Pd(II)-catalyzed diastereoselective and enantioselective domino cyclization/cycloaddition reactions of alkenyl oximes for polycyclic heterocycles with four chiral stereogenic centers

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ABSTRACT

Diastereoselective and enantioselective domino cyclization/cycloaddition reactions of alkenyl oximes were established using a Pd(II)-(R)-Tol-SDP complex and triflic acid. The present process gave polycyclic heterocycles with four chiral stereogenic centers in almost quantitative yields and high stereoselectivities (up to 70% ee, *exo/endo* = 97/3).

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The development of a facile construction of polycyclic heterocycles is a subject of intensive research because of their potential use in medicinal chemistry.^{1,2} Among them, domino cyclization has become a powerful strategy for the formation of two or more rings in a single operation. In the domino cyclization, multiple chiral centers can often be formed with high stereoselectivities.² Nitrones derived from the reaction of oximes and alkenes are widely used 1,3-dipoles that endure cycloadditions with alkenes affording versatile isoxazolidine derivatives.³ In 1994, Grigg *et al.* developed Pd(II)-catalyzed cyclization/cycloaddition cascade reaction of alkenyl oximes, effectively furnishing isoxazolidines with multiple stereocenters.⁴ Despite the potential of this transformation, no enantioselective domino cyclization process has been reported.⁵ Herein, we present the first enantioselective protocol of a cyclization/cycloaddition sequence of alkenyl oxime (*E*)-**1** with enedione **2** catalyzed by a Pd(II)-(R)-Tol-SDP complex and triflic acid (TfOH) (Scheme 1).

Scheme 1 Pd(II)-catalyzed diastereoselective and enantioselective domino cyclization/cycloaddition reaction of alkenyl oxime **1** and enedione **2**.

With the aim of developing a diastereoselective and enantioselective cyclization/cycloaddition sequence, the reaction of alkenyl oxime (*E*)-**1a** and *N*-methyl maleimide (**2a**) as prototypical substrates was attempted (Table 1).⁴ Although a chiral complex derived from PdCl₂(MeCN)₂ with (*S*)-BINAP was used, no desired cyclic product **3a** was obtained. ESI-MS studies of the reaction indicated the formation of intermediate **4**.^{4,6} To promote the protonolysis of the Pd-C bond in **4** that lead to the domino process, various Brønsted acids as proton sources were employed. Among the acids tested (HClO₄, HCl_{aq}, *p*-Tol-SO₃H, CF₃CO₂H, *o*-NO₂-C₆H₄-CO₂H, HCO₂H, and AcOH), the addition of TfOH was found to promote the domino process effectively, resulting in the formation of **3a** with 70% yields in the ratio of *exo/endo*-**3a** to 93/7; the *exo*-cycloadduct **3a** was obtained as a major product in 37% enantiomeric excess (ee) (Entry 2). Encouraged by these results, we further studied the effects of other reaction conditions such as solvents, Pd salts, a ratio of substrates, and temperature. The use of CHCl₃ as a reaction solvent resulted in the formation of **3a** with 46% ee (Entry 4). Chiral Pd complexes prepared from Pd(acac)₂ with (*S*)-BINAP were found to give **3a** in higher enantioselectivity (55% ee, Entry 7) than those prepared from other Pd salts. The optimal result (quant, *exo/endo* = 93/7, 56% ee) with Pd(II)-(S)-BINAP was obtained when the reaction of **1a** with **2a** in a ratio of **2** to **1** was performed in CHCl₃ at 45 °C (Entry 10).

Next, we focused on searching for an appropriate chiral ligand to construct isoxazolidine **3a** with high optical purity (Table 2). The catalysts derived from Pd(acac)₂ with (*S*)-Tol-BINAP, (*R*)-C₃-Tunephos, or (*R*)-Segphos were virtually ineffective in improving

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Table 1 Screening of reaction conditions.^a

Entry	Pd salt	Ratio (1a : 2a)	Solvent	Time (h)	Total yields of 3a (%) ^a	Ratio of <i>exo</i> / <i>endo</i> - 3a ^b	ee of <i>exo</i> - 3a (%) ^b
1	PdCl ₂ (MeCN) ₂	1:1	CH ₂ Cl ₂	24	trace ^c	—	—
2	PdCl ₂ (MeCN) ₂	1:1	CH ₂ Cl ₂	12	70	93/7	37
3	PdCl ₂ (MeCN) ₂	1:1	THF	6	64	91/9	37
4	PdCl ₂ (MeCN) ₂	1:1	CHCl ₃	6	60	92/8	46
5	PdCl ₂ (PhCN) ₂	1:1	CHCl ₃	6	79	90/10	47
6	PdCl ₂ (COD)	1:1	CHCl ₃	6	85	91/9	46
7	Pd(acac) ₂	1:1	CHCl ₃	6	67	91/9	55
8	Pd(acac) ₂	1:2	CHCl ₃	6	36	92/8	41
9	Pd(acac) ₂	2:1	CHCl ₃	6	83	91/9	46
10 ^d	Pd(acac) ₂	2:1	CHCl ₃	10	Quant	93/7	56

^a Isolated yield.^b Determined by HPLC.^c In the absence of TfOH.^d At 45 °C

the stereoselectivity (Entries 1–3). Because a larger bite angle of the chiral ligand is suggested to increase the ee value of domino product **3a**,⁷ we shifted our attention to utilizing a chiral spiro-type ligand having a wide bite angle. A spiro-type ligand would provide a geometrically distinct and more rigid chiral pocket than its BINOL-derived counterpart.⁸ As expected, the Pd(acac)₂/(*R*)-SDP system was found to be efficient in affording good enantioselectivity (62% ee, Entry 4). An ee of 70% was achieved with the Pd(acac)₂/(*R*)-Tol-SDP catalyst (Entry 5). The use of

(*R*)-Xyl-SDP possessing bulky substituents on the phosphine region resulted in diminished enantioselectivity (Entry 6). Pd(II) complexes of other chiral monodentate phosphine ligands, (*S*)-MOP, and chiral bidentate nitrogen ligands, such as (*S,S*)-*t*-BuBOX or (*P,R,R*)-*i*-Pr-SPRIX,^{8a,9} failed to induce enantioselectivity (Entries 7–9). The relatively weakly coordinated ligands might be replaced by the substrate, allowing the background reaction to afford the racemic product.^{8d} In fact, after the addition of (*E*)-**1a** to the chiral Pd(II) complex derived from SPRIX, only the dissociated free ligand signals were observed in the ¹H-NMR spectra.

Table 2 Screening of chiral ligands.^a

Entry	Chiral ligand	Time (h)	Total yields of 3a (%) ^a	Ratio of <i>exo</i> / <i>endo</i> - 3a (%) ^b	ee of <i>exo</i> - 3a (%) ^b
1	(<i>S</i>)-Tol-BINAP	10	94	92:8	46
2	(<i>R</i>)-C ₃ -Tunephos	15	43	92:8	-55 ^c
3	(<i>R</i>)-Segphos	15	quant	92:8	-58 ^c
4	(<i>R</i>)-SDP	8	72	92:8	62
5	(<i>R</i>)-Tol-SDP	8	quant	94:6	70
6	(<i>R</i>)-Xyl-SDP	8	quant	90:10	48
7	(<i>S</i>)-MOP	15	78	93:7	0
8	(<i>S,S</i>)- <i>t</i> -Bu-BOX	12	78	93:7	0
9	(<i>P,R,R</i>)- <i>i</i> -Pr-SPRIX	12	92	90:10	4

^a Isolated yield.^b determined by HPLC.^c Opposite enantiomer was obtained. **Scheme 2** Substrate scope.¹¹

The scope and limitations of this protocol were then studied by employing the optimized reaction conditions (Pd(acac)₂/(*R*)-Tol-SDP, 45 °C, CHCl₃) to the enantioselective domino cyclization (Scheme 2). The reaction of alkenyl oxime (*E*)-**1a** and maleimides **2** bearing various substituents on the nitrogen atom afforded the corresponding tetracycles **3a–3g** with four chiral stereogenic centers in quantitative yields with good stereoselectivities (68%–70% ee, *exo/endo* = 93/7–97/3). Alkenyl oximes (*E*)-**1h** and (*E*)-**1i** bearing an electron-withdrawing or electron-donating substituent on the aromatic rings also afforded domino products **3h** and **3i** in excellent yields with moderate enantioselectivities. When using (*E*)-**1a** and dimethyl maleate for the domino reaction, the corresponding *exo*- and *endo*-cycloadduct **3j** in a ratio of 1 : 1 were obtained in 68% ees, respectively. No desired product was formed when using **1k**, having a phenyl substituent at the terminal olefin moiety, and ketoxime **1l**,¹⁰ presumably because of the bulky substituents preventing catalyst activation.

A plausible reaction mechanism for the Pd(II)-catalyzed enantioselective domino cyclization/cycloaddition reactions is shown in Figure 1. The initial coordination of the chiral Pd(II)-(*R*)-Tol-SDP complex with alkenyl oxime **1** led to transition state **I**. The subsequent nucleopalladation of **I** afforded the cyclic intermediate **II** and **III**, thus controlling the enantioselectivity. The protonation of generated Pd(II) intermediate **II** (or **III**) made the releasing catalyst, together with the formation of nitrene **IV**. Finally, 1,3-dipolar cycloaddition of **IV** with **2** gave domino product **3**.

Figure 1 Plausible reaction mechanism.

In summary, we have developed a domino cyclization/cycloaddition of alkenyl oximes catalyzed by the chiral Pd(II) complex and TfOH. The use of the (*R*)-Tol-SDP ligand led to the formation of polycyclic heterocycles having four chiral stereogenic centers in almost quantitative yields with high stereoselectivities. A fine-tuning of the spiro catalysts, investigation into the detailed reaction mechanism, scope, as well as its application to the enantioselective synthesis of biologically active compounds are currently underway.

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10. Although the corresponding intermediate **IV** was formed when using ketoxime **11**, no cycloaddition with *N*-ethyl maleimide (**2c**) was occurred
11. Yields of isolated **3**. The ee and ratio of *exo/endo*-**3** were determined by HPLC. Determination of absolute configuration of **3** is in progress.

+Supporting Information

Pd(II)-catalyzed diastereoselective and enantioselective domino cyclization/cycloaddition reactions of alkenyl oximes for polycyclic heterocycles with four chiral stereogenic centers

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A. General information

All reactions were performed with standard Schlenk technique under N₂ atmosphere. ¹H-, ¹³C- and ¹⁹F-NMR spectra were recorded with JEOL JMN LA-400 FT NMR or JNM ECA600 FT NMR (¹H-NMR 600 or 400 MHz, ¹³C-NMR 150 or 100 MHz). ¹H-NMR spectra are reported in ppm (δ) relative to the chemical shift of tetramethylsilane. Multiplicity (s = singlet, d = doublet, q = quartet, t = triplet, m = multiplet). ¹³C-NMR spectra reported in ppm (δ) relative to the central line of triplet for CDCl₃ at 77.16 ppm. CF₃CO₂H used as external standards for ¹⁹F-NMR. ESI-MS spectra were obtained with JMS-T100LC (JEOL). Optical rotations were measured with JASCO P-1030 polarimeter. HPLC analyses were performed on a JASCO HPLC system (JASCO PU 980 pump and UV-975 UV/Vis detector) using a mixture of hexane and *i*-PrOH eluents. FT-IR spectra were recorded on a JASCO FT-IR system (FT/IR4100). Melting point was measured with SHIMADZU DSC-60. Column chromatography on SiO₂ was performed with Kanto Silica Gel 60 (40-100 μm). Commercially available organic and inorganic compounds were used without further purification. The solvents were purified and dried by the standard procedures. 2-Allyl-5-fluorobenzaldehyde (**S1b**)¹, 2-allyl-3-methoxybenzaldehyde (**S1c**)² and (*E*)-**1a**³ were synthesized according to the reported procedures. Domino products **3a-j** are inseparable diastereomeric mixtures. In the case of minor diastereomer, only the representative peaks were exhibited in the ¹H-NMR data. The relative stereochemistry of the domino products **3a-3i** was assigned based on Grigg's analogy.³ The relative stereochemistry of domino product **3j** was assigned using gradient 1D-NOE studies. The indicated $[\alpha]_D^T$ value for the domino products **3a-i** were measured for the diastereomeric mixture (inseparable) except for the domino product **3j** in which the two diastereomers are separable.

B. Preparation of starting material 1

To a mixture of aldehyde (1.37 mmol) and pyridine (165 μL, 2.05 mmol, 1.5 eq.) in methanol (2 mL), a solution of hydroxylamine hydrochloride (95.2 mg, 1.37 mmol) in water (0.28 mL) was added and the mixture was stirred at room temperature overnight. The solvent was removed *in vacuo* and the residue was treated with 2M HCl (8.2 mL). The organic material was extracted into diethyl ether (3×10 mL). The combined organic layers were dried over anhydrous sodium sulphate and the solvent was removed *in vacuo*. The remaining residue was further purified by column chromatography on silica (Hexane : Et₂O = 95 : 5) to give the pure alkenyl oximes **1b-c**.

1b: colorless oil (79%); $^1\text{H-NMR}$ (CDCl_3) δ 8.33 (d, 1H, CH=NOH , $J = 1.60$ Hz), 7.66 (s, 1H, OH), 7.45 (dd, 1H, H-6, $J = 2.80, 9.60$ Hz), 7.16 (dd, 1H, H-3, $J = 5.20, 8.00$ Hz), 7.03 (td, 1H, H-4, $J = 2.80, 8.00, 10.80$ Hz), 6.00-5.90 (m, 1H, CH=CH_2), 5.10 (dd, 1H, CH=CH_{2a} , $J = 1.20, 10.00$ Hz), 4.94 (dd, 1H, CH=CH_{2b} , $J = 1.20, 18.80$ Hz), 3.47 (d, 2H, $\text{CH}_2\text{CH=CH}_2$, $J = 6.00$ Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 148.1, 136.6, 132.1, 132.0, 117.2, 117.0, 116.7, 113.0, 112.9, 36.5; $^{19}\text{F-NMR}$ (CDCl_3): δ -115.8; HRMS (ESI) calcd for $\text{C}_{10}\text{H}_{10}\text{FNNaO}$, $m/z = 202.0639$ $[(\text{M}+\text{Na})^+]$, found $m/z = 202.0637$; IR (KBr): ν 3357, 3082, 3006, 2980, 2923, 1638, 1609, 1580, 1496, 1421 cm^{-1} .

1c: yellow solid (81%); 92-93 $^\circ\text{C}$; $^1\text{H-NMR}$ (CDCl_3) δ 8.63 (s, 1H, OH), 8.4 (s, 1H, CH=NOH), 7.35 (d, 1H, H-6, $J = 7.60$ Hz), 7.22 (dd, 1H, H-5, $J = 7.60, 8.40$ Hz), 6.91 (d, 1H, H-4, $J = 8.40$ Hz), 5.99-5.89 (m, 1H, CH=CH_2), 5.00 (dd, 1H, CH=CH_{2a} , $J = 1.60, 10.00$ Hz), 4.89 (dd, 1H, CH=CH_{2b} , $J = 1.60, 15.60$ Hz), 3.54 (s, 3H, OCH_3), 3.54 (d, 2H, $\text{CH}_2\text{CH=CH}_2$, $J = 5.60$ Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 157.7, 149.0, 136.0, 131.7, 127.5, 127.4, 118.7, 115.4, 112.0, 55.9, 29.4; HRMS (ESI) calcd for $\text{C}_{11}\text{H}_{13}\text{NNaO}_2$, $m/z = 214.0838$ $[(\text{M}+\text{Na})^+]$, found $m/z = 214.0838$; IR (KBr): ν 3345, 3081, 3006, 3918, 2838, 1634, 1578, 1470, 1449, 1437, 1406 cm^{-1} .

C. Ligand screening with $\text{Pd}(\text{F}_6\text{-acac})_2$ at 40 $^\circ\text{C}$

Table S1

Table S1 (continue)

(R,R)-QuinoxP* (12h) 80%, -24% ee exo/endo = 95/5	(S,S)-BenzP* (12h) 80%, 31% ee exo/endo = 94/6	(R,R,S,S)-Duanphos (12h) 79%, <i>rac.</i> exo/endo = 94/6	iPr-Duphos (12h) 63%, 8% ee exo/endo = 94/6
(R,R)-Ph-BPE (12h) 80%, 52% ee exo/endo = 95/5	(R,R)-Chiraphos (8h) 69%, -7% ee exo/endo = 94/6	(S,S)-Norphos (12h) 58%, -5% ee exo/endo = 96/4	[(1R,2R,3S)-(+)-1,2-Dimethyl-2,3-bis(diphenylphosphinomethyl)cyclopentyl]methanol (48h) 74%, 34% ee exo/endo = 97/3
(R,R)-DIOP (12h) 72%, <i>rac.</i> exo/endo = 94/6	(R)-Phanephos (5 days) 55%, 18% ee exo/endo = 94/6	(R,R)-Chiraphite (36h) 55%, <i>rac.</i> exo/endo = 95/5	
(R,S)-BPPFOAc (24h) 46%, -17% ee exo/endo = 94/6	Josiphos (J002-2) (48h) 15 % (Con. = 71%), 9% ee exo/endo = 95/5	(R)-BINAM-P (24h) 83%, <i>rac.</i> exo/endo = 93/7	(R)-QUINAP (4days) No reaction
(S)-Monophos (12h) 61%, -7% ee exo/endo = 96/4	(R)-SDP (18h) 68%, 68% ee exo/endo = 94/6	(R)-Tol-SDP At 40 °C (12h): 63%, 73% ee exo/endo = 94/6 At 45 °C (8h): 69%, 74% ee exo/endo = 94/6	(R)-Xyl-SDP (12h) 64%, 68% ee exo/endo = 94/6

D. General procedure for Pd(II)-catalyzed diastereoselective and enantioselective domino cyclization/cycloaddition reactions of alkenyl oximes

In 10 ml R.B. flask, a mixture of (*R*)-Tol-SDP (6 mg, 0.0093 mmol, 15 mol %) and Pd(acac)₂ (1.9 mg, 0.0062 mmol, 10 mol %) was dissolved in CH₂Cl₂ (1 mL) followed by stirring at room temperature under nitrogen atmosphere. After 1 h, the solvent was distilled off and the resulting yellow Pd-complex was kept under vacuum for 10 min. The remaining yellow solid was dissolved in CHCl₃ (0.5 mL) followed by adding of triflic acid (1.1 μ L, 0.012 mmol, 20 mol %) under nitrogen. The solution was stirred for few minutes until deep yellow color was observed. In other 10 ml R.B. flask, a mixture of alkenyl oxime **1** (0.124 mmol) and endione **2** (0.062 mmol) was dissolved in CHCl₃ (0.5 mL) under nitrogen atmosphere. The resulting reaction mixture was transferred to the first flask that contains Pd-complex under nitrogen atmosphere. After the complete consumption of the endione **2** on TLC monitoring, the solvent was removed under vacuum. The remaining syrup was purified by silica gel column chromatography (Hex: Et₂O = 1 : 1) to give the pure domino products **3**.

3a: White solid (quant., *exo/endo* = 94/6, 8h); m.p. 175-176 °C; ¹H-NMR (CDCl₃) Major diastereomer: δ 7.47 (d, 1H, ArH, *J* = 7.20 Hz), 7.33-7.19 (m, 2H, ArH), 7.09 (d, 1H, ArH, *J* = 7.60 Hz), 4.85 (d, 1H, H-8a, *J* = 7.20 Hz), 4.71 (d, 1H, H-11b, *J* = 4.00 Hz), 3.72 (dd, 1H, H-11a, *J* = 4.00, 7.20 Hz), 3.49-3.42 (m, 1H, H-6), 3.13-3.09 (m, 4H, H-5a, NCH₃), 2.55 (dd, 1H, H-5b, *J* = 6.00, 16.40 Hz), 1.21 (d, 3H, CH₃, *J* = 6.40); Minor diastereomer (representative peaks): δ 4.66 (d, 1H, H-11b, *J* = 7.20 Hz), 3.01 (s, 3H, NCH₃), 1.37 (d, 3H, CH₃, *J* = 6.40 Hz); ¹³C-NMR (CDCl₃) δ 175.7, 174.0, 132.8, 132.7, 128.9, 127.6, 127.5, 127.1, 76.0, 64.2, 56.7, 52.1, 32.0, 25.4, 18.0; enantiomeric excess: 70%, determined by HPLC (Chiralpak IC, hexane/2-propanol = 5/1, flow rate = 1 ml/min, 25°C, 214 nm) minor peak: *t_R* = 26.6 min, major peak: *t_R* = 16.5 min; [α]_D¹⁹ = -91.8 (*c* 0.85, CHCl₃).

3b: White solid (quant., *exo/endo* = 93/7, 12h); m.p. 150-151 °C; ¹H-NMR (CDCl₃) Major diastereomer: δ 8.12 (brs, 1H, NH, hydrogen bonded), 7.43 (d, 1H, ArH, *J* = 7.20 Hz), 7.29-7.21 (m, 2H, ArH), 7.10 (d, 1H, ArH, *J* = 7.20 Hz), 4.87 (d, 1H, H-8a, *J* = 8.00 Hz), 4.80 (d, 1H, H-11b, *J* = 3.60 Hz), 3.76 (dd, 1H, H-11a, *J* = 3.60, 7.60 Hz), 3.50-3.44 (m, 1H, H-6), 3.12 (dd, 1H, H-5a, *J* = 4.80), 2.64 (s, 1H, NH, non-hydrogen bonded), 2.57 (dd, 1H, H-5b, *J* = 6.00, 16.80 Hz), 1.24 (d, 3H, CH₃, *J* = 6.80); Minor diastereomer (representative peaks): δ 4.89 (brs, 1H, H-8a), 4.70 (d, 1H, H-11b, *J* = 7.20 Hz), 3.80 (brs, 1H, H-11a), 3.31-3.27 (m, 1H, H-6), 3.02 (dd, 1H, H-5a, *J* = 12.00, 16.00), 2.51 (dd, 1H, H-5b, *J* = 4.00, 16.00 Hz), 1.40 (d, 3H, CH₃, *J* = 6.40 Hz); ¹³C-NMR (CDCl₃) δ 175.3, 173.7, 132.7, 132.5, 129.0, 127.7, 127.4, 127.1, 64.3, 57.7, 52.1, 31.9, 29.8, 18.0; HRMS (ESI)

calcd for $C_{14}H_{14}N_2NaO_3$, $m/z = 281.0897 [(M+Na)^+]$, found $m/z = 281.0895$; enantiomeric excess: 68%, determined by HPLC (Chiralpak IC, hexane/2-propanol = 5/1, flow rate = 1 ml/min, 25°C, 214 nm) minor peak: $t_R = 28.6$ min, major peak: $t_R = 19.3$ min; $[\alpha]_D^{19} = -15.3$ (c 0.49, $CHCl_3$); IR (KBr): ν 3171, 3071, 2920, 1780, 1707 cm^{-1} .

3c: White solid (quant., *exo/endo* = 97/3, 8h); 111-112 °C; 1H -NMR ($CDCl_3$) Major diastereomer: δ 7.48 (d, 1H, ArH, $J = 7.60$ Hz), 7.33-7.19 (m, 2H, ArH), 7.09 (d, 1H, ArH, $J = 7.20$ Hz), 4.84 (d, 1H, H-8a, $J = 7.20$ Hz), 4.71 (d, 1H, H-11b, $J = 4.40$ Hz), 3.71-3.62 (m, 3H, H-11a, $\underline{CH_2CH_3}$), 3.47-3.39 (m, 1H, H-6), 3.09 (dd, 1H, H-5a, $J = 4.40, 16.40$ Hz), 2.57 (dd, 1H, H-5b, $J = 6.40, 10.00$ Hz), 1.25-1.21 (m, 6H, $\underline{CHCH_3}$, $\underline{CH_2CH_3}$); Minor diastereomer (representative peaks): δ 4.63 (d, 1H, H-11b, $J = 7.60$ Hz), 3.28-3.22 (m, 1H, H-6), 3.01 (dd, 1H, H-5a, $J = 12.40, 16.40$ Hz), 2.49 (dd, 1H, H-5b, $J = 4.00, 16.40$ Hz), 1.37 (d, 3H, $\underline{CHCH_3}$, $J = 6.80$ Hz); ^{13}C -NMR ($CDCl_3$) δ 175.5, 173.7, 132.8 (2C), 128.8, 127.6, 127.5, 127.1, 76.0, 64.4, 56.6, 52.1, 34.3, 32.3, 18.1, 13.1; HRMS (ESI) calcd for $C_{16}H_{18}N_2NaO_3$, $m/z = 309.1210 [(M+Na)^+]$, found $m/z = 309.1207$; enantiomeric excess: 68%, determined by HPLC (Chiralpak IC-3, hexane/2-propanol = 10/1, flow rate = 1 ml/min, 25°C, 214 nm) minor peak: $t_R = 38.0$ min, major peak: $t_R = 31.9$ min; $[\alpha]_D^{19} = -34.4$ (c 0.41, $CHCl_3$); IR (KBr): ν 2987, 2920, 2851, 1781, 1694, 1405 cm^{-1} .

3d: White solid (quant., *exo/endo* = 95/5, 8h); 144-145 °C; 1H -NMR ($CDCl_3$) Major diastereomer: δ 7.45 (d, 1H, ArH, $J = 7.20$ Hz), 7.41-7.20 (m, 7H, ArH), 7.09 (d, 1H, ArH, $J = 7.20$ Hz), 4.87-4.64 (m, 4H, H-8a, H-11b, $\underline{NCH_2Ph}$), 3.70 (dd, 1H, H-11a, $J = 4.40, 7.60$ Hz), 3.48-3.40 (m, 1H, H-6), 3.09 (dd, 1H, H-5a, $J = 4.00, 16.40$ Hz), 2.56 (dd, 1H, H-5b, $J = 6.40, 16.40$ Hz), 1.22 (d, 3H, $\underline{CH_3}$, $J = 6.40$); Minor diastereomer (representative peaks): δ 1.38 (d, 3H, $\underline{CH_3}$, $J = 6.40$ Hz); ^{13}C -NMR ($CDCl_3$) δ 175.4, 173.5, 135.3, 132.8, 132.7, 128.9 (2C), 128.8, 128.6 (2C), 128.2, 127.6, 127.5, 127.1, 76.1, 64.4, 56.6, 52.1, 42.8, 32.2, 18.1; HRMS (ESI) calcd for $C_{21}H_{20}N_2NaO_3$, $m/z = 371.1366 [(M+Na)^+]$, found $m/z = 371.1362$; enantiomeric excess: 70 %, determined by HPLC (Chiralcel IC-3, hexane/2-propanol = 10/1, flow rate = 1 ml/min, 25°C, 214 nm) minor peak: $t_R = 38.4$ min, major peak: $t_R = 32.4$ min; $[\alpha]_D^{18} = -26.8$ (c 0.69, $CHCl_3$); IR (KBr): ν 2961, 2926, 2853, 1776, 1704, 1496, 1456, 1433 cm^{-1} .

3e: Yellow solid (quant., *exo/endo* = 93/7, 4h); 175-176 °C; ¹H-NMR (CDCl₃) Major diastereomer: δ 7.49-7.46 (m, 3H, ArH), 7.37-7.22 (m, 4H, ArH), 7.12 (d, 1H, ArH, *J* = 7.60 Hz), 4.99 (d, 1H, H-8a, *J* = 8.00 Hz), 4.86 (d, 1H, H-11b, *J* = 3.60 Hz), 3.88 (dd, 1H, H-11a, *J* = 4.40, 8 Hz), 3.55-3.47 (m, 1H, H-6), 3.15 (dd, 1H, H-5a, *J* = 4.80, 16.80 Hz), 2.59 (dd, 1H, H-5b, *J* = 6.00, 16.80 Hz), 1.26 (d, 3H, CH₃, *J* = 6.40); Minor diastereomer (representative peaks): 4.96 (brs, 1H, H-8a), 4.81 (d, 1H, H-11b, *J* = 8.00 Hz), 3.33-3.28 (m, 1H, H-6), 3.05 (dd, 1H, H-5a, *J* = 12.00, 16.00 Hz), 2.53 (dd, 1H, H-5b, *J* = 4.00, 16.40 Hz), 1.41 (d, 3H, CH₃, *J* = 7.20 Hz); ¹³C-NMR (CDCl₃) δ 163.6, 161.7, 123.9, 121.8, 121.5, 118.9, 118.63 (2C), 118.56, 118.0, 116.8, 116.4, 116.2, 64.8, 53.7, 45.6, 41.2, 21.0, 7.1; HRMS (ESI) calcd for C₂₀H₁₇ClN₂NaO₃, *m/z* = 391.0820 [(M+Na)⁺], found *m/z* = 391.0817; enantiomeric excess: 70%, determined by HPLC (Chiralpak IE, hexane/2-propanol = 10/1, flow rate 1 = ml/min, 25°C, 214 nm) minor peak: *t_R* = 53.3 min, major peak: *t_R* = 39.4 min; [α]_D²⁴ = -29.5 (c 0.57, CHCl₃); IR (KBr): ν 3011, 2930, 2855, 1782, 1713, 1496, 1456 cm⁻¹.

3f: Pale yellow solid (quant., *exo/endo* = 94/6, 4h); 157-158 °C; ¹H-NMR (CDCl₃) Major diastereomer: δ 7.53-7.49 (m, 3H, ArH), 7.46-7.42 (m, 1H, ArH), 7.39-7.36 (m, 2H, ArH), 7.31-7.23 (m, 2H, ArH), 7.12 (d, 1H, ArH, *J* = 8.00 Hz), 5.01 (d, 1H, H-8a, *J* = 7.60 Hz), 4.88 (d, 1H, H-11b, *J* = 4.00 Hz), 3.88 (dd, 1H, H-11a, *J* = 4.40, 7.60 Hz), 3.53-3.46 (m, 1H, H-6), 3.13 (dd, 1H, H-5a, *J* = 4.40, 16.40 Hz), 2.61 (dd, 1H, H-5b, *J* = 6.40, 18.80 Hz), 1.27 (d, 3H, CH₃, *J* = 6.40); Minor diastereomer (representative peaks): δ 4.97 (brs, 1H, H-8a), 4.81 (d, 1H, H-11b, *J* = 7.60 Hz), 3.33-3.28 (m, 1H, H-6), 3.05 (dd, 1H, H-5a, *J* = 12.00, 16.80 Hz), 2.53 (dd, 1H, H-5b, *J* = 4.00, 16.40 Hz), 1.41 (d, 3H, CH₃, *J* = 6.40 Hz); ¹³C-NMR (CDCl₃) δ 174.8, 172.8, 132.9, 132.7, 129.4 (2C), 129.1, 128.9, 127.7, 127.6, 127.2, 126.5 (2C), 76.0, 64.9, 56.7, 52.3, 32.3, 29.9, 18.2; HRMS (ESI) calcd for C₂₀H₁₈N₂NaO₃, *m/z* = 357.1210 [(M+Na)⁺], found *m/z* = 357.1206; enantiomeric excess: 70 %, determined by HPLC (Chiralpak IE, hexane/2-propanol = 10/1, flow rate = 1 ml/min, 25°C, 214 nm) minor peak: *t_R* = 69.9 min, major peak: *t_R* = 56.5 min; [α]_D²³ = -34.4 (c 0.52, CHCl₃); IR (KBr): ν 2927, 2854, 1778, 1717, 1498, 1456 cm⁻¹.

3g: Pale yellow solid (quant., *exo/endo* = 94/6, 4h); 162-163 °C; ¹H-NMR (CDCl₃) Major diastereomer: δ 7.51 (d, 1H, ArH, *J* = 7.20 Hz), 7.32-7.21 (m, 6H, ArH), 7.11 (d, 1H, ArH, *J* = 8.00 Hz), 4.99 (d, 1H, H-8a, *J* = 7.60 Hz), 4.86 (d, 1H, H-11b, *J* = 4.00 Hz), 3.86 (dd, 1H, H-11a, *J* = 4.40, 7.60 Hz), 3.51-3.44 (m, 1H, H-6), 3.12 (dd, 1H, H-5a, *J* = 4.80, 16.40 Hz), 2.61 (dd, 1H, H-5b, *J* = 6.40, 16.80 Hz), 2.40 (s, 3H, C₆H₄-CH₃), 1.27 (d, 3H, CH₃, *J* = 6.40); Minor diastereomer (representative peaks): δ 7.37 (d, 1H, ArH, *J* = 7.60 Hz), 4.96 (brs, 1H, H-8a), 4.79 (d, 1H, H-11b, *J* = 8.00 Hz), 3.32-3.28 (m, 1H, H-6), 3.05 (dd, 1H, H-5a, *J* = 11.60, 16.40 Hz), 2.52 (dd, 1H, H-5b, *J* = 4.00, 16.40 Hz), 1.41 (d, 3H, CH₃, *J* = 6.80 Hz); ¹³C-NMR (CDCl₃) δ 174.9, 172.9,

139.2, 132.9, 132.8, 130.0, 128.9, 128.8, 127.7, 127.6, 127.1, 126.3, 76.0, 65.0, 56.6, 52.2, 32.4, 21.4, 18.2; HRMS (ESI) calcd for $C_{21}H_{20}N_2NaO_3$, $m/z = 371.1366 [(M+Na)^+]$, found $m/z = 371.1363$; enantiomeric excess: 70%, determined by HPLC (Chiralpak IC-3, hexane/2-propanol = 10/1, flow rate = 1 ml/min, 25°C, 214 nm) minor peak: $t_R = 49.1$ min, major peak: $t_R = 53.8$ min; $[\alpha]_D^{25} = -43.1$ (c 1.08, $CHCl_3$); IR (KBr): ν 2924, 2882, 2853, 1781, 1719, 1516, 1793, 1455 cm^{-1} .

3h: White solid (92%, *exo/endo* = 96/4, 12h); 138-139 °C; 1H -NMR ($CDCl_3$) Major diastereomer: δ 7.20 (dd, 1H, H-1, $J = 2.40, 9.20$ Hz), 7.06 (dd, 1H, H-4, $J = 5.60, 8.40$ Hz), 6.93 (td, 1H, H-3, $J = 2.00, 8.00$ Hz), 4.83 (d, 1H, H-8a, $J = 7.20$ Hz), 4.66 (d, 1H, H-11b, $J = 3.60$ Hz), 3.68-3.62 (m, 3H, H-11a, $\underline{CH_2CH_3}$), 3.49-3.41 (m, 1H, H-6), 3.05 (dd, 1H, H-5a, $J = 4.00, 16.40$ Hz), 2.52 (dd, 1H, H-5b, $J = 6.40, 16.40$ Hz), 1.25-1.20 (m, 6H, $\underline{CHCH_3}$, $\underline{CH_2CH_3}$); Minor diastereomer z(representative peaks): δ 4.79 (brs, 1H, H-8a), 4.63 (brs, 1H, H-11b), 1.37 (d, 3H, $\underline{CHCH_3}$, $J = 6.40$ Hz); ^{13}C -NMR ($CDCl_3$) δ 175.3, 173.6, 161.7 (d, $^1J_{C-F} = 245.0$ Hz), 134.6 (d, $^3J_{C-F} = 6.7$ Hz), 130.5 (d, $^3J_{C-F} = 7.6$ Hz), 128.4 (d, $^4J_{C-F} = 2.9$ Hz), 115.0 (d, $^2J_{C-F} = 21.0$ Hz), 113.9 (d, $^2J_{C-F} = 21.9$ Hz), 75.8, 64.1, 56.4, 52.1, 34.4, 31.3, 18.0, 13.1; ^{19}F -NMR ($CDCl_3$): δ -114.7; HRMS (ESI) calcd for $C_{16}H_{17}FN_2NaO_3$, $m/z = 327.1115 [(M+Na)^+]$, found $m/z = 327.1111$; enantiomeric excess: 60%, determined by HPLC (Chiralpak IF, hexane/2-propanol = 5/1, flow rate 1 ml/min, 25°C, 214 nm) minor peak: $t_R = 44.9$ min, major peak: $t_R = 31.2$ min; $[\alpha]_D^{25} = -30.4$ (c 0.25, $CHCl_3$); IR (KBr): ν 2997, 2925, 2897, 2851, 1780, 1712, 1616, 1503, 1404 cm^{-1} .

3i: White solid (92%, *exo/endo* = 95/5, 12h); 147-148 °C; 1H -NMR ($CDCl_3$) Major diastereomer: δ 7.27-7.23 (m, 1H, H-2), 7.1 (d, 1H, H-1, $J = 7.60$ Hz), 6.76 (d, 1H, H-3, $J = 8.40$ Hz), 4.84 (d, 1H, H-8a, $J = 8.00$ Hz), 4.68 (d, 1H, H-11b, $J = 4.00$ Hz), 3.83 (s, 3H, OCH₃), 3.70-3.62 (m, 3H, H-11a, $\underline{CH_2CH_3}$), 3.42-3.34 (m, 1H, H-6), 2.99 (dd, 1H, H-5a, $J = 4.40, 17.20$ Hz), 2.48 (dd, 1H, H-5b, $J = 6.40, 17.20$ Hz), 1.24-1.21 (m, 6H, $\underline{CHCH_3}$, $\underline{CH_2CH_3}$); Minor diastereomer (representative peaks): δ 1.39 (d, 3H, $\underline{CHCH_3}$, $J = 6.80$ Hz); ^{13}C -NMR ($CDCl_3$) δ 175.5, 173.6, 156.7, 133.8, 127.6, 121.9, 119.4, 108.6, 76.0, 64.4, 56.5, 55.5, 51.7, 34.3, 26.6, 18.4, 13.1; HRMS (ESI) calcd for $C_{17}H_{20}N_2NaO_4$, $m/z = 339.1315 [(M+Na)^+]$, found $m/z = 339.1313$; enantiomeric excess: 52 %, determined by HPLC (Chiralpak IF, hexane/2-propanol = 5/1, flow rate 1 ml/min, 25°C, 214 nm) minor peak: $t_R = 134.3$ min, major peak: $t_R = 26.4$ min; $[\alpha]_D^{19} = -27.1$ (c 0.41, $CHCl_3$); IR (KBr): ν 3015, 2976, 2856, 1772, 1713, 1593, 1472, 1401 cm^{-1} .

3j: (quant., *exo/endo* = 1/1, 12h); **exo-3j**: White solid; 150-151 °C; $^1\text{H-NMR}$ (CDCl_3) δ 7.21 (t, 1H, ArH, J = 7.20 Hz), 7.17 (t, 1H, ArH, J = 7.20 Hz), 7.10 (d, 1H, ArH, J = 7.20 Hz), 7.07 (d, 1H, ArH, J = 7.20 Hz), 5.00 (2 overlapping d, 2H, H-9, H-11), 3.80 (s, 3H, COOCH_3), 3.79 (s, 3H, COOCH_3), 3.72 (t, 1H, H-10, J = 9.60 Hz), 3.09-3.06 (m, 1H, H-6), 2.86 (dd, 1H, H-5a, J = 4.20, 16.20 Hz), 2.80 (dd, 1H, H-5b, J = 10.20, 16.80 Hz), 1.34 (d, 3H, CHCH_3 , J = 6.00 Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 170.8, 169.6, 133.2, 133.0, 128.3, 127.7, 126.9, 126.7, 77.9, 66.7, 57.9, 53.1, 52.8, 52.7, 36.9, 19.1; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{19}\text{NNaO}_5$, m/z = 328.1155 $[(\text{M}+\text{Na})^+]$, found m/z = 328.1151; enantiomeric excess: 68%, determined by HPLC (Chiralpak IF, hexane/2-propanol = 5/1, flow rate 1.0 ml/min, 25°C, 214 nm) minor peak: t_R = 73.8 min, major peak: t_R = 26.2 min; $[\alpha]_D^{18}$ = -84 (c 0.05, CHCl_3); IR (KBr): ν 2923, 2852, 1752, 1725, 1439 cm^{-1} .

endo-3j: White solid; 116-117 °C; $^1\text{H-NMR}$ (CDCl_3) δ 7.17-7.13 (m, 2H, ArH), 7.10-7.06 (m, 2H, ArH), 5.03 (d, 1H, H-9, J = 9.60 Hz), 5.01 (d, 1H, H-11, J = 10.80 Hz), 4.27 (t, 1H, H-10, J = 9.60 Hz), 3.87-3.84 (m, 1H, H-6), 3.70 (s, 3H, COOCH_3), 3.21 (s, 3H, COOCH_3), 2.82 (dd, 1H, H-5a, J = 3.60, 16.20 Hz), 2.70 (dd, 1H, H-5b, J = 10.80, 16.20 Hz), 1.46 (d, 3H, CHCH_3 , J = 6.60 Hz); $^{13}\text{C-NMR}$ (CDCl_3) δ 171.1, 170.8, 134.7, 130.7, 128.0, 127.7, 127.5, 125.6, 80.0, 66.4, 57.8, 52.4, 51.9, 51.8, 37.1, 19.9; HRMS (ESI) calcd for $\text{C}_{16}\text{H}_{19}\text{NNaO}_5$, m/z = 328.1155 $[(\text{M}+\text{Na})^+]$, found m/z = 328.1151; enantiomeric excess: 68%, determined by HPLC (Chiralpak IF, hexane/2-propanol = 5/1, flow rate 1.0 ml/min, 25°C, 214 nm) minor peak: t_R = 12.4 min, major peak: t_R = 21.2 min; $[\alpha]_D^{18}$ = +40 (c 0.1, CHCl_3); IR (KBr): ν 2925, 2851, 1762, 1730, 1436 cm^{-1} .

E. References

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F. NMR charts

G. HPLC charts

#	Peak Name	CH	RT [min]	Area [μVsec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	49.14	2167836	24113	15.42%	17.19%	N/A	7178	1.904	1.843	
2	Unknown	9	53.76	11884459	116106	84.57%	82.80%	N/A	7125	N/A	1.958

#	Peak Name	CH	RT [min]	Area [μVsec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	1	31.19	67716317	73317	79.66%	89.47%	N/A	2722	3.688	2.228	
2	Unknown	1	44.85	17281254	8628	20.33%	10.53%	N/A	1250	N/A	2.653

#	Peak Name	CH	RT [min]	Area [μVsec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	26.43	81257203	75761	75.71%	91.39%	N/A	1958	18.402	6.322	
2	Unknown	9	134.30	26063350	7131	24.28%	8.60%	N/A	3292	N/A	2.962

#	Peak Name	CH	RT [min]	Area [μVsec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	26.23	21056398	300015	83.97%	90.30%	N/A	3723	19.568	2.737	
2	Unknown	9	73.76	4017009	3222	16.02%	9.70%	N/A	8754	N/A	1.424	

#	Peak Name	CH	RT [min]	Area [μVsec]	Height [μV]	Area%	Height%	Quantity	NTP	Resolution	Symmetry Factor	Warning
1	Unknown	9	12.43	2438191	95648	15.78%	21.05%	N/A	5602	11.050	1.322	
2	Unknown	9	21.18	12996355	35858	84.20%	78.94%	N/A	8348	N/A	1.284	