1
Recent Advance of 'Combined Acid' Strategy for Asymmetric Catalysis

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Lewis acid can be utilized as a more effective tool for chemical reactions by sophisticated engineering ('*designer acid catalysis*') [1]. The goal of such 'designer Lewis acid' is to achieve high reactivity, selectivity, and versatility, upon which the full potential of acid catalysts has not yet been realized.

1.1
Combined Acid Catalysis

One possible way to take advantage of such abilities may be to apply a 'combined acids system' [2] to the catalyst design. The concept of combined acids, which can be classified into Brønsted acid-assisted Lewis acid (BLA), Lewis acid-assisted Lewis acid (LLA), Lewis acid-assisted Brønsted acid (LBA), and Brønsted acid-assisted Brønsted acid (BBA), can be a particularly useful tool for the design of asymmetric catalysis, because combining such acids will bring out their inherent reactivity by associative interaction, and also provide more organized structure, which will allow an effective asymmetric environment to be secured.

These combined acid catalysts can be classified as shown in Table 1.1. It should be emphasized that we anticipated a more or less intramolecular assembly of such combined systems rather than intermolecular arrangements because the intramolecular assembly should generate a well-organized chiral environment, leading to high stereocontrol. Thus, proper design of the catalyst structure is essential for success.

Since we have already summarized examples of combined acid catalysis [2], only recent representative examples of such catalysis are discussed with emphasis on the area of asymmetric catalysis in the following sections.

1.1.1
Brønsted Acid-Assisted Chiral Lewis Acid (BLA)

Since the first report of chiral oxazaborolidine-based Brønsted acid-assisted chiral Lewis acid (BLA) for enantioselective Diels–Alder reactions by Corey and coworkers

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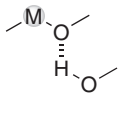
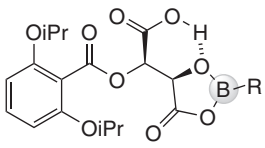
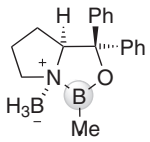
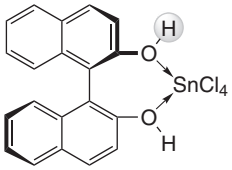
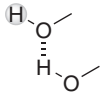
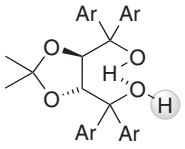
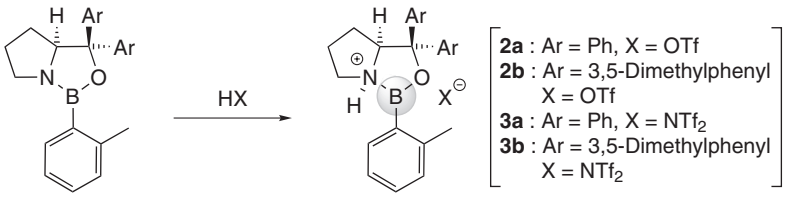
Table 1.1 The general classifications of combined acid catalysis.

Type of combined acid catalysts	General structure	Examples
Brønsted acid-assisted Lewis acid catalyst (BLA) Enhancement of Lewis acidity by the combination with Brønsted acid		
Lewis acid-assisted Lewis acid catalyst (LLA) Enhancement of Lewis acidity by the combination with Lewis acid		
Lewis acid-assisted Brønsted acid catalyst (LBA) Enhancement of Brønsted acidity by the combination with Lewis acid		
Brønsted acid-assisted Brønsted acid catalyst (BBA) Enhancement of Brønsted acidity by the combination with Brønsted acid		



Scheme 1.1 Generation of Corey's BLAs from the corresponding chiral oxazaborolidine (**1a**) or (**1b**) and strong Brønsted acid.

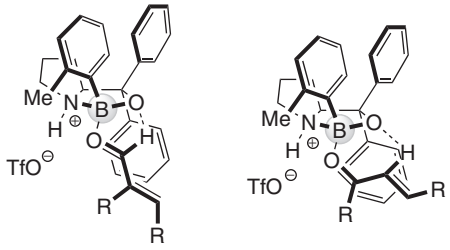


Fig. 1.1 Proposed pretransition state assemblies.

in 2002 [3a], recent studies by Corey group have demonstrated that these chiral BLAs are exceptionally potent and versatile chiral Lewis acids for catalytic enantioselective Diels–Alder reactions [3].

These chiral BLAs ((**2a–b**), (**3a–b**)) are generated simply by protonation of the chiral oxazaborolidine of type (**1**) by strong Brønsted acids such as triflic acid or triflimide (Scheme 1.1).

The absolute stereochemical outcome of the Diels–Alder reactions via these catalysts can be successfully predicted on the basis of the pretransition state assemblies shown in Figure 1.1.

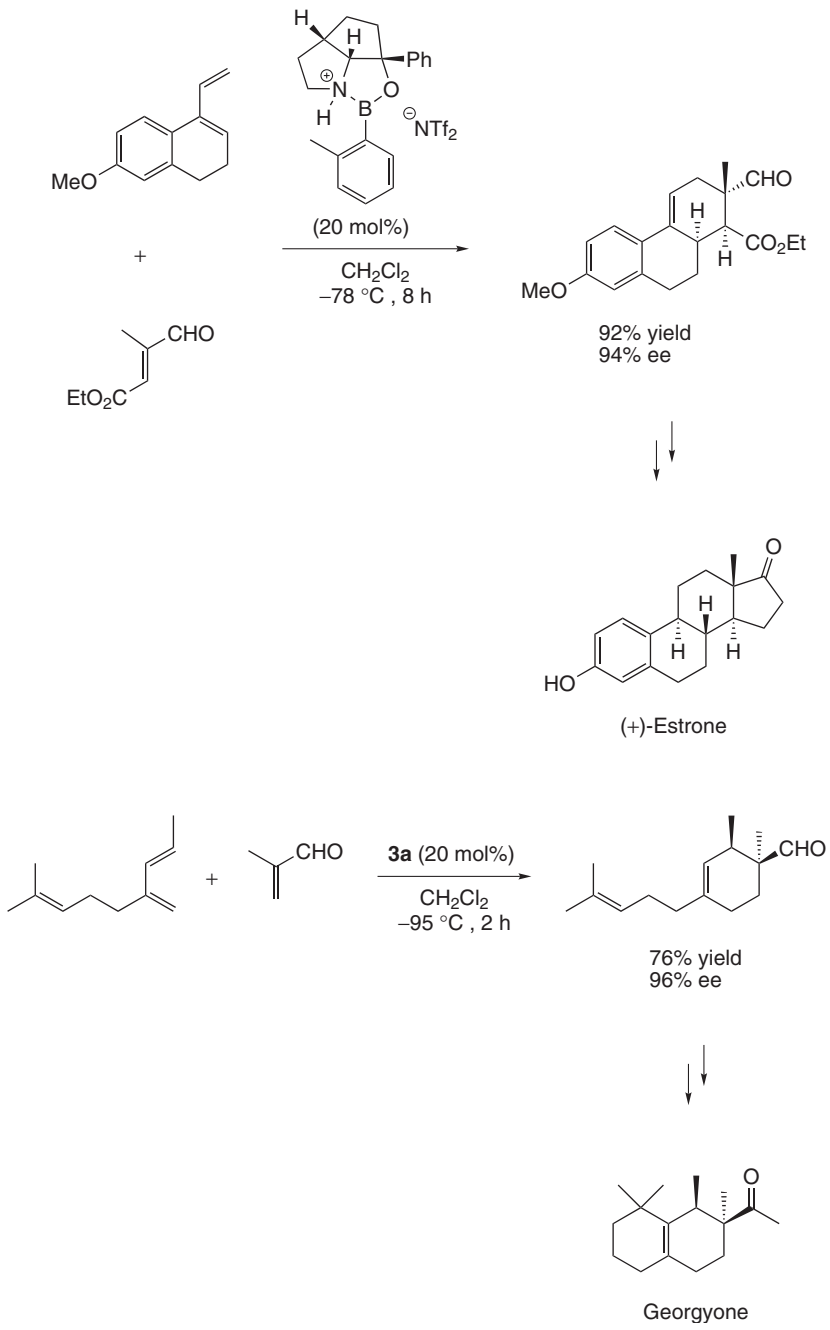
The synthetic power of Corey's BLAs has been well demonstrated by their applications to the enantioselective syntheses of biologically important complex molecules through catalytic enantioselective Diels–Alder reactions as key steps (Scheme 1.2) [3g–i, 4]. The key Diels–Alder reactions proceed in excellent chemical yield with high enantioselectivity in all cases and the absolute configurations of the product are consistent with the proposed transition state assembly.

The synthetic utility of Corey's chiral BLAs is quite obvious from many successful applications to other carbon–carbon bond-forming reactions described below.

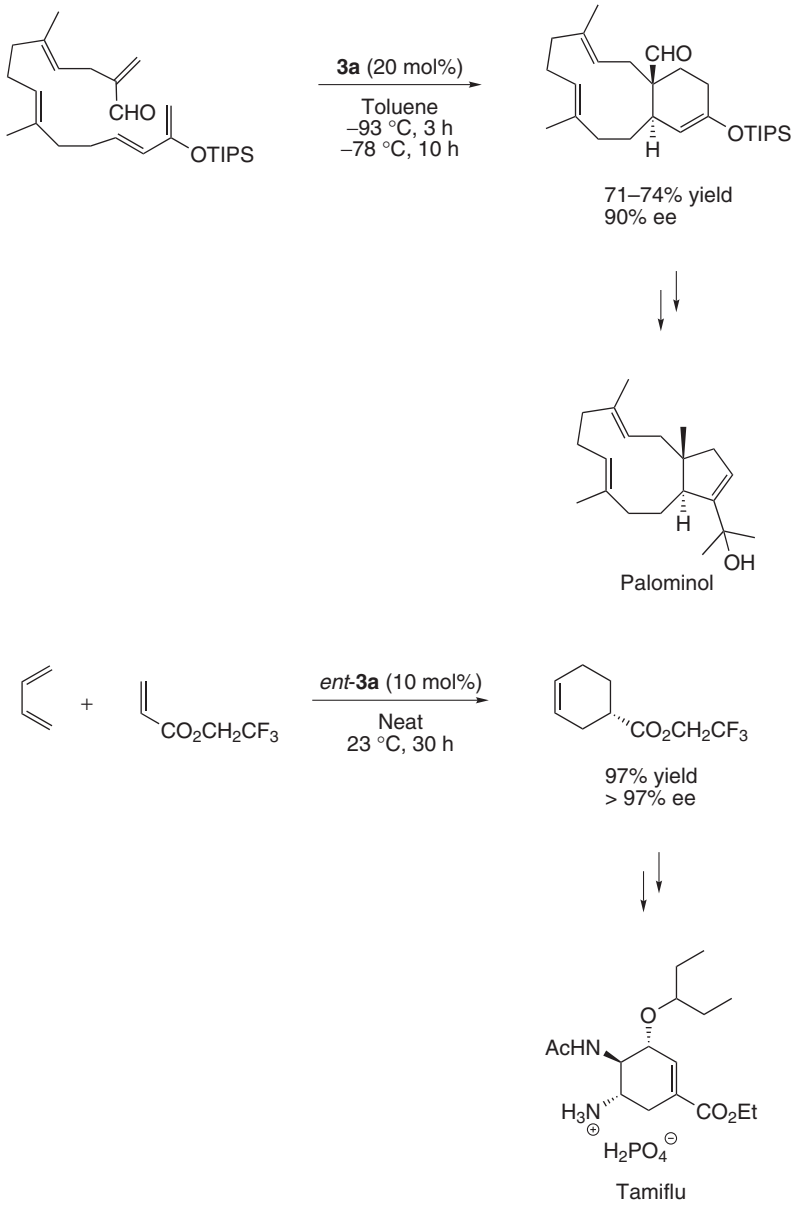
In 2004, Corey reported highly enantioselective cyanosilylation of aldehydes catalyzed by chiral BLA (**3b**) (Scheme 1.3) [5]. Under the standard conditions (10 mol% of (**3b**) and 20 mol% of Ph_3PO in toluene at 0 °C), a variety of both aromatic and aliphatic aldehydes have been transformed into cyanohydrins with >90% enantiomeric purity.

Noteworthy is that the reaction between trimethylsilyl (TMS) cyanide and triphenylphosphine oxide seems to generate a new reactive cyanide donor, isocyanophosphorane $Ph_3P(OTMS)(N{=}C{:})$ and this species is crucial for high enantioselectivity. The novel process described herein has several other advantages such as: (i) predictability of absolute configuration of cyanohydrin products from a mechanistic model as described in Scheme 1.3; (ii) easy and efficient recovery of the catalytic ligand.

The subsequent study revealed that the chiral BLA (**2b**) is a potent chiral Lewis acid for enantioselective cyanosilylation of methyl ketones promoted by TMS cyanide and diphenylmethyl phosphine oxide as coreactants (to generate $Ph_2MeP(OTMS)(N{=}C{:}$ as a reactive intermediate) (Scheme 1.4) [6]. The rational for the observed face selectivity can be explained by a transition state assembly in



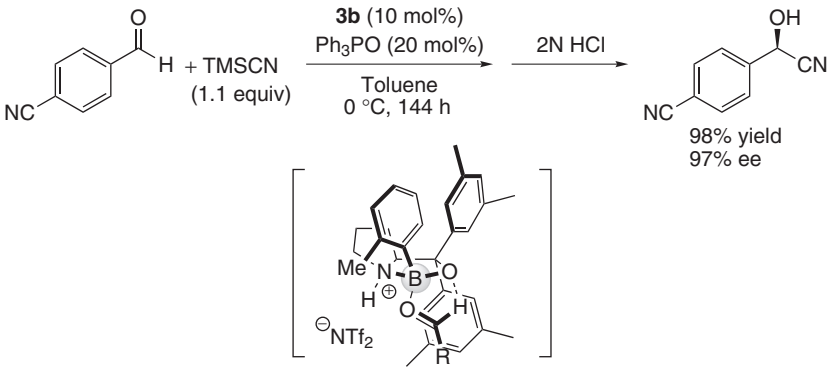
Scheme 1.2 Enantioselective total syntheses of biologically important molecules using Corey's BLAs.



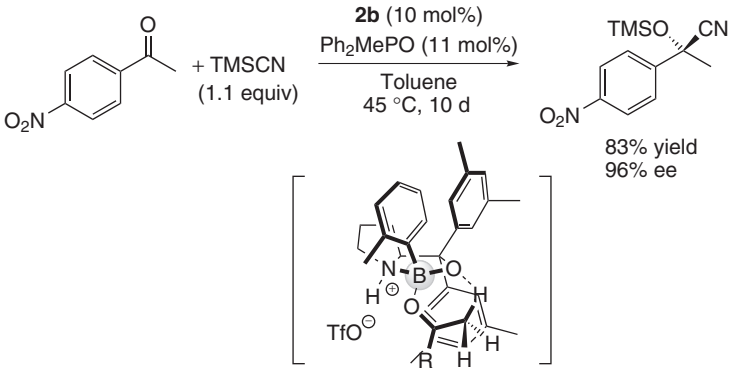
Scheme 1.2 (*continued*)

Scheme 1.4, which involves the hydrogen bonding between the oxygen atom of the chiral oxazaborolidine and α-hydrogen atom of the methyl ketone.

In 2005, a highly enantioselective [3 + 2]-cycloaddition reaction of 2,3-dihydrofuran with 1,4-benzoquinones using a chiral BLA (**3a**) as catalyst was developed, which



Scheme 1.3 Enantioselective cyanosilylation of aldehydes catalyzed by (**3b**).

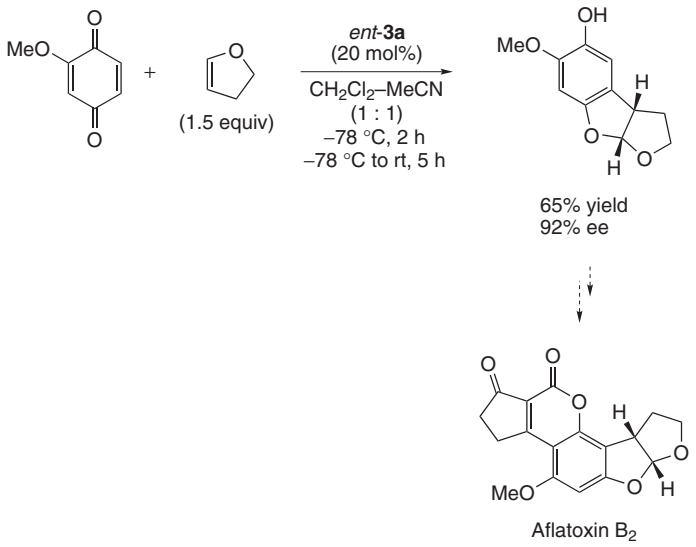


Scheme 1.4 Enantioselective cyanosilylation of methyl ketones catalyzed by (**2b**).

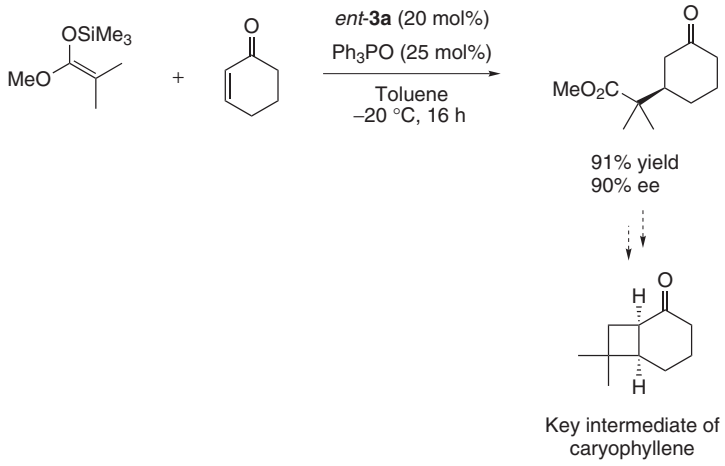
allows rapid access to a variety of chiral phenolic tricycles with high enantioselectivity (up to 98% ee). The utility of this new methodology was demonstrated by a short synthesis of the important pentacyclic natural product, aflatoxin B_2 (Scheme 1.5) [7].

In 2006, catalytic enantioselective Michael addition of ketene silyl acetals to cyclic and acyclic α, β-enones was devised using the chiral BLA (**3a**) (Scheme 1.6) [8]. Various Michael donors and ketene silyl acetals can be employed for this process. Here again, the use of triphenylphosphine oxide is crucial to trap any catalytically active silyl cation species. In addition, the combined use of triphenylphosphine oxide and a stoichiometric amount of 2,6-diisopropylphenol (which acts as a scavenger of silyl cation species) is sometimes required to get both high enantioselectivity and the chemical yield. This enantioselective methodology was applied to the asymmetric synthesis of a key intermediate of caryophyllene.

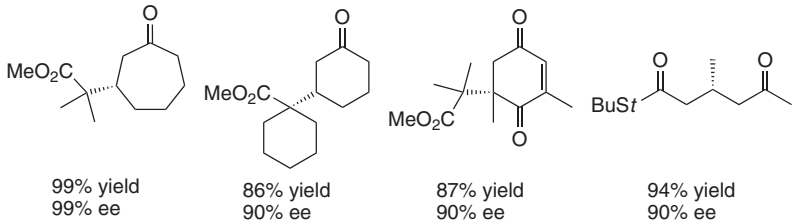
An enantioselective total synthesis of the apoptosis-inducing natural product, (−)-rasfonin has been reported by Boeckman Jr. and coworkers in 2006 (Scheme 1.7) [9]. The crucial asymmetric vinylogous Mukaiyama aldol addition was achieved with high diastereoselectivity with chiral BLA (**2b**) through Corey's transition state model.



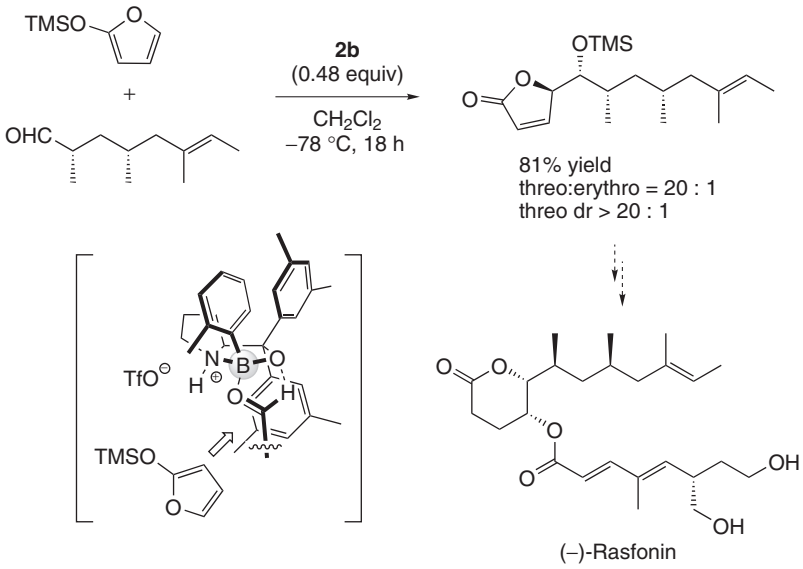
Scheme 1.5 Asymmetric [3 + 2] cycloaddition of 1,4-benzoquinones catalyzed by (**3a**).



Other examples (**3a** as a chiral Lewis acid)



Scheme 1.6 Enantioselective Michael addition of ketene silyl acetals catalyzed by (**3a**).



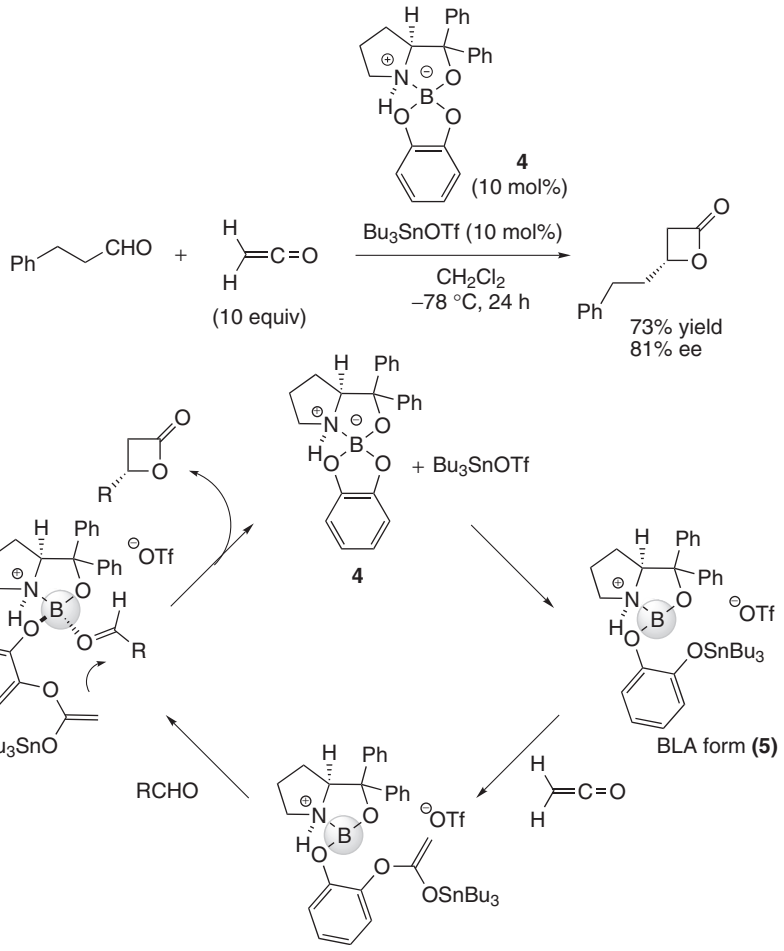
Scheme 1.7 Total synthesis of (–)-rasfonin through diastereoselective vinylogous Mukaiyama aldol reaction promoted by chiral BLA (**2b**).

A novel catalytic system was developed for the enantioselective synthesis of β-lactones from ketene and aldehydes by Corey group in 2006 (Scheme 1.8) [10].

A range of aliphatic aldehydes have been converted to the corresponding chiral β-lactones by the reaction with ketene in the presence of the chiral oxazaborolidine and tributyltin triflate as catalysts with up to 84% ee.

The authors proposed that the chiral BLA (**5**), generated by the reaction of the chiral oxazaborolidine (**4**) and tributyltin triflate, acts as a chiral Lewis acid catalyst in this system. Noteworthy is the fact that the absolute configuration of the β-lactone can be predicted by the transition state assembly in Scheme 1.8, which is analogous to that of well-known CBS reduction.

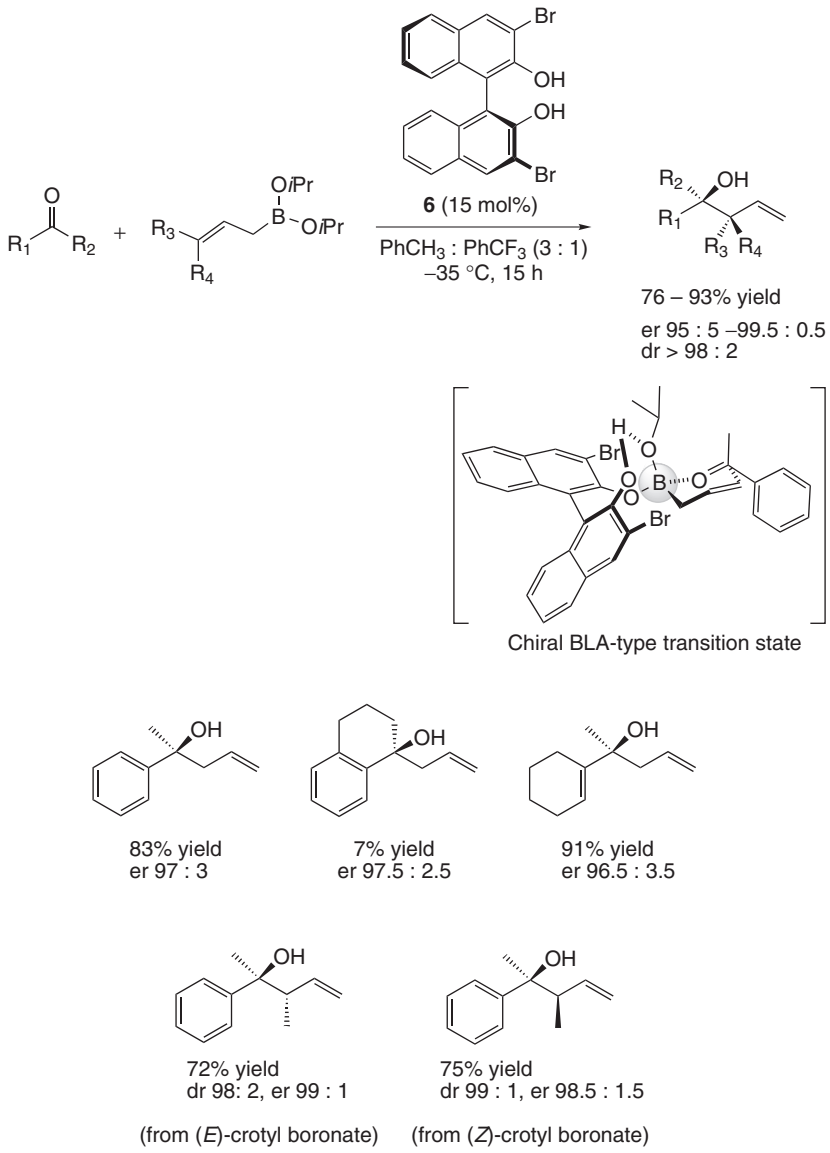
In 2006, Schaus group reported that chiral BINOL-derived diols catalyze the enantioselective asymmetric allylboration of ketones (Scheme 1.9) [11]. The reaction requires 15 mol% of 3,3′-Br_2-BINOL (**6**) as the catalyst and allyldiisopropoxyborane as the nucleophile. The reaction products are generally obtained in good yields and high enantiomeric ratios (up to 99.5 : 0.5). In addition, high diastereoselectivities (dr 98 : 2) and enantioselectivities (er 98 : 2) are obtained in the reactions of acetophenone with crotyldiisopropoxyboranes through Zimmerman–Traxler transition state model. On the basis of a series of experiments, the authors proposed chiral BLA-type transition state assembly in which the acidic proton coordinates to the alkoxy ligand of the chiral boronate complex through hydrogen bonding. To support this hypothesis, the reaction using monomethylated analog of (**6**) resulted in lower yield and virtually no asymmetric induction, highlighting the importance of the diol functionality for BLA-type activation.



Scheme 1.8 Enantioselective β-lactone formation catalyzed by the chiral oxazaborolidine.

Hall and coworkers developed the novel enantioselective allylboration of aldehydes catalyzed by chiral Brønsted acid in 2006 (Scheme 1.10) [12]. Moderate to good enantioselectivities (up to 80% ee) were observed in the reactions of allylboronate and both aromatic and aliphatic aldehydes with 10 mol% of chiral Brønsted acid (**7**) [13], a Lewis acid-assisted chiral Brønsted acid (chiral LBA) developed by Yamamoto group. On the basis of their previous studies on allylboration reactions, the authors proposed that the use of the strong chiral Brønsted acid provides the chiral recognition event through BLA-type cyclic transition state with coordination to the oxygen atom of the allylboronate.

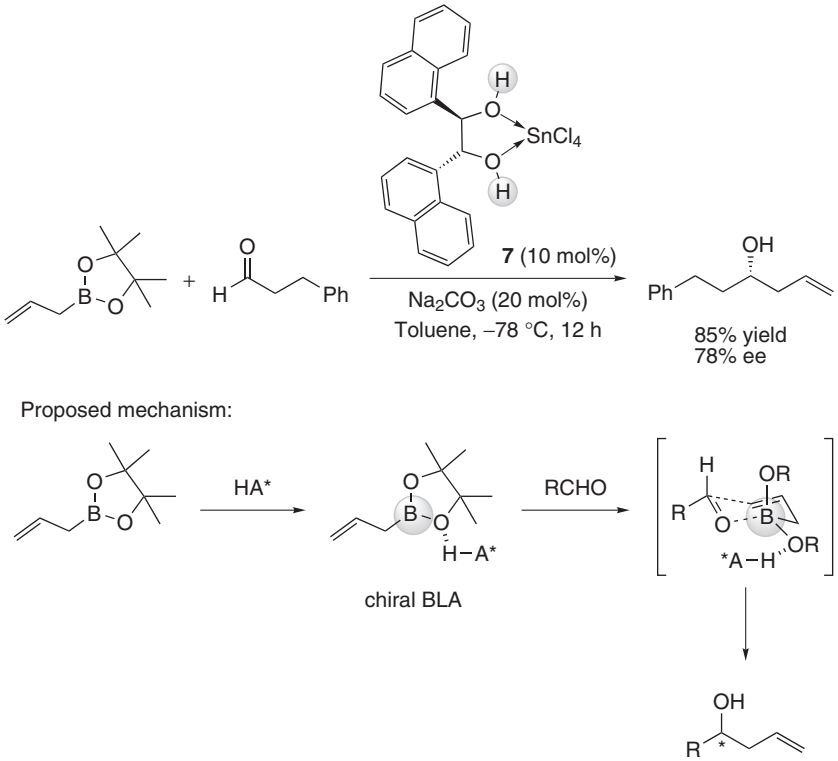
A highly practical enantioselective allylation of aldehyde or ketone-derived acrylhydrazones was developed by Leighton group in 2003 [14a] and 2004 [14b] (Scheme 1.11). The chiral allylsilane reagent (**8**) can be prepared easily in bulk and is stable to storage. Mechanistic studies have revealed that the acylhydrazone



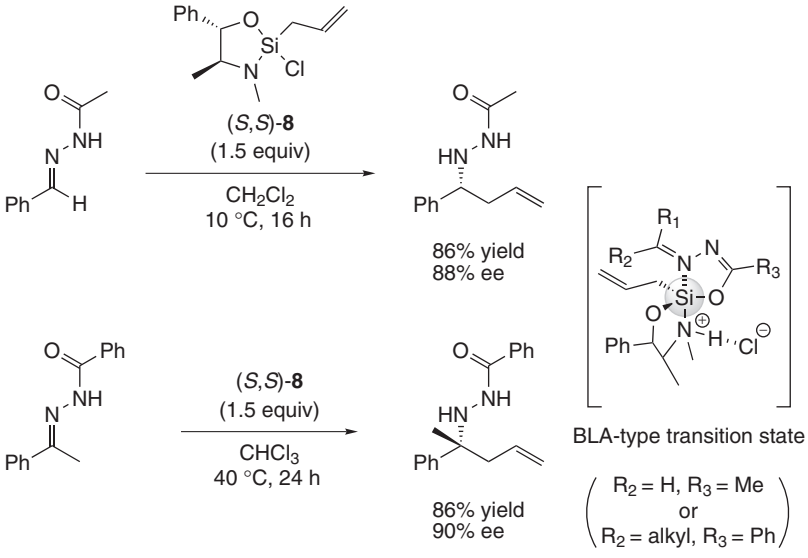
Scheme 1.9 Catalytic enantioselective allyl and crotylboration of ketones by Schaus group.

reactions operate by nucleophilic displacement of the chloride on the silicon center by the oxygen of the acylhydrazone. This reaction generates one equivalent of HCl, which protonates the amino group of the pseudoephedrine chiral controller, resulting in a significant increase in the Lewis acidity of the silicon center.

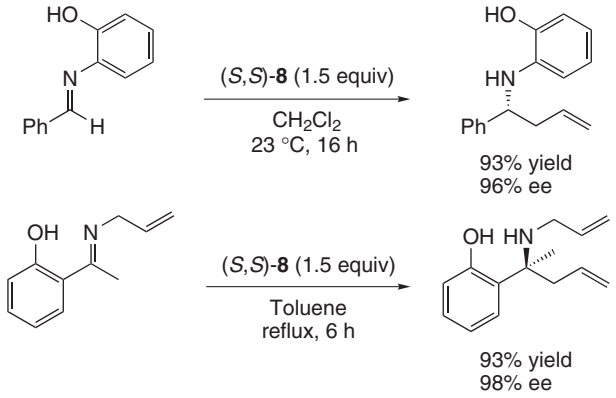
A similar enantioselective allylation and crotylation system was developed by Leighton group in 2006 (Schemes 1.12 [15] and 1.13 [16]). In these reactions,



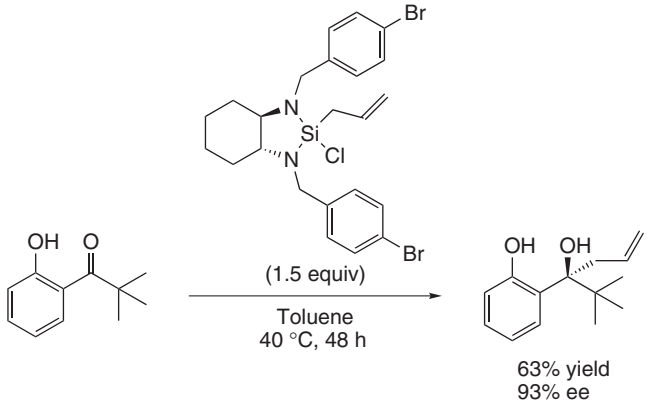
Scheme 1.10 Catalytic enantioselective allylboration of aldehydes by Hall and coworkers.



Scheme 1.11 Enantioselective allylation of acylhydrazones by Leighton and coworkers.



Scheme 1.12 Enantioselective allylation of phenol-derived imines by Leighton group.

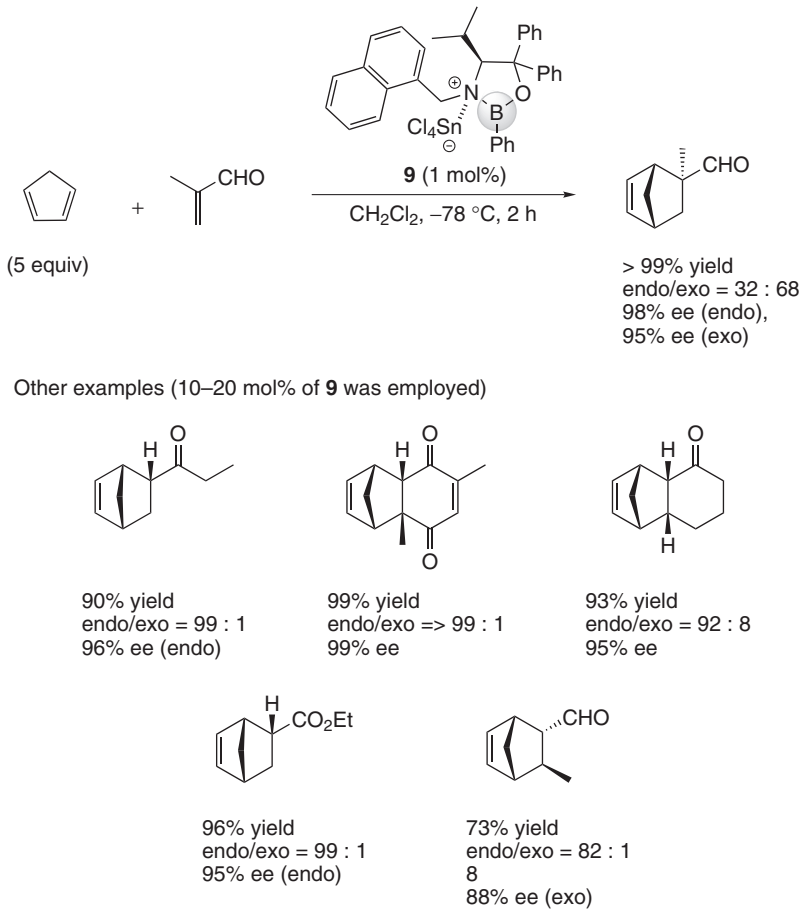


Scheme 1.13 Enantioselective allylation of phenol-derived ketones by Leighton group.

BLA-type transition states, similar to those discussed above, are likely to operate through the activation of the chiral allylsilane reagent by HCl generated after the nucleophilic displacement of the chloride by the phenolic oxygen atom.

1.1.2
Lewis Acid-Assisted Chiral Lewis Acid (LLA)

In 2005, Yamamoto group recognized that a new Lewis acid-assisted chiral Lewis acid (LLA, **9**), generated from the corresponding chiral oxazaborolidine and $SnCl_4$, is a highly reactive and enantioselective Diels–Alder catalyst for various classes of substrates (88–99% ee) (Scheme 1.14) [17]. Importantly, the enantioselectivity of Diels–Alder reactions can be preserved even in the presence of a large excess amount of $SnCl_4$, which implicates the high reactivity of the chiral LLA. Furthermore, this catalyst system is tolerant of a small amount of moisture, oxygen, and other Lewis bases without any significant loss of enantioselectivity.

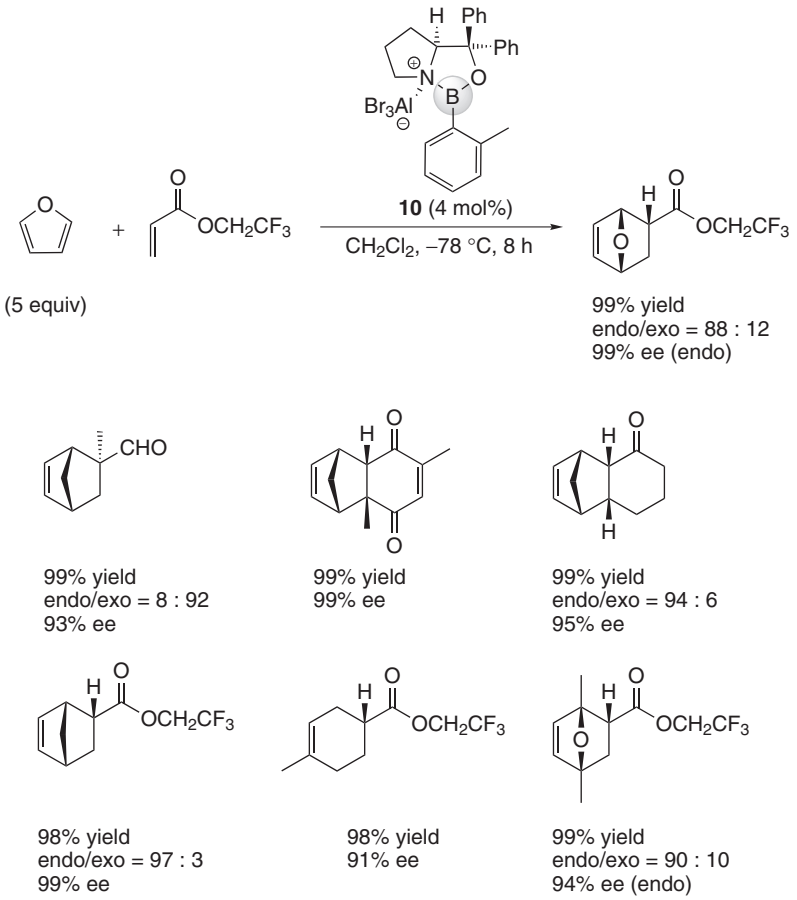


Scheme 1.14 Enantioselective Diels–Alder reactions catalyzed by LLA (**9**).

The plausible generation of chiral LLA (**9**) is considered to be analogous to that of the CBS reduction system [18–20] and Corey's chiral BLAs [3–9]. Thus, the coordination of the achiral Lewis acid to the nitrogen atom of the chiral oxazaborolidine should serve to increase the Lewis acidity of boron atom.

In 2007, Corey group has reinvestigated Lewis acid activation of the chiral oxazaborolidine (**1a**) instead of the use of the strong Brønsted acid triflimide, leading to the identification of $AlBr_3$-(**1a**) complex (**10**) as an unusually powerful and effective chiral Lewis acid catalyst for enantioselective Diels–Alder reactions (Scheme 1.15) [21].

Using the very strong Lewis acid $AlBr_3$, the complete complexation to form chiral LLA (**10**) was observed with 1 equivalent each of (**1a**) and $AlBr_3$ by ^1H NMR analysis. Excellent Diels–Alder conversions were generally observed with only 4 mol% of (**10**) using even less reactive substrates and the absolute configurations of the Diels–Alder adducts were consistent with the transition state model for the

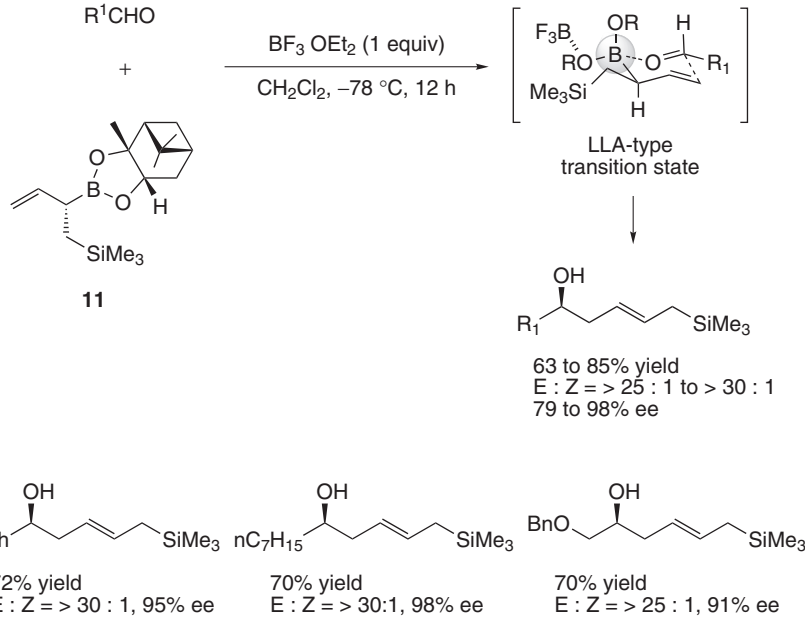


Scheme 1.15 Enantioselective Diels–Alder reactions catalyzed by LLA (**10**) derived from $AlBr_3$ and (**1a**).

triflimide-activated chiral BLA (**3a**). These data clearly indicate that LLA (**10**) is considerably more efficient than the corresponding BLA (**3a**) since 10–20 mol% of (**3a**) is generally required for the optimum results. The authors concluded that the greater turnover efficiency of LLA (**10**) may be the result of greater steric screening of the catalytic boron site by the adjacent $AlBr_3$ subunit and diminished product inhibition.

In 2007, Hall and coworkers have disclosed a new family of simple and efficient double allylating reagents of type (**11**) as stable bimetallic reagents for stereoselective allylation reaction of aldehydes (Scheme 1.16) [22].

Chiral hydroxyl-functionalized allylic silanes were obtained by the reaction of various aldehydes and chiral double allylating reagent (**11**) with high enantioselectivities (up to 98% ee) and excellent E/Z ratio ($> 25 : 1$ to $> 30 : 1$) using 1 equivalent of $BF_3{\bullet}OEt_2$ as a Lewis acid promoter. The resulting chiral allylic silanes can be



Scheme 1.16 Asymmetric allylation of aldehydes with a new double-allylation reagent (**11**).

further transformed to the various compound classes such as propionate units, polysubstituted furans, vinylcyclopropanes, and larger carbocycles. The authors proposed that the high degree of E/Z selectivity can be explained by an LLA-type transition state involving coordination of the Lewis acid BF_3•OEt_2 to a boronate oxygen as described in Scheme 1.16.

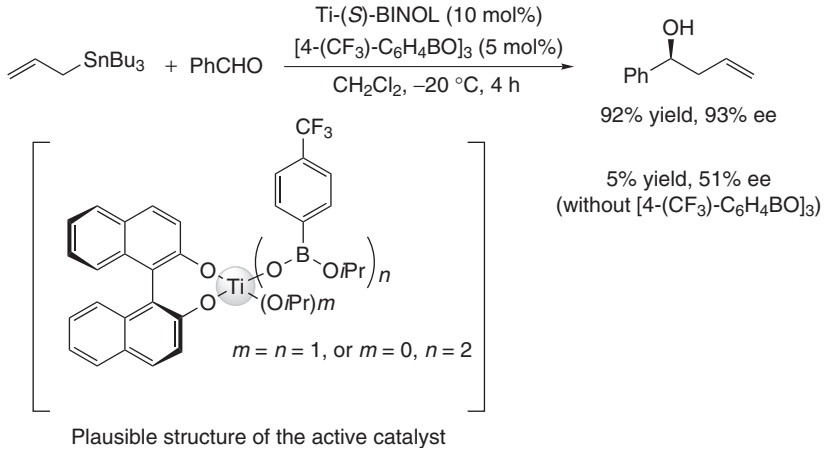
A Ti-BINOL based LLA system was developed for asymmetric allylation by Yamamoto group in 2004 (Scheme 1.17) [23]. Allylation reaction of benzaldehyde with allyltributyltin has been found to be dramatically accelerated by addition of 5 mol% of 4-(trifluoromethyl)boroxine to Ti-(*S*)-BINOL catalyst.

It is important to note that both reactivity and enantioselectivity increased with addition of this boron Lewis acid, demonstrating the power of LLA system. This result can be attributed to the enhancement of Lewis acidity of titanium by coordination of boron to the oxygen atom of BINOL as in the proposed structure of the active catalyst.

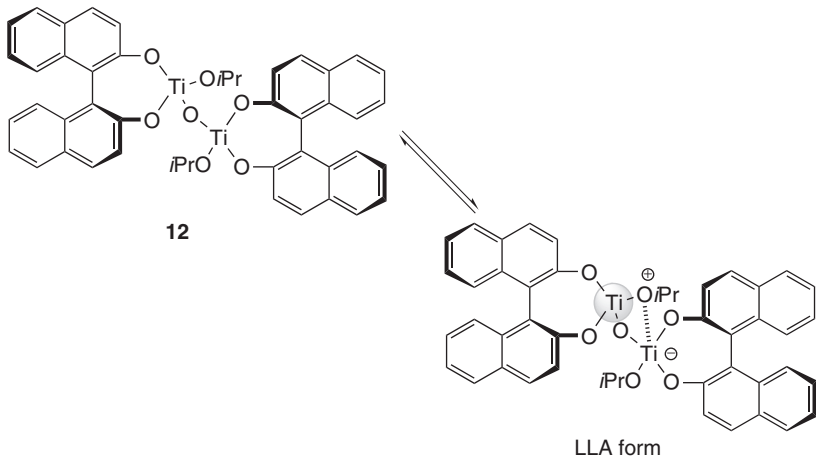
Maruoka's chiral bis-titanium Lewis acid (**12**) [24] can be regarded as an excellent example of chiral LLA. In this catalytic system, it is proposed that the Lewis acidity of one titanium center might be enhanced by the intramolecular coordination of the oxygen atom of isoproxy group to the other titanium (Scheme 1.18).

Following the first report of catalytic enantioselective allylation reactions with (**12**) by Maruoka group in 2003 [24a], the synthetic utility of this type of chiral LLA was recently broadened.

In 2005, Maruoka and coworkers reported asymmetric 1,3-dipolar cycloaddition reaction of nitrones and acrolein catalyzed by (**12**) (Scheme 1.19) [24c].



Scheme 1.17 Enantioselective allylation of aldehydes catalyzed by Ti-BINOL-Boroxine combined system.

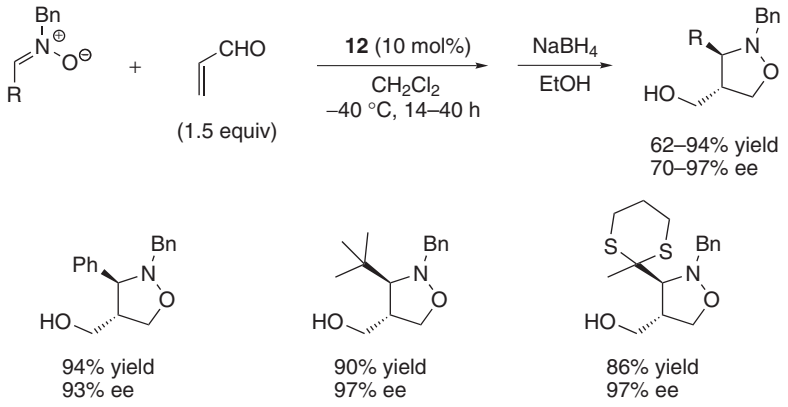


Scheme 1.18 Plausible formation of LLA species from chiral bis-titanium Lewis acid (**12**).

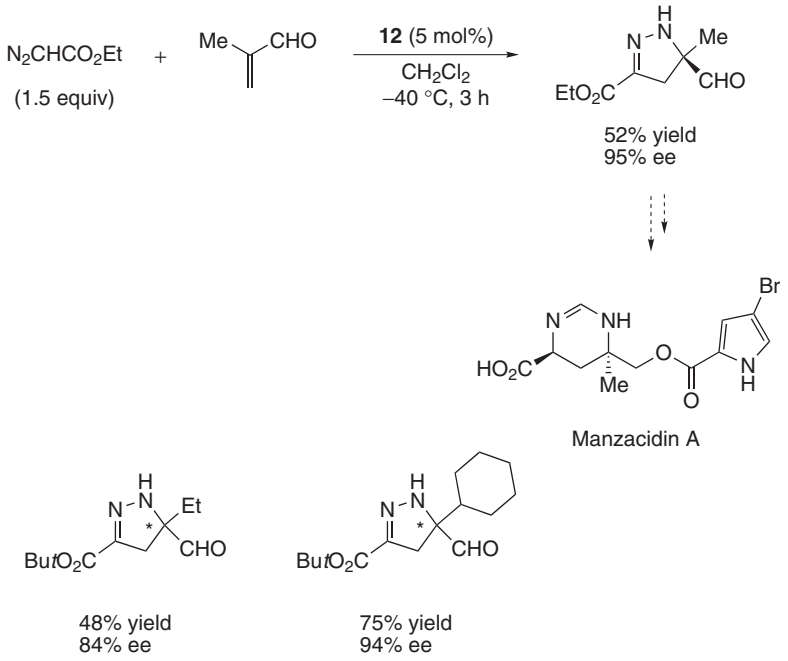
The reactions of various aryl-substituted nitrones and sterically hindered alkyl-substituted nitrones with 10 mol% of (**12**) as a chiral Lewis acid provided the corresponding chiral isoxazolidines with high to excellent enantioselectivities (70–97% ee).

Noteworthy is the fact that the use of Ti(IV)-(*S*)-BINOL complexes resulted in low yields with moderate enantioselectivities, implicating the importance of enhanced Lewis acidity in chiral bis-titanium catalyst (**12**).

Subsequently, Maruoka group developed an enantioselective 1,3-dipolar cycloaddition reaction between diazoacetates and α-substituted acroleins (Scheme 1.20) [24d]. The reactions of 1.5 equivalent of ethyl or *tert*-butyl diazoacetate and various α-substituted acrolein derivatives afford chiral 2-pyrazolines with high



Scheme 1.19 Enantioselective 1,3-dipolar cycloaddition reactions of nitrones catalyzed by chiral bis-titanium catalyst (**12**).

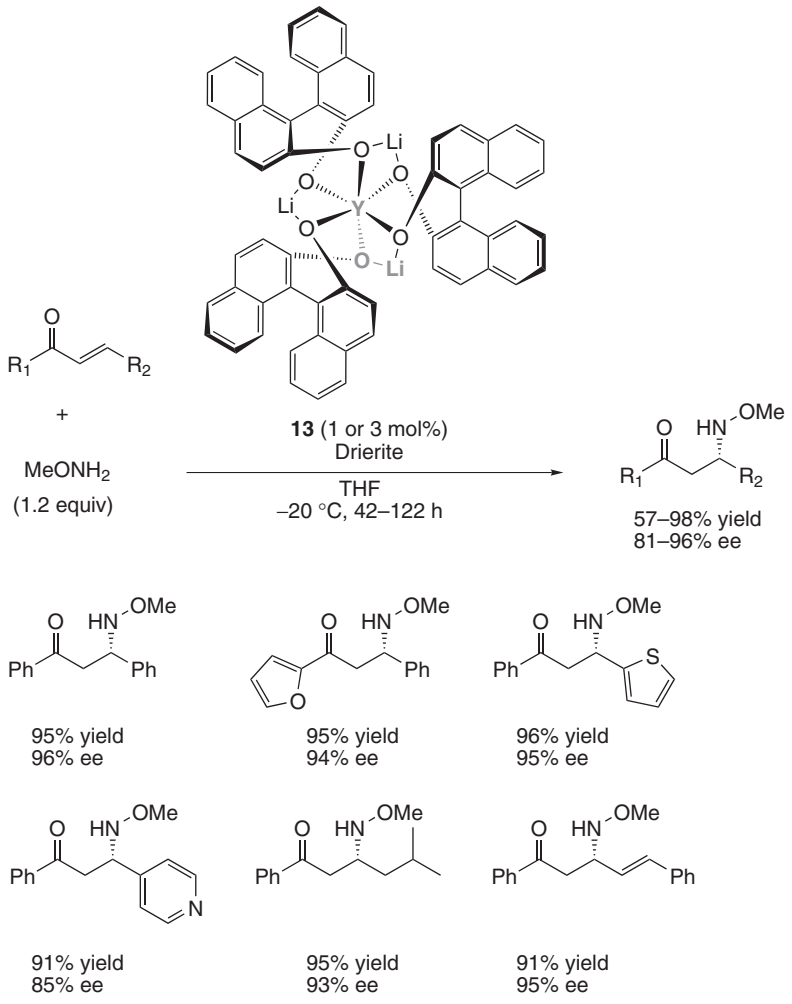


Scheme 1.20 Enantioselective 1,3-dipolar cycloaddition reactions of diazoacetates catalyzed by (**12**).

enantioselectivities with 5 mol% of (**12**) as a chiral Lewis acid (84–94% ee). Interestingly, possible side reactions such as 1,2- and 1,4-addition of diazoacetates to α-substituted acroleins or cyclopropanation were somewhat suppressed under these reaction conditions.

The synthetic utility of this methodology has been demonstrated by the short enantioselective total synthesis of manzacidin A in five steps, starting from commercially available methacrolein and ethyl diazoacetate.

Related to the concept of Lewis acid-assisted chiral Lewis acid, Shibasaki and coworkers demonstrated the concept of 'Lewis acid-Lewis acid cooperative catalysis' through the development of highly enantioselective aza-Michael reactions of methoxyamine catalyzed by (*S*,*S*,*S*)-YLi_3tris(binaphthoxide) (YLB) complex (**13**) (Scheme 1.21) [25a,b].



Scheme 1.21 Enantioselective aza-Michael reactions catalyzed by YLB (**13**).

The working hypothesis of 'Lewis acid-Lewis acid cooperative catalysis' is proposed by the authors as described in Figure 1.2.

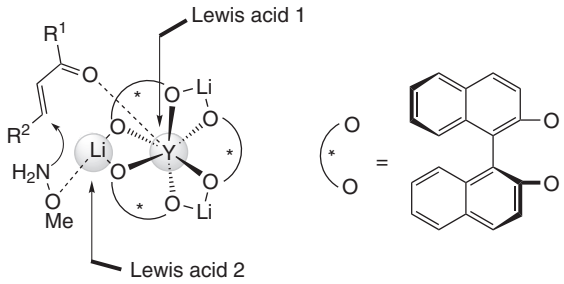
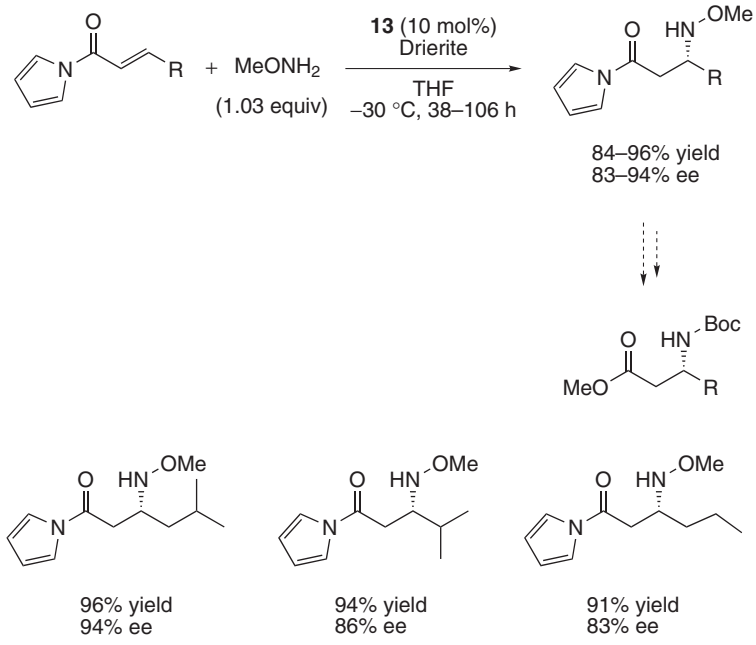


Fig. 1.2 Proposed working model of Lewis acid-Lewis acid cooperative catalysis using YLB (**13**).

The authors hypothesized that two Lewis acidic centers in YLB complex (Y and Li) work cooperatively to control the orientations of both the electrophile and the nucleophile, leading to the highly organized transition state to give rise to high enantioselectivity (Figure 1.2). This hypothesis has been proved by a series of detailed mechanistic studies and the effectiveness of this concept is clear from the excellent results in Scheme 1.21.

In a subsequent study, the synthetic utility of this methodology has been broadened by the use of α, β-unsaturated *N*-acylpyrroles as substrates (Scheme 1.22) [25b].

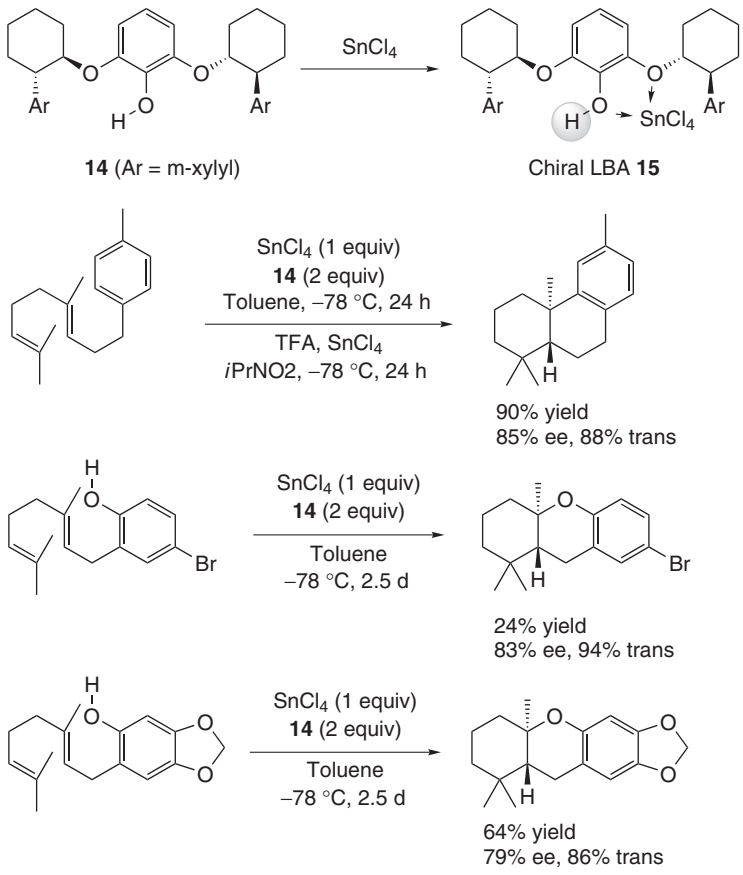
The resulting 1,4-adducts have been successfully transformed into important chiral building blocks, including chiral β-amino acid derivatives.



Scheme 1.22 Enantioselective aza-Michael reactions of *N*-acylpyrroles catalyzed by YLB (**13**).

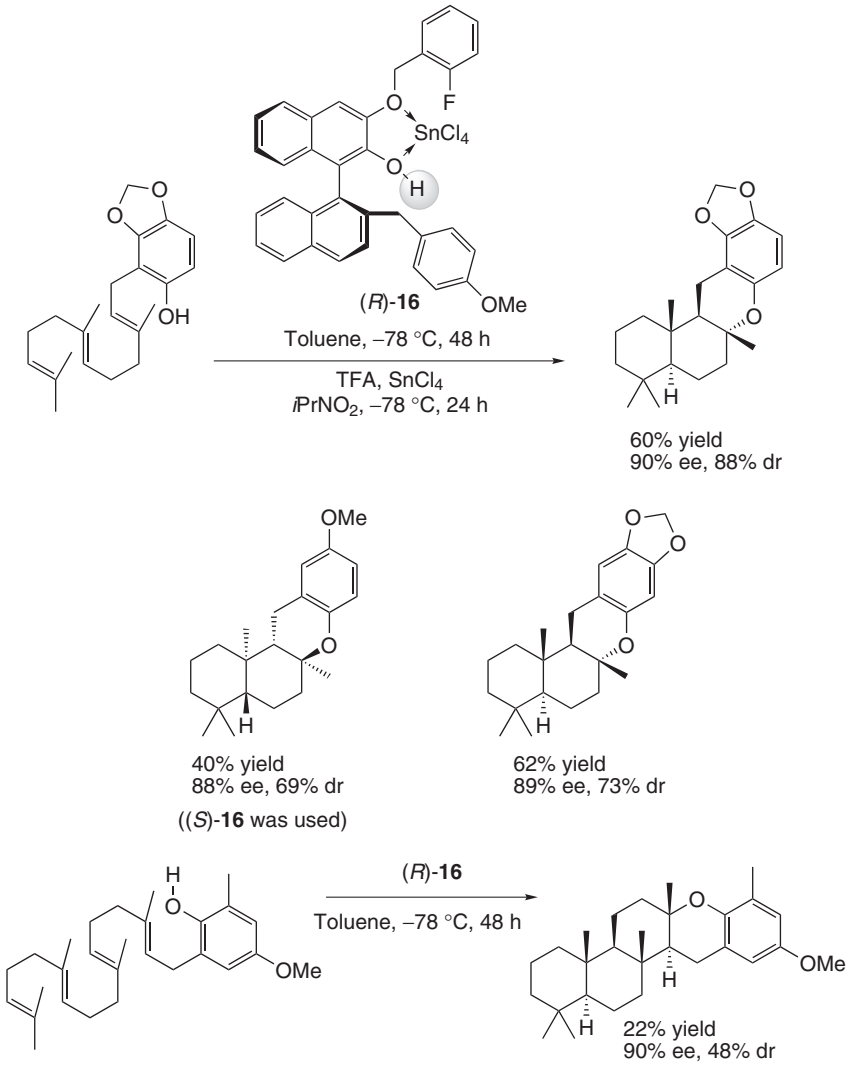
1.1.3
Lewis Acid-Assisted Chiral Brønsted Acid (LBA)

Chiral pyrogallol (**14**) derived LBA (**15**) was developed for enantioselective polyene cyclization reaction as an 'artificial cyclase' by Yamamoto, Ishihara and coworkers in 2004 (Scheme 1.23) [26]. Various tricyclic skeletons have been synthesized with good enantioselectivities (79–85% ee) in the presence of chiral LBA (**15**).



Scheme 1.23 $SnCl_4$-chiral pyrogallol complex (**15**) as a new LBA for enantioselective polyene cyclization.

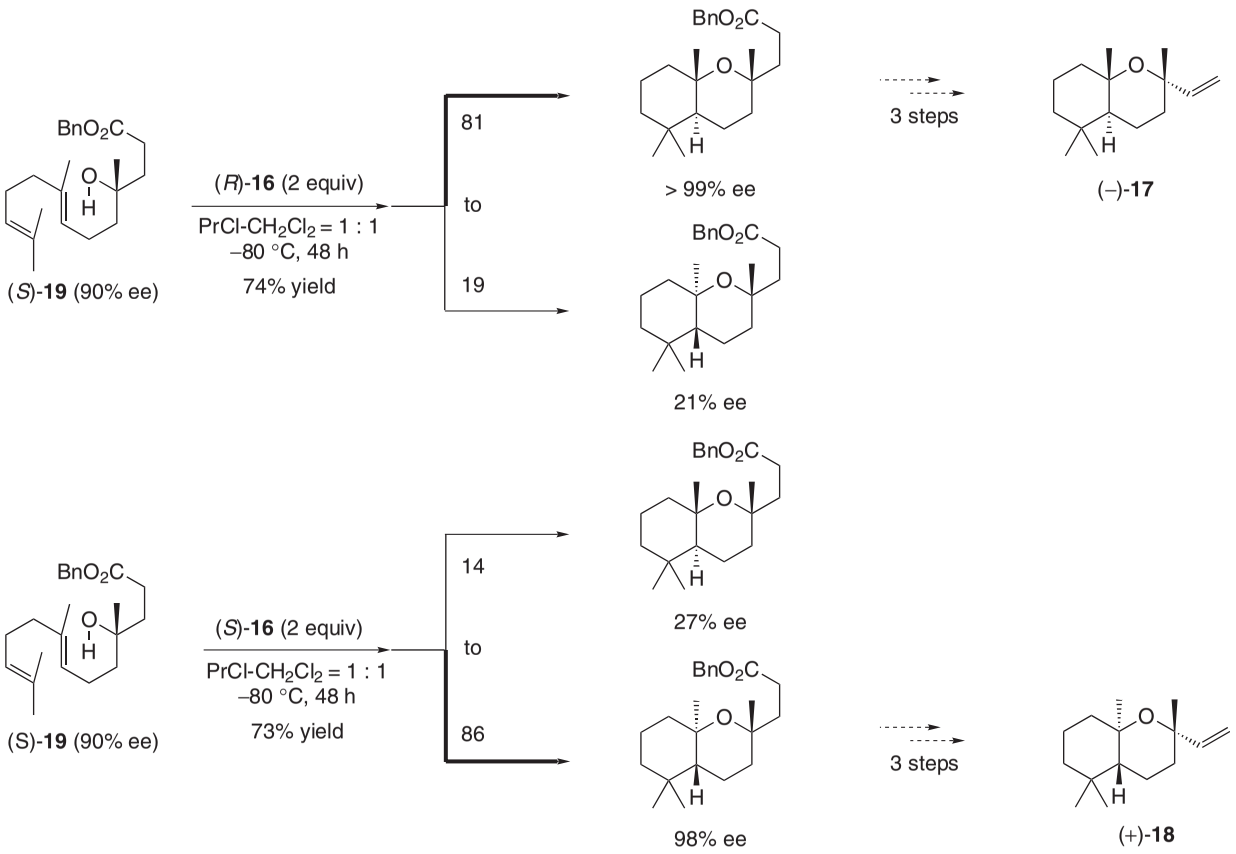
Chiral catechol-derived LBA (**16**) was devised as a new artificial cyclase for polyprenoids by the same group in 2004 (Scheme 1.24) [27]. The synthetic power of the new chiral LBA (**16**) has been well demonstrated by enantioselective cyclizations of various 2-(polyprenyl)phenol derivatives with good to excellent enantioselectivities (88–90% ee), leading to the efficient asymmetric syntheses of (−)-chromazonarol, (+)-8-epi-puupehedione, and (−)-11′-deoxytaondiol methyl ether.



Scheme 1.24 $SnCl_4$-chiral catechol complex (**16**) as a new LBA for enantioselective synthesis of polyprenoids.

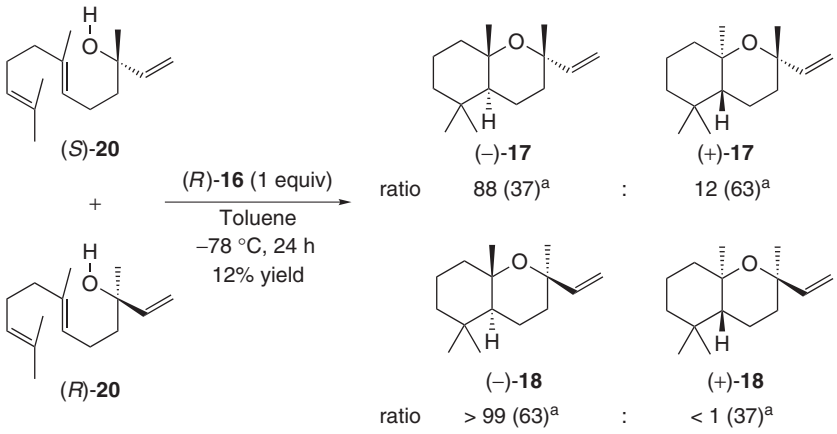
Subsequent study revealed that the chiral LBA (**16**) can be used as artificial cyclases for the asymmetric syntheses of (−)-caparrapi oxide (**17**) and (+)-8-epicaparrapi oxide (**18**) [28a,b]. (**17**) and (**18**) can be diastereoselectively synthesized from (*S*)-(**19**) (prepared in three steps from commercially available farnesol) by reagent control of (*R*)-**16** and (*S*)-**16**, respectively, regardless of the chirality of (*S*)-**19** (Scheme 1.25).

In addition, (−)-(**17**) can be obtained directly from (*S*)-**20** by reagent control of (*R*)-LBA **16** overcoming the substrate control, while (−)-**18** can be synthesized directly from (*R*)-**20** by the double asymmetric induction (both the reagent control



Scheme 1.25 Reagent-controlled diastereoselective polyene cyclization of (*S*)-**19** promoted by (*R*) or (*S*)-**16**.

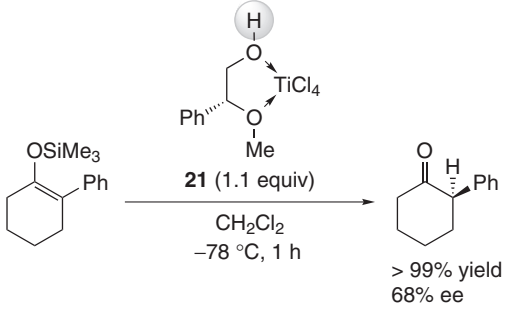
by (*R*)-LBA (**16**) and the substrate control) in the diastereoselective polyene cyclization of racemic (**20**) (Scheme 1.26) [28a,b]. Although the total sequence for the asymmetric synthesis of (−)-(**17**) is the shortest, the reaction gave only 12% yield of inseparable mixture of four products.



[a] 2-methoxyphenol–$SnCl_4$ complex was used as an achiral LBA.

Scheme 1.26 Diastereoselective polyene cyclization of racemic nerolidol (**20**) promoted by (*R*)-(**16**).

A highly reactive chiral LBA (**21**) was prepared from $TiCl_4$ and (*R*)-2-phenyl-2-methoxyethanol for enantioselective protonation of silyl enol ether by Yamamoto group in 2006 (Scheme 1.27) [29]. It is interesting to note that the enantioselectivity of the product strongly depends on the preparation conditions of chiral LBA. The authors found that relatively high reaction temperature (0 °C, 30 minutes) is required to get the optimal enantioselectivity owing to the insufficient generation of the chiral LBA complex (**21**) caused by the strong aggregation of $TiCl_4$.



Scheme 1.27 $TiCl_4$-(*R*)-2-phenyl-2-methoxyethanol complex (**21**) as a new LBA for enantioselective protonation.

1.1.4
Brønsted Acid-Assisted Chiral Brønsted Acid (BBA)

Since the first discovery of the enantioselective catalysis through hydrogen bond activation by Rawal group in 2003 [30a], TADDOL (Figure 1.3) has represented a 'privileged' chiral scaffold for this type of asymmetric catalysis [31]. In addition, TADDOL can be regarded as Brønsted acid-assisted chiral Brønsted acid (BBA) by virtue of its intramolecular hydrogen bonding ability as shown in Figure 1.3.

As further applications of their concept of 'hydrogen bond catalysis', Rawal and coworkers demonstrated the use of hydrogen bonding catalysis in enantioselective vinylogous Mukaiyama aldol reactions in 2005 (Scheme 1.28) [30c]. The reaction of the silyldienol ether (**23**) and a range of reactive aldehydes proceeds regiospecifically

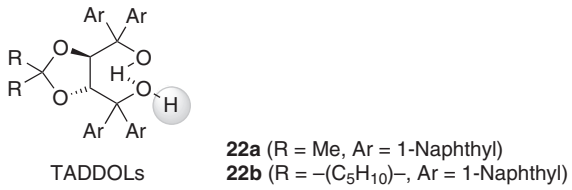
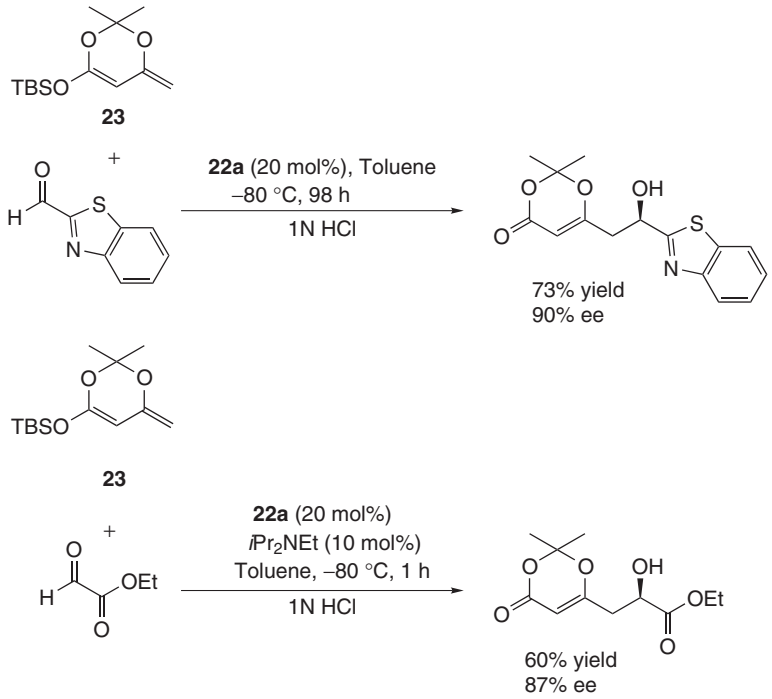


Fig. 1.3 Representative structures of TADDOL.

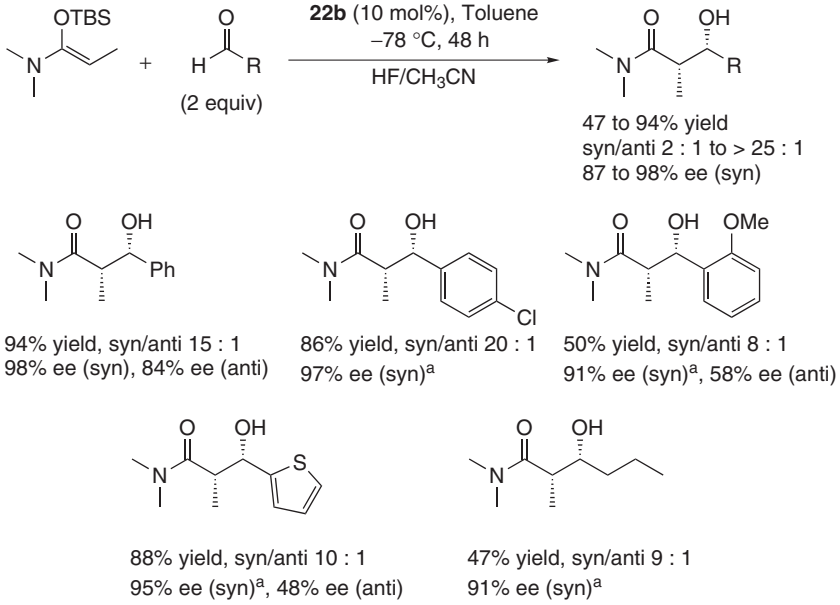


Scheme 1.28 Enantioselective vinylogous Mukaiyama aldol reactions catalyzed by TADDOL (**22a**).

using 20 mol% of TADDOL (**22a**), affording the addition products in good yield with moderate to high enantiomeric excess (up to 90% ee).

Subsequently, Rawal group disclosed the hydrogen bond catalysis of highly diastereo- and enantioselective Mukaiyama aldol reactions of *O*-silyl-*N,O*-ketene acetals by the use of TADDOL (**22b**) as a catalyst (Scheme 1.29) [30d]. The reaction is effective for a range of aldehydes and affords the corresponding adducts in synthetically useful yields with excellent enantioselectivities (up to 98% ee).

In this study, the authors have succeeded in obtaining the first crystal structure of a complex between a racemic TADDOL (**22a**) and *p*-anisaldehyde. The X-ray structure analysis clearly indicated the formation of BBA through intramolecular hydrogen bonding between the two hydroxyl groups and a single point activation of the carbonyl group through intermolecular hydrogen bonding, thus confirming the proposed mode of activation of the carbonyl group by TADDOL (Figure 1.4).



[a] The absolute configuration of the product was assigned by analogy.

Scheme 1.29 Enantioselective Mukaiyama aldol reactions catalyzed by TADDOL (**22b**).

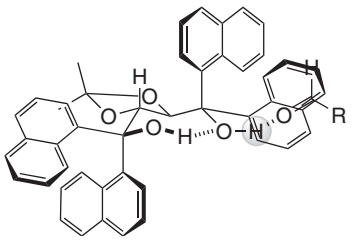
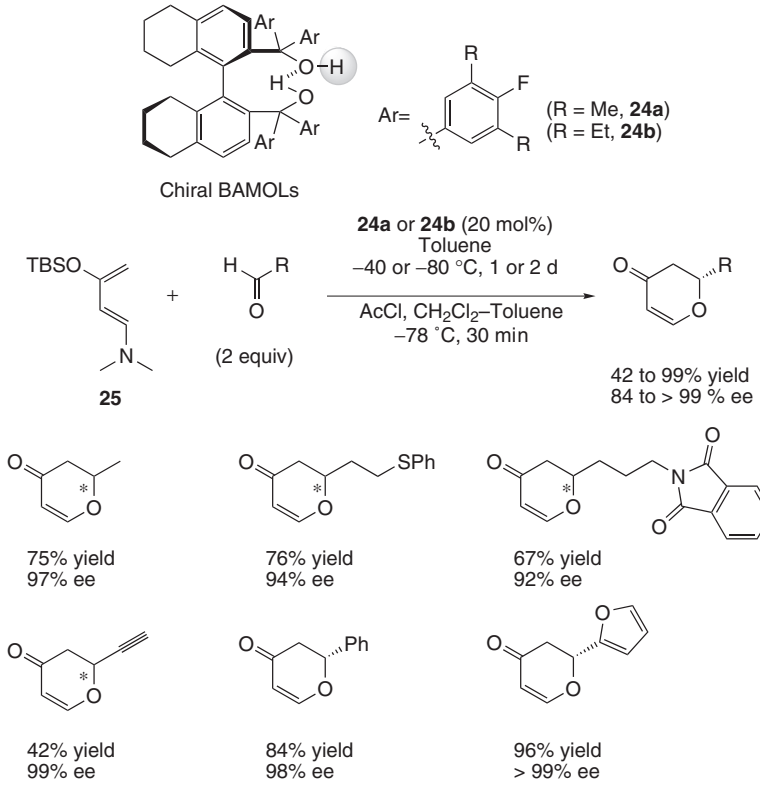


Fig. 1.4 Proposed mode of activation of the carbonyl group by TADDOL.

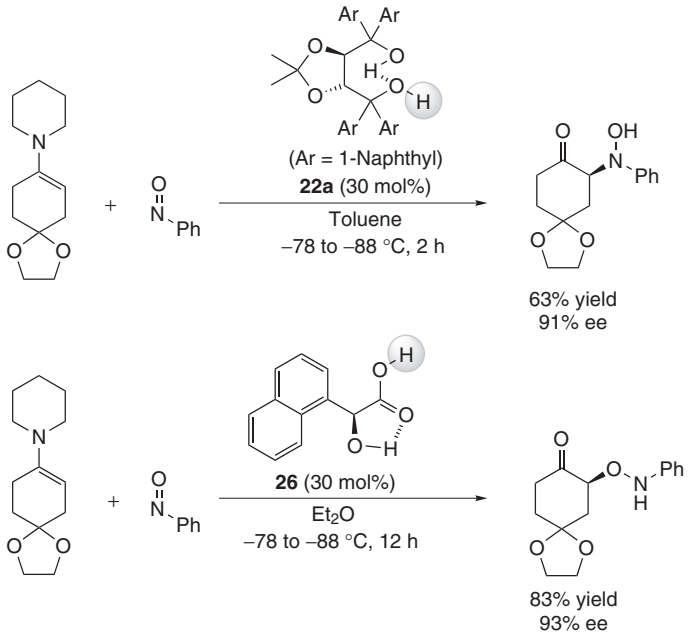


Scheme 1.30 Enantioselective hetero Diels–Alder reactions catalyzed by chiral BAMOLs.

Again, the intramolecular hydrogen bonding in TADDOL plays an important role not only to increase Brønsted acidity of the free alcoholic proton for the effective activation of the carbonyl group, but also to keep well-organized chiral scaffold.

In 2005, Yamamoto, Rawal and coworkers reported that axially chiral 1,1′-biaryl-2,2′-dimethanol (BAMOL) family of diols (**24a**) and (**24b**) is a highly effective catalyst for enantioselective hetero Diels–Alder reactions between aminosiloxydiene (**25**) and a wide variety of unactivated aldehydes (Scheme 1.30) [32]. The reactions proceed in useful yields and excellent enantioselectivities (84 to > 99% ee). The diols function in the same capacity as Lewis acids, by activating the aldehyde carbonyl group through hydrogen bonding. A similar mode of activation of the carbonyl group with TADDOL was indicated by the X-ray structure analysis of 1 : 1 complex of the related BAMOL derivative and benzaldehyde, suggesting the formation of BBA through intramolecular hydrogen bonding between the two hydroxyl groups and a single point activation of the carbonyl group through intermolecular hydrogen bonding.

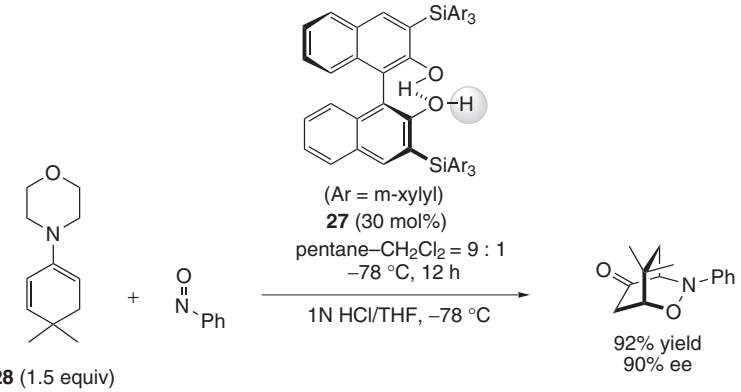
In 2005, Yamamoto group developed Brønsted acid catalysis of achiral enamines for regio- and enantioselective nitroso aldol synthesis (Scheme 1.31) [33]. The exclusive formation of a single regioisomer (*N*-adduct or *O*-adduct) has been



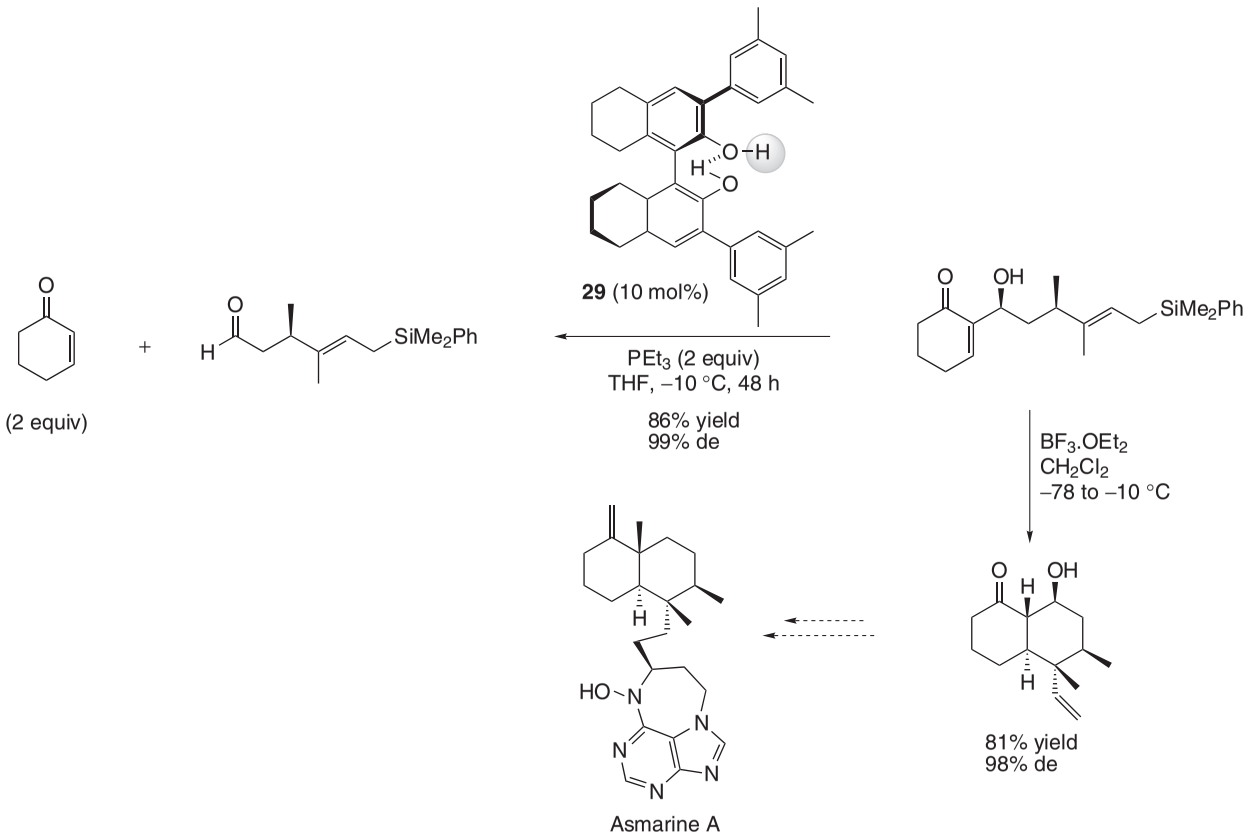
Scheme 1.31 Regioselective synthesis of *N*- or *O*-adduct in enantioselective 'Nitroso aldol' reactions.

achieved simply by the choice of chiral Brønsted acid catalysts with high enantioselectivities. Although the rationale for the regioselectivity is still unclear, the possible generation of BBAs through intramolecular hydrogen bonding was proposed to explain high enantioselectivities in both processes by the authors.

Yamamoto group subsequently reported diastereo- and enantioselective synthesis of 2-oxo-3-azabicycloketones catalyzed by chiral Brønsted acid (**27**) (Scheme 1.32) [34]. The reaction of dienamine (**28**) and nitrosobenzene proceeded in high yield



Scheme 1.32 Enantioselective bicycloketone synthesis with achiral dienamines catalyzed by (**27**).



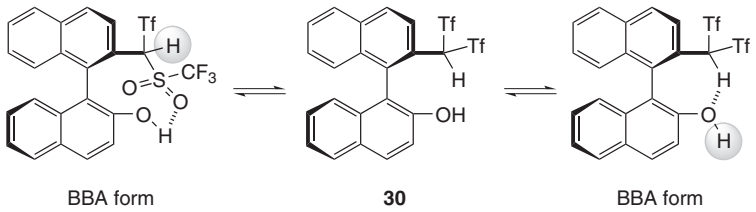
Scheme 1.33 Asymmetric Morita–Baylis–Hillman reaction/Lewis acid promoted annulation reaction for the synthesis of Clerodane decalin core.

with excellent enantioselectivity in the presence of 30 mol% of chiral BINOL derivative (**27**). The authors proposed that the BBA form of (**27**) is responsible for the active catalyst in this system and the reaction proceeds in a stepwise fashion initiated with *N*-nitroso aldol reaction, followed by Michael addition of the resulting anionic oxygen atom.

Schaus and coworkers have developed a general route to the Clerodane diterpene core by the use of previously developed Brønsted acid catalyzed asymmetric Morita–Baylis–Hillman (MBH) reaction/Lewis acid mediated ring-annulation process (Scheme 1.33) [31]. Excellent diastereoselectivity was achieved in the key MBH reaction in the presence of 10 mol% of the chiral BINOL derivative (**29**), affording the key intermediate for the synthesis of Clerodane decalin core.

A similar mode of activation of the carbonyl group through BBA system may be expected for this reaction since two hydroxyl groups are crucial to obtain high yield and enantioselectivity.

A new type of Brønsted acid-assisted chiral Brønsted acid (chiral BBA) catalyst (**30**) possessing a bis(triflyl)methyl group was developed for enantioselective Mannich-type reaction by Yamamoto, Ishihara and coworkers [35]. The authors proposed the two possible chiral BBA form generated through intramolecular hydrogen bonding as shown in Scheme 1.34.



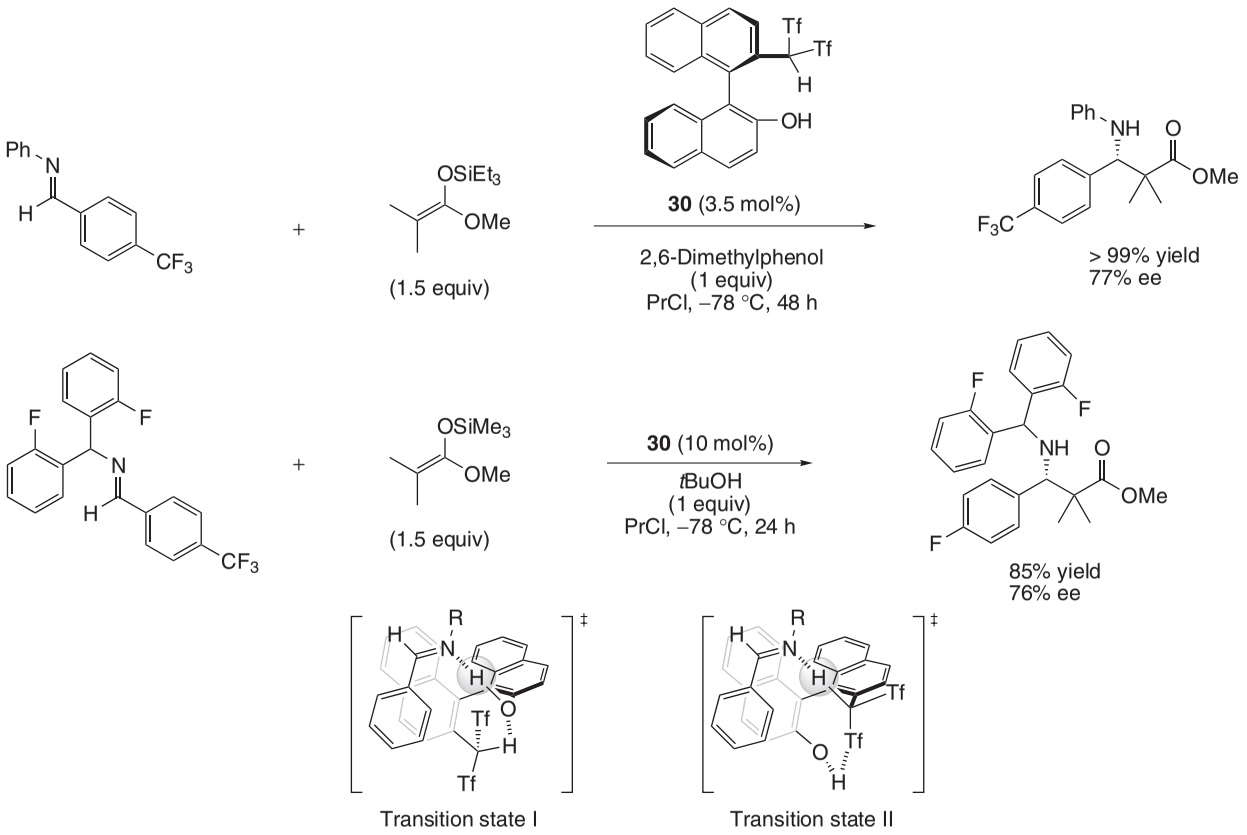
Scheme 1.34 Possible formations of chiral BBAs from (**30**) through intramolecular hydrogen bonding.

Chiral BBA (**30**) has been shown to be effective as a Brønsted acid catalyst for Mannich-type reaction of ketene silyl acetals and aldimines and good enantioselectivity was observed (up to 77% ee) using 3.5 or 10 mol% of chiral BBA (**30**) (Scheme 1.35).

It is important to note that a stoichiometric use of the achiral proton source is crucial to obtain high enantioselectivity for this catalytic system to scavenge a cationic silicon species. The authors proposed two plausible transition states for each BBA form (Scheme 1.35). As in the case of TADDOL, BBA formation should lead to high enantioselectivity by virtue of their well-organized chiral cavities.

1.2
Super Brønsted Acid Catalyst

Acidity of organic compounds is affected by structural features. For example, March's Advanced Organic Chemistry (fifth edition) summarizes major effects



Scheme 1.35 Enantioselective Mannich-type reactions catalyzed by chiral BBA (**30**).

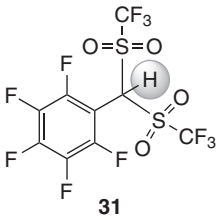


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Fig. 1.5 Pentafluorophenyl bis(triflyl)methane as a super Brønsted acid.

that influence the acid strength as follows [36]: (i) field effect, (ii) resonance effect, (iii) periodic table correlations, (iv) statistical effect, (v) hydrogen bonding, and (vi) steric effect.

Basically, the acidity of the compound AH increases by stronger stabilizing interaction with A^- and for this reason, TfOH, Tf_2NH, and Tf_3CH are a nice set of acid catalysts. Thus, we can expect better reactivity by choosing more electron-withdrawing and/or nice resonance stabilizing A^- for acid catalysis. For example, our previously developed pentafluorophenyl bis(triflyl)methane (Figure 1.5) was shown to be an excellent super Brønsted acid catalysis for a number of organic transformations [37]. In this example, the high reactivity of the catalyst may come not only from the inductive effects of two Tf and a C_6F_5 group but also from a relatively large resonance effect.

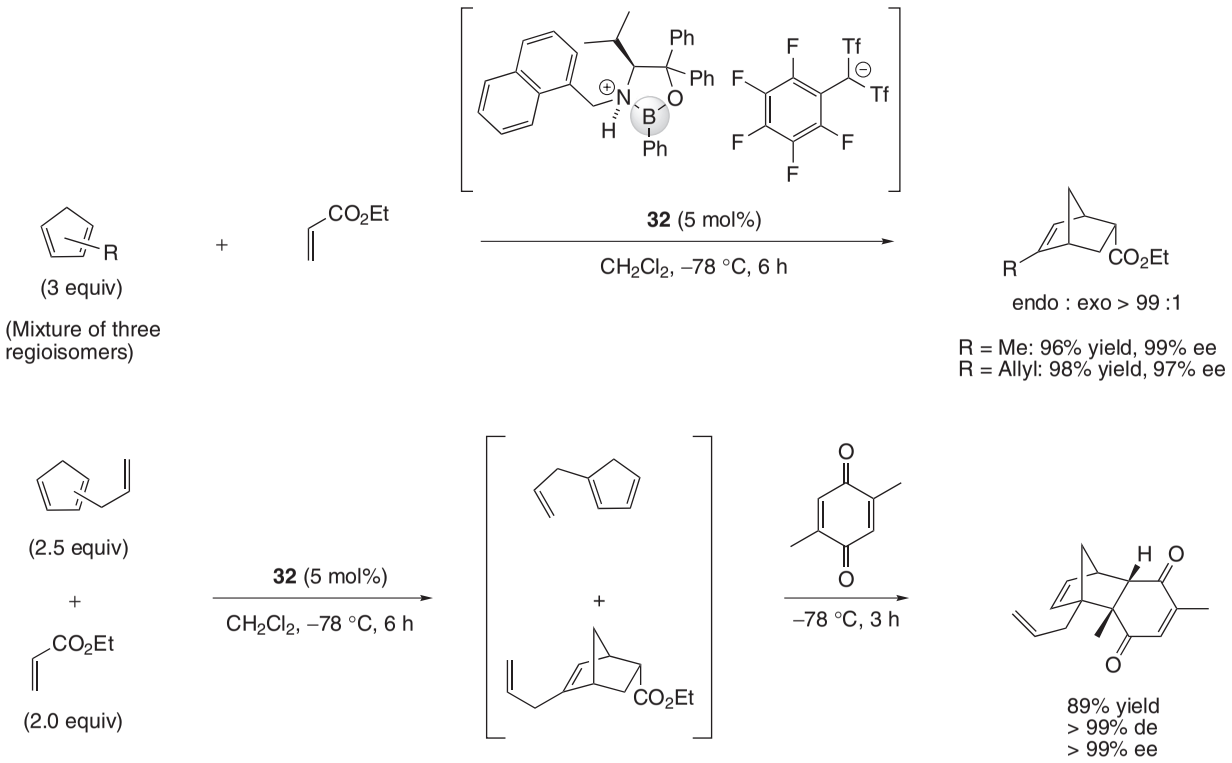
1.3
Combined Super Brønsted Acid and Lewis Acid System

Combination of super Brønsted acid with simple Brønsted acid or Lewis acid would be a new system for acid catalysis in organic synthesis. The example of super BLA would be an interesting tool for selective organic transformations. We have already shown excellent examples in Scheme 1.3 using the Tf_2NH–chiral Lewis acid combined system. Scheme 1.36 exemplifies some additional recent reactions based on pentafluorophenyl bis(triflyl)methane and chiral Lewis acid catalyst [38].

1.4
Conclusion

In recent years, the power of designer acid catalysis has greatly increased as a result of the development of catalytic enantioselective versions, as described herein. Yet it is likely that there is much more to learn with regard to new reactivity. The concept of 'combined acid catalysis' is still very much in a state of infancy and detailed mechanistic study of the true nature of this type of catalysis is required.

Since the introduction of our review article of combined acid catalysis in 2005 [2], this concept has clearly continued to interpenetrate the area of asymmetric catalysis and rapidly evolving, as is apparent from the summary described herein.



Scheme 1.36 Super BLA for selective Diels–Alder reaction.

The ultimate goal is to apparently develop a more reactive, more selective, and more versatile catalyst. We believe that the realization of such an objective would be a tremendous benefit for the development of organic synthesis including green chemistry.

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