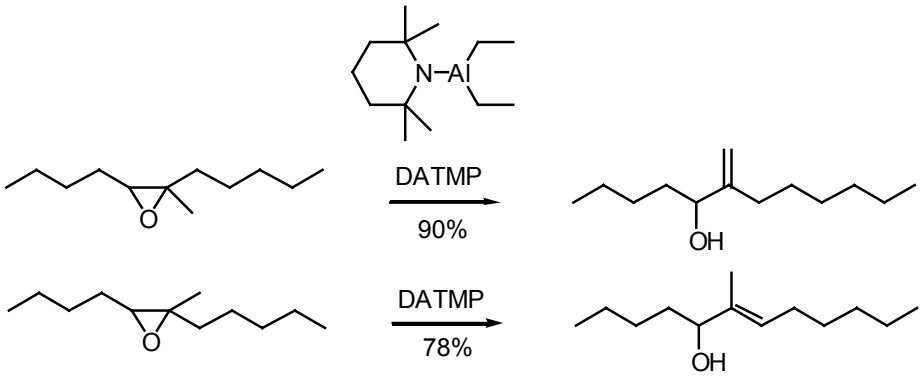
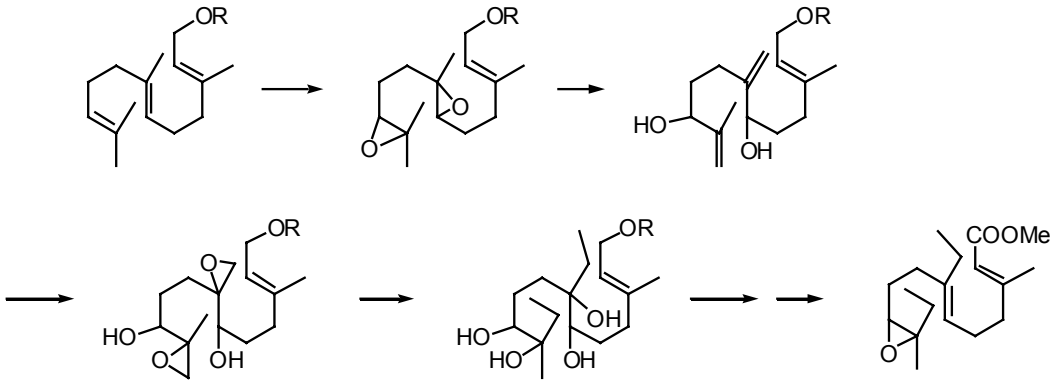
Chapter 1 Organoaluminum Reagents for Selective Organic Transformation

1.1. Epoxide – Allylic Alcohol Rearrangement

The reaction of epoxides with a strong base constitutes a well-known synthetic method for the preparation of allylic alcohols. In his early days at Kyoto, Yamamoto demonstrated the reaction proceeded stereo- and regioselectively with organoaluminum amides [29].

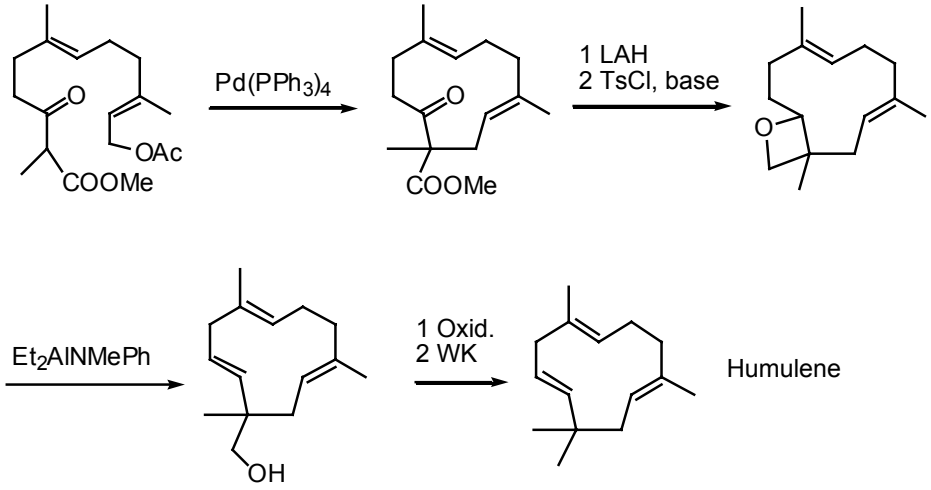


The method was used for his straightforward synthesis of trans-α-farnesene and juvenile hormone from farnesol [26].



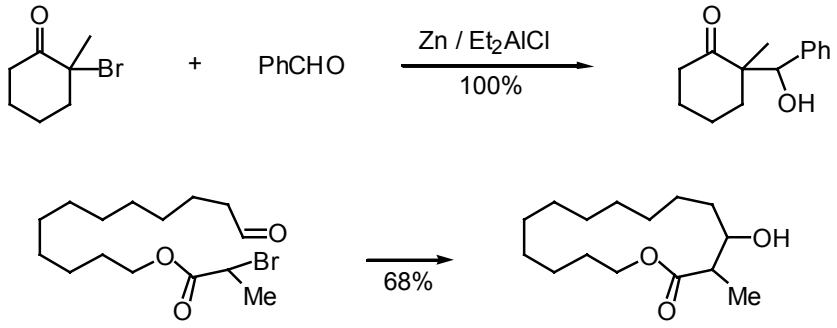
Cecropia juvenile hormone

In 1974, Yamamoto synthesized humulene in a highly stereoselective manner. This is the first example of palladium catalyzed medium ring cyclization. Another key step of the synthesis is the base catalyzed elimination of oxetane, a similar transformation using aluminum amide reagent to that described above [39].



1.2. Aldol Synthesis

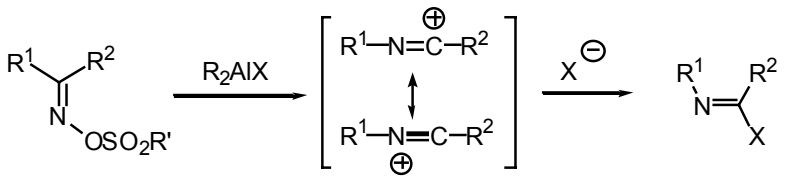
Complexes of organoaluminum compounds and ketones led to a variety of reactions. An example is the reaction of haloketone and aldehyde developed by Yamamoto. The critical part of the process is the coupled attack of the α-haloketone by diakylakuminum chloride and zinc dust which generates an aluminum enolate regioselectively. The method was used for short synthesis of medium and large ring compounds [43].



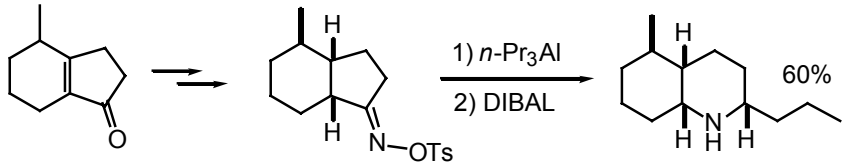
1.3. Beckmann Rearrangement Using Organoaluminum Reagent

The Beckmann rearrangement is the skeletal rearrangement of ketoximes in the presence of certain acids under aqueous conditions to give amides or lactams. Reexamination of this reaction using organoaluminum reagents under aprotic conditions led to the abstraction of the sulfonyl group, followed by capture of the intermediary iminocarbocation or alkylidyneammonium ion with the nucleophilic group (X; R_2AlX (X = R, SR', SeR')) on the aluminum. Thus, aluminum reagents act not only as a

Lewis acid but also as a base [73].

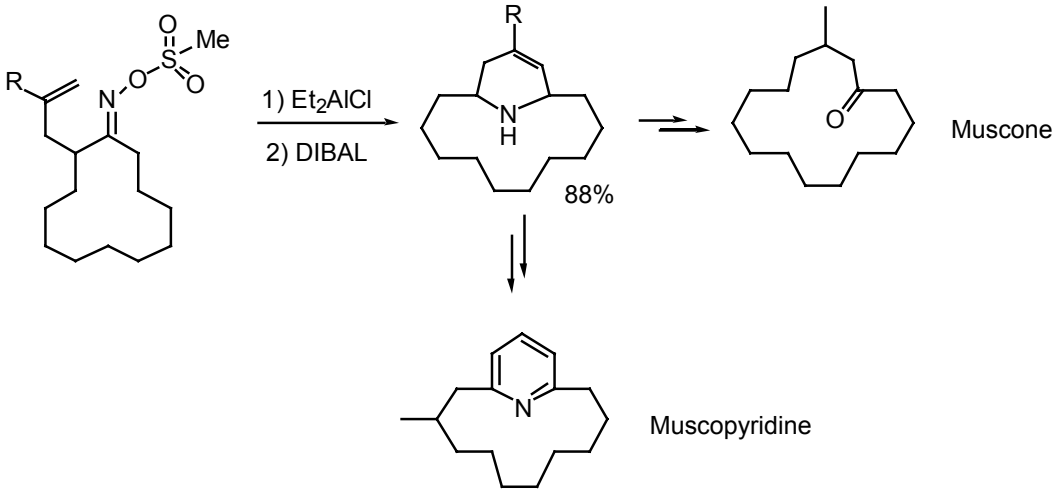


This method opens a new synthetic entry to a variety of alkaloides such as Pumiliotoxin C [60].



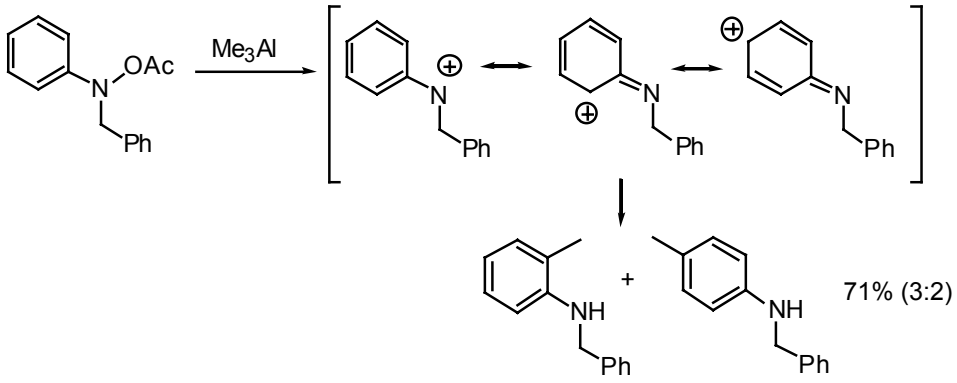
Pumiliotoxin C

The intermediary iminocarbocation or alkylidyneammonium ion generated by an organoaluminum can also be trapped intramolecularly with olefinic groups [71] . This interesting rearrangement–cyclization sequence can be extended to an efficient synthesis of muscopyridine [72].

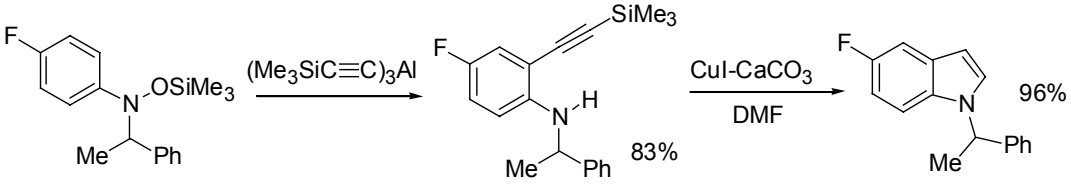


1.4. Nucleophilic Aromatic Substitution

Arylhydroxyamines behave in a different manner from alkylhydroxyamines on treatment with organoaluminum compounds [80]. The highly oxygenophilic organoaluminum reagent can cleave the N–O bond heterolytically to yield a phenylaminyl cation, which undergoes nucleophilic attack by an alkylaluminum at the *ortho* or *para* position of the aromatic ring.

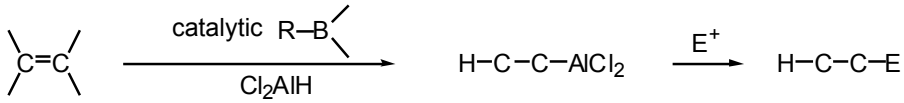


The synthetic potential of this novel reaction has been demonstrated by the synthesis of indol derivatives [80].



1.5. Hydroalumination of Olefins Catalyzed by Organoborane

Phenylboric acid catalyzed hydroalumination of Cl_2AlH to various olefins in high yields. Regio- and chemoselectivity of the reaction is exceedingly high [119].

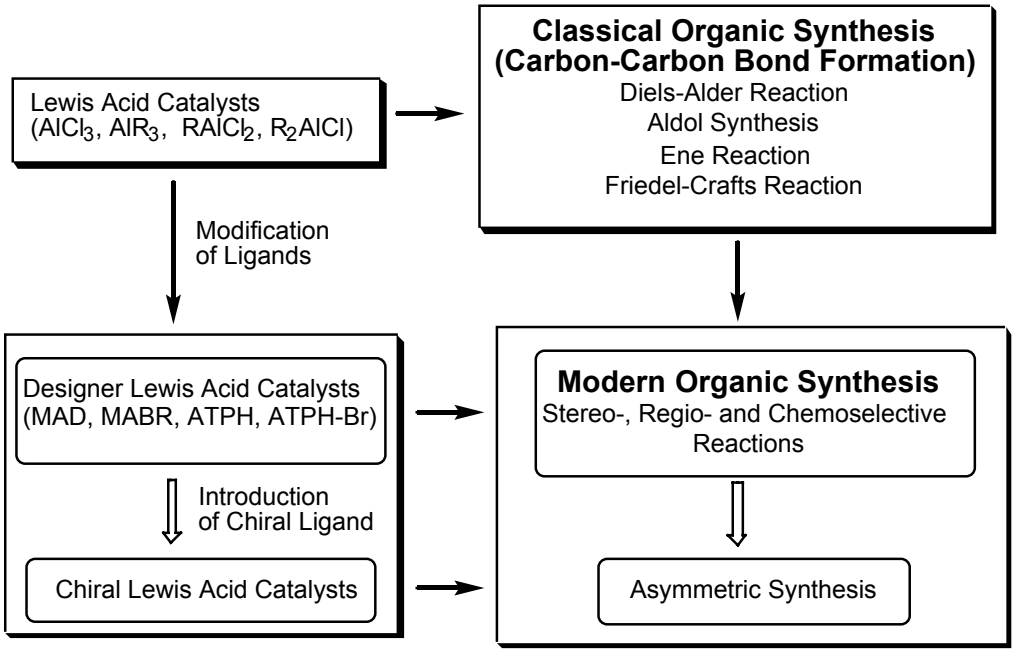


1.6. Biomimetic Heterolysis of Allyl Phosphates

Reactions of dialkyl phosphates of a variety of terpene alcohols were exposed to organoaluminum reagents. After careful investigation of these systems, Yamamoto achieved biomimetic synthesis of many terpenes with this technology [34].

Chapter 2. Development of Designer Lewis Acids

Classical Lewis acids activate a wide variety of functional groups of substrates, and the reactions usually proceed efficiently but with relatively low stereo-, regio-, and chemoselectivities. Relatively simple design of the ligands of these Lewis acids leads to monomeric Lewis acids in organic solvent and consequently to high Lewis-acidity and reactivity. Furthermore, upon coordination with designed ligand(s), the well designed Lewis acid exhibits new selectivity.



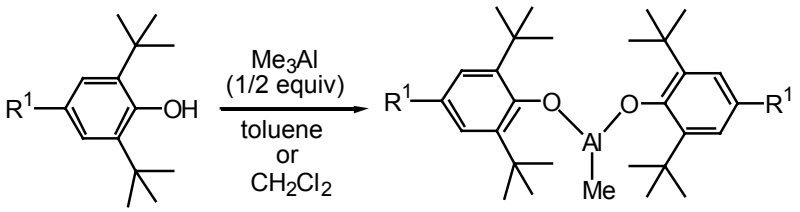
In the early 1970', Yamamoto, together with H. Nozaki, reported the first and a variety of examples of such designer Lewis acid catalysts using organoaluminum reagents [44]. These results encouraged further work by a large number of scientists in various laboratories worldwide and Yamamoto's principle is now accepted as one of the fundamental chemical means of organic synthesis.

2.1. Preparation of Various Aluminum Phenoxides

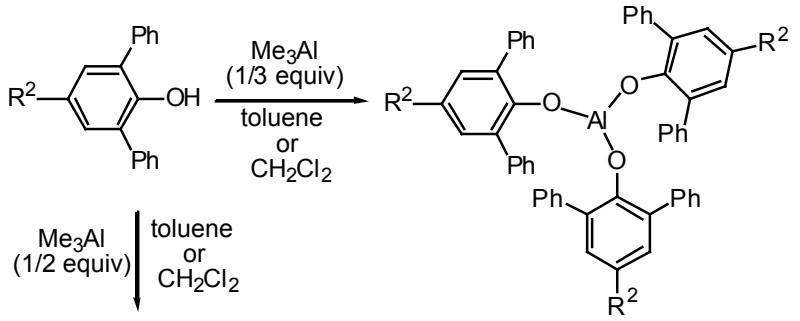
Several bulky aluminum reagents can be prepared from sterically hindered phenols. Most aluminum reagents in solution exist as dimeric, trimeric, or higher oligomeric structures. In contrast, methylaluminum bis(2,6-di-*tert*-butyl-4-methylphenoxide)(MAD) and aluminum tris(2,6-diphenylphenoxide)(ATPH) are monomeric in organic solvent. Lewis-acidity

of these reagents decreases with the coordination of more electron-donating aryloxides, but this can be compensated for by loosening of the aggregation. Compared with classical Lewis acids, the steric effect of our aluminum reagents also plays an important role in selective organic synthesis [R-27, 28, 323].

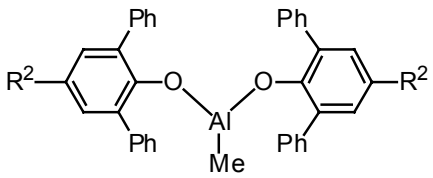
Thus, MAD, ATPH, methylaluminum bis(4-bromo-2,6-di-*tert*-butylphenoxide) (MABR) and methylaluminum bis(2,6-diphenylphenoxide)(MAPH) are readily prepared by treatment of Me_3Al with a corresponding amount of the phenol in toluene (or in CH_2Cl_2) at room temperature for 0.5~1 hour with rigorous exclusion of air and moisture. The reactivity of a phenol toward Me_3Al largely depends on the stereochemistry of the phenol. For example, treatment of 3 equiv of 2,6-di-*tert*-butyl-4-methylphenol with Me_3Al in CH_2Cl_2 at room temperature under argon results in the generation of bisphenoxide MAD together with the unreacted phenol. In contrast, 3 equiv of 2,6-diphenylphenol completely reacts with 1 equiv of Me_3Al to produce the trisphenoxide ATPH.



MAD : R^1 = Me
MABR : R^1 = Br



ATPH : R^2 = H
ATPH-Br : R^2 = Br



MAPH : R^2 = H

2.2. Structural Features of ATPH

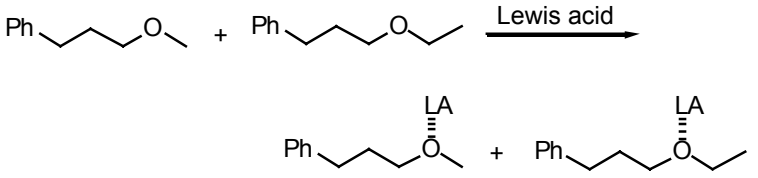
The X-ray crystal structure of the N,N-dimethylformamide-ATPH complex [251] disclosed that three arene rings of ATPH form a propeller-like arrangement around the aluminum center, and hence ATPH has a cavity with C_3 symmetry. By contrast, the X-ray crystal structure of the benzaldehyde-ATPH complex shows that the cavity surrounds the carbonyl substrate upon complexation with slight distortion from C_3 symmetry. A particularly notable structural feature of these aluminum-carbonyl complexes is the Al-O-C angles and Al-O distances, which clarify that the size and the shape of the cavity change flexibly depending on the substrates. According to these models, the cavity should be able to differentiate carbonyl substrates, which when accepted into the cavity should exhibit unprecedented reactivity under the steric and electronic environment of the arene rings. ^{1}H NMR measurement of crotonaldehyde-ATPH complex (300 MHz, CD_2Cl_2) revealed that the original chemical shifts of the aldehydic proton (H_a) at δ 9.50, and the α- and β-carbon protons (H_b and H_c) at δ 6.13 and δ 6.89, were significantly shifted upfield to δ 6.21, δ 4.92 and δ 6.40, respectively. The largest Δδ value of H_a of 3.29 ppm suggests that the carbonyl is effectively shielded by the arene rings of the cavity. This observation is in contrast to the resonance frequencies of the crotonaldehyde-Et_2AlCl complex at -60 °C (H_a: δ 9.32; H_b: δ 6.65; H_c: δ 7.84), and those of crotonaldehyde complexes with other ordinary Lewis acids.

2.3. Molecular Recognition with Bulky Aluminum Reagents

The monomeric aluminum phenoxides have sufficient Lewis-acidity and thus bind with polar functionalities. The complexation heavily depends on the structural features of these functional groups. Thus, functional groups outside a molecule bind to bulky aluminum reagents rather tightly and functional groups inside a molecule cannot form stable complexes. In other words, the steric bulk of aluminum reagents appears to play a crucial role in discriminating among structurally or electronically similar substrates.

2.3.1. Discrimination of Two Different Ethers with MAD

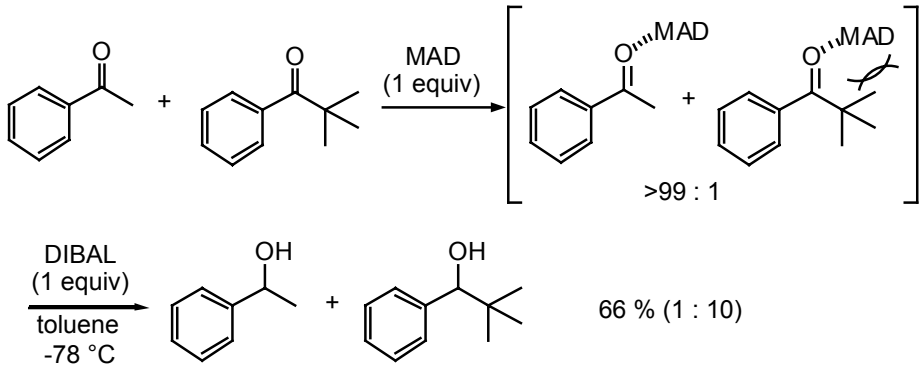
The 125-MHz ^{13}C NMR measurement of a mixture of 1 equiv each of MAD, methyl 3-phenylpropyl ether, and ethyl 3-phenylpropyl ether in $CDCl_3$ (0.4 M solution) at -50 °C showed that the original signal of methyl ether at δ 58.7 shifted downfield to δ 60.1, whereas the signal of the α-methylene carbon of ethyl ether remained unchanged. The unusual selectivity could not be observed with other Lewis acids as shown below. This method could be extended to the use of a polymeric aluminum aryloxide in complexation chromatography: heteroatom-containing solutes can be separated by complexation with stationary, insolubilized organoaluminum polymer [174].



MAD	: >99 : 1
i-Bu_3Al	: 4 : 1
$SnCl_4$	: 2 equiv of ethers coordinated to $SnCl_4$ to form a 2 : 1 complex
BF_3•OEt_2	: no complexation
BEt_3	: 5 : 3

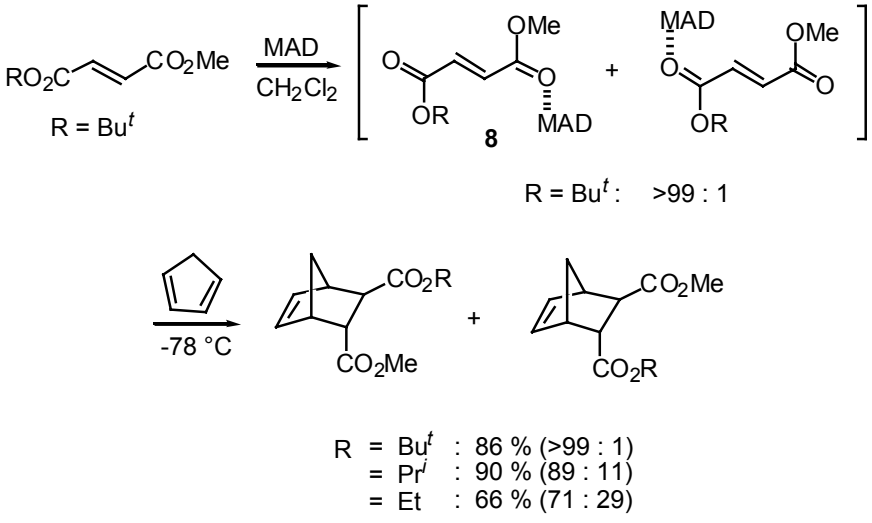
2.3.2. Discrimination of Two Different Ketones with MAD

Selective reduction of more hindered or electronically less polarizable ketones can be accomplished using MAD as a selective stabilizer of the carbonyls of less hindered or electronically more polarizable ketones [138, 140].



2.3.3. Discrimination of two Different Esters with MAD

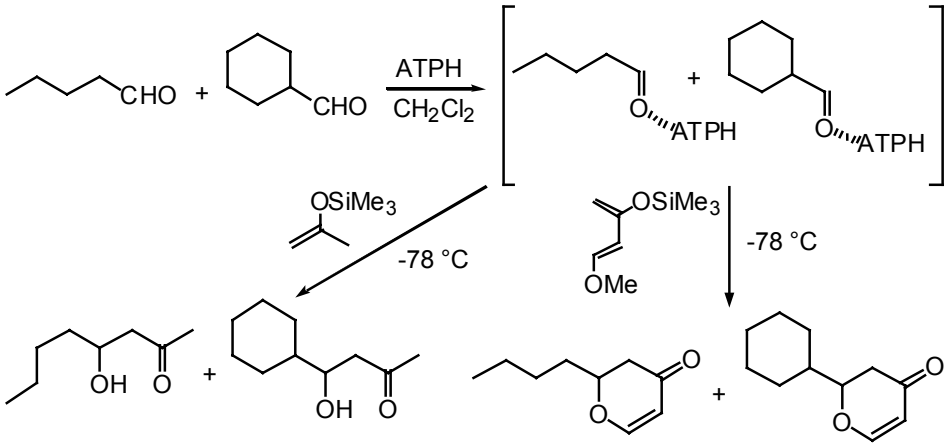
Discrimination of two different ester carbonyls can be similarly achieved with MAD [201, 222]. For example, reaction of *tert*butyl methyl fumarate with 1.1 equiv of MAD in CH_2Cl_2 at -78 °C gave new organoaluminum fumarate exclusively, the structure of which was rigorously established by low-temperature ^{13}C NMR spectroscopy. Diels-Alder reaction of a complex with cyclopentadiene gave a single isomer, predominantly with *endo* orientation of the methoxycarbonyl group. Thus, the methyl ester coordinated with the aluminum reagent gave us high *endo*-selectivity of the Diels-Alder reaction.



2.3.4. Discrimination of Two Different Aldehydes with MAPH and ATPH

ATPH can discriminate between structurally similar aldehydes, thereby facilitating the selective functionalization of the less hindered aldehyde carbonyl. Treatment of an equimolar mixture of valeraldehyde and cyclohexane-carboxaldehyde with 1.1 equiv of ATPH in CH_2Cl_2 at -78 °C, followed by addition of Danishefsky's

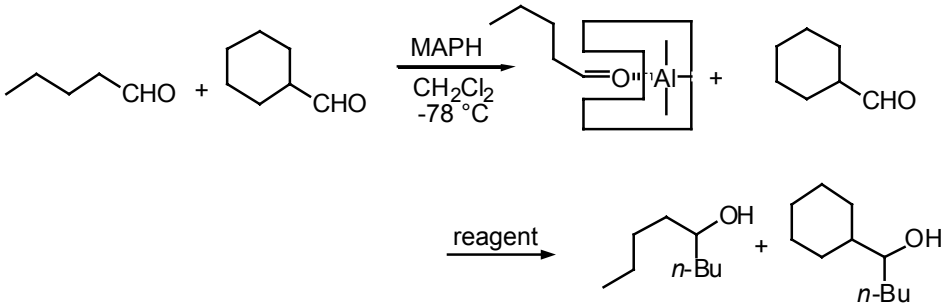
diene at this temperature proceeded hetero-Diels-Alder selectively. It should be noted that the complexed aldehyde could only react with the diene [258].



75 % (>99 : 1)

87 % (>99 : 1)

Obviously, the coordinated aldehyde is electronically activated but sterically deactivated with bulky aluminum reagents. The selective functionalization of more sterically hindered aldehydes was accomplished by the combined use of MAPH and alkyllithiums (RLi; R= *n*-Bu or Ph) [218] In this system, MAPH acted as a carbonyl protector of a less hindered aldehyde [175, 226], and therefore the carboanions preferentially react with more hindered carbonyl groups.

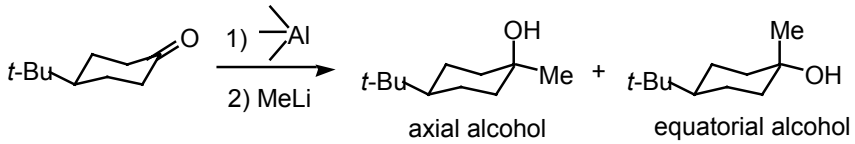


n-BuTi(OPr^i)$_3$ (1 *eq*.) : 31 % (2.5 : 1)
MAPH (1 *eq*.)/ *n*-BuLi (1 *eq*.) : 76 % (1 : 6.5)
MAPH (2 *eq*.)/ *n*-BuLi (2 *eq*.) : 45 % (1 :14)

Chapter 3. Bulky Aluminum Reagents for Selective Organic Synthesis

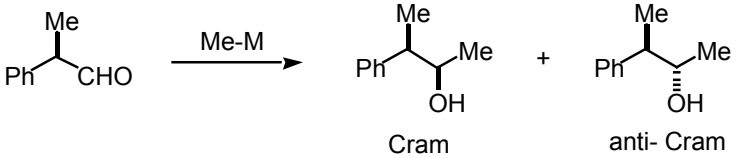
In chapter 2 we discussed several excellent methods of discriminating various functional groups using bulky aluminum reagents. In this section we focus on the reactions promoted with bulky aluminum reagents which could not be achieved with ordinary Lewis acid catalysts.

The following is a typical example which shows the potential of a bulky aluminum reagent for a new selectivity. When MAD was mixed with the carbonyl compound 4-tert-butylcyclohexanone, MAD gave a stable 1:1 complex. This complex was treated with methyllithium at low temperature to yield an equatorial alcohol, the stereochemistry of which was opposite that of the product from reaction of cyclohexanone with methyllithium. The equatorial selectivity achieved with MAD was found to be perfect [102, 139].



MeLi : 85% (79:21)
MAD/MeLi : 84% (1:99)

Such complexation also allows inversion of nucleophilic addition to chiral aldehydes. While ethylmagnesium bromide, on reaction with 2-phenylpropanol, obeys Cram's rule, the opposite mode is largely favored in the presence of MAD [102, 139].

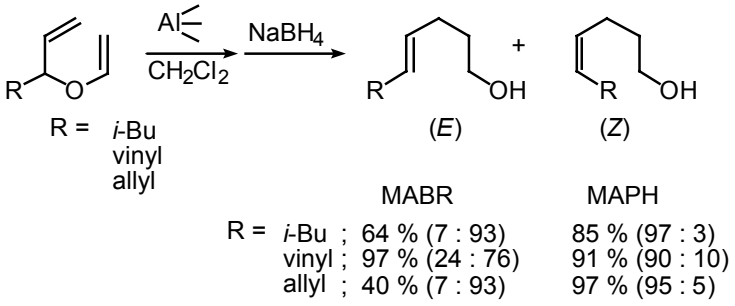


EtMgBr : 78% (84:16)
MAD/EtMgBr : 90% (25:75)

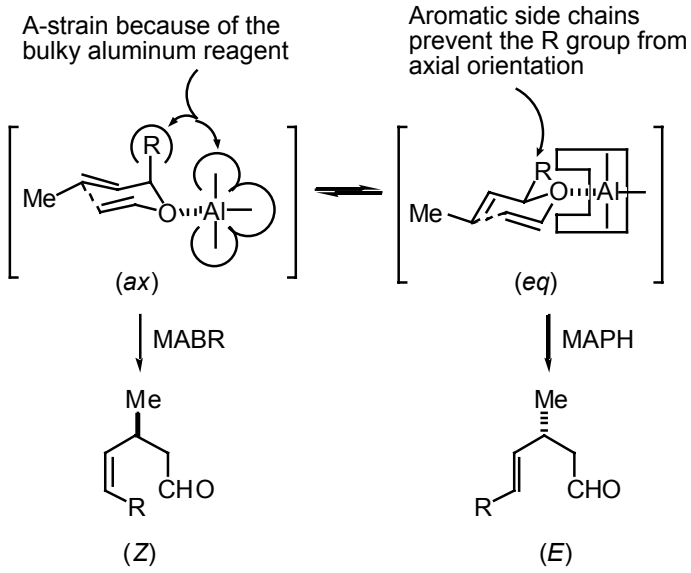
3.1. Stereoselective Claisen Rearrangement

Claisen rearrangement is accelerated significantly by bulky aluminum reagents [151, 167]. With MABR, the rearrangement of 1-substituted-2-propenyl vinyl ether derivatives takes place in a few seconds even at -78 °C to give the 4-(*Z*)-alkenols after reduction with $NaBH_4$. When MABR is replaced by MAPH, (*E*)-isomers are formed

preferentially.

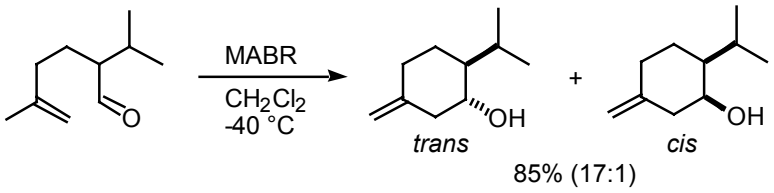


This stereochemical reversal observed with MABR and MAPH can be accounted for by two possible chair-like transition state structures, which was proposed by the absolute configuration of the double bonds and the allylic carbons of the produced aldehydes.



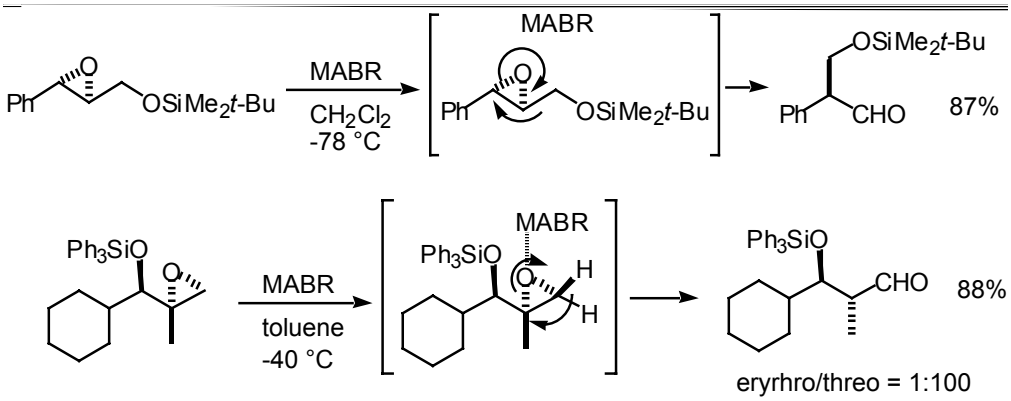
3.2. Stereoselective ene-Reaction

Intramolecular ene reactions of α-substituted-δ,ε-unsaturated aldehydes were achieved in a stereoselective manner using MABR [180]. The reaction shows unprecedented *trans*-selectivity, in contrast to the *cis*-selectivity frequently observed in the type II ene reaction with other ordinary Lewis acids.



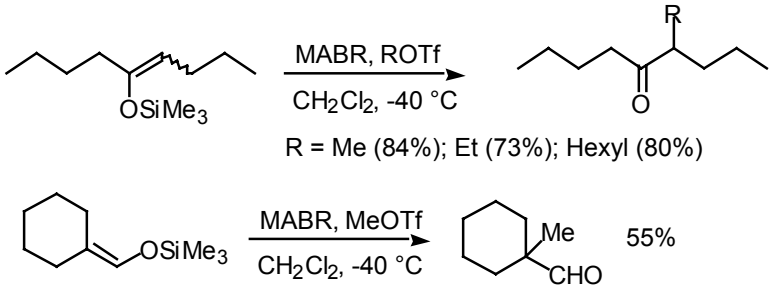
3.3. Stereoselective Epoxide Rearrangement

Two different rearrangement modes of β-siloxy epoxides gave distinct β-siloxy aldehydes using MABR as a key reagent depending on the substrate employed [160, 185]. Since optically pure α-siloxyepoxides are easily accessible by the Katsuki–Sharpless asymmetric epoxidation, this rearrangement protocol is very useful to obtain optically pure β-siloxyaldehydes which are often key building blocks in natural product syntheses.



3.4. Primary α-Alkylation of Carbonyl Compounds

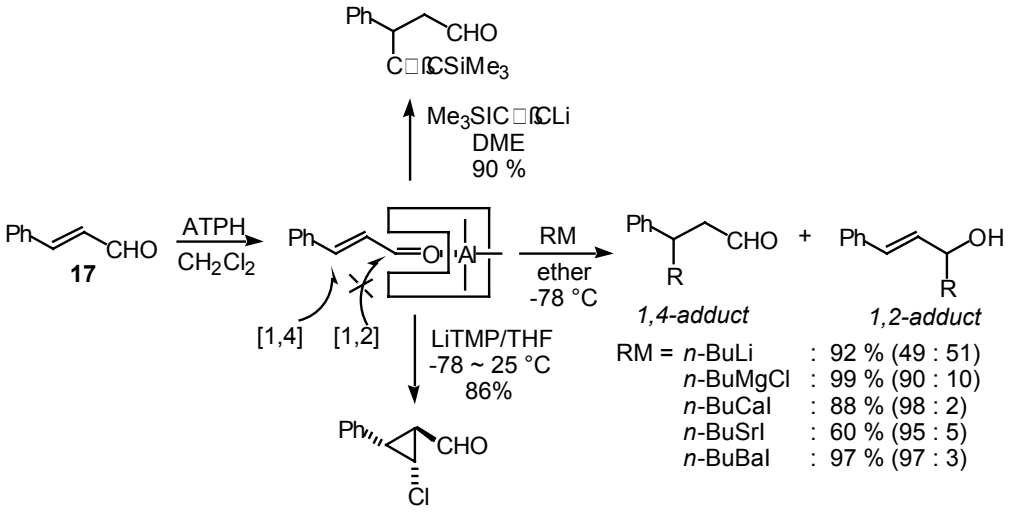
Primary α-alkylation of carbonyl compounds proceeded with silyl enol ethers, MABR and alkyltriflates under non-basic conditions. This is tolerated by base-sensitive functional groups [207].



3.5. Conjugate Addition to α,β-Unsaturated Carbonyl Compounds

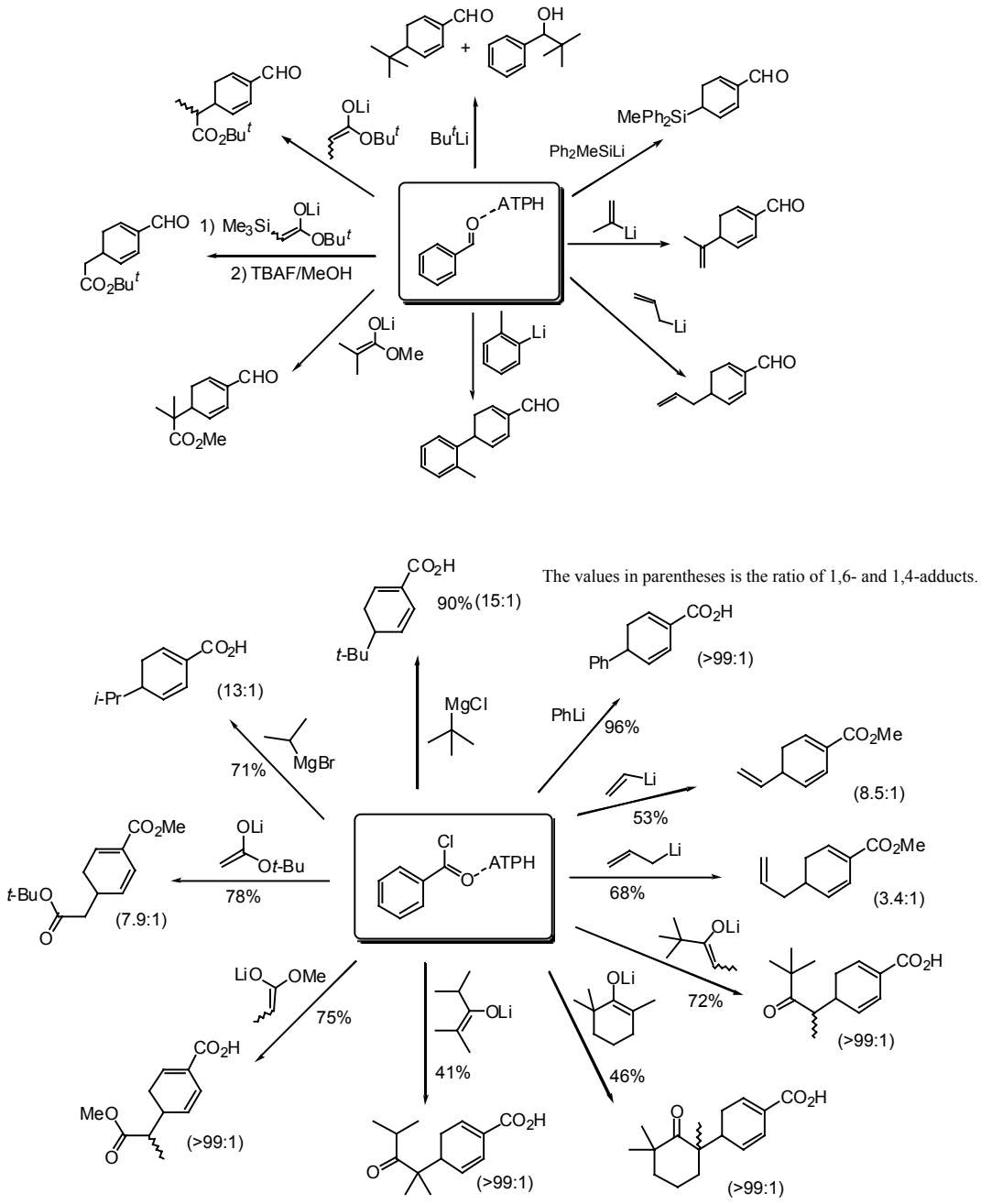
Organocuprates are the most widely used reagents for Michael addition to

α,β-unsaturated ketones, and for one of the most powerful and important carbon-carbon bond-forming reactions. ATPH can be used as a carbonyl protector upon complexation, which facilitates 1,4-addition to even α,β-unsaturated aldehydes for which 1,4-addition is virtually unexplored [251]. Complexation of cinnamaldehyde with 1.1 equiv of ATPH in CH_2Cl_2 at -78 °C, followed by subsequent addition of 1.5 equiv of *n*-butylmagnesium bromide (*n*-BuMgBr), gave the 1,4-addition product preferentially. The alkylation of cinnamaldehyde with MAD and *n*-BuMgBr gave unsatisfactory results (95 %; 1,4/1,2-adduct ratio = 7 : 93). The combination of MAPH with the same butylating agent gave an equal mixture of 1,4- and 1,2-adducts (98 %; ratio = 49 : 51). Replacing organomagnesium reagents with organocalcium, strontium, and barium enhanced 1,4-selectivity.



One advantage of this method over organocopper-mediated conjugate addition is the availability of lithium alkynides and thermally unstable lithium carbenoids as Michael donors. With alkynides, raising the reaction temperature after the Michael addition afforded cyclopropanation to give a sole diastereomer.

Selective 1,6-addition of alkyllithiums to aromatic carbonyl substrates such as benzaldehyde or acetophenone was achieved with ATPH to give functionalized cyclohexadienyl compounds [285]. According to the molecular structure of the benzaldehyde-ATPH complex, it is obvious that the *para*- position of benzaldehyde is deshielded by the three arene rings, which effectively block the *ortho*- position as well as the carbonyl carbon from nucleophilic attack.

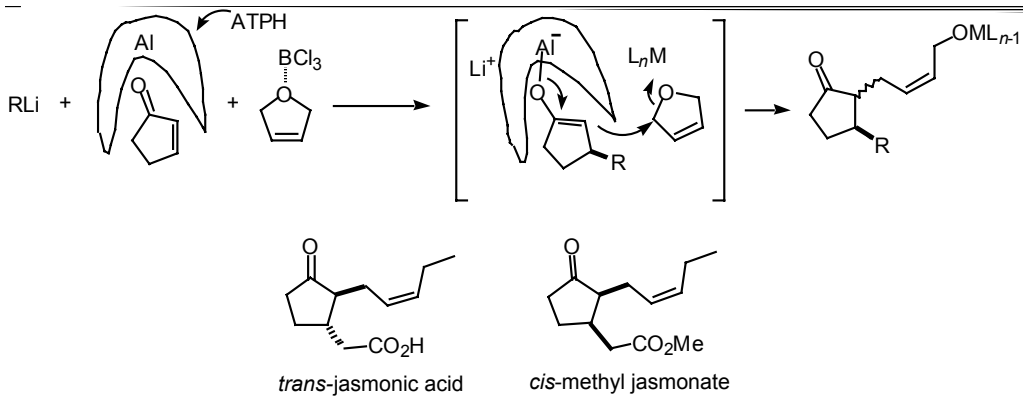


Unfortunately, however, conjugate addition to the ATPH–PhCHO complex did not proceed effectively with smaller nucleophiles. Yamamoto and his colleagues

recently illustrated that ATPH–ArCOCl is superior to ATPH–PhCHO for the nucleophilic dearomatic functionalization. Several analytical and spectral data showed that the ATPH–PhCOCl complex was more reactive than ATPH–PhCHO[367].

X-ray crystal structure (space-filling model) of the ATPH-benzaldehyde complex, which shows more facile nucleophilic attack at the *para*-position.

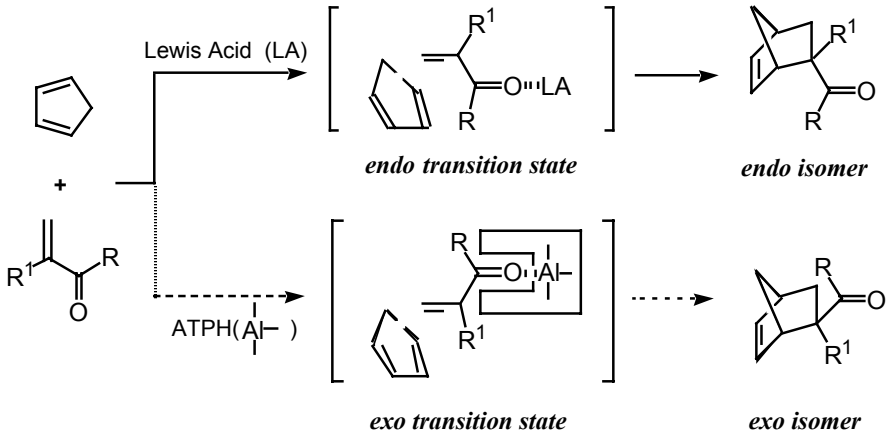
The 1,4-addtion process was the key step of the synthesis of jasmonates. The synthesis involves the combined use of: (1) organolithium reagent (RLi); (2) aluminum tris(2,6-diphenylphenoxide) (ATPH)-cyclopentenone complex; and (3) 2,5-dihydrofuran (DHF)–BCl_3 complex[387].



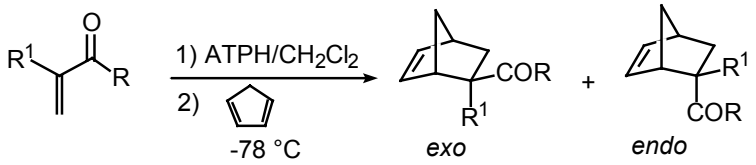
3.6. *Exo*-Selective Diels-Alder Reaction

One characteristic stereochemical feature of the Diels-Alder reaction is *endo*-selectivity. The origin of the *endo*-preference in Diels-Alder reactions can be ascribed to "secondary orbital interactions". If the carbonyl functions of dienophilic

α,β-unsaturated carbonyl substrates are effectively shielded by complexation with ATPH, secondary interaction is decreased, thereby disfavoring the hitherto preferred *endo* transition state.



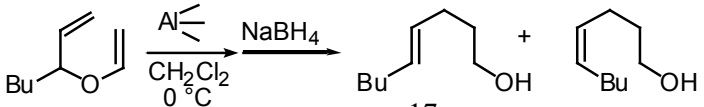
As expected, precomplexation of α,β-unsaturated ketone with ATPH in CH_2Cl_2 at -78 °C, followed by cyclization with cyclopentadiene, resulted in the stereochemical reversal to furnish *exo*-adduct as a major product [269].



R = Ph, R^1 = H ; 81 % (73 : 27)
R = Ph, R^1 = Me : 81 % (96 : 4)
R = R^1 = Me : 87 % (87 : 13)

3.7. Stereoselective Claisen Rearrangement

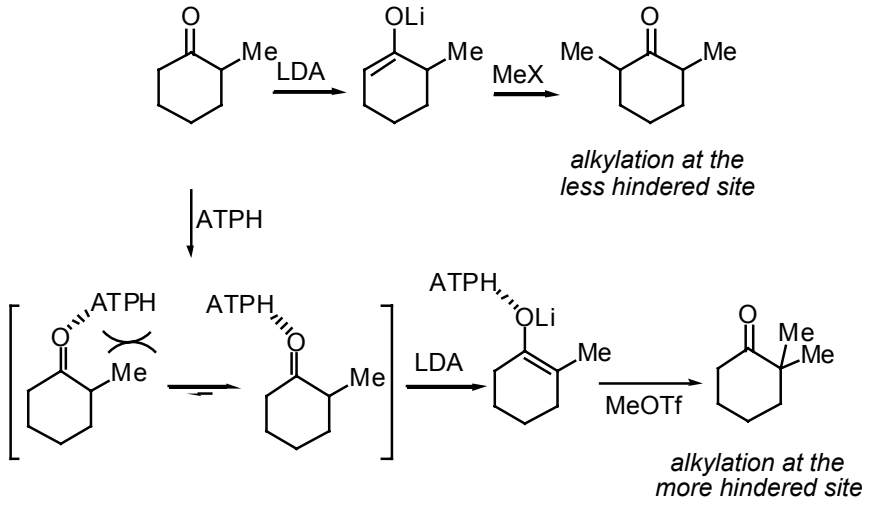
Claisen rearrangement is believed to proceed *via* a six-membered transition state. The preferential conformation of the reactant in the transition state might be due to the shape and the size of the cavity of ATPH. This hypothesis can be verified by treatment of 1-butyl-2-propenyl vinyl ether with ATPH at 0 °C to give isomeric rearrangement products in 87% yield in a ratio of 16 : 1 [273].



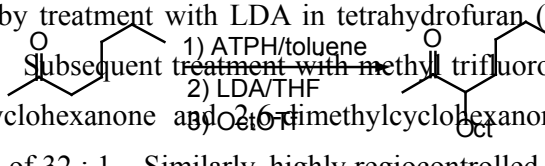
MAPH : 75 % (5 : 1)
ATPH : 87 % (16 : 1)

3.8. Selective Alkylation at the α-Carbon of Unsymmetrical Ketones

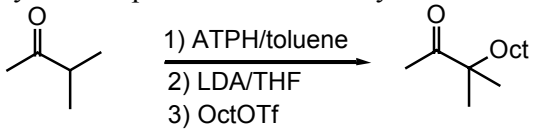
An unsymmetrical dialkyl ketone can form two regioisomeric enolates upon deprotonation under either kinetic or thermodynamic control. Ideal conditions for the kinetic control of less-substituted enolate formation are those in which deprotonation is irreversible using lithium diisopropylamide (LDA). On the other hand, at equilibrium, the more substituted enolate is the dominant species with moderate selectivity. A hitherto unknown method, i.e., the kinetically controlled generation of the more substituted enolate, was realized by the combined use of ATPH and LDA [306].



Precomplexation of ATPH with 2-methylcyclohexanone at -78 °C in toluene was followed by treatment with LDA in tetrahydrofuran (THF), and the mixture was stirred for 1 h. Subsequent treatment with methyl trifluoromethanesulfonate furnished 2,2-dimethylcyclohexanone and 2,6-dimethylcyclohexanone in an isolated yield of 53 % in a ratio of 32 : 1. Similarly, highly regiocontrolled alkylation of unsymmetrical ketones with octyl triflate proceeded selectively as shown below (>99 : 1).



89% (> 99 % selectivity)



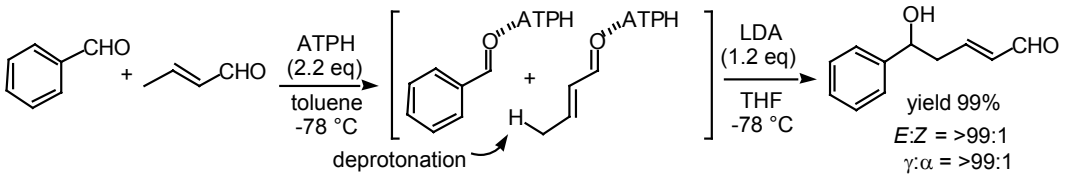
71% (>99 % selectivity)

Generation of the kinetically deprotonated more substituted enolate can be explained in terms of the effect of ATPH on the inherent coordination preference of unsymmetrical ketones. Most likely, the bulky aluminum reagent ATPH prefers coordination with one of the lone pairs *anti* to the more hindered α-carbon of the unsymmetrical ketones. As a consequence, the aluminum reagent surrounds the less hindered site of the carbonyl group, thus obstructing the trajectory of the nucleophilic attack of LDA.

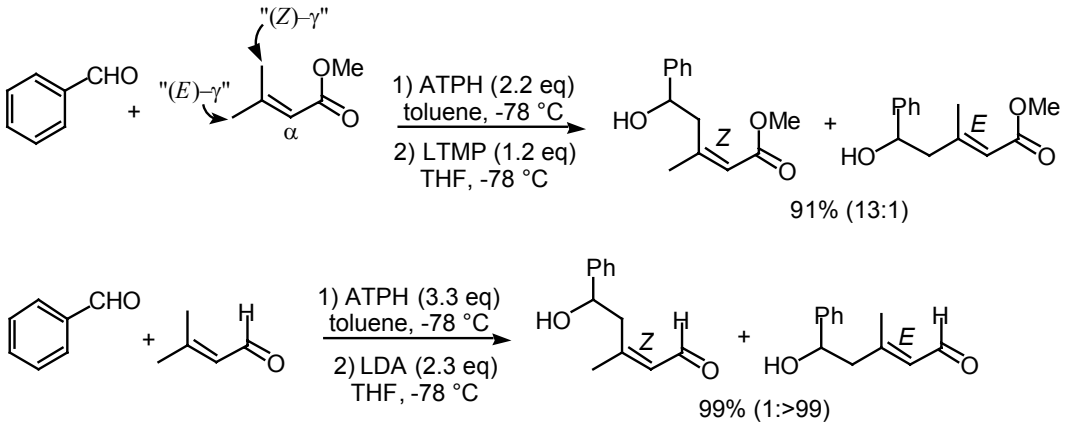
Space-filling model of the ATPH-methylcyclohexanone complex.
LDA attacking is more feasible at the more substituted α-carbon

3.9. New Directed Aldol Condensation between two Different Carbonyl Compounds

The mixed aldol condensation between two different carbonyl compounds which present several possible sites for enolization is very difficult including proton transfer and over-alkylation. Recent progress has been made in the directed mixed crossed aldol condensation of two different carbonyl compounds which involves the control of reactivity and selectivity of the activated enolates using ATPH [R-34, 329]. Precomplexation of PhCHO and crotonaldehyde with ATPH was followed by treatment with LDA to give γ-aldol adduct in 99% yield. The reaction generally proceeds even with other carbonyl substrates with high *E* and γ selctivity.

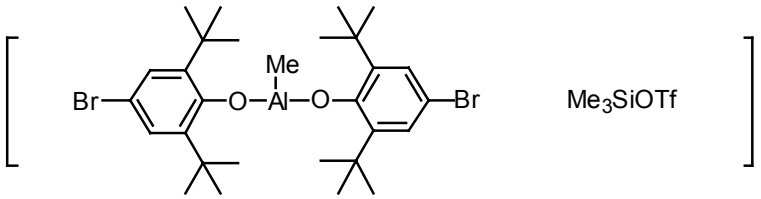


However, when β,β-disubstituted-α,β-unsaturated carbonyl compounds complexed with ATPH were subjected to the alkylation reaction with an aldehyde in the presence of LDA or LTMP, different selectivity was observed depending on the carbonyl functionality employed: the predominant alkylation site was at the (*Z*)–γ position of methyl 3-methyl-2-butenoate, whereas senecialdehyde gave the (*E*)–γ-addition product exclusively. This could be ascribed to a specific complexation of ATPH with a different carbonyl compound by molecular recognition, which was rigorously ascertained by X-ray crystal analysis and NOE measurement.



3.10. Remarkable Enhancement of Catalyst Activity of Trialkylsilyl Sulfonates on the Mukaiyama Aldol Reaction

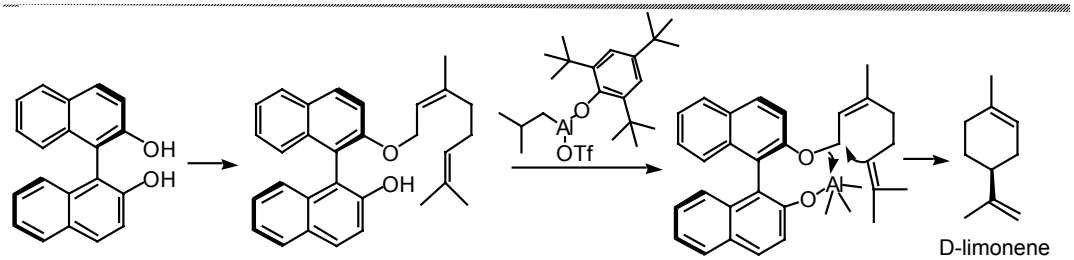
Yamamoto and his colleagues disclosed the remarkable rate enhancement on the trialkylsilyl triflate-catalyzed Mukaiyama aldol reaction of silyl enol ethers by using a bulky organoaluminum reagent, i.e., MAD or MABR, as a cocatalyst [334]. Thus, a more strongly Lewis acidic species forms from two different Lewis acids of the bulky organoaluminum reagent and Me_3SiOTf in the presence of an aldehyde.



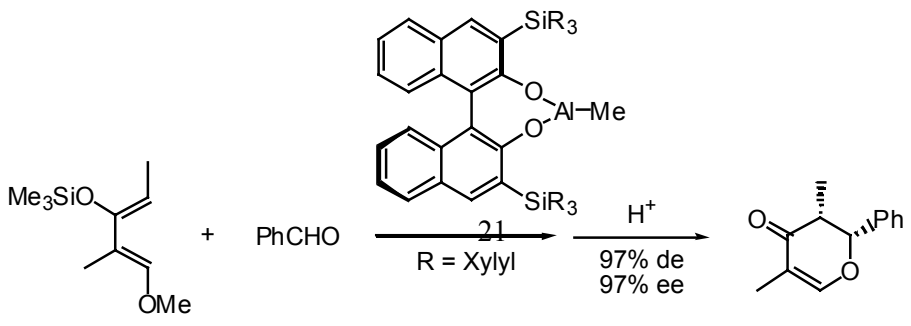
Highly reactive Lewis acid catalyst

3.11. Chiral Aluminum Reagents in Asymmetric Synthesis

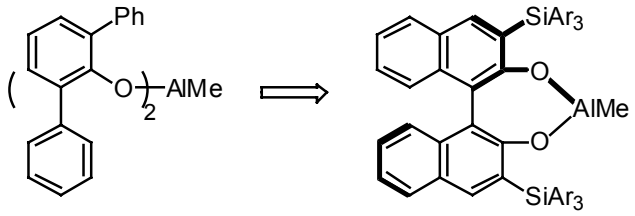
Biomimetic synthetic approach involving the organoaluminum-accelerated cyclization of chiral alkoxides to limonene was highlighted by chiral leaving group strategy [79]. A modfied aluminum reagent which has a bulky phenoxy ligand and a strong electron-withdrawing group (-OTf) was devised to obtain high reactivity and selectivity. The reaction of (*R*)-(+)-binaphthol mononeryl ether with this bulky aluminum reagent proceeded via effective activation of the allyl ether and subsequent elimination of binaphthol to give D-limonene in 77% ee.



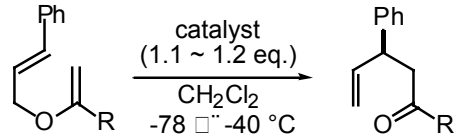
Asymmetric hetero-Diels-Alder reaction was found to be catalyzed by the optically pure bulky aluminum reagent [134]. Thus, treatment of a mixture of benzaldehyde and siloxydiene under the influence of catalytic amount of binaphthol derived reagent furnished cis-dihydropyrone in 93% yield with 97% diastereoselectivity and 97% ee. The same catalyst was used as in the first asymmetric ene reaction.



The same optically pure aluminum reagent is an excellent promoter for the asymmetric Claisen rearrangement of allyl vinyl ethers which possess bulky substituents such as trialkylsilyl- or trialkylgermanium groups [176].

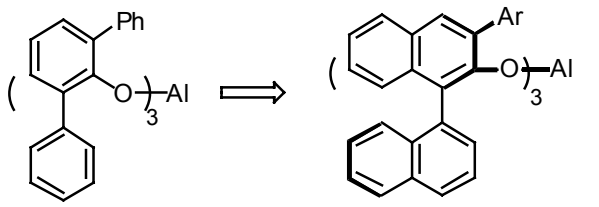


MAPH Ar_3 = *t*-$BuPh_2$



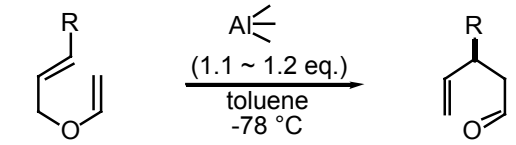
R = $SiMe_3$ R = $SiMe_3$: 76 % (90 %ee)
= $GeMe_3$ = $GeMe_3$: 68 % (93 %ee)

Based on the structure of ATPH, an optically active catalyst, aluminum tris((*R*)-1-α-naphthyl-3-phenyl-2-naphthoxide)((*R*)-ATBN), was synthesized, and was subjected to the asymmetric Claisen rearrangement of to give the corresponding aldehydes in moderate enantioselectivities (>60% ee). In contrast, the more elaborate (*R*)-ATBN analogue, aluminum tris((*R*)-1-α-naphthyl-3-*p*-fluorophenyl-2-naphthoxide) ((*R*)-ATBN-F), generated products of up to 92% ee [273].



ATPH

Ar = Ph : (*R*)-ATBN
= *p*-F-Ph : (*R*)-ATBN-F

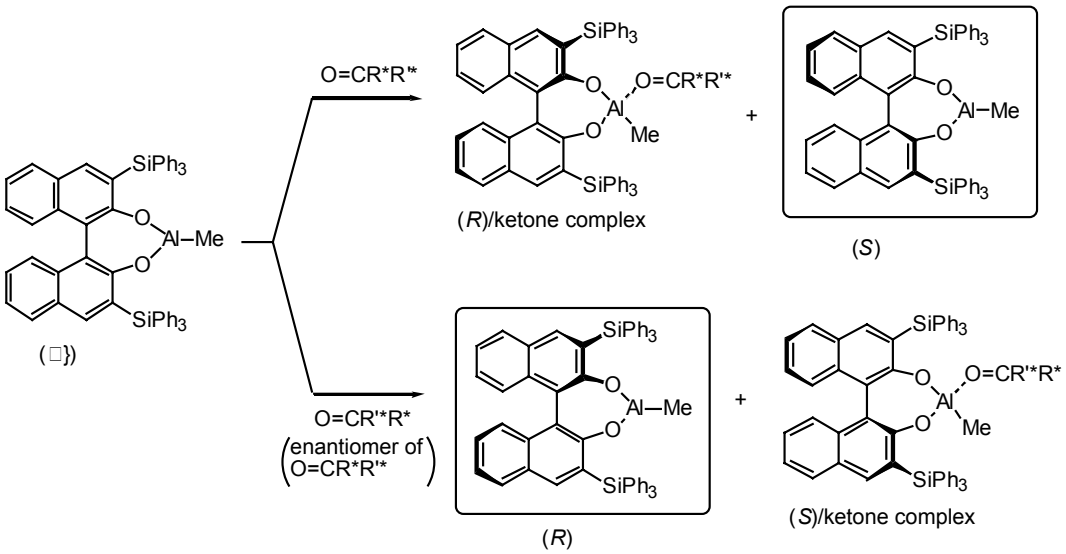


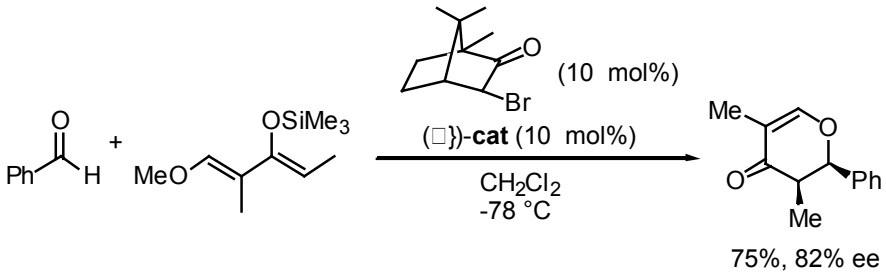
R = Ph
c-hexyl
t-Bu
Me_3Si

R = Ph : (*R*)-ATBN : 93 % (61 %ee)
: (*R*)-ATBN-F : 97 % (76 %ee)

R = *c*-hexyl : (*R*)-ATBN-F : 85 % (86 %ee)
t-Bu : (*R*)-ATBN-F : 70 % (91 % ee)
Me_3Si : (*R*)-ATBN-F : 78 % (92 % ee)

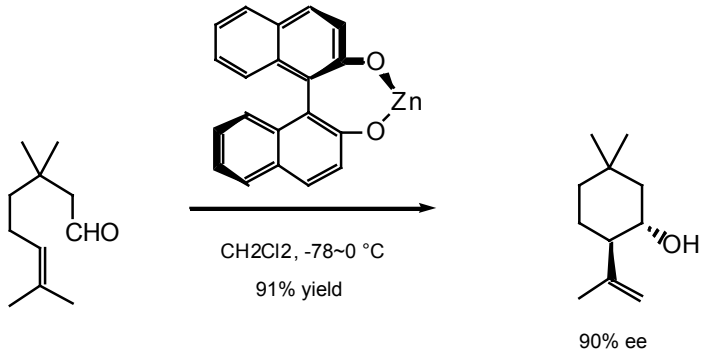
It is reasonable to anticipate that certain chiral ketones may discriminate between racemic organoaluminum reagents by diastereoselective complexation: preferential formation of one of the diastereomers. Indeed, the Lewis acidic enantiomer that *in situ* remained intact promoted the asymmetric hetero-Diels-Alder reaction of several aldehydes with substituted Danishefsky diene in high enantioselectivity [155]. The so-called concept of "chiral poisoning" of one of two active enantiomers triggers the selective and relative activation of another enantiomer. Similar approaches using this strategic chiral poisoning for asymmetric synthesis have also been reported.


SiPh3
O
Al–Me
O
SiPh3
(□})
O=CR*R'*
O=CR'*R*
(enantiomer of O=CR*R'*)
SiPh3
O
Al
O=CR*R'*
Me
SiPh3
(R)/ketone complex
+
SiPh3
O
Al–Me
O
SiPh3
(S)
SiPh3
O
Al–Me
O
SiPh3
(R)
+
SiPh3
O
Al
O=CR'*R*
O
Me
SiPh3
(S)/ketone complex


O
Ph
H
+
MeO
OSiMe3
O
Br
(10 mol%)
(□})-cat (10 mol%)
CH2Cl2
-78 °C
Me
O
O
Ph
Me
75%, 82% ee

Chapter 4. Enantioselective Synthesis Using Chiral Lewis Acids

In 1985 Yamamoto and his colleagues reported the first logically designed chiral Lewis acid catalyst for asymmetric synthesis: an asymmetric cyclization took place efficiently using chiral zinc reagent derived dimethylzinc and optically active binaphthol. The reaction proceeds smoothly at low temperature to generate the cyclization product in reasonable asymmetric induction. Since then, a great number of chiral Lewis acid catalysts have been reported in the literature and the resulting process is now an essential tool for many asymmetric syntheses [98].

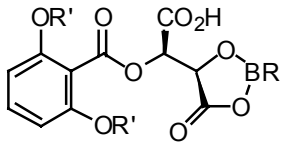


4.1. Chiral (Acyloxy)boranes (CAB)

Yamamoto and his colleagues found that the action of a controlled amount of diborane on a carboxylic acid leads to an (acyloxy)borane $RCO_2BR'_2$ which behaves as a Lewis acid: the chiral (acyloxy)borane (CAB) complex that is formed *in situ* from monoacyl tartaric acid and diborane [147]. Yamamoto and his colleagues has achieved highly enantioselective carbo-Diels–Alder [147, 156, 165, 215, 240, 243], hetero-Diels–Alder [206, 246], aldol [182, 193, 239], and allylation [194, 241] reactions using a common CAB catalyst.

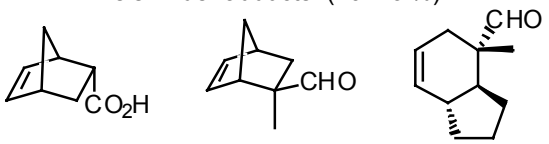
The CAB (R' = Me, R = H) is an excellent asymmetric catalyst for the Diels–Alder reaction between cyclopentadiene and acrylic acid [147] or methacrolein [156, 240]. The reaction with acrylic acid deserves special attention, since usually it is not a good component in Diels–Alder reactions. The α-substituent on the α,β-enals increased the enantioselectivity. When there was a β-substitution on the α,β-enals, the cycloadduct was almost racemic, but for a substrate having substituents at both α- and β-positions, high ee's were observed. According to NOE studies of the CAB-coordinated methacrolein and crotonaldehyde, the effective shielding of the *si*-face of the coordinated α,β-enal arises from π-stacking of 2,6-dialkoxybenzene ring

and the coordinated aldehyde [243].



CAB

Diels–Alder adducts (10 mol%)

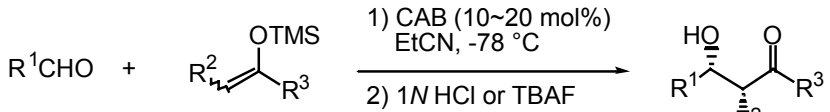


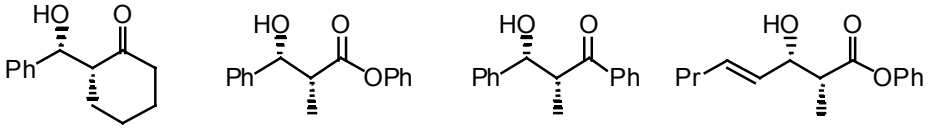
exo/endo: 4/96
endo: 78% ee

exo/endo: 89/11
exo: 96% ee

exo/endo: 4/96
exo: 92% ee

A little later Yamamoto and his colleagues reported that CAB (R' = i-Pr, R = H) is also an excellent catalyst for the Mukaiyama condensation of simple enol silyl ethers of achiral ketones with various aldehydes [182]. Furthermore, the reactivity of aldol reactions can be improved without reducing the enantioselectivity by using CAB (R = 3,5-$(CF_3)_2C_6H_3$ or R = *o*-$PhOC_6H_4$) [239]. The CAB-catalyzed aldol process allows the formation of adducts in a highly diastereo- and enantioselective manner (up to 99% ee) under mild reaction conditions. Another aldol-type reaction of ketene silyl acetal derived from phenyl esters with achiral aldehydes also proceeds smoothly with **2** and can furnish erythro β-hydroxy esters with high optical purity [193]. Regardless of the stereochemistry of enol silyl ethers, syn aldols are highly selectively obtained via the acyclic extended transition-state mechanism. Judging from the product configurations, CAB catalyst (from natural tartaric acid) should effectively cover the *si* face of carbonyl following its coordination.



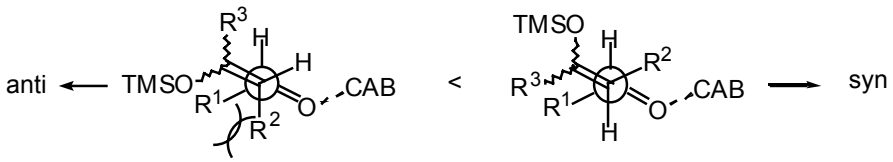


(83%), 97% ee syn
syn:anti=>95:5
(R=3,5-$(CF_3)_2C_6H_3$)

92% ee syn
syn:anti=79:21
(R' = iPr; R = H)

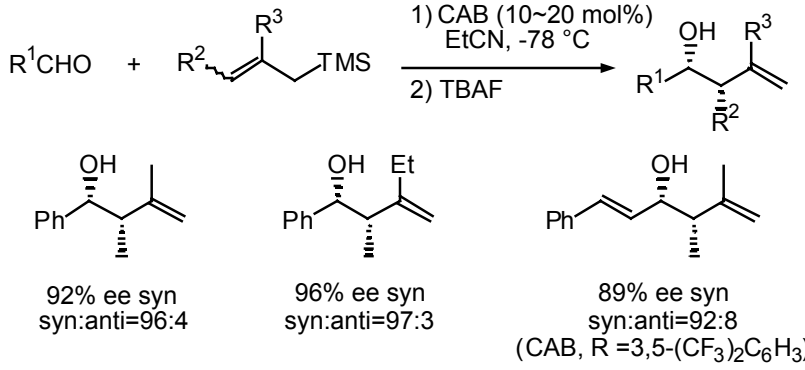
(92%), 96% ee syn
syn:anti=99:1
(R=3,5-$(CF_3)_2C_6H_3$)

97% ee syn
syn:anti=96:4
(R' = iPr, R = H)



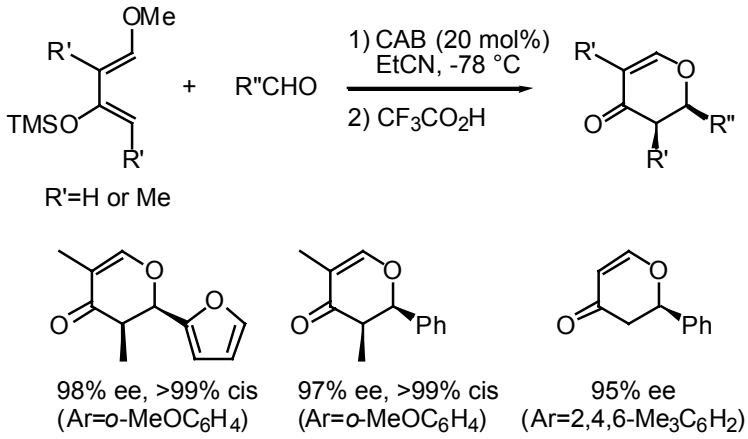
Extended Transition-State Model

Yamamoto and his colleagues found for the first time that chiral Lewis acid catalyzed the Sakurai-Hosomi reaction asymmetrically. Thus, CAB has a powerful activity for the reaction to furnish homoallylic alcohols in excellent enantiomeric excess [194]. Alkyl substitution at the olefin moiety of allylsilanes increases the reactivity, permitting a lower reaction temperature with improved asymmetric induction. γ-Alkylated allylsilanes exhibit excellent diastereo- and enantioselectivities affording erythro homoallylic alcohols of higher optical purity. Regardless of the geometry of starting allylsilanes, the predominant isomer in this reaction had erythro configuration. The observed preference for relative and absolute configurations for the adducts is predicted on the basis of an extended transition-state model similar to that for the CAB-catalyzed aldol reaction. The boron substituent of **3** has strong influence on the chemical yield and the enantiomeric excess of allylation adduct, and the 3,5-bis(trifluoromethyl)phenyl group is most effective [241].

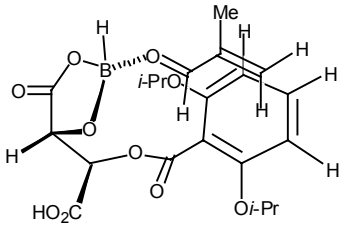


CAB was also effective in catalyzing the hetero Diels-Alder reaction of aldehydes with a Danishefsky diene to produce dihydropyrone derivatives of high optical purity (up to 98%ee) [206]. The extent of asymmetric induction is largely dependent on the structure of the boronic acid. In general, bulky phenylboronic acid (Ar=2,4,6-$Me_3C_6H_2$, *o*-$MeOC_6H_4$) results in excellent asymmetric induction [246]. Judging from the product configuration, CAB (from natural tartaric acid) should

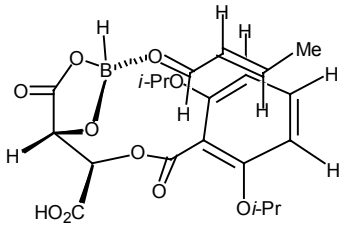
effectively cover the *si* face of carbonyl when coordinated, and the selective approach of nucleophiles from the *re* face should agree well with the results of other CAB-catalyzed asymmetric reactions.



The mechanism of CAB-catalyzed asymmetric Diels-Alder reaction has been studied carefully using NMR [243]. α-Substituted methacrolein favors *s*-trans conformation in the transition-state assembly independent of the steric feature of boron-substituent. On the other hand, the sp2-sp2 conformational preference of α-nonsubstituted acrolein and crotonaldehyde are reversed by altering the structure of the boron-substituent: *s*-trans conformation is preferred when the boron substituent is small, while *s*-cis conformation is preferred when it is bulky.



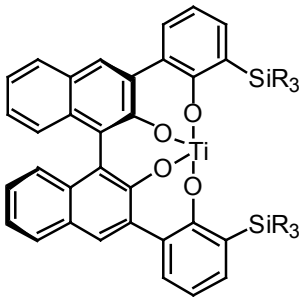
methacrolein

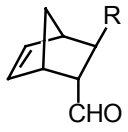


crotonaldehyde

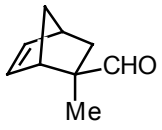
4.2. Chiral Helical Lewis Acid

Chiral helical titanium reagents have been prepared and as an efficent chiral template for asymmetric Diels-alder reaction with dienes, regardless of reaction temperature and structure of dienophiles [225].





95-96% ee exo
exo:endo=85:15

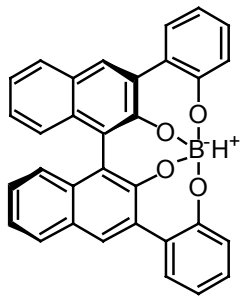


94% ee exo
exo:endo=>99:1

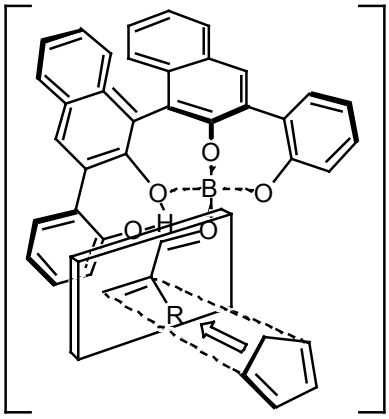
4.3. Enantioselective Synthesis Using Chiral Brønsted–Lewis Acids

4.3.1. Brønsted Acid-assisted Chiral Lewis Acids (BLA)

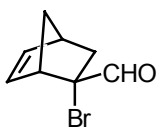
Yamamoto and his colleagues found that Brønsted acid assisted chiral Lewis acid: BLA achieved high selectivity through the double effect of intramolecular hydrogen binding interaction and attractive π–π donor-acceptor interaction in the transition-state [249, 330]. Extremely high enantioselectivity (>99 to 92% ee) and exo selectivity (>99 to 97% exo) are obtained for cycloadditions of α-substituted α,β-enals with dienes in the presence of BLA. The absolute stereopreference in the reaction can be easily understood in terms of the most favorable transition-state assembly. The coordination of a proton of 2-hydroxyphenyl group with an oxygen of the adjacent B-O bond in complex should play an important role in asymmetric induction; this hydrogen binding interaction via Brønsted acid would cause Lewis acidity of boron and π-basicity of phenoxy moiety to increase.



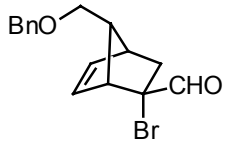
BLA (5~10 mol%)



Non-Helical Transition-State

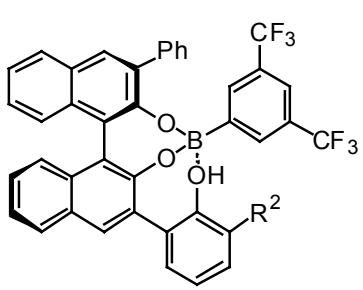


>99% ee exo
exo:endo=>99:1

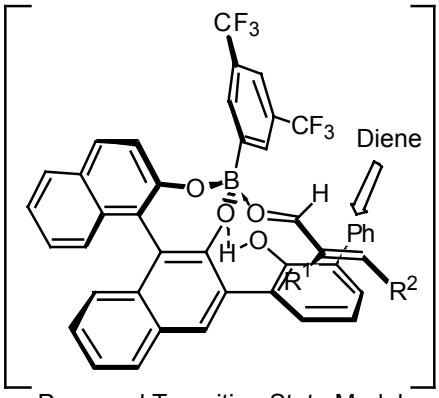


94% ee exo
exo:endo=>99:1

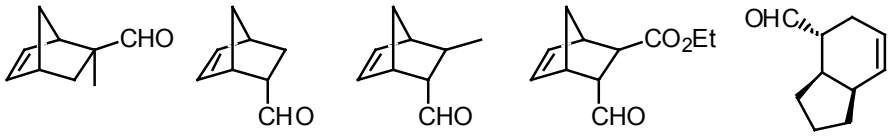
Diels–Alder reactions of α-unsubstituted α,β-enals with BLA as well as most chiral Lewis acids exhibit low enantioselectivity and/or reactivity. Yamamoto and his colleagues developed a new type of BLA, which was prepared from a chiral triol and 3,5-bis(trifluoromethyl)benzeneboronic acid [291, 331]. This catalyst was extremely effective in enantioselective cycloaddition of both α-substituted and α-unsubstituted



BLA



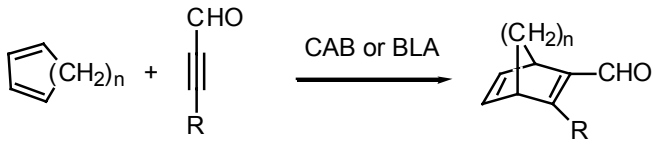
Proposed Transition State Model

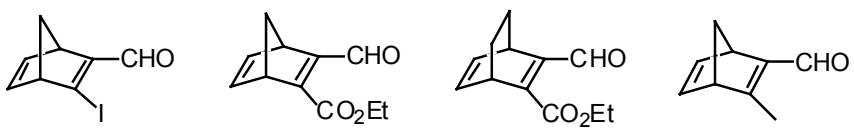


99% ee (*S*) 95% ee (*S*) 95% ee (*S*) 95% ee (*R*) 80% ee (*R*)

α,β-enals with various dienes. The Brønsted acid in the new BLA catalysts clearly accelerates the cycloaddition.

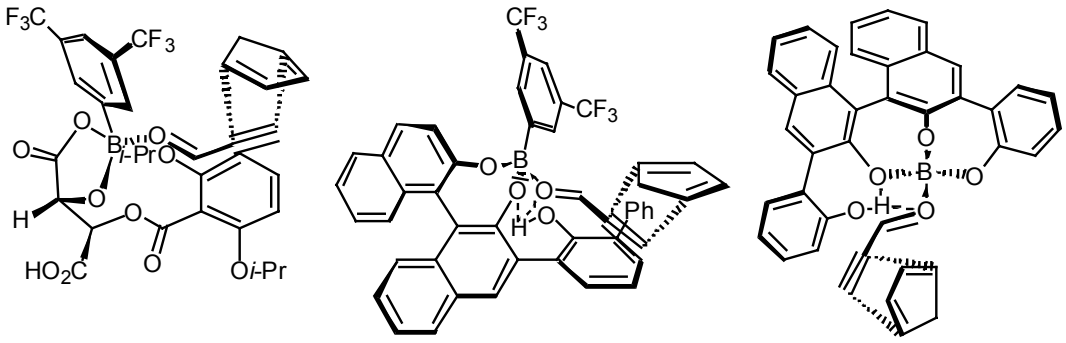
Yamamoto and his colleagues reported the first example of an enantioselective reaction of dienes and acetylenic aldehydes catalyzed by chiral Lewis acids and an *ab initio* study which supports the predominance of an exo-transition structure, thus clarifying the origin of the enantioselectivity observed upon catalysis [305]. The reaction catalyzed by BLA proceeded with good enantioselectivity and conversion, although the use of CAB or BLA gave higher enantioselectivity in some cases.





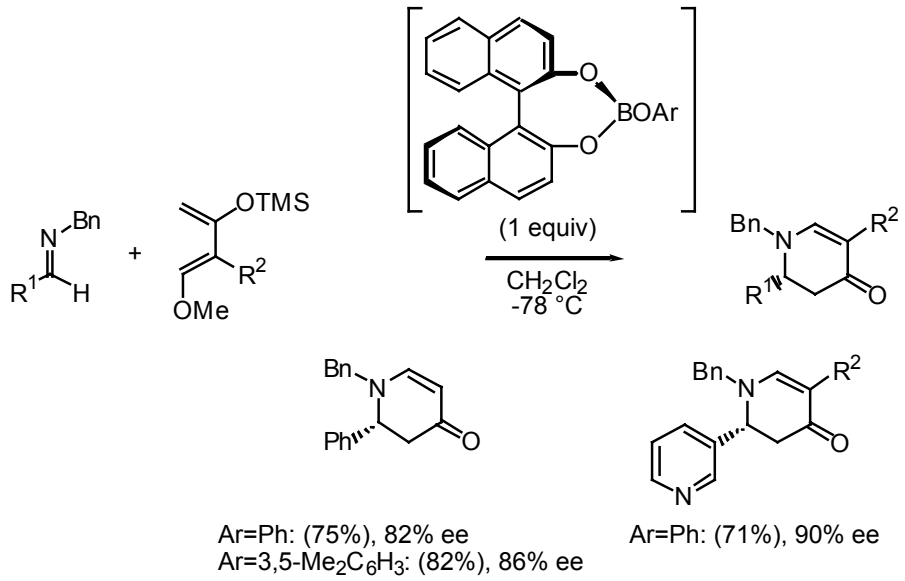
85% ee (BLA) 95% ee (BLA) 86% ee (CAB) 89% ee (CAB)

The absolute stereochemical outcomes attained in these reactions can be explained in terms of the anti-exo-transition-state models which are analogous to those previously proposed for the reaction of dienes and olefinic dienophiles. Simple *ab initio* molecular orbital calculations at the RHF/6-31G* level identified the transition structures of the processes: acid-free and BF_3-promoted reactions of cyclopentadiene and propynal. As expected, the calculations showed that the exo-transition structures are more stable than the endo structures by 0.8 kcal/mol for the former reaction and by 2.0 and 2.4 kcal/mol for anti and syn pairs, respectively, for the latter.

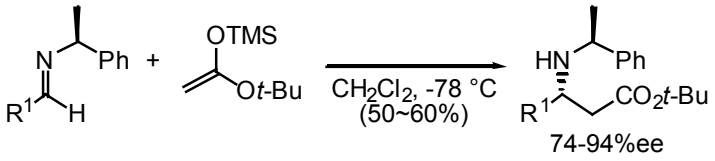


Proposed anti-exo-transition structures.

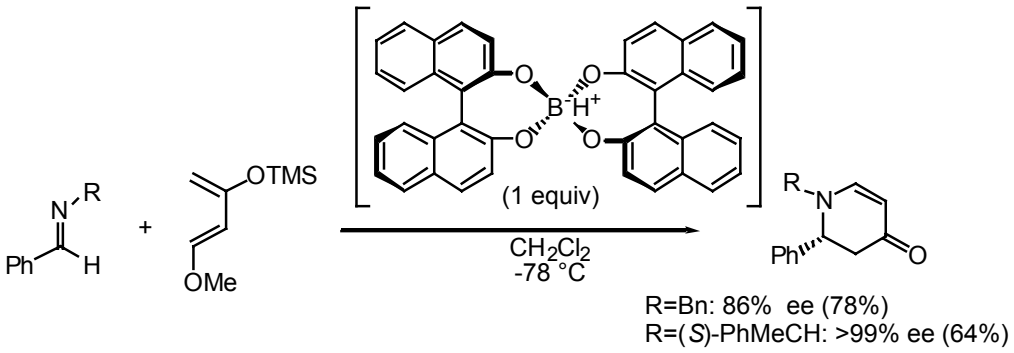
The aza-Diels-Alder reaction with a Danishefsky diene is promoted by another boron catalyst which was prepared from optically active binaphthol and traiarylborate [209, 220, 221, 223].



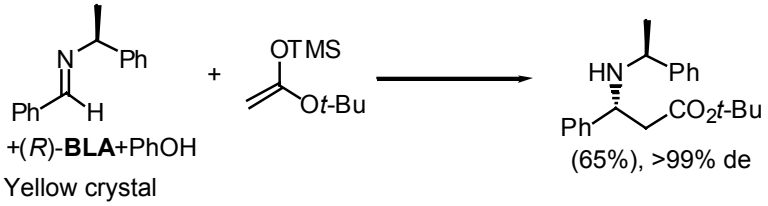
The same catalyst was effective for the stereoselective aldol-type reaction of aldimines with ketene silyl acetals [217, 233, 234, 253]. This method can be effectively applied to the preparation of β-lactam compounds including thienamycin and related carbapenems.



BLA, which is prepared from a 1:2 molar ratio mixture of a trialkylborate and optically pure binaphthol, is also an excellent chiral promoter for the aza Diels-Alder reaction of imines with Danishefsky dienes [265].

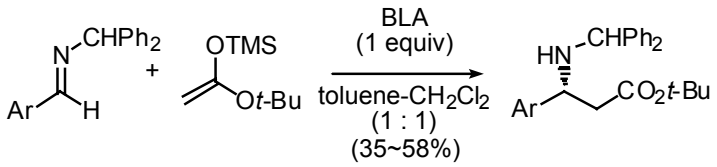


The same BLA is very useful in the double stereodifferentiation of aldol-type reactions of chiral imines [265]. The aldol-type reaction with trimethylsilyl ketene acetal derived from *tert*-butyl acetate using yellow crystals of (*R*)-**9**·(*S*)-benzylidene-α-methylbenzylamine·PhOH proceeds with unprecedented diastereoselectivity.



Based on the above results, Yamamoto developed the first method of

enantioselective synthesis of chiral β-amino acid esters from achiral imines and ketene silyl acetals using BLA [265, 271].

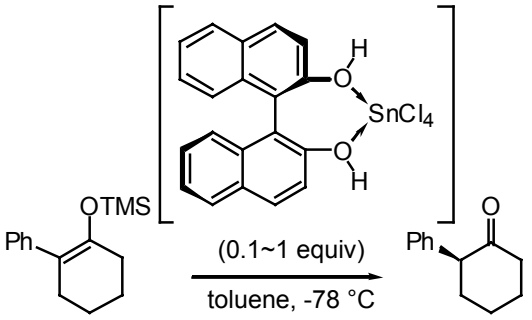


Ar=Ph: 96% ee (*R*) Ar=*p*-ClC_6H_4: 98% ee Ar=2,4-$Cl_2C_6H_3$: 95% ee
Ar=*p*-MeC_6H_4: 97% ee Ar=*p*-$AcOC_6H_4$: 98% ee Ar=2-naphthyl: 96% ee

4.3.2. Lewis Acid-assisted Chiral Brønsted Acids (LBA)

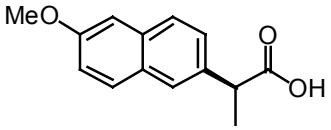
Enantioselective protonation of prochiral silyl enol ethers is a very simple but attractive route for preparing optically active carbonyl compounds. However, it is difficult to achieve high enantioselectivity using simple chiral Brønsted acids because of the conformational flexibility in the neighborhood of the proton. The coordination of a Lewis acid to a Brønsted acid would restrict the direction of the proton and increase its acidity. In 1994, Yamamoto and his colleagues found that the *Lewis acid assisted chiral Brønsted acid (LBA)* is a highly effective chiral proton donor for the enantioselective protonation [266, 304].

LBA is generated *in situ* from optically pure binaphthol and tin tetrachloride in toluene, and is stable in the solution even at room temperature. In the presence of a stoichiometric amount of (*R*)-LBA, the protonation of the TMS enol ether derived from 2-phenylcyclohexanone proceeded at -78 °C to give the (*S*)-isomer with 97% ee. This reagent is applicable to various ketene bis(trialkylsilyl) acetals derived from α-arylcarboxylic acids. The observed absolute stereopreference can be understood in terms of the proposed transition state assembly. The trialkylsiloxy group is directed opposite to the binaphthyl moiety in order to avoid any steric interaction, and the aryl group stacks on this naphthyl group.

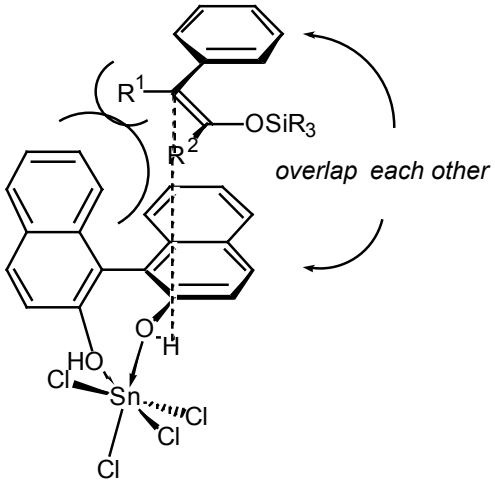


>95%, 97% ee (*S*)

Another example:

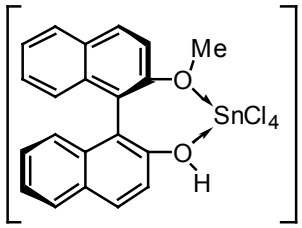


92% ee (*S*)
naproxen

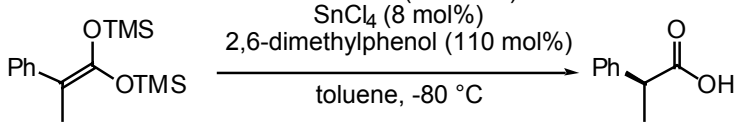


The Proposed Transition State Assembly

In further studies, Yamamoto and his colleagues succeeded in the enantioselective protonation using a stoichiometric amount of an achiral proton source and a catalytic amount of LBA [302].



BINOL-Me (10 mol%)
$SnCl_4$ (8 mol%)
2,6-dimethylphenol (110 mol%)

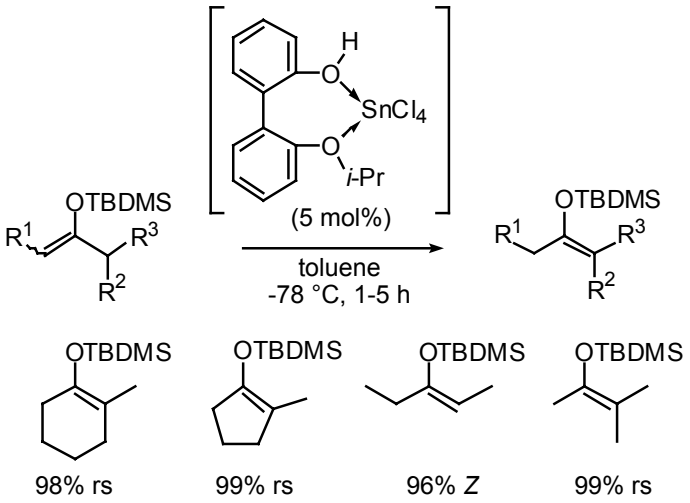


(addition over 1 h)

100% conv.

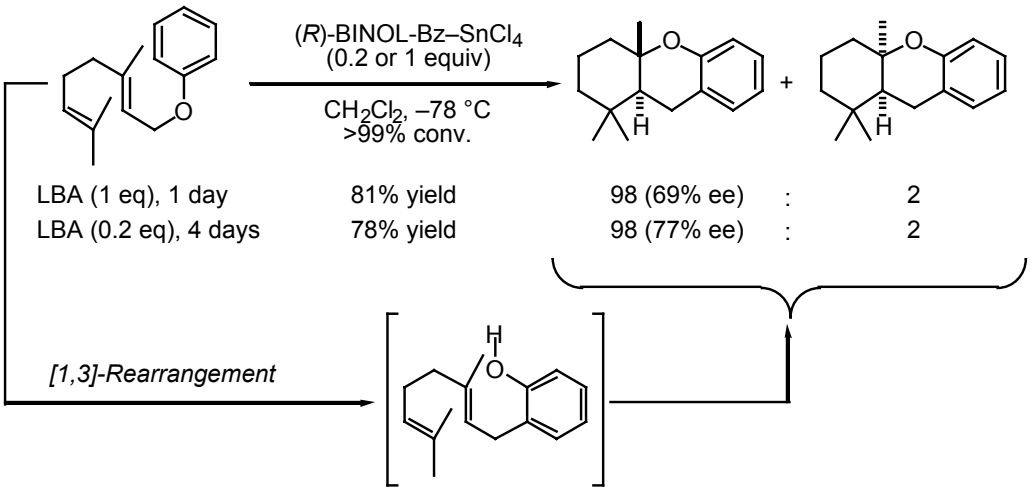
94% ee

The regio- and stereoselective isomerization of a “kinetic” silyl enol ether to a “thermodynamic” one was catalyzed by LBA [336]. “Kinetic” TBDMS enol ethers were isomerized to the “thermodynamic” ones in the presence of catalytic amounts of the coordinate complexes of tin tetrachloride and the monoalkyl ethers of BINOL or biphenol. For the various structurally diverse substrates, the isomerization cleanly proceeded in the presence of 5 mol% of the achiral LBA.



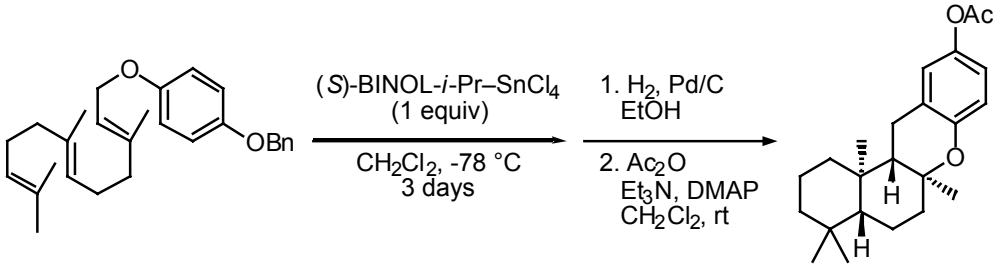
Despite extensive studies on acid-catalyzed diastereoselective polyene-cyclizations, their enantioselective processes have not yet been reported. Very recently, Yamamoto and his colleagues succeeded in the first enantioselective biomimetic cyclization of polyprenoids catalyzed by LBA [341].

Cyclization of *o*-geranylphenol with the monobenzoyl ester of (*R*)-BINOL ((*R*)-BINOL-Bz)-$SnCl_4$ complex in dichloromethane at –78 °C was completed within 1 day, and the transfused tricyclic compound was obtained as a major diastereomer (95% ds) in good yield with moderate induction of 54% ee. The same tricyclic ether was obtained with much better selectivity from geranyl phenyl ether. Surprisingly, the reaction proceeded smoothly even in the presence of 20 mol% of this LBA to give the desired compound with 77% ee and 98% ds. Geranyl phenyl ether is more reactive than *o*-geranylphenol due to the lack of a hydroxy group.



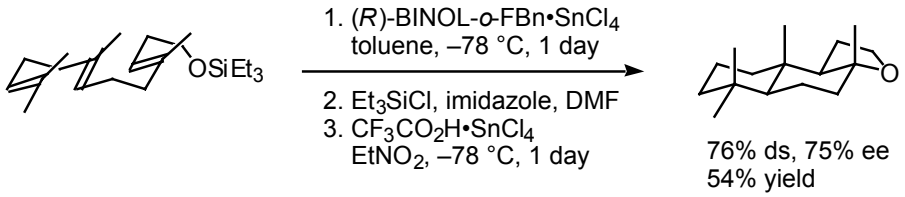
It is surmised that this reaction takes place *via* a [1,3]-rearrangement and subsequent cyclization,. The use of this LBA without exception resulted in the high enantioselectivity (up to 90%ee) and diastereoselectivity.

To demonstrate the effectiveness of the LBA-promoted enantioselective cyclization, the biomimetic synthesis of (–)-chromazonarol, a minor constituent of the brown Pacific seaweed., was performed. The cyclization of 4-benzyloxyphenyl farnesyl ether with (*S*)-LBA gave the desired tetracyclic compound as the major diastereomer.

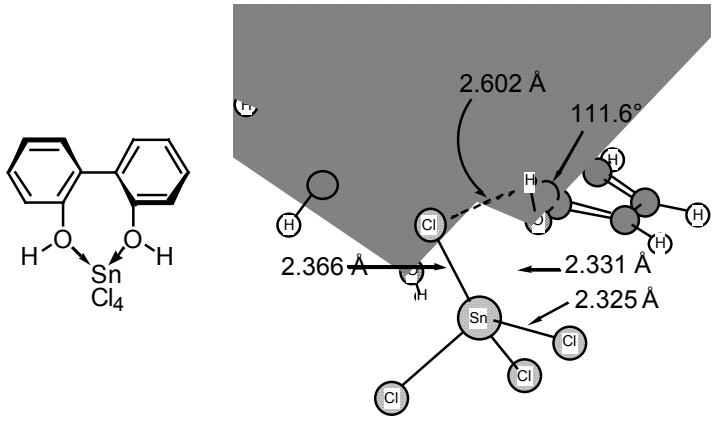


ca. 40% overall yield, 44% ee

(–)-Ambrox® was synthesized via the enantioselective cyclization of (*E*,*E*)-homofarnesyl triethylsilyl ether with tin(IV) chloride-coordinated (*R*)-2-(*o*-fluorobenzyloxy)-2'-hydroxy-1,1'-binaphthyl ((*R*)-BINOL-*o*-FBn) and subsequent diastereoselective cyclization with CF_3CO_2H•$SnCl_4$ as key steps [391].

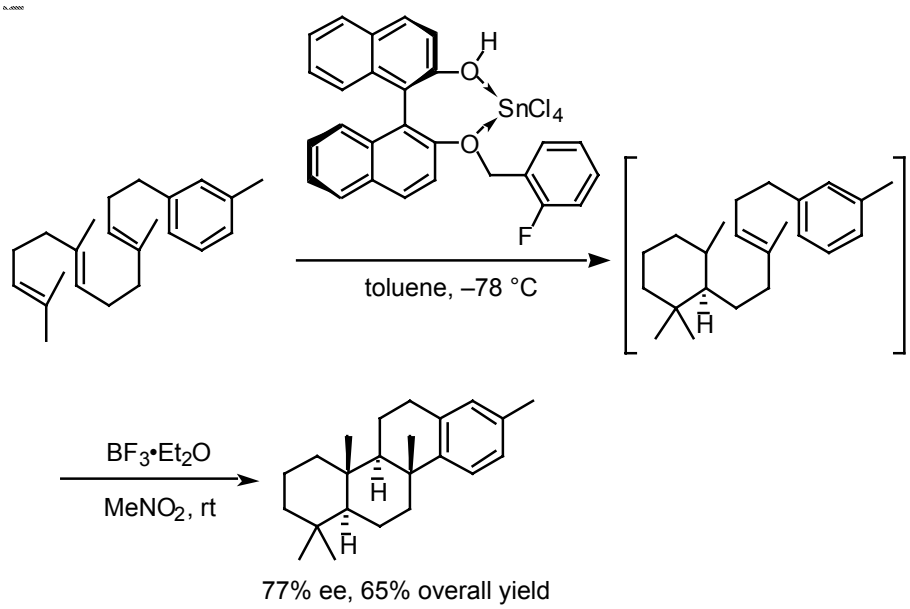


The optimized structure of a BIPOL–$SnCl_4$ complex was determined at the B3LYP/LANL2DZ level to understand the absolute stereochemical outcome of the cyclizations. It is noteworthy that two acidic protons are probably located at pseudo-axial sites parallel to the apical axis of the tin atom, and an electrostatic interaction between the acidic protons and the apical chlorines is expected.



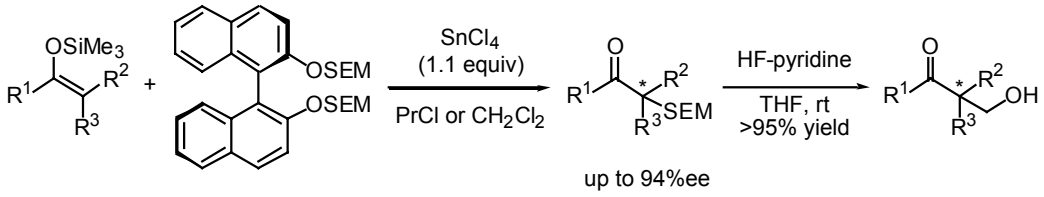
Optimized geometry of a biphenol–$SnCl_4$ complex

Nonenzymatic enantioselective polyene cyclization of homo(polyprenyl)arenes is an attractive application of the new method. Yamamoto and his colleagues have demonstrated the effectiveness of chiral LBAs for absolute stereocontrol in the initial cyclization step of homo(polyprenyl)arenes to form an A-ring and the importance of the nucleophilicity of the internal terminator in homo(polyprenyl)arenes for the relative stereocontrol in the subsequent step. For example, a tetracyclic polyprenoid from Eocene Messel shale (Germany) was synthesized with 77% ee in good yield by using the LBA-induced enantioselective cyclization as a key step.



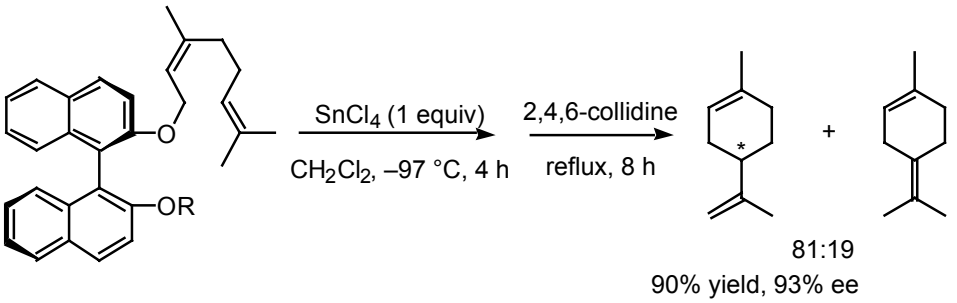
4.3.3. Enantioselective SEM Addition Reaction Using $SnCl_4$–BINOL(SEM)$_2$

Yamamoto and his colleagues developed the enantioselective alkoxymethylation of silyl enol ethers by introducing suitable carbon-electrophiles in place of the activated-protons of LBA [348]. Thus, the reaction of the trimethylsilyl enol ether derived from 2-phenylcyclohexanone with the bis[trimethylsilyl(ethoxy)methyl (SEM)] ether of (*R*)-BINOL was promoted in the presence of $SnCl_4$, and the (*R*)-α-SEM ketone was obtained in 91% yield with up to 94% ee.



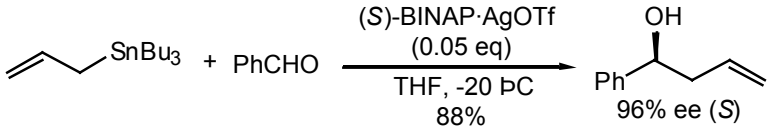
4.3.4. Asymmetric Synthesis of (*R*)-Limonene Using a Chiral Leaving Group

A six-membered monocyclic terpene, (*R*)-limonene have been synthesized by new enantioselective intramolecular cyclization reactions of neryl ether using an (*R*)-1,1'-binaphthyl-2-benzoxy-2'-oxy auxiliary as a chiral leaving group in the presence of tin(IV) chloride [377, 393].



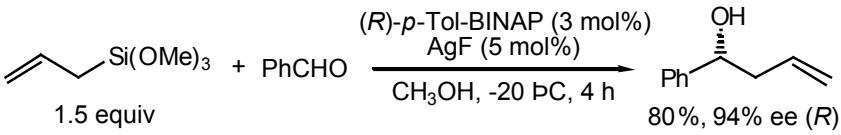
4.4. Catalytic Asymmetric Allylation and Aldol Reaction with Aldehydes Using a Chiral Silver(I) Complex

Yamamoto and his colleagues found that a BINAP·silver(I) complex also catalyzes the asymmetric allylation of aldehydes with allylic stannanes, and high γ-, anti-, and enantioselectivities are obtained by this method [R-27, R-30, R-31, 296, 308, 321]. The chiral phosphine-silver(I) catalyst can be prepared simply by stirring an equimolar mixture of chiral phosphine and silver(I) compound in THF at room temperature. Treatment of benzaldehyde with allyltributyltin under the influence of 5 mol % of (*S*)-BINAP·silver(I) triflate in THF at -20 ˚C provides the corresponding (*S*)-enriched homoallylic alcohol in 88% yield with 96% ee. The reaction furnishes high yields and remarkable enantioselectivities not only with aromatic aldehydes but also with α,β-unsaturated aldehydes and aliphatic aldehydes [296]. Enantioselective addition of methallyltributylstannane to aldehydes can also be achieved using this method [308].

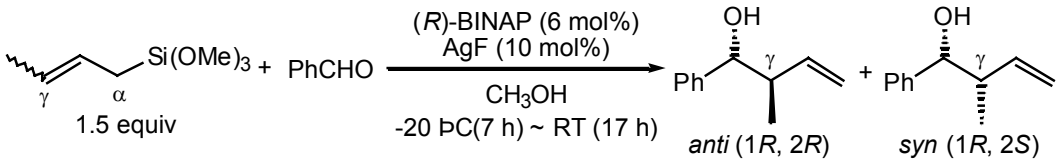


4.4.1. Enantioselective Addition of Allylic Trimethoxysilanes to Aldehydes Catalyzed by *p*-Tol-BINAP·AgF [349]

Treatment of benzaldehyde with allyltrimethoxysilane in MeOH under the influence of (*R*)-BINAP·AgF complex (10 mol %) at -20 ˚C for 4 h gave the corresponding (*R*)-enriched homoallylic alcohol in 72% yield with 91% ee. It should be noted that, when (*R*)-BINAP·AgOTf complex was used as a catalyst, a racemic homoallylic alcohol was obtained in only 5% yield. After careful investigation to optimize the reaction conditions and the allylation proceeded in higher yield and enantioselectivity when only 3 mol % of (*R*)-*p*-Tol-BINAP was present.



The BINAP·AgF-catalyzed reaction of (*E*)- and (*Z*)-crotyltrimethoxysilane with benzaldehyde gave remarkable γ- and *anti* selectivities for the reaction with crotylsilanes, irrespective of the configuration at the double bond. Thus, addition of (*E*)-enriched crotyltrimethoxysilane (*E*/*Z* = 83/17) to benzaldehyde in the presence of 6 mol % of (*R*)-BINAP and 10 mol % of AgF in MeOH at -20 ˚C ~ r.t. exclusively gives the γ-adducts with an *anti/syn* ratio of 92/8. The *anti*-isomer indicates 96% ee with a 1*R*,2*R* configuration. Use of (*Z*)-crotyltributyltin (*E*/*Z* < 1/99) or a nearly 1:1 mixture of the (*E*)- and (*Z*)- crotyltrimethoxysilane also results in a similar *anti/syn* ratio and enantioselectivity.

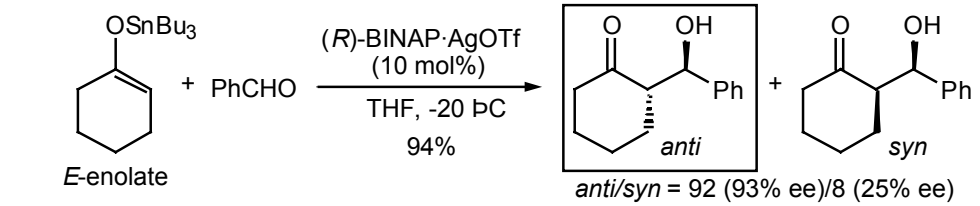


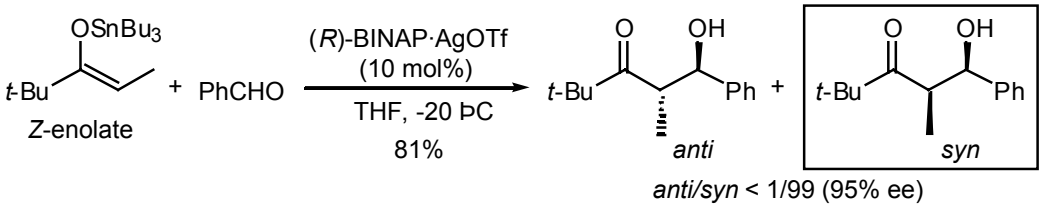
E/*Z* ratio	Yield (%)	*anti* (% *ee*)/*syn* (% *ee*)
83/17	77	92 (96)/8 (62)
<1/99	82	94 (94)/6 (60)
45/55	99	93 (94)/7 (60)

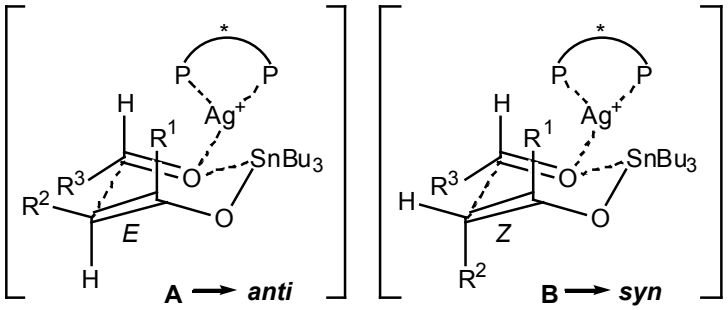
4.4.2. Enantioselective Aldol Reaction of Tin Enolates with Aldehydes Catalyzed by BINAP·Silver(I) Complex [R-27, 324]

The aldol reaction of tributyltin enolates with aldehydes is catalyzed by a BINAP·silver(I) complex with high diastereo- and enantioselectivities. The catalytic aldol reaction of a variety of tributyltin enolates with typical aromatic, α,β-unsaturated, and aliphatic aldehydes was obtained in up to 95% ee. Addition of substituted enol stannanes to aldehydes also proceeds to furnish high diastereo- and enantioselectivities using this chiral catalyst. For example, treatment of the tributyltin enolate of cyclohexanone (1 equiv) with benzaldehyde (1 equiv) under the influence of 10 mol % of (*R*)-BINAP·AgOTf complex in dry THF at -20 ˚C gives the optically active *anti* aldol product preferentially with an *anti/syn* ratio of 92/8. The *anti*-isomer indicates 93% ee with a 2*S*,1'*R* configuration. In contrast, the *Z*-enolate derived from *tert*-butyl ethyl ketone provides the *syn* aldol adduct nearly exclusively with 95% ee. These results

show that the diastereoselectivity depends on the geometry of enol stannane and that six-membered cyclic transition-state structures **A** and **B** are probable models.



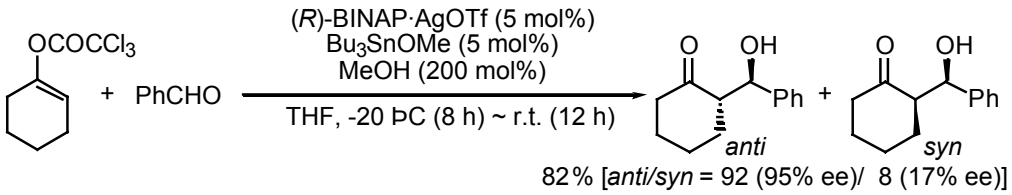




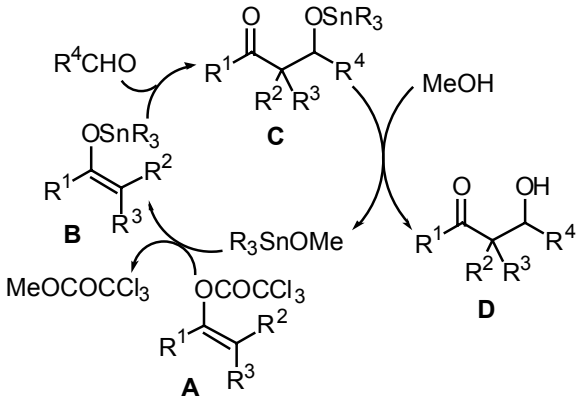
Probable cyclic transition-state structures.

4.4.3. Enantioselective Aldol Reactions Catalyzed by Tin Methoxide and BINAP·Silver(I) Complex [351]

Since the aldol process has the disadvantage of requiring the stoichiometric use of toxic trialkyltin compounds [324], Yamamoto and his colleagues achieved the aldol reaction using a catalytic amount of tin enolate and the asymmetric version with BINAP·silver(I) catalyst. Thus, treatment of benzaldehyde with the aforementioned enol trichloroacetate in the presence of (*R*)-BINAP·AgOTf complex (5 mol %), tributyltin methoxide (5 mol %), and MeOH (200 mol %) in dry THF at -20 ˚C for 8 h and then at room temperature for 12 h gave a 92:8 mixture of optically active *anti* and *syn* aldol adduct in 82% combined yield. The *anti* isomer showed 95% ee with (2*S*,1'*R*)-configuration, a level of enantioselectivity similar to that observed for a BINAP·silver(I) catalyzed aldol reaction of tributyltin enolates.



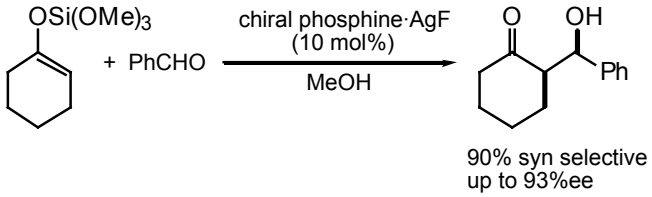
A possible catalytic cycle of this aldol reaction is shown below. First, Bu_3SnOMe reacts with an enol trichloroacetate **A** to generate the trialkyltin enolate **B** and methyl trichloroacetate. Subsequently, the tin enolate **B** can be added to benzaldehyde to give the aldol adduct **C**. Finally, protonolysis of the alkoxide **C** by MeOH produces the product **D** and regenerates the tin methoxide. The rate of methanolysis is regarded as the key to success in the catalytic cycle.



A possible catalytic cycle.

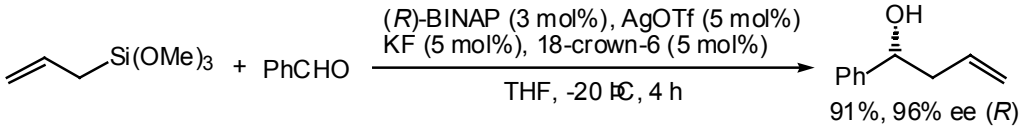
4.4.4 Enantioselective Aldol Reaction of Trimethoxysilyl Enol Ethers with Aldehydes Catalyzed by *p*-Tol-BINAP·AgF Complex

Recently, Yamamoto and his colleagues has achieved novel and practical asymmetric aldol reaction with trimethoxysilyl enol ethers catalyzed by *p*-Tol-BINAP·AgF complex. The procedure can be performed without any difficulty employing readily available chemicals and can provide various optically active β-hydroxy ketones with high enantioselectivity up to 97% ee. Furthermore, remarkable *syn* selectivity was observed for the reaction independent of the *E/Z* stereochemistry of the silyl enol ethers.



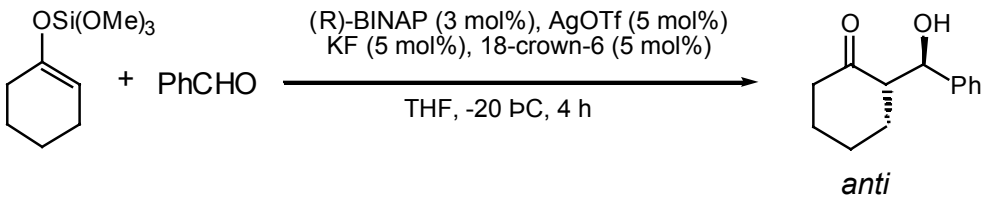
4.4.5 Enantioselective Addition of Allyltrimethylsilane to Aldehydes Catalyzed by BINAP·AgOTf, KF, and 18-Crown-6

More recently, Yamamoto and his colleagues have achieved an asymmetric Sakurai-Hosomi allylation of aldehydes with allylic trimethoxysilanes catalyzed by BINAP·AgOTf complex, KF, and 18-crown-6. He attempted KF and 18-crown-6 as co-catalysts for the reaction anticipating that the fluoride ion would activate the allylic silanes. Treatment of benzaldehyde with 3 equiv of allyltrimethoxysilane in THF under the influence of (*R*)-BINAP (3 mol%), AgOTf (5 mol%), KF (5 mol%), and 18-crown-6 (5 mol%) at -20 ˚C for 4 h gave the corresponding (*R*)-enriched homoallylic alcohol in 91% yield with 96% ee .



4.4.6 Enantioselective Aldol Reaction of Trimethylsilyl Enol Ethers with Aldehydes Catalyzed by BINAP·AgOTf, KF, and 18-Crown-6

The new chiral catalytic system (BINAP·AgOTf/KF/18-crown-6) described above was further successfully applied to the catalytic asymmetric aldol condensation of trimethoxysilyl enol ethers with aldehydes. Treatement of trimethoxysilyl enol ether of cyclohexanone (1 equiv) with benzaldehyde (1 equiv) in the presence of (*R*)-BINAP (3 mol%), AgOTf (5 mol%), KF (5 mol%), and 18-crown-6 (5 mol%) in dry THF at -20 ˚C gave the optically active *anti* aldol product preferentially with an *anti/syn* ratio of 92/8. The *anti*-isomer indicates 93% ee with a 2*S*,1'*R* configuration.



52% [anti/syn = 92 (93% ee)/8]

Chapter 5 Other New Synthetic Reactions

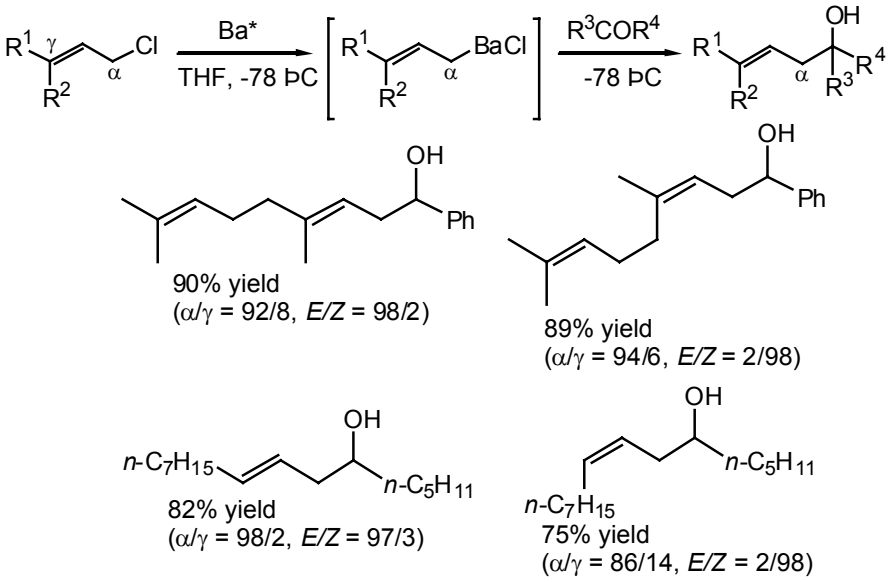
5.1. Allylbarium and Related Allylmetal Reagents for Organic Synthesis

5.1.1 Allylbarium in Organic Synthesis: α-Selective and Stereospecific Allylation of Carbonyl Compounds [R-22, R-23, R-31]

The allylic organometallic compounds of heavier alkaline-earth metals have found little application in organic synthesis, since they do not offer any particular advantages over simple Grignard reagents. Yamamoto and his colleagues have been interested in using barium or strontium reagents with the anticipation that such species would exhibit stereochemical stability markedly different from that of the ordinary magnesium reagents. Allylic barium reagents, generated from the corresponding allylic chlorides and reactive barium, undergo reaction with carbonyl compounds with high α-selectivity and stereospecificity.

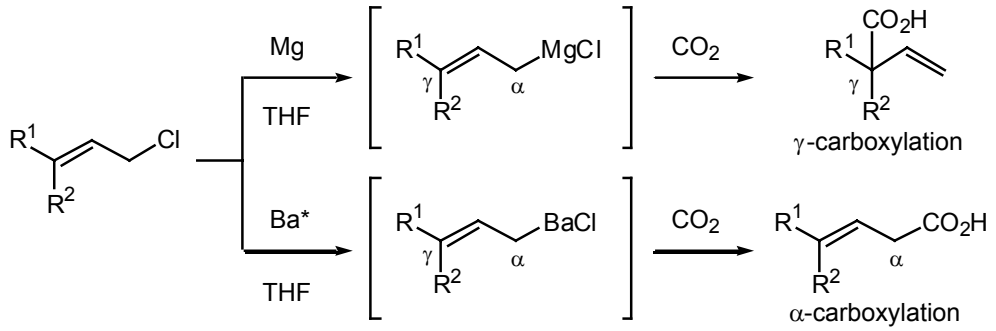
5.1.2 Allylbarium Reagents: Regio- and Stereoselective Allylation Reactions of Carbonyl Compounds [197, 211, 230, 255]

The first direct preparation of allylbarium reagents by reaction of *in situ* generated reactive barium with various allylic chlorides, and their new and unexpected selective allylation reactions of carbonyl compounds are disclosed. Highly reactive barium was readily prepared by the reduction of barium iodide with 2 equiv of lithium biphenylide in dry THF at room temperature. A variety of carbonyl compounds reacted with barium reagents generated from (E)- or (Z)-allylic chlorides in THF at -78 °C [197, 255].



All reactions resulted in high yields with remarkable selectivities not only with aldehydes but also with ketones. The double bond geometry of the starting allylic chloride was completely retained in each case.

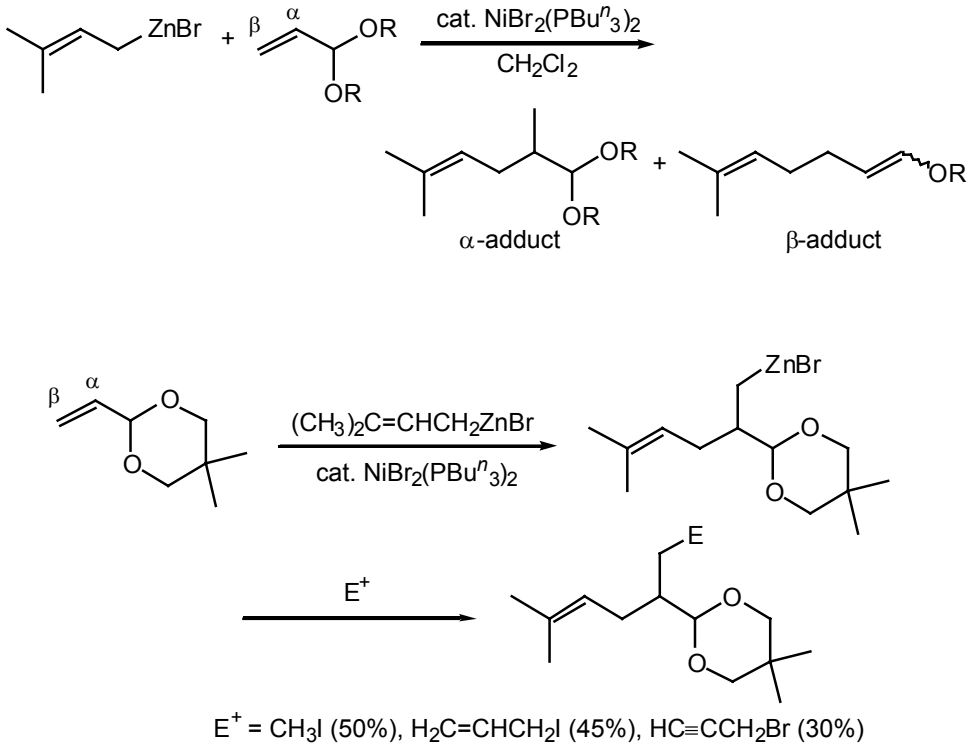
β,γ-Unsaturated carboxylic acids and their derivatives are valuable synthetic intermediates of various natural products. One straightforward way to obtain β,γ-unsaturated acids is by the carboxylation of an allylmetal. In the substituted allylic series, the reaction usually occurs at the more sterically hindered terminus. However, carboxylation of allylic barium reagent shows α-selectivity without loss of the double bond geometry [211, 230, 255].



5.1.3 Double Alkylation of α,β-Unsaturated Acetals. An Inverse Polarity Approach [153]

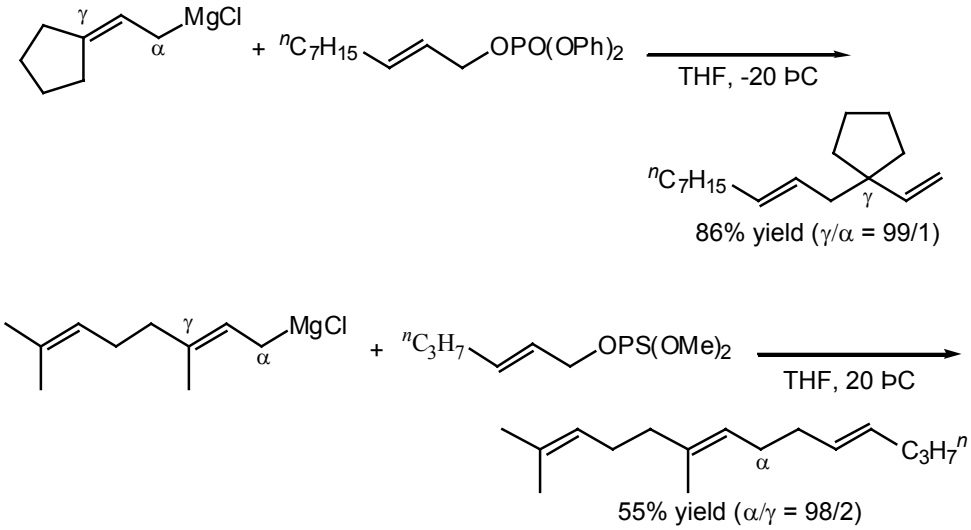
Yamamoto and his colleagues have found that an α,β-unsaturated acetal undergoes rapid metallation upon treatment with allylic zinc reagents in the presence of a nickel catalyst.

Copper or nickel-catalyzed reaction of Grignard reagent with α,β-unsaturated acetals was reported to produce only the corresponding Michael-type addition (β-alkylation) products in moderate yields. In some cases, the more reactive allylic Grignard reagent reacts with nonactivated double bonds. Allylic zinc reagents, in contrast, are relatively unreactive toward alkenic bonds. Treatment of 1 equiv of the α.β–unsaturated acetal with a solution of prenylzinc bromide (3.5 equiv) under the influence of catalytic $NiBr_2(PBu_3)_2$ (10 mol %) at 40 °C for 30 min gave an α-adduct almost exclusively.

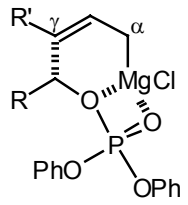


5.1.4. γ-Selective Nucleophilic Substitution Reaction of Allylmetal Reagents: A New Cross-Coupling of Diphenylphosphates with Allylic Grignard Reagents [227]

The highly γ-selective cross-coupling reaction of allylic Grignard reagent was achieved using diphenylphosphate as electrophile. Yamamoto and his colleagues examined the various kinds of leaving groups and the diphenylphosphate ester revealed this unique regioselectivity. For example, treatment of (E)-2-decenyl-1-diphenylphosphate with 2-cyclopentylideneethylmagnesium chloride in THF at -20 °C afforded the γ-alkylated product in 86% yield with an γ/α ratio of 99/1. In contrast, the dimethylthiophosphates, for which the longer P-S bond would be expected, showed entirely different results and afforded the α-coupling product nearly exclusively.



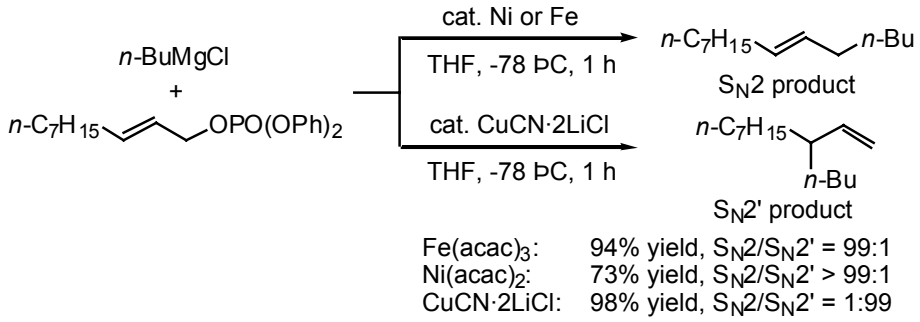
The reason for these striking features in regioselectivity may be the fact that, in the normal alkylation of an allyl metal to an alkyl halide, an acyclic transition structure is formed that brings a mixture of α- and γ-alkylation products. With diphenylphosphates, on the other hand, bidentate leaving groups coordinate with magnesium metal to produce a γ-alkylation product selectively via a rigid bicyclic transition structure.



5.1.5. Transition Metal-Catalyzed Substitution Reaction of Allylic Phosphates with Grignard Reagents [R-31, 242, 248]

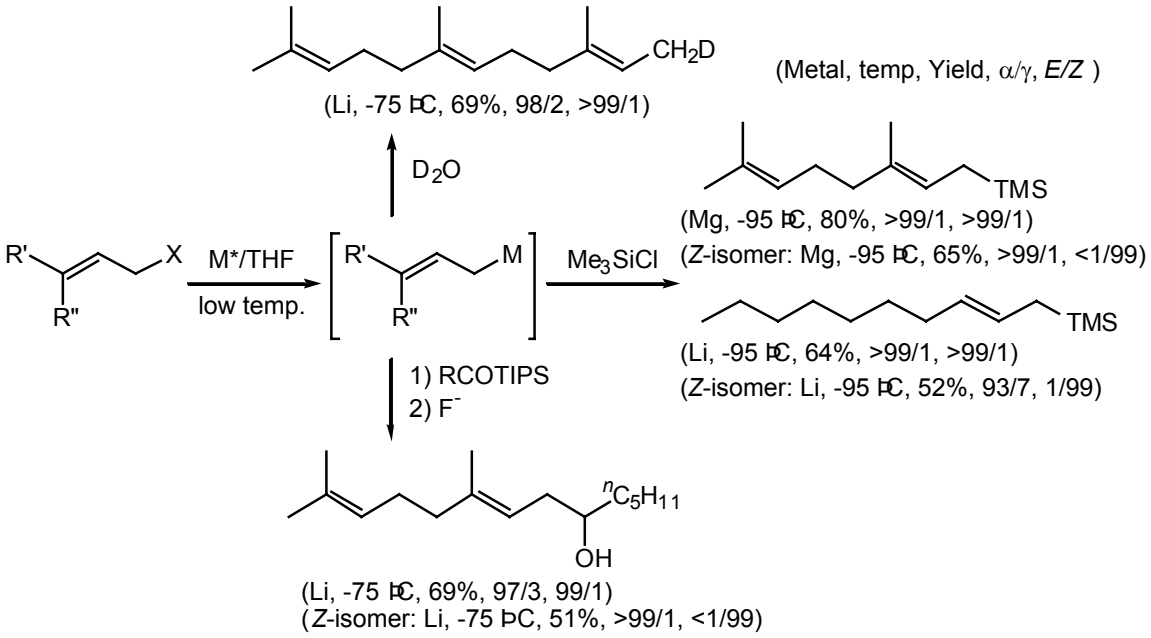
Transition metal-catalyzed substitution reaction of alkyl halides with Grignard reagents is generally described as the Kharasch reaction. In the cross-coupling reaction of allylic substrates, the regioselectivity has been actively studied with a variety of leaving groups but to a lesser extent with phosphate leaving groups. Yamamoto and his colleagues examined the transition metal catalysts most suitable for the regioselective coupling of allylic phosphates with Grignard reagents and found that iron, nickel, and copper compounds showed remarkable catalytic activities. In addition, nearly exclusive S_N2-regioselectivities were obtained using Fe and Ni catalysts, while S_N2'-

regioselectivity was observed for CuCN-2LiCl.



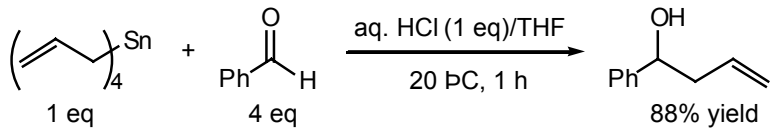
5.1.6. Direct Insertion of Alkali (Alkaline-Earth) Metals into Allylic Carbon-Halogen Bonds Avoiding Stereorandomization [R-22, R-23, R-31, 188, 255]

Allylic alkali and alkaline-earth metal compounds are popular allylating reagents that exhibit high reactivity toward various functional groups of organic molecules. However, these allylic organometallics readily isomerize between the E- and Z-isomers. If the stereo-randomization of an allylic metal is due to rapid isomerization through metallotropic 1,3-rearrangements that are temperature dependent, a stereochemically pure allylic metal should be generated from the corresponding allylic halide by its reaction with reactive metal below the isomerization temperature. Thus, Yamamoto and his colleagues investigated the temperature dependence of the E/Z ratio of geranyl, neryl, and 2-decenylmetals (Mg, Li, Na, and K), directly prepared from the corresponding allylic halides and reactive metals. The result was that extremely high stereoretention was observed below -95 °C for geranyl and neryl magnesium chloride. In contrast, the double bond geometry of the alkali allylmetals was retained even at higher temperature. The versatility of stereochemically homogeneous mono- and disubstituted allylmetals in synthesis is noteworthy, as is their complementary relationship to other key functional groups. Stereochemically pure allylic silanes can be prepared easily from the corresponding Grignard or lithium derivatives. Deuteration can be accomplished smoothly and selectively. Reaction of carbonyl derivatives selectively produced the stereochemically homogeneous homoallylic alcohols.



5.1.7. Highly Chemoselective Allylation of Carbonyl Compounds with Tetraallyltin in Acidic Aqueous Media [229]

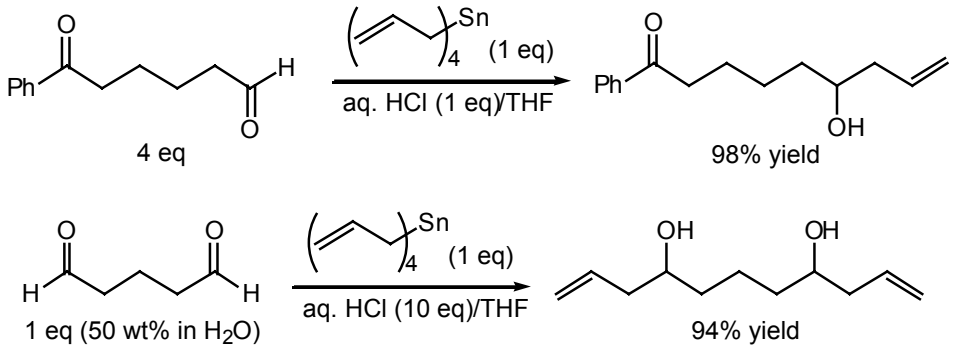
Yamamoto and his colleagues has found a novel allylation reaction of carbonyl compounds by tetraallyltin in acidic aqueous media which shows exclusive chemoselectivity toward aldehydes. Reaction of 4 equiv of benzaldehyde with tetraallyltin (1 equiv) in a 1:8 mixture of 2N HCl (1 equiv) and THF at 20 °C exclusively afforded the corresponding homoallyl alcohol.



Noteworthy is the fact that tetraallyltin decomposes relatively slowly in acidic aqueous media and four of the allyl groups on tin metal reacted with carbonyl compounds in the presence of 1 equiv of hydrochloric acid. None of the organic tin compound was produced and thus the work-up of the reaction proceeded quite smoothly.

Ketone was inert under the standard reaction conditions except for cyclohexanone, which showed a relatively high reactivity. The above results suggested a possibility of chemoselective addition of tetraallyltin to aldehydes in the presence of ketones. Indeed, in a competitive reaction of benzaldehyde and acetophenone with tetraallyltin, only the aldehyde adduct was obtained with 99.98% selectivity.

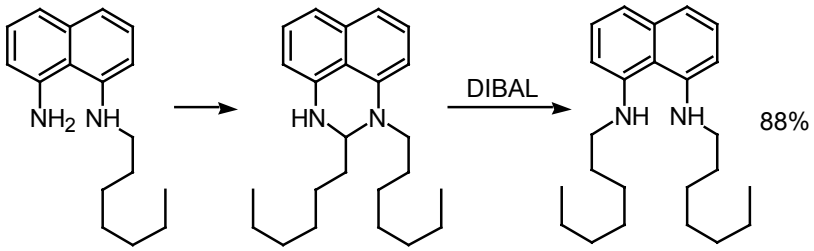
Intramolecular discrimination of carbonyl groups is also possible with tetraallyltin under acidic media. Thus, reaction of keto-aldehyde with tetraallyltin resulted in complete chemoselectivity (>99%) towards aldehyde. Water-soluble aldehyde was used without any difficulty and treatment of an aqueous solution of glutaraldehyde with tetraallyltin in the presence of excess acid afforded the diallylated product in 94% yield.



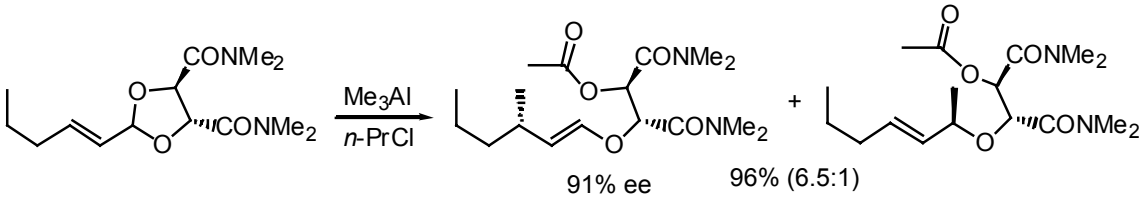
5.2. Selective Cleavage of Acetals

5.2.1. Cleavage of C-O and C-N Bond

Organoaluminum has strong Lewis acidity and thus strongly coordinates with heteroatoms such as N or O. This characteristic advantage was used elegantly for the cleavage of aminals or acetals. DIBAL is an effective and selective reducing agent that cleanly converts 1-heptyl-2-hexyl-2,3-dihydropyrimidine to 1,8-bis(heptylamino)naphthalene in a high yield [57].

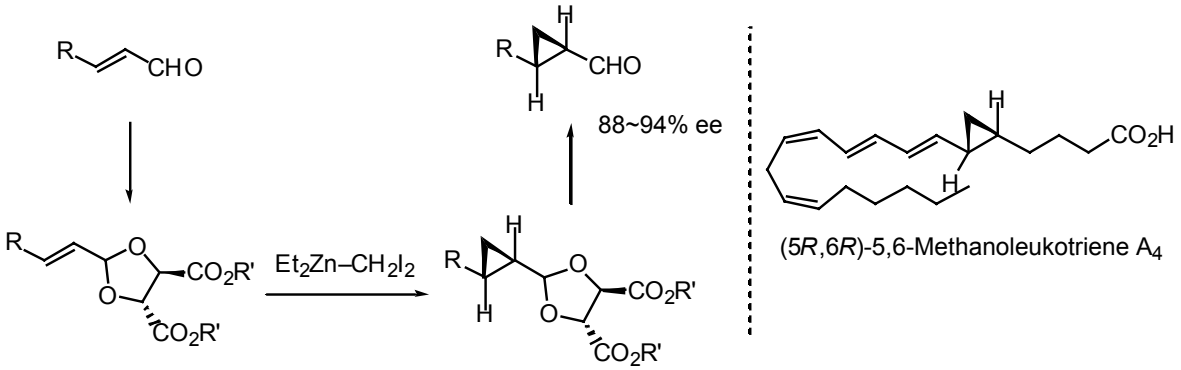


Optically active acetals were cleaved regio- and stereoselectively by organoaluminum reagents [90]. Chiral unsaturated acetals derived from tartaric acid undergoes ring-opening alkylation in the presence of a trialkylaluminum to give 1,4- and 1,2-adduct in high optical purity.



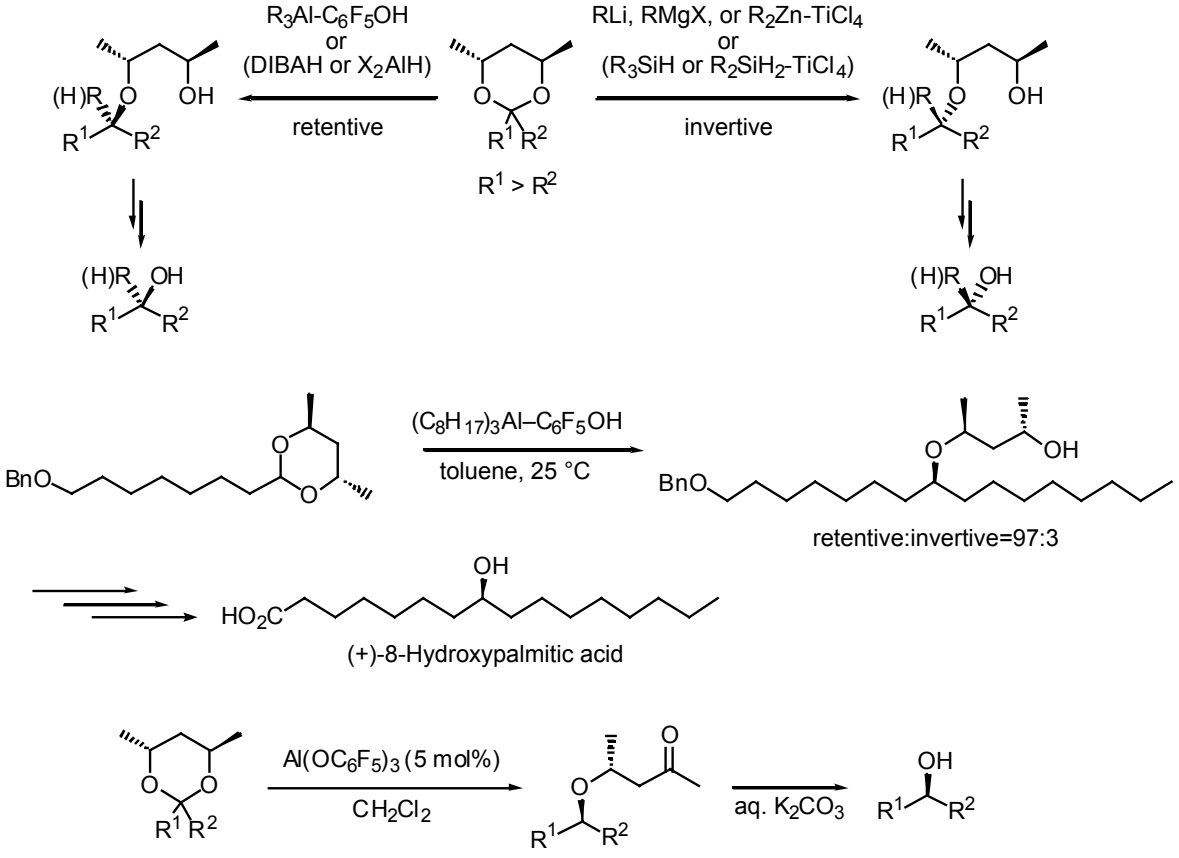
5.2.2. Diastereoselective Synthesis Using Chiral Acetals

Diastereoselective Simmons-Smith reactions of α,β-unsaturated acetals derived from chiral dialkyl tartarate or (2R,4R)-2,4-pentanediol were developed [105, 122]. Treatment of the acetal with diethylzinc and methylene iodide gives a cyclopropane with high diastereoselectivity. The acetal group is readily transformed to the aldehyde or the ester group. In addition, the method is successfully applied to the enantioselective synthesis of 5,6-methanoleukotriene A4, a stable and selective inhibitor of leukotriene biosynthesis.

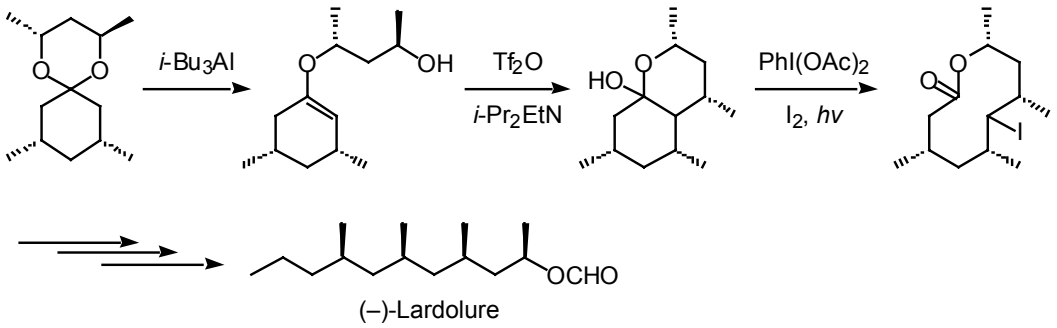


Chiral acetals derived from aldehydes and (2R,4R)-2,4-pentanediol are cleaved selectively by organoaluminum reagents [78 , 89, 95, 111, 112, 172]. The reaction proceeds via the retentive-alkylation process with >95% selectivities in most cases. Trialkylaluminum reagent is utilized for higher alkyl transfers, but for smaller alkyl transfers, a new reagent system, combining trialkylaluminum and the halophenols such as pentafluorophenol and 2,4,6-trichlorophenol is employed [185, 237]. Chiral acetals derived from aldehydes and 1,3-butanediol are cleaved selectively by trialkylaluminum, even for smaller alkyl transfers. The reaction of acetals derived from (2R,4R)-2,4-pentanediol and ketones in the presence of a catalytic amount of aluminum pentafluorophenoxide produces reductively cleaved products with high diastereoselectivity. The reaction is a new means of diastereoselective cleavage of acetals: an intramolecular Meerwein-Ponndorf-Verley reductive and Oppenauer

oxidative reaction on an acetal template [219]. In contrast, alkylative cleavage of the same chiral acetals using Lewis acid-alkylmetal systems and reductive cleavage of the same acetals using Lewis acid-trialkylsilane or dialkylsilane systems occur inversely [112, 123, 130, 157, 171].



(-)-Lardolure has been synthesized elegantly by intramolecular cyclization of vinyl ether alcohol derived from spiroacetal via triisobutylaluminium [150] and further ring enlargement of the afforded bicyclic hemiacetals [173, 278, 294]. The same method was utilized for new stereospecific ring enlargement to yield medium and large rings from simple ketones [173, 278, 294].



□□ Lewis Acid-Catalyzed Esterification and Amidation

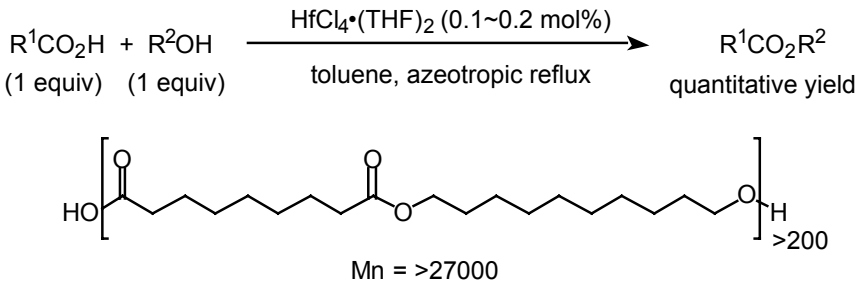
5.3.1. Esterification

Scandium trifluoromethanesulfonate (triflate), which is commercially available, is a practical and useful Lewis acid catalyst for acylation of alcohols with acid anhydrides or the esterification of alcohols by carboxylic acids in the presence of *p*-nitrobenzoic anhydrides. The remarkably high catalytic activity of scandium triflate can be used to assist the acylation by acid anhydrides of not only primary alcohols but also sterically-hindered secondary or tertiary alcohols. The method presented is essentially effective for selective macrolactonization of ω-hydroxy carboxylic acids [274, 299].

$$R^2OH + (R^1CO)_2O \xrightarrow[CH_3CN]{\text{cat. } Sc(OTf)_3} R^1CO_2R^2$$

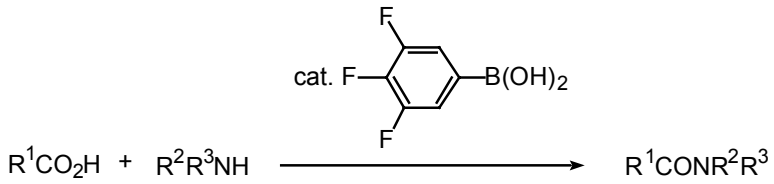
$$R^2OH + R^1CO_2H \xrightarrow[(p\text{-}NO_2C_6H_4CO)_2O,\ CH_3CN]{\text{cat. } Sc(OTf)_3} R^1CO_2R^2$$

In order to promote atom efficiency in synthesis and to avoid the generation of environmental waste, the use of stochiometric amounts of condensing reagents or excess substrates should be avoided. In esterification, excesses of either carboxylic acids or alcohols are normally needed. Yamamoto and his colleagues showed that the direct condensation of equimolar amounts of carboxylic acids and alcohols can be achieved with the use of hafnium(IV) salts such as commercially available hafnium(IV) chloride and hafnium(IV) *tert*-butoxide. He also synthesized polyesters by polycondensing ω-hydroxycarboxylic acids and aliphatic diols in the presence of 0.2 mol% of $HfCl_4$•$(THF)_2$ in *o*-xylene with the removal of water for 1 day. In most cases, polycondensation proceeded quantitatively [371].

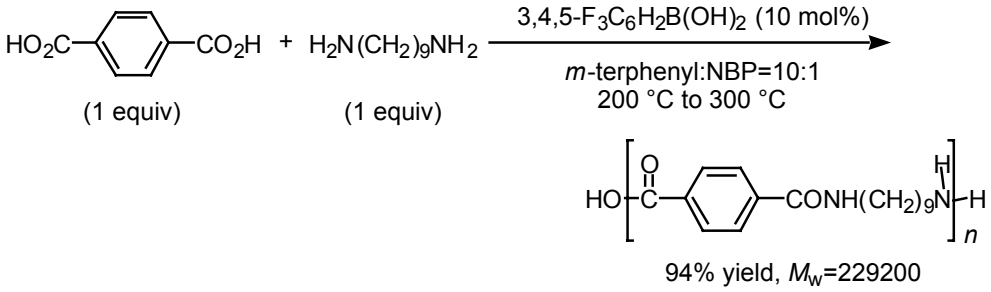


1 Amidation [297, 359,384]

Trifluorophenylboronic acid is a highly effective amidation catalyst between carboxylic acids and amines [297]. In the presence of a catalytic amount of catalyst the condensation proceeds in almost quantitative yields.

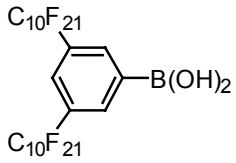


Polyamides are used in the production of synthetic fibers and engineering resins. Aromatic polyamides are particularly well-known as high-performance polymers due to their excellent thermal, mechanical, and chemical properties. Direct polycondensation that produces only a stoichiometric amount of water as a byproduct is the most ideal route, both environmentally and industrially. However, it is difficult to obtain aromatic polyamides with a high molecular weight by molten polycondensation. This has been explained primarily by the low reactivity of aromatic amines compared with that of aliphatic amines because of the resonance effect of phenyl groups. 3,45-Trifluorophenylboronic acid was for the first time shown to be a highly effective catalyst for the direct polycondensation to aramids, semiaromatic nylons, and polyimides [359].

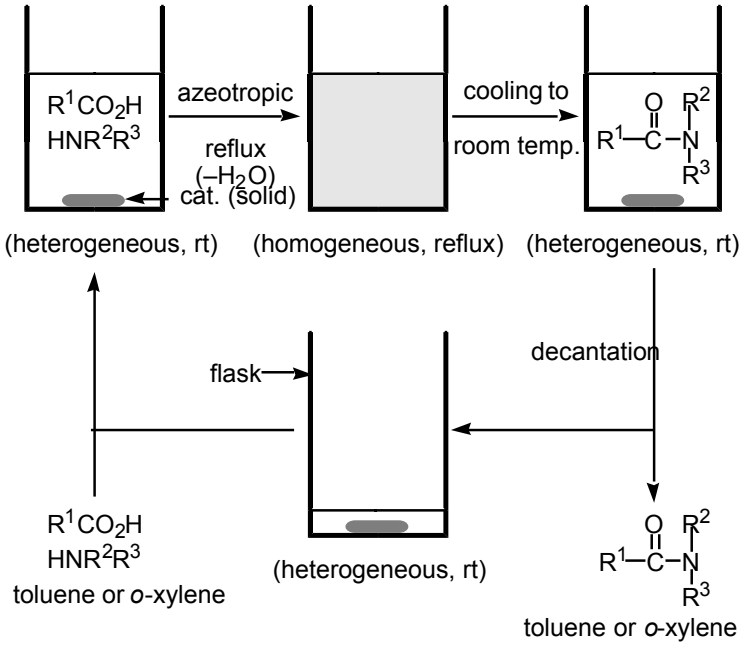


94% yield, M_w=229200

3,5-Bis(perfluorodecyl)phenylboronic acid has been synthesized based on the direct coupling of perfluorodecyl iodide with 1,3-diiodobenzene [384]. This new boronic acid is shown to be a fluorous catalyst for the direct amide condensation reaction by virtue of the strong electron-withdrawing effect and the immobility in the fluorous recyclable phase of the perfluorodecyl group.



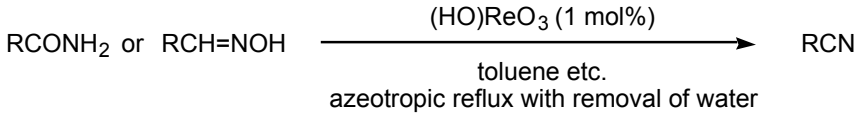
Fluorous esterification catalyst



Recovery of a catalyst by decantation and its reuse without isolation

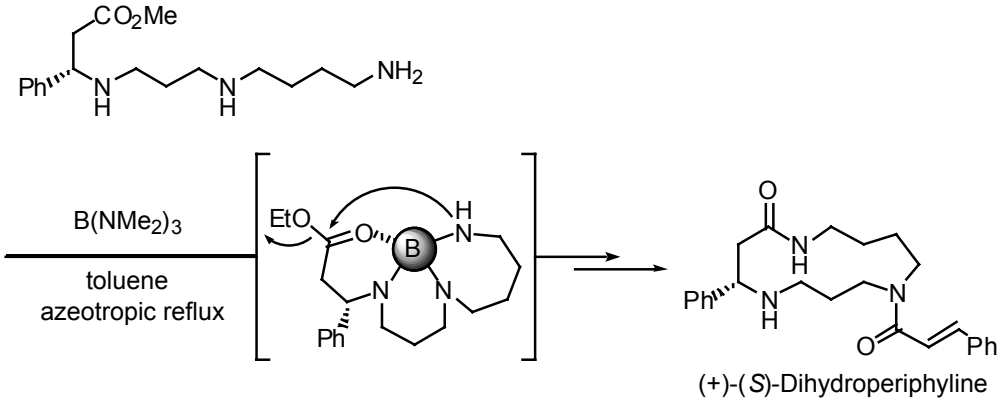
5..3.3 Synthesis of Nitrile

Yamamoto and colleagues have found rhenium(VII) oxo complexes as extremely active catalysts (1 mol%) for dehydration of not only primary amides but also aldoximes to the corresponding nitriles. The reaction proceeds under essentially neutral conditions, and the present method is mild and simple to conduct. This protocol can be readily applied to large-scale processes with high efficiency and selectivity, making it an economical and environmentally benign process for the preparation of nitriles.

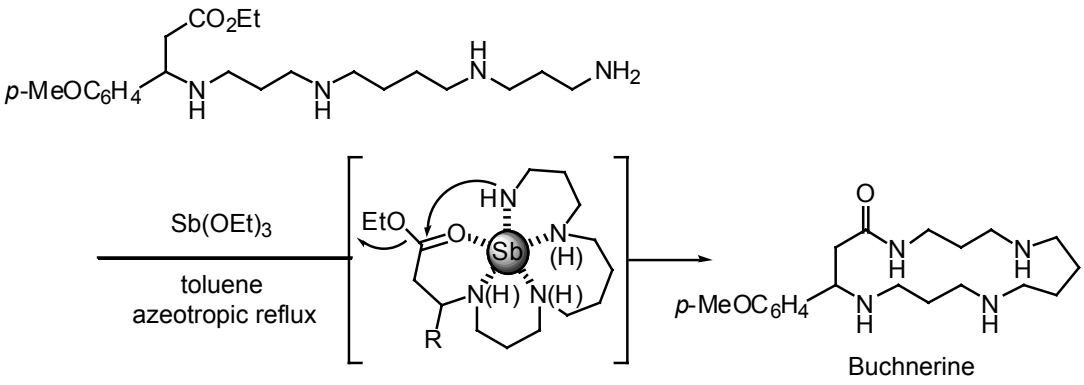


5.4. Templated Cyclization of Polyamino Compounds [58, 288, 330]

Tris(dimethylamino)borane is effective for the metal-templated cyclization of triamino esters to give macrocyclic spermidine alkaloids such as (+)-(S)-dihydroperiphylline and celacinnine.

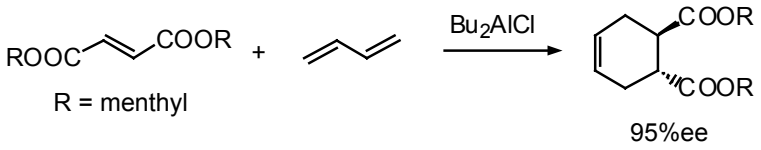


Antimony(III) ethoxide is also effective for the metal-templated cyclization of tetramino esters to give the macrocyclic spermine alkaloids buchnerine, verbacine, verbaskine, and verbascenine. The accelerated rates and high regioselectivities of therse polyamino systems suggest a mechanism in which the acyclic tri and tetramino esters are covalently or coordinately attached to the boron or antimony before the final cyclization step.

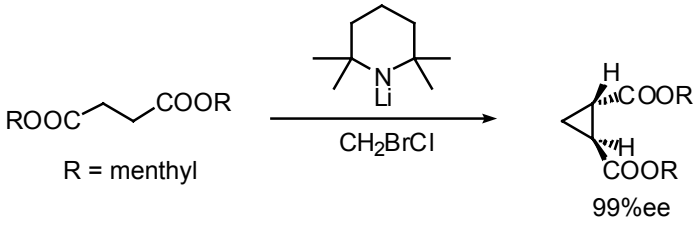


5.5. Cooperative Blocking Effect

In the study of the influence of concave-convex topological features on asymmetric Diels-Alder reaction, readily available dimenthyl fumarate appears to deserve reinvestigations since its primitive topological features seem have been underestimated. Indeed, a series of dienes was subjected to Diels-Alder reaction with orgnoaluminum reagent and all the attempted reaction proceeded with excellent stereoselection [115].



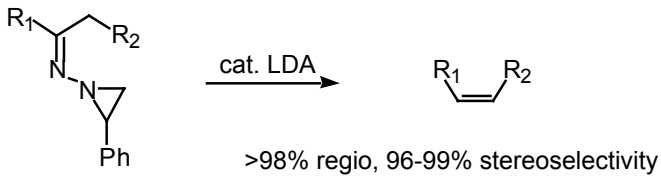
The observed rigorous selectivity in the present system can adequately prove the concept of cooperative blocking which is working effectively even for the dianion alkylative cyclizations [99].



5.6. Stereoselective Catalytic Shapiro Reaction

Shapiro reaction is one of the most powerful techniques for regioselective preparation of alkenes. Yamamoto and his colleagues disclosed an excellent regio- and stereoselectivity obtained using the combination of ketone phenylaziridinylhydrazone as arenesulfonylhydrazone equivalents with a catalytic amount of lithium amide. The

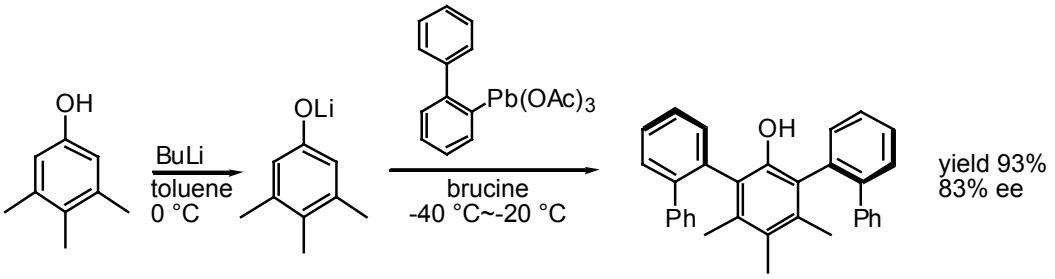
preparation proceeded with highly regio-(>98%) and stereoselectivities (cis/trans 96-99%) [292].



5.7. New Cross coupling Reaction Using Aryllead

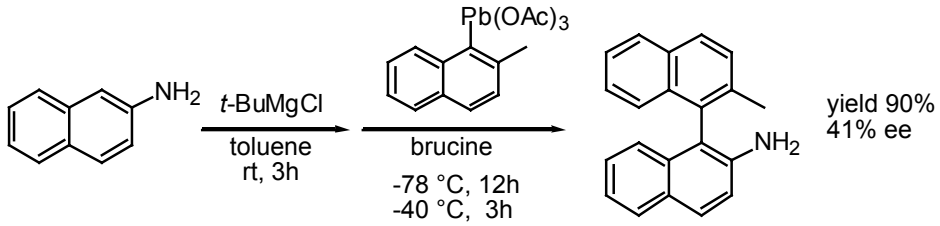
5.7.1. Aryl-aryl Coupling Reaction Using Aryllead Compounds - Asymmetric Coupling of Phenols with Arylleads

The asymmetric coupling of various phenol derivatives with aryllead triacetates was investigated for the first time using optically active amines including strychnine and brucine. Yamamoto and his colleagues found that conformationally restricted tertiary amines, as well as the effect of lithium aryloxides and molecular sieves are essential for accelerating the rate of this coupling process. Consequently, the reaction can be carried out at a low temperature, giving a high degree of diastereo- and enantioselectivities [345].



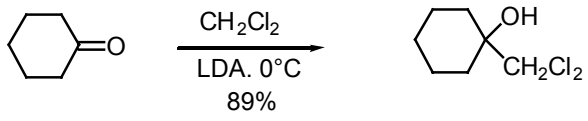
5.7.2. Asymmetric Coupling of Anilines with Arylleads

Although Barton pointed out that no reaction occurred between amines and organolead derivatives alone, simple magnesation of anilines proved to be effective for transmetallation and subsequent arylation with aryllead compounds. This finding was extended to an asymmetric version of this novel process using brucine.

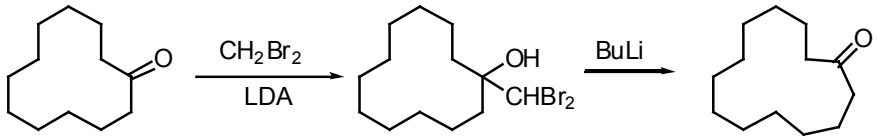


5.8. Polyhalomethyllithium as a Useful Synthetic Reagents

Dihalomethyllithium can be generated from dihalomethane with LDA or butylllithium. However, generation of this highly useful reagent required the conditions of very low temperature and careful temperature control. Yamamoto reported an easy *in-situ* generation method which is now widely used for many synthetic transformations of this reagent [25].

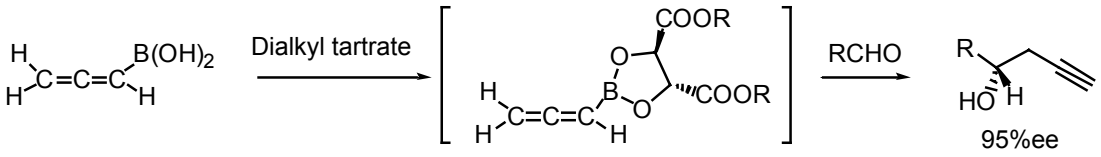


The technique was used for ring enlargement reaction including synthesis of muscone [28, 36].



5.9. Asymmetric Propargylation using Chiral Allenylboronic Esters

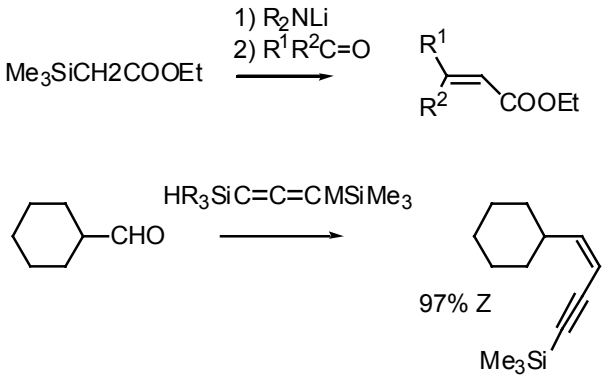
Yamamoto reported condensations of aldehydes with chiral allenylboronic esters to provide β-acetylenic alcohols with a high degree of enantioselectivity. Similar reagents derived from allylboronic ester and dalkyl tartrate are now widely used for asymmetric allylation processes [69, 114]. □



5.10. Peterson Olefination for Stereoselective Synthesis

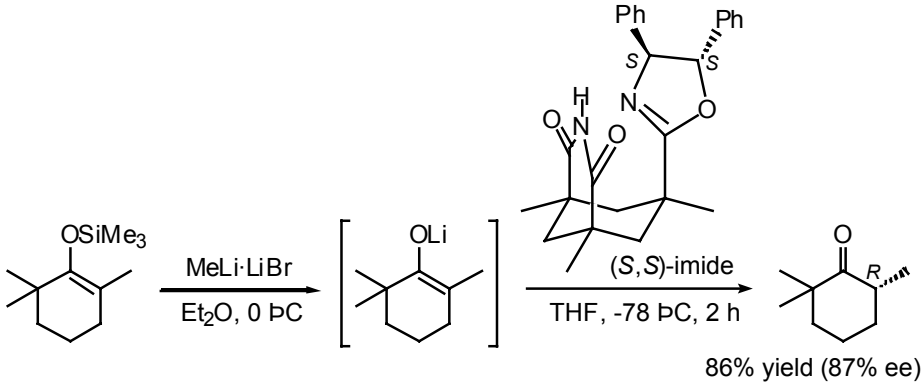
In his early research at Kyoto, Yamamoto reported an efficient silicon-mediated

alkene synthesis which directly produces Z-alkenyl derivatives [24, 59].



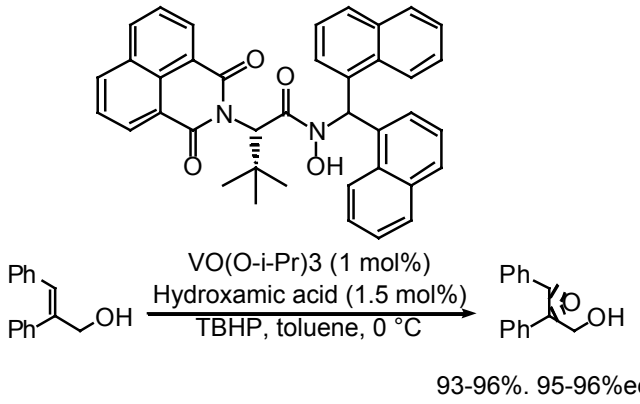
5.11. Enantioselective Protonation of Simple Enolates: Chiral Imide as a Chiral Proton Source [R-25, R-33, 245, 332]

Asymmetric protonation of prochiral metal enolates is an effective route to produce optically active carbonyl compounds. Although a number of groups have made important contributions to the continuing progress in this process, most of these are the reactions of enolates having polar groups including amino, hydroxyl, or phenyl groups, and there have been few satisfactory reports on the asymmetric induction of enolates of simple ketones such as 2-methylcyclohexanone. New chiral proton sources possessing an asymmetric 2-oxazoline ring, (S,S)-imide and related imides, were synthesized from Kemp's triacid and optically active 2-amino alcohols. With these chiral imides, various lithium enolates of α-monoalkylated cycloalkanones were effectively protonated with excellent to moderate enantioselectivity.

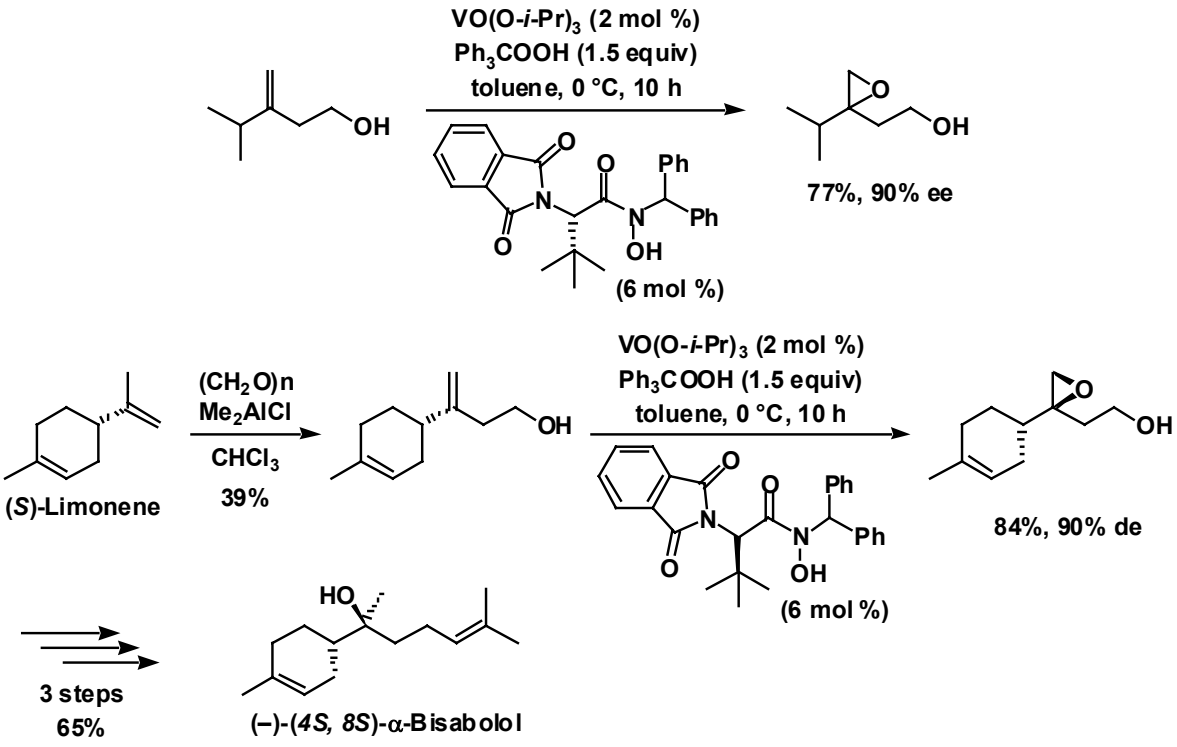


1.3. Novel α-Amino Acid-based Hydroxamic Acid Ligand for Vanadium-Catalyzed Asymmetric Epoxidation of Allylic Alcohols

Irrational and facile design of acyclic chiral hydroxamic acid ligands for asymmetric epoxidation has been achieved. In a study on asymmetric epoxidation of allylic alcohols the catalyst structure optimization was carried out step by step with varying structure of the ligand, *i.e.*, three components of α-amino acid, *N*-protecting group, and hydroxylamine. As a result of the above screening, the new structure was discovered to be the best ligand whose vanadium complex reaches unprecedented catalytic performance of productivity and selectivity. For instance, in the presence of new catalyst (0.1 mol%) a mixture of (*E*)-2,3-diphenyl-2-propenol and *tert*-butylhydroperoxide in toluene was stirred at 25 °C for 15 h to afforded the corresponding epoxide in high yield and good selectivity (99% yield, 86% ee).

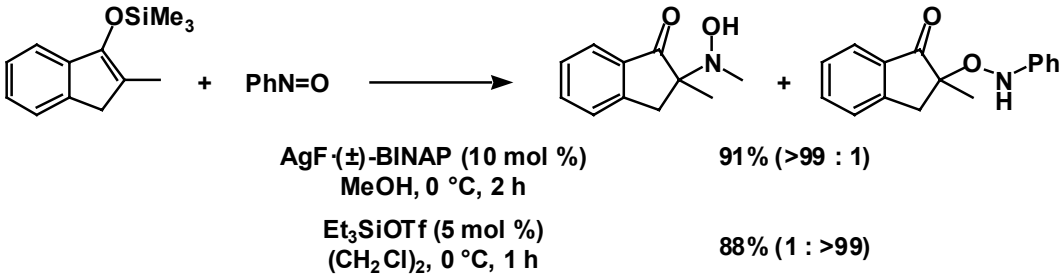


The new chiral catalytic system described above was further successfully applied to the catalytic asymmetric epoxidation of homoallylic alcohols. The asymmetric epoxidation of a variety of 3-substituted homoallylic alcohols was obtained in up to 91% ee. Using this catalyst concise synthesis of (–)-Bisabolol was achieved.



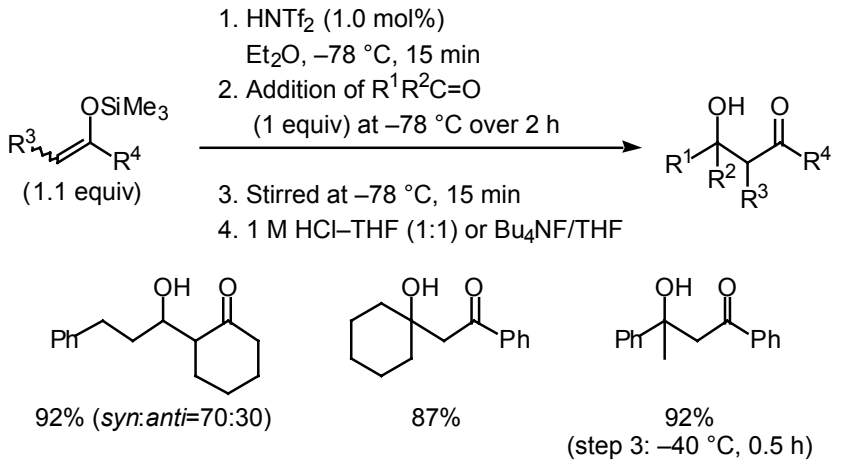
5.13. Regioselective Nucleophilic Addition to Nitrosobenzen Catalyzed by Lewis Acid

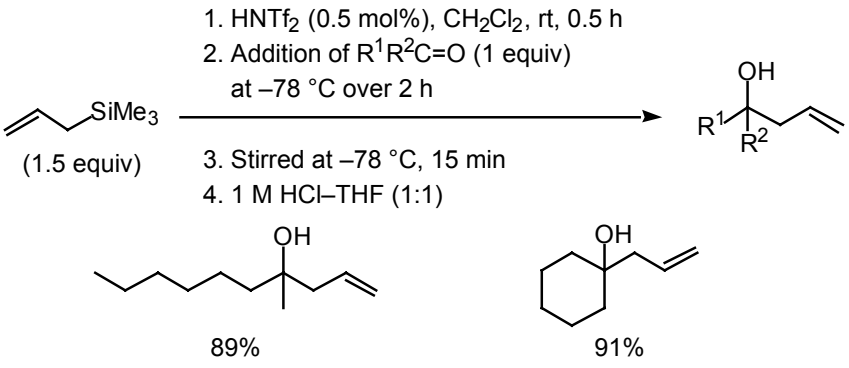
Yamamoto and his colleagues found that the nucleophilic attack by enol silyl ethers to nitroso compounds was regioselectively occurred in the presence of Lewis acid. For instance, *N*-hydroxy-2-aminoketone and 2-aminooxyketone were obtained using 10 mol % of AgF·(±)-BINAP and 5 mol % of Et_3SiOTf, respectively. Especially, the regioselective nucleophilic attack by various enol silyl ethers in the presence of 5 mol % of Et_3SiTOf was obtained with high selectivities to give 2-aminooxyketone. The process of the reaction using Me_3SiTOf was pursued by ReactIR, and suggested that the dimerization of nitrosobenzene was promoted by Me_3SiTOf.



5.14. The Me_3SiNTf_2-induced Carbon–Carbon Bond-forming Reactions of Silyl Nucleophiles with Carbonyl Compounds

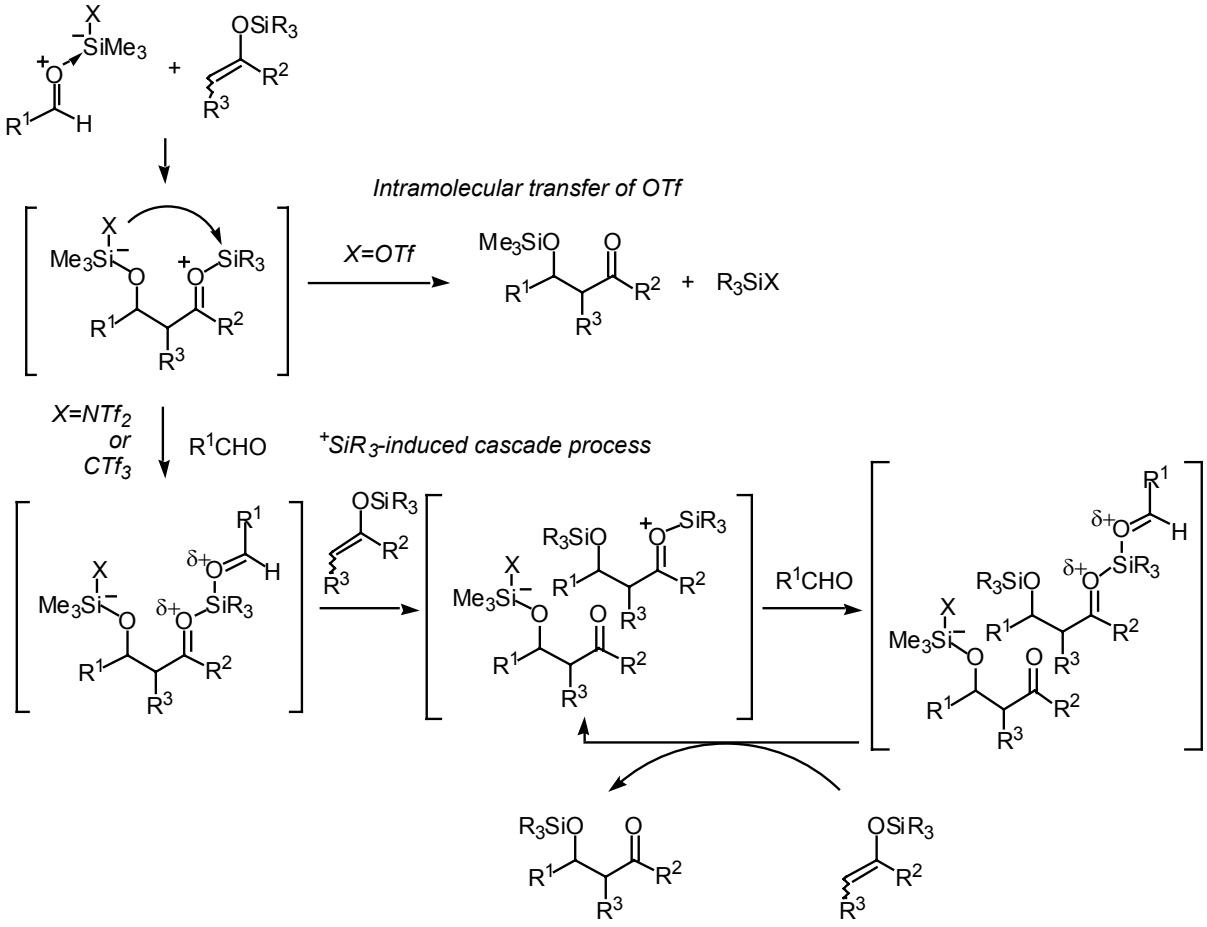
Yamamoto and colleagues have demonstrated the efficiency of Me_3SiNTf_2 (0.3~1.0 mol%) as a strong Lewis acid catalyst for the Mukaiyama aldol and Sakurai–Hosomi allylation reactions, and that the slow addition of carbonyl compounds to a solution of acid catalyst and Me_3Si–Nu is very important for suppressing side products; this may be widely accepted as a common and reasonable general procedure for the Lewis acid-induced reaction of Me_3Si–Nu with carbonyl compounds [388].





The Me_3SiX-induced Mukaiyama aldol reaction proceeds through each catalytic cycle under the influence of X^-: the silyl group of Me_3SiNTf_2 does not release from $^-NTf_2$ and that of silyl enol ether intermolecularly transfers to the product, while the silyl group of Me_3SiOTf remains in the product and that of the silyl enol ether becomes the catalyst for the next catalytic cycle . These findings may provide a basis for the

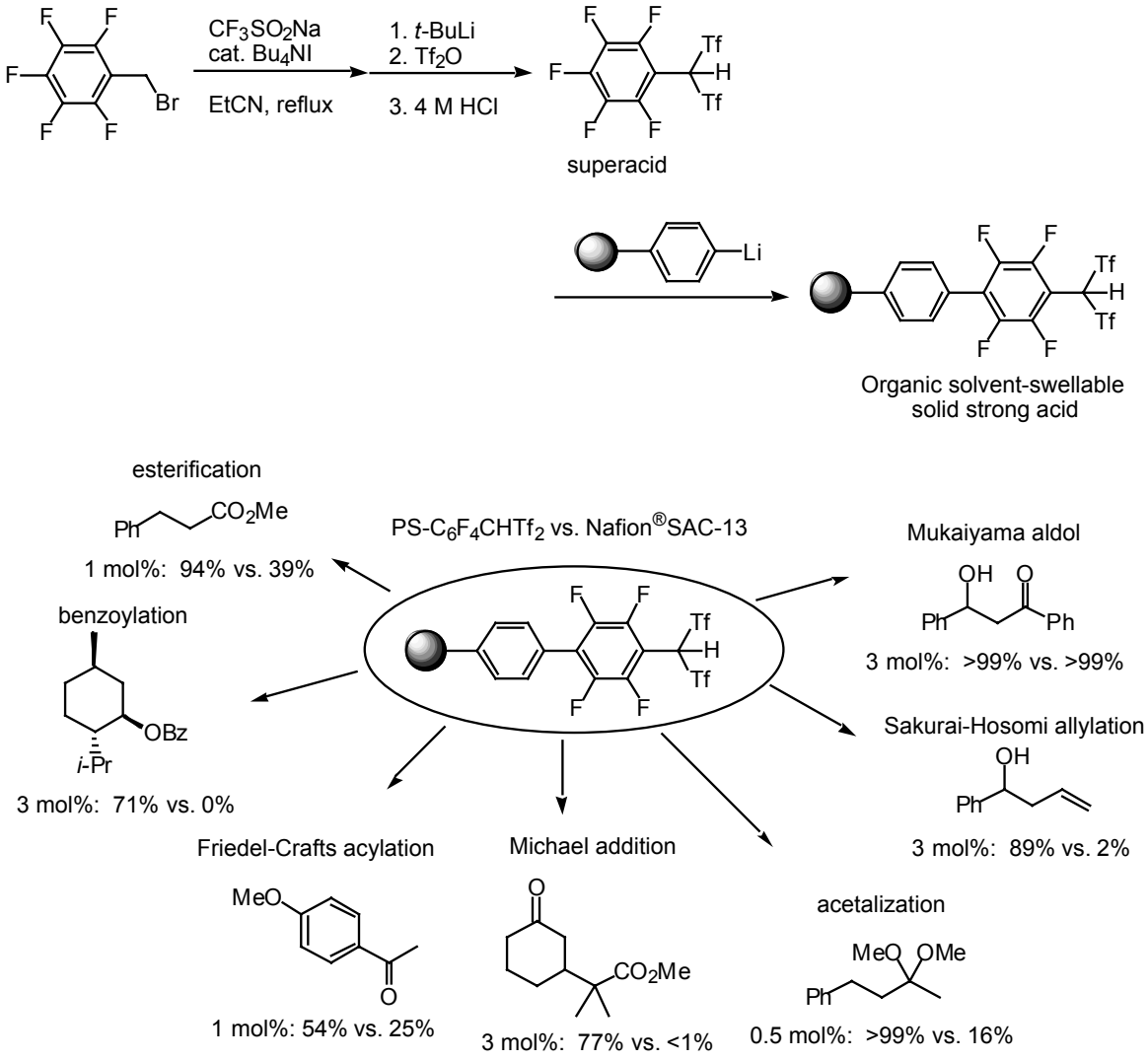
future development of not only chiral silyl Lewis acid catalysts but also other chiral metal catalysts for carbon–carbon bond-forming reactions of silyl nucleophiles with carbonyl compounds



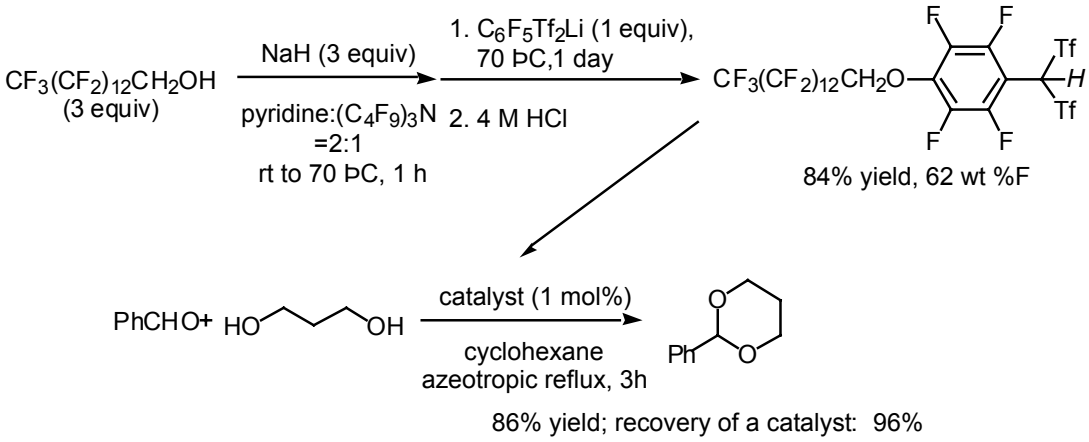
Chapter 6 Development of Designer Brønsted Acid

6.1. Polystyrene-Bound Tetrafluorophenylbis(triflyl)methane as an Organic Solvent-Swellable and Strong Brønsted Acid Catalyst

The trifluoromethanesulfonyl (triflyl, Tf) group is one of the strongest neutral electron-withdrawing groups. In particular, it greatly increases the acidity of hydrogen atoms at α-positions. For example, bis(triflyl)methane (pK_a in water = –1) and phenylbis(triflyl)methane (pK_a in MeCN = 7.83). The steric and electronic factors of the aromatic ring on arylbis(triflyl)methanes are expected to greatly influence their Brønsted acidity and their catalytic activity and selectivity for organic reactions. We have developed new strong carbon Brønsted acids, pentafluorophenylbis(triflyl)methane and polystyrene-bound tetrafluorophenylbis(triflyl)methane [389]. The synthesis of the resin-bound Brønsted acid has been accomplished by using the nucleophilic *para*-substitution reaction of lithium pentafluorophenylbis(triflyl)methide with lithiated polystyrenes as a key step. To the best of our knowledge, this is the first example of a highly acidic heterogeneous Brønsted acid catalyst that is effectively swollen by non-polar organic solvents, and its catalytic activities are superior to those of Nafion® SAC-13. Organic solvent-swellable superacids should make a great contribution to green chemistry and the growth of the chemical industry.



Recently, Yamamoto and colleagues [384] demonstrated that perfluorocarbon solvent isn't essential for fluorous biphasic catalysis: the perfluorocarbon solvent can be skipped by designing fluorinated catalysts that themselves have a temperature-dependent phase miscibility–that is solubility–in ordinary organic solvents. We have developed a fluorous super Brønsted acid catalyst, 4-(1*H*,1*H*-perfluorotetradecanoxy)-2,3,5,6-tetrafluorophenylbis(trifluoromethanesulfon yl)methane . The fluorous catalyst can be recycled based upon liquid/solid phase separation without fluorous solvents. Now, perfluorocarbon solvent isn't essential for fluorous biphasic catalysis..


CF3(CF2)12CH2OH
(3 equiv)
NaH (3 equiv)
pyridine:(C4F9)3N
=2:1
rt to 70 ÞC, 1 h
1. C6F5Tf2Li (1 equiv),
70 ÞC,1 day
2. 4 M HCl
CF3(CF2)12CH2O
F
F
Tf
H
Tf
F
F
84% yield, 62 wt %F
PhCHO+
HO
OH
catalyst (1 mol%)
cyclohexane
azeotropic reflux, 3h
O
Ph
O
86% yield; recovery of a catalyst: 96%