

Novel, air-stable, lanthanide catalysts for the hetero Diels–Alder reaction

Claude Spino, Laurel Clouston, and David Berg

Abstract: Novel, air-stable, yttrium and ytterbium complexes were found effective in the catalysis of the typical hetero Diels–Alder reaction of crotonaldehyde and ethylvinyl ether. They represent an attractive solution to the problem of ligand lability in the realm of lanthanide catalysts.

Key words: lanthanide, catalyst, hetero Diels–Alder, yttrium, ytterbium.

Résumé : Deux nouveaux complexes d'yttrium et d'ytterbium, stable à l'air, se sont avérés très efficace comme catalyseurs d'une réaction typique de Diels–Alder hétéro impliquant la crotonaldéhyde et l'éther d'éthylevinyle. Ils représentent une solution attrayante au problème chronique de la labilité des ligands chez les catalyseurs de lanthanide.

Mots clés : lanthanide, catalyseur, Diels–Alder hétéro, yttrium, ytterbium.

Lanthanides are increasingly used in organic synthesis as mild reagents and catalysts that can spare many sensitive functional groups (1 and, for reviews, 2). Catalytic systems based on lanthanide metals have been found for many organic reactions, including the Friedel–Crafts reaction, acetal and ether formation, reduction and oxidation, and the Diels–Alder cycloaddition or, more particularly, the hetero Diels–Alder reaction involving an oxygen on the dienophile or diene (1, 3). Complex and sensitive molecules give high yields of products with few side reactions, testimony to the mildness of these catalysts (1–3). Asymmetric versions of the latter type of Diels–Alder reactions have been limited to only a few isolated examples (4–6) with little success in the cycloaddition of vinyl ethers to α,β -unsaturated aldehydes (3). All of the lanthanide complexes tried as catalysts were in fact either NMR shift reagents or commercially available complexes designed for other uses (1–3). Part of the obstacle to achieving high asymmetric induction with lanthanide catalysts can be attributed to the lability of the ligands around the metal. In reality, this lability confers a degree of uncertainty about the actual structure of the active catalyst. In addition, it may impair induction because of ligand displacement during catalysis.

We felt that a necessary step in designing efficient lanthanide catalysts for that reaction was to find suitable ligands

with low lability and to make complexes of a well-defined structure. Only then could we rationally design chiral complexes with the hope of increasing the enantioselectivities so far achieved with lanthanide systems. We describe herein our success in synthesizing two novel, air-stable, and effective yttrium and ytterbium complexes that show low ligand lability and are efficient catalysts for the hetero Diels–Alder reaction. To the best of our knowledge, these are the first examples of well-defined hexadentate² ligand–metal complexes of a lanthanide or yttrium that are effective catalysts.³ Their stability in air is a good indicator of low ligand lability and we believe they are strong forerunners of chiral complexes.

The rationale for using tripodal ligands was to contribute extra stability to the complex, in effect “locking” the ligand in place.⁴ Well-defined monomeric tripodal structures would thus provide a solid base from which to design and develop highly effective chiral catalysts. Starting from the observation that lanthanide complexes derived from trifluoromethyl- β -diketone-type ligands are effective catalysts for the hetero Diels–Alder reaction (1, 2, 8), we initially believed that derivatives such as ligand 2 would be well suited for our purpose, being tripodal in nature, easily prepared, and easily altered for the eventuality of chiral design. Ligand 2 was prepared in 80% purified yield by refluxing 1,1,1-trifluoroacetoacetate in a benzene solution of tris(aminoethyl)amine 1 with concurrent

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Claude Spino.¹ Université de Sherbrooke, Département de Chimie, Sherbrooke, QC J1K 2R1, Canada.

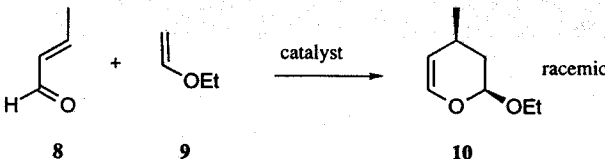
Laurel Clouston and David Berg.¹ University of Victoria, Chemistry Department, P.O. Box 3055, Victoria, BC V8W 3P6, Canada.

¹ Authors to whom correspondence may be addressed.
C.S.: Telephone: (819) 821-7087. Fax: (819) 821-8017.
D.B.: Telephone: (604) 721-7161. Fax: (604) 721-7147.

² The complex is hexadentate assuming there is no interaction between the arene ring and the metal. This interaction may exist and would be interesting. It has not yet been examined.

³ Similar but non-catalytic heptadentate lanthanide complexes can be found in ref. 7.

⁴ Even though a “hinging motion” is possible, it is unlikely that more than one arm would do this at any one time. “Hinging” specifically refers to partial dissociation of one arm, i.e., bidentate to monodentate for that arm.

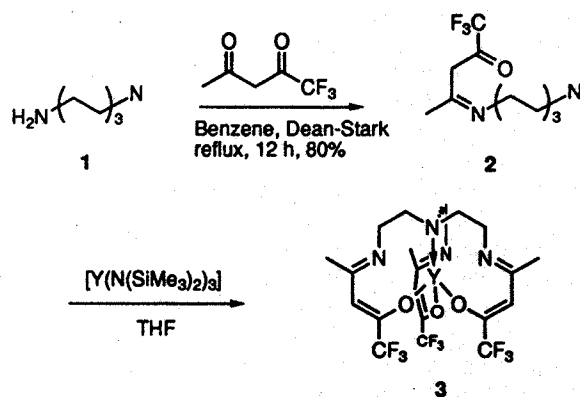
Table 1. Efficiency of the different catalysts on the hetero Diels–Alder of **8** and **9**.


Entry	Catalyst	Conditions ^a	Time (h)	Conversion ^b	Yield ^c
1	3	A	96	0	0
2	7a	A	72	98	95
3	7b	A	96	80	80
4	Yb(fod) ₃	A	96	98	90
5	ZnCl ₂	A	48	98	46
6	BF ₃ ·Et ₂ O	A	48	98	12
7	7a	B	96	69	69
8	Yb(fod) ₃	B	96	69	65
9	7a	C	96	89	89
10	7b	C	96	89	89
11	Yb(fod) ₃	C	96	0	0

^aMethod A = ethylvinyl ether as solvent, 2 mol% catalyst; Method B = method A + dioxane (0.5 equiv.) (similar results if **7** is prepared in a coordinating solvent); Method C = method A + deliberately exposed to air for 7 days.

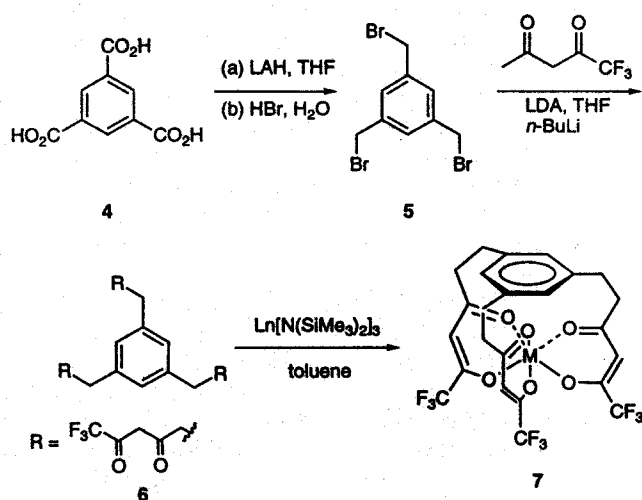
^bDisappearance of starting materials analysed by gas chromatography.

^cIsolated yield after distillation.

Scheme 1.

removal of water (Scheme 1). The metal complex **3** was prepared by mixing the ligand with a solution of yttrium tris(bis-trimethylsilyl)amide (**9**) in tetrahydrofuran. It was characterized by single-crystal X-ray diffraction.

We were surprised to find that this complex showed no catalytic behaviour toward the cycloaddition reaction of crotonaldehyde and ethylvinyl ether (see Table 1). Several factors could be responsible for this lack of activity and we suspected that either the imine nitrogen or the coordinating amine nitrogen could electronically saturate the metal and thereby lower its Lewis acidity. Nevertheless, we reasoned that the needed ligand should possess the unaltered trifluoromethyl- β -diketone functionality. Such units could be linked by the end methyl group via a number of linkers, thereby leaving the β -diketone unit intact. 1,3,5-Tribromomesitylene **5** caught our

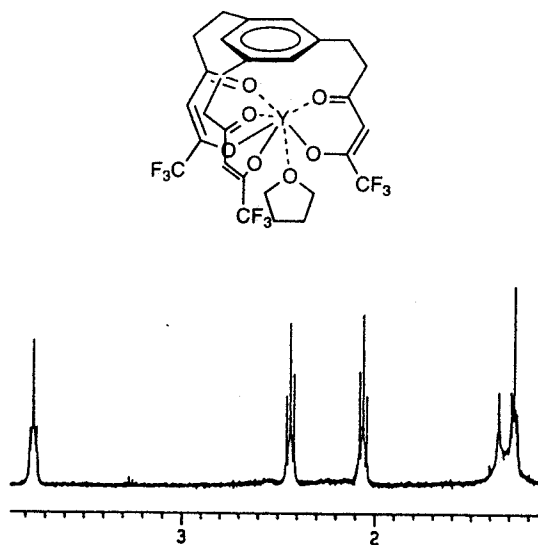
Scheme 2.

attention as being a useful linker because of its relative ease of preparation and high reactivity toward alkylation.

We looked at several ligands before ultimately settling for the tribenzyltrifluoroacetoacetate ligand **6** (Scheme 2). Ligand **6** was thus prepared starting from 1,3,5-benzenetricarboxylic acid **4**. The aluminium salts resulting from the reduction of **4** with LAH are directly treated with aqueous hydrobromic acid to give an 80% yield of **5**.

The dianion of 1,1,1-trifluoroacetylacetone was generated using slight modifications of a standard procedure (**10**). Though its reactivity was lower than that of non-fluorinated β -diketones, effective alkylation in THF at room temperature

Fig. 1. Partial NMR spectrum of yttrium complex **7a** showing a coordinated THF molecule.



with tribromomesitylene **5** could be achieved. The tripodal ligand **6** was thus obtained in 40% yield after recrystallization and sublimation at 140°C / 10⁻² Torr (1 Torr = 133.3 Pa).

The metal complexes **7a** (M = Y) and **7b** (M = Yb) were prepared by mixing the ligand with a solution of yttrium or ytterbium tris(bis(trimethylsilyl)amide in toluene (**9**). In each case, an instantaneous reaction occurred with concomitant precipitation of the complex, which was washed several times with toluene. Unfortunately, we could not grow crystals of adequate quality to perform a single-crystal X-ray crystallographic analysis on either of the complexes and neither were soluble in non-coordinating solvents. To secure the structure of the yttrium complex **7a**, we prepared it in THF and isolated the powdery material by simple reduced pressure evaporation of the solvent. Although no X-ray quality crystals could be grown, the proton NMR analysis of the complex in benzene-*d*₆ was unequivocal and established the coordination of a molecule of THF (Fig. 1). Mass spectral data, Exact Mass measurement, and elemental analysis on this compound were satisfactory. The structure of the ytterbium complex **7b** was inferred only from mass spectral data and by analogy to **7a**.

Catalytic activities were tested on the hetero Diels-Alder cycloaddition of crotonaldehyde and ethylvinyl ether, the latter serving as solvent, with 2 mol% of catalyst (Table 1). In each example involving lanthanide or yttrium catalysts, with the exception of **3**, the isolated yields of the respective dihydropyran product **10** were excellent, testimony to their mildness (entries 2–4). In contrast, zinc chloride and BF₃-etherate gave 46 and 12% isolated yield, respectively, of **10** (entries 5 and 6). The thermal reaction proceeds at 175°C to give product **10** in 87% yield (**8**). The same reaction can also be carried out under high-pressure conditions (15 kbar (1 bar = 100 kPa), 75°C, 24 h) to give 89% of the *endo* adduct (**11**).

Each reaction was monitored by gas chromatography at specific time intervals. The yttrium catalyst **7a** was superior to all others, including the commonly used Yb(fod)₃ (**12**), having the fastest conversion rate and giving a good isolated yield of **10** (entry 2). As expected, the product isolated was regiochem-

ically and diastereomerically pure (racemic) and was derived from the *endo* approach of the dienophile as verified by proton NMR (**12a**). If dioxane was utilized as an internal standard for quantitative work, the reaction rate between **8** and **9** dropped (entries 7 and 8), indicating a competition for the active site between the coordinating solvent and crotonaldehyde **8**. We found that when the complexes **7** were prepared in or came in contact with coordinating solvents, the reaction rate dropped also, presumably due to the incorporation of a coordinating solvent molecule. In turn, this coordinating solvent molecule may compete with crotonaldehyde for the active site or simply reduce the Lewis acidity of the complex. More importantly, both catalysts **7** remained active even after several days of exposure to the ambient air (entries 9 and 10), even though the complexes may have picked up water molecules from exposure to air. A 3-month-old sample of complex **7a** stored in an opened vial still retained complete catalytic activity. In contrast, all other catalysts including Yb(fod)₃ had to be kept in a rigorously dry atmosphere to remain active (entry 11). The air and moisture stability of these complexes is undoubtedly linked to the low p*K*_a coupled with the tripodal nature of the ligand **6**.

In conclusion, we have prepared the first lanthanide complexes that possess a tripodal ligand and are active catalysts. Their high stability, even in air, is not only desirable in terms of handling but is also very promising as a base from which to develop chiral catalysts showing high asymmetric induction.

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