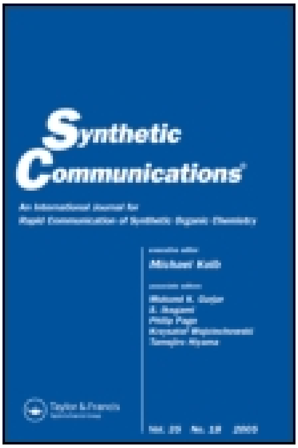

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Ytterbium Trichloride-Catalyzed Diels-Alder Reactions of Unactivated Dienes

Xinggao Fang [a] , Benjamin P. Warner [a] & John G. Watkin [a]

[a] Chemical Science and Technology (CST) Division, Los Alamos National Laboratory, Los Alamos, NM, 87545

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YTTERBIUM TRICHLORIDE-CATALYZED DIELS-ALDER REACTIONS OF UNACTIVATED DIENES

Xinggao Fang, Benjamin P. Warner* and John G. Watkin

Chemical Science and Technology (CST) Division,
Los Alamos National Laboratory, Los Alamos, NM 87545

ABSTRACT: Ytterbium chloride ($YbCl_3$) is an effective and reusable catalyst for Diels-Alder reactions of unactivated dienes with α,β-unsaturated ketones and aldehydes at room temperature, leading to products with high regio- and stereoselectivities.

In recent years, a number of reports have appeared which describe the use of lanthanide-containing complexes as Lewis acid catalysts to facilitate a range of organic transformations. Initially, lanthanide shift reagents such as $Yb(fod)_3$ and $Eu(hfc)_3$ were reported to effectively catalyze Diels-Alder (D-A) reactions,[1] and more recently lanthanide triflates, $Ln(OTf)_3$, have found increasing applicability as hard Lewis acid catalysts for both D-A[2] and aza- (or hetero-) D-A reactions.[3] In contrast to traditional Lewis acids such as $TiCl_4$, $SnCl_4$, and BF_3 which are extremely moisture sensitive and can promote side reactions, $Ln(OTf)_3$ reagents are water-stable and reusable. Kobayashi and co-workers have reported that $Yb(OTf)_3$ and its derivatives are particularly useful catalysts for D-A reactions between the highly reactive cyclopentadiene (Cp) and carbonyl-containing

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*To whom correspondence should be addressed; E-mail: warner@lanl.gov.

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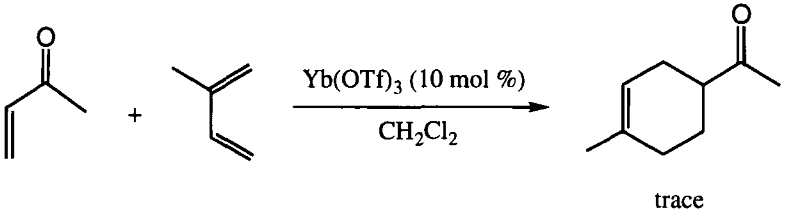
dienophiles.[4] However Yb(OTf)$_3$ was found to be ineffective in catalyzing Diels-Alder reactions involving an unactivated diene such as isoprene (eq. 1).[5,6] These workers had to employ the considerably more expensive scandium triflate in order to achieve reasonable product yields from this reaction.



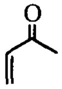
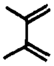
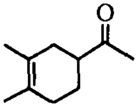
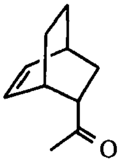
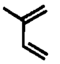
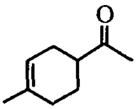
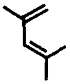
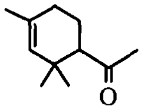
(1)

During our current investigations of the use of lanthanide compounds in organic syntheses, we found that the above reaction was efficiently catalyzed both by Yb(OTf)$_3$ and by anhydrous YbCl$_3$ at room temperature. Since lanthanide trichlorides (LnCl$_3$) are more readily available than the respective triflates, it was of interest to explore the scope of LnCl$_3$ catalyzed D-A reactions. Lanthanide trichlorides are simple, low-cost and commercially-available reagents. They have been employed previously to catalyze thioacetalization,[7] the cycloaddition of epoxides to isocyanates,[8] Friedel-Crafts reactions[9] and nucleophilic substitutions.[10] Ligand-modified lanthanide chlorides have also been used as catalysts for the asymmetric addition of trimethylsilyl cyanide to aldehydes.[11] Certain lanthanide chlorides have been found to be extremely active in catalyzing hetero-Diels-Alder reactions at elevated temperature, and also facilitating D-A reactions between highly activated cyclopentadiene and certain carbonyl-containing dienophiles under inert atmosphere.[12] Gadolinium chloride has also very recently been reported as an effective catalyst for the imino D-A reaction of aromatic imines with dihydropyran and dihydrofuran.[13] Here we would like to report that YbCl$_3$ is an efficient and reusable catalyst for D-A reactions of readily available unactivated dienes with high regio- and stereoselectivities.

Methyl vinyl ketone (MVK) was found to react with a range of dienes using 10 mol % of $YbCl_3$ catalyst at room temperature over approximately 16 hours to give the desired products with moderate to excellent yields (Table 1). Methacrolein was also found to be a suitable dienophile (Table 2). Methylene chloride was found to be the optimal solvent for the reaction. The use of THF gave low yields of products, while attempted use of water as solvent gave only trace quantities of the desired products.

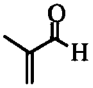
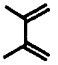
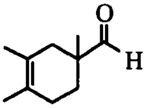
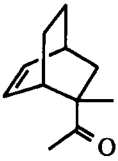
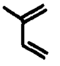
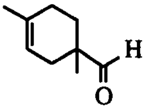
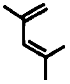
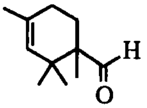
As can been seen from Tables 1 and 2, regio- and stereoselectivities of the products are very high for both MVK and methacrolein. In addition, the reactions may be run under atmospheric conditions with results comparable to those obtained under inert atmosphere.

Table 1.

Entry	Dienophile	Diene	Major Product	Yield
1	 1		 5	86
2	1		 6	86 - 94[a]
3	1		 7	70
4	1		 8	49

[a] Endo:Exo ratio = 45:1.

Table 2

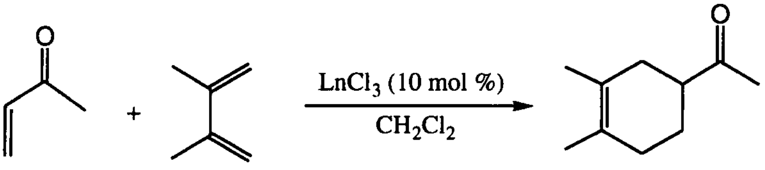
Entry	Dienophile	Diene	Major Product	Yield
1	 2		 9	79
2	2		 10	57[b]
3	2		 11	48
4	2		 12	65

[b] Endo:Exo ratio = 7:1.

Since the lanthanide trichlorides have very limited solubility in CH_2Cl_2, the reactions are essentially heterogeneous, and the yield generally increases with increasing reaction time. As an example, a reaction between MVK and 2,3-dimethyl-1,3-butadiene to form adduct **5**, employing 10 mol % $YbCl_3$ as catalyst, was monitored over time. **5** could be isolated in 47 % yield after 1 h of reaction time, 69 % after 3 h, and 92 % after 66 h. It should be noted that the heterogeneous nature of the reaction medium simplifies catalyst separation and enables reuse of the ytterbium trichloride. For example, following the isolation of adduct **5** in 92 % yield in the above-described reaction, the solid catalyst was filtered off, dried under reduced pressure for 30 mins. at room temperature and reused. The yield of **5** for the second run was found to be 80 %. The catalyst was again filtered off and dried, and was then used to obtain a 72 % yield of **5** in a third reaction.[14]

During investigations of catalyst loading, it was found that the use of smaller quantities of $YbCl_3$ was still effective in promoting the Diels-Alder reactions. Thus we were able to employ catalyst loadings as low as 2 mol % while maintaining reasonable yields of product. For example, adduct **6** may be isolated in 62 % yield by utilizing a 2 mol % loading of $YbCl_3$, and the yield increases to 78 % when 5 mol % of $YbCl_3$ is employed. The yield can presumably be raised with prolonged reaction time.

In a study of the effect of changing the metal center, the following results were obtained (eq. 2):



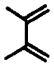
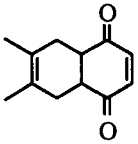
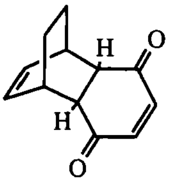
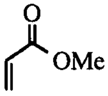
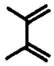
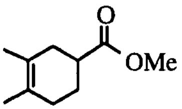
(2)

$LnCl_3$	$PrCl_3$	$GdCl_3$	$DyCl_3$	$ErCl_3$	$LuCl_3$
Yield (%)	1	2	42	54	62

These results tend to confirm the observations of previous workers. As one progresses across the lanthanide series the ionic radius of the metal gradually decreases, which serves to increase the charge/size ratio and produce a more electrophilic and Lewis acidic metal center.

In further studies (Table 3), it was found that reactions involving 1,4-benzoquinone and methyl acrylate were catalyzed to varying extents, whereas

Table 3

Entry	Dienophile	Diene	Major Product	Yield
9	 3		 13	52
10	3		 14	71
11	 4		 15	9

attempted D-A reaction of cyclohexenone with 2,3-dimethyl-1,3-butadiene led to the formation of only trace amounts of product.

In summary, we have demonstrated that $YbCl_3$ is a practical Lewis acid catalyst for the Diels-Alder reactions of readily available dienes with carbonyl-containing dienophiles under very mild and convenient conditions. Asymmetric versions of this catalyst are currently being explored in our laboratory.

Experimental

Anhydrous lanthanide trichlorides $LnCl_3$ (Ln = Pr, Gd, Dy, Er, Yb, Lu) were purchased from Strem Chemical Co. and used as received. Initial manipulations and weighings of lanthanide trichlorides were carried out under a helium atmosphere in an Innovative Technologies drybox. NMR spectra were recorded at 22°C on a Varian Unity 300 spectrometer.

In a typical experiment, the dienophile (10 equivalents) was added to a stirred suspension of $YbCl_3$ (0.050 g) in CH_2Cl_2 (5 mL) at room temperature in air followed by addition of the appropriate diene (10 equivalents). The resulting mixture was stirred overnight (*ca.* 16 h) at ambient temperature. Volatiles were removed under reduced pressure, the residue extracted with hexane and the extract filtered. Solvent was then removed from the filtrate and product was purified by flash silica gel column chromatography or crystallization from hexane where appropriate. All of the Diels-Alder products have been previously reported in the literature. Therefore products were analyzed by ^1H NMR and GC-MS spectroscopy and characterizing data were compared with those previously reported.

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14. The use of extracting hexane likely will introduce water which may convert $YbCl_3$ into $YbCl_3{\bullet}xH_2O$ that serves as an active catalyst for these Diels-Alder reactions. However, it should be noted that $YbCl_3$ treated with excess of H_2O does not catalyze the reaction.

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