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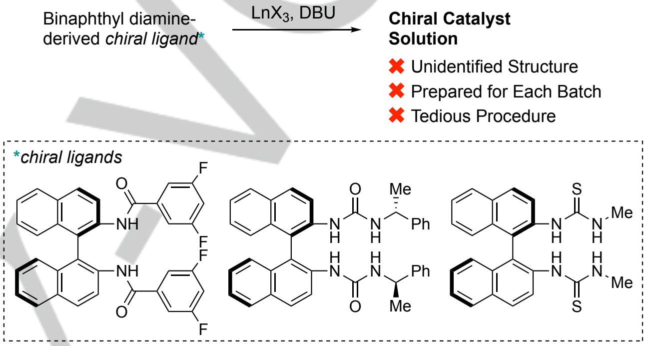
Optically Active Helical Lanthanide Complexes: Storable Chiral Lewis Acidic Catalysts for Enantioselective Diels-Alder Reaction of Siloxydienes

Shinji Harada,*[a],[b] Saki Nakashima,[a] Shihori Sekino,[a] Wakana Oishi,[a] and Atsushi Nishida*[a],[b]

Abstract: Lanthanide triflates and a series of hexadentate chiral ligands complexes were synthesized. X-ray-quality crystals were obtained from mixtures of the lanthanide complexes, which were helical in shape. The complexes showed Lewis acidity and catalyzed the enantioselective Diels-Alder reaction of electron-rich siloxydienes. The complexes were stable enough to be stored at ambient temperature on a laboratory bench and retained their Lewis acidity even after a month.

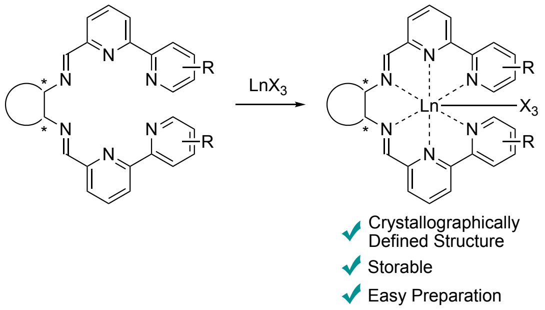
The Diels-Alder reaction, which gives a six-membered ring from a diene and a dienophile, is one of the fundamental reactions in organic synthesis.[1] Among frequently used dienes, siloxydiene is a highly reactive substrate, and the siloxy group can be used after the reaction as a versatile functional group.[2] However, a challenge with the use of siloxydiene is its acid-lability. In general, the Diels-Alder reaction is accelerated by acidic reagents. Diastereo- and enantioselective variant could be also achieved by acidic reagents. Thus, for the reaction using siloxydienes, the applicable Lewis acidic catalyst is limited because acidic reagents decompose the siloxydiene before promoting the desired reaction. The product derived from siloxydiene is also unstable under acidic conditions.

Our group has overcome this problem by using a lanthanide catalyst (Scheme 1).[3],[4],[5] Lanthanides are reactive electropositive metals, and their salts are often used as hard Lewis acids.[6] They also accept large numbers of ligands with a variety of coordination environments. By taking advantage of these unique properties, we could control the Lewis acidity of the metal center by adding proper ligands without saturating the coordination site. In addition, their chemical and physical properties are similar, but differ slightly according to the atomic number.[7] Thus, we can tailor-make a suitable catalyst for a specific substrate by screening the metal center. However, our ternary lanthanide catalyst was not a crystalline complex, and the structure is still unknown. Additionally, the catalyst was not storable and each time had to be prepared in situ under rigorously dried conditions prior to use.



Scheme 1. Our Previous Chiral Ternary Catalytic System for Enantioselective Diels-Alder Reaction of Siloxydienes.

We report here a synthesis of new lanthanide complexes (Scheme 2), which were prepared using a simple procedure and were stable at ambient temperature. We elucidated the structure unambiguously by X-ray crystallographic analysis. The Lewis acidity of the metal center would be properly tuned by a hexadentate ligand, and the catalytic and enantioselective Diels-Alder reaction of siloxydiene was performed as an application of the complex.



Scheme 2. Preparation of Chiral Lanthanide Catalyst for Enantioselective Diels-Alder Reaction of Siloxydienes.

We synthesized bis[imino-bipyridyl] (ImBpy) chiral ligand **1** from (*S*,*S*)-cyclohexanediamine.[8],[9] When we mixed **1** and lanthanide triflate, we obtained a crystalline compound (Scheme 3). This complex is stable enough to store at ambient temperature on a

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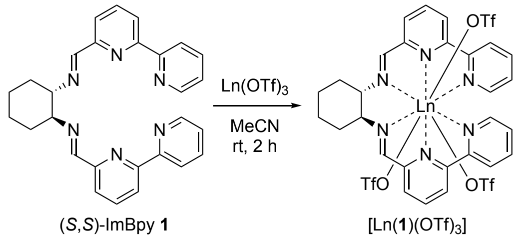
laboratory bench for at least one month. Figure 1 shows the X-ray crystallographic analysis of gadolinium complex as an example.[10] The chiral ligand **1** wound around the metal center with a chiral coordination sphere to form a *P*-helix.[11] We focused on the structure in which the metal center was multiply coordinated by nitrogen functionalities. The genuine Lewis acidity of the metal center would be decreased, and we envisioned that the complex may act as a mild Lewis acidic catalyst. Incidentally, Hasegawa reported the synthesis of racemic helical lanthanide complexes from lanthanide nitrates and an ethylene-tethered variant of ligand **1**.[12]



Scheme 3. Synthesis of Chiral Lanthanide Complexes ($[\mathrm{Ln}(\mathbf{1})(\mathrm{OTf})_3]$)

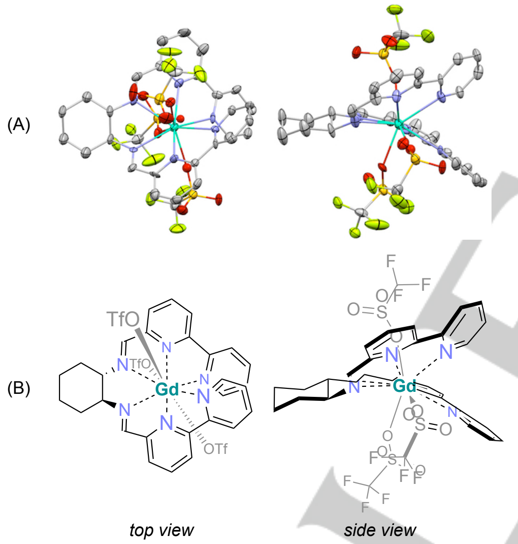
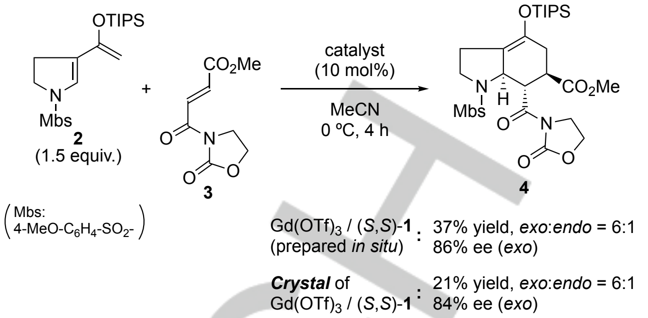


Figure 1. Crystallographic Characterization of the Chiral Gadolinium Complex $[\mathrm{Gd}(\mathbf{1})(\mathrm{OTf})_3]$. ORTEP Drawings (A) and ChemDraw Drawings (B). Hydrogen atoms and disordered atoms have been omitted for clarity. Ellipsoids are drawn at the 50% probability level.

To verify the catalytic ability of this new lanthanide complex, we considered the Diels-Alder reaction of pyrrolidine-incorporated siloxydiene **2**[4e] and dienophile **3**. The solution of the complex was first used as a catalyst, and the product **4** with a silyl enol ether was obtained in 37% yield with 86% ee (Scheme 4). When the isolated single crystal was used as a catalyst, it still showed a similar high stereoselectivity. These results indicated that this new lanthanide complex acted as a chiral Lewis acidic catalyst, and we speculated that a helical lanthanide complex $[\mathrm{Ln}(\mathbf{1})]^{(3-n)+}\bullet n(\mathrm{OTf})^{-}$ would be the active catalyst.



Scheme 4. Enantioselective Diels-Alder Reaction Using the New Binary Lanthanide Complex as a Chiral Lewis Acidic Catalyst

We briefly surveyed rare-earth triflates to tailor-make the best-suited catalytic composition for the Diels-Alder reaction of **2** and **3** (Table 1). While scandium catalyst gave the product with only 28% ee (entry 1), yttrium and other lanthanides showed high enantioselectivity (entries 2-9). For lanthanides, the yields tended to improve as the Lewis acidity of the elements increased.[7] Regarding stereoselectivity, a smaller ionic radius was associated with a higher ee of the product. Based on both the yield and stereoselectivity, the ytterbium catalyst was considered to give the best results.[13],[14]

Table 1. Screening of Rare-Earth Triflates in the Asymmetric Diels-Alder Reaction

$$\underset{(1.5\text{ equiv.})}{\mathbf{2}} + \mathbf{3} \xrightarrow[\text{MeCN, 0 °C, 4 h}]{\text{rare earth triflate (10 mol\%)},\ (S,S)\text{-}\mathbf{1}\text{ (10 mol\%)}} \mathbf{4}$$

Entry	Ln(OTf)3	Yield (%)	*exo*:*endo*[a]	% ee (*exo*)
1	Sc(OTf)3	69	14:1	28
2	Y(OTf)3	65	4:1	77
3	La(OTf)3	42	4:1	71
4	Nd(OTf)3	29	4:1	76
5	Gd(OTf)3	37	6:1	86
6	Ho(OTf)3	60	9:1	83
7	Er(OTf)3	60	4:1	78
8	Tm(OTf)3	79	5:1	78
9	Yb(OTf)3	77	16:1	89

[a] calculated by ^{1}H NMR of diastereomixture.

We proposed the reaction mechanism shown in Scheme 5 based on the X-ray crystallographic analysis of the catalyst. The dienophile **3** would coordinate to the lanthanide catalyst in a bidentate manner by the ligand exchange with triflates to form a corresponding complex **5**, while a complex **6** had a steric

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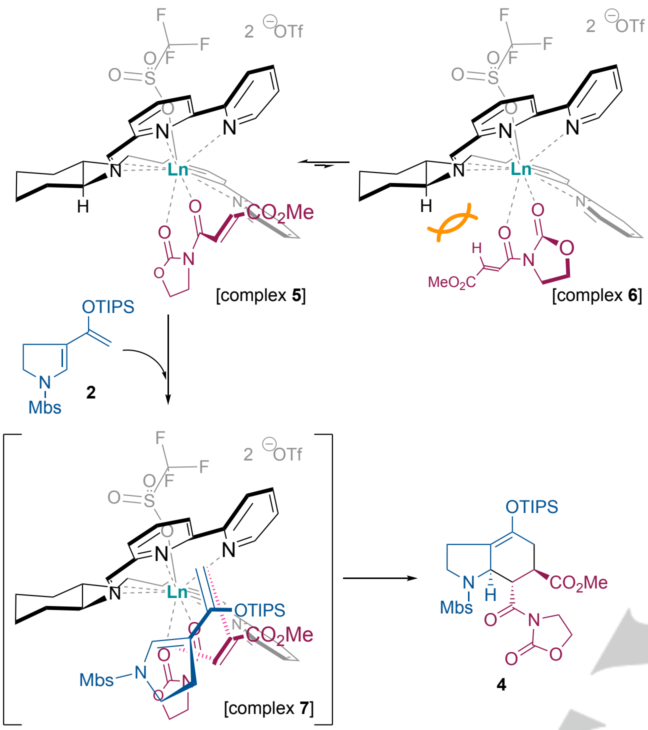
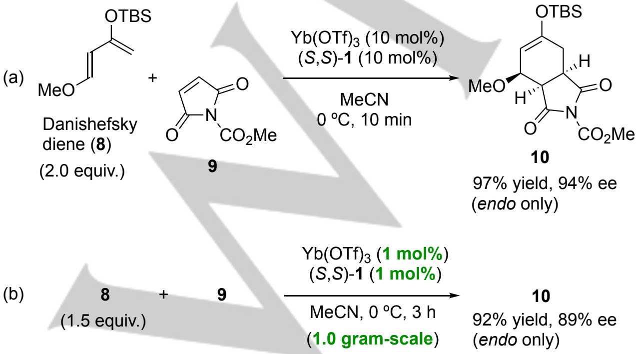
repulsion and would be unstable. Next, the diene **2** would approach the complex from the front-left side, because the opposite side (back-right) of the dienophile was blocked by the bipyridyl unit of the chiral ligand. Finally, the product **4** with the actual stereochemistry was obtained *via* transition state **7**.



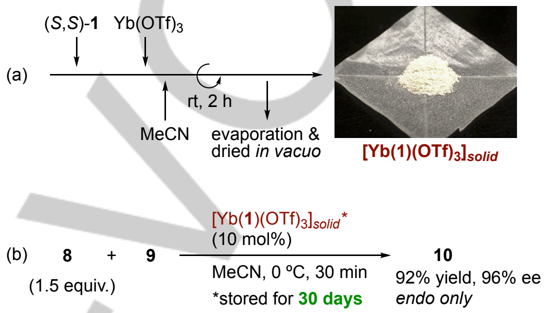
Scheme 5. Proposed Reaction Mechanism

We then tried the Diels-Alder reaction using a combination of more common substrates: Danishefsky diene (**8**) and maleimide **9** (Scheme 6 (a)).[15] The desired hydroisoindole **10** with a silyl enol ether was obtained in 97% yield with 94% ee. Our previous ternary catalyst[3a] gave **10** in only 85% yield with 65% ee.[16] Thus the enantio-inductive potential of Yb(**1**)(OTf)$_3$ catalyst for this reaction was superior to that of our previous ternary catalyst. In addition, we confirmed that a gram-scale reaction with 1 mol% of the catalyst also gave comparable results (Scheme 6 (b), 92% yield, 89% ee).



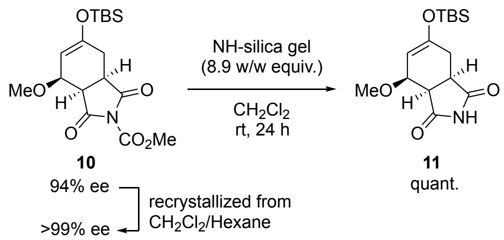
Scheme 6. Enantioselective Diels-Alder Reaction of Danishefsky Diene (**8**) and Maleimide **9**.

The catalytic activity of the lanthanide complex was maintained even after isolation of the complex as a powdery reagent. We prepared the reagent by simply removing volatiles (Scheme 7 (a)), and the resulting powdery solid was placed in a vial and sealed with argon. After storage for 30 days, it was used as a catalyst for the Diels-Alder reaction of **8** and **9** (Scheme 7 (b)), and product **10** was obtained in 94% yield with comparable stereoselectivity.



Scheme 7. Chiral Ytterbium Powdery Complex as a Storable Catalyst

The enantiomeric excess of the Diels-Alder adduct **10** could be enriched by recrystallization (Scheme 8).[17] A methoxy carbonyl moiety was successfully removed by mixing with NH-silica gel. Through these operations, the silyl enol ether was intact, and compound **11** could be used as a versatile building block.



Scheme 8. Enantio-enrichment of **10**, and Its Transformation in the Presence of Silyl Enol Ether.

In conclusion, we synthesized novel lanthanide complexes having a chiral helical shape. Their chiral helicity served as a powerful structural motif in the induction of enantioselectivity, and they exhibited catalytic activity for the enantioselective Diels-Alder reaction of electron-rich siloxydienes. We also successfully isolated the chiral catalyst as a storable reagent. Studies on the optical properties of these complexes are now ongoing.

Acknowledgements

We thank Prof. M. Hasegawa (Aoyama Gakuin University) for her fruitful discussions regarding lanthanide complexes. We thank Prof. T. Yoneda (Hokkaido University) for his help with X-ray crystallographic analyses. We are grateful to Mr. Sakamoto, Mr. Emori, and Mr. Ikeda (Chiba University) for their support with the preliminary survey. This work was supported by the Japan Society for the Promotion of Science (JSPS) KAKENHI [Grant Numbers 16K08154 & 19K06991 (SH), and 17H03969 (AN)], and the Tokyo Biochemical Research Foundation [Grant Number 16-B1-5 (SH)]. We acknowledge the Institute for Global Prominent Research, Chiba University, for providing financial support.

Conflict of Interest

A patent application on storable chiral lanthanide catalyst has been filed, where S.H., S.N., and A.N. are listed as inventors.

Keywords: asymmetric synthesis • lanthanides • Diels-Alder reaction • Lewis acid • helical structure

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[10] CCDC 1961513 contains the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

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[13] We constructed an ImBpy library. For the results using those ligands in combination with other lanthanide salts, see Supporting Information.

[14] We succeeded in the X-ray crystallographic analyses of chiral complexes synthesized from other lanthanide salts and ImBpy derivatives which had similar helical structures. CCDC 1961514, 1961516, and 1961517 contain the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif. See also Supporting Information.

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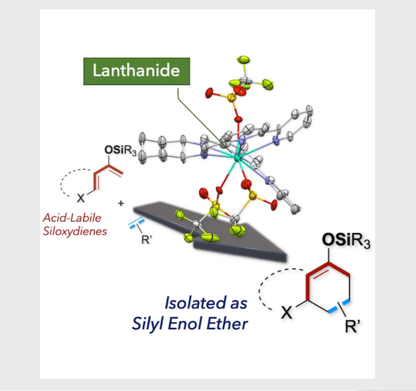
[16] For details, see Supporting Information.

[17] The absolute configuration of **10** was unambiguously assigned by X-ray crystallographic analysis using the optically pure sample. CCDC 1968368 contains the supplementary crystallographic data. These data can be obtained free of charge from the Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/data_request/cif.

Entry for the Table of Contents

COMMUNICATION

New chiral lanthanide complexes were synthesized and applied to the enantioselective Diels-Alder reaction of siloxydienes. The complex was stable enough to be stored at room temperature.



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