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$Hf(OTf)_4$-CATALYZED 1,4-ADDITION REACTIONS OF INDOLE TO ENONE IN THE PRESENCE OF MESO AND CHIRAL PYRIDINE-DIAMINE LIGANDS

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Abstract – $Hf(OTf)_4$-catalyzed 1,4-addition reactions of indole to enones in the presence of pyridinediamine are described. Although a dimer and a trimer of indole were produced under the $Hf(OTf)_4$ catalyzed reaction conditions of indole, the addition of pyridinediamines (**La-f**) inhibited such oligomerization reactions. A 1:1 mixture of $Hf(OTf)_4$ and a pyridinediamine ligand formed a $Hf(OTf)_4$-pyridinediamine complex, which catalyzed the 1,4-addition reaction very efficiently without the formation of dimer and trimer of indole. The stereochemistry of the pyridinediamine ligands was found to play an important role in the relative rate of the reactions.

INTRODUCTION

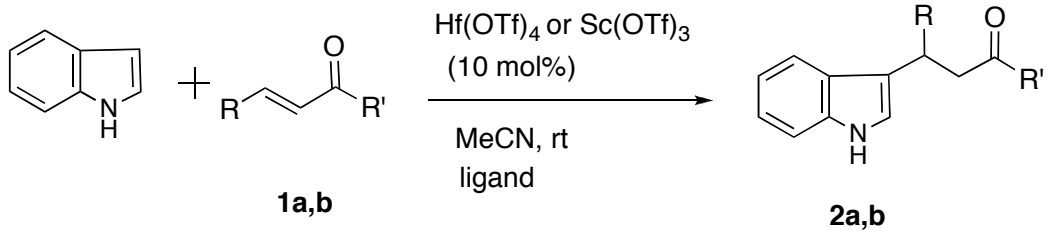
Indoles are widely present in the unit of biologically active natural products and are very important heterocycles in the structure of many medicines.[1] Due to the electron-rich nature of indole, the nucleophilic addition reactions of indole to α,β-unsaturated carbonyl compounds occur at the C-3 position and are employed for the synthesis of 3-substituted indoles.[2] Although 1,4-additions of indole to enones promoted by various kinds of Lewis acids such as $InCl_3$,[3a] $InBr_3$,[3b] $Sc(DS)_3$,[3c] $Sc(OTf)_3$,[3c] Clay,[3d] $Yb(OTf)_3$,[3e] $CeCl_3$,[3f] $Bi(NO)_3$,[3g] $Bi(OTf)_3$,[3h,i] $CuBr_2$,[3j] $ZrOCl_2 \cdot 8H_2O$,[3k] and others[3l,m] have been reported, there continues to be a lot of research into these reactions, including those of asymmetric addition.[4] Recently, we have investigated $Sc(OTf)_3$- and $Hf(OTf)_4$-catalyzed 1,4-addition of indoles to enones,[5] and found that i) the reaction rate using $Hf(OTf)_4$ is faster than that using $Sc(OTf)_3$, and ii) the chemical yield obtained by using $Sc(OTf)_3$ is better than that by using $Hf(OTf)_4$. In an extension of the results, we have studied further improvement of the reactions. In this paper, we report that the $Hf(OTf)_4$-catalyzed

1,4-addition of indole to enone in the presence of a pyridinediamine ligand proceeds very cleanly without formation of by-products and that the reaction rate largely depends on the stereochemistry of the ligands.

RESULTS AND DISCUSSION

The reaction of indole to enone **1** was conducted in MeCN at room temperature in the presence of 10 mol% of $Hf(OTf)_4$ or $Sc(OTf)_3$ as shown in Scheme 1. The results are summarized in Table 1. When $Sc(OTf)_3$ was used with enone **1a**, the adduct **2a** was obtained in 62% yield along with unreacted indole in 32% yield after 3 h (entry 1). On the other hand, when $Hf(OTf)_4$ was used as a catalyst, the reaction was completed within 15 min and **2a** was obtained in 78% yield along with a mixture of dimer and/or trimer of indole in 19% yield (entry 2). A similar trend was observed in the reaction of **1b**. When it was catalyzed by $Sc(OTf)_3$, it proceeded slowly after 2 h to give **2b** in 23% yield with good recovery of indole in 64% yield (entry 3). When it was catalyzed by $Hf(OTf)_4$, in contrast, the reaction occurred much faster than that by $Sc(OTf)_3$ to give **2b** in 60% yield with a formation of dimer and trimer of indole in 32% yield (entry 4). In fact, when the reaction was carried out in the absence of enone **1**, dimer and trimer of indole were formed in 34% combined yield after 1 h in the presence of $Hf(OTf)_4$ but none of them was formed in the presence of $Sc(OTf)_3$ (entries 5 and 6). Interestingly, when 12 mol% of the meso pyridinediamine ligand, **L1,**[6] was added to the reaction mixture of **1a**, the reaction was accelerated and completed within 30 min to give **2a** in quantitative yield. The use of diastereo-isomeric chiral pyridinediamine ligand **L2**[6] also gave **2a** quantitaively with no formation of dimer and trimer.

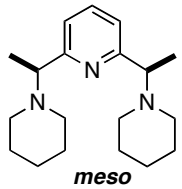
Scheme 1. $Hf(OTf)_4$ and $Sc(OTf)_3$ catalyzed 1,4-addition of indole to enones



a; R = Me, R' = Ph

b; R = Ph, R' = Me

L1;



L2;

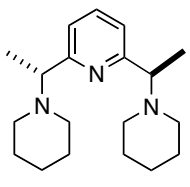


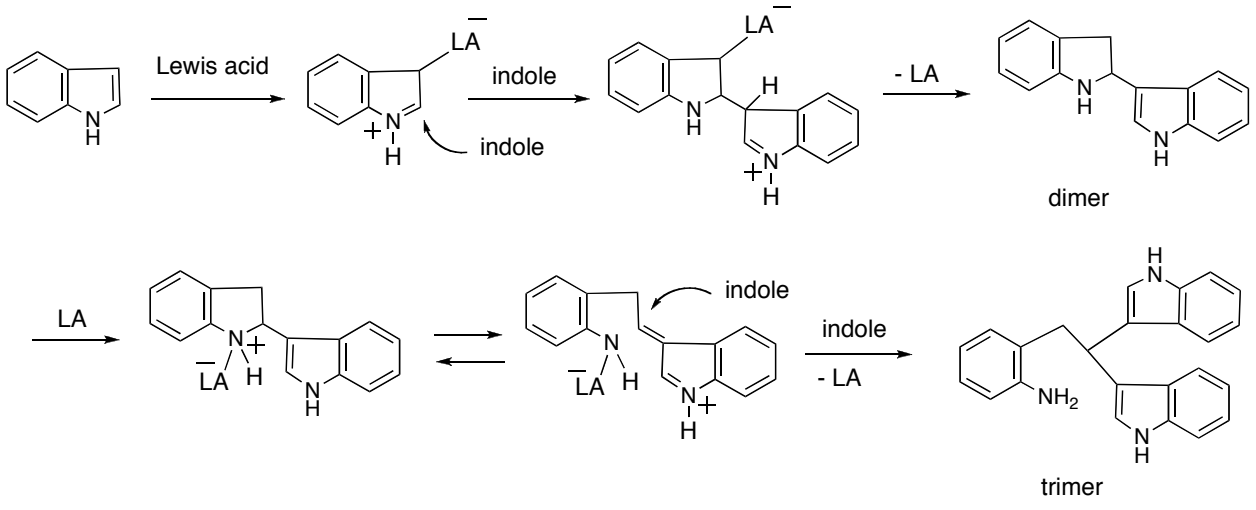
Table 1. $Hf(OTf)_4$- and $Sc(OTf)_3$-catalyzed addition of indole to enones

Entry	Catalyst[a]	Enone[b]	Ligand[c]	Time	Product (%)		Dimer and Trimer (%)	Indole (%)[d]
1	$Sc(OTf)_3$	**1a**	——	3 h	**2a**	62	——	32
2	$Hf(OTf)_4$	**1a**	——	15 min	**2a**	78	19	——
3	$Sc(OTf)_3$	**1b**	——	2 h	**2b**	23	——	64
4	$Hf(OTf)_4$	**1b**	——	2 h	**2b**	60	32	——
5	$Sc(OTf)_3$	——	——	1 h	——		——	95
6	$Hf(OTf)_4$	——	——	1 h	——		34	55
7	$Hf(OTf)_4$	**1a**	**L1**, *meso*	30 min	**2a**	quant.	0	0
8	$Hf(OTf)_4$	**1a**	**L2**, *R,R*	1 h	**2a**	quant.	0	0

[a] 10 mol%. [b] 1.5 eq. [c] 12 mol%. [d] recovery.

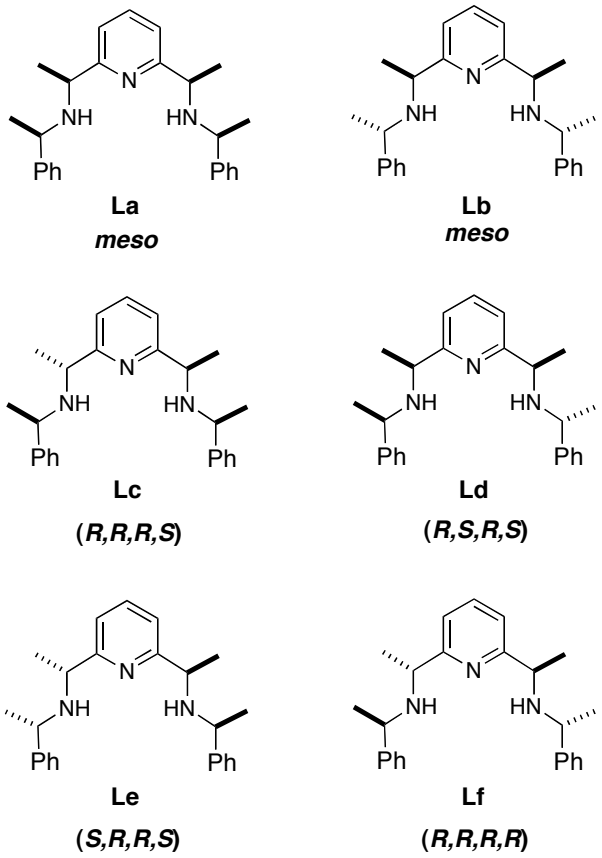
Although the mechanism for the formation of dimer and trimer of indole under acidic conditions has been documented,[7] $Hf(OTf)_4$ may play as an acid to produce them. Its mechanism is described in Scheme 2. First, Lewis acid promotes indole to form indolenium cation intermediate. Another indole attacks the indolenium cation to form a dimer, which is again activated by $Hf(OTf)_4$ to form another indolenium cation. Addition of indole to the cation results in the formation of a trimer. However, when the pydirinediamine such as **L1** or **L2** was added to the reaction mixture, $Hf(OTf)_4$ enhanced the catalytic acitivity for the addition reaction but lost the activity for the formation of dimer and trimer, presumably by the formation of $Hf(OTf)_4$-triamine complex. Interestingly, by the addition of an equimolar of pyridinetriamine, the reaction became clean and the activity of $Hf(OTf)_4$ was maintained or even enhanced. Therefore, we next investigated the study of other pyridinediamine ligands.

Scheme 2. Formation of dimer and trimer of indole



Recently, we have reported the synthesis of meso and chiral pyridinediamines, **La** to **Lf**,[8] by stereospecific substitution reactions of chiral pyridinylethanols.[9] The structures of two meso isomers, **La** and **Lb**, and four chiral isomers, **Lc**, **Ld**, **Le**, and **Lf**, are shown in Figure 1. When an equimolar of **La** to the catalyst $Hf(OTf)_4$ was added to the reaction mixture of indole and enone **1a**, the reaction took only 10 min at room temperature and gave **2a** quantitatively (Table 2, entry 1). The reaction using meso **Lb** was slower, and took 30 min to complete (entry 3). The reaction rates with the four chiral ligands were even slower than those of the meso ligands. The order is **Lf** > **Lc** > **Le** >> **Ld**. There seems to be a relation between the symmetrical structure of ligands and the reaction rate; possibly, that the more stable the $Hf(OTf)_4$-ligand complex, the faster the reaction.

Figure1. Structures of chiral pyridinediamines



La ***meso*** **Lb** ***meso***

Lc (***R,R,R,S***) **Ld** (***R,S,R,S***)

Le (***S,R,R,S***) **Lf** (***R,R,R,R***)

Table 2. $Hf(OTf)_4$-catalyzed reaction of **1a** and indole with chiral pyridinediamine ligands[a]

Entry	Ligand	Time[b] (min)	Yield
1	**La**[c]	10	quant.
2	**Lf**[c]	15	quant.
3	**Lb**	30	quant.
4	**Lc**	40	quant.
5	**Le**	60	quant.
6	**Ld**	240	quant.

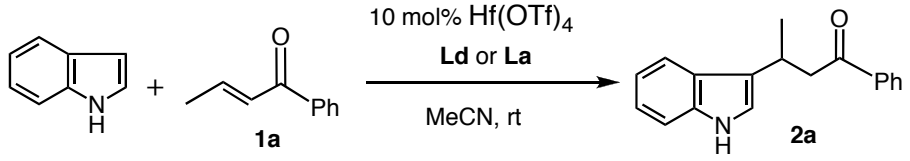
[a] Indole (0.1 mmol), **1a** (0.15 mmol), $Hf(OTf)_4$ (0.01 mmol), and ligand (0.012 mmol) were used. [b] rt in CH_3CN. c The results have been reported in ref 5a.

We expected chiral induction in this $Hf(OTf)_4$-catalyzed addition of indole using the above chiral ligands. However, the best result was obtained when ligand **Lf** was used, though only 10% ee was observed in the preferential formation of (*R*)-enantiomer.[10]

Since it has been revealed that a combination of $Hf(OTf)_4$ and a pyridinediamine ligand is important, reactions using different ratios of $Hf(OTf)_4$ and ligand were examined next. $Hf(OTf)_4$ was maintained at 10 mol%, while the percentage of the ligands **Ld** and **La** varied from 2.5 to 40 mol%. The reaction time

and yields are shown in Table 3. When ligand **Ld** was used less than 10 mol% in entries 1-3, oligomers were detected partially. This suggests ligand-free $Hf(OTf)_4$ is present and promotes the formation of oligomers. However, when an equal ratio of $Hf(OTf)_4$ and **Ld** was used, **2a** was obtained quantitatively without the formation of oligomers (entry 4). When an excess of **Ld** was used, the reactions took longer (entries 5 and 6). However, the yields of **2a** were quantitative. When two or more equivalents of **Ld** with respect to $Hf(OTf)_4$ were used, **2a** was not produced at all (entries 7-9). These results indicate that a 1:1 complex of $Hf(OTf)_4$ and **Ld** might produce the catalytic 1,4-addition reaction, but that a 1:2 complex loses its catalytic activity completely. In entries 1-3, both the 1:1 complex and free $Hf(OTf)_4$ existed and catalyzed not only the 1,4-addition reaction but also oligomerization. In entries 5 and 6, both the 1:1 complex and the 1:2 complex might exist in the reaction mixture, though only the former complex catalyzed the 1,4-addition reaction. Although reaction rates differed when ligand **La** was used instead of ligand **Ld**, the similar results were obtained.

Table 3. Reactions of **1a** and indole with the use of 10 mol% of $Hf(OTf)_4$ and variable mol% of ligands **Ld** and **La**



Entry	Hf / **Ld** (mol%)	Time	Yield (%)	Entry	Hf / **La** (mol%)	Time	Yield (%)
1	10 : 2.5	15 min	85[a]	10	10 : 2.5	10 min	80[a]
2	10 : 5	15 min	82[a]	11	10 : 5	10 min	80[a]
3	10 : 7.5	0.5 h	90[a]	12	10 : 7.5	10 min	94[a]
4	10 : 10	2.5 h	quant.	13	10 : 10	10 min	quant.
5	10 : 12	4 h	quant.	14	10 : 12	10 min	quant.
6	10 : 15	12 h	quant.	15	10 : 15	2 h	quant.
7	10 : 20	24 h	—[b]	16	10 : 20	24 h	—[b]
8	10 : 24	24 h	—[b]	17	10 : 24	24 h	—[b]
9	10 : 40	24 h	—[b]	18	10 : 40	24 h	—[b]

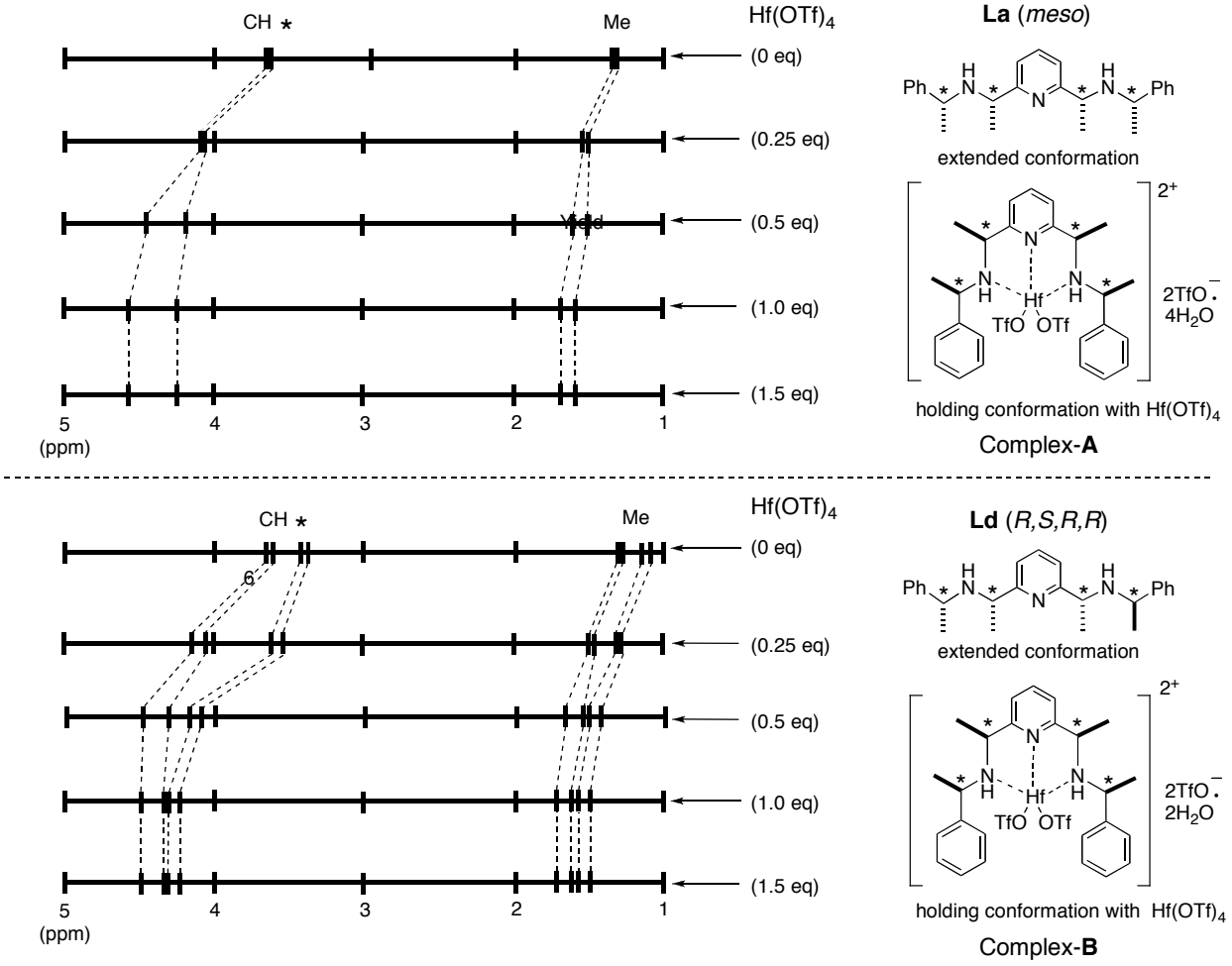
[a] A small amount of dimer and trimer of indole was formed. [b] Indole and **1a** were recovered.

From these results we assumed that the real catalyst is the 1:1 complex, so we attempted its synthesis. After a 1:1 ratio of $Hf(OTf)_4$ and **La** were stirred in MeCN for 30 min at room temperature, evaporation of the solvent gave a white powder, complex-**A**, which was recrystallized in EtOH. Complex-**B** was prepared similarly, only with a 1:1 ratio of $Hf(OTf)_4$ and **Ld**, and also formed a white powder. When

complex-**A** (10 mol%) was used instead of $Hf(OTf)_4$ and **La**, the reaction of indole and **1a** was completed within 10 min at room temperature in MeCN. This result is compatible with the result in entry 13 in Table 3. Complex-**B** produced a result similar to $Hf(OTf)_4$ and **Ld** in entry 4 in Table 3.

Next, we prepared a 1:2 complex of $Hf(OTf)_4$ and **La** and **Ld**, which gave complex-**A'** and complex-**B'**, respectively. However, both complex-**A'** and complex-**B'** were totally inactive as a catalyst for the addition reaction. The results were also compatible to those listed in entries 7-9 and 16-18 in Table 3.

Chart 1. Proton NMR shift values of Me and CH groups of **La** and **Ld** in CD_3CN



Titration experiments for the formation of these complexes were carried out by proton NMR. To a CD_3CN solution of pyridinediamine ligands **La** and **Ld**, was added $Hf(OTf)_4$, respectively. The results are shown in Chart 1. In the experiment of **La**, chemical shifts of two methyl and two methine protons moved downfield by the addition of $Hf(OTf)_4$. When 0.5 eq of $Hf(OTf)_4$ was added, a 1:2 complex was formed. In fact, its spectrum was identical to the NMR spectrum of complex-**A'**. When 1.0 eq of $Hf(OTf)_4$ was added, the spectrum was identical to that of the complex-**A**. When more $Hf(OTf)_4$ was added, no change was observed in the spectrum. Similar titration spectra were observed by the addition of $Hf(OTf)_4$ to a CD_3CN solution of **Ld**, in which diastereomeric four methyl and four methine protons shifted downfield.

The NMR spectra of 1 eq and 0.5 eq of $Hf(OTf)_4$ with respect to **Ld** were identical to those of the complex-**B** and the complex-**B'** prepared independently.

In summary, a 1:1 mixture of catalytic $Hf(OTf)_4$ and pyridinediamine was found to be very effective for the 1,4-addition reaction of indole to enone. The reaction takes place remarkably mild and clean. The complex-**A** and complex-**B** prepared by $Hf(OTf)_4$ and an equimolar of pyridinediamines **La** or **Ld** were identified to be the real catalytic species in that reaction. However, the complex-**A'** and complex-**B'** prepared by a 1:2 mixture of $Hf(OTf)_4$ and pyridinediamines **La** and **Ld**, respectively, show no catalytic activity in the same reaction.

EXPERIMENTAL

^1H NMR and ^{13}C NMR spectra were recorded on JEOL JNM-AL-300 (300 MHz and 75 MHz) spectrometer in CD_3CN or $CDCl_3$ with tetramethylsilane or $CDCl_3$ as an internal standard. IR spectra were recorded on JASCO FT/IR-410 instrument. Optical rotation was measured on a JASCO DIP-360 instrument. Column chromatography was carried out using Merck silica gel 60 (230-400 mesh).

$Hf(OTf)_4$ and $Sc(OTf)_3$ catalyzed reaction of indole with 1 in the absence of pyridinediamine ligand. A mixture of indole (0.2 mmol), **1** (0.3 mmol), and $Hf(OTf)_4$ or $Sc(OTf)_3$ (0.02 mmol) in MeCN (1 mL) was stirred at rt. The mixture was quenched with water and extracted with $CHCl_3$. The extract was washed with water, dried over $MgSO_4$ and condensed. The residue was purified by flash column chromatography on silica gel eluted with 20% EtOAc in hexane to give **2**.

$Hf(OTf)_4$ catalyzed oligomerization reaction of indole. A mixture of indole (1 mmol) and $Hf(OTf)_4$ (0.1 mmol) was stirred for 1 h at rt. The reaction was quenched with water and extracted with $CHCl_3$. The extract was washed with water and dried over $MgSO_4$. The crude product was purified by flash column chromatography on silica gel eluted with 20-50% EtOAc in hexane to give dimer[7a] in 21% yield, trimer[7a,b] in 13% yield, and recovery of indole in 55% yield. Dimer; 2,3-dihydro-1*H*,1'*H*-[2,3']biindolyl. Yellow oil. ^1H-NMR (300 MHz, $CDCl_3$) δ: 7.84 (1H, brs), 7.49 (1H, d, *J* = 7.7 Hz), 7.21 (1H, d, *J* = 8.1 Hz), 7.12-6.96 (5H, m), 6.66 (1H, td, *J* = 7.3, 0.7 Hz), 6.56 (1H, d, *J* = 7.7 Hz), 5.14 (1H, t, *J* = 8.4 Hz), 3.95 (1H, brs), 3.37 (1H, dd, *J* = 15.8, 9.2 Hz), 3.10 (1H, dd, *J* = 15.8, 8.4 Hz). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 150.9, 136.7, 128.8, 127.4, 125.7, 124.6, 122.2, 121.1, 119.5, 119.4, 119.3, 118.7, 111.3, 109.2, 56.3, 37.6. Trimer; 2-[2,2-bis-(1*H*-indol-3-yl)ethyl]phenylamine. White powder. Mp 163-164 °C. ^1H-NMR (300 MHz, $CDCl_3$) δ: 7.79 (2H, brs), 7.39 (2H, d, *J* = 8.1 Hz), 7.21 (2H, d, *J* = 8.1 Hz), 7.05 (2H, td, *J* = 8.1, 1.1 Hz), 6.92-6.86 (6H, m), 6.53 (1H, td, *J* = 7.3, 1.1 Hz), 6.46 (1H, dd, *J* =8.4, 1.1 Hz), 4.77 (1H, t, *J* =

7.3 Hz), 3.33 (2H, d, *J* = 7.3 Hz), 3.17 (2H, brs). ^{13}C-NMR (75 MHz, $CDCl_3$) δ: 144.7 (2C), 136.5 (2C), 130.3, 125.9, 126.8 (2C), 121.8 (4C), 119.6 (2C), 119.1 (2C), 118.7 (2C), 115.6 (2C), 111.0 (2C), 37.1, 34.4.

$Hf(OTf)_4$ catalyzed addition reaction of indole with 1a in the presence of pyridinediamine ligand. A mixture of $Hf(OTf)_4$ (0.01 mmol) and pyridinediamine ligand (0.012 mmol) was stirred in MeCN (0.1 mL) at rt for 30 min. To this solution, a solution of **1a** (0.15 mmol) in MeCN (0.2 mL) and indole (0.1 mol) in MeCN (0.2 mL) were added and the mixture was stirred at rt for appropriate time indicated in Table 2. After the reaction was completed, the reaction mixture was quenched with water (10 mL) and extracted with $CHCl_3$ (15 mL×2). The combined extracts were dried over $MgSO_4$ and condensed in vacuo. The residual oil was purified by flash column chromatography on silica gel eluted with 20% EtOAc in hexane to give **2a** in quantitative yield.

Preparation of complex-A and complex-B. A mixture of $Hf(OTf)_4$ (77 mg, 0.1 mmol) and pyridinediamine (37 mg, 0.1 mmol) was stirred in MeCN (2 mL) for 30 min at rt. Solvent was removed and resulting solid was recrystallized from EtOH. The white solid was dried at 70 °C for 12 h under reduced pressure in the presence of P_4O_{10}. Complex-**A** (meso) from **La** and $Hf(OTf)_4$; 90% yield. Mp 100-102 °C. ^{1}H-NMR (300 MHz, CD_3CN) δ: 7.78 (1H, t, *J* = 7.7 Hz), 7.55-7.46 (10H, m), 7.22 (2H, d, *J* = 7.7 Hz), 4.61 (2H, q, *J* = 6.6 Hz), 4.22 (2H, q, *J* = 6.6 Hz), 1.76 (6H, d, *J* = 6.6 Hz), 1.60 (6H, d, *J* = 6.6 Hz). *Anal*. Calcd for $C_{29}H_{39}F_{12}HfN_3O_{16}S_4$ (hydrate with $4H_2O$).: C, 28.54; H, 3.44; N, 3.22. Found: C, 28.50; H, 3.49; N, 3.42. IR (KBr) cm^{-1}: 3076, 3418 (O-H, N-H). Complex-**B** (chiral) from **Ld** and $Hf(OTf)_4$; 79% yield. Mp 100-102 °C. $[\alpha]_D^{27}$ +35 (*c* 0.4, MeOH). ^{1}H-NMR (300 MHz, CD_3CN) δ: 7.91 (1H, t, *J* = 7.7 Hz), 7.58-7.28 (11H, m), 7.24 (1H, d, *J* = 7.7 Hz), 4.59 (1H, q, *J* = 6.6 Hz), 4.37 (1H, q, *J* = 6.6 Hz), 4.31 (1H, q, *J* = 6.6 Hz), 4.23 (1H, q, *J* = 6.6 Hz), 1.75 (3H, d, *J* = 6.6 Hz), 1.65 (3H, d, *J* = 6.6 Hz), 1.62 (3H, d, *J* = 6.6 Hz), 1.51 (3H, d, *J* = 6.6 Hz). *Anal*. Calcd $C_{29}H_{35}F_{12}HfN_3O_{14}S_4$ (hydrate with $2H_2O$): C, 29.41; H, 2.98; N, 3.55. Found: C, 29.34; H, 3.16; N, 3.56. IR (KBr) cm^{-1}: 3048, 3420 (O-H, N-H).

Preparation of complex-A' and complex-B'. A mixture of $Hf(OTf)_4$ (77 mg, 0.1 mmol) and pyridinediamine (74 mg, 0.2 mmol) was stirred in MeCN (2 mL) for 30 min at rt. Removal of solvent gave hygroscopic white solid. Due to a difficulty of recrystallization or other purification, we could not yield pure material. Only their NMR data are given. Complex-**A'** (meso) from **La** and $Hf(OTf)_4$; ^{1}H-NMR (300 MHz, CD_3CN) δ: 7.75 (2H, t, *J* = 7.7 Hz), 7.58-7.41 (20H, m), 7.20 (4H, d, *J* = 7.7 Hz), 4.47 (4H, q, *J* = 6.6 Hz), 4.18 (4H, q, *J* = 6.6 Hz), 1.68 (12H, d, *J* = 6.6 Hz), 1.56 (12H, d, *J* = 6.6 Hz). Complex-**B'** (chiral) from **Ld** and $Hf(OTf)_4$; ^{1}H-NMR (300 MHz, CD_3CN) δ: 7.82 (2H, t, *J* = 7.7 Hz), 7.48-7.30 (20H, m), 7.28 (2H, d, *J* = 7.7 Hz), 7.17 (2H, d, *J* = 7.7 Hz), 4.45 (2H, q, *J* = 6.6 Hz), 4.34 (2H, q, *J* = 6.6 Hz),

4.13 (2H, q, *J* = 6.6 Hz), 4.04 (2H, q, *J* = 6.6 Hz), 1.70 (6H, d, *J* = 6.6 Hz), 1.58 (6H, d, *J* = 6.6 Hz), 1.54 (6H, d, *J* = 6.6 Hz), 1.44 (6H, d, *J* = 6.6 Hz).

Proton NMR of pyridinediamines La and Ld in CD_3CN. La; ^{1}H-NMR (300 MHz, CD_3CN) δ: 7.55 (1H, t, *J* = 7.7 Hz), 7.27-7.17 (10H, m), 7.09 (2H, d, *J* = 7.7 Hz), 3.74 (2H, q, *J* = 6.6 Hz), 3.72 (2H, q, *J* = 6.6 Hz), 1.29 (6H, d, *J* = 6.6 Hz), 1.28 (6H, d, *J* = 6.6 Hz). **Ld**; ^{1}H-NMR (300 MHz, CD_3CN) δ: 7.58 (1H, t, *J* = 7.7 Hz), 7.33-7.17 (10H, m), 7.13 (1H, dd, *J* = 7.7, 1.1 Hz), 7.01 (1H, dd, *J* = 7.7, 1.1 Hz), 3.78 (1H, q, *J* = 6.6 Hz), 3.72 (1H, q, *J* = 6.6 Hz), 3.45 (1H, q, *J* = 6.6 Hz), 3.38 (1H, q, *J* = 6.6 Hz), 1.32 (3H, d, *J* = 6.6 Hz), 1.30 (3H, d, *J* = 6.6 Hz), 1.19 (3H, d, *J* = 6.6 Hz), 1.11 (3H, d, *J* = 6.6 Hz). Their proton NMR in $CDCl_3$ was already reported in ref. 8.

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REFERENCES AND NOTES

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10. The chiral ligands **L2**, and **Lc-f** gave a slight excess of (*R*)-enantiomer in less than 10% ee. Separations of the enantiomers by chiral HPLC were performed by the conditions reported in ref 4b.