Scandium Triflate in Organic Synthesis

Shū Kobayashi[a]

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$Sc(OTf)_3$ is a new type of a Lewis acid that is different from typical Lewis acids such as $AlCl_3$, BF_3, $SnCl_4$, etc. While most Lewis acids are decomposed or deactivated in the presence of water, $Sc(OTf)_3$ is stable and works as a Lewis acid in water solutions. Many nitrogen-containing compounds such as imines and hydrazones are also successfully activated by using a small amount of $Sc(OTf)_3$ in both organic and aqueous solvents. In addition, $Sc(OTf)_3$ can be recovered after reactions are completed and can be reused. While lanthanide triflates [$Ln(OTf)_3$] have similar properties, the catalytic activity of $Sc(OTf)_3$ is higher than that of $Ln(OTf)_3$ in several cases.

1. Introduction

While the element scandium (Sc) is in group 3 and lies above La and Y, its radius is appreciably smaller than those of any other rare earth elements. The chemical behavior of scandium is known to be intermediate between that of aluminum and lanthanides.[1] Scandium has been uncommon probably due to the lack of rich sources and to difficulties in separation, and its use in organic synthesis is rather limited although unique characteristics might be expected. In 1993, we first introduced scandium trifluoromethanesulfonate [$Sc(OTf)_3$] as a promising Lewis acid in organic synthesis.[2] While Lewis acid catalyzed carbon−carbon bond-forming reactions are now of great interest in organic synthesis, these reactions must be carried out under strictly anhydrous conditions, because most Lewis acids immediately react with water rather than the substrates and are decomposed or deactivated. On the other hand, $Sc(OTf)_3$ was readily prepared from scandium oxide (Sc_2O_3) and aqueous trifluoromethanesulfonic acid (TfOH) solution, and was found to be stable in water. In addition, $Sc(OTf)_3$ effectively activated carbonyl and related compounds as a Lewis acid in water. While we had already found that lanthanide triflates [$Ln(OTf)_3$; Ln = La, Ce, Pr, Nd, Sm, Eu, Gd, Tb, Dy, Ho, Er, Tm, Yb, Lu] and yttrium triflate [$Y(OTf)_3$] are stable in water and can act as Lewis acid catalysts in aqueous media,[3] $Sc(OTf)_3$ has remarkably excellent properties even compared to $Ln(OTf)_3$ in some cases. Moreover, $Sc(OTf)_3$ worked well as a Lewis acid catalyst in several organic solvents and chiral scandium triflates have also been developed.

In this article, useful synthetic reactions using $Sc(OTf)_3$ as a catalyst, especially focused on carbon−carbon bond-forming reactions, are discussed.

2. Aldol Reactions

Aldol Reactions in Organic Solvents

$Sc(OTf)_3$ was found to be an effective catalyst in aldol reactions of silyl enol ethers with aldehydes.[4,5] The activi-

Shū Kobayashi was born in 1959 in Tokyo, Japan. He studied chemistry at the University of Tokyo and received his Ph. D. under the supervision of Professor Teruaki Mukaiyama in 1988. He became Assistant Professor (1987), Lecturer (1991), and Associate Professor (1992) of Science University of Tokyo (SUT). In 1998, he moved to the University of Tokyo to become Professor of Pharmaceutical Sciences. He was Visiting Professor of Universite Louis Pasteur, Strasbourg (1993), Kyoto University (1995), Nijmegen University (1996), and Philipps-Universität Marburg (1997). His research interests include development of new synthetic methods and catalysts, development of new methodologies for library synthesis, aqueous reactions, total synthesis of biologically important compounds, and organometallic chemistry. He received the Chemical Society of Japan Award for Young Chemists (1991), Teijin Award in Synthetic Organic Chemistry, Japan (1992), and Springer Award in Organometallic Chemistry (1997).

MICROREVIEWS: This feature introduces the readers to the authors' research through a concise overview of the selected topic. Reference to important work from others in the field is included.

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[a] Graduate School of Pharmaceutical Sciences, The University of Tokyo,
Hongo, Bunkyo-ku, Tokyo 113-0033, Japan
Fax: (internat.) + 81-3/5684-0634
E-mail: skobayas@mol.f.u-tokyo.ac.jp

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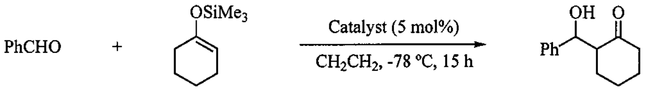
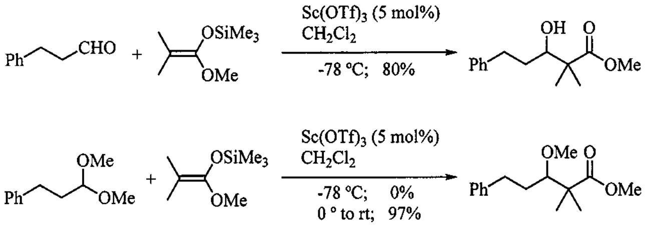
ties of typical rare earth triflates [Sc, Y, Yb(OTf)$_3$] were evaluated in the reaction of 1-trimethylsiloxycyclohexene with benzaldehyde in dichloromethane (Table 1). While the reaction scarcely proceeded at −78°C in the presence of Yb(OTf)$_3$ or Y(OTf)$_3$,[3b] the aldol adduct was obtained in an 81% yield in the presence of Sc(OTf)$_3$. Obviously, Sc(OTf)$_3$ was more active than Y(OTf)$_3$ or Yb(OTf)$_3$ in this case.

Table 1. Effect of catalysts



Entry	Catalyst	Yield/%
1	Sc(OTf)$_3$	81
2	Y(OTf)$_3$	trace
3	Yb(OTf)$_3$	trace

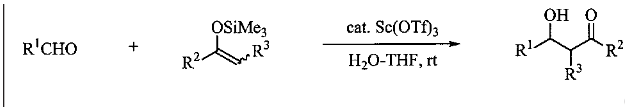
Several examples of the Sc(OTf)$_3$-catalyzed aldol reactions of silyl enolates with aldehydes were examined. Silyl enolates derived from ketones, thioesters, and esters reacted smoothly with various types of aldehydes in the presence of 5 mol-% of Sc(OTf)$_3$ to afford the aldol adducts in high yields. Sc(OTf)$_3$ was also found to be an effective catalyst in aldol-type reactions of silyl enolates with acetals. The reactions proceeded smoothly at −78°C or room temperature to give the corresponding aldol-type adducts in high yields without side reaction products. It should be noted that aldehydes were more reactive than acetals. For example, while 3-phenylpropionaldehyde reacted with the ketene silyl acetal of methyl isobutyrate at −78°C to give the aldol adduct in an 80% yield, no aldol-type adduct was obtained at −78°C in the reaction of the same ketene silyl acetal with 3-phenylpropionaldehyde dimethyl acetal. The acetal reacted with the ketene silyl acetal at 0°C to room temperature to give the adduct in a 97% yield (Scheme 1).



Scheme 1. Sc(OTf)$_3$-catalyzed aldol reactions

Aldol Reactions in Aqueous Media

The importance of aqueous reactions is now generally recognized, and development of carbon−carbon bond-forming reactions that can be carried out in aqueous media is now one of the most challenging topics in organic synthesis.[6] It was found that Sc(OTf)$_3$ was effective in the aldol reactions of silyl enolates with aldehydes in aqueous media (water/THF; Equation 1).[4] The reactions of aromatic and aliphatic aldehydes such as benzaldehyde and 3-phenylpropionaldehyde with silyl enolates were successfully carried out in aqueous solvents. In addition, water-soluble formaldehyde and chloroacetaldehyde were directly treated as water solutions with silyl enolates to afford the corresponding aldol adducts in good yields. It is noted that water-sensitive silyl enolates could be used in water solutions using Sc(OTf)$_3$ as a catalyst.



(1)

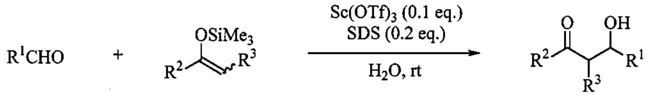
Aldol Reactions in Micellar Systems

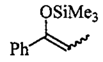
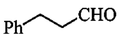
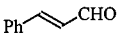
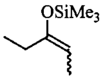
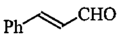
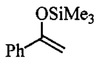
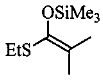
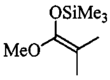
Quite recently, the Sc(OTf)$_3$-catalyzed aldol reactions of silyl enol ethers with aldehydes were successfully performed in micellar systems.[7] While the reaction proceeded sluggishly in water (without organic solvents), remarkable enhancement of the reactivity was observed in the presence of a small amount of a surfactant. In these systems, versatile carbon−carbon bond-forming reactions proceeded smoothly in water without using any organic solvents.

Lewis acid catalysis in micellar systems was first found in the model reaction of the silyl enol ether of propiophenone with benzaldehyde. While the reaction proceeded sluggishly in the presence of 0.2 equiv. of Yb(OTf)$_3$ in water, remarkable enhancement of the reactivity was observed when the reaction was carried out in the presence of 0.2 equiv. of Yb(OTf)$_3$ in an aqueous solution of sodium dodecyl sulfate (SDS, 0.2 equiv., 35 mM), and the corresponding aldol adduct was obtained in a 50% yield. The yield was improved to 88% when Sc(OTf)$_3$ (0.1 equiv.) was used as a Lewis acid catalyst. Judging from the critical micelle concentration, micelles would be formed in these reactions. It was also found that the surfactants influenced the yield, and that Triton X-100 was effective in the aldol reaction (but required a longer reaction time), while only a trace amount of the adduct was detected when using cetyltrimethylammonium bromide (CTAB) as a surfactant. Although several organic reactions in micelles were reported,[8] this is the first report of Lewis acid catalysis in micellar systems.

Several examples of the Sc(OTf)$_3$-catalyzed aldol reactions in micellar systems are shown in Table 2. Not only aromatic, but also aliphatic and α,β-unsaturated aldehydes reacted with silyl enol ethers to afford the corresponding aldol adducts in high yields. Aqueous formaldehyde solution also worked well. Even the ketene silyl acetals, which are known to hydrolyze very easily in the presence of a small amount of water, reacted with aldehydes in the present micellar systems to afford the corresponding aldol adducts in high yields. It should be noted that work-up procedures including phase separation are easy since only a small amount of the surfactant was used.

Table 2. $Sc(OTf)_3$-catalyzed aldol reactions in micellar systems

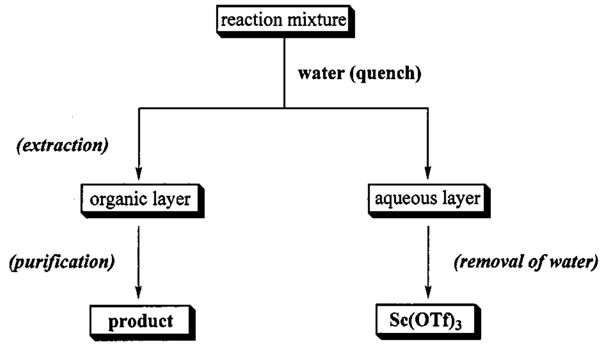


Aldehyde	Silyl Enol Ether	Yield/%
PhCHO	 1	88 [a]
	1	86 [b]
	1	88 [c]
HCHO	1	82 [d]
PhCHO	 2	88 [e]
	2	80 [f]
PhCHO		75 [g, h]
PhCHO		94
PhCHO	 3	84 [h]

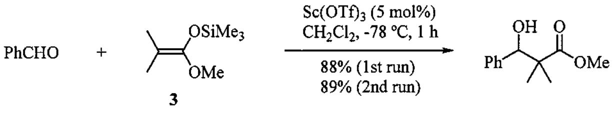
[a] *syn/anti* = 50:50. – [b] *syn/anti* = 45:55. – [c] *syn/anti* = 41:59. – [d] Commercially available HCHO aq. (3 ml), **1** (0.5 mmol), $Sc(OTf)_3$ (0.1 mmol), and SDS (0.1 mmol) were combined. – [e] *syn/anti* = 57:43. – [f] *syn/anti* = 69:31. – [g] $Sc(OTf)_3$ (0.2 equiv.) was used. – [h] Additional silyl enolate (1.5 equiv.) was charged after 6 h.

Recovery and Reuse of the Catalysts

$Sc(OTf)_3$ is more soluble in water than that in organic solvents such as dichloromethane. The catalyst could be recovered almost quantitatively from the aqueous layer after the reaction was completed (Scheme 2) and it could be reused. The recovered catalyst was also effective in the 2nd reaction, and the yield of the 2nd run was comparable to that of the 1st run (Equation 2).[4] $Sc(OTf)_3$ is expected to solve some severe environmental problems caused by mineral or Lewis acid promoted reactions in the chemical industry.



Scheme 2. Recover of the catalyst



(2)

Aldol Reactions Using Polymer-Supported Silyl Enol Ethers

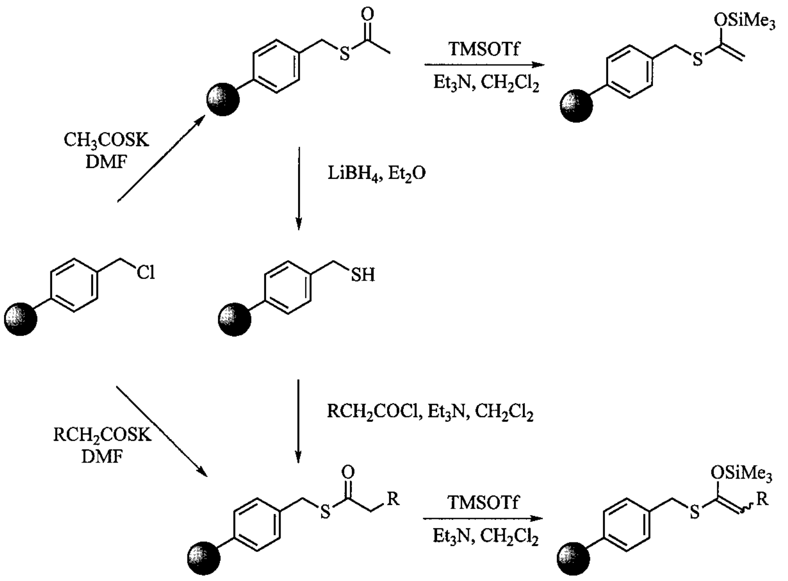
Silyl enol ethers are versatile reagents in organic synthesis.[9] They are used as isolable enolate equivalents and many useful reactions using silyl enol ethers have been developed.[9] As a new approach to exploit an efficient method for combinatorial synthesis,[10] silyl enol ethers were successfully immobilized onto a polymer. Polymer-supported silyl enol ethers (PSSEEs) were prepared according to Scheme 3.[11] In aldol reactions of PSSEEs with aldehydes, it was also revealed that $Sc(OTf)_3$ was an efficient catalyst.[12] An example of the preparation of a 1,3-diol library using PSSEEs is shown in Scheme 4. In all cases, the reactions proceeded smoothly to afford the corresponding 1,3-diols in good yields. While 1,3-diols are successfully cleaved from the support by treatment with $LiBH_4$, it is also possible to produce β-hydroxy aldehydes or β-hydroxy carboxylic acids directly using appropriate cleavage (Scheme 5).

3. Michael Reactions

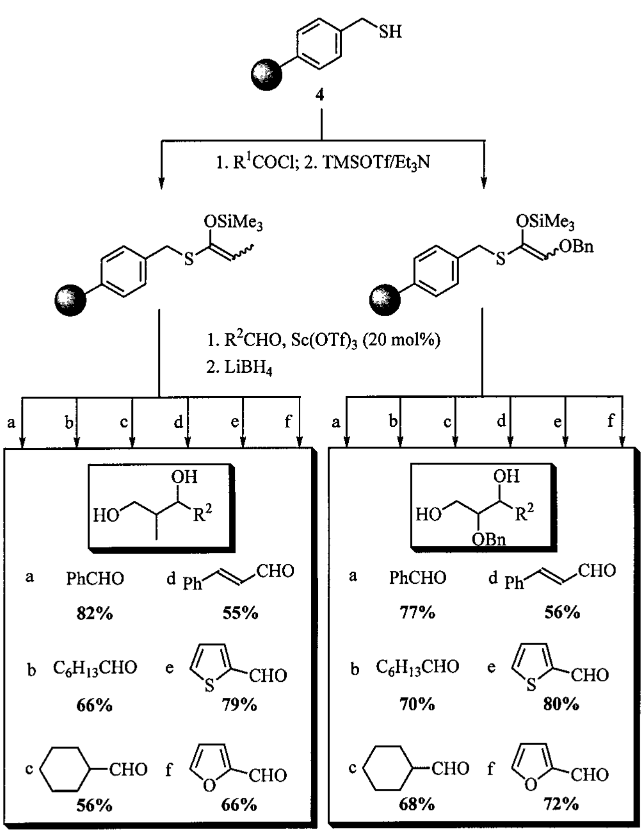
The Michael reactions of silyl enol ethers or ketene silyl acetals with α,β-unsaturated carbonyl compounds are among the most important carbon−carbon bond-forming processes in organic synthesis. $Sc(OTf)_3$ was found to be an effective and reusable catalyst in these reactions.[4] The reactions proceeded smoothly in the presence of a catalytic amount of $Sc(OTf)_3$ under extremely mild conditions to give the corresponding 1,5-dicarbonyl compounds in high yields after acid work-up (Equation 3). Silyl enolates derived from ketones, thioesters, and esters were applicable, and no 1,2-addition products were obtained. Furthermore, the products could be isolated as synthetically valuable silyl enol ethers (**5**) when the crude adducts were worked up without acid. The catalyst could be recovered almost quantitatively and could be reused.

4. Allylation Reactions

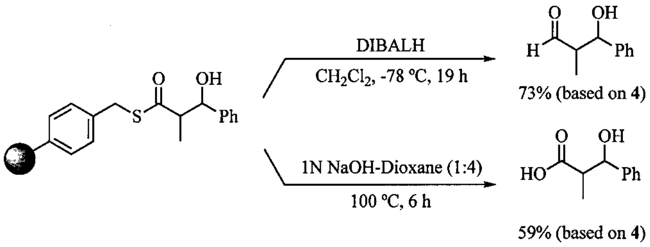
Synthesis of homoallylic alcohols by the reaction of organometallic allyl compounds with carbonyl compounds is one of the most important processes in organic synthesis.[13] The allylation reactions of carbonyl compounds with tetraallyltin[13][14] proceeded smoothly under the influence of a catalytic amount of $Sc(OTf)_3$[15] to afford the adducts,



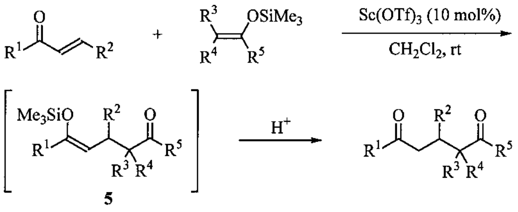
Scheme 3. Synthesis of polymer-supported silyl enol ethers



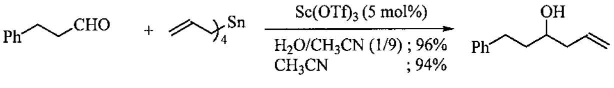
Scheme 4. 1,3-Diol library based on aldol reactions



Scheme 5. Conversion to β-hydroxy aldehyde or β-hydroxy carboxylic acid



(3)



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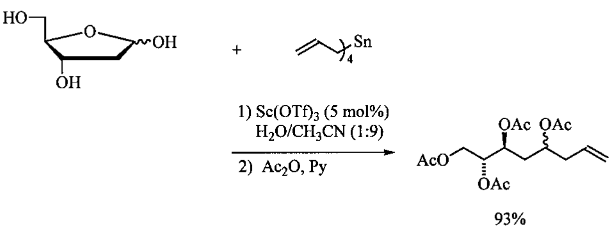
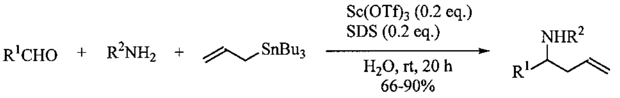


(5)

homoallylic alcohols, in high yields under extremely mild conditions.[16] In most cases, the reactions were successfully carried out in aqueous media (Equation 4). It is noteworthy that unprotected sugars reacted directly to give the adducts in high yields (Equation 5). The allylated adducts are intermediates for the synthesis of higher sugars.[17] The allylation reactions of aldehydes with tetraallyltin also proceeded smoothly in micellar systems using Sc(OTf)$_3$ as a catalyst.[18a] No organic solvents were used in these cases.

Furthermore, three-component reactions of aldehydes, amines, and allyltributyltin proceeded smoothly in micellar systems using Sc(OTf)$_3$ as a Lewis acid catalyst (Equation

6) to afford the corresponding homoallylic amines in high yields.[18b] Not only aromatic aldehydes but also aliphatic, unsaturated, and heterocyclic aldehydes worked well. The procedure is very simple; just mixing an aldehyde, an amine, and allyltributyltin in the presence of $Sc(OTf)_3$ and SDS in water, and no homoallylic alcohol (an adduct between an aldehyde and allyltributyltin) was produced. It was suggested that imine formation from aldehydes and amines was very fast under these conditions, and that the selective activation of imines rather than aldehydes was achieved.

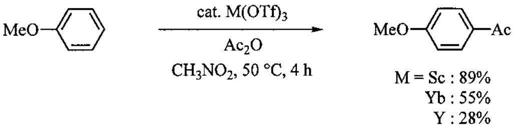


(6)

It is noteworthy that the use of the recoverable scandium catalyst and water as the solvent would result in clean and environmentally friendly systems.

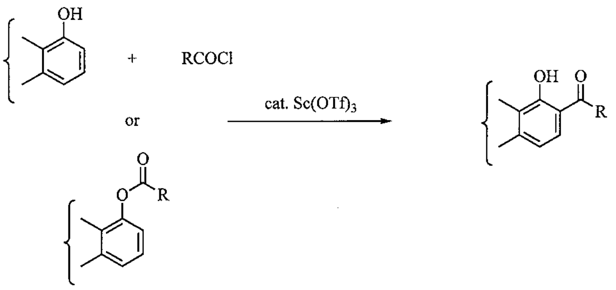
5. Friedel-Crafts Acylation and Fries Rearrangement

While Friedel−Crafts acylation reactions are fundamental and important processes in organic synthesis as well as in industrial chemistry,[19] more than a stoichiometric amount of a Lewis acid such as $AlCl_3$ or BF_3 is needed due to the consumption of the Lewis acid by coordination to aromatic ketones produced. It was found that a small amount of $Sc(OTf)_3$ catalyzed some Friedel−Crafts acylation reactions.[20] The catalytic activity of $Sc(OTf)_3$ was found to be much higher than that of $Ln(OTf)_3$ (Equation 7). Although the acylation of benzene or chlorobenzene did not occur, introduction of an electron-donating group was effective for the promotion of the acylation. For example, in the acetylation of thioanisole, *o*- or *m*-dimethoxybenzene gave a single acetylated product in an excellent yield. Benzoylation of anisole also proceeded smoothly in the presence of a catalytic amount of $Sc(OTf)_3$. Although both benzoic anhydride and benzoyl chloride were effective in the reactions, benzoic anhydride gave a slightly higher yield of 4-methoxybenzophenone. In each reaction, formation of the other isomers was not detected by GLC. Also in this reaction, $Sc(OTf)_3$ could be easily recovered from aqueous layers and reused. In addition, it was found that addition of lithium perchlorate ($LiClO_4$) as a co-catalyst improved the yields dramatically.[21] This novel $Sc(OTf)_3$-catalyzed Friedel−Crafts acylation reaction is remarkable and has advantages over the conventional $AlCl_3$-promoted reaction.



(7)

The Fries rearrangement of acyloxybenzene or naphthalene derivatives proceeded smoothly in the presence of a catalytic amount of $Sc(OTf)_3$ (Equation 8).[22] It was also found that the triflate was an efficient catalyst in 2-acylation (direct acylation) reactions of phenol or naphthol derivatives with acid chlorides. Both reactions were successfully carried out using a small amount of $Sc(OTf)_3$.



(8)

6. Diels−Alder Reactions

The Diels−Alder reaction is one of the most useful synthetic conversions used to form cyclic structures. Although many Diels−Alder reactions have been carried out at high reaction temperatures without catalysts, heat-sensitive compounds in complex and multistep syntheses cannot be employed. Furthermore, the Diels−Alder reaction is reversible, and the lowest possible temperatures are generally used. 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 the catalyst are often needed to catalyze carbonyl-containing dienophiles.[23]

Lanthanide triflates are also efficient catalysts in some Diels−Alder reactions, although $Sc(OTf)_3$ is clearly more effective than lanthanide triflates as a catalyst.[2,24] In the presence of 10 mol-% of $Y(OTf)_3$ or $Yb(OTf)_3$, only a trace amount of the adduct was obtained in the Diels−Alder reaction of methyl vinyl ketone (MVK) with isoprene. However, the reaction proceeded smoothly to give the adduct in a 91% yield in the presence of 10 mol-% of $Sc(OTf)_3$.[2] Several examples of the $Sc(OTf)_3$-catalyzed Diels−Alder reactions are shown in Table 3. In all cases, the Diels−Alder adducts were obtained in high yields with high *endo* selectivities.

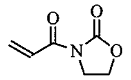
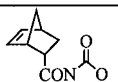
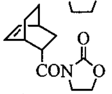
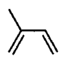
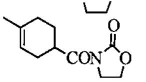
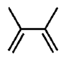
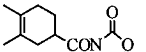
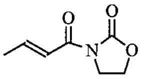
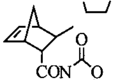
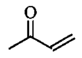
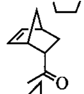
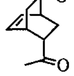
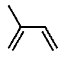
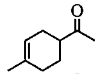
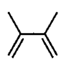
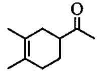
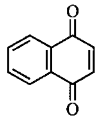
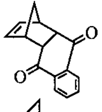
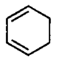
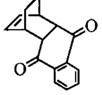
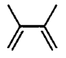
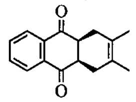
The present Diels−Alder reaction even proceeded in aqueous media.[25] Thus, naphthoquinone reacted with cyclopentadiene in THF/H_2O (9:1) at room temperature to give the corresponding adduct in a 93% yield (*endo*/*exo* = 100:0) (Equation 9).

7. Aza Cycloaddition Reactions

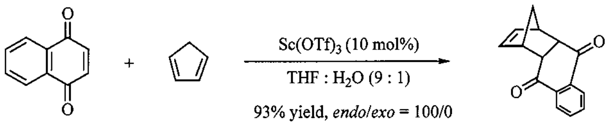
Aza Diels−Alder Reactions

The Diels−Alder reactions of imines (aza Diels−Alder reactions, imino Diels−Alder reactions) are recognized as being among the most useful synthetic tools for the preparation of nitrogen-containing six-membered heterocycles.[26] Although Lewis acids often promote these reactions, more than stoichiometric amounts of the acids are

Table 3. $Sc(OTf)_3$-catalyzed Diels−Alder reaction[a]

Entry	Dienophile	Diene	Major Product	Yield/%[b]	endo/exo[c]
1				95	87/13
2				89	100/0
3				90	—
4				86	—
5				97	84/16
6				96	89/11
7				83	>95/5
8				91	—
9				88	—
10				83	100/0
11				89	94/6
12				92	—

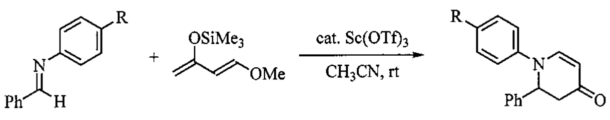
[a] Reaction conditions; $Sc(OTf)_3$ 10 mol-%, CH_2Cl_2, 0°C. − [b] Isolated yield. − [c] Determined by ^1H and/or ^{13}C NMR.



(9)

required due to the strong coordination of the acids to nitrogen atoms.[26] $Sc(OTf)_3$ was proved to be an efficient catalyst in these reactions.

In the presence of 10 mol-% of $Sc(OTf)_3$, *N*-benzylideneaniline reacted with 2-*trans*-1-methoxy-3-trimethylsiloxy-1,3-butadiene (Danishefsky′s diene)[27] to afford the corresponding imino Diels−Alder adduct, a tetrahydropyridine derivative, quantitatively (Equation 10).[28] On the other hand, in the reaction of *N*-benzylideneaniline with cyclopentadiene under the same conditions, the reaction course changed and a tetrahydroquinoline derivative was obtained (Equation 11). In this reaction, the imine acted as an azadiene toward one of the double bonds of cyclopentadiene as a dienophile.[29] In the reaction using 2,3-dimethylbutadiene, a mixture of tetrahydropyridine and tetrahydroquinoline derivatives was obtained. A vinyl sulfide, a vinyl ether, and a silyl enol ether worked well as dienophiles to afford the tetrahydroquinoline derivatives in high yields.[30][31]



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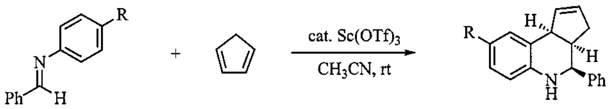
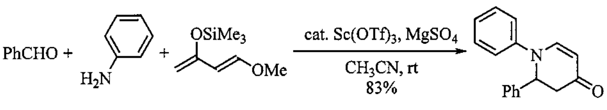


(11)

One synthetic problem in the imino Diels−Alder reactions is the stability of imines under the influence of Lewis acids. It is desirable that the imines activated by Lewis acids are immediately trapped by dienes or dienophiles. In 1989, 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 *N*-sulfonylimine produced in situ, by using a stoichiometric amount of $BF_3{\cdot}OEt_2$ as a promoter.[32]

$Sc(OTf)_3$-catalyzed three-component coupling reactions of aldehydes, amines, and dienes were examined. In the presence of 10 mol-% of $Sc(OTf)_3$ and magnesium sulfate, benzaldehyde was treated with aniline and Danishefsky's diene. The desired three-component reaction proceeded smoothly to afford the corresponding tetrahydropyridine derivative in an 83% yield (Equation 12).[28b] Under the same reaction conditions, cyclopentadiene was used instead of Danishefsky′s diene to afford the corresponding tetrahydroquinoline derivative (Equation 13). Various combinations of aldehydes, amines, and alkenes are possible in these reactions to afford diverse tetrahydroquinoline derivatives in high yields.



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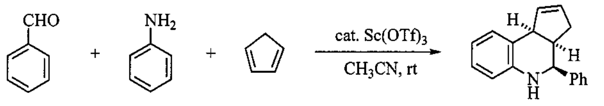
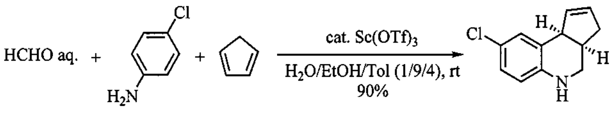


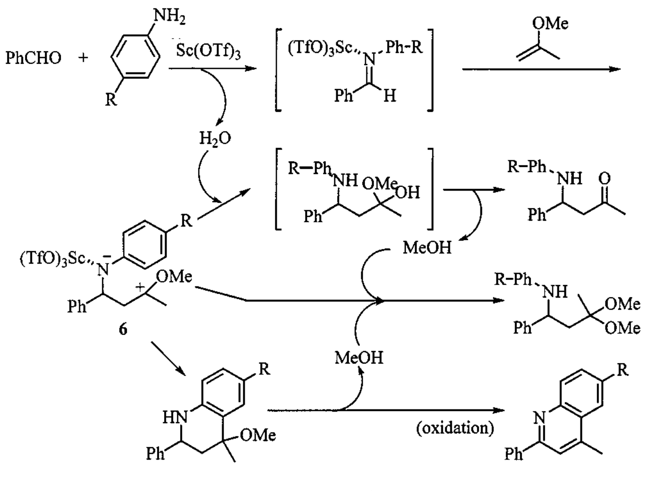
(13)

Moreover, the three component coupling reactions proceeded smoothly in aqueous solution, and commercial formaldehyde water solution could be used directly (Equation 14).



(14)

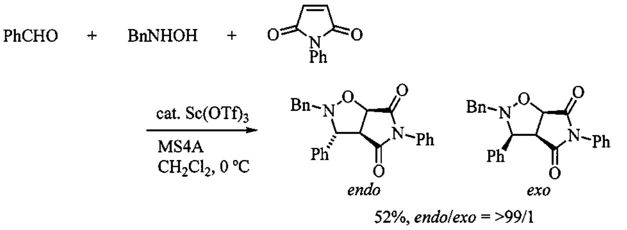
A possible mechanism of these reactions is shown in Scheme 6.[28b] It is noted that a stepwise mechanism including intermediate **6** is suggested in these types of aza Diels–Alder reactions.[33]



Scheme 6. A possible mechanism of the three-component coupling reaction

1,3-Dipolar Cycloadditions

The 1,3-dipolar cycloaddition of nitrones to alkenes provides a useful route to isoxazolidine derivatives, whose reductive cleavage gives a range of compounds such as β-hydroxy ketones, β-amino alcohols, etc.[34] Although Lewis acids are known to promote the cycloaddition,[34][35] some nitrones, especially aliphatic nitrones, are unstable under these conditions and lower yields are sometimes observed. The three-component coupling reaction of benzaldehyde, *N*-benzylhydroxylamine, and *N*-phenylmaleimide proceeded smoothly in the presence of a catalytic amount of a $Sc(OTf)_3$, to afford the corresponding isoxazolidine derivative in a good yield with a high diastereoselectivity (Equation 15).[36]



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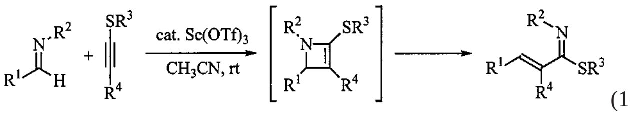
[2 + 2] Cycloaddition Reactions of Imines with Alkynyl Sulfides

α,β-Unsaturated thioimidates are useful intermediates in organic synthesis.[37] Recently, it was found that a new reaction of imines with alkynyl sulfides proceeded smoothly in the presence of a catalytic amount of $Sc(OTf)_3$ affording α,β-unsaturated thioimidates.[38] These reactions are assumed to proceed by [2 + 2] cycloaddition and successive fragmentation. Thus, the [2 + 2] cycloaddition of imines to alkynyl sulfides proceeds smoothly to form azetine intermediates which are unstable and immediately fragment to the corresponding α,β-unsaturated thioimidates (Equation 16).



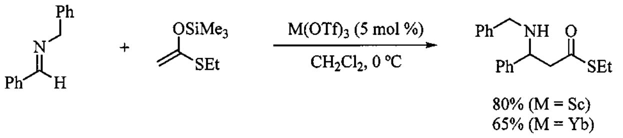
(16)

8. Mannich-Type Reactions

Mannich-Type Reactions in Organic Solvents

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.[39] In the classical Mannich routes to β-amino ketones and esters, yields are sometimes low because significant side reactions, such as deamination, occur under the rather drastic reaction conditions. To perform the reactions under milder conditions, new modifications using preformed iminium salts[40] and imines[41] were introduced. However, these intermediates are often hygroscopic and/or thermally unstable. As for the reactions using silyl enolates, use of a stoichiometric amount of $TiCl_4$ as a promoter was first reported in 1977[41a], and since then, some efficient catalysts have been developed.[41c−41g,42]

It was first observed that reactions of imines with ketene silyl acetals proceeded smoothly in the presence of 5 mol-% of $Yb(OTf)_3$ (a representative lanthanide triflate) to afford the corresponding β-amino ester derivative in a moderate yield. The yield was improved when $Sc(OTf)_3$ was used instead of $Yb(OTf)_3$ as a catalyst (Equation 17).[43] Not only silyl enolates derived from esters, but also one derived from a thioester worked well to give the desired β-amino esters and thioester with high yields. In the reactions of the silyl enolate derived from benzyl propionate, *anti* adducts were obtained in good selectivities. In addition, the catalyst could be recovered after the reaction was completed and could be reused.

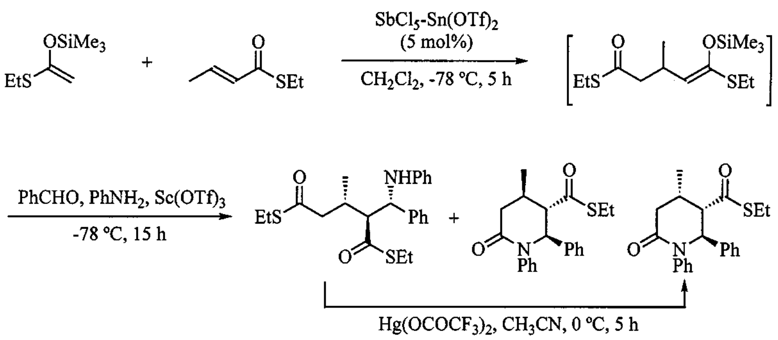


(17)

A novel Mannich-type reaction of *N*-(β-aminoalkyl)benzotriazoles with silyl enolates has also been developed.[44] Four-component (silyl enolates, α,β-unsaturated thioesters, amines, and aldehydes) coupling reactions were successfully carried out using $Sc(OTf)_3$ as a catalyst, to afford the corresponding amino thioester and γ-acyl-δ-lactam derivatives stereoselectively in high yields (Scheme 7).[45]

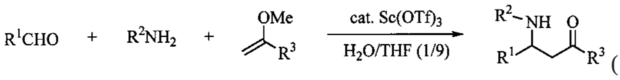
Mannich-Type Reactions in Aqueous Media

Mannich-type reactions of aldehydes, amines, and vinyl ethers proceeded smoothly in the presence of a catalytic



Scheme 7. Synthesis of γ-acyl-δ-lactam derivatives

amount of $Sc(OTf)_3$ in aqueous media (Equation 18).[46] Commercially available formaldehyde and chloroacetaldehyde aqueous solutions were used directly and the corresponding β-amino ketones were obtained in good yields. Phenylglyoxal monohydrate, methyl glyoxylate, an aliphatic aldehyde, and an α,β-unsaturated aldehyde also worked well to give the corresponding β-amino esters in high yields. It should be noted that dehydration accompanied by imine formation and successive addition of a vinyl ether proceeded smoothly in aqueous solution. Use of $Sc(OTf)_3$, a water-stable Lewis acid, is a key feature in this reaction.

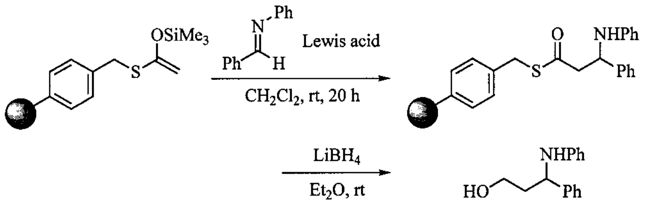


(18)

Mannich-Type Reactions Using PSSEE

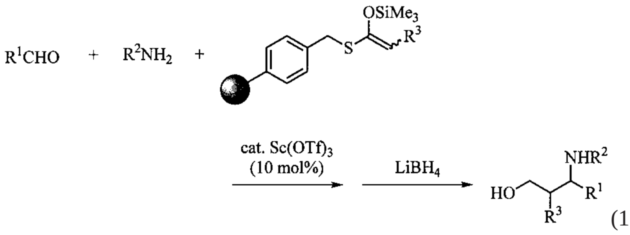
PSSEEs reacted with imines in the presence of a Lewis acid to afford β-amino thioesters, which were reduced to give amino alcohols (Table 4).[11] In this reaction, although typical Lewis acids such as $TiCl_4$, $SnCl_4$, and $BF_3{\cdot}OEt_2$ gave poor results, a catalytic amount of $Sc(OTf)_3$ or $Hf(OTf)_4$ gave better results. This process provides a convenient method for the construction of an amino alcohol library.

Table 4. Effect of Lewis acids



Lewis Acid/mol%	Yield/%	Lewis Acid/mol%	Yield/%
$SnCl_4$ (100)	2	$Zr(OTf)_4$ (10)	23
$TiCl_4$ (100)	3	$Hf(OTf)_4$ (10)	70
$BF_3{\cdot}OEt_2$ (100)	10	$Sn(OTf)_2$ (10)	40
$Sc(OTf)_3$ (10)	65	TMSOTf (10)	47

In the solid phase, $Sc(OTf)_3$ also effectively catalyzed the Mannich-type three-component reactions of aldehydes, amines, and PSSEEs to afford polymer-supported β-amino thioesters (Equation 19). Reductive cleavage from the supports gave the amino alcohols in good to high yields.[47] β-Amino acid and β-lactam libraries are also constructed according to the present method (Equation 20).



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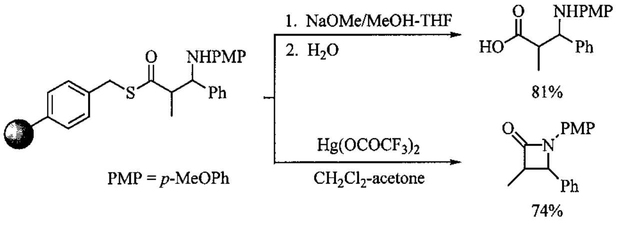
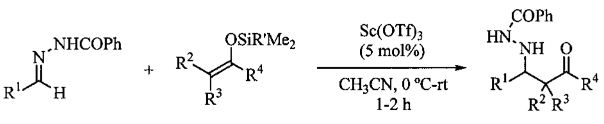


(20)

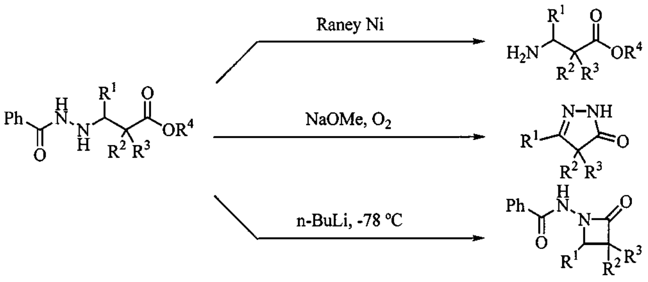
9. Mannich-Type Reactions Using Hydrazones

Acylhydrazones are aldehyde and ketone equivalents as well as imines. Their stability is much higher than imines and indeed acylhydrazones derived from aliphatic aldehydes are often crystalline and can be stored, although their reactivity as electrophiles is known to be low. 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 (Equation 21).[48] Not only aromatic but also aliphatic, α,β-unsaturated aldehydes, and glyoxylate benzoylhydrazones worked well. On the other hand, the catalytic activation of benzoylhydrazones using a typical Lewis acid such as $TiCl_4$, $SnCl_4$, or $BF_3{\cdot}OEt_2$, etc. was not effective in this reaction.



(21)

The β-*N′*-benzoylhydrazino esters were readily converted to the various N-containing compounds. Reductive cleavage of the nitrogen−nitrogen bond of the hydrazino compounds was successfully carried out using Raney Ni under H_2[49] to afford the β-amino esters. Cyclization of β-*N′*-benzoylhydrazino esters was also carried out under basic conditions, and β-lactams were obtained by treatment with *n*BuLi at −78 °C, while pyrazolones were produced in the presence of NaOMe in MeOH at room temperature or under reflux conditions (Scheme 8).



Scheme 8. Conversion to β-amino esters, pyrozolones, or β-lactams

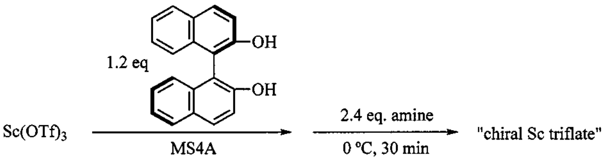
10. Asymmetric Catalysts

Asymmetric Diels−Alder Reactions

Recently, some efficient asymmetric Diels−Alder reactions catalyzed by chiral Lewis acids have been reported.[50] Although rare-earth compounds were expected to be promising Lewis acid reagents, only a few asymmetric reactions catalyzed by chiral rare-earth Lewis acids were reported.[51] On the other hand, rare-earth triflates, especially $Yb(OTf)_3$ and $Sc(OTf)_3$, are good catalysts in the Diels−Alder reactions of various dienophiles with cyclic and acyclic dienes (as mentioned in Section 6).

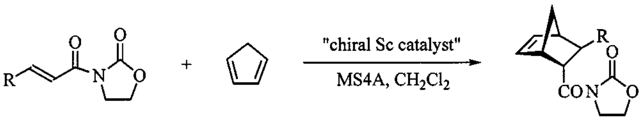
It was first found that a chiral Yb catalyst, prepared in situ from $Yb(OTf)_3$, (*R*)-(+)-1,1′-bi-2-naphthol [(*R*)-BINOL], and a tertiary amine in dichloromethane, was quite effective in enantioselective Diels−Alder reactions.[52] Moreover, some additives were found to be effective not only in stabilizing the catalyst but also in controlling the enantiofacial selectivities in the Diels−Alder reaction. When 3-acetyl-1,3-oxazolidin-2-one was combined with the chiral catalyst as an additive, the *endo* adduct was obtained in 93% ee as (2*S*,3*R*) form. On the other hand, when 3-phenylacetylacetone was mixed with the catalyst as an additive, the *endo* adduct was obtained in 81% ee as (2*R*,3*S*) form.[53]

The chiral Sc catalyst could be prepared similarly from $Sc(OTf)_3$, (*R*)-BINOL, and a tertiary amine in dichloromethane (Equation 22).[54] The catalyst was also found to be effective for the Diels−Alder reactions of an acrylic acid derivative with dienes (Table 5). The amines employed in the preparation of the catalyst influenced the enantioselectivities strongly. The highest enantioselectivities were observed when *cis*-1,2,6-trimethylpiperidine was employed as the amine. It should be noted that even 3 mol-% of the catalyst was sufficient to complete the reaction yielding the *endo* adduct with a 92% ee.



(22)

Table 5. Enantioselective Diels−Alder reactions using a chiral scandium catalyst

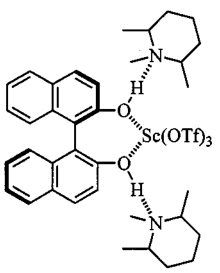


R	Catalyst/mol%	Yield/%	*endo/exo*	ee/% (*endo*)
Me	20	94	89/11	92 (2*S*, 3*R*)
	10	84	86/14	96 (2*S*, 3*R*)
	5	84	87/13	93 (2*S*, 3*R*)
	3	83	87/13	92 (2*S*, 3*R*)
Ph	20	99	89/11	93 (2*R*, 3*R*)
	10	96	90/10	97 (2*R*, 3*R*)
Pr	20	95	78/22	74 (2*S*, 3*R*)
	10	86	78/22	75 (2*S*, 3*R*)

It was found that 3-acetyl-1,3-oxazolin-2-one or 3-benzoyl-1,3-oxazolin-2-one was a good additive for stabilization of the chiral Sc catalyst, but that reverse enantioselectivities by using additives were not observed. In this way it differs from the chiral Yb catalyst. This can be explained by the coordination number of Sc^{III} and Yb^{III}; while Sc^{III} has up to seven ligands, specific coordination numbers of Yb^{III} allow it to have up to twelve ligands.[55]

For the chiral Sc catalyst, the structure shown in Scheme 9 was postulated.[56] The unique structure was indicated by ^{13}C-NMR and IR spectra. The most characteristic point of the catalyst was the existence of hydrogen bonds between the phenolic hydrogen atoms of binaphthol and the nitrogen atoms of the tertiary amines. The coordination form 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,[57] boron,[58] or titanium.[59] In the present chiral catalyst, the axial chirality of (*R*)-BINOL is transferred through the hydrogen bonds to the amine parts, which shield one side of the dienophile effectively. This is consistent with the experimental results showing that amines employed in the preparation of the chiral catalysts strongly influenced the selectivities and that bulky amines gave better selectivities.

The sense of asymmetric induction in the chiral Sc^{III}-catalyzed reactions can be rationalized by assuming an intermediate octahedral Sc^{III}−dienophile complex (Scheme 10).



Scheme 9. Chiral scandium catalysts

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.

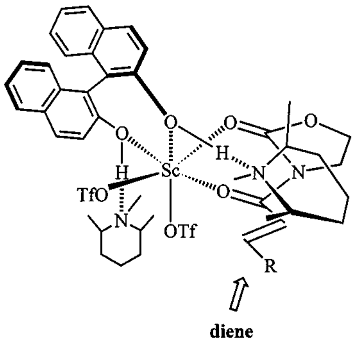
Since the amine part can be freely chosen, the design of efficient catalyst systems is easier compared to other catalysts based on (*R*)-BINOL.

Asymmetric Aza Diels−Alder Reactions

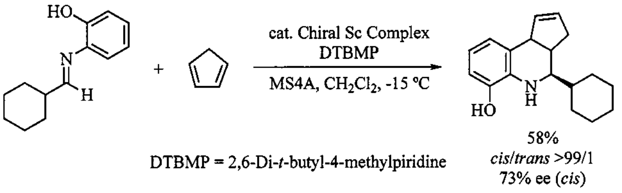
While asymmetric versions of aza Diels−Alder reactions using chiral auxiliaries were reported, only one example using a stoichiometric amount of a chiral Lewis acid was reported.[60] The first example of a catalytic enantioselective aza Diels−Alder reaction has been reported by using a chiral lanthanide catalyst.[61] A chiral ytterbium or scandium catalyst, prepared from $Yb(OTf)_3$ or $Sc(OTf)_3$, (*R*)-BINOL, and DBU, was effective in enantioselective aza Diels−Alder reactions. 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 corresponding 8-hydroxyquinoline derivatives in good to high yields with good to excellent diastereo- and enantioselectivities (Equation 23).

Asymmetric 1,3-Dipolar Cycloaddition Reactions

Catalytic asymmetric 1,3-dipolar cycloaddition of a nitrone with a dipolarophile was carried out using a chiral scandium catalyst.[36] The chiral catalyst, which was effective in asymmetric Diels−Alder reactions, was readily prepared from $Sc(OTf)_3$, (*R*)-(+)-BINOL, and *cis*-1,2,6-trimethylpiperidine. The reaction of benzylbenzylideneamine *N*-oxide with 3-(2-butenoyl)-1,3-oxazolidin-2-one was performed in the presence of the chiral catalyst to yield the desired isoxazolidine in a 69% ee with perfect diastereoselectivity (*endo*/*exo* > 99:1) (Scheme 11).[36,62] On the other hand, it was found that reverse enantioselectivity was observed when a chiral Yb catalyst, prepared from $Yb(OTf)_3$, the same (*R*)-(+)-BINOL, and *cis*-1,2,6-trimethylpiperidine, was used instead of the Sc catalyst under the same reaction conditions.



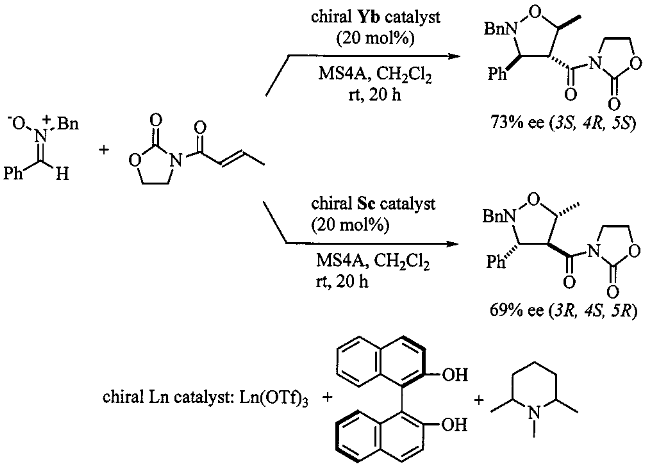
Scheme 10. Assumed transition state



(23)

11. Miscellaneous Reactions

$Sc(OTf)_3$ also catalyzes acetalization reactions,[63a,63b] acylal formation,[63c] β-selective glycosilation reactions with thioglycosides,[64] and acylation reactions of alcohols.[65] Guanidium formation reactions of carbodiimide with benzylamine,[66] intermolecular stereoselective radical additions to *N*-enoyloxazolidinones,[67] and rearrangement of epoxides[68] have also been reported. Some elimination reactions such as decarbonylation of aromatic aldehydes[69] and dehydration reactions of aldoximes to nitriles[70] proceed in the presence of $Sc(OTf)_3$. Finally, nitration of simple aromatic compounds,[71] alkylation of hydroquinone with allylic alcohols[72a] or 1,3-diene,[72b] Friedel−Crafts alkylation reactions,[73] ene reactions[74] etc. are also recent topics investigated using $Sc(OTf)_3$ as a Lewis acid catalyst.



Scheme 11. Asymmetric 1,3-dipolar cycloaddition; synthesis of both enantiomers using the same chiral source and a choice of rare earths

12. Conclusions

Sc(OTf)$_3$ is a new type of a Lewis acid that is different from typical Lewis acids such as AlCl$_3$, BF$_3$, SnCl$_4$, etc. While most Lewis acids are decomposed or deactivated in the presence of water, Sc(OTf)$_3$ is stable and works as a Lewis acid in aqueous solutions. Many nitrogen-containing compounds such as imines and hydrazones are also successfully activated by using a small amount of Sc(OTf)$_3$. Sc(OTf)$_3$ is also an excellent Lewis acid catalyst in organic solvents. A catalytic amount of Sc(OTf)$_3$ is sufficient to complete reactions in most cases. In addition, Sc(OTf)$_3$ can be recovered after reactions are completed and can be reused. While lanthanide triflates [Ln(OTf)$_3$] have similar properties, the catalytic activity of Sc(OTf)$_3$ is higher than that of Ln(OTf)$_3$ in several cases. On the other hand, while Ln(OTf)$_3$ has 9 to 12 ligands, Sc(OTf)$_3$ has up to 7 ligands and its ionic radius is smaller than those of lanthanides. Furthermore, Sc(OTf)$_3$ catalysis in micellar systems will lead to clean and environmentally friendly processes, and it will become a more important topic in the future

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