

# Recent Advances in Rare Earth-Metal Triflate Catalyzed Organic Synthesis in Green Media

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**Abstract:** Rare-earth metal triflates have been well established as potent environmentally-benign Lewis acids. This review summarizes the recent progress of RE(OTf)<sub>3</sub> catalyzed organic synthesis in green media including water, ionic liquids, super critical CO<sub>2</sub>, solvent-free conditions as well as solid supported synthesis.

**Keywords:** Rare-earth metal triflates, aqueous phase, ionic liquids, super critical CO<sub>2</sub>, solvent free, solid support, organic synthesis, Green chemistry.

## I. INTRODUCTION

Lewis acid has been of great interest in organic synthesis [1]. Although various kinds of Lewis acids have been applied in organic synthesis, and many of them are successfully utilized in industry, most of such transformations were carried out under strictly anhydrous condition and in many cases, stoichiometric amount of catalyst was needed. In the presence of even a small amount of water, the Lewis acid was immediately decomposed and deactivated leaving the substrates inactivated. These have limited the utilization of Lewis acid in organic synthesis. On the other hand, the use of water as reaction media has captured great interests in organic synthesis in term of Green chemistry [2].

Recently, rare earth metal triflates (RE(OTf)<sub>3</sub>), including lanthanide triflates (Trifluoro-methanesulfonates, Ln(OTf)<sub>3</sub>, Ln= La, Ce, Pr, Nd, Sm, Gd, Dy, Yb, Lu) together with Sc(OTf)<sub>3</sub> and Y(OTf)<sub>3</sub>, have been established as water-tolerable unique Lewis acid, which can catalyze various organic transformations in protic media [3]. Rare earth metal triflates were readily prepared from the corresponding oxide (RE<sub>2</sub>O<sub>3</sub>) and aqueous trifluoromethanesulfonic acid (TfOH) solution. In 1987, Forsberg firstly introduced RE(OTf)<sub>3</sub> into organic synthesis in the addition of amine to nitrile under anhydrous condition [4]. In 1991, Kobayashi demonstrated the remarkable catalytic effect of RE(OTf)<sub>3</sub> in water for the first time [5]. Since then, the advance in this field has been explosive.

In the passing two decades, there has been increasing recognition for the necessity to replace the volatile organic compounds (VOCs) traditionally used as solvents both in academic research and industry [6]. In addition to water, alternative green media for chemical processes include ionic liquid, supercritical fluids, fluoruous phase, and solvent free

environments such as the surfaces or interiors of clays, zeolites, silical gel, and alumina. In the past 5 or 6 years, RE(OTf)<sub>3</sub> has been successfully applied in these reaction media. The use of RE(OTf)<sub>3</sub> and green media in combination inspires great impact on synthetic organic chemistry, as well as other fields of chemistry and industry application. As testimony to the dramatic progress in this field, several reviews have appeared [3, 7], which mainly focused on the catalyzed reactions in aqueous media. The current review covers all the recent progress on the application of RE(OTf)<sub>3</sub> in environmentally friendly media, especially of ionic liquid, solvent free condition and solid supported reactions and catalysts.

## II. UNDERSTANDING OF RE(OTf)<sub>3</sub>

Rare earth metal triflates are now frequently used as Lewis acid catalysts. Owing to their higher Lewis acidities, RE(OTf)<sub>3</sub> can activate carbonyl and imine groups in organic compounds. However, the intrinsic chemical properties, as well as their reactivity and catalytic mechanism, still remains unclear.

Recently, quantitative evaluation of the relative Lewis acid was made by the use of tandem mass spectrometry (MS)[8]. Three series of Lanthanide triflates complex, M(OTf)<sub>3</sub>(hmpa)<sub>4</sub> (hmpa= hexamethyl phosphoramide), M(OTf)<sub>3</sub>(tepo)<sub>4</sub> (tepo= triethylphosphine oxide) and M(OTf)<sub>3</sub>(tmp)<sub>4</sub> (tmp= trimethyl phosphine), (M= rare earth metal) were synthesized and introduced into the tandem MS using collision-activated decomposition (CAD). Two obvious characteristics were observed among the lanthanoid complexes studied: (1) the extremely reproducible fragmentation of precursor ions, and (2) the significant difference of the intensity ratio between the ion due to losing a triflate group and that from losing a coordinating ligand.

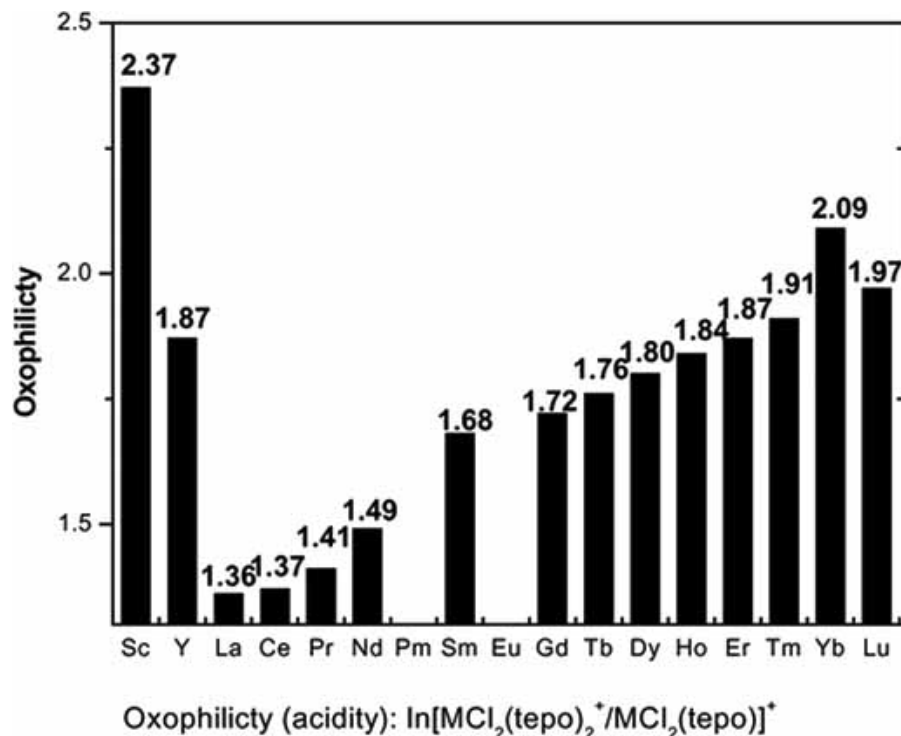
Based on other kinetic studies, the electronic property of each central element was suggested directly related to the stability of these fragmentation ions. The acidity (or oxophilicity) was evaluated according to the intensity ratio

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mentioned above. Similar results were obtained among three different complexes. Pure oxophilicity was estimated using  $[\text{MCl}_2(\text{tppo})_3]^+$ , the data was shown in Scheme 1. It was clearly demonstrated that Sc and Yb have the highest Lewis acidity, which is mainly ascribed to their small ionic radii. Lu has the smaller ionic radii, but the unoccupied 4f orbital of Yb render Yb more electron-attracting. Therefore, Yb has

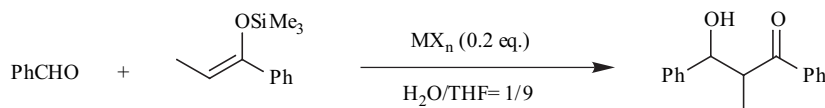
stronger Lewis acidity than Lu. Nakagawa's recent report verified this acidity scale [9]. The catalytic effect profile of  $\text{M}(\text{OTf})_3/\text{TMS}-\text{Cl}$  in the imino-ene reaction was found to be nearly consistent with the oxophilicity scale.

The most notable feature of  $\text{RE}(\text{OTf})_3$  is their stability in water, which renders them remarkable effective Lewis acids



Scheme 1. Acidity Scale of  $\text{RE}(\text{OTf})_3$ .

Table 1. Catalytic Effect of Metal Salts in Aqueous Aldol Reaction



$\text{MX}_n$	Yield/ %	$\text{pK}_h$	WERC	$\text{MX}_n$	Yield/ %	$\text{pK}_h$	WERC
$\text{AlCl}_3$	trace	1.14	1.64	$\text{Pr}(\text{OTf})_3$	83	8.1	$3.1 \times 10^8$
$\text{Co}(\text{ClO}_4)_2$	17	9.65	$2.0 \times 10^5$	$\text{Nd}(\text{OTf})_3$	78	8.0	$3.9 \times 10^8$
$\text{Ni}(\text{ClO}_4)_2$	17	9.86	$2.7 \times 10^4$	$\text{Sm}(\text{OTf})_3$	85	7.9	$5.9 \times 10^8$
$\text{InCl}_3$	68	4.00	$4.0 \times 10^4$	$\text{Eu}(\text{OTf})_3$	88	7.8	$6.5 \times 10^8$
$\text{Zn}(\text{ClO}_4)_2$	57 <sup>a</sup>	8.96	$5.0 \times 10^8$	$\text{Gd}(\text{OTf})_3$	90	8.0	$6.3 \times 10^7$
$\text{Fe}(\text{ClO}_4)_2$	55 <sup>a</sup>	9.5	$3.2 \times 10^6$	$\text{Tb}(\text{OTf})_3$	81	7.9	$7.8 \times 10^7$
$\text{Pb}(\text{ClO}_4)_2$	65 <sup>a</sup>	7.71	$7.5 \times 10^9$	$\text{Dy}(\text{OTf})_3$	85	8.0	$6.3 \times 10^7$
$\text{Cu}(\text{ClO}_4)_2$	81 <sup>a</sup>	7.53	$2.0 \times 10^8$	$\text{Ho}(\text{OTf})_3$	89	8.0	$6.1 \times 10^7$
$\text{ScCl}_3$	78 <sup>a</sup>	4.3	$4.8 \times 10^7$	$\text{Er}(\text{OTf})_3$	86	7.9	$1.4 \times 10^8$
$\text{YCl}_3$	86 <sup>a</sup>	7.7	$1.3 \times 10^7$	$\text{Tm}(\text{OTf})_3$	85	7.7	$6.4 \times 10^6$
$\text{La}(\text{OTf})_3$	80	8.5	$2.1 \times 10^8$	$\text{Yb}(\text{OTf})_3$	92	7.7	$8 \times 10^7$
$\text{Ce}(\text{OTf})_3$	81	8.3	$2.7 \times 10^8$	$\text{Lu}(\text{OTf})_3$	84	7.6	$6 \times 10^7$

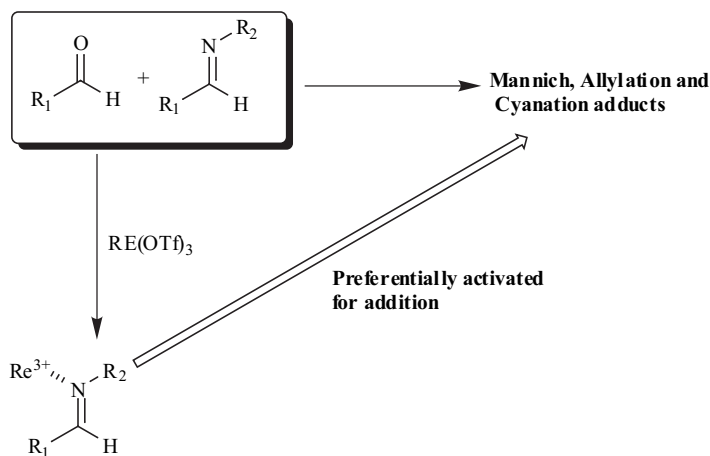
<sup>a</sup> Solvent system:  $\text{H}_2\text{O}:\text{EtOH}:\text{toluene}=1:7:3$

in aqueous media. Tolerable of water as they are, the hydrolysis of the metal center ions does occur to some extent. The center ions are surrounded with water molecules and other counter ions in aqueous media.

The catalytic effect of Lewis acids in water was systematically investigated by Kobayashi *et al.* [10]. They found that catalytic effect of Lewis acids in water was correlated to their hydrolysis constants and water exchange rate constants (WERC) for substitution of inner-sphere water ligands. A model reaction of benzaldehyde and (*Z*)-1-phenyl-1-(trimethylsiloxy) propene was chosen to screen various metal salts including RE(OTf)<sub>3</sub> (Table 1). In the cases the yield exceeding 50%, the metal salts have the pK<sub>h</sub> (K<sub>h</sub>= hydrolysis constant) values from 4.3-10.08, and WERC greater than 3.2×10<sup>6</sup> M<sup>-1</sup>s<sup>-1</sup>. A notable exception is InCl<sub>3</sub>

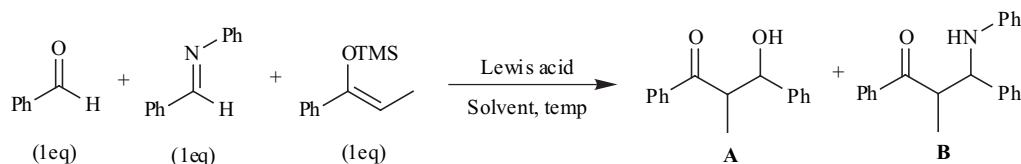
[11], which was reported to catalyze Mukaiyama reaction in water effectively but with a pK<sub>h</sub> of 4.00 and WERC of 4.0×10<sup>4</sup>. Obviously, all rare earth metal triflates work well in water with the pK<sub>h</sub> and WERC values falling in the range. Intrinsically, these two values are closely related to the (electron)<sup>2</sup>/(ionic radii) value. The Lewis acids working well in water are strictly consistent with the requirements of pK<sub>h</sub> and WERC.

The mechanism of RE(OTf)<sub>3</sub> catalysis can be deduced by judging from these findings. Upon the addition of RE(OTf)<sub>3</sub> to water, the dissociation and hydration of the metal center ion occur, the exchange of intermolecular water and intramolecular water gives chances for the substrate to coordinate with the center ion. The substrate is activated and the reaction is readily to occur. After the reaction, the



Scheme 2. Preferential activation of aldimine.

Table 2. Effect of Lewis Acid



Lewis acid (equiv.)	Temp (°C)	Yield (%)		A/B
		A	B	
SnCl <sub>4</sub> (1.0)	-78	93	1	99/1 <sup>a</sup>
TiCl <sub>4</sub> (1.0)	-78	86	1	99/1 <sup>a</sup>
TMSOTf(1.0)	-23	87	trace	>99/1 <sup>a</sup>
SnCl <sub>4</sub> (0.2)	-78	18	trace	>99/1 <sup>a</sup>
TiCl <sub>4</sub> (0.2)	-78	12	trace	>99/1 <sup>a</sup>
BF <sub>3</sub> ·OEt <sub>2</sub> (0.2)	-78	26	7	79/21 <sup>a</sup>
Yb(OTf) <sub>3</sub> (1.0)	-23	40	31	56/44 <sup>a</sup>
Yb(OTf) <sub>3</sub> (0.2)	-23	2	92	2/98 <sup>a</sup>
Yb(OTf) <sub>3</sub> (0.2)	-45	trace	69	<1/>99 <sup>a</sup>
Yb(OTf) <sub>3</sub> (0.2)	rt	41	48	46/54 <sup>a</sup>
Yb(OTf) <sub>3</sub> (0.2)	-45	trace	83	<1/>99 <sup>b</sup>

<sup>a</sup> CH<sub>2</sub>Cl<sub>2</sub> as solvent. <sup>b</sup> C<sub>2</sub>H<sub>5</sub>CN as solvent

products are extracted and the catalysts remain in the aqueous phase, and could be easily recovered and reused.

Another feature noteworthy of  $\text{RE}(\text{OTf})_3$  is that they can effectively interact with carbonyl and imine functionalities in organic compounds, particularly the ability to preferentially coordinate with imine group in the nucleophilic additions (Scheme 2) [12].

It's well recognized that aldimines are less reactive than aldehydes. The nucleophilic addition to aldehydes occurred more readily than to aldimines. Recent publication showed an unprecedented change in reactivity [12]. Namely, the preferential reactions of aldimines over aldehydes with silyl enolate, allyl metal, and cyanotrimethyl silane in the presence of catalytic amount of lanthanide triflate. Under the influence of traditional Lewis acid such as  $\text{TiCl}_4$ ,  $\text{SnCl}_4$ ,  $\text{TMSOTf}$ , selective reaction of aldehyde with silyl enolate occurred exclusively, while the use of lanthanide reversed the selectivity completely (Table 2). This selectivity was also temperature-dependent. At 0 °C or room temperature, both aldehydes and aldimines reacted, while only aldimines reacted at -45 °C to afford the desired adducts in high yield. Among the lanthanide triflates screened, La, Ce, Pr, Nd, Eu, Gd, Ho, Tm, Yb and  $\text{Lu}(\text{OTf})_3$  gave reasonable yields with excellent selectivities, of which  $\text{Yb}(\text{OTf})_3$  showed higher activity. Cyanation and allylation demonstrated similar high aldimine selectivity. Nuclear magnetic resonance studies revealed the selective formation of aldimine- $\text{Yb}(\text{OTf})_3$  complex in the coexistence of aldehyde when 0.2 equiv. of  $\text{Yb}(\text{OTf})_3$  was applied.

Beside the unique coordination feature,  $\text{RE}(\text{OTf})_3$  is also thermal stable. Stability up to 300 °C was observed [13].

As a conclusion, rare earth metal triflates have the following advantages compared with the traditional Lewis acids:

- $\text{RE}(\text{OTf})_3$  are readily prepared in aqueous media, and are air- and water- stable, can be used in pure water system or protic media (mixture of water with organic solvents or alcohols).
- $\text{RE}(\text{OTf})_3$  have strong Lewis acidity due to the electron-withdrawing trimethanesulfonyl group and can effectively activate carbonyl and imine functionalities.
- $\text{RE}(\text{OTf})_3$  have the strong affinity to imine group, particularly in nucleophilic addition reactions,

preferentially coordinate with aldimine in the coexistence of aldehyde.

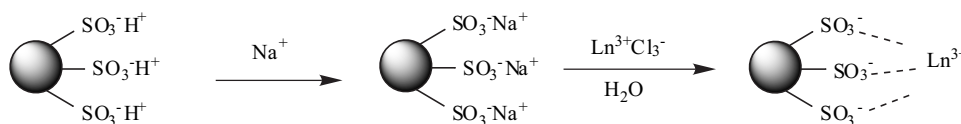
- $\text{RE}(\text{OTf})_3$  are more soluble in water than in organic solvents, and easily recovered and reused.
- $\text{RE}(\text{OTf})_3$  are thermal stable and less toxic.

### III. REUSE AND RECYCLE OF $\text{LN}(\text{OTf})_3$

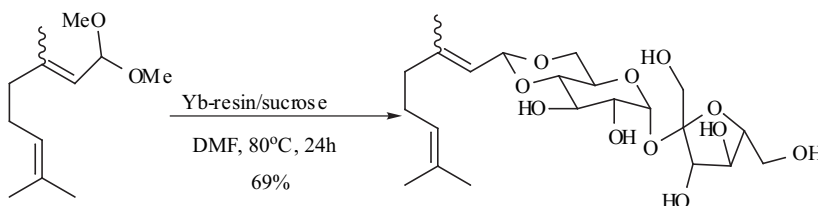
An inherent limitation of lanthanide triflates is that they are rare in nature, thus may be expensive for large scale synthesis. In order to expand the application of rare earth metal triflates, various immobilization techniques have been developed to further modify the catalyst for a greener and more economic catalytic procedure.

The first effort toward this aim is solid-supported lanthanide. Wang's group developed a series of polymer-supported lanthanides catalysts based on cation exchange resins [14]. The catalysts were introduced employing an ion-exchange process (Scheme 3). In order to evaluate the efficiency of Ln-resins catalysts, a series of organic reactions were carried out including acetalization, Aldol, allylation, aza Diels-Alder, glycosylation and epoxide ring opening reactions. In most cases, the Ln-resins demonstrated good to excellent catalytic effect. One noted exception is the aza-Diels-Alder reaction. In this case, the Ln-resin was not so effective as the  $\text{Yb}(\text{OTf})_3$  in aqueous media. It is worthy to note that the Ln-resins can be successfully applied in aqueous media, consequently offer the advantage of ease recycle of catalyst in protic solvent where lanthanides removal may be problematic. Ln-resin was recently utilized in the acetalization of sucrose (Scheme 4) [15].

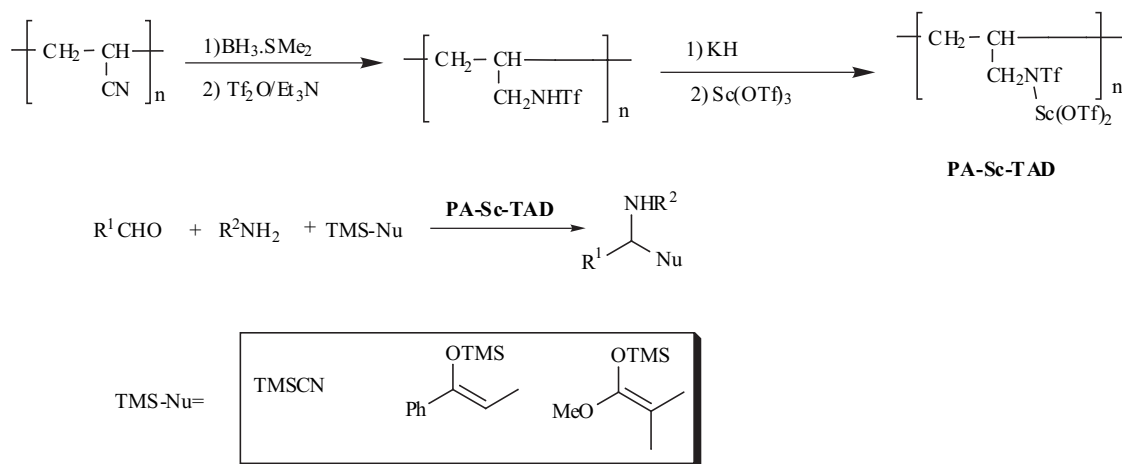
Similarly to Ln-resin, Kobayashi *et al.* developed a Nafion-Sc catalyst [16]. Nafion-Sc was prepared by treatment of three equivalents of Nafion with  $\text{ScCl}_3 \cdot \text{H}_2\text{O}$  in refluxing acetonitrile. Nafion-Sc was shown to be an effective Lewis acid catalyst in the Allylation, Diels-Alder, Friedel-Crafts acylation, and aza Diels-Alder reaction. As a continuation, Kobayashi developed a new strategy for the construction of quinoline library using polyacrylonitrile supported scandium catalyst, polyallyl scandium triflylamide ditriflate (PA-Sc-TAD) [17]. PA-Sc-TAD was prepared as show in Scheme 5 and was partially soluble in the  $\text{DCM}-\text{CH}_3\text{CN}$  (2:1) solvent system.



Scheme 3.

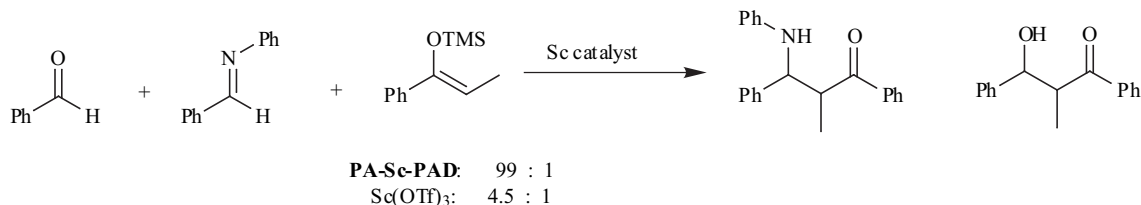


Scheme 4.

**Scheme 5.**

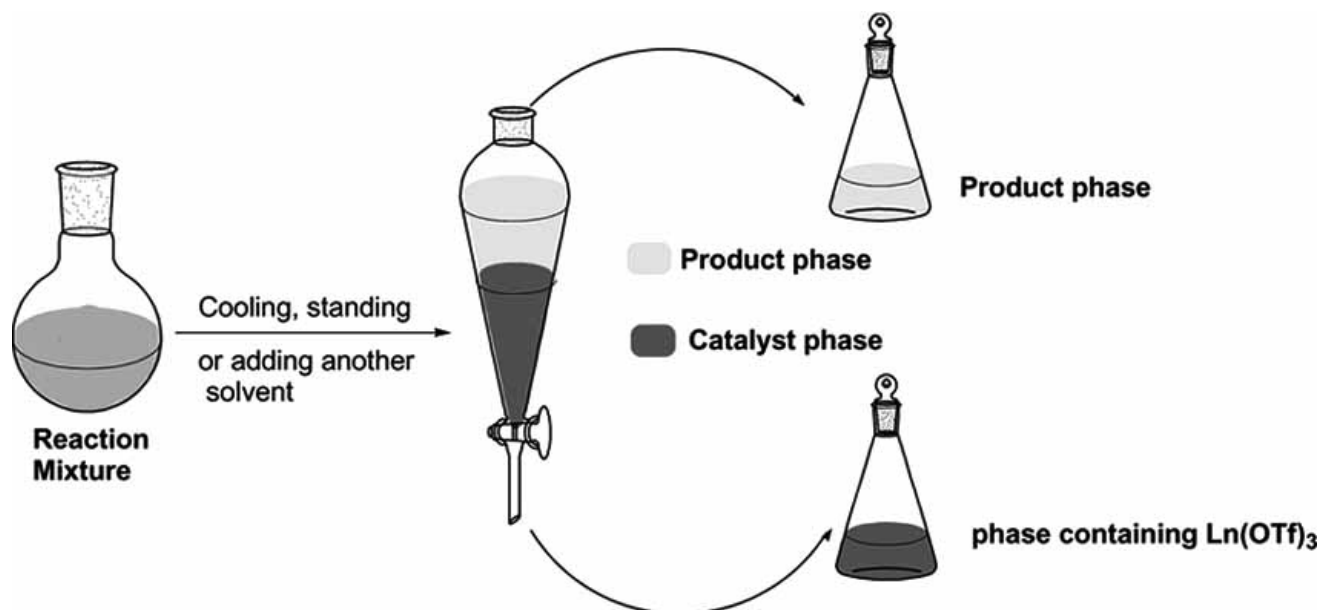
The same catalyst was also applied in the nucleophilic addition to *in situ* generated imines with silylated nucleophiles [18]. (Scheme 5) Moreover, PA-Sc-TAD was found to preferentially activate imines in the coexistence of aldehydes [18b]. Thus, treatment of 1:1:1 solution of aldehyde, imine and silyl enol ether in the presence of catalytic amount of PA-Sc-TAD afford predominantly  $\beta$ -amino ketones (99/1 selectivity over  $\beta$ -hydroxyl ketones), while the same reaction catalyzed by  $\text{Sc}(\text{OTf})_3$  resulted in decreased selectivity (4.5/1) (Scheme 6).

solid-phase immobilization of Lewis acid catalysts. Kobayashi and coworkers initially developed microencapsulated scandium triflate (MC- $\text{Sc}(\text{OTf})_3$ ) [20]. This MC- $\text{Sc}(\text{OTf})_3$  is easy to prepare and more active than other solid-supported scandium such as Nafion-Sc, PA-Sc-TAD and non-supported  $\text{Sc}(\text{OTf})_3$ . It's also recoverable and reusable, and effective in catalysis of a variety of carbon-carbon bond forming reaction. Compared with the non-encapsulated catalyst, MC- $\text{Sc}(\text{OTf})_3$  shows remarkable ability to activate aldimine group and can be used to catalyze

**Scheme 6.**

Microcapsule [19], traditionally used as protection of food and medicine, now emerging as a new protocol for

Mannich, aza Diels-Alder, cyanation, and allylation reaction of aldimines. It's also a carbonyl group activator, catalyzing

**Scheme 7.**

Friedel-Crafts acylation and alkylation, Michael addition, Aldol, allylation, and cyanation of aldehydes [20].

Another strategy for recycling of  $\text{Ln}(\text{OTf})_3$  is based on the biphasic catalysis (Scheme 7). In such system, the reaction is generally carried out under homogeneous condition, and different phases are separated after reaction. The lanthanide catalyst resides in one phase (normally water or ionic liquids), whereas the organic products and starting materials are dissolved in the other phase (organic solvents or super-critical liquid phase). Due to their high solubility in water, lanthanide triflates are generally recovered through aqueous work-up. The aqueous phase containing catalyst may be reused directly or, in most cases, after re-activation upon removal of water. Wang's group has developed a "Lantech" technology [21], which uses recyclable lanthanide triflate water solution for a variety of transformations in aqueous media. Besides being benign with respect to environment aspects by replacing volatile organic solvents, the use of water may also provide a number of advantages regarding activity and selectivity of the reaction as well as the simplicity of work-up procedure. However, the solubility and stability of reactants and catalysts have limited the use of water in biphasic catalysis.

Recently, room temperature ionic liquids [22], now emerging as novel "designer's solvent", have drawn more and more attention in biphasic system and served as a promising alternative for water. Unlike the common volatile solvents (VOLs), ionic liquids have practically no vapor pressure, which makes them more economical and environmentally benign in product separation. Most importantly, ionic liquid can form biphasic system with

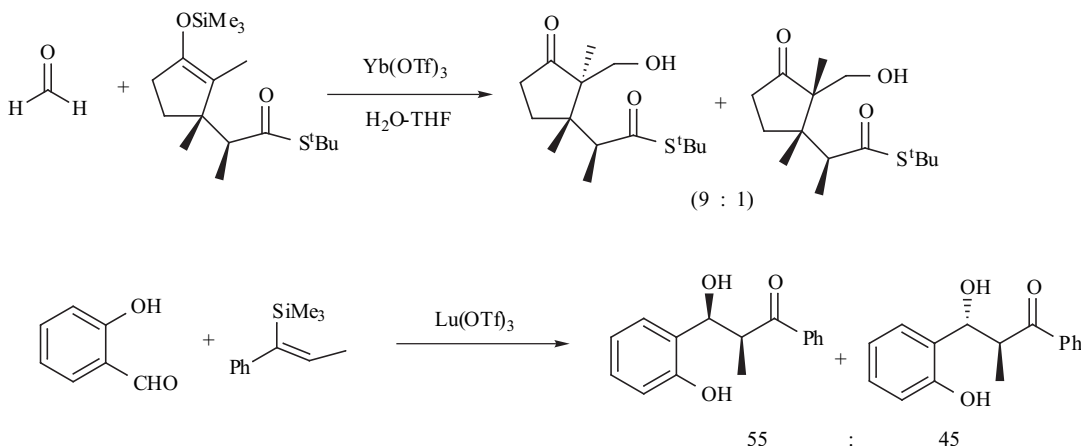
most of organic substrates, and this makes the possibility for a multiphasic reaction to have much easier isolation and recovery of homogenous catalyst. Accordingly, lanthanide triflates have been successfully immobilized in ionic liquids for a number of reactions [22]. The immobilized  $\text{Ln}(\text{OTf})_3$  is easily recycled and can be reused directly, which offers potential environmental and economic benefits. In most cases, the lanthanide catalysis in ionic liquid demonstrates superior catalytic activity and selectivity than in other media.

#### IV. $\text{RE}(\text{OTf})_3$ -CATALYZED ORGANIC SYNTHESIS IN AQUEOUS MEDIA

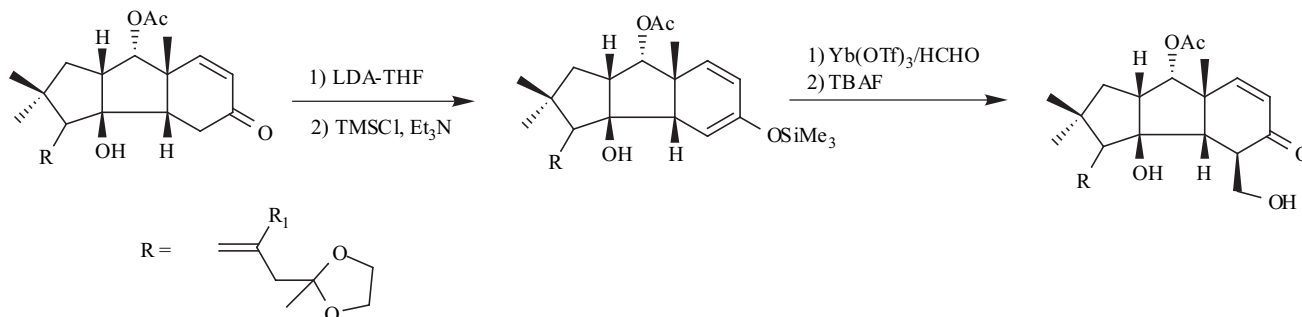
##### A. Aldol Reaction

The Aldol reaction is one of the most important synthetic tools for carbon-carbon bond formation. The  $\text{TiCl}_4$ -mediated Aldol reaction between silyl enol ether (or silyl ketene acetal) and aldehyde was reported in 1973, known as Mukaiyama reaction [23]. This reaction is distinguished from the conventional Aldol reaction carried out under basic conditions in that it proceeds in highly regioselective manner to afford cross Aldol adducts in high yield. However, the reaction must be carried out in strictly anhydrous condition, which is the major drawback for this reaction in term of Green chemistry. Due to the unique feature of  $\text{RE}(\text{OTf})_3$ , they have been widely used in Mukaiyama-Aldol reaction, and greatly expanded the scope of the reaction.

The significance of using water as reaction media has been well recognized. Development of carbon-carbon bond



Scheme 8.



Scheme 9.

formation in water remains as a challenge for organic synthetic chemists [2b]. In 1986, Lubineau successfully performed Mukaiyama reaction in water [24]. Hydrophobic effect was proposed to promote the reaction in a similar fashion as under high pressure [25]. However, the reaction suffered long reaction time. In 1991, Kobayashi demonstrated that Mukaiyama reaction in aqueous media could be greatly enhanced when lanthanide triflates were used as catalysts [5]. The reaction was carried out with commercially available water solution of formaldehyde and silyl enolates in the presence of catalytic amount of  $\text{Ln}(\text{OTf})_3$  (Scheme 8). The reaction rates were enhanced and the yields were greatly improved. Among the lanthanide triflates screened,  $\text{Yb}(\text{OTf})_3$ ,  $\text{Ga}(\text{OTf})_3$ , and  $\text{Lu}(\text{OTf})_3$  generally gave the best results. This method of hydroxymethylation in aqueous media has been successfully used in the studies toward the total synthesis of an A-seco taxane (Scheme 9) [26].

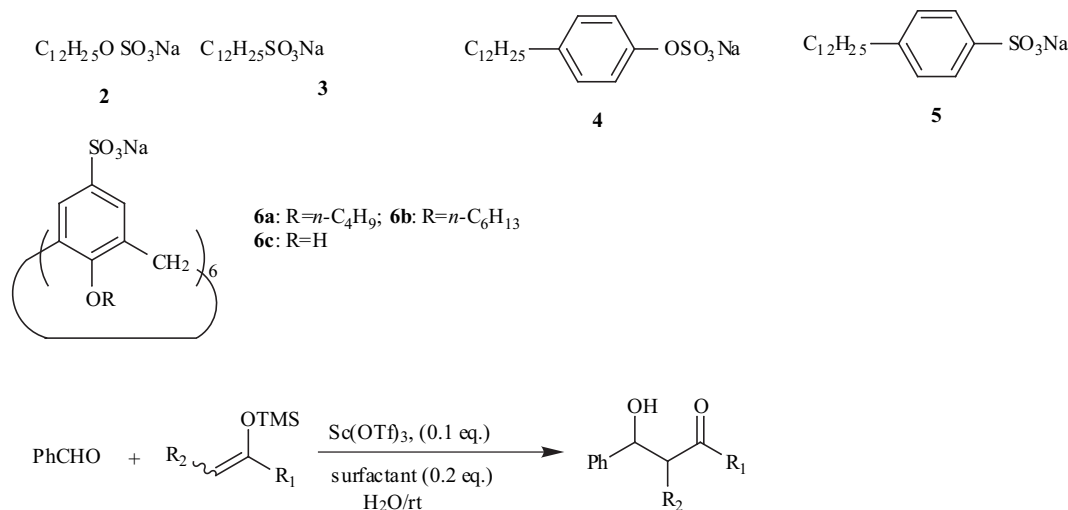
Aldehydes other than formaldehyde can also be employed in this aqueous Mukaiyama reaction (Scheme 8) [27, 28].  $\text{Ln}(\text{OTf})_3$ , especially of  $\text{Yb}(\text{OTf})_3$ , can effectively promote

these reactions. It was found that  $\text{Sc}(\text{OTf})_3$  was also effective in aqueous Mukaiyama reaction [28b]. One notable feature of the present reaction is that water solution of acetaldehyde, acrolein, chloroacetaldehyde can be directly used to afford the corresponding crossed-Aldol adducts with high yields.

Aldol type reaction of ketene silyl acetal with aldehyde is another important carbon-carbon bond forming reaction similar to the reaction of silyl enol ether. However, when the reaction was conducted in aqueous media, no Aldol adducts were obtained [29]. The hydrolysis of ketene silyl acetal precedes the desired Aldol reaction in aqueous media.

In the present aqueous Aldol reaction, it was revealed that the amounts of water used influenced the yield significantly [27]. In anhydrous THF, the reaction proceeded much slower with lower yields. On the other hand, the yield decreased when large quantity of water was employed. The best yields were obtained when 10-20% of water in THF was utilized. The diastereoselectivity of these reactions were shown to be modest. The selectivity inverse from *anti* to *syn* compared with the classical Mukaiyama reaction catalyzed by  $\text{TiCl}_4$ .

**Table 3. The Use of Surfactants in Aldol Reaction**



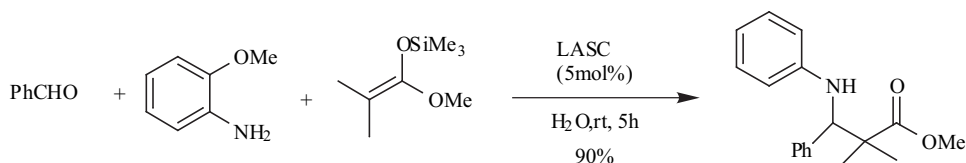
Silyl enol ether	surfactant	Time (h)	Yield (%) (Syn/anti)
	<b>2</b>	2	90(40/60)
<b>1</b>	<b>6a</b>	8	90(31/69)
<b>1</b>	<b>6b</b>	3.5	92(40/60)
	<b>2</b>	1	47(72/28)
<b>7</b>	<b>3</b>	1	55(68/32)
<b>7</b>	<b>4</b>	1	99(80/20)
<b>7</b>	<b>5</b>	1	85(75/25)
<b>7</b>	<b>6a</b>	7	88(75/25)
<b>7</b>	<b>6b</b>	4	94(77/23)
<b>7</b>	<b>6c</b>	--	None

Due to the insolubility of organic substrate, organic solvent such as THF was added to solubilize the substrates in aqueous reaction. Recent publications showed that catalytic surfactant can promote the Mukaiyama reaction in pure water together with  $\text{Ln}(\text{OTf})_3$  as Lewis acid catalysts [30, 31]. The surfactant can be anionic such as sodium dodecyl sulfate, or nonionic. The sort of surfactant affects the reaction yield dramatically. Generally, the anionic surfactant was the most effective surfactant. Triton X-100 was also effective in the Aldol reaction but the reaction suffered length reaction time, while only trace Aldol adducts were obtained when CTAB (cetyl-trimethyl-ammonium bromide), a cation type of surfactant, was used.

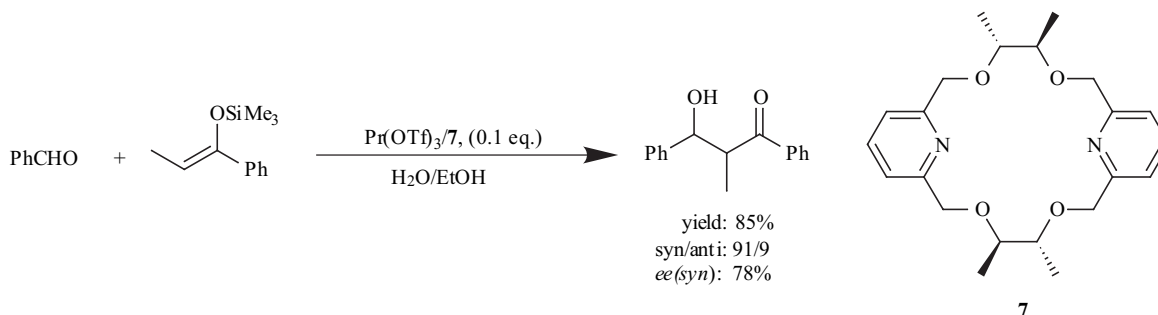
According to the CMC (critical micelle concentration), micelles could be formed in these reactions to result in a hydrophobic reaction sphere, which can accommodate the labile silyl enolate and inhibit its hydrolysis. In this way, enhancement of the reaction was achieved [32]. However, the Aldol reaction outside the micelles could not be excluded in these cases.

The use of various anionic surfactants has been reported and the results were collected in Table 3. It was revealed that sulfate surfactant **2**, **4** was more effect than sulfonate surfactant [30b]. When aromatic aldehydes were employed, aromatic surfactant favor the Aldol reaction compared with the aliphatic surfactant. Tian and Li *et al.* developed sulfonated calix[6]arene derivatives **6** as surfactants in Mukaiyama reaction in water [30]. The sulfated calix[6]arene was modified in the lower rim with alkyl group. These alkyl groups played the key role in the reaction.

Further along this line, Kobayashi and coworkers developed Lewis acid-surfactant-combined catalyst (LASC). The LASC, readily prepared from  $\text{LnCl}_3$  and SDS, was shown to have good catalytic activity in pure water for various organic transformation including Aldol, Mannich, and allylation reactions [33]. For example, in the presence of LASC, aldehyde, amine, and silyl enol ether were combined and reacted to afford the Mannich product in high yields (Scheme 10). Upon treatment with LASCs, stable colloidal



Scheme 10.



Scheme 11.

dispersions formed immediately with the reaction substrates. It was suggested that most of the substrates were concentrated in the spherical particles, which served as a hydrophobic reaction field, in this way rapid organic reactions were achieved in water.

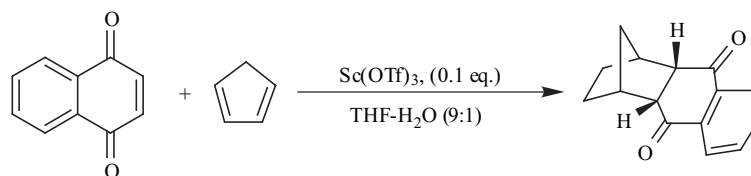
Although it was well known that rare earth metal triflates are water-stable Lewis acids, asymmetric transformations catalyzed by  $\text{Re}(\text{OTf})_3$  in aqueous media have not been very successful. To carry out asymmetric reaction in aqueous media, the choice of a proper chiral ligand remains a great challenge at present. A promising chiral ligand requires strictly controlled coordinating ability. Namely, a ligand with strong coordination ability and does not significantly reduce the acidity of  $\text{RE}(\text{OTf})_3$  [34].

Recent studies have shown that chiral crown ether can be used as a chiral ligand in asymmetric aqueous Aldol reaction [35]. Based on the size-fitting effect of macrocyclic ligands, chiral crown ether **7** and larger cations such as La, Ce, Pr, Nd were found to be effective catalysts for the asymmetric aqueous Aldol reaction (Scheme 11). The reaction of benzaldehyde and silyl enol ether in aqueous media (water/ethanol=1/9) gave the desired Aldol product in high yield (85%) and with high selectivity (syn/anti=91/9, ee for syn isomer: 78%), while the same reaction in DCM resulted in much lower yield and selectivity (3% yield after 185h, 28% de, 22% ee).

## B. Diels-Alder Reaction

Among the organic reactions investigated in aqueous media, DA reaction is the most widely studied. Because of its unique solubility and stability in water,  $\text{RE}(\text{OTf})_3$  can be used as Lewis acid catalysts not only in organic solvents but also in aqueous media. Scandium triflate catalyzed the reaction of naphthoquinone with cyclopentadiene in aqueous THF solution at room temperature [36]. The yield was improved compared with the same reaction in DCM. Moreover, the reaction was highly selective by affording only the *endo* product (Scheme 12).

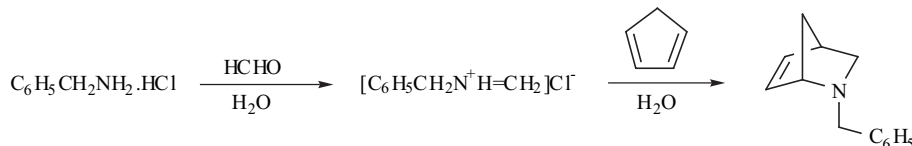




Scheme 12.

### C. Aza-Cycloaddition Reactions

Aza Diels-Alder reaction holds enormous potential in the synthesis of natural products such as alkaloid. However, simple imines are poor dienophiles and the imines used are usually substituted with one or more electron-withdrawing groups [37]. Imines can also be activated through protonation or coordination to Lewis acid catalysts. In 1985, Grieco [38] found that protonated imine group generated from an aqueous solution of formaldehyde and benzylamine hydrochloride, reacted with cyclopentadiene to afford the aza-DA adducts (Scheme 13). This aza DA reaction conveniently combined three reactive components (aldehyde, amine salt, and diene) in aqueous media to generate nitrogen-containing heterocyclic structures. C-acyl iminium ions [39] and amino acids [40] could also be employed in this reaction.



Scheme 13.

**Table 4. Aqueous Aza Diels-Alder Reactions Catalyzed by Ln(OTf)<sub>3</sub>**

RCHO	Diene	Amine	Ln	Yield (%)	Yield (%) without Ln
Et		BnNH <sub>3</sub> <sup>+</sup> Cl <sup>-</sup>	La	64 <sup>a</sup>	4
Bn		BnNH <sub>3</sub> <sup>+</sup> Cl <sup>-</sup>	Yb	72 <sup>b</sup>	3
H		BnNH <sub>3</sub> <sup>+</sup> Cl <sup>-</sup>	Nd	92	23
H		L-PAME	Nd	84 <sup>c</sup>	27
H		L-PAME	Nd	98	58
H		L-PAME	Nd	96	37

<sup>a</sup> *exo/endo*=2.5/1; <sup>b</sup> *exo/endo*=4/1; <sup>c</sup> *exo/endo*=1/3. L-PAME = L-phenylalanine methyl ester

In spite of the synthetic potentials, this reaction has been limited to use of activated substrate, (aldehydes such as formaldehyde, glyoxylates, dienes such as cyclopentadiene, and Danishefsky's diene). Inactivated substrates showed much lower reactivity. Yu and Wang found that lanthanide triflates could efficiently catalyze the three-component aza Diels-Alder reaction in water [41]. The aza DA reaction of hexanal and benzylamine hydrochloride with cyclopentadiene was greatly accelerated and the yield was increased significantly (Scheme 14).

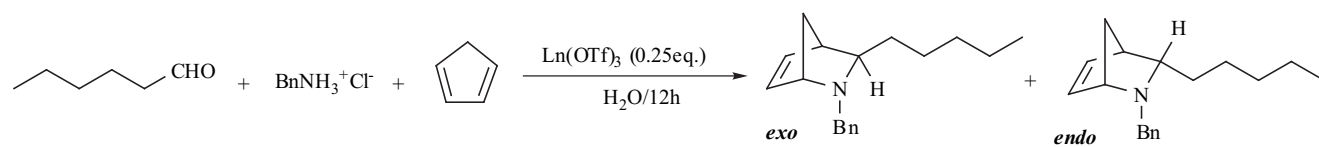
Among the lanthanide triflate employed, Yb(OTf)<sub>3</sub>, Pr(OTf)<sub>3</sub> and Nd(OTf)<sub>3</sub> appeared to be the most effective catalysts. The catalysts did not affect the diastereoselectivity of the reaction compared to the uncatalyzed reaction in water. The reactions of aldehyde other than formaldehyde and

glyoxylate proceeded in good yields. The reactions of formaldehyde with a variety of dienes also afforded products with excellent yields. Several examples are shown in Table 4. However, the reactions of larger aldehydes with the diene other than cyclopentadiene did not occur with the catalysis of lanthanide.

The lanthanide-catalyzed aza-DA reaction has been successfully used to synthesize aza-sugars analogs [42]. Aqueous media allows the use of unprotected carbohydrates and their derivatives as one of the components in the reaction. In the presence of Nd(OTf)<sub>3</sub>, cycloaddition of optical pure glyceraldehyde acetonide, benzylamine hydrochloride and cyclopentadiene afford three adducts **8**, **9**, **10** (1:8:3).

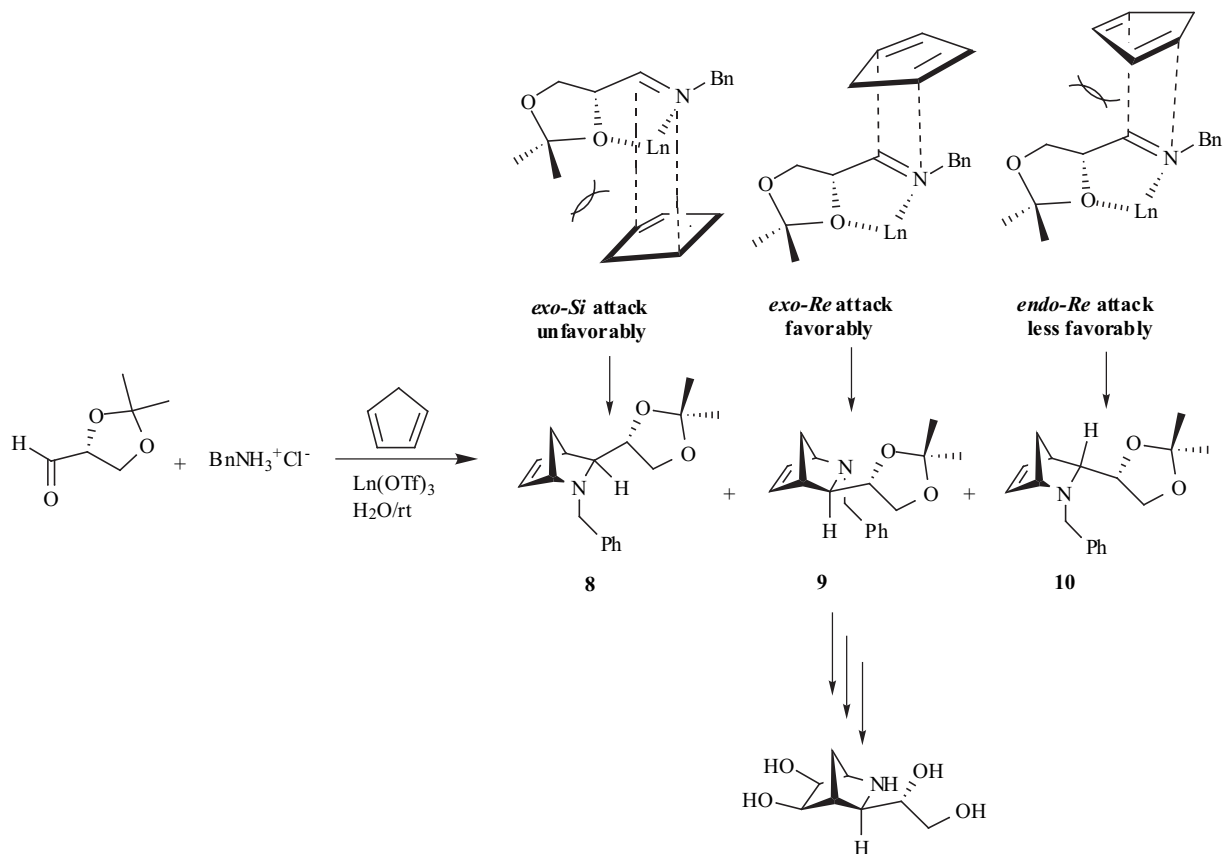
It was revealed that the lanthanide ions coordinated to the Schiff base nitrogen and the adjacent oxygen atom to form a five-membered ring intermediate and the lanthanide possessing medium radii favor the ring formation, thus gave **9** with the highest yield. On the base of the proposed intermediate, the *exo-Si* addition to the aldimine for the formation of **8** would be unfavorable due to steric hindrance. Between the *exo-Re* attack and *endo-Re* attack, the former pathway should be more favorable, this is consistent with the experimental results (Scheme 15).

The corresponding reaction using another chiral aldehyde **11**, prepared *in situ* via diazotization of glucosamine hydrochloride, exclusively gave the *exo* adduct **12** from *Si* attack to a five-membered ring intermediate (Scheme 16).

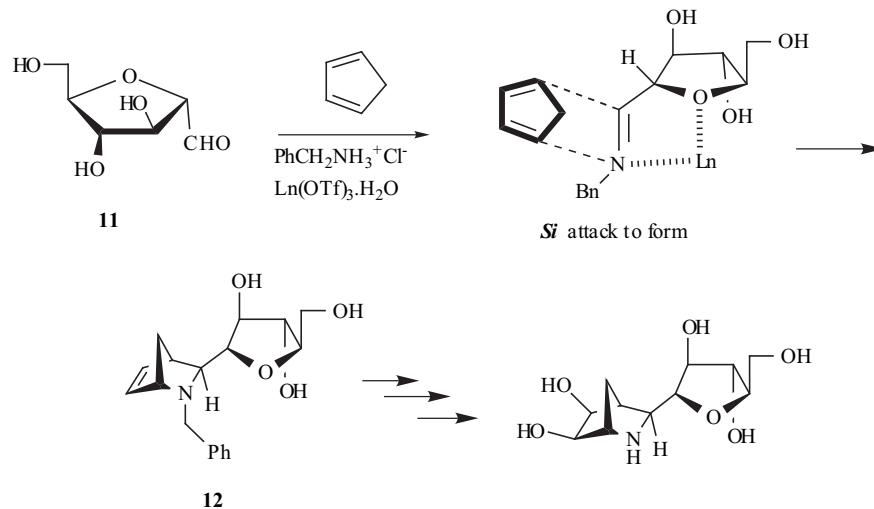


Ln	-	La	Pr	Nd	Gd	Dy	Er	Yb
Yield(%)	4	47	68	57	19	49	46	62

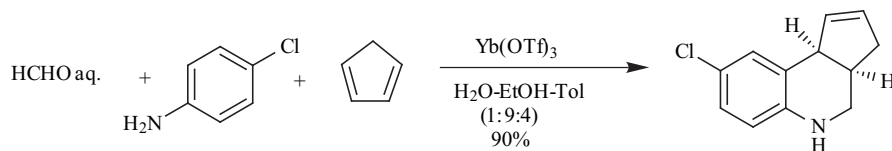
Scheme 14.



Scheme 15.



Scheme 16.



Scheme 17.

The main products of these aza-adducts were subsequently converted into azasugars analogs, which are potential inhibitors against glycoprocessing enzyme [43].

With ytterbium triflate as the catalyst, a three-component reaction of aniline, aldehyde and cyclopentadiene was successfully carried out in aqueous media to produce the desired tetrahydroquinolines in high yields (Scheme 17) [44].

This multi-component coupling reaction was recently used the total synthesis of the alkaloid matinelline **13** and martinellinic acid **14** [45]. Endocyclic enamine derivatives such as *N*-substituted 2-pyrroline were employed as the alkene component. Dy(OTf)<sub>3</sub> demonstrated better results than other lanthanide triflate in the outcome of the reaction. The selectivity of the reaction can be improved considerably when carrying out the reaction in aqueous media (THF/H<sub>2</sub>O=4/1) at the cost of low yields. This was ascribed to the hydrophobic effect by which a more compact transition state induces *endo*-selectivity. Interestingly, it was found that in the absence of aldehyde, aniline would couple with two equivalents of pyrroline to afford coupling product **15** in high yield with the *endo* diastereomer dominating. Presumably, the reaction occurred *via* the imine formed from condensation of aniline with the hydrolysis product of 2-pyrroline or the nucleophilic addition of aniline to 2-pyrroline (Scheme 18).

#### D. Lanthanide-promoted Synthesis of 2,3-Dihydropyridinium and Pyrimidium Derivatives

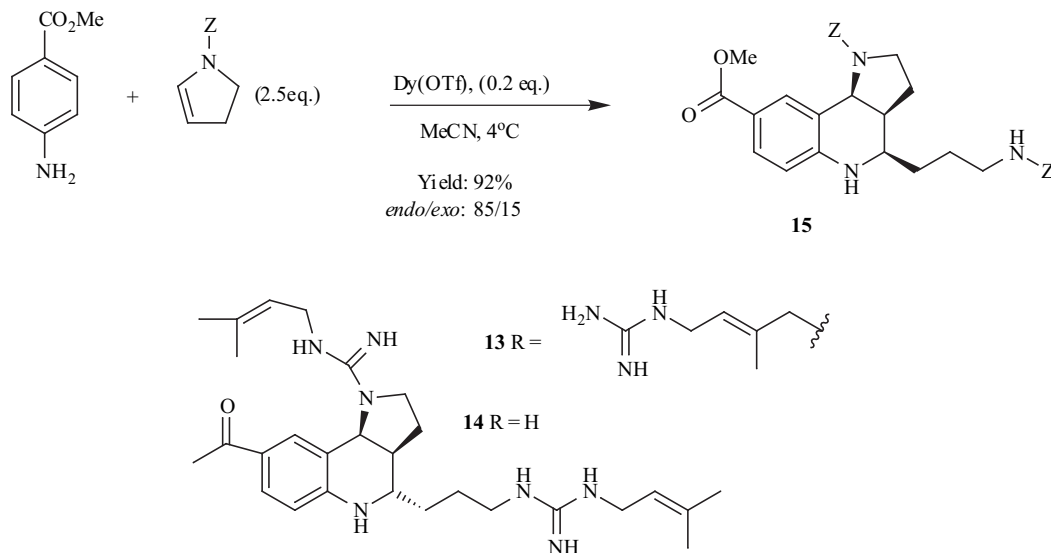
It has been shown that 1,4- and 2,3- dihydropyridines played important role in biological functions [46]. In addition, they were considered versatile intermediates in

alkaloid synthesis [47]. The general synthetic route to dihydropyridines involved the cyclization of the starting materials followed by reduction to afford the target products [48]. However, 2,3-dihydropyridines are unstable without an electron-withdrawing group at the nitrogen atom, and a few synthetic methods are available for the formation of 2,3-dihydropyridines from acyclic materials [49].

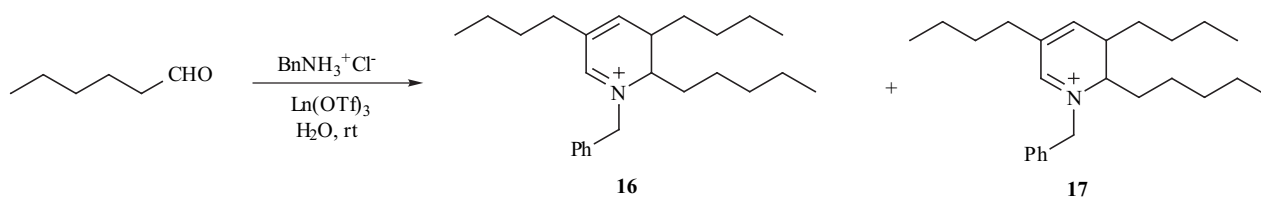
In the course of Wang's study, it was found that lanthanide triflate could promote the reaction of aldehydes and amine hydrochlorides in water to afford 2,3-dihydropyridiniums **16** and pyridinium derivatives **17** [50]. The former could be further transformed into pyridine derivatives following de-hydrogenation and de-benzylation. The counterions can be OTf<sup>-</sup> or Cl<sup>-</sup> depending on the workup conditions. Various lanthanides were screened and it was indicated that lighter lanthanides such as Pr and La exhibited better catalytic activity (Scheme 19). The reactions apparently proceed through sequential condensation of three molecules of the Schiff base formed between the aldehyde and the amine. The pyridinium products resulted from oxidation of the corresponding 2,3-dihydropyridiniums (Scheme 20). This method is a milder extension of Chichibabin pyridine synthesis, which normally requires high temperature, high pressure, or vapor phase reaction conditions [51].

#### E. Synthesis of Aziridine in Aqueous Media

Aziridines are versatile building blocks for the synthesis of various biologically important molecules. A simple way to aziridine synthesis is the addition of a carbene moiety to an imine group. Transition metal has been reported to catalyze this reaction [52]. Templeton and co-workers found that Lewis acid such as BF<sub>3</sub>·OEt<sub>2</sub>, AlCl<sub>3</sub>, and TiCl<sub>4</sub> are

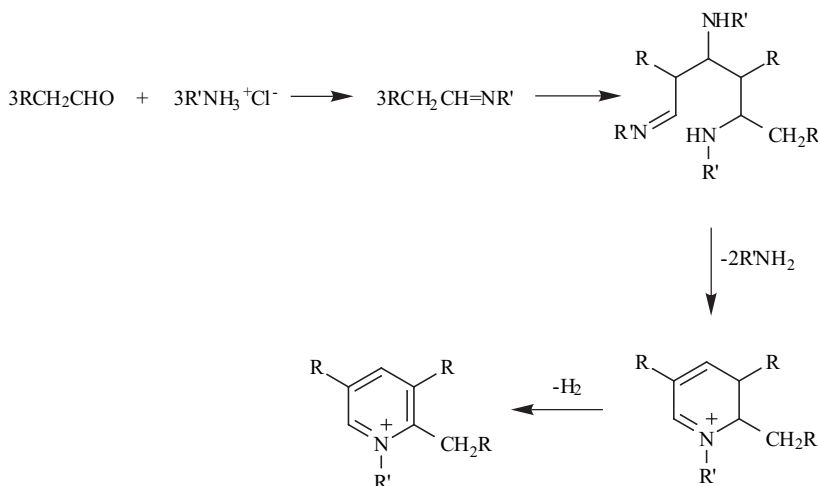


Scheme 18.

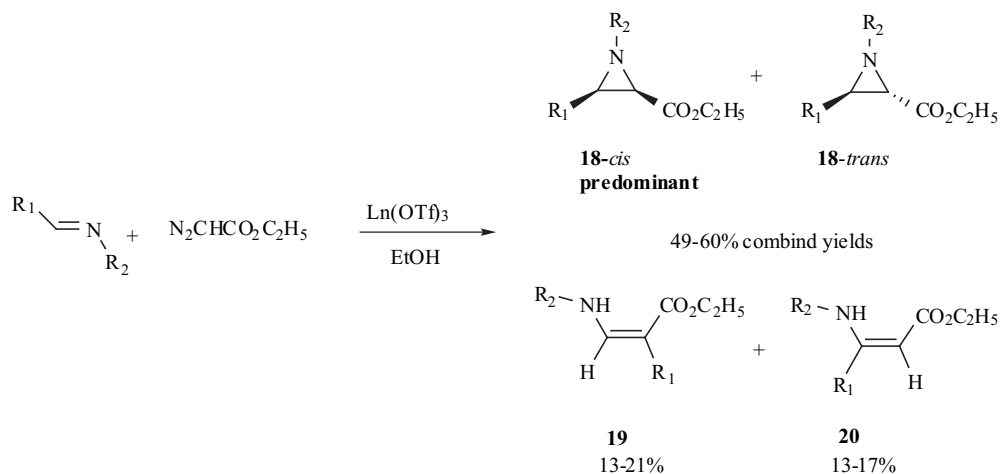


Ln(OTf) <sub>3</sub>	La	Pr	Nd	Gd	Dy	Er	Yb
16+17(%)	73	82	74	57	38	64	56
16/17	3.1	3.2	3.2	3.1	3.2	3.1	3.1

Scheme 19.



Scheme 20.



Scheme 21.

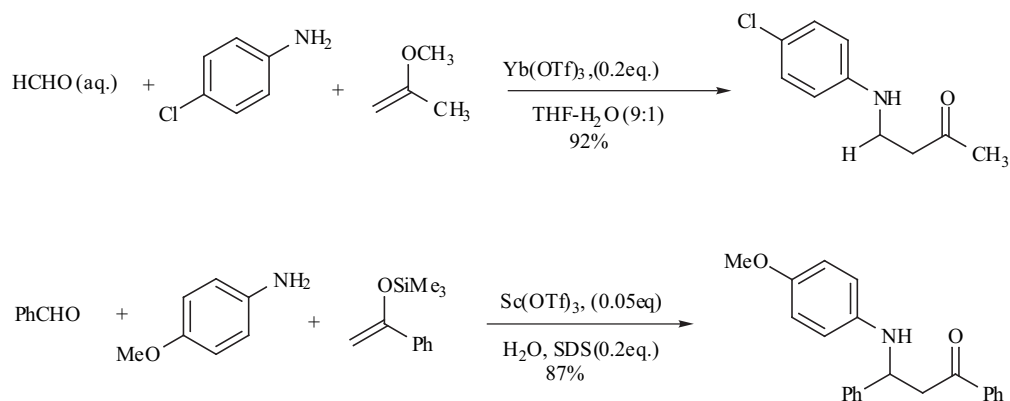
efficient catalysts in the aziridination reaction [53]. Unlike the transition metal catalyzed reaction where a transition metal carbene was involved, the Lewis acids catalyzed reactions occurred through activation of imine followed by nucleophilic addition of diazoacetate (EDA).

Quite recently, Xie and Wang accomplished the aziridation reaction in protic media by using of lanthanide [54]. The reaction proceeded readily under mild conditions and were highly selective, affording predominantly the *cis* products. The use of heavier lanthanides such as Yb and Er were found to reduce the selectivity.

No carbene-coupling product was detected under the experimental conditions. However, in several cases, by-products **19** and **20** accompanied the formation of aziridines **18** (Scheme 21). Although the carbene insertion of EDA and aziridine opening reaction can occur in the presence of lanthanide triflates, the aziridination reactions precede these by-pathways, due to their lower reaction rates.

## F. Mannich-Type Reactions

In the presence of rare earth triflates, Mannich reaction between amine, aldehyde and vinyl ether proceeded



Scheme 22.

smoothly in aqueous media to produce  $\beta$ -amino ketones [55]. In this case, the commercial available formaldehyde and chloroacetaldehyde water solutions were used directly and the desired  $\beta$ -amino ketones were obtained in high yield. Similar reaction using ketene silyl acetal proceeded smoothly and cleanly in micellar system with  $\text{Ln}(\text{OTf})_3$  as catalysts [56]. This reaction was applied to a wide range of aldehydes including heterocyclic, unsaturated, aromatic as well as aliphatic aldehydes (Scheme 22).

Mannich-type reactions of nucleophilic aromatic heterocycles have been studied extensively for the synthesis of heterocyclic compounds that are often biologically active. The use of primary amine in this reaction usually leads to low yield due to the significant side reactions. For better results, new modifications using preformed imines were introduced in the presence of protic acid [57].

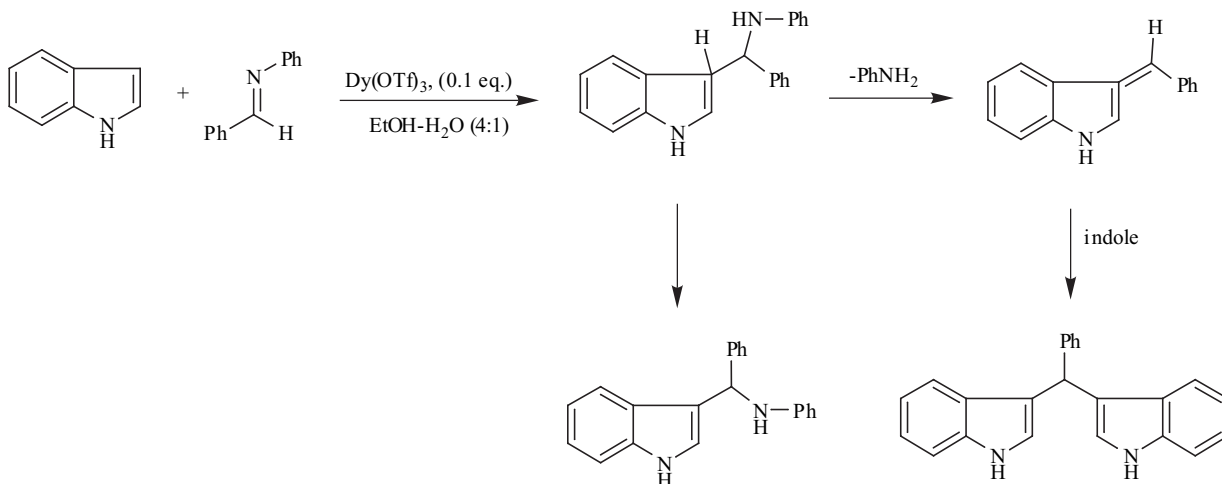
Recently, Wang found that catalytic amount of lanthanide triflate could promote the reactions of indoles with a variety of imines in protic media [58]. The reaction

provided the desired Mannich-type products as the predominant products. Minor by-products bis-indolyl methane was also isolated and a plausible pathway of the by-products was shown in Scheme 23. Among the lanthanide tested,  $\text{Dy}(\text{OTf})_3$  and  $\text{Yb}(\text{OTf})_3$  gave the best results in term of yield.

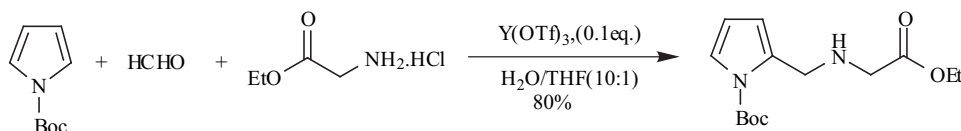
In the presence of  $\text{Y}(\text{OTf})_3$ , a three-component Mannich reaction of *N*-alkoxycarbonyl pyrroles, formaldehyde and primary amine hydrochlorides was successful carried out in aqueous media [59] (Scheme 24). The reaction gave the desired Mannich adducts in moderate to good yields. The use of aldehydes other than formaldehyde showed no reaction.

### G. Michael Reactions

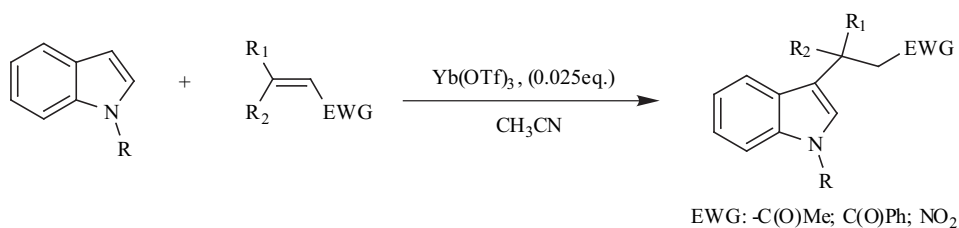
Under the influence of  $\text{Yb}(\text{OTf})_3 \cdot 3\text{H}_2\text{O}$ , indoles reacts with various electron-deficient olefins leading to 3-alkylated indoles in moderate to excellent yield [60].  $\alpha$ ,  $\beta$ -Unsaturated



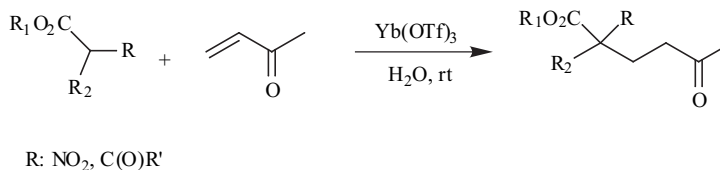
Scheme 23.



Scheme 24.



Scheme 25.



Scheme 26.

ketones showed particularly good reactivity, however,  $\beta$ -disubstituted and cyclic enones were less reactive (Scheme 25).

Feringa successfully conducted the Michael reaction in water in the presence of Yb(OTf)<sub>3</sub> [61, 62]. The reaction of  $\alpha$ ,  $\beta$ -unsaturated enones, especially of methyl vinyl ketone (MVK), with  $\beta$ -ketoesters or  $\alpha$ -nitroesters proceeded smoothly in the presence of 10mol% Yb(OTf)<sub>3</sub> in water (Scheme 26).

#### H. Allylation Reaction [63]

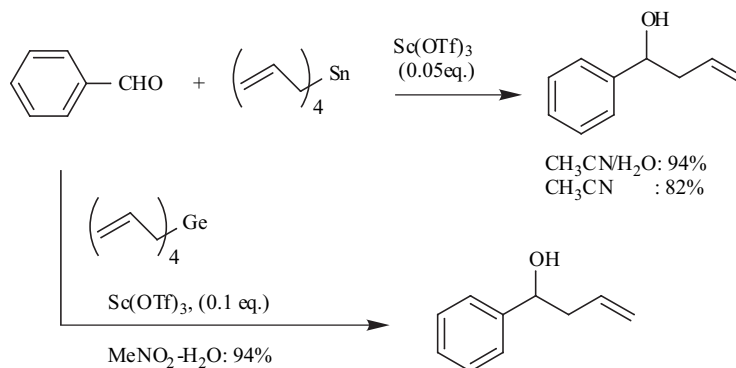
Allylation reaction of carbonyl group introduces both a hydroxyl group and a C=C bond into the substrate simultaneously. The reaction has been extensively explored

in the passing decade with much success. A variety of allyl reagents and carbonyl-containing compounds have been explored in this reaction. Rare earth triflates were found to promote allylation reaction effectively. Recent literatures on RE(OTf)<sub>3</sub> catalyzed allylation reactions are summarized in Table 5.

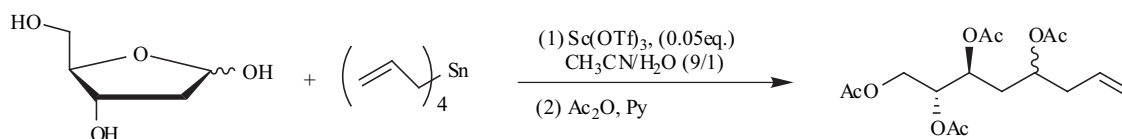
It is noted that allylation of carbonyl compounds with tetra-allyltin or tetraallylgermane occurred smoothly in aqueous media *via* the catalysis of rare earth triflates [66-68, 72] (Scheme 27). Unprotected sugar can be used directly to give the desired allyl adducts in high yield. The allyl carbohydrate derivatives can be used for the synthesis of higher sugars [66] (Scheme 28).

Table 5. Allylation Reaction Catalyzed by RE(OTf)<sub>3</sub>

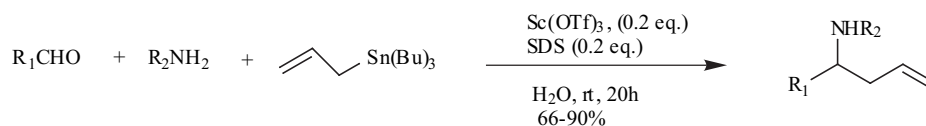
Allyl reagent	Substrate	Media	Ln(OTf) <sub>3</sub>	Ref.
SiMe <sub>3</sub>	RCHO	MeNO <sub>2</sub>	Yb(OTf) <sub>3</sub>	64
SiMe <sub>3</sub>	RCOCH(OH) <sub>2</sub>	DCM	Yb(OTf) <sub>3</sub>	65
Sn	RCHO, sugar	H <sub>2</sub> O-CH <sub>3</sub> CN	Sc(OTf) <sub>3</sub>	66
Sn	acylhydrazone	H <sub>2</sub> O-THF	Sc(OTf) <sub>3</sub>	67
Sn	RCHO	Micelle	Sc(OTf) <sub>3</sub>	68
Sn(Bu) <sub>3</sub>	RCHO	CH <sub>3</sub> CN	Yb(OTf) <sub>3</sub>	69
Sn(Bu) <sub>3</sub>	RCH=NR'	DCM	Sc(OTf) <sub>3</sub>	70
Sn(Bu) <sub>3</sub>	RCHO+RNH <sub>2</sub>	Micelle	Sc(OTf) <sub>3</sub>	71
Ge	RCHO	MeNO <sub>2</sub> -H <sub>2</sub> O	Sc(OTf) <sub>3</sub>	72



Scheme 27.



Scheme 28.



Scheme 29.

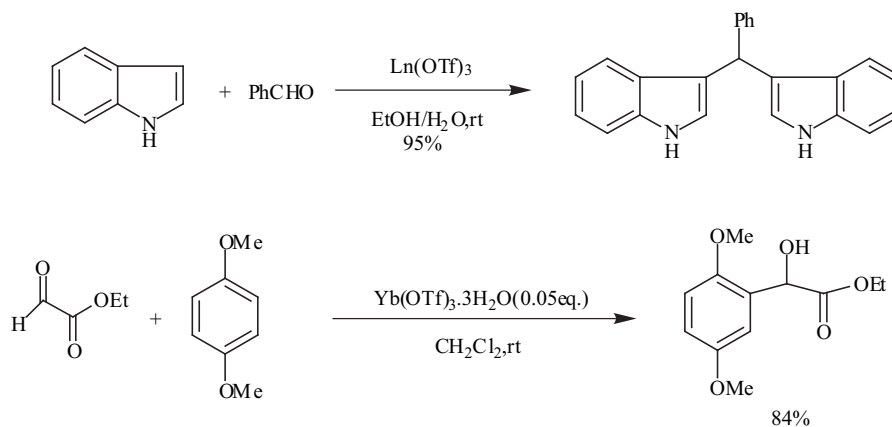
Without using of any organic solvent, the allylation reaction of tetraallyltin with aldehyde occurred smoothly in micelle system with  $\text{Sc}(\text{OTf})_3$  as catalysts. Three-component reactions of aldehydes, amines and allyltributyltin were also achieved in micelle system using SDS [71]. The reaction provided the desired homoallylic amines in high yield. This three-component reaction tolerates a wide range of aldehydes including aromatic aldehydes, heterocyclic aldehydes as well as aliphatic aldehydes. No homoallylic alcohols were detected under experimental conditions (Scheme 29).

### I. Friedel-Crafts Reaction

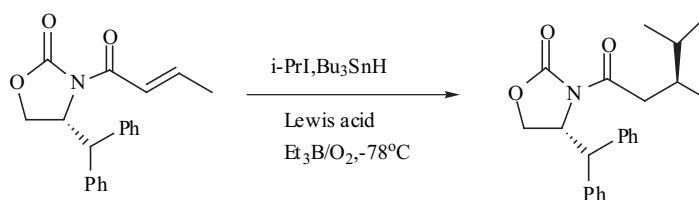
Wang found that in the presence of  $\text{Ln}(\text{OTf})_3$ , indoles reacted smoothly with aldehydes and ketones furnishing the bis-indolyl methane derivatives in high to excellent yield in aqueous media [73] (Scheme 30). Epoxides [74] and aziridines [75] are also used as alkylating reagents for indoles in the presence of catalytic amount of  $\text{RE}(\text{OTf})_3$ .

In recent years, Friedel-Crafts type hydroxyalkylation of phenol systems with  $\alpha$ -keto esters have been studied by Citterio [76] and Bigi [77]. These reactions were originally carried out using stoichiometric  $\text{TiCl}_4$ , or  $\text{SnCl}_4$  under strictly anhydrous conditions.

Zhang and Wang found that  $\text{Yb}(\text{OTf})_3$  could effectively catalyze the direct hydroxyalkylation of glyoxylate with electron-rich aromatic systems including phenols, phenol ethers, and heterocycles [78]. In the presence of 5% mol equivalent of  $\text{Yb}(\text{OTf})_3$ , the reaction occurred smoothly at room temperature in  $\text{CH}_2\text{Cl}_2$ . The use of hydrated or anhydrous catalyst gave similar results. Common Lewis acids such as  $\text{AlCl}_3$ ,  $\text{ZnCl}_2$  were not active and did not give the desired products. Various electron-rich aromatics were explored and the desired products were obtained in high yields (Scheme 30).



Scheme 30.



Yb(OTf)<sub>3</sub>(0.3eq.) : yield, 90% β/α =95:5  
 ZnCl<sub>2</sub>(1.0eq.) : yield, 90% β/α =87:13

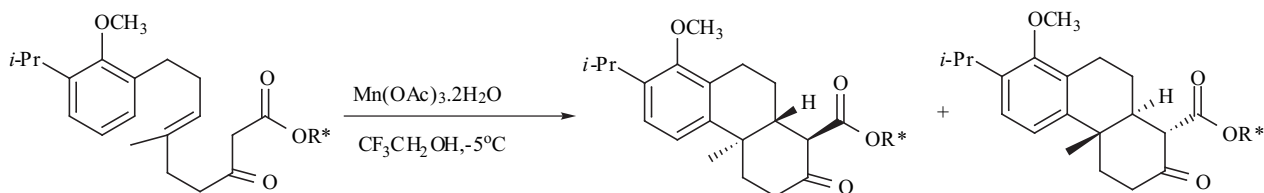
Scheme 31.

## J. Free-Radical Reaction

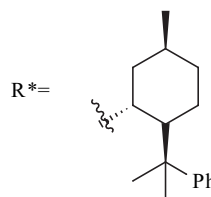
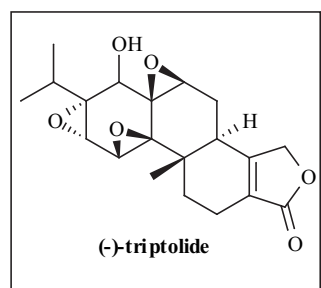
Free radicals have long been considered mainly as interesting reaction intermediates but with limited synthetic potential. However, during the past 15 years, free radical synthetic methods have been extensively explored and the progress in this field was extremely rapid. A new field was opened up by the use of Lewis acids, which was believed to influence the reactivity as well as the regioselectivity and stereoselectivity of free radical reactions [79]. Lanthanide triflates were recently revealed to be effective Lewis acid in radical reaction. Unprecedented results were obtained due to the unique feature of Ln(OTf)<sub>3</sub>.

Sibi and Ji reported good β-stereoselectivity in radical addition to *N*-butenyloxazolidinone (Scheme 31) [80]. The use of lanthanide triflates provided the maximum stereoselectivity and yield, with ytterbium giving the highest diastereoselectivity. A further advantage of Yb(OTf)<sub>3</sub> is its compatibility with small amounts of water, which is a problem for classical Lewis acids.

Yb(OTf)<sub>3</sub> was also utilized in radical pericyclization reactions [81]. In the total synthesis of Triptolide, Yang *et al.* found that Yb(OTf)<sub>3</sub> could greatly promote the reaction. Both the reaction rate and the selectivity were dramatically improved (Scheme 32). This was rationalized on the chelating of lanthanide metal ion with the substrates.



Lewis acid: None, yield: 42%; *dr*: 9:1  
 Yb(OTf)<sub>3</sub>·H<sub>2</sub>O, yield: 77%; *dr*: 38:1



## V. RE(OTf)<sub>3</sub>-CATALYZED ORGANIC SYNTHESIS IN IONIC LIQUID

### a. Diels-Alder Reaction

Ionic liquid, *i.e.* a salt mixture with a melting point below ambient temperature, is now emerging as green “designer solvents” [22]. Their properties can be adjusted by simply alternating the structure of the ions to fit the requirements of a particular process. The past few years has witnessed a growing interest in ionic liquids as solvent and catalyst for certain organic reaction, in which, the ionic liquids consisting of 1,3-dialkylimidazolium cations are of special interests due to their air and moisture stability. Unlike common volatile solvents (VOLs), ionic liquids have practically no vapor pressure, which make them more economical and environmentally benign in products separation. Most importantly, ionic liquids can form biphasic systems with most organic substrates, this make the possibility of a multiphasic reaction procedure with much easier isolation and recovery of homogenous catalysts.

Of many reports on metal catalysts immobilized in ionic liquids, few are on rare earth metal salts. Quite recently, Song and Choi reported the first immobilized RE(OTf)<sub>3</sub> as Lewis acid catalyst in Diels-Alder reaction [82]. The scandium triflate immobilized in **21** showed novel and unusual reactivity in Diels-Alder reaction between 1,4-naphthoquinone and 1,3-dimethylbutadiene. It was sufficient

Scheme 32.



**Table 6.** The Effect of Ionic Liquid on Sc(OTf)<sub>3</sub>-Catalyzed Diels-Alder Reactions

Entry	Solvent	Yield (%) <sup>a</sup>
1	CD <sub>2</sub> Cl <sub>2</sub>	22
2	<b>21a</b> (0.1 eq.)+CD <sub>2</sub> Cl <sub>2</sub>	46
3	<b>21a</b> (0.5 eq.)+CD <sub>2</sub> Cl <sub>2</sub>	85
4	<b>21a</b> (1 eq.)+CD <sub>2</sub> Cl <sub>2</sub>	>99
5	<b>21a</b>	>99
6	<b>21b</b>	>99
7	<b>21c</b>	>99

<sup>a</sup> yield estimated by HNMR

to complete the reaction with Only 0.1mol% of Sc(OTf)<sub>3</sub>. The extraordinary catalytic effect of the immobilized catalyst was shown in Table 6. It was found that the use of one equivalent of ionic liquid **21a** as additive in DCM gave the satisfactory rate enhancement.

The catalyst can be recovered by a simple extraction of the reaction mixture with Et<sub>2</sub>O. The residue ionic liquid containing the catalyst can be used for 11 times without any loss of activity. This novel immobilization methodology has great potential in the recovering of homogeneous catalysts such as RE(OTf)<sub>3</sub> usually used in aqueous media, which avoid the tedious recycle of the catalysts.

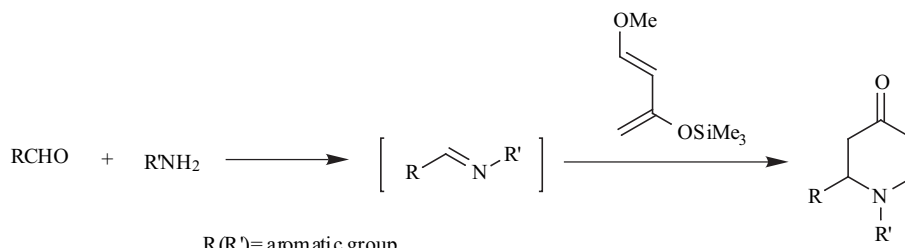
### b. Aza-Diels-Alder Reaction

One pot, three-component aza-Diels-Alder reactions were realized in ionic liquid using microencapsulated Sc(OTf)<sub>3</sub> as the Lewis acid [83]. The aza-Diels-Alder reactions of Danishefsky's Diene proceeded smoothly in imidazolium (1-ethyl-3-methyl imidazolium trifluoromethanesulfonate) or DBU centered (8-ethyl-1,8-diazobicyclo [5.4.0]-7-undecenium trifluoromethanesulfonate) ionic liquid affording

the desired *N*-aryl-6-aryl-5, 6-dihydro-4-pyridones with high yields (Scheme 33). The ionic liquid immobilized scandium catalyst was easily recovered and reused after ether extraction of the products. Similarly, one-pot Mannich type reactions occurred smoothly in ionic liquids in the presence of Yb(OTf)<sub>3</sub> [84].

### c. Friedel-Crafts Reaction

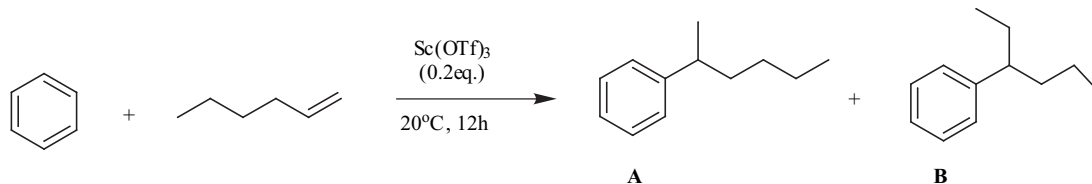
Friedel-Crafts alkylation and acylation are of great synthetic significance in view of laboratory synthesis and particularly industrial production [85]. Generally these reactions are performed using more than stoichiometric amounts of Lewis acids such as AlCl<sub>3</sub> and have to be carried out under strict anhydrous conditions. The catalysts can not be recycled. Furthermore, excess use of traditional Lewis acids and their disposal have caused serious environmental problems. In order to address these problems, much effort has been put to develop milder and more effective Lewis acid catalysts, of which the use of rare earth metal triflates represents attractive alternatives to the traditional Lewis acids.



5 examples, 75-99% yields

**Scheme 33.**

Table 7. Friedel-Crafts Alkylation in Ionic Liquid



Entry	Solvent	Yield (%) of the monoalkylated products (A:B)
1	None	0
2	CH <sub>2</sub> Cl <sub>2</sub>	0
3	CH <sub>3</sub> CN	0
4	CH <sub>3</sub> NO <sub>2</sub>	0
5	PhNO <sub>2</sub>	0
6	H <sub>2</sub> O	0
7	<b>21a</b>	96 (2:1)
8	<b>21b</b>	93 (1.5:1)
9	<b>21c</b>	0
10	<b>21d</b>	0

Sc(OTf)<sub>3</sub> immobilized in organic ionic liquid (OIL) showed unprecedented catalytic effect for the Friedel-Crafts alkylation using alkene as alkylating agent [86]. The reaction will not occur in common organic solvents and water at all. (Table 7) However, the reaction proceeded smoothly in air and moisture-stable room temperature ionic liquids consisting of 1,3-dialkylimidazolium cations. It was found that the catalytic effect of Sc(OTf)<sub>3</sub> was strongly influenced by the nature of anions X. While the reaction in hydrophobic OILs (X=PF<sub>6</sub><sup>-</sup>; SbF<sub>6</sub><sup>-</sup>) occurred smoothly to afford the desired alkylated products quantitatively, the reaction in hydrophilic OILs (X=BF<sub>4</sub><sup>-</sup>, OTf<sup>-</sup>) did not occur at all (Table 7). It is worthy to note that the catalyst immobilized in OIL was easily recovered by simple decanting the organic layer, and the recovered catalyst can be used directly without loss of activity.

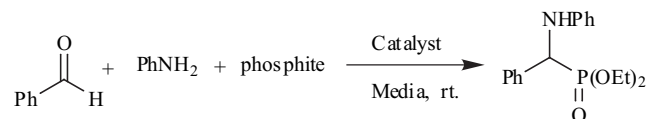
#### d. One-pot Synthesis of $\alpha$ -Amino Phosphonates

$\alpha$ -Amino phosphonates represents an important class of biologically active compounds, and their synthesis has attracted increasing attention recently [87]. Rare earth metal triflates were found to efficiently catalyze the three-component coupling reaction of aldehyde, amine and phosphonate or phosphite toward the synthesis of  $\alpha$ -amino phosphonates. Up to now, this reaction has been successfully performed in three different reaction media [88]. It is interesting to note that the media affects the RE(OTf)<sub>3</sub> catalyzed reaction dramatically. The catalytic activity was changed in different media, and minor modification of the catalyst and substrates is required for optimum outcomes. The best reaction systems in different media are summarized in Table 8.

When the reaction was conducted in DCM and OIL **21a** with diethyl phosphite as the substrate, water was found to

be detrimental to the reaction due to the hydrolysis of diethyl phosphite. In contrast, the reaction proceeded smoothly in micelle system in water to afford the desired products in good yields when triethyl phosphate was used. In this case, Lewis-acid and surfactant combined catalyst (LASC) Sc(O<sub>3</sub>SOC<sub>12</sub>H<sub>25</sub>)<sub>3</sub> (Sc(SDS)<sub>3</sub>) were used instead of the common RE(OTf)<sub>3</sub>. Compared with the reaction in DCM, the reaction rates in water and OIL were enhanced and the loading of catalyst was reduced. These methodologies were applied to a variety of aldehydes and amines to afford the desired  $\alpha$ -amino phosphonates in good to excellent yields.

Table 8. The Optimal Reaction System in Different Media

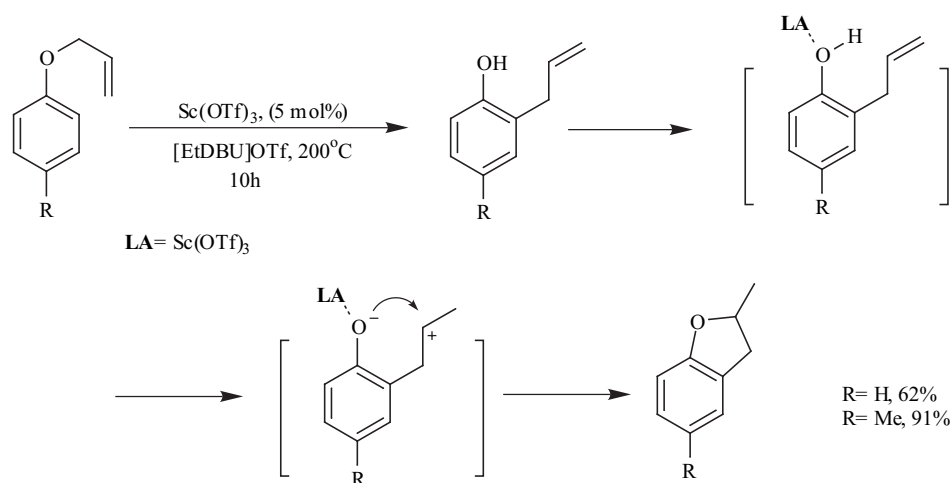


Media	phosphite	Catalyst (mol%)	t	Yield (%)
DCM	HO-P(OEt) <sub>2</sub>	Yb(OTf) <sub>3</sub> <sup>a</sup>	5h	89
Micelle/H <sub>2</sub> O	P(OEt) <sub>3</sub>	Sc(SDS) <sub>3</sub>	20 min	88
<b>21a</b>	HO-P(OEt) <sub>2</sub>	Sm(OTf) <sub>3</sub>	27h	99
<b>21a</b>	P(OEt) <sub>3</sub>	Sc(OTf) <sub>3</sub>	2h	97

<sup>a</sup> additive: MgSO<sub>4</sub>

#### e. Sequential Claisen Rearrangement and Cyclization

Under the influence of scandium triflate at high temperature (200 °C), allyl phenyl ether was transformed



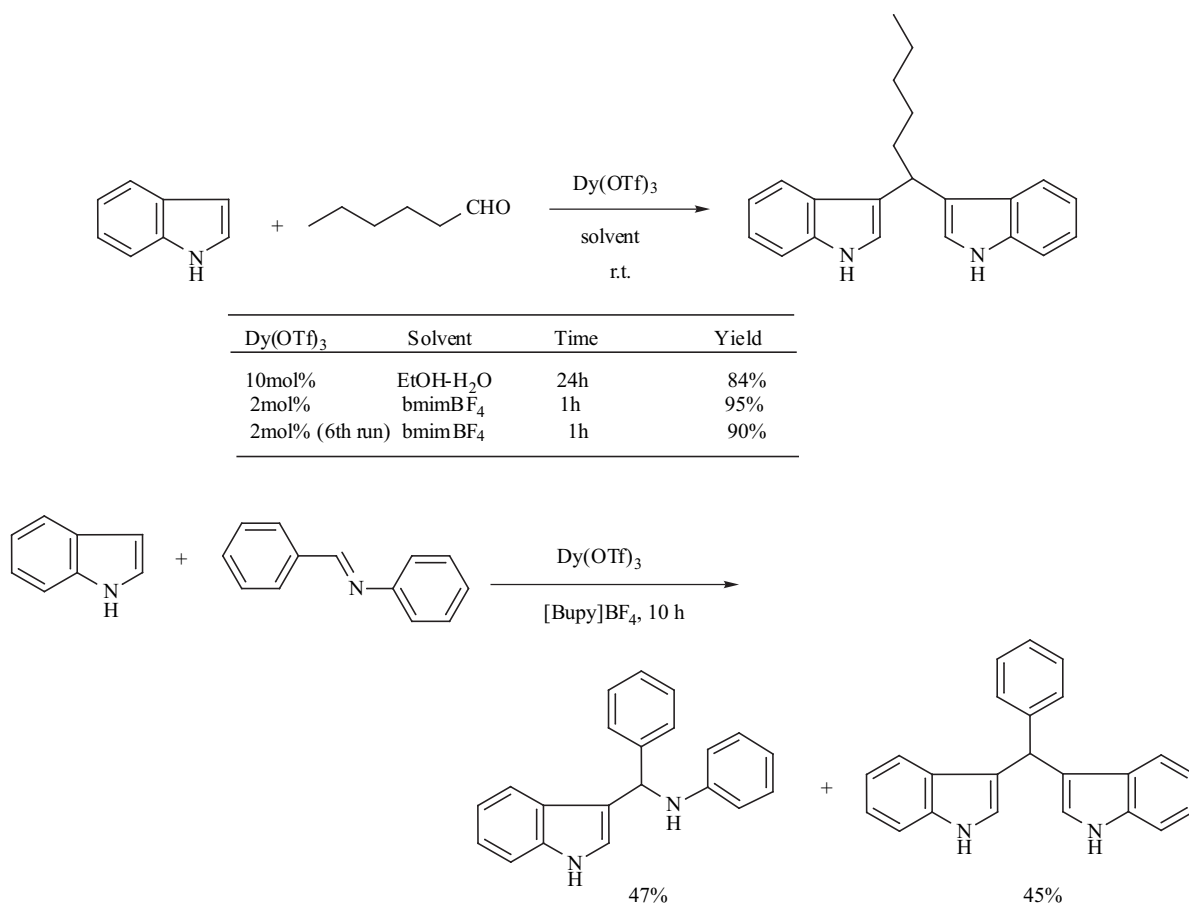
Scheme 34.

into 2-methyl-2,3-dihydrobenzofuran through domino Claisen rearrangement and an intramolecular cyclization catalyzed by Lewis acid [89] (Scheme 34). The ionic liquid (8-ethyl-1,8-diazobicyclo [5.4.0]-7-undecenium trifluoromethanesulfonate) immobilized catalyst was easily reused without loss of activity.

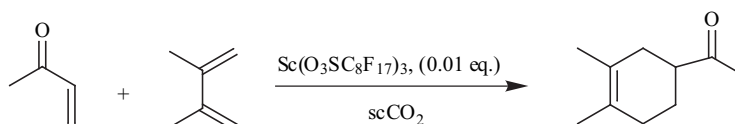
#### f. The Reaction of Indole with Aldehydes and Imines

We found that the ionic liquid immobilized Dy(OTf)<sub>3</sub> acted as powerful catalyst for electrophilic substitution of

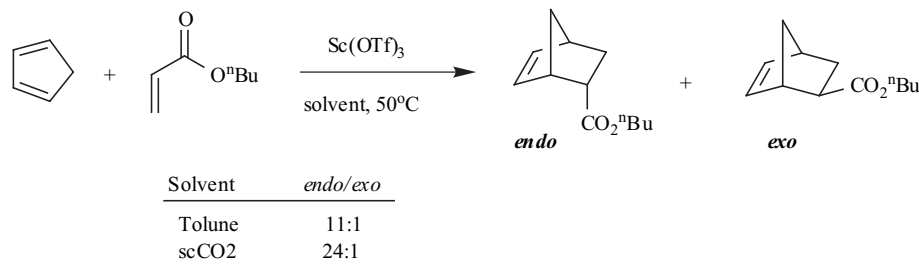
indole with aldehydes, ketones, and imines [90]. Both the reaction rates and yields are improved considerably by conducting the reaction in ionic liquids in place of aqueous ethanol. Notably, the immobilized Dy(OTf)<sub>3</sub> could be reused for at least six times with little loss of activity (Scheme 35). The reaction of imines afforded the desired secondary amine product together with by-product, bisindolyl methane (Scheme 35) in [Bupy]BF<sub>4</sub> (*N*-butyl pyridinium tetrafluoroborate).



Scheme 35.



Scheme 36.



Scheme 37.

## VI. RE(OTf)<sub>3</sub>-CATALYZED ORGANIC SYNTHESIS IN scCO<sub>2</sub>

Supercritical carbon dioxide (scCO<sub>2</sub>) [91] has now been regarded as another desirable environmental-friendly non-toxic alternative to volatile organic solvents (VOSs). Due to the low solubility of RE(OTf)<sub>3</sub> in scCO<sub>2</sub>, perfluorinated catalyst such as Sc(O<sub>3</sub>SC<sub>8</sub>F<sub>17</sub>)<sub>3</sub> were generally used [92]. Diels-Alder reactions of carbonyl dienophiles with dienes were successfully carried out using perfluoroalkylated scandium Lewis acid in scCO<sub>2</sub> (Scheme 36). The desired products were obtained in high yields with high selectivities. Beside the environmental aspects, it was also revealed that the use of scCO<sub>2</sub> could also enhance the diastereoselectivity considerably compared to the reaction in common organic solvents.

Although perfluorinated catalysts exhibit superiority when employing in scCO<sub>2</sub>, they are expensive. From this point of view, the use of unmodified catalyst is desirable. Rayner [93] found that the diastereoselectivity of the reaction between acrylate and cyclopentadiene was improved considerably when using Sc(OTf)<sub>3</sub> in scCO<sub>2</sub>. A maximum of 24:1 *endo:exo* ratio was achieved, while the same reaction in toluene gave a ratio of 10:1 (Scheme 37). Recently, Kobayashi found that Yb(OTf)<sub>3</sub>-catalyzed Mannich reactions proceeded smoothly in scCO<sub>2</sub> in the presence of

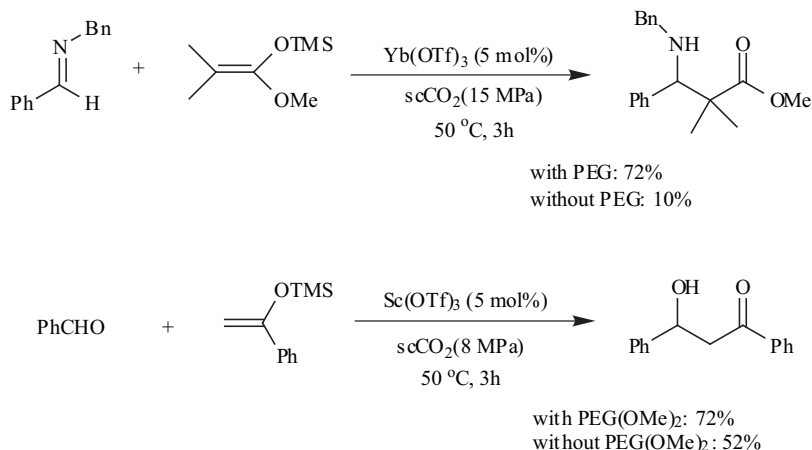
PEG [94]. PEG served as a “surfactant” in scCO<sub>2</sub> to form emulsions, which enhances the solubility of the catalyst and substrates leading to acceleration of the reaction. Similar effect was also observed in Sc(OTf)<sub>3</sub>-catalyzed Aldol reaction of enol ethers (Scheme 38).

Although the synthetic application has not been fully established, the combination of water-stable rare earth metal catalyst and scCO<sub>2</sub> is expected to lead to benign chemical process.

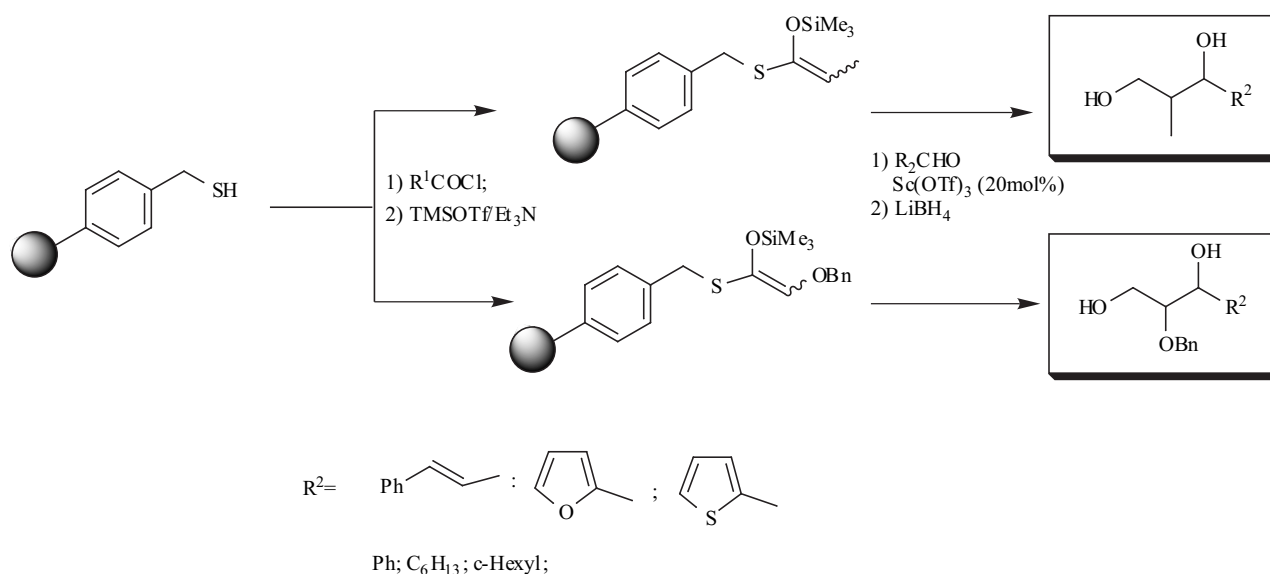
## VII. RE(OTf)<sub>3</sub>-CATALYZED ORGANIC SYNTHESIS ON SOLID SUPPORT OR SOLVENT-FREE CONDITIONS

### a. Aldol Reaction

As one of the powerful organic reaction, the solid phase version of Aldol reaction has also been widely studied. Sc(OTf)<sub>3</sub> was found to catalyze solid phase Aldol reaction effectively [95]. This reaction was developed using polystyrene supported silyl enol ethers (PSSEEs) [96]. In the presence of catalytic amount of Sc(OTf)<sub>3</sub>, PSSEEs reacted smoothly with aldehydes in DCM (dichloromethane). The products were successfully cleaved from the support by treatment with LiBH<sub>4</sub> to afford a library



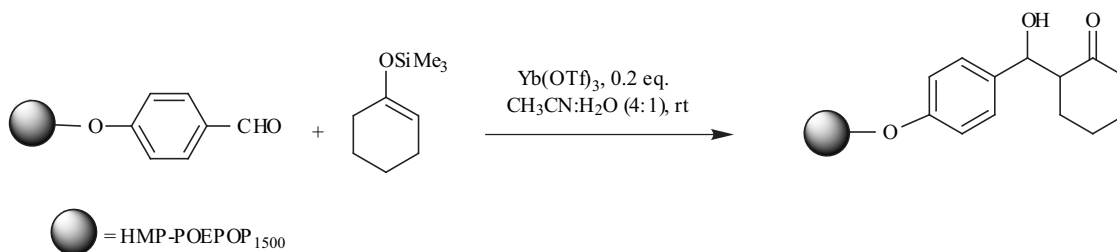
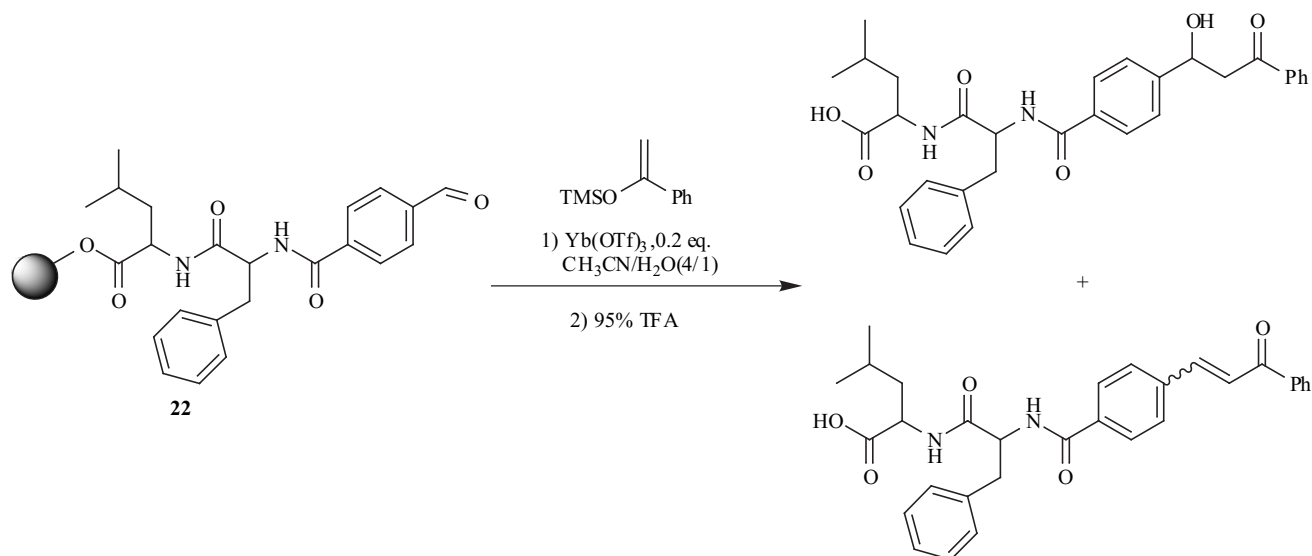
Scheme 38.

**Scheme 39.** Solid phase Aldol reaction.

of 1, 3-diols (Scheme 39). When the supported products were treated with DIBALH or hydrolyzed under aqueous base condition, the corresponding  $\beta$ -hydroxy aldehyde or  $\beta$ -hydroxy carboxylic acids were obtained.

Recently, hydrophilic solid supported aqueous Aldol reaction was reported by Meldal [97]. Polar polyoxyethylene-polyoxypropylene (POEPOP), which

containing only ether and hydroxyl functionality, was used as solid support for lanthanide triflate catalyzed aqueous Mukaiyama Aldol reaction. The resin was derivatized with a 4-hydroxymethyl-phenoxy (HMP) linker. In the optimized conditions, the resin bound 4-alkoxybenzaldehyde reacted smoothly with 1-trimethylsiloxy-cyclohex-1-ene to afford the Aldol adduct in high yield in aqueous media (Scheme 40).

**Scheme 40.** Hydrophilic solid-phase Aldol reaction.**Scheme 41.** Synthesis of peptide isostere library.

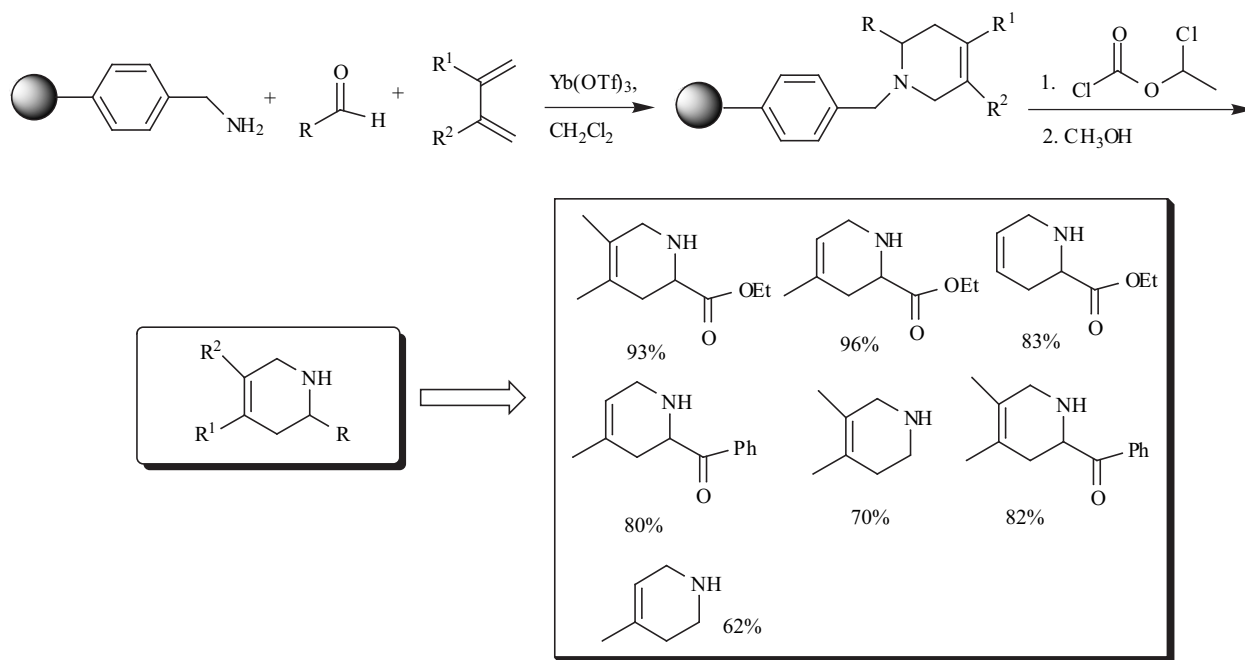
Control studies revealed that the use of water was crucial. In the absence of water, no Aldol reaction was observed. This was rationalized on the passivation of the catalyst caused by chelation with resin polyethyleneglycol in the absence of water.

This novel solid-phase Aldol reaction was utilized to prepare the peptide isostere libraries. Peptide **22** was selected as the N-terminal aldehyde model substrate. In presence of 0.2 equivalents of  $\text{Yb}(\text{OTf})_3$ , peptide **22** was shown to undergo nearly quantitative reaction with 1-trimethylsiloxy-1-phenyl-ethylene affording the Aldol or Aldol condensation products (Scheme 41). The existence of amide and ester carbonyl groups has no effect on catalyst.  $\text{Yb}(\text{OTf})_3$  preferentially coordinate to the aldehyde carbonyl group, facilitating sufficiently rapid Aldol reactions which suppress the hydrolysis of silyl enol ether.

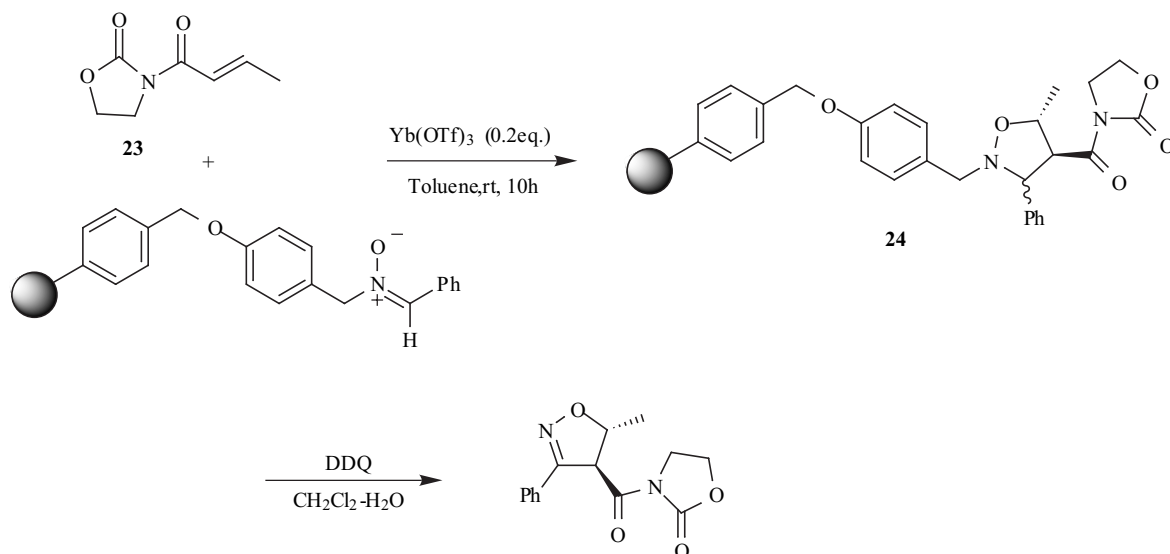
## b. Aza-Diels-Alder Reaction

As an extension of the work on aza DA reactions, Wang *et al.* developed a solid-supported aza-Diels-Alder reaction employing trace-less cleavage technique [98]. Amino-methylated polystyrene resin was used as the amine component without modification. The resin, diene, aldehyde, and lanthanide triflate were combined and reacted at room temperature in DCM. The resin was then cleaved off utilizing 1-chloroethyl chloroformate to afford a library of tetrahydropyridine (Scheme 42).

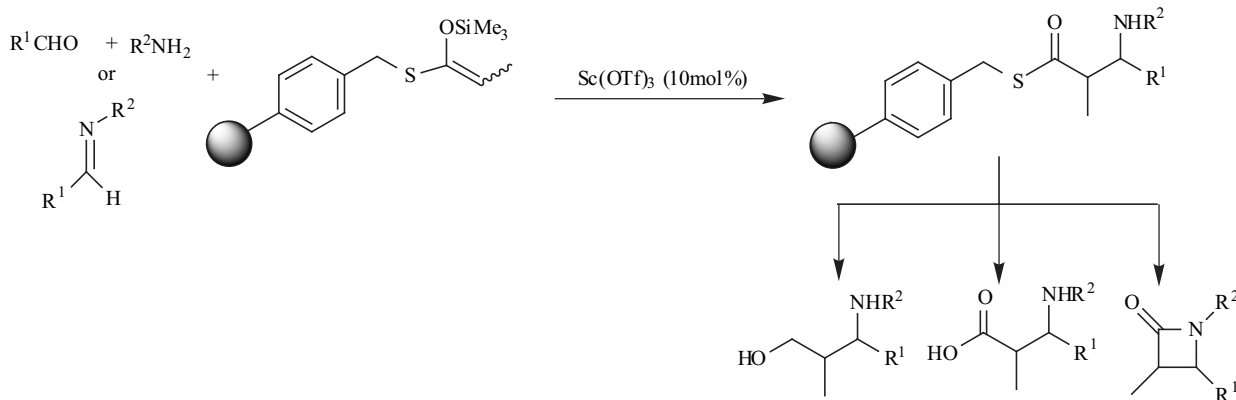
Moreover, there was no observed negative effect of water. This was believed partly resulting from the aqueous stability of the lanthanide triflate. Among the lanthanide triflates screened,  $\text{Yb}(\text{OTf})_3$  gave the best results. The advantage of the cleavage allowed for high purity as well as effective



Scheme 42.



Scheme 43.



Scheme 44.

debenzylation of product. It left the double bond intact for further synthetic manipulations, which normal hydrogenation of the benzyl moiety could not achieve.

### c. 1, 3-Dipolar Cycloaddition

A solid-supported 1,3-dipolar cycloaddition was developed based on polystyrene-supported nitrones [99]. In the presence of 20 mol%  $\text{Yb}(\text{OTf})_3$ , the polymer-supported nitrones reacted with **23** to afford the supported isoxazolidine derivatives **24** in high yields. The products were oxidative cleavage from the support using 2,3-dichloro-5,6-dicyanobenzoquinone (DDQ) (Scheme 43).

### d. Mannich Reaction

Using polystyrene supported silyl enol ether, two or three component Mannich reactions were successfully carried out on solid phase with  $\text{Sc}(\text{OTf})_3$  as the catalyst [100]. The reaction was utilized toward the construction of  $\beta$ -amino alcohol,  $\beta$ -amino acid and  $\beta$ -lactam libraries (Scheme 44).

### e. Solvent-Free Reactions

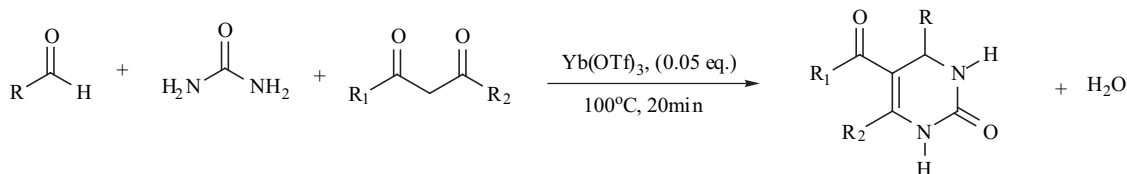
Bignelli reaction, one-pot reaction of aldehyde,  $\beta$ -dicarbonyl compounds and urea or thiourea, provides a useful route to dihydropyrimidinones and their derivatives, which are pharmacologically important as calcium channel

blockers, antihypertensive agents, and  $\alpha_1$ -a-antagonists [101].

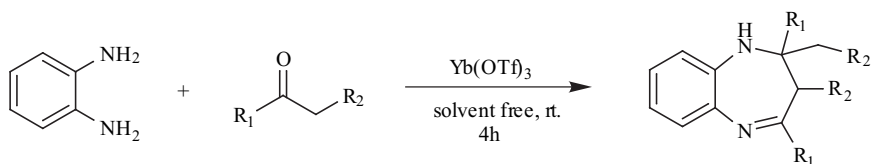
Lewis acids have been used as highly effective catalysts in this multi-component reaction [102]. It was reported recently by Ma and Qian that  $\text{Yb}(\text{OTf})_3$  could effectively catalyze the Bignelli reaction under solvent free conditions [103] (Scheme 45). The yields of the reaction were increased from 20-50% to 81-99%. Moreover, the reaction time was shortened from 18-48 h to 20 min. The “dry media”, *i.e.* solvent-free conditions, of the reaction was especially appealing environmentally. This allows the reaction to be performed with an open vessel, thus avoiding the risk of high internal pressure development. Another notable feature of this reaction is its ability to tolerate a wide range of substrates.

Under solvent-free condition,  $\text{Yb}(\text{OTf})_3$  promoted the synthesis of 1,5-benzodiazepene derivatives by condensation of *o*-phenylenediamine with ketone (Scheme 46) [104].

Epoxide-opening products of azoles have been of interest particularly in pharmacological applications and as chiral ligands in asymmetric catalyzed reactions [105]. However, the reaction of epoxides and azoles normally requires harsh conditions, such as prolonged high temperature with concomitant use of strong base. Recently, it was reported that high-pressure and microwave could promote ring opening of epoxides with azoles under relatively mild conditions [106]. Our lab found that  $\text{Yb}(\text{OTf})_3$  could

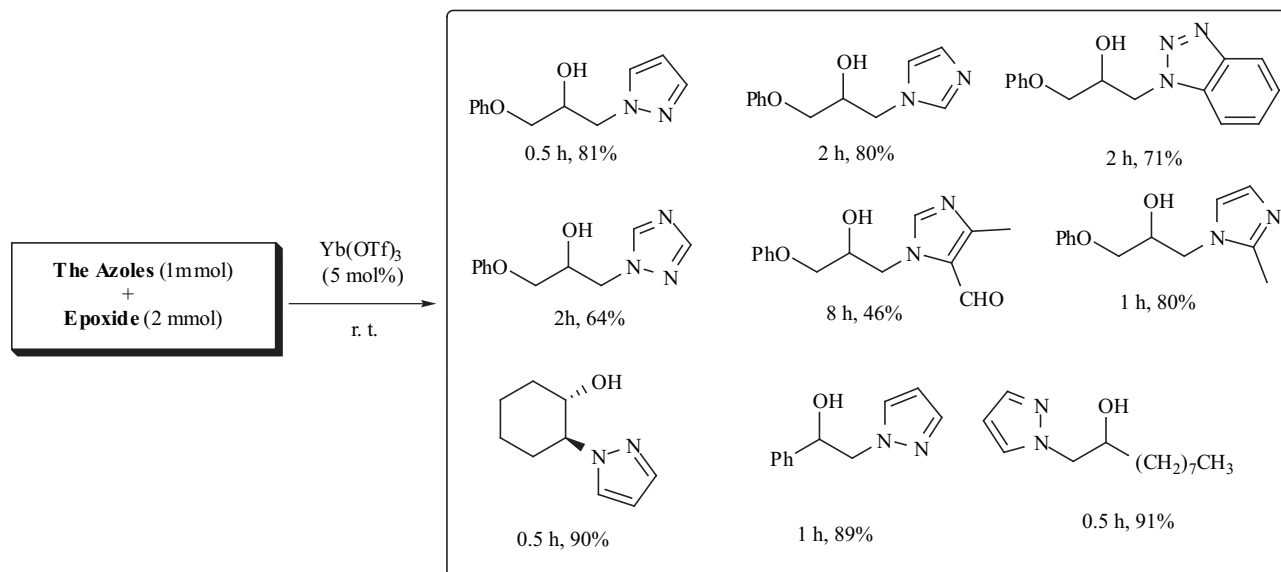


Scheme 45.



8 examples, 88-99% yields

Scheme 46.



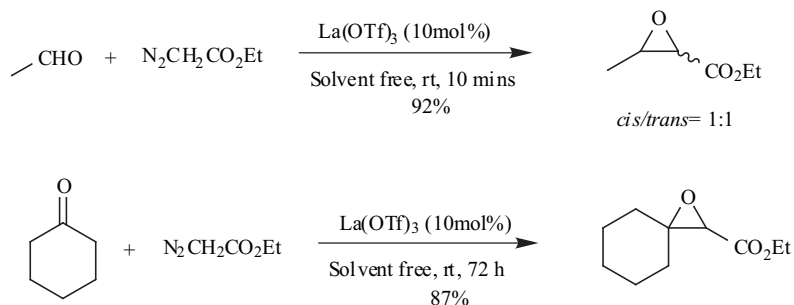
Scheme 47.

effectively catalyze the reaction of epoxides with nitrogen heterocycles under solvent free conditions [107]. Besides the environmental concern, the reaction under solvent free conditions may also offer advantages such as easy handling, time and energy efficiency, and most importantly reactivity enhancement for difficult substrates. Under optimized conditions, a library of the hydroxyl-alkylated nitrogen heterocycles was constructed with high efficiency (Scheme 47).

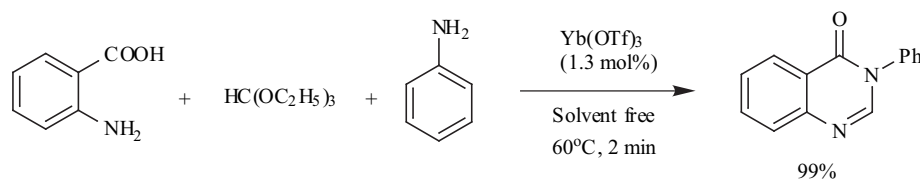
La(OTf)<sub>3</sub> was shown to promote the synthesis of glycidyl ether from the reaction of reactive carbonyl compounds such as aldehydes and cyclohexanones with ethyl diazoacetate under solvent free conditions [108] (Scheme 48). Quite recently, Qian and coworkers reported that Yb(OTf)<sub>3</sub> could catalyze the three-component coupling of anthranilic acid, ortho esters (or formic acid) and aniline under solvent free conditions. The reactions afforded the biologically important quinazolin-4(3*H*)-ones with high yields [109] (Scheme 49).

## VIII. CONCLUSION

The review has shown the unique feature and diversity usefulness of RE(OTf)<sub>3</sub> in organic synthesis, especially in environmentally benign media. However, the detailed mechanism of catalyzed reactions is still not well understood. Nevertheless, the advantages of using RE(OTf)<sub>3</sub> together with green media are numerous. Rare earth metal triflates are water and air stable, and can be easily recycled and reused. They have been applied to various green media such as water, ionic liquid, scCO<sub>2</sub> and solvent free condition which is both economic and environment-friendly. An inherent limitation of lanthanide triflates is that they are rare in nature, thus may be expensive for large-scale synthesis. The development of immobilized lanthanide catalysts based on new strategies will pave the way for their general applications. It is also noted that the unique properties of lanthanides will possibly lead to some novel synthetic processes. Although the cutting-edge research progress has been extraordinarily rapid in this field, the field of RE(OTf)<sub>3</sub>



Scheme 48.



Scheme 49.



catalyzed organic synthesis in green media is still embryonic. As the present growing recognition for persistent development, one can envision a rapid development in this field in the near future.

## ACKNOWLEDGEMENTS

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