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Aqueous Aza Diels-Alder Reactions Catalyzed by Lanthanide(III) Trifluoromethanesulfonates

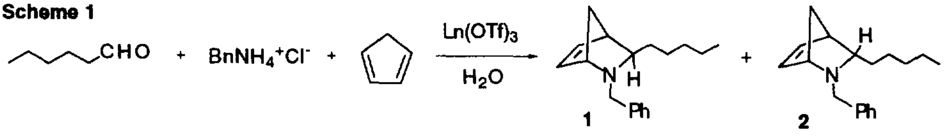
Libing Yu, Depu Chen, Peng George Wang*

Department of Chemistry, University of Miami, P. O. Box 249118, Coral Gables, FL 33124.

Abstract *Lanthanide(III) trifluoromethanesulfonates have been demonstrated to catalyze aqueous aza Diels-Alder reactions of an aldehyde and an amine hydrochloride with a diene.*

In 1985, Grieco reported an aza Diels-Alder (DA) reaction in aqueous solution between simple inactivated iminium salts generated in situ from aldehydes and amine hydrochlorides under Mannich-like conditions with dienes.[1] This hetero DA reaction conveniently combined three reactant components (an aldehyde, an amine salt and a diene) in aqueous solution and generated nitrogen-containing heterocyclic products.[2] Following this seminal work, chiral amines[3] and amino acids[4] have been employed as chiral sources to synthesize optically pure heterocyclic compounds. In spite of the potential synthetic applications, the reaction has been limited to either the smallest aldehyde (formaldehyde) or activated aldehydes such as glyoxylates. Inactivated higher aldehydes such as acetaldehyde showed much lower reactivity.[1] The dienes other than cyclopentadiene also gave poor to moderate yields. We have recently found that lanthanide(III) trifluoromethanesulfonates (triflates) in aqueous solution can serve as effective catalysts for this type of reaction.

Scheme 1

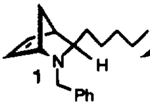
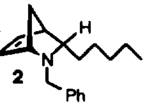
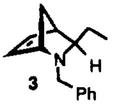
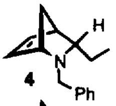
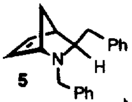
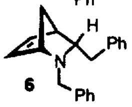
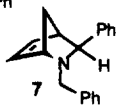
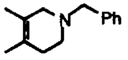
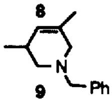
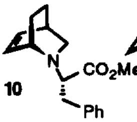
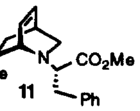
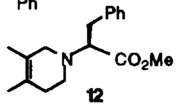
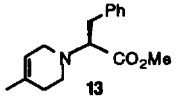


Lanthanide(III) triflates have recently been used by Kobayashi and other researchers to catalyze a variety of reactions[5] including achiral DA reactions[6] and asymmetric DA reactions in organic solvents.[7] As stable Lewis acids in aqueous media, they have been shown to catalyze aldol and allylation reactions in aqueous solutions.[8] Also, Lewis acid catalyzed cycloaddition of inactivated imine in organic solvent has been reported.[9] We found that the rate of the aza DA reaction of hexanal and benzylamine hydrochloride with cyclopentadiene in aqueous solution was quite slow and the reaction afforded only 4% adducts (**1** + **2**) after separation (**Scheme 1**). In sharp contrast, the rate of the reaction was increased by a factor of 27 during the first six hours of the reaction in 0.25 M of lanthanide triflate solution (pH 5-7) and the reaction yield was greatly enhanced as well.

Table 1. Effect of Lanthanide (III) Triflate (0.25 M) on the Aza DA Reaction Shown in **Scheme 1**

$Ln(OTf)_3$	H_2O (only)	La	Pr	Nd	Gd	Dy	Er	Yb
ratio (**1**/**2**)	2.7	2.6	2.9	3.1	2.7	2.8	2.6	2.8
Yield (% for **1** + **2**)	4	47	68	57	19	49	46	62

Table 2. Aqueous Aza Diels-Alder Reactions Catalyzed by $Ln(OTf)_3$

	Starting Materials [a]			Catalysts				
Entry	aldehyde	diene	amine	$Ln(OTf)_3$	Products	Ratio	Yield [b]	
1	$CH_3(CH_2)_4CHO$		$BnNH_3^+Cl^-$	$Pr(OTf)_3$	 1  2	(2.9/1)	68	7
2	CH_3CH_2CHO		$BnNH_3^+Cl^-$	$La(OTf)_3$	 3  4	(2.5/1)	64	4
3	$PhCH_2CHO$		$BnNH_3^+Cl^-$	$Yb(OTf)_3$	 5  6	(4/1)	72	3
4	$PhCHO$		$BnNH_3^+Cl^-$	$Yb(OTf)_3$	 7		7	0
5	$CH_3(CH_2)_4CHO$		$BnNH_3^+Cl^-$	$Ln(OTf)_3$	no products			
6	$CH_3(CH_2)_4CHO$		$BnNH_3^+Cl^-$	$Ln(OTf)_3$	no products			
7	CH_2O		$BnNH_3^+Cl^-$	$Nd(OTf)_3$	 8		93	23
8	CH_2O		$BnNH_3^+Cl^-$	$Yb(OTf)_3$	 9		92	54
9	CH_2O		L-phenylalanine methyl ester	$Nd(OTf)_3$	 10  11	(1/3)	84	27
10	CH_2O		L-phenylalanine methyl ester	$Nd(OTf)_3$	 12		98	58
11	CH_2O		L-phenylalanine methyl ester	$Nd(OTf)_3$	 13		96	37

(a) Entry 1-6, aldehyde 1 mmol, benzylamine hydrochloride 1.1 mmol and cyclopentadiene 2 mmol. Entry 7-11, amine hydrochloride 1 mmol, formaldehyde 1.2 mmol, and diene 1.5 mmol. (b) The isolated yields of entry 1-4 and entry 7-11 were based on the aldehyde and the amine hydrochloride, respectively. The first column are for the reactions with lanthanides. In comparison, the second column are for the reactions without lanthanides.

A typical reaction procedure is as follows: an aldehyde, an amine hydrochloride and a diene was added to a 5 mL vial containing 1 mL of 0.25 M lanthanide triflate. The vial was sealed tightly and shaken for 12-20 h. The reaction mixture was extracted with chloroform (2 mL x 4). The combined organic phase was washed with 1 M sodium hydroxide until pH ~ 9 and dried over anhydrous magnesium sulfate. The solvent was evaporated *in vacuo* to give an oil which was purified via silica gel column chromatography eluting with a mixture of hexane, ethyl acetate and methyl alcohol. The aqueous phase with the catalyst from the workup was re-used for the second round of the reaction and showed the same catalytic effect.

Among the seven lanthanide (III) triflates screened, praseodymium (III) triflate ($Pr(OTf)_3$) and ytterbium (III) triflate ($Yb(OTf)_3$) were most effective; while the yield of the DA adducts was lower in the presence of gadolinium (III) triflate ($Gd(OTf)_3$) (**Table 1**). In comparison to the uncatalyzed reaction, the lanthanide catalyst did not change the ratio of *exo* and *endo* products. It is worth mentioning that no catalytic effect was found in 0.25 M solutions of magnesium chloride or lithium chloride for this aza DA reaction. This should exclude the possibility that the large catalytic effect of the lanthanide comes only from the pure salt effect.[10] The lanthanide triflate most likely functions as a stable Lewis acid in the aqueous solution and the ionic radius and specific coordination of the lanthanide also play a role. In addition, we suspect that the lanthanide triflate may catalyze the formation of the Shiff base intermediate for the aza DA reaction. Studies on the detailed catalysis mechanism are underway in our laboratory.

The catalytic effect of lanthanide(III) triflates on aza DA reactions was also demonstrated with other aldehydes (**Table 2**). In the reaction of propionaldehyde with benzylamine hydrochloride and cyclopentadiene, lanthanum(III) triflate was the most effective catalyst and the catalyzed reaction gave a combined yield of 64% for two isomers (*exo* **3** and *endo* **4**, 2.5/1, entry 2); in contrast, gadolinium(III) triflate played a moderate catalytic role and the yield was 24%. All seven lanthanides tested had similar catalytic effect on the reaction of phenylacetaldehyde and afforded *exo* **5** and *endo* **6** (4/1) with the combined yields ranging from 63% to 72% (entry 3). The reactivity of benzaldehyde was relatively weak and the cycloaddition of benzaldehyde and benzylamine hydrochloride with cyclopentadiene gave the adduct (*exo* **7**) with a 7% yield in the presence of 0.25 M ytterbium(III) triflate (entry 4). Without the mediation of lanthanides, no DA adduct could be detected for this reaction.

Next, the effect of lanthanide salts was studied with different dienes and amines. It was found that in the presence of 0.25 M of lanthanide(III) triflate the reaction of hexanal and benzylamine hydrochloride with 1,3-cyclohexadiene or 2,3-dimethyl-1,3-butadiene did not afford any significant amount of adducts (**Table 2**, entry 5-6). However, when formaldehyde served as the aldehyde component, the lanthanide catalyzed reactions gave excellent yields with shortened reaction times at room temperature in comparison to the poor yields, prolonged reaction time and promoted reaction conditions (e.g higher temperature) without the lanthanide (**Table 2**, entry 7 - 8). The seven lanthanides were screened for every reaction and the best result was shown in **Table 2**. For example, the yield of the reaction of formaldehyde and benzylamine hydrochloride with 2,3-dimethyl-1,3-butadiene was improved from 23% in aqueous solution to 93% in 0.25 M neodymium(III) triflate. In addition, the lanthanide(III) triflate also exhibited good catalytic effects for the reaction of formaldehyde and L-phenylalanine methyl ester with 1,3-cyclohexadiene, or 2, 3-dimethyl-1,3-butadiene or isoprene (**Table 2**, entry 9-11). For example, the neodymium(III) triflate-mediated reaction of 1,3-cyclohexadiene gave two diastereomers **10** and **11** (1/3) with a combined yield of 84%. In comparison, the uncatalyzed reaction gave a yield of 27% (**10/11**, 1/2.7).

In summary, we have demonstrated that lanthanide(III) triflate can be used as an effective catalyst in aqueous solution for aza Diels-Alder reactions. For a given reaction, different lanthanide salts exhibited different catalytic effects, although ytterbium (III) triflate and neodymium (III) triflate were found to be the best in most cases in this study. The scope of the catalytic process covered larger aldehydes, different amines and a variety of dienes. In particular, the reactions of aldehydes with cyclopentadiene or the reactions of formaldehyde with a variety of dienes gave moderate to excellent yields of DA adducts. However, the reactions of larger aldehydes with dienes other than cyclopentadiene did not occur with the catalysis of the lanthanide. Due to its facile manipulation, this lanthanide catalyzed aqueous aza DA reaction is expected to have many practical synthetic applications.

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11. All products (**1-13**) were charaterized by proton NMR and mass spectra. Data will be provided upon request.

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