

# Chiral Holmium Complex-Catalyzed Diels–Alder Reaction of Silyloxyvinylindoles: Stereoselective Synthesis of Hydrocarbazoles

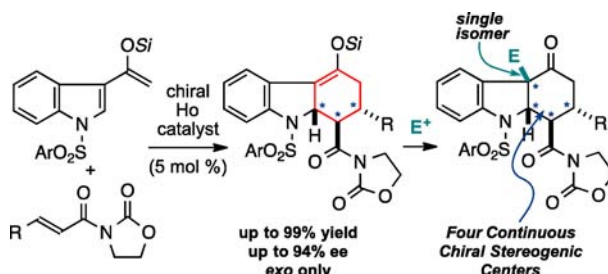
Shinji Harada, Takahiro Morikawa, and Atsushi Nishida\*

Graduate School of Pharmaceutical Sciences, Chiba University, 1-8-1 Inohana,  
Chuo-ku, Chiba 260-8675, Japan

anishida@faculty.chiba-u.jp

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## ABSTRACT



The catalytic and asymmetric cycloaddition between 3-[1-(silyloxy)vinyl]indoles and electron-deficient olefins gave substituted hydrocarbazoles in up to 99% yield and 94% ee. This reaction was catalyzed by a novel chiral holmium(III) complex. Alkylation of the cycloadduct gave a tricyclic compound with four continuous chiral centers, one of which was a quaternary carbon.

Hydrocarbazoles, which possess a heterotricyclic ring system, are an important class of organic compounds. This motif is a common scaffold of many natural and biologically active alkaloids (Figure 1).<sup>1</sup> Although

hydrocarbazoles are quite important structures, methods for constructing them are limited. The most common approach is the cycloaddition of indole derivatives. Previous reports have used 3-vinylindoles<sup>2</sup> or 2-vinylindoles<sup>3</sup> as a diene.<sup>4</sup> However, in these cases, the obtained cycloadducts mostly suffered from air-oxidation or a thermal [1,3]-hydride shift, resulting in the loss of a chiral center (Scheme 1, X = H).<sup>5</sup> Therefore, a reliable and versatile method for obtaining highly substituted chiral hydrocarbazoles in a single step is still needed.



**Figure 1.** Selected examples of natural and biologically active compounds that contain hydrocarbazole.

(1) For reviews, see: (a) Saxton, J. E. *Nat. Prod. Rep.* **1997**, *14*, 559. (b) Knölker, H. -J.; Reddy, K. R. *Chem. Rev.* **2002**, *102*, 4303.

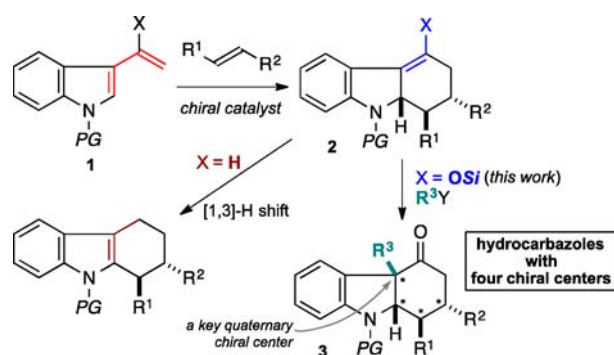
(2) (a) Saroja, B.; Srinivasan, P. C. *Synthesis* **1986**, 748. (b) Murase, M.; Hosaka, T.; Koike, T.; Tobinaga, S. *Chem. Pharm. Bull.* **1989**, *37*, 1999. (c) Pindur, U.; Lutz, G.; Fischer, G.; Schollmeyer, D.; Massa, W.; Schröder, L. *Tetrahedron* **1993**, *49*, 2863. (d) Bleile, M.; Wagner, T.; Otto, H. -H. *Helv. Chim. Acta* **2005**, *88*, 2879. (e) Gioia, C.; Hauville, A.; Bernardi, L.; Fini, F.; Ricci, A. *Angew. Chem., Int. Ed.* **2008**, *47*, 9236. (f) Tan, B.; Hernández-Torres, G.; Barbas, C. F., III. *J. Am. Chem. Soc.* **2011**, *133*, 12354.

(3) (a) Eitel, M.; Pindur, U. *J. Org. Chem.* **1990**, *55*, 5368. (b) Jones, S. B.; Simmons, B.; MacMillan, D. W. C. *J. Am. Chem. Soc.* **2009**, *131*, 13606. (c) Cao, Y. -J.; Cheng, H. -G.; Lu, L. -Q.; Zhang, J. -J.; Cheng, Y.; Chen, J. -R.; Xiao, W. -J. *Adv. Synth. Catal.* **2011**, *353*, 617. (d) Jones, S. B.; Simmons, B.; Mastracchio, A.; MacMillan, D. W. C. *Nature* **2012**, *475*, 183. See also ref 2c.

(4) For other recent strategies, see: (a) Liu, Y.; Nappi, M.; Arceo, E.; Vera, S.; Melchiorre, P. *J. Am. Chem. Soc.* **2011**, *133*, 15212. (b) Liu, Y.; Nappi, M.; Escudero-Adán, E. C.; Melchiorre, P. *Org. Lett.* **2012**, *14*, 1310. (c) Xiao, Y. -C.; Zhou, Q. -Q.; Dong, L.; Liu, T. -Y.; Chen, Y. -C. *Org. Lett.* **2012**, *14*, 5940. (d) Kawano, M.; Kiuchi, T.; Negishi, S.; Tanaka, H.; Hoshikawa, T.; Matsuo, J. -I.; Ishibashi, H. *Angew. Chem., Int. Ed.* **2013**, *52*, 906.

Based on our previous studies<sup>6</sup> using a Danishefsky diene,<sup>7</sup> we envisioned that 3-[1-(silyloxy)vinyl]indole (siloxyvinylindole) (**1**, X = OSi) could be used as a diene, which would exhibit high reactivity and allow direct access to hydrocarbazole **2** by [4 + 2] cycloaddition, as outlined in Scheme 1. Ordinary transformation of the cycloadduct provides hydrocarbazolone **3** with a quaternary carbon. To our surprise, there is no synthetically useful example of the use of siloxyvinyl-substituted heteroaromatics as a diene for catalytic and enantioselective [4 + 2] cycloaddition.<sup>8</sup> We report here a method for the catalytic synthesis of optically active hydrocarbazoles using siloxyvinylindole as a diene, in which new holmium (Ho) salt and chiral bis-thiourea complexes were used as a catalyst.

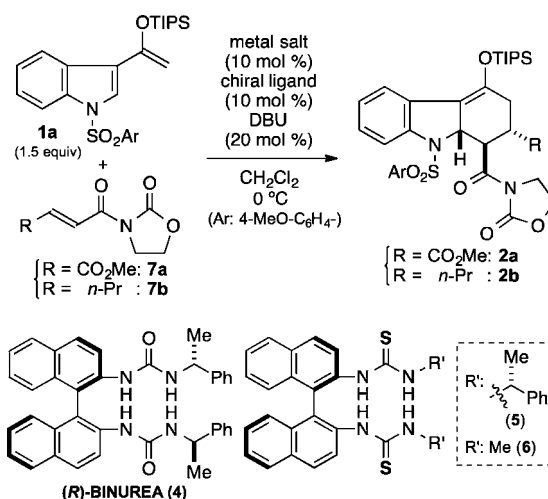
**Scheme 1.** Diels–Alder Reaction of 3-Siloxyvinylindole Followed by Alkylation To Construct Hydrocarbazoles with Four Continuous Chiral Centers



We initiated screening using our chiral Yb complex,<sup>6</sup> fumaric acid derivative **7a**, and **1** (X = OSi) with various *N*-protective groups and silyl groups. After concise screening, *N*-(*p*-methoxybenzenesulfonyl)-3-[1-(triisopropylsiloxy)vinyl]indole (**1a**) was found to be both sufficiently stable and reactive as a diene.<sup>9</sup> With our Yb catalyst, **1a** and **7a** gave encouraging results (Table 1, entry 1).<sup>10</sup> Notably, the silyl enol ether moiety of the adduct **2a** was intact under

the reaction conditions as well as under silica gel column chromatography. The perfect regioselectivity suggested that the Lewis acidic activation of dienophile **7a** occurred site-specifically at *N*-acyloxazolidinone. With the use of bis-thiourea ligand **5** (entry 2), the chemical yield was dramatically increased to be quantitative and the diastereoselectivity was perfect, yet the ee was still unsatisfactory. By changing the side chain of the ligand, we found that smaller substituents gave better enantioselectivity, and a methyl group gave the best results: 75% ee (entry 3).<sup>11</sup> For the development of a catalytic system with broader substrate generality, **7b** with a simple alkyl chain was used. However, **2b** was obtained in only 9% yield and 16% ee. Screening of other lanthanide triflates<sup>12</sup> revealed that holmium triflate (entry 5) was the most effective in terms of enantioselectivity: 32% ee. Further investigation of metal sources showed that trifluoromethanesulfonimide salt<sup>13</sup> dramatically improved the results: 90% yield,

**Table 1.** Optimization of the Catalyst



entry	R	metal salt	ligand	time (h)	yield (%)	ee (%)	dr <sup>b</sup> (exo/endo)
1 <sup>a</sup>	<b>7a</b>	Yb(OTf) <sub>3</sub>	<b>4</b>	5	18	52	9/1
2	<b>7a</b>	Yb(OTf) <sub>3</sub>	<b>5</b>	3	quant	59	exo only
3	<b>7a</b>	Yb(OTf) <sub>3</sub>	<b>6</b>	3	quant	75	exo only
4 <sup>c</sup>	<b>7b</b>	Yb(OTf) <sub>3</sub>	<b>6</b>	2	9	16	exo only
5 <sup>c</sup>	<b>7b</b>	Ho(OTf) <sub>3</sub>	<b>6</b>	2	8	32	exo only
6	<b>7b</b>	Ho(NTf <sub>2</sub> ) <sub>3</sub>	<b>6</b>	2	90	87	exo only
7 <sup>d</sup>	<b>7b</b>	Ho(NTf <sub>2</sub> ) <sub>3</sub>	<b>6</b>	3	86	93	exo only

<sup>a</sup> 2.0 equiv of **1a** was used. <sup>b</sup> Determined from the <sup>1</sup>H NMR spectrum of the crude mixture. <sup>c</sup> Carried out at rt. <sup>d</sup> 5 mol % of Ho(NTf<sub>2</sub>)<sub>3</sub>, 10 mol % of **6**, and 10 mol % of DBU were used.

(11) For the screening of other ligands, see the Supporting Information. For the organocatalytic use of binaphthylidene-derived bis-thiourea, see: (a) Fleming, E. M.; McCabe, T.; Connon, S. J. *Tetrahedron Lett.* **2006**, 47, 7037. (b) Liu, X.-G.; Jiang, J.-J.; Shi, M. *Tetrahedron: Asymmetry* **2007**, 18, 2773. (c) Rampalagos, C.; Wulff, W. D. *Adv. Synth. Catal.* **2008**, 350, 1785. (d) Crespo-Peña, A.; Monge, D.; Martín-Zamora, E.; Álvarez, E.; Fernández, R.; Lassaletta, J. M. *J. Am. Chem. Soc.* **2012**, 134, 12912.

(12) For details, see the Supporting Information.

(5) Prof. MacMillan's group avoided these problems by using the strategy of a cascade sequence: ref 3b,3d. See also ref 2c,2e.

(6) Catalytic and asymmetric Diels–Alder reaction of Danishefsky diene and electron-deficient olefins reported by our group, see: (a) Sudo, Y.; Shirasaki, D.; Harada, S.; Nishida, A. *J. Am. Chem. Soc.* **2008**, 130, 12588. (b) Harada, S.; Toudou, N.; Hiraoka, S.; Nishida, A. *Tetrahedron Lett.* **2009**, 50, 5652. (c) Hiraoka, S.; Harada, S.; Nishida, A. *J. Org. Chem.* **2010**, 75, 3871. (d) Harada, S.; Morikawa, T.; Hiraoka, S.; Nishida, A. *J. Synth. Org. Chem. Jpn.* **2013**, 71, 818. The reaction above reported by other group, see: (e) Orimoto, K.; Oyama, H.; Namera, Y.; Niwa, T.; Nakada, M. *Org. Lett.* **2013**, 15, 768.

(7) Danishefsky, S.; Kitahara, T. *J. Am. Chem. Soc.* **1974**, 96, 7807.

(8) See ref 2d. For furan derivatives, see: Benítez, A.; Herrera, F. R.; Romero, M.; Talamás, F. X. *J. Org. Chem.* **1996**, 61, 1487.

(9) *N*-Benzyl-protected siloxyvinylindole **1** predominately underwent Michael addition to **7a**. For the silyl group of **1**, TMS was rather unstable and decomposed under the reaction conditions. Compound **1a** is stable against water and can be purified by silica gel column chromatography. Moreover, it can be stored in a freezer for months.

(10) This reaction between **1a** and **7** catalyzed by lanthanide metal is *exo* selective with or without chiral ligand. For details, see the Supporting Information.

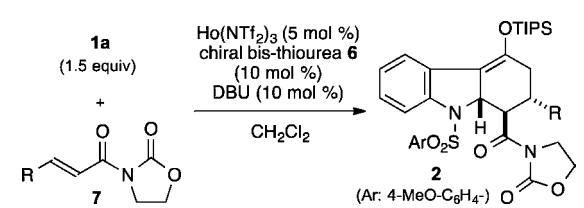
87% ee (entry 6). When a  $\text{Ho}(\text{NTf}_2)_3/(R)\text{-6}/\text{DBU} = 1/2/2$  complex was used, both the reactivity and enantioselectivity were improved to give the cycloadduct in 86% yield and 93% ee even with 5 mol % of the catalyst (entry 7).<sup>14</sup> The ee of **2** could be enriched by recrystallization. In particular, with an 86% ee sample of **2a**, we obtained optically enriched **2a** in 99% ee after a single recrystallization.<sup>15</sup> Under these conditions, we examined the scope and limitations of the dienophile.<sup>16</sup>

The reaction with thioester **7c** proceeded smoothly to give the desired product in 94% yield, but the enantioselectivity decreased to 78% ee (Table 2, entry 2). Acetyl, cyano, and trifluoromethyl groups gave similarly good results with respect to reactivity and enantioselectivity (entries 3–5). A phenyl substituent (entry 6) was associated with a slight decrease in enantioselectivity. Alkyl-substituted dienophiles (**7h–j**, and **7b**, entries 7–10) gave excellent

yields (86–96%) and good ee's (90–94% ee), although **7i** had relatively low reactivity. Acrylate derivative **7k** (entry 11) was unstable under these conditions. Therefore, the substrate was added at  $-20^\circ\text{C}$ , and the reaction mixture was stirred at the same temperature for 30 min to give the desired product **2k** in 95% yield and 86% ee.

This holmium chemistry could be extended to dienes from other heterocycles (Figure 2). Pyrrole-type substrate gave hydroindole **8** in 92% yield, and the enantioselectivity was still good, i.e., 87% ee. Similar to the results in Table 2, we did not observe the generation of an *endo* isomer. Benzofuran derivative could also be used in this reaction, although 10 mol % of the catalyst was required to complete the reaction: 96% yield and 81% ee. The formation of chiral **8** and **9** is noteworthy, since there is no previous report on the synthesis of these skeletons as well as **2** using a single catalytic system.

**Table 2.** Scope and Limitation of the Substituent on the Dienophile **7**



entry	R <sup>a</sup> (substrate)	conditions	yield of <b>2</b> <sup>b</sup> (%)	ee of <b>2</b> (%)
1	CO <sub>2</sub> CH <sub>3</sub>	<b>7a</b> 0 °C, 30 min	96	87
2	COSPh	<b>7c</b> 0 °C, 30 min	94	78
3	COCH <sub>3</sub>	<b>7d</b> 0 °C, 30 min	95	90
4	CN	<b>7e</b> 0 °C, 30 min	94	92
5	CF <sub>3</sub>	<b>7f</b> 0 °C, 1 h	99	94
6 <sup>c</sup>	Ph	<b>7g</b> 0 °C, 30 min; rt, 2 h	99	75
7	CH <sub>2</sub> Cl	<b>7h</b> 0 °C, 1 h	90	94
8 <sup>c</sup>	CH <sub>2</sub> OBn	<b>7i</b> 0 °C, 2 h	92	90
9	Me	<b>7j</b> 0 °C, 2 h	96	90
10	<i>n</i> -Pr	<b>7b</b> 0 °C, 2 h	86	93
11	H	<b>7k</b> $-20^\circ\text{C}$ , 30 min	95	86

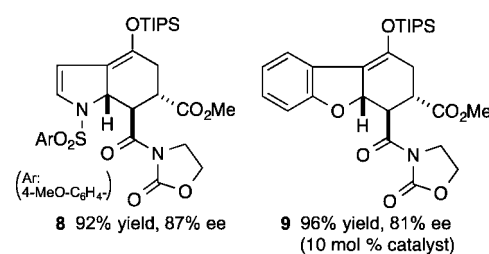
<sup>a</sup> 0.4 mmol of **7** was used in each entry. <sup>b</sup> In all entries, only the *exo* adduct was observed in the crude <sup>1</sup>H NMR spectrum. <sup>c</sup> 0.2 mmol of **7** was used with 10 mol %  $\text{Ho}(\text{NTf}_2)_3$ , 20 mol % **6**, and 20 mol % DBU.

(13) (a) Kobayashi, H.; Nie, J.; Sonoda, T. *Chem. Lett.* **1995**, 307. (b) Mikami, K.; Kotera, O.; Motoyama, Y.; Sakaguchi, H.; Murata, M. *Synlett* **1996**, 171. (c) Baudry, D. B.; Dormond, A.; Duris, F.; Bernard, J. M.; Desmurs, J. R. *J. Fluor. Chem.* **2003**, 121, 233. (d) Takasu, A.; Makino, T.; Yamada, S. *Macromolecules* **2010**, 43, 144. (e) Oshimura, M.; Takasu, A. *Macromolecules* **2010**, 43, 2283.

(14) The catalyst might compose oligomers and be in equilibrium. The composition of  $\text{Ho}$ , **6**, and DBU would affect the amount of the active catalyst complex. From the experimental results, we hypothesized that the active catalyst was predominantly generated in the case of  $\text{Ho}/\text{6}/\text{DBU} = 1/2/2$ , which enabled us to reduce the catalyst loading.

(15) The absolute configuration of **2a** was unambiguously assigned by X-ray crystallographic analysis after conversion to *p*-Br-benzoate. For details, see the Supporting Information and CCDC 925631. This result, together with NMR analyses, was used to establish the relative and absolute configurations of our compounds.

(16) While holmium salts are rarely used in organic synthesis, they cost the same as or even less than scandium or ytterbium salts. For selected examples of the use of holmium catalysts in organic synthesis, see: Trost, B. M.; Schroeder, G. M. *J. Am. Chem. Soc.* **2000**, 122, 3785.



**Figure 2.** Scope of dienes. The reactions were performed in  $\text{CH}_2\text{Cl}_2$  in the presence of the holmium catalyst.

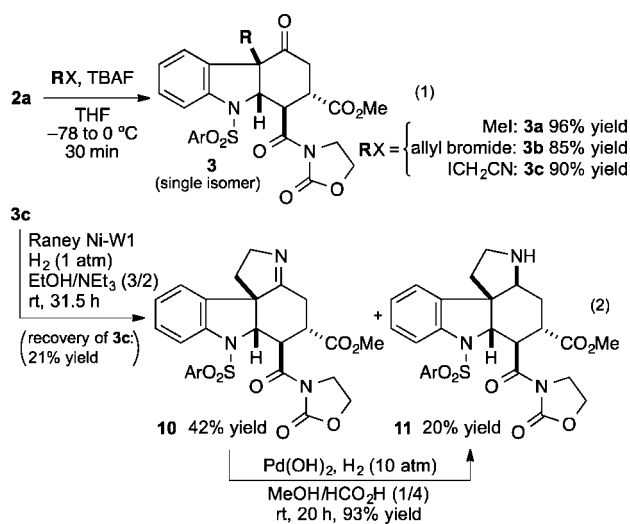
With cycloadducts in hand, we turned to conversion of the silyl enol ether moiety. When the adduct **2a** was treated with methyl iodide and tetrabutylammonium fluoride, the corresponding methylated product **3a** was obtained as a single isomer (Scheme 2, eq 1). Similarly, allylation was performed, and the product **3b** was obtained in 85% yield. Cyanomethylation gave **3c** in 90% yield. Remarkably, these compounds **3a–c** have a chiral quaternary carbon among four continuous chiral stereocenters, which were synthesized in two steps. Compound **3c** could be a potential synthetic intermediate for *strychnos* alkaloids.<sup>17</sup> Reductive cyclization of **3c** with Raney-Ni gave **10** and **11** (Scheme 2, eq 2). Compound **10** could be converted to **11** by hydrogenation with  $\text{Pd}(\text{OH})_2$ . Other transformations are depicted in Scheme 3. Thioesterification of **2b** proceeded smoothly to give **12** in quantitative yield. Fukuyama reduction<sup>18</sup> afforded aldehyde **13**. Primary alcohol **14** was obtained by the reduction of thioester **12** with LAH. Deprotection of indole-nitrogen using Na/anthracene<sup>19</sup> gave **15** in 84% yield. Neither epimerization nor racemization was observed during these transformations.

(17) (a) Azzouzi, A.; Perrin, B.; Sinibaldi, M.-E.; Gramain, J.-C. *Tetrahedron Lett.* **1993**, 34, 5451. (b) Bencheikroun-Mounir, N.; Dugat, D.; Gramain, J.-C.; Husson, H.-P. *J. Org. Chem.* **1993**, 58, 6457. (c) Beemelmans, C.; Reißig, H.-U. *Angew. Chem., Int. Ed.* **2010**, 49, 8021.

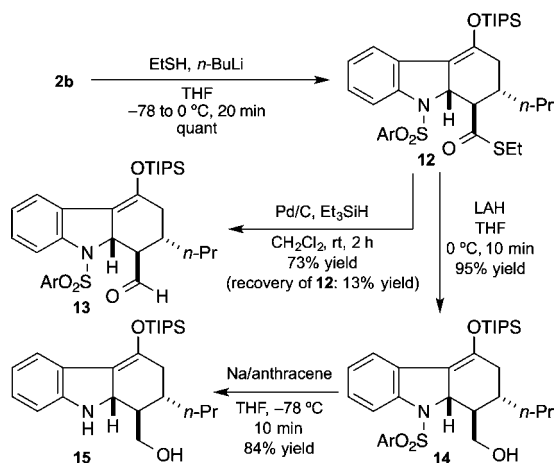
(18) Fukuyama, T.; Lin, S.-C.; Li, L. *J. Am. Chem. Soc.* **1990**, 112, 7050.

(19) Magnus, P.; Giles, M.; Bonnert, R.; Kim, C. S.; McQuire, L.; Merritt, A.; Vicker, N. *J. Am. Chem. Soc.* **1992**, 114, 4403.

**Scheme 2.** Alkylation for the Construction of a Quaternary Carbon and Further Transformation to a Tetracyclic Skeleton



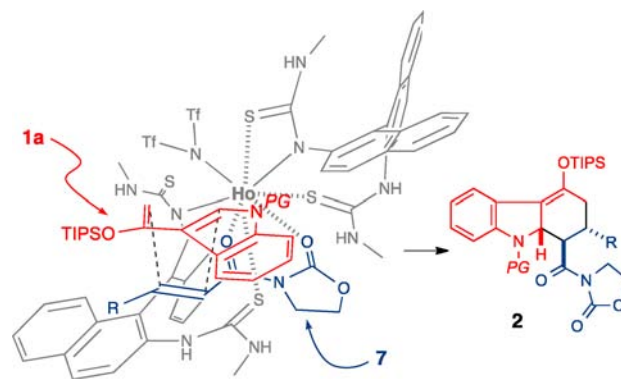
**Scheme 3.** Other Transformations and Deprotection



To obtain insight into the structure of the catalyst, the catalyst solution was monitored by ESI-TOF-MS analysis.<sup>20</sup>

(20) See the Supporting Information. For selected discussions of the mechanism of a lanthanide-based catalyst using ESI-MS analysis, see: (a) Horiuchi, Y.; Gnanadesikan, V.; Ohshima, T.; Masu, H.; Katagiri, K.; Sei, Y.; Yamaguchi, K.; Shibasaki, M. *Chem.—Eur. J.* **2005**, *11*, 5195. (b) Tosaki, S.-Y.; Hara, K.; Gnanadesikan, V.; Morimoto, H.; Harada, S.; Sugita, M.; Yamagiwa, N.; Matsunaga, S.; Shibasaki, M. *J. Am. Chem. Soc.* **2006**, *128*, 11776. (c) Comelles, J.; Pericas, A.; Moreno-Mañas, M.; Vallribera, A.; Drudis-Solé, G.; Lledos, A.; Parella, T.; Roglans, A.; Garcia-Granda, S.; Rocas-Fernández, L. *J. Org. Chem.* **2007**, *72*, 2077. (d) Mashiko, T.; Kumagai, N.; Shibasaki, M. *J. Am. Chem. Soc.* **2009**, *131*, 14990. (e) Shen, K.; Liu, X.; Zheng, K.; Li, W.; Hu, X.; Lin, L.; Feng, X. *Chem.—Eur. J.* **2010**, *16*, 3736.

(21) Lippard, S. J.; Russ, B. J. *Inorg. Chem.* **1968**, *7*, 1686. For selected examples of the X-ray crystallographic analysis of a holmium complex, see: (a) Horrocks, W. D., Jr.; Sipe, J. P., III; Luber, J. R. *J. Am. Chem. Soc.* **1971**, *93*, 5258. (b) Kav, J.; Moore, J. W.; Glick, M. D. *Inorg. Chem.* **1972**, *11*, 2818. (c) Arndt, S.; Beckerle, K.; Zeimentz, P. M.; Spaniol, T. P.; Okuda, J. *Angew. Chem., Int. Ed.* **2005**, *44*, 7473. (d) Baisch, U.; Pagano, S.; Zeuner, M.; auf der Günne, J. S.; Oeckler, O.; Schnick, W. *Organometallics* **2006**, *25*, 3027.



**Figure 3.** Proposed transition-state model of a holmium catalyst, dienophile **7**, and diene **1a** complex.

In the solution of  $\text{Ho}(\text{NTf}_2)_3$  and ligand **6**, a peak of  $\text{Ho}$  salt/ligand **6** = 1/2 was observed. This observed ratio is associated with the best catalytic composition (Table 1). The subsequent addition of DBU induced a significant change in the MS spectrum and gave a series of peaks derived from DBU salts. DBU was strongly suggested to deprotonate NH of ligand. Based on these experimental results and the high coordination number of lanthanide as well as flexible coordination modes, we offer the hypothetical structure of active catalyst complex shown in Figure 3: the eight-coordinate dienophile adduct of  $\text{Ho}(\text{NTf}_2)_3/(\text{6-H})_2$ .<sup>21</sup> In this structure, the diene could approach from only one side of the dienophile due to the steric barrier of the naphthyl ring and the thiourea side chain of the ligand, and we can rationalize the absolute configuration of **2**.

In summary, we have developed a new catalytic and enantioselective method for the synthesis of hydrocarbazoles by the [4 + 2] cycloaddition of silyloxyvinylindoles and electron-deficient olefins. This reaction was catalyzed by a novel chiral holmium complex to give adduct without the decomposition of silyl enol ether, which should be useful for the synthesis of various intermediates with a quaternary carbon. Synthetic applications of the cycloadducts and a mechanistic study of the holmium catalyst are underway.

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**Supporting Information Available.** Experimental details, substrates supply, spectral data, and supporting figures. This material is available free of charge via the Internet at <http://pubs.acs.org>.

The authors declare no competing financial interest.