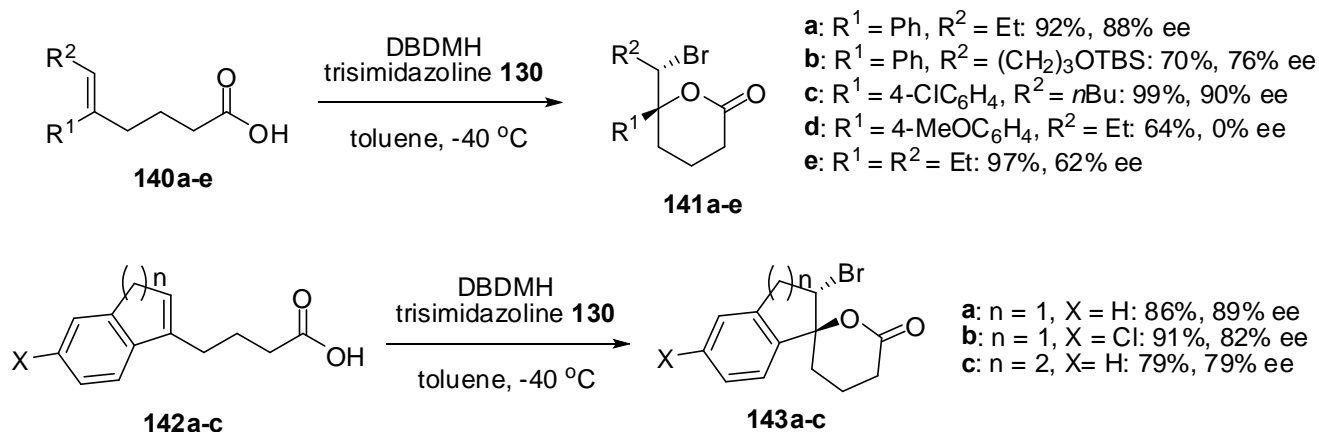
Along with 1,1-disubstituted olefinic substrates, trisubstituted internal olefin containing substrates participate this reaction system when trisimidazoline **130** is employed as the catalyst (Scheme 39).

**Table 3.** Reactions of 1,1-disubstituted olefinic acids **138** catalyzed by trisimidazole **130**

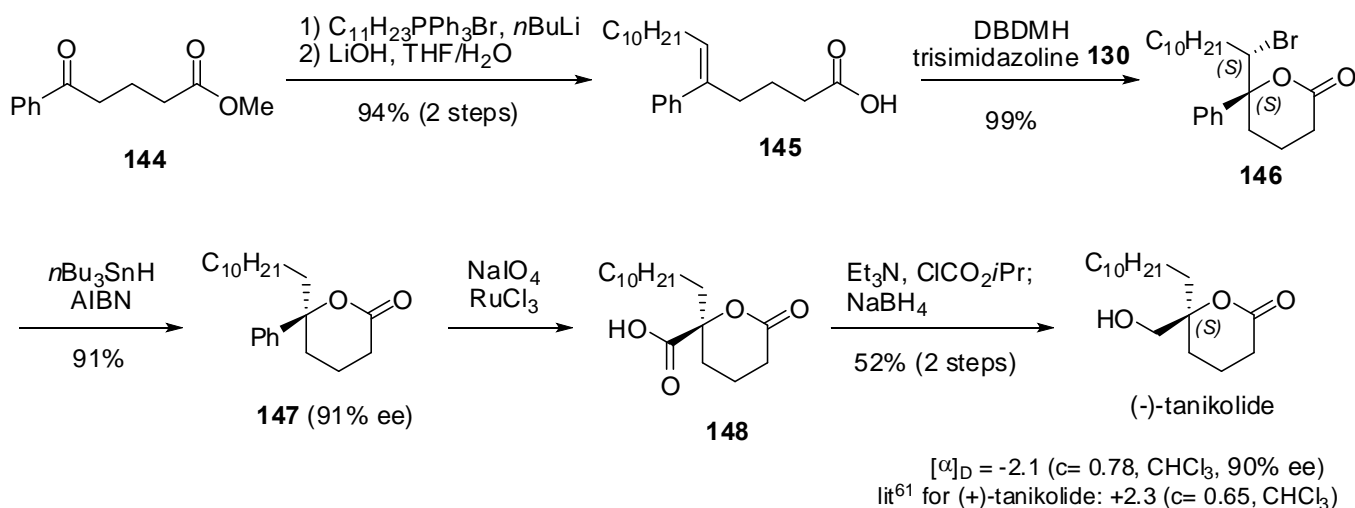
| entry | substrates  | yield (%)                               | ee (%)                  | entry           | substrates   | yield (%)          | ee (%) |
|-------|---|---|-------------------------|-----------------|--|--------------------|--------|
| 1     | <br>R = Ph ( <b>138a</b> ) | 99 ( <b>139a</b> )<br>(96) <sup>a</sup> | 91<br>(90) <sup>a</sup> | 7 <sup>b</sup>  | R = 4-MeOC <sub>6</sub> H <sub>4</sub> ( <b>138g</b> )                             | 74 ( <b>139g</b> ) | 80     |
| 2     | R = 4-ClC <sub>6</sub> H <sub>4</sub> ( <b>138b</b> )   | 93 ( <b>139b</b> )                      | 87                      | 8               | R = 2,4-diMeC <sub>6</sub> H <sub>3</sub> ( <b>138h</b> )                          | 91 ( <b>139h</b> ) | 75     |
| 3     | R = 4-BrC <sub>6</sub> H <sub>4</sub> ( <b>138c</b> )   | 93 ( <b>139c</b> )                      | 89                      | 9               | R = 2-naphthyl ( <b>138i</b> )   | 82 ( <b>139i</b> ) | 89     |
| 4     | R = 4-FC <sub>6</sub> H <sub>4</sub> ( <b>138d</b> )  | 94 ( <b>139d</b> )                      | 87                      | 10 <sup>c</sup> | R = cyclohexyl ( <b>138j</b> )   | 95 ( <b>139j</b> ) | 72     |
| 5     | R = 4-CF <sub>3</sub> C <sub>6</sub> H <sub>4</sub> ( <b>138e</b> )   | 96 ( <b>139e</b> )                      | 89                      |                 |  |                    |        |
| 6     | R = 4-MeC <sub>6</sub> H <sub>4</sub> ( <b>138f</b> )   | 96 ( <b>139f</b> )                      | 90                      | 11              | X = CMe <sub>2</sub> ( <b>138k</b> )   | 96 ( <b>139k</b> ) | 81     |
|       |   |   |                         | 12 <sup>c</sup> | X = O ( <b>138l</b> )  | 74 ( <b>139l</b> ) | 71     |
|       |   |   |                         | 13 <sup>c</sup> | X = NTs ( <b>138m</b> )  | 89 ( <b>139m</b> ) | 75     |

a) trisimidazole (2.5 mol%); b) DBDMH (2.0 eq.), -78 °C; c) -60 °C

A study probing the effect of the olefin geometry showed that substrates **140** with R<sup>1</sup> and R<sup>2</sup> having a *cis*-geometry react with higher levels of enantioselectivity than their *trans* analogs. As expected based on this observation, cyclic olefinic substrates, such as indene and dihydronaphthalene derivatives **142**, also undergo halocyclizations to form the corresponding spirocyclic lactones **143** with high enantioselectivities.

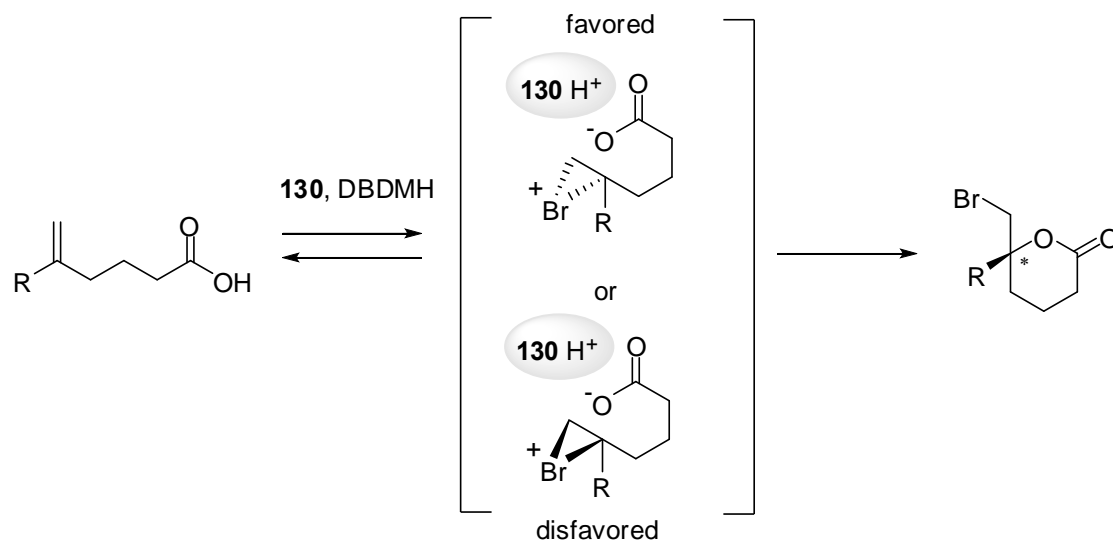
**Scheme 39.** Bromolactonization reactions of internal olefinic substrates

The synthetic utility of the methodology was demonstrated by its application to a concise asymmetric synthesis of tanikolide,<sup>61,62</sup> a natural product that possesses a tetrasubstituted carbon containing  $\delta$ -lactone ring system (Scheme 40). In the synthetic sequence, alkenoic acid **145**, prepared from  $\delta$ -keto ester **144** through the Wittig olefination and basic hydrolysis, was subjected to the bromolactonization to give bromolactone **146** in high yield. Radical reduction with  $n\text{Bu}_3\text{SnH}$  and AIBN was used to remove bromine from this substance that generated the corresponding lactone **147** in 91% yield. At this stage, the ee of lactone **147** was determined to be 91% by using HPLC analysis. The benzene moiety in **147** was then oxidized to form the corresponding carboxylic acid **148** by using  $\text{RuCl}_3/\text{NaIO}_4$ . Sequential one-pot mixed anhydride formation with **148** and reduction using  $\text{NaBH}_4$  then led to generation of the alcohol moiety in the target tanikolide in 52% yield from **148**.



**Scheme 40.** Asymmetric synthesis of tanikolide

The mechanism of bromocyclization reactions catalyzed by trisimidazoline **130** is not known at this time. However, the results of preliminary studies suggest that trisimidazoline **130** and substrate carboxylic acids interact at the initial stages of the reaction. In addition, we have observed that analogous bromocyclization reactions of ene-alcohols using **130** give almost racemic products. Therefore, we believe that interaction of **130** with the carboxylic acid moiety in the substrate forms an ion pair that is crucial for creating a chiral environment for the cyclization process (Scheme 41). Further detailed investigations of the reaction mechanism are required in order to determine, for example, if **130** operates as a bifunctional catalyst with one imidazoline activating the carboxylic acid and another activating the brominating agent (NBS or DBDMH).



**Scheme 41.** Proposed reaction mechanism for catalysis by trisimidazole **130**

## 9. CONCLUSION

In this review, we have summarized recent progress that has been made in studies of on enantioselective halocyclization reactions catalyzed by various types of organocatalysts. Although high levels of enantioselectivity accompany several of the transformations, methods that lead to highly enantioselective halocyclization as well as related halogenation reactions are still required. One significant issue that remains to be addressed in this area is the development of realistic and experimentally tested mechanistic models that both explain the observed asymmetric induction and enable the design of more effective catalysts. In addition, a reliable method for asymmetric olefin halogenations needs to be discovered. Moreover, studies that define substrate scope of the processes are important because they will lead to predictions of the types of products (for example heterocycles) that can be prepared utilizing catalytic halocyclization reactions. Finally, because of the potential applicability of halocyclization reaction to the synthesis of complex molecules including natural products, studies probing the efficiencies and stereoselectivities of these processes in the context of functionally, structurally and stereochemically complex substrates need to be carried out. Particularly interesting in this regard is the effect of preexisting stereochemistry in the reactants on the stereochemical control of newly formed chiral centers (for example, double asymmetric induction). There is no doubt that further investigations in this area will provide valuable tools to the synthetic organic chemistry community.

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