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A Synthetic Route to Chiral Benzo-Fused N-Heterocycles via Sequential Intramolecular Hydroamination and Asymmetric Hydrogenation of Anilino-Alkynes

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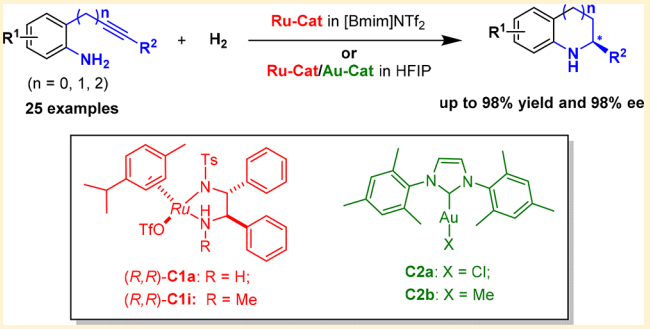
Supporting Information

ABSTRACT: An efficient sequential intramolecular hydroamination/asymmetric hydrogenation reaction under catalysis of a single chiral ruthenium complex or a binary system consisting of achiral gold complex and chiral ruthenium complex has been reported. A diverse range of enantioenriched benzo-fused N-heterocycles, including 1,2,3,4-tetrahydroquinoline, indoline, and 2,3,4,5-tetrahydro-1*H*-benzo[*b*]-azepine derivatives, were obtained from anilino-alkynes in high yields (up to 98%) with moderate to excellent enantioselectivities (up to 98% ee) under mild conditions. This protocol features good functional group tolerance and high atom economy. Furthermore, this catalytic protocol is applicable to gram-scale synthesis of a naturally occurring alkaloid, (−)-Angustureine.



INTRODUCTION

Benzo-fused *N*-heterocycles (BFNHs) are core structural elements in a large number of biologically active molecules, including natural alkaloids and pharmaceuticals.[1−3] Among these BFNHs, tetrahydroquinoline and indoline derivatives are regarded as privileged structures in medicine chemistry.[2,3] Consequently, many efforts have been made to develop new methods for the synthesis of optically active BFNHs through asymmetric metal- or organocatalysis.[4] In the past decade, highly enantioselective catalytic reduction of the presynthesized quinolines and indoles has been well established (Scheme 1a).[5,6] Alternatively, intramolecular asymmetric reductive amination (ARA) of ketones provides another efficient and direct route toward chiral tetrahydroquinolines and indolines (Scheme 1b).[7] Despite these remarkable advances, highly efficient catalytic systems capable of furnishing structurally diverse chiral BFNHs with different ring size remain rare and thus highly desirable.

The metal-catalyzed asymmetric hydroamination of an unsaturated C−C bond has proven to be an attractive alternative approach for the construction of chiral nitrogen heterocycles because of its high atom economy.[8] Recently, various chiral pyrrolidine and piperidine alkaloids, and derivatives thereof, have been prepared using asymmetric intramolecular hydroamination of alkenes.[9] Although alkynes are more reactive than alkenes, only a few successful examples of asymmetric hydroamination of alkynes to access chiral nitrogen-containing compounds were reported.[10] Instead, most catalytic systems provide enamine or imine products.[8d] To achieve step-economic synthesis of such chiral nitrogen-containing products, the one-pot cascade reaction strategy involving hydroamination of alkynes and a subsequent asymmetric transformation has been developed.[11,12] Among the reported examples, asymmetric reduction of the imine/enamine intermediates is a straightforward and efficient route to access the chiral amines or chiral nitrogen heterocycles.[12] However, most catalytic systems constituted two-type catalysts and required stepwise addition of the second chiral catalyst and/or reducing reagent. In 2009, Gong and co-workers reported a notable example,[12c] in which a consecutive intramolecular hydroamination/asymmetric transfer hydrogenation of alkynes were carried out under relay catalysis of an achiral gold(I) complex and chiral phosphoric acid binary system, giving chiral tetrahydroquinolines with excellent enantioselectivity (Scheme 1c). This method, however, still suffers from some drawbacks, such as the use of stoichiometric Hantzsch esters as reductant and the lack of substrate generality. Therefore, it is still highly desirable to develop a general and more efficient atom- and step-economic approach to allow the synthesis of structurally diverse chiral BFNHs with different ring size.

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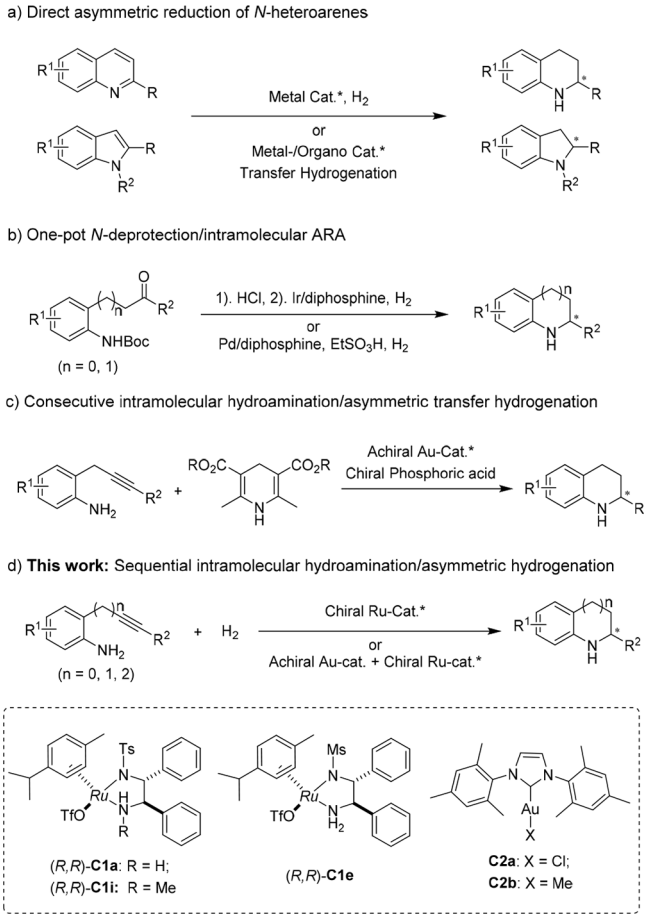
Scheme 1. Strategy for Enantioselective Synthesis of Chiral Benzo-Fused N-Heterocycles (BFNHs)



Recently, we have demonstrated that the cationic ruthenium complexes of chiral monosulfonated diamines[13] are very efficient catalysts for the asymmetric hydrogenation of various challenging substrates, such as quinolines, indoles and cyclic ketimines.[5c,d,14] Most recently, we found that this catalytic system is well compatible with some π-Lewis acidic metal complexes like $Cu(OTf)_2$, and could efficiently catalyzed the asymmetric tandem reaction of ortho-(alkynyl)aryl ketones, giving chiral 1*H*-isochromenes with excellent enantioselectivity.[15] Intrigued by this result and inspired by the aforementioned advances achieved in the asymmetric hydroamination of alkynes,[12c] we envision that alkynyl amines could be directly transferred into chiral BFNHs under relay catalysis of a bimetallic system (Scheme 1d). Herein, we report an efficient route to chiral tetrahydroquinolines and indolines in high yields (up to 98%) with moderate to excellent enantioselectivities (up to 98% ee) through sequential intramolecular hydroamination and asymmetric hydrogenation of various anilino-alkynes.

RESULTS AND DISCUSSION

The Sequential Intramolecular Hydroamination/Asymmetric Hydrogenation Reaction. Synthesis of Tetrahydroquinolines. To explore the viability of this strategy, 2-(hex-2-yn-1-yl)aniline (**1a**) was chosen as the model substrate for optimization of the reaction conditions of the sequential intramolecular hydroamination/asymmetric hydrogenation reaction. As a starting point, we used the conditions previously reported by our research group:[15] $Cu(OTf)_2$ (10 mol %) and (*R*,*R*)-**C1a** (10 mol %) as a binary metal catalysts, THF as a solvent (Table 1, entry 1). Unexpectedly, the reaction gave the expected product 2-propyl-1,2,3,4-tetrahydroquinoline **2a** with only moderate conversion, and poor chemoselectivity and enantioselectivity. Then, several other π-Lewis acidic metal complexes, such as AgOTf, $PtCl_2$, IMesAuCl **C2a**, and IMesAuMe **C2b** were studied (entries 2−5). It was found that **C2a** gave the best result for this process, which afforded the desired product **2a** in 76% yield with 73% ee (entry 4). In addition, the enantioselectivity could not be further improved after an examination of different solvents (Table S1, entries 6−11 in Supporting Information). Notably, a control experiment in the presence of only a gold catalyst **C2a** (10 mol %) gave the racemic product **2a** in 25% yield (entry 6), suggesting that the achiral gold catalyst might participate in the second catalytic hydrogenation step. To our delight, the sequential reaction could be catalyzed by a single chiral ruthenium catalyst (*R*,*R*)-**C1a** (10 mol %), affording **2a** with high enantioselectivity albeit moderate reactivity and chemoselectivity (entry 7). This result indicated that the ruthenium catalyst can also activate the alkyne group and realize the hydroamination reaction.[16] To achieve this sequential reaction with only a single catalyst, we further screened several reaction solvents (entry 8 and entries 1−6 in Table S2, Supporting Information). Unexpectedly, full conversion and excellent enantioselectivity were only observed in neat room-temperature ionic liquid [Bmim]SbF_6 (entry 9). Notably, the enantioselectivity were influenced by the nature of the counteranion (entries 9−13 in Table 1),[14b] and [Bmim]NTf_2 gave the highest enantioselectivity (97% ee). Subsequently, several chiral ruthenium catalysts were screened in [Bmim]NTf_2 (entries 13−15 in Table 1 and entries 12−21 in Table S2, Supporting Information), and (*R*,*R*)-**C1a** was found to be the optimal catalyst in terms of both catalytic activity and enantioselectivity. In addition, the experiments of other reaction parameters, including hydrogen pressure and temperature, revealed that 50 atm of hydrogen gas and 25 °C were the optimal reaction conditions (entries 22−24 in Table S2, Supporting Information). Notably, reducing the catalyst loading to 5 mol % still provided almost complete conversion and the same high enantioselectivity (Table S2, entry 25).

Under the optimized reaction conditions (entry 13 in Table 1), we further investigated the substrate scope of the Ru-catalyzed sequential hydroamination/asymmetric hydrogenation of various 2-(2-propynyl)aniline derivatives in [Bmim]-NTf_2. As shown in Scheme 2, all reactions proceeded smoothly affording the corresponding chiral 2-alkyl substituted tetrahydroquinolines in high yields with excellent enantioselectivities (88−98% ee). It was found that there is no obvious effect on either reactivity or enantioselectivity when the length of the alkyl chain (R^2) prolonged (**2a**−**2c**). However, slight lowered yields and enantioselectivities were observed when steric hindrance R^2 group such as cyclohexyl or isopropyl introduced (**2d** and **2e**). Moreover, substrates bearing both electron-donating (**2h** and **2i**) and electron-withdrawing groups (**2j**−**2l**) on the aniline moiety similarly provided the corresponding chiral products in excellent reactivity and enantioselectivity. Encouraged by these results, the aryl-substituted substrate 2-(3-phenyl-2-propynyl)aniline was also studied. When a single chiral ruthenium catalyst (*R*,*R*)-**C1a** was used, only low yield and moderate enantioselectivity were observed (entries 1−7 in Table S3, Supporting Information). We then investigated this

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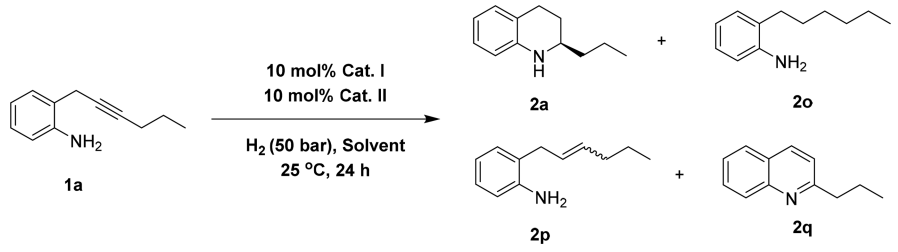
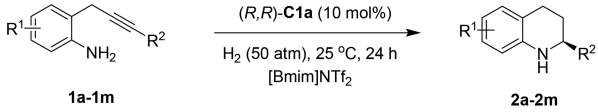
Table 1. Optimization of Reaction Conditions[a]

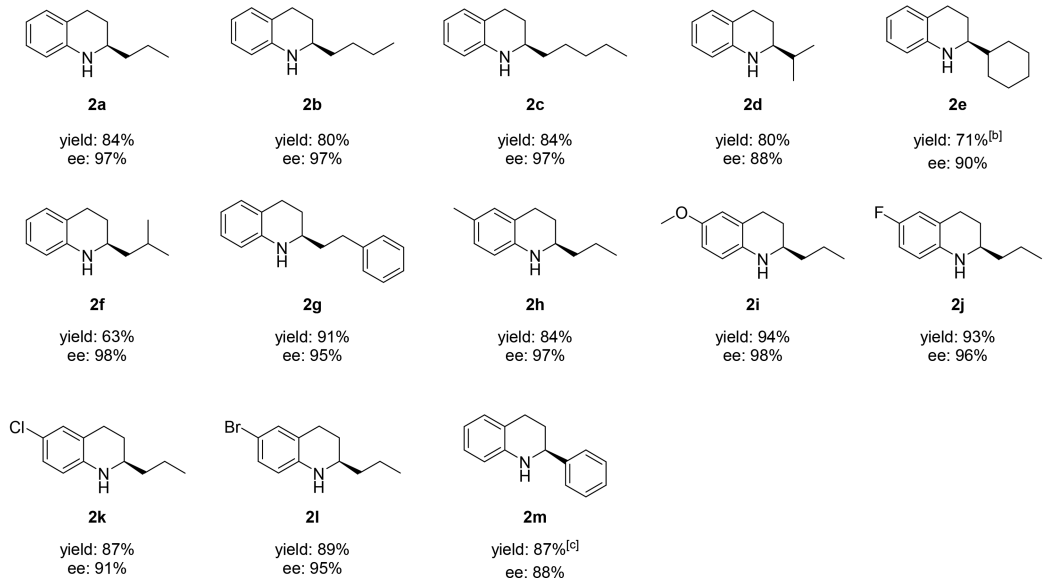


entry	solvent	catalyst I	catalyst II	conv [%][b]	ratio [%][b] 2a:2o:2p:2q	ee of 2a [%][c]
1	THF	$Cu(OTf)_2$	(*R*,*R*)-**C1a**	68	43:9:48:0	30
2	THF	AgOTf	(*R*,*R*)-**C1a**	60	31:15:54:0	38
3	THF	$PtCl_2$	(*R*,*R*)-**C1a**	83	32:68:0:0	10
4	THF	**C2a**	(*R*,*R*)-**C1a**	>95	76:14:10:0	73
5	THF	**C2b**	(*R*,*R*)-**C1a**	67	29:20:51:0	87
6	THF	**C2a**	–	82	25:11:0:64	0
7	THF	–	(*R*,*R*)-**C1a**	75	36:28:37:0	89
8	MeOH	–	(*R*,*R*)-**C1a**	80	56:13:31:0	93
9	$[Bmim]SbF_6$	–	(*R*,*R*)-**C1a**	>95	95:4:1:0	95
10	$[Bmim]PF_6$	–	(*R*,*R*)-**C1a**	>95	95:5:0:0	96
11	$[Bmim]BF_4$	–	(*R*,*R*)-**C1a**	>95	94:5:1:0	93
12	[Bmim]OTf	–	(*R*,*R*)-**C1a**	>95	93:7:0:0	92
13	**$[Bmim]NTf_2$**	–	(*R*,*R*)-**C1a**	**>95**	**94:6:0:0**	**97**
14	$[Bmim]NTf_2$	–	(*R*,*R*)-**C1e**	>95	92:5:3:0	96
15	$[Bmim]NTf_2$	–	(*R*,*R*)-**C1i**	49	57:24:19:0	98

[a]Standard reaction conditions: substrate **1a** (0.1 mmol), solvent (0.5 mL), catalyst **I** (10 mol %), catalyst **II** (10 mol %), H_2 (50 atm), 25 °C, 24 h. [b]Determined by ^1H NMR analysis of the crude product. [c]Determined by HPLC analysis.

Scheme 2. Synthesis of Chiral 2-Substituented Tetrahydroquinolines: Substrate Scope[a]





[a]Reactions were carried out on a 0.2 mmol scale using (*R*,*R*)-**C1a** (10 mol %) in $[Bmim]NTf_2$ (1.0 mL) under H_2 atmosphere (50 atm) at room temperature for 24 h. [b]50 °C. [c](*R*,*R*)-**C1e** (10 mol %) and **C2a** (10 mol %) were stirred at 0 °C in 2-propanol. Yield of isolated product given. The absolute configurations of the products were determined by comparison with literature data.

sequential reaction by using a binary catalytic system consisting of achiral gold catalyst and chiral ruthenium catalyst. Notably, IMesAuCl **C2a** was found to be the best partner of ruthenium catalyst (*R*,*R*)-**C1a**, and afforded **2m** in 94% yield with 71% ee in methanol (entries 8 in Table S3, Supporting Information). Upon a brief screening of several ruthenium catalysts, solvents

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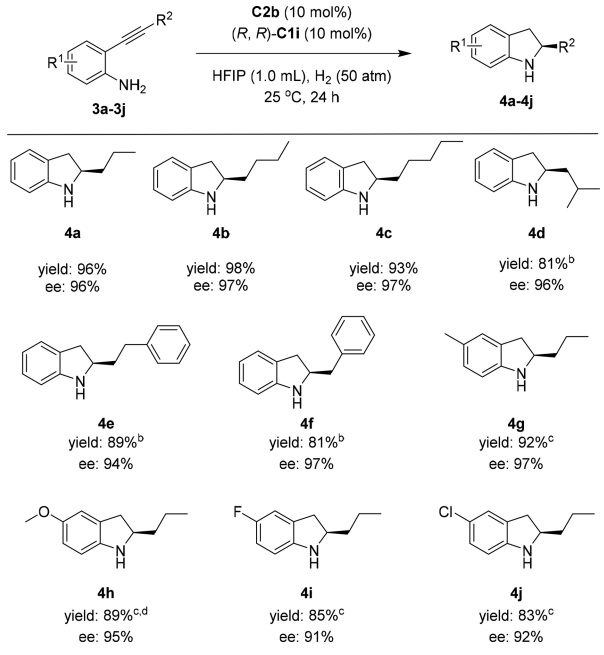
and temperature (entries 10−17 in Table S3, Supporting Information), very good yield and enantioselectivity (87% yield with 88% ee) were achieved.

Synthesis of Indoline Derivatives. Encouraged by the excellent results obtained above, we then expand this protocol to fabricate chiral indoline derivatives. As refer to our previous work,[6c] hexafluoro-2-propanol (HFIP) was the optimal solvent in the asymmetric hydrogenation of indoles. Thus, we first chose the sequential hydroamination/asymmetric hydrogenation of 2-(pent-1-yn-1-yl)aniline (**3a**) in the presence of 10 mol % (*R*,*R*)-C**1a** in HFIP as a standard reaction. However, no conversion was observed and all starting material were recovered (entry 1 in Table S4, Supporting Information). Then, we investigated this one-pot sequential reaction by using a binary catalytic system consisting of achiral gold catalyst and chiral ruthenium catalyst (entries 2−11 in Table S4, Supporting Information). A series of Lewis acids and ruthenium catalysts were screened, and the results are listed in Table S4 in Supporting Information. It was found that IMesAuMe **C2b** (10 mol %) and (*R*,*R*)-**C1i** (10 mol %) binary catalytic system gave the best catalytic performance. An examination of other reaction parameters, including hydrogen pressure and temperature, revealed that 50 atm of hydrogen gas and 25 °C were the optimal reaction conditions (entries 12−13 in Table S4, Supporting Information).

With the optimized sequential reaction conditions in hand, a variety of 2-ethynylaniline derivatives **3b**−**3j** with different substituents at the alkyne and the aromatic ring were investigated. As summarized in Scheme 3, all reactions proceeded smoothly to give full conversions and afforded the corresponding chiral indoline derivatives with excellent enantioselectivities (91−97% ee). Notably, the reaction was found to be insensitive to the length of the alkyl side chain (**4b**, **4c**), and a comparable reactivities and better enantioselectivities were observed as compared with **4a**. The substrates bearing phenyl groups (**4e**, **4f**) or more steric isobutyl groups (**4d**) on the side chain gave only slightly lower yields (81−89%) and comparable enantioselectivities (94−97%), albeit needing long reaction time (48 h). Moreover, the substrates bearing methyl group and electron-donating substitution like methoxy on the aniline moiety also gave very good yields (89−92%) with excellent enantioselectivities (95−97%) (**4g**, **4h**). Notably, substrates bearing electron-withdrawing substituents (F or Cl) on the aniline moiety gave only slightly lower enantioselectivities (91−92% ee) and yields (83−85%) upon prolonged reaction time (**4i**, **4j**).

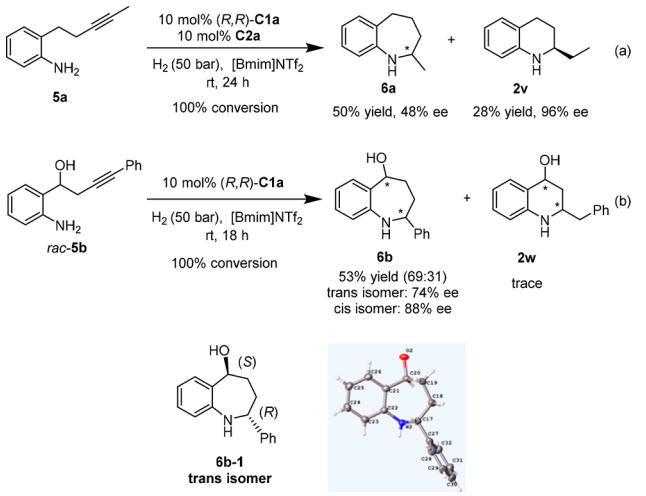
Scheme 3. Synthesis of Chiral 2-Substituented Indolines: Substrate Scope[a]



[a]Reactions were carried out on a 0.15 mmol scale using (*R*,*R*)-**C1i** (10 mol %) and **C2b** (10 mol %) in HFIP (1.0 mL) under H_2 atmosphere (50 atm) at room temperature for 24 h. Yield of isolated product given. [b]48 h. [c]72 h. [d]50 °C.

Synthesis of 2,3,4,5-Tetrahydro-1*H*-benzo[*b*]azepine Derivatives. Benzo-fused seven-membered aza-heterocycles, such as benzazepine, are widely present in a variety of drugs and bioactive molecules.[17] However, the direct catalytic asymmetric synthesis of benzazepine framework is less studied.[14d,17b,c] Encouraged by the excellent results obtained above, we attempted to employ this effective approach for the construction of 2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine derivatives (Scheme 4). In contrast to anilino-alkyne **1a**, substrate **5a**

Scheme 4. Synthesis of Chiral 2,3,4,5-Tetrahydro-1*H*-benzo[*b*]azepine Derivatives



was less reactive in [Bmim]NTf_2 in the presence of (*R*,*R*)-**C1a**, and the six-membered 2-ethyl-1,2,3,4-tetrahydroquinoline **2v** was found to be the main product (Table S5, entry 1 in Supporting Information). When this reaction was carried out under a binary catalytic system of **C2a** and (*R*,*R*)-**C1a** in [Bmim]NTf_2, full conversion of **5a** was observed (Scheme 4a). The seven-membered 2-methyl-1*H*-benzo[*b*]azepine **6a** was obtained in 50% isolated yield with 48% ee, and **2v** was also observed in 28% isolated yield with 96% ee. Notably, sequential reaction of racemic substrate **5b** bearing a hydroxyl group proceeded smoothly in [Bmim]NTf_2 in the presence of (*R*,*R*)-**C1a**, affording the seven-membered ring isomers as the main product in 53% totally isolated yield with 74% ee (trans isomer, **6b-1**) and 88% ee (cis isomer, **6b-2**), respectively (Scheme 4b). The absolute configuration of trans isomer **6b-1** was determined to be (2*R*,5*S*) based on the single-crystal X-ray analysis (see Scheme S2, Supporting Information).

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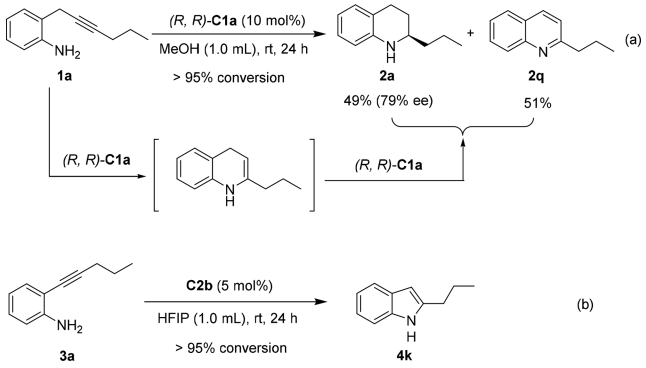
Catalytic Pathway. In our initial study with this sequential hydroamination/asymmetric hydrogenation protocol, we proposed a catalytic reaction pathway, including hydroamination of anilino-alkyne, isomerization, and asymmetric hydrogenation of imine. Despite such a general understanding, however, some key issues of this sequential reaction were unclear. In order to further investigate the catalytic mechanism, several control experiments were carried out (Scheme 5).

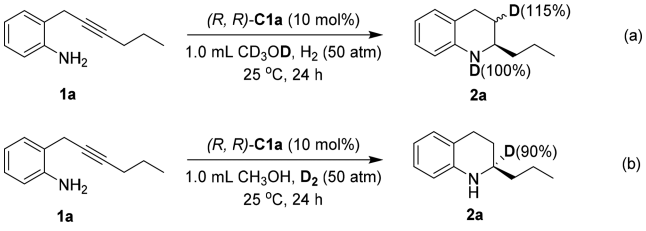
Scheme 5. Control Experiments



Reaction of **1a** in the presence of 10 mol % (*R*,*R*)-**C1a** in methanol led to the formation of chiral tetrahydroquinoline (*R*)-**2a** in 49% yield with 79% ee and the corresponding quinoline **2q** in 51% yield (Scheme 5a). This result indicated that the chiral ruthenium complex first functioning as a π-Lewis acid catalyst catalyzed hydroamination of **1a**, furnishing a 1,4-dihydroquinoline intermediate, followed by asymmetric disproportionation of 1,4-dihydroquinoline catalyzed by (*R*,*R*)-**C1a**.[4q] In the case of synthesizing chiral indolines with a binary catalytic system, reaction of **3a** in the presence of only a π-Lewis acid catalyst **C2b** resulted in the formation of 2-propyl-1*H*-indole in 99% conversion (Scheme 5b). These results demonstrated that both the ruthenium catalyst and the gold catalyst can catalyze the hydroamination of anilino-alkyne.

To further confirm the catalytic pathway, isotope labeling experiments using deuterated hydrogen gas and solvents were carried out, and the concentration of deuterium in the various positions of the targeted product was determined by ^{1}H NMR spectroscopy. As shown in Scheme 6a, the reaction of **1a** was

Scheme 6. Deuterium-Labeling Studies



performed with 10 mol % (*R*,*R*)-**C1a** under 50 atm H_2 in CD_3OD for 24 h. The isolated product **2a** bearing 100% D at 1-position and 115% D at 3-position was obtained. Instead, when the sequential reaction was carried out under 50 atm D_2 in CH_3OH, the D atoms were found only at 2-position of **2a** with 90% D (Scheme 6b).

On the basis of these results obtained from the above experiments, as well as relevant study on asymmetric hydrogenation of quinolines and indoles with this ruthenium catalytic system by our group,[5d,6c] a plausible mechanism was proposed for the synthesis of tetrahydroquinolines via sequential reaction (Scheme 7). In the hydroamination step, the anilino-alkyne substrates **1** were activated by ruthenium catalyst (*R*,*R*)-**C1a** to generate 1,4-dihydroquinoline intermediate. Then, 1,4-dihydroquinoline was activated by Brønsted acid HOTf to form the iminium cation, and the subsequent asymmetric hydrogenation catalyzed by (*R*,*R*)-**C1a** leads to the desired product.[5d] Considering that the D atoms were not found at 4-position of the product (as shown in Scheme 6b), the asymmetric disproportionation of 1,4-dihydroquinoline intermediate do not occur in the presence of hydrogen gas. In the case of synthesizing chiral indolines, similar catalytic pathway can be proposed, which involves gold-catalyzed hydroamination of anilino-alkyne to generate indoles, followed by asymmetric hydrogenation of indoles catalyzed by (*R*,*R*)-**C1i** to give the desired chiral products.[6c]

Product Elaboration. As a specific synthetic application, we developed a gram-scale synthesis of (−)-Angustureine, a natural product with multiple biological activities.[18] Sequential hydroamination/asymmetric hydrogenation of **1c** catalyzed by (*R*,*R*)-**C1a** (10 mol %) was carried out in [Bmim]NTf_2 at room temperature for 48 h, affording (*R*)-**2c** in full conversion with 97% ee. Subsequent *N*-methylation of **2c** under mild reaction conditions gave (−)-Angustureine in 98% isolated yields (1.2 g) with 97% ee (Scheme 8).

CONCLUSIONS

In summary, we have developed an efficient and facile protocol for the one-pot synthesis of enantioenriched benzo-fused *N*-heterocycles from anilino-alkynes through the relay catalysis using a single chiral ruthenium catalyst or using a binary system consisting of achiral gold complex and chiral ruthenium complex. Series of chiral benzo-fused *N*-heterocycles, including tetrahydroquinoline, indoline, and benzazepine derivatives were obtained in high yields with moderate to excellent enantioselectivities. The chiral ruthenium catalysts worked well for the synthesis of 2-alkyl 1,2,3,4-tetrahydroquinolines. Instead, the Au/Ru binary catalytic system provided better results for the synthesis of 2-phenyl 1,2,3,4-tetrahydroquinoline and indoline derivatives. Notably, the use of ionic liquids enhanced the chemo- and enantioselectivities. Further control and deuteration labeling experiments demonstrated that these sequential reactions comprise π-Lewis acid-catalyzed intramolecular hydroamination and ruthenium-catalyzed asymmetric hydrogenation reactions. In addition, this new protocol was further applied in the gram-scale synthesis of naturally occurring tetrahydroquinoline alkaloid, (−)-Angustureine.

EXPERIMENTAL SECTION

General Methods. Unless otherwise noted, all experiments were carried out under an atmosphere of nitrogen using standard Schlenk techniques or in a nitrogen-filled glovebox. ^{1}H NMR and ^{13}C NMR spectra were recorded on Bruker Model Avance DMX 300 Spectrometer (^{1}H 300 MHz and ^{13}C 75 MHz, respectively), Bruker Model Avance DMX 400 Spectrometer (^{1}H 400 MHz and ^{13}C 100 MHz, respectively) and Bruker Model Avance DMX 500 Spectrometer (^{1}H 500 MHz and ^{13}C 125 MHz, respectively). Chemical shifts (δ) were given in ppm and were referenced to residual solvent or TMS peaks. Optical rotations were measured with Rudolph Autopl VI polarimeter. High resolution mass spectra (HRMS) were obtained on Thermo Fisher Q Exactive Mass Spectrometer. All organic solvents were dried using standard, published methods and were distilled before use. All other chemicals were used as received

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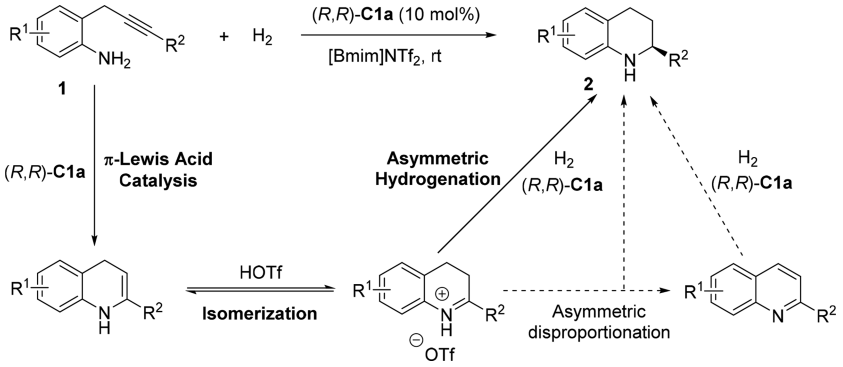
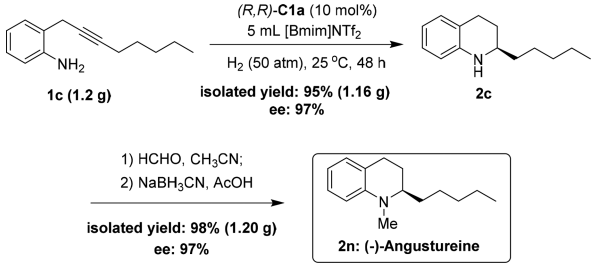
Scheme 7. Proposed Mechanism for This One-Pot Sequential Reaction



Scheme 8. Ru-Catalyzed Sequential Hydroamination/Asymmetric Hydrogenation of 1c on Gram-Scale and the Synthesis of (−)-Angustureine[1b]



from Aldrich or Acros without further purification. The enantiomeric excess of the chiral compounds was determined by HPLC (Varian Prostar 210 liquid chromatography) with a chiral column using racemic compounds as references. The absolute configuration of 1,2,3,4-tetrahydroquinoline[5c,d] and indoline[6c,21] derivatives were determined by comparison of optical rotation with literature data. The catalysts[5d,13b] and substrates[12c,d,19] were synthesized according to the modified literature methods.

Typical Procedure for Sequential Hydroamination/Asymmetric Hydrogenation Reaction: Synthesis of 2-Alkyl-tetrahydroquinoline Derivatives. A 30 mL glass-lined stainless-steel reactor equipped with a magnetic stirrer bar was charged with substrate **1a**−**1l** (0.2 mmol), Ru-catalyst (*R*,*R*)-**C1a** (0.02 mmol) in 1.0 mL of [Bmim]NTf_2 under N_2 atmosphere in a glovebox. The autoclave was closed, and the final pressure of the hydrogen gas was adjusted to 50 atm after purging the autoclave with hydrogen gas several times. The reaction mixture was stirred at room temperature for 24 h. Then the hydrogen gas was carefully released, the reduced product was extracted with diethyl ether (6 × 1 mL). The combined diethyl ether layer was concentrated under vacuum to give the crude product **2a**. The conversion was determined by 1H NMR spectroscopy of crude mixture. The crude mixture was filtered through a short pad of silica eluted with petroleum ether and EtOAc (PE:EA = 15:1, v/v) to give the isolated pure product **2a**−**2l**.

*(R)-2-Propyl-1,2,3,4-tetrahydroquinoline (**2a**).* Colorless oil, isolated yield: 84%, 26 mg. 97% ee, $[\alpha]_D^{20}$ = +94.7 (*c* 0.42, $CHCl_3$) (literature data[5a] $[\alpha]_D^{25}$ = +72.7 (*c* 1.58, $CHCl_3$) for the *R*-isomer 93% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.99 (t, *J* = 7.2 Hz, 2H), 6.64 (t, *J* = 7.4 Hz, 1H), 6.54 (d, *J* = 8.4 Hz, 1H), 3.80 (brs, 1H), 3.29−3.28 (m, 1H), 2.88−2.72 (m, 2H), 2.01−1.97 (m, 1H), 1.69−1.59 (m, 1H), 1.56−1.42 (m, 4H), 0.99 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 144.4, 129.4, 126.8, 121.8, 117.4, 114.5, 51.6, 38.8, 28.1, 26.5, 19.0, 14.3. The enantiomeric excess was determined by HPLC (Chiralcel OJ-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, *T* = 25 °C, 254 nm) t_R = 9.7 min (major), t_R = 7.9 min (minor).

*(R)-2-n-Butyl-1,2,3,4-tetrahydroquinoline (**2b**).* Colorless oil, isolated yield: 80%, 28 mg. 97% ee, $[\alpha]_D^{20}$ = +92.5 (*c* 0.40, $CHCl_3$) (literature data[5a] $[\alpha]_D^{25}$ = +79.9 (*c* 1.0, $CHCl_3$) for the *R*-isomer 92% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.96 (t, *J* = 7.5 Hz, 2H), 6.60 (t, *J* = 7.3 Hz, 1H), 6.48 (d, *J* = 7.5 Hz, 1H), 3.80 (brs, 1H), 3.26−3.21 (m, 1H), 2.85−2.71 (m, 2H), 1.99−1.94 (m, 1H), 1.64−1.56 (m, 1H), 1.51−1.48 (m, 2H), 1.38 (s, 4H), 0.94 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 144.9, 129.4, 126.8, 121.5, 117.0, 114.2, 51.7, 36.5, 28.2, 28.0, 26.6, 23.0, 14.2. The enantiomeric excess was determined by HPLC (Chiralcel OJ-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, *T* = 25 °C, 254 nm) t_R = 8.0 min (major), t_R = 7.0 min (minor).

*(R)-2-n-Pentyl-1,2,3,4-tetrahydroquinoline (**2c**).* Colorless oil, isolated yield: 84%, 31 mg. 97% ee, $[\alpha]_D^{20}$ = +92.3 (*c* 0.40, $CHCl_3$) (literature data[5a] $[\alpha]_D^{25}$ = +74.4 (*c* 1.03, $CHCl_3$) for the *R*-isomer 94% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.98 (t, *J* = 7.5 Hz, 2H), 6.62 (t, *J* = 7.3 Hz, 1H), 6.49 (d, *J* = 7.5 Hz,1H), 3.70 (brs, 1H), 3.28−3.23 (m, 1H), 2.87−2.72 (m, 2H), 2.01−1.96 (m, 1H), 1.66−1.58 (m, 1H), 1.53−1.49 (m, 2H), 1.46−1.34 (m, 6H), 0.94 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 144.9, 129.4, 126.8, 121.5, 117.0, 114.2, 51.7, 36.8, 32.1, 28.3, 26.6, 25.5, 22.8, 14.2. The enantiomeric excess was determined by HPLC (Chiralcel OJ-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, *T* = 25 °C, 254 nm) t_R = 6.9 min (major), t_R = 6.4 min (minor).

*(S)-2-Isopropyl-1,2,3,4-tetrahydroquinoline (**2d**).* Colorless oil, isolated yield: 80%, 24 mg. 88% ee, $[\alpha]_D^{20}$ = +60.3 (*c* 0.33, $CHCl_3$) (literature data[5a] $[\alpha]_D^{25}$ = +21.1 (*c* 0.32, $CHCl_3$) for the *S*-isomer 94% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.97 (t, *J* = 7.2 Hz, 2H), 6.60 (t, *J* = 7.2 Hz, 1H), 6.50 (d, *J* = 7.8 Hz, 1H), 3.72 (brs, 1H), 3.08−3.02 (m, 1H), 2.88−2.70 (m, 2H), 1.97−1.89 (m, 1H), 1.78−1.61 (m, 2H), 1.00 (t, *J* = 7.4 Hz, 6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 145.1, 129.3, 126.8, 121.6, 116.9, 114.2, 57.4, 32.6, 26.8, 24.6, 18.7, 18.4. The enantiomeric excess was determined by HPLC (Chiralcel OJ-H, *n*-hexane/isopropanol = 98/2, flow rate 1.0 mL/min, *T* = 25 °C, 254 nm) t_R = 17.9 min (major), t_R = 17.2 min (minor).

*(S)-2-Cyclohexyl-1,2,3,4-tetrahydroquinoline (**2e**).* Colorless oil, isolated yield: 71%, 14 mg. 90% ee, $[\alpha]_D^{20}$ = +49.9 (*c* 0.46, $CHCl_3$) (literature data[20] $[\alpha]_D^{25}$ = +56.5 (*c* 0.40, $CHCl_3$) for the *S*-isomer 95% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.97 (t, *J* = 8.3 Hz, 2H), 6.61 (t, *J* = 7.3 Hz, 1H), 6.52 (d, *J* = 7.5 Hz, 1H), 4.01 (brs, 1H), 3.07−3.04 (m, 1H), 2.83−2.71 (m, 2H), 1.96−1.91 (m, 1H), 1.82(t, *J* = 14.5 Hz, 4H), 1.75−1.67 (m, 2H), 1.42−1.01 (m, 7H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 144.8, 129.3, 126.8, 121.8, 117.1, 114.4, 56.8, 42.5, 29.3, 28.9, 26.7, 26.6, 26.5, 26.5, 24.7. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, *T* = 25 °C, 254 nm) t_R = 5.4 min (major), t_R = 5.0 min (minor).

*(S)-2-Isobutyl-1,2,3,4-tetrahydroquinoline (**2f**).* Colorless oil, isolated yield: 63%, 20 mg. 98% ee, $[\alpha]_D^{20}$ = +85.0 (*c* 0.30, $CHCl_3$) (literature data[5d] $[\alpha]_D^{25}$ = +88.7 (*c* 0.21, $CHCl_3$) for the *S*-isomer 99% ee); ^{1}H NMR (300 MHz, $CDCl_3$) δ (ppm) 6.97 (t, *J* = 6.6 Hz, 2H), 6.61 (t, *J* = 7.2 Hz, 1H), 6.49 (d, *J* = 7.8 Hz, 1H), 3.38−3.30 (m, 1H), 2.89−2.69 (m, 2H), 2.00−1.92 (m, 1H), 1.84−1.68 (m, 1H), 1.66−1.54 (m, 1H), 1.50−1.27 (m, 2H), 0.96 (d, *J* = 6.3 Hz,

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6H); ^{13}C NMR (75 MHz, $CDCl_3$) δ (ppm) 144.8, 129.4, 126.8, 121.6, 117.1, 114.3, 49.4, 46.0, 28.7, 26.6, 24.6, 23.3, 22.6. The enantiomeric excess was determined by HPLC (Chiralcel OJ-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 8.1 min (major), t_R = 6.3 min (minor).

*(R)-2-Phenethyl-1,2,3,4-tetrahydroquinoline (**2g**).* Colorless oil, isolated yield: 91%, 22 mg. 95% ee, $[\alpha]_D^{20}$ = +87.5 (*c* 0.20, $CHCl_3$) (literature data[5d] $[\alpha]_D^{25}$ = +88.9 (*c* 0.27, $CHCl_3$) for the *R*-isomer 99% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.31−7.28 (m, 2H), 7.24−7.18 (m, 3H), 6.95 (t, J = 7.3 Hz, 2H), 6.60 (t, J = 7.3 Hz, 1H), 6.45 (d, J = 7.5 Hz, 1H), 3.87 (brs, 1H), 3.32−3.28 (m, 1H), 2.83−2.72 (m, 4H), 2.02−1.98 (m, 1H), 1.86−1.81 (m, 2H), 1.71−1.64 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 144.5, 142.0, 129.4, 128.6, 128.5, 126.9, 126.1, 121.5, 117.3, 114.4, 51.3, 38.3, 32.3, 28.1, 26.3. HR-ESI calculated for $C_{17}H_{20}N$ ($[M + H]^+$): 238.15903, found 238.15892. The enantiomeric excess was determined by HPLC (Chiralcel OJ-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 22.6 min (major), t_R = 21.5 min (minor).

*(R)-6-Methyl-2-propyl-1,2,3,4-tetrahydroquinoline (**2h**).* Colorless oil, isolated yield: 84%, 32 mg. 97% ee, $[\alpha]_D^{20}$ = +61.8 (*c* 0.44, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.80 (d, J = 6.0 Hz, 2H), 6.49−6.47 (m, 1H), 4.03 (brs, 1H), 3.27−3.21 (m, 1H), 2.85−2.68 (m, 2H), 2.22 (s, 3H), 2.01−1.94 (m, 1H), 1.67−1.57 (m, 1H), 1.55−1.35 (m, 4H), 0.97 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 142.2, 129.9, 127.4, 126.6, 121.8, 114.6, 51.7, 38.9, 28.4, 26.5, 20.5, 19.1, 14.3. HR-ESI calculated for $C_{13}H_{20}N$ ($[M + H]^+$): 190.15903, found 190.15889. The enantiomeric excess was determined by HPLC (Chiralcel OJ-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 12.3 min (major), t_R = 8.8 min (minor).

*(R)-6-Methoxy-2-propyl-1,2,3,4-tetrahydroquinoline (**2i**).* Colorless oil, isolated yield: 94%, 39 mg. 98% ee, $[\alpha]_D^{20}$ = +97.0 (*c* 0.95, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.61−6.57 (m, 2H), 6.47 (d, J = 8.5 Hz, 1H), 3.73 (s, 3H), 3.63 (brs, 1H), 3.22−3.17 (m, 1H), 2.86−2.69 (m, 2H), 1.98−1.93 (m, 1H), 1.63−1.55 (m, 1H), 1.52−1.38 (m, 4H), 0.97 (t, J = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 152.0, 138.8, 123.0, 115.5, 114.8, 113.0, 55.9, 51.8, 38.9, 28.4, 26.9, 19.1, 14.3. HR-ESI calculated for $C_{13}H_{20}ON$ ($[M + H]^+$): 206.15394, found 206.15414. The enantiomeric excess was determined by HPLC (Chiralcel OJ-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 17.1 min (major), t_R = 11.8 min (minor).

*(R)-6-Fluoro-2-propyl-1,2,3,4-tetrahydroquinoline (**2j**).* Colorless oil, isolated yield: 93%, 36 mg. 96% ee, $[\alpha]_D^{20}$ = +87.0 (*c* 0.38, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.68−6.65 (m, 2H), 6.41−6.39 (m, 1H), 3.64 (brs, 1H), 3.22−3.17 (m, 1H), 2.83−2.67 (m, 2H), 1.97−1.92 (m, 1H), 1.60−1.53 (m, 1H), 1.49−1.36 (m, 4H), 0.96 (t, J = 7.0 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 155.6 (d, J_{C-F} = 232.9 Hz), 141.0 (d, J_{C-F} = 2.5 Hz), 122.9 (d, J_{C-F} = 6.3 Hz), 115.5 (d, J_{C-F} = 21.4 Hz), 114.9 (d, J_{C-F} = 7.5 Hz), 113.3 (d, J_{C-F} = 21.4 Hz), 51.6, 38.9, 28.0, 26.7, 19.0, 14.3. HR-ESI calculated for $C_{12}H_{17}NF$ ($[M + H]^+$): 194.13450, found 194.13425. The enantiomeric excess was determined by HPLC (Chiralcel OJ-H, *n*-hexane/isopropanol = 99/1, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 11.0 min (major), t_R = 10.1 min (minor).

*(R)-6-Chloro-2-propyl-1,2,3,4-tetrahydroquinoline (**2k**).* Colorless oil, isolated yield: 87%, 28 mg. 91% ee, $[\alpha]_D^{20}$ = +84.8 (*c* 0.50, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.92−6.89 (m, 2H), 6.39 (d, J = 8.0 Hz, 1H), 3.79 (brs, 1H), 3.26−3.20 (m, 1H), 2.82−2.66 (m, 2H), 1.98−1.92 (m, 1H), 1.61−1.53 (m, 1H), 1.52−1.37 (m, 4H), 0.97 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 143.3, 128.9, 126.6, 123.1, 121.4, 115.1, 51.4, 38.8, 27.8, 26.4, 19.0, 14.3. HR-ESI calculated for $C_{12}H_{17}NCl$ ($[M + H]^+$): 210.10440, found 210.10419. The enantiomeric excess was determined by HPLC (Chiralcel OJ-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 7.7 min (major), t_R = 7.1 min (minor).

*(R)-6-Bromo-2-propyl-1,2,3,4-tetrahydroquinoline (**2l**).* Colorless oil, isolated yield: 89%, 11 mg. 95% ee, $[\alpha]_D^{20}$ = +76.0 (*c* 0.20, $CHCl_3$); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.06−7.02 (m, 2H), 6.36 (d, J = 8.4 Hz, 1H), 3.90 (brs, 1H), 3.26−3.20 (m, 1H), 2.82−2.66 (m, 2H), 1.98−1.91 (m, 1H), 1.61−1.53 (m, 1H), 1.51−1.37 (m, 4H), 0.97 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 143.7, 131.8, 129.5, 123.6, 115.6, 108.5, 51.4, 38.8, 27.7, 26.3, 19.0, 14.3. HR-ESI calculated for $C_{12}H_{17}NBr$ ($[M + H]^+$): 254.05389, found 254.05348. The enantiomeric excess was determined by HPLC (Chiralcel OJ-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 8.6 min (major), t_R = 7.8 min (minor).

Typical Procedure for Sequential Hydroamination/Asymmetric Hydrogenation Reaction: Synthesis of 2-Aryl-tetrahydroquinoline Derivatives. A 30 mL glass-lined stainless-steel reactor equipped with a magnetic stirrer bar was charged with substrate **1m** (0.1 mmol), Ru-catalyst (*R*,*R*)-**C1e** (0.01 mmol) and IMesAuCl **C2a** (0.01 mmol) in 1.0 mL IPA under N_2 atmosphere in a glovebox. The autoclave was closed, and the final pressure of the hydrogen gas was adjusted to 50 atm after purging the autoclave with hydrogen gas several times. The reaction mixture was stirred at 0 °C for 24 h. Then the hydrogen gas was carefully released. The conversion was determined by ^{1}H NMR spectroscopy of crude mixture. The crude mixture was filtered through a short pad of silica eluted with petroleum ether and EtOAc (PE:EA = 10:1, v/v) to give the isolated pure product **2m**.

*(S)-2-Phenyl-1,2,3,4-tetrahydroquinoline (**2m**).* Colorless oil, isolated yield: 87%, 18 mg. 88% ee, $[\alpha]_D^{20}$ = −110.0 (*c* 0.40, $CHCl_3$) (literature data[5d] $[\alpha]_D^{25}$ = +36.8 (*c* 0.95, $CHCl_3$) for the *R*-isomer 92% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.41−7.26 (m, 5H), 7.02−6.99 (m, 2H), 6.67 (t, J = 7.2 Hz, 1H), 6.55 (d, J = 8.0 Hz, 1H), 4.43 (dd, J_1 = 9.4 Hz, J_2 = 3.4 Hz, 1H), 2.96−2.88 (m, 1H), 2.75(t, J = 4.6 Hz, 1H), 2.71 (t, J = 4.6 Hz, 1H), 2.16−2.09 (m, 1H), 2.06−1.96 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 144.5, 144.3, 129.4, 128.7, 127.6, 127.1, 126.8, 121.4, 117.8, 114.5, 56.5, 30.9, 26.5. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 9.3 min (major), t_R = 11.6 min (minor).

Typical Procedure for Sequential Hydroamination/Asymmetric Hydrogenation Reaction: Synthesis of Indolines Derivatives. A 30 mL glass-lined stainless-steel reactor equipped with a magnetic stirrer bar was charged with substrate **3a**−**3j** (0.15 mmol), Ru-catalyst (*R*,*R*)-**C1i** (0.015 mmol), **C2b** (0.015 mmol) in 1.0 mL of HFIP under N_2 atmosphere in a glovebox. The autoclave was closed, and the final pressure of the hydrogen gas was adjusted to 50 atm after purging the autoclave with hydrogen gas several times. The reaction mixture was stirred at room temperature for specific time. Then the hydrogen gas was carefully released and the conversion was determined by 1H NMR spectroscopy. The reaction mixture was filtered through a short pad of silica (ethyl acetate/petroleum ether/Et_3N, 40/1/1, v/v) to give the pure products **4a**−**4j**.

*(R)-2-Propylindoline (**4a**).* Colorless oil, isolated yield: 96%, 16 mg. 96% ee, $[\alpha]_D^{20}$ = +16.7 (*c* 0.18, $CHCl_3$) (literature data[6c] $[\alpha]_D^{25}$ = +9.3 (*c* 0.3, $CHCl_3$) for the *R*-isomer 96% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.07 (d, J = 7.5 Hz, 1H), 7.01 (t, J = 7.5 Hz, 1H), 6.69 (t, J = 7.5 Hz, 1H), 6.61 (d, J = 7.5 Hz, 1H), 3.89−3.83 (m, 1H), 3.13 (dd, J_1 = 15.3 Hz, J_2 = 8.8 Hz, 1H), 2.68 (dd, J_1 = 15.5 Hz, J_2 = 8.5 Hz, 1H), 1.71−1.55 (m, 2H), 1.49−1.34 (m, 2H), 0.97 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 151.0, 129.1, 127.3, 124.8, 118.7, 109.3, 60.0, 39.1, 36.3, 19.9, 14.3. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 6.3 min (major), t_R = 8.0 min (minor).

*(R)-2-Butylindoline (**4b**).* Colorless oil, isolated yield: 98%, 25 mg. 97% ee, $[\alpha]_D^{20}$ = +14.3 (*c* 0.60, $CHCl_3$) (literature data[6c] $[\alpha]_D^{25}$ = +11.8 (*c* 0.6, $CHCl_3$) for the *R*-isomer 97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.09 (d, J = 7.2 Hz, 1H), 7.03 (t, J = 7.6 Hz, 1H), 6.76−6.70 (m, 2H), 3.92−3.84 (m, 1H), 3.15 (dd, J_1 = 15.4 Hz, J_2 = 8.6 Hz, 1H), 2.71 (dd, J_1 = 15.6 Hz, J_2 = 8.4 Hz, 1H), 1.74−1.59 (m, 2H), 1.44−1.31 (m, 4H), 0.93 (t, J = 7.0 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.7, 129.2, 127.4, 124.8, 118.8, 109.5, 60.3, 36.6, 36.3, 28.9, 22.9, 14.2. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol = 90/10, flow rate

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1.0 mL/min, T = 25 °C, 254 nm) t_R = 5.5 min (major), t_R = 6.8 min (minor).

*(R)-2-Pentylindoline (**4c**).* Colorless oil, isolated yield: 93%, 26 mg. 97% ee, $[\alpha]_D^{20}$ = +16.6 (c 0.70, $CHCl_3$) (literature data[6c] $[\alpha]_D^{25}$ = +16.4 (c 0.5, $CHCl_3$) for the *R*-isomer 96% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.08 (d, J = 7.0 Hz, 1H), 7.02 (t, J = 7.5 Hz, 1H), 6.71 (t, J = 7.5 Hz, 1H), 6.65 (d, J = 8.0 Hz, 1H), 4.10 (brs, 1H), 3.89−3.83 (m, 2H), 3.14 (dd, J_1 = 15.5 Hz, J_2 = 8.5 Hz, 1H), 2.70 (dd, J_1 = 15.0 Hz, J_2 = 8.5 Hz, 1H), 1.67−1.59 (m, 2H), 1.43−1.34 (m, 6H), 0.92 (t, J = 6.5 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 150.6, 129.3, 127.4, 124.8, 119.0, 109.6, 60.3, 36.8, 36.3, 32.0, 26.4, 22.8, 14.2. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 5.4 min (major), t_R = 6.6 min (minor).

*(R)-2-Isobutylindoline (**4d**).* Colorless oil, isolated yield: 81%, 21 mg. 96% ee, $[\alpha]_D^{20}$ = +18.0 (c 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.94 (d, J = 7.0 Hz, 1H), 6.88 (t, J = 7.5 Hz, 1H), 6.57 (t, J = 7.3 Hz, 1H), 6.51(d, J = 8.0 Hz, 1H), 4.18 (brs, 1H), 3.85−3.79 (m, 1H), 3.00 (dd, J_1 = 15.5 Hz, J_2 = 8.5 Hz, 1H), 2.54 (dd, J_1 = 15.5 Hz, J_2 = 8.5 Hz, 1H), 1.64−1.55 (m, 1H), 1.49−1.43 (m, 1H), 1.37−1.31 (m, 1H), 0.83 (d, J = 6.5 Hz, 6H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 150.6, 129.3, 127.4, 124.8, 119.0, 109.7, 58.3, 46.0, 36.6, 25.8, 23.2, 22.6. HR-ESI calculated for $C_{12}H_{18}N$ ([M + H]$^+$): 176.14338, found 176.14352. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 6.5 min (major), t_R = 7.8 min (minor).

*(R)-2-Phenethylindoline (**4e**).* Colorless oil, isolated yield: 89%, 31 mg. 94% ee, $[\alpha]_D^{20}$ = +14.6 (c 0.65, $CHCl_3$), (literature data[21] $[\alpha]_D^{25}$ = +12.0 (c 0.17, $CHCl_3$) for the *R*-isomer 98% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.30−7.27 (m, 2H), 7.23−7.18 (m, 3H), 7.07 (d, J = 7.0 Hz, 1H), 7.00 (t, J = 7.5 Hz, 1H), 6.69 (t, J = 7.5 Hz, 1H), 6.60 (d, J = 7.5 Hz, 1H), 3.91−3.84 (m, 1H), 3.15 (dd, J_1 = 15.5 Hz, J_2 = 8.5 Hz, 1H), 2.75−2.67 (m, 3H), 2.01−1.90 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 150.7, 141.8, 128.9, 128.6, 128.5, 127.4, 126.1, 124.8, 118.9, 109.5, 59.7, 38.5, 36.2, 33.1. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 9.9 min (major), t_R = 13.9 min (minor).

*(R)-2-Benzylindoline (**4f**).* Colorless oil, isolated yield: 81%, 25 mg. 97% ee, $[\alpha]_D^{20}$ = +77.1 (c 0.55, $CHCl_3$) (literature data[6c] $[\alpha]_D^{25}$ = +78.6 (c 0.5, $CHCl_3$) for the *R*-isomer 97% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.35−7.31 (m, 2H), 7.26−7.22 (m, 3H), 7.08 (d, J = 7.2 Hz, 1H), 7.01 (t, J = 7.6 Hz, 1H), 6.69 (t, J = 7.4 Hz, 1H), 6.57 (d, J = 7.6 Hz, 1H), 4.12−4.05 (m, 1H), 3.16−3.08 (m, 1H), 2.93−2.77 (m, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 150.4, 139.2, 129.3, 128.8, 128.6, 127.5, 126.6, 124.9, 118.8, 109.4, 61.1, 42.8, 36.0. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 7.6 min (major), t_R = 8.4 min (minor).

*(R)-5-Methyl-2-propylindoline (**4g**).* Colorless oil, isolated yield: 92%, 24 mg. 97% ee, $[\alpha]_D^{20}$ = +22.2 (c 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.93 (s, 1H), 6.85 (d, J = 8.0 Hz, 1H), 6.63 (d, J = 8.0 Hz, 1H), 4.97 (brs, 1H), 3.90−3.84 (m, 1H), 3.11 (dd, J_1 = 15.5 Hz, J_2 = 8.5 Hz, 1H), 2.68 (dd, J_1 = 15.5 Hz, J_2 = 8.5 Hz, 1H), 2.26 (s, 3H), 1.71−1.58 (m, 2H), 1.51−1.36 (m, 2H), 0.98 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 147.2, 129.9, 129.1, 127.7, 125.6, 110.3, 60.3, 38.7, 36.3, 21.0, 19.9, 14.2. HR-ESI calculated for $C_{12}H_{18}N$ ([M + H]$^+$): 176.14338, found 176.14395. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 5.3 min (major), t_R = 7.4 min (minor).

*(R)-5-Methoxy-2-propylindoline (**4h**).* Colorless oil, isolated yield: 89%, 25 mg. 95% ee, $[\alpha]_D^{20}$ = +21.6 (c 0.50, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.71(s, 1H), 6.59−6.55 (m, 2H), 3.87−3.81 (m, 1H), 3.74 (s, 3H), 3.10 (dd, J_1 = 15.3 Hz, J_2 = 8.3 Hz, 1H), 2.66 (dd, J_1 = 15.5 Hz, J_2 = 8.5 Hz, 1H), 1.66−1.54 (m, 2H), 1.47−1.35 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 153.7, 144.5, 131.0, 112.2, 111.8, 110.2, 60.5, 56.1, 39.0, 36.8, 20.0, 14.3. HR-ESI calculated for $C_{12}H_{18}ON$ ([M + H]$^+$): 192.13829, found 192.13872. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 6.6 min (major), t_R = 13.8 min (minor).

*(R)-5-Fluoro-2-propylindoline (**4i**).* Colorless oil, isolated yield: 85%, 22 mg. 91% ee. $[\alpha]_D^{20}$ = +9.8 (c 0.40, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 6.80−6.78 (m, 1H), 6.71−6.67 (m, 1H), 6.51−6.49 (m, 1H), 3.90−3.84 (m, 1H), 3.10 (dd, J_1 = 15.8 Hz, J_2 = 8.3 Hz, 1H), 2.66 (dd, J_1 = 16.0 Hz, J_2 = 8.5 Hz, 1H), 1.65−1.54 (m, 2H), 1.47−1.32 (m, 2H), 0.96 (t, J = 7.3 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 157.1 (d, J_{C-F} = 235.5 Hz), 146.9, 130.9 (d, J_{C-F} = 8.1 Hz), 113.2 (d, J_{C-F} = 23.1 Hz), 112.2 (d, J_{C-F} = 23.1 Hz), 109.5 (d, J_{C-F} = 9.1 Hz), 60.7, 39.0, 36.5, 19.9, 14.2. HR-ESI calculated for $C_{11}H_{15}NF$ ([M + H]$^+$): 180.11830, found 180.11871. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 5.1 min (major), t_R = 7.8 min (minor).

*(R)-5-Chloro-2-propylindoline (**4j**).* Colorless oil, isolated yield: 83%, 24 mg. 92% ee, $[\alpha]_D^{20}$ = +11.5 (c 0.80, $CHCl_3$); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.02 (s, 1H), 6.95 (d, J = 8.5 Hz, 1H), 6.52 (d, J = 8.0 Hz, 1H), 3.91−3.85 (m, 1H), 3.15−3.08 (m, 1H), 2.66 (dd, J_1 = 15.5 Hz, J_2 = 8.5 Hz, 1H), 1.65−1.53 (m, 2H), 1.47−1.32 (m, 2H), 0.96 (t, J = 7.5 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 149.2, 131.2, 127.1, 125.0, 123.5, 110.2, 60.4, 38.9, 36.1, 19.8, 14.2. HR-ESI calculated for $C_{11}H_{15}NCl$ ([M + H]$^+$): 196.08875, found 196.08888. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 5.4 min (major), t_R = 10.4 min (minor).

Typical Procedure for Sequential Hydroamination/Asymmetric Hydrogenation Reaction: Synthesis of 2-Methyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepine. A 30 mL glass-lined stainless-steel reactor equipped with a magnetic stirrer bar was charged with substrate **5a** (0.16 mmol), (*R*,*R*)-**C1a** (0.016 mmol), and **C2a** (0.016 mmol) in 1.0 mL of [Bmim]NTf_2 under N_2 atmosphere in a glovebox. The autoclave was closed, and the final pressure of the hydrogen gas was adjusted to 50 atm after purging the autoclave with hydrogen gas several times. The reaction mixture was stirred at room temperature for 24 h. Then the hydrogen gas was carefully released, the reduced product was extracted with diethyl ether (6 × 1 mL). The combined diethyl ether layer was concentrated under vacuum to give the crude product. the conversion was determined by ^{1}H NMR spectroscopy of crude mixture. The crude mixture was filtered through a short pad of silica eluted with petroleum ether and ethyl acetate (PE:EA = 15:1, v/v) to give the isolated pure product **6a**.

*(+)-2-Methyl-2,3,4,5-tetrahydro-1H-benzo[b]azepine (**6a**).*[22] White solid, Melting point: 57−60 °C, isolated yield: 50%, 13 mg. 48% ee, $[\alpha]_D^{20}$ = +15.5 (c = 0.40, $CHCl_3$). ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 7.09−7.02 (m, 2H), 6.84 (td, J_1 = 7.4 Hz, J_2 = 0.8 Hz, 1H), 6.75 (d, J = 7.6 Hz, 1H), 3.47 (brs, 1H), 2.98−2.89 (m, 1H), 2.84−2.79 (m, 1H), 2.74−2.68 (m, 1H), 1.96−1.83 (m, 2H), 1.55−1.35 (m, 2H), 1.25 (d, J = 6.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 148.9, 134.0, 130.7, 126.7, 121.2, 120.0, 53.9, 39.4, 35.7, 26.4, 24.2. HR-ESI calculated for $C_{11}H_{16}N$ ([M + H]$^+$): 162.12827, found 162.12766. The enantiomeric excess was determined by HPLC (Chiralcel OJ-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 7.9 min (major), t_R = 7.4 min (minor).

*(R)-2-Ethyl-1,2,3,4-tetrahydroquinoline (**2v**).* Colorless oil, isolated yield 28%, 8 mg. 96% ee, $[\alpha]_D^{20}$ = +100.0 (c 0.45, $CHCl_3$) (literature data[5d] $[\alpha]_D^{25}$ = +80.3 (c 0.19, $CHCl_3$) for the *R*-isomer 99% ee); ^{1}H NMR (400 MHz, $CDCl_3$) δ (ppm) 6.97 (t, J = 7.2 Hz, 2H), 6.61 (t, J = 7.2 Hz, 1H), 6.49 (d, J = 8.0 Hz, 1H), 3.90 (brs, 1H), 3.19−3.17 (m, 1H), 2.86−2.70 (m, 2H), 1.99−1.97 (m, 1H), 1.65−1.50 (m, 3H), 1.00 (t, J = 7.4 Hz, 3H); ^{13}C NMR (100 MHz, $CDCl_3$) δ (ppm) 144.7, 129.4, 126.8, 121.6, 117.1, 114.2, 53.2, 29.5, 27.7, 26.5, 10.2. The enantiomeric excess was determined by HPLC (Chiralcel OJ-H, *n*-hexane/isopropanol = 90/10, flow rate 1.0 mL/min, T = 25 °C, 254 nm) t_R = 9.4 min (major), t_R = 8.6 min (minor).

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Typical Procedure for Sequential Hydroamination/Asymmetric Hydrogenation Reaction: Synthesis of 2-Phenyl-2,3,4,5-tetrahydro-1*H*-benzo[*b*]azepin-5-ol. A 30 mL glass-lined stainless-steel reactor equipped with a magnetic stirrer bar was charged with substrate **5b** (0.2 mmol), (*R*,*R*)-**C1a** (0.02 mmol) in 2.0 mL of [Bmim]NTf_2 under N_2 atmosphere in a glovebox. The autoclave was closed, and the final pressure of the hydrogen gas was adjusted to 50 atm after purging the autoclave with hydrogen gas several times. The reaction mixture was stirred at room temperature for 18 h. Then the hydrogen gas was carefully released, the reduced product was extracted with diethyl ether (6 × 1 mL). The combined diethyl ether layer was concentrated under vacuum to give the crude product. the conversion and diastereoselectivity was determined by ^{1}H NMR spectroscopy of crude mixture. The crude mixture was filtered through a short pad of silica eluted with petroleum ether and EtOAc (PE:EA = 2:1, v/v) to give the isolated mixed product **6b** (25 mg, 53% yield), two isomers were isolated through silica eluted with petroleum ether, ethyl acetate and Et_3N (PE:EA:Et_3N = 10:2:1, v/v) to achieve the *trans* isomer **6b-1** and *cis* isomer **6b-2**, respectively.

*(2R,5S)-2-Phenyl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-5-ol (**6b-1**).* *trans* isomer. White solid, melting point: 124−127 °C, isolated yield: 36%, 17 mg. 74% ee, $[\alpha]_D^{20}$ = +26.0 (*c* 0.20, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.53 (d, *J* = 7.5 Hz, 1H), 7.42−7.37 (m, 4H), 7.32 (t, *J* = 7.0 Hz, 1H), 7.12 (t, *J* = 7.5 Hz, 1H), 7.02 (t, *J* = 7.3 Hz, 1H), 6.74 (d, *J* = 7.5 Hz, 1H), 4.94 (d, *J* = 9.0 Hz, 1H), 3.91 (dd, J_1 = 11.0 Hz, J_2 = 2.5 Hz, 1H), 3.71 (brs, 1H), 2.29 (brs, 1H), 2.22−2.17 (m, 1H), 2.11−1.97 (m, 2H), 1.86−1.78 (m, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 146.5, 145.5, 135.4, 129.0, 127.8, 127.6, 126.2, 125.9, 121.8, 120.5, 72.4, 62.8, 36.0, 34.8. HR-ESI calculated for $C_{16}H_{18}NO$ ($[M + H]^+$): 240.13829, found 240.13861. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol = 80/20, flow rate 1.0 mL/min, *T* = 25 °C, 254 nm) t_R = 13.1 min (major), t_R = 6.4 min (minor).

*(2R,5R)-2-Phenyl-2,3,4,5-tetrahydro-1H-benzo[b]azepin-5-ol (**6b-2**).* *cis* isomer. Yellow oil, isolated yield: 17%, 8 mg. 88% ee, $[\alpha]_D^{20}$ = +83.5 (*c* 0.20, $CHCl_3$). ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.43−7.38 (m, 4H), 7.33 (t, *J* = 6.8 Hz, 1H), 7.22 (d, *J* = 7.5 Hz, 1H), 7.13 (t, *J* = 7.3 Hz, 1H), 6.98 (t, *J* = 7.3 Hz, 1H), 6.77 (d, *J* = 7.5 Hz, 1H), 4.86 (d, *J* = 6.5 Hz, 1H), 3.90 (d, *J* = 11.0 Hz, 1H), 3.79 (brs, 2H, containing NH and OH), 2.47−2.39 (m, 1H), 2.31−2.26 (m, 1H), 1.89−1.83 (m, 2H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 147.1, 145.4, 135.8, 129.4, 129.1, 128.6, 127.9, 126.5, 122.7, 121.4, 74.9, 64.7, 32.6, 32.6. HR-ESI calculated for $C_{16}H_{18}NO$ ($[M + H]^+$): 240.13829, found 240.13861. The enantiomeric excess was determined by HPLC (Chiralcel OD-H, *n*-hexane/isopropanol = 80/20, flow rate 1.0 mL/min, *T* = 25 °C, 254 nm) t_R = 19.9 min (major), t_R = 8.3 min (minor).

Synthesis of (−)-Angustureine (2n). In a 50 mL glass-lined stainless steel reactor with a magnetic stirring bar was charged with (*R*,*R*)-**C1a** (460 mg, 0.6 mmol), substrate **1c** (1.2 g, 6.0 mmol) and [Bmim]NTf_2 (5 mL). The autoclave was closed, and hydrogen was initially introduced into the autoclave at a pressure of 50 atm, before being reduced to 1 atm. After this procedure was repeated three times, the autoclave was pressurized with H_2 to 50 atm. Then, the mixture was stirred under this H_2 pressure at room temperature for 48 h. After carefully releasing the hydrogen, the reaction mixture was extracted with diethyl ether. The combined diethyl ether layer was concentrated under vacuum to give the crude product **2c** (100% conversion), which was further purified through flash chromatography on silica gel to afford pure **2c** (1.16 g, 95% yield, 97% ee). To a solution of **2c** (1.16 g, 5.7 mmol) obtained in the above step in CH_3CN (50 mL) at room temperature was added aqueous formaldehyde (37% w/w, 2.9 mL, 34.0 mmol). The mixture was stirred at room temperature for 15 min. $NaBH_3CN$ (723 mg, 11.4 mmol) was added, and stirred for another 15 min. Then, glacial acetic acid (2 mL) was added and further stirred at room temperature for 2 h. The reaction mixture was diluted with 2% CH_3OH−CH_2Cl_2 (10 mL), washed with 1 M NaOH (3 × 10 mL), and dried over Na_2SO_4. The organic solvent was removed in vacuo to afford pure (−)-Angustureine (**2n**) as a pale yellow oil (1.2 g, 98% yield, 97% ee). $[\alpha]_D^{20}$ = −11.6 (*c* = 0.73, $CHCl_3$) (literature data[5a] $[\alpha]_D^{15}$ = −6.7 (*c* 1.00, $CHCl_3$) for the *R*-isomer 94% ee); ^{1}H NMR (500 MHz, $CDCl_3$) δ (ppm) 7.10 (t, *J* = 7.5 Hz, 1H), 6.99 (d, *J* = 7.0 Hz,1H), 6.60 (t, *J* = 7.3 Hz, 1H), 6.54 (d, *J* = 8.5 Hz, 1H), 3.27−3.23 (m, 1H), 2.95 (s, 3H), 2.86−2.79 (m, 1H), 2.70−2.65 (m, 1H), 1.95−1.86 (m, 2H), 1.64−1.60 (m, 1H), 1.46−1.25 (m, 7H), 0.92 (t, *J* = 6.8 Hz, 3H); ^{13}C NMR (125 MHz, $CDCl_3$) δ (ppm) 145.5, 128.8, 127.2, 122.0, 115.3, 110.5, 59.1, 38.1, 32.2, 31.3, 25.9, 24.5, 23.7, 22.8, 14.2. The enantiomeric excess was determined by HPLC (Chiralcel OJ-H, *n*-hexane/isopropanol = 99/1, flow rate 1.0 mL/min, *T* = 25 °C, 254 nm) t_R = 5.3 min (major), t_R = 5.9 min (minor).

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.organomet.9b00183.

Additional experiments data (Table S1−S7, Scheme S1−S2); NMR and HPLC spectra of all substrates and chiral products (Figures S1−S60) (PDF)

Accession Codes

CCDC 1908845 contains the supplementary crystallographic data for this paper. These data can be obtained free of charge via www.ccdc.cam.ac.uk/data_request/cif, or by emailing data_request@ccdc.cam.ac.uk, or by contacting The Cambridge Crystallographic Data Centre, 12 Union Road, Cambridge CB2 1EZ, UK; fax: +44 1223 336033.

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Notes

The authors declare no competing financial interest.

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