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Tetrahedron: *Asymmetry* 17 (2006) 590–597

Studies on Cu-catalyzed asymmetric alkynylation of tetrahydroisoquinoline derivatives

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Received 4 January 2006; accepted 3 February 2006
Available online 10 March 2006

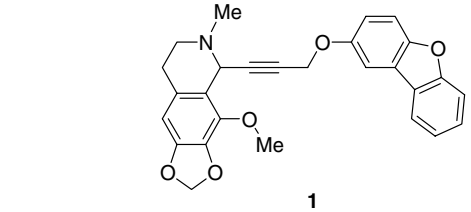
Dedicated to Professor Jack Halpern on the occasion of his 80th birthday

Abstract—Enantioselective C–C bond formations between the sp^3 C–H bond of prochiral CH_2 and terminal alkynes via the cross-dehydrogenative coupling (CDC) reaction were studied. Efficient asymmetric syntheses of alkynyl tetrahydroisoquinoline derivatives were achieved by using a catalytic amount of CuOTf together with PyBox chiral ligand. When dihydroisoquinolinium salts were used as electrophiles, the combination of CuBr/QUINAP provided the best results for asymmetric syntheses of alkynyl tetrahydroisoquinoline derivatives. The factors influencing the enantioselectivity were studied.

1. Introduction

Tetrahydroisoquinoline derivatives are common substructures in natural products.[1] Tetrahydroisoquinoline alkaloids with a stereocenter at the C-1 carbon are compounds of extensive interest, due to their biological and pharmacological properties.[2] Various methodologies have been developed to construct this stereogenic center.[3] Among them, the main synthetic strategies are diastereoselective and enantioselective nucleophilic additions, Friedel–Crafts reactions, and asymmetric hydrogenation of acyclic or cyclic imines or iminium intermediates.

Alkynyl tetrahydroisoquinoline derivatives, such as compound **1**,[4] are potential D3 dopamine receptor ligands in neurological and neuropsychiatric therapeutics. As part of our interest in such compounds, we recently reported a highly efficient new method to build C1-alkynyl tetrahydroisoquinoline derivatives via cross-dehydrogenative coupling (CDC) reactions (Eq. 1).[5] This novel methodology opens a new way to functionalized tetrahydroisoquinoline derivatives, otherwise difficult to obtain.[6] Enantioselective catalytic syntheses of C1-alkynylation of tetrahydroisoquinoline derivatives are rare. Recently, important progress has been made in asymmetric C–C bond formations based on the addition of various C–H bonds to prochiral double bonds.[7] On the other hand, an even greater challenge is to achieve enantioselective C–C bond formations based on the enantioselective reaction of sp^3 C–H bonds of prochiral CH_2 groups.[8] Recently, we reported the preliminary studies of the first Cu-catalyzed asymmetric C–C bond formations based on the reaction of sp^3 C–H bonds of prochiral CH_2 groups.[9] Herein, we report the detailed studies and the mechanistic insights of this novel enantioselective CDC coupling reaction.



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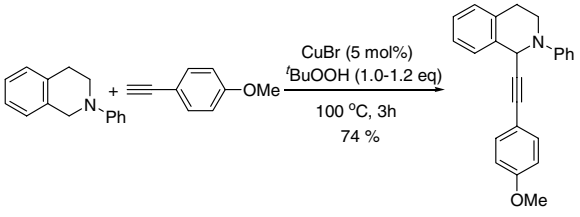

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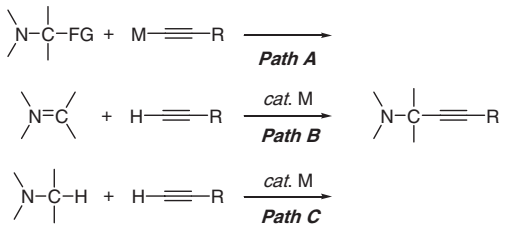
doi:10.1016/j.tetasy.2006.02.007

2. Results and discussion

There are three main methods to construct propargylic amines (Scheme 1): *Path A* represents stoichiometric nucleophilic reactions;[10] *Path B* is the transition-metal catalyzed reactions of alkynes and imines generated from aldehydes and amines. There are many excellent examples of these two methods. Recently, we[11] and others[12] described the direct addition of terminal alkynes to aldehyde and imines to afford propargyl alcohols and propargyl amines. With Cu(I)–PyBox as a chiral catalyst, the first highly enantioselective imine addition in either water or toluene was also developed by us.[13] We also developed the coupling of alkynes with *N*-acylimines and *N*-acyliminium ions by a CuBr catalyst, and the gold or silver-catalyzed coupling reaction of alkyne, aldehyde, and amine in water.[14] Although these are effective methods, they need a leaving group or imines formed from aldehyde and amine. Therefore, the direct construction of propargylic amines by the catalytic coupling of sp^3 C–H adjacent to nitrogen with a terminal alkyne is an attractive alternative method (Path C).[15]



Scheme 1. Various methods for forming propargyl amines.

In our previous study,[5] we established that the desired propargyl amines could be synthesized via a CDC reaction in the presence of a CuBr catalyst (5 mol %) and *tert*-butyl hydroperoxide (1.0–1.2 equiv) at 100 °C for 3 h. Under the same reaction conditions, cyclic amines, such as tetrahydroisoquinoline, can be selectively converted into the corresponding alkynylation product in 74% isolated yield (Eq. 1). This discovery opened an opportunity for us to enantioselectively synthesize C1-alkynyl tetrahydroisoquinoline derivatives by this method.

Chiral bisoxazolines **L1**–**L6**,[16] QUINAP **L7** and BINAP **L8** have been shown to be excellent ligands in copper-catalyzed reactions (Fig. 1). Therefore, various copper salts and chiral compounds **L1**–**L8** were examined as ligands for the asymmetric CDC reaction under various conditions (such as different solvents and reaction temperatures). The use of ligand **L1** provided the highest enantioselectivity in the CDC reaction (Table 1). Various solvents, such as 1,4-dioxane, dimethyl ether, 2-methoxyethyl ether, THF, dichloromethane, 1,2-dichloroethane, toluene, and 18-crown ether were examined and all provided the corresponding alkynylation product in varied yields. The catalytic asymmetric alkynylation also proceeded in water and under solvent-free conditions; however, both the yields and the enantioselectivities were decreased. The best enantioselectivity was obtained by using THF as a solvent. Both

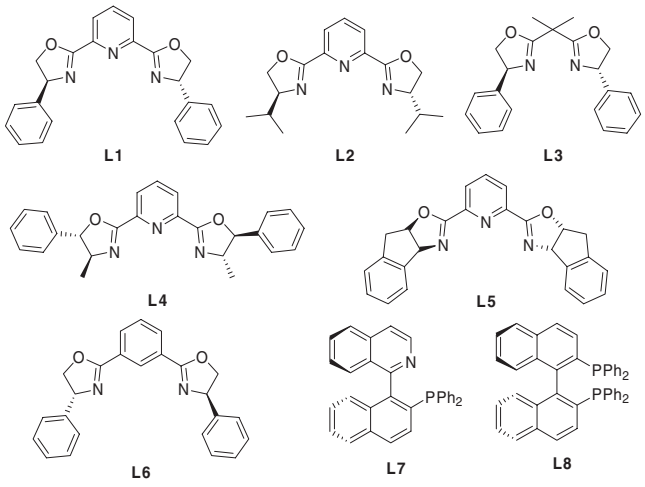
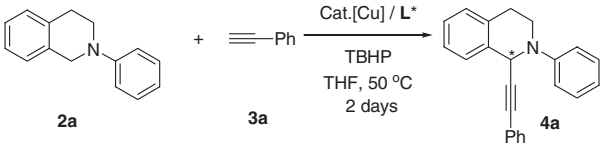


Figure 1. Various chiral ligands.

Table 1. Effect of chiral ligands on the enantioselectivity[a]



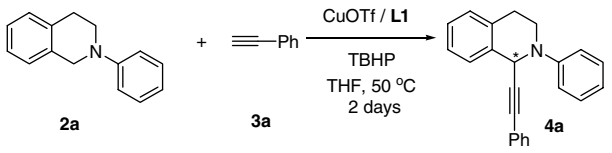
Entry	Catalyst	Ligand	ee (%)[b]
1	CuOTf	**L1**	56
2	CuOTf	**L2**	9[c]
3	CuOTf	**L3**	14
4	CuOTf	**L4**	13
5	CuOTf	**L5**	13
6	CuOTf	**L6**	2
7	CuOTf	**L7**	20
8	CuBr	**L7**	4
9	CuOTf	**L8**	8
10	CuOTf	**L1**	63[d]

[a] Conditions: 0.1 mmol tetrahydroisoquinoline, 0.1 mmol phenylacetylene, 0.01 mmol copper salt, 0.015 mmol ligand, and 0.1 mmol TBHP (5–6 M in decane).
[b] The enantiomeric excess was determined with HPLC by using a Chiralcel OD-H column and 5:95 hexane/isopropanol as eluent.
[c] Dichloromethane was used as solvent.
[d] In this case, ca. 50 mg 4 Å molecular sieve was used.

Cu(I) and Cu(II) were found to be effective as the catalysts, which suggests that Cu(II) may be the active catalyst during the reaction. However, slightly higher enantioselectivities were observed with Cu(I) catalysts. The use of Cu(OTf) provided better enantioselectivities than CuBr. Lowering the reaction temperature (50 °C) was found to be beneficial to the enantioselectivities. Unfortunately, the desired product **4** was not formed at room temperature under the present reaction conditions; the isolated products were mainly the dimer of phenylacetylene and 1-*tert*-butylperoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline **5**.[17]

In order to improve the enantioselectivity, different ratios and amounts of the chiral ligand were also examined under standard reaction conditions (Table 2). The selectivities were diminished when either the ratio of

Table 2. Effect of the amounts of catalyst and chiral ligands[a]



Entry	CuOTf (equiv)	**L1** (equiv)	ee (%)[b]
1	0.1	0.11	55
2	0.1	0.15	58
3	0.1	0.2	27
4	0.01	0.015	20[c]
5	0.05	0.075	54
6	0.2	0.3	56

[a] Conditions: 0.1 mmol tetrahydroisoquinoline, 0.1 mmol phenylacetylene, and 0.1 mmol TBHP (5–6 M in decane).
[b] Enantiomeric excess was determined with HPLC by using a Chiralcel OD-H column and 5:95 hexane/isopropanol as eluent.
[c] In this case, 0.5 mmol tetrahydroisoquinoline, 0.5 mmol phenylacetylene, and 0.5 mmol TBHP (5–6 M in decane) were used.

the chiral ligand relative to copper catalyst was increased or when decreasing the amounts of the chiral ligand and copper catalyst. The best selectivity was obtained by using 10 mol % of copper catalyst together with 15 mol % PyBox chiral ligand **L1**.

Subsequently, the asymmetric CDC reaction of a variety of substrates was examined by using the combination of Cu(I)OTf/**L1** as the chiral catalyst (Table 3). For aryl alkynes, the reaction usually provided both good yields and enantiomeric excesses. Electron-withdrawing groups or electron-donating group R^2 on the aryl ring of the aryl alkynes did not substantially influence the isolated yields or enantioselectivities of the desired products. For alkyl substituted alkynes, fair or low enantiomeric excesses were obtained. Studies showed that the presence of a 4-methoxy substituent on the aryl ring (R^1) did not influence the enantioselectivity of the reaction. Interestingly, the presence of an *ortho*-methoxy substitutent on the aryl ring (R^1) did improve the enantiomeric excess up to 74%. The enhanced enantioselectivity was initially attributed to the presence of the oxygen-based moieties, which allows for chelation and increases rigidity around the metal center. To test this hypothesis, compound **2d** (which allows an even stronger chelation) was synthesized and used in the reactions under standard conditions (Eq. 2). No significant effect of this extended chelation on the enantioselectivity of the alkynylation was observed. The slightly higher enantioselectivity could be the result of an increased steric hindrance near the nitrogen atom.

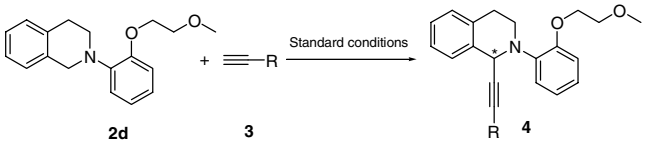


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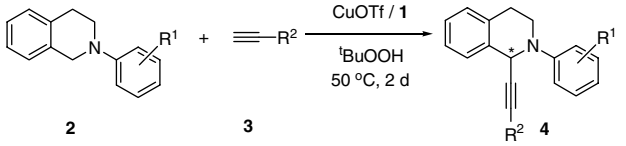
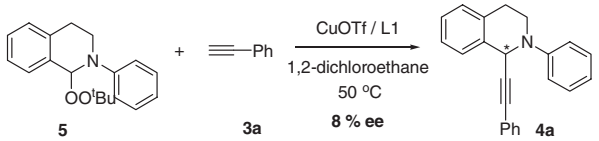
Table 3. CDC reactions of tetrahydroisoquinolines with terminal acetylenes[a]



Entry	R^1	R^2	Product **4**	Yield (%)[b]	ee (%)[c]
1	H (**2a**)	Ph	**4a**	67	63
2	**2a**	4-$MeOC_6H_4$	**4b**	65	41
3	**2a**	4-BrC_6H_4	**4c**	72	64
4	**2a**	Hex	**4d**	65	26
5	**2a**	TMS	**4e**	11	30
6	4-MeO (**2b**)	Ph	**4f**	59	60
7	**2b**	Hex	**4g**	48	5
8	2-MeO (**2c**)	Ph	**4h**	54	73
9	**2c**	4-$MeOC_6H_4$	**4i**	56	69
10	**2c**	4-BrC_6H_4	**4j**	61	74
11	**2c**	Py	**4k**	57	36

[a] Conditions: 0.4 mmol tetrahydroisoquinoline, 0.2 mmol phenylacetylene, 0.02 mmol copper salt, 0.03 mmol ligand, and 0.2 mmol ^{t}BuOOH (5–6 M in decane).
[b] Isolated yields based on alkynes.
[c] The enantiomeric excess was determined with HPLC by using a Chiralcel OD-H column and 5:95 hexane/isopropanol or 100 hexane as eluent.

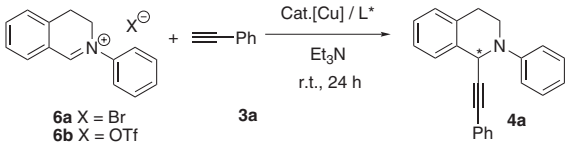
For the mechanism of this novel coupling reaction, it was hypothesized that two relatively stable intermediates, peroxide product **5** and iminium salt **6**, might be involved as possible intermediates in the present reactions.[5] Therefore, in order to gain mechanistic insights as well as to improve the enantioselectivities of the final products, we decided to investigate the asymmetric alkynylation of these two types of compounds. Moreover, it was of interest to determine if the C1-alkynation product of tetrahydroisoquinoline derivatives could be formed from these compounds. Subsequently, it was found that the alkynylation product was in fact obtained with both possible intermediates. However, although 1-*tert*-butylperoxy-2-phenyl-1,2,3,4-tetrahydroisoquinoline **5** was transformed into the desired product **4a**, the enantioselectivity of the reaction is quite low with only 8% ee (Eq. 3). Therefore, our attention was focused on the asymmetric alkynylation of dihydroisoquinoline iminium salts.[18]



(3)

Dihydroisoquinolinium bromide **6a** was synthesized in two steps from isochroman following the literature procedures.[19] Dihydroisoquinolinium triflate **6b** was obtained by the reaction of **6a** with silver triflate.

Table 4. Enantioselectivity of the reaction of iminiums and phenylacetylene[a]



6a X = Br
6b X = OTf

3a **4a**

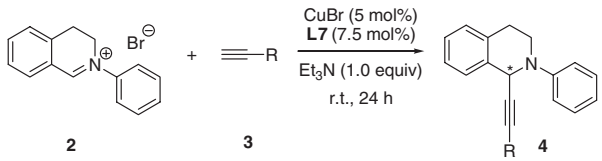
Entry	X	[Cu] (mol %)	Ligand (mol %)	Solvent	Yield (%)[b]	ee (%)[c]
1	Br	CuOTf (10)	**L1** (15)	THF	55	5
2[d]	Br	CuOTf (10)	**L1** (15)	THF	—	—
3	Br	CuBr (10)	**L7** (15)	CH_2Cl_2	71	76
4[e]	Br	CuBr (10)	**L7** (15)	CH_2Cl_2	55	64
5	Br	CuBr (5)	**L7** (7.5)	CH_2Cl_2	83	75
6[f]	Br	CuBr (5)	**L7** (7.5)	CH_2Cl_2	73	76
7	OTf	CuOTf (5)	**L1** (7.5)	CH_2Cl_2	81	14
8	OTf	CuBr (5)	**L7** (7.5)	CH_2Cl_2	90	81

[a] Conditions: 0.2 mmol iminium salt, 0.2 mmol phenylacetylene, 0.2 mmol triethylamine, room temperature, and 24 h; otherwise mentioned.
[b] Isolated yields.
[c] The enantiomeric excess was determined with HPLC by using a Chiralcel OD-H column and 95:5 hexane/isopropanol as eluent.
[d] Without Et_3N.
[e] At −18 °C.
[f] At 40 °C.

Subsequently, the iminium compound was examined with different chiral catalysts: the CuOTf/PyBox system[13] gave low enantioselectivities (Table 4, entries 1 and 7), while the CuBr/QUINAP system[20] provided good enantioselectivities (Table 4, entries 3–6 and 8). In all cases, the desired product **4a** was obtained in good isolated yields. However, triethylamine was found to be essential in this reaction and no product was formed in its absence (Table 4, entry 2).

Subsequently, various alkynes were reacted with dihydroisoquinoline iminium bromide **6a** with a CuBr/QUINAP system in dichloromethane at room temperature. The desired products were obtained in high yields and good to high enantiomeric excesses (Table 5). When ethynyltrimethylsilane was used, the desired product **4e** was obtained with 94% ee.

Table 5. The reactions of iminium salts with terminal acetylenes[a]



2 **3** **4**

Entry	R	Product **4**	Yield (%)[b]	ee (%)[c]
1	Ph	**4a**	83	75
2	4-$MeOC_6H_4$	**4b**	78	73
3	4-BrC_6H_4	**4c**	80	81
4	Hex	**4d**	52	81
5	TMS	**4e**	66	94

[a] Conditions: 0.2 mmol iminium salt, 0.2 mmol phenylacetylene, room temperature, and 24 h.
[b] Isolated yields.
[c] The enantiomeric excess was determined with HPLC by using a Chiralcel OD-H column and 95:5 hexane/isopropanol or 100 hexane as eluent.

3. Conclusion

Alkynyl tetrahydroisoquinoline derivatives were efficiently obtained under a new concept of cross-coupling reaction, the Cross-Dehydrogenative Coupling reaction. The catalytic enantioselective version of this new methodology was established for the first time. Good enantioselectivities were obtained by combining CuOTf and PyBox chiral ligand. When dihydroisoquinolinium salts were used, CuBr/QUINAP combination was found to be a more effective enantioselective catalyst for coupling with terminal alkynes. Further improvement of the enantioselectivities of this type of coupling reaction is underway in our laboratory.

4. Experimental

4.1. General

^{1}H NMR spectra were recorded on Varian 300, 400, and 500 MHz spectrometer in $CDCl_3$ solution and the chemical shifts are reported in parts per million (δ) relative to internal standard TMS (0 ppm). ^{13}C NMR spectra were obtained at 75, 100, and 125 MHz and referenced to the internal solvent signals (central peak is 77.00 ppm). MS data were obtained by Agilent 6890N Network GC System/Agilent 5973 Mass Selective Detector. HRMS were made by McGill University. IR spectra were recorded by an ABB Bomem MB100 instrument. Enantiomeric excess was determined with HPLC by using a Chiralcel OD-H column and 5:95 isopropanol/hexane or 100 hexane as eluent. Thin layer chromatography was performed using Sorbent Silica Gel 60 F254 TLC plates and visualized with ultraviolet light. All reagents were weighed and handled in air, and backfilled under an inert atmosphere of nitrogen at room temperature. All reagents were purchased from Aldrich, Strem, and Acros

and used without further purification. THF and CH_2Cl_2 were refluxed and distilled from sodium/benzophenone and CaH_2 respectively under a nitrogen atmosphere.

4.2. General procedure

4.2.1. General procedure for preparing 2-aryl-1,2,3,4-tetrahydroisoquinolines 2.[21] Copper(I) iodide (200 mg, 1.0 mmol) and potassium phosphate (4.25 g, 20.0 mmol) were put into a Schlenk-tube. The tube was evacuated and back filled with nitrogen. 2-Propanol (10.0 mL), ethylene glycol (1.11 mL, 20.0 mmol), 1,2,3,4-tetrahydroisoquinoline (2.0 mL, 15 mmol), and iodobenzene (1.12 mL, 10.0 mmol) were added successively with a micro-syringe at room temperature. The reaction mixture was heated at 85–90 °C for 24 h and then allowed to cool to room temperature. Diethyl ether (20 mL) and water (20 mL) were then added to the reaction mixture. The organic layer was extracted with diethyl ether (2×20 mL). The combined organic phases were washed with brine and dried over magnesium sulfate. The solvent was removed by rotary evaporation and purified by column chromatography on silica gel (hexane/ethyl acetate = 20:1). The fraction with an $R_f = 0.7$ was collected to give the desired product **2a**.

4.2.1.1. 1,2,3,4-Tetrahydro-2-phenylisoquinoline 2a. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 7.29–7.25 (m, 2H), 7.17–7.12 (m, 4H), 6.96 (d, $J = 8.5$ Hz, 2H), 6.81 (dd, $J = 7.5$, 7.5 Hz, 1H), 4.38 (s, 2H), 3.53 (dd, $J = 6.0$, 6.0 Hz, 2H), 2.96 (dd, $J = 6.0$, 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz, ppm) δ 150.50, 134.82, 134.42, 129.15, 128.47, 126.49, 126.27, 125.97, 118.61, 115.09, 50.68, 46.46, 29.07; MS (EI) *m*/*z* (%) 209, 208 (100), 115, 104, 91, 78, 77, 51.

4.2.1.2. 1,2,3,4-Tetrahydro-2-(4-methoxyphenyl)isoquinoline 2b. ^{1}H NMR ($CDCl_3$, 400 MHz, ppm) δ 7.15–7.08 (m, 4H), 6.95 (d, $J = 8.8$ Hz, 2H), 6.84 (d, $J = 8.8$ Hz, 2H), 4.28 (s, 2H), 3.75 (s, 3H), 3.42 (dd, $J = 6.0$, 6.0 Hz, 2H), 2.97 (dd, $J = 6.0$, 6.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 100 MHz, ppm) δ 153.26, 145.11, 134.40, 134.34, 128.51, 126.34, 126.09, 125.74, 117.88, 114.41, 55.62, 52.68, 48.47, 29.18; MS (EI) *m*/*z* (%) 239 (100), 238, 224, 135, 120, 104, 91, 77, 65, 51.

4.2.1.3. 1,2,3,4-Tetrahydro-2-(2-methoxyphenyl)isoquinoline 2c. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 7.15–7.12 (m, 3H), 7.10–7.07 (m, 1H), 6.99 (d, $J = 8.0$ Hz, 2H), 6.90 (t, $J = 8.0$ Hz, 1H), 6.89 (t, $J = 8.0$ Hz, 1H), 4.28 (s, 2H), 3.87 (s, 3H), 3.40 (dd, $J = 5.5$, 5.5 Hz, 2H), 2.97 (dd, $J = 5.0$, 5.0 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz, ppm) δ 152.53, 141.08, 135.10, 134.49, 128.81, 126.29, 126.03, 125.64, 122.88, 120.85, 118.88, 111.25, 55.40, 53.01, 48.91, 28.83.

4.2.1.4. 2-(2-(2-Methoxyethoxy)phenyl)-1,2,3,4-tetrahydroisoquinoline 2d. ^{1}H NMR ($CDCl_3$, 500 MHz, ppm) δ 7.23–7.21 (m, 3H), 7.18–7.17 (m, 1H), 7.07 (d, $J = 8.0$ Hz, 1H), 7.03 (t, $J = 7.5$ Hz, 2H), 6.96 (d, $J = 7.5$ Hz, 1H), 4.38 (s, 2H), 4.21 (t, $J = 5.0$ Hz, 2H), 3.81 (t, $J = 5.0$ Hz, 2H), 3.51 (t, $J = 5.0$ Hz, 2H), 3.48 (s, 3H), 3.08 (dd, $J = 5.5$, 5.5 Hz, 2H); ^{13}C NMR ($CDCl_3$, 125 MHz, ppm) δ 151.26, 141.32, 134.92, 134.31, 128.45, 126.03, 125.68, 125.25, 122.10, 121.12, 118.18, 112.98, 70.83, 67.23, 58.58, 52.36, 48.72, 28.93.

4.2.2. General procedure for 3,4-dihydro-2-phenyl-isoquinolinium salt 6.[19] Bromine (3.0 g) was added slowly to an ice-cooled solution of isochroman (2.5 g) in carbon tetrachloride (10 mL). The mixture was then heated at reflux until the color of the mixture changed from dark brown to pale yellow (ca. 1 h). The solvent was removed under a reduced pressure and aqueous hydrobromic acid (48%, 3.8 mL) added. The mixture was heated at reflux (ca. 15 min). The obtained solution was allowed to cool to room temperature and extracted with diethyl ether. The organic extract was washed with water and saturated aqueous sodium bicarbonate and dried over magnesium sulfate. The crude 2-(2-bromoethyl)benzaldehyde (3.3 g) was obtained by evaporation of the solvent under reduced pressure. The crude 2-(2-bromoethyl)benzaldehyde was dissolved in 20 mL dioxane. Aniline (1.63 g) was added slowly to the solution. 3,4-Dihydro-2-phenyl-isoquinolinium bromide **6a** was obtained as a solid by filtration and washed with diethyl ether. 3,4-Dihydro-2-phenyl-isoquinolinium triflate **6b** was obtained as a solid by adding 1 equiv of silver triflate to the methanol solution of **6a**.

4.2.2.1. 3,4-Dihydro-2-phenyl-isoquinolinium bromide 6a. ^{1}H NMR (CD_3OD, 400 MHz, ppm) δ 9.52 (s, 1H), 8.05 (dd, $J = 7.6$, 0.8 Hz, 1H), 7.90–7.85 (m, 2H), 7.68–7.65 (m, 2H), 7.62–7.58 (m, 2H), 7.55–7.48 (m, 1H), 7.44–7.42 (m, 1H), 4.66 (td, $J = 8.0$, 1.2 Hz, 2H), 3.53 (d, $J = 8.0$ Hz, 2H); ^{13}C NMR (CD_3OD, 100 MHz, ppm) δ 168.27, 168.17, 144.24, 139.93, 138.32, 136.19, 132.12, 131.20, 131.07, 130.00, 129.50, 129.38, 126.62, 123.93, 123.57, 52.79, 26.58.

4.2.2.2. 3,4-Dihydro-2-phenyl-isoquinolinium triflate 6b. ^{1}H NMR (CD_3OD, 300 MHz, ppm) δ 9.42 (s, 1H), 8.00 (d, $J = 7.5$ Hz, 1H), 7.89–7.77 (m, 3H), 7.68–7.62 (m, 2H), 7.59–7.55 (m, 2H), 7.42–7.29 (m, 1H), 4.62 (t, $J = 8.1$ Hz, 2H), 3.49 (d, $J = 8.1$ Hz, 2H); ^{13}C NMR (CD_3OD, 75 MHz, ppm) δ 168.40, 168.33, 144.27, 140.02, 138.32, 136.16, 132.17, 131.23, 130.97, 129.54, 129.38, 128.71, 126.56, 123.48, 122.96, 52.65, 26.43.

4.2.3. General procedure for product 4. *Method A*: To a mixture of $(CuOTf)_2$toluene complex (5.4 mg, 0.02 mmol), [*S*-(*R**,*R**)]-2,6-bis-(4,5-dihydro-4-phenyl-2-oxazolyl)pyridine (PyBox) (10.8 mg, 0.03 mmol), 2-phenyl-1,2,3,4-tetrahydroisoquinoline (42 mg, 0.4 mmol), phenylacetylene (0.022 mL, 0.2 mmol), ca. 50 mg of 4 Å MS, and 1 mL of THF was added. Then *tert*-butyl hydroperoxide (0.04 mL, 5–6 M in decane) was added dropwise into the mixture under nitrogen at room temperature. The reaction temperature was raised to 50 °C over 10 min and stirred at the same temperature for 2 days. The reaction mixture was cooled to room temperature; the resulting suspension was diluted with diethyl ether and filtered through a short silica gel in a pipette eluting with diethyl ether. Solvent was evaporated and the residue purified by thin layer chromatography (hexane/

methylene chloride/diethyl ether = 100:60:1), and the fraction with an $R_f = 0.6$ was collected to give the desired product **4a**.

Method B: To a mixture of copper catalyst (5 mol %), chiral ligand (7.5 mol %), 3,4-dihydro-2-phenyl-isoquinolinium salt (0.2 mmol), and 1 mL THF or dichloromethylene were added while stirring. Then phenylacetylene (0.2 mmol) and triethyl amine (0.2 mmol) were added dropwise into the mixture under nitrogen at room temperature and stirred for 24 h. The work-up procedure was the same as that of Method A.

4.2.3.1. *rac*-2-Phenyl-1-phenylethynyl-1,2,3,4-tetrahydroisoquinoline 4a. Isolated by thin layer chromatography (hexane/methylene chloride/diethyl ether = 100:60:1, $R_f = 0.6$). HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 95:5, flow rate = 0.5 mL/min) t_R = 12.0 min, t_R = 13.3 min, ee = 0%; IR (neat liquid): ν_{max} 3061, 3024, 2920, 2832, 2210, 1950, 1598, 1503, 1489, 1451, 1442, 1377, 1287, 1201, 1069, 1029, 932 cm^{-1}; ^1H NMR (400 MHz, ppm) δ 7.35–7.25 (m, 5H), 7.22–7.14 (m, 6H), 7.09 (dd, $J = 8.4$, 0.8 Hz, 2H), 6.86 (dt, $J = 7.2$, 0.8 Hz, 1H), 5.62 (s, 1H), 3.75–3.61 (m, 2H), 3.09 (ddd, $J = 16.8$, 10.4, 6.4 Hz, 1H), 2.95 (dt, $J = 16.0$, 4.0 Hz, 1H); ^{13}C NMR (100 MHz, ppm) δ 149.31, 135.20, 134.19, 131.55, 128.95, 128.75, 127.90, 127.84, 127.25, 127.04, 126.10, 122.83, 119.47, 116.54, 88.53, 84.71, 52.31, 43.46, 28.98; MS (EI) *m/z* (%) 309, 308 (100), 293, 253, 204, 203, 202, 73, 51; HRMS calcd for $C_{23}H_{19}N$: 309.1517; found: 309.1511.

4.2.3.2. *rac*-1-(4-Methoxy-phenylethynyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline 4b. Isolated by thin layer chromatography (hexane/ethyl acetate = 20:1, R_f = 0.4). HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 95:5, flow rate = 0.5 mL/min) $t_R = 16.1$ min, $t_R = 18.8$ min, ee = 0%; IR (neat liquid): ν_{max} 3061, 3025, 2932, 2836, 2206, 1600, 1499, 1374, 1246, 1172, 1106, 1033, 832, 756, 692 cm^{-1}; ^1H NMR (ppm) δ 7.34–7.31 (m, 1H), 7.30–7.26 (m, 2H), 7.21–7.16 (m, 4H), 7.15–7.12 (m, 1H), 7.08 (d, $J = 8.0$ Hz, 2H), 6.84 (dd, $J = 7.6$, 7.6 Hz, 1H), 6.69 (dt, $J = 8.8$, 2.4 Hz, 2H), 5.60 (s, 1H), 3.73–3.60 (m, 2H), 3.68 (s, 3H), 3.09 (ddd, $J = 16.0$, 9.6, 6.0 Hz, 1H), 2.92 (dt, $J = 16.0$, 4.0 Hz, 1H); ^{13}C NMR (ppm) δ 159.10, 149.32, 135.40, 134.14, 132.93, 128.92, 128.70, 127.23, 126.94, 126.04, 119.34, 116.46, 114.95, 113.54, 87.03, 84.52, 55.17, 52.25, 43.41, 28.95; MS (EI) *m/z* (%) 340, 339, 338, 324, 223, 220, 219, 208, 191, 189, 118, 104, 77; HRMS calcd for $C_{24}H_{20}NO$ (M−1): 338.1545; found: 338.1540; $C_{24}H_{21}NO$: 339.1623; found: 339.1604.

4.2.3.3. *rac*-1-(4-Bromo-phenylethynyl)-2-phenyl-1,2,3,4-tetrahydroisoquinoline 4c. Isolated by thin layer chromatography (hexane/methylene chloride/diethyl ether = 100:60:1, $R_f = 0.5$). HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 95:5, flow rate = 0.5 mL/min) t_R = 12.9 min, t_R = 14.9 min, ee = 0%; IR (neat liquid): ν_{max} 3065, 3029, 2921, 2833, 2393, 1902, 1597, 1504, 1485, 1451, 1393, 1377, 1354, 1286, 1261, 1205, 1153, 1070, 1011 cm^{-1}; ^1H NMR (300 MHz, ppm) δ 7.35–7.29 (m, 4H), 7.24–7.15 (m, 4H), 7.14–7.07 (m, 4H), 6.87 (dt, $J = 7.2$, 1.2 Hz, 1H), 5.61 (s, 1H), 3.77–3.58 (m, 2H), 3.13 (ddd, $J = 15.6$, 9.9, 5.7 Hz, 1H), 2.95 (dt, $J = 15.9$, 4.2 Hz, 1H); ^{13}C NMR (75 MHz, ppm) δ 149.29, 134.93, 134.26, 133.06, 131.20, 129.04, 128.85, 127.26, 127.20, 126.20, 122.11, 121.81, 119.64, 116.58, 89.78, 83.67, 52.35, 43.47, 28.94; MS (EI) *m/z* (%) 389, 388 (100), 387, 386 (100), 373, 360, 307, 284, 258, 206, 182, 153, 140, 75, 50; HRMS calcd for $C_{23}H_{17}BrN$ (M−1): 386.0536; found: 386.0544; $C_{23}H_{18}BrN$: 387.0631; found: 387.0623.

4.2.3.4. *rac*-1-Oct-1-ynyl-2-phenyl-1,2,3,4-tetrahydroisoquinoline 4d. Isolated by thin layer chromatography (hexane/methylene chloride/diethyl ether = 100:60:1, $R_f = 0.6$). HPLC (Daicel Chiralcel OD-H, hexane, flow rate = 0.3 mL/min) $t_R = 46.6$ min, $t_R = 66.2$ min, ee = 0%; IR (neat liquid): ν_{max} 3062, 3025, 2954, 2928, 2856, 2260, 1598, 1504, 1452, 1428, 1377, 1287, 1224, 1201, 1152, 1123, 1033, 932 cm^{-1}; ^1H NMR (300 MHz, ppm) δ 7.30–7.23 (m, 3H), 7.20–7.11 (m, 3H), 7.03 (dt, $J = 7.8$, 1.2 Hz, 2H), 6.83 (tt, $J = 7.2$, 1.2 Hz, 1H), 5.39 (s, 1H), 3.73–3.65 (m, 1H), 3.61–3.52 (m, 1H), 3.08 (ddd, $J = 15.9$, 10.1, 5.8 Hz, 1H), 2.91 (dt, $J = 15.9$, 3.9 Hz, 1H), 2.08 (dt, $J = 6.9$, 2.8 Hz, 2H), 1.39–1.32 (m, 2H), 1.28–1.15 (m, 6H), 0.84 (t, $J = 6.9$ Hz, 3H); ^{13}C NMR (75 MHz, ppm) δ 149.67, 136.10, 134.00, 128.89, 128.69, 127.18, 126.82, 126.00, 119.21, 116.45, 85.28, 79.13, 51.77, 43.21, 31.32, 28.96, 28.71, 28.42, 22.60, 18.84, 14.12; MS (EI) *m/z* (%) 317, 316 (100), 246, 232, 206, 155, 142, 141, 128, 116, 115, 91, 77, 55; HRMS calcd for $C_{23}H_{27}N$: 317.2144; found: 317.2155.

4.2.3.5. *rac*-2-Phenyl-1-trimethylsilanylethynyl-1,2,3,4-tetrahydroisoquinoline 4e. Isolated by thin layer chromatography (hexane/methylene chloride/diethyl ether = 100:60:1, $R_f = 0.8$). HPLC (Daicel Chiralcel OD-H, hexane, flow rate = 0.3 mL/min) $t_R = 58.9$ min, $t_R = 87.6$ min, ee = 0%; IR (neat liquid): ν_{max} 3065, 3029, 2958, 2904, 2835, 2381, 2352, 2161, 1598, 1503, 1451, 1376, 1249, 1201, 1020, 992 cm^{-1}; ^1H NMR (ppm) δ 7.29–7.25 (m, 3H), 7.21–7.13 (m, 3H), 7.04 (d, $J = 6.0$ Hz, 2H), 6.86 (t, $J = 5.4$ Hz, 1H), 5.40 (s, 1H), 3.69–3.64 (m, 1H), 3.60–3.54 (m, 1H), 3.09 (ddd, $J = 16.2$, 10.2, 6.0 Hz, 1H), 2.91 (dt, $J = 16.0$, 3.6 Hz, 1H), 0.05 (s, 9H); ^{13}C NMR (ppm) δ 149.37, 135.04, 134.17, 128.85, 128.73, 127.29, 126.97, 126.04, 119.52, 116.80, 104.61, 88.98, 52.72, 43.38, 28.87, 0.13; MS (EI) *m/z* (%) 305, 304 (100), 290, 232, 208, 206, 185, 172, 155, 145, 128, 115, 104, 91, 77, 59; HRMS calcd for $C_{20}H_{23}NSi$: 305.1600; found: 305.1611.

4.2.3.6. *rac*-2-(4-Methoxy-phenyl)-1-phenylethynyl-1,2,3,4-tetrahydroisoquinoline 4f. Isolated by thin layer chromatography (hexane/methylene chloride/diethyl ether = 100:60:1, $R_f = 0.4$). HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 95:5, flow rate = 0.5 mL/min) $t_R = 15.7$ min, $t_R = 23.8$ min, ee = 0%; IR (neat liquid): ν_{max} 3061, 3022, 2997, 2952, 2930, 2907, 2832, 2248, 1597, 1511, 1489, 1463, 1452, 1442, 1374, 1261, 1243, 1201, 1183, 1037, 956 cm^{-1}; ^1H NMR (ppm) δ 7.34–7.32 (m, 1H), 7.27–7.25 (m, 2H), 7.22–7.15 (m, 6H), 7.09 (d, $J = 8.8$ Hz, 2H), 6.87 (d, $J = 8.8$ Hz, 2H),

5.49 (s, 1H), 3.78 (s, 3H), 3.69–3.52 (m, 2H), 3.14 (ddd, $J = 16.6$, 10.6, 3.2 Hz, 1H), 2.92 (dt, $J = 16.0$, 3.6 Hz, 1H); ^{13}C NMR (ppm) δ 154.03, 143.95, 135.27, 133.87, 131.53, 128.91, 127.90, 127.81, 127.35, 126.98, 125.97, 122.92, 120.06, 114.24, 88.38, 85.44, 55.61, 54.42, 44.27, 29.12; MS (EI) m/z (%) 339 (100), 338, 327, 267, 253, 236, 204, 203, 202, 191, 178, 165, 147, 135, 120, 96, 73; HRMS calcd for $C_{24}H_{21}NO$: 339.1623; found: 339.1620.

4.2.3.7. *rac*-2-(4-Methoxy-phenyl)-1-oct-1-ynyl-1,2,3,4-tetrahydroisoquinoline 4g. Isolated by thin layer chromatography (hexane/methylene chloride/diethyl ether = 100:60:1, $R_f = 0.4$). HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 95:5, flow rate = 0.5 mL/min) $t_R = 11.6$ min, $t_R = 13.1$ min, ee = 0%; IR (neat liquid): ν_{max} 2953, 2930, 2856, 2832, 2252, 1579, 1511, 1464, 1441, 1376, 1261, 1243, 1201, 1182, 1122, 1039 cm^{-1}; ^{1}H NMR (ppm) δ 7.26–7.25 (m, 1H), 7.18–7.13 (m, 3H), 7.03 (d, $J = 8.8$ Hz, 2H), 6.85 (d, $J = 9.2$ Hz, 2H), 5.27 (s, 1H), 3.77 (s, 3H), 3.57–3.49 (m, 2H), 3.09 (ddd, $J = 16.4$, 10.0, 6.4 Hz, 1H), 2.88 (dt, $J = 16.4$, 3.2 Hz, 1H), 2.07 (dt, $J = 7.2$, 2.0 Hz, 2H), 1.37–1.32 (m, 2H), 1.26–1.17 (m, 6H), 0.85 (t, $J = 6.0$ Hz, 3H); ^{13}C NMR (ppm) δ 153.78, 144.05, 136.10, 133.63, 128.80, 127.23, 126.72, 125.83, 119.79, 114.13, 85.98, 78.86, 55.56, 53.79, 44.06, 31.39, 29.09, 28.78, 28.45, 22.65, 18.88, 14.18; MS (EI) m/z (%) 347 (100), 346, 276, 262, 236, 194, 169, 155, 142, 141, 129, 128, 115, 92, 91, 77, 55; HRMS calcd for $C_{24}H_{29}NO$: 347.2249; found: 347.2242.

4.2.3.8. *rac*-2-(2-Methoxy-phenyl)-1-phenylethynyl-1,2,3,4-tetrahydroisoquinoline 4h. Isolated by thin layer chromatography (hexane/methylene chloride/diethyl ether = 100:60:1, $R_f = 0.3$). HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 95:5, flow rate = 0.5 mL/min) $t_R = 12.4$ min, $t_R = 21.2$ min, ee = 0%; IR (neat liquid): ν_{max} 3062, 3022, 3006, 2958, 2925, 2834, 2384, 2349, 1712, 1595, 1500, 1490, 1463, 1454, 1442, 1374, 1273, 1253, 1241, 1217, 1199, 1179, 1138, 1106, 1028 cm^{-1}; ^{1}H NMR (ppm) δ 7.32–7.30 (m, 1H), 7.22–7.15 (m, 9H), 7.05 (dt, $J = 7.6$, 1.6 Hz, 1H), 6.96 (dt, $J = 7.6$, 1.6 Hz, 1H), 6.89 (dd, $J = 8.0$, 0.8 Hz, 1H), 5.74 (s, 1H), 3.87 (s, 3H), 3.68 (dt, $J = 11.6$, 4.0 Hz, 1H), 3.43 (dd, $J = 11.6$, 11.6 Hz, 1H), 3.24 (ddd, $J = 16.8$, 11.2, 5.6 Hz, 1H), 2.90 (dt, $J = 16.4$, 2.4 Hz, 1H); ^{13}C NMR (ppm) δ 159.10, 149.32, 135.40, 134.14, 132.93, 128.92, 128.70, 127.23, 126.94, 126.04, 119.34, 116.46, 114.95, 113.54, 87.03, 84.52, 55.17, 52.25, 43.41, 28.95; MS (EI) m/z (%) 339, 338, 322, 308 (100), 293, 262, 246, 232, 217, 203, 202, 189, 165, 152, 115, 92, 91, 77, 64; HRMS calcd for $C_{24}H_{20}NO$: 339.1623; found: 339.1627.

4.2.3.9. *rac*-2-(2-Methoxy-phenyl)-1-(4-methoxy-phenylethynyl)-1,2,3,4-tetrahydroisoquinoline 4i. Isolated by thin layer chromatography (hexane/methylene chloride/diethyl ether = 100:60:1, $R_f = 0.4$). HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 95:5, flow rate = 0.5 mL/min) $t_R = 16.1$ min, $t_R = 18.8$ min, ee = 0%; IR (neat liquid): ν_{max} 3061, 3025, 2932, 2836, 2206, 1600, 1499, 1374, 1246, 1172, 1106, 1033, 832, 756, 692 cm^{-1}; ^{1}H NMR (ppm) δ 7.34–7.31 (m, 1H), 7.30–7.26 (m, 2H), 7.21–7.16 (m, 4H), 7.15–7.12 (m, 1H), 7.08 (d, $J = 8.0$ Hz, 2H), 6.84 (dd, $J = 7.6$, 7.6 Hz, 1H), 6.69 (dt, $J = 8.8$, 2.4 Hz, 2H), 5.60 (s, 1H), 3.73–3.60 (m, 2H), 3.68 (s, 3H), 3.09 (ddd, $J = 16.0$, 9.6, 6.0 Hz, 1H), 2.92 (dt, $J = 16.0$, 4.0 Hz, 1H); ^{13}C NMR (ppm) δ 159.10, 149.32, 135.40, 134.14, 132.93, 128.92, 128.70, 127.23, 126.94, 126.04, 119.34, 116.46, 114.95, 113.54, 87.03, 84.52, 55.17, 52.25, 43.41, 28.95; MS (EI) m/z (%) 369, 368, 338 (100), 262, 247, 220, 191, 189, 165, 115, 91, 77, 63.

4.2.3.10. *rac*-1-(4-Bromo-phenylethynyl)-2-(2-methoxy-phenyl)-1,2,3,4-tetrahydroisoquinoline 4j. Isolated yield by thin layer chromatography (hexane/methylene chloride/diethyl ether = 100:60:1, $R_f = 0.7$). HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 95:5, flow rate = 0.5 mL/min) $t_R = 12.9$ min, $t_R = 14.9$ min, ee = 0%; IR (neat liquid): ν_{max} 3065, 3029, 2921, 2833, 2393, 1902, 1597, 1504, 1485, 1451, 1393, 1377, 1354, 1286, 1261, 1205, 1153, 1070, 1011 cm^{-1}; ^{1}H NMR (300 MHz, ppm) δ 7.35–7.29 (m, 4H), 7.24–7.15 (m, 4H), 7.14–7.07 (m, 4H), 6.87 (dt, $J = 7.2$, 1.2 Hz, 1H), 5.61 (s, 1H), 3.77–3.58 (m, 2H), 3.13 (ddd, $J = 15.6$, 9.9, 5.7 Hz, 1H), 2.95 (dt, $J = 15.9$, 4.2 Hz, 1H); ^{13}C NMR (75 MHz, ppm) δ 149.29, 134.93, 134.26, 133.06, 131.20, 129.04, 128.85, 127.26, 127.20, 126.20, 122.11, 121.81, 119.64, 116.58, 89.78, 83.67, 52.35, 43.47, 28.94; MS (EI) m/z (%) 418, 416, 402, 388 (100), 386 (100), 373, 355, 341, 327, 312, 297, 262, 207, 203, 193, 152, 135, 105, 91, 73, 51.

4.2.3.11. *rac*-2-(2-Methoxy-phenyl)-1-pyridin-2-yl-ethynyl-1,2,3,4-tetrahydroisoquinoline 4k. Isolated by thin layer chromatography (hexane/ethyl acetate = 5:1, $R_f = 0.3$). HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 95:5, flow rate = 0.5 mL/min) $t_R = 12.9$ min, $t_R = 14.9$ min, ee = 0%; IR (neat liquid): ν_{max} 3065, 3029, 2921, 2833, 2393, 1902, 1597, 1504, 1485, 1451, 1393, 1377, 1354, 1286, 1261, 1205, 1153, 1070, 1011 cm^{-1}; ^{1}H NMR (300 MHz, ppm) δ 7.35–7.29 (m, 4H), 7.24–7.15 (m, 4H), 7.14–7.07 (m, 4H), 6.87 (dt, $J = 7.2$, 1.2 Hz, 1H), 5.61 (s, 1H), 3.77–3.58 (m, 2H), 3.13 (ddd, $J = 15.6$, 9.9, 5.7 Hz, 1H), 2.95 (dt, $J = 15.9$, 4.2 Hz, 1H); ^{13}C NMR (75 MHz, ppm) δ 149.29, 134.93, 134.26, 133.06, 131.20, 129.04, 128.85, 127.26, 127.20, 126.20, 122.11, 121.81, 119.64, 116.58, 89.78, 83.67, 52.35, 43.47, 28.94; MS (EI) m/z (%) 340, 339, 309 (100), 294, 281, 262, 233, 218, 205, 204, 191, 176, 155, 133, 120, 92, 76, 51, 50.

4.2.3.12. *rac*-2-(2-(2-Methoxyethoxy)phenyl)-1,2,3,4-tetrahydro-1-(2-phenylethynyl)isoquinoline 4l. Isolated by thin layer chromatography (methylene chloride, $R_f = 0.4$) HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 95:5, flow rate = 0.5 mL/min) $t_R = 20.1$ min, $t_R = 23.7$ min, ee = 0%; IR (neat liquid): ν_{max} 3059, 3022, 2923, 2878, 2832, 1595, 1499, 1450, 1371, 1241, 1198, 1128 cm^{-1}; ^{1}H NMR (500 MHz, ppm) δ 7.32–7.30 (m, 1H), 7.24–7.15 (m, 9H), 7.03–6.97 (m, 2H), 6.90 (dd, $J = 7.5$, 1.0 Hz, 1H), 5.85 (s, 1H), 4.16 (t, $J = 4.5$ Hz, 2H), 3.75–3.65 (m, 3H), 3.51 (dd, $J = 11.0$, 6.0 Hz, 1H), 3.23 (ddd, $J = 17.0$, 11.5,

6.0 Hz, 1H), 2.88 (dd, $J = 16.0$, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, ppm) δ 151.68, 140.33, 135.91, 133.83, 131.59, 129.08, 127.96, 127.71, 127.44, 126.80, 125.73, 123.28, 123.15, 121.41, 120.88, 113.29, 89.01, 85.46, 71.07, 67.80, 59.07, 52.64, 43.79, 29.07; MS (ESI) m/z (%) 406 (100, M+Na$^+$), 384, 352, 324, 308, 282, 232.

4.2.3.13. *rac*-2-(2-(2-Methoxyethoxy)phenyl)-1-(2-(4-bromophenyl)ethynyl)-1,2,3,4-tetrahydroisoquinoline 4m. Isolated by thin layer chromatography (methylene chloride, $R_f = 0.4$) HPLC (Daicel Chiralcel OD-H, hexane/isopropanol = 95:5, flow rate = 0.5 mL/min) $t_R =$ 20.0 min, $t_R = 23.3$ min, ee = 0%; IR (neat liquid): ν_{max} 3062, 3025, 2923, 2832, 1594, 1499, 1485, 1450, 1241, 11998, 1128, 1010 cm^{-1}; ^{1}H NMR (500 MHz, ppm) δ 7.33–7.28 (m, 3H), 7.21–7.16 (m, 4H), 7.08 (d, $J =$ 9.0 Hz, 2H), 7.04–6.96 (m, 2H), 6.90 (dd, $J = 8.0$, 1.5 Hz, 1H), 5.86 (s, 1H), 4.18–4.14 (m, 2H), 3.74–3.62 (m, 2H), 3.63 (dd, $J = 11.5$, 4.0 Hz, 1H), 3.50 (ddd, $J = 12.0$, 6.5, 1.5 Hz, 1H), 3.23 (ddd, $J = 17.0$, 11.5, 6.0 Hz, 1H), 2.88 (dd, $J = 16.5$, 3.0 Hz, 1H); ^{13}C NMR (125 MHz, ppm) δ 151.67, 140.21, 135.57, 133.81, 133.06, 131.21, 129.12, 127.40, 126.91, 125.78, 123.26, 122.22, 121.86, 121.39, 120.81, 113.31, 113.30, 90.30, 84.36, 71.06, 67.81, 59.08, 52.62, 43.78, 29.04; MS (ESI) m/z (%) 486 (M+Na$^+$), 484 (M+Na$^+$), 464, 462, 430, 404, 402, 388, 386, 306, 282 (100), 231.

Acknowledgments

We are grateful to the Canada Research Chair (Tier I) foundation (to C.J.L.), the CFI, NSERC, FQRNT, Merck Frosst, CIC (AstraZeneca/Boehringer Ingelheim/Merck Frosst), and McGill University for support of our research.

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