# Highly efficient and enantioselective hydrogenation of quinolines and pyridines with Ir-Difluorphos catalyst†

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The combination of the readily available chiral bisphosphine ligand Difluorphos with $[Ir(COD)Cl]_2$ in THF resulted in a highly efficient catalyst system for asymmetric hydrogenation of quinolines at quite low catalyst loadings (0.05–0.002 mol%), affording the corresponding products with high enantioselectivities (up to 96%), excellent catalytic activities (TOF up to 3510 $h^{-1}$) and productivities (TON up to 43000). The same catalyst was also successfully applied to the asymmetric hydrogenation of trisubstituted pyridines with nearly quantitative yields and up to 98% ee. In these two reactions, the addition of $I_2$ additive is indispensable; but the amount of $I_2$ has a different effect on catalytic performance.

## Introduction

The synthesis of enantioenriched heterocycles has attracted ever-increasing interest due to the significance of these intermediates for the preparation of a variety of biologically active compounds in the pharmaceutical, agrochemical and fine chemical industries.[1] However, using the traditional direct cyclization strategy is difficult to prepare these chiral compounds. Alternatively, the transition-metal catalyzed asymmetric hydrogenation of readily available heteroaromatic precursors affords a straightforward, efficient and atom-economic route to these optically active compounds. However, in comparison with the relative maturity of asymmetric hydrogenation of unsaturated olefins, ketones and imines, enantioselective hydrogenation of heteroaromatic compounds remains underdeveloped.[2]

Recently some exciting advances have been achieved in transition-metal catalyzed asymmetric hydrogenation of heteroaromatic compounds,[3] and a series of heteroaryl compounds, such as quinolines,[4] quinoxalines,[5] furans,[6] pyrroles,[7] pyridines[8] and indoles[9] have been successfully subjected to enantioselective hydrogenation, providing high yields and more than 90% ee values. Among these reported catalytic systems, a range of chiral atropisomeric biaryl bisphosphine ligands, such as MeO-BIPHEP,[4a,4b,4f,8f] Segphos,[4d] P-Phos,[4g] dendrimer-supported BINAP (GnDenBINAP),[4k] PQ-Phos,[4i] Cl–MeO-BIPHEP,[4l] Synphos[4l,4q] and Difluorphos[4l,4q,4u] have demonstrated their strong ability to transfer chiral information to the desired heterocycles in the Ir-catalyzed hydrogenation reactions. Despite these advances, less attention has been placed on making these hydrogenations more economical and practical.[4c,4j-14v,5f] It is worth noting that Fan and coworkers reported that a chiral iridium complex formed *in situ* from GnDenBINAP and $[Ir(COD)Cl]_2$ could efficiently catalyze asymmetric hydrogenation of quinolines, providing up to 93% ee with excellent catalytic activities (TOF up to 3450 $h^{-1}$) and productivities (TON up to 43000).[4k] However, the preparation of GnDenBINAP requires tedious synthetic procedures, rendering Fan's catalyst system less attractive for commercial application. In this context, it is very appealing to develop high-performance catalyst systems with readily available biaryl bisphosphines as ligands. Herein, we wish to report that the combination of the commercially available diphosphine ligand DifluorPhos with $[Ir(COD)Cl]_2$ served as an exceedingly efficient catalyst to enantioselectively hydrogenate a series of quinolines at high substrate-to-catalyst (S/C) ratios, affording up to 96% ee with up to 43000 TON and up to 3510 $h^{-1}$ TOF. Furthermore, this catalyst system also exhibited superb activity and excellent enantioselectivity in the asymmetric hydrogenation of trisubstituted pyridines.

## Results and discussion

The asymmetric hydrogenation of quinoline derivatives offers an especially attractive route to chiral tetrahydroquinolines, which are useful intermediates and building blocks for the construction of a variety of biologically active compounds.[1] Since Zhou's pioneering report about Ir-catalyzed asymmetric hydrogenation of quinolines, a number of efficient catalyst systems have been developed.[4,10] However, most of the reported examples suffered from low catalytic efficiency. In order to achieve satisfactory yield and enantioselectivity, high catalyst loading is generally required, 1 mol% in most cases. From the viewpoints of both scientific interest and practical applications, it is highly desirable to develop more efficient catalyst systems for enantioselective hydrogenation of quinolines.

With quinaldine **1a** as the model compound, we first examined the catalytic performance of several readily available chiral diaryl bisphosphine ligands (Scheme 1) at a low catalyst loading (0.01 mmol%) with iodine (2.5 mmol%) as the additive. All

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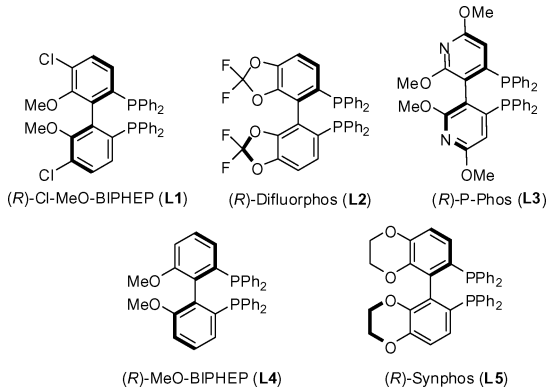
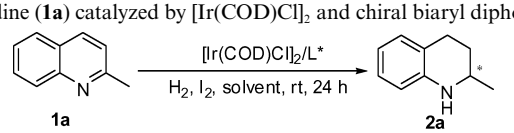



**Scheme 1** Chiral biaryl diphosphine ligands for asymmetric hydrogenation.

catalysts were prepared *via in situ* reaction of $[Ir(COD)Cl]_2$ with a chiral ligand in THF in the presence of $I_2$ additive. After 24 h, it was found that the employment of Ir complexes of electronic-withdrawing Cl–MeO-BIPHEP (**L1**), Difluorphos (**L2**) and P-Phos (**L3**) ligands furnished more than 90% conversions and excellent enantioselectivities (Table 1, entries 1–3), whereas using electronic-donating ligands (**L4** and **L5**) led to lower conversions and ee values (Table 1, entries 4–5). Of particular note is that the Ir-**L2** catalyst gave the highest enantioselectivity (94% ee) and a full conversion, and thus it was selected for further investigation.

Next the effect of solvent was investigated with an aim to further improve the enantioselectivity. The solvent screening indicated that the reaction exhibited strong solvent-dependency, and THF was the best choice in terms of both reactivity and enantioselectivity (Table 1, entries 2 *vs.* 6–10). The hydrogenation in other aprotic solvent, such as toluene, ether, $CH_2Cl_2$ and mixed THF and $CH_2Cl_2$ (v/v = 1/1) furnished unsatisfactory results (Table 1, entries 6–9). The use of methanol resulted in a much lower conversion and enantioselectivity (Table 1, entry 10). Decreasing the reaction temperature led to a slight increase in enantioselectivity (Table 1, entry 11). Slightly lower conversion and enantioselectivity was achieved at lower hydrogen pressure (Table 1, entry 12). In light of the remarkable impact of additives on catalytic performance in asymmetric hydrogenation of heteroaryl compounds,[3] we also examined the effect of NaI and HI (Table 1, entries 13–14). Neither of them worked as effectively as iodine. According to Zhou's recent report,[4f] it is believed that iodine could oxidize Ir(I) to form the highly active Ir(III) species. It is noticed that the catalytic performance is also related to the amount of additive $I_2$ (Table 1, entries 2 *vs.* 15–17). In the absence of any $I_2$, no reaction took place (Table 1, entry 15). Increasing the amount of $I_2$ to 10 mol% had no effect on both the reactivity and enantioselectivity, but the conversion was observed to decrease with 1.25 mol% $I_2$ (Table 1, entries 16–17). Similar observations have been reported by Fan and coworkers.[4k] Gratifyingly, it was noted that a high initial TOF of 3510 $h^{-1}$ was observed in the first 20 min (Table 1, entry 18). This result is better than Fan's GnDenBINAP.[4k] To further evaluate the efficiency of this catalyst system, the S/C ratio was increased to 20000, and the reaction ran well in the presence of a lower amount of $I_2$ with retained catalytic activity and enantioselectivity (Table 1, entry 19). It appeared that decreasing the amount of $I_2$ is favorable for high reactivity and enantioselectivity at low catalyst loading. It is worth noting that the reaction still proceeded smoothly under a very low catalyst

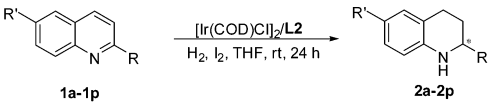
**Table 1** Asymmetric hydrogenation of quinaldine (**1a**) catalyzed by $[Ir(COD)Cl]_2$ and chiral biaryl diphosphine ligands[a]




| Entry | Solvent | L* | $I_2$ (mol%) | S/C | Conv. (%)[b] | Ee (%)[c] |
|---|---|---|---|---|---|---|
| 1 | THF | **L1** | 2.5 | 10000 | 93 | 91 (*R*) |
| 2 | THF | **L2** | 2.5 | 10000 | 100 | 94 (*R*) |
| 3 | THF | **L3** | 2.5 | 10000 | 100 | 91 (*R*) |
| 4 | THF | **L4** | 2.5 | 10000 | 61 | 80 (*R*) |
| 5 | THF | **L5** | 2.5 | 10000 | 78 | 89 (*R*) |
| 6 | toluene | **L2** | 2.5 | 10000 | 12 | 56 (*R*) |
| 7 | $Et_2O$ | **L2** | 2.5 | 10000 | 15 | 65 (*R*) |
| 8 | $CH_2Cl_2$ | **L2** | 2.5 | 10000 | 2 | 8 (*R*) |
| 9 | THF–$CH_2Cl_2$(1/1) | **L2** | 2.5 | 10000 | 46 | 89 (*R*) |
| 10 | MeOH | **L2** | 2.5 | 10000 | 4 | 5 (*R*) |
| 11[d] | THF | **L2** | 2.5 | 10000 | 100 | 95 (*R*) |
| 12[e] | THF | **L2** | 2.5 | 10000 | 94 | 94 (*R*) |
| 13[f] | THF | **L2** | 2.5 | 10000 | 5 | 8 (*R*) |
| 14[g] | THF | **L2** | 2.5 | 10000 | 25 | 94 (*R*) |
| 15 | THF | **L2** | 0 | 10000 | < 1 | ND |
| 16 | THF | **L2** | 10 | 10000 | 100 | 94 (*R*) |
| 17 | THF | **L2** | 1.25 | 10000 | 95 | 94 (*R*) |
| 18[h] | THF | **L2** | 2.5 | 10000 | 11.7 | 94 (*R*) |
| 19[i] | THF | **L2** | 1.25 | 20000 | 100 | 94 (*R*) |
| 20[j] | THF | **L2** | 1.25 | 50000 | 86 | 92 (*R*) |

[a] Reaction conditions: **1a** (1 mmol), $[Ir(COD)Cl]_2$/ligand (0.5/1.1), $I_2$ (1.25–2.5 mol%), 1 mL solvent, $H_2$ (700 psi), rt, 24 h. [b] The conversions were determined by $^1H$ NMR and the enantioselectivities of products were determined by HPLC analysis with OJ-H column. [c] The absolute configuration was assigned by comparing the HPLC retention time with those reported in the literature data. [d] The reaction temperature is 0 °C. [e] The $H_2$ pressure is 200 psi. [f] NaI as the additive. [g] Aqueous HI as the additive. [h] The reaction time is 20 min. [i] 2 mmol **1a**. [j] 5 mmol **1a**.

**Table 2** Asymmetric hydrogenation of quinoline derivatives[a]



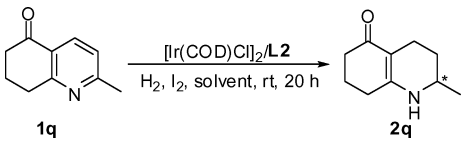

1a-1p 2a-2p

**a**: R = $CH_3$, R'= H; **b**: R = $C_2H_5$, R' = H; **c**: R = $nC_3H_7$, R' = H; **d**: R = $iC_3H_7$, R' = H; **e**: R = $nC_4H_9$, R' = H; **f**: R = $iC_4H_9$, R' = H; **g**: R = $nC_5H_{11}$, R' = H; **h**: R = cyclohexyl, R' = H; **i**: R = $CH_2CH_2C_6H_5$, R' = H; **j**: R = $CH_2CH_2CH{=}C(CH_3)_2$, R' = H; **k**: R = $CH_3$, R' = F; **l**: R = $CH_3$, R' = $OCH_3$; **m**: R = $CH_3$, R' = $CH_3$; **n**: R = $CH_2C(CH_3)_2OH$, R' = H; **o**: R = $CH_2(c\text{-}C_6H_{10})(OH)$, R' = H; **p**: R = $CH_2C(C_6H_5)_2OH$, R' = H;

| Entry | Substrate | S/C | Yield (%)[b] | Ee (%)[c], [d] |
|---|---|---|---|---|
| 1 | **1a** | 10000 | 99 | 94 (*R*) |
| 2 | **1b** | 10000 | 98 | 96 (*R*) |
| 3 | **1c** | 10000 | 98 | 94 (*R*) |
| 4 | **1d** | 10000 | 97 | 96 (*S*) |
| 5 | **1e** | 10000 | 96 | 94 (*R*) |
| 6 | **1f** | 10000 | 97 | 95 (*S*) |
| 7 | **1g** | 10000 | 98 | 96 (*R*) |
| 8 | **1h** | 10000 | 98 | 96 (*S*) |
| 9 | **1i** | 10000 | 99 | 96 (*R*) |
| 10 | **1j** | 10000 | 96 | 96 (*S*) |
| 11 | **1k** | 10000 | 99 | 85 (*R*) |
| 12 | **1l** | 2000 | 91 | 93 (*R*) |
| 13 | **1m** | 2000 | 99 | 92 (*R*) |
| 14 | **1n** | 2000 | 98 | 92 (*S*) |
| 15 | **1o** | 2000 | 98 | 95 (*S*) |
| 16 | **1p** | 2000 | 99 | 88 (*S*) |

[a] Reaction conditions: 0.3 mmol substrate, $I_2$ (2.5 mol% for **1a–k**; 5 mol% for **1l–p**), 0.6 mL degassed THF, $H_2$ (700 psi), rt, 24 h. [b] Isolated yield. [c] The enantioselectivities of product were determined by HPLC analysis with OJ-H (**2a–c, 2e, 2 g, 2l–m**), OD-H (**2d**, **2f**, **2h**, **2j**, **2k**, **2n**, **2p**), AS-H (**2i**) and OJ (**2o**) columns. [d] The absolute configurations were determined by comparison with the literature data.

**Table 3** Asymmetric hydrogenation of **1q** with Ir-**L2** catalyst[a]




1q 2q

| Entry | Solvent | $I_2$ (mol%) | Conv. (%)[b] | Ee (%)[c] |
|---|---|---|---|---|
| 1 | $CH_2Cl_2$ | 20 | 100 | 95 (*R*) |
| 2 | THF | 20 | 100 | 94 (*R*) |
| 3 | $ClCH_2CH_2Cl$ | 20 | 100 | 98 (*R*) |
| 4 | $MeOCH_2CH_2OMe$ | 20 | 100 | 91 (*R*) |
| 5 | toluene | 20 | 100 | 90 (*R*) |
| 6 | dioxane | 20 | 100 | 85 (*R*) |
| 7 | MeOH | 20 | 100 | 67 (*R*) |
| 8 | $ClCH_2CH_2Cl$ | 0 | < 1 | ND |
| 9 | $ClCH_2CH_2Cl$ | 15 | 100 | 98 (*R*) |
| 10 | $ClCH_2CH_2Cl$ | 10 | 100 | 95 (*R*) |
| 11[d] | $ClCH_2CH_2Cl$ | 15 | 100 | 98(*R*) |
| 12[e] | $ClCH_2CH_2Cl$ | 15 | 100 | 96 (*R*) |
| 13[f] | $ClCH_2CH_2Cl$ | 15 | 100 | 92 (*R*) |
| 14[g] | $ClCH_2CH_2Cl$ | 15 | 96 | 91 (*R*) |

[a] Reaction conditions: **1q** (0.15 mmol), $[Ir(COD)Cl]_2$ (0.5 mol%), **L2** (1.1 mol%), 0.7 mL degassed solvent, $H_2$ (700 psi), rt, 20 h. [b] The conversions were determined by $^1H$ NMR. [c] The enantioselectivities of the product were determined by HPLC analysis with OD-H column, and the absolute configurations were determined by comparison with the literature data. [d] The reaction was carried out at 0 °C. [e] S/C = 200. [f] S/C = 500. [g] S/C = 1000.

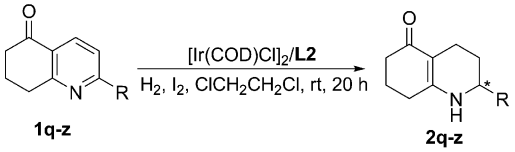
loading (S/C = 50000), giving 92% ee and 86% conversion with up to 43000 TON (Table 1, entry 20). In Fan's catalyst system, the use of dendritic support played a key role on the catalytic activity.[4k] Very recently, Zhou *et al.* found the introduction of bulky groups on the coordination phosphorous atoms of P,P and P,N ligands in Ir-catalyzed asymmetric hydrogenation of quinolines could also improve the catalytic activity.[4v] In comparison with the above-mentioned two examples, our current catalyst system required no modification of the chiral ligand, but attained the same or better level of productivity and higher enantioselectivity.

Under the optimal reaction conditions, a variety of 2-substituted quinoline derivatives were tested to examine the reaction scope at a low catalyst loading (0.05–0.01 mol%). As can be seen from Table 2, 2-alkylated quinolines could undergo smooth hydrogenation at a high S/C ratio of 10000, furnishing high isolated yields and excellent enantioselectivities irrespective of the length of the side chain (Table 2, entries 1–8). The best enantioselectivity of 96% was achieved with ethyl, isopropyl, pentyl, cyclohexyl and phenylethyl-substituted quinoline (Table 2, entries 2, 4, 7–9). Interestingly, the C=C double bond in the side chain of substrate **1j** was tolerated (Table 2, entry 10). A similar result has been reported by Xiao and coworkers under transfer hydrogenation conditions, but the S/C was only 100.[10e] The substrate possessing an electron-withdrawing group on the 6-position was more reactive than that with an electron-donating substituent. For example, hydrogenation of **1k** could result in a nearly quantitative yield with a high S/C ratio of 10000, albeit with a lower enantioselectivity of 85% (Table 2, entry 11). In the case of substrates **1l** and **1m**, a lower S/C ratio of 2000 was necessary to provide more than 90% yields and better enantioselectivities (Table 2, entries 12–13). The presence of a hydroxyl group at the side chain did not significantly disturb the catalytic performance, and nearly quantitative yields and good to excellent enantioselectivities were achieved at an S/C ratio of 2000 (Table 2, entries 14–16).

Encouraged by the excellent performance of Ir-**L2** catalyst in asymmetric hydrogenation of quinolines, we decided to investigate its application in the asymmetric hydrogenation of trisubstituted pyridines. So far there have been only two reports about enantioselective reduction of trisubstituted pyridines in the literature.[8f,11] Although good to excellent enantioselectivities have been reported, high catalyst loadings (2–5 mol%) were employed. We started our investigation by using **1q** as a model substrate with a catalyst loading of 1 mol%. The initial study aimed to investigate the effect of solvents on reactivity and enantioselectivity. From the data in Table 3, it can be seen that full conversion was achieved in all the tested solvents, but the enantioselectivities were different. Good to excellent ee values were achieved in aprotic solvents (Table 3, entries 1–6), and the reaction performed in $ClCH_2CH_2Cl$ turned out to be the most enantioselective (Table 3, entry 3). It should be noted that no reaction was observed in the absence of $I_2$ (Table 3, entry 8). When the amount of the additive $I_2$ was reduced to 15 mol%, the hydrogenation still proceeded smoothly with retained reactivity and enantioselectivity (Table 3, entry 9). Further decreasing the amount to 10 mol% resulted in the same conversion, but the enantioselectivity dropped to 95% (Table 3, entry 10). Accordingly, 15 mol% of $I_2$ was employed for further study. The reaction at lower temperature led to unchanged reactivity and enantioselectivity (Table 3,

**Table 4** Asymmetric hydrogenation of trisubstituted pyridine derivatives[a]




**q**: R = $CH_3$; **r**: R = $nC_3H_7$; **s**: R = $nC_5H_{11}$; **t**: R = $nC_6H_{13}$; **u**: R = $nC_7H_{15}$; **v**: R = $nC_8H_{17}$; **w**: R = $nC_{10}H_{21}$; **x**: R = $C_6H_5$; **y**: R = $CH_2C_6H_5$; **z**: R = $CH_2CH_2C_6H_5$

| Entry | Substrate | Yield (%)[b] | Ee (%)[c] |
|---|---|---|---|
| 1 | **1q** | 97 | 98 (*R*) |
| 2 | **1r** | 97 | 95 (*R*) |
| 3 | **1s** | 98 | 97 (*R*) |
| 4 | **1t** | 97 | 98 (*R*) |
| 5 | **1u** | 98 | 95 (*R*) |
| 6 | **1v** | 96 | 92 (*R*) |
| 7 | **1w** | 99 | 92 (*R*) |
| 8 | **1x** | 99 | 89 (*S*) |
| 9 | **1y** | 99 | 97 (*S*) |
| 10 | **1z** | 98 | 90 (*R*) |

[a] Reaction conditions: 0.15 mmol substrate, $[Ir(COD)Cl]_2$ (0.5 mol%), **L2** (1.1 mol%), $I_2$ (15 mol%), 0.7 mL degassed $ClCH_2CH_2Cl$, $H_2$ (700 psi), rt, 20 h. [b] Isolated yield. [c] The enantioselectivities of products were determined by HPLC analysis with OD-H (**2q–w, 2y–z**) and AS-H (**2x**) columns, and the absolute configurations were determined by comparison with literature data.

entry 11). Increasing the S/C ratio did not substantially affect the reactivity, but the enantioselectivity decreased gradually (Table 3, entries 9 *vs.* 12–14).

With the optimal conditions in hand, the application of Ir-**L2** was extended to the hydrogenation of a number of trisubstituted pyridines, and the results are listed in Table 4. The catalyst showed superb reactivity and enantioselectivity, and nearly quantitative yields and good to excellent enantioselectivities were achieved for all the substrates tested. The length of the side chain of 2-alkyl substituted substrates showed no obvious influence on the catalytic performance (Table 4 entries 1–7), but lower ee was obtained in the hydrogenation of aryl substituted substrate (Table 4 entry 8). Substrates with 2-benzyl and 2-phenethyl groups could also be successfully hydrogenated to give the corresponding products with high enantioselectivities (Table 4 entries 9–10). Compared to Zhou's Ir-**L3** catalyst (S/C = 50),[8f] the current catalyst system is more reactive (S/C = 100) with comparable or better chirality-inducing ability.

## Conclusions

In summary, we have shown that highly efficient asymmetric hydrogenation of quinoline derivatives could be carried out at high S/C ratios (2000–50000) by employing readily available $[Ir(COD)Cl]_2$/Difluorphos/$I_2$ catalyst system without recourse to tedious ligand modification, providing high yields and excellent enantioselectivities (up to 96%) with up to 3510 $h^{-1}$ TOF and up to 43000 TON. The same catalyst also showed superb reactivity and enantioselectivity in the hydrogenation of trisubstituted pyridines with nearly quantitative yields and up to 98% ee. The remarkable performance of the current catalyst system offers high potential for practical applications.

## Experimental

### General

Unless otherwise noted, all experiments were carried out under an atmosphere of nitrogen using standard Schlenk techniques or in a nitrogen-filled glovebox, and all commercially available chemicals were used as received from Aldrich, Acros or Strem without further purification. $^1H$ NMR and $^{13}C$ NMR spectra were recorded on a Bruker Model Avance DMX 400 Spectrometer ($^1H$ 400 MHz and $^{13}C$ 106 MHz, respectively). Chemical shifts ($\delta$) are given in ppm and are referenced to residual solvent peaks. Quinolines **2b–j**, **2n–p** were prepared according to the literature procedure.[4a,10e,12] Pyridine **2q** was synthesized according to the literature report.[13] All the organic solvents were dried using standard, published methods and were distilled before use.

### Typical procedure for asymmetric hydrogenation of quinolines

A mixture of $[Ir(COD)Cl]_2$ (1.0 mg, 0.0015 mmol) and the ligand (*R*)-Difluorophos (2.25 mg, 0.0033 mmol) in THF (2.0 mL) was stirred at room temperature for 10 min in a glovebox. The catalyst (40–200 μl) was transferred by a syringe to a stainless steel autoclave, in which $I_2$ and a quinoline substrate (0.3–5.0 mmol) in THF (0.6–10.0 mL) were placed beforehand. The hydrogenation was performed at room temperature under $H_2$ (700 psi) for 24 h. After carefully releasing the hydrogen, the reaction mixture was diluted with $CH_2Cl_2$ (5.0–20.0 mL) followed by the addition of saturated $Na_2CO_3$ aqueous solution (2.0–10.0 mL). After stirring for 15 min, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 3.0 mL). The combined organic layers were dried with $Na_2SO_4$ and concentrated in vacuum to give the crude product. Purification on a silica gel column gave the pure product. The enantiomeric excess was determined by HPLC with a chiral column (OJ-H, OD-H, or AS-H).

**(*R*)-2-Methyl-1,2,3,4-tetrahydroquinoline (2a)**[4a,10a,10c]**.** 94% ee, $[\alpha]_D^{20}$ = +83.1 (*c* 0.1, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 6.87–6.90 (m, 2H), 6.53 (t, 1H, *J* = 7.0 Hz), 6.40 (d, 1H, *J* = 8.0 Hz), 3.29–3.35 (m, 1H), 2.62–2.79 (m, 3H), 1.83–1.88 (m, 1H), 1.47–1.55 (m, 1H), 1.13 (d, 3H, *J* = 6.5 Hz); $^{13}C$ NMR (106.6 MHz, $CDCl_3$): $\delta$ 144.9, 129.5, 126.9, 121.4, 117.3, 47.4, 30.4, 26.8, 22.8; HRMS (ESI) calcd. for $C_{10}H_{14}N$ $[M + 1]^+$: 148.1126; found: 148.1131; HPLC (OJ-H, elute: hexane/*i*PrOH = 95/5, detector: 254 nm, flow rate: 0.5 ml $min^{-1}$), (*S*) $t_1$ = 25.6 min, (*R*) $t_2$ = 28.7 min.

**(*R*)-2-Ethyl-1,2,3,4-tetrahydroquinoline (2b)**[4a,10c]**.** 96% ee, $[\alpha]_D^{20}$ = +75.5 (*c* 0.1, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 6.99 (t, 2H, *J* = 7.52 Hz), 6.63 (t, 1H, *J* = 7.52 Hz), 6.51 (d, 1H, *J* = 8.01 Hz), 3.17–3.22 (m, 1H), 2.74–2.88 (m, 2H), 1.98–2.03 (m, 1H), 1.53–1.66 (m, 3H), 1.02 (t, 3H, *J* = 7.46 Hz); $^{13}C$ NMR (106.6 MHz, $CDCl_3$): $\delta$ 145.0, 129.5, 127.0, 121.7, 117.2, 114.3, 53.3, 29.7, 27.8, 26.7, 10.3; HRMS (ESI) calcd. for $C_{11}H_{16}N$ $[M + 1]^+$: 162.1283; found: 162.1286; HPLC (OJ-H, elute: hexane/*i*PrOH = 95/5, detector: 254 nm, flow rate: 0.5 ml $min^{-1}$), (*S*) $t_1$ = 22.1 min, (*R*) $t_2$ = 24.8 min.

**(*R*)-2-Propyl-1,2,3,4-tetrahydroquinoline (2c)[4a,10c].** 94% ee, $[\alpha]_D^{20} = +79.7$ (*c* 0.1, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 6.98 (t, 2H, $J = 7.51$ Hz), 6.62 (t, 1H, $J = 7.02$ Hz), 6.50 (d, 1H, $J = 8.01$ Hz), 3.25–3.29 (m, 1H), 2.72–2.87 (m, 2H), 1.95–2.00 (m, 1H), 1.58–1.67 (m, 1H), 1.42–1.53 (m, 4H), 0.99 (t, 3H, $J = 7.50$ Hz); $^{13}C$ NMR (106.6 MHz, $CDCl_3$): $\delta$ 144.9, 129.5, 126.9, 121.7, 117.2, 114.3, 51.6, 39.1, 28.4, 26.7, 19.2, 14.5; HRMS (ESI) calcd. for $C_{12}H_{18}N$ [M + 1]$^+$: 176.1439; found: 176.1443; HPLC (OJ-H, elute: hexane/*i*PrOH = 95/5, detector: 254 nm, flow rate: 0.5 ml min$^{-1}$), (*S*) $t_1 = 20.3$ min, (*R*) $t_2 = 26.4$ min.

**(*S*)-2-Isopropyl-1,2,3,4-tetrahydroquinoline (2d)[4a,10c].** 96% ee, $[\alpha]_D^{20} = +26.6$ (*c* 0.1, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 6.95 (t, $J = 7.7$ Hz, 2H), 6.58 (t, $J = 7.3$ Hz, 1H), 6.47 (d, $J = 7.7$ Hz, 1H), 3.77 (brs, 1H), 3.05–3.01 (m, 1H), 2.84–2.69 (m, 2H), 1.94–1.88 (m, 1H), 1.74–1.60 (m, 2H), 0.98 (dd, $J = 10.5$, 6.7 Hz, 6H); $^{13}C$ NMR (106.6 MHz, $CDCl_3$) $\delta$ 145.4, 129.6, 127.1, 121.8, 117.1, 114.4, 57.7, 32.9, 27.1, 24.9, 19.0, 18.7; HRMS (ESI) calcd. for $C_{12}H_{18}N$ [M + 1]$^+$: 176.1439, found 176.1439; HPLC (OD-H, elute: hexane/*i*PrOH = 98/2, detector: 254 nm, flow rate: 0.5 ml min$^{-1}$), (*S*) $t_1 = 18.4$ min, (*R*) $t_2 = 34.6$ min.

**(*R*)-2-Butyl-1,2,3,4-tetrahydroquinoline (2e)[4a,10a,10c].** 94% ee, $[\alpha]_D^{20} = +82.3$ (*c* 0.1, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 6.98 (t, 2H, $J = 7.51$ Hz), 6.62 (t, 1H, $J = 7.02$ Hz), 6.50 (d, 1H, $J = 8.01$ Hz), 3.27–3.31 (m, 1H), 2.73–2.89 (m, 2H), 1.97–2.00 (m, 1H), 1.60–1.65 (m, 1H), 1.51–1.53 (m, 2H), 1.37–1.46 (m, 4H), 0.97 (t, 3H, $J = 7.50$ Hz); $^{13}C$ NMR (106.6 MHz, $CDCl_3$): $\delta$ 145.0, 129.5, 126.9, 121.7, 117.2, 114.3, 51.8, 36.7, 28.4, 26.7, 23.1, 14.4; HRMS (ESI) calcd. for $C_{13}H_{20}N$ [M + 1]$^+$: 190.1596; found: 190.1598; HPLC (OJ-H, elute: hexane/*i*PrOH = 95/5, detector: 254 nm, flow rate: 0.5 ml min$^{-1}$), (*S*) $t_1 = 17.7$ min, (*R*) $t_2 = 21.1$ min.

**(*S*)-2-Isobutyl-1,2,3,4-tetrahydroquinoline (2f)[10c].** 95% ee, $[\alpha]_D^{20} = +54.5$ (*c* 0.1, $CHCl_3$). $^1H$ NMR ($CDCl_3$,400 MHz): $\delta$ 6.97–6.93 (m, 2H), 6.59 (t, $J = 7.3$ Hz, 1H), 6.46 (d, $J = 8.2$ Hz, 1H), 3.73 (brs, 1H), 3.35–3.28 (m, 1H), 2.86–2.69 (m, 2H), 1.97–1.90 (m, 1H), 1.80–1.72 (m,1H), 1.62–1.53 (m, 1H), 1.43–1.29 (m, 2H), 0.94 (d, $J = 6.5$ Hz, 6H); $^{13}C$ NMR (106.6 MHz, $CDCl_3$): $\delta$ 145.1, 129.7, 127.1, 121.8, 117.4, 114.5, 49.7, 46.3, 29.0, 26.9, 24.9,23.6, 22.9; HRMS (ESI) calcd. For $C_{13}H_{20}N$ [M + 1]$^+$: 190.1596; found: 190.1599; HPLC (OD-H, elute: hexane/*i*PrOH = 98/2, detector: 254 nm, flow rate: 0.5 ml min$^{-1}$): (*S*) $t_1 = 18.2$ min, (*R*) $t_2 = 27.2$ min.

**(*R*)-2-Pentyl-1,2,3,4-tetrahydroquinoline (2g)[4a,10a,10c].** 96% ee, $[\alpha]_D^{20} = +79.2$ (*c* 0.1, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 6.88 (t, 2H, $J = 7.01$ Hz), 6.52 (t, 1H, $J = 7.52$ Hz), 6.40 (d, 1H, $J = 8.01$ Hz), 3.13–3.18 (m, 1H), 2.62–2.77 (m, 2H), 1.86–1.91 (m, 1H), 1.48–1.56 (m, 1H), 1.18–1.43 (m, 9H), 0.83 (t, 3H, $J = 6.50$ Hz); $^{13}C$ NMR (106.6 MHz, $CDCl_3$): $\delta$ 145.0, 129.5, 126.9, 121.7, 117.2, 114.3, 51.9, 36.9, 32.2, 28.4, 26.7, 25.7, 22.9, 14.3; HRMS (ESI) calcd. for $C_{14}H_{22}N$ [M + 1]$^+$: 204.1752; found: 204.1757; HPLC (OJ-H, elute: hexane/*i*PrOH = 95/5, detector: 254 nm, flow rate: 0.5 ml min$^{-1}$), (*S*) $t_1 = 15.7$ min, (*R*) $t_2 = 17.3$ min.

**(*S*)-2-Cyclohexyl-1,2,3,4-tetrahydroquinoline (2h)[10c].** 96% ee, $[\alpha]_D^{20} = +48.3$ (*c* 0.1, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 6.97–6.93 (m, 2H), 6.58 (t, $J = 7.3$ Hz, 1H), 6.46 (d, $J = 7.7$ Hz, 1H), 3.81 (brs, 1H), 3.05–3.01 (m, 1H), 2.82–2.68 (m, 2H), 1.95–1.63 (m, 7H), 1.41–0.97 (m, 6H); $^{13}C$ NMR (106.6 MHz, $CDCl_3$): $\delta$ 145.4, 129.6, 127.1, 121.9, 117.1, 114.4, 57.0, 42.9, 29.6, 29.2, 27.0, 26.9, 26.8, 26.7, 25.0; HRMS (ESI) calcd. for $C_{15}H_{22}N$ [M + 1]$^+$: 216.1752; found 216.1758; HPLC (OD-H, elute: hexane/*i*PrOH = 98/2, detector: 254 nm, flow rate: 0.5 ml min$^{-1}$), (*S*) $t_1 = 18.4$ min, (*R*) $t_2 = 26.0$ min.

**(*R*)-2-Phenethyl-1,2,3,4-tetrahydroquinoline (2i)[4a,10a].** 96% ee, $[\alpha]_D^{20} = +73.1$ (*c* 0.1, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 7.38 (t, 2H, $J = 6.5$ Hz), 7.28 (t, 3H, $J = 6.50$ Hz), 7.04 (t, 2H, $J = 8.01$ Hz), 6.69 (t, 1H, $J = 7.50$ Hz), 6.53 (d, 1H, $J = 8.50$ Hz), 3.34–3.39 (m, 1H), 2.79–2.92 (m, 4H), 2.05–2.08 (m, 1H), 1.86–1.96 (m, 2H), 1.71–1.79 (m, 1H); $^{13}C$ NMR (106.6 MHz, $CDCl_3$): $\delta$ 144.7, 142.2, 129.6, 128.9, 128.8, 128.7, 127.1, 126.3, 121.7, 117.4, 114.6, 51.5, 38.5, 32.5, 28.3, 26.5; HRMS (ESI) calcd. for $C_{17}H_{20}N$ [M + 1]$^+$: 238.1596; found: 238.1602; HPLC (AS-H, elute: hexane/*i*PrOH = 90/10, detector: 254 nm, flow rate: 1.0 ml min$^{-1}$), (*S*) $t_1 = 18.8$ min, (*R*) $t_2 = 20.5$ min.

**(*S*)-2-(4-Methylpent-3-enyl)-1,2,3,4-tetrahydroquinoline (2j)[10c].** 97% ee, $[\alpha]_D^{20} = +56.7$ (*c* 0.1, $CHCl_3$). $^1H$ NMR ($CDCl_3$, 400 MHz): $\delta$ 6.97–6.93 (m, 2H), 6.59 (t, $J = 7.4$ Hz, 1H), 6.45 (d, $J = 8.3$ Hz, 1H), 5.16–5.13 (m, 1H), 3.79 (brs, 1H), 3.28–3.22 (m, 1H), 2.85–2.69 (m, 2H), 2.13–2.07 (m, 2H), 1.99–1.92 (m, 1H), 1.70 (s, 3H), 1.66–1.50 (m, 6H); $^{13}C$ NMR (106.6 MHz, $CDCl_3$): $\delta$ 145.1, 132.5, 129.7, 127.1, 124.4, 121.8, 117.4, 114.5, 51.7, 37.0, 28.5, 26.8, 26.2, 24.8, 18.2; HRMS (ESI) calcd. for $C_{15}H_{22}N$ [M + 1]$^+$: 216.1752; found: 216.1752; HPLC (OD-H, elute: hexane/*i*PrOH = 98/2, detector: 254 nm, flow rate: 0.5 ml min$^{-1}$): (*S*) $t_1 = 18.0$ min, (*R*) $t_2 = 23.5$ min.

**(*R*)-6-Fluoro-2-methyl-1,2,3,4-tetrahydroquinoline (2k)[4a,10c].** 85% ee, $[\alpha]_D^{20} = +72.8$ (*c* 0.1, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 6.64–6.70 (m, 2H), 6.37–6.42 (m, 1H), 3.29–3.49 (m, 1H), 2.79–2.88 (m, 1H), 2.68–2.75 (m, 1H), 1.90–1.95 (m, 1H), 1.53–1.61 (m, 1H), 1.21 (d, 3H, $J = 6.00$ Hz); $^{13}C$ NMR (106.6 MHz, $CDCl_3$): $\delta$ 156.7, 154.8, 141.2, 122.7, 115.7, 115.5, 115.0, 114.9, 113.5, 113.3, 47.5, 30.1, 26.9, 22.7; HRMS (ESI) calcd. for $C_{10}H_{13}NF$ [M + 1]$^+$: 166.1032; found: 166.1036; HPLC (OD-H, elute: hexane/*i*PrOH = 94/6, detector: 254 nm, flow rate: 1.0 ml min$^{-1}$), (*S*) $t_1 = 5.2$ min, (*R*) $t_2 = 6.4$ min.

**(*R*)-6-Methoxy-2-methyl-1,2,3,4-tetrahydroquinoline (2l)[4a,10c].** 93% ee, $[\alpha]_D^{20} = +70.4$ (*c* 0.1, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 6.51 (t, 2H, $J = 8.50$ Hz), 6.39 (d, 1H, $J = 8.50$ Hz), 3.65 (s, 3H), 3.24–3.28 (m, 1H), 2.73–2.80 (m, 1H), 2.61–2.66 (m, 1H), 1.82–1.87 (m, 1H), 1.46–1.54 (m, 1H), 1.13 (d, 3H, $J = 6.00$ Hz); $^{13}C$ NMR (106.6 MHz, $CDCl_3$): $\delta$ 152.2, 139.0, 122.9, 115.7, 114.9, 113.1, 56.0, 47.76, 30.5, 27.1, 22.7; HRMS (ESI) calcd. for $C_{11}H_{16}NO$ [M + 1]$^+$: 178.1232; found: 178.1239; HPLC (OJ-H, elute: hexane/*i*PrOH = 90/10, detector: 254 nm, flow rate: 0.5 ml min$^{-1}$), (*S*) $t_1 = 35.2$ min, (*R*) $t_2 = 42.7$ min.

**(*R*)-2,6-Dimethyl-1,2,3,4-tetrahydroquinoline (2m)[4a,10c].** 92% ee, $[\alpha]_D^{20} = +82.7$ (*c* 0.1, $CHCl_3$). $^1H$ NMR (400 MHz, $CDCl_3$): $\delta$ 6.80 (d, 2H, $J = 8.01$ Hz), 6.43 (d, 1H, $J = 8.01$ Hz), 3.36–3.40 (m, 1H), 2.69–2.87 (m, 2H), 2.23 (s, 3H), 1.91–1.96 (m, 1H), 1.56–1.64 (m, 1H), 1.22 (d, 3H, $J = 6.50$ Hz); $^{13}C$ NMR (106.6 MHz, $CDCl_3$): $\delta$ 142.6, 130.1, 127.5, 126.6, 121.5, 114.5, 47.6, 30.6, 26.8, 22.8, 20.7; HRMS (ESI) calcd. for $C_{11}H_{16}N$ [M + 1]$^+$: 162.1283; found: 162.1288; HPLC (OJ-H, elute: hexane/*i*PrOH = 90/10,

detector: 254 nm, flow rate: 0.5 ml min$^{-1}$), (*S*) $t_1 = 24.2$ min, (*R*) $t_2 = 29.8$ min.

**(*S*)-2-Methyl-1-(1,2,3,4-tetrahydroquinolin-2-yl)-propan-2-ol (2n)[4a].** 92% ee, $[\alpha]_D^{20} = +48.1$ (*c* 0.1, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.88 (t, 2H, $J = 7.50$ Hz), 6.53 (t, 1H, $J = 7.50$ Hz), 6.43 (d, 1H, $J = 8.01$ Hz), 3.48–3.52 (m, 1H), 2.77–2.84 (m, 1H), 2.63–2.68 (m, 2H), 1.75–1.80 (m, 1H), 1.50–1.69 (m, 3H), 1.25 (d, 7H, $J = 5.50$ Hz); $^{13}$C NMR (106.6 MHz, $CDCl_3$): $\delta$ 144.6, 129.5, 127.0, 121.3, 117.2, 114.9, 72.2, 49.1, 48.6, 33.0, 30.0, 28.0, 26.8; HRMS (ESI) calcd. for $C_{13}H_{20}NO$ [M + 1]$^+$ : 206.1545: found: 206.1549; HPLC (OD-H, elute: hexane/*i*PrOH = 94/6, detector: 254 nm, flow rate: 1.0 ml min$^{-1}$), (*S*) $t_1 = 9.0$ min, (*R*) $t_2 = 11.1$ min.

**(*S*)-1-(1,2,3,4-Tetrahydroquinolin-2-ylmethyl)-cyclohexanol (2o)[4a].** 95% ee, $[\alpha]_D^{20} = +38.5$ (*c* 0.1, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 6.87 (t, 2H, $J = 8.50$ Hz), 6.52 (t, 1H, $J = 8.50$ Hz), 6.42 (d, 1H, $J = 7.51$ Hz), 3.48–3.53 (m, 1H), 2.76–2.83 (m, 1H), 2.63–2.68 (m, 1H), 1.74–1.79 (m, 1H), 1.38–1.68 (m, 13H), 1.23–1.27 (m, 1H); $^{13}$C NMR (106.6 MHz, $CDCl_3$): $\delta$ 144.7, 129.5, 126.9, 121.3, 117.1, 114.8, 72.8, 48.1, 47.4, 40.8, 36.0, 30.1, 26.8, 26.0, 22.5, 22.4; HRMS (ESI) calcd. for $C_{16}H_{24}NO$ [M + 1]$^+$: 246.1858: found: 246.1861; HPLC (OJ, elute: hexane/*i*PrOH = 85/15, detector: 254 nm, flow rate: 1.0 ml min$^{-1}$), (*S*) $t_1 = 5.1$ min, (*R*) $t_2 = 7.9$ min.

**(*S*)-1,1-Diphenyl-2-(1,2,3,4-tetrahydroquinolin-2-yl)ethanol (2p)[4a,4k].** 88% ee, $[\alpha]_D^{20} = +95.8$ (*c* 0.1, $CHCl_3$). $^1$H NMR (400 MHz, $CDCl_3$): $\delta$ 7.45–7.50 (m, 4H), 7.30–7.39 (m, 4H), 7.26–7.29 (m, 2H), 6.95–7.00 (m, 2H), 6.66 (t, 1H, $J = 7.5$ Hz), 6.44 (d, 1H, $J = 8.0$ Hz), 4.14–4.18 (m, 1H), 3.33–3.38 (m, 1H), 2.74–2.79 (m, 2H), 2.51 (d, 2H, $J = 5.0$ Hz), 1.74–1.84 (m, 2H), 1.29–1.34 (m, 1H) ppm; $^{13}$C NMR (106.6 MHz, $CDCl_3$): $\delta$ 148.5, 146.7, 144. 6, 129.9, 129.0, 128.9, 127.9, 127.5, 127.3, 126.7, 126.6, 122.2, 118.1, 116.0, 79.5, 48.9, 47.6, 29.9, 26.4; HRMS (ESI) calcd. for $C_{23}H_{24}NO$ [M + 1]$^+$: 330.1858; found 330.1855; HPLC (OD-H, elute: hexane/*i*PrOH = 94/6, detector: 254 nm, flow rate: 1.0 ml min$^{-1}$), (*S*) $t_1 = 12.1$ min, (*R*) $t_2 = 14.5$ min.

### Typical procedure for asymmetric hydrogenation of pyridine derivatives

A mixture of $[Ir(COD)Cl]_2$ (1.0 mg, 0.0015 mmol) and (*R*)-Difluorophos (2.25 mg, 0.0033 mmol) in $ClCH_2CH_2Cl$ (2.0 ml) was stirred at room temperature for 10 min in a glovebox. The catalyst was transferred by a syringe to a stainless steel autoclave, in which $I_2$ (11.4 mg, 0.045 mmol) and a pyridine substrate (0.3 mmol) were placed beforehand. The hydrogenation was performed at room temperature under $H_2$ (700 psi) for 20 h. After carefully releasing the hydrogen gas, the reaction mixture was diluted with $CH_2Cl_2$ (5.0 mL) followed by the addition of saturated $Na_2CO_3$ aqueous solution (2.0 mL). After stirring for 15 min, the aqueous layer was extracted with $CH_2Cl_2$ (3 × 3.0 mL). The combined organic layers were dried with $Na_2SO_4$ and concentrated under vacuum to give the crude product. Purification on an $Al_2O_3$ column gave the pure product. The enantiomeric excess was determined by HPLC with a chiral column (OD-H, or AS-H).

**(2*R*)-2-Methyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one (2q).** 98% ee, $[\alpha]_D^{24} = +259.1$ (*c* 0.05, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.82 (br, 1H), 3.53–3.54 (m, 1H), 2.60–2.63 (m, 2H), 2.40–2.47 (m, 3H), 2.16–2.23 (m, 1H), 1.81–1.90 (m, 3H), 1.40–1.45 (m, 1H), 1.29–1.31 (m, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 189.8, 168.0, 104.2, 48.8, 33.8, 29.8, 28.8, 21.9, 21.7, 18.4; HRMS (ESI) calcd. for $C_{10}H_{16}NO$ [M + H]$^+$: 166.1232; found: 166.1235; HPLC (OD-H, elute: hexane/*i*PrOH = 90/10, detector: 254 nm, flow rate: 1 mL min$^{-1}$), (*R*) $t_1 = 12.6$ min, (*S*) $t_2 = 15.4$ min.

**(2*R*)-2-Propyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one (2r)[11].** 95% ee, $[\alpha]_D^{24} = +263.5$ (*c* 0.06, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.36 (br, s, 1H), 3.22–3.23 (m, 1H), 2.47–2.52 (m, 1H), 2.26–2.34 (m, 4H), 2.15–2.23 (m, 1H), 1.86–1.96 (m, 3H), 1.36–1.48 (m, 5H), 0.93–0.97 (m, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 195.2, 159.1, 106.0, 52.1, 38.7, 37.2, 30.3, 27.8, 22.3, 19.6, 19.1, 14.8; HRMS (ESI) calcd. for $C_{12}H_{20}O$ [M + H]$^+$: 194.1545, found: 194.1553; HPLC (OD-H, elute: hexane/*i*PrOH = 90/10, detector: 254 nm, flow rate: 1 mL min$^{-1}$), (*R*) $t_1 = 11.0$ min, (*S*) $t_2 = 14.9$ min.

**(2*R*)-2-Pentyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one (2s)[11].** 97% ee, $[\alpha]_D^{24} = +194.6$ (*c* 0.05, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.43 (br, s, 1H), 3.20–3.21 (m, 1H), 2.46–2.52 (dt, 1H, $J = 5.10$, 16.18 Hz), 2.26–2.34 (m, 4H), 2.15–2.23 (m, 1H), 1.85–1.95 (m, 3H), 1.29–1.49 (m, 9H), 0.87–0.91 (m, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 195.2, 159.2, 105.9, 52.4, 37.2, 36.5, 32.5, 30.3, 27.8, 26.1, 23.3, 22.5, 19.1, 14.8; HRMS (ESI) calcd. for $C_{14}H_{24}NO$ [M + H]$^+$: 222.1858, found: 222.1866; HPLC (OD-H, elute: hexane/*i*PrOH = 90/10, detector: 254 nm, flow rate: 1 mL min$^{-1}$), (*R*) $t_1 = 9.5$ min, (*S*) $t_2 = 12.3$ min.

**(2*R*)-2-Hexyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one (2t).** 98% ee, $[\alpha]_D^{24} = +216.3$ (*c* 0.05, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.94 (br, s, 1H), 3.19–3.21 (m, 1H), 2.46–2.51 (dt, 1H, $J = 4.78$, 16.30 Hz), 2.26–2.33 (m, 4H), 2.17–2.23 (m, 1H), 1.86–1.95 (m, 3H), 1.28–1.46 (m, 11H), 0.86–0.88 (m, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 195.13, 159.1, 105.9, 52.4, 37.2, 36.5, 32.5, 30.3, 30.0, 27.8, 26.4, 23.3, 22.5, 19.1, 14.8; HRMS (ESI) calcd. for $C_{15}H_{26}NO$ [M + H]$^+$: 236.2014; found: 236.2021; HPLC (OD-H, elute: hexane/*i*PrOH = 90/10, detector: 254 nm, flow rate: 1.0 mL min$^{-1}$), (*R*) $t_1 = 9.2$ min, (*S*) $t_2 = 12.0$ min.

**(2*R*)-2-Heptyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one (2u).** 95% ee, $[\alpha]_D^{24} = +201.5$ (*c* 0.1, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.61 (br, s, 1H), 3.18–3.20 (m, 1H), 2.44–2.49 (dt, 1H, $J = 5.04$, 16.18 Hz), 2.14–2.32 (m, 5H), 1.84–1.93 (m, 3H), 1.16–1.47 (m, 13H), 0.84–0.88 (m, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 195.1, 159.3, 105.8, 52.4, 37.3, 36.5, 32.5, 30.3, 30.2, 30.0, 27.8, 26.4, 23.4, 22.5, 19.1, 14.8; HRMS (ESI) calcd. for $C_{16}H_{28}NO$ [M + H]$^+$: 250.2171; found: 250.2177; HPLC (OD-H, elute: hexane/*i*PrOH = 90/10, detector: 254 nm, flow rate: 1.0 mL min$^{-1}$), (*R*) $t_1 = 9.1$ min, (*S*) $t_2 = 11.8$ min.

**(2*R*)-2-Octyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one (2v).** 92% ee, $[\alpha]_D^{24} = +162.8$ (*c* 0.06, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.62 (br, s, 1H), 3.18–3.20 (m, 1H), 2.44–2.49 (dt, 1H, $J = 4.95$, 16.16 Hz), 2.14–2.32 (m, 5H), 1.84–1.93 (m, 3H), 1.25–1.47 (m, 15H), 0.84–0.88 (m, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 195.1, 159.3, 105.8, 52.4, 37.3, 36.5, 30.4, 30.3, 30.2, 30.0, 27.8, 26.4, 23.4, 22.5, 19.1, 14.9; HRMS (ESI) calcd. for $C_{17}H_{30}NO$ [M + H]$^+$: 264.2327; found: 264.2336; HPLC (OD-H, elute: hexane/*i*PrOH = 90/10, detector: 254 nm, flow rate: 1.0 mL min$^{-1}$), (*R*) $t_1 = 8.7$ min, (*S*) $t_2 = 11.4$ min.

**(2*R*)-2-Decyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one (2w)[11].** 92% ee, $[\alpha]_D^{24} = +112.7$ (*c* 0.06, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 4.43 (br, s, 1H), 3.19–3.21 (m, 1H), 2.47–2.51 (dt, 1H, $J = 4.86, 16.08$ Hz), 2.26–2.33 (m, 4H), 2.19–2.21 (m, 1H), 1.86–1.95 (m, 3H), 1.25–1.48 (m, 19H), 0.85–0.89 (m, 3H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 195.2, 159.2, 106.0, 52.4, 37.3, 36.6, 32.7, 30.41, 30.39, 30.35, 30.33, 30.1, 27.9, 26.5, 23.5, 22.6, 19.2, 14.9; HRMS (ESI) calcd. for $C_{19}H_{34}NO$ [M + H]$^+$: 292.2640, found: 292.2646; HPLC (OD-H, elute: hexane/*i*PrOH = 90/10, detector: 254 nm, flow rate: 1.0 mL min$^{-1}$), (*R*) $t_1 = 8.2$ min, (*S*) $t_2 = 10.8$ min.

**(2*S*)-2-Phenyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one (2x).** 89% ee, $[\alpha]_D^{24} = +199.1$ (c 0.05, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.25–7.38 (m, 5H), 4.96 (br, s, 1H), 4.38–4.40 (m, 1H), 2.32–2.42 (m, 6H), 1.95–2.06 (m, 3H), 1.79–1.83 (m, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 195.3, 159.5, 143.5, 129.5, 128.6, 127.1, 105.9, 56.7, 37.3, 30.7, 30.1, 22.6, 18.8; HRMS (ESI) calcd. for $C_{15}H_{18}NO$ [M + H]$^+$: 228.1388, found: 228.1385; HPLC (AS-H, elute: hexane/*i*PrOH = 80/20, detector: 254 nm, flow rate: 1.0 mL min$^{-1}$), (*S*) $t_1 = 29.4$ min, (*R*) $t_2 = 38.6$ min.

**(2*S*)-2-Benzyl-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one (2y).** 97% ee, $[\alpha]_D^{24} = +107.8$ (*c* 0.05, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.33–7.37 (m, 2H), 7.26–7.29 (m, 1H), 7.19–7.21 (m, 2H), 4.51 (br, s, 1H), 3.49–3.51 (m, 1H), 2.84–2.89 (dd, 1H, $J =$ 5.6, 13.46 Hz), 2.67–2.72 (dd, 1H, $J = 8.82, 13.44$ Hz), 2.51–2.58 (dt, 1H, $J = 5.36, 16.16$ Hz), 2.21–2.35 (m, 5H), 1.90–1.98 (m, 3H), 1.55–1.60 (m, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 195.3, 159.0, 138.4, 129.9, 129.6, 127.6, 106.0, 53.35, 42.8, 37.3, 30.2, 27.9, 22.5, 18.9; HRMS (ESI) calcd. for $C_{16}H_{20}NO$ [M + H]$^+$: 242.1545, found: 242.1550; HPLC (OD-H, elute: hexane/*i*PrOH = 90/10, detector: 254 nm, flow rate: 1.0 mL min$^{-1}$), (*R*) $t_1 = 22.2$ min, (*S*) $t_2 = 24.9$ min.

**(2*R*)-2-(2-Phenylethyl)-2,3,4,6,7,8-hexahydroquinolin-5(1*H*)-one (2z)[11].** 90% ee, $[\alpha]_D^{24} = +209.5$ (*c* 0.1, $CH_2Cl_2$). $^1$H NMR (400 MHz, $CDCl_3$) $\delta$ 7.18–7.31 (m, 5H), 4.40 (br, s, 1H), 3.26–3.28 (m, 1H), 2.66–2.79 (m, 1H), 2.44–2.50 (dt, 1H, $J = 5.36, 16.15$ Hz), 2.29–2.32 (m, 2H), 2.18–2.26 (m, 3H), 1.79–1.92 (m, 5H), 1.50–1.54 (m, 1H); $^{13}$C NMR (100.6 MHz, $CDCl_3$) $\delta$ 195.2, 159.0, 142.1, 129.4, 129.1, 127.0, 105.9, 52.0, 37.9, 37.3, 33.0, 30.2, 27.7, 22.5, 18.8; HRMS (ESI) calcd. for $C_{17}H_{22}NO$ [M + H]$^+$: 256.1701, found: 256.1708; HPLC (OD-H, elute: hexane/*i*PrOH = 80/20, detector: 254 nm, flow rate: 1.0 mL min$^{-1}$), (*R*) $t_1 = 10.1$ min, (*S*) $t_2 = 12.1$ min.

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