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Enantioselective Synthesis of 4-Silyl-1,2,3,4-tetrahydroquinolines via Copper(I) Hydride Catalyzed Asymmetric Hydrosilylation of 1,2-Dihydroquinolines

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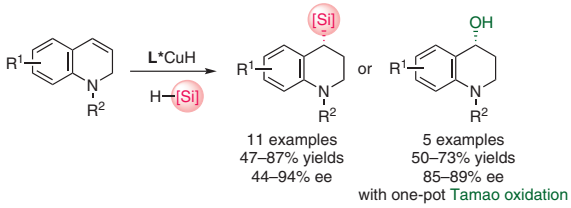
Dedicated to Prof. Barry M. Trost

Published as part of the Cluster *The Power of Transition Metals: An Unending Well-Spring of New Reactivity*



Received: 22.04.2020
Accepted after revision: 08.05.2020
Published online: 16.04.2020
DOI: 10.1055/s-0040-1707134; Art ID: st-2020-b0238-c

Crowd-Reviewed

Abstract C–Si bonds were constructed by utilizing copper hydride-catalyzed asymmetric hydrosilylation of 1,2-dihydroquinolines, affording various chiral 4-silyl-1,2,3,4-tetrahydroquinolines in good yields and enantioselectivity. In addition, the C–Si bonds were transformed into C–O bonds with retention of stereochemistry through the Tamao oxidation, giving a series of useful 4-hydroxy-1,2,3,4-tetrahydroquinolines. This method with the enantioselective introduction of silyl groups provides an option to adjust bioactive properties of tetrahydroquinolines.

Key words 1,2-dihydroquinoline, 1,2,3,4-tetrahydroquinoline, copper hydride, asymmetric catalysis, hydrosilylation, dearomatization

Silicon is regarded as a bio-isostere of carbon in clinical studies due to their similarity.[1] In fact, the introduction of silicon-containing groups to known bioactive compounds provides opportunities to alter their properties (Scheme 1).[2] For example, the larger covalent radius of silicon and the longer Si–C covalent bond lengths (compared to C–C bonds) may lead to different conformations of the biomolecules, thus providing beneficial influence on their biological activities.[3] Furthermore, introducing the silyl group to biomolecules may adjust their pharmacokinetic pathway.[4,5] In this regard, numerous methods were developed for the synthesis of potential bioactive silicon-containing compounds, which could be roughly classified into two types. One is the installation of a silicon-containing moiety on known lead compounds or drugs[6] (e.g., Camptothecin versus Karenitecin)[6b] albeit with slightly low efficiency.[1d,7] The second is the introduction of silyl groups or carbon-to-silicon switch on a bioactive skeleton.[8] However, the latter remains underexplored and most of the reported studies are restricted to the modification of amino acids.[9] Despite the considerable progress, incorporation of silicon moieties on diverse bioactive scaffolds is still in great demand.

1,2,3,4-Tetrahydroquinolines (THQs) represent an important bioactive skeleton because of their ubiquitous presence in pharmaceuticals and natural products.[10] Diverse methods have been developed for the synthesis of chiral THQs such as assorted cyclizations (e.g., Povarov reaction,[11] Michael addition,[12] C–H bond functionalization[13]),[14] kinetic resolution[15] and dearomatization. In particular, asymmetric dearomatization of quinolines constitutes a straightforward approach. By utilizing (transfer) hydrogenation[16] or the Reissert type reaction,[17] various enantioenriched THQs were obtained from readily available quinolines. Recently, a stepwise reduction of quinolines and asymmetric catalytic transformation of the generated dihydroquinolines emerged as an attractive method to access chiral THQs with no need for preactivation of quinoline substrates.[18] Thus the combination of this strategy with the introduction of silyl groups would be an appealing approach for the synthesis of silyl substituted THQs.[19] Compared with other methods of forging C(sp^3)–Si bonds,[20] transition-metal-catalyzed asymmetric hydrosilylation of unsaturated compounds[21] represents a direct and atom-economic approach.[22] In this regard, we envisioned that copper-catalyzed asymmetric hydrosilylation of 1,2-dihydroquinolines would efficiently introduce a C–Si bond at the 4-position of THQs.[23] Herein, we report the results of this study.

At the outset, *N*-CO_2Me 1,2-dihydroquinoline (**1a**) was chosen as the substrate in the hydrosilylation reaction (Table 1). Considering the relatively high reactivity of arylsilanes over alkylsilanes, we chose diphenylsilane for the initial

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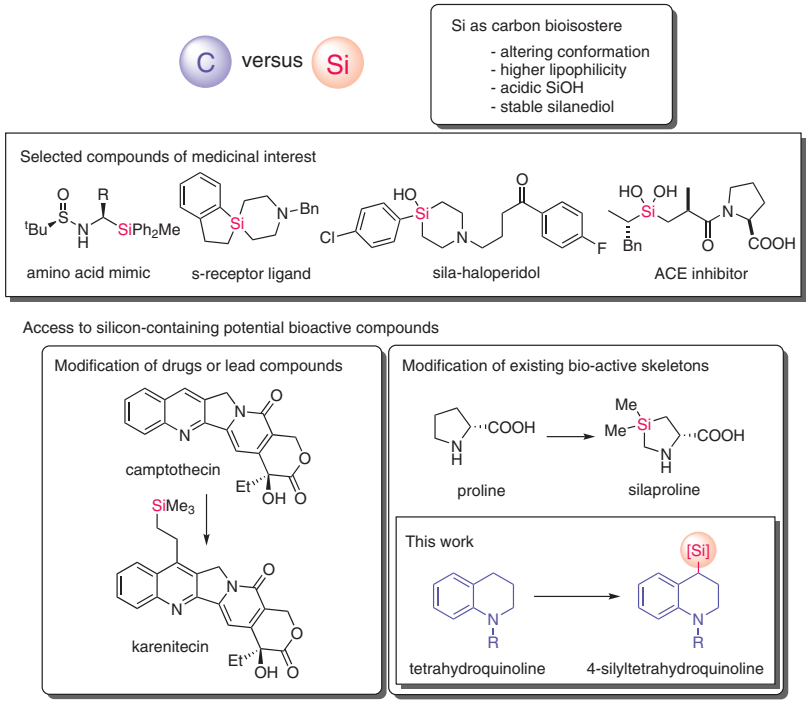

Scheme 1 Application of silicon in pharmaceutical chemistry

attempt. Compound **1a** was treated with 3 equivalents of diphenylsilane in the presence of the catalyst derived from copper(II) acetate and **L1** at 40 ° under neat conditions for 36 h. To our delight, the desired product **2a** was afforded in 56% yield and 87% ee (entry 1). Notably, the addition of a mono-phosphine as the secondary ligand[24] resulted in an improved yield (entries 2–5; see the Supporting Information for more details), and $(p\text{-tolyl})_3P$ gave the optimal results (86% yield and 87% ee; entry 4).[25] Subsequent screening of chiral ligands revealed that **L1** is the most effective ligand (entries 6–11).

With the optimal conditions in hand, the substrate scope was then explored (Scheme 2; see also the Supporting Information and Procedure A).[26] The substrates with various N-protecting groups (Ac, CO_2Bn, $CO_2{}^iBu$) gave the desired products with good yields and enantioselectivities (**2b–d**, 74–83% yields, 83–90% ee). A series of substituents at the 6-position of 1,2-dihydroquinolines were explored. A moderate yield and poor enantioselectivity were observed for the bromo-bearing substrate (**2e**, 50% yield, 46% ee). The substrate with an electron-withdrawing group (CO_2Me) worked well, affording the desired THQ in 87% yield and 89% ee (**2f**). 6-Thienyl-1,2-dihydroquinoline was transformed into its corresponding product **2g** in moderate yield with slightly decreased ee value (47% yield, 76% ee). The THQs with electron-donating groups (OMe and SMe) were obtained with good results (**2h**, 87% yield, 94% ee; **2i**, 82% yield, 86% ee). Substituent effects were also investigated for the 7-methyl (**2j**) and 7-methoxy (**2k**) substrates, giving 77% yield with 82% ee and 62% yield with 82% ee, respectively. Subsequently, by utilizing phenylsilane as the silyl reagent, the desired 4-silyl THQs were generated and an extra Tamao oxidation was performed in a one-pot fashion, yielding 4-hydroxy THQs (Scheme 3; see also the Supporting Information and Procedure B).[27] The *N*-CO_2Me and *N*-CO_2Bn 1,2-dihydroquinolines were well tolerated, leading to the desired products **3a**[28] and **3b** in 63% yield with 89% ee and 73% yield with 88% ee, respectively. 1,2-Dihydroquinolines bearing varied substituents (6-OMe, 6-Ph and 7-Me) reacted smoothly with phenylsilane, and moderate yields with good enantioselectivities were obtained (**3c–e**, 50–68% yields, 85–89% ee). Notably, other silanes such as Et_2SiH_2 and Et_2MeSiH were also tested, but failed to give any desired product.

To demonstrate the practicality of this protocol, we next performed scale-up reactions (Scheme 4). The hydrosilylation of **1a** with diphenylsilane at 5 mmol scale under the standard conditions gave an improved yield and slightly decreased enantioselectivity (eq. 1, 1.76 g, 94% yield, 85% ee). The one-pot hydrosilylation/Tamao oxidation reaction occurred smoothly with 2.5 mol% catalyst loading (eq. 2, 168 mg, 81% yield, 89% ee). The 4-silyl THQ product **2a** could be oxidized to the desired silanol in 83% yield with 85% ee (Scheme 5). The absolute configuration of **4** was determined to be *R* by the X-ray crystallographic analysis of its optically pure single crystal and the absolute configurations

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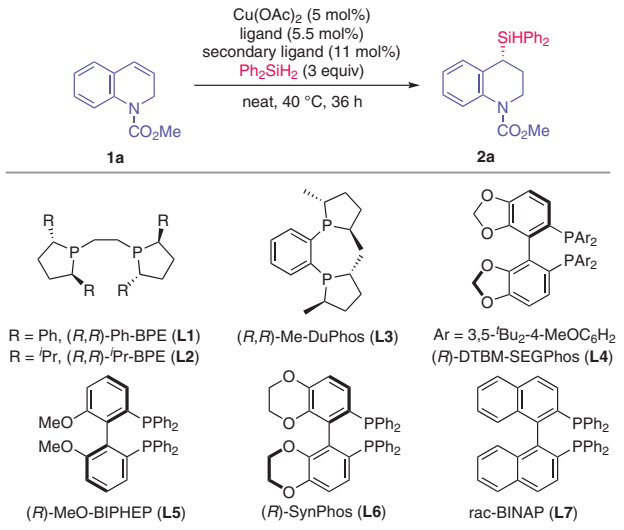
Table 1 Optimization of the Reaction Conditions[a]

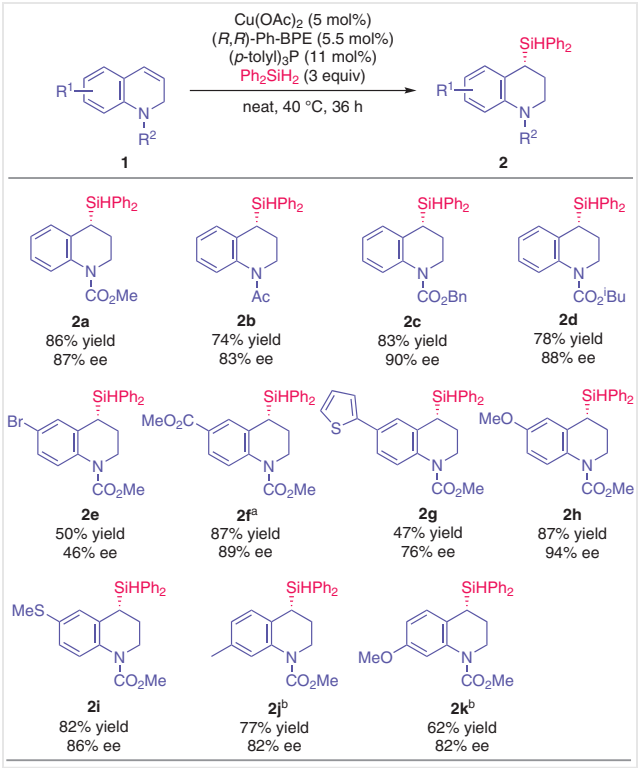


Entry	Secondary ligand	Ligand	Yield (%)[b]	ee (%)[c]
1	none	**L1**	56	87
2	PPh_3	**L1**	84	86
3	$(4\text{-}MeOC_6H_4)_3P$	**L1**	64	85
4	$(p\text{-tolyl})_3P$	**L1**	86	87
5	PCy_3	**L1**	80	56
6	$(p\text{-tolyl})_3P$	**L2**	22	1
7	$(p\text{-tolyl})_3P$	**L3**	8	1
8	$(p\text{-tolyl})_3P$	**L4**	0	n.a.
9	$(p\text{-tolyl})_3P$	**L5**	0	n.a.
10	$(p\text{-tolyl})_3P$	**L6**	0	n.a.
11	$(p\text{-tolyl})_3P$	**L7**	0	n.a.

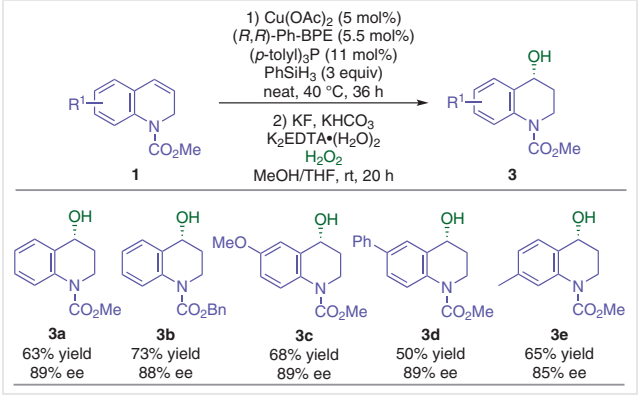
[a] Reaction conditions: $Cu(OAc)_2$ (0.010 mmol), ligand (0.011 mmol), secondary ligand (0.022 mmol, if used), **1a** (0.2 mmol) and diphenylsilane (0.6 mmol) were stirred at 40 °C under neat conditions for 36 h.
[b] Isolated yield.
[c] The ee value was determined based on HPLC analysis; n.a. = not applicable.

of the products **2** and **3** were assigned based on the assignment of **4**.[29]

A deuterium experiment utilizing Ph_2SiD_2 as the hydride source revealed that hydrogen atoms at both the 3-position and in the silyl group were deuterated, which demonstrated the excellent atom-economy of this protocol (Scheme 6). A plausible mechanism was thus proposed as exemplified by the reaction between **1a** and diphenylsilane (Scheme 7). Ligated copper hydride (**L**CuH) is generated in situ from the copper(II) acetate, the ligand (**L**) and diphenylsilane. The activated species then inserts into **1a** with formation of intermediate **A** containing the stereogenic center with a C–Cu bond. Subsequent stereoretentive σ-metathesis between **A** and another silane molecule results in the desired product **2a** and the regeneration of **L**CuH.[30]



Scheme 2 Substrate scope for the asymmetric hydrosilylation. *Reagents and conditions*: $Cu(OAc)_2$ (0.010 mmol), (*R*,*R*)-Ph-BPE (0.011 mmol), $(p\text{-tolyl})_3P$ (0.022 mmol), **1** (0.2 mmol) and diphenylsilane (0.6 mmol) were stirred at 40 °C under neat condition for 36 h. Isolated yields are reported and the ee value was determined based on HPLC or SFC analysis. [a] 5 equiv of silane were used. [b] The reaction time was 48 h.



Scheme 3 Substrate scope for the asymmetric hydrosilylation and Tamao oxidation. *Reagents and conditions*: $Cu(OAc)_2$ (0.010 mmol), (*R*,*R*)-Ph-BPE (0.011 mmol), $(p\text{-tolyl})_3P$ (0.022 mmol), **1** (0.2 mmol) and phenylsilane (0.6 mmol) were stirred at 40 °C under neat conditions for 36 h. Then KF (0.8 mmol), $KHCO_3$ (0.8 mmol), $K_2EDTA{\cdot}(H_2O)_2$ (0.2 mmol), MeOH (1.2 mL) and H_2O_2 (1.8 mmol) were added and stirred at r.t. in THF (1.2 mL) for 20 h. Isolated yields are given and the ee values were determined based on HPLC or SFC analysis.

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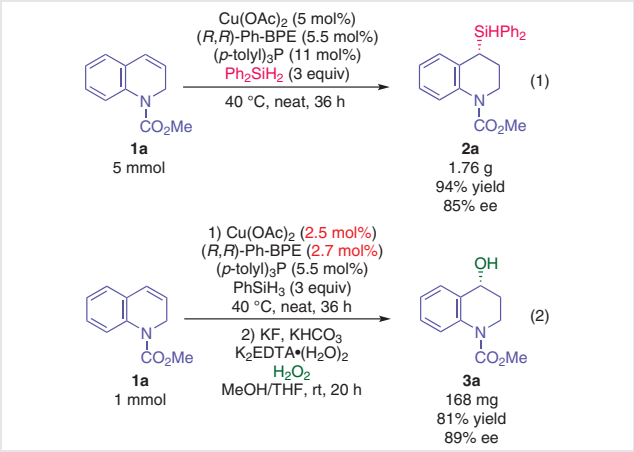
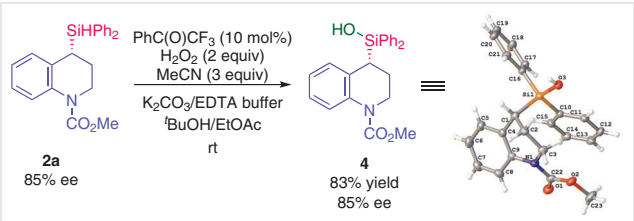
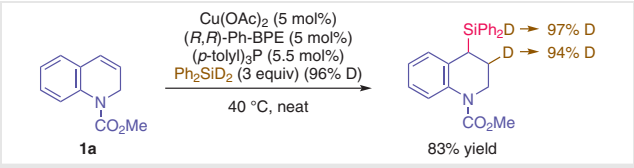


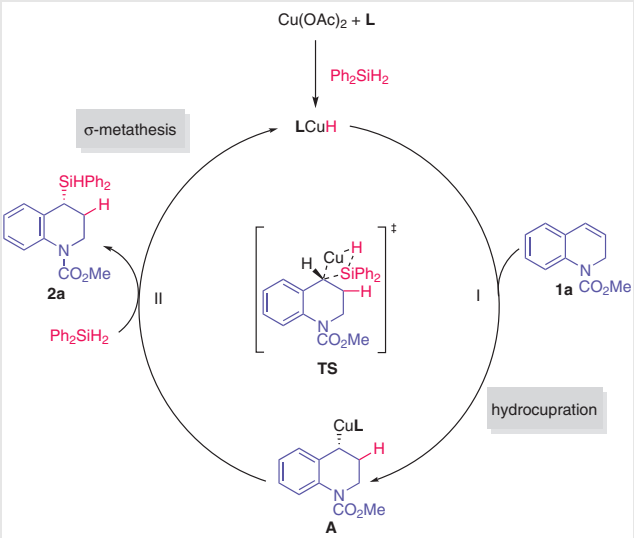
Scheme 4 Scale-up reactions



Scheme 5 Transformation into product **4**



Scheme 6 Deuterium experiment



Scheme 7 Plausible mechanism

In conclusion, a copper(II) acetate/(*R*,*R*)-Ph-BPE/(*p*-tolyl)$_3$P catalyzed asymmetric hydrosilylation of 1,2-dihydroquinolines with hydrosilanes was developed. Various 4-silyl and 4-hydroxy 1,2,3,4-tetrahydroquinolines were obtained with good enantioselectivities. The enantioselective incorporation of a silyl group on the tetrahydroquinoline skeleton might find application in medicinal chemistry.

Funding Information

We thank MOST (2016YFA0202900), the NSFC (21821002, 21801248), the Chinese Academy of Sciences (XDB20030000, QYZDY-SSW-SLH012), the Science and Technology Commission of Shanghai Municipality (18JC1411302, 18YF1428900, 19590750400) for generous financial support.

Supporting Information

Supporting information for this article is available online at https://doi.org/10.1055/s-0040-1707134.

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(25) **Methyl (*R*)-4-(Diphenylsilyl)-3,4-dihydroquinoline-1(2*H*)-carboxylate (2a):** Yield: 64.1 mg (86%); colorless oil; 87% ee [Daicel Chiralpak OD-H (0.46 cm × 25 cm), *n*-hexane/2-propanol = 90/10, *v* = 0.7 mL·min^{-1}, λ = 230 nm, t_R (major) = 12.59 min, t_R (minor) = 10.58 min]; $[\alpha]_D^{28}$ = +18.9 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.65–7.50 (m, 1 H), 7.50–7.44 (m, 2 H), 7.44–7.35 (m, 4 H), 7.35–7.26 (m, 4 H), 7.12–7.05 (m, 1 H), 6.92–6.85 (m, 2 H), 4.92 (d, *J* = 2.8 Hz, 1 H), 3.93 (dt, *J* = 12.4, 6.4 Hz, 1 H), 3.65 (s, 3 H), 3.31 (dt, *J* = 12.0, 6.0 Hz, 1 H), 2.99 (td, *J* = 6.8, 3.2 Hz, 1 H), 2.24–2.06 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 138.1, 135.7, 135.6, 132.6, 132.5, 131.7, 130.0, 129.9, 128.5, 128.2, 128.1, 125.2, 124.7, 123.8, 52.8, 44.2, 26.2, 25.7. IR (thin film): 3057, 3010, 2945, 2123, 1699, 1587, 1487, 1435, 1377, 1329, 1249, 1193, 1113, 1048, 803, 736, 698, 582, 481, 434 cm^{-1}. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{23}H_{23}NNaO_2Si$: 396.1390; found: 396.1390.

(26) **General Procedure A:** An oven-dried 10 mL screw-cap reaction tube with magnetic stir bar was charged with copper acetate (1.8 mg, 0.010 mmol, 5.0 mol%), (*R*,*R*)-Ph-BPE (5.6 mg, 0.011 mmol, 5.5 mol%) and tri(*p*-tolyl)phosphine (6.7 mg, 0.022 mmol, 11 mol%). It was evacuated and backfilled with argon three times. Diphenylsilane (111 μL, 0.6 mmol) was added by using a syringe and the resulting mixture was premixed for 30 min at 30 °C on a heating block. To the resulting orange mixture, 1,2-dihydroquinoline **1** (0.2 mmol) was added under argon atmosphere. The mixture was stirred for 36 h at 40 °C on a heating block. The mixture was diluted with ethyl acetate (20 mL), then the organic phase was allowed to pass through a short pad of silica gel with extra ethyl acetate (20 mL) as eluent. The filtrate was concentrated in vacuo and the crude mixture was purified by silica gel column chromatography (PE/EtOAc = 100:1 to 40:1, v/v) or preparative TLC (PE/EtOAc = 40:1, v/v) affording product **2**.

(27) **General Procedure B:** An oven-dried 10 mL screw-cap reaction tube with magnetic stir bar was charged with copper acetate (1.8 mg, 0.010 mmol, 5.0 mol%), (*R*,*R*)-Ph-BPE (5.6 mg, 0.011 mmol, 5.5 mol%) and tri(*p*-tolyl)phosphine (6.7 mg, 0.022 mmol, 11 mol%). It was evacuated and backfilled with argon for three times. Phenylsilane (74 μL, 0.6 mmol) was added by using a syringe and the resulting mixture was premixed at r.t. for 5 min. To the resulting orange mixture, 1,2-dihydroquinoline **1** (0.2 mmol) was added under argon atmosphere. The mixture was stirred for 36 h at 40 °C on a heating block. The volatiles were removed in vacuo with an oil pump at room temperature and the crude product was used for the next step without further purification. To a 25 mL Schlenk tube were added potassium fluoride (46.5 mg, 0.8 mmol), $K_2EDTA{\cdot}(H_2O)_2$ (80.9 mg, 0.2 mmol) and potassium bicarbonate (80.1 mg, 0.8 mmol) and the tube was evacuated and backfilled with argon for three times. The crude product was dissolved in THF (1 mL) and transferred to the Schlenk tube by using a syringe. The residue was further rinsed with THF (0.1 mL × 2) and added to the tube. To the resulting mixture was added methanol (1.2 mL) dropwise and gas was released. The mixture was stirred at room temperature for 40 min, then hydrogen peroxide (0.23 g, 27% w/w in water, 1.8 mmol) was added and the suspension was stirred at room temperature for 20 h. The reaction was quenched with sodium thiosulfate (0.85 g, 5.4 mmol) with extra methanol (2 mL). After peroxide residue was quenched completely as indicated by starch-iodine indicator paper, the mixture was diluted by ethyl acetate (5 mL), dried over magnesium sulfate, filtered by glass-sintered filter, rinsed with extra ethyl acetate (20 mL) and concentrated in vacuo. The crude product was purified by silica gel column chromatography (PE/EtOAc = 10:1 to 2:1, v/v) or preparative TLC (PE/EtOAc = 2:1, v/v) afford product **3**.

(28) **Methyl (*R*)-4-Hydroxy-3,4-dihydroquinoline-1(2*H*)-carboxylate (3a):** Yield: 26.0 mg (63%); colorless oil; 89% ee [Daicel Chiralpak IG (0.46 cm × 25 cm), *n*-hexane/2-propanol = 95:5, *v* = 1.0 mL·min^{-1}, λ = 230 nm, t_R (major) = 36.31 min, t_R (minor) = 33.64 min]; $[\alpha]_D^{21}$ = +25.6 (*c* = 1.0, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.80 (d, *J* = 8.4 Hz, 1 H), 7.38 (d, *J* = 7.6 Hz, 1 H), 7.26 (t, *J* = 8.0 Hz, 1 H), 7.09 (t, *J* = 7.6 Hz, 1 H), 4.80–4.70 (m, 1 H), 4.07 (dt, *J* = 13.2, 5.2 Hz, 1 H), 3.79 (s, 3 H), 3.64 (ddd, *J* = 13.6, 10.0, 4.4 Hz, 1 H), 2.18 (s, 1 H), 2.14–1.93 (m, 2 H). ^{13}C NMR (100 MHz, $CDCl_3$): δ = 155.1, 137.4, 130.8, 128.4, 128.3, 124.0, 123.4, 65.8, 53.1, 40.7, 31.9. IR (thin film): 3399, 2953, 1681, 1605, 1581, 1490, 1439, 1377, 1331, 1245, 1217, 1192, 1134, 1083, 1054, 1037, 1021, 976, 943, 911, 865, 821, 756, 702, 591, 560, 530, 491 cm^{-1}. HRMS (ESI): *m*/*z* [M + Na]$^+$ calcd for $C_{11}H_{13}NNaO_3$: 230.0788; found: 230.0791.

(29) CCDC 1996641 contains the supplementary crystallographic data for compound **4**. The data can be obtained free of charge from The Cambridge Crystallographic Data Centre via www.ccdc.cam.ac.uk/getstructures.

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