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The improved synthesis of ROCKYPhos and its application for the asymmetric hydrogenation of dihydroisoquinoline derivatives

Abstract

An optimized approach to the multigram synthesis of [(1*R*,2*R*,3*S*)-(+)-1,2-dimethyl-2,3-bis(diphenylphosphinomethyl)cyclopentyl]methanol (ROCKYPhos, CatASium I®), a camphor-derived chiral diphosphine ligand, has been developed. The key improvement in the synthetic scheme involved the oxidative cleavage of 3,9-dibromocamphor with $V_2O_5 – HNO_3$ or $NH_4VO_3 – Cu(NO_3)_2 – HNO_3$ system, which gave the corresponding dicarboxylic acid in the yield of 28% and significantly reduced the reaction sequence. The NMR study of a diselenide derivative of ROCKYPhos showed that one of the PPh_2 groups had strong donor properties comparable to those of trialkylphosphines. The asymmetric hydrogenation of *N*-acetyl-1,2-dihydroisoquinoline-4-carboxylates in the presence of ROCKYPhos provided target tetrahydroisoquinolines with up to 52% *ee* – an outstanding result for this substrate class.

Keywords: asymmetric synthesis; phosphine ligands; nitrogen heterocycles; isoquinoline

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Удосконалений синтез ROCKYPhos та його застосування для асиметричного гідрування похідних дигідроізохіноліну

Анотація

Було розроблено оптимізований підхід до багатограмового синтезу [(1*R*,2*R*,3*S*)-(+)-1,2-диметил-2,3-біс(дифенілфосфінометил)циклопентил]метанолу (ROCKYPhos, CatASium I®) – хірального дифосфінового ліганду, похідної камфори. Ключове покращення синтетичної схеми полягало в окиснювальному розщепленні 3,9-дибромкамфори системою $V_2O_5 – HNO_3$ або $NH_4VO_3 – Cu(NO_3)_2 – HNO_3$, що дало відповідну дикарбонову кислоту з виходом 28% і суттєво скоротило послідовність реакцій. Дослідження методом ЯМР діселенідного похідного ROCKYPhos показало, що одна з груп PPh_2 має сильні донорні властивості, близькі до відповідних значень для триалкілфосфінів. Асиметричне гідрування *N*-ацетил-1,2-дигідроізохінолін-4-карбоксилатів у присутності ROCKYPhos забезпечило утворення цільових тетрагідроізохінолінів з енантіомерним надлишком до 52% *ee*, що є видатним результатом для цього класу субстратів.

Ключові слова: асиметричний синтез; фосфінові ліганди; азотовмісні гетероцикли; ізохінолін

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Introduction

Chiral diphosphines are widely used in various areas of organic synthesis, but became most famous for their Nobel prize-winning application in the asymmetric hydrogenation [1]. Ligands like BINAP, DIPAMP, or DuPhos (**Figure 1**) became classical in this area, and many others were synthesized and evaluated for the preparation of various enantioenriched products [2]. Nevertheless, most of them demonstrated a narrow substrate scope in the case of the asymmetric C=C bond hydrogenation, and despite numerous efforts and considerable achievements for specific substrate classes (e.g., α-dehydroamino acid derivatives), there is still no general method. Therefore, any new information on the possible extension of the asymmetric olefin hydrogenation scope remains valuable.

In 2001, Komarov, Börner, and co-authors reported the synthesis of camphor-derived hydroxydiphosphine ligand **1** (later named ROCKYPhos or CatASium I®) and illustrated its efficiency for the asymmetric hydrogenation of several α- and ß-dehydroamino acid derivatives [3]. The original synthetic approach to compound **1** proposed by authors was lengthy and the involved Bayer-Villiger oxidation of 9-bromocamphor (**4**) as one of the key steps (**Scheme 1**). This reaction provided modest yield of target lactone **5** (33%). An alternative approach included even more steps, i.e., the oxidation of ketone **4** with SeO_2, the Bayer-Villiger reaction, and the reduction of the resulting anhydride **9** (**Scheme 2**).

In this work, we report our efforts on further optimization of the synthesis of ligand **1**. In addition to that, we characterized its donor properties and evaluated it in the asymmetric

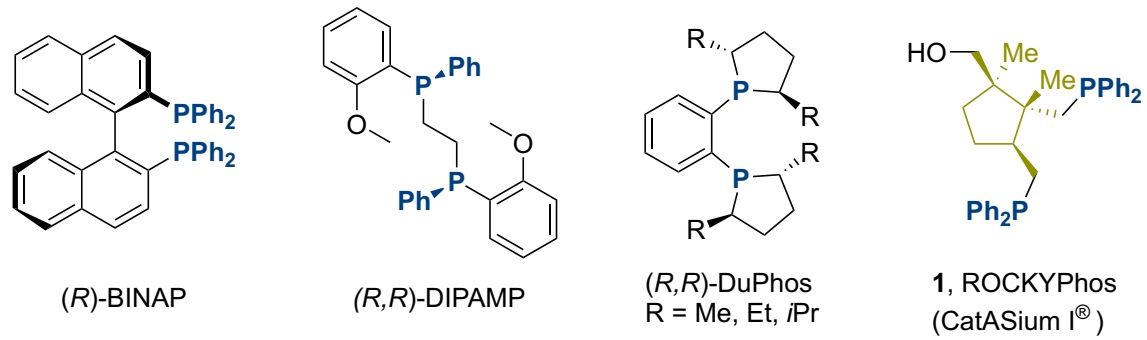
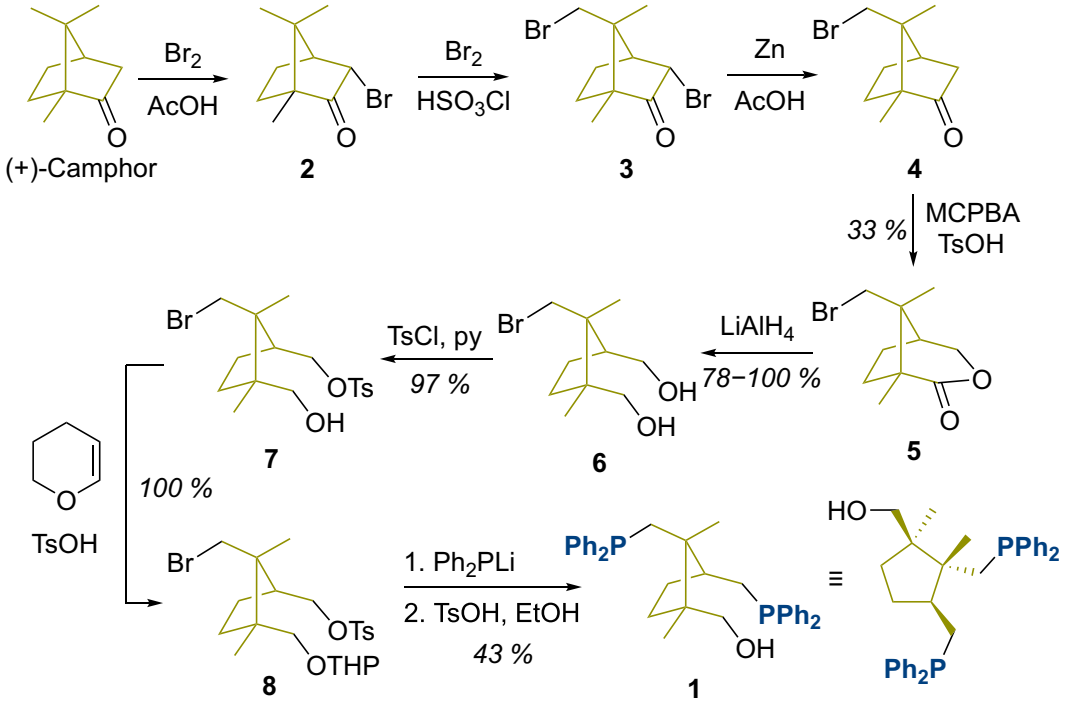


Figure 1. Diphosphine-based ligands used in the asymmetric hydrogenation



Scheme 1. The original synthetic approach to compound **1** proposed by Komarov, Börner, and co-authors in 2001

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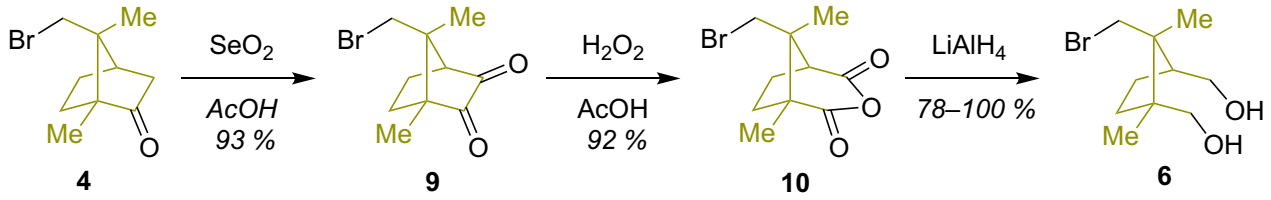


Scheme 2. An alternative approach to **6**

hydrogenation of *N*-acetyl-1,2-dihydroisoquinoline-4-carboxylates. It should be noted that while examples of the asymmetric hydrogenation of ß-dehydroamino acid derivatives were reported in the literature [4, 5], to the best of our knowledge, the method was never applied to the synthesis of enantioenriched tetrahydroisoquinoline derivatives.

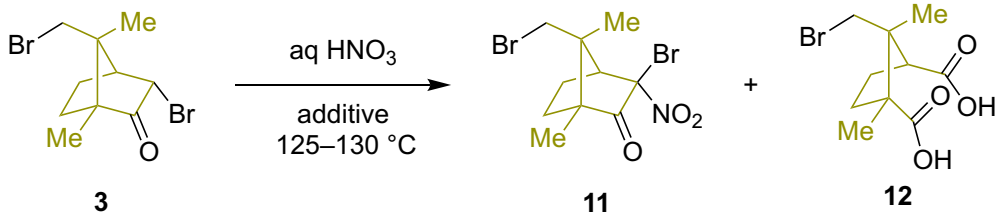
To further shorten the synthetic scheme used for the preparation of ligand **1**, we considered a direct oxidative cleavage of 3,9-dibromocamphor (**3**) as a possible alternative. We found that the reaction of compound **3** with 63% aq. HNO_3 at 130 °C, nitro derivative **11** was formed in an isolated yield of 68% (**Table 1**). The addition of V_2O_5 led to a mixture of compound **11** (65% yield) and target dicarboxylic acid **12** (15% yield). Decreasing the HNO_3 concentration to 53% improved the yield of **12** to 28%. Further dilution (to 30% HNO_3) was ineffective since the reaction became too slow. One more variation included the use of NH_4VO_3 – $Cu(NO_3)_2$ as additives (as reported by Whittaker and co-authors for the oxidation of cyclohexanol to adipic acid [6]). In this case, the yield of compound **12** was also 28%.

Unfortunately, a prolonged heating of compound **11** under the reaction conditions did not result in its transformation to target compound **12**.

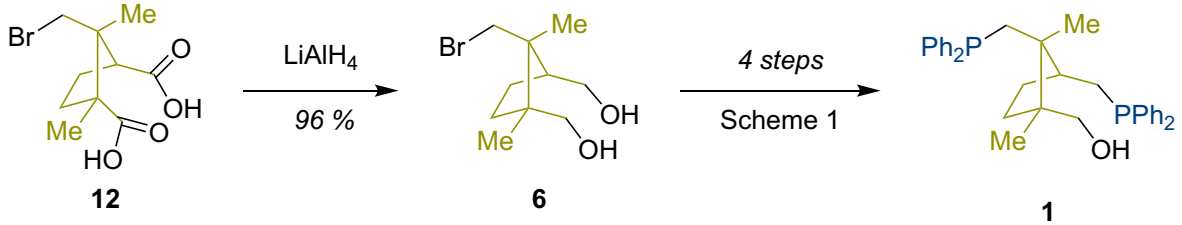
The reduction of dicarboxylic acid **12** with $LiAlH_4$ proceeded smoothly and gave target diol **6** in the yield of 96% (**Scheme 3**). Further transformation of compound **6** into ligand **1** followed the reaction sequence shown in **Scheme 1**.

To estimate the donor properties of diphosphine ligand **1**, we applied the method based on the analysis of $^1J(^{31}P–^{77}Se)$ coupling constants in the corresponding diselenides. The value of this constant correlated with electron-donating

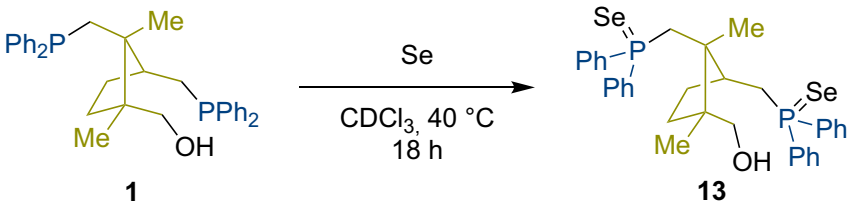
Table 1. The oxidative cleavage of 3,9-dibromocamphor (3) with HNO_3



No.	Reaction time, h	HNO_3 concentration	Additive	Yield, %		
				3	11	12
1	18	63	–	–	40	–
2	78	63	–	–	68	–
3	78	63	V_2O_5	–	65	15
4	78	53	V_2O_5	–	58	28
5	78	30	V_2O_5	35	12	13
6	78	30	NH_4VO_3 – $Cu(NO_3)_2$	traces	46	28



Scheme 3. Further access to **1** from **12**



1 **13**

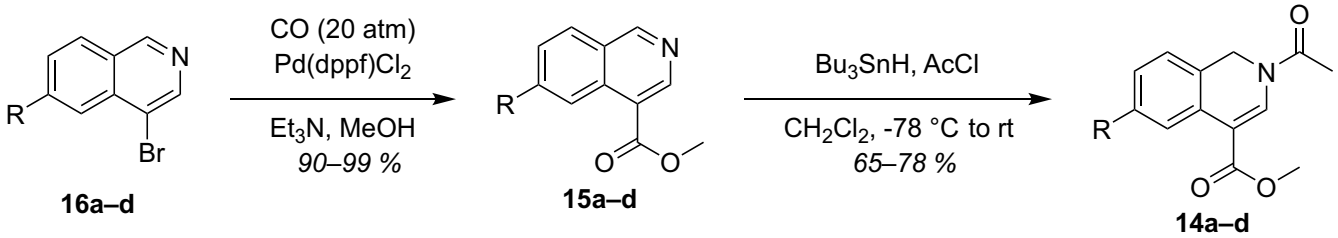
Scheme 4. The reaction of **1** with Se

properties of the substituents attached to the phosphorus atom [7]. The corresponding diselenide **13** was prepared by the reaction of compound **1** with Se (**Scheme 4**).

It was found that the $^{1}J(^{31}P–^{77}Se)$ values for compound **13** were 702 Hz and 720 Hz, which was comparable to those for a bis(dimethylphosphino)-ethane derivative ($^{1}J(^{31}P–^{77}Se)$ = 706 Hz). This result suggests that ligand **1** is highly P-donating, which can be used as a rationale for its high efficiency potential.

As a further illustration of the promising properties of ligand **1** in the asymmetric catalysis (in addition to the previous work [3]), we evaluated the hydrogenation of *N*-acetyl-1,2-dihydroisoquinoline-4-carboxylates **14a–d**. Compounds **14a–d** were obtained from the corresponding esters **15a–d** (**Scheme 5**). For the first step, we used methoxycarbonylation of commercially available bromides **16a–d**, and the obtained esters **15a–d** were reduced with tributylstannane in the presence of acetyl chloride to form **14a–d**. It was found that the parent substrate underwent the hydrogenation smoothly: the conversion was complete after 18 h, and product **17a** was obtained with 52% *ee* (according to the chiral stationary phase HPLC) (**Table 2**). Substituted derivatives **14b–d** reacted much slower. Derivative **14b** with the electron-donating OMe group reached a 90% conversion after a week; the corresponding product **17b** was formed with 45% *ee*. The hydrogenation of substrates with electron-withdrawing substituents (**14c**, R = Cl, or **14d**, R = CF_3) was virtually inefficient.

To confirm the absolute configuration of the major enantiomer in product **17a**, it was transformed

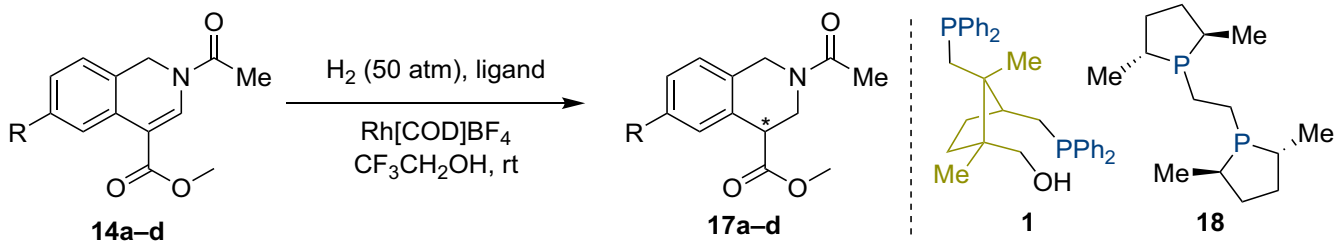


16a–d **15a–d** **14a–d**

a: R = H; **b:** R = OMe; **c:** R = Cl; **d:** R = CF_3

Scheme 5. Obtaining substrates for the hydrogenation

Table 2. The asymmetric hydrogenation of isoquinoline derivatives **14a–d**



14a–d **17a–d** **1** **18**

No.	Substrate	R	Ligand	Time, d	Conversion, %	*ee*, %
1	14a	H	1	0.75	100	52
2	14b	OMe	1	7	90	45
3	14c	Cl	1	7	67	7
4	14d	CF_3	1	7	6	–
5	14a	H	18	0.75	21	–
6	14a	H	18	3	100	0

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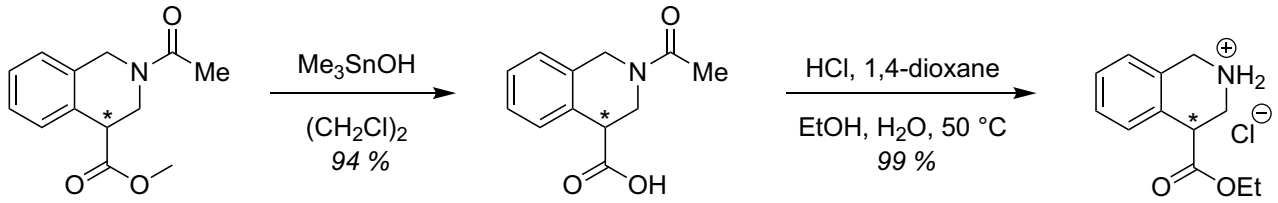

17a **19** **20**·HCl

Scheme 6. The confirmation of the absolute configuration of the major enantiomer in product **17a**

into the known ester **20**. The main challenge here was to avoid racemization at the hydrolysis/esterification steps. We achieved this by performing the ester hydrolysis with Me_3SnOH in 1,2-dichloroethane [8] and then, simultaneously, the amide hydrolysis and esterification of **19** with HCl in EtOH at 50 °C (**Scheme 6**). Product **20**×HCl had $[\alpha]_D$ = +19.7° (*c* 1.0, MeOH), which corresponded to (*S*) enantiomer (according to the literature data, $[\alpha]_D$ = –42.3° (*c* 1.0, MeOH) for (*R*) isomer [8]).

■ Conclusions

An improved and scalable route to the camphor-derived chiral diphosphine ligand ROCKYPhos has been developed and validated for the multigram synthesis. The key advancement of the updated strategy is an efficient oxidative cleavage of 3,9-dibromocamphor upon action of $V_2O_5 – HNO_3$ or NH_4VO_3–$Cu(NO_3)_2$–HNO_3, providing the corresponding dicarboxylic acid in the yield of 28% while significantly shortening the overall synthetic sequence.

The electronic properties of ROCKYPhos were investigated by the thNMR analysis of its diselenide derivative, revealing the pronounced donor ability of one of the PPh_2 fragment comparable to that of trialkylphosphines.

Finally, ROCKYPhos was successfully applied in the asymmetric hydrogenation of *N*-acetyl-1,2-dihydroisoquinoline-4-carboxylates, giving the corresponding tetrahydroisoquinolines with enantioselectivities of up to 52% *ee*. This level of stereocontrol represents a considerable advancement for this challenging substrate class and demonstrates the practical value of ROCKYPhos as a promising ligand for the asymmetric hydrogenation.

■ Experimental part

General part

The solvents were purified according to the standard procedures [9]. [1,1'-Bis(diphenylphosphino)ferrocene]dichloropalladium(II) ($Pd(dppf)Cl_2$), (+)-3,9-dibromocamphor **3**, and other starting reagents were available commercially and obtained from Enamine Ltd. All operations with compounds **14a–d** were performed under the argon atmosphere in a glove box. Melting points were measured on the MPA100 OptiMelt automated melting point system. ^1H, $^{13}C\{^1H\}$, $^{19}F\{^1H\}$ and $^{31}P\{^1H\}$ NMR spectra were recorded on a Bruker 170 Avance 500 spectrometer (at 500 MHz for ^1H NMR and 126 MHz for $^{13}C\{^1H\}$ NMR) or a Varian Unity Plus 400 spectrometer (at 400 MHz for ^1H NMR, 101 MHz for $^{13}C\{^1H\}$ NMR, and 376 MHz for $^{19}F\{^1H\}$ NMR), as well as using an Agilent ProPulse 600 spectrometer (at 600 MHz for ^1H, 151 MHz for $^{13}C\{^1H\}$ and 243 MHz for $^{31}P\{^1H\}$). NMR chemical shifts are reported in ppm (δ scale) downfield from TMS or $CFCl_3$ (^{19}F) as an internal standard, and are referenced using residual NMR solvent peaks in $CDCl_3$ at 7.26 ppm for ^1H and 77.16 ppm for $^{13}C\{^1H\}$ respectively, in DMSO-d_6 at 2.50 ppm for ^1H and 39.52 ppm for $^{13}C\{^1H\}$, 4.78 and 3.31 ppm for ^1H or 49.15 ppm for $^{13}C\{^1H\}$ in CD_3OD. H_3PO_4 (85% in H_2O) used as an external $^{31}P\{^1H\}$ standard. Coupling constants (*J*) are given in Hz. Elemental analyses were performed at the Laboratory of Organic Analysis, Department of Chemistry, Taras Shevchenko National University of Kyiv. Mass spectra were recorded on an Agilent 1100 LC/MSD SL instrument (APCI atmospheric pressure chemical ionization). High-resolution mass spectra (HRMS) were obtained on an Agilent 1260 Infinity UHPLC instrument coupled with an Agilent 6224 Accurate Mass TOF mass spectrometer. Enantiomeric excess determinations were obtained by high-performance liquid chromatography (HPLC) with chiral columns Chiralpak IA-U (for **17a**), Chiralcel OJ-H (for **19**) and Chiralpak IC (for **20**·HCl). *ee* Values for **17a**, **19**, and **20**·HCl were not corrected for the chromatogram baseline and may include minor errors.

(1*S*,3*R*,4*S*,7*R*)-3-Bromo-7-(bromomethyl)-1,7-dimethyl-3-nitrobicyclo[2.2.1]heptan-2-one (11)

The mixture of 3,9-dibromocamphor **3** (0.76 g, 2.45 mmol) and the aq. nitric acid (13 M, 10 mL) was heated to reflux, and then stirred at this

temperature under the argon atmosphere for 78 h. The solvents were removed under reduced pressure, and distilled water (50 mL) was added to the residue. The mixture obtained was extracted with toluene (3×20 mL). The combined organic phases were dried over Na_2SO_4, and then concentrated under reduced pressure. The crude product was purified by crystallization from 2-propanol.

A colorless solid. Yield – 0.590 g (68%). M. p. 98–99 °C. $[\alpha]_D^{20}$ = +43.8 (*c* 0.5, MeOH). ^{1}H NMR (500 MHz, CD_3OD), δ, ppm: 1.08 (3H, s, CH_3), 1.31–1.40 (4H, m, CH_3 and CH_2), 1.64–1.74 (1H, m, CH_2), 1.90–2.00 (1H, m, CH_2), 2.08–2.20 (1H, m, CH_2), 3.15 (1H, d, *J* = 4.3 Hz, CH), 3.38 (1H, dd, *J* = 10.8, 1.5 Hz, CH_2), 3.82 (1H, d, *J* = 10.8 Hz, CH_2). ^{13}C{^{1}H} NMR (126 MHz, CD_3OD), δ, ppm: 10.3, 20.6, 24.8, 28.9, 39.7, 48.9, 55.8, 60.7, 92.3, 199.9. HRMS (ESI/QTOF), *m*/*z*: calculated for $C_{10}H_{14}Br_2NO_3^+$ 353.9335 $[M + H]^+$; found 353.9342.

1-(1*S*,2*R*,3*S*)-2-(Bromomethyl)-1,2-dimethylcyclopentane-1,3-dicarboxylic acid (12)

The mixture of 3,9-dibromocamphor **3** (5.00 g, 16.1 mmol) and vanadium (V) oxide (0.292 g, 1.60 mmol) in the aq. nitric acid (11.3 M, 80 mL, ca. 53% in water) was heated to reflux, and then stirred at the same temperature under the argon atmosphere for 78 h. Nitric acid was removed under reduced pressure, a fresh portion of distilled water (20 mL) was added to the residue, and the resulting mixture was re-evaporated under reduced pressure. The residue was mixed with water (100 mL) and extracted with EtOAc (3×200 mL). The combined organic phases were dried over Na_2SO_4 and concentrated under reduced pressure. The residue obtained was triturated with benzene to give 1,3-dicarboxylic acid **12** (1.26 g, 4.5 mmol, 28% yield).

A colorless solid. Yield – 1.26 g (28 %). M. p. 199–201 °C. ^{1}H NMR (500 MHz, DMSO-d_6), δ, ppm: 1.04 (3H, s, CH_3), 1.22 (3H, s, CH_3), 1.40–1.49 (1H, m, CH_2), 1.80–1.99 (2H, m, CH_2), 2.38 (1H, td, *J* = 12.2, 7.6 Hz, CH_2), 3.00 (1H, t, *J* = 9.3 Hz, CH), 3.79 (1H, d, *J* = 10.5 Hz, CH_2), 3.89 (1H, d, *J* = 10.5 Hz, CH_2), 12.34 (2H, s, OH). ^{13}C{^{1}H} NMR (126 MHz, DMSO-d_6), δ, ppm: 18.7, 21.3, 23.6, 33.7, 41.6, 48.7, 50.0, 55.8, 174.6, 176.3. HRMS (ESI/QTOF), *m*/*z*: calculated for $C_{10}H_{15}BrO_4Na^+$ 301.0046 $[M + Na]^+$; found 301.0039.

((1*S*,2*R*,3*S*)-2-(Bromomethyl)-1,2-dimethylcyclopentane-1,3-diyl)dimethanol (6)

To the stirred solution of dicarboxylic acid **12** (1.26 g, 4.52 mmol) in THF (50 mL), $LiAlH_4$ (0.690 g, 18.1 mmol) was added in portions under the gentle argon gas flow. The suspension obtained was heated at reflux for 5 h. Upon the completion, the mixture was cooled to 0 °C using an ice/water bath and quenched by the addition of water (1.5 mL) under vigorous stirring. Then EtOAc (300 mL) was added, the cooling bath was removed, and the resulting suspension was stirred for 2 h at r.t., then dried over Na_2SO_4 (50.0 g), filtered, and the filtrate was concentrated under reduced pressure. The residual viscous oil was dissolved in the CH_2Cl_2/MeOH mixture (300 mL, 9:1, v/v) and filtered through a small column packed with SiO_2 (approx. 100 g). The eluate containing the product was collected and concentrated under reduced pressure to give the title compound **6**, which was used further as obtained.

A colorless powder. Yield 1.08 g (96%). The spectral and physical data are consistent with those previously reported [3].

{[(1*R*,2*S*,3*S*)-2-{[diphenyl(selanylidene)-λ^5-phosphanyl]methyl}-3-(hydroxymethyl)-2,3-dimethylcyclopentyl]methyl}diphenyl-λ^5-phosphaneselone (13)

In an NMR vial, selenium (16.5 mg, 0.208 μmol) was added to the solution of diphosphine **1** (65 mg, 0.095 μmol) in $CDCl_3$ under the argon atmosphere. The reaction mixture was heated to 40 °C and shaken vigorously at that temperature overnight. The compound was characterized directly by the NMR analysis without further isolation or purification.

An orange solution. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 0.69–0.91 (1H, m), 1.07 (3H, s, CH_3), 1.14 (3H, s, CH_3), 1.17–1.36 (3H, m, CH_2), 2.32 (1H, dt, *J* = 14.2, 9.9 Hz), 2.56–2.73 (1H, m), 2.82 (1H, t, *J* = 14.8 Hz, CH), 3.11–3.23 (2H, m, CH_2), 3.45 (1H, t, *J* = 15.6 Hz, CH_2), 3.81 (1H, d, *J* = 11.9 Hz, CH_2), 7.22–7.33 (2H, m, Ph), 7.32–7.53 (10H, m, Ph), 7.70–7.81 (2H, m, Ph), 7.79–7.93 (2H, m, Ph), 7.92–8.07 (4H, m, Ph). ^{13}C{^{1}H} NMR (101 MHz, $CDCl_3$), δ, ppm: 14.7 (d, J_{CP} = 10.5 Hz), 33.9 (d, J_{CP} = 46.2 Hz), 34.2, 35.4 (d, J_{CP} = 46.5 Hz), 44.9 (d, J_{CP} = 6.2 Hz), 48.8 (dd, J_{CP} = 12.5, 4.5 Hz), 48.9 (d, J_{CP} = 12.9 Hz), 49.9 (d, J_{CP} = 4.8 Hz), 67.6, 128.5 (d, J_{CP} = 12.2 Hz), 128.7 (d, J_{CP} = 12.0 Hz), 131.4 (dd, J_{CP} = 9.2, 3.0 Hz), 131.6 (d, J_{CP} = 14.3 Hz), 131.7 (d, J_{CP} = 14.6 Hz), 132.5 (t, J_{CP} = 11.4 Hz), 133.4 (dd, J_{CP} = 74.2, 5.76 Hz). ^{31}P{^{1}H} NMR (243 MHz, $CDCl_3$), δ, ppm: 28.0 (J_{PSe} = 702.8 Hz), 36.6 (J_{PSe} = 720.0 Hz).

The general procedure for the preparation of compounds 15a–d

In an autoclave, to the solution of the corresponding 4-bromoisoquinoline **16** (10.0 mmol) in MeOH (100 mL), $Pd(dppf)Cl_2$ (0.220 g, 0.3 mmol)

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and Et_3N (1.7 mL, 12.0 mmol, 1.22 g) were subsequently added at 25 °C. The reaction vessel was purged with argon for 5 min, then filled with CO from a gas cylinder. The reaction mixture was vigorously stirred at the temperatures indicated (80 °C for **15a**,**c**; 120 °C for **15b**; 110 °C for **15d**) under the CO atmosphere at 20 bar for 16 h (with the conversion monitored by the LC-MS analysis of the reaction aliquots). Upon the completion, the reaction mixture was concentrated under reduced pressure, and the residue was triturated with the anhydrous THF (10 mL) and filtered. The filtrate was evaporated under reduced pressure, and the residual crude product was used in the next step without further purification.

Methyl isoquinoline-4-carboxylate (**15a**)

The compound was synthesized according to the General Procedure from **16a** (3.00 g, 14.4 mmol). The reaction mixture was stirred at 80 °C for 16 h.

Beige crystals. Yield – 2.64 g (98%). M. p. 81–82 °C. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.97 (3H, s, CH_3), 7.79 (1H, t, J = 7.6 Hz, Ar), 7.95 (1H, t, J = 7.7 Hz, Ar), 8.26 (1H, d, J = 8.2 Hz, Ar), 8.76 (1H, d, J = 8.7 Hz, Ar), 9.05 (1H, s, Ar), 9.53 (1H, s, Ar). LC-MS, *m/z* (APCI): 188 $[M+H]^+$. The analytical data are consistent with those previously reported [10].

Methyl 6-methoxyisoquinoline-4-carboxylate (**15b**)

The compound was synthesized according to the General Procedure from **16b** (2.50 g, 10.5 mmol). The reaction mixture was stirred at 120 °C overnight.

A colorless powder. Yield – 2.04 g (90 %). M. p. 122–124 °C. Anal. Calcd. for $C_{12}H_{11}NO_3$, %: C 66.35; H 5.10; N 6.45. Found, %: C 66.07; H 5.47; N 6.38. ^{1}H NMR (400 MHz, $CDCl_3$), δ, ppm: 4.01 (3H, s, CH_3), 4.02 (3H, s, CH_3), 7.29 (1H, dd, J = 9.0, 2.5 Hz, Ar), 7.91 (1H, d, J = 9.0 Hz, Ar), 8.40 (1H, d, J = 2.5 Hz, Ar), 9.18 (1H, s, Ar), 9.22 (1H, s, Ar). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$), δ, ppm: 52.2, 55.7, 103.1, 119.0, 120.9, 124.5, 130.1, 136.5, 148.0, 156.0, 162.8, 167.3. LC-MS, *m/z* (APCI): 218 $[M+H]^+$.

Methyl 6-chloroisoquinoline-4-carboxylate (**15c**)

The compound was synthesized according to the General Procedure from **16c** (2.44 g, 10.0 mmol). The reaction mixture was stirred at 80 °C for 18 h.

A light-brown powder. Yield – 2.03 g (92 %). M. p. 111–112 °C. Anal. Calcd. for $C_{11}H_8ClNO_2$, %: C 59.61; H 3.64; N 6.32; Cl 15.99. Found, %: C 59.93; H 3.82; N 6.60; Cl 16.11. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 3.96 (3H, s, CH_3), 7.83 (1H, dt, J = 8.8, 2.0 Hz, Ar), 8.31 (1H, dd, J = 8.8, 1.8 Hz, Ar), 8.82 (1H, s, Ar), 9.10 (1H, s, Ar), 9.55 (1H, s, Ar). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6), δ, ppm: 52.5, 118.8, 123.2, 126.4, 128.6, 130.9, 133.3, 137.7, 147.0, 157.1, 165.8. HRMS (ESI/QTOF), *m/z*: calculated for $C_{11}H_9ClNO_2^+$ 222.0316 $[M+H]^+$; found 222.0314.

Methyl 6-(trifluoromethyl)isoquinoline-4-carboxylate (**15d**)

The compound was synthesized according to the General Procedure from **16d** (2.80 g, 10.2 mmol). The reaction mixture was stirred at 110 °C overnight.

A brown powder. Yield – 2.57 g (99 %). M. p. 76–78 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 4.06 (3H, s, CH_3), 7.87 (1H, dd, J = 8.5, 1.7 Hz, Ar), 8.18 (1H, d, J = 8.5 Hz, Ar), 9.31 (1H, s, Ar), 9.37 (1H, s, Ar,), 9.47 (1H, s, Ar). ^{13}C{^{1}H} NMR (126 MHz, $CDCl_3$), δ, ppm: 52.7, 121.0, 123.4 (q, $^3J_{CF}$ = 4.7 Hz), 123.7 (q, $^3J_{CF}$ = 2.6 Hz), 123.8 (q, $^1J_{CF}$ = 272.9 Hz), 129.3, 129.5, 133.3, 133.8 (q, $^2J_{CF}$ = 32.5 Hz), 148.1, 157.1, 166.4. ^{19}F{^{1}H} NMR (376 MHz, DMSO-d_6), δ, ppm: −62.2. HRMS (ESI/QTOF), *m/z*: calculated for $C_{12}H_9F_3NO_2^+$ 256.0580 $[M+H]^+$; found 256.0575.

The general procedure for the preparation of compounds 14a–d

To a pre-cooled to −78 °C solution of the corresponding ester **15a–d** (1 mmol) in CH_2Cl_2 (6 mL), Bu_3SnH (0.292 g, 1 mmol), and neat acetyl chloride (79.0 µL, 1.1 mmol, 87.0 mg) were sequentially added with stirring under the argon atmosphere. The reaction mixture was stirred, maintaining the same temperature for 2 h. The cooling bath was then removed, and the reaction mixture gradually warmed to rt with stirring. In case of the incomplete conversion (as determined by LC-MS of a small aliquot of the reaction mixture), the reaction mixture was treated with additional separate portions of Bu_3SnH and acetyl chloride at −40 °C, with stirring maintained at this temperature under the argon atmosphere for 2 h before warming to rt. Once the reaction was complete, a sat. aq. NH_4Cl solution was added, and the mixture was stirred overnight. The layers were separated, the organic layer was then dried over Na_2SO_4 and concentrated under reduced pressure. The residual crude product was purified by the trituration with hexane/*t*BuOMe mixture (5 mL, 4:1, v/v).

Methyl 2-acetyl-1,2-dihydroisoquinoline-4-carboxylate (**14a**)

The compound was synthesized according to the General Procedure from **15a** (0.750 g, 4.00 mmol).

A beige powder. Yield – 0.668 g (72 %). M.p. 88–91 °C. ^{1}H NMR (500 MHz, $CDCl_3$), δ, ppm: 2.34 (3H, s, CH_3), 3.86 (3H, s, CH_3), 4.88 (2H,

s, CH_2), 7.11 (1H, d, J = 7.5 Hz, Ar), 7.21 (1H, t, J = 7.4 Hz, Ar), 7.28 (1H, t, J = 7.7 Hz, Ar), 7.86 (1H, s, CH), 8.16 (1H, d, J = 8.0 Hz, Ar). $^{13}C\{^1H\}$ NMR (151 MHz, $CDCl_3$), δ, ppm: 21.5, 44.9, 51.8, 110.4, 125.1, 126.1, 127.8, 128.1, 128.2, 128.9, 136.7, 166.1, 169.3. HRMS (ESI/QTOF), *m/z*: calculated for $C_{13}H_{14}NO_3^+$ 232.0968 $[M + H]^+$; found 232.0971.

Methyl 2-acetyl-6-methoxy-1,2-dihydroisoquinoline-4-carboxylate (**14b**)

The compound was synthesized according to the General Procedure from **15b** (0.560 g, 2.58 mmol).

A colorless powder. Yield – 0.522 g (78 %). M.p. 86–87 °C. Anal. Calcd. for $C_{14}H_{15}NO_4$, %: C 64.36; H 5.79; N 5.36. Found, %: C 64.43; H 5.83; N 5.06. ^1H NMR (500 MHz, $CDCl_3$), δ, ppm: 2.34 (3H, s, CH_3), 3.83 (3H, s, CH_3), 3.86 (3H, s), 4.83 (2H, s, CH_2), 6.77 (1H, dd, J = 8.8, 2.3 Hz, Ar), 7.02 (1H, d, J = 8.5 Hz, Ar), 7.83 (1H, s, Ar), 7.89 (1H, s, CH). $^{13}C\{^1H\}$ NMR (126 MHz, $CDCl_3$), δ, ppm: 21.5, 44.5, 51.8, 55.5, 103.4, 110.6, 113.6, 121.0, 127.0, 129.3, 137.2, 159.5, 166.1, 169.3 (the compound demonstrated a significant decomposition rate in the solution). LC-MS, *m/z* (APCI): 262 $[M+H]^+$.

Methyl 2-acetyl-6-chloro-1,2-dihydroisoquinoline-4-carboxylate (**14c**)

The compound was synthesized according to the General Procedure from **15c** (0.325 g, 1.50 mmol).

A yellowish solid. Yield 0.260 g (67 %). M.p. 112–114 °C. Anal. Calcd. for $C_{13}H_{12}ClNO_3$, %: C 58.77; H 4.55; N 5.27; Cl 13.34. Found, %: C 58.81; H 4.68; N 5.40; Cl 13.22. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: 2.35 (3H, s, CH_3), 3.87 (3H, s, CH_3), 4.85 (2H, s, CH_2), 7.03 (1H, d, J = 8.1 Hz, Ar), 7.18 (1H, dd, J = 8.1, 2.2 Hz, Ar), 7.91 (1H, s, CH), 8.23 (1H, s, Ar). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$), δ, ppm: 21.5, 44.5, 52.0, 109.1, 125.2, 127.0, 127.3, 127.6, 129.8, 134.1, 137.7, 165.7, 169.3. LC-MS, *m/z* (APCI): 266 $[M+H]^+$.

Methyl 2-acetyl-6-(trifluoromethyl)-1,2-dihydroisoquinoline-4-carboxylate (**14d**)

The compound was synthesized according to the General Procedure from **15d** (0.250 g, 1.00 mmol).

A beige powder. Yield – 0.192 g (65 %). M.p. 104–106 °C. Anal. Calcd. for $C_{14}H_{12}F_3NO_3$, %: C 56.19; H 4.04; N 4.68. Found, %: C 56.42; H 4.25; N 4.72. ^1H NMR (400 MHz, $CDCl_3$), δ, ppm: δ 2.37 (3H, s, CH_3), 3.89 (3H, s, CH_3), 4.95 (2H, s, CH_2), 7.22 (1H, d, J = 8.0 Hz, Ar), 7.47 (1H, d, J = 8.5 Hz, Ar), 7.96 (1H, s, CH), 8.54 (1H, s, Ar). $^{13}C\{^1H\}$ NMR, δ, ppm: the spectrum is uninformative due to the compound decomposition during NMR processing. LC-MS, *m/z* (APCI): 300 $[M+H]^+$.

Methyl 2-acetyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylate (17a)

The mixture of isoquinoline methyl carboxylate **14a** (500.0 mg, 2.16 mmol), bis(1,5-cyclooctadiene)rhodium(I) tetrafluoroborate (43.9 mg, 108.1 μmol) and [(1*R*,2*R*,3*S*)-2,3-bis[(diphenylphosphanyl)methyl]-1,2-dimethylcyclopentyl]methanol **1** (56.7 mg, 108.1 μmol) was dissolved in degassed CF_3CH_2OH (5 mL). All operations with reagents for the asymmetric hydrogenation were performed in a glove box. The solution obtained was transferred to the autoclave. Subsequently, the autoclave was evacuated and backfilled with H_2 (50 bar) from a gas cylinder. The reaction mixture was vigorously stirred at 20 °C for 18 h. The solvent was evaporated under reduced pressure, and the residue was purified by the flash column chromatography (*t*BuOMe/MeOH = 1:0 to 5:1, v/v as an eluent) to give tetrahydroisoquinoline methyl carboxylate **17a**.

A viscous oil. Yield – 451.0 mg (1.94 mmol, 89%). ^1H NMR (400 MHz, $CDCl_3$), the compound exists as a mixture of rotamers (ca. 2:1) δ, ppm: 2.18 (0.36×3H, s, CH_3), 2.25 (0.64×3H, s, CH_3), 3.57 (0.64×1H, dd, J = 13.4, 4.1 Hz, CH_2), 3.64–3.69 (0.36×1H, m, CH_2), 3.71 (3H, m, CH_3), 3.87 (1H, dt, J = 12.7, 4.3 Hz, CH), 4.34 (0.64×1H, dd, J = 13.4, 3.6 Hz, CH_2), 4.42 (0.64×1H, d, J = 17.4 Hz, CH_2 AB system), 4.47 (0.36×1H, dd, J = 13.3, 5.1 Hz, CH_2), 4.60 (0.36×1H, d, J = 16.2 Hz, CH_2 AB system), 4.74 (0.36×1H, d, J = 16.2 Hz, CH_2 AB system), 5.06 (0.64×1H, d, J = 17.6 Hz, CH_2 AB system), 7.12–7.25 (2H, m, Ph), 7.28 (2H, t, J = 6.6 Hz, Ph). $^{13}C\{^1H\}$ NMR (101 MHz, $CDCl_3$), the compound exists as a mixture of rotamers (ca. 2:1) δ, ppm: 21.5 and 21.9, 41.6 and 44.2, 44.3 and 45.0, 45.5 and 48.1, 52.5 and 52.6, 126.5 and 126.7, 127.0 and 127.3, 127.8 and 128.0, 129.2 and 129.7, 129.9 and 130.6, 133.3 and 133.8, 169.9 and 170.3, 172.0 and 172.5. HRMS (ESI/QTOF), *m/z*: calcd. for $C_{13}H_{15}NO_3Na^+$ 256.0944 $[M + Na]^+$; found 256.0951. *ee* = 52% (determined by chiral HPLC).

The general procedure for the synthesis of tetrahydroisoquinoline-4-carboxylates *rac*-17 (prepared for the *ee* determination)

In a high-pressure vessel to the solution of the corresponding dihydroisoquinoline-4-carboxylate **14a** (0.50 mol) in MeOH (5 mL), Pd/C (10% w/w, 50.0 mg) was added in one portion. The reaction vessel was evacuated and backfilled with H_2 from a gas cylinder (repeated twice), and the suspension was kept at rt with intensive stirring under the H_2 atmosphere at 50 bar for 24 h.

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The catalyst was filtered off, the filter cake was washed with MeOH (3×2 mL). The filtrate was concentrated under reduced pressure, the remained solid was dried under a high vacuum (1 mmHg) to give the title product **(±)-17a**.

2-Acetyl-1,2,3,4-tetrahydroisoquinoline-4-carboxylic acid (19)

To the solution of tetrahydroisoquinoline methyl carboxylate (0.400 g, 1.72 mmol) in dichloroethane (50 mL), neat trimethylstannanol (0.936 g, 5.17 mmol) was added. The reaction mixture was heated to reflux and kept with stirring at that temperature for 18 h. After cooling to room temperature, the resulting solution was diluted with CH_2Cl_2 (100 mL), washed with the aq. 1 M solution of $NaHSO_4$ (2×50 mL), then a sat. aq. solution of NaCl (40 mL). The organic layer was separated, dried over Na_2SO_4, and concentrated under reduced pressure to give the crude title compound, which was used in the next step without further purification. The analytical sample was obtained after the purification by the reverse-phase HPLC (performed on a puriFlash C18-HP column using CH_3CN–H_2O–0.1%HCOOH gradients).

A colorless powder. Yield – 0.353 g (94%). M. p. 155–157 °C. *ee* 53% (determined by HPLC). ^{1}H NMR (400 MHz, CD_3OD), the compound exists as a mixture of rotamers (ca. 2:1) δ, ppm: 2.18 (0.34×3H, s, CH_3), 2.24 (0.66×3H, s, CH_3), 3.50 (0.34×1H, dd, J = 13.2, 4.6 Hz, CH_2), 3.58 (0.64×1H, dd, J = 13.6, 4.1 Hz, CH_2), 3.88 (0.34×1H, t, J = 4.4 Hz, CH), 3.91 (0.64×1H, t, J = 3.6 Hz, CH), 4.34 (0.64×1H, d, J = 17.3 Hz, CH_2 AB system), 4.35–4.47 (0.66×1H, m, CH_2), 4.56 (0.34×1H, dd, J = 13.2, 4.2 Hz, CH_2), 4.65 (0.34×1H, d, J = 16.4 Hz, CH_2 AB system), 4.79 (0.34×1H, d, J = 16.4 Hz, CH_2 AB system), 5.01 (0.64×1H, d, J = 17.3 Hz, CH_2 AB system), 7.15–7.36 (4H, m, Ph). ^{13}C{^{1}H} NMR (101 MHz, CD_3OD), the compound exists as a mixture of rotamers (ca. 2:1) δ, ppm: 21.4 and 21.7, 42.8, 45.5 and 45.7, 45.1 and 46.7, 127.5 and 127.64, 127.60, 128.0 and 128.7, 130.1 and 130.8, 132.8 and 133.5, 134.0 and 134.1, 172.6 and 172.9, 175.1 and 175.6. HRMS (ESI/QTOF), *m/z*: calculated for $C_{12}H_{14}NO_3^+$ 220.0968 $[M + H]^+$; found 220.0964.

Ethyl 1,2,3,4-tetrahydroisoquinoline-4-carboxylate hydrochloride (20×HCl)

To the solution of tetrahydroisoquinoline carboxylic acid **19** (100.0 mg, 0.456 mol) in EtOH (5 mL), aq. HCl (0.2 mL, 10 M) was added. The resulting mixture was stirred at 50 °C for 9 days. After the completion of the reaction (by ^{1}H NMR spectra of the small aliquots of the reaction mixture) all volatiles were removed under reduced pressure. The residue was dissolved in a dry EtOH (4 mL), the solution was acidified with an anhydrous HCl (0.2 mL, *ca.* 3.6 M in 1,4-dioxane) and then stirred at 50 °C for 36 h. The reaction mixture was concentrated under reduced pressure to give tetrahydroisoquinoline hydrochloride **20** with a sufficient purity.

A colorless powder. Yield 109.6 mg (99 %). M. p. 124–126 °C. *ee* 57 % (determined by HPLC). $[\alpha]_D^{20}$ = +19.7 (*c* 1.0, MeOH) (lit. $[\alpha]_D$ = –42.3° (*c* 1.0, MeOH) [8]). Anal. Calcd. for $C_{12}H_{16}ClNO_2$: C 59.63; H 6.67; N 5.79; Cl 14.67. Found: C 60.02; H 6.39; N 5.62; Cl 14.59. ^{1}H NMR (400 MHz, DMSO-d_6), δ, ppm: 1.23 (3H, t, J = 7.1 Hz, CH_3), 3.54 (2H, d, J = 6.2 Hz, CH_2), 4.18 (2H, q, J = 7.1 Hz, CH_2), 4.22–4.31 (3H, m, CH_2 and CH), 7.25–7.30 (1H, m, Ph), 7.32 (2H, dt, J = 7.2, 3.6 Hz, Ph), 7.35–7.39 (1H, m, Ph). ^{13}C{^{1}H} NMR (101 MHz, DMSO-d_6), δ, ppm: 14.4, 40.9, 42.2, 43.8, 61.8, 127.6, 128.1, 128.2, 128.9, 129.6, 129.7, 171.2. LC-MS, *m/z* (APCI): 206 $[M+H]^+$. The spectral and physical data were consistent with those previously reported [8].

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