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Rare-Earth Metal Triflates in Organic Synthesis

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Contents

1. Introduction

Lewis-acid (LA)-catalyzed reactions are of great interest because of their unique reactivities and selectivities and mild reaction conditions used.[1,2] A wide variety of reactions using Lewis acids have been developed, and they have been applied to the synthesis of natural and unnatural compounds. Traditionally, Lewis acids such as $AlCl_3$, BF_3, $TiCl_4$, $SnCl_4$, etc., have been employed in these reactions; however, more than stoichiometric amounts of the Lewis acids are needed in many cases. Moreover, these Lewis acids are moisture sensitive and easily decomposed or deactivated in the presence of even a small amount of water. Furthermore, these Lewis acids cannot be recovered and reused after the reactions are completed. In 1991, the first report on water-compatible Lewis acids, lanthanide triflates [$Ln(OTf)_3$], appeared.[3,4] Lanthanide triflates were literature-known compounds at that time, but their use in organic synthesis had been limited. Before 1991, indeed, only one report on amidine synthesis in an organic solvent using a lanthanide triflate as a catalyst was known.[5] This synthesis was reported to be carried out under strictly anhydrous conditions. Including this synthesis, it was generally accepted that Lewis-acid catalysis had to be performed under strictly anhydrous conditions.

The most characteristic feature of $Ln(OTf)_3$ is that they are stable and work as Lewis acids in water. After the first report, not only $Ln(OTf)_3$ (Ln = La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu) but also scandium (Sc) and yttrium (Y) triflates were shown to be water-compatible Lewis acids, and these *rare-earth metal triflates* [$RE(OTf)_3$] have been regarded as new types of Lewis acids. Many useful reactions are catalyzed by rare-earth metal triflates in aqueous media. Only catalytic amounts of the triflates are enough to complete the reactions in most cases. Furthermore, rare-earth metal triflates can be recovered easily after reactions and reused without loss of activity.

Rare-earth metal triflates are available not only in aqueous media but also in many organic solvents. The triflates are still active in the coexistence of many Lewis bases containing nitrogen, oxygen, phos-

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phorus, and sulfur atoms. In almost all cases, catalytic use, recovery, and reuse of the triflates are possible. While large amounts of conventional Lewis acids are required and treatment of the residues of the Lewis acids after reactions may induce some serious environmental problems, rare-earth metal triflate-catalyzed reactions are clean and the triflates are regarded as environmentally friendly catalysts. The catalytic efficiency of rare-earth metal triflates vary from one reaction to another. Generally, $Sc(OTf)_3$ shows a higher catalytic activity than $Ln(OTf)_3$ and $Y(OTf)_3$. Recently, the relative Lewis acidity of rare-earth metal triflates were evaluated based on their competitive ligand dissociation from complexes, $M(OTf)_3(L)_4$ (L = hexamethylphosphoramide, triethylphosphine oxide, or trimethyl phosphate) using tandem mass spectrometry.[6] The results are in accordance to the extraordinary catalytic activity of Sc(III) and Yb(III) in the Lewis-acid-catalyzed reactions. The high Lewis acidity of Sc(III) and Yb(III) may be attributed to their small ionic radii.[7]

Rare-earth metal triflates are readily prepared by heating the corresponding metal oxides or chlorides in an aqueous trifluoromethanesulfonic acid (TfOH) solution.[8,9] They are also prepared by the reaction of aqueous solutions of the corresponding metal halides with silver triflate. Typically, eight or nine molecules of water are contained in the triflates after removal of water at room temperature. Anhydrous samples are obtained after drying at elevated temperature under high vacuum.

In this review, useful organic transformations employing rare-earth metal triflates as Lewis-acid catalysts are discussed. The authors did their best to cover all related papers which were accessible before October 2001. In addition, special attention is focused upon comparison of these new types of Lewis acids with other conventional Lewis acids and their applications in aqueous media.

2. C–C Bond Formation

2.1. Nucleophilic Addition

2.1.1. Aldol Reaction

The titanium tetrachloride-mediated aldol reaction of silyl enol ethers with aldehydes was first reported in 1973.[10] The reaction is notably distinguished from the conventional aldol reactions performed under basic conditions; it proceeds in a highly regioselective manner to provide cross aldols in high yields.[11] Since the pioneer contribution by Mukaiyama's group, several efficient promoters such as trityl salts,[12] Clay montmorillonite,[13] fluoride anions,[14] etc.,[15] have been developed to realize the reaction in high yields and selectivities. Although the reaction is considered to be one of the most important carbon–carbon bond-forming reactions in organic synthesis, it should be performed under strictly anhydrous conditions. The presence of even a small amount of water causes lower yields, probably due to rapid decomposition or deactivation of the promoters and hydrolysis of silyl enol ethers.

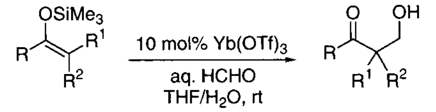
Kobayashi and his group reported the use of $Yb(OTf)_3$ for hydroxymethylation reaction of silyl enol ethers with commercial aqueous formaldehyde solution (Table 1).[4]

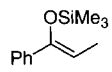
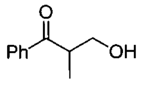
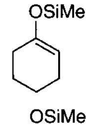
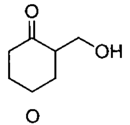
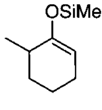
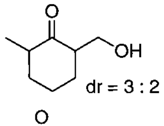
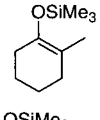
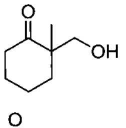
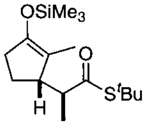
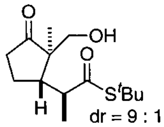
In a total asymmetric synthesis of (−)-sclerophytin A, Paquette et al. later utilized this methodology to construct a complex molecule (Scheme 1).[16]

The efficiency of $RE(OTf)_3$ in a model reaction of 1-trimethylsiloxycyclohexene with benzaldehyde was examined in aqueous medium (H_2O/THF 1/4).[17,18] Of the lanthanide triflates screened, neodymium (Nd), gadolinium (Gd), ytterbium (Yb), and lutetium (Lu) triflates were very effective in terms of yield (Table 2). Interestingly, the product yields were low when water or THF was used alone instead of their mixtures. Table 3 shows the effect of ytterbium salts in this reaction. It is suggested that not only the cations but also the counteranions are very important for the catalytic activity.

In the presence of a catalytic amount of $Yb(OTf)_3$, other water-soluble aldehydes, for instance, acetaldehyde, acrolein, and chloroacetaldehyde, reacted with the silyl enol ether of propiophenone to afford the corresponding cross aldol adducts in high yields with moderate diastereoselectivities (Table 4). Remarkably, salicylaldehyde and 2-pyridinecarboxaldehyde were successfully employed in this reaction. The former has a free hydroxy group, which is

Table 1. $Yb(OTf)_3$-Catalyzed Hydroxymethylation of Silyl Enol Ethers with Aqueous Formaldehyde Solution



silyl enol ether	product	yield/%
		94
		82
	 dr = 3 : 2	86
		92
	 dr = 9 : 1	90

Scheme 1. $Yb(OTf)_3$-Catalyzed Hydroxymethylation of a Silyloxy Diene in a Total Synthesis

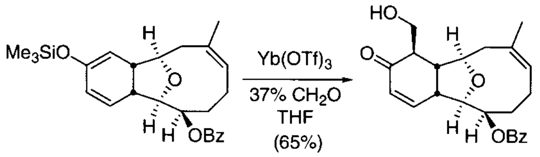
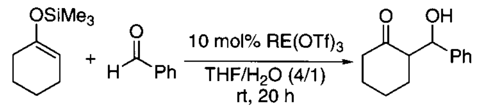


Table 2. Efficiency of $RE(OTf)_3$ on Mukaiyama Aldol Reaction



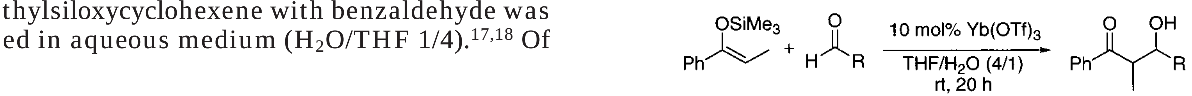
RE	yield/%	RE	yield/%
Sc	81[a]	Gd	89
Y	trace[a]	Dy	73
La	8	Ho	47
Pr	28	Er	52
Nd	83	Tm	20
Sm	46	Yb	91 (trace)[a]
Eu	34	Lu	88

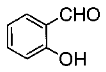
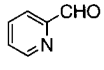
[a] The reaction was performed in CH_2Cl_2 at −78 °C for 15 h.

Table 3. Effect of Counteranions of Yb(III) Salts

Yb salt	yield/%	Yb salt	yield/%
$Yb(OTf)_3$	91	$Yb(OAc)_3{\cdot}8H_2O$	14
$Yb(ClO_4)_3$	88	$Yb(NO_3)_3{\cdot}5H_2O$	7
$YbCl_3$	3	$Yb_2(SO_4)_3{\cdot}5H_2O$	trace

Table 4. $Yb(OTf)_3$-Catalyzed Aldol Reactions in Aqueous Medium



aldehyde	yield/%	aldehyde	yield/%
aq. HCHO	94		81
CH_3CHO	93		
$CH_2{=}CHCHO$	82		97
$ClCH_2CHO$	95		
$PhCOCHO{\cdot}H_2O$	67		

incompatible with metal enolates or Lewis acids, while the latter would form complexes with Lewis acids through coordination with nitrogen atoms, resulting in deactivation of the catalyst.

The fact that lanthanide triflates are more soluble in water than in common organic solvents allows easy recovery of the catalysts from the aqueous phase in almost quantitative yields. The catalyst can be reused without attenuated activity. For example, in the presence of 20 mol % of $Yb(OTf)_3$, the reaction of the silyl enol ether derived from propiophenone with aqueous formaldehyde solution gave excellent yields in three consecutive cycles (1st, 94%; 2nd, 91%; 3rd, 93% yield).

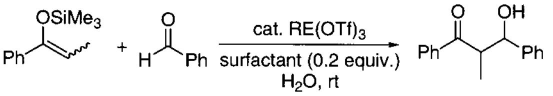
It was found that the amount of water had a great influence on both yields and diastereoselectivities. The best yields were obtained with 10−20% of water in THF, after which the yield began to drop until two phases were observed. Only 18% yield of the product was isolated in pure water. In addition, when water was not added or 1−5 equiv of water was added, the aldol adducts were obtained in low yield (ca. 10% yield). It was found that the yield was improved with increasing amounts of water up to 50 equiv.

In addition, the amount of water has an important role in dictating the diastereoselectivies of the reactions. In the absence of water, the reaction proceeded with *anti* preference. This trend was changed as the amount of water increased, and the *syn* aldol was dominant when more than 3 equiv (with respect to catalyst) of water was added. The selectivity was improved in accordance to the amount of water; however, almost the same selectivities were obtained when more than 15 equiv of water was added to the reaction mixture.

Although hydrolysis of ketene silyl acetals (KSA) preceded the desired aldol reactions in aqueous medium, KSA reacted with benzaldehyde in the presence of 10 mol % of $Yb(OTf)_3$ in dichloromethane.[19] Comparable yields were obtained when the reactions were performed in other organic solvents such as toluene, THF, acetonitrile, and DMF. It was showed that other lanthanide triflates [$Ln(OTf)_3$; Ln = La, Pr, Nd, Sm, Eu, Gd, Dy, Ho, Er, Tm, and Lu] also catalyzed the addition of KSA effectively in CH_2Cl_2 (85−95% yields). The superior catalytic activity of $Sc(OTf)_3$ allowed the reaction to proceed at −78 °C.[20] Silyl enol ethers derived from esters, thioesters, and ketones reacted with aldehydes to give the corresponding adducts in high yields. Furthermore, acetals reacted with silyl enol ethers to afford the corresponding aldols.[21]

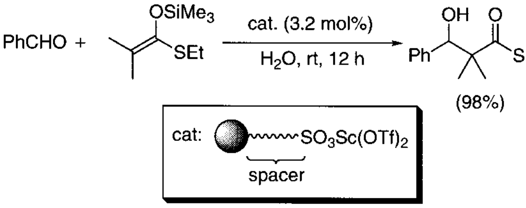
As stated before, aldol reactions proceeded sluggishly in pure water (without organic solvents); however, remarkable rate enhancement was observed in the presence of a small amount of a surfactant (Table 5).[22] When the reaction was carried out in the presence of 20 mol % of $Yb(OTf)_3$ in an aqueous solution of sodium dodecyl sulfate (SDS, 35 mM), the corresponding aldol adduct was obtained in 50% yield, which was further improved to 88% when using 10 mol % of $Sc(OTf)_3$. It was found that the surfactants employed influenced the yield and that Triton X-100 was also effective in the aldol reaction, albeit with a longer reaction time, while only a trace amount of the adduct was detected with cetyltrimethylammonium bromide (CTAB). Surprisingly, KSA derived from methyl isobutyrate, which was expected to be easily hydrolyzed in the presence of water, reacted with benzaldehyde in this micellar system to give the corresponding adduct in high yield (84%). It was also reported that amphiphilic calix[6]arene derivatives were efficient surfactants in $Sc(OTf)_3$-catalyzed Mukaiyama aldol reactions in water.[23]

Table 5. $RE(OTf)_3$-Catalyzed Aldol Reaction in Water



$RE(OTf)_3$ (mol %)	surfactant	time/h	yield/%
$Yb(OTf)_3$ (20)	SDS	48	50
$Sc(OTf)_3$ (20)	SDS	17	73
$Sc(OTf)_3$ (10)	SDS	4	88
$Sc(OTf)_3$ (10)	TritonX-100	60	89
$Sc(OTf)_3$ (10)	CTAB	4	trace

Scheme 2. Aldol Reaction in Pure Water Using a Polymer-Supported Scandium Catalyst



Moreover, aldol reactions of silyl enol ethers with aldehydes proceed in pure water using a polymer-supported scandium catalyst, which can be easily recovered and reused (Scheme 2).[24]

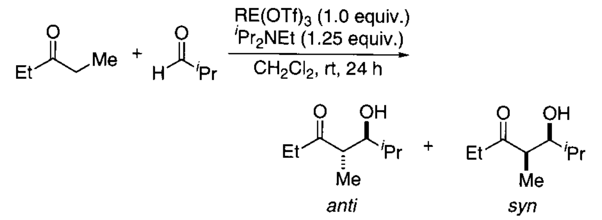
A combination of stoichiometric amounts of $Ln(OTf)_3$ and a tertiary amine promoted diastereoselective (*anti*-selective) cross-aldol reactions between ketones and aldehydes.[25] Formation of Yb enolate was confirmed by in situ trapping with trimethylsilyl chloride (TMSCl). The efficiency of $RE(OTf)_3$ in the reaction of 3-pentanone with isobutyraldehyde was examined (Table 6). $Nd(OTf)_3$ and $Sm(OTf)_3$ were inactive, while $Sc(OTf)_3$, $Y(OTf)_3$, and $Yb(OTf)_3$ gave the aldol product in good yields.

Comparison of several different Lewis-acid catalysts in the reaction of 1-*tert*-butoxycarbonyl-2-*tert*-butyldimethylsiloxypyrrole (TBSOP) with benzaldehyde was reported (Table 7).[26] A stoichiometric amount of $BF_3{\cdot}OEt_2$ or $SnCl_4$ was used to form *threo* or *erythro* isomer preferentially. Other Lewis acids, including $Yb(OTf)_3$ and $Sc(OTf)_3$, were less effective in terms of selectivity, while use of a catalytic amount of $Sc(OTf)_3$ was enough to obtain the desired adduct in 70% yield.

$RE(OTf)_3$ also catalyzes highly diastereoselective addition of silyl enol ethers to chiral benzaldehyde−$Cr(CO)_3$ complexes at ambient temperature. In this reaction, the product was obtained as a single diastereomer (Scheme 3).[27]

Vogel and his group reported a new carbon−carbon bond-forming reaction through oxyallylation of an

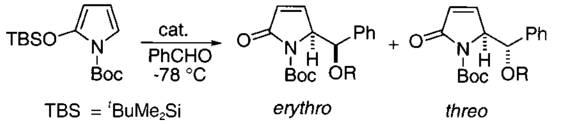
Table 6. Cross Aldol Reaction of Rare-Earth Metal Enolate



RE	yield/%	*anti*/*syn*[a]
Sc	82	85/15
Y	71	80/20
Nd	trace	
Sm	trace	
Yb[b]	76	84/16

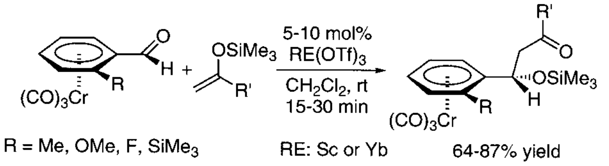
[a] Determined by 400 MHz ^{1}H NMR spectroscopy. [b] Reaction time; 48 h.

Table 7. Diastereoselective Reaction of a Pyrrole Derivative with Benzaldehyde



catalyst (mol %)	solvent	yield/%	*erythro*/*threo*
$BF_3 \cdot OEt_2$ (100)	Et_2O	75	19/81
$TiCl_4$ (100)	CH_2Cl_2	70	60/40
$SnCl_4$ (150)	Et_2O	83	90/10
$Yb(OTf)_3$ (30)	CH_3CN	19	71/29
$Sc(OTf)_3$ (5)	CH_3CN	70	64/36

Scheme 3. Diastereoselective Reactions of Acyclic Silyl Enol Ethers with η^6-(*ortho*-substituted Benzaldehyde)−Cr(CO)$_3$ Complexes



Scheme 4. Generation of an Oxyallylating Agent

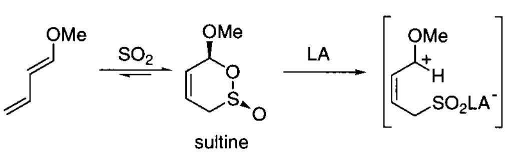
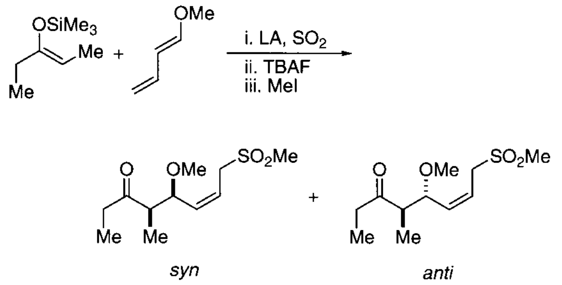
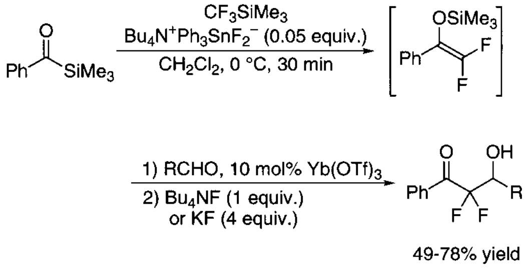


Table 8. Oxyallylation of Silyl Enol Ether



LA (mol %)	yield/%	*syn*/*anti*
$Sn(OTf)_2$ (4)	76	70/30
Me_3SiOTf (37)	78	75/25
$^tBuMe_2SiOTf$ (43)	63	81/19
$Sc(OTf)_3$ (3)	81	70/30
$Yb(OTf)_3$ (2)	89	70/30

Scheme 5. One-Pot Synthesis of Difluoroaldols



enolsilane with the SO_2 adduct of 1-methoxybutadiene.[28] Sultine was formed rapidly at low temperature (−60 °C) from electron-rich 1-methoxybutadiene and excess SO_2 without any acid catalysis. However, in the presence of a Lewis acid, it underwent ring opening to give a zwitterionic intermediate, which reacted as an oxyallylating agent with electron-rich alkenes, such as enolsilanes (Scheme 4). The effect of Lewis-acid catalysts for the reaction with the (*Z*)-enol silane derived from 2-pentanone was summarized in Table 8. In all cases, only *Z*-olefinic products were obtained, and *tert*-butyldimethylsilyl triflate (TBSOTf) resulted in the best *syn* selectivity. $Sc(OTf)_3$ and $Yb(OTf)_3$ performed equally well to afford good yields of the product with moderate selectivities.

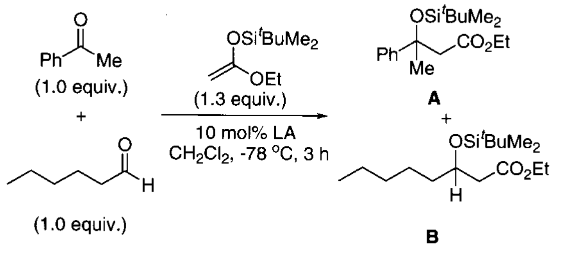
It was reported that difluoroaldol compounds were synthesized in a one-pot procedure. A difluoroenoxysilane generated from benzoyltrimethylsilane and trifluoromethyltrimethylsilane undergoes the aldol-type reaction with an aldehyde. $Yb(OTf)_3$ proved to be a very efficient catalyst for promoting the aldol-type reactions under very mild conditions (Scheme 5).[29]

Differentiation between carbonyl functions in the competitive reactions is a difficult task in organic synthesis.[30] Although carbonyl functions possess different reactivities, highly selective discrimination between them is generally difficult to attain. One of the most popular solutions is to protect or convert a more reactive function into other functions and thus allow reactions of less reactive functions. For example, a recent success has been achieved in the preferential addition reactions of ketals over acetals.[31] However, the differentiation between the parent ketones and aldehydes or between ketones and acetals is more challenging. Toward this end, preferential addition reactions of ketones over aldehydes (Table 9) or acetals with silyl enol ethers (Table 10) were reported in the presence of $(C_6F_5)_2SnBr_2$, TMSOTf, or $Sc(OTf)_3$.[32] Classical Lewis acid $SnCl_4$ was less effective, giving products in low yields.

It was shown that $Yb(OTf)_3$ was moderately effective as $InCl_3$ to promote asymmetric aldol reaction of the D-glucose-derived silyl enol ether with commercial formaldehyde in water (Table 11).[33]

Chiral lanthanide catalysts generated from $Ln(OTf)_3$ and chiral bis-triflamide of (1*S*,2*S*)-1,2-diphenyl-

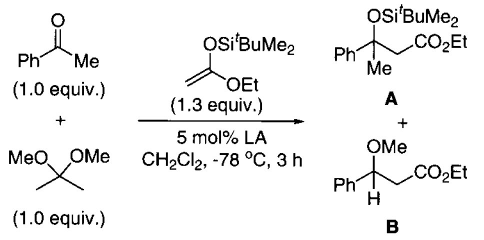
Table 9. Competition Reaction between a Ketone and an Aldehyde



LA	yield/% (**A**/**B**)
$(C_6F_5)_2SnBr_2$	75/7
Me_3SiOTf	90/12
$Sc(OTf)_3$	72/6
$SnCl_4$[a]	26/6

[a] One equivalent was used.

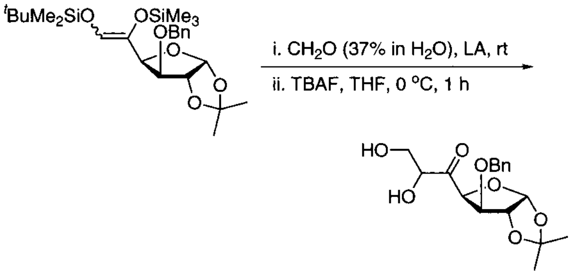
Table 10. Competition Reaction between a Ketone and an Acetal



LA	yield/% (**A**/**B**)
$(C_6F_5)_2SnBr_2$	91/0
Me_3SiOTf	91/0
$Sc(OTf)_3$	91/0
$SnCl_4$[a]	1/3

[a] One equivalent was used.

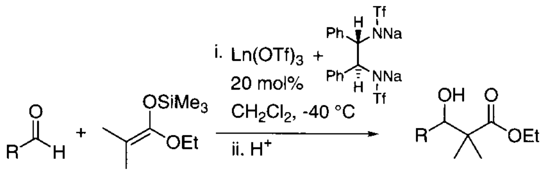
Table 11. Lewis-Acid-Catalyzed Asymmetric Aldol Reaction of D-Glucose-Derived Silyl Enol Ether with Formaldehyde in Water



E/*Z*	LA (mol %)	yield/%	*R*/*S*
0/100	$Yb(OTf)_3$ (40)	35	54/46
0/100	$InCl_3$ (40)	68	82/18
80/20	$Yb(OTf)_3$ (40)	40	88/12
80/20	$InCl_3$ (40)	73	96/4

ethylenediamine have been applied for catalytic Mukaiyama aldol reactions.[34] A ketene silyl acetal reacted with various aldehydes to give adducts with moderate enantiomeric excesses (Table 12).

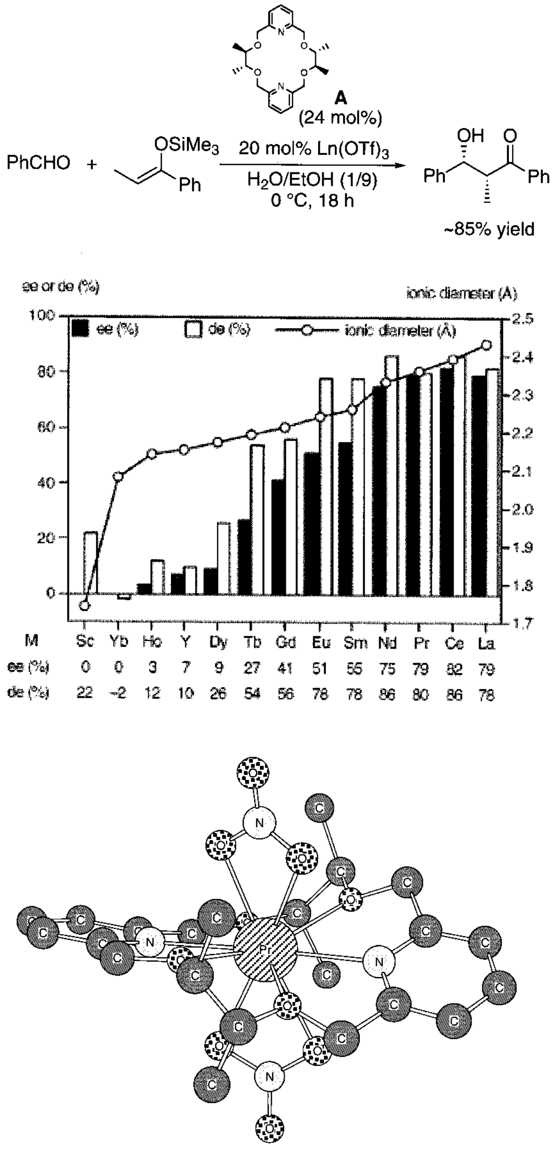
Table 12. Asymmetric Aldol Reaction Promoted by Chiral Lanthanide Complexes



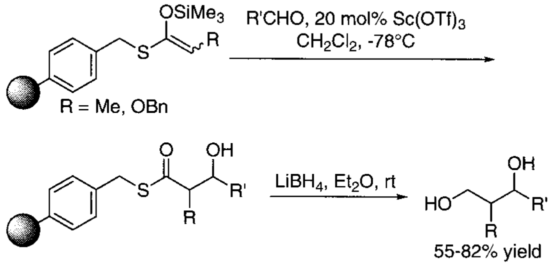
	La	Eu	Yb
RCHO	yield/% (ee)	yield/% (ee)	yield/% (ee)
PhCHO	42 (47)	59 (40)	71 (33)
p-NO_2PhCHO	86 (41)	92 (40)	98 (44)
$PhCH_2CH_2CHO$	19 (39)	34 (39)	55 (40)

One of the most characteristic features of rare-earth metal triflates as Lewis acids is that they are stable in water and can be used as catalysts in aqueous media. While many useful reactions using rare-earth metal triflates in aqueous media have been developed, no report on asymmetric catalysis in aqueous media using rare-earth metal triflates appeared before 2000. In 2001, asymmetric aldol reactions of silyl enol ethers with aldehydes catalyzed by $Ln(OTf)_3$ in aqueous media using a chiral crown ether have been reported (Scheme 6).[35] When

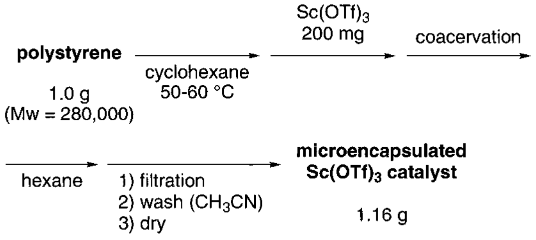
Scheme 6. Asymmetric Aldol Reaction Promoted by $Ln(OTf)_3$ Using a Chiral Crown Ether



Scheme 7. Sc(OTf)$_3$-Catalyzed Aldol Reactions of Polymer-Supported Silyl Enol Ethers with Aldehydes



Scheme 8. Preparation of Microencapsulated Sc(OTf)$_3$ Catalyst



Pr(OTf)$_3$ with a crown ether **A** was used as a catalyst, the reaction proceeded in high diastereo- (82% de) and enantioselectivities (78% ee). In this reaction, water plays an essential role for the high yield and selectivities. When the reaction was carried out in pure EtOH or CH$_2$Cl$_2$, lower yields and selectivities were observed (51% yield, 70% de, 23% ee in EtOH; 3% yield, 28% de, 22% ee in CH$_2$Cl$_2$). It was found in this reaction that ionic diameters of the metal cations significantly affected the selectivity. For the larger cations such as La, Ce, Pr, and Nd, both diastereo- and enantioselectivities were high. The smaller cations such as Sc and Yb showed no enantioselection. It was found in this reaction that ionic diameters of the metal cations significantly affected the selectivity. For the larger cations such as La, Ce, Pr, and Nd, both diastereo- and enantioselectivities were high. The smaller cations such as Sc and Yb showed no enantioselection.

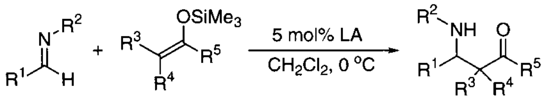
Polymer-supported thioketene silyl acetals reacted with aldehydes in the presence of a catalytic amount of Sc(OTf)$_3$ to give the corresponding β-hydroxy thioester derivatives, which were reduced to 1,3-diols and β-hydroxy aldehyde derivatives or hydrolyzed to β-hydroxy carboxylic acid derivatives (Scheme 7).[36]

A new type of polymer-supported Lewis acid, microencapsulated Sc(OTf)$_3$, was developed and successfully used in the aldol reaction and other reactions. Microencapsulated Sc(OTf)$_3$, which was prepared by the immobilization of Sc(OTf)$_3$ onto polymer, is easily recovered and reusable (Scheme 8).[37]

2.1.2. Mannich-type Reaction

The Mannich and related reactions provide one of the most fundamental and useful methods for the synthesis of β-amino ketones or β-amino esters, leading to β-lactam derivatives.[38] In the classical Mannich routes to β-amino ketones and esters, yields are sometimes low due to significant side reaction, such as deamination under rather drastic reaction conditions. To perform the reactions under milder conditions, some modifications using preformed iminium salts[39] and imines[40] were introduced. However, these intermediates are often hygroscopic and/or thermally unstable. In 1977, the reactions of imines with silyl enol ethers in the presence of a stoichiometric amount of TiCl$_4$ as a promoter were first reported,[40a] and since then, some efficient catalysts have been developed.[40c-g, 41]

Table 13. Mannich-type Reactions Using a Lewis Acid as a Catalyst



R^1	R^2	R^3	R^4	R^5	LA	yield/%
Ph	Ph	Me	Me	OMe	Yb(OTf)$_3$	97
Ph	Ph	Me	Me	OMe	Y(OTf)$_3$	81
Ph	Ph	Me	Me	OMe	TiCl$_4$ (1.0 eq.)	85
Ph	Bn	H	Me	OBn	Yb(OTf)$_3$	80[a]
Ph	Bn	H	H	SEt	Yb(OTf)$_3$	65
Ph	Bn	H	H	SEt	Sc(OTf)$_3$	80

[a] *Syn*/*anti* = 18/82.

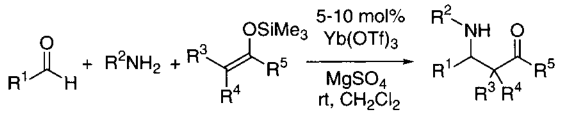
2.1.2.1. Mannich-type Reaction of Imines. Reactions of imines with ketene silyl acetals proceeded smoothly in the presence of 5 mol % of Yb(OTf)$_3$ to afford the corresponding β-amino ester derivatives in moderate to excellent yields (Table 13).[42] A catalytic amount of Yb(OTf)$_3$ is enough to complete the reactions, whereas a stoichiometric amount of TiCl$_4$ was required for the reaction (Table 13). In the reactions of the ketene silyl acetal derived from benzyl propionate, *anti* adducts were obtained in good selectivities. Generally, Sc(OTf)$_3$ has higher activity than Yb(OTf)$_3$ in the reaction with thioketene acetals. Again, these catalysts could be recovered and reused without loss of activities.

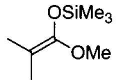
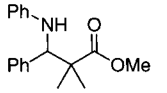
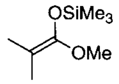
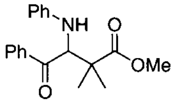
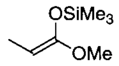
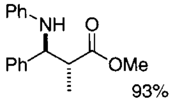
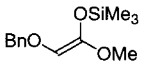
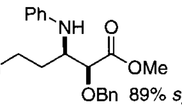
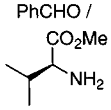
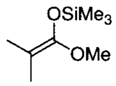
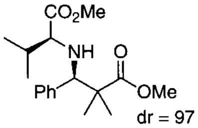
A novel Mannich-type reaction of *N*-(β-aminoalkyl)-benzotriazoles with silyl enol ethers has been developed.[43] Yb(OTf)$_3$ was also useful for three-component coupling reactions of aldehydes, amines, and silyl enol ethers (Table 14).[44] The reactions with chiral amines provided β-aminocarbonyl compounds in moderate to excellent diastereoselectivties.[45] It has been shown recently that Sc(OTf)$_3$ and Cu(OTf)$_2$ promoted Mannich-type reactions of aldehydes, amines, and silyl enol ethers in micellar systems.[46] It was also reported that Mannich-type reactions of 4-phenyl-2-trimethylsiloxy-1,3-butadiene with imines proceeded in the presence of Sc(OTf)$_3$ to give the corresponding adducts in good yield.[47]

Four-component coupling reactions of silyl enol ethers, α,β-unsaturated thioesters, amines, and aldehydes were also catalyzed by Sc(OTf)$_3$, affording the corresponding amino thioester and γ-acyl-δ-lactam derivatives stereoselectively in high yields (Scheme 9).[48]

A two-step procedure involving addition of ketene silyl acetals to imines and subsequent ring closure has been used for the construction of β-lactam derivatives.[38,49] The procedure was later improved by Cozzi, Cinquini,[50] and others,[51] who demonstrated that ketene silyl acetals derived from 2-pyridyl

Table 14. Three-Component Coupling Reactions of Aldehydes, Amines, and Silyl Enol Ethers Catalyzed by Yb(OTf)$_3$



aldehyde / amine	KSA	product	yield/%
PhCHO / PhNH$_2$			89[a]
PhCOCHO•H$_2$O / PhNH$_2$			82[a]
PhCHO / BnNH$_2$		 93% *anti*	90[a]
Ph(CH$_2$)$_2$CHO / Ph$_2$CHNH$_2$		 89% *syn*	88[a]
PhCHO / 		 dr = 97 : 3	70[b]

[a] Reference 44. [b] Reference 45.

Scheme 9. Synthesis of γ-Acyl-δ-lactam Derivatives Using Four-Component Coupling Reactions Catalyzed by Sc(OTf)$_3$

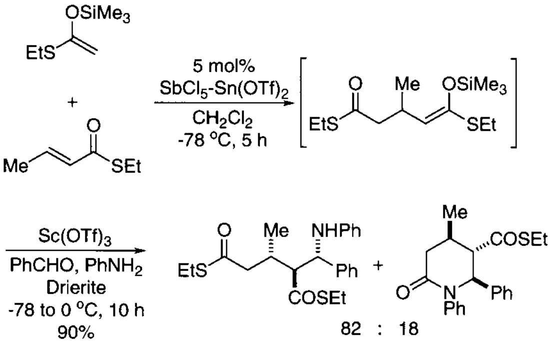
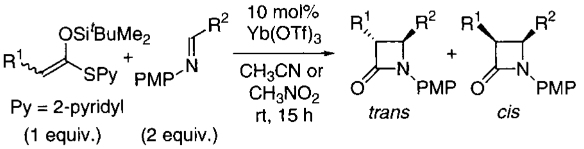
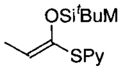
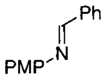
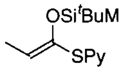
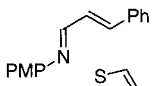
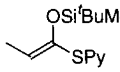
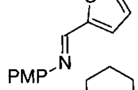
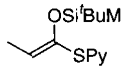
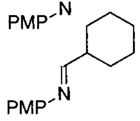
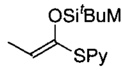
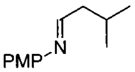
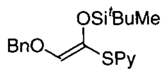
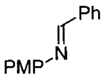
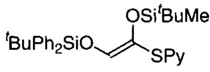
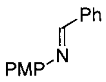


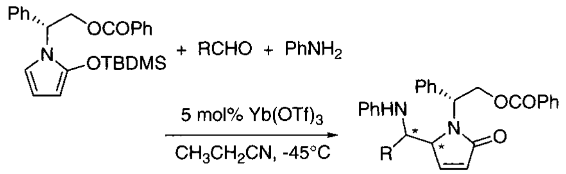
Table 15. Yb(OTf)$_3$-Catalyzed Synthesis of β-Lactams



KSA	imines	yield/%	*trans*/*cis*
		62[a] 99[b]	95 / 5 89 / 11
		64[a] 90[b]	84 / 16 60 / 40
		57[b]	87 / 13
		89[a]	37 / 63
		36[b]	63 / 37
 60% *E*		49[a]	60 / 40
 92% *E*		21[a]	40 / 60

[a] In CH$_3$CN. [b] In CH$_3$NO$_2$.

Table 16. Yb(OTf)$_3$-Catalyzed Mannich-type Reactions of a Chiral Silyloxypyrrole



R	dr		yield/%
	erythro	*threo*	
Ph	45/27	19/9	71
Furan	53/34	10/3	86
^{t}Bu	73/27	0/0	81
CH$_3$	74/16	8/2	82
PhCH$_2$	85/15	0/0	80
CH$_3$(CH$_2$)$_6$	81/13	6/0	85
PhCH$_2$CH$_2$	80/14	6/0	77

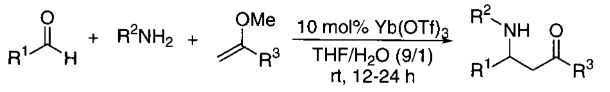
thioesters reacted with imines[52] to afford β-lactams directly in the presence of a stoichiometric amount of a Lewis acid. Meanwhile, it was also found that a catalytic amount of Yb(OTf)$_3$ mediated synthesis of β-lactams directly using preformed or in situ generated imines (Table 15).[53]

Diastereoselective Mannich-type reactions using a siloxypyrrole were also catalyzed by Yb(OTf)$_3$.[54] The three-component reactions of nonracemic siloxypyrrole, aldehyde including aromatic as well as aliphatic enolizable aldehydes, and aniline proceeded smoothly at −45 °C in propionitrile to afford the corresponding Mannich-type adducts (Table 16).

Mannich-type reactions of aldehydes, amines, and vinyl ethers proceeded smoothly in the presence of a catalytic amount of Yb(OTf)$_3$ in aqueous media (Table 17).[55] Remarkably, commercially available aqueous formaldehyde and chloroacetaldehyde solutions could be used directly, and the corresponding β-amino ketones were obtained in good yields. Wide varieties of aldehyde, including phenylglyoxal monohydrate, methyl glyoxylate, an aliphatic aldehyde, and an α,β-unsaturated aldehyde, gave the corresponding β-amino esters in high yields. It is noted that the condensation of aldehydes and amines proceeds in aqueous solution. Other rare-earth triflates also showed similar catalytic activities.

When compared to aldehydes, aldimines are less reactive toward nucleophilic additions.[56] Recently it

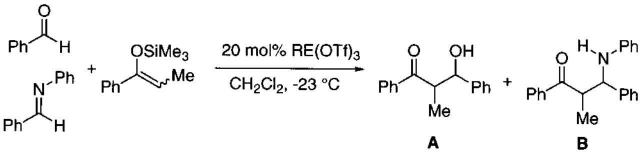
Table 17. Three-Component Mannich-type Reactions Catalyzed by $Yb(OTf)_3$ in Aqueous Media



R^1CHO	R^2NH_2	R^3	yield/%
aq. HCHO	p-$ClPhNH_2$	Me	92
aq. HCHO	p-anisidine	Ph	quant.
PhCHO	p-$ClPhNH_2$	Me	90
$Ph(CH_2)_2CHO$	p-$ClPhNH_2$	Me	55
aq. $ClCH_2CHO$	p-$ClPhNH_2$	Me	59
PhCH=CH	p-$ClPhNH_2$	Me	73
$PhCOCHO{\cdot}H_2O$	p-$ClPhNH_2$	Me	93[a]
MeO_2CCHO	p-anisidine	Me	67

[a] 91% yield with $Sc(OTf)_3$, 90% yield with $Sm(OTf)_3$, 94% yield with $Tm(OTf)_3$.

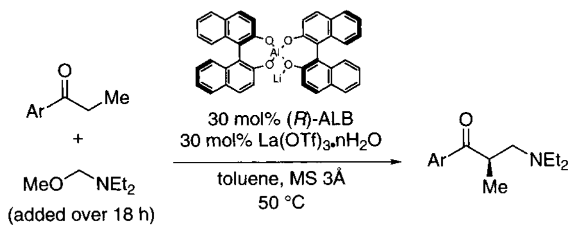
Table 18. Selective Activation of Aldimines over Aldehydes for Nucleophilic Addition Reactions in the Presence of a Catalytic Amount of $RE(OTf)_3$



RE	yield/% A	yield/% B	A/B	RE	yield/% A	yield/% B	A/B
Sc	24	65	27/73	Gd	3	81	4/96
Y	19	64	23/77	Dy	12	46	21/79
La	3	82	4/96	Ho	2	78	3/97
Ce	2	77	3/97	Er	22	63	26/74
Pr	1	55	2/98	Tm	3	82	4/96
Nd	5	72	6/94	Yb	2	92	2/98
Sm	10	34	23/77	Lu	trace	70	<1/>99
Eu	2	78	3/97	$SnCl_4$[a]	93	1	99/1

[a] 100 mol% of $SnCl_4$ was used at −78 °C.

Table 19. Direct Catalytic Asymmetric Mannich Reactions of Propiophenone



Ar	yield/%	ee/%
Ph	65	40
4-$MeOC_6H_4$	76	31
2-naphtyl	61	44
6-MeO-2-naphtyl	69	44

Scheme 10. Polymer-Supported Scandium-Catalyzed Three-Component Reactions

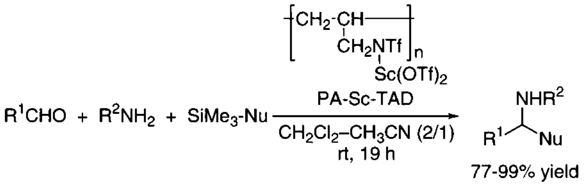
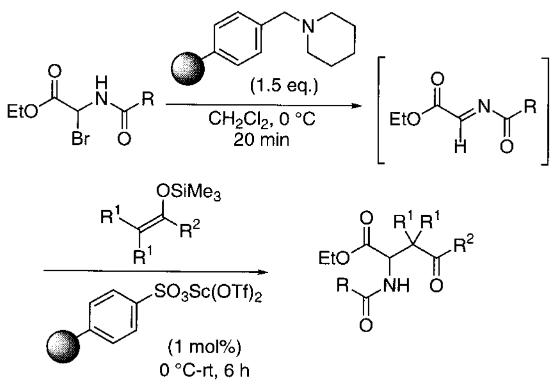


Table 20. Direct Formation of N-Acylated Amino Acid Derivatives



R	R^1	R^2	yield/%
Ph	H	Ph	79
	H	p-$MeOC_6H_4$	85
	H	p-ClC_6H_4	76
	Me	OMe	91
	H	SEt	86
Me	H	p-$MeOC_6H_4$	74
$(CH_2)_{10}CH_3$	H	p-$MeOC_6H_4$	86
OEt	H	p-$MeOC_6H_4$	71

has been shown that a dramatic change in their reactivities is observed by employing $Yb(OTf)_3$ as a catalyst.[57] Thus, aldimines are preferentially activated by a catalytic amount of $Yb(OTf)_3$ in the coexistence of aldehydes for nucleophilic additions with silyl enol ethers and ketene silyl acetals (Table 18).[58] On the other hand, excess $SnCl_4$ promoted the addition to aldehyde exclusively. Selective formation of an aldimine−$Yb(OTf)_3$ complex over an aldehyde−$Yb(OTf)_3$ complex was indicated by ^{13}C NMR analyses.

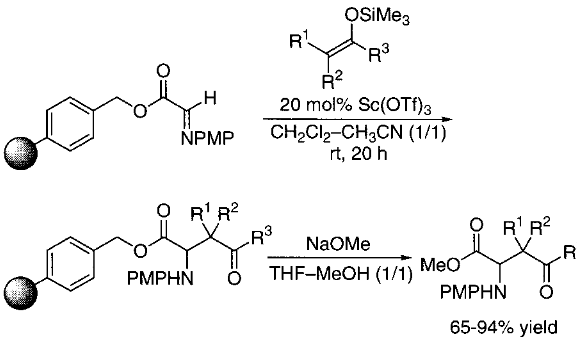
Shibasaki and co-workers reported the first example of direct catalytic asymmetric Mannich-type reactions of unmodified ketones using a combination of AlLibis[(*R*)-binaphthoxide] complex [(*R*)-ALB] and $La(OTf)_3$ hydrate (Table 19).[59] (*R*)-ALB alone was not sufficient to promote the reaction, and other rare-earth triflates resulted in lower enantiomeric excesses.

A polymer-supported scandium catalyst was successfully used in three-component reactions. In the presence of polyallylscandium trifylamide ditriflate (PA-Sc-TAD), three-component reactions proceeded smoothly to afford β-amino ketones, β-amino esters, and β-amino nitriles in high yields (Scheme 10). Aldimine-selective reactions in the coexistence of aldehydes using PA-Sc-TAD proceeded to afford the corresponding adducts in high yield.[60] Microencapsulated $Sc(OTf)_3$-catalyzed Mannich-type reactions were also reported. The catalyst was easily recovered and reusable.[37]

In the presence of a polymer-supported scandium catalyst, Mannich-type reactions of *N*-acylimino esters prepared from α-bromoglycine derivatives and a polymer-supported amine proceeded smoothly to afford the N-acylated amino acid derivatives directly (Table 20).[61]

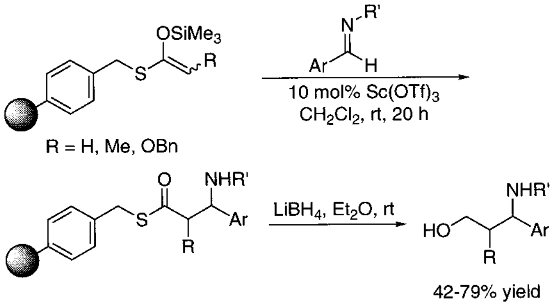
Mannich-type reactions of polymer-supported α-imino esters proceeded in the presence of a catalytic

Scheme 11. Mannich-type Reactions of Polymer-Supported α-Imino Esters



PMP = *p*-methoxyphenyl

Scheme 12. $Sc(OTf)_3$-Catalyzed Mannich-type Reactions of Polymer-Supported Silyl Enol Ethers with Imines



amount of $Sc(OTf)_3$ to give the corresponding α-amino esters after cleavage from the polymer support (Scheme 11).[62]

Polymer-supported thioketene silyl acetals reacted with imines in the presence of a catalytic amount of $Sc(OTf)_3$ to give the corresponding β-amino thioester derivatives, which were converted to β-amino alcohol, β-amino acid, and β-lactam derivatives (Scheme 12).[63] Three-component reactions using polymer-supported thioketene silyl acetals proceeded under similar conditions.

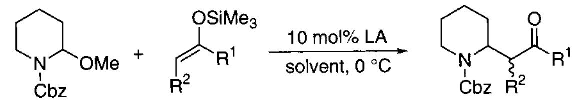
Mannich-type reactions of iminium ions generated from 2-methoxypiperidines proceeded smoothly to afford the corresponding piperidine derivatives in high yield. In this reaction, conventional Lewis acids such as $SnCl_4$ and $BF_3 \cdot Et_2O$ gave only trace amounts of the adducts (Table 21).[64]

It was reported that $Sc(OTf)_3$-catalyzed addition of 1-trimethylsilyl nitropropanate to imines proceeded to give β-nitro amines in good yields (Table 22).[65]

2.1.2.2. Mannich-type Reactions of Other C═N Groups. Recently, it was found that in the presence of a catalytic amount of $Sc(OTf)_3$, benzoylhydrazones reacted with ketene silyl acetals to afford the corresponding adducts, β-*N*′-benzoylhydrazino esters, in high yields (Table 23).[66] Typical Lewis acids such as $TiCl_4$, $SnCl_4$, and $BF_3 \cdot OEt_2$, etc., were not effective in this reaction. β-*N*′-Benzoylhydrazino esters were readily converted to various nitrogen-containing compounds. Thus, reductive cleavage of the nitrogen–nitrogen bonds of the hydrazino compounds afforded β-amino esters. Cyclization of β-*N*′-benzoylhydrazino esters with ^{n}BuLi at −78 °C provided β-lactams, while pyrazolones were produced in the presence of NaOMe in MeOH at room temperature or under reflux conditions (Scheme 13). Polymer-supported acylhydrazones have been developed, and the reactions with ketene silyl acetals proceeded smoothly in the presence of a catalytic amount of $Sc(OTf)_3$.[67]

It was reported that rare-earth metal triflate-catalyzed addition of ketene silyl acetals to nitrones proceeded smoothly to afforded the corresponding adducts in good yields under mild conditions. $La(OTf)_3$ was the most effective as a catalyst in this reaction (Table 24).[68]

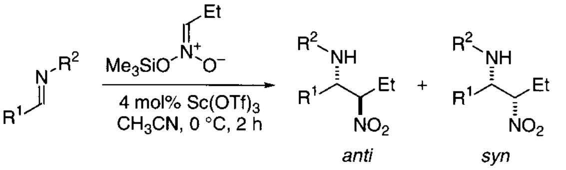
Table 21. Nucleophilic Substitution Reactions of a 2-Methoxypiperidine



LA	R^1	R^2	solvent	yield/%
$SnCl_4$	Ph	H	CH_2Cl_2	trace
$BF_3 \cdot Et_2O$	Ph	H	CH_2Cl_2	trace
$Sc(OTf)_3$[a]	Ph	H	CH_2Cl_2	89
$Sc(OTf)_3$	Ph	H	CH_3CN	95
$Sc(OTf)_3$	^{t}Bu	H	CH_3CN	89[b]
$Sc(OTf)_3$	Ph	Me	CH_3CN	91[b,c]

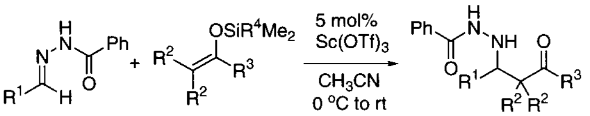
[a] 0.5 equiv of $LiClO_4$ was used as an additive. [b] Performed at room temperature. [c] Diastereomeric ratio was 90/10.

Table 22. $Sc(OTf)_3$-Catalyzed Addition of 1-Trimethylsilyl Nitropropanate



R^1	R^2	yield/%	*anti*/*syn*
Ph	*p*-$MeOC_6H_4CH_2$	70	2/1
^{c}Hex		68	1/1
^{n}Pent		66	3/2
$(CH_2)_4Ph$		90	4/1
2-furyl		90	5/3
Ph	*p*-MeOC6H4	90	8/1
^{c}Hex		99	9/1
^{n}Pent		72	2/1
$(CH_2)_4Ph$		53	3/1
2-furyl		65	6/5

Table 23. $Sc(OTf)_3$-Catalyzed Mannich-type Reactions of Hydrazones



R^1	R^2	R^3	R^4	yield/%
Ph	Me	OMe	Me	81
PhCH═CH	Me	OMe	Me	63
$Ph(CH_2)_2$	Me	OMe	Me	98
^{i}Bu	Me	OMe	^{t}Bu	quant.
^{i}Bu	Me	SEt	Me	53
^{i}Bu	H	SEt	Me	36
EtO_2C	Me	OMe	^{i}Bu	76

Scheme 13. Conversion of β-*N'*-Benzoylhydrazino Esters to β-Amino Esters, Pyrazolones, and β-Lactams

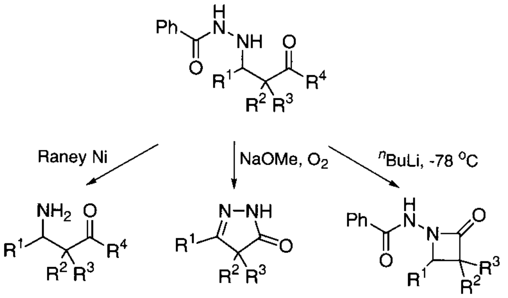
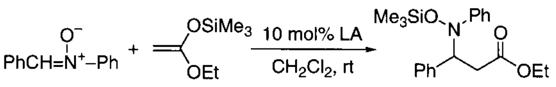
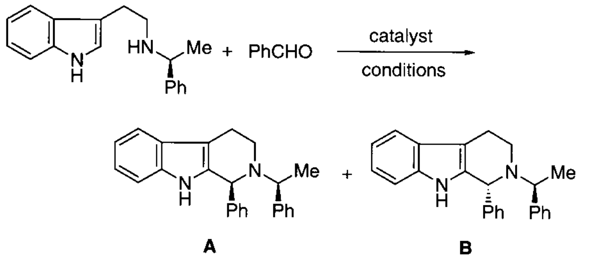


Table 24. Ln(OTf)$_3$-Catalyzed Addition of Ketene Silyl Acetals to Nitrones



LA	yield/%	LA	yield/%
Yb(OTf)$_3$	58	BF$_3$·OEt$_2$	21
La(OTf)$_3$	80	AlCl$_3$	17
Sc(OTf)$_3$	14	TiCl$_4$	8
Sm(OTf)$_3$	59	ZnI$_2$	39

Table 25. Effect of Acid Catalysts on Pictet–Spengler Reaction

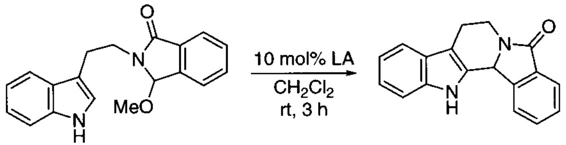


cat. (mol %)	conditions	time/h	yield/% (**A**/**B**)
none	PhH, reflux	48	96 (53/47)
Yb(OTf)$_3$ (5)	CH$_2$Cl$_2$, reflux	24	40 (55/45)
BF$_3$·OEt$_2$ (50)	PhH, reflux	24	54 (71/29)
B(OPh)$_3$ (100)	PhH, reflux	5	96 (60/40)
Et$_2$AlCl (100)	CH$_2$Cl$_2$, rt	24	50 (67/33)
TFA (50)	PhH, reflux	24	71 (86/14)

2.1.2.3. Pictet–Spengler Reaction. Pictet–Spengler reaction has been used for construction of tetrahydro-β-carbolines and tetrahydroisoquinolines, whose structures are widely distributed in many alkaloids.[69] Asymmetric reactions with tryptophan alkyl esters,[70] chiral aldehydes,[71] or *N*-β-(3-indolyl)ethyl amino acid esters[72] have been reported in the literature. Nakagawa and her group studied acid-catalyzed asymmetric Pictet–Spengler reaction of tryptamine derivatives with α-methylbenzylamine as chiral auxiliary (Table 25).[73] Although TFA (0.5–1 equiv) provided the best result, a catalytic amount of Yb(OTf)$_3$ was also effective.

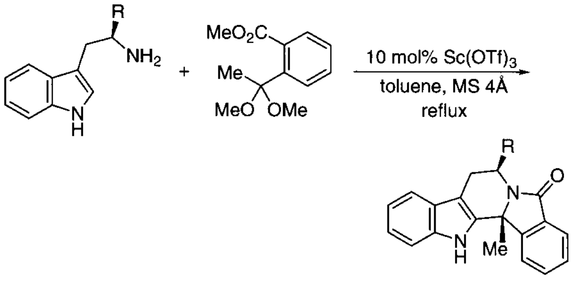
Sc(OTf)$_3$ catalyzed in situ generation of the acyliminium ion from α-methoxyindolone and subsequent cyclization to give the corresponding β-carboline in moderate yield (Scheme 14).[74] The same reaction was also mediated by Cu(OTf)$_2$ in a better yield.

Scheme 14. Lewis-Acid-Catalyzed Intramolecular Acylaminoalkylation



Sc(OTf)$_3$: 56% yield
Cu(OTf)$_2$: 94% yield

Scheme 15. Sc(OTf)$_3$-Catalyzed Reactions of an Acetal with Amines and Cascade Cyclization Reactions



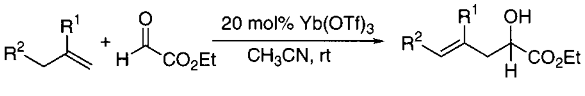
R= H: 91% yield
R= CO$_2$Et: 36% yield

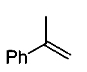
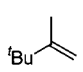
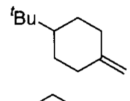
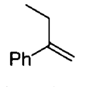
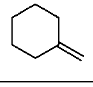
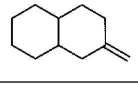
It was also found that heating a solution of tryptamine and methyl 2-(1,1-dimethoxyethyl)benzoate in toluene in the presence of 10 mol % of Sc(OTf)$_3$ and MS 4A gave the β-carboline derivative in excellent yield (Scheme 15).[75] A similar reaction with the ethyl ester of tryptophane gave the desired product as a single diastereomer.

2.1.3. Ene Reaction

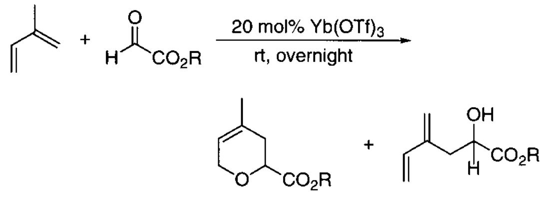
Carbonyl–ene reactions between glyoxylates and simple alkenes were efficiently catalyzed by Yb(OTf)$_3$ (Table 26).[76] Other Ln(OTf)$_3$ also constituted effective catalysts, while lanthanide(III) chlorides and alkoxides did not promote the reaction. 2-Methyl-1,3-butadiene (isoprene) is known to react with glyoxylate to form a hetero-Diels–Alder product and an ene product.[77] The Yb(OTf)$_3$-catalyzed reaction of isoprene with a glyoxylate in CH$_3$CN gave the hetero-Diels–Alders adduct as a major product (Scheme 16). In contrast, the ene product was formed in CH$_2$Cl$_2$ preferentially. Chiral ytterbium catalysts generated from Yb(OTf)$_3$ and chiral ligands (BINOL derivatives or Pybox derivatives) were used in an asymmetric carbonyl–ene reaction (Table 27).

Table 26. Yb(OTf)$_3$-Catalyzed Carbonyl–Ene Reactions



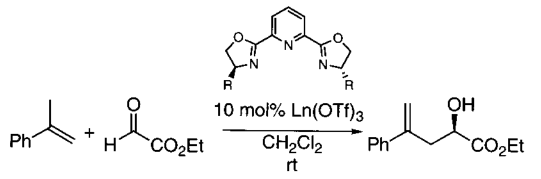
alkene	yield/%	alkene	yield/%
	85		65
	72		91 (84% *E*)
	63		72 (69 / 31)

Scheme 16. Competitive Hetero-Diels–Alders Reaction and Carbonyl–Ene Reaction of Isoprene Catalyzed by Yb(OTf)$_3$



in CH_3CN: 73-87% yield (78/22 to 65/35)
in CH_2Cl_2: 69-81% yield (25/75 to 33/67)

Table 27. Asymmetric Carbonyl–Ene Reaction Catalyzed by Chiral Rare-Earth Metal Triflates



Ln(OTf)$_3$	R	time/h	yield/%	ee/%
Sc(OTf)$_3$	^{i}Pr	40	26	27
Dy(OTf)$_3$	^{i}Pr	40	44	20
Sm(OTf)$_3$	^{i}Pr	40	42	16
Yb(OTf)$_3$	^{i}Pr	8	31	46
Yb(OTf)$_3$	Ph	36	71	50

Scheme 17. Sc(OTf)$_3$-Catalyzed Reactions of Methylenecyclohexane with Aldehydes

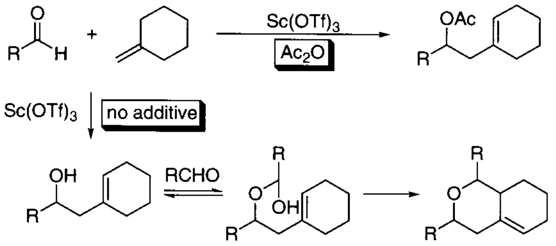
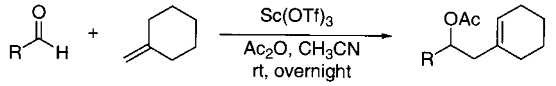


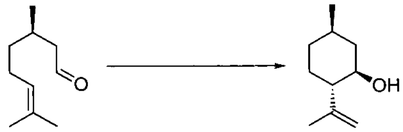
Table 28. Sc(OTf)$_3$-Catalyzed Intermolecular Carbonyl–Ene Reactions



R	Sc(OTf)$_3$/mol%	yield/%
Ph	10	68
p-MeC_6H_4	5	61
p-$MeOC_6H_4$	5	0
m-$MeOC_6H_4$	5	29

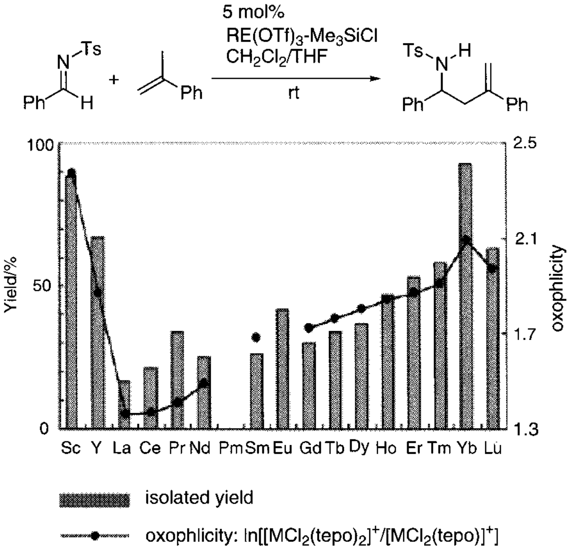
Sc(OTf)$_3$ was found to catalyze intermolecular carbonyl–ene reactions of methylene cyclohexane with aromatic and aliphatic aldehydes.[78] Interestingly, without any additive, the reaction gave a pyran instead of the ene adduct (Scheme 17). Formation of the pyran was presumably via initial addition of the alkene to the aldehyde, followed by rapid formation of hemiacetal, generation of an oxonium ion, and cyclization. In the presence of acetic anhydride, the ene product was then trapped in situ as an acetate (Table 28). It was found that the electronic effect controlled the reaction; highly electron-rich aromatic aldehydes failed to react, whereas highly electron-deficient aldehydes and aliphatic aldehydes furnished unexpected geminal diacetates (acylals). The intramolecular ene cyclization of citronellal was originally promoted by a stoichiometric amount (1 equiv) of $ZnBr_2$.[79] Notably, a catalytic amount of Sc(OTf)$_3$ could be used without affecting the selectivity (Scheme 18).

Scheme 18. Sc(OTf)$_3$-Catalyzed Intramolecular Carbonyl–Ene Cyclization of Citronellal



5 mol% Sc(OTf)$_3$: >95%, isopulegol/other isomers: 94/6
100 mol% $ZnBr_2$: 70%, isopulegol/other isomers: 94/6

Scheme 19. Imine–Ene Reaction Catalyzed by a Combination of Yb(OTf)$_3$ and TMSCl



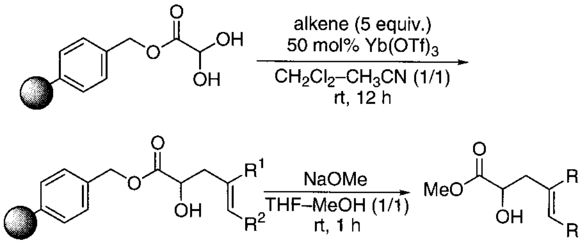
The imino ene reaction of *N*-tosyl benzaldimine with α-methylstyrene was catalyzed by Yb(OTf)$_3$.[80] Addition of a catalytic amount of TMSCl dramatically enhanced the reaction (Scheme 19). TMSCl alone did not catalyze the reaction, while TMSOTf or TfOH was less effective to promote the reaction. Moreover, a combination of 50 mol % each of Yb(OTf)$_3$ and TMSOTf catalyzed three-component coupling of aromatic or aliphatic aldehydes, tosylamine, and α-methylstyrene to afford the desired products in good yields (76–90%). Among rare-earth metal triflates screened, Sc(OTf)$_3$ and Yb(OTf)$_3$ gave the best yields.

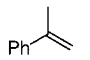
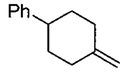
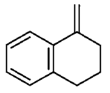
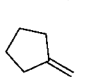
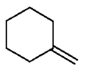
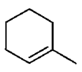
Ene reactions of polymer-supported glyoxylate with alkenes were effectively catalyzed by Yb(OTf)$_3$ (Table 29).[62b]

2.1.4. Allylation

The Lewis-acid-catalyzed reaction of allyl organometallics with carbonyl compounds provides synthetically useful homoallylic alcohols.[81] Yb(OTf)$_3$ proved to be a catalyst for allylation of aldehydes with allyltributyltin (Table 30).[82] In the coexistence of a stoichiometric amount of benzoic acid, the rate of allylation with some less reactive aldehydes was much enhanced (Table 31).[83] The added protic acid

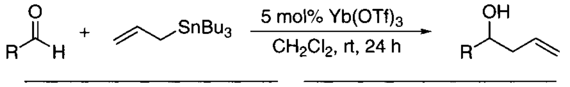
Table 29. Ene Reactions of a Polymer-Supported Glyoxylate



alkene	yield/%	alkene	yield/%
	74		64
	79		61
	71		$59^{a,b}$

[a] 100 mol % of Yb(OTf)_3 was used. [b] 6% of the exo-methylene isomer was included.

Table 30. Allylation of Aldehydes with Allyltributyltin Catalyzed by Yb(OTf)_3



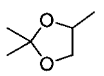
R	yield/%	R	yield/%
Ph	85		66
p-$NO_2C_6H_4$	93		
^{c}Hex	94		
1-naphthyl	88	^{n}pent	93
PhCHMe	87	^{i}Pr	86
2-furyl	85		

Table 31. Effect of Benzoic Acid on Allylation of Aldehydes Catalyzed by Yb(OTf)_3[a]

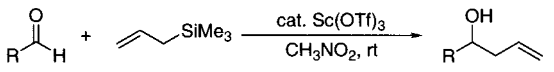
R	$PhCO_2H$/equiv	time/h	yield/%
C_6H_{11}	0	48	33
C_6H_{11}	1	1.5	100
p-$MeSC_6H_4$	0	48	27
p-$MeSC_6H_4$	1	0.75	100
Ph	1	0.25	100
Ph	1	48	0[b]

[a] 2 mol % of Yb(OTf)_3. [b] In the absence of Yb(OTf)_3.

was suggested to promote the catalyst regeneration step where a ytterbium alkoxide intermediate might decompose to Yb(OTf)_3 and a homoallylic alcohol.

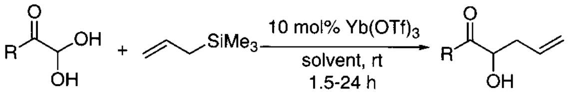
Although the allylation reaction with less reactive allyltrimethylsilane was not catalyzed by Yb(OTf)_3, it proceeded smoothly in the presence of Sc(OTf)_3 (Table 32).[84] Moreover, in the coexistence of aldehydes and ketones, aldehydes reacted exclusively under the conditions and high chemoselectivity was demonstrated.[85] $YbCl_3$ was also effective in this reaction.[86]

Table 32. Allylation of Aldehydes with Allyltrimethylsilane Catalyzed by Sc(OTf)_3



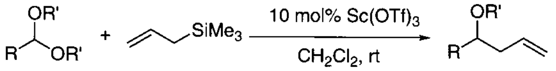
R	Sc(OTf)_3/mol%	time/h	yield/%
Ph	2	14	79
2-naphthyl	2	14	73
p-ClC_6H_4	2	14	98
p-$NO_2C_6H_4$	2	14	84
$PhCH_2$	10	14	53
nBu	10	18	56
^{c}Hex	10	18	62
^{t}Bu	10	18	71

Table 33. Yb(OTf)_3-Catalyzed Allylation Reactions of α-Keto Aldehydes and Glyoxylates



R	solvent	time/h	yield/%
Ph	CH_2Cl_2	2	71
p-HOC_6H_4	MeCN	20	74
p-$MeOC_6H_4$	MeCN	20	65
BuO	CH_2Cl_2	1.5	76
(−)-menthyloxy	dioxane	20	76 (30% de)

Table 34. Sc(OTf)_3-Catalyzed Allylation of Acetals and *gem*-Diacetes

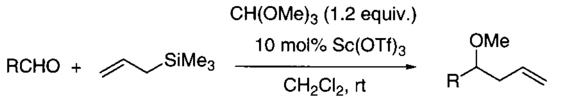


	R′ = Me		R′ = Ac	
Ar	time/h	yield/%	time/h	yield/%
Ph	6	90	4	90
3,4-$(OCH_2O)C_6H_3$	6	87	4	87
3,4-$(MeO)_2C_6H_3$	5	81	5	78
3,4-$Cl_2C_6H_3$	4	87	6	90
3-$PhOC_6H_4$	5	78	5	89
p-BrC_6H_4	6	85	4	81
m-$MeOC_6H_4$	6	75	6	80
p-MeC_6H_4	7	90	5	87
o-ClC_6H_4	6	85	4	84
2-naphthyl	6	77	8	88
9-anthracenyl	8	74	10	83
2-thienyl	5	80	7	62
$Ph(CH_2)_2$	6	71	6	65
^{c}Hex	8	68	8	70

Anhydrous α-keto aldehydes and glyoxylates are unstable and easily polymerized, and thus, they are usefully prepared and stored as hydrates. It is desirable to use these hydrates directly for Lewis-acid-catalyzed reactions. Toward this end, It was shown that Yb(OTf)_3 catalyzed reactions of the hydrates from α-keto aldehydes and glyoxylates with allyltrimethylsilane affording α-keto and α-ester homoallylic alcohols, respectively (Table 33).[87] It is noted that allylation reactions of the corresponding dimethyl acetals were not successful even in the presence of 20 mol % of Yb(OTf)_3.

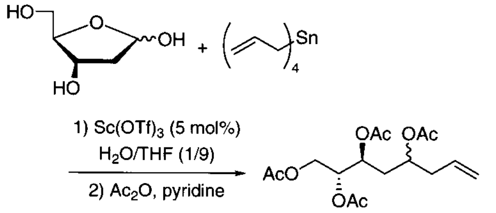
Scandium triflate catalyzes also allylation of acetals and *gem*-diacetates with allyltrimethylsilane to give homoallyl ethers in high yields (Table 34).[88] In the presence of trimethylorthoformate, the direct formation of homoallyl methyl ethers from aldehydes and allyltrimethylsilane proceeds smoothly (Table 35).

Table 35. $Sc(OTf)_3$-Catalyzed Direct Allylation of Aldehyde in the Presence of Trimethylorthoformate



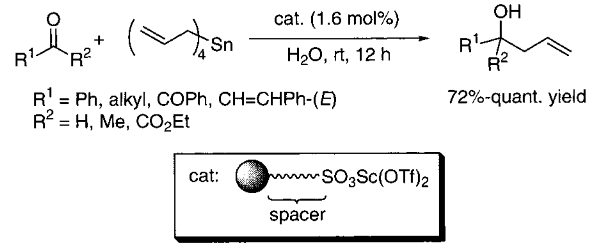
R	time/ h	yield/ %	R	time/ h	yield/ %
Ph	5	90	p-MeC_6H_4	5	90
3,4-$(OCH_2O)C_6H_3$	7	85	3,4,5-$(MeO)_3C_6H_4$	8	75
3,4-$(MeO)_2C_6H_3$	7	81	2-naphthyl	8	84
3,4-$Cl_2C_6H_3$	8	90	2-thienyl	5	90
3-$PhOC_6H_4$	6	80	$Ph(CH_2)_2$	8	75
p-BrC_6H_4	5	85	PhCH=CH	5	70
m-$MeOC_6H_4$	6	82	^{c}Hex	8	74

Scheme 20. Allylation with Tetraallyltin in Aqueous Media Using $Sc(OTf)_3$



89% yield
dr=88/12

Scheme 21. Allylation in Water Using a Polymer-Supported Scandium Catalyst



R^1 = Ph, alkyl, COPh, CH=CHPh-(E)
R^2 = H, Me, CO_2Et

72%-quant. yield

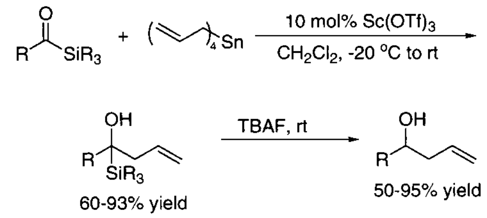
Likewise, other allyl organometallics were subjected for allylation reactions. For example, in the presence of a catalytic amount of $Sc(OTf)_3$, tetraallyltin[89] and tetraallylgermane[90] reacted with aldehydes to afford homoallylic alcohol, in high yields (Scheme 20). In most cases, the reactions were performed in organic solvent—water mixtures. Remarkably, unprotected sugars reacted directly to give the corresponding adducts in high yields, which provided an easy entry to higher sugars (Scheme 20).[89] It was possible to conduct reactions without using organic solvents; allylation of aldehydes with tetraallyltin proceeded in water in the presence of a surfactant (SDS).[91]

As stated before, ketones are unreactive for allylation.[85] However, a polymer-supported scandium catalyst showed high activity even toward ketones in pure water. The allylation of carbonyl compounds proceeded smoothly in the presence of the catalyst to afford the corresponding homoallylic alcohols in high yields (Scheme 21).[24]

Acylsilanes reacted smoothly with tetraallyltin in the presence of $Sc(OTf)_3$.[92] The silyl groups in the products were easily removed by tetrabutylammonium fluoride (TBAF) to give secondary alcohols. When compared to the original procedures, this two-step protocol allows facile access to a wide range of homoallylic alcohols in good yields (Scheme 22). An interesting result was observed with a chiral acylsilane; a complete reversal of diastereoselectivity was observed using $Sc(OTf)_3$ in place of a traditional Lewis acid, $TiCl_4$ (Scheme 23).

La$(OTf)_3$ was introduced to induce allylation of aldehydes with metallic indium in water (Table 36).[93] The reaction was highly *anti*-selective regardless of the geometry of the starting allyl bromides. Given

Scheme 22. $Sc(OTf)_3$-Catalyzed Allylation of Acylsilanes



Scheme 23. Reversal of Diastereoselectivity: $Sc(OTf)_3$ vs $TiCl_4$

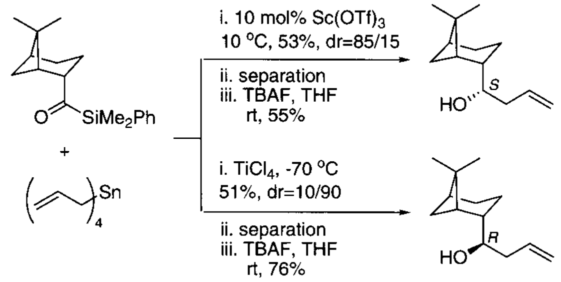
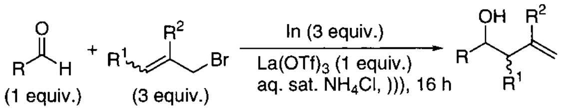
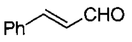
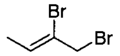
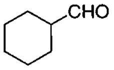
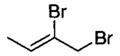
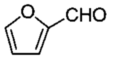
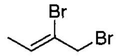
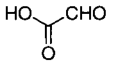
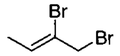
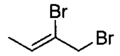
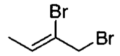
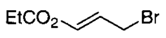
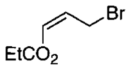


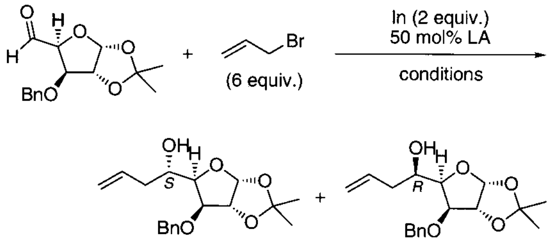
Table 36. La$(OTf)_3$-Catalyzed Allylation of Aldehydes Using Metallic Indium in Water



RCHO	allylic bromide	% yield (*anti* / *syn*)
		80% (78 / 22)
		100% (50 / 50)
		88% (81 / 19)
		95% (76 / 24)
TMS—≡—CHO		93% (77 / 23)
PhCHO		70% (100 / 0)
PhCHO		99% (90 / 10)[a]
PhCHO		90% (99 / 1)[a]

[a] Aldehyde (1 equiv), bromide (3 equiv), In (2 equiv), and La$(OTf)_3$ (2 equiv) were used.

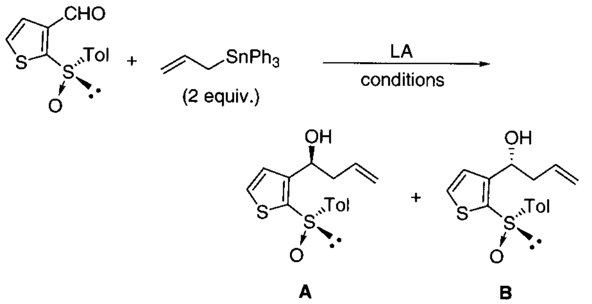
Table 37. Yb(OTf)$_3$-Promoted Indium-Mediated Allylation in Aqueous Medium



LA	conditions	yield/%	S/R^a
none	H_2O, 10 h	66	41/59
none	DMF/H_2O (6/4), 2 h	82	17/83
Yb(OTf)$_3$	DMF/H_2O (6/4), 1 h	88	6/94
$SnCl_4{}^b$	CH_2Cl_2, −78 °C	76	88/12

[a] Determined by ^{13}C NMR spectroscopy. [b] Allyltrimethylsilane was used instead of a combination of In and allyl bromide.

Table 38. Lewis-Acid-Catalyzed Diasteroselective Allylation with a Chiral Sufinyl Aldehyde



LA (equiv)	solvent	time/h	temp/°C	yield/%	dr
Sm(OTf)$_3$ (2.0)	THF	4	25	77	6.4/1
Nd(OTf)$_3$ (2.0)	THF	3	25	77	3.4/1
Yb(OTf)$_3$ (3.0)^a	THF	5	25	84	50/1
$TiCl_4$ (2.0)	CH_2Cl_2	3	−85	87	20.5/1
$SnCl_4$ (2.0)	CH_2Cl_2	2	−80	97	1/7.5

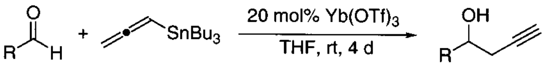
[a] With 2 equiv of Yb(OTf)$_3$ at 0 °C, the same reaction gave products in 43% yield (dr 19/1) after 20 h.

the lower reactivity of γ-substituted allylic reagents, the reaction was much accelerated with sonication.

Loh and his group reported that Yb(OTf)$_3$ accelerated the indium-mediated allylation reaction of sugar-derived chiral aldehyde in an aqueous medium giving high *anti* diastereoselectivity (Table 37).[94] The reaction proceeded slowly in pure water, and adducts were obtained with poor diastereoselectivity. DMF as a cosolvent resulted in a significant improvement in selectivity, and the best result was obtained with Yb(OTf)$_3$. Addition of $SnCl_4$ reversed the diastereofacial selectivity.

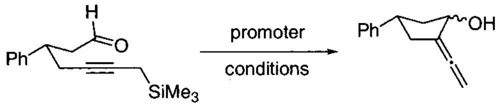
Diastereoselective allylation reactions of a chiral sulfinyl-substituted thiophene carboxaldehyde using different Lewis acids were examined.[95] The reaction with allyltriphenylsilane in the presence of Ln(OTf)$_3$ gave homoallylic alcohols with different selectivities, and Yb(OTf)$_3$ provided the best result (Table 38). $TiCl_4$ gave the same diastereomer as the major product, presumably through a chelation-controlled addition. On the other hand, $SnCl_4$ gave the other diastereomer predominantly.

Table 39. Yb(OTf)$_3$-Catalyzed Propargylation of Aldehydes



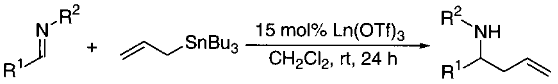
R	yield/%	R	yield/%
Ph	82	p-MeOC$_6$H$_4$	41
p-NO$_2$C$_6$H$_4$	91	2-furyl	71
m-MeOC$_6$H$_4$	60	^{n}Oct	66

Table 40. Intramolecular Allenylation of an Allenyl Aldehyde



promoter	conditions	yield/% (dr)
Sc(OTf)$_3$	CH_3NO_2, rt, 12 h	70 (50/50)
$ZnCl_2$	CH_2Cl_2, 0 °C to room temperature, 14 h	26
TBAF	THF, 0 °C, 1 h	78 (55/25)

Table 41. RE(OTf)$_3$-Catalyzed Allylation of Imines



R^1	R^2	Ln(OTf)$_3$	yield/%
Ph	Ph	Yb(OTf)$_3$	56
Ph	Ph	La(OTf)$_3$	62
Ph	Ph	Sc(OTf)$_3$	66
Ph	p-MeOC$_6$H$_4$	Yb(OTf)$_3$	73
Ph	Bn	Sc(OTf)$_3$	29
2-furyl	Bn	Yb(OTf)$_3$	30
PhCH=CH	p-MeOC$_6$H$_4$	Yb(OTf)$_3$	32
^{c}Hex	Ph$_2$CH	La(OTf)$_3$	53
EtCO$_2$	p-MeOC$_6$H$_4$	Yb(OTf)$_3$	46

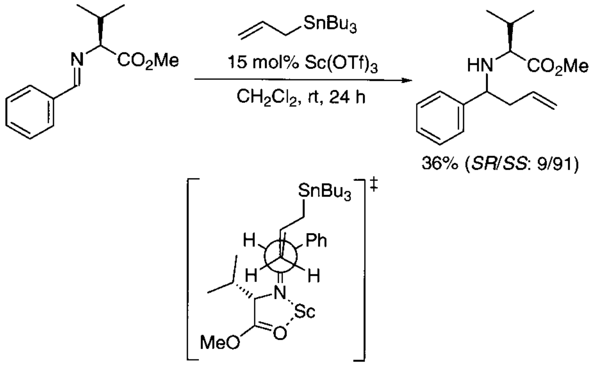
Homopropargyl alcohols were prepared in good yields by Yb(OTf)$_3$-catalyzed addition of allenyltributylstannane to various aldehydes (Table 39).[96] A similar result was obtained using Sc(OTf)$_3$ in the propargylation of benzaldehyde. When La(OTf)$_3$ was used as a catalyst, only a trace amount of product was observed.

Intramolecular allenylation of a propargyl silane aldehyde was studied under different conditions, and it was reported that an allenic product was obtained in moderate to good yields (Table 40).[97] Sc(OTf)$_3$ was as good as TBAF to promote the reaction.

Recently, highly enanioselective addition and annulation reactions of allenylsilanes with ethyl glyoxylate were reported. The reactions are catalyzed by Sc(OTf)$_3$/a chiral pybox ligand complex to give homopropargylic alcohols or dihydrofuranes depending on the silyl group of allenylsilanes used.[98]

It was reported that RE(OTf)$_3$ catalyzed allylation reactions of imines with allyltributylstannane to furnish homoallylic amines in moderate yields (Table 41).[99] The choice of the amine partners of the imines was crucial to achieve good yields, e.g., with 15 mol % of Yb(OTf)$_3$, benzaldehyde imines derived from benzylamine and aniline gave products in 8% and 56% yield, respectively. Sc, La, and Yb triflates were

Scheme 24. Sc(OTf)$_3$−Catalyzed Diastereoselective Allylation of a Chiral Imine



Scheme 25. Selective Activation of Aldimines over Aldehydes in Nucleophilic Addition Reactions Using Yb(OTf)$_3$ as a Catalyst

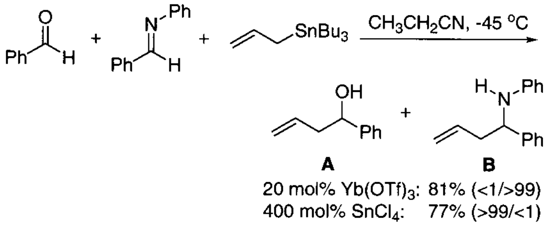
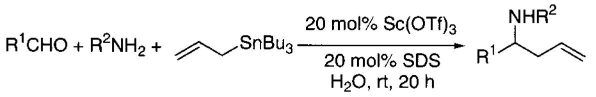
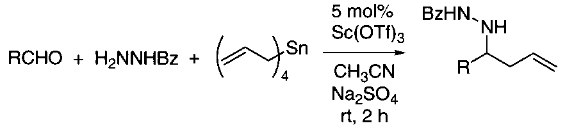


Table 42. Sc(OTf)$_3$-Catalyzed Three-Component Reactions of Aldehydes, Amines, and Allyltributyltin in a Micellar System



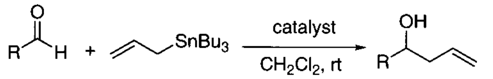
R^1	R^2	yield/%
Ph	Ph	83
Ph	p-ClC$_6$H$_4$	90
Ph	p-MeOC$_6$H$_4$	81
p-ClC$_6$H$_4$	p-ClC$_6$H$_4$	70
2-furyl	p-ClC$_6$H$_4$	67
2-thienyl	p-ClC$_6$H$_4$	67
Ph(CH$_2$)$_2$	p-ClC$_6$H$_4$	78
^{n}Oct	p-ClC$_6$H$_4$	66
^{c}Hex	Ph	80
PhCO	p-ClC$_6$H$_4$	71
(E)-PhCH=CH	p-ClC$_6$H$_4$	80

Table 43. Three-Component Allylation Reactions Using Acylhydrazines as a Imine Equivalent

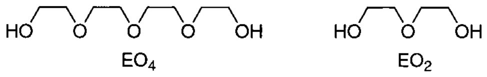


R	yield/%	R	yield/%
Ph(CH$_2$)$_2$	quant.	Ph	92
^{n}Hex	94	p-NCC$_6$H$_4$	90
^{i}Bu	99	PhCH=CH	93
^{c}Hex	84		

Table 44. Use of Polyethylene Glycol−Ln(OTf)$_3$ Complexes in Allylation of Imines



catalyst	mol%	time	yield/%
fresh Yb(OTf)$_3$	5	90 min	100
1-year-old Yb(OTf)$_3$	5	90 min	48
[Yb(OTf)$_3$(EO$_4$)]	10	4 h	77
[Yb(OTf)$_3$(EO$_4$)]	10	24 h	94
[Yb(OTf)$_3$(EO$_2$)]	10	4 h	85
[Yb(OTf)$_3$(EO$_2$)]	10	24 h	96



used to get optimum yields with different imines. The chiral imine derived from valine methyl ester gave the allylated product in high diastereoselectivity (Scheme 24). The observed selectivity was attributed to a nucleophilic attack in a chelated transition state.

Selective allylation of aldimines over aldehydes can be achieved using 20 mol % of Yb(OTf)$_3$ as a catalyst (Scheme 25).[58] Again, an excess of SnCl$_4$ promoted the addition to an aldehyde exclusively.

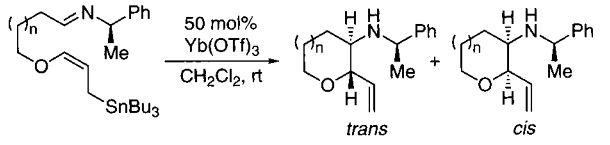
Three-component reactions of aldehydes, amines, and allyltributyltin were achieved in water using Sc(OTf)$_3$ as a Lewis-acid catalyst and a surfactant (SDS) (Table 42).[100] Homoallylic amines were obtained in high yields with a wide range of aldehydes including aromatic, aliphatic, unsaturated, and heteroaromatic aldehydes. No homoallylic alcohol resulting from reactions of allyltributyltin with aldehydes was detected. It was proposed that imine formation from aldehydes and amines was significantly fast to allow selective activation of imines over aldehydes. Allyltriethylgermane was used in the same type of three-component reactions in CH$_3$NO$_2$ in the presence of Sc(OTf)$_3$.[101]

Sc(OTf)$_3$ catalyzed reactions of benzoylhydrazones with tetraallyltin, and three-component reactions of aldehydes, benzoylhydrazine, and tetraallyltin also proceeded smoothly to give the corresponding homoallylic hydrazines, which were readily converted to homoallylic amines (Table 43).[102] This reaction was also successfully performed in aqueous media [H$_2$O/THF (1/9)].[103]

It was suggested that modification of the coordination sphere of Ln(OTf)$_3$ might lead to different reactivity or selectivity. Some lanthanide complexes with multidentate polyethers and poly(ethylene glycol)s ligands were prepared (Table 44).[104] These complexes were more soluble in organic solvents and less hygroscopic than Ln(OTf)$_3$. Polyether complexes did not catalyze the allylation of aldehydes with allyltributylstannane; however, poly(ethylene glycol)s complexes were effective to promote the reaction. These complexes show improved handling properties compared with the parent Ln(OTf)$_3$ and are not subject to the aging process observed for Yb(OTf)$_3$.

Intramolecular allylation of imines in the presence of various Lewis acids and protic acids was studied (Table 45).[105] The reaction with γ-alkoxyallylstannane ($n = 1$) gave *trans* isomer mainly with excellent diastereoselectivity when Yb(OTf)$_3$, TiCl$_2$(O^{i}Pr)$_2$, ZrCl$_4$, or aqueous HCl was employed as a catalyst. On the other hand, the reaction using BF$_3$·OEt$_2$, ZnCl$_2$, or CF$_3$CO$_2$H provided high diastereoselectivities of the

Table 45. Lewis-Acid- and Protic-Acid-Promoted Intramolecular Allylation ($n = 1$)



catalyst	temp/°C	yield/%	*trans* (de)/*cis* (de)[a]
Yb(OTf)$_3$	rt	70	84 (>95)/16 (36)
TiCl$_2$(O^r)$_2$	−78	63	77 (>95)/23 (36)
BF$_3$•OEt$_2$	−78	88	90 (81)/10 (>95)
ZnCl$_2$	0	94	91 (68)/ 9 (88)
ZrCl$_4$	−78	97	100 (91)/0 (- -)
aqueous HCl	0	98	100 (92)/0 (- -)
CF$_3$CO$_2$H	0	97	87 (63)/13 (>95)

[a] Diastereomeric excesses were determined by ^{1}H NMR spectroscopy.

Table 46. Yb(OTf)$_3$-Catalyzed Intramolecular Allylation

n	time	yield/%	*trans* (de)/*cis* (de)[a]
0	10 min	90	88 (12)/12 (100)
1	3 h	70	84 (>95)/16 (36)
2	24 h	62	>98 (−)/2 (−)

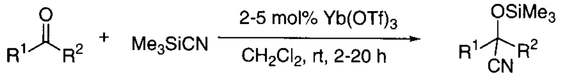
[a] Diastereomeric excesses were determined by ^{1}H NMR spectroscopy.

cis isomer, albeit in low yields. It was found that reactivity and diastereoselectivity observed in this reaction depended on the tether length of the γ-alkoxyalkylstannanes ($n = 0-2$) (Table 46).

2.1.5. Cyanation

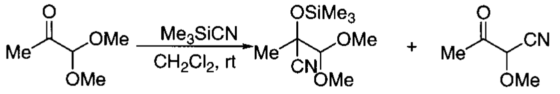
Yb(OTf)$_3$ was found to catalyze the addition of TMSCN to various carbonyl compounds (Table 47).[106] Aliphatic aldehydes, aliphatic ketones, and glyoxylates exhibit high reactivity for cyanation, whereas aromatic aldehydes are less reactive. Aromatic ketones and acetals are unreactive. The observed difference in reactivities allows chemoselective cyanation of α-keto aldehyde dimethyl acetals, in which the reaction occurred exclusively in the carbonyl moiety when Yb(OTf)$_3$ was used as a catalyst (Scheme 26). In a sharp contrast, both carbonyl and acetal group reacted with Me$_3$SiCN in the presence of AlCl$_3$, forming a 63:37 mixture of the addition and substitution products. Acetophenone was found to be unreactive for cyanation with TMSCN, but an independent study carried out by Jenner revealed that acetophenone did react with TMSCN to give the silylated cyanohydrin in 41% yield.[107]

Table 47. Yb(OTf)$_3$-Catalyzed Cyanation of Aldehydes, Ketones, and Glyoxylates



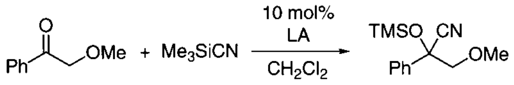
R^1	R^2	mol%	time/h	yield/%
Ph	H	5	15	86
^{n}Hex	H	2	2	95
BuCO$_2$	H	5	2	94
PhCH=CH	H	5	2	81
Ph(CH$_2$)$_2$	Me	5	2	85
Ph	Me	5	20	0

Scheme 26. Yb(OTf)$_3$-Catalyzed Chemoselective Cyanation of α-Keto Aldehyde Dimethylacetal



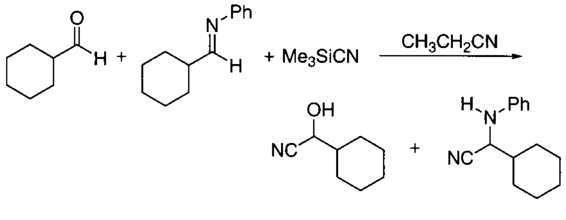
5 mol% Yb(OTf)$_3$: 87% yield (100/0)
5 mol% AlCl$_3$: 92% yield (63/37)

Table 48. Lewis-Acid Catalytsts in Trimethylsilylcyanation of a α-Alkoxyketone



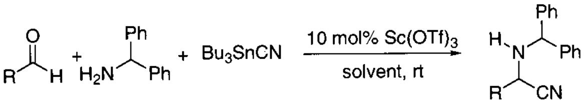
LA	yield/%
ZnI$_2$	97
InCl$_3$	90
InBr$_3$	99
Sc(OTf)$_3$	91
Sn(OTf)$_2$	93

Scheme 27. Selective Activation of Aldimines over Aldehydes for Nucleophilic Addition Reactions Using Yb(OTf)$_3$



20 mol% Yb(OTf)$_3$, -45 °C: 100% (<1/>99)
400 mol% SnCl$_4$, -78 °C: 91% (>99/<1)

Table 49. Sc(OTf)$_3$-Catalyzed Strecker-type Reactions of Aldehydes, Amines, and Bu$_3$SnCN



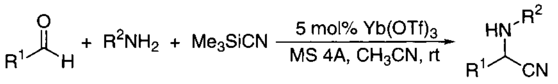
R	yield/% [in MeCN/toluene (1/1)]	yield/% [in H$_2$O]
Ph	88	88
PhCH=CH	83	84
2-furyl	88	89
Ph(CH$_2$)$_2$	94	79
Bu	84	94
^{c}Hex	86	94

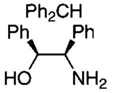
Meanwhile, in the trimethylsilylcyanation of an α-alkoxyketone, scandium triflate was found to be one of the effective catalysts (Table 48).[108]

Selective cyanation of aldimines or aldehydes can be achieved with either Yb(OTf)$_3$ or SnCl$_4$ (Scheme 27).[58]

Sc(OTf)$_3$ was used to achieve Strecker-type reaction of aldehydes, amines, and tributyltin cyanide (Bu$_3$SnCN) in both CH$_3$CN/toluene (1/1) and water (Table 49).[109] Remarkably, dehydrative formation of imines occurred in water. The reaction rate in water was almost the same as that in organic medium, even when surfactant was not added to the reaction mixture. In both media, products resulting from cyanation of aldehyde were not observed. Similar

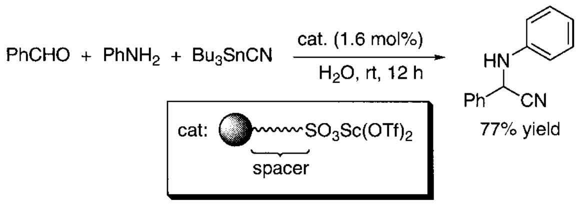
Table 50. Yb(OTf)$_3$-Catalyzed Strecker-type Reactions of Aldehydes, Amines, and Me$_3$SiCN



R^1	R^2	yield/%
Ph	$MeOC_6H_4$	92
Ph	Ph_2CH	88
1-naphthyl	$MeOC_6H_4$	91
1-naphthyl	Ph_2CH	85
^{c}Hex	$MeOC_6H_4$	86
^{c}Hex	Ph_2CH	85
Ph		78 (dr = 16/1)[a]

[a] In the presence of 2,6-di-*tert*-butyl-4-methylpyridine (100 mol %).

Scheme 28. Strecker-type Reaction Using a Polymer-Supported Scandium Catalyst in Water



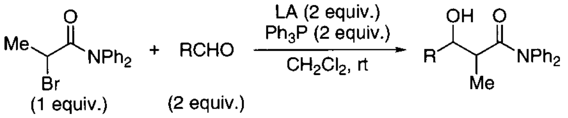
reactions with Me$_3$SiCN were catalyzed by Yb(OTf)$_3$ in organic medium in the presence of MS 4 (Table 50).[110]

Strecker-type reactions of benzaldehyde using polymer-supported scandium catalyst were reported.[24] The reaction proceeded cleanly in water to afford the corresponding α-amino nitrile derivatives in high yields (Scheme 28).

2.1.6. Reformatsky-type Reaction

Hashimoto, Saigo, and co-workers disclosed that a combination of Ph$_3$P and Sc(OTf)$_3$ mediated Reformatsky-type reaction of α-bromoamide with several aldehydes and that β-hydroxyamides were obtained in good yields with *syn*-selectivities (Table 51).[111] Other Lewis acids including BF$_3$·OEt$_2$, TiCl$_4$, and Yb(OTf)$_3$ were less efficient, resulting in low reaction rate and/or poor selectivity.

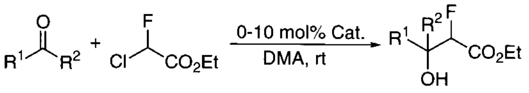
Table 51. Reformatsky-type Reactions of α-Bromoamides with Aldehydes in the Presence of Lewis Acids and Ph$_3$P



LA	R	time	yield/%	*syn*/*anti*[a]
BF$_3$·OEt$_2$	Ph	48 h	82	95/5
TiCl$_4$	Ph	15 min	92	76/24
Yb(OTf)$_3$	Ph	15 h	83	83/17
Sc(OTf)$_3$	Ph	15 min	93	98/2
Sc(OTf)$_3$[b]	^{n}Pr	24 h	71	97/3

[a] Determined by 300 MHz ^{1}H NMR spectroscopy. [b] The reaction was performed with 1.2 equivalents each of aldehyde, Lewis acid and Ph$_3$P.

Table 52. Synthesis of α-Fluoro-β-hydroxy Esters by Reformatsky-type Reaction



DMA = *N,N*-dimethylacetamide

R^1, R^2	cat. (mol %)	yield/%	dr
Ph, H	none	81	1/1
Ph, H	CeCl$_3$ (5)	80	n.r.[a]
$-(CH_2)_4-$	CeCl$_3$ (5)	45	
$-(CH_2)_4-$	Yb(OTf)$_3$ (5)	40	

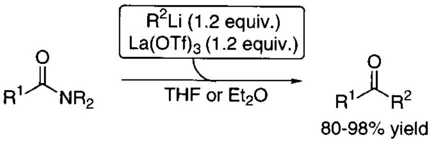
[a] Not reported.

It was also reported that Reformatsky-type reactions of ethyl chlorofluoroacetate with less reactive aliphatic aldehydes or ketones were efficiently catalyzed by CeCl$_3$ or Yb(OTf)$_3$ (Table 52).[112] In the absence of the catalyst, only low yields (5−10% yields) of products were obtained, while aromatic aldehydes reacted without catalyst.

2.1.7. Nucleophilic Addition Using Organolanthanide Reagents

It has been reported that lanthanum reagents prepared from La(OTf)$_3$ and organolithium reagents add to amides giving ketones in a highly selective manner.[113] MeLi reacted with *N,N*-diethylbenzamide to give acetophenone and 2-phenyl propan-2-ol in 26% and 15% yields, respectively. *N,N*-Diethyl benzamide was recovered in 54% yield. The same reaction in the presence of La(OTf)$_3$ gave acetophenone as the sole product (95% yield). Likewise, other alkyllithium reagents reacted with substituted aryl amides to afford high yields of alkyl aryl ketones (Scheme 29).

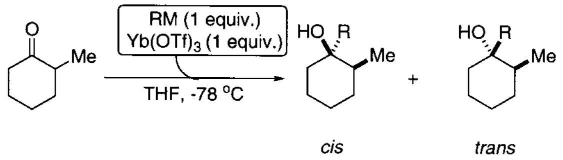
Scheme 29. Preparation of Ketones by Addition of Organolanthanum Reagents to Amides



Organoytterbium reagents, prepared form of common organolithiums or organomagnesiums and Yb(OTf)$_3$, reacted with various 2-, 3-, or 4-substituted cyclohexanones in a highly diastereoselective manner (Table 53).[114] In the carbonyl addition with 2-methylcyclohexanone, better selectivities of equatorial to axial attacks were achieved with organoytterbium reagents than with typical organotitanium,[115] organolithium,[116] or organomagnesium reagents.[117]

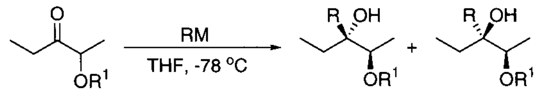
Although addition of Yb(OTf)$_3$ did not reverse the diastereoselectivity of the reactions of 2-methylcyclohexanone with oxygenated organolithiums, the reversal of diastereoselectivity was observed in the reactions of α-benzyloxy ketones with common organolithiums; thus, the addition of Yb(OTf)$_3$ favored formation of Felkin−Anh addition products (Table 54).[118] Meanwhile, both the yields and diastereoselectivities in the reactions with

Table 53. Diastereoselective Addition of Organoytterbium Reagents to 2-Methylcyclohexane



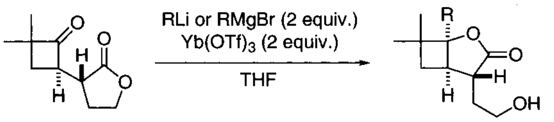
RM	yield/%	*cis*/*trans*
^{n}BuLi	91	99.0:1.0
PhLi	73	>99:<1
(E)-^{n}BuCH=CHLi	75	96.7:3.3
(Z)-^{n}BuCH=CHLi	78	97.4:2.6
CH_2=CHMgBr	89	97.5:2.5
^{t}BuLi	53	200:1

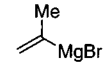
Table 54. Effect of Yb(OTf)$_3$ on Diastereoselective Addition of Organolithiums to Chiral Chelating Aldehydes

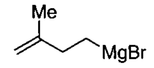
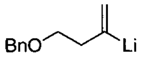


RM	R^1	Yb(OTf)$_3$	yield/%	dr
MeLi	Bn	−	84	70/30
MeLI	Bn	+	96	27/73
BuLi	Bn	−	83	76/34
BuLi	Bn	+	85	22/78
MeLi	^{t}BuMe$_2$Si	−	75	11/89
MeLi	^{t}BuMe$_2$Si	+	86	3/97
BuLi	^{t}BuMe$_2$Si	−	83	4/96
BuLi	^{t}BuMe$_2$Si	+	87	<1/>99

Table 55. Efficient Addition of Organoytterbium Reagents to a Cyclobutanones



RLi or RMgBr	yield/%
MeLi	68
	67
	78

RLi or RMgBr	yield/%
	85
	50

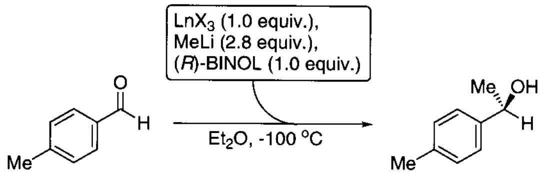
other 2- and 3- silyloxy ketones were improved by employing Yb(OTf)$_3$.

Recently, organoytterbium reagents were shown to add to a cyclobutanone derivative efficiently, while MeMgBr or MeLi in the absence of Yb(OTf)$_3$ or less basic organocerium reagents led to substantial epimerization of the ketone (Table 55).[119]

Homochiral organolanthanide reagents, prepared by the reaction of (R)-BINOL with in situ generated trimethyllanthanides, were used for enantioselective addition to 4-methylbenzaldehyde (Scheme 30).[120] While Yb(OTf)$_3$ and Ce(OTf)$_3$ gave products with moderate enantiomeric excesses, CeCl$_3$ gave better selectivity.

Recently, it was revealed that the 1,2-addition of Grignard reagents to N-p-methoxyphenyl (PMP) aldimines proceeded effectively in the presence of catalytic amounts of Sc(OTf)$_3$.[121]

Scheme 30. Enantioselective Addition of Organolanthanide Reagents to an Aldehyde



Yb(OTf)$_3$: 56% yield; 65% ee
Ce(OTf)$_3$: 62% yield; 57% ee
CeCl$_3$: 69% yield; 77% ee

2.1.8 Michael Reaction

1,4-Conjugate additions of either stabilized or nonstabilized carbanions and heteroanions to activated alkenes and alkynes are one of the most convenient, intensely studied, and useful synthetic methods.[122] The reactions using more selective and less basic organometallic nucleophiles, such as silyl enol ethers and ketene silyl acetals, were introduced by Mukaiyama,[123] and the so-called Mukaiyama–Michael reaction was effected with various Lewis acids.[124] In contrast to other enolate additions, the Lewis-acid-catalyzed reaction permits using base-sensitive Michael acceptors, prevents 1,2-additions and enolate scrambling, and creates β-quaternary centers in high yields.

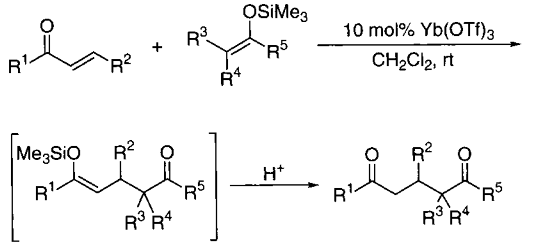
It has been reported that Ln(OTf)$_3$ catalyzed conjugate addition of silyl enol ethers to α,β-unsaturated carbonyl compounds to give the corresponding 1,5-dicarbonyl compounds (Table 56).[125] Silyl enol ethers derived from ketones, thioesters, and esters were applicable, and no 1,2-addition products were obtained. Products could be isolated as synthetically valuable silyl enol ethers when the crude adducts were isolated without acidic workup. Easily recoverable and reusable microencapsulated Sc(OTf)$_3$ was also effective for the Michael reaction of silyl enol ethers with α,β-unsaturated carbonyl compounds.[37]

Lewis-acid-catalyzed conjugate addition reactions of silyl enol ethers derived from a lactone and lactams with nitroenamines proceeded equally well in the presence of a catalytic amount of Sm(OTf)$_3$ or (^{i}PrO)$_2$TiBr$_2$ (Table 57).[126]

It is well-known that Michael additions of β-ketoesters and dialkyl malonates are catalyzed by various Lewis acids under nonaqueous conditions[127] and that Michael additions of β-ketoesters are sluggish in water under neutral conditions.[122,128] A report from Feringa and co-workers has shown that water-tolerant Yb(OTf)$_3$ catalyzed Michael addition of β-ketoesters to *β-unsubstituted* enones in water (Scheme 31).[129] Surprisingly, no acid-catalyzed hydrolysis of the ester was observed. The same reaction hardly occurred in organic solvents such as THF, dioxane, and CH$_2$Cl$_2$.[127]

It was found that Yb(OTf)$_3$ on silica gel support catalyzed additions of β-ketoesters to *β-substituted* enones without using any solvent (Scheme 32), while high pressure and temperature facilitated the reactions with acrylic esters.[130]

Table 56. Yb(OTf)$_3$-Catalyzed Mukaiyama–Michael Reactions



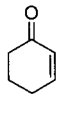
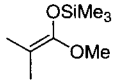
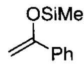
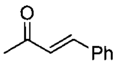
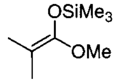
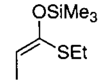
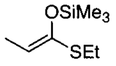
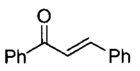
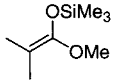
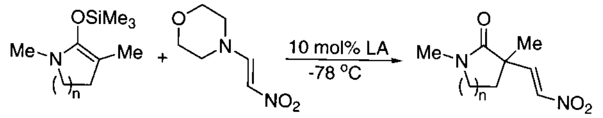
enone	silicon enolate	yield/% (1st run)	yield/% (2nd run)
		92	95
		75	74
		85	85
		87 (51% *anti*)	87 (51% *anti*)
		82 (61% *anti*)	78 (62% *anti*)
		92	93

Table 57. Lewis Acid-catalyzed Conjugate Addition of Lactam-derived Silyl Enol Ethers to a Nitroenamine



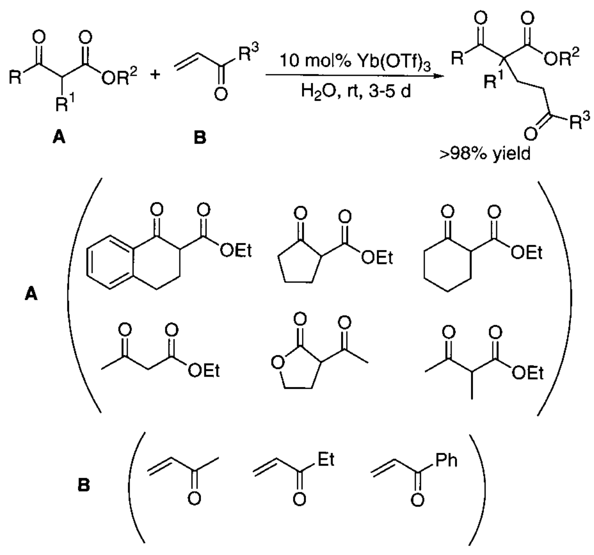
n	LA (mol %)	solvent	time/min	yield/%
1	Sm(OTf)$_3$ (10)	THF	18	75
1	(^{i}PrO)$_2$TiBr$_2$ (10)	CH$_2$Cl$_2$	18	77
2	Sm(OTf)$_3$ (10)	THF	18	70
2	(^{i}PrO)$_2$TiBr$_2$ (10)	CH$_2$Cl$_2$	18	71

On the other hand, Michael addition with α-nitroesters proceeds in water using Yb(OTf)$_3$ as a catalyst (Scheme 33).[131] The Michael adducts serve as versatile building blocks for making amino acid derivatives.

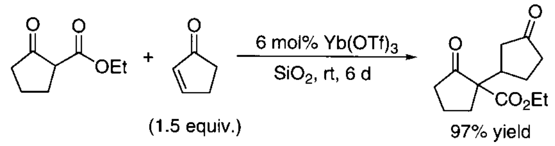
The conjugate addition of indoles to α,β-unsaturated carbonyl compounds has been limited because strong acidic conditions, long reaction time, and constraint on substrates employed were required.[132] For instance, only highly reactive methyl vinyl ketone[132a] and β-nitrostyrene[132b] can react with indoles. Clay[132c] and Lewis-acid[132d] catalysts have been reported to accelerate the reactions of methyl vinyl ketone and some activated substrates.

It was found that Yb(OTf)$_3$ catalyzed conjugate additions of both *N*-substituted and unsubstituted indoles to various electron-deficient olefins, including β-substituted enones and esters (Table 58).[133] Unfortunately, other Michael acceptors, such as phenyl vinyl sulfone, ethyl cinnamate, methyl acrylate, acylonitrile, and several α,β-unsaturated aldehydes, failed to react in this process.

Scheme 31. Michael Addition of β-Keto Esters in Water in the Presence of Yb(OTf)$_3$



Scheme 32. Michael Addition of Cyclopent-2-enone Catalyzed by Yb(OTf)$_3$ on a Silica Gel Support



Scheme 33. Michael Addition of α-Nitroesters in Water in the Presence of Yb(OTf)$_3$

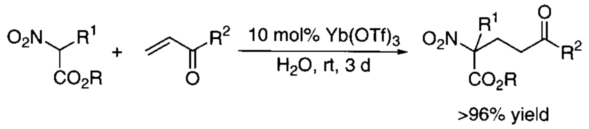
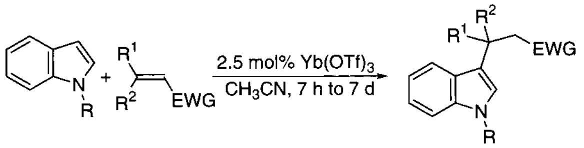
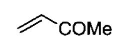
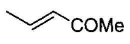
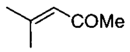
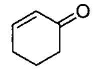


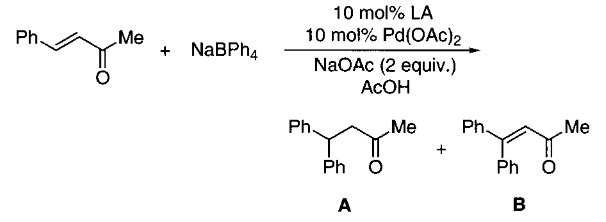
Table 58. Conjugate Addition of Indoles



R	enone	time	yield/%
Me H		7 h 22 h	73 72
Me H		10 h 14 h	95 85
Me H		7 d 7 d	38 19
Me H		7 d 7 d	37 44

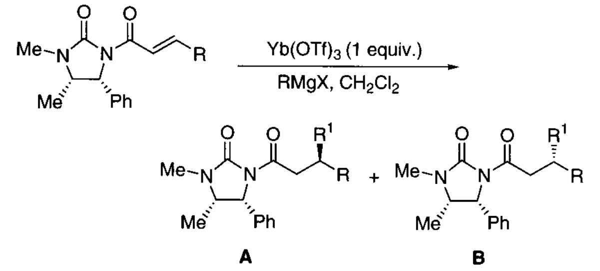
The effect of Lewis-acid catalysts on Pd-catalyzed reactions of sodium tetraphenylborate with various enones and enals was studied (Table 59).[134] In the reaction with benzalacetone, Yb(OTf)$_3$ and other conventional Lewis acids including BF$_3$·OEt$_2$, Al-

Table 59. Effect of Lewis Acids on Pd-Catalyzed Reactions of $NaBPh_4$ with Benzalacetone



LA	yield/% (**A**/**B**)	LA	yield/% (**A**/**B**)
$Yb(OTf)_3$	96 (17/83)	$SbCl_3$	92 (98/2)
$BF_3{\cdot}OEt_2$	91 (19/81)	$AsCl_3$	66 (97/3)
$Al(O^iPr)_3$	92 (21/79)	$Ti(O^iPr)_4$	83 (40/60)

Table 60. Diastereoselective Conjugate Addition of Grignard Reagents in the Presence of $Yb(OTf)_3$



RMgX	yield/%[a]	A/B
PhMgCl	20 (11)	41/59
AllylMgCl	93 (7)	75/25
AllylMgBr	92 (8)	82/18

[a] The yield in parentheses is for the 1,2-addition product.

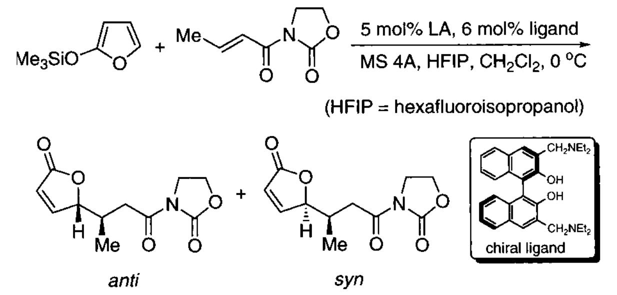
$(O^iPr)_3$, and $Ti(O^iPr)_4$ gave the usual Heck-type reaction product in high yield, whereas $SbCl_3$ and $AsCl_3$ favored formation of an unexpected Michael-type conjugate addition compound. However, the reaction with 2-cyclohexen-1-one favored conjugate addition compounds regardless of the acid catalyst employed.

Asymmetric conjugate addition of Grignard reagents to chiral imides was attempted by using a stoichiometric amount of $Yb(OTf)_3$.[135] Despite low yield and diastereoselectivity being observed with PhMgCl, allyl Grignard reagents gave better yields and selectivities (Table 60).

The chiral Lewis acid generated from a 1:1 mixture of $Sc(OTf)_3$ and 3,3′-bis(diethylaminomethyl)-1,1′-bi-2-naphthol catalyzed stereoselective Michael addition of 2-(trimethylsiloxy)furan to *N*-crotyloxazolidinone.[136] The reaction proceeded with *anti* selectivity, providing the product with moderate enantioselectivity. In a sharp contrast, other $Ln(OTf)_3$ resulted in poor selectivities (Table 61).

Nakajima and co-workers reported that a chiral *N*,*N*′-dioxide/scandium triflate complex served as an effective enantioselective catalyst in Michael addition of *β*-keto esters to methyl vinyl ketone (Table 62).[137]

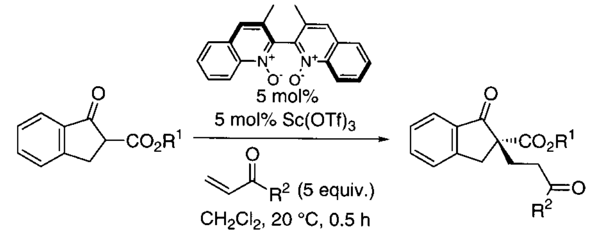
Table 61. Asymmetric Michael Addition of 2-(Trimethylsiloxy)Furan to *N*-Crotyloxazolidinone



LA	yield/%	*anti*/*syn*	ee/%[a]
$Sc(OTf)_3$[b]	80 (86)	>50/1 (>50/1)	65 (68)
$Y(OTf)_3$	87	39/1	0
$La(OTf)_3$	62	1.6/1	28
$Yb(OTf)_3$	65	12/1	10

[a] Enantiomeric excesses of the *anti* isomers. [b] The values in parentheses were obtained from the reaction with 10 mol % of LA and 12 mol % of chiral ligand.

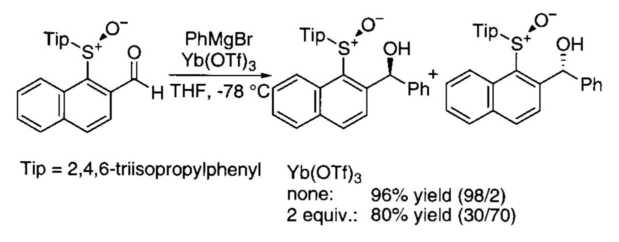
Table 62. Enantioselective Michael Addition Using a Chiral *N*,*N*′-Dioxide/Scandium Triflate Complex



R^1	R^2	yield/%	ee/%	configuration
Me	Me	98	39	R
Bn	Me	85	38	R
^iPr	Me	94	47	R
$CH(^iPr)_2$	Me	98	69	R
^tBu	Me	93	80	R
^tBu	H	73[a]	75[a]	R

[a] Determined after conversion of aldehyde to methyl ester.

Scheme 34. Diastereoselective Addition of Phenyl Grignard Reagent to 1-(Arylsulfinyl)-2-naphthaldehydes



2.1.9. Others

It was reported that the diastereoselectivity of the Grignard reaction was changed in the presence of $Yb(OTf)_3$. This can be rationalized by a chelated transition state between the sulfinyl and formyl oxygens with $Yb(OTf)_3$ (Scheme 34).[138]

The reactions of acylzirconocenes with imines proceeded in the presence of $Yb(OTf)_3/Me_3SiOTf$ to afford α-amino ketones directly (Scheme 35).[139]

Reactions of 2-methyl-2-vinyloxirane with aldehydes were reported. $Sc(OTf)_3$ induced ring opening followed by a [1,2] hydride shift to generate the *β*,*γ*-unsaturated aldehydes. This intermediate was then translated to give an enol form which reacts with aldehydes to yield the corresponding adducts in high yields (Table 63).[140]

Scheme 35. Yb(OTf)$_3$/Me$_3$SiOTf-Catalyzed Reactions of Acylzirconocene Chlorides with Imines

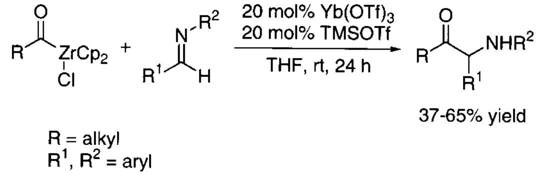
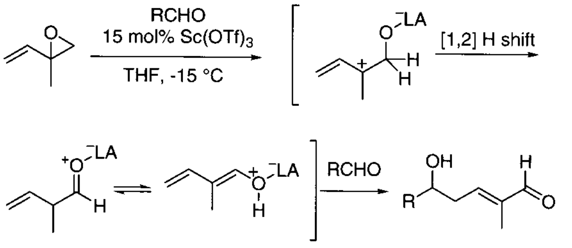
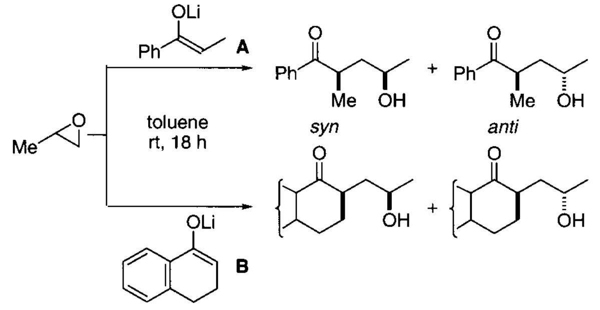


Table 63. Sc(OTf)$_3$-Catalyzed Reactions of 2-Methyl-2-vinyloxirane with Aldehydes



R	yield/%	R	yield/%
Ph	49	*p*-Brv	78
p-NO$_2$C$_6$H$_4$	88	*p*-MeOC$_6$H$_4$	55
o-NO$_2$C$_6$H$_4$	73	2-furyl	97
p-NCC$_6$H$_4$	90	PhCH=CH	91

Table 64. Lewis-Acid-Catalyzed Ring Opening of Epoxide with Lithium Enolates



enolate	catalyst	yield/%	*syn*/*anti*
A	Sc(OTf)$_3$	90	55/45
A	Y(OTf)$_3$	80	58/42
A	Ti(Cp)$_2$(OTf)$_2$	74	54/46
B	Sc(OTf)$_3$	95	45/55
B	Y(OTf)$_3$	90	45/55
B	Ti(Cp)$_2$(OTf)$_2$	62	51/49

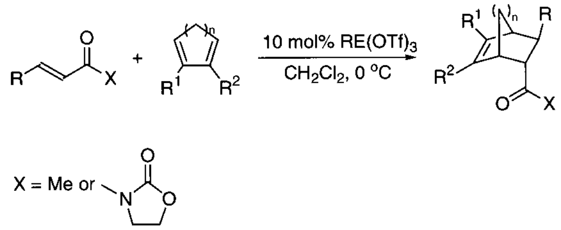
The effect of Lewis acids on ring opening of epoxide with lithium enolates was studied.[141] Sc(OTf)$_3$ catalyzed the reactions in excellent yields, whereas Y(OTf)$_3$ and a titanium-based catalyst were less effective (Table 64). It was shown that *syn*/*anti* ratios of the products were independent of the lithium enolate geometry.

2.2. Cyclization Reactions

2.2.1. Carbon Diels–Alder Reactions

Diels–Alder reactions provide powerful entries for cyclic structures with up to four consecutive stereogenic centers in a single operation. Although many Diels–Alder reactions have been carried out thermally without using catalysts, heat-sensitive compounds cannot survive under such conditions. Furthermore, Diels–Alder reactions are reversible, and the lowest possible temperatures are generally used to prevent equilibration and/or retro-Diels–Alder reactions. While Lewis-acid catalysts allow the reactions to proceed at room temperature or below with satisfactory yields, they are often accompanied by diene polymerization and excess amounts of catalysts are often needed to mediate carbonyl-containing dienophiles.[142]

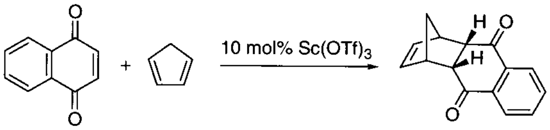
Table 65. Rare-Earth Metal Triflate-Catalyzed Diels–Alder Reactions



RE	R	R^1	R^2	X	*n*	yield/%[a] (*endo*/*exo*)[b]
Sc	H	H	H	oxazolidinone	1	95 (87/13)
Sc	H	H	H	oxazolidinone	2	89 (100/0)
Sc	H	Me	H	oxazolidinone	0[c]	90
Sc	H	Me	Me	oxazolidinone	0	86
Sc	Me	H	H	oxazolidinone	1	97 (84/16)
Sc	H	H	H	Me	1	96 (89/11)
Yb[d]	H	H	H	Me	1	86 (90/10)
Sc	H	H	H	Me	2	83 (>95/5)
Sc	H	Me	H	Me	0	91
Sc	H	Me	Me	Me	0	88

[a] Isolated yield. [b] Determined by ^{1}H and/or ^{13}C NMR spectroscopy. [c] 2,3-Dimethyl-1,3-butadiene. [d] 20 mol % of Yb(OTf)$_3$ was used.

Scheme 36. Sc(OTf)$_3$-Catalyzed Diels–Alder Reaction in Aqueous Medium



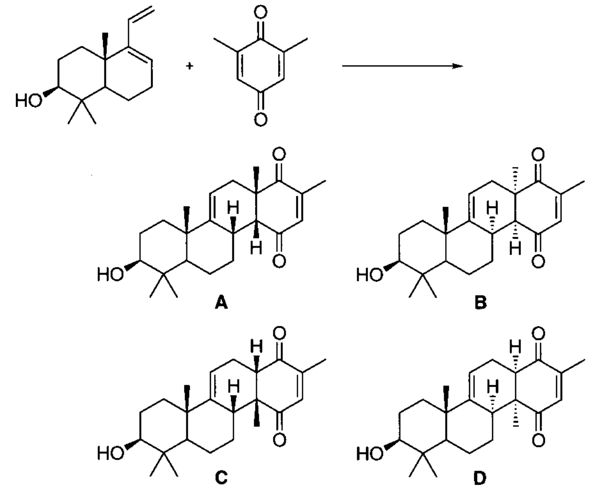
CH$_2$Cl$_2$: 83%, *endo*/*exo* (100/0)
THF/H$_2$O (9/1): 93%, *endo*/*exo* (100/0)

While Yb(OTf)$_3$ was shown to be an effective catalyst in Diels–Alder reactions,[125a] Sc(OTf)$_3$ was later found to be the most effective as a catalyst among rare-earth metal triflates (Table 65).[143] In the presence of 10 mol % of Y(OTf)$_3$ or Yb(OTf)$_3$, only a trace amount of the adduct was obtained from methyl vinyl ketone (MVK) and isoprene. However, the same reaction gave the desired adduct in 91% yield in the presence of 10 mol % of Sc(OTf)$_3$. Several examples of the Sc(OTf)$_3$-catalyzed Diels–Alder reactions are shown in the table. In all cases, the Diels–Alder adducts were obtained in high yields with high *endo*-selectivities. Scandium perfluoroalkanesulfonate is also an effective catalyst for Diels–Alder reactions.[144]

Sc(OTf)$_3$ catalyzed the Diels–Alder reaction of naphthoquinone with cyclopentadiene in aqueous media (THF/H$_2$O 9/1) to give the desired adduct in excellent yield (Scheme 36).[143,145]

In an effort to prepare isoarborinol and fernenol, the stereoselectivity of the Diels–Alder reaction of a

Table 66. Stereoselective Variation in the Diels−Alder Reaction of a Chiral Diene with 2,6-Dimethylbenzoquinone under Different Conditions



LA (mol %)	conditions	yield/%	**A**/**B**/**C**/**D**
$Sc(OTf)_3$ (100)	CH_2Cl_2, −78 °C, 8 h	92	77/15/8/0
$Sc(OTf)_3$ (100)	CH_2Cl_2/H_2O (1/10), 25 °C, 20 h	96	2/0/77/21
$Sc(OTf)_3$ (10)	THF/H_2O (9/1), 25 °C, 21 h	18	0/0/75/25
$Eu(fod)_3$ (200)	CH_2Cl_2, 25 °C, 24 h	73	0/0/42/58
none	benzene, reflux, 20 h	96	0/0/100/0
$AlCl_3$ (120)	CH_2Cl_2, −70 °C, 2 h	80	58/42/0/0
$TiCl_4$ (130)	CH_2Cl_2, −78 °C, 3 h	70	89/11/0/0
LiCl (5 M)	H_2O, 25 °C, 7 h	79	0/0/76/24
10 kbar	CH_2Cl_2, 50 °C, 24 h	96	0/0/75/25

chiral diene with 2,6-dimethylbenzoquinone was studied under different conditions (Table 66).[146] The reaction using a stoichiometric amount of $Sc(OTf)_3$ in CH_2Cl_2 favored two of the endo-products resulting from *meta* approach of the substrates. This selectivity was similar to the results obtained using $AlCl_3$ and $TiCl_4$. However, in the presence of water, the reactions gave the other *endo*-products resulting from *ortho* approach, and this selectivity was independent of the stoichiometry of the catalyst employed. The same preference was observed when $Eu(Fod)_3$ or a high concentration of LiCl (5 M) was used or under a hydrostatic pressure (10 kbar). The best conditions were in boiling benzene without a Lewis-acid catalyst, giving exclusively one of the products from *ortho* approach.

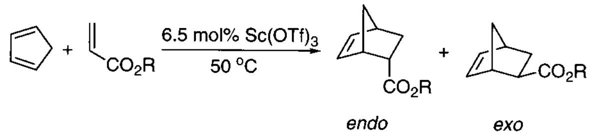
It has been demonstrated that the stereoselectivity in $Sc(OTf)_3$-catalyzed Diels−Alder reactions of alkyl acrylates with cyclopentadiene was improved by employing supercritical CO_2 ($scCO_2$) as the reaction medium (Table 67).[147]

Ionic liquids act as powerful media in scandium triflate-catalyzed Diels−Alder reactions not only for facilitating catalyst recovery but also for accelerating reaction rate and improving selectivity (Table 68).[148]

Polymer-supported scandium catalyst has high activity for Diels−Alder reactions in water (Scheme 37).[24]

Diels−Alder reactions of various electron-deficient dienophiles with 1,3-cyclohexadiene proceed smoothly in the presence of 10 mol % of $Yb(OTf)_3 \cdot H_2O$ under ultrahigh pressure (13 kbar) (Scheme 38).[149]

Table 67. Effect of Reaction Media on $Sc(OTf)_3$-Catalyzed Diels−Alder Reactions of Acrylates with Cyclopentadiene



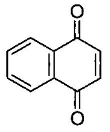
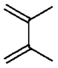
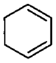
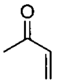
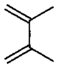
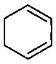
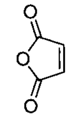
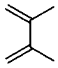
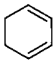
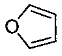
R	reaction medium	*endo*/*exo*
Bu	toluene	10/1
Bu	$CHCl_3$	11/1
Bu	$scCO_2$ (1.03 g/mL)[a]	24/1
Me	toluene	4/1
Me	$scCO_2$ (1.12 g/mL)	>10/1
Ph	toluene	2/1
Ph	$scCO_2$ (1.09 g/mL)	>8/1

[a] Density of $scCO_2$.

Table 68. Scandium Triflate-Catalyzed Diels−Alder Reactions with Ionic Liquids

$$\text{dienophile} + \text{diene} \xrightarrow[\text{rt, 2-4 h}]{0.2\text{ mol\% }Sc(OTf)_3} [4+2]\text{ adduct}$$

bmim =

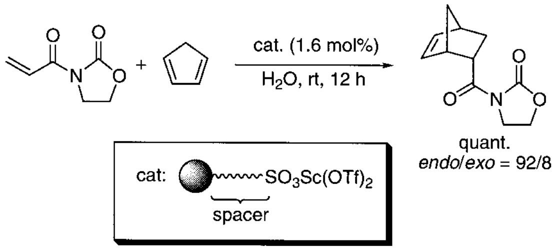
dienophile	diene	condition	yield/% (*endo*/*exo*)
		CD_2Cl_2	22
		CD_2Cl_2, $[bmim][PF_6]$ (0.5eq.)	85
		CD_2Cl_2, $[bmim][PF_6]$ (1eq.)	>99
		$[bmim][PF_6]$ (solvent)	>99
		$[bmim][OTf]$ (solvent)	>99
		$[bmim][PF_6]$	94 (>99:1)[a]
		$[bmim][PF_6]$	88
		$[bmim][OTf]$ 1 st run	94
		2 nd run	86
		3 rd run	81
		....	....
		11 th run	90
		$[bmim][PF_6]$ (solvent)	96 (>99:1)[b]
		$[bmim][PF_6]$	80
		$[bmim][PF_6]$	84 (>99:1)
		$[bmim][PF_6]$	71 (>99:1)

[a] 94% *endo*-selectivity was obtained in CH_2Cl_2. [b] 95% *endo*-selectivity was obtained in CH_2Cl_2.

The thermal [4+2] cycloaddition of in situ produced dienyl sulfide from cyclic dithioacetal of 3-methylcyclopent-2-enone reacted with dimethyl acetylene dicarboxylate to give 2-norbornanone dithioacetal in good yield (Table 69).[150] Lewis acids and a Brønsted acid were added in order to facilitate the conversion to dienyl thioacetals, but in all cases, yields were not high.

Intramolecular Diels−Alder reactions of oxazole−olefins are catalyzed by $Yb(OTf)_3$, $Sc(OTf)_3$, and most effectively $Cu(OTf)_2$ to afford pyridine derivatives (Table 70).[151]

Scheme 37. Diels-Alder Reaction in Water Using a Polymer-Supported Scandium Catalyst



Scheme 38. Diels–Alder Reaction Catalyzed by $Yb(OTf)_3 \cdot H_2O$ under Ultrahigh Pressure

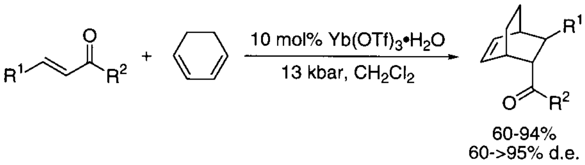
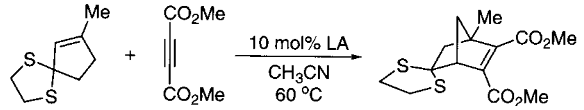


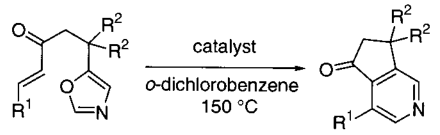
Table 69. Preparation of 2-Norbornanone Dithioacetal by [4+2] Cycloaddition



conditions[a]	time/h	conversion/%[b]	yield/%[b]
sealed tube, 120 °C	9	100	75[c]
None	48	<1	<1
CF_3CO_2H	24	63	26 (41)[d]
$Zn(OTf)_2$	12	89	31 (35)[d]
$Sc(OTf)_3$	24	100	3
$La(OTf)_3$	24	100	41
$Yb(OTf)_3$	24	100	18

[a] Reactions were performed with 1 equiv of dithioacetal and 1.7 equiv of dienophile in MeCN at 60 °C, unless otherwise stated. [b] Determined by GC. [c] Isolated yield. [d] GC yield based on the consumption of dithioacetal.

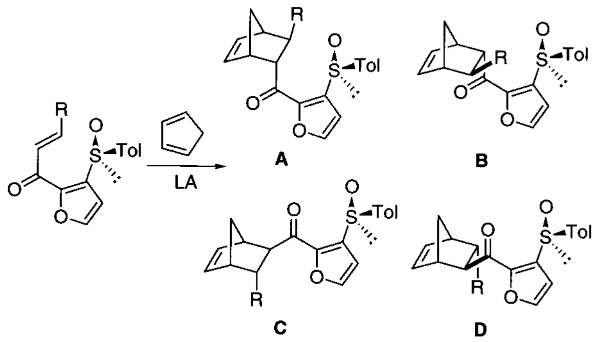
Table 70. Lewis-Acid Catalysis of Intramolecular Diels–Alder Reaction of Oxazole–Olefins



R^1	R^2	catalyst/mol%	time/h	yield/%
H	Me		24	21
		$Yb(OTf)_3$ (10)	2	37
		$Sc(OTf)_3$ (10)	3	40
		$Cu(OTf)_2$ (10)	3	48
		$Cu(OTf)_2$ (2)[a]	1	55
H	H		24	6
		$Sc(OTf)_3$ (10)	8	15
		$Cu(OTf)_2$ (10)	8	24
CO_2Me	Me	$Cu(OTf)_2$ (10)	0.5	95

[a] At 180 °C.

Table 71. Effect of Lewis Acids in Asymmetric Diels–Alder Reactions of Chiral (Sulfinyl)furyl-α,β-unsaturated Enones with Cyclopentadiene[a]



R	LA (mol %)	yield/%	**A/B/C/D**
Ph	None[b]	72	27/36/17/20
Ph	$TiCl_4$ (100)[c]	0	
Ph	$BF_3 \cdot OEt_2$ (100)[c]	100	65/32/2/1
Ph	$AlCl_3$ (20)	100	88/4/7/1
Ph	$Yb(OTf)_3$ (100)	96	84/10/4/2
Ph	$Yb(OTf)_3$ (20)	88	83/6/9/2
Ph	$Nd(OTf)_3$ (20)	100	88/4/7/1
Ph	$Sm(OTf)_3$ (20)	100	89/3/6/2
Me	$AlCl_3$ (20)	87	74/16/8/2
Me	$Yb(OTf)_3$ (20)	94	87/4/7/2
Me	$Nd(OTf)_3$ (20)	100	89/5/5/1
Me	$Sm(OTf)_3$ (20)	97	90/4/5/1

[a] The reactions were performed in CH_2Cl_2 at 25 °C unless otherwise stated. [b] The reaction was performed in benzene at 80 °C. [c] At −20 °C.

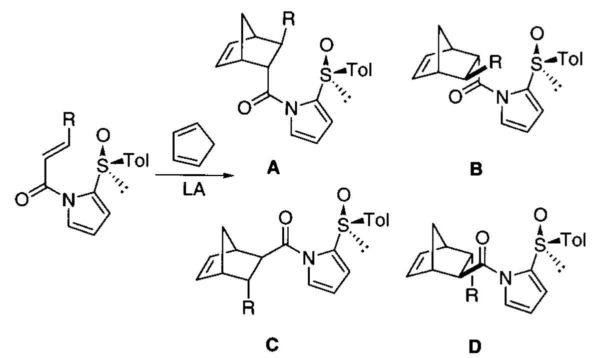
Lewis-acid-mediated asymmetric Diels–Alder reactions of 2-(3-tolyl-*p*-sufinyl)furyl-α,β-unsaturated enones with cyclopentadiene were investigated.[152] The reaction gave poor selectivity without a Lewis acid (Table 71). Conventional Lewis acids such as $TiCl_4$ and $BF_3 \cdot OEt_2$ gave disappointing results. On the other hand, catalytic amounts of $AlCl_3$ and $Ln(OTf)_3$ facilitated the reaction to give the Diels–Alder adduct in high yields and selectivities.

As an extension of this work, the use of 1-(2-tolyl-*p*-sufinyl)pyrrolyl-α,β-unsaturated enones as dienophiles was studied (Table 72).[153] Again, $AlCl_3$ and $Ln(OTf)_3$ mediated the cycloaddition reactions with cyclopentadiene in high yields and selectivities; however, stoichiometric amounts of Lewis acids were required when these chiral dienophiles were employed.

Chiral Lewis-acid-mediated asymmetric Diels–Alder reactions have been reported recently.[154] Although rare-earth metal compounds were expected to be promising Lewis-acid reagents, only a few asymmetric reactions catalyzed by chiral rare-earth metal Lewis acids have been reported.[155] On the other hand, rare-earth metal triflates, especially $Yb(OTf)_3$ and $Sc(OTf)_3$, are good catalysts in Diels–Alder reactions of various dienophiles with cyclic and acyclic dienes.[125,143]

Kobayashi and co-workers reported that a chiral ytterbium catalyst generated in situ from $Yb(OTf)_3$, (*R*)-(+)-1,1′-bi-2-naphthol [(*R*)-BINOL], and a tertiary amine in dichloromethane (Scheme 39) was quite effective in enantioselective Diels–Alder reactions (Table 74).[156] Moreover, some additives were found to be effective to stabilize the catalyst and at the same time to control enantiofacial selectivities in the Diels–Alder reactions. By employing 3-acetyl-1,3-oxazolidin-2-one as an additive, the *endo*-adduct was obtained in 93% ee with (2*S*,3*R*)-form. On the other hand, the use of 3-phenylacetylacetone as an additive

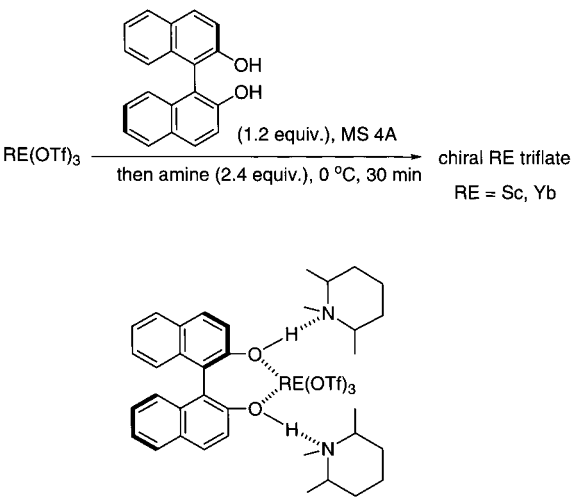
Table 72. Asymmetric Diels–Alder Reactions of Chiral (Sulfinyl)pyrrolyl-α,β-unsaturated Enones with Cyclopentadiene[a]



R	LA (mol %)	yield/%	*endo* (**A**+**B**)/ *exo* (**C**+**D**)	% de (*endo*)
Ph	$BF_3 \cdot OEt_2$ (100)	0	-	-
Ph	$ZnCl_2$ (100)	60	77/23	38
Ph	$AlCl_3$ (100)	99	95/5	98
Ph	$Yb(OTf)_3$ (100)	61	69/31	89
Ph	$Yb(OTf)_3$ (20)	33	80/20	80
Me	$Yb(OTf)_3$ (100)	93	92/8	93
Et	$Yb(OTf)_3$ (100)	99	95/5	84
Et	$Nd(OTf)_3$ (100)	100	95/5	90
Et	$Sm(OTf)_3$ (100)	96	96/4	96

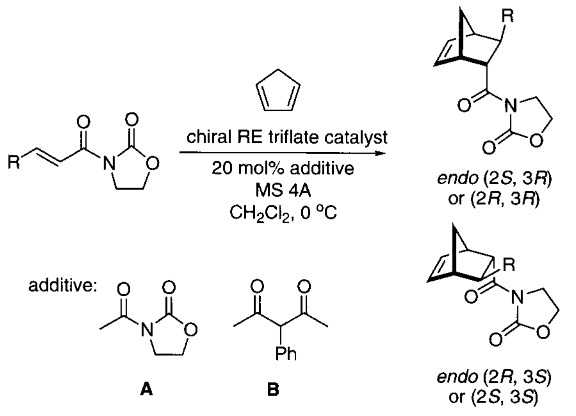
[a] The reactions were performed in CH_2Cl_2 at 25 °C.

Scheme 39. Preparation of Chiral Rare-Earth Metal Triflates



gave *endo*-adduct in 81% ee with (2*R*,3*S*)-form.[157] Following the same method, a chiral Sc catalyst was prepared from $Sc(OTf)_3$, (*R*)-BINOL, and a tertiary amine in dichloromethane (Scheme 39). The catalyst was also effective for the Diels–Alder reactions of an acrylic acid derivative with dienes (Table 73).[158] The amines employed in the preparation of the catalyst had a strong influence on enantioselectivities. The highest enantioselectivities were obtained when *cis*-1,2,6-trimethylpiperidine was used. It should be noted that even 3 mol % of the catalyst was sufficient to complete the reaction and that the *endo*-adduct was produced in 92% ee. 3-Acetyl-1,3-oxazolin-2-one and 3-benzoyl-1,3-oxazolin-2-one were also effective additives to stabilize the chiral Sc catalyst. However, unlike the similar chiral Yb catalyst, the sense of the enantioselections for these additives was the same.

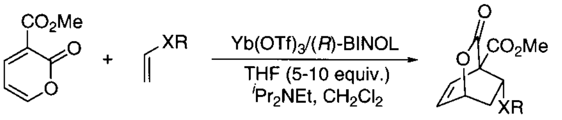
Table 73. Enantioselective Diels–Alder Reactions Using Chiral Rare-Earth Metal Triflates



R	RE catalyst[a] (mol %)	additive	yield/%	*endo*/*exo*	ee/%[b]
Me	Yb (20)	none	77	89/11	95 (2*S*,3*R*)
Me	Yb (20)	**A**	77	89/11	93 (2*S*,3*R*)
Me	Yb (20)	**B**[c]	83	93/7	81 (2*R*,3*S*)
Me	Sc (20)	none	94	89/11	92 (2*S*,3*R*)
Me	Sc (10)	none	84	86/14	96 (2*S*,3*R*)
Me	Sc (3)	none	83	87/13	92 (2*S*,3*R*)
Ph	Yb (20)	**A**	40	81/19	83 (2*R*,3*R*)
Ph	Yb (20)	**B**[c]	60	89/11	79 (2*S*,3*S*)
Ph	Sc (20)	none	99	89/11	93 (2*R*,3*R*)
Ph	Sc (10)	none	96	90/10	97 (2*R*,3*R*)
^{n}Pr	Yb (20)	none	81	80/20	83 (2*S*,3*R*)
^{n}Pr	Yb (20)	**A**	34	80/20	86 (2*S*,3*R*)
^{n}Pr	Yb (20)	**B**[c]	81	91/9	80 (2*R*,3*S*)

[a] *cis*-1,2,6-Trimethylpiperidine was used as the amine component for preparation of the chiral catalyst unless otherwise stated. [b] Enantiomeric excess of *endo*-adduct. [c] 1,2,2,6,6-Pentamethylpiperidine was used to prepare catalyst.

Table 74. Asymmetric Diels–Alder Reactions of a 2-Pyrone Derivative Using a Chiral $Yb(OTf)_3$ Catalyst



XR	THF/equiv	yield/%	ee/%
BuO	5	81	65
BuS	10	85	74
^{c}HexO	10	90	96
^{c}HexS	10	67	>95
PhS	10	92	>95

This observation may be attributed to different coordination numbers of Sc(III) and Yb(III); Sc(III) has up to seven ligands, while specific coordination numbers of Yb(III) allow it to have up to 12 ligands.[159]

A possible structure of the chiral Sc catalyst was postulated based on the observation by ^{13}C NMR and IR spectroscopy.[160] The most characteristic feature of the catalyst was the existence of hydrogen bonds between phenolic hydrogens of the binaphthol and nitrogens of the tertiary amines. The coordination of this catalyst may be similar to that of the lanthanide(III)–water or –alcohol complex. It should be noted that the structure is quite different from those of conventional chiral Lewis acids based on aluminum,[161] boron,[162] or titanium.[163] In the present chiral catalyst, the axial chirality of (*R*)-BINOL is trans-

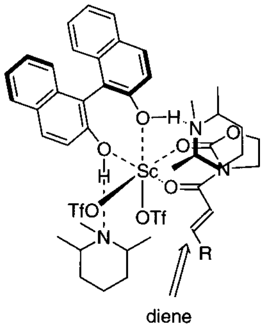


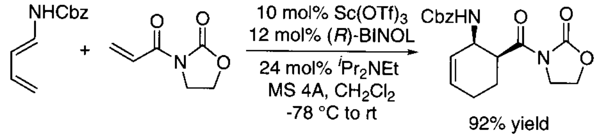
Figure 1. Assumed transition state.

ferred through the hydrogen bondings to the amines, which shield one side of the dienophile effectively. Thus, the amines employed in the preparation of the chiral catalysts strongly influenced the selectivities, and hence, bulky amines gave better selectivities.

The sense of asymmetric induction in the chiral Sc(III)-catalyzed reactions can be rationalized by assuming an octahedral Sc(III)–dienophile complex (Figure 1). The axial chirality of (*R*)-BINOL is transferred to the amine, the *re* face of the acyl-1,3-oxazolidin-2-one is effectively shielded by the amine part, and a diene approaches the dienophile from the *si* face to afford the adduct with a high enantioselectivity. Since the amine part can be freely chosen, the design of efficient catalyst systems is easier when compared to other chiral Lewis-acid catalysts based on (*R*)-BINOL.

Wipf and his group reported that catalytic asymmetric Diels–Alder reaction of an aminodiene proceeded enantioselectively in the presence of the chiral scandium catalyst prepared from $Sc(OTf)_3$ and BINOL (Scheme 40).[164]

Scheme 40. Catalytic Asymmetric Diels–Alder Reaction of an Aminodiene

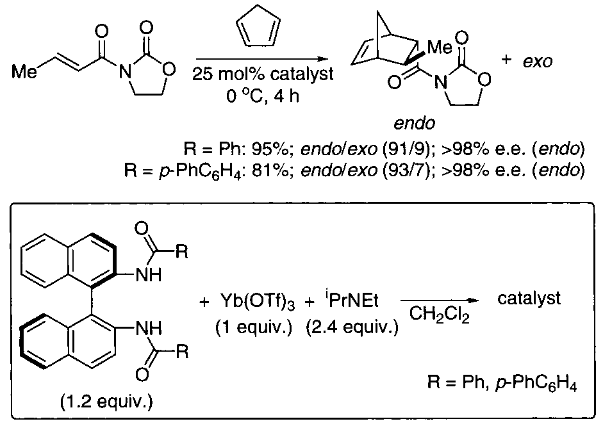


Enantioselective cycloaddition reactions of 3-carbomethoxy-2-pyrone with various vinyl ethers and sulfides were mediated by a catalyst consisting of $Yb(OTf)_3$ and BINOL to afford bicyclic lactones in good to excellent enantiomeric excesses (Table 74).[165] It should be noted that $Yb(OTf)_3$ itself did not promote the reaction of 3-carbomethoxy-2-pyrone with butyl vinyl ether and that Lewis acids such as $BF_3{\cdot}OEt_2$, $TiCl_4$, and Et_2AlCl coordinated strongly to 3-carbomethoxy-2-pyrone to give complexed pyrylium cations, hampering the reaction.

Nakagawa and co-workers utilized catalysts prepared from chiral 1,1′-(2,2′-bisacylamino)binaphthalenes, $Yb(OTf)_3$, and $^{i}Pr_2NEt$ in asymmetric Diels–Alder reactions of 3-crotonyloxazolidinones with cyclopentadiene (Scheme 41).[166]

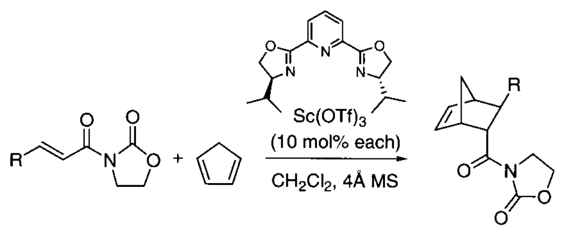
Fukuzawa and co-workers investigated enantioselective Diels–Alder reactions of 3-(2-alkenoyl)-oxazolidinones with 1,3-dienes using chiral nitrogen-donor ligands–$Sc(OTf)_3$ complex.[167] Among chiral ligands tested, isopropyl pybox was found to be the most effective, providing up to 90% ee (Table 75). The reactions can be carried out in less toxic benzotrifluoride and supercritical carbon dioxide with slightly inferior selectivities.

Scheme 41. Enantioselective Diels–Alder Reaction Catalyzed by 1,1′-(2,2′-Bisacylamino)binaphthalene–$Yb(OTf)_3$ Complexes



R = Ph: 95%; *endo*/*exo* (91/9); >98% e.e. (*endo*)
R = *p*-PhC_6H_4: 81%; *endo*/*exo* (93/7); >98% e.e. (*endo*)

Table 75. Enantioselective Diels–Alder Reaction Using a Chiral Pybox-$Sc(OTf)_3$ Complex



R	temp/°C	yield/%	*endo*/*exo*	ee/% (*endo*)	configuration
H	0	63	92/8	82	*S*
H[a]	0	60	98/2	90	*S*
Me	0	99	89/11	78	2*S*,3*R*
Me[a]	0	94	91/9	83	2*S*,3*R*
Ph	25	27	78/22	75	2*R*,3*R*

[a] The complex was prepared at -78 °C.

2.2.2. Aza-Diels–Alder Reactions

The Diels–Alder reactions of imines (aza-Diels–Alder reactions, imino Diels–Alder reactions) allow an easy access to nitrogen-containing six-membered heterocycles.[168] Although Lewis acids often promote these reactions, more than a stoichiometric amount of the acids is required due to strong coordination of the acids to the nitrogen atoms.

$Sc(OTf)_3$ was proved to be an efficient catalyst in aza-Diels–Alder reactions.[169] In the presence of 10 mol % $Sc(OTf)_3$, substituted *N*-benzylideneaniline reacted with 2-*trans*-1-methoxy-3-trimethylsiloxy-1,3-butadiene (Danishefsky's diene) to afford the corresponding imino Diels–Alder adducts (a tetrahydropyridine derivative in this case) quantitatively. On the other hand, the reaction course between substituted *N*-benzylideneaniline and cyclopentadiene under the same conditions was changed, and tetrahydroquinoline derivative was obtained as the sole

Scheme 42. Preparations of Tetrahydropyridines and Tetrahydroquinolines Using $Sc(OTf)_3$

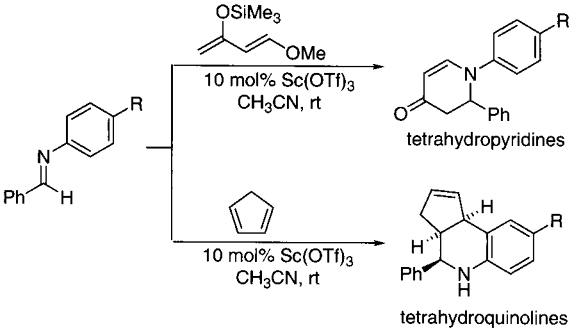
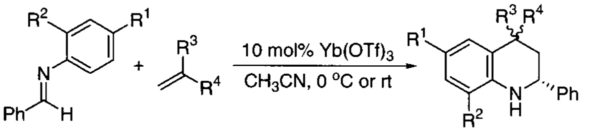


Table 76. Syntheses of Quinoline Derivatives Using $Yb(OTf)_3$



R^1	R^2	R^3	R^4	yield/%	*cis*/*trans*
H	H	H	PhS	75	57/43
Cl	H	H	PhS	quant.	n.d.[a]
MeO	H	H	PhS	0	-
H	MeO	H	PhS	70	n.d.
H	H	H	EtO	96	n.d.
MeO	H	H	EtO	77	67/33
Cl	H	H	EtO	95	n.d.
MeO	H	Ph	Me_3SiO	quant.	83/17[b]

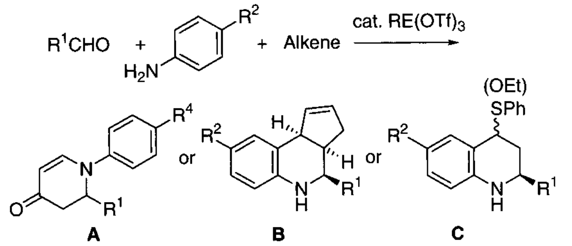
[a] Not determined. [b] Tentative assignment.

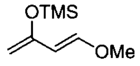
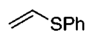
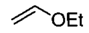
product (Scheme 42). In this reaction, the aromatic imines acted as azadienes and cyclopentadiene as a dienophile.[170] However, with 2,3-dimethylbutadiene, a mixture of tetrahydropyridine and tetrahydroquinoline derivatives was obtained. Other dienophiles, such as vinyl sulfide, vinyl ethers, and silyl enol ether, were attempted to afford the tetrahydroquinoline derivatives in high yields (Table 76).[171,172]

Sisko and Weinreb reported a convenient procedure for the imino Diels–Alder reaction of an aldehyde, a 1,3-diene, and *N*-sulfinyl *p*-toluenesulfonamide via an in situ generated *N*-sulfonyl imine using a stoichiometric amount of $BF{\cdot}OEt_3$ as a promoter.[173] The synthetic problem associated with the instability of imines under the influence of Lewis acids was overcome by trapping imines immediately by dienes or dienophiles in the reaction mixture. $Sc(OTf)_3$ catalyzed three-component coupling reactions of aldehydes, amines, and dienes.[169] With 10 mol % of $Sc(OTf)_3$ and magnesium sulfate, aldehydes were treated with aromatic amines and Danishefsky's diene or cyclopentadiene to afford the corresponding tetrahydropyridines or tetrahydroquinolines. Various aldehydes, amines, and alkenes were coupled effectively to provide two diverse libraries in high yield. Commercial aqueous formaldehyde solution could be directly used (Table 77).

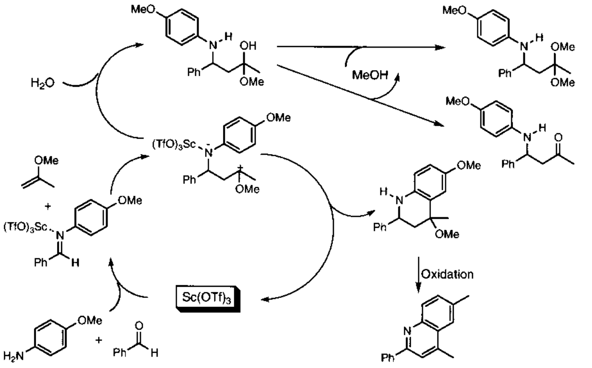
A stepwise mechanism was proposed based on experimental observations (Scheme 43).[169b,174] The reactive intermediate generated from *N*-benzylideneaniline (an azadiene) and 2-methoxypropene (an dienophile) was transformed into a hemiacetal with water (generated from condensation of the aldehyde and the amine) or an acetal with methanol (released from the hemiacetal to form the β-aminoketone), and the hemiacetal was then collapsed to give the β-aminoketone. Nevertheless, under anhydrous conditions (by using preformed imines or adding drying agent), spontaneous cyclization of the reactive intermediate would give the tetrahydroquinoline and the quinoline.

Table 77. One-Pot Synthesis of Tetrahydroquinoline Derivatives



alkene	R^1	R^2	product	RE	yield/%
	Ph	H	**A**	Yb	80
	Ph	H	**A**	Sc	83
	Ph	*p*-MeO	**A**	Yb	83
	PhCO	*p*-MeO	**A**	Yb	76
	Ph	H	**B**	Yb	56
	PhCO	*p*-MeO	**B**	Yb	94
	MeOCO	*p*-MeO	**B**	Yb	80
	Ph	H	**C**	Sc	83
	Ph	*o*-MeO	**C**	Yb	86
	Ph	*p*-MeO	**C**	Yb	60

Scheme 43. Possible Mechanism of the Three-Component Coupling Reaction

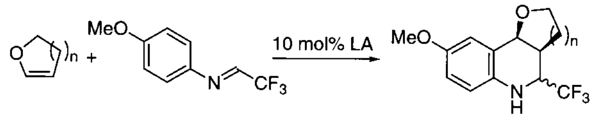


It was shown that $Yb(OTf)_3$ was as effective as $BF_3{\cdot}OEt_2$ to mediate the aza-Diels–Alder reactions shown below. Surprisingly $BF_3{\cdot}OEt_2$ could also be employed in catalytic quantity in the reaction with dihydrofuran (Table 78).[175]

It was also reported that $In(OTf)_3$ was effective for aza-Diels–Alder reactions. Cycloaddition of the imine prepared from 3-formylchromone with 3,4-dihydro-2*H*-pyran proceeded smoothly to afford the cycloadduct in good yield. $Sc(OTf)_3$ could be also used for this reaction (Table 79).[176]

The original protocol for aza-Diels–Alder reactions has been limited to either the simplest aldehyde,

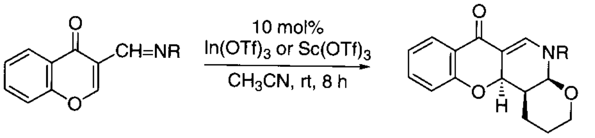
Table 78. Effect of Lewis Acids on Aza-Diels−Alder Reactions



n	LA	yield/%	cis/trans
1	BF$_3$·OEt$_2$[a]	84	90/10
1	Yb(OTf)$_3$[b]	74	70/30
2	BF$_3$·OEt$_2$[a,c]	86	64/36
2	Yb(OTf)$_3$[b]	87	70/30

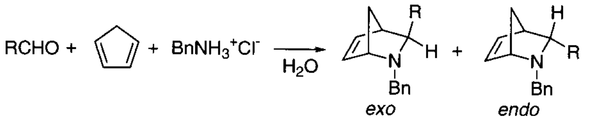
[a] The reactions were performed in toluene at −78 °C. [b] The reactions were performed in CH$_3$CN at room temperature.[c] 1 equiv of BF$_3$·OEt$_2$ was employed.

Table 79. Aza-Diels−Alder Reaction of Chromone Derivatives



R	yield/%	
	In(OTf)$_3$	Sc(OTf)$_3$
Ph	80	70
p-MeC$_6$H$_4$	78	75
p-MeC$_6$H$_4$	75	73
p-BrC$_6$H$_4$	90	70
p-ClC$_6$H$_4$	85	73
Bn	55	0

Table 80. Ln(OTf)$_3$-Catalyzed Aza-Diels−Alder Reactions of Higher Aldehydes, *N*-Benzylammonium Chloride, and Cyclopentadiene in Water



R	Ln(OTf)$_3$	yield/%	exo/endo
^{n}Pent	Pr(OTf)$_3$	68	2.9/1
Et	La(OTf)$_3$	64	2.5/1
PhCH$_2$	Yb(OTf)$_3$	72	4/1
Ph	Yb(OTf)$_3$	7	*exo* only

formaldehyde, or activated aldehydes such as glyoxylates.[177] It was found that Ln(OTf)$_3$ promoted aza-Diels−Alder reactions in water, particularly for substrates which have been difficult to use under standard conditions.[178] For instance, hexanal, propanal, and phenylethanal reacted in good yields in the presence of Ln(OTf)$_3$ (Table 80). Less reactive dienes, including 2,3-dimethyl-1,3-butadiene, 2-methyl-1,3-butadiene, and 1,3-cyclohexadiene, did not react with higher aldehydes using this protocol; however, they reacted smoothly with formaldehyde and a L-phenylalanino ester (Scheme 44).[178] Aza-sugars were prepared by using this reaction.[179]

Scheme 44. Products from Ln(OTf)$_3$-Catalyzed Aza-Diels−Alder Reaction of Different Dienes with Formaldehyde and L-Phenylalanine Methyl Ester

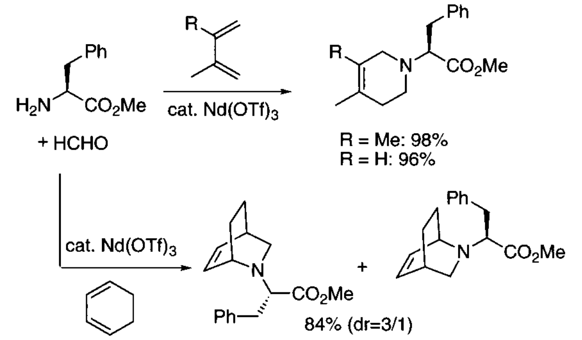
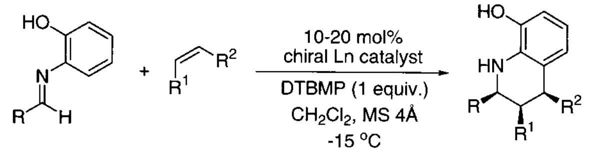


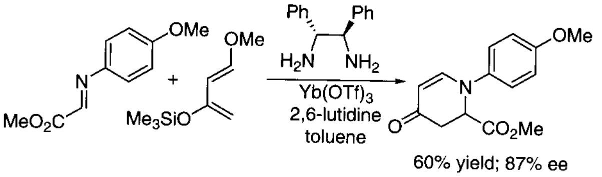
Table 81. Enantioselective Aza-Diels−Alder Reactions Using Chiral Ln Catalyst



R	R^1,R^2	Ln (mol %)	yield/%	cis/ trans	ee/%[a]
Ph	H, OEt	Yb (10)	52	94/6	77
1-naphthyl	H, OEt	Yb (20)	74	>99/1	91
1-naphthyl	H, OEt	Yb (10)	62	98/2	82
1-naphthyl	H, OBu	Yb (20)	80	66/34	70
1-naphthyl	−(CH$_2$)$_2$O−	Yb (20)	90	91/9	78
1-naphthyl	−CH$_2$CH=CH−	Yb (20)	69	>99/1	68
^{c}Hex[b]	−CH$_2$CH=CH−	Sc (20)	58	>99/1	73

[a] Enantiomeric excess of the *cis*-isomer. [b] The reaction was performed with cyclohexane carboxaldehyde and 2-aminophenol at −45 °C with 2,6-di-*tert*-butylpyridine instead of DTBMP.

Scheme 45. Asymmetric Hetero-Diels−Alder Reaction.



Unlike carbon Diels−Alder reactions, enantioselective aza-Diels−Alder reactions are far less studied and most of the available methodologies are auxiliary-based.[180] Research on using chiral Lewis acids is rather limited but not unprecedented.[181,182] The first example of a *catalytic* aza-Diels−Alder reaction was reported using chiral lanthanide catalysts that were prepared from Yb(OTf)$_3$ or Sc(OTf)$_3$, (*R*)-BINOL, and DBU.[183] The reaction of *N*-alkylidene- or *N*-arylidene-2-hydroxyaniline with cyclopentadiene proceeded in the presence of the chiral catalyst and 2,6-di-*tert*-butyl-4-methylpyridine (DTBMP) to afford the 8-hydroxyquinoline derivatives in good to high yields with good to excellent diastereo- and enantioselectivities (Table 81). The present protocol allows three-component coupling using the chiral Sc catalyst.

A parallel combinatorial approach to find chiral Lewis-acid catalysts for asymmetric aza-Diels−Alder reactions has been reported.[184] A catalyst generated from Yb(OTf)$_3$, 1,2-diphenylethylenediamine, and 2,6-lutidine in acetonitrile gave the desired product in high enantiomeric excess (Scheme 45).

Scheme 46. Polymer Scandium-Catalyzed Aza-Diels–Alder Reactions

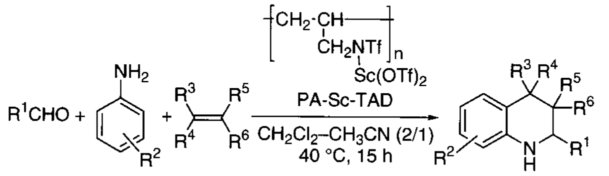
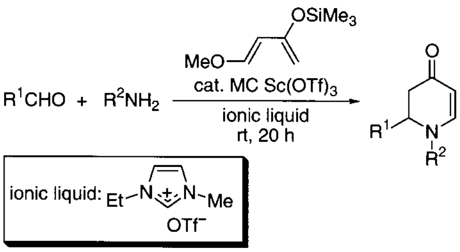


Table 82. Aza-Diels–Alder Reactions in Ionic Liquid



R^1	R^1	yield/%	recovered ionic liquid/%
Ph	Ph	80	99
Ph	3,4-FC_6H_3	99	92
Ph	4-FC_6H_4	79	97
p-FC_6H_4	Ph	95	98
p-$F_3CC_6H_4$	Ph	88	98

Three-component reactions in the presence of a polymer-supported scandium catalyst proceeded smoothly to give the corresponding adducts in good yields. This method is especially useful for construction of a quinoline library (Scheme 46).[185]

Aza-Diels–Alder reactions in ionic liquid were catalyzed effectively by microencapsulated Sc(OTf)$_3$. In view of 'green chemistry', the utility of ionic liquid as a safe recyclable reaction media and microencapsulated Sc(OTf)$_3$ (MC Sc(OTf)$_3$) as a recyclable and easy recoverable catalyst should be noted (Table 82).[186]

The aza-Diels–Alder reactions of polymer-supported α-imino esters were also catalyzed by Sc(OTf)$_3$ (Scheme 47).[62]

2.2.3. Other Hetero-Diels–Alder Reactions

The effect of Lewis acids on the asymmetric hetero-Diels–Alder reaction of chiral 3-(*p*-tolylsulfinyl)-2-furaldehyde with Danishefsky's diene was studied (Table 83).[187] ZnCl$_2$ produced a 1:1 mixture of diastereomers. In sharp contrast, LnCl$_3$ and Ln(OTf)$_3$ served as effective promoters, resulting in high yields and diastereomeric excesses. Among them, the triflates showed better selectivities. It was interesting that an Eu-based NMR shift reagent gave the other diastereomer selectively.

A catalytic enantioselective hetero-Diels–Alder reaction of butyl glyoxylate with Danishefsky's diene was reported.[188] The reaction was catalyzed by a chiral yttrium bis-trifluoromethane sulfonamide (bistriflamides) generated from Y(OTf)$_3$ and chiral bistriflamides (Scheme 48). Sc(OTf)$_3$ and Yb(OTf)$_3$ gave less satisfactory results.

Scheme 47. Aza-Diels–Alder Reactions of Polymer-Supported α-Imino Esters

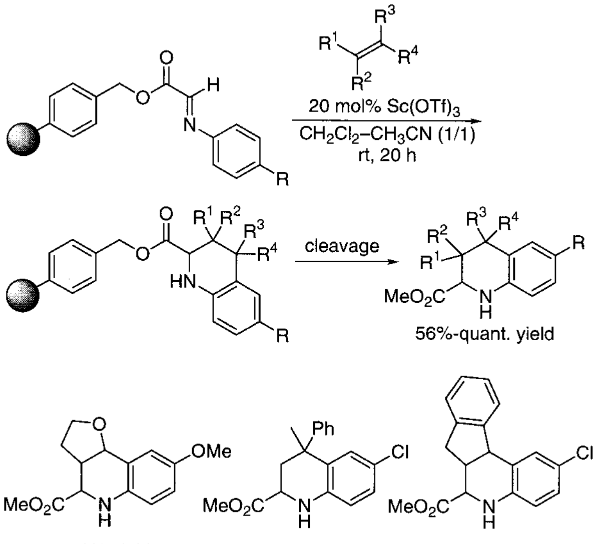
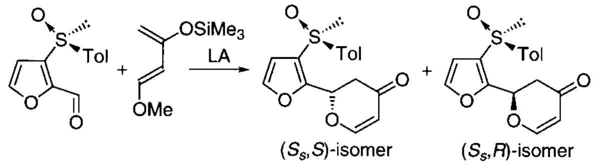


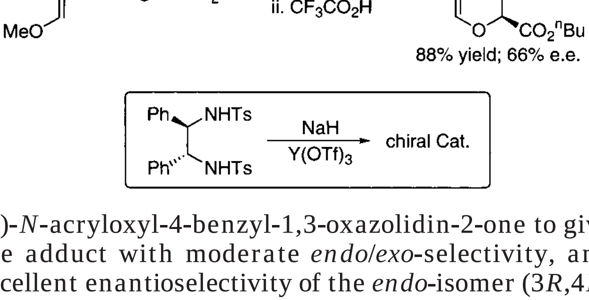
Table 83. Asymmetric Hetero-Diels–Alder Reaction of Chiral 3-(*p*-Tolylsulfinyl)-2-furaldehyde with Danishefsky's Diene



LA (equiv)	conditions	yield/%	de/%[a]
ZnCl$_2$ (1.0)	THF, 25 °C, 15 h	63	0
CeCl$_3$ (1.0)	CH$_2$Cl$_2$, 25 °C, 11 h	58	81
YbCl$_3$ (1.0)	toluene, 25 °C, 12 h	56	54
Yb(OTf)$_3$ (1.0)	THF, −20 °C, 2 h	88	93
Nd(OTf)$_3$ (1.0)	THF, −20 °C, 2 h	68	98
Sm(OTf)$_3$ (1.0)	THF, −20 °C, 2 h	73	97
Eu(thd)$_3$[b] (1.0)	CH$_2$Cl$_2$, 25 °C, 21 h	92	−77

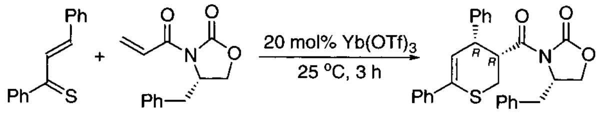
[a] Positive sign: (S_S,S)-isomer was in excess; negative sign: (S_S,R)-isomer was in excess. [b] Eu(thd)$_2$tris(2,2,6,6-tetramethyl-3,5-heptanedionate)europium.

Scheme 48. Catalytic Enantioselective Hetero-Diels–Alder Reaction of Butyl Glyoxylate with Danishefsky's Diene



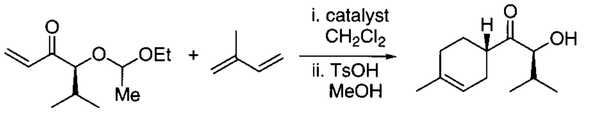
Yb(OTf)$_3$ promoted asymmetric hetero-Diels–Alder reaction of 2,4-diphenyl-1-thiabuta-1,3-diene with (*S*)-*N*-acryloxyl-4-benzyl-1,3-oxazolidin-2-one to give the adduct with moderate *endo*/*exo*-selectivity, and excellent enantioselectivity of the *endo*-isomer (3*R*,4*R*-isomer) was observed (Scheme 49).[189] The same reaction without Yb(OTf)$_3$ favored the opposite *endo*-enantiomer (3*S*,4*S*-isomer). In the stoichiometric reaction promoted by Yb(OTf)$_3$, the use of coordinating solvents, including THF, DMSO, and DMF, also

Scheme 49. $Yb(OTf)_3$-Catalyzed Hetero-Diels–Alder Reaction of 2,4-Diphenyl-1-thiabuta-1,3-diene with (*S*)-*N*-Acryloxyl-4-benzyl-1,3-oxazolidin-2-one



99% yield; *endo*/*exo* (58/42); >99% e.e. (*endo*)
without $Yb(OTf)_3$: 86% yield; *endo*/*exo* (79/21); -67% e.e. (*endo*)

Table 84. Acid-Catalyzed Ionic Diels–Alder Reaction



catalyst (mol %)	temp/°C	time/h	yield/% (dr)
$HBF_4{\cdot}OMe_2$ (2)	−45	10	70 (90/1)
$BF_3{\cdot}OEt_2$ (10)	−78	4	a
Me_2AlCl (100)	−78	2	75 (44/1)
$Zn(OTf)_2$ (10)	rt	24	0
$Sc(OTf)_3$ (10)	−20	20	67 (5.3/1)

[a] Decomposition of the substrate.

favored the (3*S*,4*S*)-*endo*-isomer. For hetero cycloaddition of *N*-acylimines with chiral vinyl ethers, $Yb(OTf)_3$ activation caused dominant decomposition of *N*-acylimines.[190]

2.2.4. Ionic Diels–Alder Reaction

The Gassman ionic Diels–Alder reactions of α,β-unsaturated acetals provide substituted cyclohexanes under mild conditions.[191] Efficiency of various acid catalysts in a diastereoselective reaction of chiral dienophiles with isoprene was investigated (Table 84).[192] The reaction proceeded with catalytic amounts of $HBF_4{\cdot}OMe_2$ or $Sc(OTf)_3$ or a stoichiometric amount of Me_2AlCl. Other Lewis acid, including $BF_3{\cdot}OEt_2$ and $Zn(OTf)_2$ were not effective to promote the reaction.

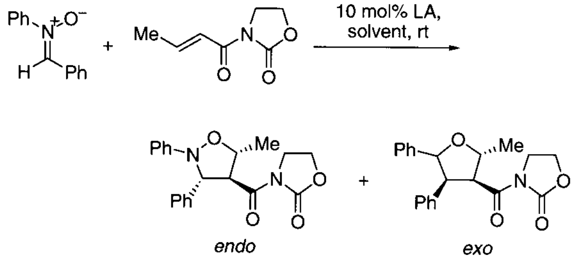
2.2.5. 1,3-Dipolar Cycloadditions

The 1,3-dipolar cycloaddition of nitrones to alkenes provides a useful route to isoxazolidine derivatives. Their reductive cleavage gives a range of compounds, such as β-hydroxy ketones, β-amino alcohols, etc.,[193] which in turn are versatile intermediates and chiral auxilaries for organic synthesis.

A detailed study of the effect of lanthanide triflates for 1,3-dipolar cycloaddition was reported,[194] and an excellent *endo*/*exo*-selectivity was observed using $Yb(OTf)_3$ in toluene (Table 85). Interestingly, the same reaction in acetonitrile was moderately selective for an *exo*-adduct, which was also formed preferentially using other classical Lewis-acid catalysts.

The three-component coupling reaction of benzaldehyde, *N*-benzylhydroxylamine, and *N*-phenylmaleimide was investigated in the presence of a catalytic amount of $Sc(OTf)_3$. The corresponding isoxazolidine derivative was obtained in good yield with high *endo*-selectivity (Table 86).[195]

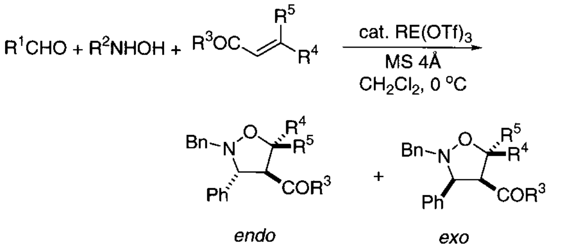
Table 85. Effect of Lewis Acid Catalysts for 1,3-Dipolar Cycloaddition of 3-Crotonoyl-1,3-oxazolidinone with Benzylidenephenylamine *N*-Oxide

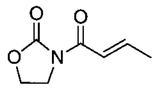
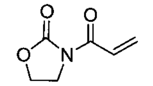
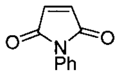


Lewis acid	solvent	yield/%	*endo*/*exo*
$La(OTf)_3$	toluene	23	53/47
$Sm(OTf)_3$	toluene	88	76/24
$Eu(OTf)_3$	toluene	78	67/33
$Yb(OTf)_3$	toluene	87	95/5
$Yb(OTf)_3$	CH_3CN	63	18/82
$Ti(^iPrO)_2Cl_2$	CH_2Cl_2	68[a]	13/87
MgI_2–I_2	CH_2Cl_2	>90[a]	15/85
None	CH_2Cl_2	<2[a]	–

[a] Percentage conversion.

Table 86. $RE(OTf)_3$-Catalyzed Three-Component Coupling Reaction of Benzaldehyde, *N*-Benzylhydroxylamine, and *N*-Phenylmaleimide



R^1	R^2	dipolarophile	RE	yield/%	*endo*/*exo*
Ph	Bn		Yb	82	94/6
$Ph(CH_2)_2$	Bn		Yb	93	98/2
Ph	Ph		Yb	88	85/15
Ph	Ph		Sc[a]	quant.	91/9
1-naphthyl	Ph		Yb	68	88/12
2-furyl	Ph		Sc[a]	99	89/11
Ph	Bn		Yb	90	>99/1
Ph	Bn		Yb	53	>99/1

[a] In CH_2Cl_2.

1,3-Dipolar cycloaddition of polymer-supported nitrones with alkenes proceed smoothly in the presence of a catalytic amount of $Yb(OTf)_3$. Diverse 2-isoxazoline derivartives were prepared based on these solid-phase reactions (Scheme 50).[196]

Rare-earth metal triflate-catalyzed 1,3-dipolar cycloaddtion of carbonyl ylides generated from α-diazocarbonyl compounds are discussed in section 2.7.

Substituted indenones reacted smoothly with a variety of in situ generated nitrones in the presence

Scheme 50. 1,3-Dipolar Cycloaddition Reactions of Polymer-Supported Nitrones

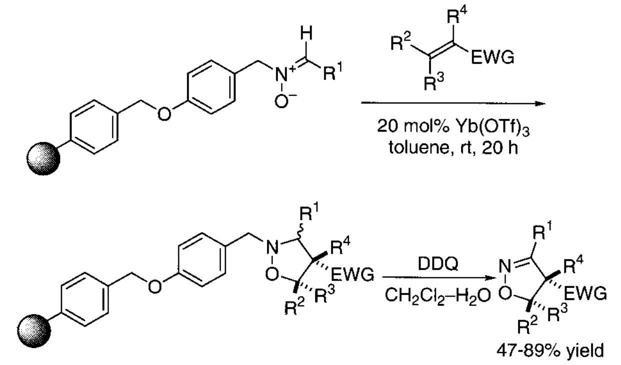
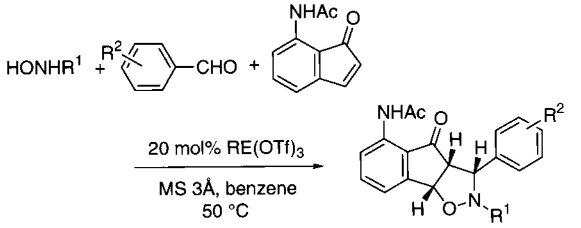
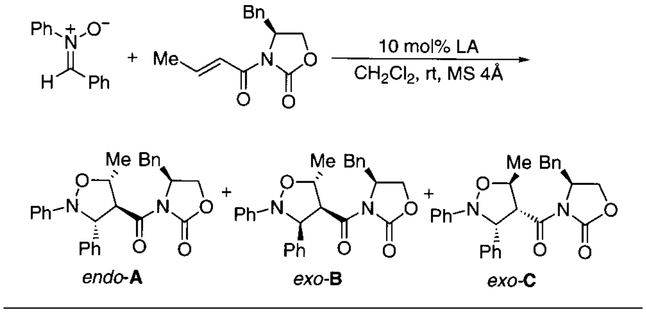


Table 87. Ln(OTf)$_3$-Catalyzed 1,3-Dipolar Cycloadditions of an Indenone



R^1	R^2	RE	yield/%	*exo*/*endo*
PhCH$_2$	*p*-MeO	Yb	88	98/2
4-MeOPhCH$_2$	*p*-MeO	Yb	84	98/2
3,4-(MeO)$_2$PhCH$_2$	*p*-MeO	Yb	81	98/2
3,4-(MeO)$_2$PhCH$_2$	*p*-MeO	Sc	86	98/2
3,4-(MeO)$_2$PhCH$_2$	*p*-NO$_2$	Sc	78	98/2
3,4-(MeO)$_2$PhCH$_2$	H	Sc	69	98/2
3,4-(MeO)$_2$PhCH$_2$	*p*-MeO	none	0	–

Table 88. Effect of Lewis-Acid Catalysts on Diastereoselective 1,3-Dipolar Cycloaddition Using a Chiral Dipolarophile

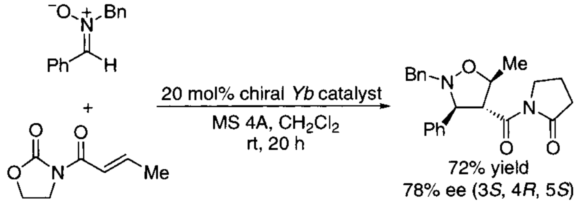


Lewis acid	time	yield/%	**A**/**B**/**C**
Sc(OTf)$_3$	5 h	>95	95/5/0
Yb(OTf)$_3$	12 h	>95	94/6/0
Mg(ClO$_4$)$_2$	60 h	>95	92/8/0
none	15 d	95	17/7/76

of lanthanide triflates to give exclusive *exo*-adducts (Table 87).[197]

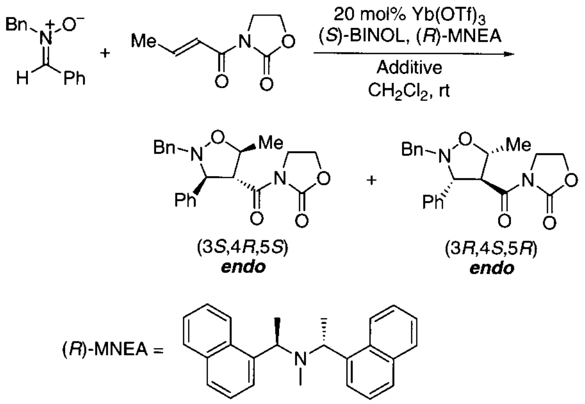
Sc(OTf)$_3$ was used for asymmetric 1,3-dipolar cycloaddition with chiral dipolarophiles (Table 88).[198] A higher reaction rate was achieved with Sc(OTf)$_3$ than Yb(OTf)$_3$, and in both cases, excellent *endo*-selectivities were observed. The reaction with Mg(ClO$_4$)$_2$ was less selective and much slower. It was noteworthy that in the absence of a catalyst, the reaction proceeded slowly to give predominantly *exo*-isomers.

Scheme 51. Asymmetric 1,3-Dipolar Cycloaddition Catalyzed by a Chiral Ytterbium Triflate



chiral *Yb* catalyst: Yb(OTf)$_3$, (*R*)-BINOL, *cis*-1,2,6-trimethylpiperidine

Table 89. Effect of Additive on Selectivity of 1,3-Dipolar Cycloaddition



additive	yield/%	*endo*/*exo*	ee/%	isomer
MS 4 Å[a]	92	99/1	96	3*R*,4*S*,5*R*
NMO (20 mol %)[b]	68	98/2	81	3*S*,4*R*,5*S*
benzylidenebenzylamine *N*-oxide (20 mol %)[b]	90	99/1	83	3*S*,4*R*,5*S*

[a] Reference 199. [b] Reference 200.

Catalytic asymmetric 1,3-dipolar cycloaddition of a nitrone with a dipolarophile was carried out using a chiral Yb catalyst, which was readily prepared from Yb(OTf)$_3$, (*R*)-(+)-BINOL, and *cis*-1,2,6-trimethylpiperidine.[195] The reaction of benzylbenzylideneamine *N*-oxide with 3-(2-butenoyl)-1,3-oxazolidin-2-one gave the desired isoxazolidine in 78% ee with perfect diastereoselectivity (*endo*/*exo* ≥ 99/1) (Scheme 51). On the other hand, it was found that reverse enantioselection was observed with a chiral scandium catalyst generated in a similar way.

The chiral Yb catalyst for asymmetric 1,3-dipolar cycloaddition was improved by addition of a chiral amine, *N*-methyl-bis[(*R*)-1-(1-naphthyl)ethyl]amine [(*R*)-MNEA] (Table 89).[199] Thus, a combination of Yb(OTf)$_3$, (*S*)-BINOL, and (*R*)-MNEA gave 1,3-dipolar adducts with good to excellent *endo*- and enantioselectivities. A reverse of the selectivity was achieved using the same chiral catalyst simply by replacing molecular sieves with *N*-methylmorpholine *N*-oxide or benzylidenebenzylamine *N*-oxide (Table 89).[200]

A chiral scandium catalyst prepared from Sc(OTf)$_3$ and a BINOL-Box ligands (Figure 2) also catalyzes the same asymmetric 1,3-dipolar cycloaddition to provide the (3*R*,4*S*,5*R*)-adduct with high diastereo- and enantioselectivity (94% yield, 97% *endo*, 87% ee).[201]

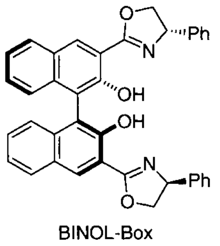


Figure 2. BINOL-Box ligand.

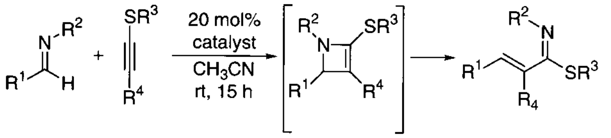
2.2.6. Other Cycloaddition Reactions

α,β-Unsaturated thioimidates are useful intermediates in organic synthesis.[202] Sc(OTf)$_3$ catalyzes reactions of imines with alkynyl sulfides providing α,β-unsaturated thioimidates (Table 90).[203] These reactions are assumed to proceed via [2+2]-cycloaddition of imines to alkynyl sulfides, forming azetine intermediates, which are unstable and immediately fragment to give the corresponding α,β-unsaturated thioimidates. Yb(OTf)$_3$ and BF$_3$·OEt$_2$ were less effective in this reaction.

Recently, it has been reported that analogous reactions with alkynyl selenides are also catalyzed by Sc(OTf)$_3$ (Scheme 52).[204] Again, other Lewis acids, including Yb(OTf)$_3$, BF$_3$·OEt$_2$, ZnCl$_2$, MgBr$_2$, and ScCl$_3$, were less effective for the process.

A Lewis-acid-catalyzed stereoselective method for preparation of α-(trifluoromethyl)-α,β-unsaturated amides was reported (Table 91).[205] The reaction of *N*,*N*-dibutyl-(3,3,3-trifluoro-1-propynyl)amine with benzaldehyde was mediated by La(OTf)$_3$ to give the enamide as a major product with high *Z* stereoselectivity. Other classical Lewis acids were more effective than La(OTf)$_3$ to promote the stereoselective reaction in high yields in the presence of MS 4 (Table 91).

Table 90. Preparation of α,β-Unsaturated Thioimidates from [2+2] Cycloaddition of Imines and Alkynyl Sulfides



R^1	R^2	catalyst	conditions[a]	yield/%
Ph	Bn	Sc(OTf)$_3$	A	40
Ph	Ts	Sc(OTf)$_3$	A	95
Ph	Ts	Yb(OTf)$_3$	A	80
Ph	Ts	BF$_3$·OEt$_2$	A[b]	66
p-MeOPh	Ts	Sc(OTf)$_3$	A	75
p-ClPh	Ts	Sc(OTf)$_3$	A[b]	80
2-furyl	Ts	Sc(OTf)$_3$	A	73
PhCJC	Ts	Sc(OTf)$_3$	B	65
c-Hex	Ts	Sc(OTf)$_3$	B[b]	80
Ph(CH$_2$)$_2$	Ts	Sc(OTf)$_3$	B	62

[a] A: isolated imine was used. B: imine was prepared in situ. [b] In CH$_2$Cl$_2$.

Scheme 52. Preparation of α,β-Unsaturated Selenylimidates from [2+2] Cycloaddition of Imines and Alkynyl Selenides

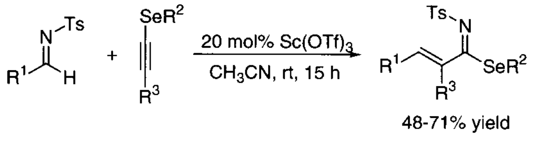
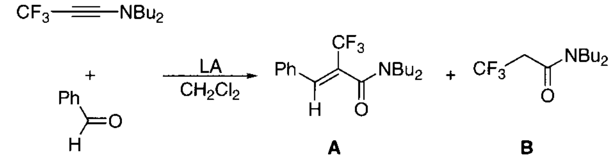


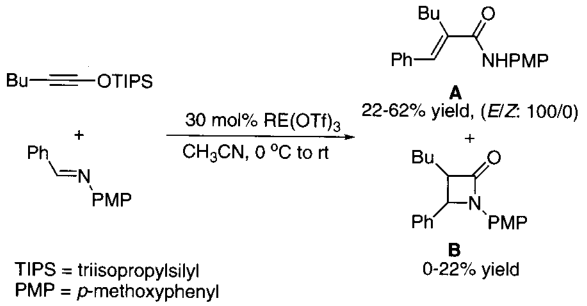
Table 91. Lewis-Acid-Catalyzed Stereoselective Synthesis of α-(Trifluoromethyl)-α,β-unsaturated Amides[a]



LA (mol %)	time/h	yield/% **A** (*E*/*Z*)	yield/% **B**
La(OTf)$_3$ (30)	24	71 (<3/>97)	8
BF$_3$·OEt$_2$ (10)	1	98 (<3/>97)	trace
TiCl$_4$ (10)	1	80 (<3/>97)	12
ZnBr$_2$ (10)	1	90 (<3/>97)	5
SnCl$_4$ (10)	1	81 (<3/>97)	5

[a] The reactions were performed at room temperature in the presence of MS 4 Å, unless otherwise stated. [b] In the absence of MS 4 Å.

Table 92. RE(OTf)$_3$-Catalyzed Reaction of Silyl Ynolate with Aldimine



	yield/%			yield/%	
RE	**A** (*E*/*Z*)	**B**[a]	RE	**A** (*E*/*Z*)	B
Sc	35 (100/0)	4	Tb	46 (100/0)	15
Y[b]	52 (100/0)	0	Dy	61 (100/0)	4
La	22 (100/0)	9	Ho	56 (100/0)	6
Pr	43 (100/0)	22	Er	54 (100/0)	7
Nd	38 (100/0)	13	Tm	36 (100/0)	16
Sm	32 (100/0)	0	Yb	38 (100/0)	0
Eu	45 (100/0)	0	Lu	56 (100/0)	0
Gd	62 (100/9)	7			

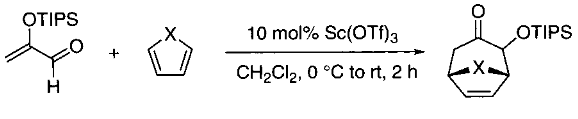
[a] Only *cis*-isomer was obtained. [b] Y(OTf)$_3$·3H$_2$O was used instead of anhydrous sample.

TiCl$_4$ catalyzed the reaction of silyl ynolates with aldehydes but did not catalyze the reaction with imines.[206] RE(OTf)$_3$ was introduced as effective catalysts to the later reaction, and the reaction gave enamides as the major products with perfect *E* stereoselectivity (Table 92).[207]

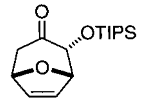
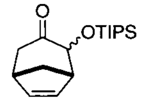
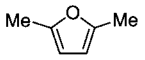
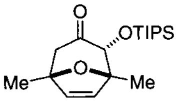
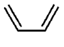
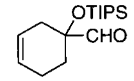
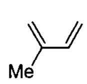
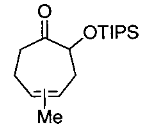
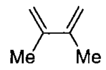
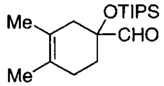
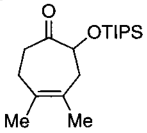
2-(Triisopropylsilyloxy)acrolein reacted with various dienes in the presence of a catalytic amount of Sc(OTf)$_3$ to afford the corresponding [4+3] cycloadducts (Table 93).[208] Although TiCl$_4$ (1.1 equiv) promoted the reaction with furan to give the adduct in 88%, Ti(O^{i}Pr)$_4$ and Ti(O^{i}Pr)$_2$Cl$_2$ were ineffective.

Sc(OTf)$_3$ was recently shown to be effective for [5+2] cycloaddition of a η^3-pyridinylmolybdenum complex to a methyleneoxindole (Scheme 53).[209] The reaction is reversible, and the yield of the cycloadduct

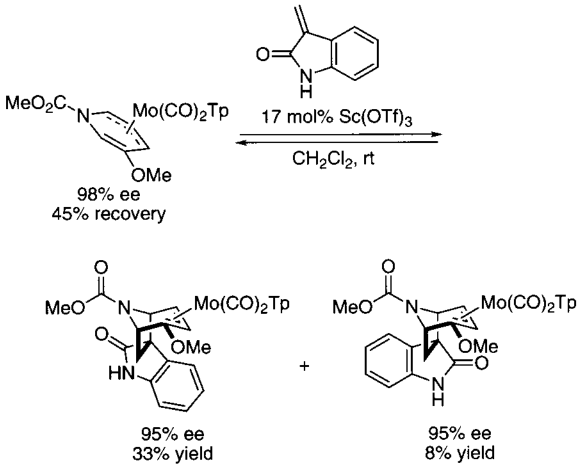
Table 93. Reactions of 2-(Triisopropylsiloxy)acrolein



TIPS = triisopropylsilyl

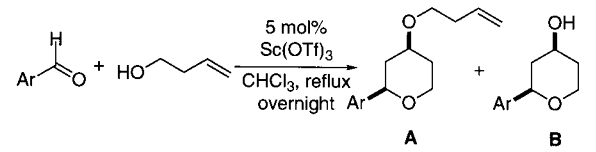
diene	adduct	yield/%
		90
		72 (dr = 3/1)
		55
		67
		17
		22
		17

Scheme 53. [5+2] Cycloaddtion of a η^3-Pyridinylmolybdenum Complex



is dependent on the reaction time and the amount and nature of the Lewis acid. The adducts were obtained in good ee, and the starting material was recovered with high enantiopurity.

Table 94. Sc(OTf)$_3$-Catalyzed Formations of 4-Tetrahydropyranols and Their Ethers



	yield/%			yield/%	
Ar	A	B	Ar	A	B
Ph	63	14	1,3-$Cl_2C_6H_3$	49	17
o-FC_6H_4	50	19	*m*-BrC_6H_4	72	14
m-FC_6H_4	57	12	*o*-MeC_6H_4	58	20
p-FC_6H_4	69	16	*m*-MeC_6H_4	62	13
o-ClC_6H_4	71	13	*p*-MeC_6H_4	64	18
m-ClC_6H_4	65	11	*p*-EtC_6H_4	56	10
p-ClC_6H_4	83	15	naphthyl	70	9

Recently, it was reported that 1-benzyl-4-*tert*-butyl-1,4-dihydronicotinamide (*t*-BuBNAH) reacts with *p*-benzoquinone (Q) to yield a [2+3] cycloadduct in the presence of Sc(OTf)$_3$ in acetonitrile at room temperature. On the other hand, when a weaker Lewis acid such as Lu(OTf)$_3$, Y(OTf)$_3$, or Mg(ClO$_4$)$_2$ is used, the hydride transfer reaction from BNAH to Q occurs besides the cycloaddition reaction.[210]

2.2.7. Prins-type Cyclization

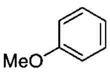
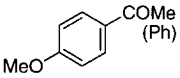
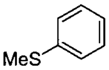
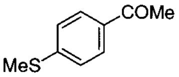
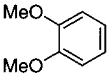
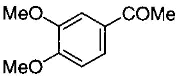
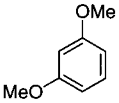
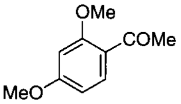
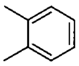
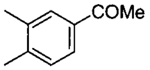
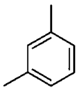
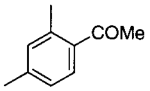
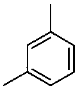
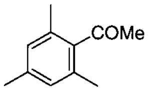
The acid-catalyzed condensation of an aldehyde and an olefin is well-known as the Prins reaction.[211] The reaction is usually promoted by strong acids and high reaction temperatures and resulted in a mixture of products. Recently, it was shown that Sc(OTf)$_3$ catalyzed Prins-type cyclization of aromatic aldehydes and a homoallylic alcohol to provide synthetically useful 4-tetrahydropyranols and their homoallylic ethers (Table 94).[212] It is noted that *cis*-adducts were obtained exclusively and that aliphatic aldehydes were less effective for the reactions. A mechanism of a tandem carbonyl acetalization—Prins reaction was postulated.

2.3. Friedel–Crafts Acylation and Alkylation

While Friedel—Crafts acylation reactions are fundamental and important processes in organic synthesis as well as in industrial chemistry,[213] more than a stoichiometric amount of a Lewis acid such as AlCl$_3$ or BF$_3$ is needed due to coordination of the Lewis acids to aromatic ketones produced. It has been reported that a small amount of Sc(OTf)$_3$[214a] or Ln(OTf)$_3$[214b] catalyzes Friedel—Crafts acylation reactions efficiently.[215] The catalytic activity of Sc(OTf)$_3$ was much higher than that of Ln(OTf)$_3$ in several cases. An example of acetylation of anisole is shown in Table 95.[216] Moreover, acetylation of other electron-rich aromatics, e.g., thioanisole or *o*- or *m*-dimethoxybenzene, gave a single regioisomer in excellent yield. It was found that the regioselectivity of acetylation of 2-methoxynaphthalene depended on the amounts of the catalyst (Table 96). While 1-acetylated product was obtained in the presence of a catalytic amount of Yb(OTf)$_3$ or Sc(OTf)$_3$, 6-acetylated product was yielded in the presence of a stoichiometric amount of the catalyst. Benzoylation of anisole also proceeded smoothly in the presence of a catalytic amount of Sc(OTf)$_3$, which was easily recovered and reused after the reaction. In addition, it was found that the addition of lithium perchlorate (LiClO$_4$) as a cocatalyst improved the yields dramatically (Table 95).[217]

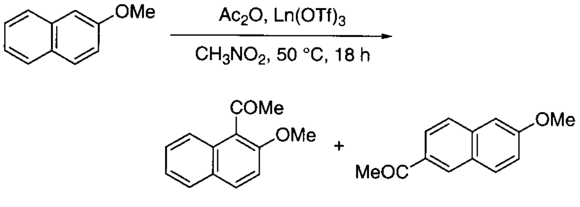
Table 95. Effect of Lewis Acids on Friedel-Craft Acetylation of Anisole

$$\text{Ar-H} + \text{Acylating Agent} \xrightarrow[\text{CH}_3\text{NO}_2\text{, }50^\circ\text{C}]{20\text{ mol\% RE(OTf)}_3} \text{Ar-COR}$$

Ar-H	Acylating Agent	product	RE	time /h	yield /%
	Ac_2O		Yb	4	55
	Ac_2O		Sc	4	89
	PhCOCl		Sc	18	79
	$(PhCO)_2O$		Sc	18	90
	Ac_2O		Yb	42	83
	Ac_2O		Sc	1	97
	Ac_2O		Sc	1	99
	Ac_2O		Sc	1	89
	Ac_2O		Yb	18	22
	Ac_2O		Sc	1	14
	Ac_2O		Sc[a]	1	55
	Ac_2O		Yb	18	25
	Ac_2O		Sc	1	11
	Ac_2O		Sc[a]	1	61
	Ac_2O		Yb	18	55
	Ac_2O		Sc	1	89
	Ac_2O		Sc[a]	1	93

[a] $LiClO_4$ (4 equiv) was added.

Table 96. RE(OTf)$_3$-Catalyzed Acylations of 2-Methoxynaphthalene



1-Ac **6-Ac**

$Ln(OTf)_3$ (mol %)	yield/%[a]	**1-Ac/6-Ac**
$Yb(OTf)_3$ (20)	76	88/12
$Yb(OTf)_3$ (50)	78	85/15
$Yb(OTf)_3$ (100)	51	8/92
$Sc(OTf)_3$ (20)	86	85/15
$Sc(OTf)_3$ (100)	77	5/95

[a] Determined by GLC analyses using an internal standard.

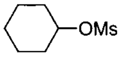
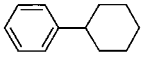
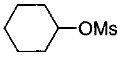
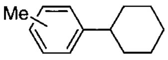
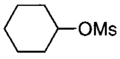
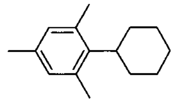
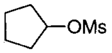
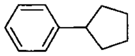
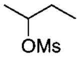
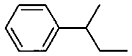
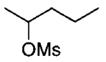
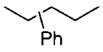
A microencapsulated $Sc(OTf)_3$ was also effective for Friedel–Crafts acylation reactions.[37]

The catalytic effect of $Sc(OTf)_3$ and $Ln(OTf)_3$ on Friedel–Crafts alkylation with mesylates of secondary alcohols was systematically investigated.[218] Among the rare-earth metal triflates tested, $Sc(OTf)_3$ and $Yb(OTf)_3$ gave the most outstanding performance and $Sc(OTf)_3$ was more active than $Yb(OTf)_3$ (Table 97). Surprisingly, TfOH was even more active than the rare-earth metal triflates screened.

Conventional Friedel–Crafts alkylation employs alkyl halides and a Lewis acid. However, hydrogen halide produced during the reaction often induces side reactions. Moreover, reactions with alcohols require more than stoichiometric amounts of Lewis acids due to deactivation of the Lewis acids by alcohols and/or water produced during the reaction. It was reported that catalytic Friedel–Crafts alkylation with benzylic and allylic alcohols proceeded using a water-tolerant Lewis acid, $Sc(OTf)_3$.[219] Chemical yields ranging from moderate to excellent yields were obtained with 10 mol % of the catalyst (Table 98). The effect of other Lewis-acid catalysts for benzylation of benzene with benzyl alcohol was studied, and $Sc(OTf)_3$ gave the best result. Interestingly, the reaction of arenes with an aromatic aldehyde and 1,3-propanediol or with their acetal affords diarylmethane as a sole product. This reaction is considered to proceed through a redox process including a hydride shift from 1,3-propanediol.[219]

Table 97. Catalytic Friedel–Crafts Alkylation with Mesylates of Secondary Alcohols

$$\text{R-OMs} + \underset{\text{(excess)}}{\text{Ar-H}} \xrightarrow[80^\circ\text{C}]{10\text{ mol\% Sc(OTf)}_3} \text{Ar-R}$$

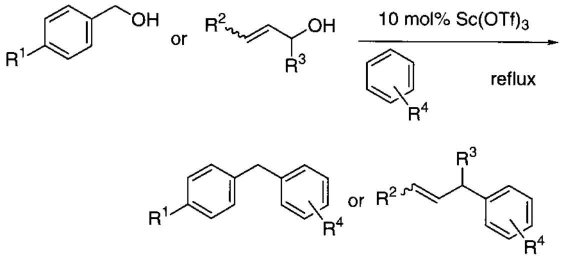
R-OMs	Ar-H	product	time /h	yield /%
	benzene		4	92
	toluene	 *o*-/*p*- = 50/50	3	98
	mesitylene		2	93
	benzene		1	87
	benzene		2	92
	benzene	 2-/3- = 76/24	2	93

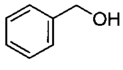
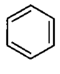
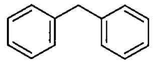
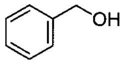
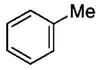
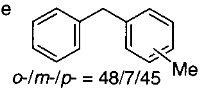
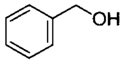
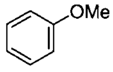
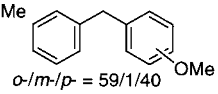
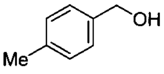
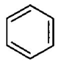
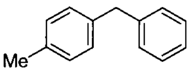
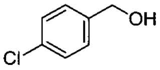
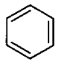
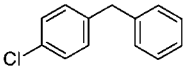
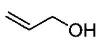
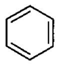
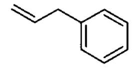
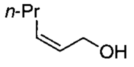
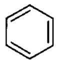
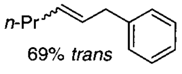
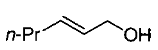
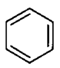
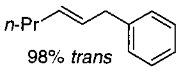
Friedel–Crafts alkylation reactions of aromatic compounds with α-chloro-α-(ethylthio)acetate were effectively catalyzed by $Yb(OTf)_3$ (Table 99).[220] Even the reaction of acid-sensitive furan proceeded well to afford the mono-alkylated product in good yield, while both mono- and dialkylated products were obtained when $ZnCl_2$ was used as a Lewis acid.

It was also reported that Friedel–Crafts alkylation reactions of aromatic compounds with alkenes proceeded in the presence of $Sc(OTf)_3$ immobilized in ionic liquid (Scheme 54).[221]

Calix[4]resorcinarenes are used as host compounds for ions, sugars, and other organic molecules.[222] They are usually prepared by condensation of resorcinol with aldehydes in the presence of mineral acids.[223] Two examples using classical Lewis acids ($AlCl_3$[224] and $SnCl_4$[225]) were reported in the literature, where only aromatic aldehydes reacted to give moderate to good yields in the presence of large amounts of Lewis acids (50–200 mol %). $Yb(OTf)_3$ nonahydrate was employed for the condensation reaction, and both

Table 98. Catalytic Friedel–Crafts Alkylation Using Alcohols



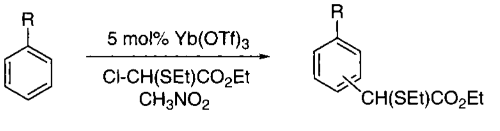
alcohol	ArH	product	time/h	yield/%
			6	91
			4	quant.
			1	quant.
			3	85
			3	93
			8	48
			2	91
			1.5	95

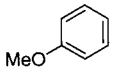
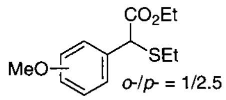
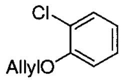
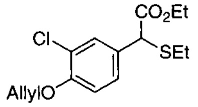
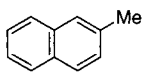
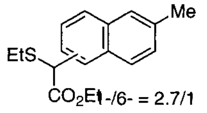
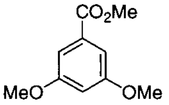
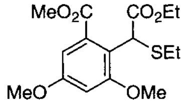
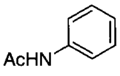
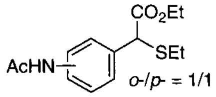
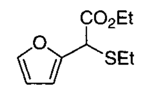
aromatic and aliphatic aldehydes gave the desired resorcinarenes in 71–94% yield (Scheme 55).[226] The thermodynamically more stable all-*cis* (bowl-shaped) isomer was obtained with aliphatic aldehydes. In contrast, benzaldehyde gave the kinetically favored α,α,β,β-isomer along with the all-*cis* configuration. The catalyst was recovered without loss of activity.

Substituted indoles can be used for Friedel–Crafts alkylation with stabilized carbinols in the presence of $Sc(OTf)_3$ (Scheme 56).[227] No selectivity was observed in the reaction with a chiral carbinol.

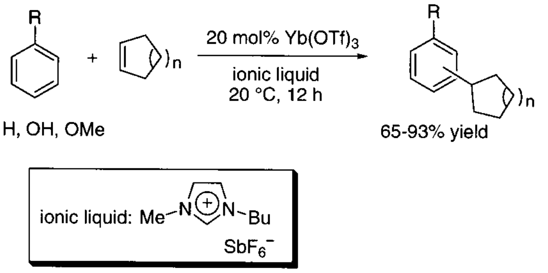
Protic acids[228] and Lewis acids[229] (e.g., $AlCl_3$) have been successfully employed in reactions of indole with aromatic and aliphatic aldehydes and ketones to form bisindolyl-methanes.[230] The same chemistry was catalyzed by $Ln(OTf)_3$ in aqueous media.[231] $Dy(OTf)_3$ gave the best result, mediating reactions of substituted indoles with aldehydes and ketones smoothly (Table 100). It has been reported that a complicated mixture was obtained by using $BF_3{\cdot}OEt_2$ or $AlCl_3$ as a promoter in the reaction of indole with acetone.[229] Other main-group triflates such as NaOTf and $Mg(OTf)_2$ were not effective. The reaction of indole-3-acetic acid with hexanal gave different products in different reaction solvents. Bisindolylmethane was isolated as a sole product in chloroform ($CHCl_3$), while 1:1 indole–aldehyde ethanolysis product was produced in aqueous ethanol (Scheme 57).

Table 99. Friedel–Crafts Alkylation Reactions with α-Chloro-α-(ethylthio)acetate

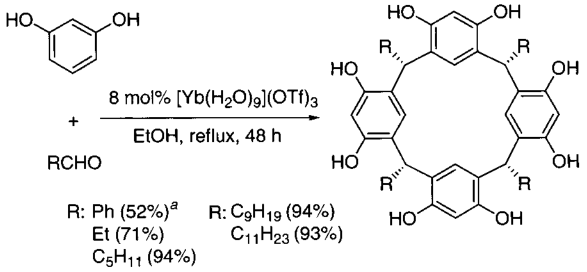


ArH	product	time/h	yield/%
		1	92
		5	85
		10	50
		4	58
		16	29
		6	81

Scheme 54. Friedel–Crafts Alkylation Reactions in Ionic Liquids



Scheme 55. Yb(OTf)₃-Catalyzed Preparation of Calix[4]resorcinarenes



[a] All-*cis* isomer. Another isomer (37%) was obtained.

Smith and co-workers utilized a catalytic amount of $Sc(OTf)_3$ in the cascade reaction involving intramolecular Friedel–Crafts alkylation of an indole in total synthesis of (–)-Penitrem D (Scheme 58).[232] The reaction proceeded in a highly stereoselective fashion (>95:5).

Scheme 56. Sc(OTf)$_3$-Catalyzed Friedel–Crafts Alkylation of 1,2-Dimethylindole with Carbinols

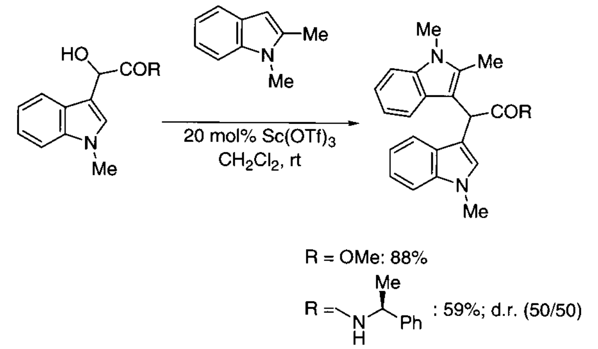
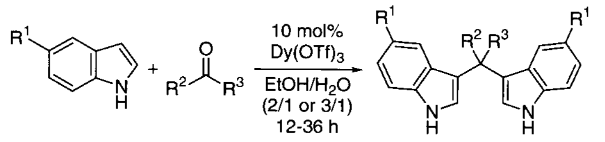
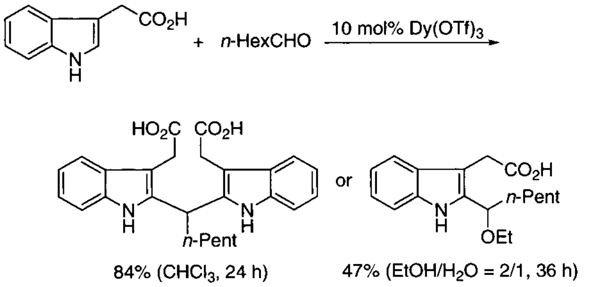


Table 100. Dy(OTf)$_3$-Catalyzed Reaction of Indoles with Aldehydes and Ketones



R^1	R^2	R^3	yield/%
H	Ph	H	95
H	p-MeOC$_6$H$_4$	H	98
H	p-ClC$_6$H$_4$	H	99
H	n-Pent	H	84
MeO	n-Pent	H	81
H	-(CH$_2$)$_5$-		90
H	Me	Me	76
H	Ph	Me	77

Scheme 57. 2:1 and 1:1 Products Resulted from Dy(OTf)$_3$-Catalyzed Reactions of Indole-3-acetic Acid with Hexanal in Different Reaction Media



It was reported that rare-earth metal triflates [La(OTf)$_3$, Nd(OTf)$_3$, Dy(OTf)$_3$, Sc(OTf)$_3$, Yb(OTf)$_3$] catalyzed effectively electrophilic substitution of arenes with ethyl glyoxylate.[233] When Yb(OTf)$_3$ was used as a catalyst, the best result was obtained. In this reaction, no desired product was observed when commonly used Lewis acids (AlCl$_3$, MgCl$_2$, ZnCl$_2$) were examined (Table 101).

Indole has been reported to react with a number of imines in the presence of a protic acid to afford the desired secondary amines in moderate yields.[234] Wang and his research group found that Dy(OTf)$_3$ catalyzed the reactions of indole with imines in protic media (Table 102).[235] Other lanthanide triflates (La, Nd, Eu, Gd, Yb, and Er triflates) and lanthanide chloride hydrates (Nd, Dy, and Y chloride hexahydrates) also promoted the reactions of indole with N-benzylidene anilines, while no reaction occurred without catalyst. Dy(OTf)$_3$ and Yb(OTf)$_3$ gave the best yield of the desired secondary amine, and Dy(OTf)$_3$ was chosen as a catalyst for the reactions with other imines.

Scheme 58. Sc(OTf)$_3$-Catalyzed Cascade Reaction as a Key Step in Total Synthesis of (−)-Penitrem D

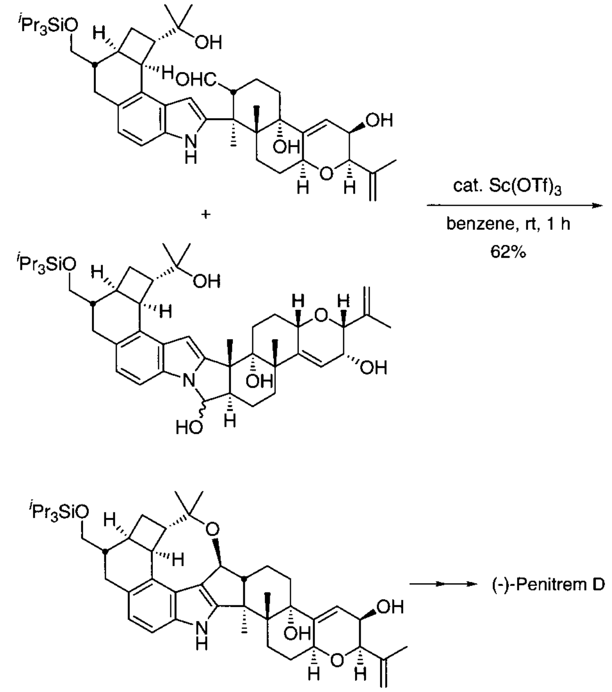
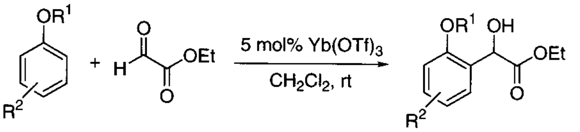


Table 101. Yb(OTf)$_3$-Catalyzed Electrophilic Substitution of Arenes with Ethyl Glyoxylate



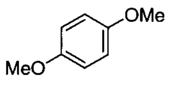
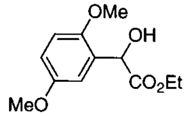
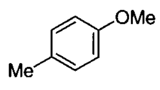
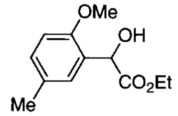
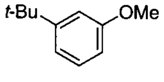
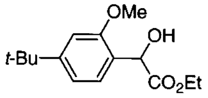
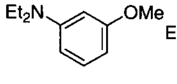
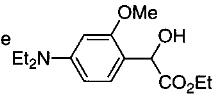
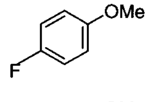
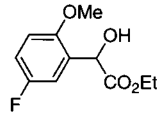
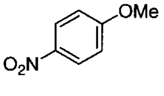
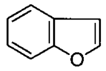
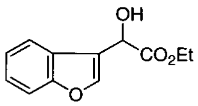
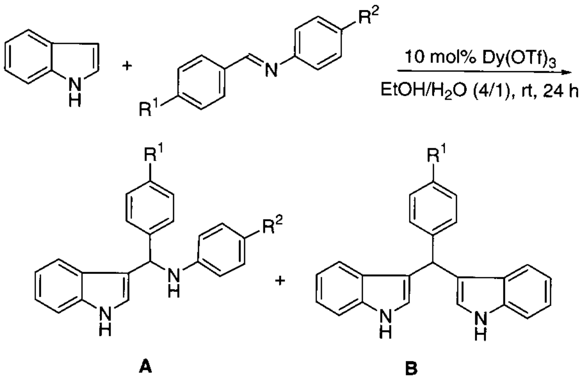
arene	product	time/h	yield/%
		5	84
		24	80
		3	90
		2	68
		6	81
	no reaction		
		24	76

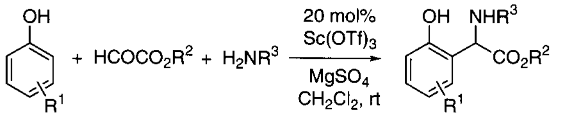
Table 102. Dy(OTf)$_3$-Catalyzed Reactions of Indole with Imines



R^1	R^2	yield/% A	yield/% B
H	H	57	12
H	H	83	10[a]
Cl	H	63	21
Cl	Cl	60	17
Me	Cl	53	14
Me	Cl	71	8[a]
Me	OMe	47	9

[a] At 0 °C for 96 h.

Table 103. Friedel–Crafts Reaction of Phenol with α-Iminoesters



R^1	R^2	R^3	yield/%
p-MeO	Me	2,4-$Cl_2C_6H_3$	70
p-MeO	^{i}Pr	2,4-$Cl_2C_6H_3$	72
p-Ph	^{i}Pr	2,4-$Cl_2C_6H_3$	57
m-^{t}Bu	^{i}Pr	2,4-$Cl_2C_6H_3$	86
H	^{i}Pr	2,4-$Cl_2C_6H_3$	61
p-MeO	Et	4-ClC_6H_4	43
m-^{t}Bu	Et	4-FC_6H_4	65
o-Br	^{n}Bu	4-FC_6H_4	trace

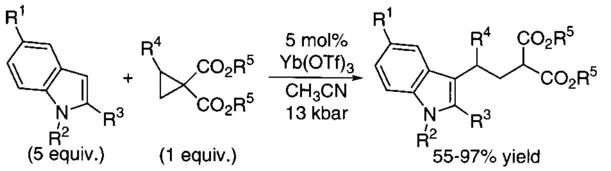
It was reported that Friedel–Crafts reaction of phenol with α-imino esters proceeded smoothly in the presence of 20 mol % of Sc(OTf)$_3$.[236] In addition, three-component reactions of phenols, glyoxylates, and amines have been achieved under similar conditions (Table 103).

The fact that the use of ultra-high-pressure facilitates Yb(OTf)$_3$-catalyzed addition of indole to α,β-saturated ketones[133] motivated the study of homologous processes, i.e., homo-Michael addition.[237] In fact, a combination of Yb(OTf)$_3$ and high pressure promoted nucleophilic ring opening of activated cyclopropanes with indoles to give homo-Michael adducts (Table 104). It was unexpected that the nucleophilic attack occurred exclusively at the more substituted carbons.

The reaction of a substituted indole with an aziridine was also mediated by a stoichiometric amount of Sc(OTf)$_3$ (Table 105).[238]

Yb(OTf)$_3$ was found to be effective for the corrole formation via condensation of a dipyrromethane and an aldehyde as well as protic acids (Table 106).[239]

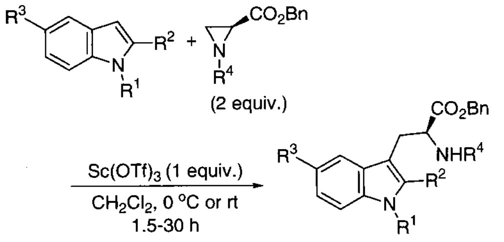
Table 104. Yb(OTf)$_3$-Catalyzed Reactions of Indoles with Activated Cyclopropanes



R^1	R^2	R^3	R^4	R^5	yield/%
H	Me	H	H	Et	75[a]
H	Me	H	Me	Me	55
H	Me	H	Ph	Et	97
H	^{i}Pr$_3$Si	H	Ph	Et	49[b]
MeO	4-$BrPhCH_2$	Me	Me	Me	79

[a] Yield based on 75% conversion. [b] Desilylation product was obtained in 27%.

Table 105. Sc(OTf)$_3$-Promoted Reactions of Indoles with Aziridines



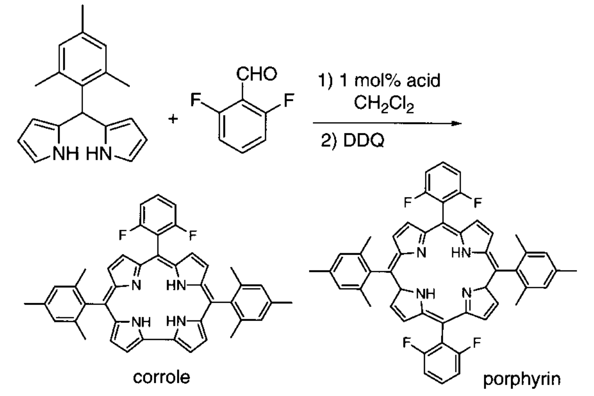
R^1	R^2	R^3	R^4	yield/%
H	H	H	Cbz	31[a]
Me	Me	H	Cbz	84
Me	Me	H	Fmoc	85
H	Me	H	Cbz	66
Me	H	H	Cbz	69
H	Me	MeO	Cbz	72
Bn	H	H	Cbz	42
H	Me	NO_2	Cbz	22

[a] 2 equiv of Sc(OTf)$_3$ was used.

2.4. Baylis–Hillman Reaction

The classical Baylis–Hillman reaction suffers from low reaction rates, especially when acrylate esters are involved as the substrates.[240] Although significant rate enhancement has been observed using high pressure,[241] water as solvent,[242] sonication,[243] or microwave irradiation,[244] these methods are often lacking of substrate generality. The rate-determining step of the Baylis–Hillman reaction is believed to be a nucleophilic attack to the aldehyde, and thus, activation of the aldehyde through coordination with a Lewis acid should accelerate the reaction.[245] However, the classical Lewis acids bind irreversibly with nucleophilic amine bases such as DABCO and shut down the catalytic cycle. By careful examination on the promotion by Lewis-acid catalysts, it was found that oxophilic scandium and lanthanide triflates accelerated the reaction (Table 107).[246] Importantly, the addition of diols such as (+)-BINOL caused a further acceleration. Although the product obtained was racemic, this observation will provide a promising basis for future development of asymmetric catalysis.

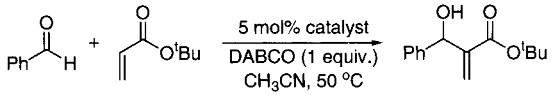
Table 106. Yb(OTf)$_3$-Catalyzed Synthesis of Corroles



acid	yield/% corrole	porphyrin
none	18	3
TFA	19	4
HOAc	8	2
BF$_3$·OEt$_2$	12	12
TfOH	13	5
Yb(OTf)$_3$[a]	18	3
K-10	18	3

[a] 0.005 mmol of the acid and 0.4 mmol of the bispyrrole were used.

Table 107. Relative Rate of Baylis–Hillman Reaction between *tert*-Butyl Acrylate and Benzaldehyde Using 100 mol % DABCO and 5 mol % Catalyst



DABCO = 1,4-diazabicyclo[2.2.2]octane

catalyst	time/h	yield/%	$k_{\rm rel}$
none	24	3.8	1
Sc(OTf)$_3$	24	11.6	3.3
Yb(OTf)$_3$	24	12.3	3.6
Gd(OTf)$_3$	24	13.2	3.9
Eu(OTf)$_3$	24	12.1	3.5
Sm(OTf)$_3$	24	16.3	4.9
La(OTf)$_3$	24	15.9	4.7
La(OTf)$_3$ + N(CH$_2$CH$_2$OH)$_3$[a]	72	74	
N(CH$_2$CH$_2$OH)$_3$[b]	72	65	
MeOH[c]	48	35	

[a] 50 mol%. [b] 80 mol%. [c] 240 mol%.

Recently, it was reported that the aza-version of the Baylis–Hillman reaction, a three-component coupling reaction of aromatic aldehydes, sulfonamides, and activated alkenes, was efficiently catalyzed by La(OTf)$_3$ and a base such as DABCO.[247]

2.5. Radical Addition

Although stereoselective acyclic radical addition has received much attention,[248] the use of Lewis acids in the reactions is rather limited due to its incompatibility with typical conditions for radical generation.[249] Until recently, Lewis acids have been used to control a population of interconverting rotamers through chelation (Scheme 59).[248] A variety of Lewis acids were evaluated by Sibi and co-workers for their ability to control acyclic diastereoselection in β-radical addition (Table 108).[250] In the absence of a Lewis acid or with a monodentate Lewis acid, the product was also formed regioselectively (no α-addition was detected) with a diastereomeric ratio of 1.3/1. Conventional Lewis acids gave β-adducts with varying yields and moderate selectivities. In some cases, significant amounts of the alkene reduction products were observed. However, maximum yields and selectivities were achieved using Ln(OTf)$_3$, and among Ln(OTf)$_3$, Yb(OTf)$_3$ provided the product with the highest diastereoselectivity, which was comparable to or better than the results obtained in the reactions under ionic conditions. For the lanthanides, the selectivity increased (from La, Sm, to Yb) with reducing ionic radius. The β-substituent in the alkene had a great influence on diastereoselectivity; cinnamate as compared to crotonate gave a better selectivity. A substoichiometric amount of Yb(OTf)$_3$ allowed radical addition to crotonate with minimal change in yield and selectivity.

Scheme 59. Conformation Control by Chelation with Lewis Acids

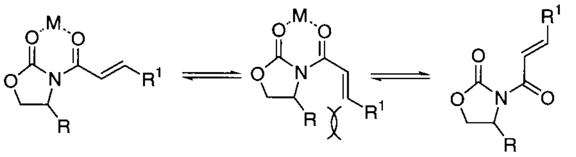
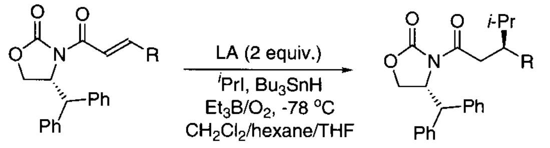


Table 108. Effect of Lewis Acids on Regio- and Diastereoselective Radical Addition to *N*-Enoyloxazolidinones

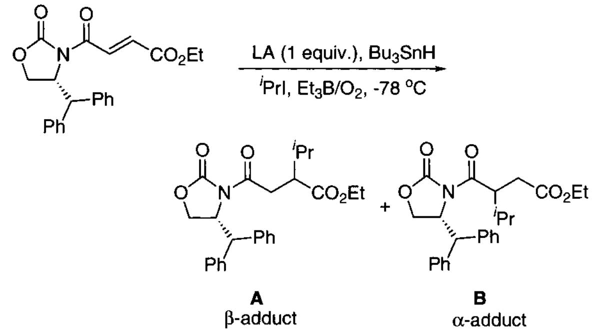


R	LA (equiv)	yield/%[a]	diastereoselectivity *RS*/*RR*
Me	none[b]	60	1.3/1
Me	BF$_3$·OEt$_2$ (2.0)[b]	80 (5)	1.3/1
Me	MgBr$_2$ (2.0)	90	6/1
Me	SnCl$_4$ (2.0)[b]	30 (60)	3/1
Me	Sc(OTf)$_3$ (2.0)	90	15/1
Me	La(OTf)$_3$ (2.0)	80	7/1
Me	Sm(OTf)$_3$ (2.0)	90	18/1
Me	Yb(OTf)$_3$ (2.0)	93	25/1
Me	Yb(OTf)$_3$(1.0)	90	25/1
Me	Yb (OTf)$_3$ (0.3)	90	20/1
Ph	MgBr$_2$ (2.0)[c]	90	20/1
Ph	ZnCl$_2$ (2.0)[c]	70	9/1
Ph	La(OTf)$_3$ (2.0)	80	12/1
Ph	Yb(OTf)$_3$ (2.0)	89	45/1

[a] Yields in parentheses are for alkene reduction product. [b] Run in CH$_2$Cl$_2$/hexane. [c] Run in CH$_2$Cl$_2$/hexane/ether.

In connection with a total synthesis of butyrolactone natural products, a highly regio- and stereoselective method for addition of radicals to a desymmetrized fumarate was reported.[251] The reaction was nonselective without using a Lewis acid, while conventional Lewis acids and Sc(OTf)$_3$ gave quite poor selectivities (Table 109). On the other hand, Ln(OTf)$_3$ gave good to excellent selectivities.

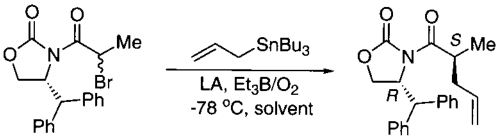
Table 109. Effect of Lewis Acids on Regio- and Diastereoselectivity of Radical Addition to a Desymmetrized Fumarate



LA	solvent	yield/%	β/α^a	dr^a (β-adduct)
none	CH_2Cl_2	92	11/1	1.6/1
$BF_3{\cdot}OEt_2$	CH_2Cl_2	86	9/1	1.2/1
$Mg(OTf)_2$	CH_2Cl_2	87	7/1	1/1
$Zn(OTf)_2$	CH_2Cl_2	88	33/1	1.6/1
$Sc(OTf)_3$	CH_2Cl_2/toluene (4/1)	95	6/1	2.1/1
$Y(OTf)_3$	CH_2Cl_2/toluene (4/1)	90	>100/1	21/1
$Sm(OTf)_3$	CH_2Cl_2/toluene (4/1)	95	>100/1	29/1
$Ho(OTf)_3$	CH_2Cl_2/toluene (4/1)	88	>100/1	13/1
$Tm(OTf)_3$	CH_2Cl_2/toluene (4/1)	92	>100/1	47/1
$Yb(OTf)_3$	CH_2Cl_2/toluene (4/1)	91	80/1	10/1
$Lu(OTf)_3$	CH_2Cl_2/toluene (4/1)	95	87/1	31/1
$Er(OTf)_3$	CH_2Cl_2/toluene (4/1)	90	>100/1	33/1

[a] Determined by 400 MHz ^{1}H NMR spectroscopy.

Table 110. Effect of Lewis Acids on ρ-Selective Radical Addition



LA (equiv)	conditions	yield/%	dr^a
none	CH_2Cl_2, 3 h	93	1/1.8
$BF_3{\cdot}OEt_2$ (2.0)	CH_2Cl_2, 2.5 h	85	1/1.4
$ZnCl_2$ (2.0)	CH_2Cl_2, 2 h	95	6/1
MgI_2 (2.0)	CH_2Cl_2, 2 h	57 (39)	≥100/1
$MgBr_2$ (2.0)	CH_2Cl_2, 2 h	94	≥100/1
$Yb(OTf)_3$ (1.0)	CH_2Cl_2/THF (1.1), 2 h	64 (14)	5/1
$Yb(OTf)_3$ (1.0)	THF, 2 h	86 (5)	5/1
$Yb(OTf)_3$ (1.0)	Et_2O, 2 h	91	16/1
$Yb(OTf)_3$ (1.0)	Et_2O, H_2O (10 equiv), 2 h	77 (3)	9/1
$Sm(OTf)_3$ (1.0)	Et_2O, 2 h	90	7/1
$Sc(OTf)_3$ (1.0)	Et_2O, 2 h	94	≥100/1

[a] Determined by 400 MHz ^{1}H NMR spectroscopy.

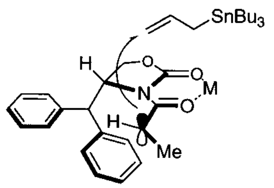
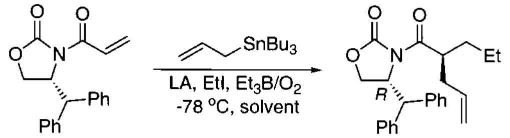


Figure 3. Working model for diastereoselective radical addition with a chelating Lewis acid.

Table 111. Diastereoselective Tandem Radical Addition with Lewis Acids



LA (equiv)	yield/%	dr^a
none	90	1/1
$BF_3{\cdot}OEt_2$ (2.0)	90	1/1.8
ZnI_2 (2.0)	85	2.2/1
$ZnCl_2$ (2.0)	90	4.1/1
$Zn(OTf)_2$ (2.0)	85	1.3/1
$MgBr_2{\cdot}OEt_2$ (2.0)	93	>100/1
$Yb(OTf)_3$ (1.0)	90	>100/1
$Sm(OTf)_3$ (1.0)	90	>100/1
$La(OTf)_3$ (1.0)	71	>100/1

[a] Determined by 400 MHz ^{1}H NMR spectroscopy.

Sibi's group extended the idea of conformational restriction using chelating Lewis acids for acyclic ρ-diastereoselective radical addition (Table 110).[252] In the absence of Lewis acids, the newly formed stereogenic center for the major diastereomer had an (*R*)-configuration. This preference was maintained in the presence of monodentate Lewis acids, while it was reversed with multidentate Lewis acids. Of the Lewis acids attempted, MgI_2, $MgBr_2$, and $Sc(OTf)_3$ resulted in the best selectivity. Among them, $Sc(OTf)_3$ was the most efficient in terms of catalyst loading. In this case, lanthanide triflates were not as efficient as $Sc(OTf)_3$. The authors proposed a working model to account for the observed stereoselectivity (Table 110). Coordination of the substrate with a Lewis acid leads to a chelated intermediate with a σ-(*Z*) orientation of the bond linked with α-substituent (Figure 3). The addition of allylic tin species will then occur from the face away from the bulky diphenylmethyl group, leading to the adduct with the observed stereochemistry. It was also reported that $Yb(OTf)_3$ was moderately effective for radical allylation of xylose-derived α-bromoacetates with allyltributyltin.[253]

It was interesting that a radical could be trapped diastereoselectively with a proper choice of chelating Lewis acids. In addition, the use of a stoichiometric amount of a chiral Lewis acid for enantioselective tandem addition processes with *N*-propenoxyl-oxazolidinone was reported. Encouraged by these results, tandem radical addition with chiral *N*-enoxyloxazolidinone was investigated (Table 111).[254] Diastereoselectivities of the reaction were generally poor without a Lewis acid or with a boron- and zinc-based Lewis acid. Lanthanide triflates were as effective as $MgBr_2$ in achieving high diastereoselectivities. It was of particular note that functionalized radical-possessing Lewis-basic sites such as methoxymethyl radical and acyl radical could also be used. With methoxymethyl radical, $Yb(OTf)_3$ gave 58/1 selectivity while $MgBr_2$ gave only 1.8/1 (Scheme 60). This result may be attributed to the higher coordinating ability of the oxophilic ytterbium(III) cation.

The classical Kharasch reaction, which results in an overall addition of alkyl halides to alkenes (an atom economy process), requires high reaction temperatures, long reaction times, and large excesses of alkyl halides to ensure good yields.[255] It was found that the reactivity of this sluggish atom-transfer process could be much improved by employing α-halo

Scheme 60. Comparison of Diastereoselective Tandem Radical Processes with $Yb(OTf)_3$ and $MgBr_2$

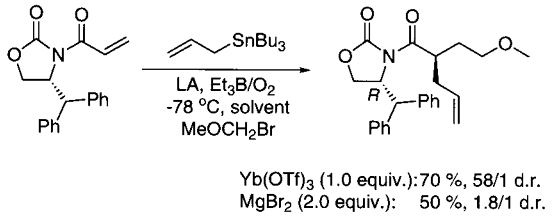
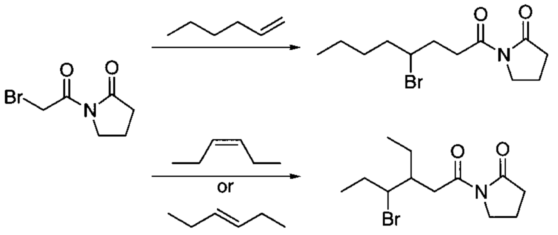


Table 112. Effect of Lewis Acids on Conversion of Bromoacetyl 2-Oxazolidinone Amide with Terminal and Internal Alkenes[a]



LA	conversion/%[b] 1-hexene	*cis*−3-hexene	*trans*−3-hexene
none	25	<10	<10
$MgBr_2$	34	<10	<10
$Mg(OTf)_2$	37	16	<10
$Zn(OTf)_2$	37	<10	<10
$Sc(OTf)_3$	86	47	23
$La(OTf)_3$	46	20	<10
$Eu(OTf)_3$	54	19	11
$Yb(OTf)_3$	100	100	63

[a] Reagents and conditions: bromide (1 equiv), alkene (5 equiv), LA (1 equiv), Et_3B (0.5 equiv), 1,2-dichloroethane, 25 °C. [b] Determined by NMR of the crude product.

esters, nitriles, or amides without Lewis acid.[256] The effect of chelating Lewis acids on atom-transfer addition of bromoacetyl 2-oxazolidinone amide to terminal and internal alkenes was reported (Table 112).[257] Poor conversion was observed with a Lewis acid. $MgBr_2$, $Zn(OTf)_2$, and $La(OTf)_3$, which were used successfully for radical additions with allyl tributylstannane, gave only slight improvement. On the other hand, $Sc(OTf)_3$ resulted in good conversion with 1-hexene, and quantitative conversions were obtained with $Yb(OTf)_3$ for addition to both 1-hexene and *cis*-3-hexene.

A secondary bromide reacts with 1-hexene in the presence of scandium or ytterbium triflate, but very low conversion resulted with *cis*- or *trans*-3-hexene. The tertiary bromide does not react with both terminal and internal alkenes under otherwise the same conditions. A diastereoselective atom-transfer reaction with 1-hexene was promoted by $Sc(OTf)_3$, and up to 92% diastereomeric excesses was obtained using a benzyl-substituted chiral oxazolidinone (Scheme 61). This result clearly showed a possibility to extend radical addition reactions with simple alkenes and a proper choice of a Lewis acid.

An intermolecular alkyl radical addition to carbon−nitrogen double bonds of oxime ethers and hydrazones was studied.[258] In a model reaction with an oxime ether, $Yb(OTf)_3$ as well as most of the traditional acid catalysts showed poor results, while 2 equiv of $BF_3{\cdot}OEt_2$ promoted the reaction in excellent yield (Table 113).

Scheme 61. Diastereoselective Radical Addition

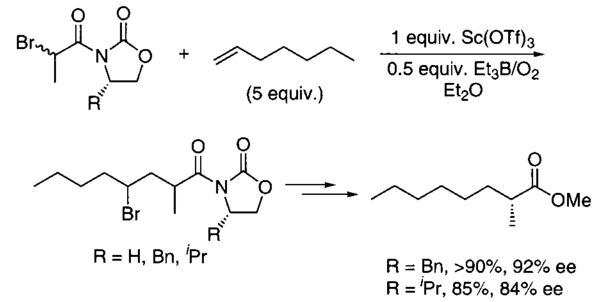
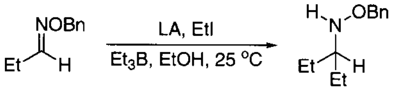


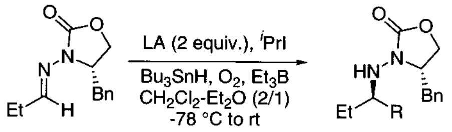
Table 113. Effect of Lewis Acids on Radical Addition to Imine[a]



LA	yield/%[b]	LA	yield/%[b]
none	0 (94)	$Zn(OTf)_2$	28 (70)
$BF_3{\cdot}OEt_2$	95	$Yb(OTf)_3$	17 (68)
Et_2AlCl	14 (78)	TFA	13 (83)

[a] LA (2 equiv), EtI (5 equiv), Et_3B (2.5 equiv), and EtOH (2.5 equiv) in CH_2Cl_2. [b] Yields in parentheses are the yields of the recovered starting material.

Table 114. Radical Addition of Alkyliodides to Hydrazones



catalyst	yield/%	product ratio R = ^{i}Pr	Et	H
none	NR			
$BF_3{\cdot}OEt_2$	0	0	0	100
$MgBr_2$	NR			
$Yb(OTf)_3$	32	96	4	0
$InCl_3$	55	92	8	0
$ZnCl_2$	60	91	9	0
$Zn(OTf)_2$	53	93	7	0

Radical additions of hydrazones took place using $Yb(OTf)_3$ as a catalyst to afford the corresponding adducts in moderate yield (Table 114).[259]

$Yb(OTf)_3$-promoted diastereoselective radical cyclization was investigated. The cyclization of a chiral bromoenoate in the presence of 2 equiv of $Yb(OTf)_3$ proceeded to give the corresponding cyclic compound in good yield with low selectivity (Scheme 62).[260]

A highly diastereoselective radical cyclization method has been developed for construction of a tricyclic intermediate in formal synthesis of a natural product.[261] The $Mn(OAc)_3$-mediated oxidative radical cyclization reaction has been applied to construction of polycyclic ring systems, and this reaction was much accelerated in the presence of $Ln(OTf)_3$ to give the products in higher yields and better diastereoselectivities. When a stoichiometric amount of $Yb(OTf)_3$ was employed, the cyclization reaction of

Scheme 62. Diastereoselective Radical Cyclization of a Chiral Enoate

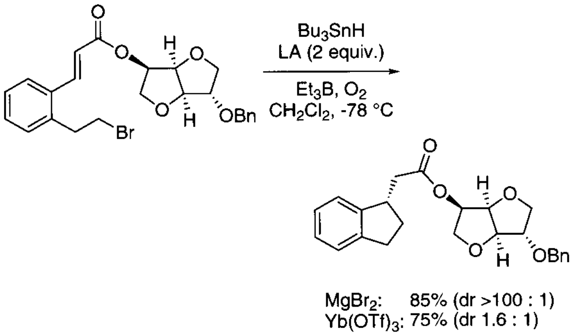
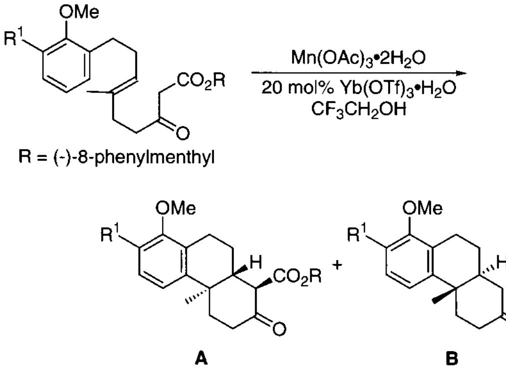


Table 115. Diastereoselective Radical Cyclization Promoted by Yb(OTf)$_3$



R^1	catalyst (equiv)	yield/%	**A/B**
^{i}Pr	Yb(OTf)$_3$·H$_2$O (1.0)	77	38/1
^{i}Pr	Yb(OTf)$_3$·H$_2$O (0.2)	71	26/1
H	Yb(OTf)$_3$·H$_2$O (0.2)	66	36/1
^{i}Pr	Sm(OTf)$_3$ (0.2)	73	28/1
^{i}Pr	Pr(OTf)$_3$ (0.2)	76	24/1
^{i}Pr	Eu(OTf)$_3$ (0.2)	68	26/1
H	Er(OTf)$_3$ (0.2)	67	27/1

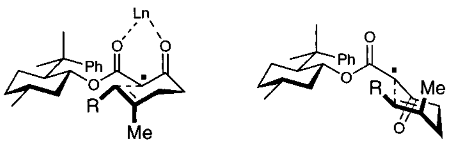
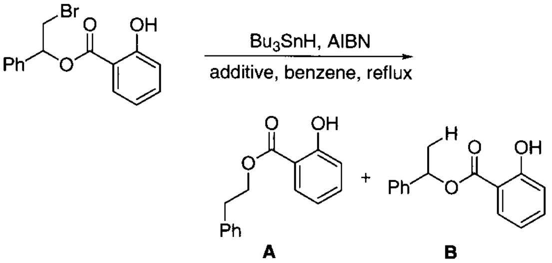


Figure 4. Conformational restriction of radical rotamers by chelation with Ln(OTf)$_3$; a highly diastereoselective radical cyclization.

isopropyl-substituted ester afforded *trans* products with a diastereomeric ratio of 1/38 (Table 115). The use of a catalytic amount (20 mol %) of Yb(OTf)$_3$ gave the product in a similar yield but with a declined selectivity. However, improved selectivity was observed by using the ester (R^1 = H). Similar selectivities were obtained when other Ln(OTf)$_3$ were employed. The resulting stereoselectivity was attributed to bidentate chelation of the β-ketoester to oxophilic Ln(OTf)$_3$, which fixed the two carbonyl groups in a *syn*-orientation. The chiral auxiliary then blocked the *si* face of the radical and thus allowed the cyclization to occur from the *re* face (Figure 4).

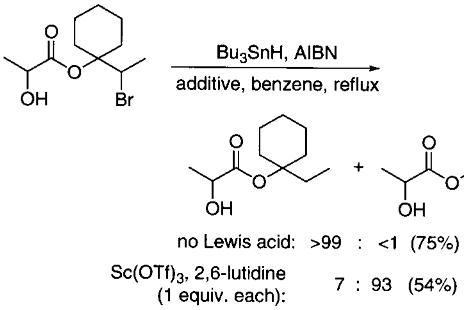
Table 116. Radical 1,2-Acyloxy Shift Promoted by a Lewis Acid



	procedure A^a		procedure B^b	
additive	yield/%	**A/B**	yield/%	**A/B**
none	88	3/97	78	25/75
MeAl(O-*p*-Tol)$_2$	68	38/62	73	88/12
La(OTf)$_3$, Et$_3$N	78	9/91		
Sc(OTf)$_3$, Et$_3$N	75	25/75		
Sc(OTf)$_3$, 2,6-lutidine	71 (86)	33/67 (2/98)	76	83/17

^{a} 0.02 M in Bu$_3$SnH. ^{b} Bu$_3$SnH was added over 12 h with a syringe pump.

Scheme 63. Lewis-Acid-Promoted Radical 1,2-Acyloxy Shift of a Lactate Derivative



1,2-Acyloxy shift of β-(acyloxy)alkyl radicals, so-called Surzur–Tanner rearrangement,[262] has been used as an efficient method for making 2-deoxy sugars.[263] However, the rate of the rearrangement of many β-(acyloxy)alkyl radicals is too slow to allow synthetic utilities. A recent computational investigation has shown that the rate of the rearrangement could be accelerated by a protic acid.[264] This theoretical argument was later verified experimentally.[265] In the absence of a Lewis acid, the product of direct reduction was formed as a major product, while slow addition of Bu$_3$SnH improved the amount of the rearranged product (Table 116). Complexation of the substrate with an aluminum-based Lewis acid has proven to enhance the rate of the rearrangement; methylation of the phenolic hydroxyl group fully inhibited the effect of the Lewis acid. Among the RE(OTf)$_3$ tested, Sc(OTf)$_3$ was again found to be an effective promoter of the rearrangement, and by using a combination with 2,6-lutidine and slow addition of Bu$_3$SnH, the yield of the rearranged product was much improved. An even greater increase in the rearrangement rate was observed in a lactate-derived bromide (Scheme 63).

2.6. Heterocycle Synthesis

The first utilization of Ln(OTf)$_3$ in organic synthesis was reported by Forsberg and co-workers in amidine synthesis. In the presence of a catalytic amount of Ln(OTf)$_3$, amines reacted with nitriles to give a variety of products including *N*,*N*′-disubsti-

Scheme 64. Yb(OTf)$_3$-Catalyzed Syntheses of *N,N′*-Disubstituted Amidines and Triazines

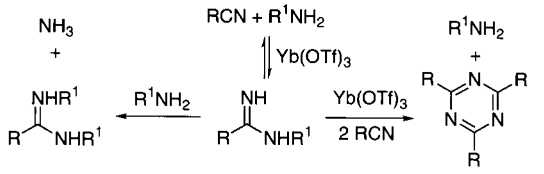
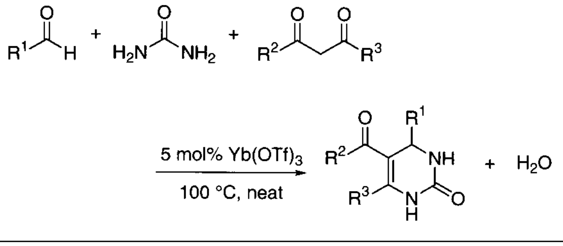


Table 117. Yb(OTf)$_3$-Catalyzed Biginelli Reaction



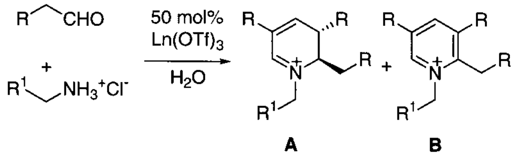
R^1	R^2	R^3	yield/%	R^1	R^2	R^3	yield/%
Ph	EtO	Me	98	^{n}Bu	EtO	Me	87
p-MeOC$_6$H$_4$	EtO	Me	96	^{i}Pr	EtO	Me	83
p-NO$_2$C$_6$H$_4$	EtO	Me	94	Ph	Me	Me	94
p-ClC$_6$H$_4$	EtO	Me	97	p-MeOC$_6$H$_4$	Me	Me	91
2,4-Cl$_2$C$_6$H$_4$	EtO	Me	89	p-NO$_2$C$_6$H$_4$	Me	Me	90
PhCH=CH	EtO	Me	81	Ph	Ph	CF$_3$	96

tuted amidines and triazines depending on the molar ratios of the amines to the nitriles (Scheme 64).[5] Excess amines favored formation of *N,N′*-disubstituted amidines, while excess nitriles gave predominantly triazines. It was reported that the reactions had to be carried out under strictly anhydrous conditions. The authors showed that the catalytic activities of Ln^{3+} ions depended on their effective ionic potential (or effective nuclear charge) and that higher turnover rates were observed for smaller ions (Ho^{3+} to Lu^{3+}) than for larger ions (La^{3+} to Sm^{3+}). The results highlighted the ability of a Ln^{3+} ion to activate nitriles in the presence of a strongly coordinating *N*-donor ligand (an amine).

Multiple component condensations (MCCs), such as Ugi,[266] Passerini,[267] and Bidinelli[268] reactions, etc.,[269] are particular attractive for parallel synthesis of large arrays (libraries) of small-molecule compounds used for evaluation of biological activities.

The Biginelli reactions proceeded in the presence of a catalytic amount of Ln(OTf)$_3$ to give the corresponding compounds in high yields. The Biginelli reaction, first described more than a century ago, is a one-pot but low yielding (20−50%) condensation of 1,3-dicarbonyl compounds with aldehydes and urea or thiourea in the presence of a catalytic amount of an acid.[270] Among the rare-earth metal triflates [La(OTf)$_3$, Sc(OTf)$_3$, Yb(OTf)$_3$], Yb(OTf)$_3$ was particularly effective for this transformation (Table 117).[271]

Table 119. Ln(OTf)$_3$-Catalyzed Synthesis of 2,3-Dihydropyridinium and Pyridinium Derivatives in Water



R	R^1	Ln	yield/%	A/B
Et	Ph	Dy	31	100/0
Pr	Ph	Pr	56	100/0
^{i}Bu	Ph	Pr	61	90/10
^{n}Pent	Ph	Pr	82	76/24
^{n}Pent	Et	Pr	51	72/28
PhCH$_2$	Ph	Yb	75	0/100

Recently, the preparation of a dihydropyrimidine library via microwave-assisted Biginelli three-component condensation was investigated. Yb(OTf)$_3$ as a catalyst in AcOH/EtOH (3/1) proved to be successful, leading to an average isolated yield of 52% of dihydropyrimidines with >90% purity.[272]

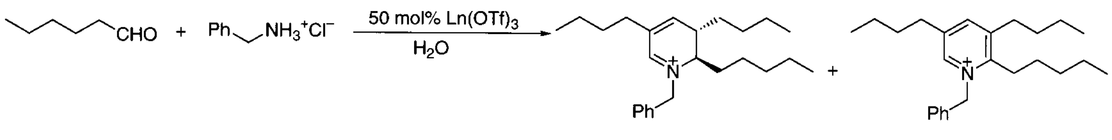
2,3-Dihydropyridines[273] are generally prepared either by nucleophilic addition of organometallic reagents or metal hydrides to pyridines or by cyclization of acyclic materials. In nucleophilic addition, a mixture of 1,4- and 2,3-dihydropyridines is obtained, and few general methods for the preparation from acyclic precursors have been reported in the literature.[274] It was found that Ln(OTf)$_3$ promoted reactions of aldehydes and amine hydrochlorides in water to provide the corresponding 2,3-dihydropyridinium and pyridinium derivatives.[275] In a model reaction, La and Pr triflates showed high activities and the product ratios of 2,3-dihydropyridinium to pyridinium were almost independent of Ln(OTf)$_3$ used (Table 118). Other aldehydes and amine hydrochlorides gave the desired products in good yields, and the product ratio was dependent on the aldehydes and the amines employed (Table 119).

Recently, pyridine formation from enamino esters and alkynones (Bohlamm−Rahtz heteroannulation) was found to be effectively catalyzed by Yb(OTf)$_3$ or ZnBr$_2$.[276]

Sm(OTf)$_3$ and Sc(OTf)$_3$ were used to promote the condensation of butylamine, propionaldehyde, and nitroethane to give the substituted pyrrole.[277] Their catalytic efficiencies were inferior to samarium(III) chloride and samarium(II) iodide but were comparable to classical Lewis acids such as AlCl$_3$ and TiCl$_4$. In the absence of a Lewis acid, no reaction took place (Table 120).

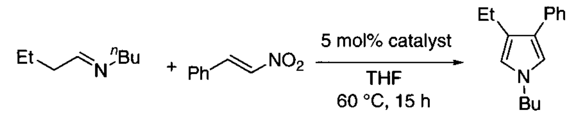
Blackburn and his group reported a new Sc(OTf)$_3$-catalyzed three-component condensation (3CC) reac-

Table 118. Synthesis of 2,3-Dihydropyridinium and Pyridinium Derivatives with Different Ln(OTf)$_3$



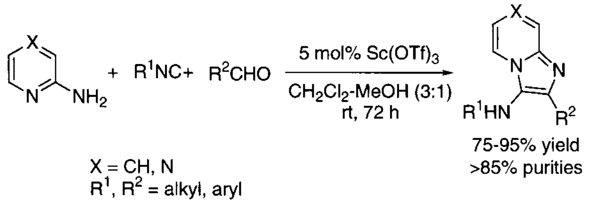
Ln(OTf)$_3$	La	Pr	Nd	Gd	Dy	Er	Yb
yield/% (**A**/**B**)	73 (3.1)	82 (3.2)	74 (3.2)	57 (3.1)	38 (3.2)	64 (3.1)	56 (3.1)

Table 120. Lewis Acid-Promoted Synthesis of a Substituted Pyrrole

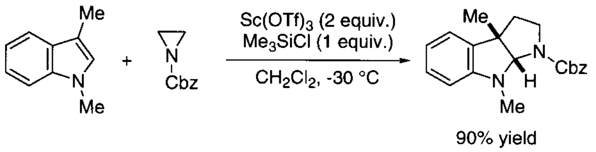


catalyst	yield/%	catalyst	yield/%
$Sm(O^iPr)_3$	63	$Sm(OTf)_3$	7
$Cp^*Sm(thf)_2$	45	$Yb(O^iPr)_3$	58
SmI_2	20	$La(O^iPr)_3$	45
$SmCl_3$	12		

Scheme 65. Sc(OTf)$_3$-Catalyzed Three-Component Condensation



Scheme 66. Alkylative Cyclization of 1,3-Dimethylindole



tion between 2-aminopyridine or 2-aminopyrazine, an aldehyde, and an isonitrile to afford 3-aminoimidazo-[1,2-*a*]pyridines or pyrazines (Scheme 65).[278] The reaction was proposed to follow the initial stage of the Ugi reaction with the in situ generated imine attacked by an isonitrile to form a nitrilium ion, which was then cyclized (instead of being attacked by a carboxylic acid in Ugi reaction). This three-component condensation was applied to the solid-phase synthesis with any of the three reacting partners tethered to an amide resin.[279]

It was reported that the alkylative cyclization of 1,3-dimethylindole with *N*-Cbz-aziridine proceeded in the presence of Sc(OTf)$_3$ and Me$_3$SiCl to give the corresponding cyclic compound in 90% yield (Scheme 66).[280]

Recently, it was found that phenyl aziridines undergo 1,3-dipolar cycloaddition efficiently with olefins such as cyclic enol ethers and trimethylsilane in the presence of Sc(OTf)$_3$ at ambient temperature to afford the corresponding pyrrolidine derivatives in high yields with high regioselectivity.[281]

D-Glucal undergoes sequences of rearrangement and dehydration reactions catalyzed by mercuric ion in aqueous sulfuric acid to yield 2-(D-glycero-1,2-dihydroxyethyl) furan.[282] However, this transformation required highly toxic metal and acidic conditions. Yb(OTf)$_3$ and Sm(OTf)$_3$ were found to promote the same reaction under milder conditions (Scheme 67).[283] The product is a versatile chiral synthon for further transformations.

Scheme 67. Ln(OTf)$_3$-Catalyzed Transformation of D-Glucal to Chiral Furan Diol

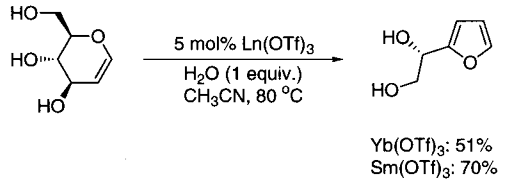
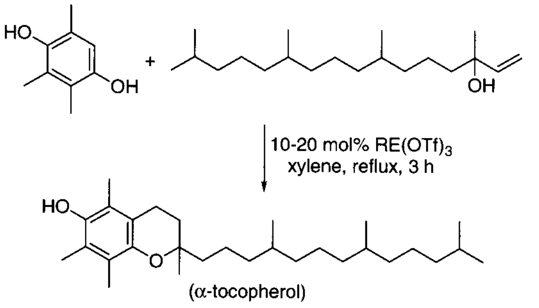


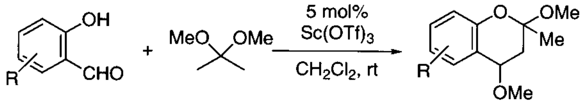
Table 121. Efficiency of RE(OTf)$_3$ in Synthesis of α-Tocopherol



RE (mol %)	yield/%	RE (mol %)	yield/%
Sc (20)	88 (98)[a]	Dy (10)	47
Y (20)	42	Ho (10)	63
La (20)	<1	Er (10)	33
Pr (10)	32	Tm (10)	<1
Sm (10)	<1	Yb (20)	59
Eu (20)	84	Lu (10)	59
Gd (10)	<1		

[a] The yield of the reactions performed in toluene.

Table 122. Sc(OTf)$_3$-Catalyzed Formation of 2,4-Dimethoxy-2-methylbenzopyrans



R	time/min	yield/%	R	time/min	yield/%
H	20	92	4-^{i}Pr	25	88
3-MeO	25	93	3,4-(MeO)$_2$	30	90
3-EtO	20	95	4-Cl	40	86
4-Me	30	90	4-Br	45	85

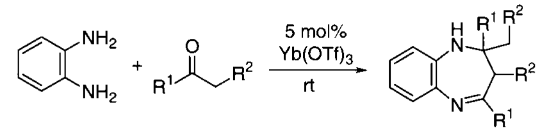
α-Tocopherol was prepared by ZnCl$_2$-catalyzed condensation of trimethylhydroquinone and isophytol.[284] A stoichiometric amount of the Lewis acid was required for the reaction because of the deactivation of the catalyst by water produced. Therefore, water-tolerant rare-earth metal triflates were examined in this reaction, and their efficiencies are summarized in Table 121. Sc(OTf)$_3$ was the most effective, whereas other Ln(OTf)$_3$ gave lower yields.[285]

It was reported that Sc(OTf)$_3$ catalyzed an unusual cyclocondensation of *o*-hydroxybenzaldehydes with 2,2-dimethoxypropane to afford a class of 2,4-dimethoxy-2-methylbenzopyrans in high yields (Table 122).[286]

2,3-Dihydro-1*H*-1,5-benzodiazepines have been synthesized in very good yields in solvent-free conditions from *o*-phenylendiamine and ketones in the presence of Yb(OTf)$_3$ as catalyst (Table 123).[287]

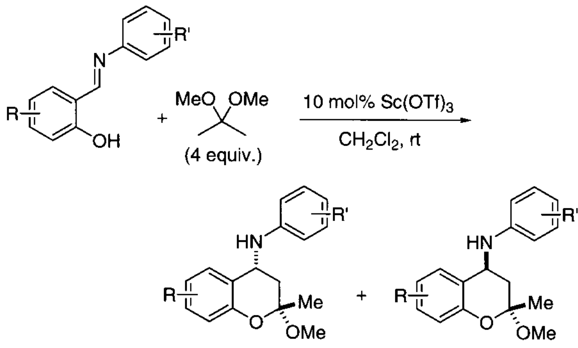
Meanwhile, 2,3-dihydro-4-amino-2*H*-1-benzopyrans have been synthesized from salicylaldehyde−Schiff's bases and 2,2-dimethoxypropane in the presence of Sc(OTf)$_3$ or BF$_3$·OEt$_2$ as catalyst (Table 124).[288]

Table 123. Yb(OTf)$_3$-Catalyzed Formation 2,3-Dihydro-1*H*-1,5-benzodiazepines from *o*-Phenylendiamine and Ketones



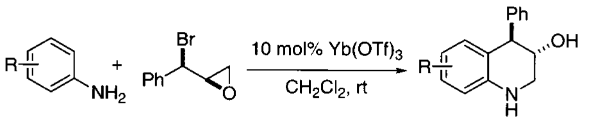
R^1, R^2	yield/%
Me, H	96
Ph, H	99
Et, Me	95
Me, Me	93
Me$_2$C=CH(CH$_2$)$_2$, H	99
−(CH$_2$)$_3$−	99
−(CH$_2$)$_4$−	89
−(CH$_2$)$_5$−	88

Table 124. Sc(OTf)$_3$-Catalyzed Synthesis of 3,4-Dihydro-4-amino-2*H*-1-benzopyranes



R	R′	time/h	yield/%	R	R′	time/h	yield/%
H	H	3.0	88	H	4-CN	7.5	45
H	4-Cl	4.5	86	3-EtO	4-Me	4.5	84
5-Cl	H	6.0	87	3-EtO	4-Cl	5.0	85
H	4-MeO	3.0	89	3-MeO	4-Me	3.5	89
3-EtO	H	4.5	84	3-MeO	4-Me	5.5	80
3-OMe	H	4.0	81	5-Cl	4-Cl	7.0	74
H	4-Me	3.5	83	5-Cl	4-Me	5.0	83

Table 125. Yb(OTf)$_3$-Catalyzed Quinoline Formation



aniline R	temp/°C, time/h	product R	yield/%
H	rt, 0.5	H	43
o-MeO	rt, 12	8-MeO	61
m-MeO	rt, 1	7-MeO	15
		5-MeO	48
p-MeO	rt, l	6-MeO	42
o-Me	rt, 1	8-Me	51
m-Me	rt, 1	7-Me	14
		5-Me	29
p-Me	rt, 1	6-Me	56
2-MeO-5-Me	rt, 1	8-MeO-5-Me	47
2-MeO-5-Cl	rt, 1	8-MeO-5-Cl	49

Yb(OTf)$_3$ was found to be effective as a catalyst for the quinoline formation from aromatic amines with (2*R**,1′*R**)-2-(α-bromobenzyl)oxiranes (Table 125).[289] The tandem ring-opening reaction of the oxirane/ring closure via intramolecular Friedel−Crafts alkylation proceeded stereoselectively. The second step is suggested to proceed with inversion at the benzyl carbon.

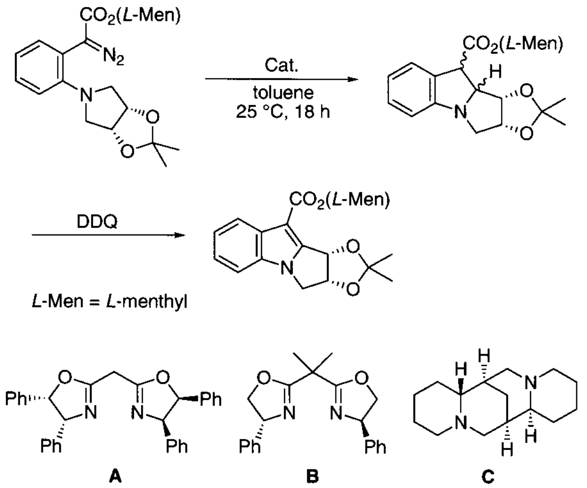
Recently, an efficient synthesis of pyranoquinolinones was achieved by ytterbium triflate-catalyzed reaction of 4-hydroxy-2-quinolones with a variety of α,β-unsaturated aldehydes in moderate yields.[290] This new method has been applied to the synthesis of pyranoquinolinone alkaloids.

2.7. Diazocarbonyl Insertion

The diazocarbonyl insertion reactions have been used for the synthesis of α-heteroatom-substituted carbonyl compounds.[291] The traditional protocols employed $Rh_2(OAc)_2$ and $RuCl_2(PPh_3)_3$ as catalysts to promote the reactions of diazoketones or diazoesters with alcohols, thiols, or amines.[292] A high-throughput catalyst screening for the C−H insertion reaction was investigated (Table 126).[293,294] The best stereoselectivity was found with a typical copper catalyst. Surprisingly, comparable yields and diastereoselectivities were observed when Sc(OTf)$_3$ was used. Less satisfactory results were obtained by using La(OTf)$_3$ and Yb(OTf)$_3$.

It has been demonstrated that the product distribution resulting from Rh(II)-catalyzed decomposition of α-diazoimide can be controlled by proper choice of catalysts and solvents.[295] In the reaction of *N*-phenylmaleimide as a dipolarophile, an epoxide was formed exclusively via attack of rhodium carbenoid on the ester carbonyl in nonpolar solvents, such as PhH, $CHCl_3$, and pentane (Table 127). On the other hand, the *exo*-cycloadduct was obtained as a sole product via [3+2]-cycloaddition of the intermediate dipolar resulting from the attack of the rhodium

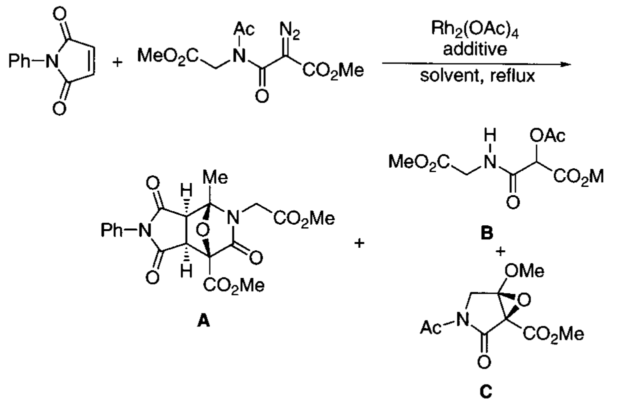
Table 126. Metal-Catalyzed C−H Insertion Reaction[a]



metal salt	ligand	yield/%	dr
Sc(OTf)$_3$	**A**	36	1.6/1
La(OTf)$_3$	**A**	19	1/1.3
Yb(OTf)$_3$	**A**	0.40	1/1.4
CuOTf·PhH	**A**	47	1.7/1
Sc(OTf)$_3$	**B**	43	1/1.5
CuOTf·PhH	**B**	21	1/1.3
Sc(OTf)$_3$	**C**	34	1/1.1
CuOTf·PhH	**C**	44	1.3/1

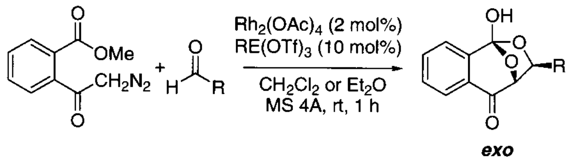
[a] The reactions were performed with 10 mol % each of metal salt and ligand in PhMe.

Table 127. Site Selectivity in Rh(II)-Catalyzed Reaction of α-Diazoimides



additive (mol %)	solvent	A	B	C
none	PhH	0	0	90
none	$CHCl_3$	0	0	90
none	Pentane	0	0	50
none	$MeNO_2$	90	0	0
none	MeCN	50	0	0
$Sc(OTf)_3$ (10)	PhH	38	26	0

Table 128. 1,3-Dipolar Cycloaddition Reactions of *o*-(Methoxycarbonyl)-α-diazoacetophenone with Aldehydes

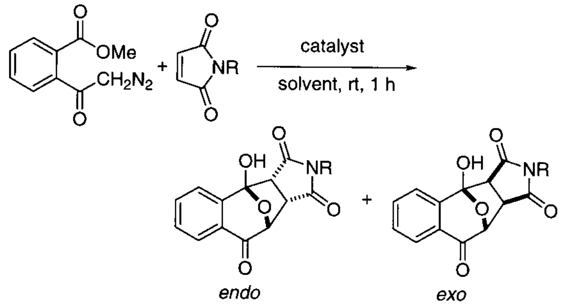


R	RE	solvent	yield/%	*exo*/*endo*
Ph		CH_2Cl_2	83	50/50
	Sc		82	69/31
	Yb		96	90/10
	Lu		quant.	89/11
	Tm		96	87/13
	Ho		93	83/17
	Eu		99	73/27
	Sm		91	70/30
	La		87	55/45
Ph	Yb	Et_2O	89	97/3
p-MeOPh	Yb	Et_2O	77	87/13
p-NO_2Ph	–	CH_2Cl_2	93	27/75
p-NO_2Ph	Yb	Et_2O	99	82/18
^{n}Pr	Yb	CH_2Cl_2	89	45/55
^{i}Pr	Yb	CH_2Cl_2	65	34/66
^{c}Hex	Yb	CH_2Cl_2	95	69/31
$PhCH_2OCH_2$	Yb	CH_2Cl_2	97	93/7

carbenoid on the acetyl group in polar solvents including CH_3NO_2 and CH_3CN. Addition of a catalytic amount of $Sc(OTf)_3$ to the reaction mixture in refluxing benzene modified the selectivity and gave the *exo*-cycloadduct and the acetate inserted product. Other Lewis-acid additives such as $MgBr_2$ and $ZnCl_2$ caused side reactions of the starting material and/or the reaction product.

1,3-Dipolar cycloaddtion reactions of *o*-(methoxycarbonyl)-α-diazoacetophenone with aldehydes proceeded in the presence of $Rh(OAc)_2$ and $Yb(OTf)_3$ to give the adducts in good yields with high diastereoselectivities (Table 128).[296]

Table 129. Metal-Catalyzed Decomposition of *o*-(Methoxycarbonyl)-α-diazoacetophenone in the Presence of *N*-Methylmaleimide



R	catalyst (mol%)	solvent	yield/%	*endo*/*exo*
Me	CuOTf (5)	benzene^b	49	87/13
	CuCl (5)	benzene^b	81	26/74
	CuCl (5), $Yb(OTf)_3$ (5)	benzene^b	52	94/6
	$Cu(OTf)_2$ (5)	benzene^b	24	82/18
	$Cu(acac)_2$ (5)	benzene^b	66	24/76
	$Rh_2(OAc)_4$ (5)	benzene^b	70	11/89
	$Rh_2(OAc)_4$ (5), Yb $(OTf)_3$ (5)	benzene^b	64	61/39
	$Rh_2(OAc)_4$ (2), Yb $(OTf)_3$ (10)	benzene	98	93/3
	$Rh_2(OAc)_4$ (2), Yb $(OTf)_3$ (10)	CH_2Cl_2	quant.	95/5
	Yb $(OTf)_3$ (10)	CH_2Cl_2	36	98/2
	Yb $(OTf)_3$ (10)	CH_2Cl_2	60	77/23
Et	$Rh_2(OAc)_4$ (2), Yb $(OTf)_3$ (10)	CH_2Cl_2	76	95/5
	$Rh_2(QAc)_4$ (2), Yb $(QTf)_3$ (10)^a	CH_2Cl_2	80	90/10
Ph	$Rh_2(OAc)_4$ (2), Yb $(OTf)_3$ (10)	CH_2Cl_2	57	54/46
	$Rh_2(OAc)_4$ (2), Yb $(OTf)_3$ (10)	Et_2O	10	92/8
	$Rh_2(OAc)_4$ (2), Yb $(OTf)_3$ (10)^a	Et_2O	89	78/22
	$Rh_2(OAc)_4$ (2), Yb $(OTf)_3$ (10)	CH_2Cl_2	50	84/16
	$Rh_2(OAc)_4$ (2), Yb $(OTf)_3$ (10)^a	CH_2Cl_2	82	49/51

[a] In the presence of 4A MS. [b] Under refluxing.

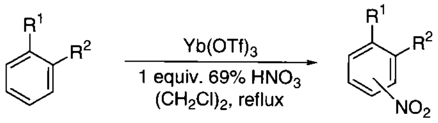
A combination of CuCl and $Yb(OTf)_3$ catalyzed a reaction of *o*-(methoxycarbonyl)-α-diazoacetophenone with *N*-methylmaleimide to give the 1,3-dipolar cycloaddition product in high *endo*-selectivity (Table 129).[297] It was of particular note that CuCl alone favored formation of the *exo*-adduct, which was a dominant product in a typical Rh(II)-catalyzed process.

3. C–X (X = N, O, P, Etc.) Bond Formation

3.1. Aromatic Nitration and Sulfonylation

Aromatic nitrates are versatile building blocks in pharmaceutical, dye, plastics, and perfumes industries, and conventionally their preparation involves using mixtures of concentrated HNO_3 and H_2SO_4.[298] Like Friedel–Crafts reactions, disposal of acidic wastes after the reaction is problematic. Recently, it was reported a catalytic aromatic nitration using $Yb(OTf)_3$ as a catalyst and 1 equiv of commercially available 69% HNO_3 reacted cleanly with electron-rich arenes in refluxing dichloroethane to give the corresponding nitrates in good to excellent yields (Table 130).[299] The effect of $RE(OTf)_3$ on nitration of *m*-xylene is summarized in Table 131. Moderate electron-deficient 2-nitrotoluene was nitrated in the presence of a stoichiometric amount of $Yb(OTf)_3$.[300] The catalytic efficiency of $Ln(OTf)_3$ for aromatic nitration of bromobenzene was quantified according to tripositive lanthanides,[301] and as in many other similar studies, an inverse correlation between them

Table 130. Catalytic Aromatic Nitration Using $Yb(OTf)_3$



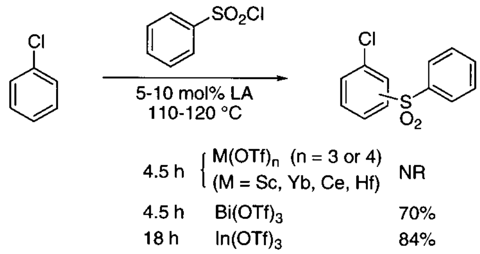
R^1	R^2	time/h	yield/%	isomeric ratio
Me	H	12	>95	*o*/*m*/*p* (52/7/41)
Me	NO_2	14	88	2,4-DNT/2,6-DNT (65/35)
Br	H	6	62	*o*/*p* (40/60)

Table 131. Effect of Catalysts on Nitration of *m*-Xylene[a]

catalyst (mol %)	HNO_3 (equiv)	time/ h	conversion/ %	(4-NO_2/ 2-NO_2)
$Sc(OTf)_3$ (10)	69% (1.0)	12	85	85/15
$La(OTf)_3$ (10)	69% (1.0)	12	22	86/14
$Eu(OTf)_3$ (10)	69% (1.0)	12	36	86/14
$Pr(OTf)_3$ (10)	69% (1.0)	12	65	88/12
$Yb(OTf)_3$ (10)	69% (1.0)	12	88	85/15
TfOH (420)	100% (2.1)	1	n.r.[c]	62/37[d]

[a] The reactions were performed in refluxing dichloroethane unless otherwise stated. [b] The reaction was performed in CH_2Cl_2 at 25 °C. [c] Not reported. [d] About 1% of other isomers.

Scheme 68. Sulfonylation of Toluene under Microwaves



was reported. By extrapolation, it is not unexpected that trivalent $Sc(OTf)_3$ and tetravalent $Hf(OTf)_4$ showed superior activity over $Ln(OTf)_3$.[300,301]

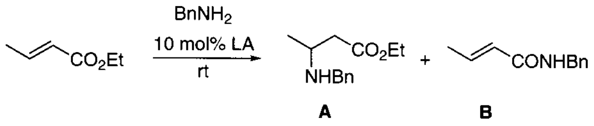
It has been shown that $Yb(OTf)_3$ increases the Brønsted acidity of an acidic reagent.[226,299,302] It was argued that binding of Yb^{3+} to acidic ligands such as HNO_3[299] and HOAc[302] would form the corresponding chelates, which are stronger Brønsted acids. These chelates may undergo equilibrium loss of triflic acid (TfOH), a very efficient catalyst used in some organic transformations. The isomer distribution in the electrophilic aromatic nitration supports the Brønsted-acid-catalyzed mechanism rather than the Lewis-acid-catalyzed one.[299] Other related reaction systems such as $Yb(Fod)_3-HOAc$[303] and $Yb(OTf)_3-PhCO_2H$[83] have been reported recently.

It was reported that RE (Sc, Yb, Ce) triflates were ineffective for aromatic sulfonylation using benzenesulfonyl chloride whereas $Bi(OTf)_3$ and $In(OTf)_3$ are efficient catalysts (Scheme 68).[304]

3.2. Michael Reaction

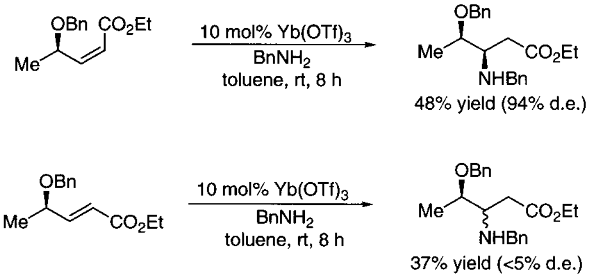
The conjugate addition of amines to α,*β*-unsaturated esters requires drastic conditions,[305] such as high temperature and/or high pressure, and is extremely sensitive to steric hindrance imposed by the substrates.[306] The efficiency of different Lewis-acid catalysts in the conjugate addition of benzylamine to ethyl crotonate was examined (Table 132).[307] In the absence of a catalyst or using a classical Lewis acid like $BF_3 \cdot OEt_2$, no conjugate adduct was detected. The reaction using $TiCl_4$ gave a low yield of the adduct accompanied by formation of *N*-benzylamide. On the other hand, $Ln(OTf)_3$ gave an excellent yield with a wide range of solvents including CH_2Cl_2, THF, ethanol, and toluene. Notably, $YbCl_3$ was less efficient for the reaction, resulting in low yield and formation of *N*-benzylamide.

Table 132. Efficacy of Lewis Acids in Michael Addition of Benzylamine to Ethyl Crotonate



LA (mol %)	solvent	time/h	yield/% **A**/**B**
none	CH_2Cl_2	12	0/0
$BF_3 \cdot OEt_2$	CH_2Cl_2	12	0/0
$TiCl_4$	CH_2Cl_2	4.5	28/26
$La(OTf)_3$	CH_2Cl_2	6	95/0
$Sm(OTf)_3$	CH_2Cl_2	6	95/0
$Yb(OTf)_3$	CH_2Cl_2	2.5	92/0
$Yb(OTf)_3$	THF	6	97/0
$Yb(OTf)_3$	EtOH	6	95/0
$Yb(OTf)_3$	PhMe	6	92/0
$YbCl_3$	THF	17	28/26

Scheme 69. $Yb(OTf)_3$-Catalyzed Diastereoselective Conjugate Addition of an Amine

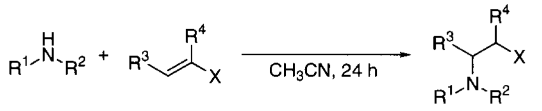


The diastereoselectivities in the $Yb(OTf)_3$-catalyzed reactions with chiral α,*β*-unsaturated esters were dependent on the geometry of the olefins (Scheme 69).[307] The *syn*-product was produced in high selectivity with the (*Z*)-isomer, whereas poor selectivity was resulted from the (*E*)-isomer.

It was disclosed that an independent study on the effect of Lewis acids and organic bases for conjugate addition of amines.[308] Also in this case, $Yb(OTf)_3$ was quite effective to promote the addition of isopropylamine to methyl crotonate, whereas other Lewis acids, such as $LiClO_4$ and $Eu(fod)_3$, or organic bases were not suitable. Surprisingly, $ZrCl_4$ was a potent catalyst, despite that its amine complexes were active catalysts for polymerization.

Meanwhile, a comprehensive study on the effects of pressure, catalyst, water, and their combinations was investigated in conjugate addition of amines to α,*β*-unsaturated ethylenic compounds.[309] Multiactivation by pressure and $Yb(OTf)_3$ was important in promoting the reactions; otherwise low reactivity resulted (Table 133). A comparison was made between the pressure effect and hydrophobic effect on

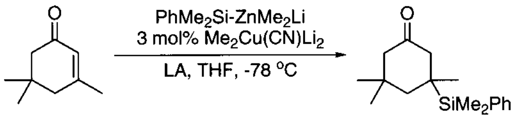
Table 133. Yb(OTf)$_3$-Catalyzed Conjugate Addition of Amines under High Pressure



amine	acrylic compound			temp/	yield/%		
R^1, R^2	R^3	R^4	X	°C	no cat.[a]	Yb(OTf)$_3$[b]	H_2O[c]
^{i}Pr, Me	H	H	CO_2Me	50	13	80 (17)[d]	0
^{i}Bu, ^{i}Bu	H	H	CN	30	11	91 (20)	40
^{i}Pr, ^{i}Pr	H	H	CN	50	8	95 (2)	69
Ph_2CH, H	H	H	CN	50	5	51 (6)	28
-$(CH_2)_5$-	H	Me	CN	20	19	36 (5)	100
-$(CH_2)_5$-	Me	H	CN	20	15	86 (18)	95
-$(CH_2)_5$-	H	Me	$CONH_2$	20	2	65 (17)	70

[a] The reactions were performed at 300 MPa pressure without a catalyst. [b] The reactions were performed at 300 MPa pressure with 2 mol % of Yb(OTf)$_3$. [c] The reaction was performed in water at ambient (0.1 MPa) pressure. [d] Yields in parentheses were for the reactions performed at ambient pressure.

Table 134. Effect of Lewis Acids on Rates of Conjugate Addition Reaction with Silylzincate/Cuprate



LA (mol %)	time	yield/%
Sc(OTf)$_3$ (5)	5 min	81
Yb(OTf)$_3$ (5)	15 min	82
BF_3·OEt_2 (120)	1 min	22[a]
Me_3SiCl (120)	5 min	63[b]
none	2.5 h	90

[a] Starting material was recovered. [b] 1,2-addition compound was the major product.

the reactivity. In some cases, the hydrophobic effect was quite pronounced. Surprisingly, a combination of Yb(OTf)$_3$ and water did not improve the yield.

In an effort to develop catalytic conjugate addition of silylcuprate, it was disclosed that rare-earth metal triflates including scandium and ytterbium triflate enhanced the rate of 1,4-addition of mixed silylcuprates to enones.[310] In the reaction with isophorone, addition of a catalytic amount of Sc(OTf)$_3$ and Yb(OTf)$_3$ shortened the reaction time from 2.5 h to 5 min and 15 min, respectively (Table 134). On the other hand, Me_3SiCl and BF_3·OEt_2 were less efficient, requiring an excess promoter and resulting in lower yields.

Aza-Michael addition of enantiopure 1-aminopyrrolidines to (*E*)-alkenyl sulfones was also reported to be catalyzed by Yb(OTf)$_3$ (Scheme 70).[311]

During development of an enantioselective conjugate addition reaction of benzyloxyamine, it was shown that a reverse in enantioselectivity using the same chiral ligand was achieved when Y(OTf)$_3$ or Yb(OTf)$_3$ instead of $MgBr_2$ was used as a Lewis-acid catalyst (Table 135).[312]

Scheme 70. Aza-Michael Addition of 1-Aminopyrrolidine to (*E*)-Alkenyl Sulfones

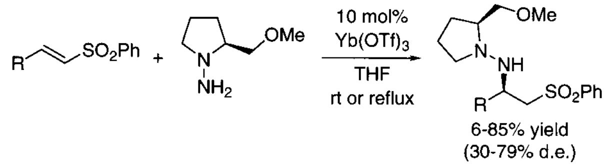
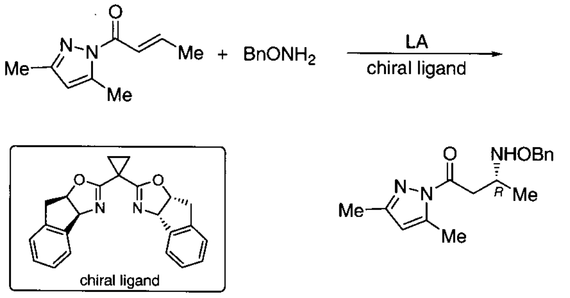
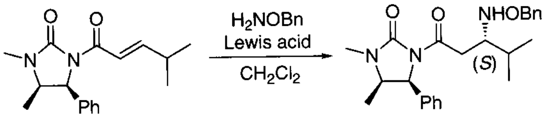


Table 135. Enantioselective Conjugate Addition Reactions



LA (equiv)	conditions	yield/%	ee/% (configuration)
$MgBr_2$ (1.0)	−80 °C, 72 h	60	97 (*R*)
$MgBr_2$ (0.3)	−60 °C, 22 h	80	92 (*R*)
Y(OTf)$_3$ (1.0)	−60 °C, 22 h	67	59 (*S*)
Yb(OTf)$_3$ (1.0)	−60 °C, 22 h	78	41 (*S*)

Table 136. Diastereoselective Conjugate Addition Reactions



Lewis acid (equiv)	temp/°C	time/h	yield/%	*S*/*R*
$AlMe_2Cl$ (1.1)	−78 to rt	18	95	70/30
$TiCl_4$ (1.1)	−60 to rt	18	10	46/54
$MgBr_2$·OEt_2 (0.5)	−10 to rt	18	95	75/25
Sc(OTf)$_3$ (0.05)	−10 to rt	18	70	65/35
BF_3·OEt_2 (1)	−10 to rt	72	50	90/10
BF_3·OEt_2 (2)	−10 to rt	72	>95	90/10

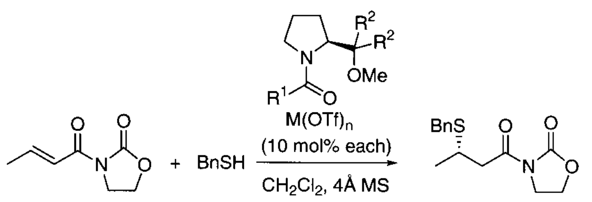
In the presence of a Lewis acid including Sc(OTf)$_3$, *O*-benzylhydroxyamine effectively adds to an unsaturated imide with a chiral auxiliary. Although a catalytic amount of Sc(OTf)$_3$ was enough to promote the reaction, the highest diastereoselectivity was obtained with over a stoichiometric amount of BF_3·OEt_2 (Table 136).[313]

It was reported that chiral catalysts prepared from metal triflates (metal = Yb, Sc, or Hf) and (*S*)-praline-derived chiral ligands were effective for asymmetric Michael addition of thiols to 3-(2-alkenoyl)-2-oxazolidinones (Table 137).[314]

3.3. Glycosylation

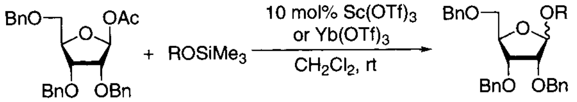
Stereoselective glycosylation has received much attention due to a wide distribution of oligosaccharides in many different types of natural compounds.[315] Several Lewis acids have been used for this transformation. Recent studies have demonstrated that RE(OTf)$_3$ promotes glycosylation of several glycosyl donors. 1-*O*-Acetyl-2,3,5-tri-*O*-benzylribofuranose reacted with trimethylsilyl ethers in the presence of a catalytic amount of Yb(OTf)$_3$ or Sc(OTf)$_3$

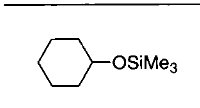
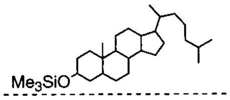
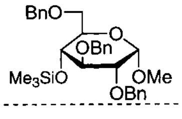
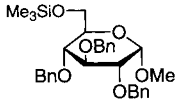
Table 137. Enantioselective Conjugate Addition Reactions of Thiols to 3-(2-Alkenoyl)-2-oxazolidinones



M(OTf)$_n$	R^1	R^2	temp/°C	yield/%	ee/%
Yb(OTf)$_3$	Ph	Ph	−45	80	62
Sc(OTf)$_3$	Ph	Ph	−45	73	57
Hf(OTf)$_4$	Ph	Ph	0	82	67
Hf(OTf)$_4$	^{t}Bu	Ph	0	82	69
Hf(OTf)$_4$	^{t}Bu	1-naphthyl	0	79	71

Table 138. Sc(OTf)$_3$- and Yb(OTf)$_3$-Catalyzed Synthesis of Ribofuranosides



ROSiMe$_3$	Ln	yield/%	α/β
	Yb	85	7/93
	Yb^a	11	52/48
	Yb^b	89	96/4
	Sc	67	7/93
	Sc^a	84	6/94
^{n}BuOSiMe$_3$	Yb	84	11/85
^{n}BuOSiMe$_3$	Yb^b	89	96/4
	Yb	83	8/92
	Yb^b	88	96/4
	Yb	77	18/82
	Yb^b	88	98/2
	Yb	75	39/61
	Yb^b	69	87/13

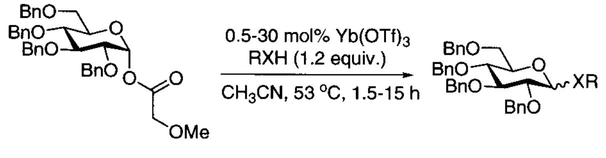
[a] At 0 °C. [b] In the presence of LiClO$_4$ (1.5 equiv).

to give the corresponding ribofuranoses in good yields and selectivities (Table 138).[316]

Yb(OTf)$_3$ promoted glycosylation of 1-*O*-methoxyacetyl pyranosides or furanosides with glycosyl acceptors, simple alcohols, and thiols (Tables 139 and 140).[317] The glycosides were obtained in almost quantitative yields with moderate to excellent selectivities. Moreover, a combination of Yb(OTf)$_3$ and methoxyacetic acid catalyzed the direct coupling of 1-hydroxy sugars with various alcohols and thiols to form the desired glycosides.[318]

In the presence of hexamethyldisiloxane and Drierite, lanthanide (Yb and La) triflates were used for glycosylation reaction of 2,3,5-tri-*O*-benzyl-D-ribofuranose with various acceptors (Table 141).[319] While formation of *β*-anomers was favored in some cases, a reverse of selectivity was noted by addition of lithium perchlorate. Similar selectivity was observed in the glycosylation of the glucose derivative.

Table 139. Stereoselective Glycosylation of a Glucose Derivative Catalyzed by Yb(OTf)$_3$



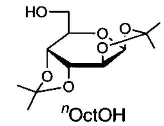
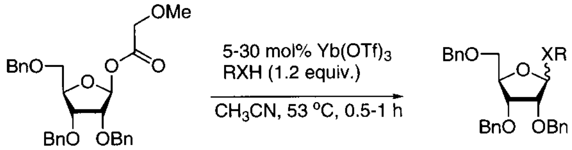
RXH	cat./mol%	time/h	yield/%	α/β
	30	15	87	27/73
^{n}OctOH	0.5	1.5	99	36/64
c-C$_6$H$_{11}$OH	0.5	6	98	36/64
cholesterol	5	6	87	33/67
1-adamantanol	5	8	51	54/46
PhSH	0.5	6	97	55/45
^{n}OctSH	5	3	99	58/42

Table 140. Stereoselective Glycosylation of a Ribose Derivative Catalyzed by Yb(OTf)$_3$



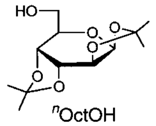
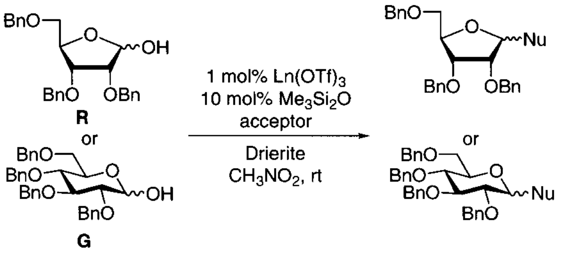
RXH	cat./mol%	time/h	yield/%	α/β
	30	1	97	0/100
^{n}OctOH	5	0.5	99	7/93
c-C$_6$H$_{11}$OH	5	0.5	98	6/94
cholesterol	5	1	98	71/29
PhSH	5	0.5	91	40/60
^{n}OctSH	5	0.25	97	19/81

Table 141. Stereoselective Glycosylation of 1-OH Ribose and Glucose Derivatives

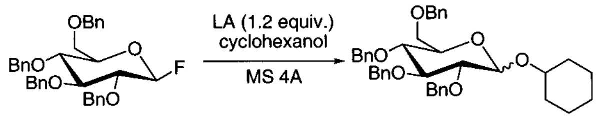


donor	acceptor	Ln	Nu	yield/%	α/β
R	*c*-C$_6$H$_{11}$OH	Yb	*c*-HexO	95	6/94
	c-C$_6$H$_{11}$OH	La	*c*-HexO	98	5/95
	Me$_3$SiN$_3$	La	N$_3$	quant.	20/80
	1,3,5-(MeO)$_3$C$_6$H$_3$	La	2,4,6-(MeO)$_3$Ph	80	0/100
	c-C$_6$H$_{11}$OH	La^a	*c*-HexO	96	93/7
	c-C$_6$H$_{11}$OH	La^a	*c*-HexO	96	94/6
	Me$_3$SiN$_3$	La^a	N$_3$	95	80/20
G	3b-cholestanol	La^a	RO	95	84/16
	1,3,5-(MeO)$_3$C$_6$H$_3$	La	2,4,6-(MeO)$_3$Ph	80	0/100

[a] In the presence of LiClO$_4$ (1.5 equiv).

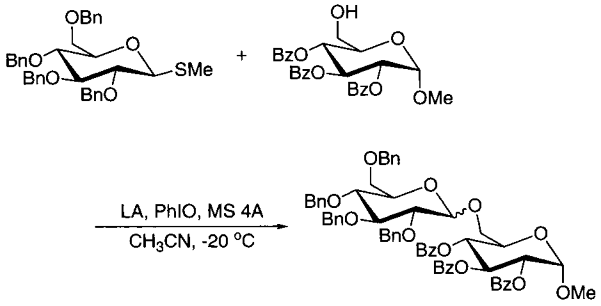
Glycosyl fluorides, which are now commonly used for complex oligosaccharide synthesis, were employed for glycosylation using Ln(OTf)$_3$.[320] Both solvents and bases proved to be important to determine

Table 142. Stereoselective Glycosylation of Glucosyl Fluoride Promoted by Ln(OTf)$_3$



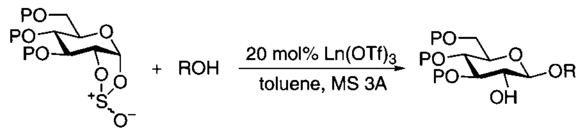
LA	conditions	yield/%	α/β
Yb(OTf)$_3$	K_2CO_3, CH_3CN, −15 °C, 3.5 h	63	6/94
Y(OTf)$_3$	$CaCO_3$, Et_2O, rt, 22 h	96	94/6
$YbCl_3$	$CaCO_3$, Et_2O, rt, 17 h	98	97/3
La(OTf)$_3$	K_2CO_3, CH_3CN, rt, 43 h	36	0/100
La(OTf)$_3$	$CaCO_3$, Et_2O, rt, 72 h	67	100/0

Table 143. Effect of Lewis Acids for Glycosylation of Thioglycoside



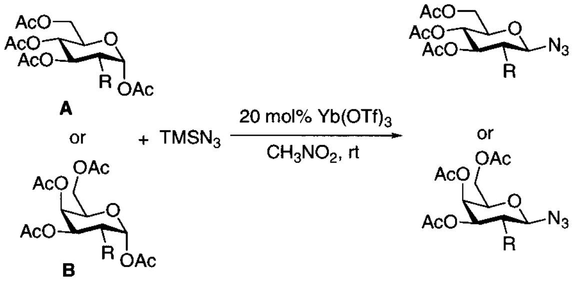
LA	time/min	yield/%	α/β
Sc(OTf)$_3$	<5	82	6/94
Yb(OTf)$_3$	20	87	7/93
Lu(OTf)$_3$	15	83	6/94
Sn(OTf)$_2$	<5	81	6/94
Me_3SiOTf	8	77	6/94
TfOH	<5	74	5/95

Table 144. Stereoselective Glycosylation of Glucose 1,2-Cyclic Sulfite Using Yb(OTf)$_3$



donor	ROH	Ln	temp/°C	yield/%	α/β
P = Bz	AllylOH	Yb	100	86	1/10
	BnOH	Yb	100	92	1/11
	c-HexOH	Ho	100	83	1/8
P = Ac	AllylOH	Yb	100	82	1/9
	BnOH	Yb	100	81	1/5
	c-HexOH	Ho	100	74	1/10
P = Bn	AllylOH	Yb	80	71	0/100
	BnOH	Yb	80	85	0/100
	c-HexOH	Yb	80	75	0/100

Table 145. Synthesis of Glycosyl Azides Using Yb(OTf)$_3$



donor	R	cat./mol%	time/h	yield/%
A	OAc	20	8	85
	NHTroc	10	3	97
B	OAc	20	6	94
	NHTroc	10	3	97

the stereochemical outcome of the reaction (Table 142).

With a combination of iodosobenzene (PhIO) and Ln(OTf)$_3$ as a catalyst, thioglycosyl donors reacted rapidly to give disaccharides in good yields and selectivities (Table 143).[321] Other acid catalysts including Sn(OTf)$_2$, Me_3SiOTf, and TfOH also promoted the reaction efficiently.

Cyclic sulfites are stable surrogates of the corresponding epoxides, and they are prepared from readily available 1,2-diols. It was reported that the activation of glucose 1,2-cyclic sulfite was performed by Yb(OTf)$_3$ and that subsequent reactions with simple alcohols gave β-*O*-glycosides stereoselectively (Table 144).[322] The hydroxyl protecting groups of the sugar had a significant influence on the resulting stereoselectivity. When tri-*O*-benzyl cyclic sulfites were employed, the best result was obtained. With other protecting groups such as benzoyl and acetyl groups, glycosylation required a higher temperature (100 °C) and gave adducts with lower selectivities (α/β = 1/5 to 1/11).

Glycosyl azides are important precursors for *N*-glycoproteins.[323] Stereoselective preparation of glycosyl azides was successfully performed by employing Yb(OTf)$_3$ as a catalyst (Table 145).[324] In all reactions, only β-azides were isolated. Surprisingly, no product was obtained when the reaction was carried out in CH_2Cl_2. This observation was consistent with the previous finding of activation of 1-*O*-methoxyacetyl sugar by Yb(OTf)$_3$.[317]

In the glycosylation of mannosyl donors and methyl glucopyranoside, α-selectivity was obtained in the absence of a Lewis acid, while β-selectivity was observed using a stoichiometric amount of Eu(OTf)$_3$ (Table 146).[325] Lanthanide(III) was supposed to coordinate to the 2-hydroxyl group of the mannosyl donor as well as the glycosyl acceptor, leading the acceptor to the β-side of the donor.

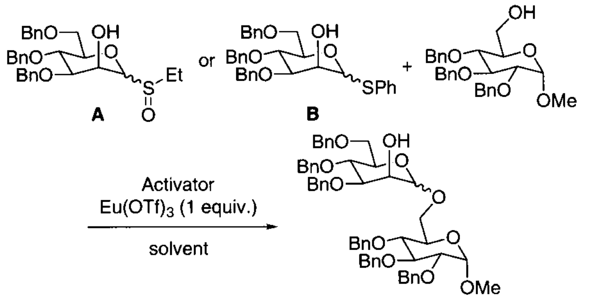
A catalytic amount of Yb(OTf)$_3$ was reported to be effective for the synthesis of aryl *O*-glycosides using triaryloxyboranes (Table 147).[326]

Recently, it was demonstrated that 1,2-*trans*-selective *O*-glycosylation with disarmed 2-*O*-methoxycarbonylated glycosyl thrichloroacetoimidates was efficiently catalyzed by Yb(OTf)$_3$. An *O*-methoxycarbonyl protection is critical in avoiding the formation of undesired ortho ester-like products.[327]

3.4. Aziridination

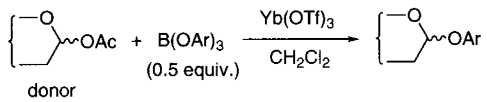
The transition-metal-catalyzed addition of a nitrene to an olefin or the addition of a carbene to an imine provides aziridines.[328,329] It was found that the reaction of imines with ethyl diazoacetate gave a mixture of *cis* and *trans* aziridines and that the ratio was dependent on the Lewis acids employed to

Table 146. Stereoselective Synthesis of β-D-Mannopyranosides



donor	activator (equiv)	Ln	solvent	temp	yield/%	α/β
A	Tf_2O		CH_3CN	−40 °C to rt	42	5/1
	Tf_2O	Eu	CH_3CN	−40 °C to rt	82	1/4.3
B	NIS (4), TfOH (cat.)		CH_2Cl_2	0 °C	56	5.3/1
	NIS (4), TfOH (cat.)	Eu	CH_2Cl_2	−78 °C	64	1/3.0

Table 147. Yb(OTf)$_3$-Catalyzed Reactions of Glycosyl Acetates and Triaryloxyboranes



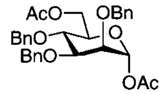
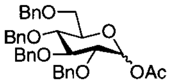
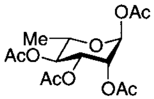
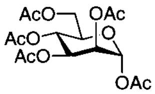
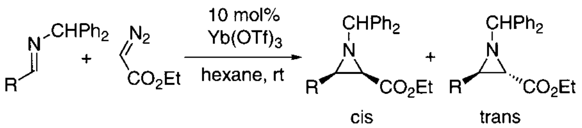
donor	Ar	cat./mol%	temp.	time	yield/%	α/β
	Ph	2	0 °C	1.5 h	86	α
	o-ClPh	4	0 °C	5 h	61	α
	p-MeO	4	0 °C	5 h	96	α
	Ph	2	0 °C	5 h	71	57/43
	o-ClPh	4	0 °C	5 h	45	70/30
	p-MeO	4	0 °C	5 h	83	65/35
	Ph	5	rt	overnight	71	α
	p-MeO	5	rt	overnight	78	α
	Ph	15	rt	2 d	75	α
	p-MeO	15	rt	2 d	72	α

Table 148. Yb(OTf)$_3$-Promoted Aziridination of an Imine with Ethyl Diazoacetate

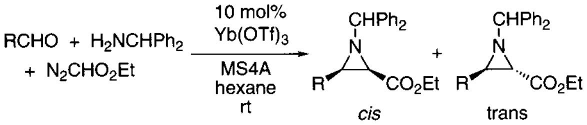


R	yield/%	cis/trans	R	yield/%	cis/trans
Ph	89	93/7	p-ClPh	81	94/6
p-MePh	75	95/5	p-NO$_2$Ph	83	93/7
p-MeOPh	90	94/6	1-naphthyl	82	94/6

promote the reaction (Table 148).[330] Main-group and transition-metal catalysts gave either poor yields or selectivities; however, Yb(OTf)$_3$ provided product with moderate yield and selectivity.

Yb(OTf)$_3$-catalyzed three-component coupling reactions of aldehydes, amines, and ethyl diazoacetate were also developed (Table 149).[330a] This process is particularly useful for the reaction of aliphatic aldehydes whose imines are generally unstable.

Table 149. Three-Component Coupling Reactions of Aldehydes, Amines, and Ethyl Diazoacetate



R	yield/%	cis/trans	R	yield/%	cis/trans
Ph	83	95/5	^{i}Pr	82	91/9
PhCO	85	94/6	^{i}Bu	86	70/30
c-C$_6$H$_{11}$	82	93/7	^{n}Bu	60	85/15

Scheme 71. Synthesis of Aziridine from Imines and Ethyl Diazoacetate Catalyzed by Ln(OTf)$_3$ in Protic Media

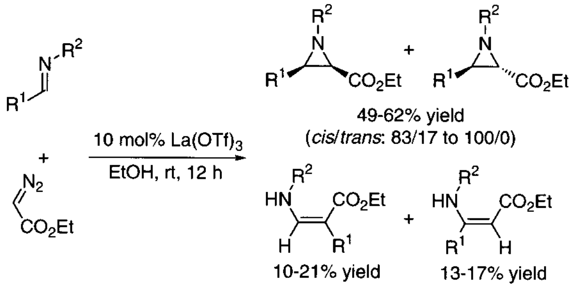
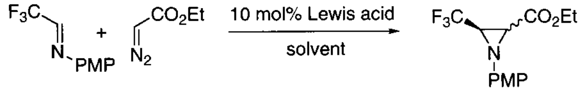


Table 150. Synthesis of Aziridines from CF$_3$-Substituted Imines and Ethyl Diazoacetate



catalyst	solvent	temp/°C	time	yield/%	cis/trans
Yb(OTf)$_3$	Hexane	rt	12 h	85	70/30
InCl$_3$	CH$_2$Cl$_2$	rt	20 h	56	72/28
BF$_3$·OEt$_2$	Et$_2$O	rt	30 min	90	84/16
BF$_3$·OEt$_2$	Et$_2$O	−78	2 h	86	95/5

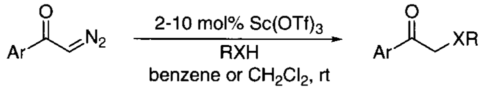
An independent study showed that lanthanum and other rare-earth metal triflates promoted the formation of aziridines from imines and ethyl diazoacetate in protic media (Scheme 71).[331] *cis*-Aziridines were formed exclusively using most of the lanthanides, except for heavier lanthanides. In some cases, the reaction was accompanied by the formation of ring-opened products.

It was also reported that aziridine formation of CF$_3$-substituted imines with ethyl diazoacetate was accelerated by a Lewis acid such as Yb(OTf)$_3$ (Table 150).[332] In terms of selectivity, BF$_3$·OEt$_2$ gave the best result.

3.5. Diazocarbonyl Insertion

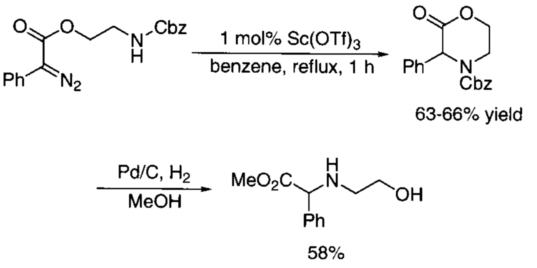
Recently, Sc(OTf)$_3$ has been shown to catalyze diazocarbonyl insertion reactions with alcohols and thiols at ambient temperature (Table 151).[333] Although Sc(OTf)$_3$ did not promote intermolecular insertion reactions with free or protected amines (such as benzyl carbamate), it catalyzed intramolecular diazoester N−H insertion reactions (Scheme 72).

Table 151. $Sc(OTf)_3$-Catalyzed Intermolecular Insertion(s) into O−H and S−H Bonds



Ar	RXH	cat./mol%	yield/%
4-EtOC$_6$H$_4$	^{i}PrOH	2	64
Ph	PhSH	5	62
Ph	CbzNHCH$_2$CH$_2$OH	5	30
4-ClC$_6$H$_4$	MeOH	5	93
4-ClC$_6$H$_4$	PhCH(CH$_3$)OH	10	64
2-thiophenyl	^{n}BuSH	10	40
2-thiophenyl	PhSH	10	46
2-thiophenyl	CbzNHCH$_2$CH$_2$OH	10	36
2-thiophenyl	BnOH	3	63

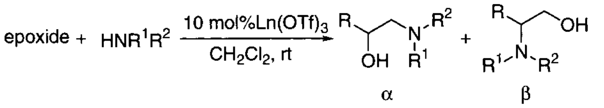
Scheme 72. $Sc(OTf)_3$-Catalyzed Intramolecular Insertion(s) into a N−H Bond

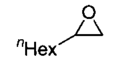
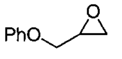
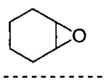
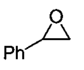


3.6. Ring-Opening Reactions

β-Amino alcohols are well-studied compounds. They act both as chiral auxiliaries for diastereoselective transformations and as ligands for metal-catalyzed enantioselective reactions. Aminolysis of 1,2-epoxides allows a simple preparation of the compounds; however, typical conditions in protic solvents suffer from low conversions when hindered amines and/or epoxides are involved.[334] Searching for a new catalyst to facilitate this reaction, it was found that Ln(OTf)$_3$ was an ideal candidate to promote aminolysis with hindered amines and/or epoxides (Table 152).[335,336] The best results were obtained in anhydrous nonpolar solvents such as toluene and CH$_2$Cl$_2$. The reaction was slowed in MeCN or in the presence of water in an aprotic solvent. The reaction proceeded sluggishly in coordinating solvents such as DMF and THF. LiClO$_4$ was also a good promoter but not as efficient as Ln(OTf)$_3$.[337] Complementary results were obtained in the reaction of *cis*-4-benzyloxy-1,2-epoxyhexane with diethylamine: LiClO$_4$ in CH$_3$CN gave predominantly C-1 product, whereas Yb(OTf)$_3$ in CH$_2$Cl$_2$ provided regioisomeric C-2 product exclusively (Scheme 73). The results were ascribed to the size of Yb^{3+} ion, which was too big to fit into the space between benzyl ethereal and epoxy oxygen atoms. More recently, it was reported that a cyclic epoxide derived from (−)-shikimic acid underwent the regioselective ring-opening reaction with benzylamine in the presence of Yb(OTf)$_3$.[338]

Table 152. Aminolysis of Epoxides



epoxide	Ln	amine	yield/%	α/β
	Yb	NHEt$_2$	97	>99/<1
	Yb	NH^{i}Pr$_2$	95	>99/<1
	Yb	HNEt$_2$	100	>99/<1
	Yb	H$_2$N^{t}Bu	95	>99/<1
	Yb	HN^{i}Pr$_2$	95	>99/<1
	Yb	H$_2$N^{t}Bu	97	-
	Gd	H$_2$N^{t}Bu	98	-
	Nd	H$_2$N^{t}Bu	85	-
	Yb	H$_2$N^{t}Bu	97	90/10
	Gd	H$_2$N^{t}Bu	96	92/8
	Nd	H$_2$N^{t}Bu	97	92/8
	Yb	HNEt$_2$	98	55/45
	Gd	HNEt$_2$	98	57/43
	Nd	HNEt$_2$	97	58/42

Scheme 73. Comparison of Regioselectivity in the Ring Opening of an Epoxide Catalyzed by $Yb(OTf)_3$ and $LiClO_4$

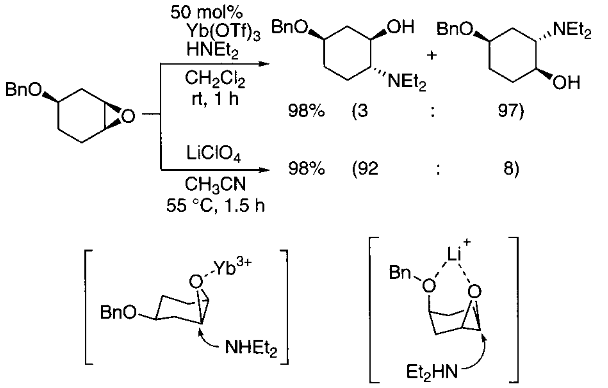
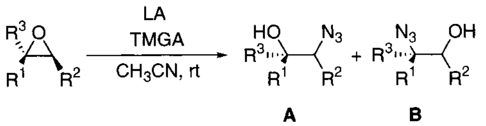


Table 153. Lewis-Acid-Catalyzed Azidolysis of Epoxides with TMGA



TMGA : 1,1,3,3-tetramethylguanidium azide

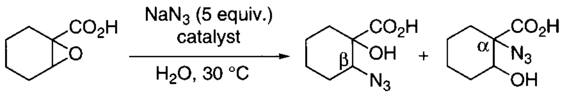
R^1,R^2	R^3	LA (mol %)	yield/% (**A**/**B**)
C$_6$H$_{13}$, H	H	Yb(OTf)$_3$ (20)	54 (93/7)
C$_6$H$_{13}$, H	H	Zr(OTf)$_3$ (20)	75 (82/18)
C$_6$H$_{13}$, H	H	Hf(OTf)$_3$ (20)	74 (82/18)
C$_6$H$_{13}$, H[a]	H	LiClO$_4$ (150)	96 (92/8)
−(CH$_2$)$_4$−	H	Yb(OTf)$_3$ (20)	78
−(CH$_2$)$_4$−	Me	Yb(OTf)$_3$ (20)	51 (80/20)
Ph, H	H	Yb(OTf)$_3$ (10)	82 (28/72)

[a] NaN$_3$ was used as a nucleophile and the reaction was performed at 80 °C.

Azidolysis of epoxides with 1,1,3,3-tetramethyl guanidinium azide (TMGA) in the presence of a Lewis-acid catalyst was reported.[339] Yb(OTf)$_3$, which was successful used for aminolysis of epoxides, gave only moderate yield in azidolysis (Table 153). Other metal triflates including Zr and Hf triflates improved yields but not regioselectivities. A stoichiometric amount of LiClO$_4$ promoted the reaction in excellent yield and selectivity.

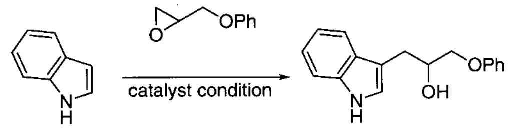
The catalytic efficiency of InCl$_3$, Yb(OTf)$_3$, and Sc(OTf)$_3$ in azidolysis of an α,β-epoxycarboxylic acid using NaN$_3$ has been evaluated in water (Table

Table 154. Effect of Lewis Acids in Azidolysis in Water



catalyst	pH	conversion/%	β/α
none	7.0	15	80/20
$InCl_3$	7.0	25	>99/<1
$Yb(OTf)_3$	7.0	32	>99/<1
$Sc(OTf)_3$	7.0	17	>99/<1
none	4.0	10	>99/<1
$InCl_3$	4.0	>99	>99/<1
$Yb(OTf)_3$	4.0	32	>99/<1
$Sc(OTf)_3$	4.0	30	>99/<1

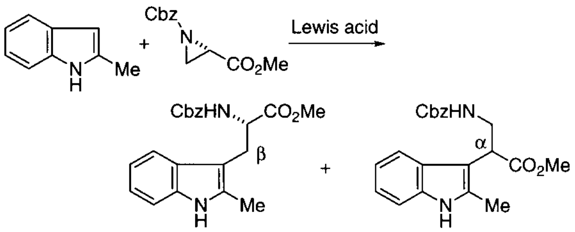
Table 155. Reaction of Indole with Glycidyl Phenyl Ether



cat. (mol %)	conditions	yield/%
none	CH_3CN, 10 kbar, 60 °C, 3 d	16
$Yb(OTf)_3$ (5)	CH_2Cl_2, 1 atm, reflux, 3 days	59 (19)[a]
$Yb(OTf)_3/H_2O$ (10)	CH_2Cl_2, 10 kbar, 60 °C, 42 h	66 (58)[b]
$PhB(OH)_2$ (10)	CH_2Cl_2, 10 kbar, 60 °C, 42 h	61
$Eu(fod)_3$ (5)	CH_2Cl_2, 10 kbar, 60 °C, 42 h	41
$LiOTf/H_2O$ (5)	CH_3CN, 10 kbar, 60 °C, 42 h	30
p-$TsOH\cdot H_2O$ (1)	CH_2Cl_2, 10 kbar, 60 °C, 42 h	4[c]

[a] CH_3CN was used instead of CH_2Cl_2. [b] 5 mol % of $Yb(OTf)_3/H_2O$ was used. [c] Decomposition of substrate was observed.

Table 156. Reaction of Indole with an Aziridinecarboxylic Acid



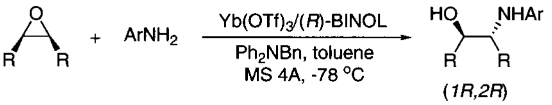
Lewis acid (equiv)	solvent	temp/°C	yield/%	α/β
$Zn(OTf)_2$ (2)	$CHCl_3$	80	69	10/1
$Sc(OTf)_3$ (1)	CH_2Cl_2	0	50	3/1-3/2
$Sc(ClO_4)_3$ (1)	CH_2Cl_2	0	80	10/1

154).[340] At pH 4.0, $InCl_3$ was found to be a better catalyst than $Yb(OTf)_3$ and $Sc(OTf)_3$.

It was shown that the reaction of indole with glycidyl phenyl ether was accelerated efficiently by $Yb(OTf)_3$ under high pressure (Table 155).[341] $PhB(OH)_2$ was as effective as $Yb(OTf)_3$ in accelerating the reaction, while other Lewis acids or Brønsted-acid catalysts were less efficient.

A similar reaction with an aziridinecarboxylic acid instead of an epoxide proceeded well in the presence of a Lewis acid such as $Sc(OTf)_3$ (Table 156).[342] In this reaction, $Sc(ClO_4)_3$ showed higher catalytic activity and regioselectivity than $Sc(OTf)_3$.

Table 157. Enantioselective Ring Opening of *meso*-Epoxides with Aromatic Amines



epoxide (R,R)	Ar	yield/%	% ee
$-(CH_2)_4-$	Ph	90	80.1
$-(CH_2)_4-$	o-EtC_6H_4	74	39.0
$-(CH_2)_4-$	p-ClC_6H_4	98	75.5
$-(CH_2)_4-$	p-BrC_6H_4	78	73.6
$-(CH_2)_4-$	p-$MeOC_6H_4$	64	37.4
$-(CH_2)_3-$	Ph	98	11.6
$-(CH_2)_6-$	Ph		
Ph,Ph	Ph	92	17.4[a]
Me,Me	Ph	99	42.7

[a] At room temperature.

Scheme 74. $Yb(OTf)_3$-Catalyzed Ring Opening of Sugar-Derived Epoxide and Aziridine with Liquid Ammonia

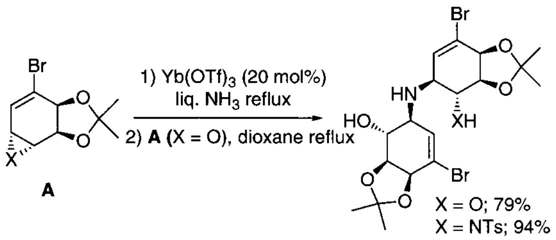
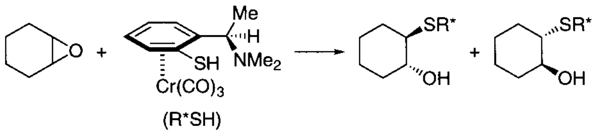


Table 158. Asymmetric Ring Opening of Cyclohexene Oxide with a Chiral Tricarbonyl Arene Thiol Chromium Complex



additive (mol %)	solvent	yield/%	de/%
none	CH_2Cl_2	93	34
none	THF	93	40
$Yb(OTf)_3$ (20)	CH_2Cl_2	70	44
$Yb(hfc)_3$ (20)	CH_2Cl_2	94	41

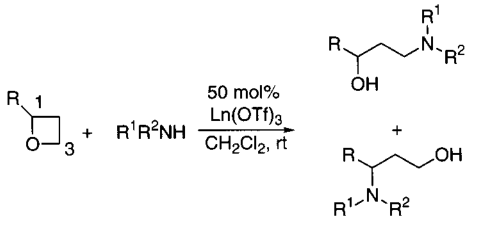
A catalyst prepared from $Yb(OTf)_3$, (*R*)-BINOL, and Ph_2NBn promoted asymmetric ring opening of *meso*-epoxides with aromatic amines in good yields and poor to good enantiomeric excesses (Table 157).[343] The chiral Yb catalyst was originally used in asymmetric Diels–Alder reactions.

$Yb(OTf)_3$ was found to be effective even for ring-opening reactions of an epoxide or the corresponding *N*-tosylaziridine with liquid ammonia (Scheme 74).[344] Thus, *N*- and *O*-linked inositol oligomers were synthesized utilizing this reaction as a key step.

A chiral tricarbonyl arene thiol chromium complex reacted with cyclohexene oxide directly to give *trans*-β-hydroxyalkyl aryl sulfide in high yield with moderate selectivity (Table 158).[345] Addition of a Yb catalyst slightly increased the diastereoselectivity of the reaction.

Aminolysis of oxetanes was studied (Table 159).[346] Although $LiBF_4$ in MeCN mediated the aminolysis of oxetanes with various primary and secondary amines, the reaction proceeded sluggishly. $Ln(OTf)_3$ gave comparable or better yields in a shorter reaction

Table 159. Aminolysis of Oxetanes



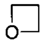
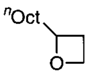
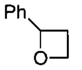
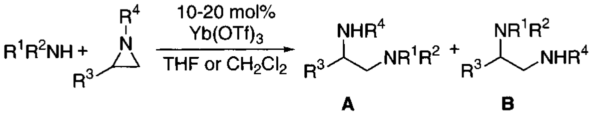
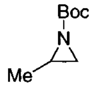
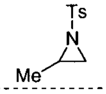
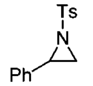
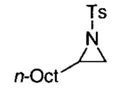
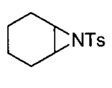
oxetanes	Ln	amine	yield/%	3-/1-attack
	Yb	H_2NBu	90	-
	Yb	HNMePh	99	-
	Gd	HNMePh	99	-
	Nd	HNMePh	96	-
	Yb	H_2N^tBu	99	>99/<1
	Gd	H_2N^tBu	50	>99/<1
	Nd	H_2N^tBu	7	>99/<1
	Yb	H_2NPh	99	>99/<1
	Yb	$HNEt_2$	99	>99/<1
	Yb	$HNEt_2$	99	83/17
	Yb	piperidine	90	75/25
	Yb	morpholine	98	65/35

Table 160. Yb(OTf)$_3$-Catalyzed Ring Opening of Aziridines with Amines

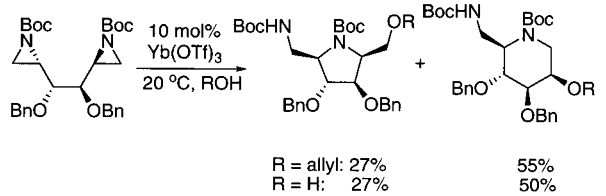


aziridine	amine	conditions	yield/%	A/B
	$HNBn_2$	THF, reflux	quant.	75/25
	$HNBn_2$	CH_2Cl_2, rt	91	62/38
	H_2NBn	CH_2Cl_2, rt	82	65/35
	$HNBn_2$	CH_2Cl_2, rt	84	77/23
	H_2NBn	CH_2Cl_2, rt	75	>99/<1
	$HNEt_2$	CH_2Cl_2, rt	95	>99/<1
	$HNBn_2$	THF, rt	77	67/33
	$HNBn_2$	THF, rt	77	>99/<1
	H_2NBn	CH_2Cl_2, reflux	quant.	-
	$HNEt_2$	CH_2Cl_2, reflux	82	-
	H_2NPh	CH_2Cl_2, reflux	98	-
	pyrroridine	CH_2Cl_2, reflux	quant.	-
	$HNBn_2$	CH_2Cl_2, reflux	NR	-

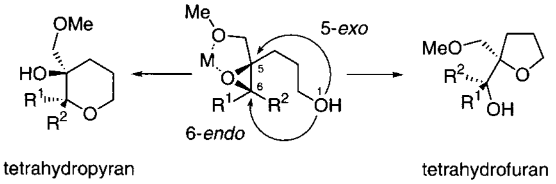
time. Of Ln(OTf)$_3$ screened, Yb(OTf)$_3$ was the most effective, allowing aminolysis with hindered amines. In addition, 2-phenyloxetane, which was resistant to aminolysis with $LiBF_4$, reacted smoothly when Yb(OTf)$_3$ was employed as a catalyst.

Ring opening of aziridines with amines has become an attractive entry to the preparation of synthetically useful 1,2-diamines.[347] It was found that the reaction of *N*-tosylcyclohexeneimine with benzylamine was sluggish and that only a 20% yield of the diamine was obtained after 1 week. Yb(OTf)$_3$ accelerated the same reaction to afford quantitative yield after 3 days at room temperature or 1 day under reflux in dichloromethane.[348] Other Ln(OTf)$_3$ including Y, La, Sm, and Pr triflates were equally effective. Reactions with monosubstituted aziridines proceeded smoothly, and regioselectivities depended on the amines employed (Table 160). On the other hand, the reactions with trisubstituted aziridines were relatively slow, resulting in low yields after prolonged reaction time. Nevertheless, Yb(OTf)$_3$ did not promote the ring opening of 1-tosylazetidine with benzylamine even in refluxing dichloromethane, and 1-tosylazetidine was recovered without decomposition.

Scheme 75. Yb(OTf)$_3$-Catalyzed Formations of Azafuranose and Azapyranose from Ring Opening of Bis-aziridine with Allyl Alcohol and Water



Scheme 76. Regioselective Ring Opening Controlled by Chelation of Lewis Acids



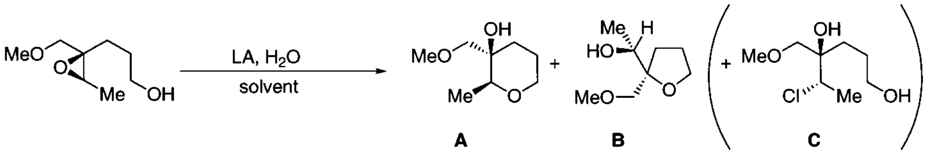
Yb(OTf)$_3$ catalyzed the ring-opening reactions of bis-aziridine with allyl alcohol and water, followed by intramolecular heterocyclization to afford a mixture of azafuranose and azapyranose (Scheme 75).[349] It was demonstrated that the Lewis acid employed for the reaction dictated the ratio of the products. For instance, $BF_3 \cdot OEt_2$ mediated the reaction with allyl alcohol in poor selectivity.

Tetrahydrofuran, tetrahydropyran, and tetrahydrooxepane ring systems are frequently found in biologically active marine polycyclic ether compounds.[350] Stereoselective intramolecular ring opening of a proper tethered epoxy alcohol allows straightforward access to tetrahydrofuran and/or tetrahydropyran (Scheme 76). It was found that in the presence of both La(OTf)$_3$ and water, the 6-*endo*-mode of cyclization was preferred over the favored 5-*exo*-mode, affording tetrahydropyrans mainly.[351] CSA, $BF_3 \cdot OEt_2$, or anhydrous La(OTf)$_3$ gave tetrahydrofuran as the sole product (Table 161). $CeCl_3$ enhanced the formation of tetrahydropyran, albeit in low yield, and the major product was the ring-opened product by chloride. However, in the presence of water (1.1−2.2 equiv), the selectivity for La(OTf)$_3$-promoted reaction was reversed and tetrahydropyran was dominant at a longer reaction time. The influence of water was less pronounced in solvents other than dichloromethane.

Biomimetic successive ring-closure reactions also proceeded under similar reaction conditions (Schemes 77 and 78).[352]

Yb(OTf)$_3$ catalyzed intermolecular ring-opening reactions of epoxides with alcohols to give *β*-alkoxy alcohols in good to high yields with high regio- and stereoselectivity (Table 162).[353]

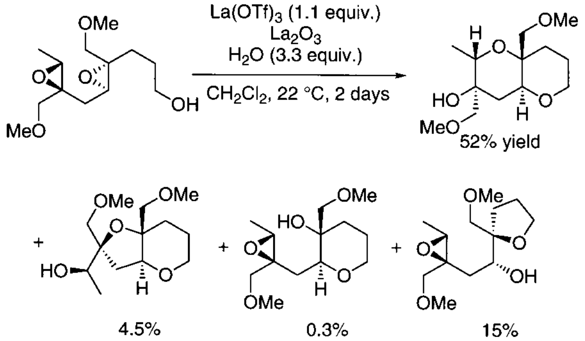
Table 161. Effect of Lewis Acids on Regioselective Intramolecular Ring Opening of an Epoxy Alcohol



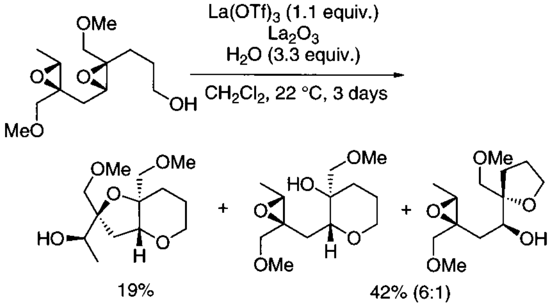
LA (equiv)	H_2O/equiv	solvent	yield/% (**A**/**B**)[a]
CSA (0.1)	0	CH_2Cl_2, 20 °C, 10 min	92 (0/100)
BF_3·OEt_2 (1.1)	0	CH_2Cl_2, −78 to 20 °C, 30 min	95 (0/100)
$CeCl_3$ (1.2)	0	CH_2Cl_2, 20 °C, 13 d	17[b] (50/50)
La(OTf)$_3$ (1.1)	0	CH_2Cl_2, 20 °C, 14 h	87 (0/100)
La(OTf)$_3$ (1.1)	1.1	CH_2Cl_2, 20 °C, 2 d	72 (70/30)
La(OTf)$_3$ (1.1)	2.2	CH_2Cl_2, 20 °C, 2 d	68 (82/18)
La(OTf)$_3$ (1.1)	2.2	Et_2O, 20 °C, 2 d	75 (0/100)
La(OTf)$_3$ (1.1)	2.2	THF, 20 °C, 2 d	92 (52/48)

[a] Determined by 400 MHz ^1H NMR spectroscopy. [b] **C** was isolated in 69% yield.

Scheme 77. Biomimetic Successive Ring-Closure Reaction Catalyzed by La(OTf)$_3$ (1)



Scheme 78. Biomimetic Successive Ring-Closure Reaction Catalyzed by La(OTf)$_3$ (2)

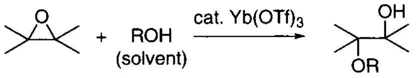


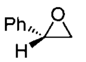
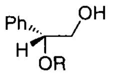
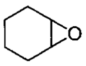
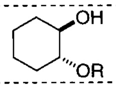
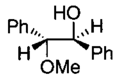
3.7. Other C–X Bond Formations

In the synthetic study of 1α,25-dihydroxyvitamin D_3 A-ring synthon, it was found that treatment of a γ-keto ester with neat acetic anhydride in the presence of a catalytic amount of Sc(OTf)$_3$ gave a bicyclic diacetate cleanly in 65% yield with high diastereoselectivity (Scheme 79).[354]

Lewis acids such as $SnCl_2$, $SnCl_4$, BF_3·OEt_2, $ZnCl_2$, and $MgBr_2$ have been employed to mediate the reactions of imines with phosphites.[355] The results varied from case to case, but a one-pot reaction from an aldehyde has never been achieved by using these conventional Lewis acids. Yb(OTf)$_3$ has been shown to be effective in the three-component coupling of aldehydes, amines, and diethyl phosphite to afford α-aminophosphonates in high yields.[356] Moderate diastereoselectivities were obtained in the reactions with chiral amines (Scheme 80).

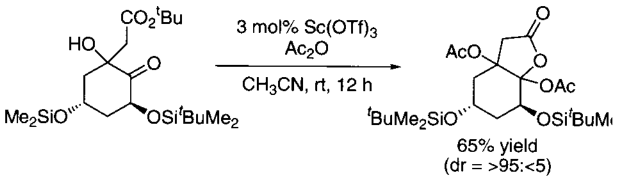
Table 162. Yb(OTf)$_3$-Catalyzed Ring-opening Reactions of Epoxides with Alcohols



epoxide	R	cat/mol%	product	yield/%
	Me	0.2		95
	Et	0.2		98
	Et	none		0
	^{n}Pr	0.2		98
	^{i}Pr	0.2		98
	^{n}Bu	0.2		96
	^{i}Bu	0.2		98
	^{t}Bu	0.2		98
	c-C_6H_{11}	0.2		89
	Allyl	0.2[a]		75
	propargyl	0.2[a]		76
	Me Et	0.15 0.15		91 95
	Me	0.2		80

[a] Alcohol (2 equiv) was used in CH_2Cl_2 under reflux conditions.

Scheme 79. Sc(OTf)$_3$-Catalyzed Cyclization Reaction of a γ-Keto Ester



It was also reported that Sc(OTf)$_3$ catalyzed the three-component synthesis of α-aminophosphonates in ionic liquids (Table 163).[357] The catalyst immobilized in an ionic liquid can be reused several times without loss of activity.

4. Oxidation and Reduction

4.1. Oxidation

A wide range of oxidants has been developed for oxidation of alcohols to aldehydes, but most of them involve using toxic heavy metals such as chromium,

Scheme 80. Yb(OTf)$_3$-Catalyzed Three-Component Coupling of Aldehydes, Chiral Amines, and Diethyl phosphite

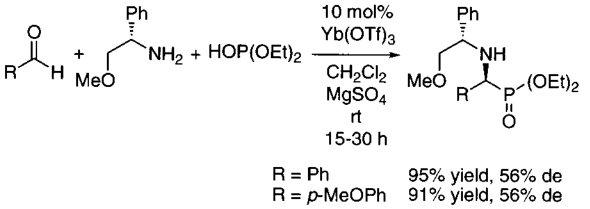
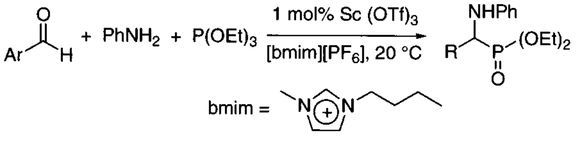
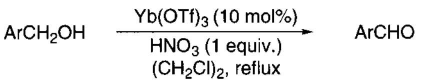


Table 163. Sc(OTf)$_3$-Catalyzed Three-Component Coupling of Aldehydes, Amines, and Triethyl Phosphite in Ionic Liquid



Ar		yield/%	Ar	yield/%
Ph	1st run	97	*m*-MeC$_6$H$_4$	>99
	2nd run	94	*p*-MeC$_6$H$_4$	>99
	3rd run	97	*p*-FC$_6$H$_4$	93
	4th run	93	*p*-CF$_3$C$_6$H$_4$	97
	5th run	>99	1-naphthyl	>99
p-MeOC$_6$H$_4$		>99	3-thianyl	93
o-MeC$_6$H$_4$		90	3-furyl	90

Table 164. Catalytic Oxidation of Benzylic Alcohols to Aromatic Aldehydes Using Yb(OTf)$_3$



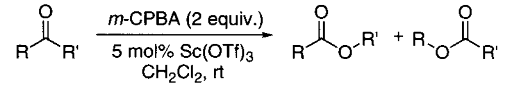
Ar	time/h	yield/%	Ar	time/h	yield/%
Ph	0.5	91	2,4-F$_2$C$_6$H$_3$	2	80
2-ClC$_6$H$_4$	0.5	86	3-CF$_3$C$_6$H$_4$	1	87
2-BrC$_6$H$_4$	0.5	84	4-MeO$_2$CC$_6$H$_4$	2	82
4-BrC$_6$H$_4$	0.5	88	3-Py	24	33
2-IC$_6$H$_4$	0.5	95	4-NO$_2$C$_6$H$_4$	12	82
2-MeC$_6$H$_4$	0.5	92	3,5-(NO$_2$)$_2$C$_6$H$_3$	24	70
4-MeC$_6$H$_4$	0.5	94			

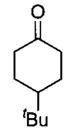
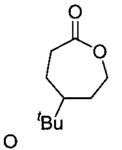
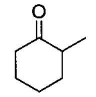
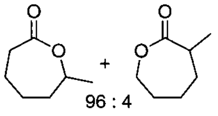
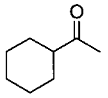
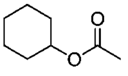
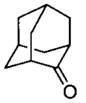
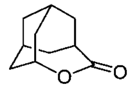
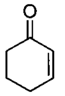
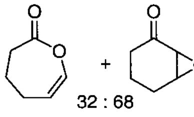
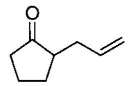
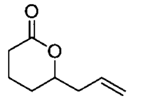
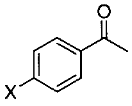
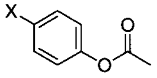
manganese, selenium, etc.[358] In related program for developing atom-economical transformations, it was shown that oxidation of benzylic alcohols to aromatic aldehydes with aqueous nitric acid (69%) was efficiently catalyzed by Yb(OTf)$_3$ (Table 164).[359] A wide range of alcohols with different electronic properties was converted into the corresponding aldehydes in high yields.

The transformation of ketones with peroxide equivalents to give esters or lactones has been known as the Baeyer–Villiger reaction. Commercially available 85% *m*-chloroperoxybenzoic acid (*m*-CPBA) is generally employed with a buffer or an acid catalyst.[360] It was shown that the rate of oxidation of 4-*tert*-butylcyclohexanone with *m*-CPBA was much enhanced when Sc(OTf)$_3$ or TfOH was employed as a catalyst (Table 165).[361]

Sc(OTf)$_3$ was found to be effective as a catalyst for the oxidative double-ring-closure reaction of porphyrins with DDQ to afford conjugated oligoporphyrins in high yields (Scheme 81).[362]

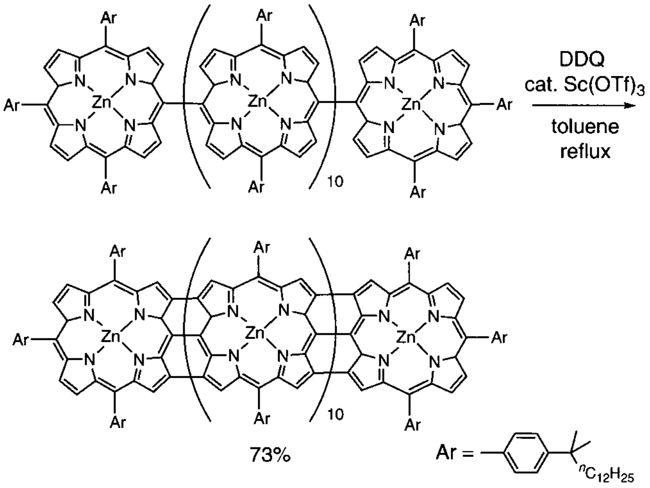
Table 165. Sc(OTf)$_3$-Catalyzed Baeyer–Villiger Oxidation



ketone	time	product	yield/%
	140 min 30 min 10 min		95[a] 99 98[b]
	12 min	 96 : 4	90
	20 h		87
	20 min		100
	3.5 h	 32 : 68	89
	3.5 h		65
	X = H, 48 h X = OMe, 1 h X = Br, 91 h		85 95 80

[a] Without catalyst. [b] With TfOH (10 mol %).

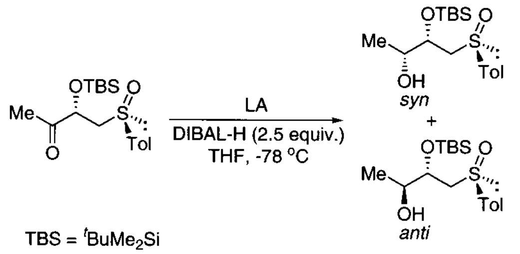
Scheme 81. Sc(OTf)$_3$-Catalyzed Oxidative Double-Ring-Closure Reaction of Porphyrins



4.2. Reduction

It was found that addition of a Lewis acid modified the yield and selectivity in the DIBAL-H reduction of β-silyloxy γ-ketosulfoxide.[363] Of the Lewis acids tested, Yb(OTf)$_3$ resulted in high selectivity for *syn* product and ZnI$_2$ for *anti* product (Table 166).

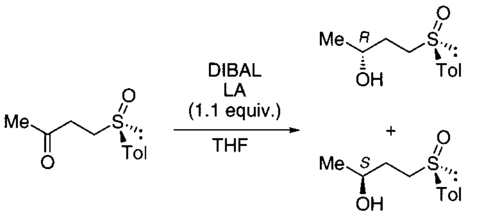
Table 166. Diastereoselective Reduction of a β-Silyloxy γ-Keto Sulfoxide



LA	conditions	yield/%	*syn*/*anti*
none	−78 °C to rt, 12 h	60	87/13
$SnCl_4$	−78 °C, 2 h	88	90/10
$Yb(OTf)_3$[a]	−78 °C, 1 h	96	96/4
ZnI_2	−78 °C, 3 h	96	3/97

[a] 0.6 equiv of the acid was used.

Table 167. Stereoselective Reduction of a γ-Keto Sulfoxide



DIBAL-H/ equiv	LA	conditions	yield/%	*S*/*R*
1.1	none	THF, −105 °C, 1.5 h	85	85/15
1.5	ZnI_2	THF, −78 °C, 3 h	84	69/31
2.5	$Yb(OTf)_3$	THF, −78 °C, 5 h	40	20/80
4.0	$Nd(OTf)_3$	THF, −78 °C, 2 h	75	25/75
3.0	$CeCl_3$	THF, −78 °C, 4 h	66	25/75

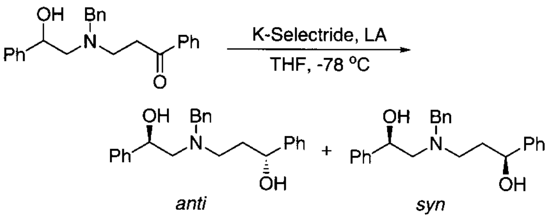
DIBAL-H was used for highly stereoselective reduction of γ-ketosulfoxide.[364] Lewis acids including ZnI_2 and $MgBr_2$ caused reduction in selectivity, whereas the use of $Yb(OTf)_3$, $Nd(OTf)_3$, or $CeCl_3$ resulted in high selectivity for the other diastereomer (Table 167).

Remote stereocontrolled reduction of 1,6-hydroxy amino ketone with K-selectride was also modified by the addition of Lewis acids.[365] $SnCl_4$ formed the product with low diastereoselectivity. $Yb(OTf)_3$ and $Ti(O^iPr)_4$ favored the *anti*-isomer, while $Zn(OTf)_2$, $Yb(O^iPr)_3$, and $Al(OEt)_3$ gave the *syn*-isomer preferentially (Table 168).

It was reported that selective reduction of carboxylic acids in the presence of aldehydes proceeded smoothly using a SmI_2−$Sm(OTf)_3$−MeOH−base system (Table 169).[366] Under this condition, acetalization of aldehydes occurs immediately and therefore aldehydes remain unreacted.

It has been reported that reduction of α-bromoamides with Ph_3P suffers from low chemoselectivity and reactivity.[367] It was shown that addition of stoichiometric amounts of Lewis acids facilitated the process and that excellent yields were be obtained in most cases when a catalytic amount of a Lewis acid was employed (Table 170).[368]

Table 168. Remote Stereocontrol in Reduction of 1,6-Hydroxy Amino Ketone



LA	yield/%[a]	*anti*/*syn*
$SnCl_4$	40 (60)	1.1/1
$Yb(OTf)_3$	51 (44)	4.8/1
$Ti(O^iPr)_4$	91	>100/1
$Zn(OTf)_2$	83	1/3.3
$Yb(O^iPr)_3$	90	1/4.3
$Al(OEt)_3$	88	1/7.1

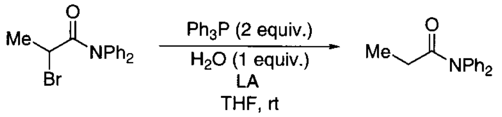
[a] The yields in parentheses were for recovery of starting material.

Table 169. Selective Reduction of Carboxylic Acids over Aldehydes

$$R^1COOH + R^2CHO \xrightarrow[\text{KOH or } H_2O,\ \text{MeOH, rt}]{20\ \text{mol\%}\ Sm(OTf)_3,\ SmI_2\ (2\ \text{equiv.})} R^1CH_2OH + R^2CH_2OH$$

R^1	R^2	time/ min	R^1CH_2OH	R^2CH_2OH
$Me(CH_2)_3CH(C_2H_5)$	ⁿOct	8	93	1
ⁿOct	ⁿHept	4.5	96	3
ⁿHept	ⁿHex	4.5	99	
c-C_6H_{11}	ⁿPent	4.5	99	
1-Me-*c*-Hex	*c*-C_6H_{11}	7	82	8
2-Me-*c*-Hex	*c*-C_6H_{11}	7	84	10
$CH_2{=}CH(CH_2)_7$	ⁿOct	5	96	trace
ⁿHept$CH_2{=}CH$	ⁿHex$CH_2{=}CH$	15	91	5
Ph	*p*-MeC_6H_4	6	96	
p-MeC_6H_4	Ph	28	53	8
p-ClC_6H_4	Ph	1	99	

Table 170. Effect of Lewis Acids on Reduction of α-Bromoamide

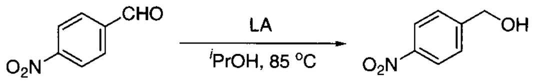


	yield/%[a]	
LA	with LA (2 equiv)	with LA (20 mol %)
Me_3SiOTf	94	88 (4)
$BF_3{\cdot}OEt_2$	96 (3)	-
$TiCl_4$[b]	92	92
$ZnCl_2$	94	-
$SnCl_4$	94	90
$GeCl_4$	96	95
$Sc(OTf)_3$	96	60 (38)

[a] Yield in parentheses was for starting material recovery. [b] The reaction was performed in CH_2Cl_2.

Castellani and his group examined rare-earth metal cation (RE^{3+})-catalyzed Meerwein−Pondorff−Verley-type reduction and etherification reactions.[369] They found that the reduction rate of 4-nitrobenzaldehyde increased with decreasing ionic radii of RE^{3+} (La = 1.05 Å, Y = 0.89 Å, Lu = 0.85 Å, Sc = 0.75 Å). This observation was consistent with the

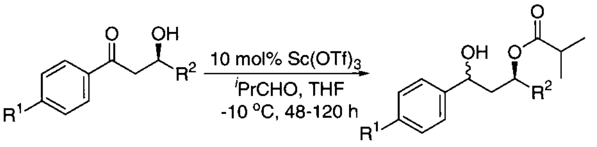
Table 171. RE^{3+}-Catalyzed Meerwein–Pondorff–Verley-type Reduction[a]



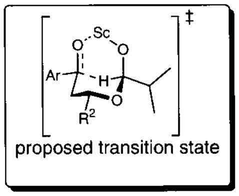
LA[a]	log k[b]	LA[a]	log k[b]
$Sc(OTf)_3$	−3.29	$Y(OTf)_3{\cdot}nH_2O$	−5.12
$LaCl_3{\cdot}nH_2O$	*c*	$Y(OTf)_3$	−4.52
$LaCl_3$	*d*	$LuCl_3{\cdot}nH_2O$	−6.68
$La(ClO_4)_3{\cdot}nH_2O$	−7.34	$Lu(ClO_4)_3{\cdot}nH_2O$	−5.49
$La(OTf)_3$	−5.46	$Lu(OTf)_3$	−4.46

[a] Molar ratio of substrate to catalyst was 3/1. [b] k is the reaction rate constant. [c] No reaction after 9 days. [d] 1% product was obtained after 6 days.

Table 172. $Sc(OTf)_3$-Catalyzed Stereoselective Tishchenko Reduction



R^1	R^2	time /h	yield /%	% de
H	Me	48	83	>95
H	^{i}Pr	48	93	>95
H	$(CH_2)_2Ph$	72	17	>95
Cl	Me	48	93	76
Cl	^{i}Pr	48	55	78
Cl	$(CH_2)_2Ph$	72	40	88
MeO	Me	120	57	88
MeO	^{i}Pr	120	38	80
MeO	$(CH_2)_2Ph$	120	59	94


proposed transition state

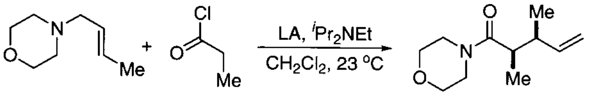
increasing Lewis acidity of the Ln^{3+} ions. Hydrated catalysts gave less satisfactory results (Table 171). Under optimized conditions, $Sc(OTf)_3$ was used for reduction of other aldehydes and ketones to give alcohols in good yields (78–99%).

Catalytic Tishchenko reduction of β-hydroxyketones with isobutyraldehyde using $Sc(OTf)_3$ has been developed (Table 172).[370] Good to excellent *anti*-selectivities were obtained using racemic β-hydroxyketones. The diastereoselectivity was rationalized using a similar transition-state model proposed by Evans and Hoveyda for the SmI_2-catalyzed reduction.[371]

5. Rearrangement

Although traditional Claisen rearrangement[372] was accomplished under thermal control, significant rate acceleration was observed by introducing cationic[373] or anionic[374] charge to the molecules before the rearrangement. Despite the synthetic utility of the reaction,[375] catalytic Claisen variants have not been the topic of intense studies.[376] It was shown that in situ generated ketene from the corresponding acid chloride and diisopropylethylamine reacted with allylic amine in the presence of a proper Lewis acid to afford Claisen adduct in high yields and with an excellent level of stereocontrol (*syn*/*anti*. >99/1).[377] In the absence of the Lewis acid, only ketene dimer was formed. Both conventional Lewis acids and $Yb(OTf)_3$ gave excellent results (Table 173). Recently, tandem acyl-Claisen rearrangement under similar conditions has been developed (Table 174).[378]

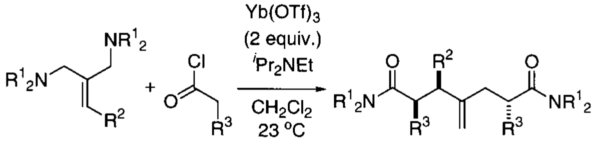
Table 173. Lewis-Acid-Catalyzed Acyl–Claisen Rearrangement



LA (mol %)	yield/%	*syn*/*anti*[a]
none	*b*	
$AlCl_3$ (10)	90	>99/1
$Ti(O^iPr)_2Cl_2$ (10)	76	>99/1
$TiCl_4{\cdot}2THF$ (5)	92	>99/1
$Yb(OTf)_3$ (10)	80	>99/1

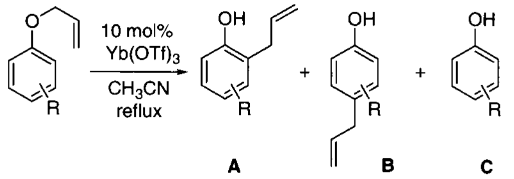
[a] Determined by GC. [b] Only ketene dimer was obtained.

Table 174. Lewis-Acid-Catalyzed Tandem Acyl–Claisen Rearrangement



NR$^1_2$	R^2	R^3	yield/%	*syn-anti*/*anti-anti*
morpholine	Me	Me	97	98:2
pyrrolidine	Me	Me	90	95:5
piperidine	Me	Me	99	96:4
morpholine	Cl	Me	98	99:1
morpholine	OBz	Me	86	91:9
morpholine	CN	Me	78	97:3
morpholine	SPh	Me	70	93:7
morpholine	Me	Me	97	98:2
morpholine	Me	Bn	99	92:8
morpholine	Me	NPhth	98	95:5
morpholine	Me	OPiv	97	97:3
morpholine	OBz	OPiv	71	92:8
morpholine	Cl	OPiv	84	95:5

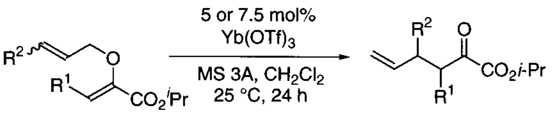
Table 175. Claisen Rearrangement of Allyl Aryl Ethers



R	yield/% A	yield/% B	yield/% C
4-MeO	70	–	4
4-^{t}Bu	44	–	27
4-F	11	–	6
2,5-Me$_2$	25	30	32
2-MeO	45	37	0
2-Ac	20	20	21

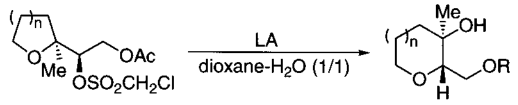
Claisen rearrangement of allyl ethers was catalyzed by $Yb(OTf)_3$ (Table 175).[379] The rearrangement of crotyl ethers also proceeded under the same reaction conditions. It was reported that $Sc(OTf)_3$ also catalyzed Claisen rearrangement of allyl ethers in ionic liquid.[380]

Table 176. Claisen Rearrangement of Allyl Vinyl Ethers



R^1	R^2	yield/%	*syn*/*anti*
Bn	(*E*)-^{n}Pr	99	34/66
Bn	(*Z*)-^{n}Pr	99	96/4
^{i}Pr	(*E*)-^{n}Pr	95	69/31
^{i}Pr	(Z)-^{n}Pr	99	91/9

Table 177. Lewis-Acid-Catalyzed Rearrangement/Ring-Expansion Reactions



n	LA (equiv)	temp/°C	time/h	R	yield/%
1	$Zn(OAc)_2$ (4.0)	50	6	Ac	97
1	$Sc(OTf)_3$ (2.0)	50	7	H	90
2	$Zn(OAc)_2$ (4.0)	80	4	H	82
2	$Sc(OTf)_3$ (2.0)	80	6.5	H	82

It was reported that $Yb(OTf)_3$ catalyzed the Claisen rearrangement of 2-alkoxycarbonyl-substituted allyl vinyl ethers (Table 176).[381] $Cu(OTf)_2$ was also effective in this reaction.

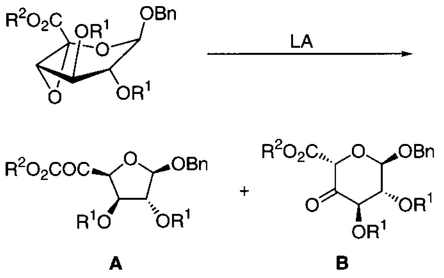
Efficient rearrangement–ring expansion reactions were reported for the synthesis of tetrahydropyrans and tetrahydrooxepanes.[382] Treatment of precursor compounds with either $Zn(OAc)_2$ or $Sc(OTf)_3$ in aqueous dioxane provided the corresponding ring-expanded compounds in excellent yields with complete stereoselectivity giving only the *trans*-isomer (Table 177).

It was found that a Lewis acid promoted rearrangement of glycan epoxides to pyranones, which were reduced to give α-L-iduronic acid derivatives.[383] BF_3·OEt_2 gave the desired pyranones from benzyl-protected epoxides in excellent yields. On the other hand, $Sc(OTf)_3$ provided the best yield and selectivity for epoxides with acid-labile groups (Table 178).

It has been reported that dienone–phenol rearrangement proceeded in the presence of a Brønsted acid or a Lewis acid.[384] However, treatment of aza-spirodienone with BF_3·OEt_2 gave a complex reaction mixture. $Yb(OTf)_3$ gave a mixture of quinoline and tetrahydroquinoline in low yields, while excess TfOH in the presence of an oxidizing agent, chloranil, provided the desired quinoline as the sole product in good yield (Table 179).[385]

Acid-catalyzed rearrangement of phenolic esters to phenolic ketones is known as Fries rearrangement, which requires a stoichiometric amount of a conventional Lewis acid such as $AlCl_3$.[386] Recently, a catalytic Fries rearrangement has been developed (Table 180).[387] The effect of Lewis acids on the Fries rearrangement of 1-naphthyl acetate was studied. Among the Lewis acids tested, $Sc(OTf)_3$ and group IV metal triflates [$Zr(OTf)_4$ and $Hf(OTf)_4$] were found to be very efficient to catalyze the Fries rearrangement. It was found later that a catalytic amount of $Sc(OTf)_3$ allowed acylation of 1-naphthols, followed by Fries rearrangement, to give 2-acyl-1-naphthols in excellent yields (90–98%). In other cases, a mech-

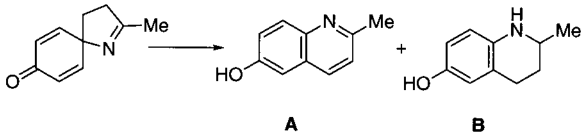
Table 178. Lewis-Acid-Promoted Rearrangement of Glycan Epoxides



R	R′	LA	yield/%	**A**/**B**
Bn	Bn	BF_3·OEt_2	100	0/100
Piv	Me	BF_3·OEt_2	*a*	
Piv	Me	$Sc(OTf)_3$	93	25/75
R,R = (^{i}$Pr_2Si)_2O$	Me	$Sc(OTf)_3$	40	79/21

[a] A complex mixture of products.

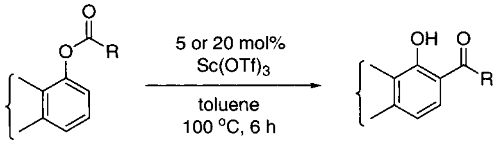
Table 179. Acid-catalyzed Dienone-Phenol Rearrangement



acid	conditions	yield/%	
		A	**B**
BF_3·OEt_2	toluene, reflux	*a*	*a*
$Yb(OTf)_3$	dichloroethane, reflux	13	12
TfOH	Chloranil (50 mol %), $PhNO_2$, 120 °C	75	0

[a] A complex mixture was obtained.

Table 180. Catalytic Fries Rearrangement



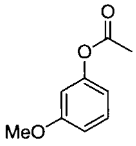
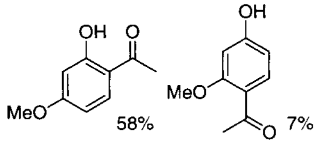
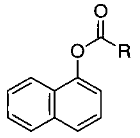
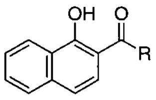
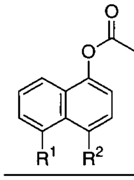
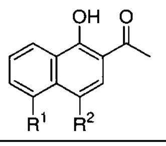
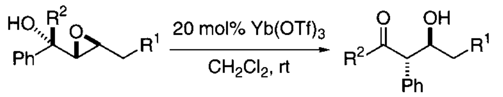
ester	$Sc(OTf)_3$ /mol%	yield
	20	 58% 7%
	5	 R = Me; 85% R = Et; 89% R = ^{n}Pent; 85% R = *c*-C_6H_{11}; 78%
	5	 R^1 = H, R^2 = OMe; 80% R^1 = OMe, R^2 = H; 66%

Table 181. Yb(OTf)$_3$-Catalyzed Semi-Pinacol Rearrangement



R^1	R^2	yield/%
Me	Me	99
OBn	Me	82
Ph	Me	100
Me	Ph	97

Scheme 82. Yb(OTf)$_3$-Catalyzed Transannular Cyclization of Lathyrane Diterpenes

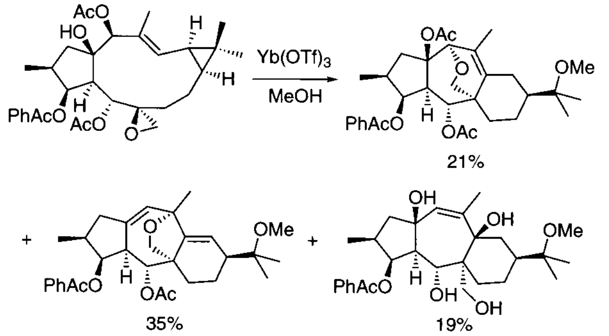
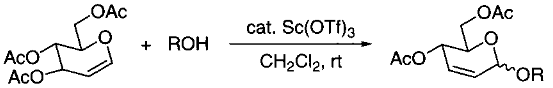


Table 182. Sc(OTf)$_3$-Catalyzed Ferrier Rearrangement with Alcohols



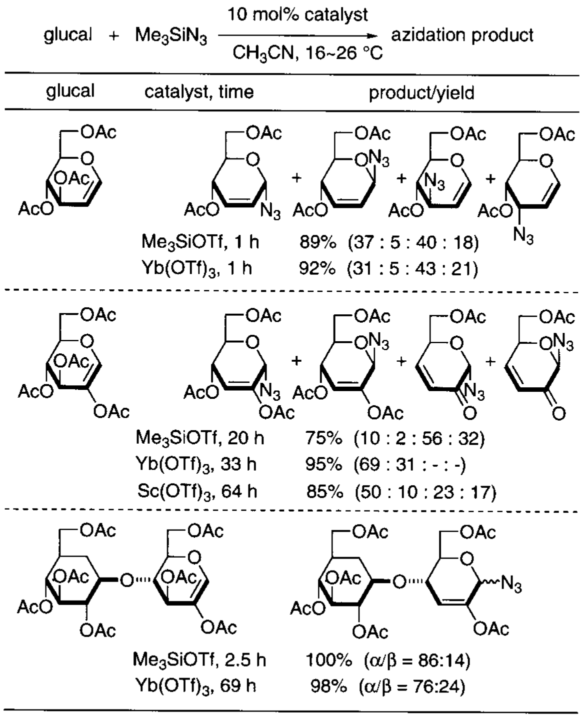
ROH	time/h	yield/%	α/β
EtOH	2.5	88	9/1
^{n}Pent	2.0	86	9/1
Ph(CH$_2$)$_2$OH	3.5	80	5/1
BnOH	3.5	85	5/1
c-C$_6$H$_{11}$OH	3.0	83	7/1
CH$_2$=CHCH$_2$OH	1.5	91	7/1
(E)-MeCH=CHCH$_2$OH	2.0	87	6/1
Me$_2$C=CHCH$_2$OH	2.0	90	7/1
(E)-PhCH=CHCH$_2$OH	2.5	92	9/1
(Z)-BnOCH$_2$CH=CHCH$_2$OH	2.0	90	6/1
HC/CCH$_2$OH	1.5	93	10/1
p-MeOC$_6$H$_4$OH	0.5	95	15/1
p-ClC$_6$H$_4$OH	1.0	90	12/1
p-NO$_2$C$_6$H$_4$OH	2.0	85	10/1
p-FC$_6$H$_4$OH	1.0	92	12/1

anism of direct 2-acylation was indicated under similar reaction conditions.

In the presence of a catalytic amount of Yb(OTf)$_3$, β,γ-epoxyalcohols were reported to undergo semi-pinacol rearrangement smoothly to afford β-hydroxy-ketones in high yields (Table 181).[388]

It was shown that Yb(OTf)$_3$ triggered transannular cyclization of a macrocyclic diterpenoid to afford a mixture of three abeomyrsinanes (Scheme 82).[389]

Table 183. Yb(OTf)$_3$-Catalyzed Ferrier Rearrangement with Azidotrimethylsilane



The acid-catalyzed allylic rearrangement of glycals, known as Ferrier rearrangement,[390] is widely used to obtain 2,3-unsaturated glycosides. A variety of reagents are employed in this transformation. Despite potential utility, however, some of these methods suffer from disadvantages such as strong oxidizing conditions, high acidity, unsatisfactory yields, and low selectivity. It was reported that mild and highly efficient Ferrier rearrangement proceeded in the presence of a catalytic amount of Sc(OTf)$_3$ to give the corresponding 2,3-unsaturated glycosides in excellent yields with high stereoselectivity (Table 182).[391]

Similarly, Ferrier rearrangement of D-glycals with azidotrimethylsilane is effectively catalyzed by Yb(OTf)$_3$ to give a mixture of rearranged products (Table 183[190]).[392]

Meanwhile, C-glycosylation of glycals via Ferrier rearrangement with silicon-based nucleophiles proceeded in the presence of a catalytic amount of Yb(OTf)$_3$ (Table 184).[393] The reactions showed high regio- and stereoselectivities.

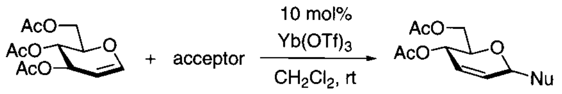
It was reported that Sc(OTf)$_3$ was also an efficient catalyst for C- and N-glycosylation of various types of glycals with allyltrimethylsilane, trimethylsilyl cyanide, and trimethylsilyl azide (Table 185).[394]

6. Protection and Deprotection

6.1. Protection

Esterification of carboxylic acids or their derivatives with alcohols is one of the most fundamental transformations in organic synthesis.[395] Bases such as 4-(dimethylamino)pyridine (DMAP) or 4-pyrrolidinopyridine (PPY) are generally used in stoichiometric amounts for couplings of alcohols with activated carboxylic acid derivatives such as acid chlorides and (mixed) acid anhydrides.[395,396] On the other hand, direct acylation of alcohols with carboxylic acids is carried out in the presence of a catalytic amount of a mineral acid or a Lewis acid (with a dehydrating agent). However, a large excess amount of alcohol or azeotropic removal of water from the reaction mix-

Table 184. Yb(OTf)$_3$-Catalyzed *C*-Glycosylation of Glycals



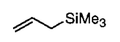
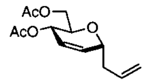
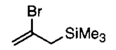
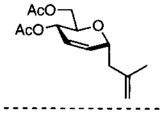
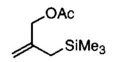
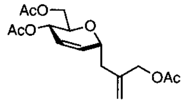
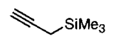
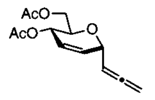
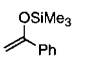
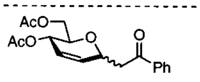
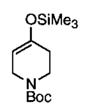
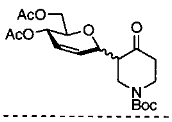
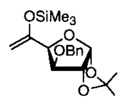
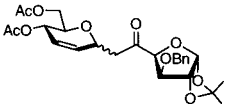
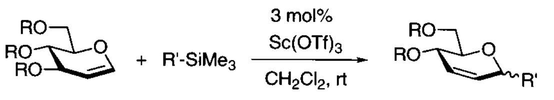
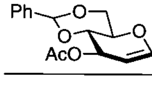
acceptor	product	time/h	yield /%	α/β
		3	94	α
		4	89	α
		4	89	α
		16	92	α
		10	90	8/1
		15	84	8/1
		12	88	5/1

Table 185. Sc(OTf)$_3$-Catalyzed *C*-Glycosylation of Glycals

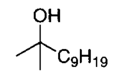
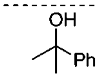
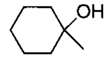
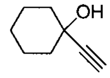
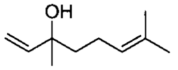
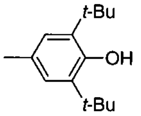
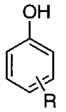


R	R'	time/h	yield /%	dr
Ac	$CH_2CH{=}CH_2$	3.5	93	9/1
	CN	4.0	90	6/4
	N_3	4.5	88	7/3
Bz	$CH_2CH{=}CH_2$	5.0	90	9/1
	CN	6.0	87	6/4
	N_3	8.0	85	7/3
Piv	$CH_2CH{=}CH_2$	4.0	95	9/1
	CN	4.5	84	6/4
	N_3	5.5	86	7/3
	$CH_2CH{=}CH_2$	3.5	90	9/1
	CN	4.0	87	6/4

ture is required to force such a reversible reaction to favor product formation. In addition, the Lewis-acid catalyst would be decomposed after the reaction.[397] The first successful catalytic acylation of alcohols with acid anhydrides or mixed anhydrides using Sc(OTf)$_3$ was reported by Yamamoto and co-workers.[398,399] With 0.1−5 mol % of the catalyst, acylation proceeded smoothly not only with primary alcohols, but also with sterically hindered secondary and tertiary alcohols (Table 186). Sc(OTf)$_3$-catalyzed acylation is superior to that catalyzed by bases such as DMAP, ^{n}Bu$_3$P, and a combination of DMAP and Et$_3$N for acetylation and benzoylation of (−)-menthol (Table 187). In addition, Sc(OTf)$_3$ catalyzed esterification of carboxylic acids with alcohols using in situ generated mixed anhydrides (Table 188). Recently, it has been shown that a combination of Sc(OTf)$_3$ and DMAP was superior to Sc(OTf)$_3$ itself for acylation of sterically hindered tertiary alcohols with carboxylic acid or amino acid derivatives.[400]

Table 186. Catalytic Acylation of Alcohols with Acid Anhydrides Using Sc(OTf)$_3$

$$R^1OH + (R^2CO)_2O \xrightarrow[CH_3CN,\ rt]{0.1\text{-}2.5\ mol\%\ Sc(OTf)_3} R^2CO_2R^1$$

R^{1}OH	(R^{2}CO)$_2$O (equiv.)	Sc(OTf)$_3$ / mol%	conditions (°C, h)	yield / %
Ph(CH$_2$)$_3$OH	Ac$_2$O (1.5)	0.1	rt, 1	>95
PhMeCHOH	Ac$_2$O (1.5)	0.1	rt, 1	>95
(-)-menthol	Ac$_2$O (1.5)	0.1	rt, 1	>95
	(EtCO)$_2$O (1.5)	1.0	0, 1	>95
	(^{t}BuCO)$_2$O (1.5)	1.0	rt, 1	>95
	(PhCO)$_2$O (3.0)	1.0	rt, 20	>95
	Ac$_2$O (3.0)	1.0	rt, 1	56 (39)^a
	Ac$_2$O (5.0)	1.0	0, 0.8	85 (9)^a
	Ac$_2$O (5.0)	1.0	rt, 1	94 (1)^a
	Ac$_2$O (5.0)	[DMAP (1.0)]	rt, 20	<1 (0)^a
	Ac$_2$O (solvent)	1.0	-40, 1.3	>95 (<1)^a
	Ac$_2$O (5.0)	1.0	-20, 5	91 (9)^a
	Ac$_2$O (3.0)	1.0	-20, 0.5	>95
	Ac$_2$O (solvent)	2.0	-20, 2.5	68 (8)^b
	Ac$_2$O (1.5)	1.0	rt, 1	>95
 R = 2,4,6-Me$_3$	(PhCO)$_2$O (3.0)	2.5	rt, 1.3	>95
R = *o*-OH			rt, 1.3	95
R = *m*-OH			rt, 1	>95
R = *p*-OH			rt, 0.5	92

^{a} Yields of elimination products. ^{b} Yield of the primary acetate.

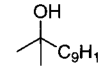
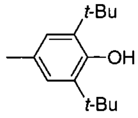
Table 187. Comparison between Sc(OTf)$_3$ and Other Base Catalysts in Acylation of (−)-Menthol in CH$_3$CN

(R^{1}CO)$_2$O (equiv)	catalyst (mol %)	temp/ °C	time	yield/ %
(MeCO)$_2$O (1.5)	Sc(OTf)$_3$ (1)	0	15 min	>95
(MeCO)$_2$O (1.5)	DMAP (1)/Et$_3$N (3 equiv)	0	55 min	75
(PhCO)$_2$O (3.0)	Sc(OTf)$_3$ (1)	23	1 h	>95
(PhCO)$_2$O (3.0)	DMAP (1)/Et$_3$N (3 equiv)	23	1 h	75^a
(PhCO)$_2$O (3.0)	DMAP (1)	23	1 h	23^a
(PhCO)$_2$O (3.0)	^{n}Bu$_3$P (1)	23	1 h	88^a

Direct acetylation of alcohols with acetic acid was performed without prior or in situ generation of mixed anhydrides (Table 189).[401] Sc(OTf)$_3$ and Ln(OTf)$_3$ were effective to catalyze the reaction, and

Table 188. Catalytic Acylation of Alcohols with Carboxylic Acids in the Presence of (p-NO$_2$PhCO)$_2$O Using Sc(OTf)$_3$

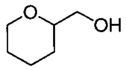
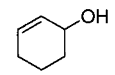
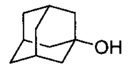
$$\mathrm{R^1OH} + \mathrm{R^2CO_2H} \xrightarrow[\substack{(p\text{-}\mathrm{NO_2PhCO})_2\mathrm{O} \\ (1.5\ \text{equiv.}) \\ \mathrm{CH_3NO_2},\ \text{rt}}]{1\ \text{mol\%}\ \mathrm{Sc(OTf)_3}} \mathrm{R_2CO_2R^1}$$

R^{1}OH	R^{2}CO$_2$H	time/h	yield/%
Ph(CH$_2$)$_3$OH	EtCO$_2$H	2	>95
	^{i}PrCO$_2$H	3	>95
(-)-menthol	EtCO$_2$H	2	>95
	^{i}PrCO$_2$H	2	>95
	(E)-MeCH=CHMeCO$_2$H	2	>95
	^{t}BuCO$_2$H	3	>95
	EtCO$_2$H	2	-[a]
	EtCO$_2$H	12.5	86[b]

[a] Although the esterification proceeded, elimination of hte acyloxy group was accompanied. [b] p-NO$_2$PhCO$_2$Ar was also obtained (2%).

Table 189. Catalytic Direct Acetylation of Alcohols with Carboxylic Acids Using Sc(OTf)$_3$

$$\underset{(\text{solvent})^a}{\mathrm{AcOH}} + \mathrm{ROH} \xrightarrow[\text{conditions}]{5\ \text{mol\%}\ \mathrm{Sc(OTf)_3}} \mathrm{ROAc}$$

ROH	conditions/°C, h	yield/%
Ph(CH$_2$)$_2$OH	rt, 24 reflux, 0.5	99 98
	rt, 24	96
	rt, 1	97
PhCHMeOH	65, 2	98
(-)-menthol	65, 24	95
	reflux, 18	81[b]

[a] AcOH (2 mL)/ROH (1mmol). [b] AcOH (25 mL)/ROH (1 mmol).

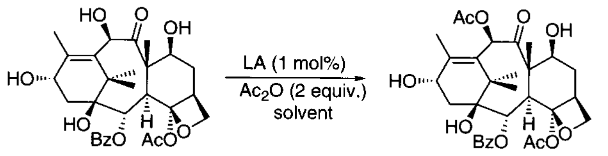
Table 190. Effect of Lanthanide Triflates (10 mol %) for Direct Acetylation of 2-Phenethyl Alcohol with Acetic Acid

Ln(OTf)$_3$	Sc	La	Pr	Eu	Yb
conversion (%)	79[a] (100)[b]	22 (63)	28 (77)	23 (70)	41 (92)

[a] After 3 h. [b] After 21 h.

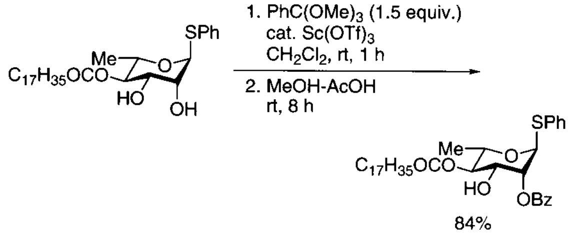
the catalysts were easily recovered and reused. The effect of various lanthanide triflates for acetylation of phenethyl alcohol was examined (Table 190). The results for catalytic efficiency were closely parallel to those obtained in other reactions.

Table 191. Effect of Lewis Acids and Solvents on Selective Acetylation

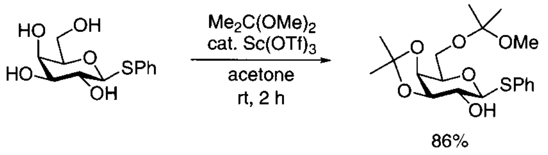


LA	solvent	time/h	yield/%
La(OTf)$_3$	THF	2	97
Yb(OTf)$_3$	CH$_2$Cl$_2$	24	>95
Yb(OTf)$_3$	THF	3	98
Yb(OTf)$_3$	AcOEt	3	>95
Lu(OTf)$_3$	THF	3	100
CeCl$_3$	THF	24	95

Scheme 83. Sc(OTf)$_3$-Catalyzed Mono-benzoylation of Diols via a Cyclic Ortho ester



Scheme 84. Sc(OTf)$_3$-Catalyzed Acetonide Protection of Triols



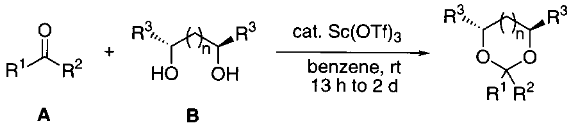
Selective acylation of a polyhydroxylated compound is a difficult task in organic synthesis.[402] Ln(OTf)$_3$ was successfully used to achieve selective acetylation of 10-deacetylbaccatin III, which was an important intermediate for the synthesis of anti-cancer taxol derivatives (Table 191).[403] Interestingly, the catalytic activity of Yb(OTf)$_3$ was solvent-dependent, and the highest activity was obtained in THF. Other metal chlorides required a large excess of acetic anhydride to obtain comparable yields.

It was reported that Sc(OTf)$_3$ was effective for the formation of a cyclic ortho ester intermediate, followed by treatment with aqueous acid to give the acylated compound (Schemes 83).[404] Sc(OTf)$_3$-catalyzed acetonide protection of a sugar-derived triol was also reported (Scheme 84).

Acetals are used as efficient protecting groups for carbonyl compounds, and their preparations are usually performed in the presence of a Brønsted acid or a Lewis acid.[402] It was reported that Sc(OTf)$_3$ was an efficient catalyst for synthesis of chiral acetals from carbonyl compounds and chiral diols (Table 192).[405] Meanwhile, a similar study revealed that Sc(OTf)$_3$ promoted acetalizations of vinyl ethers with alcohols and of aldehydes or ketones with trialkyl orthoformates or with diols in the presence of trimethyl orthoformate.[406] Similarly, Yb(OTf)$_3$ promoted formation of dimethyl acetals from aldehydes and trimethyl orthoformate in MeOH.[407]

Sc(OTf)$_3$ catalyzed highly diastereoselective preparation of 1,3-dioxolanones and 1,3-dioxanones with chiral hydroxy acids (Table 193).[406] Better yields were

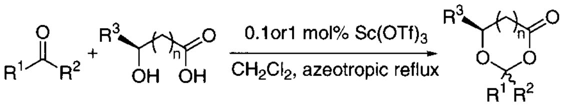
Table 192. Sc(OTf)$_3$-Catalyzed Acetalization

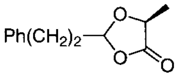
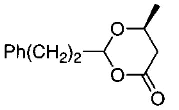
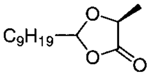
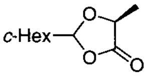
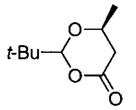
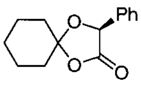


A	B R^3	B *n*	Sc(OTf)$_3$/ mol %	conditions	yield/ %
PhCHO	Me	0	10	benzane, rt, 2 days	84
PhCHO	Me	0	10	benzane, rt, 2 days^a	90
PhCHO	Me	0	10	THF, rt, 2 days	72
PhCHO	Me	0	10	CH_2Cl_2, rt, 2 days	80
PhCHO	Me	1	10	benzane, rt, 2 days	93
p-MeOPhCHO	Me	0	20	benzane, rt, 2 days^a	59
furfural	Me	0	10	benzane, rt, 2 days	38
furfural	Me	0	10	benzane, rt, 2 days^a	53
$C_5H_{11}CHO$	Me	0	5	THF, rt, 13 h	100
$C_6H_{13}CHO$	Me	0	10	THF, rt, 13 h	93
c-$C_6H_{11}CHO$	Me	0	5	THF, rt, 13 h	96
$Ph(CH_2)_2CHO$	CO_2Et	0	20	benzane, rt, 2 days	84
cinnamaldehyde	Me	0	20	benzane, rt, 2 days	75
cyclohexanone	Me	0	20	benzane, rt, 2 days	84
cyclohexanone	CO_2Et	0	20	benzane, rt, 2 days	99

^{a} With $MgSO_4$ (0.75 mmol / 1 mmol of **A**).

Table 193. Sc(OTf)$_3$-Catalyzed Diastereoselective Preparations of 1,3-Dioxolanones and 1,3-Dioxanones

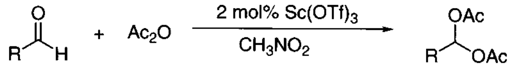


products	Sc(OTf)$_3$ /mol%	time/h	yield/%	*cis/trans*
	0.1	2	76	92/8
	1	2	96	90/10
	0.1	2	76	87/13
	0.1	2	59	97/3
	1	3	88	89/11
	1	1.5	98	-

obtained by azeotropic removal of water produced from the condensation reactions.

Formation of acylals from aromatic or aliphatic aldehydes and acetic anhydride was mediated by Sc(OTf)$_3$, which also catalyzed the reverse process causing hydrolysis of acylals (Table 194).[408] Chemoselective protection of benzaldehyde in the presence of acetophenone has been achieved using Sc(OTf)$_3$ as a catalyst (Scheme 85).

Table 194. Sc(OTf)$_3$-Catalyzed Formation and Deprotection of *gem*-Diacetates (Acylals)



RCHO	time/mins	yield/%
p-$NO_2C_6H_4CHO$	10	99
p-ClC_6H_4CHO	10	95
PhCHO	10	99
p-$MeOC_6H_4CHO$	10	95
p-$MeOC_6H_4CHO$	20	45
cinnamaldehyde	120	76
c-HexCHO	20	94

Scheme 85. Chemoselective Formation of Acylals

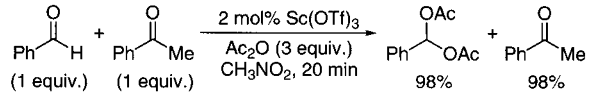
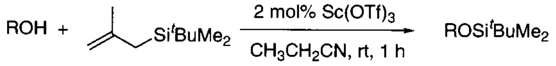
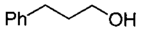
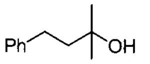
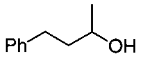
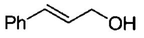
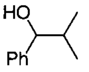
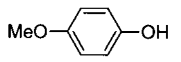
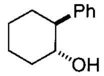
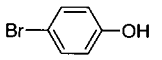


Table 195. Silylation of Alcohols Using Methallylsilane



ROH	time /h	yield /%	ROH	time /h	yield /%
	1	98		0.5	88
	0.5	93		6	91
	0.5	97		2	94
	0.5	98		2	94

It was reported that reactions of alcohols with methallylsilanes in the presence of Sc(OTf)$_3$ provided the corresponding alkyl silyl ethers in high yields. Microencapsulated Sc(OTf)$_3$ [MC Sc(OTf)$_3$] was also effective in this reaction (Table 195).[409]

Facile conversion of alcohols to diphenylmethyl (DPM) ethers was successfully performed. The reaction proceeded in the presence of Yb(OTf)$_3$ to give the corresponding DPM ethers in good yields (Table 196).[410]

N-Carbamoylation of 5-methylene-2-oxazolidione and 5-methylene-1,3-thiazoidine-2-thione with various isocyanates (formation of urethanes) was shown to be efficiently catalyzed by rare-earth metal perfluoralkanesulfonates.[411]

6.2. Deprotection

During the course of total synthesis of complex molecules, selective deprotection of similar and/or different functional groups is necessary and not trivial. Esters are stable functional groups which are difficult to remove in the substrates containing acid- and/or base-sensitive groups, and therefore, they are always used as protective groups in the early stage of a synthesis and are cleaved at the end.[402] It has been reported that selective deprotection of the methoxyacetyl group in the presence of other ester

Table 196. Conversion of Alcohols to DPM Ethers

$$\text{ROH} \xrightarrow[\text{CH}_2\text{Cl}_2\text{, rt, 0.5-1 h}]{\text{10 mol\% Yb(OTf)}_3\text{, diphenylmethanol}} \text{RODPM}$$

DPM = diphenylmethyl

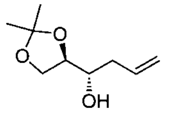
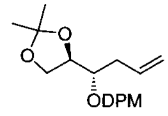
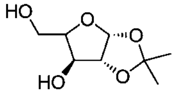
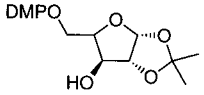
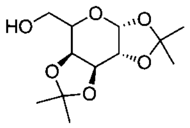
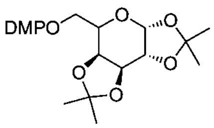
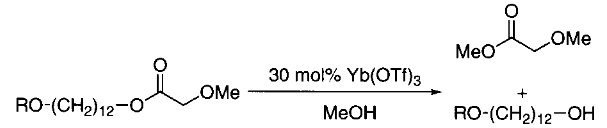
ROH	product	time /h	yield /%
$Ph(CH_2)_4OH$	$Ph(CH_2)_4ODPM$	0.5	87
(-)-menthol	(-)-menthylODPM	1	86
		0.5	80
		1	78
		0.5	92

Table 197. Selective Deprotection of Methoxyacetate Using Yb(OTf)₃



R	temp/°C	time/h	yield/%[a]
Ac	0	2	93 (7)
Ac	25	13	98 (2)
Bz	0	3	95 (1)
THP	0	2	92 (3)
TBDMS	0	1.5	94 (3)
TBDPS	0	2	99 (0)
MEM	25	0.5	99 (0)

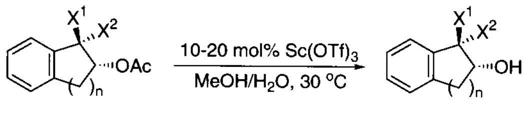
[a] Yields of 1,12-dodecanediol are given in parentheses.

groups, such as acetyl and benzoyl groups, or acid-labile ethereal groups, such as tetrahydropyranyl (THP), *tert*-butyldimethylsilyl (^{t}BuMe$_2$Si), *tert*-butyldiphenylsilyl (TBDPS), and 2-methoxyethoxymethyl (MEM) groups, was achieved by transesterification in MeOH using Yb(OTf)$_3$ as a catalyst (Table 197).[412] The chemoselectivity resulted from the preferential activation of the methoxyacetyl group through strong interaction with trivalent ytterbium.

This type of functional-group-assisted catalysis was proven to be essential for rapid hydrolysis of functionalized acetates as exemplified by recent reports that Sc(OTf)$_3$-catalyzed hydrolysis of 2-acetoxyindane was much less efficient than those of 2-acetoxy-1-indanone, 2-acetoxy-1-amidoindane, and 2-acetoxy-1,1-difluoroindane (Table 198).[413] It was of particular note that 2-acetoxy-1-indanone (99% ee) was hydrolyzed to give 2-hydroxy-1-indanone (98% ee) without racemization.

On the other hand, hydrolysis of simple acetates was achieved in refluxing 2-propanol in the presence of Yb(OTf)$_3$ (Table 199).[414]

Table 198. Functional-Group-Assisted Deprotection of Acetates Using Sc(OTf)₃



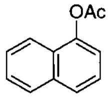
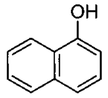
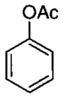
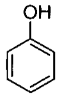
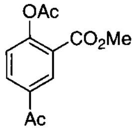
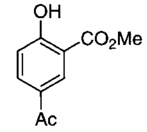
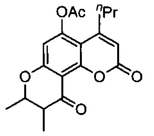
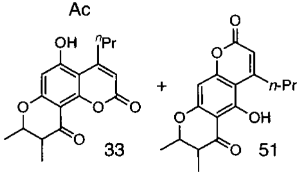
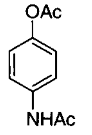
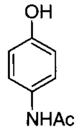
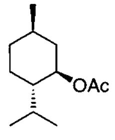
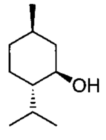
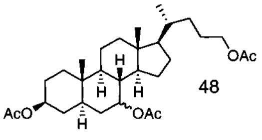
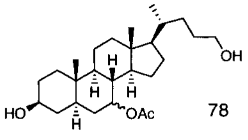
A **B**

acetate A					
X^1, X^2	*n*	%ee	time/h	%ee of **B**	yield/%
O (carbonyl)	1	99	40	98 (8)[a]	93 (75)[a]
O (carbonyl)	2	98	40	90 (26)[a]	82 (23)[a]
O (carbonyl)	3	94	40	94 (1)[a]	84 (34)[a]
H, OH	1		48		87
H, NHAc	1		26		81
H, NHBoc	1		76		73
H, H	1		28		21
F, F	1		30		93
H, F	1		48		36
F, H	1		48		29

[a] Yield and ee in parentheses are those of the hydrolysis with LiOH (1.5 equiv).

Table 199. Yb(OTf)₃-Catalyzed Deprotection of Acetates

$$\text{ROAc} \xrightarrow[{}^i\text{PrOH, reflux}]{\text{10 mol\% Yb(OTf)}_3} \text{ROH}$$

ROAc	time/h	ROH	yield/%
	9		85
	12		96
	20		95
	7		33 51
	15		96
	74		95
	48		78

The *tert*-butoxycarbonyl (Boc) group has been widely used as a nitrogen protecting group.[402] Deprotection of Boc-protected carboxamide is usually achieved

Scheme 86. Deprotection of Boc-Protected Amide Using $Yb(OTf)_3/SiO_2$

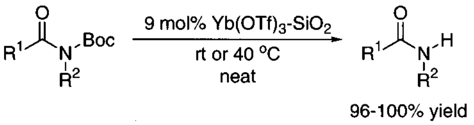
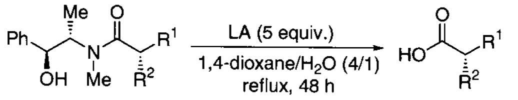


Table 200. Amide Hydrolysis Using Lewis Acids[a]



LA	R^1, R^2	yield/%	ee/%[b]
$FeCl_3$	Me, ^{n}Bu	85	98
$ZrOCl_2$	Me, ^{n}Bu	92	99
$Yb(OTf)_3$	Me, ^{n}Bu	73	98
$FeCl_3$	Me, Bn	94	98
$ZrOCl_2$	Me, Bn	92	97
$Yb(OTf)_3$	Me, Bn	91	95
$FeCl_3$	Ph, Et	91	92
$ZrOCl_2$	Ph, Et	90	93
$Yb(OTf)_3$	Ph, Et	69	82

[a] The starting materials were ≥99% de. [b] Enantiomeric excesses were determined by chiral capillary GC analysis of the corresponding (*R*)-α-methylbenzylamides.

using strong acids such as HCl and CF_3CO_2H.[402] Chemoselective deprotection of *N*-Boc carboxamides was achieved using $Yb(OTf)_3$ supported on silica gel under neat conditions (Scheme 86).[415] Other functional groups including *N*-Cbz amide, *N*-Boc amine, and pyrazole and acid-sensitive acetonide survived under the conditions.

It has been demonstrated that chiral amides of pseudoephedrine underwent highly diastereoselective alkylations and that the chiral auxiliary was easily removed by hydrolysis in the presence of excess Lewis acids (Table 200).[416] Among the Lewis acids tested, $FeCl_3$, $ZrOCl_2$, and $Yb(OTf)_3$ promoted hydrolysis efficiently with minimal racemization.

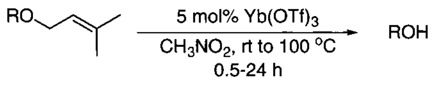
Base-promoted removal of substituted allylic groups suffers from isomerization of double bonds[417] and lack of selectivity between different allylic groups.[418] It was shown that $Yb(OTf)_3$ efficiently catalyzed deprotection of prenyl ethers (Table 201), while allyl and crotyl ethers were unaffected using this protocol.[419]

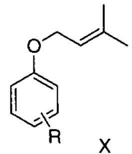
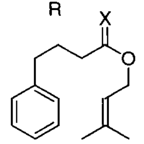
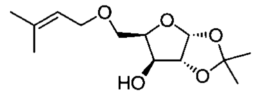
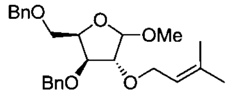
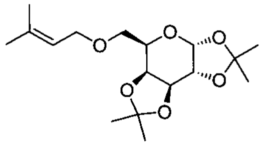
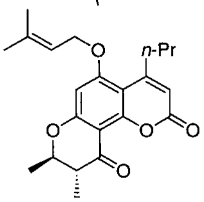
Selective deprotection of silyl ethers was achieved by using $Sc(OTf)_3$.[420] Silyl alkyl ethers were removed in the presence of silyl aryl ethers, while TBS ethers were cleaved without affecting TBDPS ether groups (Schemes 87 and 88).

$Yb(OTf)_3$ catalyzed the deprotection of tritylamines and trityl ethers to the corresponding amines and alcohols under mild conditions in high yields (Table 202).[421] Under these reaction conditions, *N*-Boc protection was unaffected.

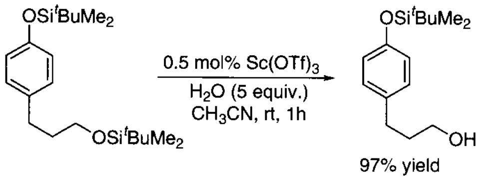
One-pot deprotection–protection was achieved by using $Sc(OTf)_3$ as a catalyst (Scheme 89).[422] Polymer-supported ether-linked disaccharides were selectively cleaved to release the benzylic alcohol, which was converted to the acetate. The procedure facilitated easy recovery of the product in the solid-phase synthesis.

Table 201. Deprotection of Prenyl Ethers Using $Yb(OTf)_3$

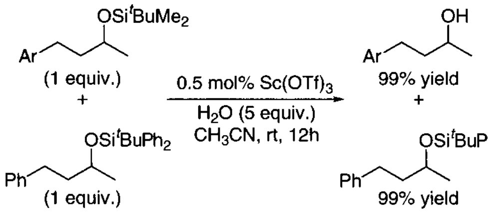


ether		time /h	yield /%
	R: *p*-OMe	0.5	79
	p-F	2	85
	p-Ac	1	90
	o-NO_2	12	72
	2-CO_2Me-4-Ac	1	74
	X: O	9	85
	H_2	24	55
		12	55
		2	80
		2	60
		12	60

Scheme 87. Chemoselective Deprotection of Silyl Ethers (1)



Scheme 88. Chemoselective Deprotection of Silyl Ethers (2)



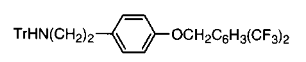
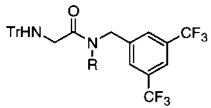
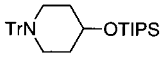
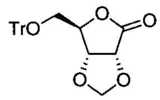
Ar = *p*-MeOPh
Si^tBuMe_2 = *tert*-butyldimethylsilyl
Si^tBuPh_2 = *tert*-butyldiphenylsilyl

A facile chemoselective hydrolysis of terminal isopropylidene acetals has been achieved using a catalytic amount of $Yb(OTf)_3 \cdot H_2O$ in acetonitrile at ambient temperature (Table 203).[423]

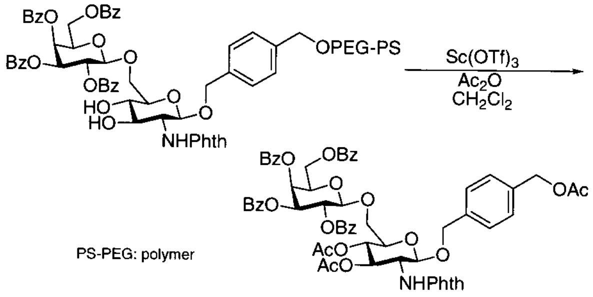
Table 202. Deprotection of Tritylamines and Trityl Ethers

$$\mathrm{RXTr} \xrightarrow[\text{THF, } H_2O\text{, rt, 4 h}]{\text{15 mol\% catalyst}} \mathrm{RXH}$$

Tr = triphenylmethyl

substrate		conditions	yield/%
		1N HCl, EtOH TFA, EtOH Yb(OTf)$_3$, THF Eu(OTf)$_3$, THF	0 0 89 78
	R = Me R = Me R= H R= H	1N HCl, EtOH Yb(OTf)$_3$, THF 1N HCl, EtOH Yb(OTf)$_3$, THF	98 94 97 93
TrNHBn		1N HCl, EtOH TFA, EtOH Yb(OTf)$_3$, THF Eu(OTf)$_3$, THF	0 0 93 89
TrOBn		Yb(OTf)$_3$, THF	92
		Yb(OTf)$_3$, THF	89
		Yb(OTf)$_3$, THF	94

Scheme 89. Sc(OTf)$_3$-Catalyzed Deprotection and in Situ Protection



THP and MOM ethers are easily deprotected in the presence of a catalytic amount of Sc(OTf)$_3$ with methanol and 1,3-propanediol, respectively (Tables 204 and 205).[424]

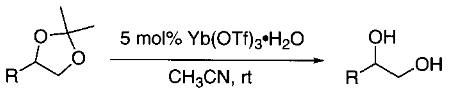
N-Acyl oxazolidinones are smoothly converted to the corresponding methyl esters by Lewis-acid-catalyzed transesterification (Table 206).[425] Mild reaction conditions suppress epimerization or racemization of chiral substrates and allow acid-sensitive groups to survive.

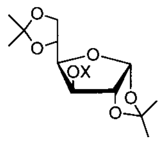
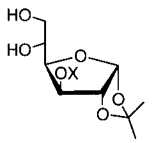
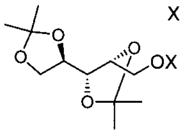
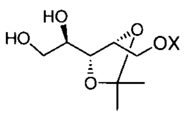
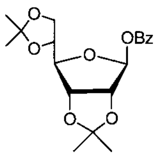
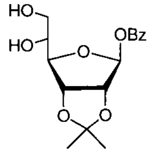
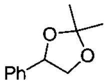
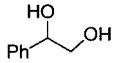
7. Polymerization

Catalytic amounts of Sc(OTf)$_3$ or Yb(OTf)$_3$ catalyzed aldol polymerization to give polymers with high molecular weights (Table 207).[426]

Rare-earth metal triflates were found to be effective for stereocontrol of the free-radical polymerization of acrylic acid derivatives (Tables 208 and 209).[427] The stereochemistry of the polymerization was significantly affected by the coordination of the Lewis acids.

Table 203. Yb(OTf)$_3$-Catalyzed Chemoselective Deprotection of Terminal Acetonide

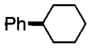


acetal		time/h	product	yield/%
	X: H Bn Allyl Me Ts PMB	3 3.5 4 3 3.5 2.5		88 90 81 91 92 90
	X: Bn Allyl Me Ts TBDPS Ac	2.5 4 3 3.5 3 2.5		91 80 87 85 81 92
		3		89
		2		90

TBDPS : Si^{t}BuPh$_2$. PMB : *p*-MeOC$_6$H$_4$CH$_2$

Table 204. Sc(OTf)$_3$-Catalyzed Deprotection of THP Ethers

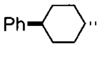
$$\mathrm{ROTHP} \xrightarrow[\text{CH}_3\text{CN-MeOH, rt, 1 h}]{\text{5 mol\% Sc(OTf)}_3} \mathrm{ROH}$$

R	yield/%	R	yield/%
Bn	84	2-Naphthyl	93
Ph(CH$_2$)$_3$	98		95
PhCHMe	84		
Ph(CH$_2$)$_2$CHMe	99		
Ph(CH$_2$)$_2$CMe$_2$	90[a]		
o-MeC$_6$H$_4$	90	BnO(CH$_2$)$_4$	95
m-MeC$_6$H$_4$	99	BzO(CH$_2$)$_4$	97
p-MeC$_6$H$_4$	96	^{t}BuPh$_2$SiO(CH$_2$)$_4$	74
p-BrC$_6$H$_4$	98	MOMO(CH$_2$)$_6$	90

[a] For 2 h.

Table 205. Sc(OTf)$_3$-Catalyzed Deprotection of MOM Ethers

$$\mathrm{ROMOM} + \mathrm{HO(CH_2)_3OH} \xrightarrow[\text{CH}_3\text{CN, rt, 1-4 h}]{\text{5 mol\% Sc(OTf)}_3} \mathrm{ROH}$$

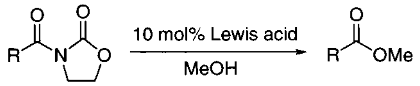
R	yield/%	R	yield/%
Bn	85	*o*-MeC$_6$H$_4$	95
Ph(CH$_2$)$_3$	97	*m*-MeC$_6$H$_4$	92
PhCH$_2$CHMe	90	*p*-MePC$_6$H$_4$	90
Ph(CH$_2$)$_2$CHMe	94	*p*-BrC$_6$H$_4$	99
		2-Naphthyl	79
	97		

Recently, Sc(OTf)$_3$ was reported to be one of the effective catalysts for the ring-opening polymerization of L-lactide with ethanol as an initiator in pyridine.[428]

8. Miscellaneous Reactions

During the course of a synthesis of (−)-tetrodotoxin, a mild method for the conversion of carbodiimide into

Table 206. Lewis-Acid-Catalyzed Transesterification *N*-Acyl Oxazolidinones



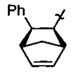
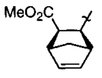
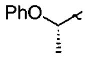
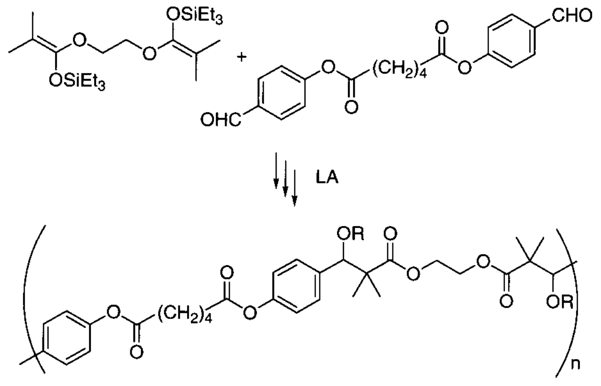
R	Lewis acid	temp./°C	time/h	yield/%
PhCH=CH	$[^t\mathrm{Bu_2SnCl(OH)}]_2$	85	24	99
	$\mathrm{MgBr_2}$	85	8	97
	$\mathrm{Sc(OTf)_3}$	85	8	94
$\mathrm{PhCHMeCH_2}$	$[^t\mathrm{Bu_2SnCl(OH)}]_2$	50	23	93
	$\mathrm{MgBr_2}$	30	2	97
	$\mathrm{Sc(OTf)_3}$	30	1	93
PhCHEt	$[^t\mathrm{Bu_2SnCl(OH)}]_2$	85	3	94
	$\mathrm{MgBr_2}$	85	3	92
	$\mathrm{Sc(OTf)_3}$	85	24	70
$\mathrm{PhCH_2CHMe}$	$[^t\mathrm{Bu_2SnCl(OH)}]_2$	40	4.5	99
	$\mathrm{MgBr_2}$	30	24	85
	$\mathrm{Sc(OTf)_3}$	85	24	90
p-$\mathrm{NO_2Ph}$	$[^t\mathrm{Bu_2SnCl(OH)}]_2$	85	3	92
	$\mathrm{MgBr_2}$	85	14	92
	$\mathrm{Sc(OTf)_3}$	85	24	82
 Ph	$[^t\mathrm{Bu_2SnCl(OH)}]_2$	85	14	91
	$\mathrm{MgBr_2}$	30	24	86
	$\mathrm{Sc(OTf)_3}$	85	14	92
 $\mathrm{MeO_2C}$	$[^t\mathrm{Bu_2SnCl(OH)}]_2$	85	24	79
	$\mathrm{MgBr_2}$	85	3	91
	$\mathrm{Sc(OTf)_3}$	85	14	92
 PhO	$[^t\mathrm{Bu_2SnCl(OH)}]_2$	85	3	92
	$\mathrm{MgBr_2}$	30	3	92
	$\mathrm{Sc(OTf)_3}$	30	1	94

Table 207. Lewis-Acid-Catalyzed Aldol Polymerization

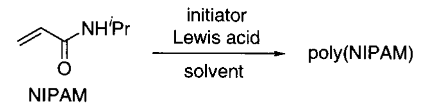


LA (mol %)	yield/%	M_n
$\mathrm{Sc(OTf)_3}$ (10)	50	55 700
$\mathrm{Yb(OTf)_3}$ (20)	15	11 300
$\mathrm{TiCl_4}$ (200)	29	2 700

guanidine was developed (Table 210).[429] Addition of a conventional Lewis acid or a Brønsted acid did not promote the reaction, presumably due to coordination of the acids to benzylamine. A 3 M ethereal solution of $\mathrm{LiClO_4}$ gave a moderate yield. Remarkably, $\mathrm{Sc(OTf)_3}$ and $\mathrm{Yb(OTf)_3}$ catalyzed the conversion in high yields.

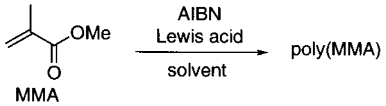
$\mathrm{Ln(OTf)_3}$ efficiently catalyzed the decarbonylation of 2,4,6-trimethoxybenzaldehyde (Table 211).[430] Less electron-rich aromatic aldehydes reacted slowly. For instance, treatment of 2,4- and 2,6-dimethoxybenzaldehyde and $\mathrm{Sc(OTf)_3}$ (16 mol %) in MeOH for 1 h afforded the decarbonylated product in ca. 10% yield, while 4-methoxybenzaldehyde failed to give any products.

Table 208. Polymerization of an Acrylic Amide in the Presence of $\mathrm{RE(OTf)_3}$



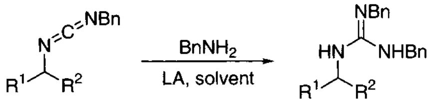
initiator	Lewis acid	solvent	temp/ °C	time/ h	yield/ %	tacticity *m*/*r*
AIBN	–	$\mathrm{CHCl_3}$	60	3	65	45/55
AIBN	$\mathrm{Yb(OTf)_3}$ (0.2 M)	$\mathrm{CHCl_3}$	60	3	39	58/42
AIBN	$\mathrm{Y(OTf)_3}$ (0.2 M)	$\mathrm{CH_3OH}$	60	3	94	80/20
$\mathrm{Na_2SO_3}$ + $\mathrm{K_2S_2O_8}$	$\mathrm{Y(OTf)_3}$ (0.2 M)	H2O	60	3	94	57/43
AIBN	$\mathrm{Y(OTf)_3}$ (0.2 M)	DMSO	60	3	96	47/53
AIBN, UV	–	$\mathrm{CH_3OH}$	−20	24	61	44/56
AIBN, UV	$\mathrm{Y(OTf)_3}$ (0.2 M)	$\mathrm{CH_3OH}$	−20	24	85	90/10
AIBN, UV	$\mathrm{Y(OTf)_3}$ (0.5 M)	$\mathrm{CH_3OH}$	−20	24	72	92/8
AIBN, UV	$\mathrm{Lu(OTf)_3}$ (0.5 M)	$\mathrm{CH_3OH}$	−20	24	62	92/8
$\mathrm{BBu_3}$, air	$\mathrm{Y(OTf)_3}$ (0.2 M)	$\mathrm{CH_3OH}$	−40	24	85	89/11
$\mathrm{BBu_3}$, air	$\mathrm{Y(OTf)_3}$ (0.2 M)	$\mathrm{CH_3OH}$	−78	24	98	80/20

Table 209. Polymerization of an Methacrylate in the Presence of $\mathrm{RE(OTf)_3}$



Lewis acid	solvent	yield/ %	M_n $\times 10^{-4}$	M_w/ M_n	tacticity *mm*/*mr*/*rr*
none	toluene	79	3.46	1.61	3/33/64
$\mathrm{Sc(OTf)_3}$ (0.2 M)	toluene	>99	5.23	2.23	14/46/40
$\mathrm{Y(OTf)_3}$ (0.2 M)	toluene	>99	4.22	5.38	3/34/63
$\mathrm{La(OTf)_3}$ (0.2 M)	toluene	95	2.66	2.6	3/34/63
$\mathrm{Sm(OTf)_3}$ (0.2 M)	toluene	92	2.68	3.42	3/34/63
$\mathrm{Er(OTf)_3}$ (0.21 M)	$\mathrm{CHCl_3}$	92	4.66	4.37	5/34/61
$\mathrm{Yb(OTf)_3}$ (0.24 M)	$\mathrm{CHCl_3}$	83	3.01	1.97	10/36/54

Table 210. Conversion of Carbodiimide into Guanidine



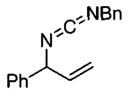
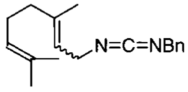
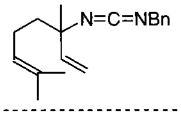
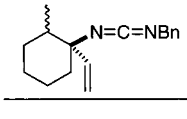
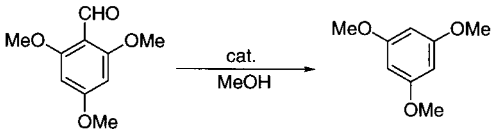
carbodiimide	conditions	yield/%
	$\mathrm{LiClO_4}$ (300 mol%), $\mathrm{Et_2O}$	49
	$\mathrm{Sc(OTf)_3}$ (10 mol%), $\mathrm{THF/H_2O}$ (9:1)	70
	$\mathrm{Yb(OTf)_3}$ (10 mol%), $\mathrm{THF/H_2O}$ (9:1)	89
	$\mathrm{Sc(OTf)_3}$ (10 mol%), $\mathrm{THF/H_2O}$ (9:1)	60
	$\mathrm{LiClO_4}$ (300 mol%), $\mathrm{Et_2O}$	17
	$\mathrm{Sc(OTf)_3}$ (120 mol%), $\mathrm{CH_2Cl_2}$	69
	$\mathrm{Yb(OTf)_3}$ (120 mol%), $\mathrm{CH_2Cl_2}$	85
	$\mathrm{Sc(OTf)_3}$ (120 mol%), $\mathrm{CH_2Cl_2}$	70
	$\mathrm{Yb(OTf)_3}$ (120 mol%), $\mathrm{CH_2Cl_2}$	75

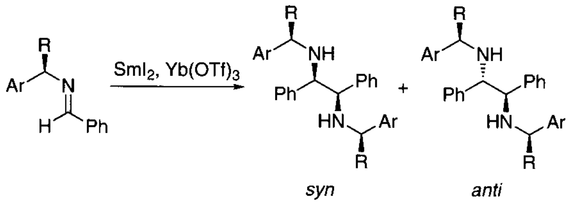
Table 211. Ln(OTf)$_3$-Catalyzed Decarbonylation of 2,4,6-Trimethoxybenzaldehyde



catalyst (mol %)	condition	time[a]
Sc(OTf)$_3$ (16)	25 °C	6 h
Sc(OTf)$_3$ (16)	reflux	15 min
Sc(OTf)$_3$ (100)	reflux	<10 min
Y(OTf)$_3$ (100)	reflux	5 h
La(OTf)$_3$ (100)	reflux	20 h

[a] Time for complete decarbonylation.

Table 212. Diastereoselective Coupling of Aldimines to Diamines



R, Ar	SmI$_2$/ equiv	Yb(OTf)$_3$/ eq.	temp/ °C	yield/% (*syn*/*anti*)
H, Ph	2	0	65	53 (57/43)
H, Ph	2	1	20	81 (>98/2)
Me, Ph	2	1	20	86 (62[a]/38)
Me, 1-naphthyl	2	1	20	23 (65[b]/35)

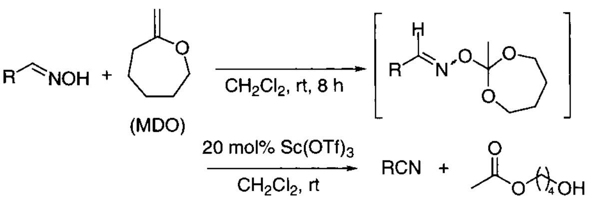
[a] Diatereomeric ratio (dr) of *syn* product (75/25). [b] dr of *syn* product (100/0).

The metal-promoted reductive coupling of aldimines provide symmetrical 1,2-diamines.[431] SmI$_2$ has been shown to be an efficient promoter for the reaction with activated aldimine in the presence of a large excess of reagents or at higher reaction temperature.[432] Yb(OTf)$_3$ accelerated the SmI$_2$-promoted aldimine coupling and improved the yield and diastereoselectivity (Table 212).[433]

Nitriles were obtained by dehydration of aldoximes with 2-methylene-1,3-dioxepane (MDO) in the presence of a Lewis acid (Table 213).[434] Sc(OTf)$_3$ was particularly effective, whereas other Ln(OTf)$_3$ mediated the reaction to different extents. Among the conventional Lewis acids tried, AlCl$_3$ gave the best result. Interestingly, the in situ generated ortho ester was susceptible to rapid hydrolysis when Nd(OTf)$_3$, BF$_3$·OEt$_2$, Ti(O^{i}Pr)$_4$, and ZnCl$_2$ were employed.

High *syn*-selectivity in BF$_3$-promoted addition of (*E*)-γ-OTBS methallyl stannane to aldehydes was observed.[435] This result prompted the search for a preparation of enantioenriched (*E*)-stannanes. It was reported that (*Z*)-γ-OTBS methallyl stannane was readily obtained by a stereospecific *anti* 1,3-isomerization of the enantioenriched α-OTBS crotyl stannane in the presence of BF$_3$·OEt$_2$ (Table 214). However, isomerization of (*Z*)-stannane to (*E*)-stannane was not achieved due to decomposition of the compound in the presence of BF$_3$·OEt$_2$. After several attempts using other Lewis acids, it was found that Yb(OTf)$_3$ promoted a thermodynamic equilibrium between (*E*)- and (*Z*)-stannanes, presumably through two consecutive *anti* 1,3-isomerizations, giving a 3/1 (*E*/*Z*) mixture. The rate of equilibration was surprisingly slow in the presence of other Ln(OTf)$_3$ such as Sc(OTf)$_3$ and La(OTf)$_3$.[436]

Table 213. Transformation of Aldoximes to Nitriles



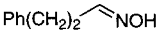
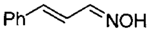
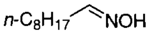
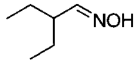
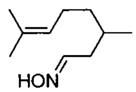
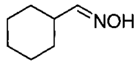
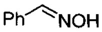
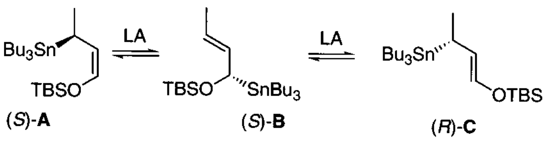
oxime	yield/%	oxime	yield/%
	90		25
	85		70
	81		94
	13		

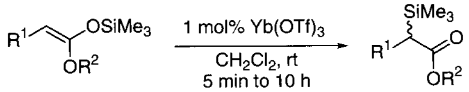
Table 214. Lewis-Acid-Catalyzed Interconversion of Nonracemic α-OTBS Crotyl and γ-OTBS Methallyl Tri-*n*-butylstannanes



stannane	LA	(*S*)-**A**/(*R*)-**C**	yield/%
A	BF$_3$·OEt$_2$	100/1	80
B	BF$_3$·OEt$_2$		*a*
A	Yb(OTf)$_3$	76/24	82
B	Yb(OTf)$_3$	76/24	71
C[b]	Yb(OTf)$_3$	77/23	56

[a] The substrate was decomposed. [b] Racemic substrate was used.

Table 215. Yb(OTf)$_3$-Catalyzed *O*- to *C*-Silyl Migration of Ketene Silyl Acetals



R^1	R^2	time	yield/%	R^1	R^2	time	yield/%
H	Et	5 min	94	Me	^{i}Pr	2 h	>99
Me	Me	2 h	95	Et	Me	7 h	>99
Me	Et	2 h	>99	Bn	Me	10 h	90

A facile isomerization of ketene silyl acetals to α-silyl esters was achieved by a catalytic amount of Yb(OTf)$_3$ (Table 215).[437] Of other Lewis acids tested, Sm(OTf)$_3$ and La(OTf)$_3$ were less efficient, whereas BF$_3$·OEt$_2$ was totally ineffective. ZnI$_2$ showed similar activity to Yb(OTf)$_3$ in CH$_2$Cl$_2$, but no activity in coordinating solvent such as THF. Yb(OTf)$_3$ mediated the isomerization in CH$_2$Cl$_2$, (CH$_2$Cl)$_2$, THF, and CH$_3$CN.

Scheme 90. Yb(OTf)$_3$-Catalyzed Enatioselective 1,2-Migration of (Dichloromethyl)borate

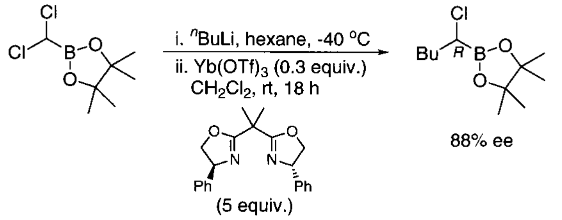
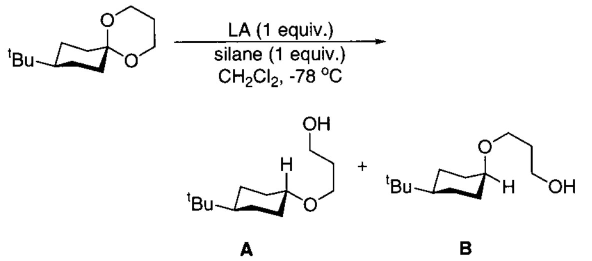


Table 216. Lewis-Acid-Mediated Cleavage of Spiro-1,3-dioxane



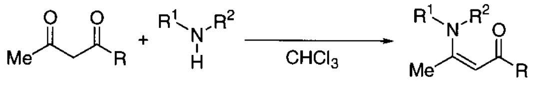
LA	silane	yield/%	A/B
Sc(OTf)$_3$	Me$_3$SiH	35	2/98
BCl$_3$	Me$_3$SiH	74	2/98
AlCl$_3$	Me$_3$SiH	72	13/87
TiCl$_4$	Me$_3$SiH	95	19/81
Sc(OTf)$_3$	Et$_3$SiH	44	51/49
BCl$_3$	Et$_3$SiH	45	42/58
AlCl$_3$	Et$_3$SiH	81	44/56
TiCl$_4$	Et$_3$SiH	83	36/64

The first example of enantiotopic differentiation of two leaving groups on a sp^3 center was reported using chiral Lewis acids.[438] The 1,2-migration of (dichloromethyl)borate gave synthetically useful (α-chlorobutyl)boronate. The best enantioselectivity (88% ee) was achieved by a combination of Yb(OTf)$_3$ and chiral bisoxazoline (Scheme 90). Combination of other Lewis acids, including Zn(OTf)$_2$, Cu(OTf)$_2$, and Lu(OTf)$_3$, with bisoxazoline provided inferior results (35−60% ee).

The Lewis-acid-mediated cleavage of spiro-1,3-dioxane has been investigated.[439] High selectivity was obtained by using Sc(OTf)$_3$ or BCl$_3$ as a catalyst and Me$_3$SiH as a hydride source (Table 216).

Enamino ketones and esters are prepared by the condensation of 1,3-diketone or *β*-ketoester with primary amines;[440] however, reactions with aromatic and hindered amines are more difficult and required the addition of an acid catalyst,[441] microwave irradiation,[442] or azeotropic removal of water formed.[443] It was found that a combination of high pressure and Yb(OTf)$_3$ catalyst dramatically activated the condensation *β*-ketoesters with aromatic and hindered amines.[444] The catalytic effect of Yb(OTf)$_3$ was minimal when 1,3-diketones were involved (Table 217).

Table 217. Pressure Effect and/or Catalytic Effect of Yb(OTf)$_3$ on Condensation of Bulky Amines with Ethyl Acetoacetate or 2,4-Pentanedione

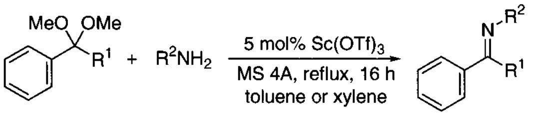


R	R^1, R^2	yield/%[a], 0.1 MPa	yield/%[a], 300 MPa
OEt	^{n}Pr, H	100	
OEt	Ph, H	4 (64)	23 (92)
OEt	^{i}Pr, Me	1 (63)	62 (81)
OEt	Bn, Bn	6 (61)	(64)
OEt	-(CH$_2$)$_5$-	8 (36)	67 (82)
Me	^{n}Pr, H	100	-
Me	Ph, H	9 (100)	85
Me	^{i}Pr, Me	0	12 (3)[c]
Me	-(CH$_2$)$_5$-	6	63

[a] The yields in parentheses were obtained in the presence of Yb(OTf)$_3$. [b] The reactions were performed at 20 °C. [c] Other products were isolated.

Traditional procedures for preparation of imines from acetals and amines required high temperatures (180−200 °C).[445] It was found that the formation of imines was achieved at lower temperatures in the presence of a catalytic amount of Sc(OTf)$_3$ (Table 218).[75] Various amines reacted with aromatic dimethyl acetals to furnish imines. The yields were comparable to or better than those resulting from using stoichiometric amounts of Lewis acids such as TiCl$_4$ and ZnCl$_2$.

Table 218. Sc(OTf)$_3$-Catalyzed Condensation Reactions of Acetals and Amines



R^1	R^{2}NH$_2$	solvent	time/h	yield/%
H	PhNH$_2$	toluene	16	92
Me	^{i}PrNH$_2$	toluene	16	41
Me	PhNH$_2$	toluene	16	89
Ph	^{i}PrNH$_2$	toluene	16	96
Ph	BnNH$_2$	toluene	16	88
Ph	(*R*)-PhCHMeNH$_2$	toluene	16	10
Ph	(*R*)-PhCHMeNH$_2$	xylene	16	90
Ph	4-aminopyridine	xylene	16	55
Ph	4-aminopyridine	xylene	96	76

It was reported that oxymercuration of homoallylic alcohols proceeded in the presence of Yb(OTf)$_3$ (Table 219).[446]

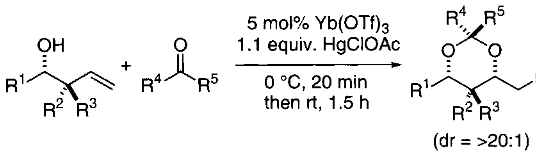
Yb(OTf)$_3$ was utilized for the formation of a diaziridine from a tosyloxime (Scheme 91).[447]

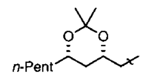
It was reported that multiple reactions in one-pot (Diels−Alder reaction, allylation of aldehyde, and acetylation of alcohol) proceeded smoothly in the presence of 40 mol % of Sc(OTf)$_3$ (Scheme 92).[448] Both yield and chemoselectivity were greatly improved when all reagents were charged in one shot.

Recently, the enantioselective oxidative homocoupling reaction of a ytterbium enolate prepared from 3-phenylacetyl-2-oxazolidinone, Yb(OTf)$_3$, Et$_3$N, and a chiral TADDOL with a ferrocenium cation as an oxidant was shown to proceed in moderate selectivity (53% yield, *dl*/*meso* = 54/46, 34% ee).[449]

In the presence of scandium triflate, an efficient photoinduced electron transfer from the triplet excited C$_{60}$ to *p*-chloranil occurs to produce C$_{60}$ radical cation, which has a diagnostic NIR (near-infrared) absorption band at 980 nm, whereas no efficient photoinduced electron transfer occurs in the absence of the triflate.[450]

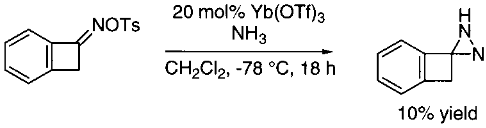
Table 219. Yb(OTf)$_3$-Catalyzed Oxymercuration



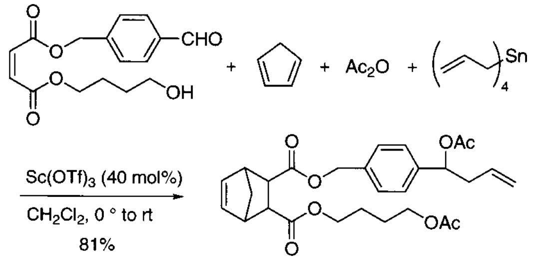
R^1	R^2	R^3	R^4	R^5	yield/%
^{i}Bu	H	H	Me	Me	85
BnO(CH$_2$)$_2$	H	H	Me	Me	85
TBDMSO(CH$_2$)$_2$	H	H	Me	Me	76
^{i}Pr	Me	H	Me	Me	72[a]
TBDMSO(CH$_2$)$_2$	H	Me	Me	Me	83[b]
(*E*)-^{i}PrCH=CH	H	H	Me	Me	54[c]
	H	H	Me	Me	60[c,d]
n-OCt	H	H	Ph	H	86
(*E*)-^{i}PrCH=CH	H	H	Ph	H	68

[a] 11:1 diasteroselectivity; 3 h at room temperature. [b] At −78 °C to room temperature. [c] At 0 °C. [d] With 10 mol % Yb(OTf)$_3$.

Scheme 91. Formation of Diaziridine from a Tosyloxime



Scheme 92. Four-Component Reaction



In a synthetic study of diphenylmethane from formalin and benzene, it was reported that Sc(OTf)$_3$ catalyzed dimerization of HCHO to HCOOMe but was inactive for the formation of diphenylmethane.[451]

9. Lanthanide(II) Triflates in Organic Synthesis

Sm(II) and Yb(II) triflates were prepared in situ by reduction of the corresponding tripositive ions with a Grignard reagent (Scheme 90). They were used for Barbier-type reactions of alkyl halides with ketones and the Reformatsky-type reactions of haloesters with ketones.[452] Salt-free Sm(OTf)$_2$ was prepared by reduction of Sm(OTf)$_3$ with Sm metal in DME (Scheme 93).[453] The DME-solvated complex was isolated, freely soluble in CH$_2$Cl$_2$, THF, and CH$_3$CN, and highly air- and water-sensitive. It acted as a stoichiometric reagent to promote pinacol coupling of acetophenone, dimerization of imines, Barbier-type reactions of alkyl halides with ketones, and the coupling reaction of cyclohexanone with methyl methacrylate to afford the corresponding lactone. Moreover, aldol reaction, Michael reaction, and Mannich-type reactions with ketene silyl acetals as well as Diels−Alder reaction of cyclopentadiene with *N*-crotonoyl oxazolidinone were also catalyzed by Sm(OTf)$_2$(DME)$_2$. It should be noted that facile enolization of carbonyl compounds with Sm(II) halides was suppressed by using Sm(OTf)$_2$(DME)$_2$.

Scheme 93. Preparation of Ln(OTf)×e2Q

$$\mathrm{Ln(OTf)_3 + EtMgBr} \xrightarrow[25\ ^\circ\mathrm{C}]{\mathrm{THF}} \mathrm{Ln(OTf)_2}$$

Ln= Sm, Yb

$$\mathrm{2[Sm(OTf)_3] + Sm} \xrightarrow[\mathrm{DME}]{\mathrm{Hg\ (cat.)}} \mathrm{3[Sm(OTf)_2(DME)_2]}$$

DME = dimethoxyethane

Recently, it was revealed that the electrochemical reduction of ytterbium and samarium triflate salts provides a simple and convenient route to solutions of divalent lanthanides.[454]

10. Conclusion

Rare-earth metal triflate(s) is a new type of Lewis acid that is different from conventional Lewis acids such as AlCl$_3$, BF$_3$, SnCl$_4$, etc. While most of the Lewis acids are decomposed or deactivated in the presence of water, rare-earth triflates are stable and work as Lewis acids in aqueous solutions as well as organic solvents. Catalytic use has been attained, and many nitrogen-containing compounds including imines and hydrazones are successfully activated with rare-earth metal triflates.

Several useful organic transformations using conventional Lewis acids have been repeated with rare-earth metal triflates, and in many cases, they show comparable and superior performance. In particular, catalytic amounts of rare-earth metal triflates have been successfully used, while stoichiometric amounts of conventional Lewis acids have been employed in many cases. It becomes a common practice to test rare-earth metal triflates in both the known and some new reactions. In addition, they can be recovered and reused without loss of activity. These properties will lead to really environmentally friendly chemical processes using rare-earth metal triflates as catalysts.

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