

## **Reduction of Carbonyl Compounds with Dicyclopentylzinc: A New Example of Asymmetric Amplifying Autocatalysis**

**Elena Sh. Saigitbatalova <sup>1†</sup>, Liliya Z. Latypova <sup>1†</sup>, Almaz A. Zagidullin <sup>2</sup>, Almira R. Kurbangalieva <sup>1,\*</sup> and Ilya D. Gridnev <sup>3,\*</sup>**

<sup>1</sup> Biofunctional Chemistry Laboratory, A. Butlerov Institute of Chemistry, Kazan Federal University, 18 Kremlyovskaya Street, 420008 Kazan, Russia

<sup>2</sup> A. E. Arbuzov Institute of Organic and Physical Chemistry, FRC Kazan Scientific Center of RAS, 8 Arbuzov Street, 420088 Kazan, Russia

<sup>3</sup> N. D. Zelinsky Institute of Organic Chemistry, Leninsky Prosp. 47, 119991 Moscow, Russia

† These authors contributed equally to this work

\* Correspondence: ilyaiochem@gmail.com (I.D.G.); akurbang@kpfu.ru (A.R.K.)

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## 1. Materials and Methods

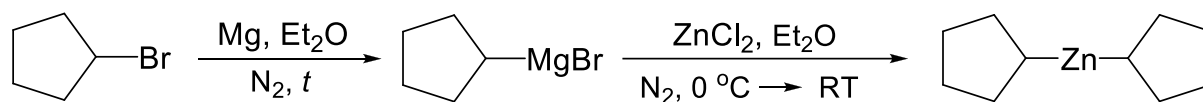
All reactions were carried out using standard Schlenk techniques under an argon atmosphere in oven-dried glassware with magnetic stirring. All solvents were purified and distilled using standard procedures. Solvents were additionally degassed by three pump–freeze–thaw cycles. Analytical thin-layer chromatography (TLC) was carried out on Sorbfil PTLC-AF-A-UF plates using UV light (254 nm) as the visualizing agent. Silica gel 60A (Acros Organics, 400–230 mesh, 0.040–0.063 mm) was used for open column chromatography. Melting points were recorded with a Boëtius melting point instrument and are uncorrected. NMR spectra were measured on a Bruker Avance III 400 spectrometer at 400.17 MHz ( $^1\text{H}$ ) and 100.62 MHz ( $^{13}\text{C}$ ), and a Bruker Avance III 500 spectrometer at 500.1 MHz ( $^1\text{H}$ ) and 125.8 MHz ( $^{13}\text{C}$ ) at 20 °C in the deuterated chloroform and benzene. The chemical shifts ( $\delta$ ) are expressed in parts per million (ppm) and are calibrated using residual undeuterated solvent peak as an internal reference ( $\text{CDCl}_3$ :  $\delta_{\text{H}}$  7.26,  $\delta_{\text{C}}$  77.16;  $\text{C}_6\text{D}_6$ :  $\delta_{\text{H}}$  7.16,  $\delta_{\text{C}}$  128.06). All coupling constants ( $J$ ) are reported in Hertz (Hz), and multiplicities are indicated as follows: s (singlet), d (doublet), dd (doublet of doublets), qd (quartet of doublets) and m (multiplet). The enantiomeric excess (ee) measurements were performed via HPLC analysis on an HPLC system equipped with chiral stationary phase columns Chiralpak (OD-H), detection at 220 nm.

4-Methoxybenzaldehyde, 4-fluorobenzaldehyde, hexanal, 2-phenylacetaldehyde, pyridine-2-carbaldehyde, pyridine-3-carbaldehyde, pyridine-4-carbaldehyde, 2-acetylpyridine (**3**), 2-acetyl-6-bromopyridine (**4**), 2-acetyl-5-bromopyridine (**5**), 2-acetyl-4-bromopyridine (**6**), 2-acetyl-3-bromopyridine (**7**), 4-acetylpyridine (**8**), 4-acetyl-2-bromopyridine (**9**), 3-acetylpyridine (**10**), 5-acetyl-2-bromopyridine (**11**), bromocyclopentane, (–)-(1*R*,2*S*)-ephedrine (**21**) (Merck), benzaldehyde, magnesium (Acros), zinc chloride (TCI), Celite (Fluka), diisopropylzinc 1 M solution in toluene (Sigma-Aldrich) were used as received without further purification.

## 2. Chemical Synthesis

2-((Trimethylsilyl)ethynyl)pyrimidine-5-carbaldehyde (**1**) was synthesized according to the known method [1].

### 2.1. Synthesis of dicyclopentylzinc



A solution of cyclopentyl bromide (7.2 mL, 67.1 mmol) in 10 mL of diethyl ether was added dropwise to a suspension of freshly calcined and iodine-activated magnesium (2.12 g, 87.2 mmol) in 20 mL of diethyl ether. The reaction mixture was refluxed for 2 h. ZnCl<sub>2</sub> (3.22 g, 23.6 mol) had been dried intensively in vacuo by flaming for 1 h. After cooling down to room temperature the solution of cyclopentylmagnesiumbromide obtained after filtration of the reaction mixture through the cannula was added to the suspension of ZnCl<sub>2</sub> in diethyl ether (5 mL) in an ice bath. The reaction mixture was stirred at room temperature for 12 h under nitrogen. Dry petroleum ether (30 mL) was added to the obtained suspension, and the resulting solution was filtered via the cannula to the round bottom Schlenk flask (this procedure was repeated twice). The volume of the filtrate was reduced in vacuo ( $1 \times 10^{-3}$  mbar), and the remaining grey residue was distilled under reduced pressure ( $p = 3.7 \times 10^{-3}$  mbar, bp = 65–67 °C (44–46 °C,  $p = 1 \times 10^{-4}$  mm [2]) to yield the desired compound.

**Dicyclopentylzinc:** colorless solid, 3.23 g (67% yield); <sup>1</sup>H NMR (C<sub>6</sub>D<sub>6</sub>, 400 MHz, ppm)  $\delta$  1.95–1.77 (m, 4H, CH<sub>2</sub>), 1.69–1.54 (m, 4H, CH<sub>2</sub>), 1.53–1.33 (m, 8H, CH<sub>2</sub>), 0.54–0.40 (m, 2H, CH); <sup>13</sup>C {<sup>1</sup>H} NMR (CDCl<sub>3</sub>, 125 MHz, ppm)  $\delta$  30.43 (CH<sub>2</sub>), 29.64 (CH), 26.56 (CH<sub>2</sub>).

For subsequent reactions,  $10^{-3}$  M solutions of dicyclopentylzinc in dry hexane (for all aldehydes, except aldehyde **1**) or in dry toluene (for all ketones) were prepared.

### 2.2. Reaction of aldehyde **1** with dicyclopentylzinc

**(2-((Trimethylsilyl)ethynyl)pyrimidin-5-yl)methanol (2).** The solution of aldehyde **1** (0.10 g, 0.50 mmol) in dry toluene (3 mL) with intense stirring was added to the mixture of  $10^{-3}$  M solution of dicyclopentylzinc (1.0 mL) with 6 mL of dry toluene under nitrogen atmosphere at –70 °C (acetone/dry ice bath). The reaction mixture was stirred for 30 min at –70 °C and for 3 h at room temperature. The mixture was then quenched with aqueous HCl solution (1 M, 5 mL). After stirring for 15 min, the reaction mixture was neutralized with a saturated solution of NaHCO<sub>3</sub> (7 mL). The organic phase was separated, and the aqueous layer was extracted with diethyl ether (4  $\times$  15 mL). The combined organic layers were dried over Na<sub>2</sub>CO<sub>3</sub>, and the solvent was removed in vacuo. The remaining orange solid was purified via column chromatography (eluent petroleum ether–acetone 8:1) to yield alcohol **2**. Spectral data are consistent with the literature [1].

### 2.3. General procedure for the reaction of aldehydes with dicyclopentylzinc

The solution of aldehyde (0.50 mmol) in dry hexane (3 mL) with intense stirring was added to the mixture of  $10^{-3}$  M solution of dicyclopentylzinc with 7 mL of dry hexane under a nitrogen atmosphere. The reaction mixture was stirred at room temperature and was then quenched with aqueous HCl solution (1 M, 3 mL). After stirring for 15 min, the reaction mixture was neutralized with a saturated solution of  $\text{NaHCO}_3$  (5 mL). The organic phase was separated, and the aqueous layer was extracted with diethyl ether ( $3 \times 20$  mL). The combined organic layer was filtered through the Celite and removed in vacuo. The residue was analyzed via NMR spectroscopy without additional purification.

**Benzyl alcohol** was obtained according to the general procedure from benzaldehyde (51  $\mu\text{L}$ , 0.50 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 0.50 mL). The reaction time was 30 min. The yield was quantitative. Spectral data are consistent with the database [3].

**(4-Methoxyphenyl)methanol** was obtained according to the general procedure from 4-methoxybenzaldehyde (61  $\mu\text{L}$ , 0.50 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 0.50 mL). The reaction time was 18 h. The yield (80%) was determined according to  $^1\text{H}$  NMR spectra of the crude product. Spectral data are consistent with the database [3].

**(4-Fluorophenyl)methanol** was obtained according to the general procedure from 4-fluorobenzaldehyde (53  $\mu\text{L}$ , 0.50 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 0.50 mL). The reaction time was 1 h. Light yellow oil was obtained, 57 mg (90% yield). Spectral data are consistent with the literature [4].

**Hexanol-1** was obtained according to the general procedure from hexanal (62  $\mu\text{L}$ , 0.50 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 0.50 mL). The reaction time was 1 h. The yield (58%) was determined according to  $^1\text{H}$  NMR spectra of the crude product. Spectral data are consistent with the database [3].

**2-Phenylethanol** was obtained according to the general procedure from 2-phenylacetaldehyde (56  $\mu\text{L}$ , 0.50 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 0.50 mL). The reaction time was 3.5 h. The yield (70%) was determined according to  $^1\text{H}$  NMR spectra of the crude product. Spectral data are consistent with the database [3].

**Pyridin-2-ylmethanol** was obtained according to the general procedure from pyridine-2-carbaldehyde (48  $\mu\text{L}$ , 0.50 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 0.50 mL). The reaction time was 30 min. The residue obtained after evaporation of the solvents was purified via column chromatography (eluent ethyl acetate–petroleum ether, 1:1). Colorless oil was obtained, 51 mg (93% yield);  $R_f$  0.29 (ethyl acetate–petroleum ether, 1:1). Spectral data are consistent with the literature [5].

**Pyridin-3-ylmethanol** was obtained according to the general procedure from pyridine-3-carbaldehyde (47  $\mu\text{L}$ , 0.50 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 0.50 mL). The reaction time was 30 min. The residue obtained after evaporation of the solvents was purified via column chromatography (eluent ethyl acetate–petroleum ether, 1:1). Colorless oil, 46 mg (84% yield);  $R_f$  0.31 (ethyl acetate–petroleum ether, 1:1). Spectral data are consistent with the literature [6].

**Pyridin-4-ylmethanol** was obtained according to the general procedure from pyridine-4-carbaldehyde (47  $\mu\text{L}$ , 0.50 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 0.50 mL). The reaction time was 30 min. The residue obtained after evaporation of the solvents was purified via column chromatography (eluent ethyl acetate–petroleum ether, 1:2). Colorless solid, 54 mg (99%

yield); mp 58–59 °C (55–57 °C [7]);  $R_f$  0.58 (ethyl acetate–petroleum ether, 1:2). Spectral data are consistent with the literature [7].

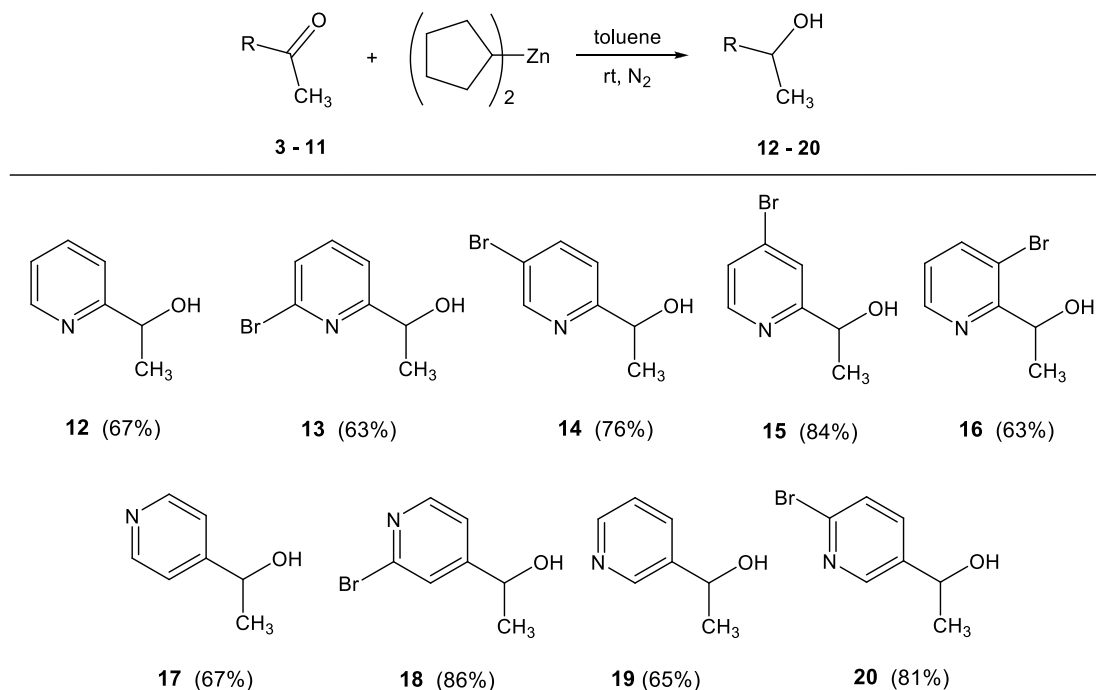
#### 2.4. Reactions of aldehydes with diisopropylzinc

To the solution of hexanal (62  $\mu$ L, 0.50 mmol) in dry hexane (5 mL), a toluene solution of (*i*Pr)<sub>2</sub>Zn (1 M, 0.5 mL) was added dropwise via syringe with intense stirring under an argon atmosphere. The reaction mixture was stirred for 3 days at room temperature and was then quenched with aqueous HCl solution (0.1 M, 5 mL). After stirring for 15 min, the reaction mixture was neutralized with a saturated solution of NaHCO<sub>3</sub> (7 mL). The organic phase was separated, and the aqueous layer was extracted with CH<sub>2</sub>Cl<sub>2</sub> (3  $\times$  10 mL). The solvent from the combined organic layers was removed in vacuo. According to the HPLC and GC–MS spectroscopy, the remaining residue contained 2-methyloctan-3-ol (9%) with other byproducts.

The reaction of benzaldehyde (51  $\mu$ L, 0.50 mmol) with (*i*Pr)<sub>2</sub>Zn (1 M, 0.5 mL) was carried out as described above for hexanal. The reaction time was 26 h. The residue obtained after evaporation of the solvents was purified via column chromatography (eluent ethyl acetate–petroleum ether, 1:6). The fraction with  $R_f$  0.86 contained starting aldehyde (37 mg, 69%), and the fraction with  $R_f$  0.75 contained **2-methyl-1-phenylpropan-1-ol**. Colorless oil was obtained, 20 mg (26% yield). Spectral data are consistent with the literature [8].

#### 2.5. General procedure for the reaction of pyridine ketones with dicyclopentylzinc

The solution of ketone (0.45 mmol) in dry toluene (3 mL) with intense stirring was added to the mixture of 10<sup>−3</sup> M solution of dicyclopentylzinc (2.3 mL) with 7 mL of dry toluene under a nitrogen atmosphere. The reaction mixture was stirred for 5 or 24 h at room temperature and was then quenched with aqueous HCl solution (1 M, 5 mL). After stirring for 15 min, the reaction mixture was neutralized with a saturated solution of NaHCO<sub>3</sub> (7 mL). The organic phase was separated, and the aqueous layer was extracted with ethyl acetate (3  $\times$  20 mL). The combined organic layer was filtered through the Celite and removed in vacuo. The remaining yellow oil was purified via column chromatography (eluent acetone–toluene) to yield the corresponding alcohol.



**1-(Pyridin-2-yl)ethanol (12)** was synthesized according to the general procedure from 2-acetylpyridine (**3**, 0.05 mL, 0.45 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 2.25 mL). The reaction time was 5 h. Eluent for the column chromatography: acetone–toluene, from 1:2 to 1:1. Colorless solid, 37 mg (67% yield); mp 37–39 °C (38–40 °C [9]);  $R_f$  0.16 (acetone–toluene, 1:2);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, ppm)  $\delta$  8.54 (d, 1H,  $\text{H}_{\text{arom.}}$ ), 7.75–7.62 (m, 1H,  $\text{H}_{\text{arom.}}$ ), 7.33–7.15 (m, 2H,  $\text{H}_{\text{arom.}}$ ), 4.89 (q, 1H,  $\text{CH-OH}$ ,  $^3J = 6.5$  Hz), 4.26 (br s, 1H, OH), 1.50 (d, 3H,  $\text{CH}_3$ ,  $^3J = 6.5$  Hz). Spectral data are consistent with match the literature [9].

**1-(6-Bromopyridin-2-yl)ethanol (13)** was synthesized according to the general procedure from 2-acetyl-6-bromopyridine (**4**, 0.09 g, 0.45 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 1.34 mL). The reaction time was 5 h. Eluent for the column chromatography: acetone–toluene, from 1:20 to 1:3. Light yellow oil, 57 mg (63% yield);  $R_f$  0.31 (acetone–toluene, 1:10). Spectral data are consistent with the literature [10].

**1-(5-Bromopyridin-2-yl)ethanol (14)** was synthesized according to the general procedure from 2-acetyl-5-bromopyridine (**5**, 0.09 g, 0.45 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 1.34 mL). The reaction time was 24 h. Eluent for the column chromatography: acetone–toluene, from 1:10 to 1:6. Colorless solid, 69 mg (76% yield); mp 77–80 °C;  $R_f$  0.32 (acetone–toluene, 1:6). Spectral data are consistent with the literature [11].

**1-(4-Bromopyridin-2-yl)ethanol (15)** was synthesized according to the general procedure from 2-acetyl-4-bromopyridine (**6**, 0.05 g, 0.25 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 0.75 mL). The reaction time was 5 h. According to the  $^1\text{H}$  NMR spectroscopy, the reaction mixture contained 10% of starting ketone **6**. Eluent for the column chromatography: acetone–toluene, from 1:10 to 1:5. Colorless crystals, 43 mg (84% yield); mp 67–69 °C;  $R_f$  0.24 (acetone–toluene, 1:5). Spectral data are consistent with the literature [12].

**1-(3-Bromopyridin-2-yl)ethanol (16)** was synthesized according to the general procedure from 2-acetyl-3-bromopyridine (**7**, 0.09 g, 0.45 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 1.34 mL). The reaction time was 24 h. Eluent for the column chromatography: acetone–toluene, 1:10. Colorless oil, 57 mg (63% yield);  $R_f$  0.34 (acetone–toluene, 1:10). Spectral data are consistent with the literature [13].

**1-(Pyridin-4-yl)ethanol (17)** was synthesized according to the general procedure from 4-acetylpyridine (**8**, 0.05 mL, 0.45 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 1.35 mL). The

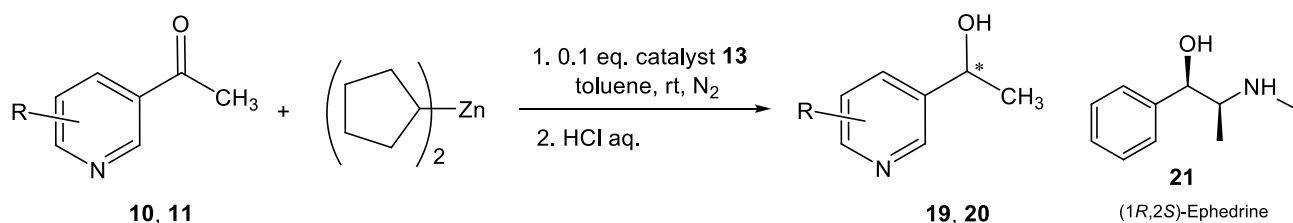
reaction time was 5 h. Eluent for the column chromatography: acetone–toluene, from 1:10 to 1:1. Colorless solid, 37 mg (67% yield); mp 53–54.5 °C (57–59 °C [14];  $R_f$  0.31 (acetone–toluene, 1:1). Spectral data are consistent with the literature [15].

**1-(2-Bromopyridin-4-yl)ethanol (18)** was synthesized according to the general procedure from 4-acetyl-2-bromopyridine (**9**, 0.05 g, 0.25 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 0.75 mL). The reaction time was 24 h. According to the  $^1\text{H}$  NMR spectroscopy, the reaction mixture contained 7% of starting ketone **9**. Eluent for the column chromatography: acetone–toluene, 1:20. Colorless oil, 43 mg (86% yield);  $R_f$  0.23 (acetone–toluene, 1:20);  $^1\text{H}$  NMR ( $\text{CDCl}_3$ , 400 MHz, ppm)  $\delta$  8.29 (d, 1H,  $\text{H}_{\text{arom}}$ ,  $^3J = 5.1$  Hz), 7.52 (br s, 1H,  $\text{H}_{\text{arom}}$ ), 7.24 (dd, 1H,  $\text{H}_{\text{arom}}$ ,  $^3J = 5.1$  Hz,  $^4J = 1.1$  Hz), 4.88 (qd, 1H,  $\text{CH-OH}$ ,  $^3J = 6.6$  Hz,  $^3J = 3.8$  Hz), 2.36 (d, 1H, OH,  $^3J = 3.8$  Hz), 1.48 (d, 3H,  $\text{CH}_3$ ,  $^3J = 6.6$  Hz);  $^{13}\text{C}\{^1\text{H}\}$  NMR ( $\text{CDCl}_3$ , 100 MHz, ppm)  $\delta$  157.81, 150.34, 142.69, 124.88, 119.73 ( $\text{C}_{\text{arom}}$ ), 68.59 (CH), 25.26 ( $\text{CH}_3$ ). Alcohol **18** is known [16, 17]; however, no spectroscopic data are available.

**1-(Pyridin-3-yl)ethanol (19)** was synthesized according to the general procedure from 3-acetylpyridine (**10**, 0.05 mL, 0.45 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 2.27 mL). The reaction time was 5 h. According to the  $^1\text{H}$  NMR spectroscopy, the reaction mixture contained 10% of starting ketone **10**. Eluent for the column chromatography: acetone–petroleum ether, from 1:2 to 1:1. Colorless oil, 36 mg (65% yield);  $R_f$  0.31 (acetone–petroleum ether, 1:1). Spectral data are consistent with the literature [9].

**1-(6-Bromopyridin-3-yl)ethanol (20)** was synthesized according to the general procedure from 5-acetyl-2-bromopyridine (**11**, 0.09 g, 0.45 mmol) and dicyclopentylzinc ( $10^{-3}$  M solution, 1.34 mL). The reaction time was 24 h. According to the  $^1\text{H}$  NMR spectroscopy, the reaction mixture contained 8% of starting ketone **11**. Eluent for the column chromatography: acetone–toluene, from 1:10 to 1:2. Colorless solid, 73 mg (81% yield); mp 47–49 °C (47–48 °C [10]);  $R_f$  0.41 (acetone–toluene, 1:2). Spectral data are consistent with the literature [10].

## 2.6. General procedure for the reaction of pyridine ketones with dicyclopentylzinc in the presence of catalyst



To the solution of dicyclopentylzinc (3 or 5 eq.) in dry toluene (20 mL), (–)-(1*R*,2*S*)-ephedrine (**21**) (0.1 eq.) was added under a nitrogen atmosphere. After stirring the mixture for 20 min at room temperature, a solution of ketone (1 eq.) in dry toluene (9 mL) was added dropwise. The reaction mixture was stirred for 5 or 24 h at room temperature and was then quenched with aqueous HCl solution (1 M, 5 mL). After stirring for 15 min, the reaction mixture was neutralized with a saturated solution of  $\text{NaHCO}_3$  (7 mL). The organic phase was separated, and the aqueous layer was extracted with ethyl acetate ( $3 \times 20$  mL). The combined organic layer was filtered through the Celite and removed in vacuo. The remaining yellow oil was purified via column chromatography to yield the corresponding alcohol. The determination of the ee values of the isolated samples was performed via chiral HPLC.

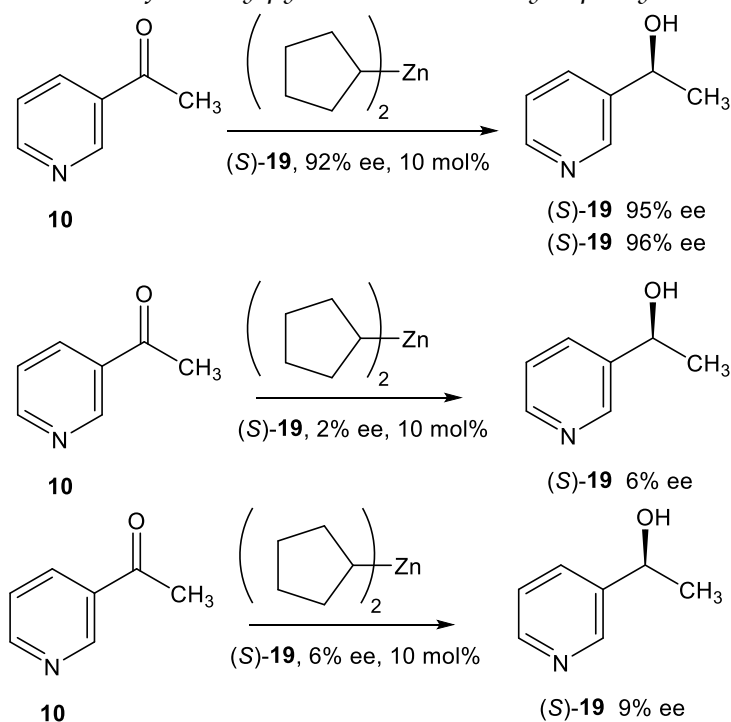


**Experiment № 1. Alcohol 19** was synthesized according to the general procedure from ketone **10** (0.15 mL, 1.34 mmol), catalyst **21** (22 mg, 0.13 mmol), and dicyclopentylzinc ( $10^{-3}$  M solution, 4.0 mL). The reaction time was 24 h. According to the  $^1\text{H}$  NMR spectroscopy, the reaction mixture contained 13% of starting ketone **10**. Eluent for the column chromatography: acetone–petroleum ether, from 1:2 to 1:1. Colorless oil, 90 mg (55% yield); 92% ee (Chiralpak, OD, 2.0 mm  $\times$  60 mm, *i*PrOH / hexane = 10 / 90, 1.0 mL/min, 20  $^\circ\text{C}$ , 220 nm UV detector, retention time = 8.49 min for the (*R*) isomer and 9.68 min for the (*S*) isomer).

**Experiment № 2. Alcohol 19** was synthesized according to the general procedure from ketone **10** (0.70 mL, 6.37 mmol), catalyst **21** (105 mg, 0.64 mmol), and dicyclopentylzinc ( $10^{-3}$  M solution, 19.1 mL). The reaction time was 5 h. Colorless oil, 0.45 g (57% yield); 99% ee (Chiralpak, OD, 2.0 mm  $\times$  60 mm, *i*PrOH / hexane = 10 / 90, 1.0 mL/min, 20  $^\circ\text{C}$ , 220 nm UV detector, retention time = 7.78 min for the (*R*) isomer and 9.77 min for the (*S*) isomer).

**Alcohol 20** was synthesized according to the general procedure from ketone **11** (0.27 g, 1.34 mmol), catalyst **21** (22 mg, 0.13 mmol), and dicyclopentylzinc ( $10^{-3}$  M solution, 4.0 mL). The reaction time was 24 h. According to the  $^1\text{H}$  NMR spectroscopy, the reaction mixture contained 6% of starting ketone **11**. Eluent for the column chromatography: acetone–toluene, from 1:10 to 1:8. Colorless solid, 173 mg (64% yield); ee 20% (Chiralpak, OD, 2.0 mm  $\times$  60 mm, *i*PrOH / hexane = 10 / 90, 1.0 mL/min, 20  $^\circ\text{C}$ , 220 nm UV detector, retention time = 8.17 min for the (*R*) isomer and 9.60 min for the (*S*) isomer).

### 2.7. Autocatalytic reaction of 3-acetylpyridine **10** with dicyclopentylzinc



**Experiment № 1:** To the solution of alcohol (S)-19 (17 mg, 0.14 mmol, 92% ee) in dry toluene (20 mL), the solution of dicyclopentylzinc ( $10^{-3}$  M solution, 4.1 mL) was added dropwise with intense stirring under a nitrogen atmosphere. The obtained mixture was stirred for 20 min at room temperature. Ketone **10** (0.15 mL, 1.38 mmol) was dissolved in 9 mL of dry toluene and

then was added dropwise to the reaction mixture under a nitrogen atmosphere. The reaction mixture was stirred for 5 h at room temperature. Workup of the reaction mixture was carried out similarly to the general procedure described above. According to the  $^1\text{H}$  NMR spectroscopy, the reaction mixture contained 30% of starting ketone **10**. The yellow oily residue was purified via column chromatography (eluent acetone–petroleum ether, from 1:2 to 1:1) to yield the corresponding alcohol **19**. Colorless oil, 88 mg (42% yield), 95% ee (Chiralpak, OD, 2.0 mm  $\times$  60 mm, *i*PrOH / hexane = 10 / 90, 1.0 mL/min, 20 °C, 220 nm UV detector, retention time = 7.93 min for the (*R*) isomer and 9.29 min for the (*S*) isomer).

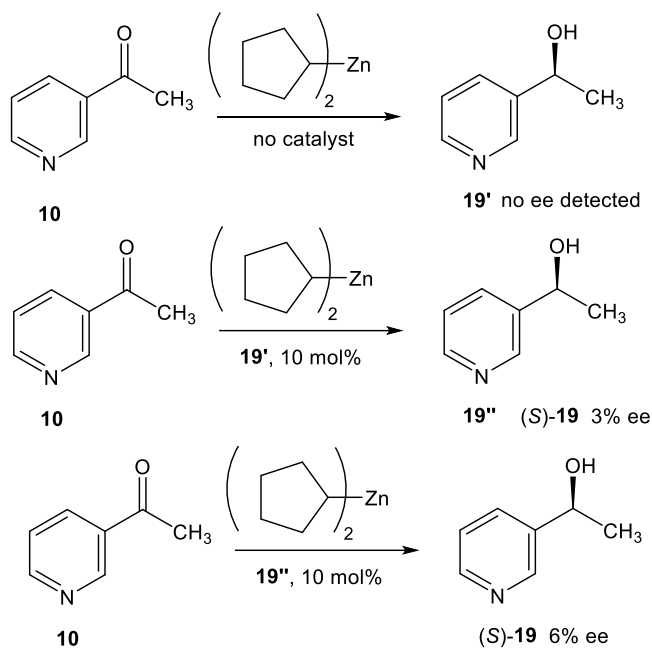
**Experiment № 2:** Reaction conditions were identical to those described above. Alcohol **19** was obtained from ketone **10** (0.14 mL, 1.29 mmol), dicyclopentylzinc ( $10^{-3}$  M solution, 6.5 mL), and alcohol (*S*)-**19** (16 mg, 0.13 mmol, 92% ee). Colorless oil, 87 mg (45% yield), 96% ee (Chiralpak, OD, 2.0 mm  $\times$  60 mm, *i*PrOH / hexane = 10 / 90, 1.0 mL/min, 20 °C, 220 nm UV detector, retention time = 8.26 min for the (*R*) isomer and 9.47 min for the (*S*) isomer).

**Experiment № 3** (2% ee of catalyst): Reaction conditions were identical to those described above. Alcohol **19** was obtained from ketone **10** (0.14 mL, 1.27 mmol), dicyclopentylzinc ( $10^{-3}$  M solution, 3.8 mL), and alcohol **19** (16 mg, 0.13 mmol, 2% ee\*). Colorless oil, 106 mg (58% yield); 6% ee (Chiralpak, OD, 2.0 mm  $\times$  60 mm, *i*PrOH / hexane = 10 / 90, 1.0 mL/min, 20 °C, 220 nm UV detector, retention time = 8.74 min for the (*R*) isomer and 9.41 min for the (*S*) isomer).

**Experiment № 4** (6% ee of catalyst): Reaction conditions were identical to those described above. Alcohol **19** was obtained from ketone **10** (0.13 mL, 1.15 mmol), dicyclopentylzinc ( $10^{-3}$  M solution, 3.5 mL), and alcohol **19** (14 mg, 0.115 mmol, 6% ee\*). The reaction mixture was stirred for 24 h at room temperature. Colorless oil, 100 mg (60% yield), 9% ee (Chiralpak, OD, 2.0 mm  $\times$  60 mm, *i*PrOH / hexane = 10 / 90, 1.0 mL/min, 20 °C, 220 nm UV detector, retention time = 8.41 min for the (*R*) isomer and 9.04 min for the (*S*) isomer).

Note: \*ee was achieved by mixing racemic alcohol **19** with the sample, obtained from experiment № 2 in section 2.6 of Supplementary materials. Racemic alcohol **19** was obtained via the reduction of ketone **10** with  $\text{NaBH}_4$  [18].

## 2.8 The three-stage reaction sequence



**Stage 2.** Reaction conditions were identical to those described above. Alcohol **19''** was obtained from ketone **10** (0.14 mL, 1.29 mmol), dicyclopentylzinc ( $10^{-3}$  M solution, 3.9 mL), and alcohol **19'** (16 mg, 0.13 mmol, 0% ee), obtained from the noncatalytic experiment described in section 2.5 of Supplementary materials. Colorless oil, 116 mg (59% yield), 3% ee (Chiralpak, OD, 2.0 mm  $\times$  60 mm, *i*PrOH / hexane = 10 / 90, 1.0 mL/min, 20 °C, 220 nm UV detector, retention time = 8.70 min for the (*R*) isomer and 9.38 min for the (*S*) isomer).

**Stage 3.** Reaction conditions were identical to those described above. Alcohol **19** was obtained from ketone **10** (0.14 mL, 1.29 mmol), dicyclopentylzinc ( $10^{-3}$  M solution, 3.9 mL), and alcohol **19''** (16 mg, 0.13 mmol, 3% ee), obtained from **Stage 2**. Colorless oil, 120 mg (65% yield), 6% ee (Chiralpak, OD, 2.0 mm  $\times$  60 mm, *i*PrOH / hexane = 10 / 90, 1.0 mL/min, 20 °C, 220 nm UV detector, retention time = 8.71 min for the (*R*) isomer and 9.41 min for the (*S*) isomer).

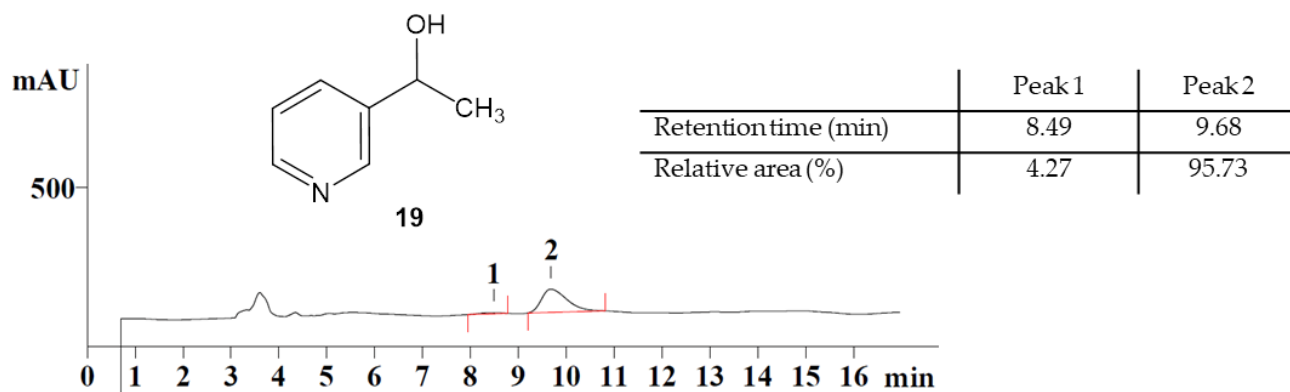
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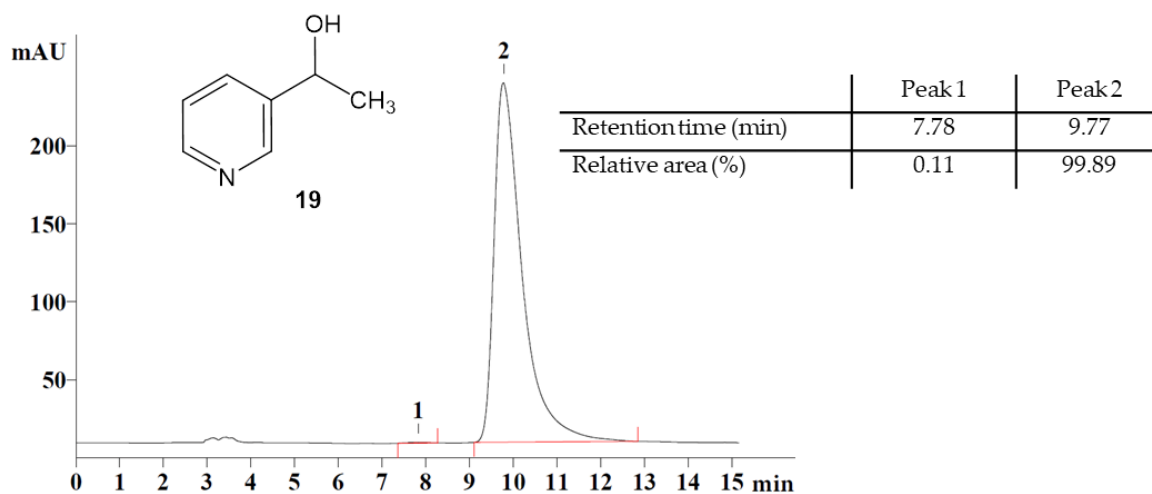
#### 4. HPLC data for alcohols 19 and 20

Conditions: *i*PrOH – hexane = 10 : 90

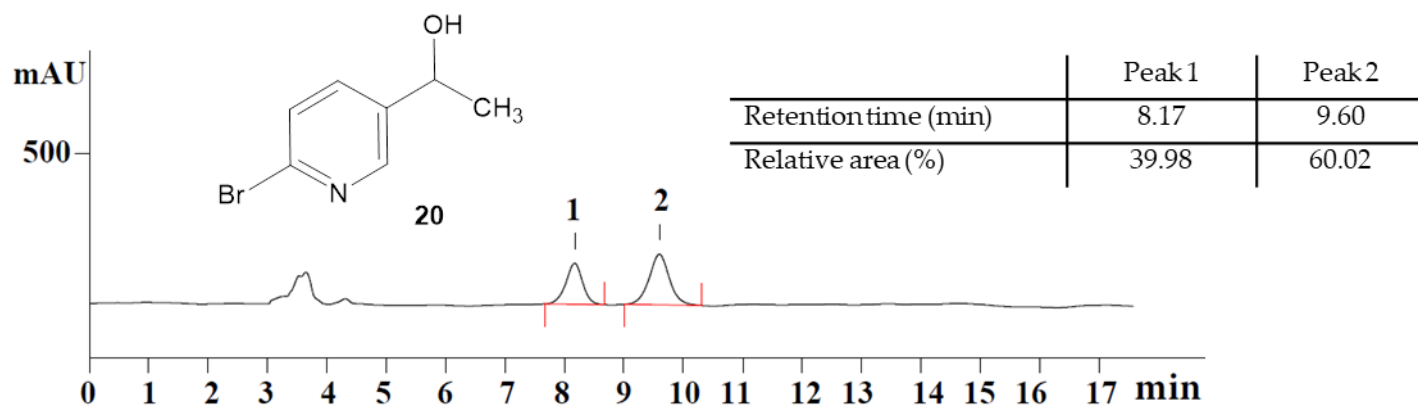
Flow rate = 1.0 mL/min,  $\lambda$  = 220 nm, Chiralpak OD



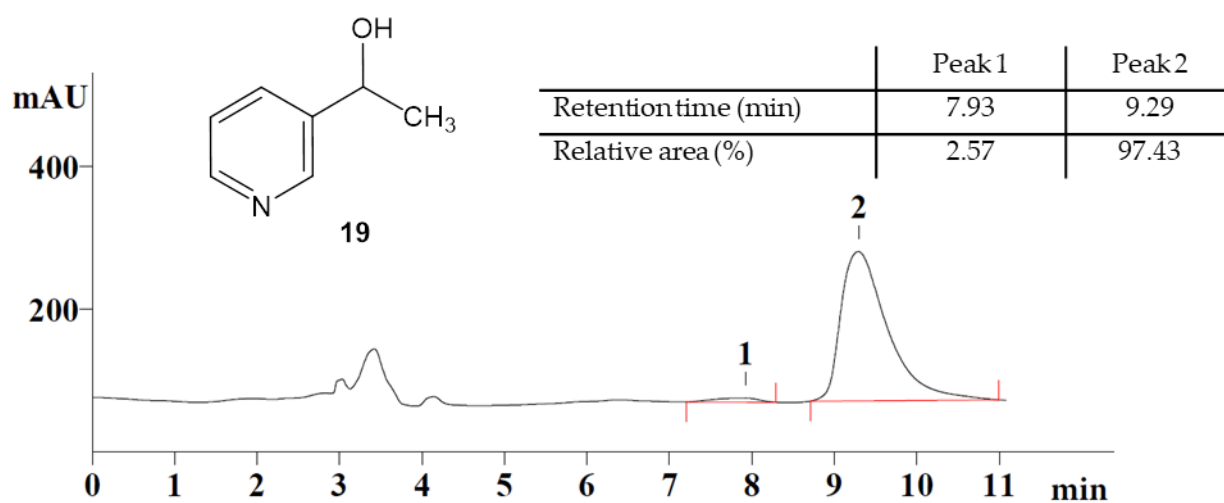
**Figure S1.** HPLC chromatogram for compound **19**, obtained in the experiment № 1 with catalyst **21**.



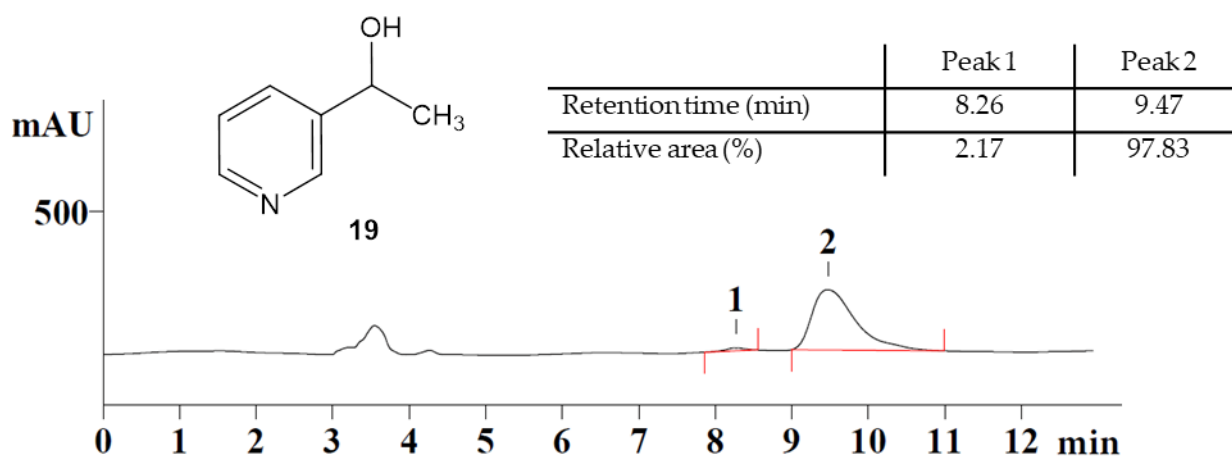
**Figure S2.** HPLC chromatogram for compound **19**, obtained in the experiment № 2 with catalyst **21**.



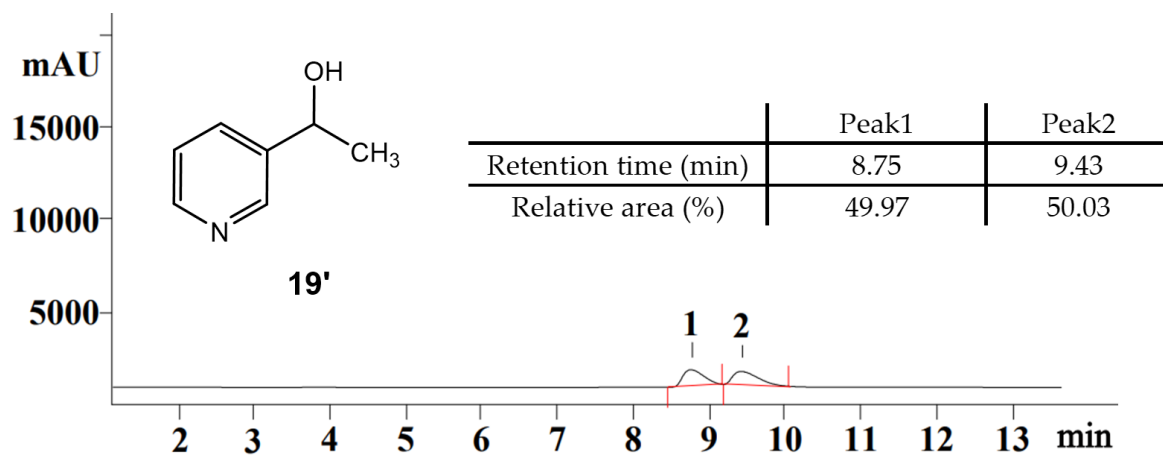
**Figure S3.** HPLC chromatogram for compound **20**, obtained in the experiment with catalyst **21**.



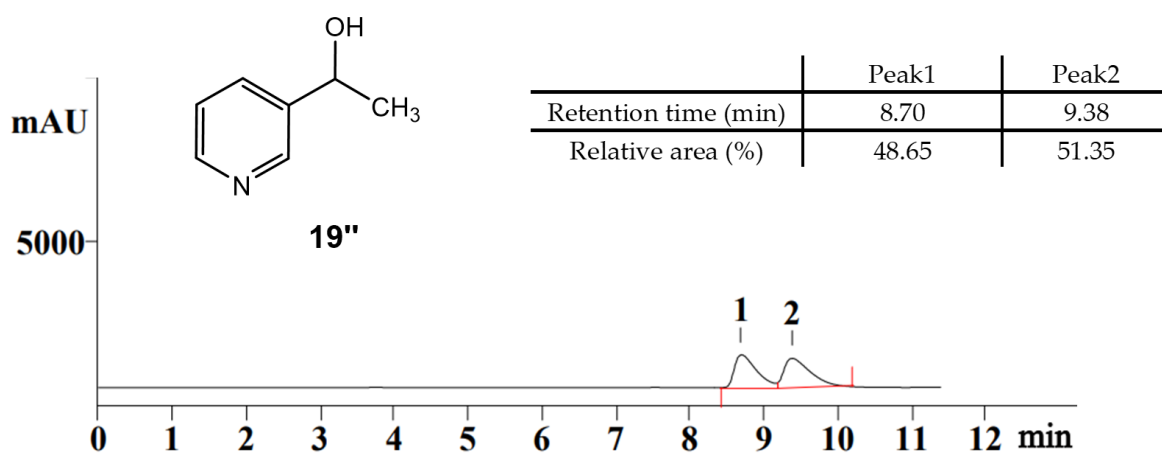
**Figure S4.** HPLC chromatogram for compound **19**, obtained in the autocatalytic reaction (experiment № 1) with catalyst (S)-**19**.



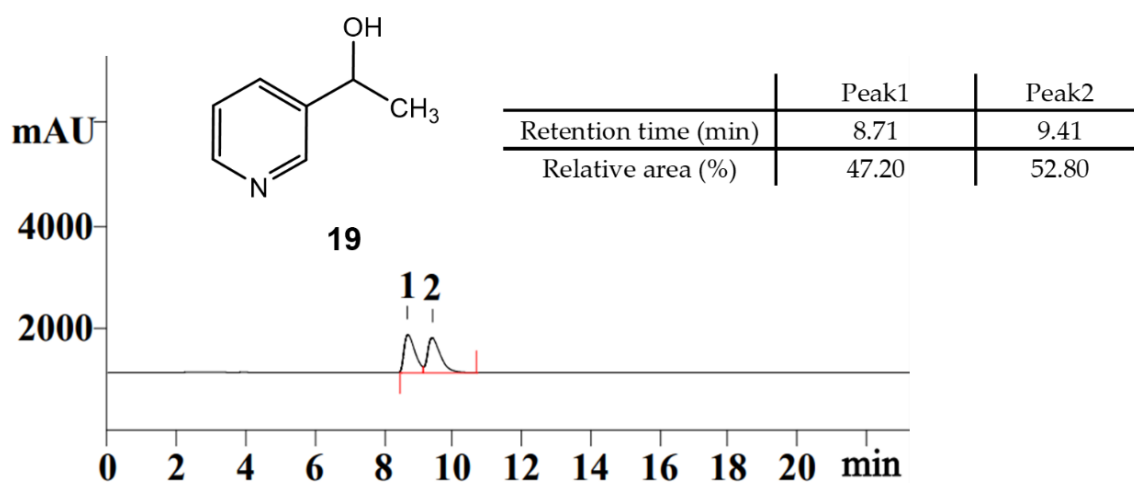
**Figure S5.** HPLC chromatogram for compound **19**, obtained in the autocatalytic reaction (experiment № 2) with catalyst (S)-**19**.



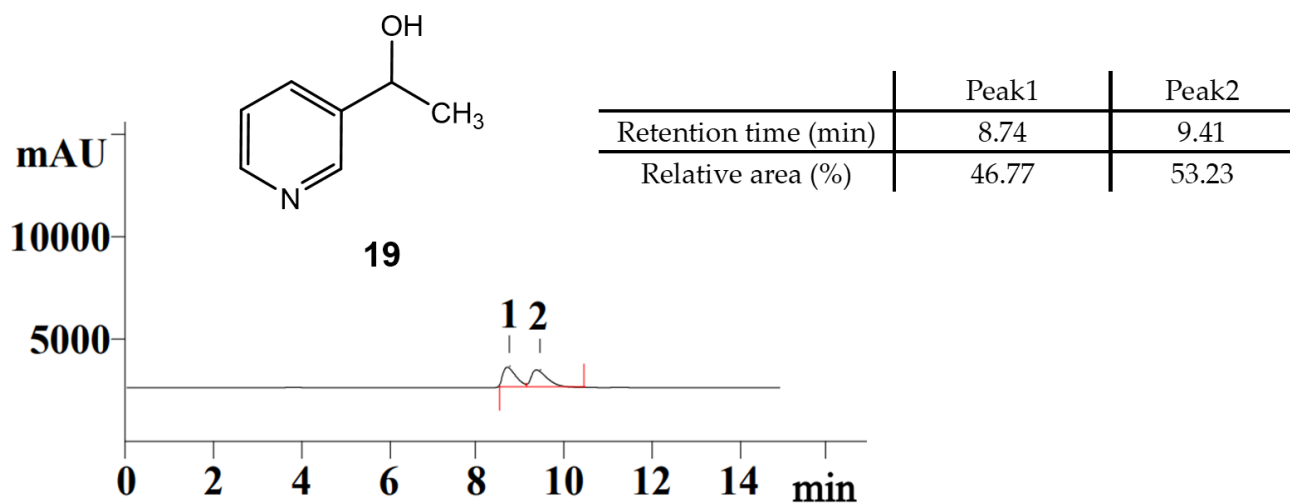
**Figure S6.** HPLC chromatogram for the sample **19'**, obtained in the non-catalytic reaction of ketone **10** with dicyclopentylzinc.



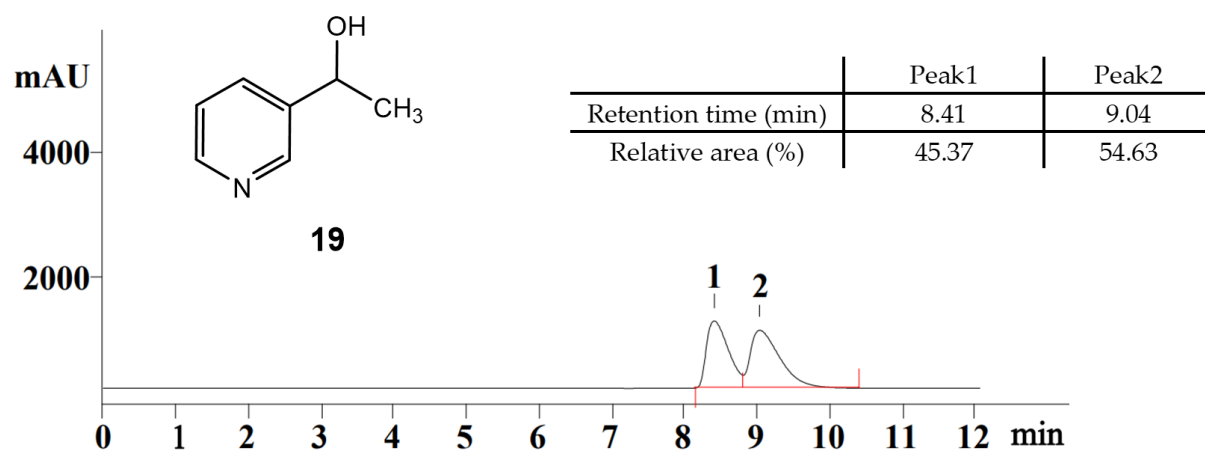
**Figure S7.** HPLC chromatogram for the sample **19''**, obtained in the autocatalytic reaction (stage 2) with catalyst **19'**.



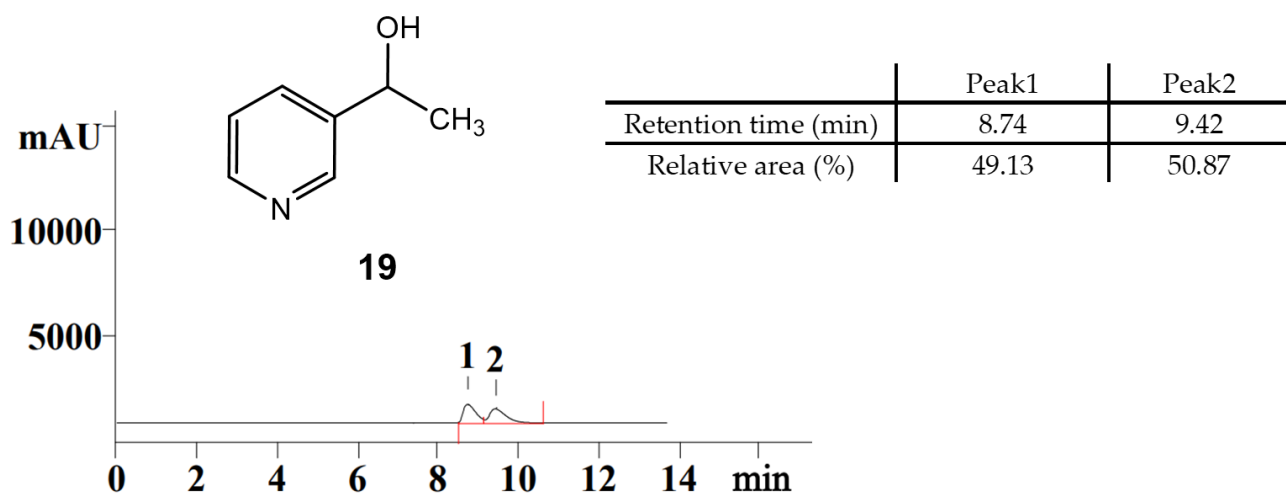
**Figure S8.** HPLC chromatogram for the sample (*S*)-**19**, obtained in the autocatalytic reaction (stage 3) with catalyst **19''**.



**Figure S9.** HPLC chromatogram for the sample (S)-19, obtained in the autocatalytic reaction with 2% ee catalyst (S)-19.

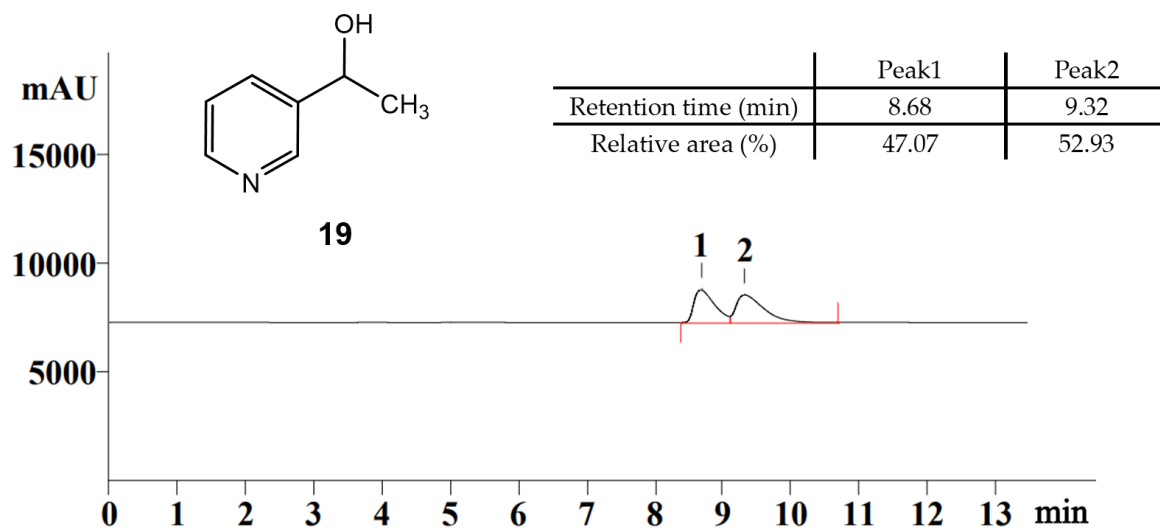


**Figure S10.** HPLC chromatogram for the sample (S)-19, obtained in the autocatalytic reaction with 6% ee catalyst (S)-19.

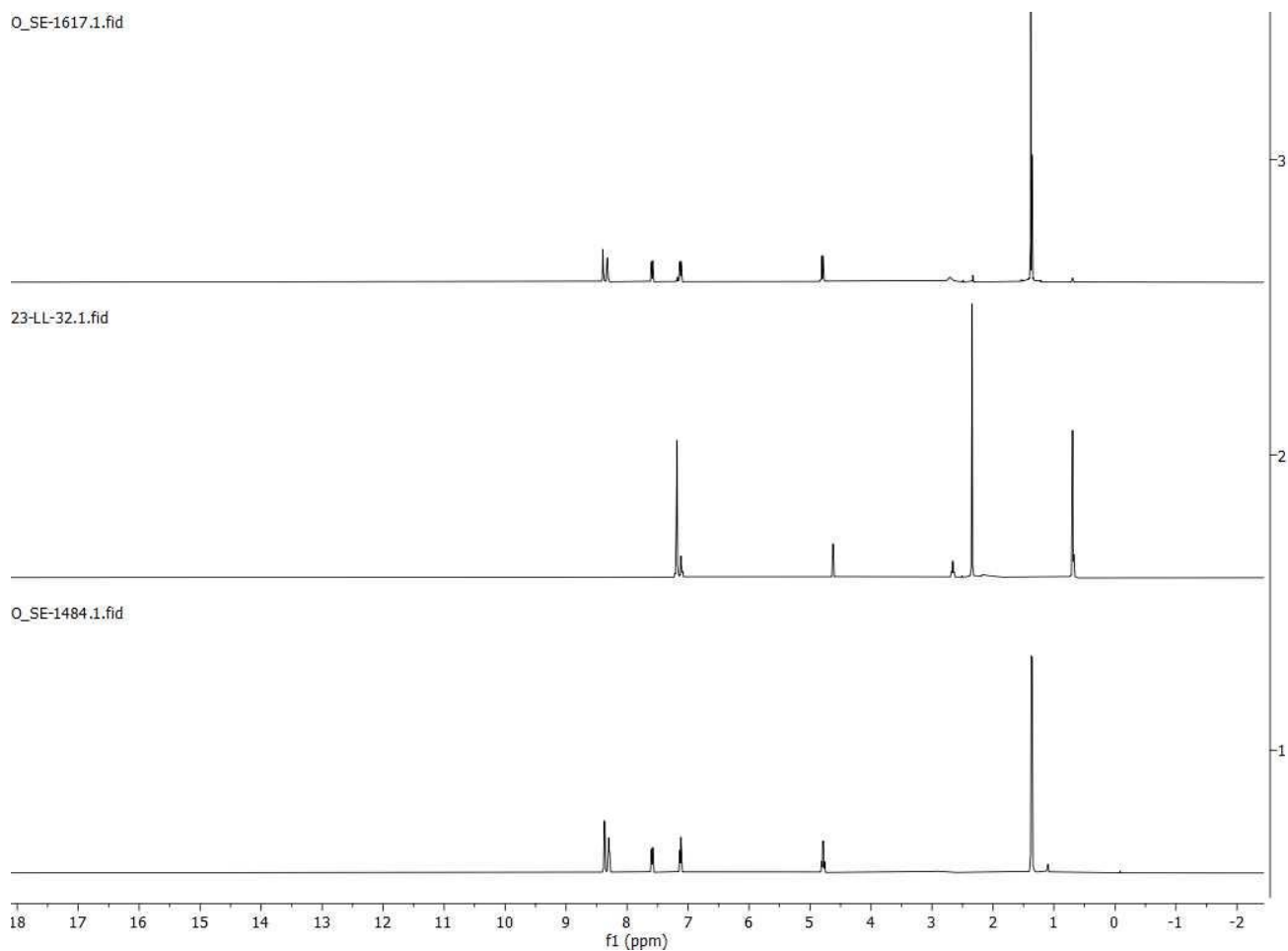


**Figure S11.** HPLC chromatogram of the catalyst (S)-19 with 2% ee.





**Figure S12.** HPLC chromatogram of the catalyst (*S*)-**19** with 6% ee.



**Figure S13:** below,  $^1\text{H}$  NMR spectrum of the alcohol **19** purified for HPLC analysis; middle:  $^1\text{H}$  NMR spectrum of Ephedrine; top:  $^1\text{H}$  NMR spectrum of the sample containing the mixture of **19** and ephedrine in a 100:1 ratio. The signals of the ephedrine in mixture are clearly visible.

## 5. Cartesian Coordinates

3

Sum of electronic and zero-point Energies= -2571.372555

Sum of electronic and thermal Energies= -2571.351382

Sum of electronic and thermal Enthalpies= -2571.350437

Sum of electronic and thermal Free Energies= -2571.425790

Standard orientation:

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Center Atomic Atomic Coordinates (Angstroms)

Number Number Type X Y Z  
-----

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6	1	0	1.424828	-2.040733	-1.126480
7	6	0	2.123967	0.071034	-1.216582
8	1	0	1.852469	0.391576	-2.235684
9	6	0	3.531367	0.578061	-0.864114
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11	1	0	4.228953	0.431609	-1.707619
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14	1	0	3.579843	0.077446	1.243640
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16	6	0	-0.104919	2.189751	1.031413
17	1	0	0.539615	2.372519	1.904237
18	6	0	-0.251684	3.477225	0.204009
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26	1	0	-1.249600	2.619798	-1.512341
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30	7	0	-0.988392	-0.619881	-0.628209
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32	6	0	-1.371670	-1.588467	0.215563
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36	6	0	-3.106534	-2.296215	-1.271686
37	1	0	-3.193345	-1.153299	-3.103246
38	1	0	-2.722632	-3.217413	0.638978
39	1	0	-3.935843	-2.950068	-1.520731
40	6	0	-0.552509	-1.671508	1.471453
41	8	0	0.407232	-0.927558	1.601606

42 6 0 -0.923528 -2.665359 2.532200  
 43 1 0 -0.236867 -2.567476 3.373765  
 44 1 0 -1.950131 -2.495889 2.875298  
 45 1 0 -0.868356 -3.685664 2.136124

## TS1

Sum of electronic and zero-point Energies= -2571.348478

Sum of electronic and thermal Energies= -2571.328753

Sum of electronic and thermal Enthalpies= -2571.327809

Sum of electronic and thermal Free Energies= -2571.397304

$\nu = i666.37$

Standard orientation:

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 Center Atomic Atomic Coordinates (Angstroms)

Number Number Type X Y Z

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 10 1 0 -3.383276 -1.098692 1.761171  
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 25 1 0 2.823759 -1.433019 -2.864330  
 26 1 0 2.051408 -0.165086 -1.911700  
 27 6 0 3.055966 -1.640339 -0.684059  
 28 1 0 3.787979 -0.889430 -0.366587  
 29 1 0 3.602577 -2.576371 -0.861818  
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 33 6 0 1.289325 2.817135 -1.540112  
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 35 6 0 2.339096 2.105934 0.497932  
 36 6 0 2.317043 2.944509 -0.606172  
 37 1 0 1.238544 3.455161 -2.415187  
 38 1 0 3.129470 2.182108 1.236214  
 39 1 0 3.092116 3.692750 -0.740419

40 6 0 1.233252 0.137208 1.742986  
 41 8 0 0.059061 -0.361415 1.928829  
 42 6 0 2.159177 0.247413 2.934998  
 43 1 0 2.058215 -0.657146 3.539748  
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## 8

Sum of electronic and zero-point Energies= -2571.395752  
 Sum of electronic and thermal Energies= -2571.373913  
 Sum of electronic and thermal Enthalpies= -2571.372969  
 Sum of electronic and thermal Free Energies= -2571.451735  
 Standard orientation:

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 Center Atomic Atomic Coordinates (Angstroms)

Number Number Type X Y Z

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39 6 0 -0.595814 2.154273 2.788255  
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 45 7 0 1.607396 3.533721 -1.741801

## TS2

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 Sum of electronic and thermal Free Energies= -2571.418965  
 $\nu = i$  687.37

Standard orientation:

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 30 6 0 1.273017 -1.914724 0.380966  
 31 6 0 3.632538 -2.196220 -0.922155  
 32 6 0 2.124781 -0.812503 0.332720  
 33 6 0 3.336774 -0.968537 -0.343775  
 34 1 0 4.572485 -2.334851 -1.451460  
 35 1 0 4.044353 -0.150987 -0.432941  
 36 1 0 0.327881 -1.855817 0.909661

37 6 0 1.688360 0.503989 0.939509  
 38 8 0 0.514129 0.512046 1.501125  
 39 6 0 2.753591 1.331862 1.637865  
 40 1 0 3.055728 0.827114 2.561407  
 41 1 0 3.643902 1.485371 1.023757  
 42 1 0 2.333250 2.304934 1.901821  
 43 6 0 1.663161 -3.101181 -0.231744  
 44 1 0 1.009225 -3.969815 -0.197336  
 45 7 0 2.819987 -3.257080 -0.878335

## 10

Sum of electronic and zero-point Energies= -2571.394233  
 Sum of electronic and thermal Energies= -2571.373560  
 Sum of electronic and thermal Enthalpies= -2571.372616  
 Sum of electronic and thermal Free Energies= -2571.446527  
 Standard orientation:

Center Atomic Atomic Coordinates (Angstroms)  
 Number Number Type X Y Z

1 6 0 1.477368 -3.242335 -0.189339  
 2 1 0 0.894383 -3.139405 0.731246  
 3 1 0 1.432330 -4.296411 -0.480840  
 4 6 0 0.914693 -2.323884 -1.297797  
 5 1 0 1.003187 -2.836171 -2.268209  
 6 1 0 -0.151550 -2.113878 -1.156637  
 7 6 0 1.814637 -1.076681 -1.272675  
 8 1 0 1.784090 -0.573419 -2.249992  
 9 6 0 3.196367 -1.719971 -1.051919  
 10 1 0 3.991160 -1.017758 -0.773946  
 11 1 0 3.533395 -2.232011 -1.967407  
 12 6 0 2.936579 -2.768358 0.042168  
 13 1 0 3.656790 -3.591923 0.014105  
 14 1 0 3.027487 -2.302181 1.031149  
 15 30 0 1.411952 0.272625 0.093836  
 16 6 0 1.422005 1.947403 1.105346  
 17 1 0 1.847343 1.750850 2.099752  
 18 6 0 2.201694 3.067719 0.396146  
 19 1 0 2.407048 3.898847 1.090339  
 20 1 0 3.166678 2.758256 -0.022101  
 21 6 0 0.031457 2.597194 1.250812  
 22 1 0 -0.777533 1.879967 1.431056  
 23 1 0 0.022564 3.294517 2.102181  
 24 6 0 1.226689 3.550847 -0.688058  
 25 1 0 1.432264 4.573485 -1.019214  
 26 1 0 1.313896 2.908378 -1.573624  
 27 6 0 -0.181387 3.398645 -0.057344  
 28 1 0 -0.860360 2.879418 -0.742390  
 29 1 0 -0.636087 4.372776 0.147953  
 30 7 0 -2.619682 0.728834 -1.687473  
 31 6 0 -3.932353 0.479814 -1.635981  
 32 6 0 -1.864084 0.190218 -0.736546  
 33 6 0 -4.530050 -0.309466 -0.657911  
 34 1 0 -4.535516 0.933693 -2.418126

35 6 0 -2.355566 -0.608071 0.300547  
 36 6 0 -3.727583 -0.865665 0.328117  
 37 1 0 -5.600356 -0.479739 -0.671587  
 38 1 0 -4.167736 -1.481714 1.105402  
 39 1 0 -0.799603 0.391146 -0.788769  
 40 6 0 -1.405326 -1.135999 1.318135  
 41 8 0 -0.231115 -0.788191 1.310250  
 42 6 0 -1.902415 -2.102320 2.355516  
 43 1 0 -2.681724 -1.638098 2.968700  
 44 1 0 -2.337912 -2.985106 1.876716  
 45 1 0 -1.072455 -2.403093 2.994189

### TS3

Sum of electronic and zero-point Energies= -2571.366809  
 Sum of electronic and thermal Energies= -2571.346535  
 Sum of electronic and thermal Enthalpies= -2571.345591  
 Sum of electronic and thermal Free Energies= -2571.419736  
 $\nu = i$  773.18  
 Standard orientation:

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 Center Atomic Atomic Coordinates (Angstroms)

Number Number Type X Y Z

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 1 6 0 -2.277001 -2.788759 -0.796560  
 2 1 0 -3.186468 -2.636779 -0.207293  
 3 1 0 -2.565945 -3.300381 -1.724085  
 4 6 0 -1.556282 -1.505119 -1.184572  
 5 1 0 -2.007118 -0.830975 -1.914585  
 6 1 0 -1.894815 -0.709483 -0.130681  
 7 6 0 -0.155066 -1.721847 -1.174053  
 8 1 0 0.428495 -1.274345 -1.979271  
 9 6 0 0.108348 -3.190871 -0.805443  
 10 1 0 1.007237 -3.370884 -0.204453  
 11 1 0 0.222860 -3.790990 -1.719534  
 12 6 0 -1.183948 -3.593610 -0.076006  
 13 1 0 -1.370159 -4.670346 -0.092438  
 14 1 0 -1.126788 -3.277720 0.970458  
 15 30 0 0.837700 -0.759466 0.400194  
 16 6 0 2.762705 -0.528500 0.623053  
 17 1 0 3.156686 -1.334562 1.256911  
 18 6 0 3.461939 -0.509116 -0.742092  
 19 1 0 4.551061 -0.630249 -0.626977  
 20 1 0 3.124803 -1.293627 -1.430596  
 21 6 0 3.158709 0.851776 1.198538  
 22 1 0 2.483615 1.222880 1.978520  
 23 1 0 4.157330 0.798340 1.656865  
 24 6 0 3.159370 0.899894 -1.267968  
 25 1 0 3.848667 1.218832 -2.055597  
 26 1 0 2.151273 0.920853 -1.703252  
 27 6 0 3.217730 1.810919 -0.017258  
 28 1 0 2.393325 2.531004 -0.008752  
 29 1 0 4.140617 2.399344 0.001378  
 30 7 0 -0.440619 3.391858 -0.004127  
 31 6 0 -1.386922 3.822654 -0.839344  
 32 6 0 -0.612226 2.192151 0.561922

33 6 0 -2.528738 3.084757 -1.147828  
34 1 0 -1.217144 4.790798 -1.305191  
35 6 0 -1.716498 1.372627 0.326826  
36 6 0 -2.693244 1.842701 -0.555002  
37 1 0 -3.259883 3.477937 -1.845447  
38 1 0 -3.558138 1.227876 -0.794935  
39 1 0 0.153524 1.863745 1.264904  
40 6 0 -1.776704 0.002678 0.958895  
41 8 0 -0.661589 -0.404567 1.506004  
42 6 0 -3.039485 -0.339007 1.731181  
43 1 0 -3.068487 0.251280 2.653362  
44 1 0 -3.950233 -0.128333 1.166562  
45 1 0 -3.024390 -1.396684 2.003424

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