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PAPER

Highly regio-, diastereo- and enantioselective one-pot gold/chiral Brønsted acid-catalysed cascade synthesis of bioactive diversely substituted tetrahydroquinolines†

Xin-Yuan Liu, Ya-Ping Xiao, Fung-Ming Siu, Li-Chen Ni, Yong Chen, Lin Wang and Chi-Ming Che*

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One-pot sequential asymmetric reactions of aminobenzaldehydes or aminophenones with alkynes catalysed by a gold(I)/Brønsted acid cooperative system are reported. This process provides a highly efficient method for the synthesis of optically active tetrahydroquinolines, with one or two chiral centres at different positions as well as highly divergent functional groups, in good to excellent yields and with high regio-, diastereo- and enantioselectivities. A preliminary study on the effect of stereochemistry on biological activity suggests a potential application of these optically active tetrahydroquinolines in drug discovery processes.

Introduction

Chiral tetrahydroquinolines with multiple chiral centres and functional substituents are ubiquitous structural motifs in numerous naturally occurring alkaloids and biologically active pharmaceuticals.[1] For example (Fig. 1), (*S*)-flumequine exhibits potent antibacterial activity and is used for treating bacterial infections.[1e] Martinella alkaloids, containing multiple-chiral tetrahydroquinoline scaffold, are bradykinin receptor antagonists.[1b] Dynemicin A (a member of the enediyne family of antibiotics), isolated from a fermentation broth of *Micromonospora chersina*, has anticancer activity in a number of cancer cell lines.[1d] The significant biological activities of these enantiomerically pure backbones have led to a demand for efficient protocols for their synthesis.[2]

The asymmetric reductions of quinolines using transition metal catalysts[3] or organocatalysts[4] are powerful methods widely used to synthesize chiral tetrahydroquinolines. Most of these methods are mainly applied to 2- or 3-substituted quinolines, thus giving products with only one chiral centre.[3,4] Enantio-enriched tetrahydroquinolines bearing two chiral centres could be synthesized diastereoselectively either by asymmetric hydrogenation or transfer hydrogenation of 2,3-disubstituted quinolines,[3h–j,4f,g] but the 2,3-substituents in these products are limited to "hard-to-remove" aliphatic or aryl groups lacking functionality. 2,3-Disubstituted quinolines with reducible groups, such as carbonyls, remain challenging substrates for such asymmetric reduction, although these functional molecules are valuable building blocks for further synthetic transformations. To the best of our knowledge, there are no reports describing asymmetric reduction of 2,4-disubstituted quinolines with high diastereo- and enantioselectivities. On the other hand, a general limitation for the existing asymmetric quinoline reduction systems with transition metal catalysts[3] or organocatalysts[4] is the requirement of prior preparation of starting quinolines by tedious chemical resolution.[5] The overall atom economy of such reduction systems could be increased through cascade processes.[6] Therefore, the development of new cascade reactions employing simple and readily available starting materials for construction of chiral diversely substituted tetrahydroquinolines through simultaneous formation of two chiral centres at different positions with readily transformable functional groups and with high diastereo- and enantioselectivity would be highly desirable.

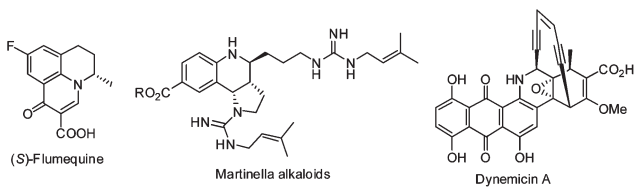

Fig. 1 Examples of biologically active chiral tetrahydroquinoline derivatives.

Cooperative catalysis combining transition metal catalysis and organocatalysis can lead to new strategies to use readily available precursors for rapid synthesis of organic compounds with

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†Electronic supplementary information (ESI) available: Tables S1 and S2, Chart S1, and ^{1}H NMR, ^{13}C NMR and HPLC spectra. CCDC 812057 (**3Dm**) and 812056 (**3Nb**). For ESI and crystallographic data in CIF or other electronic format see DOI: 10.1039/c2ob25753j

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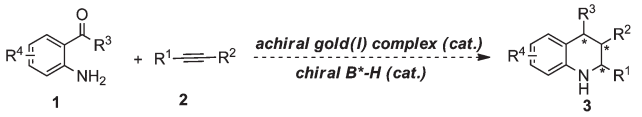


Scheme 1 Regio-, diastereo- and enantioselective one-pot reactions catalysed by a cooperative catalytic system composed of a gold(I) complex and chiral Brønsted acid.

complexity.[7,8] The cooperation of homogeneous gold catalysts[9] with organocatalysts has been shown to be an efficient approach for a variety of organic transformations.[10,11,12d] During our studies on gold-catalysed cascade reactions,[12] we recently reported a method for preparing highly substituted quinolines from 2-aminophenones and alkynes.[12a] We envisioned that a one-pot reaction could be established by starting with a gold-catalysed cascade reaction of 2-aminobenzaldehyde or 2-aminophenone with *alkyne*, to furnish a quinoline intermediate, which should undergo asymmetric transfer hydrogenation with a Hantzsch ester (HEH) catalysed by chiral Brønsted acid[13] to give optically active tetrahydroquinoline **3** (Scheme 1). This one-pot reaction could be a useful method for synthesizing chiral tetrahydroquinolines. In addition, employing various 2-aminobenzaldehydes, 2-aminophenones or terminal/internal *alkynes* bearing diverse functional groups would allow the desired chiral products to undergo further synthetically useful transformations. Herein, we describe the results on such one-pot asymmetric reactions catalysed by a gold(I)/Brønsted acid cooperative system. Using this system, a series of enantio-enriched tetrahydroquinolines with one or two chiral centres and functional groups were prepared in up to 98% yields and with excellent regio-, diastereo- and enantioselectivities from simple starting materials. After we completed this work and during our preparation of this manuscript, Gong and co-workers reported related asymmetric synthesis of tetrahydroquinolines through reaction of 2-aminobenzaldehydes or 2-aminophenyl ketones with β-*keto esters* and Hantzsch esters catalysed by $Mg(OTf)_2$ and chiral phosphoric acids.[14]

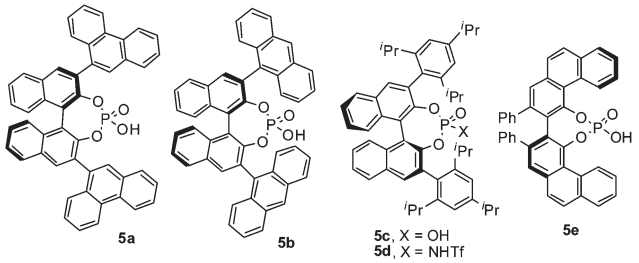
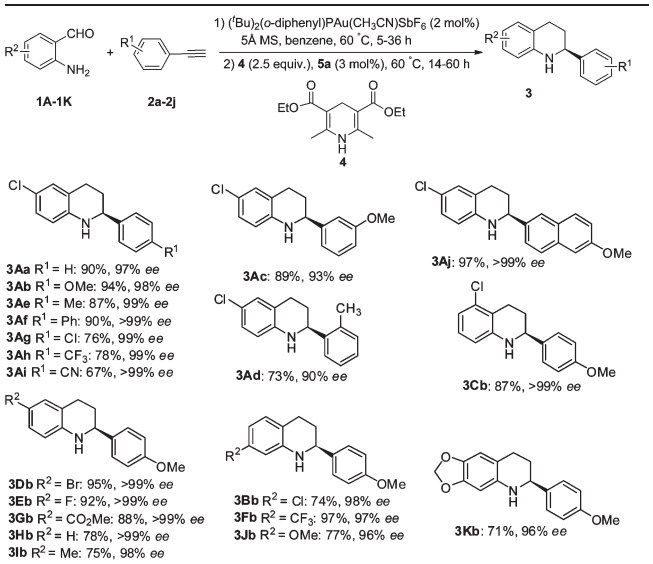


Fig. 2 Binol-based chiral phosphoric acids or phosphoramide **5a–5e**.

Table 1 Investigating the scope of alkynes and aminobenzaldehydes in asymmetric one-pot reaction[abc]



[a] Reaction conditions: aminobenzaldehyde (0.4 mmol), alkyne (0.48 mmol), ethyl Hantzsch ester (1.0 mmol), $(^tBu)_2$(*o*-diphenyl)PAu(CH_3CN)SbF_6 (2 mol%), **5a** (3 mol%), benzene (6 mL), 5 Å MS (1 g), 60 °C. [b] Isolated yield based on aminobenzaldehyde. [c] Determined by chiral HPLC analysis.

Results and discussion

Highly enantioselective synthesis of 2-substituted chiral tetrahydroquinolines

To validate the feasibility of the proposed one-pot sequential process, we began with the reaction of 2-amino-5-chlorobenzaldehyde (**1A**) with phenylacetylene (**2a**) in benzene at 60 °C in the presence of 3 mol% of $(^tBu)_2$(*o*-diphenyl)PAu(CH_3CN)SbF_6 [15] for the first step. After completion of this reaction (6 h), 10 mol% of Brønsted acid **5a** (Fig. 2) and 2.5 equivalents of Hantzsch ester **4** were added to the reaction mixture. To our delight, the desired product **3Aa** was obtained in 87% yield with 90% ee after 20 h; upon varying counteranions (for $(^tBu)_2$-(*o*-diphenyl)PAu^+), catalyst loadings, solvent and additives, we identified the following conditions as optimal: 2 mol% of $(^tBu)_2$(*o*-diphenyl)PAu(CH_3CN)SbF_6 and 3 mol% of **5a** in the presence of 5 Å MS with benzene as solvent at 60 °C, and product **3Aa** was obtained in 90% yield and 97% ee (see Table S1 in the ESI† and Table 1).

After optimizing the reaction conditions, we investigated the scope of the reaction using different types of terminal alkynes and aminobenzaldehydes (Table 1). Regardless of the position and nature of the substituent, various alkynes reacted efficiently with **1A** to afford the desired products in high yields with excellent ee values. Aryl alkynes possessing electron-donating *ortho*, *meta*, or *para* substituents were smoothly transformed into **3Aa–3Af** in 73–94% yields and with ee values of 90 to >99%. Substrates bearing electron-withdrawing *para* substituents were converted to **3Ag–3Ai** with up to >99% ee, albeit in yields (67–78%) lower than those for the substrates bearing electron-donating substituents. When 2-ethynyl-6-methoxynaphthalene (**2j**) was treated with **1A**, product **3Aj** was obtained in >99% ee with 97% yield. We then evaluated the scope of the reaction with a wide range of aminobenzaldehydes. The 2-aminobenzaldehydes possessing electron-withdrawing substituents at 4-, 5- or 6-positions were transformed into **3Bb–3Gb** in 74–97% yields with 97 to >99% ee. Notably, functional groups including ester and cyano groups could be well-tolerated under the reaction

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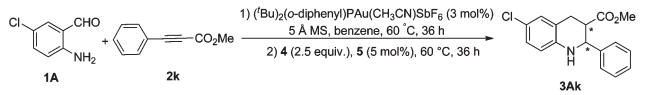
conditions. Reactions of aminobenzaldehydes having electron-neutral and -rich substituents on the aryl rings also worked well, furnishing **3Hb–3Kb** in 71–78% yields and with 96 to >99% ee.

Highly regio-, diastereo- and enantioselective formation of 2,3-disubstituted chiral tetrahydroquinolines

To assess the regio-, diastereo- and enantiocontrol, we extended the substrates to include internal alkynes **2k**. Treatment of methyl 3-phenylpropiolate (**2k**) with **1A** gave 2,3-disubstituted tetrahydroquinoline **3Ak** in 91% yield with almost complete regioselectivity, albeit with low diastereoselectivity (2 : 1) and moderate enantioselectivity (58% ee) (Table 2, entry 1). Additional binol-based chiral phosphoric acids or phosphoramide **5b–5d** (Fig. 2) were screened for this one-pot reaction of **2k** with **1A**, and the phosphoric acid **5c** was the best catalyst, giving **3Ak** in 80% yield with good diastereo- and enantioselectivity (10 : 1 d.r.; 77% ee) (Table 2, entry 3). A control experiment revealed that (^{t}Bu)$_2$(*o*-diphenyl)PAu(CH$_3$CN)SbF$_6$ can catalyse non-enantioselective transfer hydrogenation of the corresponding quinoline intermediate with Hantzsch ester **4** to give **3Ak** in 87% yield. To minimize this non-enantioselective background reaction catalysed by the gold(I) complex, we explored alternative reaction conditions that employed 4 mol% of triethylamine[16] to help deactivate gold(I) catalyst after completion of the first step reaction, which, to our delight, enhanced the enantioselectivity from 77 to 87% ee (Table 2, entry 5), suggesting that the non-enantioselective background reaction could be well suppressed by adding appropriate amount of triethylamine.

We next set out to explore the scope of this new protocol for the synthesis of 2,3-disubstituted chiral tetrahydroquinolines (Table 3). Changing the substituent of the ester in **2k** from a methyl to an ethyl group did not have an appreciable effect on the enantioselectivity, and **3Al** was obtained in 95% yield with high diastereo- and enantioselectivity (Table 3, entry 2). It is noteworthy that when the substituent R^2 on the internal alkynes was changed from ester to ketone, both the diastereo- and enantioselectivity were significantly improved. For example, **2m** or **2n** bearing methyl or phenoxymethylene substitution at the α position of carbonyl group resulted in product yields of 80–96% with enantioselectivities of 93–94% ee and diastereoselectivities of d.r. > 20 : 1 (Table 3, entries 3 and 4). The reaction also worked well for substrate **2o** bearing phenyl substituent at the α position of carbonyl group, affording **3Ao** in 93% yield

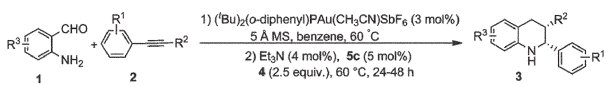
Table 2 Optimization of reaction conditions for regio-, diastereo- and enantioselective synthesis of 2,3-disubstituted tetrahydroquinoline[a]



Entry	Phosphoric acid	Yield[b] (%)	d.r.[c]	ee[d] (%)
1	(*R*)-**5a**	91	2 : 1	58
2	(*R*)-**5b**	73	1 : 1.1	39
3	(*S*)-**5c**	80	10 : 1	77
4	(*S*)-**5d**	93	11 : 1	71
5[e]	(*S*)-**5c**	87	10 : 1	87
6[f]	(*S*)-**5c**	—[g]	—	—

[a] Reaction conditions: 2-amino-5-chlorobenzaldehyde (0.2 mmol), methyl phenylpropiolate (0.24 mmol), ethyl Hantzsch ester (0.5 mmol), (^{t}Bu)$_2$(*o*-diphenyl)PAu(CH$_3$CN)SbF$_6$ (3 mol%), **5** (5 mol%), benzene (4 mL), 5 Å MS (0.5 g). [b] Isolated yield based on 2-amino-5-chlorobenzaldehyde. [c] Diastereomeric ratio determined by ^{1}H NMR spectroscopy. [d] Determined by chiral HPLC analysis. [e] 4 mol% of Et$_3$N was added after first step. [f] 15 mol% of Et$_3$N was added after first step. [g] Product was not detected.

Table 3 Scope of internal alkynes and 2-aminobenzaldehydes in asymmetric one-pot reaction catalysed by the gold(I)/chiral Brønsted acid cooperative system[a]



Entry	1	2	Product	Yield[b] (%)	d.r.[c]	ee[d] (%)
1	1A	X = Me: **2k**	X = Me: **3Ak**	87	10:1	87
2	1A	X = Et: **2l**	X = Et: **3Al**	95	16:1	87
3	1A	X = Me: **2m**	X = Me: **3Am**	80	>20:1	93
4	1A	X = PhOCH$_2$: **2n**	X = PhOCH$_2$: **3An**	96	>20:1	94
5	1A	X = Ph: **2o**	X = Ph: **3Ao**	93	5:1	82
6	1D	**2m**	**3Dm**	84	>20:1	94
7[e]	1K	**2m**	**3Km**	76	>20:1	97
8	1A	R^1 = Me: **2p**	R^1 = Me: **3Ap**	72	>20:1	94
9	1A	R^1 = Ph: **2q**	R^1 = Ph: **3Aq**	84	>20:1	93
10	1A	R^1 = Cl: **2r**	R^1 = Cl: **3Ar**	74	>20:1	96
11	1A	R^1 = CN: **2s**	R^1 = CN: **3As**	72	>20:1	97
12	1D	**2q**	**3Dq**	83	>20:1	89

[a] Reaction conditions: 2-aminobenzaldehyde (0.4 mmol), internal alkyne (0.48 mmol), ethyl Hantzsch ester (1.0 mmol), (^{t}Bu)$_2$(*o*-diphenyl)PAu(CH$_3$CN)SbF$_6$ (3 mol%), Et$_3$N (4 mol%), **5c** (5 mol%), benzene (6 mL), 5 Å MS (1.0 g) at 60 °C. [b] Isolated yield based on 2-aminobenzaldehyde. [c] Diastereomeric ratio determined by ^{1}H NMR spectroscopy; major isomer shown. [d] Determined by chiral HPLC analysis. [e] (^{t}Bu)$_2$(*o*-diphenyl)PAu(CH$_3$CN)SbF$_6$ (5 mol%), Et$_3$N (6 mol %) and **5c** (7 mol%) were required.

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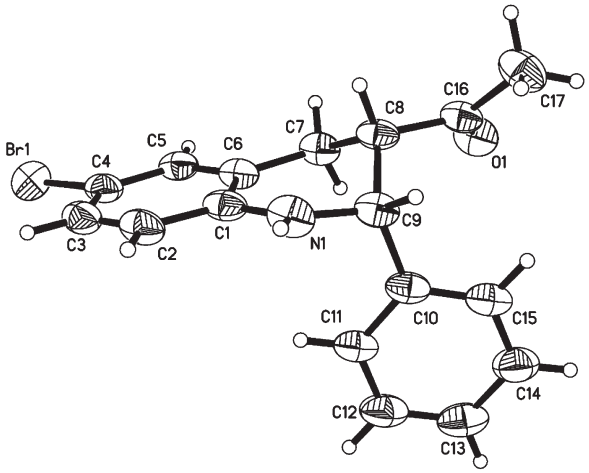


Fig. 3 Molecular structure of **3Dm** with 30% thermal ellipsoid probability.

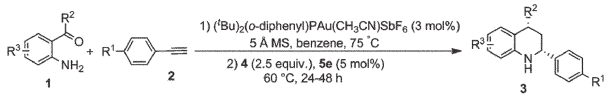
with 82% ee (d.r. = 5 : 1, Table 3, entry 5). A range of functionalized 2-aminobenzaldehydes, including those with electron-withdrawing groups (Table 3, entries 3 and 6) and electron-donating groups (Table 3, entry 7), were found to react with **2m** to give the corresponding products (**3Am**, **3Dm** and **3Km**) selectively with 93–97% ee (d.r. > 20 : 1). Investigations into the effect of substitution on the phenyl ring of the internal alkynes revealed that the reaction is highly efficient for both electron-rich and -deficient groups at the *para* position, furnishing **3Ap–3As** and **3Dq** in 72–84% yields (d.r. > 20 : 1) and with 89–97% ee (Table 3, entries 8–12). The absolute configuration of **3Dm** was determined as (2*R*,3*S*) by X-ray crystallographic analysis (Fig. 3),[17] and those of other 2,3-disubstituted tetrahydroquinolines were surmised by analogy.

Highly diastereo- and enantioselective formation of 2,4-disubstituted chiral tetrahydroquinolines

2,4-Disubstituted tetrahydroquinolines could be synthesized from one-pot sequential reactions of 2-aminophenones with alkynes using the gold(I)/Brønsted acid cooperative catalytic system. We screened a series of chiral phosphoric acids for the reaction of 2-aminobenzophenone (**1L**) with 4-ethynylbiphenyl (**2f**) under the optimal conditions (see the ESI, Table S2†). The corresponding product **3Lf** was formed in 73% yield with 86% ee and with a diastereomeric ratio of 20 : 1 by using (*R*)-VAPOL hydrogenphosphate (**5e**) as a catalyst (Table 4, entry 5).

We then extended the reaction to various 2-aminophenones and alkynes. For substituted 2-aminobenzophenones **1M** and **1N**, their reaction with 4-methoxy-phenylacetylene (**2b**) gave **3Mb** and **3Nb**, respectively, also in high enantioselectivities (88–94% ee) and diastereoselectivities (d.r. > 20 : 1, Table 4, entries 2 and 3). Substrate **1O** with a methyl group at the α position of the ketone unit was converted to **3Ob** in 94% yield and 85% ee with d.r. > 20 : 1 (Table 4, entry 4). Similar d.r. values of >20 : 1 and higher enantioselectivities of 88–94% ee were obtained for the desired products (79–93% yields) in the reactions of **1M** with terminal alkynes **2a**, **2b**, **2f** and **2u** bearing electron-rich or -neutral or -deficient aryl groups (Table 4, entries 2, and 6–8). The absolute configuration of **3Nb** is (2*R*,4*S*), as determined by X-ray crystallographic analysis (Fig. 4);[17] those of other 2,4-disubstituted tetrahydroquinolines were determined in reference to **3Nb**. These results underscore the synthetic utility of the present protocol for the synthesis of 2,4-disubstituted tetrahydroquinolines with high diastereo- and enantioselectivities from readily available precursors.

Table 4 Scope of 2-aminophenones and alkynes in asymmetric one-pot reaction catalysed by gold(I)/chiral Brønsted acid cooperative system[a]



Entry	1	2	Product	Yield[b] (%)	d.r.[c]	ee[d] (%)
1	R^3 = H: **1L**	R^1 = OMe: **2b**	**3Lb**	89	>20:1	87
2	R^3 = Cl: **1M**	**2b**	**3Mb**	93	>20:1	94
3	**1N**	**2b**	**3Nb**	98	>20:1	88
4	**1O**	**2b**	**3Ob**	94	>20:1	85
5	**1L**	R^1 = Ph: **2f**	**3Lf**	73	20:1	86
6	**1M**	R^1 = Ph: **2f**	R^1 = Ph: **3Mf**	91	>20:1	90
7	**1M**	R^1 = H: **2a**	R^1 = H: **3Ma**	81	>20:1	90
8	**1M**	R^1 = Br: **2u**	R^1 = Br: **3Mu**	79	>20:1	88

[a] Reaction conditions: 2-aminophenone (0.4 mmol), alkyne (0.48 mmol), ethyl Hantzsch ester (1.0 mmol), (^{t}Bu)$_2$(*o*-diphenyl)PAu(CH$_3$CN)SbF$_6$ (3 mol%), **5e** (5 mol%), benzene (6 mL), 5 Å MS (1.0 g). [b] Isolated yield based on 2-aminophenones. [c] Diastereomeric ratio determined by ^{1}H NMR spectroscopy; major isomer shown. [d] Determined by chiral HPLC analysis.

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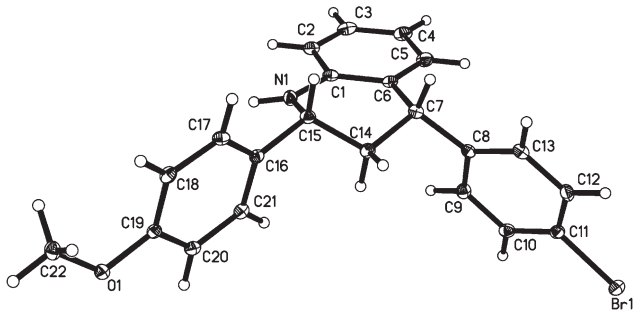

Fig. 4 Molecular structure of **3Nb** with 30% thermal ellipsoid probability.

Table 5 Chemical similarity between **3Lb** with chemical modulators of known targets

Rank	Targets
1	Tubulin chains, alpha-1
2	Norepinephrine transporter
3	Tubulin chains, beta-1
4	Dopamine transporter
5	Serotonin transporter
6	Histamine H1 receptor
7	Acetylcholine receptor protein alpha chain
8	Neurokinin 1 receptor
9	Purinergic receptor (P2Y1)

Biological activity of chiral tetrahydroquinolines

The synthesis of a library of optically active tetrahydroquinolines with one or two chiral centres at different positions by the protocol reported herein may provide an abundant resource for drug discovery research. As many of the biological targets in the cells are chiral,[18] the effect of stereochemistry on biological activity is of importance for medicinal application. Therefore, we were interested in studying the stereochemistry-biological activity relationships involving the chiral tetrahydroquinolines obtained in this work because of the diverse biological activities of such compounds.

With the use of chemical similarity search,[19] chiral tetrahydroquinoline **3Lb** was evaluated for a potential biological activity. As shown in Table 5, the chemical similarity between **3Lb** and the modulators of the known pharmaceutical targets in the ChEMBL (version 10) database was analyzed and ranked, revealing that **3Lb** could display potent activity towards different pharmaceutical targets. To further verify the hypotheses generated by the chemical similarity search and evaluate the effect of stereochemistry on biological activity, the two pure enantiomers **3Lb** and **3Lb′** (see Chart S1 in the ESI†) were subjected to the study of binding interaction with the purinergic (P2Y1) receptor, which is a G protein-coupled receptor involved in several cellular functions such as vascular reactivity, apoptosis, cytokine secretion and platelet aggregation.[20] Our experimental data[21] revealed that **3Lb′** could enhance the activity of P2Y1 by only 15%.[22] However, in the case of the opposite enantiomer **3Lb**, the activity of P2Y1 was increased by 41%, markedly higher than that for **3Lb′**. Thus, different enantiomers of the active species could demonstrate different activity towards the purinergic (P2Y1) receptor.

Conclusions

A gold(I)/chiral Brønsted acid cooperative catalytic system for efficient one-pot asymmetric synthesis of tetrahydroquinolines from reaction of 2-aminobenzaldehydes or 2-aminophenones with alkynes has been developed. This system not only results in the synthesis of 2-substituted tetrahydroquinolines with excellent enantioselectivity, but also allows access to 2,3- or 2,4-disubstituted functionalized tetrahydroquinolines through simultaneous formation of two chiral centres, with high regio-, diastereo- and enantioselectivities. The present work highlights a highly efficient and sustainable process in which optically active tetrahydroquinolines with one or two chiral centres at different positions as well as highly divergent functional groups can be formed from simple starting materials *via* independent tunability of catalyst components. A preliminary study on the effect of stereochemistry on biological activity suggests a potential application of this class of optically active tetrahydroquinolines in drug discovery processes. Further studies are under way to expand the substrate scope and to probe the origin of stereocontrol in the tetrahydroquinoline formation reactions catalysed by the gold(I)/chiral Brønsted acid cooperative system.

Experimental

General

All manipulations with air-sensitive reagents were carried out under a dry nitrogen atmosphere. Solvents were dried using standard methods and distilled before use. Starting materials and reagents were purchased from commercial sources and used without further purification. Sieves (5 Å powdered) were activated by flame under vacuum and stored at 180 °C. Unless otherwise noted, all reactions were prepared in flame or oven-dried glassware in a nitrogen-filled Vacuum Atmospheres inert atmosphere box and performed in sealed vessels. Analytical thin layer chromatography (TLC) was performed on precoated silica gel 60 F254 plates. Visualization on TLC was achieved by use of UV light (254 nm) or iodine. NMR spectra were recorded on Bruker AMX-300/400 spectrometer at 300/400 MHz for ^{1}H NMR and 75/100 MHz for ^{13}C NMR in $CDCl_3$ with tetramethylsilane (TMS) as internal standard. The chemical shifts are expressed in ppm and coupling constants are given in Hz. Data for ^{1}H NMR are recorded as follows: chemical shift (ppm), multiplicity (s, singlet; d, doublet; t, triplet; q, quartet; m, multiplet), coupling constant (Hz), integration. Data for ^{13}C NMR are reported in terms of chemical shift (δ, ppm). Mass spectra were determined on a Finnigan MAT 95 mass spectrometer. Single crystals of **3Dm** and **3Nb** suitable for X-ray diffraction analysis were obtained by slow evaporation of the CH_2Cl_2/*n*-hexane solutions. The diffraction data were collected at 296 K on a Bruker X8 PROTEUM single crystal X-ray diffractometer with MicroStar rotating-anode X-ray source (CuKα radiation, λ = 1.54178 Å). The gold(I) complexes,[15,23] and chiral phosphoric acid **5a**–**5e**[24] catalysts were prepared following literature procedures. The

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starting materials 2-aminobenzaldehydes[25] and internal alkynes **2m–2s**[26] were prepared according to literature methods.

Typical procedure for synthesis of chiral 2-substituted 1,2,3,4-tetrahydroquinolines. To a mixture of (^{t}Bu)$_2$(*o*-biphenyl)PAu(CH$_3$CN)SbF$_6$ (0.008 mmol, 2 mol%) and 5 Å molecular sieves (1 g) in dry benzene (6.0 mL) were added 2-aminobenzaldehyde (0.4 mmol) and terminal alkyne (0.48 mmol) at room temperature. The reaction mixture was stirred at 60 °C and the evolution of the reaction was monitored by TLC until completion. Then phosphoric acid **5a** (0.012 mmol, 3 mol%) and ethyl Hantzsch ester **4** (1.0 mmol) were successively added at the same reaction temperature. The resulting reaction mixture was stirred at 60 °C and monitored by TLC. Upon completion, the reaction mixture was filtered through a plug of silica (eluting with CH_2Cl_2) to remove the molecular sieves, and then concentrated *in vacuo*. The residue was purified by silica gel chromatography (eluent: hexane–ethyl acetate = 100 : 1) to afford the enantio-enriched product **3**.

(*S*)-6-Chloro-2-phenyl-1,2,3,4-tetrahydroquinoline (3Aa).[11a] Yield: 90%. ^{1}H NMR (CDCl$_3$, TMS, 300 MHz): δ 7.33 (m, 5H), 6.96 (m, 2H), 6.46 (d, J = 8.4 Hz, 1H), 4.43 (dd, J = 9.2, 3.2 Hz, 1H), 4.07 (brs, 1H), 2.88 (m, 1H), 2.70 (dt, J = 16.4, 4.8 Hz, 1H), 2.12 (m, 1H), 1.97 (m, 1H). $[\alpha]_D^{20}$ = −45.6 (*c* 1.34, EtOAc); Enantiomeric excess: 97%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 23.9 min (major), t_R = 28.9 min (minor). The absolute configuration was determined by comparison with the literature.[11a]

(*S*)-6-Chloro-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (3Ab). Yield: 94%. ^{1}H NMR (CDCl$_3$, TMS, 300 MHz): δ 7.31 (d, J = 8.6 Hz, 2H), 6.95 (m, 4H), 6.45 (d, J = 8.1 Hz, 1H), 4.38 (dd, J = 9.3, 3.1 Hz, 1H), 4.03 (brs, 1H), 3.84 (s, 3H), 2.90 (m, 1H), 2.72 (dt, J = 16.5, 4.7 Hz, 1H), 2.10 (m, 1H), 1.95 (m, 1H). ^{13}C NMR (CDCl$_3$, TMS, 75 MHz): δ 159.0, 143.4, 136.4, 128.8, 127.6, 126.7, 122.4, 121.4, 114.9, 114.0, 55.6, 55.3, 30.6, 26.3. MS: *m*/*z* (% relative intensity) 275(M$^+$ + 2, 33), 274(M$^+$ + 1, 35), 273(M$^+$, 100), 242(28), 166(43); HRMS: *m*/*z* calcd for C$_{16}$H$_{16}$ONCl (M$^+$) 273.0915, found 273.0910. $[\alpha]_D^{20}$ = −35.1 (*c* 0.97, EtOAc); Enantiomeric excess: 98%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 20.6 min (major), t_R = 43.8 min (minor). The absolute configuration was tentatively assigned by analogy.

(*S*)-6-Chloro-2-(3-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (3Ac). Yield: 89%. ^{1}H NMR (CDCl$_3$, TMS, 400 MHz): δ 7.28 (t, J = 7.8 Hz, 1H), 6.96 (m, 4H), 6.85 (d, J = 8.3 Hz, 1H), 6.46 (d, J = 8.1 Hz, 1H), 4.40 (dd, J = 8.9, 2.3 Hz, 1H), 4.07 (brs, 1H), 3.82 (s, 3H), 2.88 (m, 1H), 2.70 (dt, J = 16.4, 4.8 Hz, 1H), 2.12 (m, 1H), 1.97 (m, 1H). ^{13}C NMR (CDCl$_3$, TMS, 100 MHz): δ 159.9, 146.1, 143.2, 129.6, 128.8, 126.7, 122.4, 121.5, 118.8, 114.9, 112.8, 112.1, 56.1, 55.2, 30.4, 26.1. MS: *m*/*z* (% relative intensity) 275(M$^+$ + 2, 35), 274(M$^+$ + 1, 31), 273 (M$^+$, 100), 242(16), 166(91); HRMS: *m*/*z* calcd for C$_{16}$H$_{16}$ONCl (M$^+$) 273.0915, found 273.0907. $[\alpha]_D^{20}$ = −41.2 (*c* 1.03, EtOAc); Enantiomeric excess: 93%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.8 mL min^{-1}, λ = 254 nm): t_R = 51.9 min (major), t_R = 56.1 min (minor). The absolute configuration was tentatively assigned by analogy.

(*S*)-6-Chloro-2-*o*-tolyl-1,2,3,4-tetrahydroquinoline (3Ad). Yield: 73%. ^{1}H NMR (CDCl$_3$, TMS, 300 MHz): δ 7.48 (d, J = 5.8 Hz, 1H), 7.23 (m, 3H), 6.99 (m, 2H), 6.48 (d, J = 8.2 Hz, 1H), 4.68 (dd, J = 8.9, 3.1 Hz, 1H), 3.98 (brs, 1H), 2.91 (m, 1H), 2.74 (dt, J = 16.4, 4.8 Hz, 1H), 2.41 (s, 3H), 2.12 (m, 1H), 1.91 (m, 1H). ^{13}C NMR (CDCl$_3$, TMS, 75 MHz): δ 143.6, 142.2, 134.7, 130.6, 128.8, 127.2, 126.7, 126.4, 125.9, 122.3, 121.3, 114.9, 52.1, 28.7, 26.3, 19.0. MS: *m*/*z* (% relative intensity) 259(M$^+$ + 2, 33), 258(M$^+$ + 1, 24), 257(M$^+$, 100), 166(99); HRMS: *m*/*z* calcd for C$_{16}$H$_{16}$NCl (M$^+$) 257.0966, found 257.0964. $[\alpha]_D^{20}$ = −36.7 (*c* 0.98, EtOAc); Enantiomeric excess: 90%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 90 : 10, flow rate 1 mL min^{-1}, λ = 254 nm): t_R = 8.3 min (major), t_R = 13.9 min (minor). The absolute configuration was tentatively assigned by analogy.

(*S*)-6-Chloro-2-*p*-tolyl-1,2,3,4-tetrahydroquinoline (3Ae). Yield: 87%. ^{1}H NMR (CDCl$_3$, TMS, 400 MHz): δ 7.28 (d, J = 8.0 Hz, 2H), 7.19 (d, J = 8.0 Hz, 2H), 6.97 (m, 2H), 6.46 (d, J = 8.3 Hz, 1H), 4.40 (dd, J = 9.3, 3.2 Hz, 1H), 4.03 (brs, 1H), 2.89 (m, 1H), 2.71 (dt, J = 16.5, 4.8 Hz, 1H), 2.38 (s, 3H), 2.11 (m, 1H), 1.96 (m, 1H). ^{13}C NMR (CDCl$_3$, TMS, 100 MHz): δ 143.3, 141.4, 137.2, 129.3, 128.8, 126.7, 126.4, 122.4, 121.4, 114.9, 55.9, 30.5, 26.2, 21.1. MS: *m*/*z* (% relative intensity) 259 (M$^+$ + 2, 30), 258(M$^+$ + 1, 21), 257(M$^+$, 100), 166(52); HRMS: *m*/*z* calcd for C$_{16}$H$_{16}$NCl (M$^+$) 257.0966, found 257.0962. $[\alpha]_D^{20}$ = −30.8 (*c* 1.18, EtOAc); Enantiomeric excess: 99%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 17.0 min (major), t_R = 49.3 min (minor). The absolute configuration was tentatively assigned by analogy.

(*S*)-2-(Biphenyl-4-yl)-6-chloro-1,2,3,4-tetrahydroquinoline (3Af)

Yield: 90%. ^{1}H NMR (CDCl$_3$, TMS, 400 MHz): δ 7.62 (m, 4H), 7.47 (m, 4H), 7.38 (t, J = 7.2 Hz, 1H), 7.00 (m, 2H), 6.49 (d, J = 8.2 Hz, 1H), 4.48 (dd, J = 9.0, 2.8 Hz, 1H), 4.09 (brs, 1H), 2.92 (m, 1H), 2.74 (dt, J = 16.4, 4.7 Hz, 1H), 2.17 (m, 1H), 2.02 (m, 1H). ^{13}C NMR (CDCl$_3$, TMS, 100 MHz): δ 143.4, 143.2, 140.8, 140.5, 128.9, 128.8, 127.4, 127.1, 126.9, 126.7, 122.4, 121.5, 115.0, 55.8, 30.4, 26.1. MS: *m*/*z* (% relative intensity) 321(M$^+$ + 2, 35), 320(M$^+$ + 1, 37), 319(M$^+$, 100), 166(57); HRMS: *m*/*z* calcd for C$_{21}$H$_{18}$NCl (M$^+$) 319.1122, found 319.1116. $[\alpha]_D^{20}$ = −6.3 (*c* 0.97, EtOAc); Enantiomeric excess: >99%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 15.3 min (minor), t_R = 27.9 min (major). The absolute configuration was tentatively assigned by analogy.

(*S*)-6-Chloro-2-(4-chlorophenyl)-1,2,3,4-tetrahydroquinoline (3Ag). Yield: 76%. ^{1}H NMR (CDCl$_3$, TMS, 400 MHz): δ 7.30 (m, 4H), 6.96 (m, 2H), 6.47 (m, 1H), 4.41 (dd, J = 9.0, 3.3 Hz, 1H), 4.03 (brs, 1H), 2.86 (m, 1H), 2.67 (dt, J = 16.5, 5.0 Hz, 1H), 2.08 (m, 1H), 1.92 (m, 1H). ^{13}C NMR (CDCl$_3$, TMS, 100 MHz): δ 142.9, 142.8, 133.1, 128.8, 128.7, 127.8, 126.7, 122.3, 121.7, 115.0, 55.4, 30.4, 25.9. MS: *m*/*z* (% relative intensity) 279(M$^+$ + 2, 61), 278(M$^+$ + 1, 38), 277(M$^+$, 92), 166(100);

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HRMS: *m/z* calcd for $C_{15}H_{13}NCl_2$ (M^+) 277.0420, found 277.0417. $[\alpha]_D^{20} = -36.1$ (*c* 1.07, EtOAc); Enantiomeric excess: 99%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 20.2 min (major), t_R = 66.7 min (minor). The absolute configuration was tentatively assigned by analogy.

(*S*)-6-Chloro-2-(4-(trifluoromethyl)phenyl)-1,2,3,4-tetrahydroquinoline (3Ah). Yield: 78%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.62 (d, *J* = 8.1 Hz, 2H), 7.50 (d, *J* = 8.2 Hz, 2H), 6.98 (m, 2H), 6.50 (m, 1H), 4.52 (dd, *J* = 8.7, 3.0 Hz, 1H), 4.09 (brs, 1H), 2.88 (m, 1H), 2.68 (dt, *J* = 16.6, 5.1 Hz, 1H), 2.14 (m, 1H), 1.97 (m, 1H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 148.5, 142.8, 129.8 (q, J_{CF} = 32.1 Hz), 128.9, 126.9, 126.8, 125.6 (m), 122.8, 122.3, 121.9, 115.1, 55.6, 30.3, 25.7. MS: *m/z* (% relative intensity) 313(M^+ + 2, 31), 312(M^+ + 1, 25), 311 (M^+, 100), 166(68); HRMS: *m/z* calcd for $C_{16}H_{13}NClF_3$ (M^+) 311.0683, found 311.0677. $[\alpha]_D^{20} = -65.5$ (*c* 1.61, EtOAc); Enantiomeric excess: 99%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 17.2 min (major), t_R = 42.3 min (minor). The absolute configuration was tentatively assigned by analogy.

(*S*)-4-(6-Chloro-1,2,3,4-tetrahydroquinolin-2-yl)benzonitrile (3Ai). Yield: 67%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.63 (d, *J* = 8.4 Hz, 2H), 7.47 (d, *J* = 8.4 Hz, 2H), 6.98 (m, 2H), 6.50 (m, 1H), 4.52 (dd, *J* = 8.5, 3.6 Hz, 1H), 4.10 (brs, 1H), 2.85 (m, 1H), 2.64 (dt, *J* = 16.6, 5.2 Hz, 1H), 2.12 (m, 1H), 1.94 (m, 1H). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 149.9, 142.5, 132.5, 128.9, 127.2, 126.9, 122.2, 122.0, 118.8, 115.2, 111.3, 55.6, 30.2, 25.4. MS: *m/z* (% relative intensity) 270(M^+ + 2, 29), 269 (M^+ + 1, 24), 268(M^+, 85), 166(100); HRMS: *m/z* calcd for $C_{16}H_{13}N_2Cl$ (M^+) 268.0762, found 268.0761. $[\alpha]_D^{20} = -33.1$ (*c* 1.06, EtOAc); Enantiomeric excess: >99%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 85 : 15, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R = 16.3 min (major), t_R = 37.3 min (minor). The absolute configuration was tentatively assigned by analogy.

(*S*)-6-Chloro-2-(6-methoxynaphthalen-2-yl)-1,2,3,4-tetrahydroquinoline (3Aj). Yield: 97%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.73 (t, *J* = 10.8 Hz, 3H), 7.45 (dd, *J* = 8.5, 1.5 Hz, 1H), 7.17 (m, 2H), 6.99 (m, 2H), 6.49 (d, *J* = 8.4 Hz, 1H), 4.54 (dd, *J* = 9.1, 3.2 Hz, 1H), 4.12 (brs, 1H), 3.93 (s, 3H), 2.90 (m, 1H), 2.72 (dt, *J* = 16.4, 4.8 Hz, 1H), 2.16 (m, 1H), 2.04 (m, 1H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 157.7, 143.3, 139.4, 134.1, 129.3, 128.9, 128.8, 127.2, 126.7, 125.2, 124.9, 122.4, 121.4, 119.0, 114.9, 105.7, 56.1, 55.3, 30.4, 26.2. MS: *m/z* (% relative intensity) 325(M^+ + 2, 34), 324(M^+ + 1, 38), 323 (M^+, 100), 172(38); HRMS: *m/z* calcd for $C_{20}H_{18}ONCl$ (M^+) 323.1071, found 323.1067. $[\alpha]_D^{20} = -18.2$ (*c* 1.16, EtOAc); Enantiomeric excess: >99%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 90 : 10, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R = 14.6 min (major), t_R = 63.2 min (minor). The absolute configuration was tentatively assigned by analogy.

(*S*)-7-Chloro-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (3Bb). Yield: 74%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.28 (d, *J* = 8.6 Hz, 2H), 6.90 (m, 3H), 6.60 (dd, *J* = 8.0, 2.0 Hz, 1H), 6.50 (d, *J* = 2.0 Hz, 1H), 4.38 (dd, *J* = 9.2, 3.2 Hz, 1H), 4.06 (brs, 1H), 3.82 (s, 3H), 2.85 (m, 1H), 2.69 (dt, *J* = 16.3, 4.8 Hz, 1H), 2.08 (m, 1H), 1.93 (m, 1H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 159.0, 145.7, 136.3, 132.1, 130.2, 127.5, 119.2, 116.7, 114.0, 113.3, 55.4, 55.3, 30.7, 25.9. MS: *m/z* (% relative intensity) 275(M^+ + 2, 33), 274(M^+ + 1, 36), 273(M^+, 100), 242(30), 166(42); HRMS: *m/z* calcd for $C_{16}H_{16}ONCl$ (M^+) 273.0915, found 273.0912. $[\alpha]_D^{20} = -91.2$ (*c* 1.16, EtOAc); Enantiomeric excess: 98%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.7 mL min^{-1}, λ = 254 nm): t_R = 17.4 min (major), t_R = 34.9 min (minor). The absolute configuration was tentatively assigned by analogy.

(*S*)-5-Chloro-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (3Cb). Yield: 87%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.30 (d, *J* = 8.6 Hz, 2H), 6.93 (m, 3H), 6.73 (d, *J* = 7.8 Hz, 1H), 6.43 (d, *J* = 8.0 Hz, 1H), 4.33 (dd, *J* = 9.7, 2.9 Hz, 1H), 4.10 (brs, 1H), 3.83 (s, 3H), 2.92 (dt, *J* = 17.2, 5.3 Hz, 1H), 2.82 (m, 1H), 2.14 (m, 1H), 1.97 (m, 1H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 159.1, 146.4, 136.2, 134.7, 127.6, 127.3, 118.8, 117.7, 114.0, 112.3, 55.3, 55.2, 30.8, 24.4. MS: *m/z* (% relative intensity) 275(M^+ + 2, 35), 274(M^+ + 1, 38), 273(M^+, 100), 242 (34), 166(64); HRMS: *m/z* calcd for $C_{16}H_{16}ONCl$ (M^+) 273.0915, found 273.0908. Enantiomeric excess: >99%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.7 mL min^{-1}, λ = 254 nm): t_R = 17.2 min (major), t_R = 40.0 min (minor). The absolute configuration was tentatively assigned by analogy.

(*S*)-6-Bromo-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (3Db). Yield: 95%. ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ 7.29 (m, 2H), 7.09 (m, 2H), 6.91 (m, 2H), 6.40 (d, *J* = 8.3 Hz, 1H), 4.37 (dd, *J* = 9.2, 3.2 Hz, 1H), 4.03 (brs, 1H), 3.83 (s, 3H), 2.89 (m, 1H), 2.71 (dt, *J* = 16.5, 4.8 Hz, 1H), 2.08 (m, 1H), 1.94 (m, 1H). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 159.0, 143.8, 136.4, 131.7, 129.5, 127.6, 122.9, 115.4, 114.0, 108.4, 55.5, 55.3, 30.5, 26.3. MS: *m/z* (% relative intensity) 319(M^+ + 2, 39), 318(M^+ + 1, 24), 317(M^+, 40), 153(52), 136(66); HRMS: *m/z* calcd for $C_{16}H_{16}ONBr$ (M^+) 317.0410, found 317.0403. $[\alpha]_D^{20} = -8.8$ (*c* 0.96, EtOAc); Enantiomeric excess: >99%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.7 mL min^{-1}, λ = 254 nm): t_R = 17.8 min (major), t_R = 45.4 min (minor). The absolute configuration was tentatively assigned by analogy.

(*S*)-6-Fluoro-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (3Eb). Yield: 92%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.33 (d, *J* = 8.6 Hz, 2H), 6.92 (d, *J* = 8.5 Hz, 2H), 6.74 (m, 2H), 6.46 (m, 1H), 4.34 (dd, *J* = 9.6, 2.9 Hz, 1H), 3.91 (brs, 1H), 3.83 (s, 3H), 2.94 (m, 1H), 2.74 (dt, *J* = 16.6, 4.5 Hz, 1H), 2.09 (m, 1H), 1.98 (m, 1H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 159.0, 156.7, 154.3, 141.1 (d, J_{CF} = 1.4 Hz), 136.6, 127.6, 122.2 (d, J_{CF} = 6.5 Hz), 115.4 (d, J_{CF} = 21.5 Hz), 114.6 (d, J_{CF} = 7.6 Hz), 113.9, 113.3 (d, J_{CF} = 22.3 Hz), 55.8, 55.3, 30.8, 26.7. MS: *m/z* (% relative intensity) 257(M^+, 100), 150(46), 136(58); HRMS: *m/z* calcd for $C_{16}H_{16}ONF$ (M^+) 257.1210, found 257.1201. $[\alpha]_D^{20} = -39.1$ (*c* 0.99, EtOAc); Enantiomeric excess: >99%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.7 mL min^{-1}, λ = 254 nm): t_R = 15.0 min (major), t_R = 32.5 min (minor). The absolute configuration was tentatively assigned by analogy.

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(*S*)-2-(4-Methoxyphenyl)-7-(trifluoromethyl)-1,2,3,4-tetrahydroquinoline (3Fb). Yield: 97%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.30 (m, 2H), 7.08 (d, J = 7.8 Hz, 1H), 6.92 (m, 2H), 6.88 (d, J = 7.8 Hz, 1H), 6.74 (s, 1H), 4.43 (dd, J = 9.3, 3.3 Hz, 1H), 4.19 (brs, 1H), 3.83 (s, 3H), 2.93 (m, 1H), 2.78 (dt, J = 16.5, 4.7 Hz, 1H), 2.12 (m, 1H), 1.97 (m, 1H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 159.1, 144.8, 136.2, 129.5, 129.2 (m), 127.5, 125.8, 124.4, 123.1, 114.0, 113.2 (m), 110.1 (m), 55.5, 55.3, 30.4, 26.3. MS: *m*/*z* (% relative intensity) 307 (M^+, 100), 276(35), 198(36); HRMS: *m*/*z* calcd for $C_{17}H_{16}ONF_3$ (M^+) 307.1179, found 307.1170. $[\alpha]_D^{20}$ = −30.6 (*c* 0.94, EtOAc); Enantiomeric excess: 97%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.7 mL min^{-1}, λ = 254 nm): t_R = 11.3 min (major), t_R = 22.0 min (minor). The absolute configuration was tentatively assigned by analogy.

(*S*)-Methyl 2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline-6-carboxylate (3Gb). Yield: 88%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.73 (m, 2H), 7.26 (m, 2H), 6.89 (m, 2H), 6.47 (m, 1H), 4.46 (m, 2H), 3.84 (s, 3H), 3.81 (s, 3H), 2.88 (m, 1H), 2.75 (dt, J = 16.2, 4.9 Hz, 1H), 2.10 (m, 1H), 1.94 (m, 1H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 167.4, 159.1, 148.7, 135.9, 131.1, 129.2, 127.5, 119.7, 117.9, 114.0, 112.7, 55.5, 55.3, 51.4, 30.3, 26.0. MS: *m*/*z* (% relative intensity) 297(M^+, 100), 266 (48), 238(18), 190(29); HRMS: *m*/*z* calcd for $C_{18}H_{19}O_3N$ (M^+) 297.1359, found 297.1352. $[\alpha]_D^{20}$ = 45.8 (*c* 0.95, EtOAc); Enantiomeric excess: >99%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 85 : 15, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R = 16.8 min (major), t_R = 54.3 min (minor). The absolute configuration was tentatively assigned by analogy.

(*S*)-2-(4-Methoxyphenyl)-1,2,3,4-tetrahydroquinoline (3Hb).[11a] Yield: 78%. ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ 7.34 (m, 2H), 7.03 (m, 2H), 6.92 (m, 2H), 6.67 (m, 1H), 6.54 (dd, J = 8.1, 1.1 Hz, 1H), 4.40 (dd, J = 9.4, 3.2 Hz, 1H), 4.00 (brs, 1H), 3.84 (s, 3H), 2.95 (m, 1H), 2.76 (dt, J = 16.3, 4.6 Hz, 1H), 2.05 (m, 2H). Enantiomeric excess: >99%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 90 : 10, flow rate 0.6 mL min^{-1}, λ = 254 nm): t_R = 15.4 min (major), t_R = 25.7 min (minor). The absolute configuration was determined by comparison with the literature.[11a]

(*S*)-2-(4-Methoxyphenyl)-6-methyl-1,2,3,4-tetrahydroquinoline (3Ib). Yield: 75%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.33 (m, 2H), 6.91 (m, 2H), 6.85 (m, 2H), 6.48 (d, J = 8.6 Hz, 1H), 4.36 (dt, J = 9.6, 3.1 Hz, 1H), 3.89 (brs, 1H), 3.83 (s, 3H), 2.93 (m, 1H), 2.73 (dt, J = 16.4, 4.7 Hz, 1H), 2.26 (s, 3H), 2.08 (m, 1H), 1.99 (m, 1H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 158.9, 142.5, 137.0, 129.8, 127.6, 127.4, 126.3, 120.9, 114.1, 113.9, 55.9, 55.3, 31.3, 26.6, 20.4. MS: *m*/*z* (% relative intensity) 253(M^+, 93), 166(56), 146(32); HRMS: *m*/*z* calcd for $C_{17}H_{19}ON$ (M^+) 253.1461, found 253.1464. Enantiomeric excess: 98%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R = 8.9 min (major), t_R = 14.4 min (minor). The absolute configuration was tentatively assigned by analogy.

(*S*)-7-Methoxy-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (3Jb). Yield: 77%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.29 (m, 2H), 6.89 (m, 3H), 6.24 (dd, J = 8.2, 2.5 Hz, 1H), 6.09 (d, J = 2.5 Hz, 1H), 4.36 (dt, J = 9.5, 3.1 Hz, 1H), 4.00 (brs, 1H), 3.80 (s, 3H), 3.74 (s, 3H), 2.84 (m, 1H), 2.67 (dt, J = 16.0, 4.7 Hz, 1H), 2.06 (m, 1H), 1.95 (m, 1H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 158.9, 145.6, 136.8, 129.9, 127.6, 113.9, 113.5, 103.0, 99.2, 55.6, 55.3, 55.1, 31.3, 25.7. MS: *m*/*z* (% relative intensity) 269(M^+, 100), 254(39), 160(35); HRMS: *m*/*z* calcd for $C_{17}H_{19}O_2N$ (M^+) 269.1410, found 269.1409. Enantiomeric excess: 96%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 90 : 10, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 35.9 min (minor), t_R = 40.5 min (major). The absolute configuration was tentatively assigned by analogy.

(*S*)-6-(4-Methoxyphenyl)-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]quinoline (3Kb). Yield: 71%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.30 (m, 2H), 6.89 (m, 2H), 6.51 (s, 1H), 6.13 (s, 1H), 5.82 (q, J = 1.3 Hz, 2H), 4.30 (dt, J = 9.6, 3.0 Hz, 1H), 3.81 (s, 3H), 2.86 (m, 1H), 2.65 (dt, J = 16.3, 4.7 Hz, 1H), 2.05 (m, 1H), 1.96 (m, 1H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 158.9, 146.3, 139.5, 139.4, 136.8, 127.6, 113.9, 112.6, 109.0, 100.2, 96.4, 55.9, 55.3, 31.2, 26.6. MS: *m*/*z* (% relative intensity) 283(M^+, 100), 268(22), 174(20); HRMS: *m*/*z* calcd for $C_{17}H_{17}O_3N$ (M^+) 283.1203, found 283.1200. Enantiomeric excess: 96%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 90 : 10, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 36.4 min (major), t_R = 56.8 min (minor). The absolute configuration was tentatively assigned by analogy.

Typical procedure for synthesis of chiral 2,3-disubstituted 1,2,3,4-tetrahydroquinolines. To a mixture of (^{t}Bu)$_2$(*o*-biphenyl)-PAu(CH_3CN)SbF_6 (0.012 mmol, 3 mol%) and 5 Å molecular sieves (1 g) in dry benzene (6.0 mL) were added 2-aminobenzaldehyde (0.4 mmol) and internal alkyne (0.48 mmol) at room temperature. The reaction mixture was stirred at 60 °C and the evolution of the reaction was monitored by TLC until completion. Then triethylamine (0.016 mmol, 4 mol%), phosphoric acid **5** (0.02 mmol, 5 mol%) and ethyl Hantzsch ester **4** (1.0 mmol) were successively added at the same reaction temperature. The resulting reaction mixture was stirred at 60 °C and monitored by TLC. Upon completion, the reaction mixture was filtered through a plug of silica (eluting with CH_2Cl_2) to remove the molecular sieves, and then concentrated *in vacuo*. The residue was purified by silica gel chromatography (eluent: hexane–ethyl acetate = 20 : 1 to 6 : 1) to afford the enantioenriched product **3**.

(2*R*,3*S*)-Methyl 6-chloro-2-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (3Ak). Yield: 87%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.24 (m, 3H), 7.11 (m, 2H), 7.00 (m, 2H), 6.50 (m, 1H), 4.93 (d, J = 4.3 Hz, 1H), 4.42 (brs, 1H), 3.62 (s, 3H), 3.19 (m, 1H), 2.85 (m, 2H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 172.1, 142.0, 141.6, 129.1, 128.4, 127.9, 127.3, 126.6, 121.6, 120.3, 114.5, 55.9, 51.6, 42.9, 24.9. MS: *m*/*z* (% relative intensity) 303(M^+ + 2, 34), 302(M^+ + 1, 27), 301(M^+, 100), 242(68), 227(39); HRMS: *m*/*z* calcd for $C_{17}H_{16}O_2NCl$ (M^+) 301.0864, found 301.0865. Enantiomeric excess: 87%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.7 mL min^{-1}, λ = 254 nm): t_R = 32.7 min (minor), t_R = 69.5 min (major). The relative and absolute configurations were tentatively assigned by analogy.

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(2*R*,3*S*)-Ethyl 6-chloro-2-phenyl-1,2,3,4-tetrahydroquinoline-3-carboxylate (3Al). Yield: 95%. ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ 7.24 (m, 3H), 7.14 (m, 2H), 7.00 (m, 2H), 6.50 (m, 1H), 4.94 (d, J = 4.2 Hz, 1H), 4.42 (brs, 1H), 4.06 (m, 2H), 3.18 (m, 1H), 2.85 (m, 2H), 1.18 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 171.7, 142.1, 141.6, 129.0, 128.3, 127.8, 127.2, 126.8, 121.5, 120.4, 114.4, 60.6, 55.9, 43.0, 24.9, 14.1. MS: *m/z* (% relative intensity) 317(M^+ + 2, 10), 316(M^+ + 1, 7), 315(M^+, 21), 286(87), 240(100); HRMS: *m/z* calcd for $C_{18}H_{18}O_2NCl$ (M^+) 315.1021, found 315.1023. Enantiomeric excess: 87%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 97 : 3, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 47.7 min (minor), t_R = 101.9 min (major). The relative and absolute configurations were tentatively assigned by analogy.

1-((2*R*,3*S*)-6-Chloro-2-phenyl-1,2,3,4-tetrahydroquinolin-3-yl)-ethanone (3Am). Yield: 80%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.26 (m, 3H), 7.14 (m, 2H), 7.01 (m, 2H), 6.52 (d, J = 8.5 Hz, 1H), 4.91 (d, J = 3.8 Hz, 1H), 4.41 (brs, 1H), 3.20 (m, 1H), 2.93 (dd, J = 16.7, 9.9 Hz, 1H), 2.83 (dd, J = 16.7, 5.1 Hz, 1H), 2.02 (s, 3H). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 208.0, 142.1, 141.2, 129.0, 128.5, 127.9, 127.2, 126.6, 121.7, 120.5, 114.7, 56.0, 50.3, 29.7, 25.4. MS: *m/z* (% relative intensity) 287(M^+ + 2, 21), 286(M^+ + 1, 15), 285(M^+, 63), 242(100), 91(87); HRMS: *m/z* calcd for $C_{17}H_{16}ONCl$ (M^+) 285.0915, found 285.0914. $[\alpha]_D^{20}$ = −161.9 (*c* 1.21, EtOAc); Enantiomeric excess: 93%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 85 : 15, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R = 20.5 min (minor), t_R = 66.5 min (major). The relative and absolute configurations were tentatively assigned by analogy.

1-((2*R*,3*S*)-6-Chloro-2-phenyl-1,2,3,4-tetrahydroquinolin-3-yl)-2-phenoxyethanone (3An). Yield: 96%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.28 (m, 5H), 7.18 (m, 2H), 7.01 (m, 3H), 6.80 (d, J = 7.9 Hz, 2H), 6.53 (m, 1H), 5.04 (d, J = 3.9 Hz, 1H), 4.41 (m, 3H), 3.64 (m, 1H), 2.98 (dd, J = 16.9, 9.0 Hz, 1H), 2.90 (dd, J = 16.9, 5.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 206.0, 157.6, 142.1, 141.0, 129.7, 129.0, 128.7, 128.1, 127.3, 126.6, 122.0, 121.9, 120.3, 114.9, 114.6, 73.1, 55.8, 46.4, 25.4. MS: *m/z* (% relative intensity) 377(M^+, 16), 284(100), 266(34); HRMS: *m/z* calcd for $C_{23}H_{20}O_2NCl$ (M^+) 377.1177, found 377.1170. Enantiomeric excess: 94%, determined by HPLC (Chiralcel OD-H hexane–isopropanol = 85 : 15, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R = 57.0 min (minor), t_R = 123.1 min (major). The relative and absolute configurations were tentatively assigned by analogy.

((2*R*,3*S*)-6-Chloro-2-phenyl-1,2,3,4-tetrahydroquinolin-3-yl)-(phenyl)ethanone (3Ao). Yield: 93%. ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ 7.93 (m, 2H), 7.60 (m, 1H), 7.50 (m, 2H), 7.16 (m, 3H), 7.05 (m, 2H), 6.84 (m, 2H), 6.57 (d, J = 8.3 Hz, 1H), 5.02 (t, J = 3.2 Hz, 1H), 4.49 (d, J = 2.9 Hz, 1H), 4.17 (m, 1H), 3.09 (dd, J = 17.0, 11.2 Hz, 1H), 2.77 (dd, J = 16.5, 4.0 Hz, 1H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 199.1, 142.0, 140.9, 136.9, 133.2, 129.2, 128.9, 128.3, 128.1, 127.8, 127.2, 126.6, 121.8, 121.2, 114.4, 56.9, 44.4, 24.9. MS: *m/z* (% relative intensity) 349(M^+ + 2, 17), 348(M^+ + 1, 13), 347(M^+, 48), 242(100), 227(71); HRMS: *m/z* calcd for $C_{22}H_{18}ONCl$ (M^+) 347.1071, found 347.1069. $[\alpha]_D^{20}$ = −188.7 (*c* 1.10, EtOAc); Enantiomeric excess: 82%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 85 : 15, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R = 14.1 min (minor), t_R = 87.4 min (major). The relative and absolute configurations were tentatively assigned by analogy.

1-((2*R*,3*S*)-6-Bromo-2-phenyl-1,2,3,4-tetrahydroquinolin-3-yl)-ethanone (3Dm). Yield: 84%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.28 (m, 3H), 7.13 (m, 4H), 6.52 (d, J = 8.2 Hz, 1H), 4.90 (d, J = 3.8 Hz, 1H), 4.48 (brs, 1H), 3.18 (m, 1H), 2.92 (dd, J = 16.7, 10.1 Hz, 1H), 2.81 (dd, J = 16.7, 4.9 Hz, 1H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 207.9, 142.6, 141.2, 131.9, 130.1, 128.5, 128.0, 126.6, 121.1, 115.2, 108.9, 56.0, 50.3, 29.8, 25.4. MS: *m/z* (% relative intensity) 331 (M^+ + 2, 43), 330(M^+ + 1, 15), 329(M^+, 45), 207(100), 91(94); HRMS: *m/z* calcd for $C_{17}H_{16}ONBr$ (M^+) 329.0410, found 329.0407. Enantiomeric excess: 94%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 85 : 15, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R = 20.9 min (minor), t_R = 79.5 min (major). The relative and absolute configurations were determined by X-ray crystallographic analysis.

1-((6*R*,7*S*)-6-Phenyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-*g*]-quinolin-7-yl)ethanone (3Km). Yield: 76%. ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ 7.25 (m, 3H), 7.15 (m, 2H), 6.53 (s, 1H), 6.18 (s, 1H), 5.84 (s, 2H), 4.83 (d, J = 5.1 Hz, 1H), 4.17 (brs, 1H), 3.18 (m, 1H), 2.82 (m, 2H), 2.03 (s, 3H). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 207.9, 146.3, 141.1, 139.4, 137.5, 127.9, 127.2, 126.1, 110.1, 108.4, 99.9, 95.6, 55.8, 50.5, 29.1, 25.2. MS: *m/z* (% relative intensity) 295(M^+, 10), 210(39), 182 (70), 84(100); HRMS: *m/z* calcd for $C_{18}H_{17}O_3N$ (M^+) 295.1203, found 295.1201. $[\alpha]_D^{20}$ = −20.0 (*c* 0.63, EtOAc); Enantiomeric excess: 97%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 80 : 20, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R = 33.6 min (minor), t_R = 61.1 min (major). The relative and absolute configurations were tentatively assigned by analogy.

1-((2*R*,3*S*)-6-Chloro-2-*p*-tolyl-1,2,3,4-tetrahydroquinolin-3-yl)-ethanone (3Ap). Yield: 72%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.06 (m, 2H), 6.96 (m, 4H), 6.48 (m, 1H), 4.84 (d, J = 4.0 Hz, 1H), 4.40 (brs, 1H), 3.15 (m, 1H), 2.90 (dd, J = 16.7, 10.0 Hz, 1H), 2.76 (dd, J = 16.7, 4.9 Hz, 1H), 2.29 (s, 3H), 2.02 (s, 3H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 208.1, 142.2, 138.2, 137.6, 129.2, 129.0, 127.2, 126.5, 121.7, 120.6, 114.8, 55.9, 50.4, 29.8, 25.5, 21.0. MS: *m/z* (% relative intensity) 301(M^+ + 2, 22), 300(M^+ + 1, 17), 299(M^+, 67), 256 (100), 164(63); HRMS: *m/z* calcd for $C_{18}H_{18}ONCl$ (M^+) 299.1071, found 299.1072. Enantiomeric excess: 94%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 85 : 15, flow rate 0.7 mL min^{-1}, λ = 254 nm): t_R = 21.6 min (minor), t_R = 81.7 min (major). The relative and absolute configurations were tentatively assigned by analogy.

1-((2*R*,3*S*)-2-(Biphenyl-4-yl)-6-chloro-1,2,3,4-tetrahydroquinolin-3-yl)ethanone (3Aq). Yield: 84%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.57 (d, J = 7.2 Hz, 2H), 7.51 (d, J = 8.3 Hz, 2H), 7.45 (t, J = 7.3 Hz, 2H), 7.36 (t, J = 7.3 Hz, 1H), 7.21 (d, J = 8.2 Hz, 2H), 7.04 (m, 2H), 6.53 (m, 1H), 4.93 (d, J = 3.7 Hz, 1H), 4.50 (brs, 1H), 3.21 (m, 1H), 2.96 (dd, J = 16.7, 10.2 Hz, 1H), 2.84 (dd, J = 16.7, 4.8 Hz, 1H), 2.09 (s, 3H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 207.9, 142.2, 140.7, 140.4, 140.3,

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129.1, 128.8, 127.5, 127.3, 127.2, 127.1, 127.0, 121.9, 120.6, 114.9, 55.8, 50.4, 29.8, 25.5. MS: *m/z* (% relative intensity) 361 (M^+, 50), 342(100), 167(93), 149(63); HRMS: *m/z* calcd for $C_{23}H_{20}ONCl$ (M^+) 361.1228, found 361.1224. $[\alpha]_D^{20}$ = –161.9 (*c* 0.90, EtOAc); Enantiomeric excess: 93%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 83 : 17, flow rate 1.2 mL min^{-1}, λ = 254 nm): t_R = 45.3 min (minor), t_R = 78.3 min (major). The relative and absolute configurations were tentatively assigned by analogy.

1-((2*R*,3*S*)-6-Chloro-2-(4-chlorophenyl)-1,2,3,4-tetrahydroquinolin-3-yl)ethanone (3Ar). Yield: 74%. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 7.23 (d, *J* = 8.5 Hz, 2H), 7.06 (d, *J* = 8.5 Hz, 2H), 7.01 (m, 2H), 6.52 (m, 1H), 4.89 (d, *J* = 3.6 Hz, 1H), 4.45 (brs, 1H), 3.17 (m, 1H), 2.86 (m, 2H), 2.06 (s, 3H). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 207.7, 141.8, 139.8, 133.7, 129.1, 128.6, 128.1, 127.4, 122.1, 120.3, 114.9, 55.4, 50.1, 29.8, 25.3. MS: *m/z* (% relative intensity) 321(M^+ + 2, 37), 320(M^+ + 1, 15), 319(M^+, 58), 276(100), 240(49); HRMS: *m/z* calcd for $C_{17}H_{15}ONCl_2$ (M^+) 319.0525, found 319.0528. $[\alpha]_D^{20}$ = −206.3 (*c* 1.97, EtOAc); Enantiomeric excess: 96%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 85 : 15, flow rate 1.0 mL min^{-1}, λ = 254 nm): t_R = 16.6 min (minor), t_R = 69.0 min (major). The relative and absolute configurations were tentatively assigned by analogy.

4-((2*R*,3*S*)-3-Aceyl-6-chloro-1,2,3,4-tetrahydroquinolin-2-yl)-benzonitrile (3As). Yield: 72%. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 7.55 (d, *J* = 8.3 Hz, 2H), 7.25 (d, *J* = 8.3 Hz, 2H), 7.04 (m, 2H), 6.55 (m, 1H), 4.99 (d, *J* = 4.0 Hz, 1H), 3.22 (m, 1H), 2.85 (m, 2H), 2.12 (s, 3H). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 207.2, 146.7, 141.4, 132.2, 129.2, 127.7, 127.6, 122.5, 120.0, 118.5, 115.0, 111.7, 55.5, 49.9, 29.7, 25.2. MS: *m/z* (% relative intensity) 312(M^+ + 2, 19), 311(M^+ + 1, 9), 310 (M^+, 54), 267(100), 232(47); HRMS: *m/z* calcd for $C_{18}H_{15}ON_2Cl$ (M^+) 310.0867, found 310.0864. $[\alpha]_D^{20}$ = −170.4 (*c* 0.90, EtOAc); Enantiomeric excess: 97%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 83 : 17, flow rate 1.2 mL min^{-1}, λ = 254 nm): t_R = 31.3 min (minor), t_R = 96.1 min (major). The relative and absolute configurations were tentatively assigned by analogy.

1-((2*R*,3*S*)-2-(Biphenyl-4-yl)-6-bromo-1,2,3,4-tetrahydroquinolin-3-yl)ethanone (3Dq). Yield: 83%. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 7.45 (m, 7H), 7.19 (m, 4H), 6.50 (d, *J* = 8.2 Hz, 1H), 4.95 (d, *J* = 3.7 Hz, 1H), 4.50 (brs, 1H), 3.22 (m, 1H), 2.98 (dd, *J* = 16.7, 10.2 Hz, 1H), 2.84 (dd, *J* = 16.5, 4.8 Hz, 1H), 2.10 (s, 3H). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 207.9, 142.6, 140.7, 140.3, 140.2, 132.0, 130.1, 128.8, 127.5, 127.2, 127.1, 127.0, 121.1, 115.3, 109.0, 55.7, 50.3, 29.8, 25.4. MS: *m/z* (% relative intensity) 407(M^+ + 2, 47), 406(M^+ + 1, 22), 405(M^+, 51), 362(59), 283(69), 167(100); HRMS: *m/z* calcd for $C_{23}H_{20}ONBr$ (M^+) 405.0723, found 405.0715. $[\alpha]_D^{20}$ = –134.7 (*c* 0.80, EtOAc); Enantiomeric excess: 89%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 80 : 20, flow rate 1.2 mL min^{-1}, λ = 254 nm): t_R = 45.7 min (minor), t_R = 75.4 min (major). The relative and absolute configurations were tentatively assigned by analogy.

Typical procedure for synthesis of chiral 2,4-disubstituted 1,2,3,4-tetrahydroquinolines. To a mixture of (^{t}Bu)$_2$(*o*-biphenyl)-PAu(CH_3CN)SbF_6 (0.012 mmol, 3 mol%) and 5 Å molecular sieves (1 g) in dry benzene (6.0 mL) were added 2-aminophenone (0.4 mmol) and alkyne (0.48 mmol) at room temperature. The reaction mixture was stirred at 75 °C and the evolution of the reaction was monitored by TLC until completion. Then phosphoric acid **5** (0.02 mmol, 5 mol%) and ethyl Hantzsch ester **4** (1.0 mmol) were successively added at the same reaction temperature. The resulting reaction mixture was stirred at 60 °C and monitored by TLC. Upon completion, the reaction mixture was filtered through a plug of silica (eluting with CH_2Cl_2) to remove the molecular sieves, and then concentrated *in vacuo*. The residue was purified by silica gel chromatography (eluent: hexane–ethyl acetate = 300 : 1 to 100 : 1) to afford the enantio-enriched product **3**.

(2*R*,4*S*)-2-(4-Methoxyphenyl)-4-phenyl-1,2,3,4-tetrahydroquinoline (3Lb). Yield: 89%. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 7.25 (m, 7H), 6.98 (t, *J* = 7.2 Hz, 1H), 6.86 (d, *J* = 8.6 Hz, 2H), 6.62 (d, *J* = 7.5 Hz, 1H), 6.53 (t, *J* = 7.8 Hz, 2H), 4.52 (dd, *J* = 10.0, 3.7 Hz, 1H), 4.27 (dd, *J* = 11.1, 6.4 Hz, 1H), 3.98 (brs, 1H), 3.76 (s, 3H), 2.19 (m, 2H). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 159.1, 145.4, 145.3, 136.0, 129.6, 128.7, 128.5, 127.7, 127.2, 126.4, 124.7, 117.5, 114.2, 113.9, 56.6, 55.2, 45.0, 42.1. MS: *m/z* (% relative intensity) 315(M^+, 100), 236(74), 194 (67); HRMS: *m/z* calcd for $C_{22}H_{21}ON$ (M^+) 315.1618, found 315.1605. $[\alpha]_D^{20}$ = 49.5 (*c* 0.74, EtOAc); Enantiomeric excess: 87%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 24.9 min (minor), t_R = 35.2 min (major). The relative and absolute configurations were tentatively assigned by analogy.

(2*R*,4*S*)-6-Chloro-2-(4-methoxyphenyl)-4-phenyl-1,2,3,4-tetrahydroquinoline (3Mb). Yield: 93%. ^1H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.32 (m, 4H), 7.23 (m, 3H), 6.93 (m, 1H), 6.87 (d, *J* = 6.9 Hz, 2H), 6.59 (dd, *J* = 2.3, 1.0 Hz, 1H), 6.46 (d, *J* = 8.5 Hz, 1H), 4.51 (dd, *J* = 11.0, 2.8 Hz, 1H), 4.22 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.01 (brs, 1H), 3.78 (s, 3H), 2.18 (m, 2H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 159.2, 144.4, 144.0, 135.5, 129.2, 128.7, 128.6, 127.7, 127.1, 126.8, 126.3, 121.9, 115.3, 114.0, 56.6, 55.3, 44.9, 41.6. MS: *m/z* (% relative intensity) 351 (M^+ + 2, 34), 350(M^+ + 1, 36), 349(M^+, 100), 270(58), 193(31), 121(40); HRMS: *m/z* calcd for $C_{22}H_{20}ONCl$ (M^+) 349.1228, found 349.1221. $[\alpha]_D^{20}$ = 43.6 (*c* 0.97, EtOAc); Enantiomeric excess: 94%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 95 : 5, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 36.6 min (minor), t_R = 67.6 min (major). The relative and absolute configurations were tentatively assigned by analogy.

(2*R*,4*S*)-4-(4-Bromophenyl)-2-(4-methoxyphenyl)-1,2,3,4-tetrahydroquinoline (3Nb). Yield: 98%. ^1H NMR ($CDCl_3$, TMS, 300 MHz): δ 7.48 (d, *J* = 8.3 Hz, 2H), 7.41 (d, *J* = 8.6 Hz, 2H), 7.17 (d, *J* = 8.4 Hz, 2H), 7.06 (m, 1H), 6.95 (d, *J* = 8.6 Hz, 2H), 6.64 (m, 3H), 4.58 (dd, *J* = 10.7, 2.7 Hz, 1H), 4.32 (dd, *J* = 11.8, 5.7 Hz, 1H), 4.08 (brs, 1H), 3.85 (s, 3H), 2.22 (m, 2H). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 159.2, 145.5, 144.6, 135.8, 131.7, 130.5, 129.6, 127.8, 127.5, 124.0, 120.2, 117.7, 114.4, 114.1, 56.6, 55.4, 44.5, 42.1. MS: *m/z* (% relative intensity) 395(M^+ + 2, 50), 394(M^+ + 1, 34), 393(M^+, 53), 224(100),

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193(44); HRMS: *m/z* calcd for $C_{22}H_{20}ONBr$ (M^+) 393.0723, found 393.0714. $[\alpha]_D^{20}$ = 77.0 (*c* 0.87, EtOAc); Enantiomeric excess: 88%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 98 : 2, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 54.2 min (minor), t_R = 74.7 min (major). The relative and absolute configurations were determined by X-ray crystallographic analysis.

(2*R*,4*R*)-2-(4-Methoxyphenyl)-4-methyl-1,2,3,4-tetrahydroquinoline (3Ob). Yield: 94%. ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ 7.40 (d, *J* = 8.6 Hz, 2H), 7.25 (d, *J* = 7.5 Hz, 1H), 7.07 (t, *J* = 7.8 Hz, 1H), 6.97 (d, *J* = 8.6 Hz, 2H), 6.77 (t, *J* = 7.3 Hz, 1H), 6.56 (d, *J* = 7.9 Hz, 1H), 4.48 (dd, *J* = 11.4, 1.6 Hz, 1H), 3.93 (brs, 1H), 3.87 (s, 3H), 3.19 (m, 1H), 2.14 (m, 1H), 1.81 (q, *J* = 11.8 Hz, 1H), 1.42 (d, *J* = 6.8 Hz, 3H). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 159.1, 144.9, 136.6, 127.7, 126.9, 126.8, 126.0, 117.5, 114.1, 114.0, 56.4, 55.3, 41.7, 31.3, 20.1. MS: *m/z* (% relative intensity) 253(M^+, 100), 238(37), 144(28), 132(45); HRMS: *m/z* calcd for $C_{17}H_{19}ON$ (M^+) 253.1461, found 253.1461. $[\alpha]_D^{20}$ = 93.4 (*c* 1.13, EtOAc); Enantiomeric excess: 85%, determined by HPLC (Chiralcel AD-H, hexane–isopropanol = 95 : 5, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 17.8 min (major), t_R = 26.5 min (minor). The relative and absolute configurations were tentatively assigned by analogy.

(2*R*,4*S*)-2-(Biphenyl-4-yl)-4-phenyl-1,2,3,4-tetrahydroquinoline (3Lf). Yield: 73%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.56 (m, 6H), 7.44 (m, 2H), 7.29 (m, 6H), 7.02 (t, *J* = 7.6 Hz, 1H), 6.61 (m, 3H), 4.67 (dd, *J* = 11.0, 2.9 Hz, 1H), 4.34 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.11 (brs, 1H), 2.28 (m, 2H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 145.3, 145.2, 143.0, 140.8, 140.7, 129.7, 128.8, 128.7, 128.6, 127.4, 127.3, 127.2, 127.1, 127.0, 126.5, 124.8, 117.7, 114.3, 57.0, 45.0, 42.1. MS: *m/z* (% relative intensity) 361(M^+, 100), 356(76), 282(77), 194(47); HRMS: *m/z* calcd for $C_{27}H_{23}N$ (M^+) 361.1825, found 361.1834. $[\alpha]_D^{20}$ = 72.5 (*c* 1.25, EtOAc); Enantiomeric excess: 86%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 85 : 15, flow rate 0.7 mL min^{-1}, λ = 254 nm): t_R = 21.2 min (major), t_R = 29.7 min (minor). The relative and absolute configurations were tentatively assigned by analogy.

(2*R*,4*S*)-2-(Biphenyl-4-yl)-6-chloro-4-phenyl-1,2,3,4-tetrahydroquinoline (3Mf). Yield: 91%. ^{1}H NMR ($CDCl_3$, TMS, 400 MHz): δ 7.56 (d, *J* = 8.1 Hz, 4H), 7.47 (d, *J* = 8.0 Hz, 2H), 7.42 (t, *J* = 7.6 Hz, 2H), 7.32 (m, 3H), 7.22 (m, 3H), 6.94 (m, 1H), 6.61 (t, *J* = 1.0 Hz, 1H), 6.47 (d, *J* = 8.5 Hz, 1H), 4.58 (dd, *J* = 11.0, 2.4 Hz, 1H), 4.23 (dd, *J* = 12.0, 5.4 Hz, 1H), 4.05 (brs, 1H), 2.23 (m, 2H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 144.3, 143.9, 142.5, 140.9, 140.7, 129.2, 128.8, 128.7, 128.6, 127.5, 127.4, 127.2, 127.1, 127.0, 126.8, 126.3, 122.1, 115.4, 56.9, 44.9, 41.6. MS: *m/z* (% relative intensity) 397(M^+ + 2, 36), 396(M^+ + 1, 41), 395(M^+, 100), 316(74), 269(41), 178(42); HRMS: *m/z* calcd for $C_{27}H_{22}NCl$ (M^+) 395.1435, found 395.1416. $[\alpha]_D^{20}$ = 15.5 (*c* 0.89, EtOAc); Enantiomeric excess: 90%, determined by HPLC (Chiralcel AD-H, hexane–isopropanol = 95 : 5, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 31.7 min (major), t_R = 41.7 min (minor). The relative and absolute configurations were tentatively assigned by analogy.

(2*R*,4*S*)-6-Chloro-2,4-diphenyl-1,2,3,4-tetrahydroquinoline (3Ma). Yield: 81%. ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ 7.30 (m, 10H), 6.93 (m, 1H), 6.59 (t, *J* = 1.2 Hz, 1H), 6.46 (d, *J* = 8.5 Hz, 1H), 4.55 (dd, *J* = 10.9, 2.9 Hz, 1H), 4.22 (dd, *J* = 12.0, 5.6 Hz, 1H), 4.04 (brs, 1H), 2.19 (m, 2H). ^{13}C NMR ($CDCl_3$, TMS, 75 MHz): δ 143.8, 143.4, 142.9, 128.6, 128.2, 128.0, 127.3, 126.6, 126.3, 126.0, 125.8, 121.5, 114.8, 56.7, 44.3, 41.1. MS: *m/z* (% relative intensity) 321(M^+ + 2, 33), 320(M^+ + 1, 35), 319(M^+, 100), 240(74), 193(64), 71(61); HRMS: *m/z* calcd for $C_{21}H_{18}NCl$ (M^+) 319.1122, found 319.1120. $[\alpha]_D^{20}$ = 43.6 (*c* 1.02, EtOAc); Enantiomeric excess: 90%, determined by HPLC (Chiralcel OD-H, hexane–isopropanol = 97 : 3, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 37.2 min (minor), t_R = 51.4 min (major). The relative and absolute configurations were tentatively assigned by analogy.

(2*R*,4*S*)-2-(4-Bromophenyl)-6-chloro-4-phenyl-1,2,3,4-tetrahydroquinoline (3Mu). Yield: 79%. ^{1}H NMR ($CDCl_3$, TMS, 300 MHz): δ 7.46 (m, 2H), 7.28 (m, 7H), 6.97 (m, 1H), 6.61 (dd, *J* = 2.4, 1.1 Hz, 1H), 6.52 (d, *J* = 8.5 Hz, 1H), 4.56 (dd, *J* = 11.1, 2.8 Hz, 1H), 4.25 (dd, *J* = 12.1, 5.6 Hz, 1H), 4.04 (brs, 1H), 2.18 (m, 2H). ^{13}C NMR ($CDCl_3$, TMS, 100 MHz): δ 144.1, 143.6, 142.5, 131.8, 129.2, 128.8, 128.5, 128.3, 127.2, 126.9, 126.3, 122.3, 121.5, 115.5, 56.7, 44.7, 41.6. MS: *m/z* (% relative intensity) 399(M^+ + 2, 100), 398(M^+ + 1, 51), 397(M^+, 92), 320(79), 228(50); HRMS: *m/z* calcd for $C_{21}H_{17}NBrCl$ (M^+) 397.0227, found 397.0238. $[\alpha]_D^{20}$ = 35.8 (*c* 1.25, EtOAc); Enantiomeric excess: 88%, determined by HPLC (Chiralcel AS-H, hexane–isopropanol = 97 : 3, flow rate 0.5 mL min^{-1}, λ = 254 nm): t_R = 29.7 min (minor), t_R = 34.5 min (major). The relative and absolute configurations were tentatively assigned by analogy.

Bioinformatic analysis and experimental validation. Chemical similarity analysis[19] was performed to investigate the potential biological applications of the chiral tetrahydroquinolines studied here. Experimental validations were performed at Cerep Company. The human recombinant 1321N1 cells were firstly stimulated by 3 nM of MRS2365. The activation of P2Y1 receptor is known to enhance the intracellular Ca^{2+} level. The tested compounds were subsequently added at the dose of 5×10^{-5} M and incubated at room temperature. The intracellular Ca^{2+} level was determined by fluorimetric method. The analysis was performed using software developed at Cerep (Hill software).

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