Note

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Modular Construction of Protected 1,2/1,3-Diols, -Amino Alcohols, and -Diamines via Catalytic Asymmetric Dehydrative Allylation: An Application to Synthesis of Sphingosine

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Supporting Information Placeholder

ABSTRACT: A new enantioselective catalysis has been developed for the one-step construction of methylene-bridged chiral modules of 1,2- and 1,3-OH and/or NH function(s) from δ- or λ-OH/NHBoc-substituted allylic alcohols and "H_2C=O"/"H_2C=NBoc." A protonic nucleophile, either in situ generated CH_2OH or CH_2NHBoc, is intramolecularly allylated to furnish eight possible 1,2- or 1,3-O,O, -O,N, -N,O, and -N,N chiral modules equipped with an ethenyl group in high yields and enantioselectivities. The utility of this method has been demonstrated in the five-step synthesis of sphingosine.

Chiral 1,2- and 1,3-oxygen- and/or nitrogen-units are ubiquitous in natural products ranging from small molecules, such as sugars, amino acids, and lipids, to huge molecules.[1] Efficient construction of these chiral modules with an appropriate functionality for the continuing reaction is needed toward a target molecule, and many excellent methods have been developed on the basis of asymmetric oxydation,[2] reduction,[3] aldol reaction,[4] and allylation.[5] However, these methods lack generality; therefore, we have aimed to develop a method that can furnish all eight possible 1,2- and 1,3-O,O, -O,N, -N,O, and -N,N modules with a single chiral catalyst. **Figure 1** illustrates our basic concept. The monocationic CpRu(II) complex **1** of chiral picolinic acid, Cl-Naph-PyCOOH (6-(2-chloronaphthalen-1-yl)-5-methylpyridine-2-carboxylic acid), catalyzes an intramolecular asymmetric dehydrative Tsuji-Trost type allylation of protonic nucleophiles, e.g., OH, NHCOR, and COOH, to furnish 5- and 6-membered cyclic ethers, amides, and esters with high enantiomeric ratios (er) (**Figure 1a**).[6] **Figure 1b** illustrates our envisioned strategy that catalyzes upon the slightly acidic conditions under

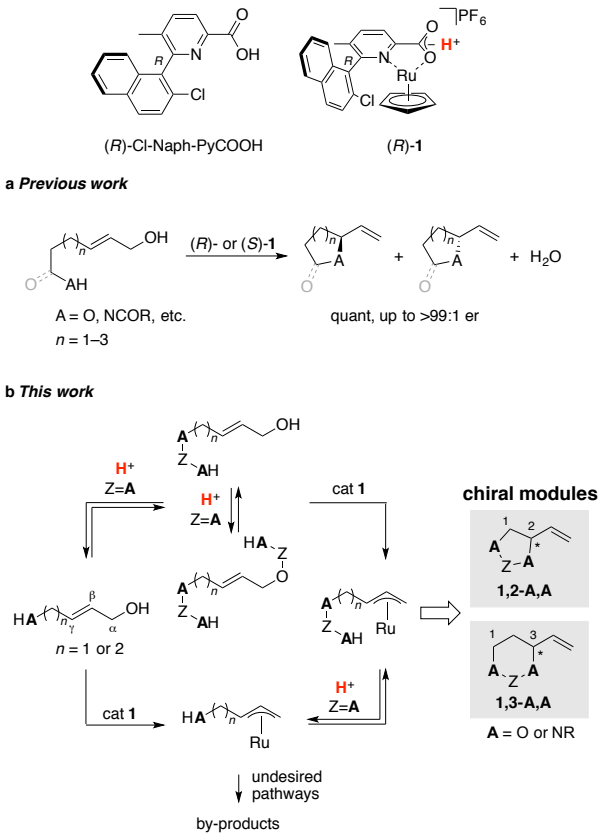


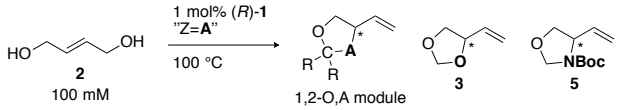
Figure 1. Dehydrative asymmetric allylation approach for construction of chiral 1,2- and 1,3-bifunctional modules.

which the CpRu/H^+ operates. Addition of the protonic nucleophile **A**H (**A** = O or NCOR) in a δ- or λ-**A**H-substituted allylic alcohol to an electron-deficient unsaturated "Z=**A**" bridging unit should be accelerated by H^+ to generate the two-atom inserted **A**–Z–**A**H species; this species would undergo a smooth cyclization to the

corresponding 5- and 6-membered 1,2- and 1,3-**A**,**A** motifs bridged by "Z." Although many possible species exist in equilibria, catalyst **1** will only furnish the product-forming species. However, if a π-allyl intermediate is generated more quickly than **A**–Z–**A**H formation, the undesired pathways would become predominant. The appropriate selection of "Z=**A**" is the key in the complex network system.

The bridging unit "Z=**A**" was screened in the reaction of (*E*)-but-2-ene-1,4-diol (**2**) under the standard conditions of "[**2**] = 100 mM; [(*R*)-**1**] = 1 mM; 10 mol amount of "Z=**A**"; DMA; 100 °C." Among many potentially usable "Z=**A**," "Z" was fixed to a C1 unit, R_2C, and "**A**" was selected as "O." **Table 1** summarizes the representative results. With the generally utilized bridging units, O=C=O, CH_3CH=O, CCl_3CH=O, and $(CH_3)_2C$=O, substrate **2** was completely consumed, but none of the desired 1,2-O,O module, 4-ethenyl-1,3-dioxorane, was obtained (entries 1–4). Most likely, the intermediary π-allyl complex underwent β-elimination to form a dienal and/or self-condensation with **2** to form allyl ethers. Use of highly electrophilic $(CF_3)_2C$=O·$n$$H_2O$ furnished the unprotected but-3-ene-1,2-diol in a 77:23 er and 52% yield (entry 5), qualitatively confirming the validity of H^+-catalyzed **A**–Z–**A**H generation, as illustrated in **Figure 1b**. Finally, use of a 37% aqueous solution of formaldehyde, HCH=O + H_2O ⇆ $HOCH_2OH$,[7] furnished the desired methylene-bridged 1,2-O,O module (**3**) with a 98:2 *R*/*S* er in 96% NMR yield (entry 6). Enantioselectivity decreased in *t*-BuOH, THF, CH_2Cl_2, and toluene. Yields tended to be lower in hydrophobic solvents (entries 7–10). Anhydrous paraformaldehyde lowered the yield,[8] and the addition of H_2O increased the yield and er (entry 11). Trioxane showed low reactivity no matter of whether the H_2O exist or not.[8] Furthermore, $HOCH_2NHBoc$ (**4**) was found to be an excellent bridging unit that facilitated the efficient construction of methylene-bridged 1,2-O,N module (**5**) with a 96:4 *R*/*S* er in 92% isolated yield (entry 12). Use of 2 mol amount of **4** was sufficient. In both cases, the absolute configurations matched the enantioselectivity observed in the (*R*)-**1**-catalyzed intramolecular OH and NHBoc allylation.[6] Replacement of Boc with Cbz, Bz, Piv, TFA, and Ts dramatically decreased the reactivity.[8] A complicated equilibria exists between various chemical species that are generated from **2**, the π-allyl intermediate and "HCH=**A**" (**A** = O or NCOR) (**Figure 1b**). The equilibrium concentration of the desired product-forming species should be strongly affected by the acidity, polarity, and the H_2O content of the reaction media. A subtle change in the bridging unit significantly affects reactivity. The H_2C=O andH_2C=NBoc bridging units satisfy the requirements for the desired reaction pathway, as shown in **Figure 1b**.

Table 1: **Screening of ''Z=A'' in the O and N Allylation of (*E*)-But-2-ene-1,4-diol (2).**[a]



entry	"Z=A"[b]	solvent	% yield[c]	*R*:*S*[d]
1	O=C=O[e]	DMA	—[f]	—
2	CH_3CH=O	DMA	—[f]	—
3	CCl_3CH=O	DMA	—[f]	—
4	$(CH_3)_2C$=O	DMA	—[f]	—
5	$(CF_3)_2C$=O·$n$$H_2O$	DMA	(52)[g]	(77:23)[g]
6	HCH=O (37% formalin)	DMA	96	98:2
7	HCH=O (37% formalin)	*t*-BuOH	94	76:24
8	HCH=O (37% formalin)	THF	94	90:10
9	HCH=O (37% formalin)	CH_2Cl_2	40	87:13
10	HCH=O (37% formalin)	toluene	45	88:12
11	HCH=O (praformaldehyde)[h]	DMA	66	96:4
12[g]	HO-CH_2-NHBoc(**4**)[i]	DMA	92[j]	96:4

[a]Conditions: [**2**] = 100 mM; [(*R*)-**1**] = 1 mM; 100 °C; 0.5 mmol scale. Allyl ester of Cl-Naph-PyCOOH was used for easier manipulation. The (*R*)-**1** catalyst is generated in situ. [b]10 mol amount of **Z**=A was used otherwize specified. [c]Determined by ^{1}H-NMR analysis otherwise specified. [d]Determined by HPLC analysis. [e]8 atm. [f]The substrate **2** was completely consumed, but no desired module was obtained. [g]The values in parentheses are the data of but-3-ene-1,2-diol obtained under the reaction conditions. [h]100 mol amount of H_2O was added. [i]2 mol amount of **4**. [j]Isolated yield.

The generality of the present method was investigated with the use of **2**, λ-OH-substituted allylic alcohol **6**, δ-BocNH-substituted allylic alcohol **7**, and λ-BocNH-substituted allylic alcohol **8**. The results are shown in **Figure 2**. All of the eight possible chiral modules, 1,2-O,O (**3**), 1,2-O,N (**5**), 1,3-O,O, 1,3-O,N, 1,2-N,O, 1,2-N,N, 1,3-N,O, and 1,3-N,N were obtained with >94:6 ers in >86% yields. Under the standard conditions, the yields of 1,3-O,N and 1,3-N,N were halved and the enantioselectivity of 1,3-O,N was low (*R*/*S* = 25:75). However, increasing the catalyst loading from 1 mol% to 10 mol% improved the yields and ers to 86% with 98:2 er and 88% with 99:1 er for 1,3-O,N and 1,3-N,N, respectively. The reliability of the present method was confirmed by the synthesis of 1,2-O,O, 1,2-O,N, and 1,3-O,O on a 1–5 g scale of **2** and **6**. The present method could not be applied to the synthesis of 1,4-type modules, because intramolecular cyclization of $HO(CH_2)_3CH$=$CHCH_2OH$ more quickly occurres.[6a]

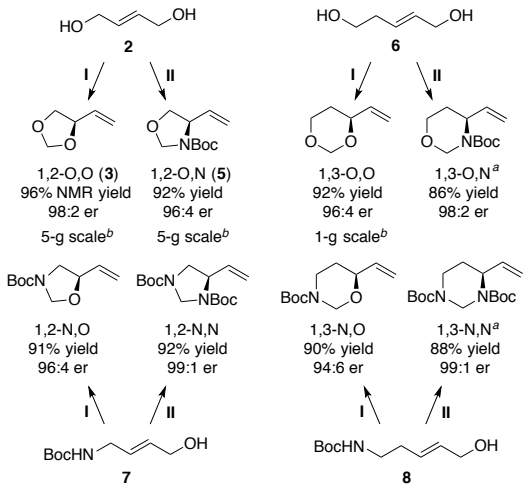


Figure 2. Synthesis of eight possible chiral modules. All of yields except for that of **3** are isolated ones. Conditions **I**: [allylic alcohol] = 100 mM, [HCHO aq] = 1 M, [(*R*)-**1**] = 1 mM, DMA, 100 °C, 3 h. Conditions **II**: [allylic alcohol] = 100 mM, [**4**] = 200 mM, [(*R*)-**1**] = 1 mM, DMA, 100 °C, 3 h. [a]Results obtained by use of 10 mM (*R*)-**1**. [b][**2**] or [**6**] = 500 mM, [HCHO aq] = 5 M or [**4**] = 1 M, [(*R*)-**1**] = 5 mM, DMA, 100 °C, 12 h. A longer time was required for completion probably due to less efficient phase separation of H_2O. Isolation of **3** was problematic.

An ethenyl group that was simultaneously installed into the chiral modules during the course of the asymmetric cyclization process is advantageous for the subsequent reaction toward a target molecule.[9] For example, metathesis with an allylic alcohol can furnish the δ-O/N substituted allylic alcohol moiety, which could be used for the next O/N introduction with our strategy. Among many potentially applicable target molecules, D-*erythro*-sphingosine (**9**), which is representative of sphingolipids, was selected for demonstration of our strategy because of its structural expediency and significant biological characteristics.[10] **Figure 3** shows the synthetic pathways. The 1,2-O,N module ((*R*)-**5**) obtained above as a 96:4 *R*/*S* mixture was subjected to olefin metathesis using 3 mol% of 2nd-generation Hoveyda-Grubbs catalyst (HG-II) in acetone containing 10 mol amount of (*Z*)-but-2-ene-1,4-diol[11] gave **10** as a 95:5 *E*/*Z* mixture, the *E* product of which was isolated in 65% yield. (*E*)-**10** was converted to **11** in a 80:20 diastereomeric ratio (dr) in the presence of (*R*)-**1** in DMA containing 60 mol amount of H_2O without the use of H_2C=O. The "NCH_2OH" unit was in situ generated from the methylene-bridged and δ-NBoc-substituted allylic alcohol (*E*)-**10**, realizing an atom economical methylene relay process. The second allylation was roughly one order slower than the first one (100 °C, 3 h: 100% conversion vs 100 °C, 15 h: 78% conversion). An 80:20 mixture of **11** (98:2 er) and *epi*-**11** (98:2 er) was isolated in 74% yield together with ca 15% recoverty of

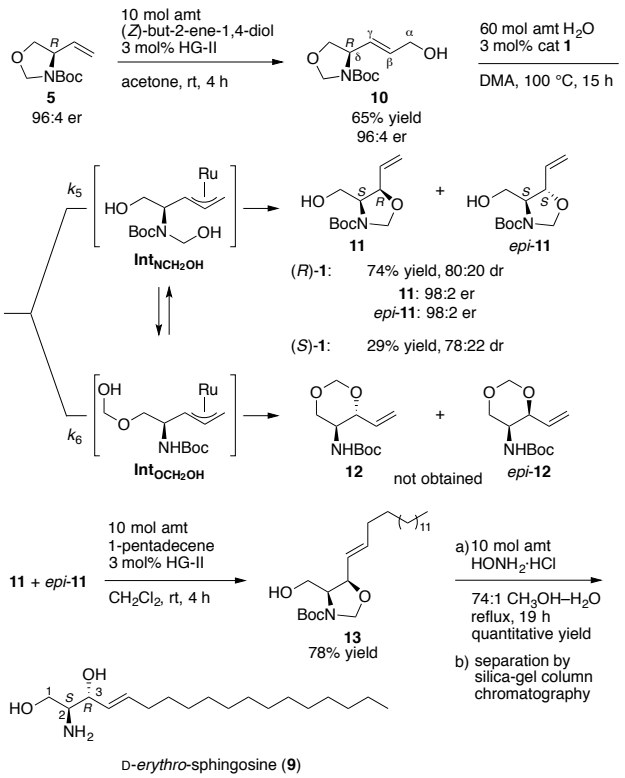


Figure 3. Synthesis of sphingosine (**9**) from 1,2-O,N module (**5**) via methylene-relayed dehydrative allylation combined with olefin metathesis. All of yields are isolated ones. amt: amount.

(*E*)-**10** with a 93:7 er. The reactivity of the enantiomeric catalyst (*S*)-**1** was significantly lowered (29% yield), and the dr hardly changed. Thus, the slight enhancement of the product er from 96:4 to 98:2 can be ascribed to the kinetic resolution of the 96:4 *R*/*S* mixture of (*E*)-**10** by (*R*)-**1**. Inthis specific case, the substrate control is predominant over the catalyst control.[12,13] In this second diastereoselective allylation, the OCH_2O-type product **12** was not generated at all, indicating that the reactivity of the 5-membered ring formation (k_5) of the NCH_2OH-type intermediate $\mathbf{Int_{NCH_2OH}}$ is much higher than that of the 6-membered ring formation (k_6) of the OCH_2OH-type intermediate $\mathbf{Int_{OCH_2OH}}$ ($k_5 >> k_6$). The oxazolidine product **11** and 1-pentadecene (10 mol amount) were coupled in CH_2Cl_2 in the presence of HG-II (3 mol%) to give **13** as a sole product in 78% isolated yield. The methylene bridge and Boc protecting group were quantitatively removed using Harding's conditions ($HONH_2$·HCl, 74:1 CH_3OH–H_2O, reflux, 19 h)[14] to furnish a 80:20 mixture of D-erythro-sphingosine (**9**) and *epi*-**9**. The mixture was purified to give the target molecule. The ^{1}H- and ^{13}C-NMR spectra, as well as the optical rotation ($[\alpha]_D^{22}$=–3.99 (*c*=0.465 in $CHCl_3$)), were all consistent with authentic **9** ($[\alpha]_D^{21}$=–3.29 (*c*=0.460 in $CHCl_3$)).[15]

In summary, we have successfully developed a general method for the construction of chiral 1,2- and 1,3-O,O, -O,N, -N,O, and -N,N eight modules equipped with a terminal ethenyl group; the reaction proceeds in the presence of our CpRu complex of chiral picolinic acid, Cl-Naph-PyCOOH, in combination with "H_2C=O" or "$HOCH_2NHBoc$" with δ- or λ-OH/NHBoc-substituted allylic alcohol substrates. The success of this method can be ascribed to two factors: i) the Ru/H^+-catalyzed allylation functioning under slightly acidic conditions; and ii) the use of a methylene bridging unit, H_2C=**A** (**A** = O or NBoc). The slightly acidic conditions facilitate the formation an acetal, aminal, and a Ru-π-allyl species directly from the allylic alcohol. The methylene bridging unit enables the facile generation of the sterically less-demanding **A**CH_2OH acetal and **A**CH_2NHBoc aminal (**A** = O or NBoc). Removal of the methylene group is straightforward, and the ethenyl group can function as the basis for the generation of the next allylic alcohol motif via HG-II-catalyzed metathesis. By using these advantages, we have realized a unique and short-step asymmetric synthesis of sphingosine from commercially available (*E*)-but-2-ene-1,4-diol. On-going projects in our group include the application of this strategy to other O/N-multi-functionalized natural products.

EXPERIMENTAL SECTION

All of **Figure S1**–**S35** and **Table S1** were attached in the supporting information.[8]

(1) Instruments. Nuclear magnetic resonance (NMR) spectra were recorded on JEOL JNM-ECA-600 (600 MHz for ^1H, 152 MHz for ^{13}C), and the chemical shifts are expressed in parts per million (ppm) downfield from $Si(CH_3)_4$ or in ppm relative to the solvent peaks (δ 7.26 ($CHCl_3$), 2.49 (CD_3SOCHD_2), and 3.31 (CHD_2OD) in ^1H NMR; δ 77.0 ($CDCl_3$) and 49.0 (CD_3OD) in ^{13}C NMR, respectively). The signal patterns of ^1H NMR are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad signal. The resolutions of ^1H- and ^{13}C-NMR spectra are 0.69 Hz and 1.44 Hz, respectively. NMR spectra were measured with samples of 5–15 mM at 25 °C unless otherwise specified. High-resolution mass spectra (HRMS) were measured by ESI ionization method on a Bruker Daltonics microTOF-QII system. High performance liquid chromatography (HPLC) analyses were performed on Shimadzu LC-10AD, LC-20AD, and LC-20TA systems. Gas chromatography (GC) analyses were performed on a Shimazu GC-2014 system. Optical rotations were measured on a JASCO P-1010-GT system.

(2) Materials.

Gases. Argon (Ar) gas was purified by being passed through a column of BASF R3-11 catalyst at 80 °C and then through a column of granular $CaSO_4$. Carbon dioxide (CO_2, >99.9% purity, H_2O <0.005%) and O_2 were purchased from AIR WATER INC. Ozone (O_3) gas was generated by NIPPON OZONE O_3 generator (100 V, 5 A, 25 mL/min O_2).

Solvents. Solvents for the present catalytic allylation and Grubbs olefin metathesis were dried and degassed at the reflux temperature in the presence of appropriate drying agents (2.5 g/L) under Ar stream for 6 h and distilled into Schlenk flasks: dichloromethane (CH_2Cl_2), *tert*-butyl alcohol (*t*BuOH), and *N*,*N*-dimethylacetamide (DMA) from CaH_2; tetrahydrofuran (THF) and toluene from Na/benzophenone; acetone from MS 4A. These were degassed by three freeze–thaw cycles before use. First grade solvents including chloroform ($CHCl_3$), CH_2Cl_2, ethanol (EtOH), 1,4-dioxane (dioxane), ethyl acetate (EtOAc), diethyl ether (Et_2O), hexane, THF, methanol (CH_3OH), pentane, and 2-propanol (*i*PrOH) were used without purification for extraction, partition, silica-gel column chromatography, measurement of optical rotations, and usual organic synthesis. Solvents for HPLC were used after filtration (0.5 μM pored PTFE filter).

Reagents and chemicals. All of reagents, which were purchased from companies, were used without further purification unless otherwise specified. These are listed below in the alphabetical order neglecting the number suffix.

Aldrich: acetaldehyde, Hoveyda-Grubbs catalyst 2nd generation ((1,3-bis-(2,4,6-trimethylphenyl)-2-imidazolidinylidene)dichloro(*o*-isopropoxyphenylmethylene)ruthenium, HG II), hydroxylamine hydrochloride ($HONH_2{\cdot}HCl$), triphenylphosphine (PPh_3), Quadrasil™ AP, and D-*erythro*-sphingosine. Ark Pharm: (1,3-dioxolan-4-yl)methanol. Kishida: pyridine. Nacalai: aqueous NH_3, distilled water (H_2O), triethylamine ($N(C_2H_5)_3$), formalin (36–38%) aqueous solution of fromaldehyde (CH_2O) (stabilized with 5–10% CH_3OH; amount of CH_2O was calculated as 37.0 wt%), and 12 M aqueous hydrogen chloride (HCl). Organo: Amberlite IR120B (H^+ form). Strem: trisacetonitrilecyclopentadienylruthenium hexafluorophosphate ($[CpRu(CH_3CN)_3]PF_6$). TCI: (*Z*)-but-2-ene-1,4-diol, di-*tert*-butyl dicarbonate (Boc_2O), *tert*-butyl methyl iminodicarbonate, trichloroacetaldehyde, trifluoroacetic acid, hexafluoroacetone hydrate, diisopropyl azodicarboxylate (DAID), 1-pentadecene, 1,1'-thiocarbonyldiimidazole (TCDI), and *p*-toluenesulfonyl chloride (TsCl).

(*E*)-But-2-ene-1,4-diol (**2**) was purchased from TCI and purified by silica-gel column chromatography before use, or synthesized from but-2-yne-1,4-diol according to the reference.[16] *N*-Boc-aminomethanol (**4**),[17] *N*-Cbz-aminomethanol,[18] *N*-Bz-aminomethanol,[19] *N*-pivaloylaminomethanol,[20] *N*-trifluoroacetylaminomethanol,[21] *N*,*N*'-bistosylaminal,[22] (*E*)-pent-2-ene-1,5-diol (**6**),[23] (*E*)-*N*-Boc-4-aminobut-2-en-1-ol (**7**),[24] and (*E*)-*N*-Boc-5-aminopent-2-en-1-ol (**8**)[25] were synthesized according to the reported methods.

Silica gels. Analytical thin-layer chromatography (TLC) and preparative TLC (PTLC) were performed using Merck Glass TLC plates, silica gel 60 coated with F_{254} (layer thickness, 0.25 mm (TLC) and 1 mm (PTLC)). The product spots were visualized by use of a solution of phosphomolybdic acid (PMA), *o*-anisaldehyde, iodine (I_2), cerium ammonium molybdate (CAM), potassium permanganate, or UV irradiation. Silica-gel column chromatography, which is abbreviated as SiO_2-chromatography afterward, was performed using AP 300.

Catalyst. CpRu(II)/H^+ catalyst (*R*)-**1** or (*S*)-**1**, which can be prepared by mixing $[CpRu(CH_3CN)_3]PF_6$ with (*R*)- or (*S*)-Cl-Naph-PyCOOH in a 1:1 ratio, is air sensitive. For the operational simplicity, the corresponding Ru(IV) π-allyl complex, $[CpRu(\eta^3\text{-}C_3H_5)((R)\text{-Cl-Naph-PyCOO})]PF_6$ or its *S* enantiomer, was used in the present asymmetric allylation. The Ru(IV) complex was prepared by mixing $[CpRu(CH_3CN)_3]PF_6$ with one mol amount of (*R*)- or (*S*)-Cl-Naph-PyCOOAll (All: $CH_2CH{=}CH_2$). In the reaction system, (*R*)-**1** or (*S*)-**1** is generated. The procedure for preparation of a 10-mM CH_2Cl_2 solution of $[CpRu(\eta^3\text{-}C_3H_5)(\text{Cl-Naph-PyCOO})]PF_6$ has been described in the supporting information of the previously reported paper.[6a]

Synthesis of authentic racemic modules. Authentic racemic samples were prepared by use of (±)-Cl-Naph-PyCOOAll instead of optically pure ligand under the same conditions as those described in sections (4), (5), and (6).

(3) General manipulation for allylation and synthesis of sphingosine. A Teflon-coated magnetic bar was used for stirring of a reaction mixture. Room temperature (rt) was in the range of 25 °C to 28 °C. Cold bath at –78 °C was prepared by use of dry-ice methanol bath or EYELA PSL-2500 equipment. Solvents after general workup process were removed by means of a rotary evaporator. Concentration of a reaction mixture in a Schlenk tube was performed by connecting to a vacuum-Ar line via a cold trap cooled by liquid N_2. Organic extract obtained by a general partition-based workup was dried over anhydrous Na_2SO_4 for ca. 30 min. "Aqueous" and "saturated" were abbreviated as "aq" and "sat," respectively. All of metal-catalyzed reactions were carried out under Ar atmosphere by use of a general Schlenk technique unless otherwise specified. A Schlenk tube with Teflon J. Young valve was specified by "Young-type Schlenk tube." Liquid reagents were introduced by use of a syringe via a septum rubber. After introduction, the septum was replaced with a glass stopper or with a Young valve. Heating in a closed system was carried out after reducing the pressure of the whole system or after raising the temperature followed by closing the system. Degassed solvents and degassed solutions of reagents, catalysts, and substrates were transferred to another Schlenk tube by use of a gas-tight syringe or cannulation method. Cannulation was performed by use of a Teflon or stainless tube through a septum rubber under a slightly positive pressure of Ar. One freeze-thaw cycle consists of i) freezing a liquid mixture, ii) evacuation of the system at the freezing stage, iii) closing the system, iv) thawing the frozen liquid, and v) releasing the negative pressure to atmospheric pressure by filling Ar gas.

(4) Synthesis of 1,2-O,O module (3). All of screening data for the reaction conditions were listed in **Table S1**.

*The boiling point of compound **3** is 110 °C,[26] therefore isolation is very difficult. The yield was determined by ^{1}H-NMR analysis using mesitylene as an internal standard, and the pure sample for measurement of the physical property was obtained in very low yield on a 5-g scale reaction. Compound **3** was isolated as a 100–300 mM pentane solution in ca. 60% yield from a 500-mM reaction mixture, and the solution was directly used for conversion to but-3-ene-1,2-diol (**14**) by hydrolysis and to (1,3-dioxolan-4-yl)methanol (**15**) by ozonolysis/$NaBH_4$ process. The details were described below.*

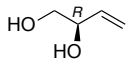
Procedure for 0.5-mmol scale reaction and determination of ^{1}H-NMR yield and conversion.

*Reactioin with 100 mM **2**.* A 10-mM CH_2Cl_2 solution of $[CpRu(CH_3CN)_3]PF_6$ (0.570 mL, 5.70 μmol (2.475 mg)) and a 10-mM CH_2Cl_2 solution of (*R*)-Cl-Naph-PyCOOAll (0.570 mL, 5.70 μmol (1.925 mg)) were charged in a 100-mL Young-type Schlenk tube, and concentrated. To this was added a 100-mM DMA solution of (*E*)-but-2-ene-1,4-diol (**2**) (5.70 mL, 0.570 mmol (50.2 mg)) and 37% formalin (424 μL, 5.70 mmol as CH_2O (171 mg)). The mixture was heated to 100 °C under Ar, and then the tube was sealed. After being stirred at 100 °C for 3 h, the resulting yellow-colored solution was cooled to rt. To this was added mesitylene (100-mM $CDCl_3$ solution; 1.90 mL, 0.190 mmol (22.8 mg)). A portion of the mixture (ca. 0.2 mL) was transferred to an NMR tube and diluted with $CDCl_3$ (0.5 mL). The solution was subjected to the ^{1}H-NMR analysis with 10-sec repetition time so that the signal intensities become accurate as much as possible. The 0.960:1.00 ratio of the signal intensities of the 1,2-O,O module product **3** (δ 4.04 (dd, *J* = 7.92, 6.89 Hz, 1H; CHC*H*HO)) and mesitylene (3H at δ 6.78 (s; 3 x ArH)) determined the yield to be 96% (**Figure S1**). No signal of the substrate **2** was observed within the error range of signal/noise (S/N) ratio (200), determining the conversion to be >99%. The reaction mixture obtained under the above conditions in a different batch was partitioned between pentane (5 mL) and H_2O (10 mL). The aq layer was extracted with pentane (5 mL x 3). The combined organic layers were washed with H_2O (5 mL x 2), dried over Na_2SO_4 (ca. 2 g), and filtrated. The filtrate was concentrated at 600 hPa by use of a rotary evaporator to ca. 1 mL, which contains ca. 10 mg of **3**. During the concentration process, a large part of **3** was evaporated. The enantiomeric ratio (er) was determined by HPLC analysis of the residue to be 98:2 (*R*:*S*) (conditions: CHIRALCEL OD-H column (0.46 cm ϕ x 250 mm); hexane–*i*PrOH 99.9:0.1 eluent; 1.0 mL/min flow rate; 254-nm light detection; t_R = 9.8 min (*S*) and 10.9 min (*R*)) (**Figure S2**).

*Reaction with 500-mM **2**.* The reaction mixture obtained under the above conditions except for the concentration of **2** (1.14 mL (500-mM DMA solution of **2**), 0.570 mmol (50.2 mg)) was used for preparation of a 100–300 mM solution of **3**. The reaction mixture was partitioned between pentane (3 mL) and H_2O (5 mL). The aq layer was further extracted with pentane (3 mL x 4). The combined organic layers were washed with H_2O (5 mL), and dried over Na_2SO_4 (ca. 2 g). Filtration gave a ca. 15 mL pentane solution of **3** containing 30% of DMA. The amount of **3** in the solution was determined to be ca. 40 mg/15 mL (ca. 25 mM) by the mesitylene method (0.100 mL; 0.500 mL (100-mM $CDCl_3$ mesitylene solution, 0.0500 mmol (6.00 mg)); 0.50 mL $CDCl_3$; 3.00:1.60 signal ratio at δ 4.04 and δ 6.78), indicating that the extraction efficiency was 80%. A 20-mL Young-type Schlenk tube was charged with the above solution (5 mL), closed, and connected to a vacuum line via a trap. The Young-type Schlenk tube was cooled to –78 °C and the trap was inserted into a liquid N_2 bath. After the inner pressure of the vacuum line reached to <0.02 mmHg, the Young's valve was carefully opened. Pentane in the Young Schlenk tube was distilled into the trap to concentrate the pentane solution to <0.5 mL (5 h). The Young's valve was closed, and the tube was warmed to rt. Another 5 mL of the 25-mM pentane solution of **3** was added to the Young-type Schlenk tube, and concentrated in the same way as described above. This concentration process was repeated 5 times. The ^{1}H-NMR analysis using mesitylene determined the amounts of **3** in the Young-type Schlenk tube and the trap to be 30 mg/mL (300 mM containing 10% DMA) and 5 mg/15 mL, respectively. Isolated yield of **3** as the pentane solution was calculated to be 60% yield. Er of 98:2 was confirmed by the HPLC analysis of the 300-mM solution of **3** under the same conditions as those described above. The 100–300 mM solution of **3** prepared in a different batch was used for conversion of **3** to other compounds.

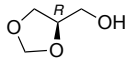
Direct conversion of 3 in the extracted pentane solution and determination of absolute configuration (abs config).

*Acid hydrolysis to but-3-ene-1,2-diol (**14**).* To the 117-mM pentane solution (1.9 mL; **3** (22.3 mg, 0.222 mmol)) derived from the reaction using (*R*)-Cl-Naph-PyCOOAll was added CH_3OH (2 mL), CH_2Cl_2 (2 mL) and Amberlite IR120B (H^+ form) (100 mg). The mixture was heated at 60 °C (oil bath temperature) for 48 h. After being cooled to rt, the whole mixture was filtered through membrane filter (1 μm pore size), and the filtrate was concentrated to give a yellow oil (ca. 120 mg). This was purified by SiO_2-chromatography (SiO_2, 5 g; $CHCl_3$–CH_3OH 50:1 eluent) to give (*R*)-but-3-ene-1,2-diol (**14**) (17.5 mg, 89% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.33 (br, 2H; OH), 3.51 (t, *J* = 11.02 Hz, 1H; C*H*HOH), 3.68 (d, *J* = 11.02 Hz, 1H; CH*H*OH), 4.26 (br, 1H; CH_2CHCH), 5.23 (d, *J* = 10.33 Hz; 1H, CH=C*H*H), 5.37 (d, *J* = 17.21 Hz; 1H, CH=CH*H*), 5.85 (ddd, *J* = 17.04, 10.33, 6.89 Hz, 1H; C*H*=CH_2). **Figure S3** shows the ^{1}H-NMR spectrum. The spectrum was consistent with the reported one.[27] Comparison of the $[\alpha]_D$ value determined the abs confign to be *R* ($[\alpha]_D^{21}$=+36.1 (*c*=0.82 in *i*PrOH); $[\alpha]_D^{20}$=–44.4 (*c*=3.02 in *i*PrOH) for *S*[27]).



14

*Ozonolysis/$NaBH_4$ reduction to (1,3-dioxolan-4-yl)methanol (**15**).* To the 130-mM pentane solution (1.9 mL; **3** (24.7 mg, 0.247 mmol)) derived from the reaction using (*R*)-Cl-Naph-PyCOOAll was added CH_3OH (2 mL) and CH_2Cl_2 (2 mL). The mixture was cooled to –78 °C, and then O_3 was introduced until the color of solution became a pale blue (10 min). $NaBH_4$ (56.1 mg, 1.48 mmol) was added at –78 °C, and the temperature was raised to rt. After being stirred for 12 h, the whole mixture was concentrated, and the residue was subjected to SiO_2-chromatography (SiO_2, 5 g; hexane–EtOAc 2:1 eluent) to give (1,3-dioxolan-4-yl)methanol (**15**) (21.7 mg, 84% yield) as colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.33 (br, 2H; OH), 3.51 (t, *J* = 11.02 Hz, 1H; C*H*HOH), 3.68 (d, *J* = 11.02 Hz, 1H; CH*H*OH), 4.26 (br, 1H; CH_2CHCH), 5.23 (d, *J* = 10.33 Hz, 1H; CH=C*H*H), 5.37 (d, *J* = 17.21 Hz, 1H; CH=CH*H*), 5.85 (ddd, *J* = 17.04, 10.33, 6.89 Hz, 1H; C*H*=CH_2); $[\alpha]_D^{20}$=+3.62 (*c*=1.09 in $CHCl_3$). **Figure S4** shows the ^{1}H-NMR spectrum of the synthetic product together with that of the commercially available sample, which is the mixture with 5-hydroxy-1,3-dioxane.[28] The spectrum was consistent with that of commercially available sample.

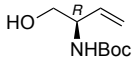


15

*Five-g scale reaction for obtaining pure sample of **3** in $CDCl_3$.* To a 200-mL Young-type Schlenk tube was added $[CpRu(CH_3CN)_3]PF_6$ (10.0-mM CH_2Cl_2 solution; 60.7 mL, 607 μmol (26.3 mg)) and (*R*)-Cl-Naph-PyCOOAll (10.0-mM CH_2Cl_2 solution; 60.7 mL, 607 μmol (20.5 mg)), the solution was concentrated under vacuum. To the orange residue was added 37% formalin (45.6 mL, 607 mmol of CH_2O (18.2 g)) and a 500-mM DMA solution of (*E*)-but-2-ene-1,4-diol (**2**) (121 mL, 60.7 mmol (5.35 g)) under Ar. The solution was stirred at 100 °C for 12 h, and then cooled to rt. The yield was determined to be 96% in the same way as that described above (0.100 mL; 0.500 mL (100-mM $CDCl_3$ mesitylene solution, 0.0500 mmol (6.00 mg)); 3.00:1.60 signal ratio at δ 4.04 and δ 6.78). The reaction mixture was partitioned between pentane (200 mL) and H_2O (300 mL). The aq layer was further extracted with pentane (200 mL x 4). The combined organic layers (ca. 1000 mL) were washed with H_2O (200 mL x 2), dried over Na_2SO_4 (ca. 20 g), and filtered. The filtrate (ca. 1000 mL) was concentrated at 40 °C to ca. 100 mL by use of a general distillation apparatus. The distillate (ca. 900 mL) and the residue (ca. 100 mL) contained 2.4 g and 2.0 g of **3**, respectively (^{1}H-NMR analysis using mesitylene). The residue was further concentrated to give a yellow oil (320 mg), which contained a small amount of DMA and no pentane. A small portion of the yellow oil (ca. 10 mg) was dissolved in $CDCl_3$ (1 mL), and passed through a pad of SiO_2 (7 mm ϕ x 7 mm). The $CDCl_3$ filtrate was subjected to the NMR measurement: ^{1}H NMR ($CDCl_3$) δ 3.54 (dd, *J* = 7.23, 6.89 Hz, 1H; OC*H*HCH), 4.05 (dd, *J* = 7.92, 6.89 Hz, 1H; OCH*H*CH), 4.44 (ddd, *J* = 6.89, 6.89, 6.89 Hz, 1H; C*H*CH=CH_2), 4.95 (s, 1H; OC*H*HO), 5.06 (s, 1H; OCH*H*O), 5.25 (d, *J* = 10.3 Hz, 1H; CH=C*H*H), 5.37 (d, *J* = 17.2 Hz, 1H; CH=CH*H*), 5.84 (ddd, *J* = 17.2, 10.3, 6.89 Hz, 1H; C*H*=CH_2); ^{13}C NMR ($CDCl_3$) δ 69.5, 77, 95.4, 118.2, 135.2, the signal resonated at 77 ppm is overlapped with the signal of $CDCl_3$, and identified by HMQC analysis; HRMS, no peak observed; $[\alpha]_D^{19}$=–57.4 (*c*=0.15 in $CDCl_3$). **Figure S5** showed ^{1}H- and ^{13}C-NMR spectra. The concentration of **3** in $CDCl_3$ was determined by use of the mesitylene method (0.1 mL $CDCl_3$ solution; 0.1 mL (100-mM $CDCl_3$ mesitylene solution, 0.0100 mmol (1.20 mg)); 0.5 mL $CDCl_3$; 0.15:3 signal ratio at δ 4.04 and d 6.78) to be *c*=0.15.

(5) Synthesis of 1,2-O,N module (5). To a 300-mL Young-type Schlenk tube was added a 10.0-mM solution of $[CpRu(CH_3CN)_3]PF_6$ and (*R*)-Cl-Naph-PyCOOAll in CH_2Cl_2 (56.8 mL, 5.68 mmol); the solution was concentrated under vacuum to furnish an orange residue. To this was added *N*-Boc-aminomethanol (**4**) (16.7 g, 114 mmol) and 500-mM solution of (*E*)-but-2-ene-1,4-diol (**2**) in DMA (113 mL, 56.8 mmol) under an Ar atmosphere. After 12-h stirring at 100 °C, the yellow solution was diluted with H_2O (120 mL) and extracted with pentane (250 mL x 4). The combined organic layers were washed with H_2O (100 mL x 2), dried over Na_2SO_4 (15 g), filtered, and evaporated under 600 hPa. The resulting crude oil (ca. 10 g) was purified by SiO_2-chromatography (SiO_2 100 g, pentane:Et_2O = 9:1) to give *N*-Boc-4-ethenyl-1,3-oxazolidine (**5**) (10.4 g, 92%) as a colorless oil: ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.45 (s, 9H; $C(CH_3)_3$), 3.73 (dd, *J* = 8.61, 4.82 Hz, 1H; OC*H*HCH), 4.09 (dd, *J* = 8.61, 6.89 Hz, 1H; OCH*H*CH), 4.31 (br, 1H; C*H*CH=CH_2), 4.76 (d, *J* = 4.13 Hz, 1H; OC*H*HN), 4.97 (d, *J* = 2.75 Hz, 1H; OCH*H*N), 5.16 (d, *J* = 10.3 Hz, 1H; CH=C*H*H), 5.22 (d, *J* = 17.2 Hz, 1H; CH=CH*H*), 5.77 (ddd, *J* = 16.9, 10.3, 6.89 Hz, 1H; C*H*=CH_2); ^{13}C NMR ($CDCl_3$, ca. 100 mM, 60 °C) δ 28.3, 57.8, 72.4, 79.1, 80.2, 116.3, 136.1 152.9; HRMS (ESI) calcd for $C_{10}H_{17}NNaO_3$ $[M+Na]^+$ 222.1106, found 222.1115; $[\alpha]_D^{19}$=–12.4 (*c*=1.06 in $CHCl_3$); *R*:*S* = 96.5:3.5 (HPLC conditions: CHIRALPAK IA-3 column (0.46 cm ϕ x 250 mm); hexane–*i*PrOH 99.7:0.3 eluent; 1.0 mL/min flow rate; 254-nm light detection; t_R = 11.5 min (*S*) and 14.6 min (*R*)). **Figure S6** and **S7** showed the ^{1}H- and ^{13}C-NMR spectra and HPLC charts, respectively.

Abs confign was determined by comparison of the optical rotation of *N*-Boc-2-aminobut-3-en-1-ol (**16**), which was obtained by deprotection of **5** followed by *N*-Boc protection.



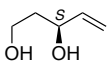
16

The compound **5** (500 mg, 2.18 mmol) dissolved in CH_2Cl_2 (8.60 mL) was charged into a 30-mL round-bottom flask. To this was added TFA (1.70 mL, 22.2 mmol). After 1-h stirring at rt, CH_3OH (9.00 mL) was added, and the mixture was heated at 65 °C for 2 h. Concentration gave crude 2-ammoniobut-3-en-1-ol trifluoroacetate (ca. 500 mg) as an oil, which was used for the next reaction without further purification. The ammonium salt (104 mg, 0.483 mmol) was dissolved in a 4:1 dioxoane–H_2O mixture, and the solution was transferred to a 5-mL Young-type Schlenk tube. To this was added $N(C_2H_5)_3$ (195 μL, 1.40 mmol) and Boc_2O (161 μL, 0.701 mmol). The mixture was stirred at rt for 2 h, and then concentrated to give a crude *N*-Boc protected compound (ca. 100 mg). This was purified by SiO_2-chromatography (SiO_2, 10 g; $CHCl_3$–CH_3OH 9:1 eluent) to afford *N*-Boc-2-aminobut-3-en-1-ol (**16**) (74.3 mg, 74%): ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.45 (s, 9H; $C(CH_3)_3$), 2.04 (s, 1H; OH), 3.64 (br, 1H; OC*H*HCH), 3.69 (br, 1H; OCH*H*CH), 4.23 (br, 1H; CH_2CH), 4.79 (br, 1H; NH), 5.22 (d, *J* = 11.0 Hz, 1H; CH=C*H*H), 5.26 (d, *J* = 17.2 Hz, 1H; CH=CH*H*), 5.77 (ddd, *J* = 17.4, 10.7, 5.51 Hz, 1H; C*H*=CH_2). **Figure S8** showed the ^{1}H-NMR spectrum. The spectrum was consistent with the reported one.[29] Comparison of the $[\alpha]_D$ value determined the abs confign to be *R* ($[\alpha]_D^{20}$=+22.4 (*c*=0.825 in $CHCl_3$); $[\alpha]_D^{20}$=+31 (*c*=1.03 in $CHCl_3$) for *R*[29]).

(6) Synthesis of other modules. The synthetic procedures using formalin and *N*-Boc-aminomethanol (**4**) followed those described in section (4) and section (5), respectively. The product isolation process is essentially the same as that for 1,2-O,N module (**5**) in all cases. Listed below are the detailed data for the reaction conditions, isolation (work up and purification), product (weight, isolated yield), and physical property. The retention times of the synthetic products with high ers were sometimes slightly different from those of the racemic samples. In these cases, the data of racemic ones were reported.

1,3-O,O module. (*E*)-Pent-2-ene-1,5-diol (**6**) (1.03 g, 12.5 mmol), 37% formalin (9.38 mL, 125 mmol), DMA (25.1 mL), $[CpRu(CH_3CN)_3]PF_6$ (12.5 mL of 10.0 mM CH_2Cl_2 solution, 125 μmol), (*R*)-Cl-Naph-PyCOOAll (12.5 mL of 10.0 mM CH_2Cl_2 solution, 125 μmol), 100 °C, 12 h. Isolation: partition between H_2O (50 mL) and pentane (50 mL); extraction of aq layer with pentane (25 mL x 5); washing of the combined organic layers with H_2O (50 mL); dryness over Na_2SO_4 (ca. 25 g); filtration/evaporation. Purification: SiO_2-chromatography (SiO_2, 50 g; pentane–Et_2O 9:1 eluent). Product: 4-ethenyl-1,3-dioxane (1,3-O,O module) (1.31 g, 92%). Physical property: ^{1}H NMR ($CDCl_3$) δ 1.61 (d, *J* = 13.1 Hz, 1H; CH_2CHHCH), 2.18 (ddd, *J* = 19.1, 13.1, 6.20 Hz, 1H; CH_2CHHCH), 3.71 (dd, *J* = 11.7, 11.4 Hz, 1H; $OCHHCH_2$), 3.88 (dd, *J* = 11.4, 4.82 Hz, 1H; $OCHHCH_2$), 4.43 (d, *J* = 10.3 Hz, 1H; OCHHO), 4.90 (br, 1H; $CH_2CHCH{=}CH_2$), 5.14 (dd, *J* = 16.9, 1.38 Hz, 1H; CH=CHH), 5.29 (dd, *J* = 11.7, 1.38 Hz, 1H; CH=CHH), 5.39 (d, *J* = 7.57 Hz, 1H; OCHHO), 5.82 (ddd, *J* = 17.6, 10.7, 4.13 Hz, 1H; $CH{=}CH_2$); ^{13}C NMR ($CDCl_3$) δ 31.8, 66.4, 76.9, 93.6, 115.6, 137.7; HRMS (ESI) calcd for $C_6H_{10}NaO_2$ $[M+Na]^+$ 137.0578, found 137.0574; $[\alpha]_D^{23}$=–11.4 (*c*=0.759 in $CHCl_3$); *R*:*S* = 4:96 (GC conditions: CHIRALDEX G-BP column (0.25 mm x 0.125 mm x 30 m); 40 °C, 40 °C/min to 100 °C; t_R = 5.1 min (*R*) and 5.3 min (*S*)). **Figure S9** and **S10** showed the ^{1}H- and ^{13}C-NMR spectra and GC charts, respectively.

Abs confign was determined by comparison of the optical rotation of pent-4-ene-1,3-diol (**17**), which was obtained by hydrolysis of the 1,3-O,O module.

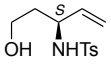


17

4-Ethenyl-1,3-dioxane (1,3-O,O module) (30.8 mg, 0.270 mmol) was dissolved in 74:1 CH_3OH–H_2O (1.5 mL), and the solution was transferred to a 20-mL Young-type Schlenk tube. To this was added $HONH_2$·HCl (188 mg, 2.70 mmol). After being stirred at 80 °C for 18 h, the whole mixture was concentrated to give the crude compound. This was purified by SiO_2-chromatography (SiO_2, 5 g; hexane–EtOAc 1:1 eluent) to give pent-4-en-1,3-diol (20.3 mg, 73%): ^{1}H NMR ($CDCl_3$) δ 1.74–1.87 (m, 2H; CH_2CH_2CH), 2.19 (br, 1H; OH), 2.30 (br, 1H; OH), 3.82–3.92 (m, 2H; OCH_2CH_2), 4.39–4.43 (br, 1H; CH_2CHCH), 5.15 (d, *J* = 11.0 Hz, 1H; CH=CHH), 5.29 (d, *J* = 17.2 Hz, 1H; CH=CHH), 5.91 (ddd, *J* = 17.0, 11.0, 6.20 Hz, 1H; $CH{=}CH_2$). **Figure S11** showed the ^{1}H-NMR spectrum. The spectrum was consistent with the reported one.[30] Comparison of the $[\alpha]_D$ value determined the abs confign to be *S* ($[\alpha]_D^{27}$=–11.0 (*c*=1.0 in CH_3OH); $[\alpha]_D$=–11 (*c*=1 in CH_3OH) for *S*[30]).

1,3-O,N module. Reaction (10 mol% (*R*)-**1**): (*E*)-pent-2-ene-1,5-diol (**6**) (204 mg, 2.00 mmol), *N*-Boc-aminomethanol (**4**) (589 mg, 4.00 mmol), DMA (20.0 mL), $[CpRu(CH_3CN)_3]PF_6$ (20.0 mL of 10.0 mM CH_2Cl_2 solution, 200 μmol), (*R*)-Cl-Naph-PyCOOAll (20.0 mL of 10.0 mM CH_2Cl_2 solution, 200 μmol), 100 °C, 3 h. Work up: partition between H_2O (50 mL) and pentane (20 mL); extraction of aq layer with pentane (20 mL x 3); washing of the combined organic layers with H_2O (30 mL); dryness over Na_2SO_4 (ca. 3 g); filtration/evaporation. Purification: SiO_2-chromatography (SiO_2, 5 g; pentane–Et_2O 8:2 eluent). Product: *N*-Boc-4-ethenyl-1,3-oxazinane (1,3-O,N module) (368 mg, 86%). Physical property: ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.47 (s, 9H; $C(CH_3)_3$), 1.61 (d, *J* = 13.1 Hz, 1H; CH_2CHHCH), 2.18 (ddd, *J* = 19.1, 13.1, 6.20 Hz, 1H; CH_2CHHCH), 3.71 (dd, *J* = 11.7, 11.4 Hz, 1H; $OCHHCH_2$), 3.88 (dd, *J* = 11.4, 4.82 Hz, 1H; $OCHHCH_2$), 4.43 (d, *J* = 10.3 Hz, 1H; OCHHN), 4.90 (br, 1H; $CH_2CHCH{=}CH_2$), 5.14 (dd, *J* = 16.9, 1.38 Hz, 1H; CH=CHH), 5.29 (dd, *J* = 11.7, 1.38 Hz, 1H; CH=CHH), 5.39 (d, *J* = 7.57 Hz, 1H; OCHHN), 5.82 (ddd, *J* = 17.6, 10.7, 4.13 Hz, 1H; $CH{=}CH_2$); ^{13}C NMR ($CDCl_3$, 60 °C) δ 28.4, 28.6, 50.7, 63.5, 72.7, 80.3, 116.5, 136.2, 154.1; HRMS (ESI) calcd for $C_{11}H_{19}NNaO_3$ $[M+Na]^+$ 236.1263, found 236.1263; $[\alpha]_D^{21}$=–44.2 (*c*=0.434 in $CHCl_3$); *R*:*S* = 2:98 (GC conditions: CP-CHIRASIL-DEX CB column (0.25 mm x 0.25 mm x 25 m); 40 °C, 10 °C/min to 150 °C; t_R = 23.0 min (*R*) and 23.9 min (*S*)). **Figure S12** and **S13** showed the ^{1}H- and ^{13}C-NMR spectra and GC charts, respectively.

Abs confign was determined by comparison of the optical rotation of *N*-(5-hydroxypent-1-en-3-yl)-4-methylbenzenesulfonamide (**18**), which was obtained by deprotection of the 1,3-O,N module followed by *N*-Ts protection.



18

Process (i): Reaction: *N*-Boc-4-ethenyl-1,3-oxazinane (1,3-O,N module) (146 mg, 685 μmol), 74:1 CH_3OH–H_2O (7.0 mL), $HONH_2$·HCl (476 mg, 6.85 mmol), 80 °C, 10 h. After the reaction mixture was cooled to rt, sat aq K_2CO_3 (5 mL) was added. Filtration/evaporation afforded a nearly pure 3-aminopent-4-en-1-ol (47.6 mg, 69% yield) as an oil, which was used for the next reaction without further purification.

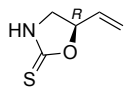
Process (ii): The amine compound (10.0 mg, 98.9 μmol) dissolved in CH_2Cl_2 (1 mL) was transferred to a 5-mL Young-type Schlenk tube. The solution was cooled to 0 °C, and to this was added TsCl (18.8 mg, 98.9 μmol) and pyridine (8.8 μL, 109 μmol). After 24-h stirring at rt, the whole mixture was concentrated in vacuo. The residue was partitioned between CH_2Cl_2 (2 mL) and H_2O (2 mL), and the aq layer was extracted with CH_2Cl_2 (2 mL x 2). Combined organic layers were washed with 1 M aq HCl (2 mL), sat aq $NaHCO_3$ (2 mL), and dried over Na_2SO_4 (ca. 1 g). Filtration/evaporation afforded a pale yellow oil (ca. 49 mg), which was purified by SiO_2-chromatography (SiO_2, 10 g; hexane–EtOAc 2:1 to 1:1 eluent) to give *N*-(5-hydroxypent-1-en-3-yl)-4-methylbenzenesulfonamide (**18**) (2.78 mg, 11% yield) as a pale yellow oil: ^{1}H NMR ($CDCl_3$) δ 1.53–1.58 (m, 1H; $CHHCH_2OH$), 1.79–1.85 (m, 1H; $CHHCH_2OH$), 2.10 (br, 1H; OH), 2.43 (s, 3H; CH_3), 3.68 (br, 1H; CHHOH), 3.88 (t, *J* = 10.33 Hz, 1H; CHHOH), 3.99–4.02 (m, 1H; NHCHCH), 4.90 (br, 1H; NH), 4.97 (d, *J* = 8.95 Hz, 1H; CH=CHH), 4.98 (d, *J* = 17.21 Hz, 1H; CH=CHH), 5.57 (ddd, *J* = 16.87, 10.33, 5.51 Hz, 1H; $CH{=}CH_2$)), 7.29 (d, *J* = 8.26 Hz, 2H; ArH), 7.75 (d, *J* = 8.26 Hz, 2H; ArH). **Figure S14** showed the ^{1}H-NMR spectrum. The spectrum was consistent with the reported one.[31] Comparison of the $[\alpha]_D$ value determined the abs confign to be *S* ($[\alpha]_D^{18}$=+20.9 (*c*=0.014 in $CHCl_3$); $[\alpha]_D^{31.2}$=+22.94 (*c*=0.017 in $CDCl_3$) for *S*[31]).

Reaction (1 mol% (R)-1). (*E*)-Pent-2-ene-1,5-diol (**6**) (235 mg, 2.28 mmol), *N*-Boc-aminomethanol (**4**) (673 mg, 4.56 mmol), DMA (22.8 mL), $[CpRu(CH_3CN)_3]PF_6$ (2.28 mL of 10.0 mM

CH_2Cl_2 solution, 22.8 μmol), (*R*)-Cl-Naph-PyCOOAll (2.28 mL of 10.0 mM CH_2Cl_2 solution, 22.8 μmol), 100 °C, 3 h. Work up: partition between H_2O (100 mL) and pentane (30 mL); extraction of aq layer with pentane (30 mL x 3); washing of the combined organic layers with H_2O (30 mL); dryness over Na_2SO_4 (ca. 5 g); filtration/evaporation. Purification: SiO_2-chromatography (SiO_2, 10 g; pentane–Et_2O 8:2 eluent). Product: *N*-Boc-4-ethenyl-1,3-oxadinane (1,3-O,N module) (224 mg, 46%); *R*:*S* = 25:75.

1,2-N,O module. (*E*)-*N*-Boc-4-aminobut-2-en-1-ol (**7**) (214 mg, 1.14 mmol), 37% formalin (856 μL, 11.4 mmol), DMA (11.4 mL), $[CpRu(CH_3CN)_3]PF_6$ (1.14 mL of 10.0 mM CH_2Cl_2 solution, 11.4 μmol), (*R*)-Cl-Naph-PyCOOAll (1.14 mL of 10.0 mM CH_2Cl_2 solution, 11.4 μmol), 100 °C, 3 h. Work up: partition between H_2O (50 mL) and pentane (30 mL); extraction of aq layer with pentane (20 mL x 4); washing of the combined organic layers with H_2O (50 mL); dryness over Na_2SO_4 (ca. 5 g); filtration/evaporation. Purification: SiO_2-chromatography (SiO_2, 5 g; pentane–Et_2O 9:1 eluent). Product: *N*-Boc-5-ethenyloxazolidine (1,2-N,O module) (207 mg, 91%). Physical property: ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.47 (s, 9H; $C(CH_3)_3$), 3.16 (dd, *J* = 8.95, 8.61 Hz, 1H; NC*H*HCH), 3.62 (dd, *J* = 9.64, 6.20 Hz, 1H; NCH*H*CH), 4.49 (ddd, *J* = 6.89, 6.54, 6.20 Hz, 1H; C*H*CH=CH_2), 4.78 (d, *J* = 3.44 Hz, 1H; NC*H*HO), 4.96 (br, 1H; NCH*H*O), 5.25 (d, *J* = 9.64 Hz, 1H; CH=C*H*H), 5.36 (d, *J* = 17.2 Hz, 1H; CH=CH*H*), 5.87 (ddd, *J* = 17.0, 10.3, 6.20 Hz, 1H; C*H*=CH_2); ^{13}C NMR ($CDCl_3$, 60 °C) δ 28.5, 48.9, 78.5, 78.9, 80.3, 118.0, 135.0, 153.0; HRMS (ESI) calcd for $C_{10}H_{17}NNaO_3$ $[M+Na]^+$ 222.1106, found 222.1105; $[\alpha]_D^{21}$=–55.87 (*c*=0.38 in $CHCl_3$); *R*:*S* = 96:4 (HPLC conditions: CHIRALCEL IA-3 column (0.46 cm ϕ x 250 mm); hexane–*i*PrOH 99.9:0.1 eluent; 1.00 mL/min flow rate; 210-nm light detection; t_R = 11.5 min (*R*), 12.5 min (*S*)). **Figure S15** and **S16** showed the ^{1}H- and ^{13}C-NMR spectra and HPLC charts, respectively.

Abs confign was determined by comparison of the optical rotation of 5-ethenyloxazolidine-2-thione (**19**), which was obtained by deprotection of the 1,2-N,O module followed by thiocarbonylation.



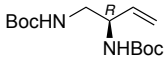
19

Process (i): Reaction: *N*-Boc-5-ethenyl-1,3-oxazolidine (1,2-N,O module) (50.1 mg, 251 μmol), 74:1 CH_3OH–H_2O (2.5 mL), $HONH_2$·HCl (175 mg, 2.52 mmol), 80 °C, 12 h. After being cooled to rt, sat aq K_2CO_3 (3 mL) was added. Filtration/evaporation afforded a white solid (ca. 200 mg), which was partitioned between CH_2Cl_2 (2 mL) and H_2O (2 mL). The aq layer was extracted with CH_2Cl_2 (2 mL x 10), and the combined organic layers were dried over Na_2SO_4 (ca. 1 g). Filtration/evaporation afforded a pale yellow solid (ca. 17 mg). This was used for the next reaction without further purification.

Process (ii): The crude amine compound (ca. 17 mg), TCDI (34.0 mg, 191 μmol), and THF (1.9 mL) were placed in a 5-mL Young-type Schlenk tube. After 15-h stirring at rt, the mixture was concentrated in vacuo. The residue was purified by SiO_2-chromatography (SiO_2, 2 g; hexane–EtOAc 2:1 eluent) to give 5-ethenyloxazolidine-2-thione (19) (13.7 mg, 42% yield) as a white solid: ^{1}H NMR ($CDCl_3$) δ 3.53 (t, *J* = 8.26 Hz, 1H; C*H*HCHCH), 3.93 (t, *J* = 8.95 Hz, 1H; CH*H*CHCH), 5.34 (q, *J* = 8.26 Hz, 1H; OC*H*CH), 5.41 (d, *J* = 10.33 Hz, 1H; CH=C*H*H), 5.47 (d, *J* = 17.21 Hz, 1H; CH=CH*H*), 5.96 (ddd, *J* =17.21, 10.33, 6.89 Hz, 1H; C*H*=CH_2), 7.39 (br, 1H; NH). **Figure S17** showed the ^{1}H-NMR spectrum. The spectrum was consistent with the reported one.[32] Comparison of the $[\alpha]_D$ value determined the abs confign to be *R* ($[\alpha]_D^{21}$=+66.8 (*c*=0.68 in $CDCl_3$); $[\alpha]_D^{23.1}$=+71 (*c*=1 in $CDCl_3$) for *R*[32]).

1,2-N,N module. (*E*)-*N*-Boc-4-aminobut-2-en-1-ol (**7**) (214 mg, 1.14 mmol), *N*-Boc-aminomethanol (**4**) (336 mg, 2.28 mmol), DMA (11.4 mL), $[CpRu(CH_3CN)_3]PF_6$ (1.14 mL of 10.0 mM CH_2Cl_2 solution, 11.4 μmol), (*R*)-Cl-Naph-PyCOOAll (1.14 mL of 10.0 mM CH_2Cl_2 solution, 11.4 μmol), 100 °C, 3 h. Work up: partition between H_2O (50 mL) and pentane (30 mL); extraction of the aq layer with pentane (20 mL x 4); washing of the combined organic layers with H_2O (50 mL); dryness over Na_2SO_4 (ca. 5 g); filtration/evaporation. Purification: SiO_2-chromatography (SiO_2, 10 g; pentane–Et_2O 9:1 eluent). Product: *N*,*N*'-diBoc-3-ethenylimidazolidine (1,2-N,N module) (313 mg, 92%). Physical property: ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.46 (s, 9H; $C(CH_3)_3$), 3.51 (d, *J* = 9.64 Hz, 1H; NC*H*HCH), 3.60 (dd, *J* = 10.7, 6.89 Hz, 1H; NCH*H*CH), 4.47 (br, 1H; C*H*CH=CH_2), 4.66 (d, *J* = 6.89 Hz, 1H; NC*H*HN), 4.73 (d, *J* = 6.89 Hz, 1H; NCH*H*N), 5.14 (d, *J* = 11.0 Hz, 1H; CH=C*H*H), 5.17 (d, *J* = 19.3 Hz, 1H; CH=CH*H*), 5.78 (ddd, *J* = 17.0, 10.7, 6.20 Hz, 1H; C*H*=CH_2); ^{13}C NMR ($CDCl_3$, 60 °C) δ 28.4, 49.7, 57.5, 60.2, 80.48, 80.51, 115.7, 136.2, 152.9, 153.4; HRMS (ESI) calcd for $C_{15}H_{26}N_2NaO_4$ $[M+Na]^+$ 321.1790, found 321.1788; $[\alpha]_D^{21}$=+14.0 (*c*=0.288 in $CHCl_3$); *R*:*S* = 99:1 (HPLC conditions: CHIRALCEL OD-H column (0.46 cm ϕ x 250 mm); hexane–*i*PrOH 99.9:0.1 eluent; 1.00 mL/min flow rate; 210-nm light detection; t_R = 16.2 min (*R*), 17.1 min (*S*)). **Figure S18** and **S19** showed the ^{1}H- and ^{13}C-NMR spectra and HPLC charts, respectively.

Abs confign was determined by comparison of the optical rotation of *N*,*N*'-diBoc-but-3-ene-1,2-diamine (**20**), which was obtained by deprotection of the 1,2-N,N module followed by Boc protection.



20

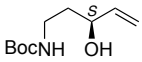
Process (i): Reaction: *N*,*N*'-diBoc-4-ethenylimidazolidine (1,2-N,N module) (30 mg, 100 μmol), 74:1 CH_3OH–H_2O (600 μL), $HONH_2$·HCl (69.5 mg, 1.00 mmol), 80 °C, 48 h. After being cooled to rt, sat aq $NaHCO_3$ (2 mL) was added. The mixture was, concentrated, and the remained solid was washed with EtOH (5 mL x 2). The washings were filtered and concentrated to give a crude but-3-ene-1,2-diamine (ca. 32 mg) as a brown solid. This was used for the next reaction without purification.

Process (ii): The crude product (ca. 32 mg) dissolved in EtOH (1 mL), $N(C_2H_5)_3$ (31 μL, 220 μmol), and Boc_2O (48 μL, 210 μmol) were charged into a 5-mL Young-type Schlenk tube. The mixture was stirred at rt for 24 h, and concentrated. The residue was partitioned between CH_2Cl_2 (2 mL) and H_2O (2 mL), and the aq layer was extracted with CH_2Cl_2 (2 mL x 2). The combined organic layers were washed with 1 M aq HCl (2 mL) and dried over Na_2SO_4 (ca. 1 g). Filtration/evaporation afforded the crude diBoc product (ca. 26 mg), which was purified by SiO_2-chromatograpy (SiO_2, 1.5 g; hexane–EtOAc 10:1 then 3:1 eluent) to give *N*,*N*'-diBoc-but-3-ene-1,2-diamine (**20**) (8.6 mg, 30% yield) as a white solid: ^{1}H NMR (DMSO-d_6, 80 °C) δ 1.389 (s, 9H; $C(CH_3)_3$), 1.392 (s, 9H; $C(CH_3)_3$), 3.02 (t, *J* = 6.20 Hz, 2H; NHCH_2), 4.04 (q, *J* = 6.20 Hz, 1H; NHC*H*CH), 5.05 (dt, *J* = 10.33, 1.38 Hz, 1H; CH=C*H*H), 5.11 (dt, *J* = 17.90, 2.07 Hz, 1H; CH=CH*H*), 5.74 (ddd, *J* = 17.04, 10.67, 6.20 Hz, 1H; C*H*=CH_2), 6.42 (br, 2H; NH). **Figure S20** showed the ^{1}H-NMR spectrum. The spectrum was consistent with the reported one.[33] Comparison of the $[\alpha]_D$ value determined the abs confign to be *R*

($[\alpha]_D^{19}$=+26.0 (*c*=0.43 in $CHCl_3$); $[\alpha]_D^{24.9}$=+26.2 (*c*=1.09 in $CDCl_3$) for *R*[33]).

1,3-N,O module. *N*-Boc-5-aminopent-2-en-1-ol (**8**) (230 mg, 1.14 mmol), 37% formalin (856 μL, 11.4 mmol), DMA (11.4 mL), $[CpRu(CH_3CN)_3]PF_6$ (1.14 mL of 10.0 mM CH_2Cl_2 solution, 11.4 μmol), (*R*)-Cl-Naph-PyCOOAll (1.14 mL of 10.0 mM CH_2Cl_2 solution, 11.4 μmol), 100 °C, 3 h. Work up: partition between H_2O (50 mL) and pentane (30 mL); extraction of the aq layer with pentane (20 mL x 4); washing of the combined organic layers with H_2O (50 mL); dryness over Na_2SO_4 (ca. 5 g); filtration/evaporation. Purification: SiO_2-chromatography (SiO_2, 5 g; pentane–Et_2O 9:1 eluent). Product: 6-ethenyl-1,3-oxadinane (1,3-N,O module) (219 mg, 90%). Physical property: ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.47 (s, 9H; $C(CH_3)_3$), 1.57–1.67 (m, 2H; NCH_2CH_2), 3.02 (br, 1H; NC*H*HCH_2), 4.00 (br, 1H; C*H*$CH=CH_2$), 4.18 (br, 1H; NCH*H*CH_2), 4.36 (d, *J* = 10.3 Hz, 1H; NC*H*HO), 5.14 (d, *J* = 11.0 Hz, 1H; CH=C*H*H), 5.26 (d, *J* = 17.2 Hz, 1H; CH=CH*H*), 5.54 (br, 1H; NCH*H*O), 5.84 (ddd, *J* = 17.0, 11.0, 6.20 Hz, 1H; C*H*$=CH_2$); ^{13}C NMR ($CDCl_3$, 60 °C) δ 28.4, 31.0, 42.4, 76.2, 77.8, 80.3, 115.5, 138.0, 154.0; HRMS (ESI) calcd for $C_{11}H_{19}NNaO_3$ $[M+Na]^+$ 236.1263, found 236.1264; $[\alpha]_D^{21}$=–31.3 (*c*=0.56 in $CHCl_3$); *R*:*S* = 6:94 (GC conditions: CP-CHIRASIL-DEX CB column (0.25 mm x 0.25 mm x 25 m); 40 °C, 10 °C/min to 150 °C; t_R = 24.1 min (*R*), 24.2 min (*S*)). **Figure S21** and **S22** showed the ^{1}H- and ^{13}C-NMR spectra and GC charts, respectively.

Abs confign was determined by comparison of the optical rotation of *N*-Boc-1-aminopent-4-en-3-ol (**21**), which was obtained by acidic hydrolysis of the 1,3-N,O module followed by *N*-Boc protection.



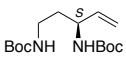
21

Process (i): A 5-mL Young-type Schlenk tube was charged with *N*-Boc-6-ethenyl-1,3-oxazinane (1,3-N,O module) (32.4 mg, 152 μmol) dissolved in CH_3OH (4.40 mL) and 12 M aq HCl (220 μL). After being stirred at rt for 12 h, the reaction mixture was concentrated to give a crude 1-aminopent-4-en-3-ol hydrochloride (20.9 mg) as an oil. This was used for the next reaction without further purification.

Process (ii): Reaction: 5-aminopent-1-en-3-ol hydrochloride (20.9 mg, 152 μmol), Boc_2O (42.0 μL, 39.9 mg, 183 μmol), $N(C_2H_5)_3$ (53.0 μL, 38.5 mg, 378 μmol) and EtOH (900 μL). Work up: concentration. Purification: SiO_2-chromatography (SiO_2, 5 g; hexane–EtOAc 8:2 eluent). Product: (3-hydroxypent-4-en-1-yl)carbamate (**21**) (26 mg, 86%): ^{1}H NMR ($CDCl_3$) δ 1.45 (s, 9H; $C(CH_3)_3$), 1.59–1.64 (m, 1H; CH_2CHHCH), 1.67–1.74 (m, 1H; CH_2CHHCH), 2.91 (br, 1H; OH), 3.12–3.19 (m, 1H; NCH*H*CH_2), 3.41–3.49 (m, 1H; NCH*H*CH_2), 4.19 (br, 1H; HOC*H*), 4.84 (br, 1H; NH), 5.12 (d, *J* = 10.3 Hz, 1H; CH=C*H*H), 5.27 (d, *J* = 17.2 Hz, 1H; CH=CH*H*), 5.90 (ddd, *J* = 17.2, 10.3, 6.2 Hz, 1H; C*H*$=CH_2$). **Figure S23** showed the ^{1}H-NMR spectrum. The spectrum was consistent with the reported one.[34] Comparison of the $[\alpha]_D$ value determined the abs confign to be *S* ($[\alpha]_D^{23}$=+8.64 (*c*=1.00 in $CHCl_3$); $[\alpha]_D^{23}$=+8.62 (*c*=1.01 in $CHCl_3$) for *S*[34]).

1,3-N,N module. Reaction (10 mol% (*R*)-**1**): (*E*)-*N*-Boc-5-aminopent-2-en-1-ol (**8**) (201 mg, 1.00 mmol), *N*-Boc-aminomethanol (**4**) (294 mg, 2.00 mmol), DMA (10.0 mL), $[CpRu(CH_3CN)_3]PF_6$ (10.0 mL of 10.0 mM CH_2Cl_2 solution, 100 μmol), (*R*)-Cl-Naph-PyCOOAll (10.0 mL of 10.0 mM CH_2Cl_2 solution, 100 μmol), 100 °C, 3 h. Work up: partition between H_2O (30 mL) and pentane (20 mL); extraction of the aq layer with pentane (20 mL x 4); washing with H_2O (30 mL); dryness over Na_2SO_4 (ca. 2 g); filtration/evaporation. Purification: SiO_2-chromatography (SiO_2, 5 g; pentane–Et_2O 9:1 eluent). Product: *N*,*N*'-diBoc-4-ethenylhexahydropyrimidine (1,3-N,N module) (275 mg, 88%). Physical property: ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.47 (s, 9H; $C(CH_3)_3$), 1.69 (ddd, *J* = 13.9, 7.57, 4.13 Hz, 1H; CH_2CHHCH), 1.97 (ddd, *J* = 18.6, 12.4, 6.20 Hz, 1H; CH_2CHHCH), 3.12 (dd, *J* = 12.4, 11.7 Hz, 1H; NC*H*HCH_2), 3.78 (br, 1H; NCH*H*CH_2), 4.10 (d, *J* = 13.1 Hz, 1H; NC*H*HN), 4.76 (br, 1H; $CH_2CHCH=CH_2$), 5.12 (d, *J* = 17.2 Hz, 1H; CH=C*H*H), 5.22 (d, *J* = 11.7 Hz, 1H; CH=CH*H*), 5.72 (d, *J* = 13.1 Hz, 1H; NCH*H*N), 5.78 (ddd, *J* = 17.4, 10.7, 4.13 Hz, 1H; C*H*$=CH_2$); ^{13}C NMR ($CDCl_3$, 60 °C) δ 27.8, 28.41, 28.44, 39.4, 51.8, 53.0, 80.1, 80.3, 116.1, 136.3, 154.2; HRMS (ESI) calcd for $C_{16}H_{29}N_2O_4$ $[M+H]^+$ 313.2127, found 313.2120; $[\alpha]_D^{21}$=–15.5 (*c*=0.288 in $CHCl_3$); *R*:*S* = 1:99 (HPLC conditions: CHIRALCEL ID-3 column (0.46 cm ϕ x 250 mm); hexane–*i*PrOH 99.9:0.1 eluent; 1.00 mL/min flow rate; 210-nm light detection; t_R = 15.0 min (*S*), 17.0 min (*R*)). **Figure S24** and **S25** showed the ^{1}H- and ^{13}C-NMR spectra and HPLC charts, respectively.

The 1,3-N,N module was converted to *N*,*N*'-diBoc-pent-4-ene-1,3-diamine (**22**). The authentic sample was synthesized from (*S*)-3-aminopent-4-en-1-ol obtained in determination of the abs confign of 1,3-O,N module. Comparison of the optical rotation determined the abs confgn to be *S*. The procedures were described below.



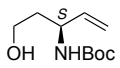
22

Process (i): Reaction: *N*,*N*'-diBoc-4-ethenylhexahydropyrimidine (1,3-N,N module) (30.0 mg, 96.0 μmol), 74:1 CH_3OH–H_2O (600 μL), $HONH_2$·HCl (66.7 mg, 960 μmol), 80 °C, 48 h. After being cooled to rt, sat aq $NaHCO_3$ (2 mL) was added. The mixture was filtered and concentrated. The remained solid was washed with EtOH (5 mL x 2), and the washing was filtered and concentrated. The crude product (ca. 30 mg) was used for the next reaction without further purification.

Process (ii): Reaction: the crude amine compound (ca. 30 mg), Boc_2O (43.7 mg, 202 μmol), $N(C_2H_5)_3$ (29 μL, 211 μmol), EtOH (1 mL), rt, 24 h. Work up: partition between CH_2Cl_2 (2 mL) and H_2O (2 mL); extraction of aq layer with CH_2Cl_2 (2 mL x 2); washing with 1 M aq HCl (2 mL) and brine (2 mL); dryness over Na_2SO_4 (ca. 1 g); filtration/evaporation. Purification: SiO_2-chromatography (SiO_2, 2.5 g; hexane–EtOAc 10:1 to 3:1 eluent). Product: *N*,*N*'-diBoc-pent-4-ene-1,3-diamine (22) (10.4 mg, 36% yield) as a white solid: ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.45 (s, 1H; $C(CH_3)_3$), 1.46 (s, 1H; $C(CH_3)_3$), 1.51–1.60 (m, 1H; CH_2CHHCH), 1.80 (dq, *J* = 13.08, 6.89 Hz, 1H; CH_2CHHCH), 3.05 (dq, *J* = 14.12, 7.57 Hz, 1H; NHC*H*HCH_2), 3.27–3.36 (br, 1H; NHCH*H*CH_2), 4.19 (br, 1H; NHC*H*CH), 4.45 (br, 1H; N*H*CHCH), 4.87 (br, 1H; N*H*CH_2CH_2), 5.11 (d, *J* = 11.02 Hz, 1H; CH=C*H*H), 5.19 (d, *J* = 17.21 Hz, 1H; CH=CH*H*), 5.79 (ddd, *J* = 17.04, 11.02, 5.51 Hz, 1H; C*H*$=CH_2$)); ^{13}C NMR ($CDCl_3$) δ 28.4, 28.5, 35.7, 37.4, 50.6, 79.2, 79.6, 114.8, 138.6, 155.7, 156.0; HRMS (ESI) calcd for $C_{15}H_{28}N_2O_4Na$ $[M+Na]^+$ 323.1947, found 323.1953; $[\alpha]_D^{19}$=–33.2 (*c*=0.15 in $CHCl_3$). **Figure S26** showed the ^{1}H- and ^{13}C-NMR spectra.

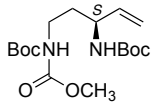
*Synthesis of authentic (S)-N,N'-diBoc-pent-4-ene-1,3-diamine ((S)-**22**) from (S)-3-aminopent-4-en-1-ol.* Reaction: the abs confign-determined (*S*)-3-aminopent-4-en-1-ol (20.0 mg, 198 μmol) obtained from 1,3-O,N module, Boc_2O (51.8 mg, 237 μmol), $N(C_2H_5)_3$ (33.1 μL, 237 μmol), EtOH (1 mL), rt, 18 h.

Work up: partition between CH_2Cl_2 (2 mL) and H_2O (2 mL); extraction of aq layer with CH_2Cl_2 (2 mL x 2); washing with 1 M aq HCl (2 mL); dryness over Na_2SO_4 (ca. 1 g); filtration/evaporation. Purification: SiO_2-chromatography (SiO_2, 10 g; hexane–EtOAc 1:3 eluent). Product: *N*-Boc-3-aminopent-4-en-1-ol (**23**) (34.6 mg, 87% yield) as a yellow oil.



23

Compound **23** (20.1 mg, 99.4 μmol) charged into a 5-mL Young-type Schlenk tube was dissolved in THF (500 μL). To this was added PPh_3 (31.3 mg, 119 μmol) and *tert*-butyl methyl iminodicarboxylate (20.9 mg, 119 μmol). To this was added DIAD (62.6 μL, 119 μmol; 1.9 M toluene). After 16-h stirring at 50 °C, the reaction mixture was concentrated in vacuo. The residue was purified by SiO_2-chromatography (SiO_2, 10 g; hexane–EtOAc 8:1 eluent) to give *tert*-butyl (3-((*tert*-butoxycarbonyl)amino)pent-4-en-1-yl)(methoxycarbonyl)carbamate (**24**) (24.7 mg, 66% yield) as colorless oil.



24

Compound **24** (12.0 mg, 33.5 μmol), 1 M aq NaOH (200 μL), EtOH (200 μL), and 1,4-dioxane (200 μL) were placed in a 5-mL Young-type Schlenk tube. After 4-h stirring at rt, the reaction mixture was concentrated in vacuo and the residue was partitioned between EtOAc (2 mL) and H_2O (2 mL). The aq layer was extracted with EtOAc (2 mL x 2), and the combined organic layers were washed with brine (2 mL), and dried over Na_2SO_4 (ca. 1 g). Filtration/evaporation afforded a pale yellow oil (ca. 16 mg), which was purified by SiO_2-chromatography (SiO_2, 2.5 g; hexane–EtOAc 3:1 eluent) to give *N*,*N*'-diBoc-pent-4-ene-1,3-diamine (**22**) (6.0 mg, 60% yield) as a white solid: $[\alpha]_D^{21}$=–31.7 (*c*=0.16 in $CHCl_3$). The sign of the optical rotation was identical with that of *N*,*N*'-diBoc-pent-4-ene-1,3-diamine (**22**) derived from (*R*)-**1**-catalyzed allylation product, determining the abs config of the 1,3-N,N module to be *S*.

*Reaction (1 mol% (R)-**1**).* *N*-Boc-5-aminopent-2-en-1-ol (**8**) (230 mg, 1.14 mmol), *N*-Boc-aminomethanol (**4**) (336 mg, 1.14 mmol), DMA (11.4 mL), $[CpRu(CH_3CN)_3]PF_6$ (1.14 mL of 10.0 mM CH_2Cl_2 solution, 11.4 μmol), (*R*)-Cl-Naph-PyCOOAll (1.14 mL of 10.0 mM CH_2Cl_2 solution, 11.4 μmol), 100 °C, 3 h. Work up: partition between H_2O (50 mL) and pentane (30 mL); extraction of the aq layer with pentane (30 mL x 3); washing of the combined organic layers with H_2O (30 mL); dryness over Na_2SO_4 (ca. 5 g); filtration/evaporation. Purification: SiO_2-chromatography (SiO_2, 10 g; pentane–Et_2O 9:1 eluent). Product: *N*,*N*'-diBoc-4-ethenylhexahydropyrimidine (1,3-N,N module) (160 mg, 45%); *R*:*S* = 7:93.

(7) Synthesis of sphingosine.

Olefin metathesis. A 80-mL Schlenk tube was charged with 1,2-O,N module (**5**) (309 mg, 1.55 mmol) dissolved in acetone (15.5 mL) and (*Z*)-but-2-ene-1,4-diol (1.28 mL, 15.6 mmol). The solution was degassed by three freeze-thaw cycles, and HG II (29.2 mg, 46.6 μmol) was added. After being stirred at rt for 4 h, a portion of the reaction mixture (ca. 100 μL) was taken and evaporated to give a pale yellow oil. This was subjected to the ^{1}H NMR analysis ($CDCl_3$), determining that the conversion was 79% and the *E*/*Z* ratio of the product was 95:5. The whole reaction mixture was concentrated and passed through a pad of silica gel (SiO_2, 15 g; hexane–EtOAc 2:1 eluent) to give a reddish crude product (ca. 300 mg). This was dissolved in CH_2Cl_2 (10 mL), and Quadrasil^{TM} AP (1.0 g) was added to the pale red solution. After being stood at rt for 8 h, the mixture was filtered and concentrated. SiO_2-chromatograpy of the residue (SiO_2, 25 g; hexane–THF 4:1 eluent) afforded the allylic alcohol **10** (233 mg, 65%): ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.45 (s, 9H; $C(CH_3)_3$), 2.12 (br, 1H; OH), 3.74 (dd, *J* = 8.95, 4.82 Hz, 1H; OC*H*HCH), 4.09 (dd, *J* = 8.26, 6.89 Hz, 1H; OCH*H*CH), 4.13 (br, 2H; CH=CHCH_2OH), 4.34 (br, 1H; C*H*CH=CH), 4.75 (d, *J* = 4.13 Hz, 1H; OC*H*HN), 4.95 (d, *J* = 2.75 Hz, 1H; OCH*H*N), 5.65 (dd, *J* = 15.8, 6.89 Hz, 1H; C*H*=CH), 5.83 (dt, *J* = 15.8, 4.82 Hz, 1H; CH=C*H*); ^{13}C NMR ($CDCl_3$, ca. 100 mM, 60 °C) δ 28.4, 56.8, 62.5, 72.5, 79.1, 80.3, 128.8, 131.9, 152.9; HRMS (ESI) calcd for $C_{11}H_{19}NNaO_4$ $[M+Na]^+$ 252.1212, found 252.1213; $[\alpha]_D^{20}$=–32.5 (*c*=1.02 in $CHCl_3$). The er was determined to be 96.5:3.5 by HPLC analysis (conditions: CHIRALPAK IA-3 column (0.46 cm ϕ x 250 mm); hexane–*i*PrOH 95:5 eluent; 1.00 mL/min flow rate; 210-nm light detection; t_R = 16.0 min (*S*), 18.3 min (*R*)). **Figure S27** and **S28** showed the ^{1}H- and ^{13}C-NMR spectra and HPLC charts, respectively.

Methylene-relayed allylation. Two 10-mM CH_2Cl_2 solutions of $[CpRu(CH_3CN)_3]PF_6$ (0.660 mL, 6.60 μmol (2.865 mg)) and (*R*)-Cl-Naph-PyCOOAll (0.660 mL, 6.60 μmol (2.23 mg))) were charged in a 20-mL Young-type Schlenk tube, and concentrated. To this was added a DMA solution (2.00 mL) of the allylic alcohol **10** (46.7 mg, 0.204 mmol) and H_2O (225 μL, 12.5 mmol). The mixture was heated to 100 °C under Ar, and then the whole system was sealed. After being stirred at 100 °C for 15 h, the yellow-colored mixture was cooled to rt. A portion of the mixture (ca. 0.2 mL) was taken and diluted with $CDCl_3$ (ca. 1 mL). The ^{1}H-NMR analysis determined the conversion to be 78%. The whole reaction solution was partitioned with Et_2O (2 mL) and H_2O (5 mL), and the aq layer was extracted by Et_2O (2 mL x 3). The combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give the crude product (ca. 100 mg). This was purified by SiO_2-chromatography (SiO_2, 15 g; hexane–EtOAc 4:1 eluent) to give a 80:20 mixture of **11** with a 97.8:2.2 *RS*/*SR* er and *epi*-**11** with a 97.6:2.4 *RR*/*SS* er (34.6 mg, 74% yield), and (*E*)-**10** with a 93.0:7.0 er was recovered (15% yield). The ways of determination of the **11**/*epi*-**11** diastereomer ratio (dr), the ers of **11** and *epi*-**11**, and the er of the recovered (*E*)-**10** were shown in **Figures S29**, **S30**, and **S31**. For the calculation of catalyst control (CC) and substrate control (SC) in the reaction, a three-digit accuracy was adopted in this particular case (see the next "Quantitative analysis of catalyst control and substrate control").

Pure **11** and *epi*-**11** were obtained by a preparative HPLC of the methylene-relayed product that was obtained in a different batch under the same conditions described above (conditions: Develosil 30-3 (2.0 cm ϕ x 250 mm) column; hexane–*i*PrOH 99:1 eluent; 9.0 mL/min flow rate; 210-nm light detection; t_R = 128.0 min (*epi*-**11**), 134.7 min (**11**); 2.5 mg in 20 μL for each injection x 100 times). **11**: ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.48 (s, 9H; $C(CH_3)_3$), 3.93 (br, 1H; HOC*H*H) 4.00–4.10 (br, 2H; HOCH*H* and CH_2CHCH), 4.31 (br, 1H; CHC*H*CH), 4.69 (d, *J* = 4.13 Hz, 1H; NC*H*HO), 4.94 (br, 1H; NCH*H*O), 5.22 (d, *J* = 11.0 Hz, 1H; CH=C*H*H), 5.36 (d, *J* = 17.2 Hz, 1H; CH=CH*H*), 5.85 (ddd, *J* = 16.9, 11.4, 5.51 Hz, 1H; C*H*=CH_2); ^{13}C NMR ($CDCl_3$, 60 °C) δ 28.4, 60.2, 68.6, 73.2, 80.0, 81.3, 116.7, 136.5, 153.9; HRMS (ESI) calcd for $C_{11}H_{19}NNaO_4$ $[M+Na]^+$ 252.1212, found 252.1215; $[\alpha]_D^{21}$=–43.4 (*c*=0.385 in $CHCl_3$). *epi*-**11**: ^{1}H NMR ($CDCl_3$, 60 °C) δ 1.49 (s, 9H; $C(CH_3)_3$), 3.83 (dd, *J* = 8.61, 4.82 Hz, 1H; HOC*H*H), 3.92 (ddd, *J* = 8.95, 6.89, 4.82 Hz, 1H;

CH_2CHCH), 3.98 (dd, J = 8.95, 6.89 Hz, 1H; HOCHH), 4.19 (dd, J = 6.54, 5.51 Hz, 1H; CHCHCH), 4.68 (d, J = 4.13 Hz, 1H; NCHHO), 4.97 (d, J = 4.82 Hz, 1H; NCHHO), 5.22 (d, J = 10.3 Hz, 1H; CH=CHH), 5.35 (d, J = 16.5 Hz, 1H; CH=CHH), 5.80 (ddd, J = 17.2, 10.3, 6.89 Hz, 1H; CH=CH_2); ^{13}C NMR ($CDCl_3$, 60 °C) δ 28.4, 60.3, 69.0, 75.0, 79.7, 81.6, 117.6, 136.8, 154.6; HRMS (ESI) calcd for $C_{11}H_{19}NNaO_4$ $[M+Na]^+$ 252.1212, found 252.1213; $[\alpha]_D^{20}$=–59.3 (c=0.395 in $CHCl_3$). The ers of **11** and *epi*-**11** were determined to be 97.8:2.2 and 97.6:2.4, respectively, by HPLC analysis (conditions: CHIRALPAK IA-3 column (0.46 cm ϕ x 250 mm); hexane–*i*PrOH 97:3 eluent; 1.00 mL/min flow rate; 210-nm light detection; t_R = 13.5 (2*R*,3*R*), 17.0 min (2*R*,3*S*), 21.1 min (2*S*,3*R*), 32.0 (2*S*,3*S*)). **Figure S32** and **S33** showed the ^{1}H- and ^{13}C-NMR spectra of the pure **11** and *epi*-**11**, respectively.

Quantitative analysis of catalyst control and substrate control. The ratio of the four stereoisomers was calculated to be (*S*,*R*):(*S*,*S*):(*R*,*R*):(*R*,*S*) = 78.2:19.5:0.5:1.8, determining the catalyst control (CC) and the substrate control (SC) to be 1.05 and 3.78, respectively (CC = $[(78.2 \times 0.5)/(19.5 \times 1.8)]^{1/2}$ = 1.05, SC = $[(78.2 \times 1.8)/(19.5 \times 0.5)]^{1/2}$ = 3.78).[13] The 78 part of the substrate (*E*)-**10** with a 96.5:3.5 *R*/*S* er is distributed to the four stereoisomers in 61.0 ((*S*,*R*)-**11**), 15.2 ((*S*,*S*)-**11** (*epi*-**11**)), 0.4 ((*R*,*R*)-**11** (*epi*-**11**)), and 1.4 ((*R*,*S*)-**11**). Therefore, 76.2 part of (*R*)-**10** (61.0 + 15.2) and 1.8 part of (*S*)-**10** (0.4 + 1.4) are transformed to the product **11** and *epi*-**11**. Taking into consideration that the er of **10** is 96.5:3.5, the 20.3 part (96.5–76.2) of (*R*)-**10** and the 1.7 part (3.5–1.8) of (*S*)-**10** are calculated to be remained intact in the reaction system, indicating that the er of the unreacted **10** is 92:8. The er value is well agreed to the experimental result (93:7). The results suggest that the reaction using the enantiomeric catalyst (*S*)-**1** should be slower than that with (*R*)-**1**, being consistent with the next result.

Reaction by use of the catalyst (S)-1. Allylic alcohol **10** (50.3 mg), DMA (2.00 mL), H_2O (220 μL), 10.0-mM solution of $[CpRu(CH_3CN)_3]PF_6$ and (*S*)-Cl-Naph-PyCOOAll in CH_2Cl_2 (660 μL). 30% convn, 29% isolated yield; 78:22 dr.

Olefin metathesis of 11. A 20-mL Young-type Schlenk tube was charged with a 80:20 **11**/*epi*-**11** mixture (49.7 mg, 0.217 mmol) dissolved in CH_2Cl_2 (2.20 mL) and 1-pentadecene (0.590 mL, 2.17 mmol). The clear solution was degassed by three freeze-thaw cycles, and then HG II (4.10 mg, 6.54 μmol) was added. The resulting pale reddish solution was stirred at rt for 4 h. A portion of the reaction mixture (ca. 100 μL) was taken. Concentration followed by the ^{1}H-NMR analysis in $CDCl_3$ determined the conversion to be 88%. The whole reaction mixture was concentrated, and the crude mixture was dissolved in CH_2Cl_2 (2.5 mL). To this was added Quadrasil^{TM} AP (0.5 g). After being stood for 8 h, the mixture was filtered and concentrated. The residue was purified by SiO_2-chromatograpy (SiO_2, 15 g; hexane–THF 6:1 eluent) to give a 8:2 diastereomer mixture of **13** and *epi*-**13** (69.9 mg, 78%). The pure **13** was obtained in 72% yield (33.6 mg) from HPLC-separated **11**. (*S*,*R*)-**13** with a 98:2 er: ^{1}H NMR ($CDCl_3$, 60 °C) δ 0.88 (t, J = 6.89 Hz, 1H; CH_3), 1.22–1.42 (m, 22H; $(CH_2)_{11}$), 1.48 (s, 9H; $C(CH_3)_3$), 2.04 (dt, J = 6.89, 6.89 Hz, 2H; CH=CHCH_2), 3.91 (br, 1H; HOCHH), 3.96–4.12 (m, 2H; HOCHH and NCH), 4.24 (br, 1H; HOCH), 4.65 (d, J = 4.13 Hz, 1H; NCHHO), 4.95 (br, 1H; NCHHO), 5.42 (dd, J = 15.5, 6.89 Hz, 1H; CHCH=CH), 5.74 (dt, J = 15.5, 6.89 Hz, 1H; CH=CHCH$_2$); ^{13}C NMR ($CDCl_3$, 60 °C) δ 14.0, 22.7, 28.4, 29.2, 29.3, 29.5, 29.6, 29.7, 31.9, 32.4, 60.4, 68.7, 73.0, 80.0, 81.1, 128.1, 134.2, 154.1; HRMS (ESI) calcd for $C_{24}H_{45}NNaO_4$ $[M+Na]^+$ 434.3246, found 434.3257; $[\alpha]_D^{21}$=–14.4 (c=0.360 in $CHCl_3$). **Figure S34** showed ^{1}H- and ^{13}C-NMR spectra of major diastereomer **13**.

Deprotection. A 20-mL Young-type Schlenk tube was charged with a 80:20 mixture of **13** and *epi*-**13** (113 mg, 0.275 mmol) dissolved in 74:1 CH_3OH–H_2O (1.8 mL) and $HONH_2$·HCl (191 mg, 2.75 mmol). After 19-h stirring at 83 °C, the reaction mixture was partitioned between CH_2Cl_2 (10 mL) and 1 M aq NaOH (50 mL). The aq layer was extracted by CH_2Cl_2 (10 mL x 9), and the combined organic layers were dried over Na_2SO_4, filtered, and concentrated to give a 80:20 mixture of sphingosine (**9**) and its epimer (81.7 mg, 98%). This was purified by SiO_2-chromatography (SiO_2, 5 g; $CHCl_3$–CH_3OH–aq NH_3 100:10:1 eluent) to give sphingosine (**9**) (30.4 mg, 37%): ^{1}H NMR (CD_3OD) δ 0.90 (t, J = 6.89 Hz, 3H; CH_3), 1.25–1.45 (m, 22H; $(CH_2)_{11}$), 2.09 (dt, J = 6.89, 6.89 Hz, 2H; CH=CHCH_2CH$_2$), 2.76 (ddd, J = 6.54, 6.54, 4.82 Hz, 1H; H_2NCH), 3.49 (dd, J = 11.0, 6.89 Hz, 1H; HOCHH), 3.68 (dd, J = 11.0, 4.82 Hz, 1H; HOCHH), 3.97 (dd, J = 6.89, 6.54 Hz, 1H; HOCH), 5.50 (dd, J = 15.5, 6.89 Hz, 1H; CHCH=CH), 5.74 (dt, J = 18.6, 6.89 Hz, 1H; CH=CHCH$_2$); ^{13}C NMR (CD_3OD) δ 15.8, 25.1, 31.7, 31.7, 31.8, 32.0, 32.1, 32.1, 32.1, 34.4, 34.8, 59.4, 65.6, 76.4, 132.1, 136.6; $[\alpha]_D^{22}$=–3.99 (c=0.465 in $CHCl_3$). **Figure S35** showed the ^{1}H-NMR spectrum together with that of the commercially obtained sphingosine (**9**).

ASSOCIATED CONTENT

The Supporting Information is available free of charge on the ACS Publications website.

NMR spectra, HPLC charts, and full screening data for the reaction conditions (PDF)

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REFERENCES

(1) (a) *Natural Products Chemistry;* Nakanishi, K., Goto, T., Ito, S., Natori, S., Nozoe, S., Eds.; Kodansha: Tokyo, 1975. (b) *Classics in Total Synthesis II: More Targets, Strategies, Methods;* Nicolaou, K. C., Snyder, S. A., Eds.; Wiley-VCH: Weinheim, 2003.

(2) (a) Kolb, H. C.; VanNieuwenhze, M. S.; Sharpless, K. B. *Chem. Rev.* **1994**, *94*, 2483–2547. (b) Jacobsen, E. N.; Wu, M. H. In *Comprehensive Asymmetric Catalysis, Vol. II;* Jacobsen, E. N., Pfaltz, A., Yamamoto, H., Eds.; Springer-Verlag: Berlin, 1999; pp 649–677.

(3) (a) Kitamura, M.; Ohkuma, T.; Inoue, S.; Sayo, N.; Kumobayashi, H.; Akutagawa, S.; Ohta, T.; Takaya, H.; Noyori, R. *J. Am. Chem. Soc.* **1988**, *110*, 629–631. (b) Ohkuma, T.; Kitamura, M.; Noyori, R. In *Catalytic Asymmetric Synthesis, 2nd Ed.;* Ojima, I., Ed.; Wiley-VCH: New York, 1999; pp 1–110.

(4) (a) Gröger, H.; Vogl, E. M.; Shibasaki, M. *Chem. Eur. J.* **1998**, *4*, 1137–1141. (b) Matsuo, J.; Murakami, M. *Angew. Chem.* **2013**, *125*, 9280–9289; *Angew. Chem. Int. Ed.* **2013**, *52*, 9109–9118. (c) Palomo, C.; Oiarbide, M.; Laso, A. *Eur. J. Org. Chem.* **2007**, *2007*, 2561–2574.

(5) Intramolecular O- and N-allylation of an in-situ generated protonic nucleophile: (a) Wang, L.; Menche, D. *Angew. Chem.* **2012**, *124*, 9559–9562; *Angew. Chem. Int. Ed.* **2012**, *51*, 9425–9427. (b) Goodwin, J. A.; Ballesteros, C. F.; Aponick, A. *Org. Lett.* **2015**, *17*,

5574–5577. (c) Yang, L.; Khan, A.; Zheng, R.; Jin, L. Y.; Zhang, Y. J. *Org. Lett.* **2015,** *17*, 6230–6233. For the C-allylation, see: (d) Wang, L.; Menche, D. *J. Org. Chem.* **2012**, *77*, 10811–10823. Intramolecular N-allylation of trichloroacetimidates and urea derivatives: (e) Xie, Y.; Yu, K.; Gu, Z. *J. Org. Chem*. **2014**, *79*, 1289–1302. (f) Morgen, M.; Bretzke, S.; Li, P.; Menche, D. *Org. Lett*. **2010**, *12*, 4494–4497. For the original paper, see: (g) Hayashi, T.; Yamamoto, A.; Ito, Y. *Tetrahedron Lett.* **1988**, *29*, 99–102. Intramolecular allylic C-H amination: (h) Nishikawa, Y.; Kimura, S.; Kato, Y.; Yamazaki, N.; Hara, O. *Org. Lett*. **2015**, *17*, 888–891.

(6) (a) Tanaka, S.; Seki, T.; Kitamura, M. *Angew. Chem.* **2009**, *121*, 9110–9113; *Angew. Chem. Int. Ed.* **2009**, *48*, 8948–8951. (b) Seki, T.; Tanaka, S.; Kitamura, M. *Org. Lett.* **2012**, *14*, 608–611. (c) Suzuki, Y.; Seki, T.; Tanaka, S.; Kitamura, M. *J. Am. Chem. Soc.* **2015**, *137*, 9539–9542.

(7) The first successfull use of formaldehyde as a bridging unit, see: Yoneda, N.; Hotta, A.; Asano, K.; Matsubara, S. *Org. Lett.* **2014**, *16*, 6264–6266.

(8) See supporting information.

(9) Lumbroso, A.; Cooke, M. L.; Breit, B. *Angew. Chem.* **2013**, *125*, 1942–1986; *Angew. Chem. Int. Ed.* **2013**, *52*, 1890–1932.

(10) (a) Koskinen, P. M.; Koskinen, A. M. P. *Synthesis* **1998**, *1998*, 1075–1091. (b) Howell, A. R.; Ndakala, A. J. *Curr. Org. Chem.* **2002**, *6*, 365–391. (c) Howell, A. R.; So, R. C.; Richardson, S. K. *Tetrahedron* **2004**, *60*, 11327–11347. (d) Morales-Serna, J. A.; Llaveria, J.; Díaz, Y.; Matheu, M. I.; Castillon, S. *Curr. Org. Chem*. **2010**, *14*, 2483–2521.

(11) (a) Xie, Y.; Floreancig, P. E. *Angew. Chem.* **2014**, *126*, 5026–5029; *Angew. Chem. Int. Ed.* **2014**, *53*, 4926–4929. See also, (b) Brendgen, T.; Fahlbusch, T.; Frank, M.; Schühle, D. T.; Seßler, M.; Schatz, J. *Adv. Synth. Catal.* **2009**, *351*, 303–307. (c) Sworen, J. C.; Pawlow, J. H.; Case, W.; Lever, J.; Wagener, K. B. *J. Mol. Catal. A: Chem.* **2003**, *194*, 69–78.

(12) For the detailed analysis of catalyst control and substrate control in this reaction, see EXPERIMENTAL SECTION.

(13) (a) Noyori, R.; Tokunaga, M.; Kitamura, M. *Bull. Chem. Soc. Jpn.* **1995**, *68*, 36–56. (b) Nakano, K.; Kitamura, M. In *Separation of Enantiomers: Synthetic Methods;* Todd, M., Ed.; Wiley-VCH: Weinheim, 2014; pp 161–215.

(14) Harding, K. E.; Marman, T. H.; Nam D. *Tetrahedron* **1988**, *44*, 5605–5614.

(15) The optical rotation of commercially available sphingosine (Aldrich: S7049) was measured.

(16) James, P.; Felpin, F.-X.; Landais, Y.; Schenk, K. *J. Org. Chem.* **2005**, *70*, 7985–7995.

(17) Fustero, S.; Jiménez, D.; Moscardó, J.; Catalán, S.; del Pozo, C. *Org. Lett*. **2007**, *9*, 5283–5286.

(18) Harding, K. E.; Marman, T. H.; Nam, D. *Tetrahedron* **1988**, *44*, 5605–5614.

(19) Branchaud, B. P.; Tsai, P. *J. Org. Chem.* **1987**, *52*, 5475–5478.

(20) Turkington, J. R.; Cocalia, V.; Kendall, K.; Morrison, C. A.; Richardson, P.; Sassi, T.; Tasker, P. A.; Bailey, P. J.; Sole, K. C. *Inorg. Chem.* **2012**, *51*, 12805–12819.

(21) Tang, S.; Si, Y.-Y.; Wang, Z.-P.; Mei, K.-R.; Chen, X.; Cheng, J.-Y.; Zheng, J.-S.; Liu, L. *Angew. Chem.* **2015**, *127*, 5805–5809; *Angew. Chem. Int. Ed.* **2015**, *54*, 5713–5717.

(22) Egginton, C. D.; Lambie, A. J. *J. Chem. Soc. C* **1969**, *1969*, 1623–1625.

(23) (a) Kang, S. H.; Jun, H. S. *Bull. Korean Chem. Soc.* **1991**, *12*, 461–463. (b) Janssen, C. G. M.; Godefroi, E. F. *Org. Prep. Proc. Intl.* **1981**, *13*, 209–216.

(24) Tosatti, P.; Horn, J.; Campbell, A. J.; House, D.; Nelson, A.; Marsden, S. P. *Adv. Synth. Catal.* **2010**, *352*, 3153–3157.

(25) Yokoyama, H.; Ejiri, H.; Miyazawa, M.; Yamaguchi, S.; Hirai, Y. *Tetrahedron: Asymmetry* **2007**, *18*, 852–856.

(26) Thomas, W. M.; Kropa, E. L. U.S. Patent 2,578,861, **1951**.

(27) Bergmeier, S. C.; Stanchina, D. M. *J. Org. Chem.* **1999**, *64,* 2852–2859.

(28) Locke, J. M.; Crumbie, R. L.; Griffith, R.; Bailey, T. D.; Boyd, S.; Roberts, J. D. *J. Org. Chem.* **2007**, *72*, 4156–4162.

(29) Trost, B. M.; Fandrick, D. R.; Brodmann, T.; Stiles, D. T. *Angew. Chem*. **2007**, *119*, 6235–6237; *Angew. Chem. Int. Ed*. **2007**, *46*, 6123–6125.

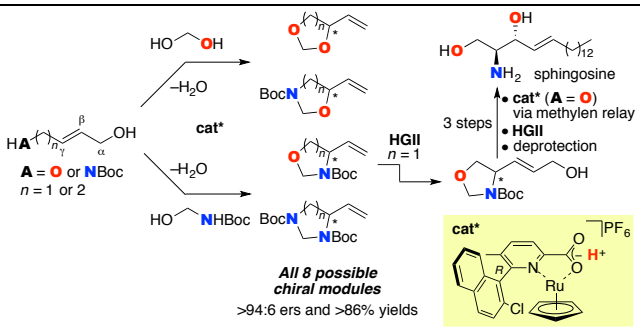
(30) Lubineau, A.; Augé, J.; Bellanger, N.; Caillebourdin, S. *Tetrahedron Lett.* **1990**, *31*, 4147–4150.

(31) Chang, M.-Y.; Lin, C.-Y.; Wu, T.-C.; Sun, P.-P. *J. Chin. Chem. Soc*. **2008**, *55*, 412–430.

(32) Yang, J.-J.; Wu, J.-Z.; Qiao, C. *Synth. Commun.* **2014**, *44*, 1240–1244.

(33) Trost, B. M.; Fandrick, D. R. *Org. Lett.* **2005**, *7*, 823–826.

(34) Honda, T.; Matsumoto, S. *Heterocycles* **2006**, *66*, 341–346.


HO OH
–H2O
cat*
–H2O
HO NHBoc
BocN
NBoc
HA
A = O or NBoc
n = 1 or 2
HGII
n = 1
3 steps
• cat* (A = O) via methylen relay
• HGII
• deprotection
OH
HO
NH2 sphingosine
OH
NBoc
All 8 possible chiral modules
>94:6 ers and >86% yields
cat*
PF6
H+
Ru
Cl