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Facile preparation of 3-aryl-4-iodoisoquinolines from *N*-(*o*-Arylethynyl)benzyl *p*-toluenesulfonamides with iodine and base

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ABSTRACT

Treatment of *N*-(*o*-arylethynyl)benzyl *p*-toluenesulfonamides with molecular iodine in the presence of $NaHCO_3$ at 60 °C, followed by the reaction with ^tBuOK at room temperature gave 3-aryl-4-iodoisoquinolines in good yields. 4-Iodo-3-phenylisoquinoline, which is one of the obtained 3-aryl-4-iodoisoquinolines, was further transformed into isoquinoline derivatives smoothly. The present approach is a novel one-pot method for the preparation of 3-aryl-4-iodoisoquinolines from *N*-(*o*-arylethynyl)benzyl *p*-toluenesulfonamides under transition-metal-free conditions. © 2021 Elsevier Science. All rights reserved.

1. Introduction

Isoquinoline is one of the important nitrogen-containing heteroaromatics and is contained as a unit in many natural products, *i.e.,* isoquinoline alkaloids [1]. Some isoquinolines possess potent biological activity. For example, Tamoxifen analogue shows antiestrogenic activity [1d], Decumbenine B exhibits antineuralgic activity [1e], and Papaverine has antispasmodic activity [1e], as shown in Fig. 1.

Therefore, in addition to the conventional methods for the preparation of the isoquinoline unit with the Pomeranz-Fritsch reaction using aromatic aldehydes and β-aminoacetals [2a,2b], and for the preparation of the 3,4-dihydroisoquinoline unit with the Bischler-Napieralski reaction using *N*-acyl β-arylethylamines and $POCl_3$ [2c], extensive synthetic studies on the preparation of the isoquinoline unit have been carried out [1b,1f]. Recent synthetic studies for the preparation of isoquinolines with alkynes are as follows:[3] the Rh(I)-catalyzed preparation of 1-substituted 3,4-diphenylisoquinolines from acetophenones, benzylamine, and diphenylacetylene [3a]; the Ni(II)-catalyzed preparation of 3,4-diarylisoquinolines from 2-iodobenzaldehydes, *tert*-butylamine, and diarylacetylenes [3b]; the Ir(III)-catalyzed preparation of 3,4-disubstituted 1-ethoxyisoquinolines from *O*-ethyl benzimidates and alkynes [3c]; the Ir(III)-catalyzed preparation of 1-substituted 3,4-diphenylisoquinolines from aryl ketoximes and diphenylacetylene [3d]; and the Rh(III)-catalyzed preparation of 1,3,5-trisubstituted isoquinolines from acetophenones, hydroxylamine-*O*-sulfonic acid, and alkynes [3e]. The preparation of 3-alkylisoquinolines from (α-benzyl,α-alkyl)tosylmethyl isocyanides with trifluoroacetic acid [3f] and of 3-ethoxycarbonyl-1-(2′,2′,2′-trifluoroethyl)isoquinolines from β-arylvinyl isocyanides with 2-iodo-1,1,1-trifluoroethane [3g] via cyclization of the isocyano group, and the preparation of isoquinolines from *o*-bromobenzaldehyde acetal, ketones, and NH_4Cl via a two-step operation [3h] were also reported.

The Pd (0)-catalyzed preparation of 3,4-disubstituted isoquinolines from *N*-(*tert*-butyl) *o*-(1-alkynyl)benzaldimines with aryl iodides (eq. 1) [4] and the electrophile-mediated preparation of 3,4-disubstituted isoquinolines from *N*-(*tert*-butyl) *o*-(1-alkynyl) benzaldimines with I_2, ICl, or PhSeCl (eq. 2) [5], are attractive, as shown in Scheme 1. In particular, the latter method does not require any transition metals, and the introduced heteroatom groups, such as iodine and phenylselenyl groups, at 4-position could be further functionalized. However, the study for 4-iodoisoquinoline synthesis in good yield with I_2, which is much less expensive than ICl and PhSeCl, is quite limited [5b]. The use of molecular iodine in organic synthesis is very attractive and important because it is a low-toxicity inorganic reagent and not a

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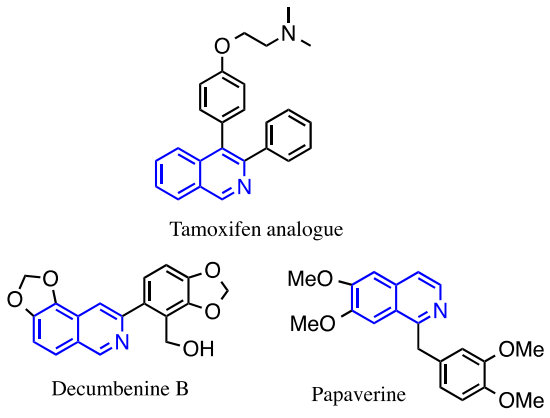
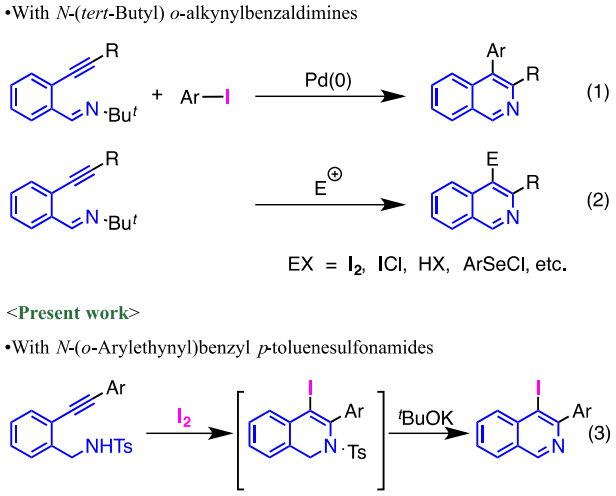


Fig. 1. Isoquinoline derivatives bearing biological activities.



Scheme 1. Preparation of Isoquinoline Cores.

transition metal. Recently, molecular iodine has been used for functional group transformation and iodocyclization [6].

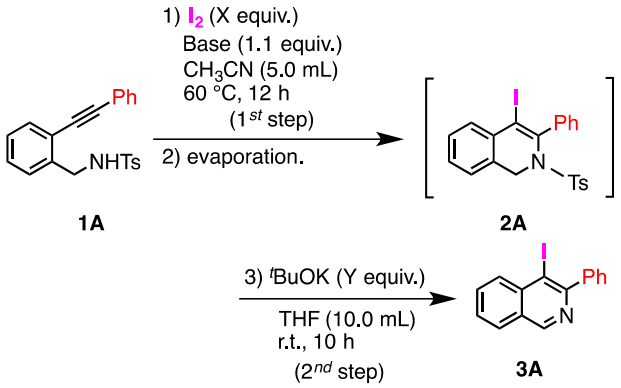
As part of our synthetic studies of nitrogen-containing heteroaromatics, such as quinolines, phenanthridines, and oxazoles, with molecular iodine and related iodine reagents [7], we would like to report herein a novel transformation of *N*-(*o*-arylethynyl)benzyl *p*-toluenesulfonamides into 3-aryl-4-iodoisoquinolines through the iodocyclization and the subsequent elimination of the tosyl group, as shown in eq. 3 (Scheme 1).

2. Results and discussion

First, iodocyclization of *N*-(*o*-phenylethynyl)benzyl *p*-toluenesulfonamide **1A** (0.5 mmol) with I_2 (1.0 equiv., 2.0 equiv., and 3.0 equiv.) in the presence of $NaHCO_3$ (1.1 equiv.) in acetonitrile at 60 °C for 12 h was studied to give 4-iodo-3-phenyl-2-tosyl-1,2-dihydroisoquinoline **2A** in 31%, 49%, and 66% yield, respectively (entries 1–3). When the iodocyclization was carried out in the absence of $NaHCO_3$ under the same conditions as those of entry 3, the yield of 1,2-dihydroisoquinoline **2A** was slightly decreased to 63% (entry 4). Thus, the use of 3.0 equiv. of I_2 with $NaHCO_3$ (1.1 equiv.) was the best to form 1,2-dihydroisoquinoline **2A** in good yield (entry 3). Further treatment of 1,2-dihydroisoquinoline **2A** with ^{t}BuOK (8.0 equiv.) in THF at room temperature for 10 h gave 4-iodo-3-phenylisoquinoline **3A** quantitatively.

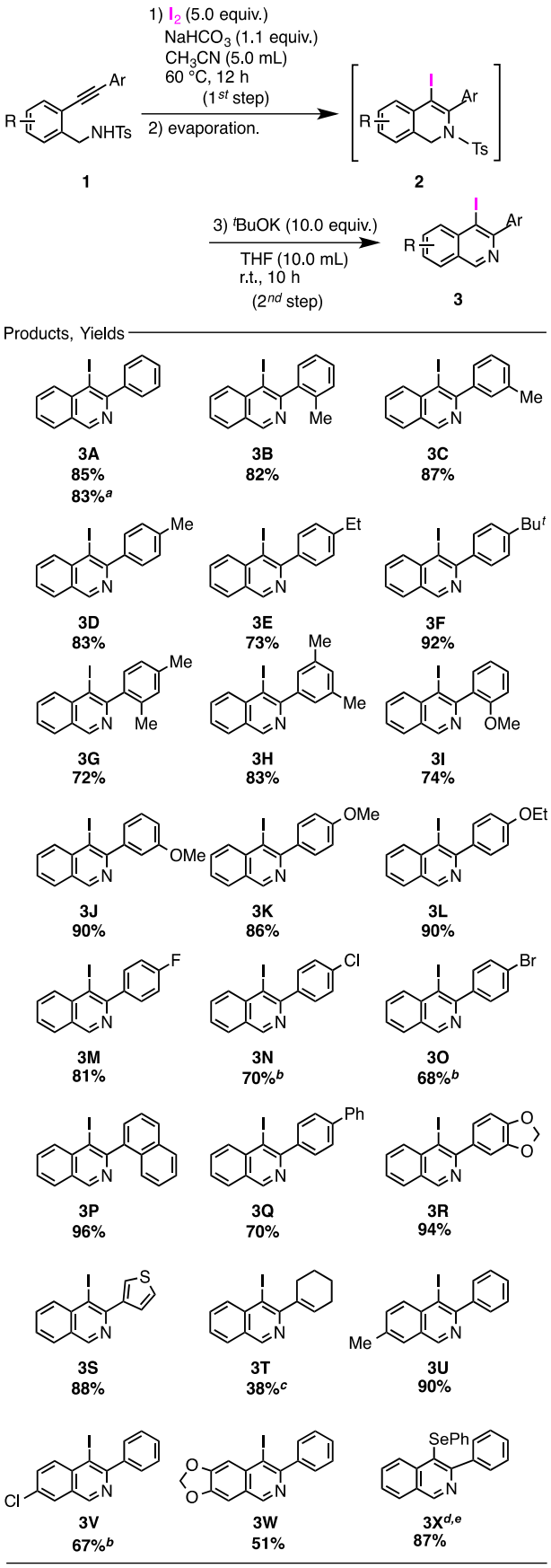
Then, sulfonamide **1A** (0.5 mmol) was treated with I_2 (3.0 equiv.) and $NaHCO_3$ (1.1 equiv.) in acetonitrile at 60 °C for 12 h (1st step). Removal of the solvent followed by reaction with ^{t}BuOK (8.0 equiv.) in THF at room temperature for 10 h (2nd step) gave 4-iodo-3-phenylisoquinoline **3A** in 65% yield in one pot, as shown in Table 1 (entry 5). However, when K_2CO_3, Na_2CO_3, Cs_2CO_3, K_3PO_4, and CH_3CO_2K were used as the base instead of $NaHCO_3$ in the 1st reaction step under the same procedure and conditions, isoquinoline **3A** was not obtained at all for the first four bases, and it was obtained in only 13% yield when CH_3CO_2K was used as the base (entries 6–10). In those reactions, sulfonamide **1A** were recovered mainly in the range of 50%–56% yields. Moreover, when the amount of $NaHCO_3$ was increased to 2.0 equiv. in the 1st reaction step under the same procedure and conditions, the yield of isoquinoline **3A** was decreased to 39% (entry 11). Increasing the

Table 1
Optimization for one-pot preparation of 4-iodo-3-phenylisoquinoline **3A**.



entry	X (equiv.)	base	Y (equiv.)	Yield (%)
1[a]	1.0	$NaHCO_3$	–	(31)[b]
2[a]	2.0	$NaHCO_3$	–	(49)[b]
3[a]	3.0	$NaHCO_3$	–	(66)[b]
4[a]	3.0	–	–	(63)[b]
5	3.0	$NaHCO_3$	8.0	65
6	3.0	K_2CO_3	8.0	0
7	3.0	Na_2CO_3	8.0	0
8	3.0	Cs_2CO_3	8.0	0
9	3.0	K_3PO_4	8.0	0
10	3.0	CH_3CO_2K	8.0	13
11[c]	3.0	$NaHCO_3$	8.0	39
12[d]	3.0	$NaHCO_3$	8.0	61
13	5.0	$NaHCO_3$	8.0	41 (42)[b]
14	**5.0**	**$NaHCO_3$**	**10.0**	**85**
15[e]	5.0	$NaHCO_3$	10.0	19 (4)[b]
16[f]	5.0	$NaHCO_3$	10.0	80
17	5.0	$NaHCO_3$	15.0	48
18[g]	5.0	$NaHCO_3$	10.0	78
19[h]	5.0	$NaHCO_3$	10.0	47
20[i]	5.0	$NaHCO_3$	10.0	0
21[a,j]	1.0	$NaHCO_3$	–	(46)[b]
22[a,k]	1.0	$NaHCO_3$	–	(40)[b]

[a] Only 1st reaction step was carried out.
[b] Yield of 4-iodo-3-phenyl-2-tosyl-1,2-dihydroisoquinoline (**2A**).
[c] In 1st reaction step, $NaHCO_3$ (2.0 equiv.) was added.
[d] Reaction was carried out at 80 °C in 1st reaction step.
[e] THF (5.0 mL) in 1st reaction step and CH_3CN (10.0 mL) in 2nd step reaction were used.
[f] 1st reaction step was carried out for 6 h.
[g] Instead of *N*-Ts group in **1A**, *N*–$SO_2C_6H_4Cl$-*p* group was used.
[h] Instead of *N*-Ts group in **1A**, *N*–$SO_2C_2H_5$ group was used.
[i] Instead of I_2, NIS (5.0 equiv.) was used.
[j] NBS (1.0 equiv.) was added in 1st reaction step.
[k] NCS (1.0 equiv.) was added in 1st reaction step.

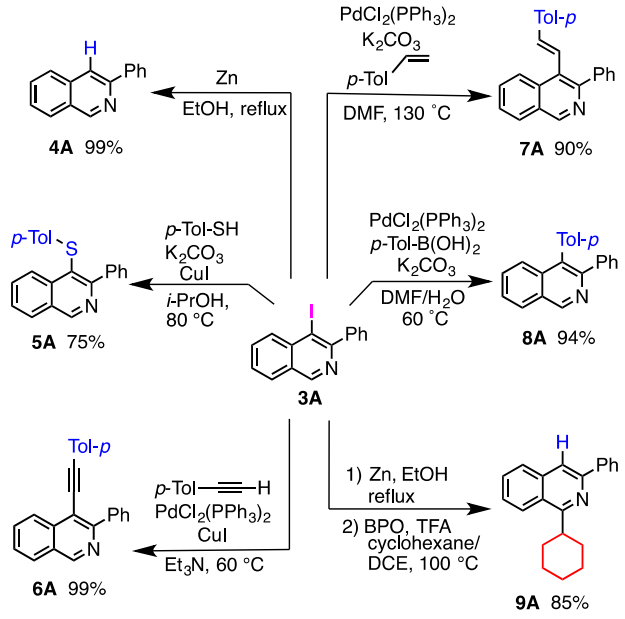


reaction temperature to 80 °C in the 1st reaction step under the same procedure and conditions gave isoquinoline **3A** in 61% yield (entry 12). On the other hand, treatment of sulfonamide **1A** with I_2 (5.0 equiv.) and $NaHCO_3$ (1.1 equiv.) at 60 °C for 12 h, followed by the removal of the solvent and the reaction with ^{t}BuOK (8.0 equiv. and 10.0 equiv.) at room temperature for 10 h gave isoquinoline **3A** in 41% yield together with **2A** (42% yield, entry 13) and **3A** in 85% yield (entry 14), respectively. When the present one-pot reaction was carried out in THF (5.0 mL) in the 1st reaction step and in acetonitrile (10.0 mL) in the 2nd reaction step (inversed solvent system) under same procedure and conditions, the yield of isoquinoline **3A** was quite decreased to 19% together with **2A** in 4% (entry 15). When the reaction time was shortened to 6 h in the 1st reaction step, the yield of isoquinoline **3A** was slightly decreased to 80% (entry 16). Increasing the amount of ^{t}BuOK (15.0 equiv.) reduced the yield of isoquinoline **3A** (entry 17). When sulfonamides **1** bearing *N*−$SO_2C_6H_4$Cl-*p* and *N*−$SO_2C_2H_5$ groups instead of the *N*-Ts group were used under the same procedure and conditions, isoquinoline **3A** was obtained in 78% and 47% yields, respectively (entries 18, 19). On the other hand, when *N*-iodosuccinimide (NIS) was used instead of I_2, isoquinoline **3A** was not formed at all (entry 20). Finally, the addition of *N*-bromosuccinimide (NBS) and *N*-chlorosuccinimide (NCS) to promote the iodocyclization through the interaction of I_2 and NBS or NCS in 1st reaction step was not so effective (entries 21, 22) [8]. Thus, treatment of sulfonamide **1A** (0.5 mmol) with I_2 (5.0 equiv.) and $NaHCO_3$ (1.1 equiv.) in acetonitrile (5.0 mL) at 60 °C for 12 h (1st step), followed by the removal of the solvent and the reaction with ^{t}BuOK (10.0 equiv.) in THF (10.0 mL) at room temperature for 10 h (2nd step) gave isoquinoline **3A** in the best yield (entry 14). As a gram-scale experiment, treatment of *N*-(*o*-phenylethynyl)benzyl *p*-toluenesulfonamide **1A** (3.0 mmol) under the best reaction conditions gave 4-iodo-3-phenylisoquinoline **3A** in 83% yield, as shown in Scheme 2.

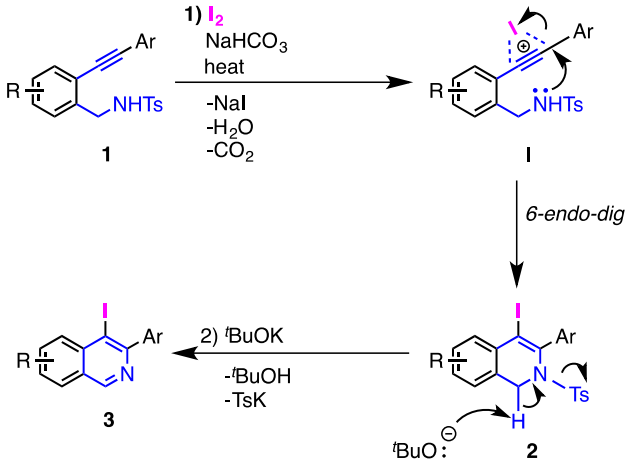
Then, to evaluate the generality of the present reaction, other *N*-(*o*-arylethynyl)benzyl *p*-toluenesulfonamides **1** were studied, as shown in Scheme 2. Treatment of *N*-(*o*-arylethynyl)benzyl *p*-toluenesulfonamides **1** bearing.

O-methylphenyl (**B**), *m*-methylphenyl (**C**), *p*-methylphenyl (**D**), *p*-ethylphenyl (**E**), *p*-*tert*-butylphenyl (**F**), 2,4-dimethylphenyl (**G**), 3,5-dimethylphenyl (**H**), *o*-methoxyphenyl (**I**), *m*-methoxyphenyl (**J**), *p*-methoxyphenyl (**K**), *p*-ethoxyphenyl (**L**), *p*-fluorophenyl (**M**), *p*-chlorophenyl (**N**), *p*-bromophenyl (**O**), naphthalen-1-yl (**P**), *p*-biphenyl (**Q**), and 1,3-benzodioxol-5-yl (**R**) groups with I_2 (5.0 equiv.) and $NaHCO_3$ (1.1 equiv.) in acetonitrile (5.0 mL) at 60 °C for 12 h (1st step), followed by the removal of the solvent and reaction with ^{t}BuOK (10.0 equiv.) in THF (10.0 mL) for 10 h at room temperature (2nd step) generated 3-aryl-4-iodoisoquinolines **3B**~**3R** in good yields, respectively. *N*-[*o*-(Thiophen-3-yl)ethynyl]benzyl *p*-toluenesulfonamide **1S** and *N*-[*o*-(cyclohexen-1-yl)ethynyl]benzyl *p*-toluenesulfonamide **1T** also underwent the reaction under the same procedure and conditions to give isoquinoline **3S** in good yield and isoquinoline **3T** in moderate yield, respectively. Treatment of *N*-(phenylethynyl)benzyl *p*-toluenesulfonamides **1U**, **1V**, and **1W** bearing substituents on the benzylic aromatic ring, such as methyl, chloro, and 1,2-methylenedioxy groups, under the same procedure and conditions generated 4-iodo-7-methyl-3-phenylisoquinoline **3U**, 7-chloro-4-iodo-3-phenylisoquinoline **3V**, and 4-iodo-6,7-methylenedioxy-3-phenylisoquinoline **3W** in good to moderate yields, respectively. As a related reagent to I_2 that has an electrophilic character, treatment of *N*-(*o*-phenylethynyl)benzyl

Scheme 2. One-pot Transformation of *N*-(*o*-Arylethynyl)benzyl *p*-Toluenesulfonamides **1** to 3-Aryl-4-iodoisoquinolines **3**. [a] Compound **1A** (3.0 mmol) was used. [b] In 1st reaction, I_2 (6.0 equiv.) was used. [c] 1st reaction step was carried out at r. t. [d] Only 1st reaction step was carried out. [e] Instead of I_2, PhSeCl (5.0 equiv.) was used.



Scheme 3. Derivatization of 4-Iodo-3-phenylisoquinoline **3A**.



Scheme 4. Possible Reaction Pathway.

p-toluenesulfonamide **1A** with PhSeCl (5.0 equiv.) and $NaHCO_3$ (1.1 equiv.) in acetonitrile (5.0 mL) at 60 °C for 12 h (1st step) gave 3-phenyl-4-phenylselenylisoquinoline **3X** in good yield, without treatment with ^{t}BuOK.

Overall, the formation of 3-aryl-4-iodo-2-tosyl-1,2-dihydroisoquinolines **2** from *N*-(*o*-arylethynyl)benzyl *p*-toluenesulfonamides **1** with I_2 in the presence of $NaHCO_3$ proceeded smoothly. However, *N*-(*o*-alkylethynyl)benzyl *p*-toluenesulfonamides **1** bearing propyl, cyclohexyl, and cyclopropyl groups were inert under the present reaction conditions (1st step). Therefore, 3-alkyl-4-iodo-2-tosyl-1,2-dihydroisoquinolines were not formed from *N*-(*o*-alkylethynyl)benzyl *p*-toluenesulfonamides.

Once 3-aryl-4-iodoisoquinolines **3** were formed, they could be smoothly transformed into various 3-arylisoquinoline derivatives because of their C—I bond. Specifically, 3-phenylisoquinoline **4A** was obtained in 99% yield by the treatment of 4-iodo-3-phenylisoquinoline **3A** with Zn in ethanol under refluxing conditions, as shown in Scheme 3. Treatment of 4-iodo-3-phenylisoquinoline **3A** with *p*-toluenethiol and K_2CO_3 in the presence of CuI in isopropanol at 80 °C gave 4-(*p*-methylbenzenesulfenyl)-3-phenylisoquinoline **5A** in 75% yield. The Pd-catalyzed C—C bond formation of 4-iodo-3-phenylisoquinoline **3A** with 4-ethynyltoluene and CuI in Et_3N at 60 °C, with 4-vinyltoluene and K_2CO_3 in DMF at 130 °C, and with 4-methylphenylboronic acid and K_2CO_3 in a mixture of DMF and water at 60 °C provided 4-(4′-methylphenyl)ethynyl-3-phenylisoquinoline **6A** in 99% yield, 4-(4′-methylphenyl)ethenyl-3-phenylisoquinoline **7A** in 90% yield, and 4-(4′-methylphenyl)-3-phenylisoquinoline **8A** in 94% yield, respectively. Treatment of 4-iodo-3-phenylisoquinoline **3A** with Zn in ethanol under refluxing conditions, followed by the reaction with benzoyl peroxide (BPO) and trifluoroacetic acid in a mixture of cyclohexane and 1,2-dichloroethane at 100 °C generated 1-cyclohexyl-3-phenylisoquinoline **9A** in 85% yield.

A possible reaction pathway for the present one-pot preparation of 3-aryl-4-iodoisoquinolines **3** from *N*-(*o*-arylethynyl)benzyl *p*-toluenesulfonamides **1** is shown in Scheme 4. I_2 activates the ethynyl group of *N*-(*o*-arylethynyl)benzyl *p*-toluenesulfonamides **1** to generate iodonium species **I**, and then the nitrogen atom of the sulfonamide group attacks the activated carbon atom via *6-endo-dig* mode to generate 3-aryl-4-iodo-2-tosyl-1,2-dihydroisoquinoline **2** (1st step). ^{t}BuOK abstracts a proton of 1-position of 3-aryl-4-iodo-2-tosyl-1,2-dihydroisoquinoline **2** via E2 reaction to generate 3-aryl-4-iodoisoquinoline **3** together with potassium *p*-toluenesulfinate, the latter of which was identified by the reaction with iodomethane as methyl *p*-methylphenyl sulfone.

3. Conclusion

3-Aryl-4-iodoisoquinolines could be efficiently obtained in good yields by the reaction of *N*-(*o*-arylethynyl)benzyl *p*-toluenesulfonamides with I_2 in the presence of $NaHCO_3$, followed by the reaction with ^{t}BuOK in one pot. The present method is a novel approach for the preparation of 3-aryl-4-iodoisoquinolines from *N*-(*o*-arylethynyl)benzyl *p*-toluenesulfonamides. We believe the present method would be useful because of its easy operation and the use of low-toxicity reagents under transition-metal-free conditions.

4. Experimental section

4.1. General

^{1}H NMR and ^{13}C NMR spectra were obtained with JEOL-JNM-ECX400 and JEOL-JNM-ECS400 spectrometers. Chemical shifts were recorded as follows: chemical shift in ppm from internal tetramethylsilane (TMS) on the δ scale, multiplicity (s = singlet; d = doublet; t = triplet; q = quartet; m = multiplet; b = broad), coupling constant (Hz) and integration. High-resolution mass spectra (HRMS) were recorded by a Thermo Fisher Scientific Exactive Orbitrap mass spectrometer. IR spectra were measured with a JASCO FT/IR-4100 spectrometer. Melting points were determined with a Yamato Melting Point Apparatus Model MP-21. Silica gel $60F_{254}$ (Merck) was used for TLC and Silica gel 60 N (63—210 mesh, Kanto Kagaku Co.) was used for short column chromatography.

4.2. Typical procedure for preparation of N-(o-arylethynyl)benzyl p-toluenesuldonamide 1

To a solution of *o*-bromobenzaldehyde (10.0 mmol, 1.85 g), $PdCl_2(PPh_3)_2$ (0.2 mmol, 140.4 mg) and CuI (0.1 mmol, 19.0 mg) in Et_3N (0.3 M) was added ethynylbenzene (12.0 mmol, 1.32 mL). The obtained mixture was stirred for 12 h at 50 °C under argon atmosphere. Sat. aq. NH_4Cl solution (15.0 mL) was added to the mixture,

and the product was extracted with $CHCl_3$ (15.0 mL × 3). The organic layer was dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography (eluent: *n*-hexane:EtOAc = 19:1) to give *o*-(phenylethynyl)benzaldehyde (1.96 g, 95%). To a solution of *o*-(phenylethynyl)benzaldehyde in EtOH (1.0 M) was added hydroxylamine hydrochloride (1.2 equiv.). The mixture was stirred for 1 h at room temperature. To the obtained mixture were slowly added Zn powder (2.5 equiv.) and hydrochloric acid (12.0 M, 4.0 equiv.) at 0 °C. The obtained mixture was stirred for 0.5 h at room temperature under argon atmosphere. A solution of ammonia (28–30%) was slowly added until pH ≧ 7, and the product was extracted with $CHCl_3$ (15.0 mL × 3). The organic layer was dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, *p*-toluenesulfonyl chloride (1.1 equiv.) and pyridine (0.5 M) were added to the residue in dichloromethane (1.0 M) at 0 °C. The obtained mixture was stirred for 12 h at room temperature under argon atmosphere. Aq. NH_4Cl solution (15.0 mL) was added to the mixture, and the product was extracted with $CHCl_3$ (15.0 mL × 3). Then, the organic layer was dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography (eluent: *n*-hexane:EtOAc = 3:1) to give *N*-(*o*-phenylethynyl)benzyl *p*-toluenesulfonamide **1A** (2.76 g, 76%). Other *N*-(*o*-arylethynyl) benzyl *p*-toluenesulfonamides **1B**–**1W** were obtained in 55%–78% yields by the same procedure.

4.2.1. *N-(o-phenylethynyl)benzyl p-toluenesulfonamide (**1A**)*

White solid; mp: 165 °C; IR (neat): 2337, 2212, 1322, 1152 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 4.37 (d, 2H, J = 6.5 Hz), 4.94 (t, 1H, J = 6.5 Hz), 7.18 (d, 2H, J = 8.1 Hz), 7.23–7.29 (m, 3H), 7.34–7.42 (m, 5H), 7.45–7.89 (m, 1H), 7.71 (d, 2H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 46.2, 86.4, 94.4, 122.2, 122.5, 127.1, 127.8, 128.4, 128.7 (2C), 128.8, 129.5, 131.5, 132.2, 136.8, 137.7, 143.2; HRMS (ESI): Calcd for $C_{22}H_{20}O_2NS$ $[M+H]^+$ = 362.1209, Found = 362.1207.

4.2.2. *N-[o-(o-methylphenyl)ethynyl]benzyl p-toluenesulfonamide (**1B**)*

White solid; mp: 108 °C; IR (neat): 2334, 2209, 1323, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 2.39 (s, 3H), 4.38 (d, 2H, J = 6.5 Hz), 4.93 (t, 1H, J = 6.4 Hz), 7.16–7.20 (m, 3H), 7.22–7.30 (m, 5H), 7.37 (d, 1H, J = 7.4 Hz), 7.45–7.49 (m, 1H), 7.69 (d, 2H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.8, 21.5, 46.2, 90.3, 93.4, 122.3, 122.4 (2C), 125.7, 127.1, 127.8, 128.6 (2C), 128.7, 129.6, 131.9, 132.3, 136.8, 137.5, 139.9, 143.3; HRMS (ESI): Calcd for $C_{23}H_{22}O_2NS$ $[M+H]^+$ = 376.1366, Found = 376.1365.

4.2.3. *N-[o-(m-methylphenyl)ethynyl]benzyl p-toluenesulfonamide (**1C**)*

White solid; mp: 122 °C; IR (neat): 2337, 2209, 1322, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 2.38 (s, 3H), 4.37 (d, 2H, J = 6.5 Hz), 4.98 (t, 1H, J = 6.5 Hz), 7.16–7.20 (m, 3H), 7.22–7.27 (m, 6H), 7.43–7.46 (m, 1H), 7.70 (d, 2H, J = 8.5 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.2, 21.4, 46.2, 86.1, 94.6, 122.2, 122.3, 127.1, 127.7, 128.3, 128.6 (2C), 128.7, 129.5, 129.6, 132.0, 132.2, 136.8, 137.7, 138.1, 143.2; HRMS (ESI): Calcd for $C_{23}H_{22}O_2NS$ $[M+H]^+$ = 376.1366, Found = 376.1361.

4.2.4. *N-[o-(p-methylphenyl)ethynyl]benzyl p-toluenesulfonamide (**1D**)*

White solid; mp: 155 °C; IR (neat): 2334, 2220, 1320, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 2.40 (s, 3H), 4.36 (d, 2H, J = 6.5 Hz), 4.96 (t, 1H, J = 6.4 Hz), 7.15–7.19 (m, 4H), 7.22–7.25 (m, 3H), 7.30 (d, 2H, J = 8.1 Hz), 7.42–7.45 (m, 1H), 7.70 (d, 2H, J = 7.4 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5 (2C), 46.3, 85.9, 94.6, 119.4, 122.4, 127.1, 127.8, 128.5, 128.8, 129.2, 129.5, 131.4, 132.2, 136.8, 137.6, 138.9, 143.2; HRMS (ESI): Calcd for $C_{23}H_{22}O_2NS$ $[M+H]^+$ = 376.1366, Found = 376.1362.

4.2.5. *N-[o-(p-ethylphenyl)ethynyl]benzyl p-toluenesulfonamide (**1E**)*

White solid; mp: 152–153 °C; IR (neat): 2331, 2212, 1321, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.27 (t, 3H, J = 7.6 Hz) 2.38 (s, 3H), 2.69 (q, 2H, J = 7.6 Hz), 4.36 (d, 2H, J = 6.5 Hz), 4.96 (t, 1H, J = 6.3 Hz), 7.17–7.20 (m, 4H), 7.22–7.25 (m, 3H), 7.33 (d, 2H, J = 8.1 Hz), 7.43–7.45 (m, 1H), 7.70 (d, 2H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.3, 21.4, 28.8, 46.2, 85.8, 94.6, 119.6, 122.4, 127.1, 127.7, 127.9, 128.5, 128.7, 129.5, 131.5, 132.1, 136.8, 137.6, 143.2, 145.2; HRMS (ESI): Calcd for $C_{24}H_{24}O_2NS$ $[M+H]^+$ = 390.1522, Found = 390.1519.

4.2.6. *N-[o-(p-tert-butylphenyl)ethynyl]benzyl) p-toluenesulfonamide (**1F**)*

White solid; mp: 111–112 °C; IR (neat): 2334, 2220, 1324, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.35 (s, 9H), 2.73 (s, 3H), 4.36 (d, 2H, J = 6.3 Hz), 4.96 (t, 1H, J = 5.8 Hz), 7.17 (d, 2H, J = 8.1 Hz), 7.21–7.26 (m, 3H), 7.33–7.39 (m, 4H), 7.43–7.45 (m, 1H), 7.70 (d, 2H, J = 8.1 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 31.1, 34.8, 46.3, 85.9, 94.6, 119.4, 122.4, 125.4, 127.1, 127.8, 128.5, 128.8, 129.5, 131.3, 132.2, 136.8, 137.6, 143.2, 152.1; HRMS (ESI): Calcd for $C_{26}H_{28}O_2NS$ $[M+H]^+$ = 418.1835, Found = 418.1832.

4.2.7. *N-[o-(2′,4′-dimethylphenyl)ethynyl]benzyl p-toluenesulfonamide (**1G**)*

White solid; mp: 123–124 °C; IR (neat): 2359, 2202, 1325, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.35 (s, 3H), 2.36 (s, 3H), 2.73 (s, 3H), 4.37 (d, 2H, J = 6.5 Hz), 4.96 (t, 1H, J = 6.3 Hz), 6.99 (d, 1H, J = 7.9 Hz), 7.05 (s, 1H), 7.16 (d, 2H, J = 7.9 Hz), 7.22–7.31 (m, 4H), 7.44–7.47 (m, 1H), 7.68 (d, 2H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.6, 21.4 (2C), 46.1, 89.6, 93.6, 119.3, 122.5, 126.4, 127.0, 127.7, 128.4 (2C), 129.5, 130.3, 131.8, 132.1, 136.8, 137.5, 138.9, 139.7, 143.2; HRMS (ESI): Calcd for $C_{24}H_{24}O_2NS$ $[M+H]^+$ = 390.1522, Found = 390.1519.

4.2.8. *N-[o-(3′,5′-dimethylphenyl)ethynyl]benzyl p-toluenesulfonamide (**1H**)*

White solid; mp: 142–143 °C; IR (neat): 2359, 2212, 1325, 1157 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.34 (s, 6H), 2.36 (s, 3H), 4.37 (d, 2H, J = 6.5 Hz), 5.01 (t, 1H, J = 6.3 Hz), 7.02 (s, 1H), 7.08 (s, 2H), 7.17 (d, 2H, J = 8.1 Hz), 7.22–7.24 (m, 3H), 7.42–7.44 (m, 1H), 7.69 (d, 2H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.1, 21.5, 46.3, 85.8, 94.9, 122.1, 122.3, 127.1, 127.8, 128.5, 128.7, 129.2, 129.5, 130.7, 132.3, 137.0, 137.7, 138.0, 143.2; HRMS (ESI): Calcd for $C_{24}H_{24}O_2NS$ $[M+H]^+$ = 390.1522, Found = 390.1521.

4.2.9. *N-[o-(o-methoxyphenyl)ethynyl]benzyl p-toluenesulfonamide (**1I**)*

White solid; mp: 115–116 °C; IR (neat): 2362, 2093, 1323, 1154, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.37 (s, 3H), 3.84 (s, 3H), 4.36 (d, 2H, J = 6.5 Hz), 4.94 (t, 1H, J = 6.5 Hz), 6.93 (d, 1H, J = 8.3 Hz), 6.98–7.01 (m, 2H), 7.19 (d, 2H, J = 8.1 Hz), 7.23–7.29 (m, 4H), 7.45–7.47 (m, 1H), 7.71 (d, 2H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 46.1, 55.3, 86.2, 94.3, 115.1, 116.4, 122.1, 123.5, 124.0, 127.0, 127.7 (2C), 128.7, 129.4, 129.5, 132.2, 136.7, 137.7, 143.3, 159.3; HRMS (ESI): Calcd for $C_{23}H_{22}O_3NS$ $[M+H]^+$ = 392.1315, Found = 392.1313.

*4.2.10. N-[o-(m-methoxyphenyl)ethynyl]benzyl p-toluenesulfonamide (**1J**)*

White solid; mp: 110 °C; IR (neat): 2331, 2210, 1322, 1153, 1047 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.26$ (s, 3H), 4.08 (s, 3H), 4.40 (d, 2H, $J = 7.2$ Hz), 6.71 (t, 1H, $J = 6.7$ Hz), 6.93–7.00 (m, 4H), 7.08–7.11 (m, 3H), 7.21–7.24 (m, 1H), 7.36–7.40 (m, 1H), 7.43–7.46 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.3$, 47.1, 55.9, 91.1, 91.5, 110.6, 111.6, 120.7, 122.4, 126.6, 127.4, 128.0, 128.8, 129.5, 130.3, 131.6, 132.6, 138.0, 138.1, 142.2, 160.2; HRMS (ESI): Calcd for $C_{23}H_{22}O_3NS$ $[M+H]^+ = 392.1315$, Found = 392.1312.

*4.2.11. N-[o-(p-methoxyphenyl)ethynyl]benzyl p-toluenesulfonamide (**1K**)*

White solid; mp: 159–161 °C; IR (neat): 2359, 2212, 1318, 1154, 1048 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.38$ (s, 3H), 3.86 (s, 3H), 4.35 (d, 2H, $J = 6.5$ Hz), 4.97 (t, 1H, $J = 6.3$ Hz), 6.88 (d, 2H, $J = 8.8$ Hz), 7.18–7.24 (m, 5H), 7.35 (d, 2H, $J = 8.5$ Hz), 7.42–7.44 (m, 1H), 7.70 (d, 2H, $J = 8.1$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 46.3, 55.3, 85.3, 94.5, 114.0, 114.5, 122.6, 127.1, 127.8, 128.3, 128.8, 129.6, 132.1, 133.0, 136.9, 137.5, 143.2, 159.9; HRMS (ESI): Calcd for $C_{23}H_{22}O_3NS$ $[M+H]^+ = 392.1315$, Found = 392.1314.

*4.2.12. N-[o-(p-ethoxyphenyl)ethynyl]benzyl p-toluenesulfonamide (**1L**)*

White solid; mp: 172 °C; IR (neat): 2209, 1319, 1175, 1052 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.45$ (t, 3H, $J = 7.0$ Hz), 2.38 (s, 3H), 4.08 (q, 2H, $J = 7.0$ Hz), 4.35 (d, 2H, $J = 6.5$ Hz), 4.96 (t, 1H, $J = 6.5$ Hz), 6.87 (d, 2H, $J = 9.0$ Hz), 7.18–7.25 (m, 5H), 7.33 (d, 2H, $J = 8.8$ Hz), 7.41–7.44 (m, 1H), 7.70 (d, 2H, $J = 8.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 14.7$, 21.5, 46.3, 63.6, 85.2, 94.6, 114.3, 114.5, 122.6, 127.1, 127.8, 128.3, 128.8, 129.5, 132.1, 133.0, 136.9, 137.4, 143.2, 159.3; HRMS (ESI): Calcd for $C_{24}H_{24}O_3NS$ $[M+H]^+ = 406.1471$, Found = 406.1470.

*4.2.13. N-[o-(p-fluorophenyl)ethynyl]benzyl p-toluenesulfonamide (**1M**)*

Gray solid; mp: 164–166 °C; IR (neat): 2362, 2216, 1318, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.39$ (s, 3H), 4.36 (d, 2H, $J = 6.3$ Hz), 4.88 (t, 1H, $J = 6.7$ Hz), 7.06 (t, 2H, $J = 8.8$ Hz), 7.21 (d, 2H, $J = 8.1$ Hz), 7.24–7.25 (m, 3H), 7.39–7.46 (m, 3H), 7.71 (d, 2H, $J = 8.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 46.2, 86.2, 93.3, 115.7 (d, $J_{C\text{-}F} = 22.6$ Hz), 118.6, 122.1, 127.1, 127.9, 128.7, 128.8, 129.6, 132.2, 133.5 (d, $J_{C\text{-}F} = 8.5$ Hz), 136.8, 137.7, 143.3, 162.7 (d, $J_{C\text{-}F} = 250.9$ Hz); HRMS (ESI): Calcd for $C_{22}H_{19}O_2NFS$ $[M+H]^+ = 380.1115$, Found = 380.1114.

*4.2.14. N-[o-(p-chlorophenyl)ethynyl]benzyl p-toluenesulfonamide (**1N**)*

Gray solid; mp: 109–110 °C; IR (neat): 2337, 2045, 1318, 1153 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.39$ (s, 3H), 4.36 (d, 2H, $J = 6.3$ Hz), 4.86 (t, 1H, $J = 6.3$ Hz), 7.21 (d, 2H, $J = 8.1$ Hz), 7.23–7.27 (m, 3H), 7.34–7.34 (m, 4H), 7.44–7.47 (m, 1H), 7.71 (d, 2H, $J = 8.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 46.1, 87.4, 93.2, 121.0, 122.2, 127.1, 127.9, 128.7, 128.8, 128.9, 129.6, 132.3, 132.7, 134.7, 136.8, 137.7, 143.4; HRMS (ESI): Calcd for $C_{22}H_{19}O_2N^{35}ClS$ $[M+H]^+ = 396.0820$, Found = 396.0818.

*4.2.15. N-[o-(p-bromophenyl)ethynyl]benzyl p-toluenesulfonamide (**1O**)*

Yellow solid; mp: 142–143 °C; IR (neat): 2359, 2170, 1382, 1226 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.39$ (s, 3H), 4.35 (d, 2H, $J = 6.5$ Hz), 4.84 (t, 1H, $J = 6.5$ Hz), 7.21 (d, 2H, $J = 8.1$ Hz), 7.24–7.28 (m, 5H), 7.44–7.53 (m, 3H), 7.71 (d, 2H, $J = 8.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 46.1, 87.6, 93.3, 121.5, 122.0, 123.0, 127.1, 128.0, 128.8, 129.0, 129.6, 131.7, 132.3, 132.9, 136.8, 137.7, 143.4; HRMS (ESI): Calcd for $C_{22}H_{19}O_2N^{79}BrS$ $[M+H]^+ = 440.0314$, Found = 440.0315, $C_{22}H_{19}O_2N^{81}BrS$ $[M+H]^+ = 442.0294$, Found = 442.0295.

*4.2.16. N-[o-(Naphthalen-1-yl)ethynyl]benzyl p-toluenesulfonamide (**1P**)*

White solid; mp: 158–159 °C; IR (neat): 2331, 2192, 1321, 1156 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.27$ (s, 3H), 4.46 (d, 2H, $J = 6.5$ Hz), 4.93 (t, 1H, $J = 6.9$ Hz), 7.05 (d, 2H, $J = 8.1$ Hz), 7.29–7.37 (m, 3H), 7.47 (t, 1H, $J = 8.3$ Hz), 7.54–7.60 (m, 3H), 7.63–7.68 (m, 3H), 7.88–7.91 (m, 2H), 8.35–8.28 (m, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.4$, 46.3, 91.2, 92.5, 120.2, 122.4, 125.2, 125.9, 126.6, 127.0 (2C), 127.9, 128.4, 128.8, 128.9, 129.2, 129.5, 130.6, 132.5, 133.0, 133.2, 136.7, 137.7, 143.2; HRMS (ESI): Calcd for $C_{26}H_{22}O_2NS$ $[M+H]^+ = 412.1366$, Found = 412.1363.

*4.2.17. N-[o-(p-biphenyl)ethynyl]benzyl p-toluenesulfonamide (**1Q**)*

Yellow solid; mp: 176–177 °C; IR (neat): 2212, 1596, 1520 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.38$ (s, 3H), 4.39 (d, 2H, $J = 6.5$ Hz), 4.96 (t, 1H, $J = 6.3$ Hz), 7.20 (d, 2H, $J = 8.1$ Hz), 7.24–7.29 (m, 3H), 7.37–7.42 (m, 1H), 7.46–7.50 (m, 5H), 7.59–7.64 (m, 4H), 7.72 (d, 2H, $J = 8.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 46.3, 87.1, 94.3, 121.3, 122.3, 127.0, 127.1 (2C), 127.8, 127.9, 128.8 (2C), 128.9, 129.6, 132.0, 132.3, 136.8, 137.7, 140.1, 141.4, 143.3; HRMS (ESI): Calcd for $C_{28}H_{24}O_2NS$ $[M+H]^+ = 438.1522$, Found = 438.1517.

*4.2.18. N-[o-(1,3-benzodioxol-5-yl)ethynyl]benzyl p-toluenesulfonamide (**1R**)*

Yellow solid; mp: 150–151 °C; IR (neat): 2362, 2205, 1323, 1154, 1033 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.40$ (s, 3H), 4.34 (d, 2H, $J = 6.5$ Hz), 4.90 (t, 1H, $J = 6.3$ Hz), 6.02 (s, 2H), 6.79 (d, 1H, $J = 8.1$ Hz), 6.81 (s, 1H), 6.94 (dd, 1H, $J = 8.1$, 1.6 Hz), 7.21–7.25 (m, 5H), 7.41–7.44 (m, 1H), 7.72 (d, 2H, $J = 8.2$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 46.3, 84.9, 94.4, 101.4, 108.5, 111.4, 115.7, 122.4, 126.3, 127.1, 127.8, 128.5, 128.8, 129.6, 132.1, 136.8, 137.5, 143.4, 147.5, 148.2; HRMS (ESI): Calcd for $C_{23}H_{20}O_4NS$ $[M+H]^+ = 406.1108$, Found = 406.1107.

*4.2.19. N-[o-(Thiophen-3-yl)ethynyl]benzyl p-toluenesulfonamide (**1S**)*

Brown solid; mp: 163–164 °C; IR (neat): 2359, 2205, 1322, 1154 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.39$ (s, 3H), 4.34 (d, 2H, $J = 6.5$ Hz), 4.92 (t, 1H, $J = 6.7$ Hz), 7.11 (dd, 1H, $J = 4.9$, 1.1 Hz), 7.19–7.25 (m, 4H), 7.32–7.34 (m, 2H), 7.43–7.45 (m, 2H), 7.71 (d, 2H, $J = 8.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.5$, 46.2, 86.0, 89.6, 121.5, 122.3, 125.6, 127.1, 127.9, 128.6, 128.8, 129.1, 129.6, 129.7, 132.2, 136.8, 137.6, 143.3; HRMS (ESI): Calcd for $C_{20}H_{18}O_2NS_2$ $[M+H]^+ = 368.0773$, Found = 368.0771.

*4.2.20. N-[o-(Cyclohexen-1-yl)ethynyl]benzyl p-toluenesulfonamide (**1T**)*

White solid; mp: 119 °C; IR (neat): 2363, 2205, 1323, 1155 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 1.67–1.71$ (m, 4H), 2.10–2.17 (m, 4H), 2.40 (s, 3H), 4.28 (d, 2H, $J = 6.5$ Hz), 5.01 (t, 1H, $J = 6.7$ Hz), 6.11–6.13 (m, 1H), 7.14–7.19 (m, 3H), 7.22 (d, 2H, $J = 8.5$ Hz), 7.30–7.33 (m, 1H), 7.69 (d, 2H, $J = 8.3$ Hz); ^{13}C NMR (100 MHz, $CDCl_3$): $\delta = 21.4$, 21.5, 22.2, 25.7, 29.0, 46.3, 84.0, 96.5, 120.2, 122.6, 127.1, 127.6, 128.1, 128.6, 129.5, 132.0, 136.0, 137.0, 137.4, 1432.2; HRMS (ESI): Calcd for $C_{22}H_{24}O_2NS$ $[M+H]^+ = 366.1522$, Found = 366.1520.

*4.2.21. N-(2-Phenylethynyl,5-methylbenzyl p-toluenesulfonamide (**1U**)*

White solid; mp: 180 °C; IR (neat): 2358, 2212, 1323, 1156 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): $\delta = 2.28$ (s, 3H), 2.37 (s, 3H), 4.33 (d, 2H,

J = 6.3 Hz), 4.95 (t, 1H, J = 6.3 Hz), 7.01–7.04 (m, 2H), 7.18 (d, 2H, J = 8.2 Hz), 7.32–7.41 (m, 6H), 7.70 (d, 2H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 21.5, 46.2, 86.6, 93.7, 119.1, 122.7, 127.1, 128.4, 128.5, 128.6, 129.5, 129.6, 131.4, 132.1, 136.9, 137.5, 139.0, 143.2; HRMS (ESI): Calcd for $C_{23}H_{22}O_2NS$ $[M+H]^+$ = 376.1366, Found = 376.1364.

4.2.22. N-(2-Phenylethynyl,5-chloro)benzyl p-toluenesulfonamide (**1V**)

White solid; mp: 142 °C; IR (neat): 2362, 2216, 1323, 1154 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 4.34 (d, 2H, J = 6.5 Hz), 4.99 (t, 1H, J = 6.3 Hz), 7.13 (s, 1H), 7.17–7.21 (m, 3H), 7.34–7.40 (m, 4H), 7.42–7.44 (m, 2H), 7.68 (d, 2H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 45.8, 85.5, 95.5, 120.5, 122.2, 127.1, 128.0, 128.5, 128.8, 129.0, 129.6, 131.5, 133.3, 134.5, 136.8, 139.5, 143.6; HRMS (ESI): Calcd for $C_{22}H_{19}O_2N^{35}ClS$ $[M+H]^+$ = 396.0820, Found = 396.0815.

4.2.23. N-(2-Phenylethynyl,4,5-methylenedioxy)benzyl p-toluenesulfonamide (**1W**)

White solid; mp: 188–189 °C; IR (neat): 2205, 1320, 1155, 1038 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 4.27 (d, 2H, J = 6.3 Hz), 4.88 (t, 1H, J = 6.7 Hz), 5.97 (s, 2H), 6.74 (s, 1H), 6.88 (s, 1H), 7.21 (d, 2H, J = 8.6 Hz), 7.32–7.39 (m, 5H), 7.71 (d, 2H, J = 8.3 Hz); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 46.1, 86.5, 92.9, 101.6, 109.5, 111.5, 115.4, 122.6, 127.1, 128.4, 128.5, 129.6, 131.4, 132.9, 136.9, 143.3, 147.1, 148.2; HRMS (ESI): Calcd for $C_{23}H_{20}O_4NS$ $[M+H]^+$ = 406.1108, Found = 406.1104.

4.3. Typical procedure for preparation of 4-iodo-3-phenyl-2-tosyl-1,2-dihydroisoquinoline **2A**

To a solution of *N*-(*o*-phenylethynyl)benzyl *p*-toluenesulfonamide **1A** (0.5 mmol, 180.7 mg) and $NaHCO_3$ (0.55 mmol, 46.2 mg) in acetonitrile (5.0 mL) was added I_2 (2.5 mmol, 634.5 mg) at room temperature. The mixture was stirred for 12 h at 60 °C under argon atmosphere. Then, aq. Na_2SO_3 solution (15.0 mL) was added to the mixture, and the obtained mixture was extracted with $CHCl_3$ (15.0 mL × 3). Then, the organic layer was dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography (eluent: *n*-hexane:EtOAc = 4:1) to give 4-iodo-3-phenyl-2-tosyl-1,2-dihydroisoquinoline **2A** (195.3 mg, 80%).

4.3.1. 4-Iodo-3-phenyl-2-tosyl-1,2-dihydroisoquinoline (**2A**)

Yield: 195.3 mg (80%); white solid; mp: 197 °C; IR (neat): 2343, 1339, 1164 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.24 (s, 3H), 4.95 (s, 2H), 6.89 (d, 2H, J = 7.7 Hz), 6.98–7.00 (m, 1H), 7.13–7.15 (m, 2H), 7.16–7.19 (m, 1H), 7.22 (d, 2H, J = 8.3 Hz), 7.39–7.41 (m, 3H), 7.60–7.62 (m, 2H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 50.8, 94.4, 124.6, 127.1, 127.5, 127.7, 128.6, 128.7, 129.1, 130.9, 131.2, 131.3, 134.7, 135.1, 139.1, 141.6, 143.3; HRMS (ESI): Calcd for $C_{22}H_{19}O_2NIS$ $[M+H]^+$ = 488.0176, Found = 488.0172.

4.4. Typical procedure for preparation of 3-aryl-4-iodoisoquinolines **3**

To a solution of *N*-(*o*-phenylethynyl)benzyl *p*-toluenesulfonamide **1A** (0.5 mmol, 180.7 mg) and $NaHCO_3$ (0.55 mmol, 46.2 mg) in acetonitrile (5.0 mL) was added I_2 (2.5 mmol, 634.5 mg) at room temperature. The mixture was stirred for 12 h at 60 °C under argon atmosphere. After removal of the solvent under reduced pressure, ^{t}BuOK (5.0 mmol, 561.0 mg) was added to the residue in THF (10.0 mL) at 0 °C. The mixture was stirred for 10 h at room temperature under argon atmosphere. Then, aq. NH_4Cl solution (15.0 mL) was added to the mixture, and the product was extracted with $CHCl_3$ (15.0 mL × 3). The organic layer was dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography (eluent: *n*-hexane:EtOAc = 4:1) to give 4-iodo-3-phenylisoquinoline **3A** (140.7 mg, 85%).

4.4.1. 4-Iodo-3-phenylisoquinoline (**3A**)

Yield: 140.7 mg (85%); white solid; mp: 82–83 °C; IR (neat): 2923, 1568, 1550 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 7.43–7.52 (m, 3H), 7.63 (d, 2H, J = 7.0 Hz), 7.69 (t, 1H, J = 7.6 Hz), 7.84 (t, 1H, J = 7.4 Hz), 7.97 (d, 1H, J = 8.1 Hz), 8.24 (d, 1H, J = 8.5 Hz), 9.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.0, 127.9 (2C), 128.0, 128.3, 129.8, 132.2 (2C), 132.3, 138.5, 143.7, 152.0, 157.1; HRMS (ESI): Calcd for $C_{15}H_{11}NI$ $[M+H]^+$ = 331.9931, Found = 331.9927.

4.4.2. 4-Iodo-3-(2′-methylphenyl)isoquinoline (**3B**)

Yield: 141.5 mg (82%); yellow oil; IR (neat): 2970, 1618, 1571 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.12 (s, 3H), 7.25 (d, 1H, J = 7.4 Hz), 7.29–7.38 (m, 3H), 7.70 (t, 1H, J = 7.6 Hz), 7.84 (t, 1H, J = 7.9 Hz), 7.98 (d, 1H, J = 8.1 Hz), 8.20 (d, 1H, J = 8.5 Hz), 9.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.6, 99.6, 125.6, 127.9 (3C), 128.4, 128.9, 130.1, 131.8, 132.1, 135.5, 138.2, 143.8, 152.0, 157.9; HRMS (ESI): Calcd for $C_{16}H_{13}NI$ $[M+H]^+$ = 346.0087, Found = 346.0082.

4.4.3. 4-Iodo-3-(3′-methylphenyl)isoquinoline (**3C**)

Yield: 150.2 mg (87%); yellow oil; IR (neat): 2989, 1615, 1568 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 7.26 (d, 1H, J = 7.2 Hz), 7.38 (t, 1H, J = 8.1 Hz), 7.42–7.44 (m, 2H), 7.68 (t, 1H, J = 7.3 Hz), 7.83 (t, 1H, J = 7.4 Hz), 7.96 (d, 1H, J = 8.3 Hz), 8.24 (d, 1H, J = 8.5 Hz), 9.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.5, 98.0, 126.9, 127.7, 127.9 (2C), 128.0, 128.1, 130.2, 132.1, 132.3, 137.6, 138.5, 143.6, 151.9, 157.2; HRMS (ESI): Calcd for $C_{16}H_{13}NI$ $[M+H]^+$ = 346.0087, Found = 346.0082.

4.4.4. 4-Iodo-3-(4′-methylphenyl)isoquinoline (**3D**)

Yield: 142.4 mg (83%); white solid; mp: 93 °C; IR (neat): 2972, 1616, 1568 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 2.45 (s, 3H), 7.30 (d, 2H, J = 7.9 Hz), 7.54 (d, 2H, J = 8.1 Hz), 7.67 (t, 1H, J = 7.4 Hz), 7.82 (t, 1H, J = 7.9 Hz), 7.96 (d, 1H, J = 8.1 Hz), 8.23 (d, 1H, J = 8.5 Hz), 9.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 98.0, 127.8, 127.9 (2C), 128.6, 129.7, 132.1, 132.3, 138.1, 138.5, 140.8, 151.9, 157.1; HRMS (ESI): Calcd for $C_{16}H_{13}NI$ $[M+H]^+$ = 346.0087, Found = 346.0084.

4.4.5. 3-(4′-Ethylphenyl)-4-iodoisoquinoline (**3E**)

Yield: 131.1 mg (73%); yellow oil; IR (neat): 2989, 1614, 1570 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.30 (t, 3H, J = 7.6 Hz), 2.75 (q, 2H, J = 7.6 Hz), 7.32 (d, 2H, J = 8.5 Hz), 7.56 (d, 2H, J = 8.3 Hz), 7.67 (t, 1H, J = 7.4 Hz), 7.82 (t, 1H, J = 7.9 Hz), 7.95 (d, 1H, J = 8.1 Hz), 8.23 (d, 1H, J = 8.5 Hz), 9.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 15.5, 28.7, 97.9, 127.4, 127.8 (2C), 127.9, 129.7, 132.1, 132.3, 138.5, 141.0, 144.4, 151.9, 157.1; HRMS (ESI): Calcd for $C_{17}H_{15}NI$ $[M+H]^+$ = 360.0244, Found = 360.0241.

4.4.6. 3-(4′-tert-Butylphenyl)-4-iodoisoquinoline (**3F**)

Yield: 178.1 mg (92%); white solid; mp: 94–95 °C; IR (neat): 2953, 1609, 1571 cm^{-1}; ^{1}H NMR (400 MHz, $CDCl_3$): δ = 1.39 (s, 9H), 7.50 (d, 2H, J = 8.5 Hz), 7.59 (d, 2H, J = 8.5 Hz), 7.67 (t, 1H, J = 7.5 Hz), 7.82 (t, 1H, J = 7.9 Hz), 7.95 (d, 1H, J = 7.9 Hz), 8.24 (d, 1H, J = 8.5 Hz), 9.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 31.3, 34.7, 97.8, 124.8, 127.8, 127.9 (2C), 129.5, 132.1, 132.3, 138.6, 140.7, 151.2, 151.9, 157.1; HRMS (ESI): Calcd for $C_{19}H_{19}NI$ $[M+H]^+$ = 388.0557, Found = 388.0554.

*4.4.7. 3-(2′,4′-Dimethylphenyl)-4-iodoisoquinoline (**3G**)*

Yield: 129.3 mg (72%); white solid; mp: 131–132 °C; IR (neat): 2982, 1616, 1568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.09 (s, 3H), 2.41 (s, 3H), 7.11–7.16 (m, 3H), 7.69 (t, 1H, J = 7.6 Hz), 7.83 (t, 1H, J = 7.9 Hz), 7.97 (d, 1H, J = 8.1 Hz), 8.19 (d, 1H, J = 8.5 Hz), 9.18 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 19.5, 21.3, 99.9, 126.3, 127.9 (3C), 128.9, 130.8, 131.8, 132.1, 135.3, 138.0, 138.2, 141.0, 152.0, 158.1; HRMS (ESI): Calcd for $C_{17}H_{15}NI$ $[M+H]^+$ = 360.0244, Found = 360.0241.

*4.4.8. 3-(3′,5′-Dimethylphenyl)-4-iodoisoquinoline (**3H**)*

Yield: 149.1 mg (83%); white solid; mp: 103 °C; IR (neat): 2913, 1603, 1568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 6H), 7.08 (s, 1H), 7.23 (s, 2H), 7.67 (t, 1H, J = 7.2 Hz), 7.82 (t, 1H, J = 7.7 Hz), 7.95 (d, 1H, J = 8.1 Hz), 8.23 (d, 1H, J = 8.5 Hz), 9.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 97.9, 127.5, 127.8, 127.9, 128.0, 129.9, 132.1, 132.4, 137.4, 138.5, 143.6, 151.9, 157.5; HRMS (ESI): Calcd for $C_{17}H_{15}NI$ $[M+H]^+$ = 360.0244, Found = 360.0241.

*4.4.9. 4-Iodo-3-(2′-methoxyphenyl)isoquinoline (**3I**)*

Yield: 133.6 mg (74%); yellow oil; IR (neat): 2987, 1579, 1568, 1549, 1065 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.88 (s, 3H), 7.00 (dd, 1H, J = 8.3, 2.6 Hz), 7.15–7.16 (m, 1H), 7.20 (d, 1H, J = 7.4 Hz), 7.41 (t, 1H, J = 7.9 Hz), 7.69 (t, 1H, J = 7.5 Hz), 7.84 (t, 1H, J = 7.9 Hz), 7.97 (d, 1H, J = 8.4 Hz), 8.24 (d, 1H, J = 7.9 Hz), 9.17 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3, 98.0, 114.3, 115.0, 122.2, 127.9, 128.0 (2C), 129.0, 132.2, 132.3, 138.5, 144.9, 151.9, 156.9, 159.1; HRMS (ESI): Calcd for $C_{16}H_{13}ONI$ $[M+H]^+$ = 362.0036, Found = 362.0035.

*4.4.10. 4-Iodo-3-(3′-methoxyphenyl)isoquinoline (**3J**)*

Yield: 162.5 mg (90%); white solid; mp: 108–109 °C; IR (neat): 2989, 1605, 1564 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.79 (s, 3H), 7.02–7.04 (m. 1H), 7.10 (t, 1H, J = 7.4 Hz), 7.30 (dd, 1H, J = 7.5, 1.6 Hz), 7.44 (t, 1H, J = 7.4 Hz), 7.68 (t, 1H, J = 7.0 Hz), 7.81 (t, 1H, J = 7.0 Hz), 7.96 (d, 1H, J = 8.1 Hz), 8.20 (d, 1H, J = 8.5 Hz), 9.20 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.5, 100.8, 111.1, 120.5, 127.9 (2C), 128.0, 129.9, 130.5, 131.9, 132.0, 133.3, 138.3, 152.0, 155.6, 156.4; HRMS (ESI): Calcd for $C_{16}H_{13}ONI$ $[M+H]^+$ = 362.0036, Found = 362.0034.

*4.4.11. 4-Iodo-3-(4′-methoxyphenyl)isoquinoline (**3K**)*

Yield: 155.3 mg (86%); white solid; mp: 113–114 °C; IR (neat): 2971, 1608, 1567, 1026 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 3.89 (s, 3H), 7.02 (d, 2H, J = 8.5 Hz), 7.61 (d, 2H, J = 8.3 Hz), 7.66 (t, 1H, J = 7.0 Hz), 7.82 (t, 1H, J = 7.4 Hz), 7.95 (d, 1H, J = 8.1 Hz), 8.23 (d, 1H, J = 8.5 Hz), 9.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 55.3, 98.0, 113.2, 127.7 (2C), 127.8, 131.2, 132.1, 132.3, 136.1, 138.6, 151.9, 156.7, 159.5; HRMS (ESI): Calcd for $C_{16}H_{13}ONI$ $[M+H]^+$ = 362.0036, Found = 362.0034.

*4.4.12. 3-(4′-Ethoxyphenyl)-4-iodoisoquinoline (**3L**)*

Yield: 168.8 mg (90%); white solid; mp: 153–155 °C; IR (neat): 2971, 1605, 1509, 1043 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.46 (t, 3H, J = 7.0 Hz), 4.12 (q, 2H, J = 7.0 Hz), 7.01 (d, 2H, J = 8.8 Hz), 7.60 (d, 2H, J = 8.8 Hz), 7.67 (t, 1H, J = 7.0 Hz), 7.82 (t, 1H, J = 7.9 Hz), 7.95 (d, 1H, J = 8.1 Hz), 8.23 (d, 1H, J = 8.5 Hz), 9.15 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 14.8, 63.4, 97.9, 113.7, 127.7, 127.8 (2C), 131.2, 132.1, 132.3 (2C), 135.9, 151.9, 156.7, 158.9; HRMS (ESI): Calcd for $C_{17}H_{15}ONI$ $[M+H]^+$ = 376.0193, Found = 376.0192.

*4.4.13. 3-(4′-Fluorophenyl)-4-iodoisoquinoline (**3M**)*

Yield: 141.4 mg (81%); white solid; mp: 98–99 °C; IR (neat): 2996, 1599, 1569 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.18 (t, 2H, J = 8.8 Hz), 7.61–7.64 (m, 2H), 7.70 (t, 1H, J = 7.5 Hz), 7.84 (t, 1H, J = 7.7 Hz), 7.97 (d, 1H, J = 8.1 Hz), 8.23 (d, 1H, J = 7.6 Hz), 9.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.1, 114.8 (d, $J_{C\text{-}F}$ = 21.6 Hz), 127.9 (2C), 128.0, 131.7 (d, $J_{C\text{-}F}$ = 21.6 Hz), 132.2, 132.3, 138.4, 139.6 (d, $J_{C\text{-}F}$ = 2.8 Hz), 152.0, 155.9, 162.6 (d, $J_{C\text{-}F}$ = 247.1 Hz); HRMS (ESI): Calcd for $C_{15}H_{10}NFI$ $[M+H]^+$ = 349.9836, Found = 349.9834.

*4.4.14. 3-(4′-Chlorophenyl)-4-iodoisoquinoline (**3N**)*

Yield: 128.0 mg (70%); white solid; mp: 149 °C; IR (neat): 2971, 1592, 1574 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.47 (d, 2H, J = 8.8 Hz), 7.59 (d, 2H, J = 8.5 Hz), 7.70 (t, 1H, J = 7.5 Hz), 7.85 (t, 1H, J = 7.9 Hz), 7.97 (d, 1H, J = 8.1 Hz), 8.23 (d, 1H, J = 8.5 Hz), 9.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.0, 127.9, 128.1 (2C), 128.2 (2C), 131.3, 132.4, 134.3, 138.5, 142.0, 152.1, 155.8; HRMS (ESI): Calcd for $C_{15}H_{10}N^{35}ClI$ $[M+H]^+$ = 365.9541, Found = 365.9537.

*4.4.15. 3-(4′-Bromophenyl)-4-iodoisoquinoline (**3O**)*

Yield: 139.4 mg (68%); white solid; mp: 148–149 °C; IR (neat): 2973, 1596, 1573 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.53 (d, 2H, J = 8.5 Hz), 7.61–7.65 (m, 2H), 7.71 (t, 1H, J = 8.1 Hz), 7.85 (t, 1H, J = 7.2 Hz), 7.97 (d, 1H, J = 8.3 Hz), 8.23 (d, 1H, J = 8.5 Hz), 9.16 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 97.9, 122.6, 127.9, 128.0, 128.2, 131.1, 131.6, 132.3 (2C), 138.5, 142.4, 152.1, 155.8; HRMS (ESI): Calcd for $C_{15}H_{10}N^{79}BrI$ $[M+H]^+$ = 409.9036, Found = 409.9034, $C_{15}H_{10}N^{81}BrI$ $[M+H]^+$ = 411.9015, Found = 411.9012.

*4.4.16. 4-Iodo-3-(naphthalen-1′-yl)isoquinoline (**3P**)*

Yield: 183.0 mg (96%); white solid; mp: 108–109 °C; IR (neat): 3044, 2985, 1569, 1551 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.39–7.40 (m, 2H), 7.48–7.55 (m, 2H), 7.61 (t, 1H, J = 8.1 Hz), 7.75 (td, 1H, J = 7.5, 1.1 Hz) 7.88 (td, 1H, J = 7.6, 1.4 Hz), 7.94–7.99 (m, 2H), 8.04 (d, 1H, J = 8.1 Hz), 9.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 100.6, 125.2, 125.5, 125.9, 126.3, 127.3, 128.0, 128.1, 128.2, 128.3, 128.7, 131.2, 132.0, 132.3, 133.6, 138.3, 141.7, 152.1, 156.8; HRMS (ESI): Calcd for $C_{19}H_{13}NI$ $[M+H]^+$ = 382.0087, Found = 382.0085.

*4.4.17. 3-(4′-Biphenyl)-4-iodoisoquinoline (**3Q**)*

Yield: 142.5 mg (70%); white solid; mp: 160–162 °C; IR (neat): 3052, 3034, 1614, 1566 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.38 (tt, 1H, J = 7.4, 1.8 Hz), 7.48 (t, 2H, J = 7.9 Hz), 7.68–7.72 (m, 3H), 7.73–7.74 (m, 4H), 7.85 (td, 1H, J = 7.9, 1.4 Hz), 7.98 (d, 1H, J = 8.1 Hz), 8.26 (d, 1H, J = 8.5 Hz), 9.19 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 97.9, 126.7, 127.2, 127.4, 128.0 (3C), 128.8, 130.3, 132.2, 132.4, 138.6, 140.7, 141.0, 142.5, 152.1, 156.7; HRMS (ESI): Calcd for $C_{21}H_{15}NI$ $[M+H]^+$ = 408.0244, Found = 408.0241.

*4.4.18. 3-(1′,3′-Benzodioxol-5′-yl)-4-iodoisoquinoline (**3R**)*

Yield: 176.3 mg (94%); white solid; mp: 81–83 °C; IR (neat): 3045, 1603, 1547, 1108 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.05 (s, 2H), 6.93 (d, 1H, J = 8.5 Hz), 7.12–7.14 (m, 2H), 7.68 (t, 1H, J = 8.1 Hz), 7.83 (t, 1H, J = 7.9 Hz), 7.95 (d, 1H, J = 7.9 Hz), 8.22 (d, 1H, J = 8.5 Hz), 9.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 98.1, 101.2, 107.8, 110.5, 124.0, 127.9 (3C), 132.2, 132.4, 137.6, 138.6, 147.1, 147.5, 151.9, 156.5; HRMS (ESI): Calcd for $C_{16}H_{11}O_2NI$ $[M+H]^+$ = 375.9829, Found = 375.9826.

*4.4.19. 4-Iodo-3-(thiophen-3′-yl)isoquinoline (**3S**)*

Yield: 148.3 mg (88%); white solid; mp: 79–82 °C; IR (neat): 3110, 2340, 1560, 1307, 1150 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.42 (dd, 1H, J = 4.9, 2.9 Hz), 7.54 (dd, 1H, J = 4.9, 1.4 Hz), 7.67 (t, 1H, J = 7.0 Hz), 7.77 (dd, 1H, J = 2.9, 1.4 Hz), 7.82 (t, 1H, J = 7.6 Hz), 7.94 (d, 1H, J = 8.1 Hz), 8.23 (d, 1H, J = 9.4 Hz), 9.14 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 97.8, 124.7, 126.5, 127.9, 128.0, 129.4, 132.2, 132.5, 138.6, 143.9, 152.0 (2C), 152.5; HRMS (ESI): Calcd for $C_{13}H_9NIS$ $[M+H]^+$ = 337.9495, Found = 337.9492.

*4.4.20. 3-(Cyclohexen-1′-yl)-4-iodoisoquinoline (**3T**)*

Yield: 63.7 mg 38%); colorless oil; IR (neat): 2997, 1616,

1568 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.74–1.80 (m, 2H), 1.85–1.91 (m, 2H), 2.24–2.30 (m, 2H), 2.41–2.44 (m, 2H), 5.86 (quint, 1H, J = 1.9 Hz), 7.62 (t, 1H, J = 7.9 Hz), 7.77 (t, 1H, J = 7.7 Hz), 7.90 (d, 1H, J = 8.5 Hz), 8.15 (d, 1H, J = 8.5 Hz), 9.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.9, 22.8.25.1, 28.3, 97.5, 127.4, 127.8, 127.9, 129.4, 131.8, 132.0, 138.4, 141.7, 152.0, 159.5; HRMS (ESI): Calcd for $C_{15}H_{15}IN$ $[M+H]^+$ = 336.0250, Found = 336.0252.

4.4.21. 4-Iodo-7-methyl-3-phenylisoquinoline (**3U**)

Yield: 155.3 mg (90%); yellow solid; mp: 94–95 °C; IR (neat): 2930, 1614, 1570 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.61 (s, 3H), 7.43–7.50 (m, 3H), 7.61–7.67 (m, 3H), 7.73 (s, 1H), 8.12 (d, 1H, J = 8.8 Hz), 9.08 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.4, 97.8, 126.6 (2C), 127.9, 128.1, 129.8, 132.1, 134.4, 136.8, 138.1, 143.7, 151.3, 156.2; HRMS (ESI): Calcd for $C_{16}H_{13}NI$ $[M+H]^+$ = 346.0087, Found = 346.0084.

4.4.22. 7-Chloro-4-iodo-3-phenylisoquinoline (**3V**)

Yield: 122.5 mg (67%); yellow solid; mp: 89–90 °C; IR (neat): 2979, 1581, 1561 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.45–7.52 (m, 3H), 7.61–7.63 (m, 2H), 7.75 (d, 1H, J = 9.1 Hz), 7.97 (s, 1H), 8.21 (d, 1H, J = 9.0 Hz), 9.10 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 97.4, 126.3, 128.0, 128.2, 128.5, 129.7, 132.9, 133.9, 134.3, 137.0, 143.3, 150.9, 157.5; HRMS (ESI): Calcd for $C_{15}H_{10}N^{35}ClI$ $[M+H]^+$ = 365.9541, Found = 365.9539.

4.4.23. 4-Iodo-6,7-methylenedioxy-3-phenylisoquinoline (**3W**)

Yield: 95.7 mg (51%); yellow solid; mp: 148–149 °C; IR (neat): 2989, 1603, 1565, 1036 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 6.18 (s, 2H), 7.19 (s, 1H), 7.40–7.49 (m, 3H), 7.59 (dd, 2H, J = 8.0, 1.2 Hz), 7.63 (s, 1H), 8.90 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 96.9, 102.1, 103.0, 109.3, 125.1, 127.9, 128.1, 129.7, 137.4, 143.9, 148.9, 149.6, 152.7, 156.4; HRMS (ESI): Calcd for $C_{16}H_{11}O_2NI$ $[M+H]^+$ = 375.9829, Found = 375.9825.

4.4.24. 3-Phenyl-4-(phenylselenyl)isoquinoline (**3X**)

Yield: 156.7 mg (87%); white solid; mp: 107–109 °C; IR (neat): 2923, 1615, 1574 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.01–7.05 (m, 2H), 7.06–7.10 (m, 3H), 7.38–7.43 (m, 3H), 7.55–7.58 (m, 2H), 7.63 (t, 1H, J = 7.5 Hz), 7.71 (t, 1H, J = 7.9 Hz), 8.03 (d, 1H, J = 8.1 Hz), 8.45 (d, 1H, J = 8.1 Hz), 9.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 121.3, 126.0, 127.4, 127.6, 128.0, 128.1, 128.5, 129.1, 129.5, 129.8, 131.6, 133.1 (2C), 138.5, 142.0, 153.2, 158.5; HRMS (ESI): Calcd for $C_{21}H_{16}N^{80}Se$ $[M+H]^+$ = 362.0442, Found = 362.0438.

4.5. Preparation of 3-phenylisoquinoline **4A**

To a solution of 4-iodo-3-phenylisoquinoline (**3A**) (0.5 mmol, 165.6 mg) in EtOH (7.5 mL) was added Zn powder (5.0 mmol, 363.3 mg) under argon atmosphere. The obtained mixture was stirred for 12 h at refluxing temperature. The cooled mixture was filtered through Celite, and then the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane/AcOEt = 4:1) to afford 3-phenylisoquinoline (**4A**) (101.6 mg, 99%).

4.5.1. 3-Phenylisoquinoline (**4A**)

Yield: 101.6 mg (99%); white solid; mp: 100 °C; IR (neat): 2923, 1623, 1573 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 7.43 (t, 1H, J = 7.2 Hz), 7.52 (t, 2H, J = 7.9 Hz), 7.60 (t, 1H, J = 7.5 Hz), 7.71 (t, 1H, J = 7.7 Hz), 7.89 (d, 1H, J = 8.3 Hz), 8.00 (d, 1H, J = 8.3 Hz), 8.08 (s, 1H), 8.12–8.14 (m, 2H), 9.35 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 116.5, 126.9, 127.0 (2C), 127.5, 127.7, 128.5, 128.8, 130.5, 136.6, 139.6, 151.3, 152.4; HRMS (ESI): Calcd for $C_{15}H_{12}N$ $[M+H]^+$ = 206.0964, Found = 206.0964.

4.6. Preparation of 4-(4′-methylbenzenesulfenyl-3-phenylisoquinoline **5A**

To a mixture of 4-iodo-3-phenylisoquinoline (**3A**) (0.5 mmol, 165.7 mg), CuI (0.1 mmol, 19.0 mg), K_2CO_3 (1.0 mmol, 138.2 mg), and *p*-Tol-SH (0.6 mmol, 74.5 mg) in *i*-PrOH (6.0 mL) was added ethylene glycol (1.0 mmol, 56 μL) under argon atmosphere. The obtained mixture was stirred for 48 h at 80 °C. H_2O (5.0 mL) was added to the reaction mixture, and the obtained mixture was extracted with $CHCl_3$ (15.0 mL × 3). The organic layer was dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography (eluent: *n*-hexane/EtOAc = 4:1) to give 3-(4′-methylbenzenesulfenyl)-4-phenylisoquinoline (**5A**) (122.8 mg, 75%).

4.6.1. 4-(4′-Methylbenzenesulfenyl)-3-phenylisoquinoline (**5A**)

Yield: 122.8 mg (75%); yellow solid; mp: 107–109 °C; IR (neat): 2921, 1615, 1549 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.23 (s, 3H), 6.83 (d, 2H, J = 8.3 Hz), 6.93 (d, 2H, J = 8.3 Hz), 7.39–7.42 (m, 3H), 7.61–7.65 (m, 3H), 7.72 (t, 1H, J = 7.6 Hz), 8.05 (d, 1H, J = 8.1 Hz), 8.42 (d, 1H, J = 8.5 Hz), 9.37 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 20.9, 122.2, 126.2, 126.9, 127.5, 127.7, 128.1 (2C), 128.2, 129.7, 129.8, 131.7, 134.4, 135.1, 138.3, 140.8, 153.2, 158.2; HRMS (ESI): Calcd for $C_{22}H_{18}NS$ $[M+H]^+$ = 328.1154, Found = 328.1152.

4.7. Preparation of 4-(4′-methylphenyl)ethynyl-3-phenylisoquinoline **6A**

To a mixture of 4-iodo-3-phenylisoquinoline (**3A**) (0.5 mmol, 165.7 mg), CuI (0.01 mmol, 1.9 mg), and $PdCl_2(PPh_3)_2$ (0.01 mmol, 7.0 mg) in Et_3N (2.0 mL) was added 4-methyl-1-ethynylbenzene (0.6 mmol, 76 μL) under argon atmosphere. The obtained mixture was stirred for 4 h at 60 °C. Aq. NH_4Cl solution (15.0 mL) was added to the mixture, and the obtained mixture was extracted with $CHCl_3$ (15.0 mL × 3). The organic layer was dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography (eluent: *n*-hexane/EtOAc = 4:1) to give 4-(4′-methylphenyl)ethynyl-3-phenylisoquinoline (**6A**) (158.1 mg, 99%).

4.7.1. 4-(4′-Methylphenyl)ethynyl-3-phenylisoquinoline (**6A**)

Yield: 158.1 mg (99%); white solid; mp: 74–77 °C; IR (neat): 2920, 2205, 1615, 1550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.39 (s, 3H), 7.18 (d, 2H, J = 7.6 Hz), 7.41–7.48 (m, 3H), 7.53 (t, 2H, J = 7.6 Hz), 7.67 (t, 1H, J = 7.5 Hz), 7.83 (t, 1H, J = 7.6 Hz), 8.03 (d, 1H, J = 8.1 Hz), 8.13–8.16 (m, 2H), 8.50 (d 1H, J = 7.4 Hz), 9.28 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.6, 85.1, 99.5, 112.7, 120.1, 125.7, 126.6, 127.5, 127.8, 127.9, 128.5, 129.2, 129.9, 131.2, 131.3, 136.6, 138.9, 140.0, 151.2, 154.2; HRMS (ESI): Calcd for $C_{24}H_{18}N$ $[M+H]^+$ = 320.1434, Found = 320.1430.

4.8. Preparation of (E)-4-(4′-methylphenyl)ethenyl-3-phenylisoquinoline (**7A**)

To a mixture of 4-iodo-3-phenylisoquinoline (**3A**) (0.5 mmol, 165.7 mg), K_2CO_3 (1.0 mmol, 138.2 mg), and $PdCl_2(PPh_3)_2$ (0.05 mmol, 35.0 mg) in DMF (5.0 mL) was added 4-methylstyrene (1.0 mmol, 131 μL) under argon atmosphere. The obtained mixture was stirred for 12 h at 130 °C. Sat. aq. $NaHCO_3$ solution (15.0 mL) was added to the reaction mixture, and the obtained mixture was extracted with $CHCl_3$ (15.0 mL × 3). The organic layer was dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column

chromatography (eluent: *n*-hexane/EtOAc = 4:1) to give (*E*)-4-(4′-methylphenyl)ethenyl-3-phenylisoquinoline (**7A**) (144.6 mg, 90% yield).

*4.8.1. (E)-4-(4′-methylphenyl)ethenyl-3-phenylisoquinoline (**7A**)*

Yield: 144.6 mg (90%); white solid; mp: 104–105 °C; IR (neat): 2924, 1609, 1550 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.38 (s, 3H), 6.87 (d, 1H, *J* = 16.4 Hz), 7.18–7.20 (m, 2H), 7.25–7.26 (m, 1H), 7.35–7.37 (m, 3H), 7.44 (t, 2H, *J* = 7.9 Hz), 7.63 (t, 1H, *J* = 7.4 Hz), 7.72–7.76 (m, 3H), 8.04 (d, 1H, *J* = 8.5 Hz), 8.39 (d 1H, *J* = 8.5 Hz), 9.27 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 123.4, 125.0, 126.4, 126.6, 126.8, 127.7 (3C), 128.0 (2C), 129.4, 130.4, 130.5, 134.4, 136.5, 137.9, 140.9, 150.5, 151.0; HRMS (ESI): Calcd for $C_{24}H_{20}N$ $[M+H]^+$ = 322.1590, Found = 322.1586.

*4.9. Preparation of 4-(4′-methylphenyl)-3-phenylisoquinoline (**8A**)*

To a mixture of 4-iodo-3-phenylisoquinoline (**3A**) (0.5 mmol, 167.1 mg) and *p*-TolB$(OH)_2$ (1.0 mmol, 136.0 mg) in DMF (10.0 mL) was added $PdCl_2(PPh_3)_2$ (0.025 mmol, 17.5 mg) under argon atmosphere. The obtained mixture was stirred for 30 min at room temperature. Then, K_2CO_3 (1.0 mmol, 138.2 mg) in H_2O (2.0 mL) was added to the mixture, and the obtained mixture was stirred for 2 h at 60 °C. Aq. NH_4Cl solution (15.0 mL) was added to the mixture, and the obtained mixture was extracted with $CHCl_3$ (15.0 mL × 3). The organic layer was dried over Na_2SO_4 and filtered. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography (eluent: *n*-hexane/EtOAc = 4:1) to give 4-(4′-methylphenyl)-3-phenylisoquinoline **(8A)** (138.8 mg, 94%).

*4.9.1. 4-(4′-Methylphenyl)-3-phenylisoquinoline (**8A**)*

Yield: 138.8 mg (94%); white solid; mp: 99–100 °C; IR (neat): 2916, 1615, 1554 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 2.40 (s, 3H), 7.12–7.25 (m, 7H), 7.37–7.40 (m, 2H), 7.59–7.63 (m, 2H), 7.69–7.71 (m, 1H), 8.03–8.06 (m, 1H), 9.36 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 21.3, 125.6, 126.8, 126.9, 127.3, 127.5, 127.6, 129.0, 130.2, 130.4, 130.6, 131.0, 134.0, 136.1, 136.9, 140.9, 150.6, 151.5; HRMS (ESI): Calcd for $C_{22}H_{18}N$ $[M+H]^+$ = 296.1434, Found = 296.1431.

*4.10. Preparation of 1-cyclohexyl-3-phenylisoquinoline **(9A)***

To a solution of 4-iodo-3-phenylisoquinoline (**3A**) (0.5 mmol, 165.6 mg) in EtOH (7.5 mL) was added Zn powder (5.0 mmol, 363.3 mg) under argon atmosphere. The obtained mixture was stirred for 12 h at refluxing temperature. The cooled mixture was filtered through Celite, and then the filtrate was concentrated under reduced pressure. The residue was purified by column chromatography on silica gel (eluent: *n*-hexane/AcOEt = 4:1) to afford 3-phenylisoquinoline (**4A**). BPO (0.65 mmol, 209.9 mg) and CF_3CO_2H (0.65 mmol, 74 μL) were added to a solution of the obtained 3-phenylisoquinoline (**4A**) in a mixture of cyclohexane and DCE (5:1; 1.5 mL) in a screw-capped flask (30 mL) at room temperature. The reaction flask was flushed with argon gas. The mixture was stirred for 4 h at 100 °C. The reaction mixture was cooled to room temperature, and the solvent was removed under reduced pressure. Then, the residual mixture was quenched with sat. aq. $NaHCO_3$ solution (15.0 mL). The product was extracted with $CHCl_3$ (15.0 mL × 3). The organic layer was dried over Na_2SO_4. After removal of the solvent under reduced pressure, the residue was purified by silica-gel column chromatography (eluent: *n*-hexane/EtOAc = 30:1) to give 1-cyclohexyl-3-phenylisoquinoline (**9A**) (122.1 mg, 85%).

*4.10.1. 1-Cyclohexyl-3-phenylisoquinoline (**9A**)*

Yield: 122.1 mg (85%); colorless oil; IR (neat): 2924, 1620, 1566 cm^{-1}; ^1H NMR (400 MHz, $CDCl_3$): δ = 1.39–1.47 (m, 1H), 1.51–1.54 (m, 1H), 1.56–1.61 (m, 1H), 1.82–1.85 (m, 1H), 1.92–2.06 (m, 6H), 3.52–3.62 (m, 1H), 7.39 (tt, 1H, *J* = 7.2, 0.9 Hz), 7.48–7.57 (m, 3H), 7.63 (t, 1H, *J* = 7.3 Hz), 7.86 (d, 1H, *J* = 7.9 Hz), 7.92 (s, 1H), 8.20–8.25 (m, 3H); ^{13}C NMR (100 MHz, $CDCl_3$): δ = 26.3, 26.9, 32.6, 41.8, 114.3, 124.7, 125.3, 126.5, 126.8, 128.0, 128.2, 128.6, 129.5, 137.2, 140.0, 149.3, 165.2; HRMS (ESI): Calcd for $C_{21}H_{22}N$ $[M+H]^+$ = 288.1747, Found = 288.1747.

Declaration of competing interest

The authors declare that they have no known competing financial interests or personal relationships that could have appeared to influence the work reported in this paper.

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Appendix A. Supplementary data

Supplementary data to this article can be found online at https://doi.org/10.1016/j.tet.2021.131993.

References

[1] (Reviews:). a) K.W. Bentley, Nat. Prod. Rep. 18 (2001) 148–170;
b) M. Chrzanowska, M.D. Rozwadowska, Chem. Rev. 104 (2004) 3341–3370;
c) K.W. Bentley, Nat. Prod. Rep. 22 (2005) 249–268;
d) M. Croisy-Delcey, A. Croisy, D. Carrez, C. Huel, A. Chiaroni, P. Ducrot, E. Bisagni, L. Jin, G. Leclercq, Bioorg. Med. Chem. 8 (2000) 2629–2641;
e) V. Reddy, A.S. Jadhav, R.V. Anand, Org. Biomol. Chem. 13 (2015) 3732–3741;
f) M. Chrzanowska, A. Grajewska, M.D. Rozwadowska, Chem. Rev. 116 (2016) 12369–12465.
[2] a) P. Fritsch, Ber. Dtsch. Chem. Ges. 26 (1893) 419–422;
b) C. Pomeranz, Monatsh. Chem. 14 (1893) 116–119;
c) A. Bischler, B. Napieralski, Ber. Dtsch. Chem. Ges. 26 (1893) 1891.
[3] a) S. Lim, J.H. Lee, C.W. Moon, J. Hong, C. Jun, Org. Lett. 5 (2003) 2759–2761;
b) J. Sun, X. Zhang, H. Yang, P. Li, B. Zhang, Eur. J. Org Chem. (2018) 4965–4969;
c) M. Liu, W. Gong, E. You, H. Zhang, L. Shi, W. Cao, J. Shi, Eur. J. Org Chem. (2018) 4991–4995;
d) W. Lin, X. Hu, C. Zhuang, Y. Wang, Tetrahedron 75 (2019) 3015–3023;
e) P. Biswal, B.V. Pati, R. Chebolu, A. Ghosh, P.C. Ravikumar, Eur. J. Org Chem. (2020) 1006–1014;
f) A. Coppola, D. Sucunza, C. Burgos, J.J. Vaquero, Org. Lett. 17 (2015) 78–81;
g) Y. Liu, Y. Kang, H. Wang, Y. Dong, T. Yang, Q. Wei, Y. Jiang, Y. Yang, H. Gao, Tetrahedron Lett. 61 (2020) 152348;
h) B.S. Pilgrim, A.E. Gatland, C.H.A. Esteves, C.T. McTernan, G.R. Jones, M.R. Tatton, P.A. Procopiou, T.J. Donohoe, Org. Biomol. Chem. 14 (2016) 1065–1090.
[4] a) G. Dai, R.C. Larock, Org. Lett. 3 (2001) 4035–4038;
b) D. Fischer, H. Tomeba, N.K. Pahadi, N.T. Patil, Z. Huo, Y. Yamamoto, J. Am. Chem. Soc. 130 (2008) 15720–15727;
c) B. Gabriele, L. Veltri, V. Maltese, R. Spina, R. Mancuso, G. Salerno, Eur. J. Org Chem. (2011) 5626–5635.
[5] a) Q. Huang, J.A. Hunter, R.C. Larock, Org. Lett. 3 (2001) 2973–2976;
b) Q. Huang, J.A. Hunter, R.C. Larock, J. Org. Chem. 67 (2002) 3437–3444;
c) Y. Hoshimoto, C. Nishimura, Y. Sasaoka, R. Kumar, S. Ogoshi, Bull. Chem. Soc. Jpn. 93 (2020) 182–186;
d) J. Yang, X. Wei, Y. Yu, Y. Zhu, Y. Zhao, W. Xie, Tetrahedron Lett. 61 (2020) 151454.
[6] (Reviews:). a) H. Togo, S. Iida, Synlett (2006) 2159–2175;
b) T. Aggarwal, S. Kumar, A.K. Verma, Org. Biomol. Chem. 14 (2016) 7639–7653.
[7] (a) A. Kishi, K. Moriyama, H. Togo, J. Org. Chem. 83 (2018) 11080–11088;
(b) E. Kobayashi, A. Kishi, H. Togo, Eur. J. Org Chem. (2019) 7335–7347;
(c) H. Naruto, H. Togo, Org. Biomol. Chem. 17 (2019) 5760–5770;
(d) H. Naruto, H. Togo, Synthesis 52 (2020) 1122–1130;
(e) A. Saitoh, H. Togo, Eur. J. Org Chem. (2020) 3320–3331;
(f) H. Naruto, H. Togo, Org. Biomol. Chem. 18 (2020) 5666–5676;
(g) K. Yanai, H. Togo, Tetrahedron 76 (2020) 131503.
[8] (a) H. Nakatsuji, Y. Sawamura, A. Sakakura, K. Ishihara, Angew. Chem. Int. Ed. 53 (2014) 6974–6977. Review:;
(b) A. Sakakura, K. Ishihara, Chem. Rec. 15 (2015) 728–742.