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Enantioselective Nitroso-Diels–Alder Reaction and Its Application for the Synthesis of (−)-Peracetylated Conduramine A-1

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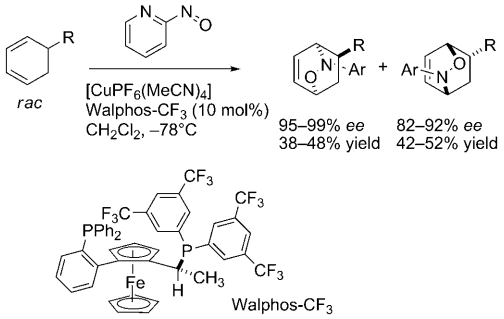
Abstract: Cu^{I}-catalyzed enantioselective nitroso-Diels–Alder reactions (NDA reactions) of 2-nitrosopyridine with various dienes are presented. The $[CuPF_6(MeCN)_4]$/Walphos-CF_3 catalyst system is best suited to catalyze the NDA reaction of various dienes by using 2-nitrosopyridine as a dienophile. In most of the cases studied, cycloadducts are obtained in quantitative yield with very good to excellent enantioselectivities. Based on DFT calculations, a model to explain the stereochemical outcome of the NDA reaction is presented. Finally, an efficient short synthesis of (−)-peracetylated conduramine A-1 by applying the enantioselective NDA reaction as a key step is described.

Keywords: copper · density functional calculations · Diels–Alder reaction · enantioselective catalysis · natural products

Introduction

Nitroso-Diels–Alder (DA) reactions have been intensively used in organic synthesis.[1] Nitroso-DA adducts can reductively be transformed to the corresponding amino alcohols, which are highly valuable building blocks for natural product synthesis. Asymmetric nitroso-DA reactions have been accomplished by using the chiral auxiliary approach. However, due to fast background reaction, it took a while to find suitable conditions for conducting catalytic enantioselective NDA reactions. To our knowledge, only very few reports on successful enantioselective metal-catalyzed NDA reactions appeared to date.[1e,2]

We have recently shown that racemic 5-substituted cyclohexa-1,3-dienes undergo highly regiodivergent enantioselective nitroso-DA reactions by using a chiral Cu^{I}-Walphos-CF_3 catalyst (Scheme 1).[3,4] It was hoped that the catalyst system identified for the more complex regiodivergent process should also perform well in enantioselective nitroso-Diels–Alder reactions that lack the regioselectivity problem. Herein we present a highly efficient catalyst for enantioselective nitroso-DA reactions. Moreover, as a first application



Scheme 1. Catalytic enantioselective regiodivergent nitroso-Diels–Alder reaction.

the synthesis of (−)-peracetylated conduramine A-1 is shown.[5] Conduramine A-1 belongs to the aminoconduritols, which are key structural moieties in many biologically active molecules.

Results and Discussion

Various Cu^{I}–bisphosphine complexes were screened as catalysts for the enantioselective nitroso-DA reaction of cyclohexa-1,3-diene with 2-nitrosopyridine (Table 1, Figure 1). Reactions were performed in CH_2Cl_2 at low temperature by using $[CuPF_6(MeCN)_4]$ (10 mol%) as a catalyst precursor in the presence of different chiral phosphine ligands. Enantio-

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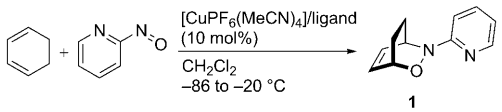
Table 1. Ligand screening.



Entry	Ligand	Yield [%]	*ee* [%][a]
1	(*S*)-Difluorphos	99	−85
2	Walphos-CH_3	99	84
3	(*R*)-Segphos	90	76
4	Walphos-CF_3	99	93
5	(*S*)-Binap	99	−55
6	(*R*)-Solphos	99	11

[a] A negative *ee* indicates formation of the enantiomer of **1**.

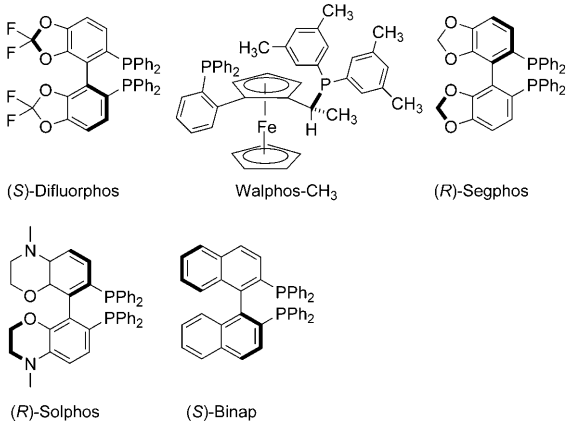
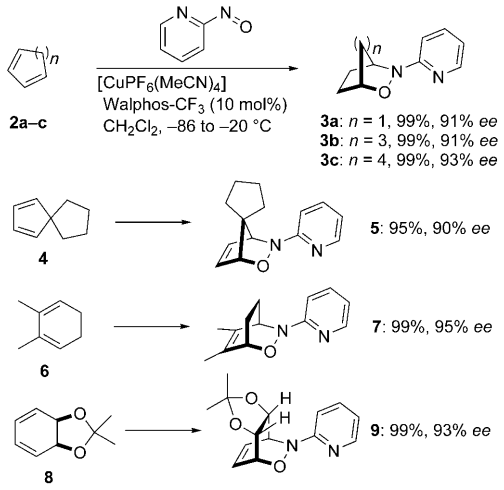


Figure 1. Various ligands that were tested.

selectivity was determined by HPLC. Good enantioselectivity was obtained when (*S*)-Difluorphos was used as ligand. The cycloadduct **1** was isolated in quantitative yield with 85% enantiomeric excess (entry 1). A similar result (99%, 84% *ee*) was achieved with the Walphos-CH_3 ligand (entry 2). (*R*)-Segphos gave a slightly lower yield and a lower selectivity (90%, 76% *ee*, entry 3), and the best result was obtained by using the Walphos-CF_3 ligand to provide the cycloadduct in quantitative yield with 93% *ee*. Moderate enantioselectivities were obtained with (*S*)-Binap (99%, 55% *ee*) and (*R*)-Solphos (99%, 11% *ee*) as ligands (entries 5, 6).

As a result of the initial ligand screening, all of the following cycloadditions were performed in CH_2Cl_2 by using the diene (1.1 equiv) and 2-nitrosopyridine in the presence of 10 mol% $[CuPF_6(MeCN)_4]$/Walphos-CF_3. For most of the reactions conducted, the product was formed with excellent yield. Enantioselectivity was determined by HPLC (see the Supporting Information).

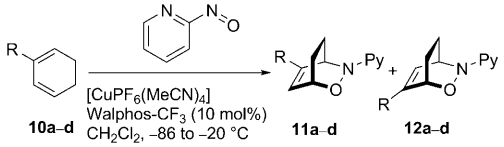
Symmetrical 1,3-dienes were studied first. Cyclopentadiene **2a** gave the adduct **3a** in a quantitative yield with high enantioselectivity (Scheme 2). The absolute configuration was assigned by comparison of the optical rotation of **3a** with the reported literature value of a similar compound.[2b] Similar results were achieved with cyclohepta-1,3-diene (**2b**) and cycloocta-1,3-diene (**2c**) to give the corresponding bicycles **3b** and **3c**, respectively. A Cu^I/Segphos system reported by Yamamoto catalyzed the cycloaddition of cyclohexa-1,3-diene with 6-methyl-2-nitrosopyridine, which is more difficult to access than the 2-nitrosopyridine used herein, in a similar selectivity (92% *ee*); however, for cycloaddition with diene **2b** an improved selectivity was obtained with the Cu^I/Walphos-CF_3 system reported herein as compared to the Cu^I/Sephos catalyst (72% *ee* versus 91% *ee*).[2b] The spirocyclopentadiene **4** underwent nitroso-DA with high yield and good enantioselectivity (→ **5**, 95%, 90% *ee*). Alkyl substituents were tolerated at positions 2 and 3 of cyclohexa-1,3-diene as shown for the transformation of **6** to **7**, which was formed in quantitative yield with high enantioselectivity (95% *ee*). Perfect diastereoselectivity and a high enantioselectivity was achieved for reaction of diene **8** with 2-nitrosopyridine (→ **9**, 99%, d.r. >99:1, 93% *ee*).



Scheme 2. Enantioselective nitroso-Diels–Alder reaction with symmetrical dienes.

We next studied the unsymmetrical cyclohexa-1,3-dienes **10a–d** bearing a substituent at the 2-position (Table 2). Silyl ether **10a** reacted highly regioselectively, and **11a** was isolated in quantitative yield with high *ee* (93%). Isomer **12a** was not identified. Perfect regioselectivity but slightly reduced

Table 2. Enantioselective nitroso-Diels–Alder Reaction with 2-substituted cyclohexa-1,3-dienes.



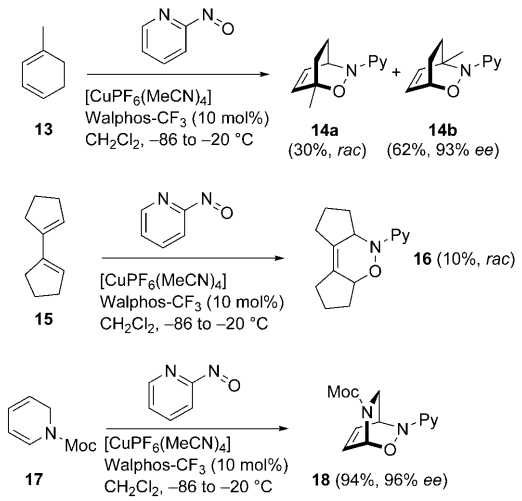
Diene	R	Yield [%] (**11a–d**)	*ee* [%] (**11a–d**)	Yield [%] (**12a–d**)	*ee* [%] (**12a–d**)
10a	OTBS	99	93	n.i.[a]	–
10b	Ph	99	88	n.i.[a]	–
10c	OTf	33	81	66	98
10d	*n*Bu	97	87	<2	n.d.[b]

[a] n.i. = not identified. [b] n.d. = not determined.

enantioselectivity was obtained for the 2-phenyl substituted diene **10b**. Regioselectivity was lower and reversed for enol triflate **10c**. Isomer **12c** was isolated in 66% yield with excellent *ee* (98%). A lower *ee* (81%) was measured for the minor isomer **11c**. As expected, the alkyl-substituted diene **10d** reacted with high regioselectivity. Hence for systems bearing electron-donating groups at the 2-position of cyclohexa-1,3-diene the nitroso-Diels–Alder reaction occurred with perfect regioselectivity and moderate to high enantioselectivity.

Structural assignment of the regioisomers in these studies was based on careful 2D NMR spectroscopic analysis. Moreover, the N–O bond in **11b** was reductively cleaved and the absolute configuration was assigned by NMR spectroscopic analysis on the corresponding Mosher ester (see the Supporting Information). The absolute configuration of all other compounds in this table was assigned by analogy. In addition, comparison of optical rotations of compounds **11a**, **11b** and **11d** with literature values of analogous compounds further supported our assignment.[2b]

As additional substrate we investigated 1-methylcyclohexadiene **13**. The minor isomer **14a** was formed as a racemate whereas **14b** was isolated with high *ee* (93%, Scheme 3). Diene **15**, which is important for the mechanistic



Scheme 3. Enantioselective nitroso-Diels–Alder reaction with dienes **13**, **15**, and **17**. Py = pyridine; Moc = methoxycarbonyl.

discussion below reacted slowly and adduct **16** was isolated in 10% yield as a racemate. Pleasingly, N-protected azacyclohexadiene **17** upon reaction with nitrosopyridine provided the cyclic N,O-acetal **18** as a single regioisomer with excellent enantioselectivity in high yield. Importantly, adduct **18** can readily be transformed to diaminodideoxylyxopyranose.[6]

To understand the stereoselectivity of the nitroso-DA reaction with substituted cyclohexa-1,3-dienes the structure of the Cu^{I}/Walphos-CF_3 catalyst complexed with 2-nitrosopyridine was studied theoretically by using DFT calculations (Figure 2).[7] As can be seen from the minimized structure,

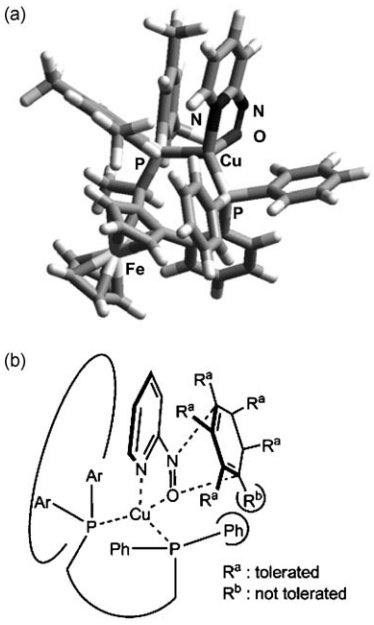
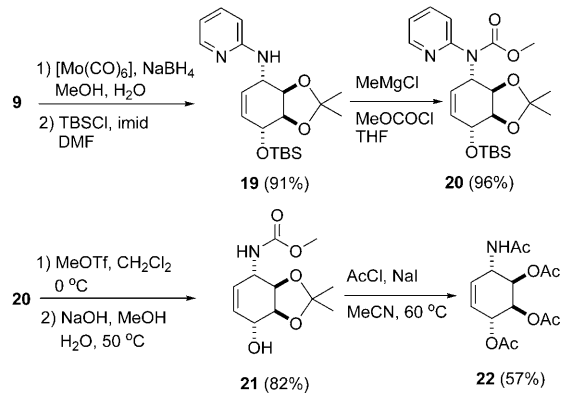


Figure 2. a) Fully optimized DFT structure of Cu^{I}/Walphos complexed with 2-nitrosopyridine. b) ChemDraw presentation of substituted cyclohexa-1,3-dienes (*endo* pathway) approaching the complexed dienophile.

the cyclohexadiene can approach the Cu-complexed nitroso compound only from the north/east direction. The north/west trajectory is well blocked by the ligand sphere. Based on calculations conducted by Houk, nitroso-DA reactions occur preferentially via the *endo* pathway.[8,9] Considering these facts, we suggest the model depicted in Figure 2b to explain the stereochemistry observed.

As shown in the experiment, substituents at the double bond were tolerated in positions 1–3 of the cyclohexadiene (R^a). However, a substituent at position 4 (R^b) of the cyclohexadiene moiety interferes with the phenyl group of the ligand while approaching the dienophile. Therefore, the *endo* approach of **13** to Cu-complexed 2-nitrosopyridine to give **14a** was probably not accessible for steric reasons. Isomer **14a**, which was isolated as a racemate likely resulted from thermal background reaction. For the same reason, diene **15** does not fit our model and should react nonselectively, as observed in the experiment. The absolute configuration of regioisomer **14b** could be predicted by our model. Positions 5 and 6 of cyclohexa-1,3-dienes can bear substituents as shown for our divergent reactions[3] and also for the transformation of diene **8**. Moreover, the 5- and 6-substituted cyclohexadienes reacted with high diastereoselectivities (*anti*-additions). The suggested model can also be applied to explain the stereochemical outcome for the DA reaction of nitrosopyridine with cyclopentadienes, cyclohepta-1,3-diene, cycloocta-1,3-diene, and of azadiene **17**.

Finally, we applied the enantioselective nitroso-DA reaction to the synthesis of (−)-peracetylated conduramine A-1 (Scheme 4). Reductive N–O bond cleavage in **9** with $Mo(CO)_6$/$NaBH_4$[10] and O-silylation afforded protected amino alcohol **19** in a good yield (91%). Carbamoylation of



Scheme 4. Synthesis of (−)-peracetylated conduramine A-1 **22**.

the amino group was performed by treatment of the corresponding Mg amide with methyl chloroformate to give **20** (96%). The pyridyl group was cleaved after N-methylation (MeOTf) and subsequent hydrolysis of the pyridinium salt (→ **21**, 82%). The final steps, namely acetal and carbamate cleavage followed by peracetylation to give protected (−)-conduramine A-1 **22** were elegantly performed as a one-pot reaction by using acetyl chloride in combination with NaI in MeCN ($[\alpha]_D^{25} = -30.6$, $c = 0.54$, $CHCl_3$; $[\alpha]_D^{25}$ (enantiomer) $= +33$, $c = 0.4$, $CHCl_3$).[5c]

Conclusions

We presented $[CuPF_6(MeCN)_4]$/Walphos-CF_3 as an efficient catalyst for enantioselective nitroso-DA reactions. In most of the cases studied, the catalyst system introduced, delivered better selectivities compared to those reported by using known catalysts. On the basis of DFT calculations a model to explain the stereochemical outcome of the nitroso-DA reaction was introduced. Finally, a first application of the method in natural product synthesis was discussed.

Experimental Section

General: All reactions involving air or moisture-sensitive reagents or intermediates were carried out in heat-gun-dried glassware under an argon atmosphere. THF was freshly distilled from potassium under argon. Diethyl ether (Et_2O) was freshly distilled from K/Na under argon. Dichloromethane (CH_2Cl_2) was freshly distilled from phosphorus(V) oxide (P_2O_5). Triethylamine (Et_3N) was distilled from CaH_2 and stored under argon. All other solvents and reagents were purified according to standard procedures or were used as received from Aldrich, Acros or Fluka. 2-Nitrosopyridine,[11] diene **8**,[12] **10a**,[13] **10b–d**[14] and **13**[15] were synthesized according to known procedures. ^1H, ^{13}C, GCOSY, GHSQC, and 1D-NOE NMR spectroscopy: Varian Unity plus 600 (at 298 K), Varian 500 Inova (at 298 K), Bruker AMX 400 (at 300 K), Bruker DPX 300 (at 300 K). Chemical shifts, δ (in ppm), are reported relative to TMS ($\delta = 0.0$ ppm), which was used as the internal reference. Otherwise the solvents residual proton resonance and carbon resonance ($CHCl_3$, $\delta(^1H) = 7.26$ ppm, $\delta(^{13}C) = 77.0$ ppm; C_6D_6, $\delta(^1H) = 7.16$ ppm, $\delta(^{13}C) = 128.0$ ppm; CD_3OD, $\delta(^1H) = 3.31$ ppm, $\delta(^{13}C)$ 49.0 ppm) were used for calibration. Polarimetry: optical rotations were measured on a Perkin–Elmer 241 & 341 polarimeter. TLC: Merck silica gel 60 F254 plates; detection with UV light or by dipping into a solution of $KMnO_4$ (1.5 g in 400 mL H_2O, 5 g $NaHCO_3$) or a solution of $Ce(SO_4)_2{\cdot}H_2O$ (10 g), phosphormolybdic acid hydrate (25 g), and concd H_2SO_4 (60 mL) in H_2O (940 mL), followed by heating. Flash column chromatography (FC): Merck or Fluka silica gel 60 (40–63 μm) at approximately 0.4 bar. HPLC: Either a KNAUER instrument, that is a High Precision KNAUER HPLC Pump, with Eurochrom V3.05 software, or a Hewlett–Packard Binary Pump coupled to a Hewlett–Packard Series 1100 ChemStation for LC were used. Column, eluent and retention times for HPLC analysis that were used for the determination of enantiomer ratios are given below with the details of the relevant experiment. IR: spectra were recorded on a Bruker IFS-28 spectrophotometer. MS: Mass spectra were recorded on a Finnigan MAT 4200S, a Bruker Daltonics MicroTof, a Waters Micromass Quatro LCZ (ESI); and peaks are given in *m/z* (% of basis peak).

General procedure for the enantioselective nitroso-Diels–Alder reaction with (R,R_p)-Walphos-CF_3 (GP 1): (R,R_p)-Walphos-CF_3 ligand (10 mol%) and $[Cu^I(CH_3CN)_4]PF_6$ (10 mol%) were added to a flame-dried Schlenk tube under an argon atmosphere. The catalyst was dried at RT for 15 min under vacuum. The Schlenk tube was recharged with argon, anhydrous CH_2Cl_2 (~6 mM with respect to ligand) was added to the mixture, and the resulting solution was stirred under argon for 1 h at RT. The solution was then cooled to −86 °C, a solution of 2-nitrosopyridine (1.0 equiv) in CH_2Cl_2 (~15 mM) was added dropwise over 10 min, and the resulting dark-blue solution was stirred for 15 min. A solution of the diene in CH_2Cl_2 (~12 mM) was added slowly over 1 h at −86 °C. After completion of addition, stirring was continued at −86 °C for 6 h. The mixture was slowly warmed to −20 °C and was stirred for 12 h at that temperature. The solvent was removed under reduced pressure, and the crude product was subjected to silica gel chromatography to afford the products.

(1*S*,4*R*)-3-Pyridin-2-yl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (1): According to GP1: (R,R_p)-Walphos-CF_3 (8.6 mg, 9.3 μmol), $[Cu^I(CH_3CN)_4]PF_6$ (3.5 mg, 9.3 μmol), CH_2Cl_2 (1.0 mL), 2-nitrosopyridine (10 mg, 93 μmol) in CH_2Cl_2 (0.5 mL), cyclohexa-1,3-diene (10.0 μL, 101 μmol) in CH_2Cl_2 (0.5 mL) and SiO_2 chromatography (pentane/MTBE 1:1) gave **1** as a colorless oil (17 mg, 93 μmol, 99%). Enantiomeric excess (93% *ee*) was determined by chiral HPLC. Column: Chiralcel OD-H; solvent: cyclohexane/*i*PrOH (95:05); flow: 1.0 mL min^{-1}; major enantiomer: $t_R = 9.0$ min, minor enantiomer: $t_R = 11.7$ min. $R_f = 0.5$ (pentane/MTBE 1:1); $[\alpha]_D^{25} = +192.2$ ($c = 0.18$, $CHCl_3$); ^1H NMR (300 MHz, $CDCl_3$): δ = 8.20–8.18 (m, 1H), 7.49 (ddd, $J = 1.8$, 7.2, 8.3 Hz, 1H), 6.91–6.89 (m, 1H), 6.75 (ddd, $J = 0.9$, 4.8, 7.2 Hz, 1H), 6.49–6.44 (m, 1H), 6.34–6.28 (m, 1H), 5.30–5.26 (m, 1H), 4.73–4.69 (m, 1H), 2.30–2.19 (m, 2H), 1.63–1.53 (m, 1H), 1.45–1.35 ppm (m, 1H);^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 164.3$, 147.4, 137.5, 132.1, 131.0, 116.7, 111.5, 69.9, 52.3, 24.4, 20.7 ppm; FTIR (neat): $\tilde{\nu}$ = 3054, 2936, 2858, 1587, 1568, 1463, 1431, 1257, 1027, 953, 881, 781, 701 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{11}H_{12}N_2OH$: 189.1033 $[M+H]^+$; found: 189.1046.

(1*S*,4*R*)-3-Pyridin-2-yl-2-oxa-3-azabicyclo[2.2.1]hept-5-ene (3a): According to GP 1: (R,R_p)-Walphos-CF_3 (12.9 mg, 13.9 μmol), $[Cu^I(CH_3CN)_4]PF_6$ (5.2 mg, 14 μmol), CH_2Cl_2 (1.5 mL), 2-nitrosopyridine (15 mg, 0.14 mmol) in CH_2Cl_2 (1.0 mL, 0.2 mL/h), cyclopentadiene (11 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) and SiO_2 chromatography (pentane/MTBE 2:1) gave **3a** as a yellow oil (23 mg, 99%). Enantiomeric excess (91% *ee*) was determined by chiral HPLC. Column: Chiralcel OD-H; solvent: cyclohexane/*i*PrOH 97:3; flow: 1.0 mL min^{-1}; major enantiomer: $t_R = 19.3$ min, minor enantiomer: $t_R = 13.6$ min. $R_f = 0.3$ (pentane/MTBE 2:1); ^1H NMR (300 MHz, $CDCl_3$): $\delta = 8.22$–8.20 (m, 1H), 7.49 (ddd, $J = 8.3$, 7.5, 1.8, 1H), 6.84–6.82 (m, 1H), 6.78 (ddd, $J = 7.2$, 4.9, 0.8, 1H), 6.31–6.28 (m, 1H), 6.14–6.11 (m, 1H), 5.49 (m, 1H), 5.21–5.20 (m, 1H), 2.14 (dt, $J = 8.7$, 1.8, 1H), 1.81 ppm (d, $J = 8.5$, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta = 163.9$, 147.5, 137.6, 135.3, 132.6, 117.2, 112.5, 83.0, 66.7, 48.3 ppm; FTIR (neat): $\tilde{\nu}$ = 3010, 2959, 2360, 2341, 1589, 1463, 1433, 1330, 1297, 1251, 929, 848, 799, 782, 735 cm^{-1}; HRMS (ESI): *m/z*: calcd for $C_{10}H_{10}N_2OH$: 175.0866 $[M+H]^+$; found: 175.0871.

(1*R*, 5*S*)-7-Pyridin-2-yl-6-oxa-7-azabicyclo[3.2.2]non-8-ene (3b): According to GP1: (R,R_p)-Walphos-CF_3 (5.8 mg, 6.2 μmol), $[Cu^I(CH_3CN)_4]PF_6$

(2.3 mg, 6.2 μmol), CH_2Cl_2 (1.0 mL), 2-nitrosopyridine (6.7 mg, 62 μmol) in CH_2Cl_2 (0.5 mL), cyclohepta-1,3-diene (8.0 μL, 74 μmol) in CH_2Cl_2 (0.5 mL) and SiO_2 chromatography (pentane/MTBE 1:1) gave **3b** as a colorless oil (12 mg, 99%). Enantiomeric excess (91% *ee*) was determined by chiral HPLC. Column: Chiralcel OD-H; solvent: cyclohexane/*i*PrOH 99.5:0.5; flow: 1.0 mL min^{-1}; major enantiomer: t_R = 23.3 min, minor enantiomer: t_R = 22.3 min. R_f = 0.5 (pentane/MTBE 1:1). $[\alpha]_D^{25}$ = +82.6 (c = 0.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19–8.18 (m, 1H), 7.57–7.50 (m, 1H), 7.03–7.00 (m, 1H), 6.76–6.72 (m, 1H), 6.26–6.19 (m, 1H), 6.08–6.03 (m, 1H), 5.38–5.34 (m, 1H), 4.82–4.81 (m, 1H), 2.11–1.90 (m, 3H), 1.79–1.71 (m, 1H), 1.66–1.60 (m, 1H), 1.51–1.35 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.8, 147.5, 137.8, 130.8, 126.2, 116.1, 111.0, 73.9, 56.8, 31.9, 27.4, 18.9 ppm; FTIR (neat): $\tilde{\nu}$ = 3052, 2932, 2863, 1591, 1568, 1463, 1432, 1280, 1146, 908, 778, 733 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{12}H_{14}N_2OH$: 203.1179 $[M+H]^+$; found: 203.1156.

(1*R*, 6*S*)-8-Pyridin-2-yl-7-oxa-8-azabicyclo[4.2.2]dec-9-ene (3c): According to GP1: (R,R_p)-Walphos-CF_3 (12.9 mg, 13.9 μmol), $[Cu^I(CH_3CN)_4]PF_6$ (5.2 mg, 14 μmol), CH_2Cl_2 (1.5 mL), 2-nitrosopyridine (15 mg, 0.14 mmol) in CH_2Cl_2 (0.5 mL), cycloocta-1,3-diene (21 μL, 0.17 mmol) in CH_2Cl_2 (1.0 mL) and SiO_2 chromatography (pentane/MTBE 10:1) gave **3c** as a colorless oil (30 mg, 99%). Enantiomeric excess (93% *ee*) was determined by chiral HPLC. Column: Chiralcel OD-H; solvent: cyclohexane/*i*PrOH 99.5:0.5; flow: 1.0 mL min^{-1}; major enantiomer: t_R = 10.1 min, minor enantiomer: t_R = 20.8 min. R_f = 0.2 (pentane/MTBE 10:1). $[\alpha]_D^{25}$ = −161.9 (c = 0.92, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19–8.18 (m, 1H), 7.59–7.53 (m, 1H), 7.08 (d, J = 8.4, 1H), 6.77–6.73 (m, 1H), 6.30 (dd, J = 6.8, 10.1, 1H), 5.72 (dd, J = 4.5, 10.1, 1H), 5.23 (m, 1H), 4.96 (m, 1H), 2.32–2.23 (m, 1H), 2.19–2.06 (m, 2H), 1.92–1.82 (m, 1H), 1.79–1.61 ppm (m, 4H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9, 147.1, 138.2, 132.0, 126.0, 115.8, 110.3, 73.7, 54.7, 34.9, 32.1, 26.3, 22.5 ppm; FTIR (neat): $\tilde{\nu}$ = 3045, 2916, 1589, 1567, 1462, 1432, 1292, 1273, 1177, 789, 778 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{13}H_{16}N_2OH$: 217.1335 $[M+H]^+$, found: 217.1333.

Spiro[cyclopentane-1,7′-(1*R*,4*S*)-3-pyridin-2-yl-2-oxa-3-azabicyclo-[2.2.1]hept-5-ene (5): According to GP1: (R,R_p)-Walphos-CF_3 (12.9 mg, 13.9 μmol), $[Cu^I(CH_3CN)_4]PF_6$ (5.2 mg, 14 μmol), CH_2Cl_2 (1.5 mL), 2-nitrosopyridine (15 mg, 0.14 mmol) in CH_2Cl_2 (0.5 mL), spiro[4.4]nona-1,3-diene (25 mg, 0.21 mmol) in CH_2Cl_2 (1.0 mL) and SiO_2 chromatography (pentane/MTBE 2:1) gave **5** as a yellow oil (30 mg, 95%). Enantiomeric excess (90% *ee*) was determined by chiral HPLC. Column: Chiralcel OD-H; solvent: cyclohexane/*i*PrOH 98:02; flow: 1.0 mL min^{-1}; major enantiomer: t_R = 7.9 min, minor enantiomer: t_R = 9.7 min. R_f = 0.6 (pentane/MTBE 2:1). $[\alpha]_D^{25}$ = +179.4 (c = 0.71, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.19–8.17 (m, 1H), 7.50–7.44 (m, 1H), 6.80–6.77 (m, 1H), 6.76–6.73 (m, 1H), 6.30–6.27 (m, 1H), 6.08 (dt, J = 5.7, 1.9, 1H), 4.91 (m, 1H), 4.56 (m, 1H), 1.92–1.35 ppm (m, 8H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.6, 147.4, 137.4, 136.2, 132.8, 116.7, 111.9, 88.1, 73.1, 68.1, 31.7, 31.3, 26.4, 26.2 ppm; HRMS (ESI): m/z: calcd for $C_{14}H_{16}N_2OH$: 229.1335 $[M+H]^+$, found: 229.1335.

(1*S*,4*R*)-5,6-Dimethyl-3-pyridin-2-yl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (7): According to GP1: (R,R_p)-Walphos-CF_3 (12.9 mg, 13.9 μmol), $[Cu^I(CH_3CN)_4]PF_6$ (5.2 mg, 14 μmol), CH_2Cl_2 (1.5 mL), 2-nitrosopyridine (15 mg, 0.14 mmol) in CH_2Cl_2 (0.5 mL), 2,3-dimethyl-cyclohexa-1,3-diene (18 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) and SiO_2 chromatography (pentane/MTBE 5:1) gave **7** as a yellow oil (30 mg, 99%). Enantiomeric excess (95% *ee*) was determined by chiral HPLC. Column: Chiralcel OD-H; solvent: cyclohexane/*i*PrOH 99:1; flow: 1.0 mL min^{-1}; major enantiomer: t_R = 9.6 min, minor enantiomer: t_R = 38.1 min. R_f = 0.25 (pentane/MTBE 5:1); $[\alpha]_D^{25}$ = +97.2 (c = 1.3, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.27–8.20 (m, 1H), 7.52–7.47 (m, 1H), 6.92–6.89 (m, 1H), 6.77–6.69 (m, 1H), 5.00 (m, 1H), 4.51–4.50 (m, 1H), 2.21–2.12 (m, 2H), 1.75 (s, 3H), 1.62 (s, 3H), 1.59–1.52 (m, 1H), 1.44–1.34 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.6, 147.1, 137.6, 132.7, 130.7, 116.4, 111.3, 75.7, 57.8, 24.9, 21.3, 16.3, 14.4 ppm; FTIR (neat): $\tilde{\nu}$ = 2934, 2856, 1588, 1463, 1431, 1293, 1254, 1141, 1064, 963, 879, 780 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{13}H_{16}N_2OH$: 217.1335 $[M+H]^+$; found: 217.1332.

(1*S*,2*R*,6*R*,7*R*)-4,4-Dimethyl-9-pyridin-2-yl-3,5,8-trioxa-9-azatricyclo[5.2.2.0^{2,6}]undec-10-ene (9): According to GP1: (R,R_p)-Walphos-CF_3 (12.9 mg, 13.9 μmol), $[Cu^I(CH_3CN)_4]PF_6$ (5.2 mg, 14 μmol), CH_2Cl_2 (1.5 mL), 2-nitrosopyridine (15 mg, 0.14 mmol) in CH_2Cl_2 (0.5 mL), 2,2-dimethyl-3a,7a-dihydro-1,3-benzodioxole (25 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) and SiO_2 chromatography (pentane/MTBE 5:1) gave **9** as white powder (36 mg, 99%). Enantiomeric excess (93% *ee*) was determined by chiral HPLC. Column: Chiralcel OD-H; solvent: cyclohexane/*i*PrOH 99:1; flow: 1.0 mL min^{-1}; major enantiomer: t_R = 12.8 min, minor enantiomer: t_R = 30.4 min. R_f = 0.3 (pentane/MTBE 5:1); $[\alpha]_D^{25}$ = +91.8 (c = 1.66, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23–8.21 (m, 1H), 7.53 (ddd, J = 1.8, 7.5, 8.4, 1H), 6.96–6.93 (m, 1H), 6.83–6.79 (m, 1H), 6.38–6.32 (m, 1H), 6.25–6.20 (m, 1H), 5.64–5.60 (m, 1H), 4.90–4.86 (m, 1H), 4.69 (dd, J = 4.1,7.0, 1H), 4.62 (dd, J = 4.5, 7.0, 1H), 1.34 ppm (s, 6H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.0, 147.5, 137.7, 130.9, 128.8, 117.4, 111.9, 110.7, 73.9, 73.6, 70.4, 55.4, 25.8, 25.6 ppm; FTIR (neat): $\tilde{\nu}$ = 2989, 2939, 1585, 1570, 1462, 1431, 1373, 1257, 1204, 1162, 1092, 881, 776 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{14}H_{16}N_2O_3H$: 261.1234 $[M+H]^+$; found: 261.1231.

(1*S*,4*R*)-5-(*tert*-Butyl-dimethyl-silanyloxy)-3-pyridin-2-yl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (11a): According to GP1: (R,R_p)-Walphos-CF_3 (12.9 mg, 13.9 μmol), $[Cu^I(CH_3CN)_4]PF_6$ (5.2 mg, 14 μmol), CH_2Cl_2 (1.5 mL), 2-nitrosopyridine (15 mg, 0.14 mmol) in CH_2Cl_2 (0.5 mL), *tert*-butyl-(cyclohexa-1,5-dienyloxy)dimethylsilane (35 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) and SiO_2 chromatography (pentane/MTBE/Et_3N 10:1:0.03) gave **11a** as a yellow oil (44 mg, 99%). Enantiomeric excess (93% *ee*) was determined by chiral HPLC. Column: Chiralcel OD-H; solvent: cyclohexane/*i*PrOH 97:3; flow: 1.0 mL min^{-1}; major enantiomer: t_R = 7.0 min, minor enantiomer: t_R = 13.9 min. R_f = 0.3 (pentane/MTBE/Et_3N 10:1:0.03); $[\alpha]_D^{25}$ = +22.3 (c = 1.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.22–8.19 (m, 1H), 7.50 (ddd, J = 1.8, 7.5, 8.3, 1H), 6.98–6.95 (m, 1H), 6.76 (ddd, J = 0.9, 4.8, 7.2, 1H), 5.14 (dd, J = 2.7, 6.6, 1H), 5.06 (dd, J = 2.8, 1H), 4.84–4.81 (m, 1H), 2.26 (s, 2H), 1.83–1.71 (m, 1H), 1.47–1.36 (m, 1H), 0.80 (s, 9H), 0.01 (s, 3H), −0.25 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.5, 153.9, 147.5, 137.4, 116.8, 111.4, 100.5, 72.2, 58.4, 26.4, 25.5, 21.1, 18.0, −4.5, −5.6 ppm; FTIR (neat): $\tilde{\nu}$ = 2932, 2895, 2858, 1638, 1587, 1463, 1432, 1306, 1251, 1214, 915, 868, 779 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{17}H_{26}N_2O_2SiH$: 319.1836; found: 319.1838 $[M+H]^+$.

(1*S*,4*R*)-5-Phenyl-3-pyridin-2-yl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (11b): According to GP1: (R,R_p)-Walphos-CF_3 (12.9 mg, 13.9 μmol), $[Cu^I(CH_3CN)_4]PF_6$ (5.2 mg, 14 μmol), CH_2Cl_2 (1.5 mL), 2-nitrosopyridine (15 mg, 0.14 mmol) in CH_2Cl_2 (0.5 mL), 2-phenylcyclohexa-1,3-diene (26 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) and SiO_2 chromatography (pentane/MTBE 8:1) gave **11b** as a colorless oil (36 mg, 99%). Enantiomeric excess (88% *ee*) was determined by chiral HPLC. Column: Chiralcel OD-H; solvent: cyclohexane/*i*PrOH (99.5:0.5); flow: 1.0 mL min^{-1}; major enantiomer: t_R = 23.8 min, minor enantiomer: t_R = 61.9 min. R_f = 0.02 (pentane/MTBE 10:1); $[\alpha]_D^{25}$ = −198.3 (c = 1.43, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.14–8.12 (m, 1H), 7.42–7.34 (m, 3H), 7.22–7.11 (m, 3H), 6.87–7.84 (m, 1H), 6.64–6.58 (m, 2H), 5.71–5.68 (m, 1H), 4.85–4.81 (m, 1H), 2.38–2.21 (m, 2H), 1.66–1.57 (m, 1H), 1.43–1.35 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.9, 147.4, 143.0, 137.6, 136.3, 128.5, 128.0, 125.6, 122.9, 116.9, 111.1, 70.3, 54.9, 24.7, 21.3 ppm; FTIR (neat): $\tilde{\nu}$ = 3054, 2935, 1586, 1462, 1431, 1249, 974, 959, 880, 780, 693 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{17}H_{16}N_2OH$: 265.1335; found: 265.1333 $[M+H]^+$.

Trifluoromethanesulfonic acid (1*S*,4*R*)-3-pyridin-2-yl-2-oxa-3-azabicyclo-[2.2.2]oct-5-en-5-yl ester (11c) and trifluoromethanesulfonic acid (1*S*,4*R*)-3-pyridin-2-yl-2-oxa-3-azabicyclo[2.2.2]oct-5-en-6-yl ester (12c): According to GP1: (R,R_p)-Walphos-CF_3 (12.9 mg, 13.9 μmol), $[Cu^I(CH_3CN)_4]PF_6$ (5.2 mg, 14 μmol), CH_2Cl_2 (1.5 mL), 2-nitrosopyridine (15 mg, 0.14 mmol) in CH_2Cl_2 (0.5 mL), trifluoromethanesulfonic acid cyclohexa-1,5-dienyl ester (38 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) and SiO_2 chromatography (pentane/MTBE 5:1) gave 46 mg (99%) of **11c** and **12c** as a mixture of isomers. The isomer ratio was determined by chiral HPLC (**11c**/**12c** 1:2). The diastereoisomers were separated by flash chromatography (pentane/MTBE 10:1) to give **11c** (15 mg, 32%) and **12c** (30 mg, 64%).

11c: Enantiomeric excess (81% *ee*) was determined by chiral HPLC. Column: Chiralcel OD-H; solvent: cyclohexane/*i*PrOH 99.5:0.5; flow:

1.0 mL min^{-1}; major enantiomer: t_R = 20.8 min, minor enantiomer: t_R = 34.5 min. R_f = 0.5 (pentane/MTBE 5:1); $[\alpha]_D^{25}$ = +25.7 (c = 0.53, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.26–8.24 (m, 1H), 7.56 (ddd, J = 1.8, 7.5, 8.3, 1H), 6.96–6.93 (m, 1H), 6.86 (ddd, J = 0.9, 4.9, 7.5, 1H), 6.15 (dd, J = 3.0, 6.6, 1H), 5.50 (dd, J = 3.0, 1H), 5.01–4.97 (m, 1H), 2.36–2.23 (m, 2H), 1.96–1.84 (m, 1H), 1.53–1.42 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.1, 147.8, 147.9, 137.9, 118.6 (q, J = 319 Hz), 118.1, 115.5, 111.9, 71.7, 55.6, 24.8, 21.0 ppm; FTIR (neat): $\tilde{\nu}$ = 2944, 1650, 1588, 1463, 1433, 1247, 1211, 1138, 1112, 888, 870 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{12}H_{11}F_3N_2O_4SH$: 337.0464 $[M+H]^+$; found: 337.0471.

12c: Enantiomeric excess (98% *ee*) was determined by chiral HPLC. Column: Chiralcel OD-H; solvent: cyclohexane/*i*PrOH 99.5:0.5; flow: 1.0 mL min^{-1}; major enantiomer: t_R = 13.2 min, minor enantiomer: t_R = 19.2 min. R_f = 0.4 (pentane/MTBE 5:1); $[\alpha]_D^{25}$ = +71.6 (c = 1.5, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21–8.19 (m, 1H), 7.55 (ddd, J = 1.8, 7.4, 8.3, 1H), 6.98–6.95 (m, 1H), 6.84 (ddd, J = 0.9, 4.9, 7.4, 1H), 6.13 (dd, J = 2.7, 6.6, 1H), 5.62–5.59 (m, 1H), 4.87–4.84 (m, 1H), 2.38–2.22 (m, 2H), 1.78–1.63 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 162.9, 147.4, 147.1, 137.9, 119.3, 118.6 (q, J = 319.2 Hz), 117.8, 111.9, 71.8, 53.2, 24.9, 21.1 ppm; FTIR (neat): $\tilde{\nu}$ = 2944, 1588, 1463, 1431, 1211, 1138, 1108, 886, 840, 780 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{12}H_{11}F_3N_2O_4SH$: 337.0464 $[M+H]^+$; found: 337.0467.

(1*S*,4*R*)-5-Butyl-3-pyridin-2-yl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (11d): According to GP1: (R,R_p)-Walphos-CF_3 (12.9 mg, 13.9 μmol), [Cu^I-($CH_3CN)_4$]PF_6 (5.2 mg, 14 μmol), CH_2Cl_2 (1.5 mL), 2-nitrosopyridine (15 mg, 0.14 mmol) in CH_2Cl_2 (0.5 mL), 2-butylcyclohexa-1,3-diene (23 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) and SiO_2 chromatography (pentane/MTBE 7.5:1) gave **11d** as a colorless oil (33 mg, 97%, ~2% other isomer formed). Enantiomeric excess (87% *ee*) was determined by chiral HPLC. Column: Chiralcel OD-H; solvent: cyclohexane/*i*PrOH (99.5:0.5); flow: 1.0 mL min^{-1}; major enantiomer: t_R = 48.2 min, minor enantiomer: t_R = 41.8 min. R_f = 0.4 (pentane/MTBE 5:1); $[\alpha]_D^{25}$ = +21.4 (c = 1.35, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.20–8.18 (m, 1H), 7.50–7.44 (m, 1H), 6.91–6.88 (m, 1H), 6.73 (ddd, J = 0.8, 4.9, 7.2, 1H), 6.03–6.00 (m, 1H), 5.10 (m, 1H), 4.71–4.68 (m, 1H), 2.28–2.14 (m, 2H), 2.01–1.87 (m, 2H), 1.57–1.46 (m, 1H), 1.41–1.06 (m, 5H), 0.77 ppm (t, J = 7.2, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 164.5, 147.3, 145.4, 137.4, 122.1, 116.5, 111.3, 70.7, 56.5, 34.2, 28.7, 25.3, 22.3, 21.1, 13.9 ppm; FTIR (neat): $\tilde{\nu}$ = 3050, 2958, 2931, 1587, 1568, 1463, 1432, 1252, 959, 881, 830, 779 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{15}H_{20}N_2OH$: 245.1648 $[M+H]^+$; found: 245.1650.

***rac*-1-Methyl-3-pyridin-2-yl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (14a) and (1*S*,4*R*)-4-methyl-3-pyridin-2-yl-2-oxa-3-azabicyclo[2.2.2]oct-5-ene (14b)**: According to GP1: (R,R_p)-Walphos-CF_3 (12.9 mg, 13.9 μmol), [Cu^I-($CH_3CN)_4$]PF_6 (5.2 mg, 14 μmol), CH_2Cl_2 (1.5 mL), 2-nitrosopyridine (15 mg, 0.14 mmol) in CH_2Cl_2 (0.5 mL), 1-methylcyclohexa-1,3-diene (16 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) and SiO_2 chromatography (pentane/MTBE 5:1) gave 26 mg (92%) of **14a** and **14b** as a mixture of isomers. The isomer ratio was determined by chiral HPLC (**14a**/**14b** 1:2.1). The diastereoisomers were separated by flash chromatography (pentane/MTBE 5:1) to get **14a** (8 mg, 28%) and **14b** (17 mg, 61%).

14a: R_f = 0.4 (pentane/MTBE 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.21–8.19 (m, 1H), 7.55–7.49 (m, 1H), 6.95–6.92 (m, 1H), 6.79–6.74 (m, 1H), 6.33–6.29 (m, 1H), 6.25–6.22 (m, 1H), 5.33–5.31 (m, 1H), 2.34–2.24 (m, 1H), 2.06–1.98 (m, 1H), 1.68–1.58 (m, 1H), 1.53 (s, 3H), 1.48–1.38 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 163.7, 146.8, 137.9, 135.2, 131.8, 116.5, 111.6, 75.0, 52.6, 30.9, 23.2, 22.1 ppm; FTIR (neat): $\tilde{\nu}$ = 3051, 2973, 2932, 1588, 1462, 1432, 1379, 1197, 850, 782 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{12}H_{14}N_2OH$: 203.1179 $[M+H]^+$; found: 203.1184.

14b: Enantiomeric excess (93% *ee*) was determined by chiral HPLC. Column: Chiralcel OD-H; solvent: cyclohexane/*i*PrOH (97:03); flow: 1.0 mL min^{-1}; major enantiomer: t_R = 22.1 min, minor enantiomer: t_R = 14.4 min. R_f = 0.3 (pentane/MTBE 5:1); $[\alpha]_D^{25}$ = −8.4 (c = 0.25, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.29–8.28 (m, 1H), 7.56–7.50 (m, 1H), 6.98 (d, J = 8.1, 1H), 6.94–6.89 (m, 1H), 6.61–6.57 (m, 1H), 5.93 (d, J = 8.1, 1H), 4.79–4.75 (m, 1H), 2.35–2.24 (m, 1H), 2.21–2.15 (m, 1H), 1.71 (s, 3H), 1.44–1.39 ppm (m, 2H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 146.5, 137.2, 134.9, 130.4, 119.0, 116.4, 69.6, 60.0, 30.4, 26.6, 25.1 ppm; FTIR (neat): $\tilde{\nu}$ = 3052, 2931, 1670, 1589, 1463, 1433, 1265, 1109, 850, 737 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{12}H_{14}N_2OH$: 203.1179 $[M+H]^+$; found: 203.1181.

5-Pyridin-2-yl-2,3,3a,5,5a,6,7,8-octahydro-1*H*-4-oxa-5-aza-*as*-indacene (16): According to GP1: (R,R_p)-Walphos-CF_3 (12.9 mg, 13.9 μmol), [Cu^I-($CH_3CN)_4$]PF_6 (5.2 mg, 14 μmol), CH_2Cl_2 (1.5 mL), 2-nitrosopyridine (15 mg, 0.14 mmol) in CH_2Cl_2 (0.5 mL), bicyclopentyl-1,1′-diene (22 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) and SiO_2 chromatography (pentane/MTBE 5:1) gave **16** as a yellow oil (4.0 mg, 11%). R_f = 0.5 (pentane/MTBE 5:1); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.23–8.21 (m, 1H), 7.56–7.50 (m, 1H), 7.11–7.08 (m, 1H), 6.68 (ddd, J = 7.1, 5.0, 0.9, 1H), 4.89–4.75 (m, 1H), 4.28–4.23 (m, 1H), 2.46–2.13 (m, 6H), 1.88–1.73 (m, 3H), 1.59–1.48 (m, 2H), 1.49–1.37 ppm (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 160.5, 147.9, 137.7, 133.1, 131.3, 114.6, 108.7, 77.3, 58.3, 30.6, 30.5, 27.6, 25.1, 21.5, 20.5 ppm; FTIR (neat): $\tilde{\nu}$ = 2960, 2869, 1593, 1564, 1464, 1434, 1361, 1298, 1259, 1176, 770, 736 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{15}H_{18}N_2OH$: 243.1492 $[M+H]^+$, found: 243.1490.

(1*S*,4*R*)-2-Pyridin-2-yl-3-oxa-2,5-diazabicyclo[2.2.2]oct-7-ene-5-carboxylic acid methyl ester (18): According to GP 1: (R,R_p)-Walphos-CF_3 (12.9 mg, 13.9 μmol), [Cu^I($CH_3CN)_4$]PF_6 (5.2 mg, 14 μmol), CH_2Cl_2 (1.5 mL), 2-nitrosopyridine (15 mg, 0.14 mmol) in CH_2Cl_2 (0.5 mL), 2*H*-pyridine-1-carboxylic acid methyl ester (23 mg, 0.17 mmol) in CH_2Cl_2 (1.0 mL) and SiO_2 chromatography (pentane/MTBE 1:1) gave **18** as a yellow oil (32 mg, 94%). Enantiomeric excess (96% *ee*) was determined by chiral HPLC. Column: Chiralcel OD-H; solvent: cyclohexane/*i*PrOH 99:1; flow: 1.0 mL min^{-1}; major enantiomer: t_R = 30.9 min, minor enantiomer: t_R = 41.6 min. R_f = 0.3 (pentane/MTB 1:1); $[\alpha]_D^{25}$ = +146.6 (c = 1.3, $CHCl_3$); ^{1}H NMR (600 MHz, $CDCl_3$): δ = 8.20–8.14 (m, 1H), 7.52–7.490 (m, 1H), 6.91–6.87 (m, 1H), 6.81–6.79 (m, 1H), 6.56–6.51 (m, 1H), 6.34–6.30 (m, 1H), 6.21–6.05 (m, 1H), 5.47–5.43 (m, 1H), 3.91–3.89 (m, 1H), 3.73–3.70 (m, 3H), 3.29–3.25 ppm (m, 1H); ^{13}C NMR (151 MHz, $CDCl_3$): δ = 161.7, 161.6, 154.4, 153.5, 146.4, 146.3, 136.9, 136.8, 129.1, 128.6, 128.5, 128.2, 116.7, 110.7, 110.6, 74.9, 74.5, 51.9, 51.9, 51.4, 51.3, 43.6 ppm; FTIR (neat): $\tilde{\nu}$ = 2955, 2250, 1709, 1590, 1433, 1395, 1339, 1293, 1124, 912, 867, 733 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{12}H_{13}N_2O_3H$: 248.1030 $[M+H]^+$, found: 248.1022.

[(3a*R*,4*S*,7*R*,7a*R*)-7-(*tert*-Butyldimethylsiloxy)-2,2-dimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxol-4-yl]-pyridin-2-yl-amine (19): The N–O bond of **9** was cleaved according to the previously reported procedure.[10] [$Mo(CO)_6$] (518 mg, 1.96 mmol) and $NaBH_4$ (79 mg, 2.1 mmol) were added to a solution of **9** (425 mg, 1.63 mmol) in MeOH/H_2O 10:1 (27 mL). The reaction mixture was heated to 65 °C and stirred for 10 h at that temperature. The precipitate was removed by filtration through a short pad of Celite, and the filtrate was concentrated in vacuo. The residue was dissolved in CH_2Cl_2, washed with brine, dried over $MgSO_4$, and concentrated under reduced pressure. The residue was passed through a short pad of silica gel (pentane/acetone 2:1) and concentrated in vacuo. The resulting mass was dissolved in DMF (3 mL), treated successively with TBSCl (353 mg, 2.35 mmol) and imidazole (320 mg, 4.70 mmol), and stirred for 24 h at RT. A sat. aq $NaHCO_3$ solution was added to the reaction mixture, and the resulting solution was extracted with MTBE. The combined organic layers were washed with brine, dried over $MgSO_4$, concentrated under vacuum, and the residue was subjected to flash column chromatography (pentane/MTBE 4:1) to give **19** as a colorless oil (560 mg, 91%, over two steps). R_f = 0.3 (pentane/MTBE 5:1); $[\alpha]_D^{25}$ = +4.2 (c = 1.15, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): δ = 8.11–8.01 (m, 1H), 7.39–7.33 (m, 1H), 6.58–6.54 (m, 1H), 6.42–6.37 (m, 1H), 5.95–5.94 (m, 2H), 4.95 (d, J = 8.1, 1H), 4.53–4.49 (m, 1H), 4.32–4.21 (m, 3H), 1.42 (s, 3H), 1.32 (s, 3H), 0.93 (s, 9H), 0.14 (s, 3H), 0.13 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): δ = 157.9, 148.3, 137.3, 132.4, 130.7, 113.3, 108.6, 108.3, 79.5, 77.0, 69.1, 50.0, 26.9, 26.0, 24.8, 18.2, −4.6, −4.6 ppm; FTIR (neat): $\tilde{\nu}$ = 2954, 2930, 1857, 1601, 1573, 1483, 1382, 1255, 1211, 1117, 1061, 897, 838, 776, 734 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{20}H_{32}N_2O_3SiH$: 377.2255 $[M+H]^+$; found: 377.2249.

[(3a*R*,4*S*,7*R*,7a*R*)-7-(*tert*-Butyldimethylsiloxy)-2,2-dimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxol-4-yl]-pyridin-2-yl-carbamic acid methyl ester (20): A 3 M solution of CH_3MgCl in THF (0.57 mL, 1.7 mmol) was added dropwise to a solution of **19** (541 mg, 1.43 mmol) in THF (8.0 mL) at RT,

and the mixture was stirred for 10 min at that temperature. Methyl chloroformate (0.34 mL, 4.3 mmol) was then added, and stirring was continued at RT for 12 h. Then the reaction was quenched with H_2O, and the resulting solution was extracted with CH_2Cl_2 (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo; the residue was subjected to flash column chromatography (pentane/MTB 2:1) to give **20** as a colorless oil (601 mg, 96%). $R_f=0.2$ (pentane/MTBE 5:1); $[\alpha]_D^{25}=+19.8$ ($c=1.33$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=8.41$–8.39 (m, 1H), 7.71–7.65 (m, 1H), 7.50–7.44 (m, 1H), 7.10 (ddd, $J=0.9$, 4.8, 7.2, 1H), 5.78 (dt, $J=2.4$, 10.1, 1H), 5.62 (ddd, $J=1.8$, 3.0, 10.1, 1H), 4.93–4.89 (m, 1H), 4.55–4.51 (m, 1H), 4.21–4.17 (m, 1H), 4.06 (dd, $J=5.3$, 7.0, 1H), 3.74 (s, 3H), 1.38 (s, 3H), 1.31 (s, 3H), 0.91 (s, 9H), 0.12 (s, 3H), 0.10 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=155.6$, 154.2, 148.2, 137.6, 131.3, 128.2, 122.1, 121.3, 108.5, 80.4, 75.8, 71.5, 58.9, 53.0, 27.7, 26.0, 25.7, 18.3, −4.4, −4.7 ppm; FTIR (neat): $\tilde{\nu}=$ 2955, 2932, 2857, 1718, 1589, 1470, 1434, 1381, 1326, 1257, 1111, 1065, 836, 777, 733 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{22}H_{34}N_2O_5SiNa$: 457.2129 $[M+Na]^+$, found: 457.2106.

((3a*R*,4*S*,7*R*,7a*S*)-7-Hydroxy-2,2-dimethyl-3a,4,7,7a-tetrahydro-1,3-benzodioxol-4-yl)-carbamic acid methyl ester (21): Methyl trifluoromethanesulfonate (0.10 mL, 0.89 mmol) was added dropwise to a solution of **20** (0.35 g, 0.81 mmol) in CH_2Cl_2 (20 mL) at 0°C, and the resulting solution was stirred for 12 h at that temperature. Then the solvent was removed under vacuum, and the residue was dissolved in MeOH (9.5 mL). A 2 M aq NaOH solution (4.7 mL) was added, and stirring was continued at 50°C for 6 h. The solvents were removed, and the resulting residue was extracted with EtOAc (3×30 mL). The combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated in vacuo. The residue was purified by flash column chromatography (pentane/acetone 2:1) to afford **21** as a colorless oil (160 mg, 82%). $R_f=0.6$ (pentane/acetone 1:1); $[\alpha]_D^{25}=+41.1$ ($c=1.3$, $CHCl_3$); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.95$–5.90 (m, 1H), 5.79 (ddd, $J=1.5$, 3.6, 9.7, 1H), 5.29–5.26 (m, 1H), 4.24–4.21 (m, 3H), 4.13–4.12 (m, 1H), 3.68 (s, 3H), 2.82 (br s, 1H), 1.44 (s, 3H), 1.34 ppm (s, 3H); ^{13}C NMR (75 MHz, $CDCl_3$): $\delta=156.7$, 131.3, 129.9, 109.3, 79.4, 69.2, 52.4, 51.3, 27.1, 24.9 ppm; FTIR (neat): $\tilde{\nu}=$ 3333, 2989, 2937, 1703, 1538, 1457, 1376, 1261, 1212, 1062, 912, 873, 732 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{11}H_{17}NO_5Na$: 266.1004 $[M+Na]^+$; found: 266.0975.

Acetic acid (1*R*,4*S*,5*R*,6*S*)-5,6-diacetoxy-4-acetylamino-cyclohex-2-enyl ester (22): Acetyl chloride (0.39 mL, 5.4 mmol) and NaI (0.81 g, 5.4 mmol) were added to a solution of **21** (88 mg, 0.36 mmol) in MeCN (6 mL) at RT. The resulting mixture was stirred at 65°C for 40 h. The reaction was cooled to 0°C and quenched with sat. aq $NaHSO_3$ and $NaHCO_3$ solutions. Then the resulting mixture was extracted with CH_2Cl_2 (3×20 mL), and the combined organic layers were washed with brine, dried over $MgSO_4$, and concentrated under vacuum. The residue was purified by flash column chromatography (pentane/acetone 2:1) to afford **22** as a colorless oil (65 mg, 57%). The physical data are in agreement with those reported in the literature.[5a,c] $R_f=0.2$ (pentane/acetone 2:1); $[\alpha]_D^{25}=-30.6$ ($c=0.45$, $CHCl_3$), (lit:[5c] $[\alpha]_D^{20}$ for *ent*-**22**$=+33$ ($c=0.4$, $CHCl_3$)); ^{1}H NMR (300 MHz, $CDCl_3$): $\delta=5.81$ (m, 2H), 5.67 (d, $J=8.4$, 1H), 5.29–5.19 (m, 34H), 4.86–4.80 (m, 1H), 2.09 (s, 3H), 2.07 (s, 6H), 1.99 ppm (s, 3H);^{13}C NMR (75 MHz, $CDCl_3$): $\delta=170.9$, 170.1, 170.0, 169.8, 131.5, 125.1, 69.8, 69.7, 68.4, 47.9, 23.4, 21.0, 21.0 ppm; FTIR (neat): $\tilde{\nu}=$ 1748, 1659, 1538, 1371, 1225, 1053, 1024, 733 cm^{-1}; HRMS (ESI): m/z: calcd for $C_{14}H_{19}NO_7Na$: 336.1054 $[M+Na]^+$, found: 336.1047.

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