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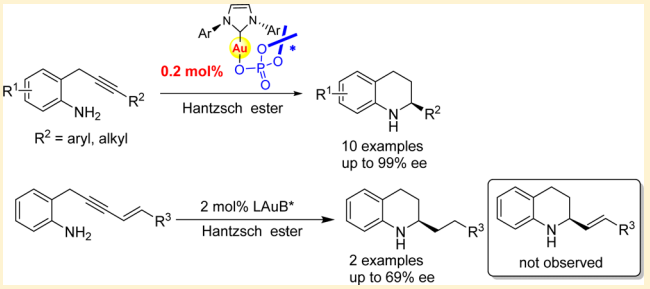
Chiral Gold Phosphate Catalyzed Tandem Hydroamination/Asymmetric Transfer Hydrogenation Enables Access to Chiral Tetrahydroquinolines

Yu-Liu Du, Yue Hu, Yi-Fan Zhu, Xi-Feng Tu, Zhi-Yong Han,* and Liu-Zhu Gong

Hefei National Laboratory for Physical Sciences at the Microscale and Department of Chemistry, University of Science and Technology of China, Hefei 230026, China

Supporting Information

ABSTRACT: A highly efficient chiral gold phosphate-catalyzed tandem hydroamination/asymmetric transfer hydrogenation reaction is described. A series of chiral tetrahydroquinolines were obtained in excellent yields and enantioselectivities. In this reaction, the gold catalyst enables both the hydroamination step as a π-Lewis acid and the asymmetric hydrogen-transfer process as an effective chiral Lewis acid.



Chiral 1,2,3,4-tetrahydroquinoline not only represents a prevalent skeleton in numerous naturally occurring alkaloids and artificial biorelated molecules but also emerges as a privileged building block in drug discovery, which has stimulated a great demand and consequent development of asymmetric synthetic methods for it.[1] Generally, catalytic asymmetric hydrogenation of prepared quinolines provides the most widely used access to chiral tetrahydroquinolines (Scheme 1, eq 1).[2] Various group VIII transition metals, such as iridium,[3] ruthenium,[4] rhodium,[5] and palladium,[6] incorporated with chiral ligands, deliver high efficiency for the enantioselective reduction of quinolines. Rueping and co-workers developed the first organocatalytic asymmetric transfer hydrogenation of quinolines.[7] Recently, we found that chiral gold phosphate is able to catalyze the asymmetric transfer hydrogenation of quinolines very efficiently.

Despite these achievements, asymmetric hydrogenation of quinolines inevitably suffers from harsh conditions and low overall step efficiency brought by preceding quinoline synthesis. To overcome this, we and other groups[7] have been involved in step-economical tetrahydroquinoline syntheses with readily available materials. From *o*-aminobenzaldehyde and β-keto esters, we developed a tandem Friedländer condensation/asymmetric transfer hydrogenation reaction via $Mg(OTf)_2$/chiral phosphoric acid relay catalysis.[8] Through the combination of gold catalysis and chiral Brønsted acid catalysis, alkynyl amines were directly transformed into chiral tetrahydroquinolines (eq 2).[9] However, this Au/organo relay catalytic process demands 5 mol % gold catalyst and 15 mol % chiral phosphoric acid,[10] thus lowering the practical applicability of this methodgy. Previously, we have found that chiral gold phosphate could serve as a highly efficient catalyst for the asymmetric transfer hydrogenation of quinolines,[11] with the stereoselectivity controlled by the chiral counteranion.[12,13] We envisioned that, with an efficient gold catalyst, the tandem process might be realized through solely gold catalysis.[14] Herein, we disclose a high yielding and enantioselective cascade hydroamination/asymmetric transfer hydrogenation reaction,

Scheme 1. Strategy for Enantioselective Synthesis of Chiral 1,2,3,4-Tetrahydroquinolines

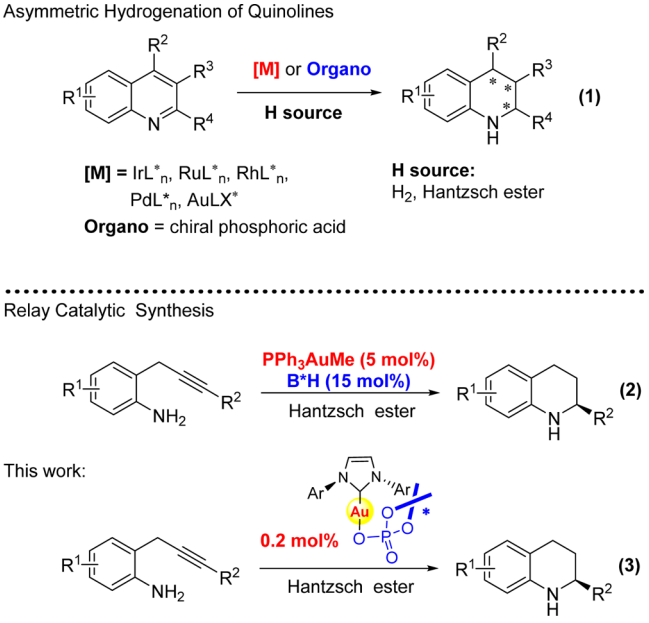


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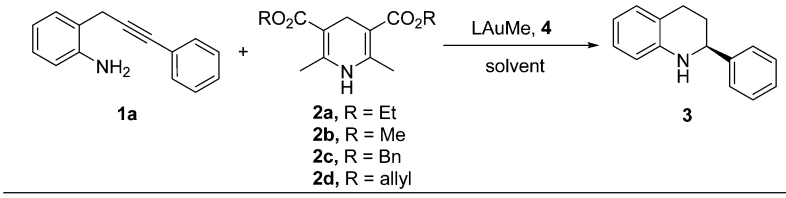
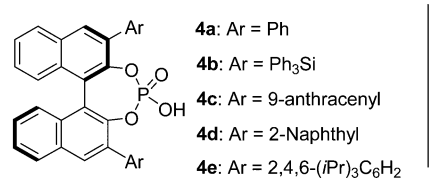
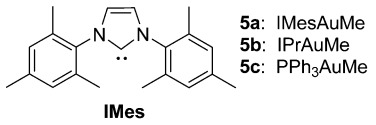
Table 1. Evaluation of Catalysts and Optimization of Reaction Conditions[a]







entry	B*−H	[Au] mol %	5	solvent	yield (%)	ee[b]
1	**4a**	1	**5a**	Tol	47	9
2	**4b**	1	**5a**	Tol	57	34
3	**4c**	1	**5a**	Tol	68	96
4	**4d**	1	**5a**	Tol	54	15
5	**4e**	1	**5a**	Tol	80	98
6	**4e**	1	**5b**	Tol	55	10
7	**4e**	1	**5c**	Tol	5	98
8	**4e**	1	**5a**	Tol	74	93[c]
9	**4e**	1	**5a**	Tol	68	90[d]
10	**4e**	1	**5a**	Tol	60	97[e]
11	**4e**	1	**5a**	CH_2Cl_2[f]	<5	97
12	**4e**	1	**5a**	THF[g]	trace	
13	**4e**	1	**5a**	*p*-xylene	59	80
14	**4e**	0.5	**5a**	Tol	80	98
15	**4e**	0.2	**5a**	Tol	81	98
16	**4e**	0.1	**5a**	Tol	59	98

[a]Unless indicated otherwise, the reaction of **1a** (0.1 mmol), **2a** (R = Et, 0.24 mmol) was carried out in toluene (1.5 mL) at 90 °C for 16 h under Ar in the presence of a gold catalyst precursor (1 mol %) and Brønsted acid (1 mol %). [b]The ee was determined by HPLC. [c]R = Me. [d]R = Bn. [e]R = Allyl. [f]Reaction was carried out at rt for 32 h. [g]Reaction was carried out at 60 °C.

catalyzed by as low as 0.2 mol % single chiral gold phosphates (eq 3).[11,15]

Our initial investigation included the reaction of 2-(3-phenyl-2-propyl)aniline (**1a**) with Hantzsch ester (**2a**) at 90 °C using chiral gold phosphates generated *in situ* from 1 mol % of IMesAuMe and 1 mol % BINOL-based phosphoric acid (**4**). Among the chiral phosphoric acids we investigated (Table 1, entries 1−5), **4e** was identified to be ideal for this process, which improved the stereochemical outcome to 98% ee with 80% yield. Then, several gold ligands were examined (entries 5−7). Carbene-type ligand IMes provided the best result in yield and enantioselectivity (entry 5) while PPh_3 gave the product with excellent stereoselectivity but only 5% yield (entry 7), and IPr ligand led to a moderate yield and poor enantioselectivity (entry 6). With the results above, an examination of different Hantzsch esters (entries 8−10) revealed that **2a** was the best hydride source. Moreover, a brief screening of solvents (entries 11−13) resulted in toluene being optimal for this reaction regarding both yield and enantioselectivity. With the optimized conditions in hand, we tried to lower the catalyst loading (entries 14−16). To our delight, 0.2 mol % of catalyst still furnished the reaction without any drop of yield and enantioselectivity. A further decrease in gold loading to 0.1 mol % led to the retention of stereoselectivity and, however, a notable reduction of target product yield.

Under the optimized reaction conditions, the general applicability of the reaction toward substituted 2-(2-propynyl)-aniline derivatives were investigated in the presence of 0.2 mol % of chiral gold phosphate generated from (IMes)AuMe and **4e** (Table 2). The gold catalytic tandem reaction tolerated a wide range of substrates. For 2-(2-propynyl)anilines bearing various aromatic substituents, from electron-deficient to electron-rich, on the propynyl moiety (entries **3a**−**3f**), the tandem reaction proceeded cleanly to give tetrahedroquinolines with good yields (from 81% to 86%) and excellent enantioselectivities (from 96% to 98% ee). An aliphatic substituent exhibited a passive effect of the enantioselectivity: *n*-propyl and *n*-butyl substituted 2-(2-propynyl)anilines (entries **3g**−**3h**) provided the desired product with good yields yet lower enantiometric excess values. Long aliphatic chain substituted aromatic substituents (entry **3i**) maintained the excellent stereoselectivity and even enhanced the yield to 91%. Moreover, substituents on the aniline moiety (entries **3j**−**3k**) were also tolerable. Both electron-withdrawing and -donating substituents were suitable for the reaction, resulting in good conversion and excellent enantioselectivity.

Vinyl substituted substrates **1l** and **1m** were investigated in the presence of 2 mol % of gold catalyst and 3.0 equiv of the Hantzsch ester (Scheme 2). Unexpectedly, aliphatic substituted products **3l** and **3m** were obtained with moderate yields and enantioselectivities. Obviously, the substituted vinyl group was

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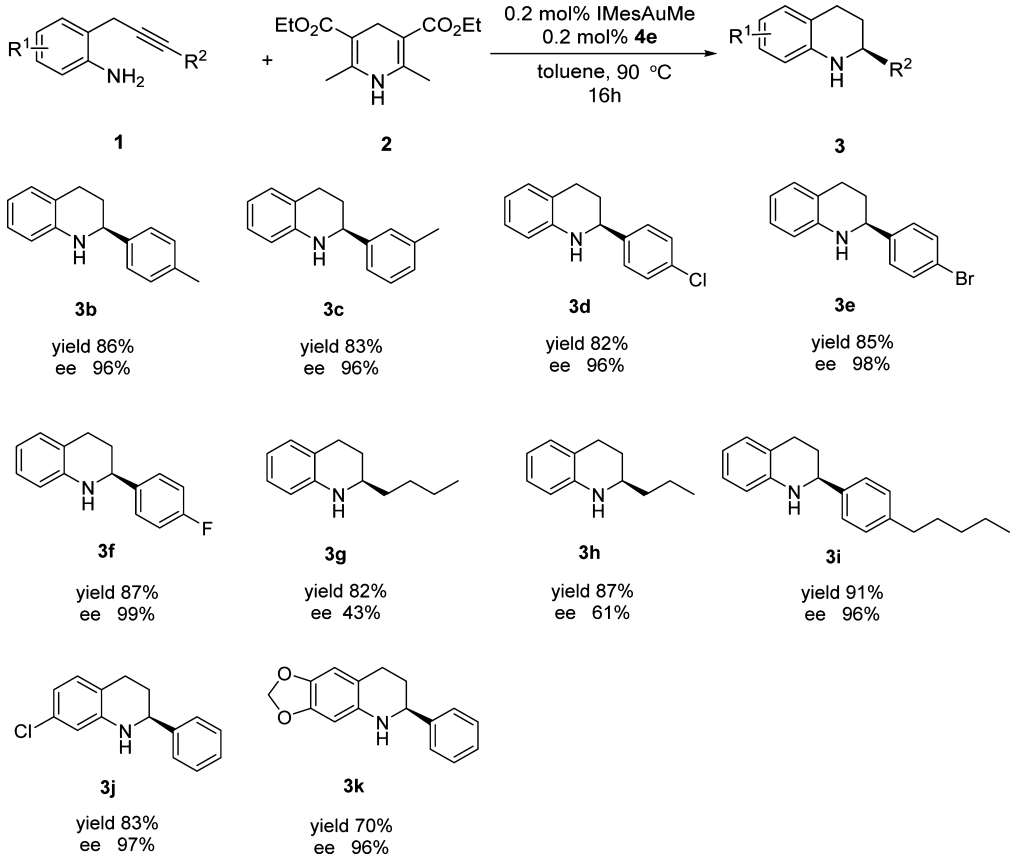
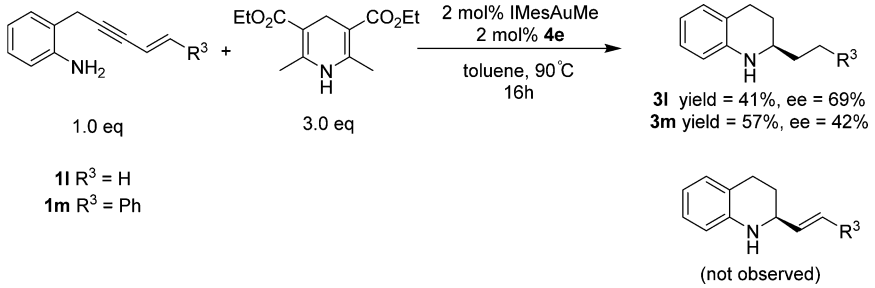
Table 2. Scope of 2-(2-Propynyl)aniline Derivatives of the Gold-Catalyzed Tandem Reaction[a,b]

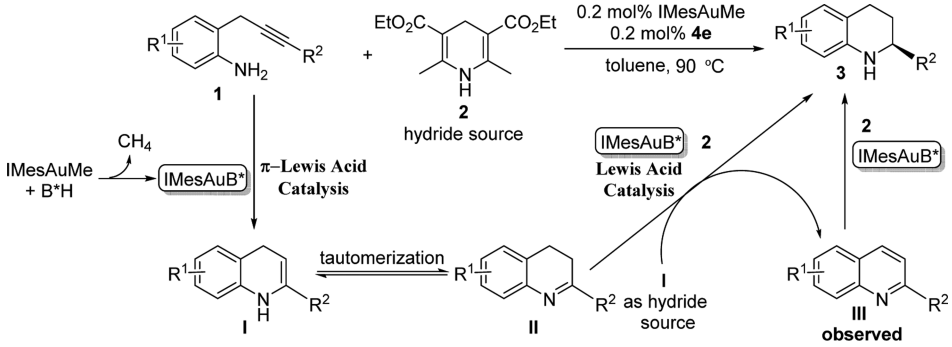


[a]Unless indicated otherwise, the reaction of **1a** (0.1 mmol), **2a** (0.24 mmol) was carried out in toluene (1.5 mL) at 90 °C for 16 h under Ar in the presence of a gold catalyst (0.2 mol %), Brønsted acid (0.2 mol %). [b]The ee was determined by HPLC.

Scheme 2. Vinyl Substituted 2-(2-Propynyl)aniline Derivatives of the Gold-Catalyzed Tandem Reaction



Scheme 3. Proposed Mechanism for This Tandem Reaction



reduced as well by a Hantzsch ester under the reaction conditions.

Interestingly, during the process of this tandem reaction, we observed the formation of quinoline **III**, which disappeared at

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the end of the reaction. Based on this, we proposed the reaction might proceed via the mechanism as shown in Scheme 3. Chiral gold phosphate formed *in situ* functions as both a π-Lewis acid catalyst and a Lewis acid catalyst. In the asymmetric transfer-hydrogenation step, both Hantzsch ester **2** and 2*H*-quinoline intermediate **I** could participate as the hydrogen source. In the latter case, quinoline **III** would be formed and underwent subsequent asymmetric reduction leading to the desired product as well.

In summary, we have developed an effective method for directly transforming 2-(2-propynyl)aniline derivatives into optically active tetrahydroquinolines in one operation with moderate to good yields and excellent enantioselectivities through the catalysis of only 0.2 mol % of chiral gold phosphate generated *in situ* from IMesAuMe and a chiral phosphoric acid. Notably in this reaction, the gold catalyst enables both the intramolecular hydroamination as a π-Lewis acid and the asymmetric reduction as a highly effective chiral Lewis acid.

EXPERIMENTAL SECTION

General Method. NMR spectra were recorded on a 400 MHz spectrometer. HRMS spectra were recorded on a TOF-Q mass spectrometer. The enantiomeric excess of the compounds was determined by chiral HPLC using racemic compounds as references. All starting materials, reagents, and solvents were purchased from commercial suppliers and used as supplied unless otherwise stated. Toluene and THF were dried over Na and distilled prior to use. MeCN and CH_2Cl_2 were dried over CaH_2 and distilled prior to use. Chloroform was washed by water and dried over Na_2SO_4. 2-(2-Propynyl)aniline derivatives **1** were synthesized according to the reported procedure.[9] The absolute configuration of 1,2,3,4-tetrahydroquinoline derivatives were determined by comparison of HPLC retention time with that reported in the literature.[7a,9,11]

General Procedures for the Synthesis of 1,2,3,4-Tetrahydroquinoline Derivatives. A mixture of IMesAuMe (0.2 mol %) and phosphoric acid **4e** (0.2 mol %), Hantzsch dihydropyridine **2a** (0.24 mmol, 2.4 equiv), and 2-(2-propynyl)aniline derivatives **1** (0.1 mmol) were flushed with argon and suspended in toluene (1.5 mL) in a screw-capped vial. The resulting mixture was allowed to stir at 90 °C for 16 h. The solvent was removed under reduced pressure and then purified through column chromatography on silica gel (ethyl acetate/petroleum ether = 20:1) to afford the product.

*2-(3-Phenylprop-2-ynyl)aniline (**1a**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.66 (s, 2H), 3.76 (brs, 2H), 6.70 (d, J = 7.6 Hz, 1H), 6.78 (t, J = 7.2 Hz, 1H), 7.11 (t, J = 7.6 Hz, 1H), 7.22−7.29 (m, 4H),7.40−7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 22.5, 82.8, 86.2, 116.0, 118.9, 121.4, 123.4, 127.9, 128.0, 128.2, 129.4, 131.6, 144.5.

*2-(3-p-Tolylprop-2-ynyl)aniline (**1b**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.33 (s, 3H), 3.66 (s, 2H), 3.91 (brs, 2H), 6.71 (d, J = 7.88 Hz, 1H), 6.77(t, J = 7.2 Hz, 1H), 7.08−7.13(m, 3H), 7.23−7.25 (m, 1H), 7.30 (d, J = 8.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 21.4, 22.7, 82.9, 85.4, 116.0, 118.9, 120.3, 121.6, 128.0, 129.0, 129.5, 131.5, 138.0, 144.6.

*2-(3-m-Tolylprop-2-ynyl)aniline (**1c**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 2.31 (s, 3H), 3.66 (s, 2H), 3.86 (brs, 2H), 6.71 (d, J = 7.6 Hz, 1H), 6.78 (t, J = 7.6 Hz, 1H), 7.11 (td, J = 8.0, 1.6 Hz, 2H), 7.17 (t, J = 7.6 Hz, 1H), 7.22−7.25 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 21.2, 22.7, 83.0, 85.8, 116.1, 118.9, 121.5, 123.2, 128.1, 128.7, 128.8, 128.9, 129.5, 132.3, 137.9, 144.6.

*2-(3-(4-Chlorophenyl)prop-2-yn-1-yl)aniline (**1d**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.66 (s, 2H), 3.84 (brs, 2H), 6.72 (d, J = 7.9 Hz, 1H), 6.78 (t, J = 7.5 Hz, 1H), 7.11 (td, J = 7.7, 1.4 Hz, 2H), 7.22−7.27 (m, 3H), 7.32−7.35 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 22.6, 81.8, 87.3, 116.0, 119.0, 121.1, 121.9, 128.2, 128.6, 128.8, 128.9, 129.4, 132.9, 134.0, 144.5; HR-ESI calculated for $C_{15}H_{12}ClN$ [M + H]: 242.0737, found: 242.0760. Mp 72−75 °C.

*2-(3-(4-Bromophenyl)prop-2-ynyl)aniline (**1e**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.64 (s, 2H), 3.86 (brs, 2H), 6.72 (dd, J = 7.6, 0.8 Hz, 1H), 6.78 (td, J = 7.2, 1.2 Hz, 1H), 7.11 (td, J = 7.6, 1.2 Hz, 1H), 7.22−7.28 (m, 3H), 7.40−7.42 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 22.6, 81.8, 87.5, 116.0, 118.9, 121.0, 122.1, 122.4, 128.1, 129.5, 131.5, 133.1, 144.5. Mp 72−77 °C.

*2-(3-(4-Fluorophenyl)prop-2-ynyl)aniline (**1f**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.64 (s, 2H), 3.80 (brs, 2H), 6.71 (d, J = 8.0 Hz, 1H), 6.78 (td, J = 7.4, 1.0 Hz, 1H), 6.97 (tt, J = 8.7, 1.8 Hz, 2H), 7.11 (td, J = 7.7, 1.3 Hz, 1H), 7.23−7.25 (m, 1H), 7.36−7.41 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 22.5, 81.7, 85.8, 115.3, 115.5, 115.9, 118.9, 121.2, 128.0, 129.4, 133.4, 133.5, 144.5, 161.0, 163.5.

*2-(Hept-2-yn-1-yl)aniline (**1g**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.90 (t, J = 7.2 Hz, 3H), 1.35−1.52 (m, 4H), 2.10 (tt, J = 6.8, 2.4 Hz, 2H), 3.41 (t, J = 2.4 Hz, 2H), 3.88 (brs, 2H), 6.69 (dd, J = 8.0, 1.2 Hz, 1H), 6.74 (td, J = 7.6, 1.2 Hz, 1H), 7.08 (td, J = 7.6, 1.2 Hz, 1H), 7.16 (d, J = 7.6 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 13.6, 18.5, 22.0, 22.1, 31.0, 76.2, 82.9, 115.8, 118.8, 122.3, 127.8, 129.3, 144.6.

*2-(Hex-2-yn-1-yl)aniline (**1h**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.97 (t, J = 7.36 Hz, 3H), 1.52 (dd, J = 14.5, 7.2 Hz, 2H), 2.16 (tt, J = 7.1, 2.4 Hz, 2H), 3.41 (t, J = 2.4 Hz, 2H), 3.88 (brs, 2H), 6.69 (dd, J = 7.9, 1.1 Hz, 1H), 6.74 (td, J = 7.4, 1.2 Hz, 1H), 7.08 (td, J = 7.8, 1.5 Hz, 1H), 7.17 (t, J = 7.5 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 13.6, 20.8, 22.1, 22.4, 76.4, 82.8, 115.9, 118.8, 122.3, 127.8, 129.3, 144.6; HR-ESI calculated for $C_{12}H_{15}N$ [M + H]: 174.1283, found: 174.1293.

*2-(3-(4-Pentylphenyl)prop-2-yn-1-yl)aniline (**1i**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 0.88 (t, J = 6.93 Hz, 3H), 1.31 (m, 4H), 1.59 (m, 2H), 2.59 (dd, J = 14.4, 6.8 Hz, 2H), 3.61 (s, 1H), 3.89 (brs, 2H), 6.59 (d, J = 8.4 Hz, 2H), 7.10 (m, 3H), 7.19 (dd, J = 8.4, 2.3 Hz, 1H), 7.31(dd, J = 9.8, 8.1 Hz, 2H), 7.36 (d, J = 2.3 Hz, 1H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 22.3, 82.7, 86.4, 98.5, 100.7, 109.4, 113.7, 123.4, 128.0, 128.2, 131.6, 138.9, 140.6, 147.1; HR-ESI calculated for $C_{20}H_{23}N$ [M + H]: 278.1909, found: 278.1913.

*5-Chloro-2-(3-phenylprop-2-yn-1-yl)aniline (**1j**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.60 (s, 2H), 3.93 (brs, 2H), 6.69 (d, J = 2.0 Hz, 1H) 6.73 (dd, J = 8.0, 2.0 Hz, 1H), 7.15 (d, J = 8.0 Hz, 1H), 7.27−7.30 (m, 3H), 7.38−7.43 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 22.1, 88.2, 85.5, 115.5, 118.6, 119.7, 123.2, 128.1, 128.3, 130.4, 131.6, 133.4, 145.7.

*6-(3-Phenylprop-2-yn-1-yl)benzo[d][1,3]dioxol-5-amine (**1k**).* ^{1}H NMR ($CDCl_3$, 400 MHz) δ (ppm) 3.58 (s, 2H), 3.67 (brs, 2H), 5.86 (s, 2H), 6.32 (s, 1H), 6.80 (s, 1H), 7.27−7.33 (m, 3H), 7.38−7.45 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz) δ (ppm) 22.3, 82.7, 86.4, 98.5, 100.7, 109.4, 113.7, 123.4, 128.0, 128.2, 131.6, 138.9, 140.6, 147.1.

*2-(Pent-4-en-2-yn-1-yl)aniline (**1l**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.17 (d, J = 7.4 Hz, 1H), 7.12−7.05 (m, 1H), 6.76 (t, J = 7.4 Hz, 1H), 6.69 (d, J = 7.9 Hz, 1H), 5.85−5.74 (m, 1H), 5.59 (dd, J = 17.5, 1.8 Hz, 1H), 5.42 (dd, J = 11.0, 2.0 Hz, 1H), 3.82 (brs, 2H), 3.55 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 129.4, 128.1, 126.5, 121.3, 118.9, 117.2, 116.0, 86.9, 81.5, 22.5. HR-ESI calculated for $C_{11}H_{11}N$ [M + H]: 158.0970, found: 158.0963.

*(E)-2-(5-Phenylpent-4-en-2-yn-1-yl)aniline (**1m**).* ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.36−7.23 (m, 1H), 7.21−7.16 (m, 1H), 7.13−7.05 (m, 1H), 6.90 (d, J = 16.3 Hz, 1H), 6.81−6.72 (m, 1H), 6.69 (d, J = 7.9 Hz, 1H), 6.15 (ddd, J = 16.2, 4.8, 2.6 Hz, 1H), 3.84 (brs, 2H), 3.60 (s, 2H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.6, 141.0, 136.4, 129.5, 128.7, 128.5, 128.1, 126.2, 121.5, 119.0, 116.1, 108.3, 88.6, 82.0, 22.9. HR-ESI calculated for $C_{17}H_{15}N$ [M + H]: 234.1283, found: 234.1274; mp 61−64 °C.

*(S)-2-Phenyl-1,2,3,4-tetrahydroquinoline (**3a**).* Yield: 81%, 16.9 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.96−2.02 (m, 1H), 2.08−2.10 (m, 1H), 2.74 (dt, J = 16.4, 4.8 Hz, 1H), 2.88−2.90 (m, 1H), 4.00 (s, 1H), 4.41 (dd, J = 9.2, 3.2 Hz, 1H), 6.51 (d, J = 7.6 Hz, 1H), 6.64 (td, J = 7.6, 0.8 Hz, 1H), 6.97−6.99 (m, 2H), 7.26−7.39 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ(ppm) 26.3, 30.9, 56.1, 113.9, 117.0, 120.7, 126.4, 126.8, 127.3, 128.5, 129.2, 144.6, 144.7; Enantiomeric excess: 98%, determined by HPLC (Chiracel-OD-H, hexane/isopropanol = 95/5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 10.44 min (major), t_R = 13.90 min (minor).

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J. Org. Chem. 2015, 80, 4754−4759

*(S)-2-(p-Tolyl)-1,2,3,4-tetrahydroquinoline (**3b**).* Yield: 86%, 19.1 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.85−1.95 (m, 1H), 1.99−2.06 (m, 1H), 2.28 (s, 3H), 2.66 (dt, J = 16.3, 4.7 Hz, 1H), 2.84 (ddd, J = 16.3, 10.8, 5.5 Hz, 1H), 3.95 (brs, 1H), 4.32 (dd, J = 9.4, 3.2 Hz, 1H), 6.45 (dd, J = 8.4, 1.0 Hz, 1H), 6.56 (td, J = 7.4, 1.0 Hz, 1H), 6.93 (t, J = 7.02 Hz, 2H), 7.08 (d, J = 7.9 Hz, 1H), 7.18−7.21 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 20.1, 25.5, 30.0, 55.0, 112.9, 116.1, 119.9, 125.4, 125.8, 128.2, 128.3, 136.1, 140.8, 143.8; Enantiomeric excess: 96%, determined by HPLC (Chiracel-OD-H, hexane/isopropanol = 95/5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 8.37 min (major), t_R = 15.11 min (minor).

*(S)-2-(m-Tolyl)-1,2,3,4-tetrahydroquinoline (**3c**).* Yield: 83%, 18.5 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.93−2.03 (m, 1H), 2.10 (ddt, J = 7.6, 5.5, 4.2 Hz, 1H), 2.35 (s, 3H), 2.74 (dt, J = 16.3, 4.6 Hz, 1H), 2.92 (ddd, J = 16.4, 10.9, 5.5 Hz, 1H), 4.01 (brs, 1H), 4.39 (dd, J = 9.5, 3.3 Hz, 1H), 6.53 (dd, J = 8.4, 1.0 Hz, 1H), 6.64 (td, J = 7.4, 1.1 Hz, 1H), 7.00 (t, J = 7.1 Hz, 2H), 7.09 (d, J = 7.4 Hz, 1H), 7.17−7.25 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 21.5, 26.6, 31.1, 56.3, 114.0, 117.1, 120.9, 123.6, 126.9, 127.3, 128.2, 128.5, 129.3, 138.3, 144.8; Enantiomeric excess: 96%, determined by HPLC (Chiracel-OD-H, hexane/isopropanol = 95/5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 8.43 min (major), t_R = 10.90 min (minor).

*(S)-2-(4-Chlorophenyl)-1,2,3,4-tetrahydroquinoline (**3d**).* Yield: 82%, 20.0 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.90−1.99 (m, 1H), 2.06−2.12 (m, 1H), 2.71 (dt, J = 16.4, 4.9 Hz, 1H), 2.90 (ddd, J = 16.1, 10.4, 5.4 Hz, 1H), 4.01 (brs, 1H), 4.42 (dd, J = 9.1, 3.3 Hz, 1H), 6.54 (d, J = 7.9 Hz, 1H), 6.67 (dd, J = 7.4, 1.0 Hz, 1H), 6.98−7.03 (m, 2H), 7.29−7.33 (m, 4H), ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 26.1, 31.0, 55.6, 114.1, 117.4, 120.8, 127.0, 127.9, 128.7, 129.3, 133.0, 143.4, 144.4; $[\alpha]_D^{20}$ = −40.9 (c 0.17, $CHCl_3$); HR-ESI calculated for $C_{15}H_{14}ClN$ [M + H]: 244.0893, found: 244.0899; Enantiomeric excess: 96%, determined by HPLC (Chiracel-OD-H, hexane/isopropanol = 95/5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 13.17 min (major), t_R = 24.42 min (minor).

*(S)-2-(4-Bromophenyl)-1,2,3,4-tetrahydroquinoline (**3e**).* Yield: 85%, 24.5 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.93 (t, J = 6.8 Hz, 3H), 1.33−1.64 (m, 7H), 1.93−1.99 (m, 1H), 2.69−2.85 (m, 2H), 3.20−3.26 (m, 1H), 3.81 (brs, 1H), 6.47 (dd, J = 8.4, 1.0 Hz, 1H), 6.59 (td, J = 7.4, 1.0 Hz, 1H), 6.93−6.97 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 14.1, 22.8, 26.4, 27.9, 28.1, 36.4, 51.6, 114.0, 116.9, 121.4, 126.7, 129.3, 144.8. Enantiomeric excess: 98%, determined by HPLC (Chiracel-OD-H, hexane/isopropanol = 95/5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 15.28 min (major), t_R = 28.83 min (minor).

*(S)-2-(4-Fluorophenyl)-1,2,3,4-tetrahydroquinoline (**3f**).* Yield: 87%, 19.7 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.91−2.00 (m, 1H), 2.04−2.12 (m, 1H), 2.72 (dt, J = 16.4, 4.8 Hz, 1H), 2.92 (ddd, J = 16.2, 10.6, 5.5 Hz, 1H), 4.02 (brs, 1H), 4.42 (dd, J = 9.3, 3.2 Hz, 1H), 6.54 (d, J = 7.7 Hz, 1H), 6.65 (td, J = 7.4, 1.1 Hz, 1H), 6.99−7.05 (m, 4H), 7.32−7.37(m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 26.3, 31.1, 55.6, 114.1, 115.2, 115.5, 117.4, 120.8, 127.0, 128.0, 128.1, 129.3, 140.5, 144.6, 160.9, 163.4. Enantiomeric excess: 99%, determined by HPLC (Chiracel-OD-H, hexane/isopropanol = 95/5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 10.95 min (major), t_R = 17.53 min (minor).

*(R)-2-Butyl-1,2,3,4-tetrahydroquinoline (**3g**).* Yield: 82%, 15.5 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.93 (t, J = 7.1 Hz, 3H), 1.33−1.40 (m, 4H), 1.46−1.52 (m, 2H), 1.55−1.64 (m, 2H), 1.93−1.99 (m, 1H), 2.17 (s, 1H), 2.69−2.85 (m, 2H), 3.20−3.26 (m, 1H), 3.81 (brs, 1H), 6.47 (dd, J = 8.4, 1.0 Hz, 1H), 6.59 (td, J = 7.4, 1.1 Hz, 1H), 6.93−6.97 (m, 2H) ; ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 14.1, 22.8, 26.4, 27.9, 28.1, 36.4, 51.6, 114.0, 116.9, 121.4, 126.7, 129.3, 144.8. Enantiomeric excess: 43%, determined by HPLC (Chiracel-IC-H, hexane/isopropanol = 99.7/0.3, flow rate 0.8 mL/min, T = 30 °C, 254 nm): t_R = 12.57 min (major), t_R = 13.67 min (minor).

*(R)-2-Propyl-1,2,3,4-tetrahydroquinoline (**3h**).* Yield: 87%, 15.3 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.96 (t, J = 7.1 Hz, 3H), 1.37−1.51 (m, 4H), 1.51−1.64 (m, 1H), 1.92−1.98 (m,1H), 2.69−2.85 (m, 2H), 3.25 (dtd, J = 9.4, 6.1, 3.0 Hz, 1H), 3.72 (brs, 1H), 6.46 (dd, J = 8.4, 1.0 Hz, 1H), 6.59 (td, J =7.4, 1.0 Hz, 1H), 6.93−6.96 (m, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 14.2, 18.9, 26.5,28.1, 38.9, 51.3, 114.0, 116.9, 121.4, 126.7, 129.3, 144.8; $[\alpha]_D^{20}$ = 17.6 (c 0.036, $CHCl_3$); HR-ESI calculated for $C_{12}H_{17}N$ [M + H]: 176.1439, found: 176.1452; Enantiomeric excess: 61%, determined by HPLC (Chiracel-IC-H, hexane/isopropanol = 99.7/0.3, flow rate 0.8 mL/min, T = 30 °C, 254 nm): t_R = 16.88 min (major), t_R = 18.86 min (minor).

*(S)-2-(4-Pentylphenyl)-1,2,3,4-tetrahydroquinoline (**3i**).* Yield: 91%, 25.4 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 0.89(t, J = 6.9 Hz, 3H), 1.28−1.36 (m, 4H), 1.61 (dt, J = 9.3, 7.5 Hz, 2H), 1.89−1.98 (m, 1H), 2.05−2.12 (m, 1H), 2.57−2.61 (m, 2H), 2.69 (dt, J = 14.8, 3.8 Hz, 1H), 2.86 (ddd, J = 16.2, 10.6, 5.4 Hz, 1H), 4.05 (brs, 1H), 4.4 (dd, J = 9.2, 3.3 Hz, 1H), 6.39 (d, J = 8.4 Hz, 1H), 7.05−7.80 (m, 2H), 7.14−7.17 (m, 2H), 7.24−7.26 (m, 3H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 14.0, 22.6, 26.2, 30.4, 31.2, 31.6, 36.0, 55.9, 108.4, 115.3, 122.9, 126.4, 127.4, 128.6, 129.1, 129.5, 131.7, 141.5, 142.4, 143.8; $[\alpha]_D^{20}$ = −22.78 (c 0.06, $CHCl_3$); HR-ESI calculated for $C_{20}H_{25}N$ [M + H]: 280.2065, found: 280.2069; Enantiomeric excess: 96%, determined by HPLC (Chiracel-OD-H, hexane/isopropanol = 95/5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 6.09 min (major), t_R = 11.08 min (minor).

*(S)-7-Chloro-2-phenyl-1,2,3,4-tetrahydroquinoline (**3j**).* Yield: 83%, 20.2 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.89−2.00 (m, 1H), 2.07−2.13 (m, 1H), 2.66 (dt, J = 16.4, 4.8 Hz, 1H), 2.78−2.86 (m, 1H), 4.10 (brs, 1H), 4.42 (dd, J = 9.2, 3.6 Hz, 1H), 6.50 (d, J = 2.0 Hz, 1H), 6.58 (dd, J = 8.0, 2.0 Hz, 1H), 6.87 (d, J = 8.0 Hz, 1H), 7.26−7.35 (m, 5H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 25.7, 30.5, 55.9, 113.3, 116.8, 119.2, 126.4, 127.5, 128.6, 130.1, 132.1, 144.3, 145.6; HR-ESI calculated for $C_{20}H_{25}N$ [M + H]: 280.2065, found: 280.2069. Enantiomeric excess: 97%, determined by HPLC (Chiracel-OD-H, hexane/isopropanol = 95/5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 12.77 min (major), t_R = 22.77 min (minor).

*(S)-6-Phenyl-5,6,7,8-tetrahydro-[1,3]dioxolo[4,5-g]quinoline (**3k**).* Yield: 70%, 17.8 mg; ^{1}H NMR ($CDCl_3$, 400 MHz): δ (ppm) 1.91−2.01 (m, 1H), 2.05−2.12 (m, 1H), 2.63 (dt, J = 16.0, 4.8 Hz, 1H), 2.81−2.89 (m, 1H), 3.81 (brs, 1H), 4.34 (dd, J = 9.6, 3.2 Hz, 1H), 5.81 (d, J = 2.4 Hz, 1H), 5.81 (d, J = 2.4 Hz, 1H), 6.14 (s, 1H), 6.50 (s, 1H), 7.24−7.29 (m, 1H), 7.29−7.39 (m, 4H); ^{13}C NMR ($CDCl_3$, 100 MHz): δ (ppm) 26.4, 31.1, 56.4, 96.4, 100.3, 109.0, 112.7, 126.5, 127.4, 128.5, 139.3, 139.6, 144.7, 146.3; Enantiomeric excess: 96%, determined by HPLC (Chiracel-OD-H, hexane/isopropanol = 95/5, flow rate 1.0 mL/min, T = 30 °C, 254 nm): t_R = 15.66 min (major), t_R = 17.91 min (minor).

*(R)-2-Ethyl-1,2,3,4-tetrahydroquinoline (**3l**).* Yield: 41%; 6.6 mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 6.96 (t, J = 7.1 Hz, 2H), 6.59 (t, J = 7.3 Hz, 1H), 6.48 (d, J = 8.0 Hz, 1H), 3.78 (brs, 1H), 3.23−3.10 (m, 1H), 2.88−2.67 (m, 2H), 2.01−1.93 (m, 1H), 1.66−1.46 (m, 3H), 0.99 (t, J = 7.5 Hz, 3H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.8, 129.3, 126.7, 121.4, 116.9, 114.0, 53.0, 29.4, 27.6, 26.4, 10.1; $[\alpha]_D^{20}$ = 81.7 (c 0.04, $CHCl_3$) HR-ESI calculated for $C_{11}H_{15}N$ [M + H]: 162.1283, found: 162.1277. Enantiomeric excess: 69%, determined by HPLC (Chiracel-IC-H, hexane/isopropanol = 99.7/0.3, flow rate 0.8 mL/min, T = 30 °C, 254 nm): t_R = 7.93 min (major), t_R = 8.56 min (minor).

*(R)-2-Phenethyl-1,2,3,4-tetrahydroquinoline (**3m**).* Yield: 57%; 13.5 mg. ^{1}H NMR (400 MHz, $CDCl_3$) δ 7.33−7.26 (m, 2H), 7.24−7.17 (m, 3H), 6.96 (t, J = 7.2 Hz, 2H), 6.60 (t, J = 7.3 Hz, 1H), 6.45 (d, J = 8.0 Hz, 1H), 3.77 (brs, 1H), 3.36−3.24 (m, 1H), 2.87−2.67 (m, 4H), 2.00 (ddd, J = 12.8, 7.9, 4.9 Hz, 1H), 1.84 (dt, J = 13.1, 6.7 Hz, 2H), 1.67 (dtd, J = 12.8, 10.3, 5.6 Hz, 1H). ^{13}C NMR (101 MHz, $CDCl_3$) δ 144.5, 141.9, 129.3, 128.5, 128.4, 126.8, 126.0, 121.3, 117.1, 114.2, 51.1, 38.3, 32.2, 28.0, 26.2; $[\alpha]_D^{20}$ = 40.4 (c 0.094, $CHCl_3$); HR-ESI calculated for $C_{17}H_{19}N$ [M + H]: 238.1596, found: 238.1588. Enantiomeric excess: 42%, determined by HPLC (Chiracel-IC-H, hexane/isopropanol = 99.7/0.3, flow rate 0.8 mL/min, T = 30 °C, 254 nm): t_R = 12.76 min (major), t_R = 14.49 min (minor).

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■ ASSOCIATED CONTENT

Supporting Information

Characterization data. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: hanzy2014@ustc.edu.cn.

Notes

The authors declare no competing financial interest.

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