Bulletin of the Chemical Society of Japan

A Chiral Picolinic Acid Ligand, Cl-Naph-PyCOOH, for CpRu-catalyzed Dehydrative Allylation: Design, Synthesis, and Properties

Shinji Tanaka, Yusuke Suzuki, Takahiro Kimura, and Masato Kitamura*

Advance Publication on the web June 20, 2019
doi:10.1246/bcsj.20190134

A Chiral Picolinic Acid Ligand, Cl-Naph-PyCOOH, for CpRu-catalyzed Dehydrative Allylation: Design, Synthesis, and Properties

Shinji Tanaka, Yusuke Suzuki, Takahiro Kimura, and Masato Kitamura*

Graduate School of Pharmaceutical Sciences and Research Center for Materials Science, Nagoya University, Chikusa, Nagoya 464-8601

E-mail: kitamura@ps.nagoya-u.ac.jp

Masato Kitamura

Masato Kitamura received his Doctor of Agriculture at Nagoya University (NU) (Professors T. Goto and M. Isobe) in 1983. After postdoctoral work with Professor G. Stork (Columbia University), he joined the Noyori group at Faculty of Science in NU as Assistant Professor (1983), and was promoted to Associate Professor (1990). In 1998, he moved to Research Center for Materials Science in NU as Full Professor. Currently, he is studying at Graduate School of Pharmaceutical Sciences in NU from 2012. He is a recipient of The CSJ Award for Young Chemists (1989) and Synthetic Organic Chemistry Award, Japan (2012).

Abstract

A CpRu/Brønsted acid-combined catalyst, CpRu(II)/picolinic acid (PyCOOH), acts as an efficient catalyst for the allyl protection/deprotection of alcohols. This discovery has resulted in the development of a new axially chiral ligand, Cl-Naph-PyCOOH (**2a**; 6-(2-chloronaphthalen-1-yl)-5-methylpyridine-2-carboxylic acid) through an investigation on the ligand structure-reactivity relationship in the CpRu-catalyzed dehydrative cyclization of (*E*)-hept-2-ene-1,7-diol (**5**) to 2-vinyltetrahydro-2*H*-pyran (**6**). A large-scale synthetic procedure for **2a** and the allyl esters **2b** has been established. The activation energy $\Delta G^{\ddagger}$ of the stereoinversion and the half-life time of (*R*)-**2b** racemization have been determined to be 33.7 kcal/mol and 16,000 years at 25 °C, respectively. The CpRu(II)/(*R*)-Cl-Naph-PyCOOH catalyst exists as a 1:1 diastereomeric mixture of (R,R_{Ru})-**3** ($\mathbf{A}_{\boldsymbol{R}}$) and ($R$,$S_{Ru}$)-**3** ($\mathbf{A}_{\boldsymbol{S}}$) because of the axial chirality of **2a** and the Ru stereogenic center. The epimerization rate of the Ru center is 19.5/sec at 30 °C with an energy barrier $\Delta G^{\ddagger}$ of 16.0 kcal/mol. Both $\mathbf{A}_{\boldsymbol{R}}$ and $\mathbf{A}_{\boldsymbol{S}}$ have their own reactivity and enantioselectivity. Nevertheless, an enantiomer ratio of up to >99:1 can be realized in the allylative cyclization of *E*-allylic alcohols possessing a protic nucleophile, OH, NHCOR, $NHSO_2R$, or COOH, at the terminal position. Questions about the mechanism have been raised as progress is being made towards a mechanistic investigation.

Keywords: Axially chiral ligand, Ruthenium, Asymmetric dehydrative allylation

1. Introduction

Picolinic acid (PyCOOH) is a simple molecule packed with significant functional groups to capture various metals. The σ donative and π acceptive sp^2N of the pyridine cooperates with the carboxylic acid moiety located at the C(2) position in capturing typical metals and transition metals with either high or low valences. The strong chelating ability plays an important role in our human body for absorbing trace elements such as Cr, Mo, Mg, Fe, Cu, and Zn to express various physiological activities.[1] An enormous number of reports on the metal complexes have been published[2] since the first discovery of metal picolinate by Webster in 1936.[3] As a result, a number of catalytic reactions have been reported during the four decades since 1979 when Mares found the utility of tungsten peroxo picolinate for the catalytic oxidation of alcohols.[4] The main use is in oxidation[4, 5] but also for carbon-carbon bond formation[6] and functional group transformation.[7] The asymmetric version is limited to the epoxidation of alkenes.[8] All applications utilize PyCOOH as an achiral supporting ligand, and the chirality of the metal complexes is introduced by highly sophisticated chiral NNN ligands. There are no reports on catalytic asymmetric reactions using metal complexes of chirally modified PyCOOH ligands.

In the course of developing a catalyst for allyl protection/deprotection through an automated combinatorial screening of metal precursors and ligands, we found that the combination of $[RuCp(CH_3CN)_3]PF_6$ (**1**) with PyCOOH shows a high reactivity in the allylation of alcohols using allyl alcohol (AllOH). Further structural optimization of the PyCOOH ligand has led to quinaldic acid (QAH), which shows a one-order higher reactivity in combination with **1**.[9] As shown in **Figure 1a**, the CpRu(II)/QAH catalyzes either dehydrative installation of an allyl group into alcohols using AllOH in aprotic solvents such as CH_2Cl_2 or removal of an allyl group from allyl ethers (AllOR) in protic solvents such as CH_3OH.[10] The CpRu(II)/QAH chemistry has contributed not only to the allyl protection/deprotection of alcohols but also to selective S-allylation of oligo peptides in aqueous media,[11] deprotection of amines and carboxylic acids,[12] and the synthesis of various important compounds.[13] **Figure 1b** illustrates our leading concept used for the combinatorial screening, which is named the Intramolecular Redox-mediated Donor-Acceptor Bifunctional Catalyst (Intramol-RDACat)[14] or transition metal/Brønsted acid-combined catalyst.[15] In the conceptual catalyst, M(n)Cp(L_s–L_hH), M(n) represents a low valence transition metal, and L_s and L_h are a soft ligating atom such as sp^3P, sp^2N, and sp^3S and a hard ligating atom such as sp^3O and sp^3N, respectively. The monoanionic and highly electron-donative cyclopentadienyl (Cp) ligand enhances the electron density of M(n) to facilitate its oxidation to M(n+2). In addition, the η^5 Cp and bidentate L_s–L_hH ligands increase the degree of coordinative saturation to suppress self-aggregation that sometimes causes catalyst deactivation. Complex M(n)Cp(L_s–L_hH) captures AllOH via a coordination of the soft C=C bond to the soft M(n) and via an interaction of the hard OH oxygen atom with the hard H^+. The resulting δ^+-δ^--δ^+-δ^--δ^+-δ^- charge-alternation including M(n) oxidation

stabilizes the transition state to facilitate the formation of M(n+2)Cp(π-allyl)(L_s–L_h) by liberation of H_2O. The subsequent reductive nucleophilic attack of ROH on the electron deficient π-allyl carbon gives AllOR. In CH_3OH, the allyloxy bond of AllOR is reversibly cleaved according to the same Intramol-RDACat mechanism to move the equilibrium to the AllOMe/ROH side.

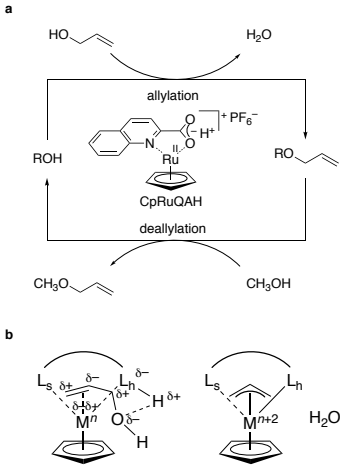

Figure 1. (**a**) Dehydrative allylation and deallylation catalyst, CpRu/quinaldic acid (QAH). (**b**) Intramolecular Redox-mediated Donor-Acceptor bifunctional Catalyst (Intramol-RDACat) concept for combinatorial screening of catalyst

The discovery of a CpRu(II)/PyCOOH-combined catalyst represents a step towards the development of the first high-performance asymmetric dehydrative allylative cyclization.[16] As shown in **Figure 2**, introduction of chirality into PyCOOH as (*R*)- or (*S*)-Cl-Naph-PyCOOH (**2a**; (*R*)- and (*S*)-6-(2-chloronaphthalen-1-yl)-5-methylpyridine-2-carboxylic acid) has led to the new chiral CpRu complexes, [RuCp((*R*)-Cl-Naph-PyCOOH)]PF_6 ((*R*)-**3**) and [RuCp(π-C_3H_5)((*R*)-Cl-Naph-PyCOO)]PF_6 ((*R*)-**4**). These complexes efficiently catalyze the asymmetric dehydrative cyclization of *E*-allylic alcohols **5** tethered with protonic nucleophiles such as OH, NHCOR, $NHSO_2R$, and COOH, furnishing the corresponding saturated heterocycles (*S*)-**6** with up to >99:1 *S*/*R* enantiomer ratio (er).[17]

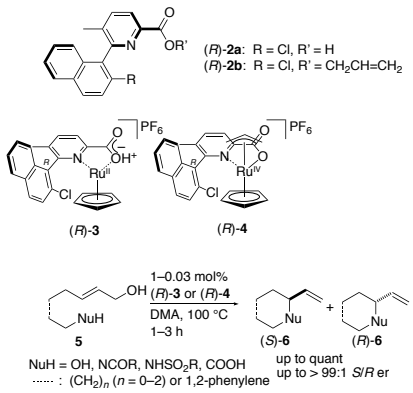

Figure 2. Asymmetric dehydrative intramolecular allylation using CpRu/Cl-Naph-PyCOOH

In this paper, we would like to report the details for the design and synthesis of Cl-Naph-PyCOOH (**2a**) and its allyl ester **2b** and propose a possible mechanism under the premise that the reaction proceeds via π-allyl Ru intermediates in a similar way to the CpRu/PyCOOH-catalyzed dehydrative allylation.[10]

2. Results and Discussion

2.1. Ligand Structure–reactivity Relationship. To design a chiral PyCOOH-type ligand for the asymmetric dehydrative allylative cyclization, the ligand structure-reactivity relationship was investigated in the reaction of (*E*)-hex-2-ene-1,6-diol (**5**) to 2-vinyltetrahydro-2*H*-pyran (**6**) using [RuCp(CH_3CN)$_3$]PF_6 (**1**) and modified PyCOOH ligand **L** under the conditions of [**5**] = 100 mM, [**1**] = [**L**] = 1 mM (1 mol%), DMA, and a 100 °C-oil bath temperature. The reaction time was set to 10 min for clarifying the reactivity difference. The yields were determined by GC analysis (column, J&W Scientific DB-5 (0.25 mm x 0.25 μm x 30 m); 50 °C for 10 min –> 10 °C increase/min –> 200 °C; 140 kPa; 100:1 split ratio; t_R of **6**, 6.9 min; t_R of **5**, 18.7 min). The results are shown in **Figure 3**. Quinaldic acid (QAH; **L1**), its allyl ester **L2**, and PyCOOH (**L4**) quantitatively afforded 6-*exo*-*trig*-cyclized product **6**. No 8-*endo*-*trig*-cyclized product was generated. Introduction of a methyl group at C(8) of QAH or a *tert*-butyl group at C(6) of PyCOOH led to no reaction (**L3** and **L5**). The reactivity was recovered by 10% by replacement of a *tert*-butyl group at C(6) with a sterically more flexible phenyl group (**L6**). Full recovery of the reactivity was attained by use of *o*-Cl-Ph- or *o*-Br-Ph-substituted PyCOOH (**L7** and **L8**). Introduction of

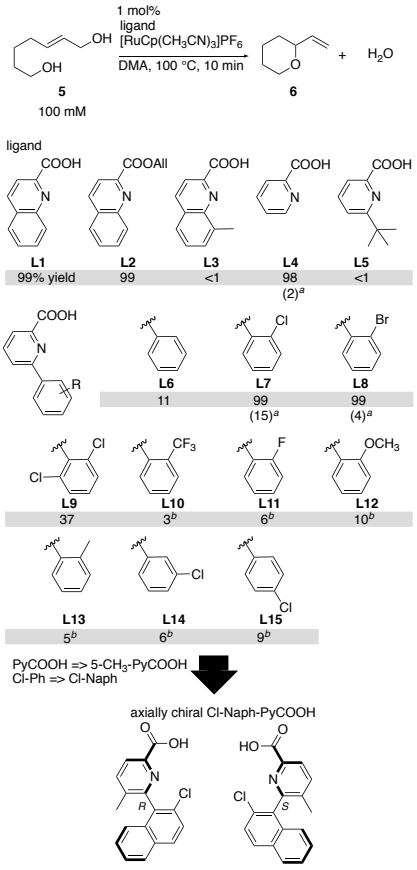

Figure 3. Ligand structure-reactivity relationship in the CpRu-catalyzed dehydrative cyclization of **5** to **6** toward the design of an axially chiral picolinic acid ligand. [a] 0.1 mol%. [b] Allyl ester was used

two ortho Cl groups led to one-fifth of the reactivity of *o*-Cl-Ph-PyCOOH (**L9** vs **L7**). More electron-withdrawing CF_3 or F groups decreased the reactivity (**L10** and **L11**), and electron-donating CH_3O or CH_3 groups were also not effective (**L12** and **L13**). Movement of the Cl substituent from the *ortho* to *meta* or *para* position eradicated the reactivity (**L14** and **L15**). Taking into consideration the ligand-structure effect on the reactivity and the higher stability of Cl-Ph toward a low valence transition metal than Br-Ph, the axially chiral Cl-Naph-PyCOOH (**2a**) ligand was designed; here, the basic skeleton of *o*-Cl-Ph-PyCOOH was modified by introducing a methyl group at C(5) of the Py moiety and by replacing the Cl-Ph group with a C(2')-Cl-naphthyl (Cl-Naph) group to suppress stereoinversion.

2.2. Ligand Synthesis. As shown in **Figure 4a**, (±)-Cl-Naph-PyCOOH ((±)-**2a**) was retrosynthesized to commercially available 2-bromo-3-methylpyridine (**7**) and naphthalen-1-ylboronic acid (**8**) via a Suzuki-Miyaura coupling between C(1') and C(6), introduction of C(2')-Cl by Py-sp^{2}N-promoted silylation followed by Si/Cl exchange, and introduction of a 2-CN group by a Reissert-Henze reaction followed by hydrolysis to COOH. **Figure 4b** shows the synthetic route. The Pd-catalyzed coupling of **7** with **8** on a 50-g scale efficiently proceeded at 100 °C in a 5:1 DME–H_2O mixed solvent containing K_2CO_3. The crude coupling product was subjected to the Murai reaction using $(C_2H_5)_3SiH$ and norbornene under the influence of $Ru_3(CO)_{12}$ in toluene,[18] giving C(2')-silylated product **9** in 93% yield in two steps. The $(C_2H_5)_3Si$ group of **9** was converted to a C(2')-Cl group by treatment with BCl_3 in CH_2Cl_2 followed by $CuCl_2$ in a 1:1 CH_3OH–H_2O mixed solvent to give **10** in 95% yield.[19] Oxidation of the Py-sp^{2}N atom of **10** by H_2O_2 in AcOH followed by reaction of the *N*-oxide product with $(CH_3)_3SiCN$ and dimethylcarbamoyl chloride introduced a CN group at C(2), which was hydrolyzed to give (±)-**2a** in 82% yield in three steps from **10**. (*S*)-Camphorsultam was introduced to (±)-**2a** and afforded the corresponding 1:1 diastereomeric mixture,

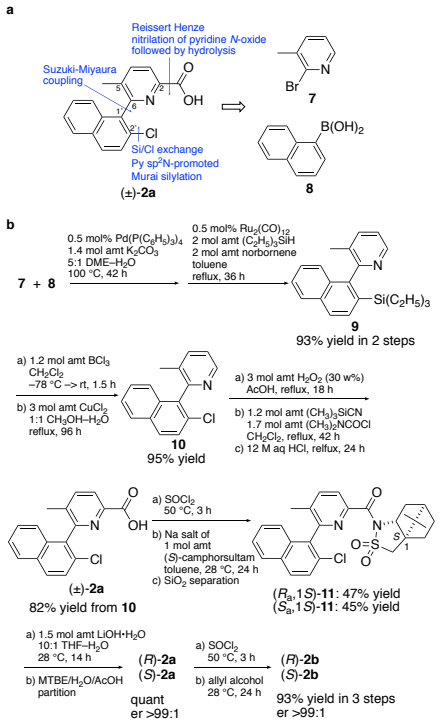

Figure 4. (**a**) Retrosynthetic analysis of (±)-**2a**. (**b**) Syntheses of (*R*)- and (*S*)-Cl-Naph-PyCOOH (**2a**) and the allyl ester **2b**

which was separated by silica-gel chromatography to give (R_a,1*S*)-**11** in 47% yield and (S_a,1*S*)-**11** in 45% yield. Hydrolysis of each diastereomer gave (*R*)-**2a** ($[\alpha]_D^{21}$ 136 (*c* 1.02, $CHCl_3$)) or (*S*)-**2a** ($[\alpha]_D^{22}$ –143 (*c* 1.06, $CHCl_3$)). Acid chlorination followed by allyl esterification afforded (*R*)-Cl-Naph-PyCOOAll ((*R*)-**2b**; $[\alpha]_D^{21}$ 122 (*c* 1.10, $CHCl_3$)) and (*S*)-**2b** ($[\alpha]_D^{20}$ –121 (*c* 0.53, $CHCl_3$)) in 93% yield from **11**.[20]

2.3. Stereochemical Stability. Possible racemization processes of **2** are illustrated in **Figure 5a**. The atropisomeric biaryl compound **2** undergoes stereochemical inversion by clockwise or anticlockwise rotation through the C(6)–C(1') bond joining the two aryl rings. The rotation proceeds via two possible transition states, $\mathbf{TS_{180}}$ and $\mathbf{TS_0}$ with the C(2')=C(1')–C(6)=N(1) dihedral angle f of 180 deg and 0 deg, respectively. The energy barrier for the stereoinversion is determined mainly by the relative steric demand between N(1) (smaller: S) and C(5)Me (larger: L) in the Py part and between C(2')Cl (smaller: S') and C(8')H (larger: L') in another aryl partner and also by electronic effects. In $\mathbf{TS_0}$, the larger substituents L and L' are located in the overcrowded fjords region[21] while the smaller S and larger L' combination in $\mathbf{TS_{180}}$ decreases the degree of the penetration across the fjords. Furthermore, $\mathbf{TS_{180}}$ is electronically favored in terms of electron flow from the Cl lone pair to N(1) in the *s-trans*-arranged Cl–C(2')=C(1')–C(6)=N(1) conjugated system, and electronic repulsion between the lone pairs of sp^{2}N(1) and the Cl atom destabilizes the *s-cis*-arranged $\mathbf{TS_0}$. The van der Waals radius of Cl is close to that of Me (effective van der Waals radius (ER): Cl 1.73 vs Me 1.80); therefore, the energy

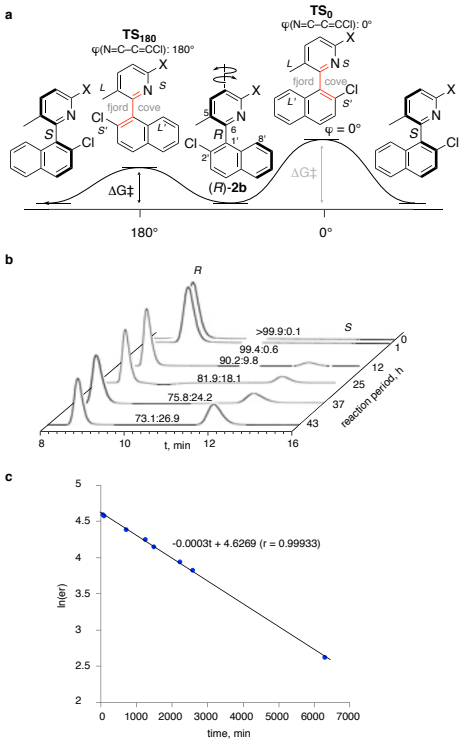

Figure 5. Possible racemization process of (*R*)-Cl-Naph-PyX (X = $COOCH_2CH{=}CH_2$, (*R*)-**2b**) and determination of the $t_{1/2}$ values. (**a**) Energy diagram in the C(6)-C(1') bond rotation of (*R*)-**2b**. (**b**) The *R*/*S* er change of (*R*)-**2b** in DMA at 130 °C as determined by HPLC analysis (CHIRALCEL OD-H (4.6 mm φ x 250 mm); 1:5 2-PrOH–hexane eluent; 1.0 mL/min flow rate; 254-nm detection; 25 °C). (**c**) Logarithmic plots of the ers over time

barrier toward **TS$_{180}$** would also be high but would be lower than that toward **TS$_0$**. To understand the racemization profile of optically pure **2** quantitatively, the time-course change in the er of (*R*)-**2b** (10 mM) in DMA at 130 °C was measured by chiral HPLC analysis (**Figure 5b**). The ers decreased from >99.9:0.1 to 99.4:0.6 (1 h), 90.2:9.8 (12 h), 81.9:18.1 (25 h), 75.8:24.2 (37 h), and 73.1:26.9 (43 h). The logarithmic plots of ers versus time gave a linear relationship with a correlation coefficient of 0.99933 ($\ln(R/S) = -3.00 \times 10^{-4} t + 4.63$), determining the rate of racemization k_{rac} to be 5.01 x 10^{-6} s^{-1}. The activation energy barrier $\Delta G^{\ddagger}$ at 25 °C and the half-life time ($t_{1/2}$) of (*R*)-**2b** racemization were calculated to be 141 kJ/mol (33.7 kcal/mol) using the Eyring equation ($\Delta G^{\ddagger} = 8.314T \ln(2.084 \times 10^{10}\, T/k_{rac})$) and 16,000 years at 25 °C using $t_{1/2} = \ln 2/k_{rac}$, respectively. In comparison to Me-Naph-PyCOOAll with the same level of ER as Cl, the half-life time is shortened by two orders of magnitude (1,500,000 years vs 16,000 years).[22] The electronically stabilized **TS$_{180}$** would be ascribed to the shorter half-life time of Cl-Naph-PyCOOAll in comparison to Me-Naph-PyCOOAll.

In the reaction of **5** using (*R*)-**3** or (*R*)-**4**, the cyclized product **6** with a 96:4 *S*/*R* er was quantitatively obtained under the conditions of [**5**] = 1000 mM, [**1**] = [(*R*)-**2b**] = 1 mM (0.1 mol%), DMA, 100 °C; 1 h. A decrease in the substrate concentration from 1000 mM to 100 mM slightly increases the er to 97:3.[16] Generation of the minor (*R*)-**6** is not due to the racemization of the chiral ligand during the course of the reaction at 100 °C, as confirmed by the recovery of the ligand without any er deterioration (**Figure 6**). The stereochemical stability of the ligand should be significantly enhanced after formation of the CpRu complex because the N(1)–RuCp part becomes the largest. The complexation of (*R*)-**2a** or (*R*)-**2b** with **1** is also thought to contribute to the stereochemical stability.

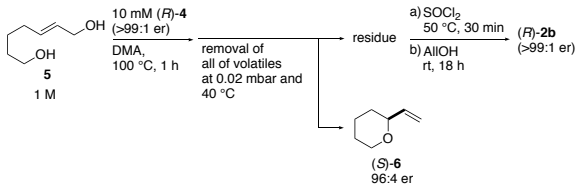

Figure 6. The process of recovering (*R*)-**2b** after the reaction of **5** at 100 °C for 1 h

2.4. Characteristics of Cl-Naph-PyCOOH/CpRu Complex. **Figure 7** shows the Cp and Cl-Naph signal regions of the ^{1}H-NMR spectra of a 1:1 mixture of (*R*)-Cl-Naph-PyCOOH ((*R*)-**2a**) and [RuCp(CH$_3$CN)$_3$]PF$_6$ (**1**) in acetone-d_6 in the absence and presence of one mol amount of Et$_3$N.

In the absence of Et$_3$N (**Figure 7a**), the Cp signals resonated at δ 3.29 ppm and δ 3.52 ppm at 18 °C. These were assignable to the two diastereomeric CpRu complexes, (*R*,*R*$_{Ru}$)-**3** (**A$_R$**) and (*R*,*S*$_{Ru}$)-**3** (**A$_S$**), which are in a rapid equilibrium as shown in **Figure 8**. The 1:1 ratio indicated that the equilibrium constant *K* is nearly 1. The two signals were broadened by raising the temperature, e.g., the half-width (*W*) of the signal at δ 3.29 ppm was widened from 4.82 Hz (18 °C) to 11.02 Hz (30 °C) and 31.67 Hz (40 °C), determining the Cp flipping rate to be 19.5/sec ($k_{30} = \pi\Delta W = \pi(11.02 - 4.82)$) at 30 °C with $\Delta G^{\ddagger}$ = 16.0 kcal/mol and 84.3/sec ($k_{40} = \pi(31.67 - 4.82)$) at 40 °C with $\Delta G^{\ddagger}$ = 15.6 kcal/mol. The complex **3** was not stable at a high temperature in the absence of the allylic alcohol substrate; an increase in temperature to 100 °C in

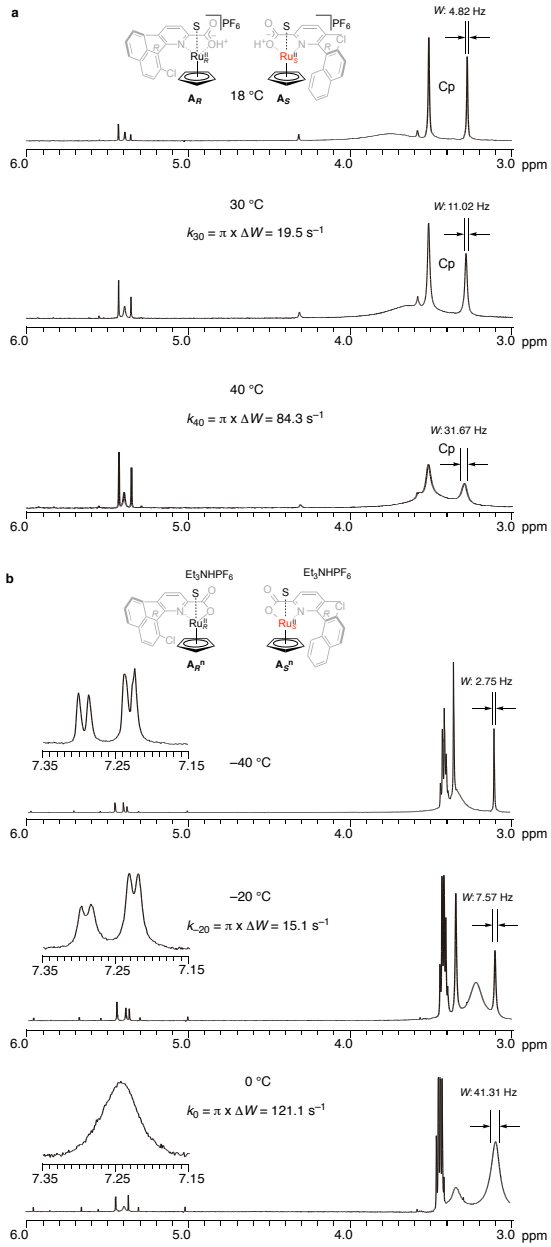

Figure 7. ^{1}H-NMR spectra of the Cp and Cl-Naph regions of (*R*)-**3** in acetone-d_6 at different temperatures. (**a**) In the absence of Et$_3$N at 18 °C, 30 °C, and 40 °C. (**b**) In the presence of one mol amount of Et$_3$N at –40 °C, –20 °C, and 0 °C. S: CH$_3$CN or acetone-d_6

DMA-d_9 liberated black precipitates probably due to disproportionation of Ru(II) to Ru(0). The chemical shift difference (0.23 ppm) of the two Cp signals are too large to coalesce at a temperature lower than 100 °C. There were no other signals that were clearly merged in the temperature range from –40 °C to 50 °C.

In the presence of Et$_3$N (**Figure 7b**), the two Cp signals appeared at δ 3.10 ppm (*W* = 2.75 Hz) and δ 3.35 ppm in a ca. 1:1 ratio at –40 °C (acetone-d_6). The *W* value of the signal at a higher field was increased to 7.57 Hz at –20 °C and to 41.31 Hz at 0 °C, determining the flipping rate to be 15.1/sec (–20 °C) and 121/sec (0 °C) with $\Delta G^{\ddagger}$ = 13.4 kcal/mol and 13.3 kcal/mol, respectively. The corresponding neutral complexes **A$_R^n$** and **A$_S^n$** are thought to be generated by liberation of a HPF$_6$/Et$_3$N salt. In this case, the ^{1}H signals at δ 7.21 ppm and δ 7.27 ppm (–40 °C) were merged at 0 °C. With the chemical shift difference of the two signals in Hz (0.06 ppm = 8.26 Hz)

and the coalescence temperature (0 °C = 273 K), the interconversion rate between $\mathbf{A}_R^n$ and $\mathbf{A}_S^n$ was determined to be 91.7/sec at 0 °C with $\Delta G^{\ddagger}$ = 13.5 kcal/mol, which qualitatively agree with the result obtained by the above half-width analysis of the Cp signal at δ 3.10 ppm.

Figure 8 illustrated the possible preequilibria of the CpRu/(*R*)-Cl-Naph-PyCOOH catalyst (*R*)-**3**. In the monocationic $\mathbf{A}_R$ and $\mathbf{A}_S$ complexes existing as a 1:1 mixture, coordination of the carboxylic acid oxygen atom of Cl-Naph-PyCOOH to the cationic Ru(II) center would enhance the acidity of the COOH to liberate HPF_6 by the formation of the corresponding neutral complexes, $\mathbf{A}_R^n$ and $\mathbf{A}_S^n$.[10e] The monocationic complex can supply H^+ for allylic alcohol substrate **5** in an intramolecular manner, whereas liberation of HPF_6 can make it possible to activate **5** intermolecularly. The two modes increase the number of the possible reaction pathways from **5** possessing a protonic nucleophile NuH at the terminus (NuH: OH, NHCOR, $NHSO_2R$, or COOH) to the major (*S*)-**6** and minor (*R*)-**6**. The coordinative regions of the chiral Brønsted acid/CpRu(II)-combined catalyst (*R*)-**3** were schematically shown by the 1st to 4th quadrants made by horizontal and vertical lines crossing the central Ru. Black and grey regions are sterically congested because of the Cl-Naph moiety. Complex $\mathbf{A}_R$ is characterized by the Ph moiety of Cl-Naph standing up in the 2nd quadrant, whereas $\mathbf{A}_S$ is characterized by the existence of a Cl atom in the 1st quadrant. The difference is supposed to realize a significant difference between the reactivities of $\mathbf{A}_R$ and$\mathbf{A}_S$ for some

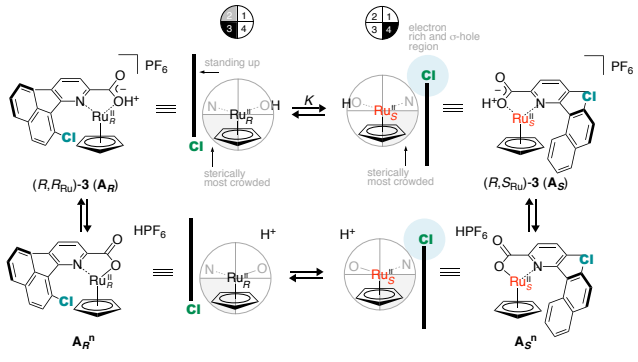

Figure 8. Diastereomeric mixture of the (*R*)-Cl-Naph-PyCOOH/CpRu complex and the neutral complexes. PF_6 or PF_6^- is omitted in the schematic view

reasons that are presently unclear.

Among many possibilities, two simplified pathways via π-allyl intermediates[23] are shown in **Figure 9**: i) π-σ-π-isomerization-involved pathways giving major (*S*)-**6** from $\mathbf{A}_R$ and minor (*R*)-**6** from $\mathbf{A}_S$ and ii) π-σ-π-isomerization-non-involved pathways giving minor (*R*)-**6** from $\mathbf{A}_R$ and major (*S*)-**6** from $\mathbf{A}_S$. Complexes $\mathbf{A}_R$ and $\mathbf{A}_S$ interact with **5** to generate catalyst/substrate complexes, $\mathbf{B}_R$-*saRe*, $\mathbf{B}_R$-*ssSi*, $\mathbf{B}_S$-*saSi*, and $\mathbf{B}_S$-*ssRe*, with equilibrium constants, K_R^1, K_R^2, K_S^1, and K_S^2, respectively. Here, "*saRe*" indicates that the C(3) substituent of **5** is *syn* to C(2)H and *anti* to the Ru carboxylato moiety and that the *Re* face of C(3) is directed to the Ru side. In terms of stereo-complementarity, inequalities $K_R^1 < K_R^2$ and $K_S^1 < K_S^2$ would be established. In the π-σ-π-isomerization-involved pathways (**Figure 9**, right), $\mathbf{B}_R$-*saRe* releases H_2O to the Ru side or inside (H_2O_{in}) to move to π-$\mathbf{C}_R$-*saRe*, which isomerizes to the sterically favored π-$\mathbf{C}_R$-*ssSi* via a Ru-C(1) bond rotation, eliminating the steric repulsion in the 2nd quadrant. Reductive nucleophilic attack of the terminal NuH to π-allyl C(3) from the Ru side (NuH_{in}) gives (*S*)-**6** as the major isomer. In a similar way to this process, the $\mathbf{B}_S$-*saSi* => H_2O_{in} => π-$\mathbf{C}_S$-*saSi* => Ru-C(1) => π-$\mathbf{C}_S$-*ssRe* => NuH_{in} process produces (*R*)-**6**. In this combination, $K_R^1 k_R^1$ must be larger than $K_S^1 k_S^1$ for the predominant generation of (*S*)-**6**. The H_2O_{in} and NuH_{in} mode is supposed to be facilitated by an intramolecular H^+ assistance from Cl-Naph-PyCOOH coordinated to Ru(II) and by an intramolecular hydrogen bond of NuH with the basic Ru carboxylato oxygen atom, respectively. π-σ-π-isomerization non-involved pathways start from the sterically favored $\mathbf{B}_R$-*ssSi* and $\mathbf{B}_S$-*ssRe* (**Figure 9**, left): $\mathbf{B}_R$-*ssSi* => H_2O_{out} => π-$\mathbf{C}_R$-*ssSi* => NuH_{out} pathway and $\mathbf{B}_S$-*ssRe* => H_2O_{out} => π-$\mathbf{C}_S$-*ssRe* => NuH_{out} pathway to generate the minor (*R*)-**6** and major (*S*)-**6**, respectively, without any intramolecular H^+ assistance or hydrogen bond assistance. In this combination, an inequality, $K_S^2 k_S^2 > K_R^2 k_R^2$, should be established for making the (*S*)-**6** major. The 3rd quadrant of $\mathbf{B}_R$-*ssSi* and the 4th quadrant of $\mathbf{B}_S$-*ssRe* are sterically congested, making the H_2O liberation to the inside impossible. These H_2O_{out}/NuH_{out} processes can be realized through an activation of **5** in $\mathbf{B}_S$-*ssRe* or $\mathbf{B}_R$-*ssSi* from the outside by the highly acidic HPF_6 which is generated from $\mathbf{A}_R$ and $\mathbf{A}_S$ by formation of the corresponding neutral complexes. Activation of **5** by another $\mathbf{A}_R$ or $\mathbf{A}_S$ is also possible.

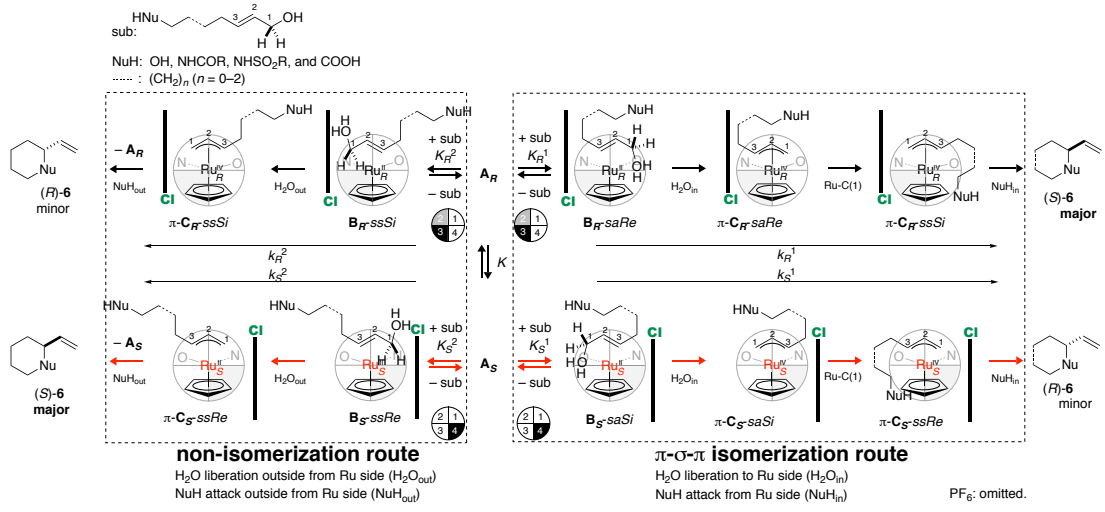

Figure 9. Reaction pathways via intramolecular and intermolecular activations of the allylic alcohol substrate **5**

The number of reaction pathways reaches 32 by 4 parameters including *ss*/*sa* and outside/inside modes both in the H_2O liberation step and in the NuH nucleophilic attack step; this is the case even with the assumptions that an *endo*-CpRu complex is formed,[24] the Ru-C(1) rotation is involved in the π-$\mathbf{C}_{\boldsymbol{R}}$-*saRe* isomerization to π-$\mathbf{C}_{\boldsymbol{R}}$-*ssSi*, and the sterically favored *syn*,*syn*-complex is not isomerized to the disfavored *syn*,*anti*-complex. The reaction pathways shown in **Figure 9** raise many questions about the mechanism: i) Is a "Redox-mediated Donor-Acceptor bifunctional Catalyst mechanism" really operating?; ii) In the case of the H_2O_{in}/NuH_{in} process, why does the reaction start from the sterically disfavored substrate/catalyst complexes?; iii) Why does $\mathbf{A}_{\boldsymbol{R}}$ more quickly turnover than $\mathbf{A}_{\boldsymbol{S}}$ in the H_2O_{in}/NuH_{in} pathway?; iv) Why does $\mathbf{A}_{\boldsymbol{S}}$ more quickly turnover than $\mathbf{A}_{\boldsymbol{R}}$ in the H_2O_{out}/NuH_{out} pathway?; v) Is a π-allyl Ru intermediate really operating, and is there any possibility for the operation of σ-allyl Ru intermediate?; and vi) What is the role of the chlorine atom, and is there any possibility for involvement of a hydrogen bond[25] or halogen bond[26]? To answer these questions, we are now trying to elucidate the mechanism via D-labeling experiments, kinetic studies, NMR studies, isolation of Ru complexes related to the present reaction and structural elucidation by X-ray diffraction, and theoretical calculations.

3. Conclusion

Discovery of the CpRu(II)/PyCOOH combined catalyst for the allyl protection/deprotection of alcohols[9,10] motivated further work on the development of an asymmetric version; 2-Cl-Ph-PyCOOH (**L7**) came up through investigation on the ligand structure-reactivity relationship in the dehydrative intramolecular allylation of ω-hydroxy allylic alcohol **5** to the corresponding cyclic ether **6**. Endowment of chirality with the basic skeleton has established a new axially chiral Cl-Naph-PyCOOH. Use of CpRu(II)/(*R*)-Cl-Naph-PyCOOH complex ((*R*)-**3**) has enabled the asymmetric construction of α-alkenyl-substituted heterocycles in quantitative yields with up to >99:1 er under the influence of even 0.01 mol% of (*R*)-**3**.[16,17] The breakaway from the traditional "salt-liberation-type" Tsuji-Trost asymmetric reaction to the new "dehydrative" process should extend a synthetic possibility for complex chiral natural and unnatural products. Establishment of a large-scale synthetic procedure for Cl-Naph-PyCOOH (**2a**) and the allyl esters **2b** has realized a reliable supply of the chiral ligands. The half-life time of (*R*)-**2b** racemization is 16,000 years at 25 °C with the activation energy barrier $\Delta G^{\ddagger}$ of 33.7 kcal/mol. The stereochemical stability is further enhanced by the formation of the corresponding Ru complexes. The monocationic CpRu(II)/(*R*)-Cl-Naph-PyCOOH complex **3** fluctuates between many species including the diastereomers, (*R*,R_{Ru})-**3** and (*R*,S_{Ru})-**3** and the neutral complex/HPF_6; therefore, there are many possible reaction pathways for generation of the major (*S*)-**6** and minor (*R*)-**6**. The number of reaction pathways reaches 32 by 4 parameters including *ss*/*sa* and outside/inside modes both in the H_2O liberation step and in the NuH nucleophilic attack step; this is the case even with the assumptions that an *endo*-CpRu π-allyl complex is formed,[24] the Ru-C(1) rotation is involved in the π-$\mathbf{C}_{\boldsymbol{R}}$-*saRe* isomerization to π-$\mathbf{C}_{\boldsymbol{R}}$-*ssSi*, and the sterically favored *syn*,*syn*-complex is not isomerized to the disfavored *syn*,*anti*-complex. Among these possible pathways, the two most probable are proposed to occur via π-allyl intermediates, although there is no proof at the present stage. D-Labeling experiments, NMR studies, isolation and structural elucidation of the related CpRu complexes, kinetic studies, and theoretical calculations are now under investigation to determine the pathway from **5** to the major (*S*)-**6**.

4. Experimental

4.1. General.

4.1.1. Instrumentation. Nuclear magnetic resonance (NMR) spectra were recorded on JEOL JNM-ECA-600 (600 MHz for ^{1}H, 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 $CHCl_3$ (δ 7.26 in ^{1}H NMR and δ 77.0 in ^{13}C NMR). The signal coupling patterns of ^{1}H and ^{13}C NMR are indicated as follows: s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet; and br, broad signal. The resolutions of ^{1}H- and ^{13}C-NMR spectra were 0.689 Hz and 1.44 Hz respectively. X-ray crystallographic analyses were conducted on a Rigaku Saturn 70 CCD system and the structures were solved by direct methods using "Crystal Structure" crystallographic software. High-resolution mass spectra (HRMS) were measured by ESI ionization method on a Bruker Daltonics micrOTOF-QII system. Shimadzu 17A and 2014 systems were used for gas chromatography (GC) analyses. High performance liquid chromatography (HPLC) analyses were performed on a Shimadzu LC-10A system. Optical rotations were measured on a JASCO P-1010-GT system. Melting points (mp) were determined on a Yanaco Micro Melting Point Apparatus.

4.1.2. Manipulation. A Teflon-coated magnetic bar was used for stirring of a reaction mixture. Room temperature (rt) was in the range of 28 °C from 25 °C. Reactions at higher temperature than rt were carried out by use of oil bath. Reactions at 0 °C and at –78 °C were carried out by use of an ice bath and of a dry ice/CH_3OH bath, respectively. 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. Brine means sat aq NaCl. All of metal-catalyzed reactions were carried out under Ar atmosphere by use of a general Schlenk technique unless otherwise specified. A Schlenk with Teflon J. Young valve was specified by "Young-type Schlenk." Schlenks were dried, before use, at ca. 250 °C by use of a heat gun under a reduced pressure, and silicon grease was used for connecting to a cold finger, a reflux condenser, and a glass stopper. 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 Schenk by use of a gas-tight syringe or cannulation method. Cannulation was performed by use of a 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. For the general synthesis of substrates under Ar atmosphere, non-degassed solvents were used.

4.2. Materials.

4.2.1. Solvents. Solvents for the the catalytic reaction and the complex preparation 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: Acetone-d_6 from molecular sieves 4A (MS 4A). 1,2-Dimethoxyethane (DME), *N*,*N*-dimethylacetamide (DMA), and dichloromethane (CH_2Cl_2) from CaH_2. Toluene from Na/benzophenone ketyl. Distilled water (H_2O) was purchased from Fujifilm Wako Pure Chemical and used without further purification. These were degassed by three freeze-thaw cycles before use. 2-Propanol (2-PrOH) for HPLC analyses, extra grade solvent was used. For the preparation of substrates, extraction, and column chromatography, first grade solvents were used without purification: dichloromethane (CH_2Cl_2), 1,4-dioxane, ethyl acetate (EtOAc), diethyl ether (Et_2O), hexane, methanol (CH_3OH), *tert*-butyl methyl ether (TBME), and *N*,*N*-dimethylformamide (DMF).

4.2.2. Silica gels and Celite. Analytical thin-layer chromatography (TLC) was performed using Merck 5715 plates precoated with silica gel 60 F_{254} (layer thickness, 0.25 mm). The product spots were visualized with a solution of phosphomolybdic acid (PMA), *p*-anisaldehyde, iodine (I_2), or cerium ammonium molybdate (CAM). Flash silica-gel column chromatography (SiO_2-chromatography) was performed using Daiko AP 300. Molecular sieves 4A (MS 4A) was purchased from Nacalai Tesque, and was activated at 250 °C under vacuum before use.

4.2.3. Reagents, chemicals, and ligands. All of reagents which were purchased from companies were used without further purification. These are listed below in the alphabetical order neglecting number suffix. Aldrich: trichloroborane (BCl_3) 1.0 M solution in heptane, copper(II) chloride ($CuCl_2$), 2-(trifluoromethyl)phenylboronic acid, and 2-fluorophenylboronic acid. Furuya metal: dodecacarbonyltriruthenium(0) ($Ru_3(CO)_{12}$). Kanto chemical: naphthalene-1-boronic acid. Kishida Chemical: 12 M aq HCl. Nacalai tesque: acetic acid (AcOH), 30% aq hydrogen peroxide (H_2O_2), lithium hydroxide monohydrate ($LiOH\cdot H_2O$), sodium bicarbonate ($NaHCO_3$), and 60 wt% sodium hydride (NaH). Tokyo Chemical Industry (TCI): 6-bromopyridine-2-carboxylic acid, 3-chlorophenylboronic acid, lithium aluminum hydride ($LiAlH_4$), 2-methoxyphenylboronic acid, *N*,*N*-dimethylcarbamoyl chloride, 2-methylphenylboronic acid, trimethylsilyl cyanide ($(CH_3)_3SiCN$), tetrakis(triphenylphosphine)palladium(0) ($Pd(PPh_3)_4$), pyridine-2-carboxylic acid (PyCOOH, **L4**), quinone-2-carboxylic acid (**L1**), and thionyl chloride ($SOCl_2$). Fujifilm Wako Pure Chemical: allyl alcohol, 2-bromo-3-methylpyridine, 70 wt% *m*-chlorobenzoyl peroxide (mCPBA), triethylsilane ($(C_2H_5)_3SiH$), and potassium carbonate (K_2CO_3). Strem: tris(acetonitrile)cyclopentadienylruthenium hexafluorophosphate ($[RuCp(CH_3CN)_3]PF_6$).

The next compounds were prepared according to the procedures reported: (1*S*)-camphorsultam,[27] 2-chlorophenylpyridine,[28] 2-(2,6-dichlorophenyl)pyridine,[28] 6-*tert*-butylpyridine-2-carboxylic acid (*t*-Bu-PyCOOH, **L5**),[29] 2-(2-bromophenyl)pyridine,[28] (*E*)-hept-2-ene-1,7-diol (**5**),[16] 8-methylquinoline-2-carboxylic acid (8-CH_3-QAH, **L3**),[30] allyl 6-phenylpyridine-2-carboxylate (Ph-PyCOOAll, **L6**),[31] allyl quinoline-2-carboxylate (QAAll, **L2**).[32] Cl-Naph-PyCOOH (**2a**), Cl-Naph-PyCOOAll (**2b**), 2-Cl-Ph-PyCOOH (**L7**), 2-Br-Ph-PyCOOH (**L8**), 2,6-Cl_2-Ph-PyCOOH (6-(2,6-dichlorophenyl)picolinic acid (**L9**)), 2-CF_3-Ph-PyCOOAll (**L10**), 2-F-Ph-PyCOOAll (**L11**), 2-CH_3O-Ph-PyCOOAll (**L12**), 2-CH_3-Ph-PyCOOAll (**L13**), 3-Cl-Ph-PyCOOAll (**L14**), and 4-Cl-Ph-PyCOOAll (**L15**) were synthesized. For the procedures, see section 4.4. The ^{1}H- and ^{13}C-NMR spectra, molecular structures of (R_a,1*S*)-**11** and (S_a,1*S*)-**11**, and the crystallographic data were listed in supporting information.

4.3. Ligand Structure-reactivity Relationship. General procedure: All manipulations were carried out under Ar by use of a general Schlenk technique, and all of solvents and solutions were degassed by three freeze-thaw cycles just before use. A 10 mM-solution of $[RuCp(CH_3CN)_3]PF_6$ (**1**) in CH_2Cl_2 (200 μL, 2.00 μmol) was charged in a dried and Ar-filled 10-mL Young Schlenk. To this was added a solution of ligand (10.0 mM in CH_2Cl_2, 200 μL, 2.00 μmol) by use of gas-tight syringes. The solution was carefully concentrated in vacuo. To this was added (*E*)-**5** (100 mM in DMA, 2.00 mL, 200 μmol) at rt. Heating to 100 °C and sealing the tube, the mixture was stirred at the temperature for 10 min. The reaction mixture was cooled to 0 °C, and 1-μL portion of the reaction mixture was subjected to GC analysis (column, J&W Scientific DB-5 (0.25 mm ϕ x 0.25 mm x 30 m); temp, 50 °C for 10 min –> 10 °C increase/min –> 200 °C; 140 kPa; splitless; t_R of **6**, 6.9 min; t_R of (*E*)-**5**, 18.7 min), and conversions were determined by comparison of the signal intensities. All of the reactions were carried on the same reaction scale. Ligand and conversion are listed below. QAH (**L1**) and 99%. QAAll (**L2**) and 99%. 8-CH_3-QAH (**L3**) and <1%. PyCOOH (**L4**) and 98%. *t*-Bu-PyCOOH (**L5**) and <1%. Ph-PyCOOH (**L6**) and 11%. 2-Cl-Ph-PyCOOH (**L7**) and 99%. 2-Br-Ph-PyCOOH (**L8**) and 99%. 2,6-Cl_2-Ph-PyCOOH (**L9**) and 37%. 2-CF_3-Ph-PyCOOAll (**L10**) and 3%. 2-F-Ph-PyCOOAll (**L11**) and 6%. 2-CH_3O-Ph-PyCOOAll (**L12**) and 10%. 2-CH_3-Ph-PyCOOAll (**L13**) and 5%. 3-Cl-Ph-PyCOOAll (**L14**) and 6%. 4-Cl-Ph-PyCOOAll (**L15**) and 9%.

4.4. Synthesis of PyCOOH-related Compounds.

4.4.1. Cl-Naph-PyCOOH (2a) and Cl-Naph-PyCOOAll (2b). The small-scale synthetic procedures to (±)-**2** without optimization of the reaction conditions have been already reported in supporting information of ref 16. In this full paper, the large-scale and optimized procedures are reported. All of the ^{1}H- and ^{13}C-NMR spectra of the synthetic intermediates were consistent with those reported in ref 16.

Process (i): A dry 1-L Schlenk tube was charged with naphthalene-2-boronic acid (**8**) (50.0 g, 291 mmol), 2-bromo-3-methylpyridine (**7**) (47.6 g, 378 mmol), DME (250 mL), K_2CO_3 (57.4 g, 415 mmol), and H_2O (50 mL). The solution was degassed by three freeze-thaw cycles, and $Pd(PPh_3)_4$ (1.60 g, 1.38 mmol) was added. Equipping a spiral condenser, the mixture was refluxed for 24 h. After being cooled to rt, all of volatiles were removed in vacuo. The residue was partitioned between EtOAc (200 mL) and H_2O (200 mL). The aq layer was extracted by three 50-mL portions of EtOAc, and the combined organic layers were washed with H_2O (200 mL) and brine (200 mL). Drying over Na_2SO_4 (10 g)/filtration/evaporation process afforded a crude product (63 g). The solid was washed with 1:2 EtOAc–hexane (300 mL) to give a nearly pure 3-methyl-2-naphthalen-1-ylpyridine (57.7 g, 95% yield). This was used for the next reaction without further purification. ^{1}H NMR ($CDCl_3$) δ 2.07 (s, 3H, CH_3), 7.26 (dd, J = 7.57, 4.82 Hz, 1H, ArH), 7.37–7.57 (m, 5H, ArH), 7.64 (d, J = 7.57 Hz, 1H, ArH), 7.88–7.91 (m, 2H, ArH), 8.59 (d, J = 7.57 Hz, 1H, ArH).

Process (ii): A dry 1-L Schlenk tube was charged with 3-methyl-2-naphthalen-1-ylpyridine (40.0 g, 182 mmol), $(C_2H_5)_3SiH$ (60.0 mL, 379 mmol), norbornene (34.4 g, 365 mmol), and toluene (160 mL). The solution was degassed by three freeze-thaw cycles, and $Ru_3(CO)_{12}$ (583 mg, 0.912 mmol) was added. Equipping a spiral condenser, the mixture was

refluxed for 36 h. After being cooled to rt, all of volatiles were removed in vacuo to give a crude product (77 g). This was purified by SiO_2-chromatogtaphy (150 g, hexane eluent then 1:10 EtOAc–hexane eluent) to give 2-(2-(triethylsilyl)naphthalen-1-yl)-3-methylpyridine (**9**) (59.6 g, 98% yield) as a brown solid. ^{1}H NMR ($CDCl_3$) δ 0.35–0.45 (m, 6H, CH_2CH$_3$), 0.70 (t, *J* = 7.76 Hz, 9H, CH$_2$CH_3), 1.95 (s, 3H, CH_3), 7.00 (d, *J* = 7.57 Hz, 1H, ArH), 7.19–7.32 (m, 4H, ArH), 7.60 (dd, *J* = 7.57, 1.1 Hz, 1H, ArH), 7.70 (d, *J* = 7.57 Hz, 1H, ArH), 7.75 (d, *J* = 7.57 Hz, 1H, ArH), 8.58 (dd, *J* = 4.92, 0.8 Hz, 1H, ArH).

Process (iii): A dry 2-L Schlenk tube was charged with **9** (59.0 g, 177 mmol) and CH_2Cl_2 (360 mL) and cooled to –78 °C. To this was added BCl_3 (1 M in heptane, 212 mL, 212 mmol). After 1.5-h stirring at the same temperature in a closed system, all volatiles were removed in vacuo. The Schlenk tube containing a yellowish brown residue was then charged with CH_3OH (180 mL), H_2O (180 mL), and $CuCl_2$ (71.4 g, 531 mmol). The tube was sealed with a cold finger, and the mixture was heated to reflux for 96 h. Cooling to rt, the whole mixture was partitioned between CH_2Cl_2 (200 mL) and 5 M aq NH_3 (200 mL). The aq layer was extracted by three 200-mL portions of CH_2Cl_2, and the combined organic layers were washed with 5 M aq NH_3 (200 mL) and brine (200 mL). Drying over Na_2SO_4 (20 g)/filtration/evaporation process afforded a light-green oil (53 g), which was purified by SiO_2-chromatography (250 g; 1:8 EtOAc–hexane) to give 2-(2-chloronaphthalen-1-yl)-3-methylpyridine (**10**) as a white solid (42.6 g, 95%). ^{1}H NMR ($CDCl_3$) δ 2.05 (s, 3H, CH_3), 7.15 (d, *J* = 8.94 Hz, 1H, ArH), 7.32 (dd, *J* = 7.56, 4.81 Hz, 1H, ArH), 7.38 (t, *J* = 7.56 Hz, 1H, ArH), 7.46 (t, *J* = 8.25 Hz, 1H, ArH), 7.55 (d, *J* = 8.94 Hz, 1H, ArH), 7.68 (d, *J* = 7.56 Hz, 1H, ArH), 7.84 (d, *J* = 8.25 Hz, 1H, ArH), 7.87 (d, *J* = 8.25 Hz, 1H, ArH), 8.64 (d, *J* = 4.81 Hz, 1H, ArH).

Process (iv): A dry 1-L Schlenk tube was charged with (±)-**10** (42.6 g, 168 mmol), AcOH (110 mL), and aq H_2O_2 (52.3 mL, 512 mmol). Equipping a spiral condenser, the mixture was refluxed for 18 h. After all volatiles were removed in vacuo, the residue was partitioned between CH_2Cl_2 (200 mL) and sat aq $NaHCO_3$ (300 mL). The aq layer was extracted by two-200 mL portions of CH_2Cl_2. The combined organic layers were washed with brine (200 mL), and then dried over Na_2SO_4 (20 g). Filtration followed by evaporation gave nearly pure (±)-2-(2-chloronaphthalen-1-yl)-3-methylpyridine-*N*-oxide (41 g) as a brown solid. A dry 1-L three-necked flask was charged with the *N*-oxide compound (41 g), CH_2Cl_2 (300 mL), *N*,*N*-dimethylcarbamoyl chloride (18.1 mL, 197 mmol), and $(CH_3)_3SiCN$ (36.1 mL, 287 mmol). The flask was equipped with a reflux condenser, and then the mixture was stirred at 60 °C for 42 h. After cooled to rt, the mixture was evaporated in vacuo. The residue was partitioned between CH_2Cl_2 (150 mL) and sat aq $NaHCO_3$ (150 mL). The aq layer was extracted with two 150-mL portions of CH_2Cl_2. The combined organic layers were washed with brine (200 mL), and dried over Na_2SO_4 (15 g). Filtration followed by evaporation gave a nearly-pure (±)-6-(2-chloronaphthalen-1-yl)-5-methylpyridine-2-carbonitrile (42 g). This was used for the next reaction without further purification.

Process (v): A 300-mL round-bottom flask was charged with the product obtained process (iv) (42 g) and 12 M aq HCl (90 mL). A spiral condenser was connected to the flask and the mixture was refluxed for 24 h in an open system. After cooled to rt, all of the volatiles were removed in vacuo to give a yellow solid. This was partitioned between CH_2Cl_2 (200 mL) and 2 M aq NaOH (150 mL). The organic layer was extracted by 2 M aq NaOH (100 mL). To the combined aq layers were added AcOH (30 mL), and this was extracted by CH_2Cl_2 (150 mL x 3). The combined organic layers were washed with brine (200 mL) and dried over Na_2SO_4 (20 g). Filtration followed by evaporation gave a nearly pure (±)-**2a** (40.8 g, 82%) as a white solid. ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H, CH_3), 7.05 (d, *J* = 8.26 Hz, 1H, ArH), 7.43 (dd, *J* = 8.26, 6.89 Hz, 1H, ArH), 7.53 (dd, *J* = 8.26, 6.89 Hz, 1H, ArH), 7.60 (d, *J* = 8.26 Hz, 1H, ArH), 7.94 (d, *J* = 8.26 Hz, 2H, ArH), 7.97 (d, *J* = 7.57 Hz, 1H, ArH), 8.27 (d, *J* = 7.57 Hz, 1H, ArH).

Process (vi): A dry 500-mL Schlenk tube was charged with (*S*)-camphorsultam (8.68 g, 40.3 mmol), 60 wt% NaH (3.22 g, 80.6 mmol), and toluene (80 mL), and the mixture was stirred for 1 h at rt. Another dry 150-mL Schlenk tube was charged with (±)-**2a** (12.0 g, 40.3 mmol) and $SOCl_2$ (30 mL) under Ar stream. The mixture was stirred at 50 °C for 3 h in a closed system, and then concentrated in vacuo. The residue was dissolved in THF (30 mL). The THF solution of (±)-**2a** was transferred to the toluene solution of (*S*)-camphorsultam, and the Schlenk of (±)-**2a** was washed with THF (30 mL x 2). The whole solution was stirred at rt for 24 h. The solution was evaporated, and the residue was partitioned between Et_2O (100 mL) and H_2O (80 mL). The aq layer was extracted with Et_2O (100-mL x 2). The combined organic layers were washed with brine (200 mL), and dried over Na_2SO_4 (20 g). Filtration followed by evaporation gave a crude product (23 g) as brown solid. This was purified two times by SiO_2-chromatography (400 g, 1:4 EtOAc–hexane eluent) to give (*R*)-6-(2-chloronaphthalen-1-yl)-5-methylpyridine-2-carbonyl (*S*)-camphorsultam imide ((*R*$_a$,1*S*)-**11**) (9.34 g, 47% yield) as a white solid and (*S*)-6-(2-chloronaphthalen-1-yl)-5-methylpyridine-2-carbonyl (*S*)-camphorsultam imide ((*S*$_a$,1*S*)-**11**) (9.04 g, 45% yield) as a white solid, respectively. (*R*$_a$,1*S*)-**11**: ^{1}H NMR ($CDCl_3$) δ 0.91 (s, 3H, CH_3), 1.00–1.05 (m, 1H, CH$_2$CC*H*CH$_2$), 1.20 (s, 3H, CH_3), 1.26 (dt, *J* = 10.3, 2.75 Hz, 1H, CHC*H*HCH), 1.71–1.77 (m, 2H, CH_2CH$_2$), 1.80–1.88 (m, 2H, CH$_2$CH_2), 1.93–1.98 (m, 1H, CHCH*H*CH), 2.07 (s, 3H, CH_3), 3.33 (d, *J* = 13.8 Hz, 1H, SC*H*H), 3.43 (d, *J* = 13.8 Hz, 1H, SCH*H*), 4.28 (m, 1H, NCH), 7.29 (d, *J* = 8.26 Hz, 1H, ArH), 7.40 (dt, *J* = 7.57, 1.38 Hz, 1H, ArH), 7.49 (dt, *J* = 7.57, 1.38 Hz, 1H, ArH), 7.54 (d, *J* = 8.26 Hz, 1H, ArH), 7.80 (d, *J* = 7.57 Hz, 1H, ArH), 7.84–7.89 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$) δ 18.8, 20.1, 21.8, 26.3, 33.3, 39.7, 45.5, 47.8, 48.9, 53.0, 66.1, 124.0, 125.7, 126.3, 127.1, 127.3, 128.3, 129.9, 131.0, 132.2, 132.5, 134.9, 136.8, 138.6, 149.4, 155.1, 166.6; HRMS (ESI) calcd for $C_{27}H_{28}ClN_2O_3S$ $[M+H]^+$ 495.1504, found 495.1501; $[\alpha]_D^{19.7}$ +42.5 (*c* 1.00, $CHCl_3$); mp. 190 °C. (*S*$_a$,1*S*)-**11**: ^{1}H NMR ($CDCl_3$) δ 0.94 (s, 3H, CH_3), 1.12–1.17 (m, 1H, CH$_2$CC*H*CH$_2$), 1.21 (s, 3H, CH_3), 1.21–1.33 (m, 2H, CHCH_2CH), 1.73–1.87 (m, 4H, CH$_2$CH$_2$), 2.09 (s, 3H, CH_3), 3.32 (d, *J* = 13.8 Hz, 1H, SC*H*H), 3.43 (d, *J* = 13.8 Hz, 1H, SCH*H*), 4.41 (m, 1H, NCH), 7.00 (d, *J* = 8.25 Hz, 1H, ArH), 7.39 (dt, *J* = 7.57, 1.37, Hz, 1H, ArH), 7.49 (ddd, *J* = 8.25, 7.57, 1.37 Hz, 1H, ArH), 7.56 (d, *J* = 8.94 Hz, 1H, ArH), 7.82 (d, *J* = 8.25 Hz, 1H, ArH), 7.87–7.89 (m, 3H, ArH); ^{13}C NMR ($CDCl_3$) δ 18.8, 20.2, 26.3, 33.2, 39.8, 45.7, 47.9, 49.4, 52.7, 65.9, 124.2, 125.5, 126.6, 127.0, 127.8, 128.3, 130.2, 130.2, 132.3, 132.9, 134.8, 136.9, 138.9, 149.6, 155.3, 165.6; HRMS (ESI) calcd for $C_{27}H_{28}ClN_2O_3S$ $[M+H]^+$ 495.1504, found 495.1496; $[\alpha]_D^{20.5}$ –204.3 (*c* 1.00, $CHCl_3$); mp. 161 °C. Compound (*R*$_a$,1*S*)-**11** (10 mg) was charged into a test tube (5 mm ϕ x 3 cm) and to this was added EtOAc (0.5 mL). The mixture was heated to be a clear solution, and this was kept at rt for 24 h to give a colorless plate crystal (7.3 mg). This was subjected to X-ray crystallographic analysis to determine the absolute stereochemistry. The *S*$_a$,1*S* isomer was also recrystallized in a similar way ((*S*$_a$,1*S*)-**11** (9.8 mg), EtOAc

(0.5 mL), colorless block crystal (8.2 mg)) and determined the absolute stereochemistry by X-ray crystallographic analysis.

Process (vii): A 1-L round-bottom flask was charged with (R_a,1*S*)-**11** (13.0 g, 26.3 mmol), LiOH·H_2O (1.65 g, 39.3 mmol), THF (260 mL), and H_2O (26.0 mL). The mixture was stirred at rt for 24 h. All of volatiles were removed in vacuo, and the residue was partitioned between TBME (200 mL) and H_2O (300 mL). The aq layer was washed by three 200-mL portions of TBME. To the aq layer was added AcOH (30 mL), and the mixture was extracted with CH_2Cl_2 (200 mL x 4). The combined organic layers were washed by brine (300 mL), and dried over Na_2SO_4 (20 g). Filtration followed by evaporation afforded a crude product (*R*)-**2a**. The product was transferred to 250-mL Schlenk tube. To this was added $SOCl_2$ (26.0 mL). After heating at 50 °C for 3 h followed by concentration in vacuo, allyl alcohol (50 mL) was introduced. The solution was stirred at rt for 24 h, and the mixture was evaporated. The residue was partitioned between CH_2Cl_2 (150 mL) and sat aq $NaHCO_3$ (150 mL). The aq layer was extracted with CH_2Cl_2 (150 mL x 2). The combined organic layers were washed by brine (200 mL) and dried over Na_2SO_4 (20 g). Filtration followed by evaporation afforded a crude product (14 g) as yellow oil, which was purified by SiO_2-chromatography (200 g; 1:6 EtOAc–hexane eluent) to give (*R*)-allyl 6-(2-chloronaphthalen-1-yl)-5-methylpyridine-2-carboxylate ((*R*)-**2b**) (8.21 g, 93% yield). ^{1}H NMR ($CDCl_3$) δ 2.08 (s, 3H, CH_3), 4.89 (d, *J* = 5.51 Hz, 2H, OCH_2), 5.26 (dd, *J* = 10.3, 1.38 Hz, 1H, CH=C*H*H), 5.38 (dd, *J* = 17.2, 1.38 Hz, 1H, CH=CH*H*), 6.00–6.08 (m, 1H, C*H*=CH_2), 7.09 (d, *J* = 8.26 Hz, 1H, ArH), 7.36 (dd, *J* = 8.26, 6.89 Hz, 1H, ArH), 7.46 (t, *J* = 7.57 Hz, 1H, ArH), 7.52 (d, *J* = 8.95 Hz, 1H, ArH), 7.80–7.87 (m, 3H, ArH), 8.17 (d, *J* = 7.57 Hz, 1H, ArH).

Process (viii): A 50-mL round-bottom flask was charged with (*R*)-**2b** (700 mg, 2.07 mmol), LiOH·H_2O (123 mg, 2.93 mmol), dioxane (18.0 mL), and H_2O (2.00 mL). The mixture was stirred at rt for 10 h. All of volatiles were removed in vacuo, and the residue was partitioned between EtOAc (50 mL) and H_2O (100 mL). The aq layer was washed with EtOAc (50 mL). To the aq layer was added AcOH (10 mL). The mixture was extracted with CH_2Cl_2 (50 mL x 3). The combined organic layers were washed with brine (100 mL) and dried over Na_2SO_4 (10 g). Filtration followed by evaporation afforded (*R*)-**2a** (570 mg, 92% yield). ^{1}H NMR ($CDCl_3$) δ 2.16 (s, 3H, CH_3), 7.05 (d, *J* = 8.26 Hz, 1H, ArH), 7.43 (dt, *J* = 8.26, 1.38 Hz, 1H, ArH), 7.54 (dt, *J* = 6.89, 1.38 Hz, 1H, ArH), 7.60 (d, *J* = 8.26 Hz, 1H, ArH), 7.94 (d, *J* = 9.64 Hz, 2H, ArH), 7.96 (d, *J* = 7.57 Hz, 1H, ArH), 8.27 (d, *J* = 7.57 Hz, 1H, ArH). All of the physical properties were consistent with those obtained on a small scale.[16]

(*S*)-Allyl 6-(2-chloronaphthalen-1-yl)-5-methylpyridine-2-carboxylate ((*S*)-**2b**) and (*S*)-6-(2-chloronaphthalen-1-yl)-5-methylpyridine-2-carboxylic acid ((*S*)-**2a**) were also prepared from (S_a,1*S*)-**11** (1.00 g, 2.02 mmol) in the same way as the *R* case. Conditions for (*S*)-**2b** synthesis: LiOH·H_2O (127 mg, 3.03 mmol), THF (18.0 mL), H_2O (2.00 mL), rt, 14 h. $SOCl_2$ (1.50 mL), 50 °C, 3 h. Allyl alcohol (2.80 mL), rt, 24 h. (*S*)-**2b** (598 mg, 91% yield). Conditions for (*S*)-**2a** synthesis: (*S*)-**2b** (300 mg, 890 mmol), LiOH·H_2O (52.4 mg, 1.25 mmol), dioxane (9.00 mL), H_2O (1.00 mL), rt, 14 h. (*S*)-**2a** (247 mg, 93% yield). All of the physical properties were consistent with those obtained on a small scale.[16]

4.4.2. 2-Cl-Ph-PyCOOH (L7). Process (i) A dry 50-mL-two-necked round bottom flask equipped with a glass stopper and a three-way stopcock was charged with 2-(2-chlorophenyl)pyridine (1.20 g, 6.32 mmol) and CH_2Cl_2 (10 mL). The resulting colorless solution was cooled to 0 °C, and mCPBA (1.64 g, 9.50 mmol) was added slowly. The temperature was gradually raised to rt, and the colorless solution was stirred for 6 h. Cooling again to 0 °C, 1 M aq NaOH (10 mL) was slowly added. The organic layer was washed with 1 M aq NaOH (10 mL) and brine (10 mL), and then dried over Na_2SO_4 (10 g). Filtration followed by evaporation gave nearly pure 2-(2-chlorophenyl)-pyridine-*N*-oxide (1.28 g) as a yellow oil. This was used for the next reaction without further purification.

Process (ii) A dry 50-mL Schlenk tube was charged with the *N*-oxide compound (750 mg, 3.65 mmol), CH_2Cl_2 (10 mL), and *N*,*N*-dimethylcarbamoyl chloride (587 mg, 5.46 mmol) in this order. After 30 min at rt, $(CH_3)_3SiCN$ (542 mg, 5.46 mmol) in CH_2Cl_2 (5 mL) was added. The Schlenk tube was equipped with a reflux condenser, and then the mixture was stirred at 50 °C for 12 h. After being cooled to rt, the mixture was added to 10 wt% aq K_2CO_3 (10 mL) and stirred for 1 h. The mixture was extracted with CH_2Cl_2 (10 mL), and the organic layer was washed with H_2O (10 mL), sat aq $NaHCO_3$ (10 mL), and brine (10 mL), and dried over Na_2SO_4 (10 g). Filtration followed by evaporation gave a yellow oil, which was purified by SiO_2-chromatography (30 g; eluent, 1:19 EtOAc–hexane) to give 6-(2-chlorophenyl)pyridine-2-carbonitrile (720 mg, 92% yield). ^{1}H NMR ($CDCl_3$) δ 7.38–7.42 (m, 2H, ArH), 7.49–7.51 (m, 1H, ArH), 7.62–7.64 (m, 1H, ArH), 7.71 (dd, *J* = 6.87, 1.37 Hz, 1H, ArH), 7.90–7.94 (m, 2H, ArH).

Process (iii) A dry 50-mL Schlenk tube was charged with 6-(2-chlorophenyl)pyridine-2-carbonitrile (1.00 g, 4.66 mmol) and 6 M aq HCl (15.5 mL). A spiral condenser was connected to the tube and the mixture was refluxed for 15 h in an open system. After being cooled to rt, all of the volatiles were removed in vacuo to give 6-(2-chlorophenyl)pyridine-2-carboxylic acid (2-Cl-Ph-PyCOOH, **L7**) (1.05 g, 97% yield) as a white solid. ^{1}H NMR ($CDCl_3$) δ 7.41–7.44 (m, 2H, ArH), 7.52–7.55 (m, 1H, ArH), 7.57–7.60 (m, 1H, ArH), 7.94 (d, *J* = 7.56 Hz, 1H, ArH), 8.05 (t, *J* = 7.56 Hz, 1H, ArH), 8.25 (d, *J* = 7.56 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 122.3, 127.2, 129.0, 130.5, 130.6, 131.4, 132.3, 137.0, 138.5, 145.7, 155.7, 163.9; HRMS (ESI) calcd for $C_{12}H_7ClNO_2$ $[M–H]^-$ 232.0171, found 232.0187; mp. 165 °C.

4.4.2. 2-Br-Ph-PyCOOH (L8). The procedures were the same as those for **L7**. The organic synthetic parameters were listed below. (i) 2-(2-Bromophenyl)pyridine (271 mg, 1.16 mmol), CH_2Cl_2 (10 mL), mCPBA (686 mg, 2.78 mmol), 0 °C –> rt, 3 h. Workup: addition of 1 M aq NaOH (10 mL) at 0 °C; washing of organic layer with 1 M aq NaOH (10 mL) and brine (10 mL); dryness over Na_2SO_4 (10 g); filtration/evaporation. Crude 2-(2-bromophenyl)pyridine-*N*-oxide (280 mg, yellow oil). (ii) The *N*-oxide compound (280 mg), CH_2Cl_2 (2.30 mL), *N*,*N*-dimethylcarbamoyl chloride (130 μL, 1.39 mmol), 30 min, rt, $(CH_3)_3SiCN$ (290 μL, 2.32 mmol) in CH_2Cl_2 (2 mL), reflux, 12 h. Workup: addition of 10 wt% aq K_2CO_3 (10 mL) at rt; extraction with CH_2Cl_2 (10 mL); washing of organic layer with H_2O (10 mL), sat aq $NaHCO_3$ (10 mL), and brine (10 mL); dryness over Na_2SO_4 (10 g); filtration/evaporation. Crude 6-(2-bromophenyl)pyridine-2-carbonitrile (620 mg, yellow oil): ^{1}H NMR (600 MHz, $CDCl_3$) δ 7.32 (ddd, *J* = 7.57, 7.57, 1.38 Hz, 1H, Ar), 7.45 (dd, *J* = 8.26, 7.57 Hz, 1H, Ar), 7.56 (dd, *J* = 7.57, 2.07 Hz, 1H, Ar), 7.70 (dd, *J* = 8.26, 1.38 Hz, 1H, Ar), 7.72 (dd, *J* = 7.57, 1.38 Hz, 1H, Ar), 7.90 (m, 2H, Ar). (iii) The crude carbonitrile (620 mg), 12 M aq HCl (3.0 mL), reflux, 24 h. Workup: evaporation in vacuo; partition between CH_2Cl_2 (10 mL) and aq $NaHCO_3$–AcOH (10 mL); adjustment of pH of the aq layer to 4 by AcOH; extraction of the aq layer with CH_2Cl_2 (10 mL x 2);

dryness of the organic layers over Na_2SO_3 (10 g); filtration/evaporation. Crude **L8** (350 mg). Purification: recrystallization from 1:1:0.5 Et_2O–2-PrOH–CH_2Cl_2. 6-(2-Bromophenyl)pyridine-2-carboxylic acid (**L8**) (290 mg, 90% yield, white solid): ^{1}H NMR ($CDCl_3$) δ 7.34 (dt, *J* = 7.57, 1.38 Hz, 1H, ArH), 7.47 (t, *J* = 7.57 Hz, 1H, ArH), 7.53 (dd, *J* = 7.57, 1.38 Hz, 1H, ArH), 7.74 (d, *J* = 7.57 Hz, 1H, ArH), 7.89 (d, *J* = 7.57 Hz, 1H, ArH), 8.05 (t, *J* = 7.57 Hz, 1H, ArH), 8.25 (d, *J* = 7.57 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 121.7, 122.4, 127.8, 128.9, 130.7, 131.3, 133.7, 138.5, 138.9, 145.6, 157.1, 164.0; HRMS (ESI) calcd for $C_{12}H_7BrNO_2$ $[M–H]^–$ 275.9666, found 275.9676; mp. 154 °C.

4.4.3. 2,6-Cl_2-Ph-PyCOOH (L9). The procedures were the same as those for **L7**. (i) 2-(2,6-Dichlorophenyl)pyridine (1.10 g, 4.91 mmol), CH_2Cl_2 (15 mL), mCPBA (1.69 g, 9.79 mmol), 0 °C –> rt, 6 h. Workup: addition of 1 M aq NaOH (10 mL) at 0 °C; washing of organic layer with 1 M aq NaOH (10 mL) and brine (10 mL); dryness over Na_2SO_4 (3 g); filtration/evaporation. Nearly pure 2-(2,6-dichlorophenyl)-pyridine-*N*-oxide (1.2 g, yellow oil). (ii) The *N*-oxide compound (1.2 g), CH_2Cl_2 (15 mL), *N*,*N*-dimethylcarbamoyl chloride (676 μL, 7.35 mmol), 30 min, rt, $(CH_3)_3SiCN$ (923 μL, 7.35 mmol) in CH_2Cl_2 (5 mL), 50 °C, 12 h. Workup: addition of 10 wt% aq K_2CO_3 (10 mL) at rt followed by 1-h stirring; extraction with CH_2Cl_2 (20 mL); washing of the organic layer with H_2O (20 mL) and brine (20 mL); dryness over Na_2SO_4 (6 g); filtration/evaporation. Purification: SiO_2-chromatography (50 g; eluent, 1:7 EtOAc–hexane). 6-(2,6-Dichlorophenyl)pyridine-2-carbonitrile (1.15 g, 94% yield): ^{1}H NMR ($CDCl_3$) δ 7.33 (dd, *J* = 8.25, 1.37 Hz, 1H, ArH), 7.42 (d, *J* = 8.25 Hz, 2H, ArH), 7.57 (d, *J* = 8.25, 1H, ArH), 7.76 (d, *J* = 8.25 Hz, 1H, ArH), 7.98 (t, *J* = 7.56 Hz, 1H, ArH). (iii) The carbonitrile compound (1.08 g, 4.33 mmol), 6 M aq HCl (8 mL), reflux, 15 h. Workup: evaporation in vacuo to liberate a white solid product. 6-(2,6-Dichlorophenyl)pyridine-2-carboxylic acid (**L9**) (1.05 g, 91% yield): ^{1}H NMR ($CDCl_3$) δ 7.36 (t, *J* = 8.26 Hz, 1H, ArH), 7.46 (d, *J* = 8.26 Hz, 2H, ArH), 7.65 (d, *J* = 7.57 Hz, 1H, ArH), 8.09 (t, *J* = 7.57 Hz, 1H, ArH), 8.29 (d, *J* = 7.57 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 123.0, 128.4, 129.6, 130.6, 134.5, 136.4, 138.9, 145.9, 154.1, 163.8; HRMS (ESI) calcd for $C_{12}H_6Cl_2NO_2$ $[M–H]^–$ 265.9781, found 265.9781; mp. 180 °C.

4.4.4. 2-CF_3-Ph-PyCOOAll (L10). Process (i): A dry 50-mL Schlenk tube was charged with 2-(trifluoromethyl)phenylboronic acid (522 mg, 2.75 mmol), DME (13 mL), 2 M aq K_2CO_3 (6.6 mL), and 6-bromopyridine-2-carboxylic acid (505 mg, 2.50 mmol). The solution was degassed by three freeze-thaw cycles, and $Pd(PPh_3)_4$ (143 mg, 124 μmol) was added. Equipping a spiral condenser, the mixture was refluxed for 12 h. After being cooled to rt, the reaction mixture was extracted with CH_2Cl_2 (10 mL). The aq layer was extracted by three 10-mL portions of CH_2Cl_2, and the combined organic layers were dried over Na_2SO_4 (10 g). Filtration/evaporation process afforded a yellow solid (ca. 1 g). This was used for the next reaction without further purification.

Process (ii): A dry 50-mL Schlenk tube was charged with 6-(2-trifluoromethylphenyl)pyridine-2-carboxylic acid (ca. 1 g) and to this was added $SOCl_2$ (3.60 mL) under Ar stream. The mixture was stirred at 50 °C for 1 h in a closed system, and then concentrated in vacuo. To this was added allyl alcohol (3.40 mL). After 6-h stirring at rt followed by concentration, the resulting residue was dissolved in CH_2Cl_2 (10 mL). This was washed with sat aq $NaHCO_3$ (5 mL) and dried over Na_2SO_4 (5 g). Filtration/evaporation process afforded a white solid, which was purified by SiO_2-chromatography (25 g; eluent, 1:3 EtOAc–hexane) to give allyl 6-(2-trifluoromethylphenyl)pyridine-2-carboxylate (**L10**) (606 mg, 81% yield) as a colorless oil. ^{1}H NMR ($CDCl_3$) δ 4.91 (dt, *J* = 5.51, 1.38 Hz, 2H, C*H*$_2$CH=CH$_2$), 5.28 (dd, *J* = 10.3, 1.38 Hz, 1H, CH$_2$CH=C*H*H), 5.42 (dd, *J* = 17.2, 1.38 Hz, 1H, CH$_2$CH=CH*H*), 6.02–6.08 (m, 1H, CH$_2$C*H*=CH$_2$), 7.52 (t, *J* = 8.26 Hz, 1H, ArH), 7.53 (d, *J* = 8.26 Hz, 1H, ArH), 7.60 (d, *J* = 7.57 Hz, 1H, ArH), 7.61 (t, *J* = 7.57 Hz, 1H, ArH), 7.75 (d, *J* = 7.57 Hz, 1H, ArH), 7.89 (t, *J* = 8.26 Hz, 1H, ArH), 8.15 (d, *J* = 7.57 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 66.4, 118.7, 123.9,124.9, 126.4, 127.2, 128.6, 131.6, 131.75, 131.81, 136.9, 139.1, 147.7, 158.0, 164.7; HRMS (ESI) calcd for $C_{16}H_{12}F_3NNaO_2$ $[M+Na]^+$ 330.0712, found 330.0717.

4.4.5. 2-F-Ph-PyCOOAll (L11). The procedures were the same as those for **L10**. (i) 2-Fluorophenylboronic acid (347 mg, 2.48 mmol), DME (13 mL), 2 M aq K_2CO_3 (6.6 mL), 6-bromopyridine-2-carboxylic acid (500 mg, 2.48 mmol), $Pd(PPh_3)_4$ (143 mg, 124 μmol), reflux, 12 h. Workup: addition of CH_2Cl_2 (10 mL); extraction of the aq layer with CH_2Cl_2 (10 mL x 3); dryness over Na_2SO_4 (10 g); filtration/evaporation process. Crude product (ca. 0.5 g, yellow solid). (ii) The carboxylic acid compound (ca. 0.5 g), $SOCl_2$ (3.60 mL), 50 °C, 1 h; concentration in vacuo; allyl alcohol (3.40 mL), 8 h, rt. Workup: concentration in vacuo; dissolving in CH_2Cl_2 (10 mL); washing with sat aq $NaHCO_3$ (5 mL); dryness over Na_2SO_4 (5 g); filtration/evaporation. Crude product (ca. 600 mg). Purification: SiO_2-chromatography (25 g; eluent, 1:3 EtOAc–hexane). Allyl 6-(2-fluorophenyl)pyridine-2-carboxylate (**L11**) (457 mg, 72% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.92 (dd, *J* = 6.20, 1.38 Hz, 1H, C*H*$_2$CH=CH$_2$), 5.31 (d, *J* = 10.3 Hz, 1H, CH$_2$CH=C*H*H), 5.46 (dd, *J* = 17.2, 1.38 Hz, 1H, CH$_2$CH=CH*H*), 6.06–6.12 (m, 1H, CH$_2$C*H*=CH$_2$), 7.14 (t, *J* = 8.95 Hz, 1H, ArH), 7.27 (t, *J* = 7.57 Hz, 1H, ArH), 7.38 (dd, *J* = 8.26, 7.57 Hz, 1H, ArH), 7.87 (dd, *J* = 7.57, 2.07 Hz, 1H, ArH), 7.97 (d, *J* = 6.89 Hz, 1H, ArH), 8.07 (d, *J* = 8.26 Hz, 1H, ArH), 8.11 (dd, *J* = 7.57, 2.07 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 66.4, 116.2, 118.8, 123.7, 124.7, 126.6, 127.7, 130.90, 131.5, 137.3, 148.2, 153.6, 159.8, 161.5, 164.9; HRMS (ESI) calcd for $C_{15}H_{12}FNNaO_2$ $[M+Na]^+$ 280.0744, found 280.0749.

4.4.6. 2-CH_3O-Ph-PyCOOAll (L12). The procedures were the same as those for **L10**. (i) 2-Methoxyphenylboronic acid (377 mg, 2.48 mmol), DME (13 mL), 2 M aq K_2CO_3 (6.6 mL), 6-bromopyridine-2-carboxylic acid (500 mg, 2.48 mmol), $Pd(PPh_3)_4$ (143 mg, 124 μmol), reflux, 12 h. Workup: addition of CH_2Cl_2 (10 mL); extraction of the aq layer with CH_2Cl_2 (10 mL x 3); dryness over Na_2SO_4 (10 g); filtration/evaporation. Crude product (ca. 0.5 g, yellow solid). (ii) The carboxylic acid compound (ca. 0.5 g), $SOCl_2$ (3.60 mL), 50 °C, 1 h; concentration in vacuo; allyl alcohol (3.40 mL), 8 h, rt. Workup: concentration in vacuo; dissolving in CH_2Cl_2 (10 mL); washing with sat aq $NaHCO_3$ (5 mL); dryness over Na_2SO_4 (5 g); filtration/evaporation. Crude product (ca. 0.5 g, white solid). Purification: SiO_2-chromatography (25 g; eluent, 1:3 EtOAc–hexane). Allyl 6-(2-methoxyphenyl)pyridine-2-carboxylate (**L12**) (425 mg, 64% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 3.84 (s, 3H, OCH_3), 4.91 (d, *J* = 5.51 Hz, 2H, C*H*$_2$CH=CH$_2$), 5.30 (d, *J* = 11.0 Hz, 1H, CH$_2$CH=C*H*H), 5.45 (dd, *J* = 17.2, 1.38 Hz, 1H, CH$_2$CH=CH*H*), 6.05–6.11 (m, 1H, CH$_2$C*H*=CH$_2$), 6.98 (d, *J* = 8.26 Hz, 1H, ArH), 7.09 (t, *J* = 7.57 Hz, 1H, ArH), 7.37 (t, *J* = 8.26 Hz, 1H, ArH), 7.81 (t, *J* = 7.57 Hz, 1H, ArH), 7.91 (dd, *J* = 7.57, 1.38 Hz, 1H, ArH), 8.03 (d, *J* = 8.26 Hz, 1H, ArH), 8.04 (d, *J* = 8.26 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 55.5, 66.1, 111.3, 118.5, 121.2, 122.9, 128.2, 128.4, 130.3, 131.5, 132.0, 136.3, 147.8, 156.2, 157.0, 165.2;

HRMS (ESI) calcd for $C_{16}H_{15}NNaO_3$ $[M+Na]^+$ 292.0944, found 292.0963.

4.4.7. 2-CH$_3$-Ph-PyCOOAll (L13). The procedures were the same as those for **L10**. (i) 2-Methylphenylboronic acid (405 mg, 2.98 mmol), DME (13 mL), 2 M aq K_2CO_3 (6.6 mL), 6-bromopyridine-2-carboxylic acid (500 mg, 2.48 mmol), $Pd(PPh_3)_4$ (143 mg, 124 μmol), reflux, 12 h. Workup: addition of CH_2Cl_2 (10 mL); extraction of the aq layer with CH_2Cl_2 (10 mL x 3); dryness over Na_2SO_4 (10 g); filtration/evaporation. Crude product (ca. 0.5 g, yellow solid). (ii) The carboxylic acid compound (ca. 0.5 g), $SOCl_2$ (3.60 mL), 50 °C, 1 h; concentration in vacuo; allyl alcohol (3.40 mL), 8 h, rt. Workup: concentration in vacuo; dissolving in CH_2Cl_2 (10 mL); washing with sat aq $NaHCO_3$ (5 mL); dryness over Na_2SO_4 (5 g); filtration/evaporation. Crude product (ca. 0.5 g, white solid). Purification: SiO_2-chromatography (25 g; eluent, 1:3 EtOAc–hexane). Allyl 6-(2-methylphenyl)pyridine-2-carboxylate (**L13**) (363 mg, 58% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 2.40 (s, 3H, CH_3), 4.92 (dt, *J* = 5.51, 1.38 Hz, 2H, C*H*$_2$CH=CH$_2$), 5.30 (dd, *J* = 10.3, 1.38 Hz, 1H, CH$_2$CH=C*H*H), 5.45 (d, *J* = 17.2, 1.38 Hz, 1H, CH$_2$CH=CH*H*), 6.04–6.11 (m, 1H, CH$_2$C*H*=CH$_2$), 7.28–7.33 (m, 2H, ArH), 7.43 (d, *J* = 7.57 Hz, 1H, ArH), 7.59 (dd, *J* = 7.57, 1.38 Hz, 1H, ArH), 7.89 (t, *J* = 7.57 Hz, 1H, ArH), 8.09 (d, *J* = 7.57 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 20.4, 66.2, 118.6, 123.0, 125.9, 127.2, 128.6, 129.8, 130.9, 131.9, 136.1, 137.0, 139.5, 147.6, 160.3, 165.1; HRMS (ESI) calcd for $C_{16}H_{15}NNaO_2$ $[M+Na]^+$ 276.0995, found 276.1024.

4.4.8. 3-Cl-Ph-PyCOOAll (L14). The procedures were the same as those for **L10**. (i) 3-Chlorophenylboronic acid (465 mg, 2.98 mmol), DME (13 mL), 2 M aq K_2CO_3 (6.6 mL), 6-bromopyridine-2-carboxylic acid (500 mg, 2.48 mmol), $Pd(PPh_3)_4$ (143 mg, 124 μmol), reflux, 24 h. Workup: addition of CH_2Cl_2 (10 mL); extraction of the aq layer with CH_2Cl_2 (10 mL x 3); dryness over Na_2SO_4 (10 g); filtration/evaporation. Crude product (ca. 0.5 g, yellow solid). Purification: recrystallization from 2:2:1 Et_2O–CH_2Cl_2–hexane (ca 1 mL). 6-(3-Chlorophenyl)pyridine-2-carboxylic acid (**L14**) (403 mg, 70% yield) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 7.48 (br, 2H, ArH), 7.86–7.87 (m, 1H, ArH), 7.99 (d, *J* = 7.57 Hz, 2H, ArH), 8.05 (t, *J* = 7.57 Hz, 1H, ArH), 8.23 (d, *J* = 7.57 Hz, 1H, ArH). (ii) The carboxylic acid compound (100 mg, 428 μmol), $SOCl_2$ (160 μL), 50 °C, 1 h; concentration in vacuo; allyl alcohol (150 μL), 6 h, rt. Workup: concentration in vacuo; dissolving in CH_2Cl_2 (10 mL); washing with sat aq $NaHCO_3$ (5 mL); dryness over Na_2SO_4 (5 g); filtration/evaporation. Crude product (ca. 0.5 g, white solid). Purification: SiO_2-chromatography (25 g; eluent, 1:3 EtOAc–hexane). Allyl 6-(3-chlorophenyl)pyridine-2-carboxylate (**L14**) (93.1 mg, 80% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.92 (d, *J* = 6.20 Hz, 2H, C*H*$_2$CH=CH$_2$), 5.33 (d, *J* = 10.3 Hz, CH$_2$CH=C*H*H), 5.48 (dd, *J* = 17.2, 1.38 Hz, 1H, CH$_2$CH=CH*H*), 6.06–6.13 (m, 1H, CH$_2$C*H*=CH$_2$), 7.38–7.42 (m, 2H, ArH), 7.86–7.93 (m, 3H, ArH), 8.06 (s, 1H, ArH), 8.07 (d, *J* = 6.89 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 66.4, 118.8, 123.5, 123.8, 125.2, 127.3, 129.4, 130.0, 131.8, 134.9, 137.8, 140.1, 148.1, 156.1, 164.8; HRMS (ESI) calcd for $C_{15}H_{12}NNaO_2$ $[M+Na]^+$ 296.0449, found 296.0469; mp. 46 °C.

4.4.9. 4-Cl-Ph-PyCOOAll (L15). The procedures were the same as those for **L10**. (i) 4-Chlorophenylboronic acid (466 mg, 2.98 mmol), DME (13 mL), 2 M aq K_2CO_3 (6.6 mL), 6-bromopyridine-2-carboxylic acid (500 mg, 2.48 mmol), $Pd(PPh_3)_4$ (143 mg, 124 μmol), reflux, 24 h. Workup: addition of CH_2Cl_2 (10 mL); extraction of the aq layer with CH_2Cl_2 (10 mL x 3); dryness over Na_2SO_4 (10 g); filtration/evaporation. Crude product (ca. 0.5 g, yellow solid). Purification: recrystallization from 2:2:1 Et_2O–CH_2Cl_2–hexane (ca 1 mL). 6-(4-Chlorophenyl)pyridine-2-carboxylic acid (419 mg, 72% yield) as a colorless solid: ^{1}H NMR ($CDCl_3$) δ 7.51 (d, *J* = 8.26 Hz, 2H, ArH), 7.94 (d, *J* = 8.26 Hz, 2H, ArH), 7.98 (d, *J* = 8.95 Hz, 1H, ArH), 8.05 (t, *J* = 8.26 Hz, 1H, ArH), 8.21 (d, *J* = 7.57 Hz, 1H, ArH). (ii) The carboxylic acid compound (110 mg, 471 μmol), $SOCl_2$ (170 μL), 50 °C, 1 h; concentration in vacuo; allyl alcohol (160 μL); 6 h, rt. Workup: concentration in vacuo; dissolving in CH_2Cl_2 (10 mL); washing with sat aq $NaHCO_3$ (5 mL); dryness over Na_2SO_4 (5 g); filtration/evaporation. Crude product (ca. 0.5 g, white solid). Purification: SiO_2-chromatography (25 g; eluent, 1:3 EtOAc–hexane). Allyl 6-(2-trifluoromethylphenyl)pyridine-2-carboxylate (**L15**) (125 mg, 97% yield) as a colorless oil: ^{1}H NMR ($CDCl_3$) δ 4.93 (d, *J* = 5.51 Hz, 2H, C*H*$_2$CH=CH$_2$), 5.34 (d, *J* = 10.3 Hz, CH$_2$CH=C*H*H), 5.48 (d, *J* = 17.2 Hz, CH$_2$CH=CH*H*), 6.07–6.13 (m, 1H, CH$_2$C*H*=CH$_2$), 7.46 (d, *J* = 8.26 Hz, 2H, ArH), 7.88–7.92 (m, 2H, ArH), 8.03 (d, *J* = 8.26 Hz, 1H, ArH), 8.07 (d, *J* = 6.89 Hz, 1H, ArH); ^{13}C NMR ($CDCl_3$) δ 66.4, 118.8, 123.2, 123.6, 128.4, 129.0, 131.9, 135.7, 136.8, 137.8, 148.1, 156.4, 164.9; HRMS (ESI) calcd for $C_{15}H_{12}ClNNaO_2$ $[M+Na]^+$ 296.0449, found 296.0427; mp. 43 °C.

4.5. Determination of the Half Life Time of (*R*)-Cl-Naph-PyCOOAll. A 20-mL Young-type Schlenk flask was charged with (*R*)-**2b** (2.98 mg, 10.0 μmol) and DMA (1.00 mL). After degassing the system by three-freeze/thaw cycles, the mixture was heated at 130 °C by use of a Riko MH-5D oil bath, which was adjusted so that the measurement temperature was kept the same throughout the whole process. After 1 h, the Schlenk flask was moved to an ice bath, and an aliquot of the mixture (ca. 0.1 mL) was sampled under Ar. Immediately after sampling (ca. 5 min), the Schlenk flask was inserted into the 130 °C-oil bath. The sample was partitioned between Et_2O (1 mL) and H_2O (1 mL). The organic layer was washed with H_2O (1 mL x 2) and concentrated in vacuo. This was subjected to er analysis by HPLC (column, CHIRALCEL OD-H (0.46 cm ϕ x 25 cm); eluent, 1:5 2-PrOH–hexane; flow rate, 1 mL min^{-1}; detection, 254-nm light; t_R, 8.9 min ((*R*)-**2b**) and 12.2 min ((*S*)-**2b**)), determining the er to be 99.4:0.6. In the same way, the ers were measured at 12 h, 25 h, 37 h, and 43 h to be 90.2:9.8, 81.9:18.1, 75.8:24.2, and 73.1:26.9, respectively. The logarithmic plot of ln(ee) versus time determined the racemization rate k_{rac} to be 5.01 x 10^{-6} s^{-1}. (ee = enantiomeric excess, ee = (100 x |[*R* isomer] – [*S* isomer]|)/([*R* isomer] + [*S* isomer])). By use of the Eyring equation ($\Delta G^{\ddagger} = 8.314T \ln(2.084 \times 10^{10}\ T/k_{rac})$), the rotational energy barrier $\Delta G^{\ddagger}$ was determined to be 140.6 kJ mol^{-1} at 403 K. The half-life time was calculated to be 16,000 year at 25 °C ($t_{1/2} = \ln 2/k_{rac}$).

4.6. ^{1}H-NMR Experiments. A Young type NMR tube was charged with (*R*)-Cl-Naph-PyCOOH ((*R*)-**2a**) (2.98 mg, 10.0 μmol), $[RuCp(CH_3CN)_3]PF_6$ (**1**) (4.34 mg, 10.0 μmol), and acetone-d_6 (900 mL). The resulting reddish solution was subjected to ^{1}H-NMR analysis at 18 °C, 30 °C, and 40 °C (**Figure 7a**). A solution of Et_3N (100 mM in acetoen-d_6, 100 μL, 10 μmol) was added to another (*R*)-**2a**/**1** solution prepared in the same way. After 30 min at 27 °C, this was subjected to ^{1}H-NMR analysis at –40 °C, –20 °C, and 0 °C (**Figure 7b**).

Acknowledgement

This work was aided by a Grant-in-Aid for Scientific Research (JP25410112, JP22750088, JP16F16339) from the Ministry of Education, Culture, Sports, Science and Technology (Japan).

References

1. R. S. Grant, S. E. Coggan, G. A. Smythe, *International Journal of Tryptophan Research*, **2009**, 271.
2. P. L. Fuchs, *Handbook of Reagents for Organic Synthesis: Catalytic Oxidation Reagents*, John Wiley & Sons, New York, **2013**. The number of substances that match the metal picolinate structure by substructure search using SciFinder exceeds 13000.
3. E. G. Cox, W. Wardlaw, K. C. Webster, *J. Chem. Soc*. **1936**, 775.
4. S. E. Jacobson, D. A. Muccigrosso, F. Mares, *J. Org. Chem.* **1979**, *44*, 921.
5. Au: a) X.-Q. Li, C. Li, F.-B. Song, C. Zhang, *J. Chem. Res.* **2007**, 722. Cu: b) M. V. Kirillova, A. M. Kirillov, M. F. C. G. da Silva, A. J. L. Pombeiro, *Eur. J. Inorg. Chem.* **2008**, 3423. Fe: c) G. Balavoine, D. H. R. Barton, J. Boivin, A. Gref, *Tetrahedron Lett*. **1990**, *31*, 659. d) C. Sheu, S. A. Richert, P. Cofré, B. Ross, A. Sobkowiak, D. T. Sawyer, J. R. Kanofsky, *J. Am. Chem. Soc.* **1990**, *112*, 1936. e) T. Chishiro, Y. Kon, T. Nakashima, M. Goto, K. Sato, *Adv. Synth. Catal.* **2014**, *356*, 623. Mo: f) N. Gharah, M. G. B. Drew, R. Bhattacharyya, *Transition Met. Chem.* **2009**, *34*, 549. Pd: g) S. Taubmann, H. G. Alt, *J. Mol. Cat. A* **2008**, *289*, 44. Re: h) A. M. Kirillov, M. Haukka, M. V. Kirillova, A. J. L. Pombeiro, *Adv. Synth. Catal*. **2005**, *347*, 1435. Ru: h) T. Kojima, Y. Hirai, T. Ishizuka, Y. Shiota, K. Yoshizawa, K. Ikemura, T. Ogura, S. Fukuzumi, *Angew. Chem. Int. Ed.* **2010**, *49*, 8449. V: i) H. Mimoun, L. Saussine, E. Daire, M. Postel, J. Fischer, R. Weiss, *J. Am. Chem. Soc.* **1983**, *105*, 3101. W: ref 4.
6. Au: a) A. S. K. Hashmi, J. P. Weyrauch, M. Rudolph, E. Kurpejovic, *Angew. Chem. Int. Ed.* **2004**, *43*, 6545. b) S. Wang, L. Zhang, *J. Am. Chem. Soc.* **2006**, *128*, 8414. c) N. D. Shapiro, F. D. Toste, *J. Am. Chem. Soc.* **2008**, *130*, 9244. d) P. W. Davies, S. J.-C. Albrecht, *Angew. Chem. Int. Ed*. **2009**, *48*, 8372. Mo: e) M. Vasconcellos-Dias, C. D. Nunes, P. D. Vaz, P. Ferreira, M. J. Calhorda, *Eur. J. Inorg. Chem.* **2007**, 2917. Mo: f) M. Vasconcellos-Dias, C. D. Nunes, P. D. Vaz, P. Ferreira, M. J. Calhorda, *Eur. J. Inorg. Chem.* **2007**, 2917. Pd: g) S. Jayasree, A. Seayad, R. V. Chaudhari, *Org. Lett.* **2000**, *2*, 203–206. Pd: h) S. Jayasree, A. Seayad, R. V. Chaudhari, *Org. Lett.* **2000**, *2*, 203. Rh: i) D. K. Dutta, P. Chutia, B. J. Sarmah, B. J. Borah, B. Deb, J. D. Woollins, *J. Mol. Cat. A* **2009**, *300*, 29. Ru: j) F. E. Hahn, M. Paas, R. Fröhlich, *J. Organomet. Chem.* **2005**, *690*, 5816. Ti: k) S. Park, Y. Do, *J. Organomet. Chem.* **2007**, *692*, 1633.
7. H. Katada, H. Seino, Y. Mizobe, J. Sumaoka, M. Komiyama, *J. Biol. Inorg. Chem.* **2008**, *13*, 249.
8. a) H. Nishiyama, T. Shimada, H. Itoh, H. Sugiyama, Y. Motoyama, *Chem. Commun.* **1997**, 1863. b) M. K. Tse, S. Bhor, M. Klawonn, C. Döbler, M. Beller, *Tetrahedron Lett.* **2003**, *44*, 7479. c) D. Chatterjee, S. Basak, A. Riahi, J. Muzart, *Catal. Commun*. **2007**, *8*, 1345.
9. S. Tanaka, H. Saburi, Y. Ishibashi, M. Kitamura, *Org. Lett.* **2004**, *6*, 1873.
10. a) H. Saburi, S. Tanaka, M. Kitamura, *Angew. Chem. Int. Ed.* **2005**, *44*, 1730. b) S. Tanaka, H. Saburi, M. Kitamura, *Adv. Synth. Catal.* **2006**, *348*, 375. c) S. Tanaka, H. Saburi, T. Hirakawa, T. Seki, M. Kitamura, *Chem. Lett.* **2009**, *38*, 188. d) T. Hirakawa, S. Tanaka, N, Usuki, H. Kanzaki, M. Kishimoto, M. Kitamura, *Eur. J. Org. Chem.* **2009**, 789. e) S. Tanaka, Y. Suzuki, H. Saburi, M. Kitamura, *Tetrahedron* **2015**, *71*, 6559.
11. P. Jaisankar, S. Tanaka, M. Kitamura, *J. Org. Chem.* **2011**, *76*, 1894.
12. a) S. Tanaka, H. Saburi, T. Murase, M. Yoshimura, M. Kitamura, *J. Org. Chem.* **2006**, *71*, 4682. b) S. Tanaka, H. Saburi, T. Murase, Y. Ishibashi, M. Kitamura, *J. Organomet. Chem.* **2007**, *692*, 295.
13. a) X. Liu, B. L. Stocker, P. H. Seeberger, *J. Am. Chem. Soc.* **2006**, *128*, 3638. b) S. Tanaka, T. Hirakawa, K. Oishi, Y. Hayakawa, M. Kitamura, *Tetrahedron Lett.* **2007**, *48*, 7320. c) J. Lauer-Fields, K. Brew, J. K. Whitehead, S. Li, R. P. Hammer, G. B. Fields, *J. Am. Chem. Soc.* **2007**, *129*, 10408. d) M. K. Kiesewetter, J. A. Edward, H. Kim, R. M. Waymouth, *J. Am. Chem. Soc.* **2011**, *133*, 16390. e) D. E. Ward, M. M. Zahedi, *Org. Lett.* **2012**, *14*, 6246. f) T. Vçlker, F. Dempwolff, P. L. Graumann, E. Meggers, *Angew. Chem. Int. Ed.* **2014**, *53*, 10536. g) T. Ohyama, M. Uchida, H. Kusama, N. Iwasawa, *Chem. Asian J.* **2015**, *10*, 1850. h) R. Hollaus, S. Ittig, A. Hofinger, M. Haegman, R. Beyaert, P. Kosma, A. Zamyatina, *Chem. Eur. J.* **2015**, *21*, 4102. i) L. Karmann, K. Schultz, J. Herrmann, R. Müller, U. Kazmaier, *Angew. Chem. Int. Ed.* **2015**, *54*, 4502. j) H.-T. Hsu, B. M. Trantow, R. M. Waymouth, P. A. Wender, *Bioconjugate Chem.* **2016**, *27*, 376. k) T. Aiba, M. Sato, D. Umegaki, T. Iwasaki, N. Kambe, K. Fukase, Y. Fujimoto, *Org. Biomol. Chem.* **2016**, *14*, 6672. l) M. Tomás-Gamasa, M. Martínez-Calvo, J. R. Couceiro, J. L. Mascareñas, *Nat. Commun.* **2016**, *7*, 12538. m) S. Inuki, J. Kishi, E. Kashiwabara, T. Aiba, Y. Fujimoto, *Org. Lett.* **2017**, *19*, 6482. n) T. Vçlker, E. Meggers, *ChemBioChem* **2017**, *18*, 1083. o) T. Aiba, S. Suehara, S.-L. Choy, Y. Maekawa, H. Lotter, T. Murai, S. Inuki, K. Fukase, Y. Fujimoto, *Chem. Eur. J.* **2017**, *23*, 8304. p) S. L. Choy, H. Bernin, T. Aiba, E. Bifeld, S. C. Lender, M. Mühlenpfordt, J. Noll, J. Eick, C. Marggra, H. Niss, N. G. Roldán, S. Tanaka, M. Kitamura, K. Fukase, J. Clos, E. Tannich, Y. Fujimoto, H. Lotter, *Sci. Rep.* **2017**, *7*, 9472. q) A. Zamyatina, *Beilstein J. Org. Chem.* **2018**, *14*, 25. r) S. Kappler, L. Karmann, C. Prudel, J. Herrmann, G. Caddeu, R. Müller, A. M. Vollmar, S. Zahler, U. Kazmaier, *Eur. J. Org. Chem.* **2018**, 6952.
14. a) R. Noyori, M. Kitamura, *Angew. Chem., Int. Ed. Engl.* **1991**, *30*, 49. For the original reaction deducing Intramolecular Metathesis-type Donor-Acceptor Bifunctional Catalyst (Intramol-MDACat) concept, see: b) M. Kitamura, S. Suga, K. Kawai, R. Noyori, *J. Am. Chem. Soc.* **1986**, *108*, 6071.
15. a) R. Noyori, M. Kitamura, T. Ohkuma, *Proc. Natl. Acad. Sci. U.S.A.* **2004**, *101*, 5356. b) M. Kitamura, H. Nakatsuka, *Chem. Commun.* **2011**, 842. For the original reaction deducing Intermol-MDACat, see: c) R. Noyori, T. Ohkuma, M. Kitamura, H. Takaya, N. Sayo, H. Kumobayashi, S. Akutagawa, *J. Am. Chem. Soc.* **1987**, *109*, 5856. d) M. Kitamura, T. Ohkuma, S. Inoue, N. Sayo, H. Kumobayashi, S. Akutagawa, T. Ohta, H. Takaya, R. Noyori, *J. Am. Chem. Soc*. **1988**, *110*, 629.
16. S. Tanaka, T. Seki, M. Kitamura, *Angew. Chem., Int. Ed*. **2009**, *48*, 8948.
17. a) T. Seki, S. Tanaka, M. Kitamura, *Org. Lett.* **2012**, *14*, 608. b) M. Kitamura, K. Miyata, T. Seki, N. Vatmurge, S. Tanaka, *Pure Appl. Chem.* **2013**, *85*, 1121. c) Y. Suzuki, T. Seki, S. Tanaka, M. Kitamura, *J. Am. Chem. Soc.* **2015**, *137*, 9539.
18. F. Kakiuchi, M. Matsumoto, K. Tsuchiya, K. Igi, T. Hayamizu, N. Chatani, S. Murai, *J. Organomet. Chem.*

2003, *686*, 134.
19. Z. Zhao, V. Snieckus, *Org. Lett.* **2005**, *7*, 2523.
20. For the preliminary report on the small scal-synthesis of (*R*)- and (*S*)-**2**, see: supporting information of ref 16.
21. J. C. Fetzer, Large (C ≥ 24) Polycyclic Aromatic Hydrocarbons, John Wiley & Sons, New York, 2000.
22. S. Tanaka, Y. Suzuki, M. Matsushita, M. Kitamura, *Bull. Chem. Soc. Jpn.* **2015**, *88*, 1726.
23. a) G. Consiglio, R. M. Waymouth, *Chem. Rev.* **1989**, *89*, 257. b) T. Kondo, T. Mitsudo, in *Ruthenium in Organic Synthesis*, ed. by S. Murahashi, Wiley-VCH, Weinheim, Germany, **2004**.
24. a) T. Kondo, H. Ono, N. Satake, T. Mitsudo, Y. Watanabe, *Organometallics* **1995**, *14*, 1945. b) Y.-M. Wuu, M. S. Wrighton, *Organometallics* **1988**, *7*, 1839. For the molecular structures of a series of CpRu(IV) π-allyl complexes of picolinate derivatives in crystals, see: ref 10e.
25. a) C. B. Aakeröy, T. A. Evans, K. R. Seddon, I. Pálinkó, *New J. Chem.* **1999**, *23*, 145. b) P. K. Thallapally, A. A. Nangia, *CrystEngComm* **2001**, *27*, 1. c) L. Brammer, E. A. Bruton, P. Sherwood, *Cryst. Growth Des.* **2001**, *1*, 277.
26. a) G. Cavallo, P. Metrangolo, R. Milani, T. Pilati, A. Priimagi, G. Resnati, G. Terraneo, *Chem. Rev.* **2016**, *116*, 2478. b) D. Bulfield, S. M. Huber, *Chem. Eur. J.* **2016**, *22*, 14434. c) T. M. Beale, M. G. Chudzinski, M. G. Sarwar, M. S. Taylor, *Chem. Soc. Rev.* **2013**, *42*, 1667.
27. M. C. Weismiller, J. C. Towson, F. A. Davis, *Org. Synth.* **1990**, *69*, 154.
28. X. Chen, X.-S. Hao, C. E. Goodhue, J.-Q. Yu, *J. Am. Chem. Soc.* **2006**, *128*, 6790.
29. S. Tanaka, P. K. Pradhan, Y. Maegawa, M. Kitamura, *Chem. Commun.* **2010**, *46*, 3996.
30. A. J. Deeming, I. P. Rothwell, *J. Organomet. Chem*. **1981**, *205*, 117.
31. T. Funaki, H. Otsuka, N. Onozawa-Komatsuzaki, K. Kasuga, K. Sayama, H. Sugihara, *Inorg. Chem. Commun.* **2014**, *46*, 137.
32. T. Völker, F. Dempwolff, P. L. Graumann, E. Meggers, *Angew. Chem., Int. Ed.* **2014**, *53*, 10536.