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Chiral counteranion-directed silver-catalyzed asymmetric synthesis of 1,2-dihydroisoquinolines by Friedel–Crafts alkylation reactions

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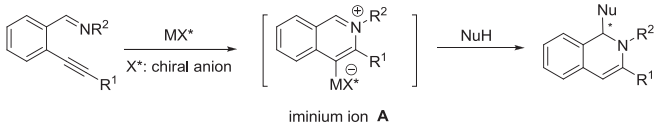
ABSTRACT

The reaction of *ortho*-alkynylaryl aldimines and indoles catalyzed by a silver binol-derived phosphate was realized to afford a series of enantioenriched 1,2-dihydroisoquinolines in moderate to good yields and ee. An interesting phenomenon that highly enantioenriched products could be obtained from their lower ee form by silica gel column chromatography was observed, providing an easy access to the enantiopure form of the product.

1. Introduction

1,2-Dihydroisoquinolines and their derivatives constitute an important class of heterocyclic compounds and are found in numerous natural products[1] and pharmaceuticals[2] that exhibit remarkable biological activities. They also often serve as key building blocks for natural products synthesis.[3] Among them, 1,2-dihydroisoquinolines bearing a stereogenic carbon center at the C1 position are particularly interesting structural motif.[3a,4] Therefore, several methodologies have been devoted to the development of novel 1,2-dihydroisoquinoline-based structures and their efficient synthesis in an asymmetric manner. These include the use of stoichiometric amount of chiral sources,[5] the asymmetric transfer hydrogenation of dihydroisoquinolines,[6] Pictet–Spengler reactions[7] and the catalytic asymmetric addition of carbon nucleophiles to C=N bonds of isoquinoline scaffolds.[8] Recently, Asao,[9] Takemoto,[10] Larock,[11] Wu,[12] and others,[13] respectively, reported AgOTf or other Lewis (π) acid-catalyzed synthesis of multi-substituted 1,2-dihydroisoquinoline skeletons by nucleophilic addition to *ortho*-alkynylaryl aldimines, which were prepared from *ortho*-alkynylaldehydes and proper amines (Scheme 1). Particularly, the group of Wu have significantly expanded the catalyst and reaction types for these reaction patterns.[12] Such processes have also been extended to one-pot procedures that employ 2-(1-alkynyl)arenecarboxaldehydes and amines to form the required imines in situ. Notably, all these above-mentioned elegant reports are limited with racemic studies despite of high efficiency of this protocol. Consequently, the development of such an asymmetric variant providing chiral multifunctionalized 1,2-dihydroisoquinoline is highly desirable but challenging due to the remote distance between the metal center and nucleophile (Scheme 1).



iminium ion **A**

Scheme 1. Asymmetric synthesis of 1,2-dihydroisoquinoline using chiral anion strategy.

Recently, chiral anions[14] have been introduced as a useful strategy for inducing asymmetry in metal-catalyzed transformations. The strategy has been demonstrated by Toste, List, and others to be capable of providing products with exceptional enantioselectivity. As shown in Scheme 1, the above discussed reaction process involves the nucleophilic attack to the iminium intermediate **A**. We envisioned that with a counteranion bearing a deep chiral pocket might display efficient enantioselective control for the nucleophilic attack. Our recent studies disclosed that chiral substituted binol phosphate could serve as a suitable counteranion

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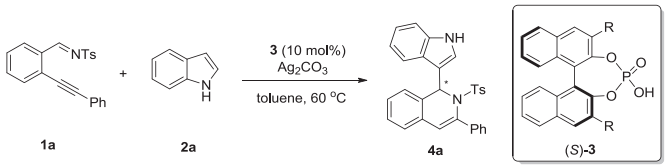
in silver-catalyzed synthesis of 1,2-dihydroisoquinoline employing indole as the nucleophile. Herein, we report our detailed studies.

2. Results and discussion

We began our investigation by testing the Friedel–Crafts type reaction of *ortho*-alkynylaryl aldimines with indole,[15,16] a privileged structural core for biologically active compounds and natural products, with various chiral phosphoric acids and Ag_2CO_3 (entries 1–13, Table 1). As summarized in Table 1, with 10 mol % of chiral phosphoric acids (**3a**–**m**) and 5 mol % of Ag_2CO_3 in toluene at 60 °C, most of the reactions proceeded smoothly to give the desired product **4a** in up to 75% yield and 38% ee except those with **3e** and **3i**. Both **3e** and **3i** contain triphenylsilyl groups that might be too sterically bulky for the reaction. Chiral phosphoric acid **3m** bearing 2,6-(^{i}Pr)$_2$-4-^{t}BuC$_6$H$_2$ group led to the formation of 1,2-dihydroisoquinoline **4a** with best enantioselectivity (38% ee, entry 13, Table 1). Gratifyingly, with the preformed sliver phosphate **3n**, prepared from **3m** and Ag_2CO_3, as the catalyst, the enantiomeric excess of the product was enhanced to 50% (entry 14, Table 1).

Table 1
Screening chiral phosphoric acid catalysts[a]



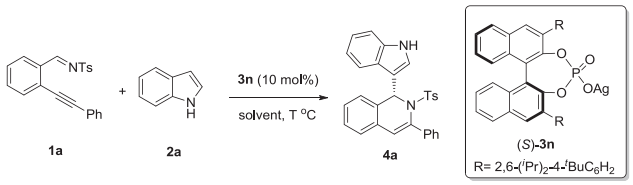
Entry	(*S*)-**3**, R	Time (h)	Yield[b] (%)	ee (%)[c]
1	**3a**, 1-Naphthyl	5	65	19
2	**3b**, 2-Naphthyl	2	71	0
3	**3c**, 4-Biphenyl	2	43	12
4	**3d**, 4-$NO_2C_6H_4$	1	75	0
5	**3e**, $SiPh_3$	24	8	27
6	**3f**, 9-Phenanthryl	2	50	16
7	**3g**, 3,5-$(CF_3)_2$–C_6H_3	1	69	4
8	**3h**, 4-[3,5-$(CF_3)_2$–C_6H_3]-C_6H_4	1	57	4
9	**3i**, $[H]_8$ $SiPh_3$	24	12	22
10	**3j**, $[H]_8$-3,5-$(CF_3)_2$-C_6H_3	1	56	19
11	**3k**, 2,6-(^{i}Pr)$_2$-4-(9-Anthryl)C_6H_2	1	71	22
12	**3l**, 2,4,6-(^{i}Pr)$_3C_6H_2$	2	70	30
13	**3m**, 2,6-(^{i}Pr)$_2$-4-^{t}BuC$_6H_2$	2.5	56	38
14[d]	**3n**, 2,6-(^{i}Pr)$_2$-4-^{t}BuC$_6H_2$	10	80	50

[a] All the reactions were performed using **1a** (0.10 mmol) and **2a** (0.20 mmol) in 1 mL of toluene with 10 mol % of catalyst CPA and 5 mol % of Ag_2CO_3 in dark.
[b] Isolated yield.
[c] Determined by HPLC.
[d] Reaction with **3n** (sliver phosphate derived from **3m** and Ag_2CO_3).

With 10 mol % of **3n** as the catalyst, various solvents were investigated. The results are summarized in Table 2. Various solvents, such as toluene, benzene, *o*-xylene, *p*-xylene, CH_2Cl_2, all led to the formation of the products in good yields and moderate enantioselectivities (50–80% yields and 46–59% ee, entries 1–5, Table 2). However, the reaction in polar solvent, such as CH_3CN only gave the product in 25% yield and 57% ee (entry 6, Table 2). The effect of reaction temperature was also examined, and the reaction at 40 °C was found to give the best result (73% yield, 56% ee, entry 10, Table 2). Either decreasing or increasing the temperature could damage the conversion or enantioselectivity of the reaction (entries 9, 11–12, Table 2). The addition of molecular sieves did not lead to any improved results (entries 13–15, Table 2).

Under the above optimized reaction conditions (10 mol % of (*S*)-**3n**, toluene, 40 °C), various substrates were carried out to test the generality of the current methodology. As summarized in Table 3, substrate **4b** bearing a methyl group at 6 position gave an improved enantioselectivity (63% ee) and comparable yield (67%) (entry 2,

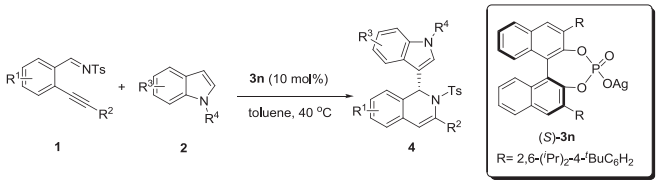
Table 2
Optimization of the reaction condition[a]

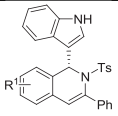
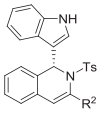
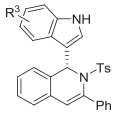
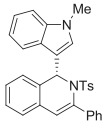


Entry	Solvent	T (°C)	Time (h)	Yield[b] (%)	ee (%)[c]
1	Toluene	60	10	80	50
2	Benzene	60	3	68	57
3	*o*-Xylene	60	4	50	59
4	*p*-Xylene	60	4	52	46
5	DCM	40	12	66	56
6	CH_3CN	60	5	25	57
7	EtOH	40	12	25	18
8	*i*-PrOH	40	12	34	33
9	Toluene	rt	36	26	52
10	Toluene	40	10	73	56
11	Toluene	80	1	73	43
12	Toluene	110	0.5	45	21
13[d]	Toluene	60	3	72	48
14[e]	Toluene	60	3	75	39
15[f]	Toluene	60	3	73	48
16[g]	Toluene	40	10	83	53

[a] All the reactions were performed using **1a** (0.10 mmol) and **2a** (0.20 mmol) in 1 mL of toluene with 10 mol % of catalyst **3n** in dark.
[b] Isolated yield.
[c] Determined by HPLC.
[d] MS (3 Å) was added.
[e] MS (4 Å) was added.
[f] MS (5 Å) was added.
[g] 20 mol % of **3n** was used.

Table 3
Ag(I)-catalyzed enantioselective synthesis of 1,2-dihydroisoquinolines[a]



Entry	Product	R	Yield	ee
1		**4a**, R^1=H	73	56
2		**4b**, R^1=6-Me	67	63
3		**4c**, R^1=6,7-$(MeO)_2$	57	32
4		**4d**, R^1=7-F	65	89
5		**4e**, R^2=Cyclopropyl	95	54
6		**4f**, R^2=*n*-Butyl	80	10
7		**4g**, R^3=7-Me	55	43
8		**4h**, R^3=5-MeO	26	48
9		**4i**, R^3=6-Cl	50	33
10		**4j**	41	59

[a] All the reactions were performed using **1** (0.10 mmol) and **2** (0.20 mmol) in 1 mL of toluene with 10 mol % of catalyst **3n** in dark.

Table 3). By introducing two methoxy groups, substrate **4c** led to decreased yield and enantioselectivity (entry 3, Table 3). Interestingly, substrate **4d** containing an electron-withdrawing group (7-F) gave much enhanced enantioselectivity (89% ee, entry 4, Table 3). In addition to the phenyl substituted alkyne, the alkyl groups, such as cyclopropyl (**4e**) and *n*-butyl (**4f**) could also be well tolerated with decent yields but decreased enantioselectivities (entries 5–6, Table 3). For nucleophile, various substituted indoles bearing either electron-donating or electron-withdrawing groups could be tolerated with moderate yields and ee values (entries 7–9, Table 3). Notably, *N*-methyl indole also gave its desired product **4j** in 41% yield and 59% ee (entry 10, Table 3).

In order to determine the absolute configuration of the product, the crystal of enantiopure **4a** was obtained and a single crystal X-ray analysis determined its configuration as *R* (Fig. 1).

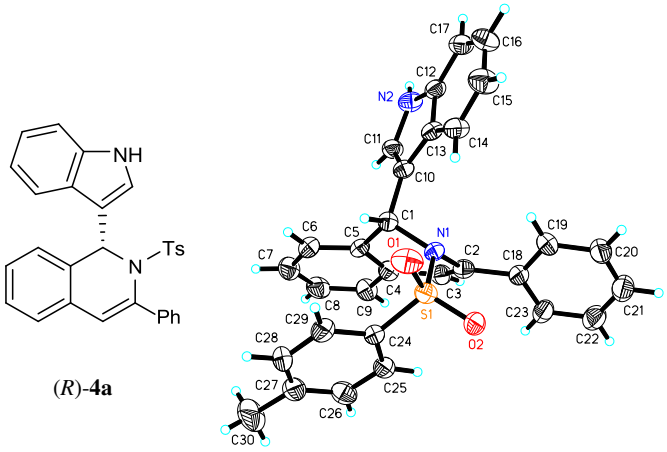


Fig. 1. X-ray structure of enantiopure (*R*)-**4a**. Ellipsoids at 30% probability.

During our studies, we have observed an interesting phenomenon with product **4a**. After the completion of the reaction, a regular silica gel column chromatography purification afforded product **4a** in 80% yield and 50% ee. However, if the reaction mixture was filtered after staying at room temperature (20 °C) overnight and then purified by silica gel column chromatography, the product from filtrate was obtained in 23% yield and 99% ee and that from filter cake was obtained in 65% yield and 33% ee. Interestingly, during the purification of the enantioenriched **4a** by silica gel column chromatography, the first collection is in very high ee but the last collection is almost racemic. This is a rare case that two enantiomers could be isolated by regular silica gel column chromatography purification. Obviously in the solid state, optically pure compounds and their racemates have significantly different crystallographic structures leading to distinctive physical properties, such as solubility.[17,18] Another notable experiment is that the racemic compound could form crystal much more easily than its enantiomeric form,[19] which also supports the above hypothesis. The intermolecular π-π stacking interactions (Fig. 2) were obviously confirmed by crystal X-ray analysis of racemic compound **4a**. As shown in Fig. 2, the distance of centroids of two six-membered rings is about 3.912(2) Å between *S* and *R* enantiomers, and the distance of centroids of five-membered ring and six-membered ring is 3.820(2) Å between *S* (or *R*) and *S* (or *R*) enantiomers. Compared with its optically pure form crystal structure, there were no any intermolecular interactions between two adjacent molecules. All these observations could strongly support that *S* and *R* enantiomers tend to aggregate together. As a result, the racemic form shows higher thermodynamic stability and lower solubility than its optically pure form. This observed different properties

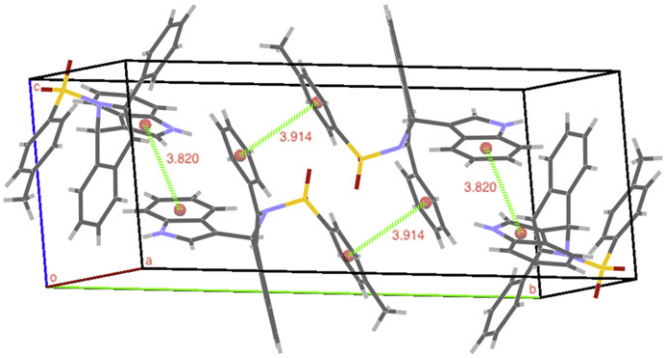


Fig. 2. Packing structure of racemic compound **4a**.

between racemic and enantiopure compounds will certainly add interesting flavors in asymmetric synthesis and might provide new thoughts for the origin of chirality in our nature.

3. Conclusions

In summary, we have developed a silver binol-derived phosphate catalyzed reaction of *ortho*-alkynylaryl aldimines and indoles affording enantioenriched 1,2-dihydroisoquinolines in moderate to good yields and ee. For product **4a**, the racemic form shows better thermodynamic stability and lower solubility than its optically pure form due to its intermolecular π–π stacking interactions between enantiomers, allowing the potential isolation of enantiopure isomer from product with low ee through silica gel column chromatography.

4. Experimental section

4.1. General procedure for the enantioselective synthesis of 1,2-dihydroisoquinolines (4a–j)

To a solution of *ortho*-alkynylarylimine **1** (0.1 mmol) in toluene (1 mL) was added indole **2** (0.2 mmol, 2 equiv) and silver phosphate **3n** (8.9 mg, 0.01 mmol). The reaction was stirred overnight at 40 °C in dark. After the reaction was complete (monitored by TLC), the mixture was purified by silica gel column chromatography (ethyl acetate/petroleum ether=1/10–1/5) to afford 1,2-dihydroisoquinoline **4**.

*4.1.1. (R)-1-(1H-Indol-3-yl)-3-phenyl-2-tosyl-1,2-dihydroisoquinoline (**4a**).* White solid (76% yield, 56% ee), following silica gel column chromatography (ethyl acetate/petroleum ether=1/10, v/v). Analytical data for **4a**: mp=209–210 °C; $[\alpha]_D^{20}$ +39.5 (*c* 0.5 acetone, 99% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.16 (s, 3H), 5.97 (s, 1H), 6.53 (s, 1H), 6.81–6.84 (m, 4H), 6.93–6.96 (m, 1H), 7.02–7.09 (m, 5H), 7.17–7.18 (m, 2H), 7.20–7.27 (m, 1H), 7.29–7.32 (m, 3H), 7.35 (s, 1H), 7.80 (br, 1H), 8.38 (d, *J*=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 56.0, 111.1, 114.2, 120.1, 120.2, 120.3, 122.4, 124.7, 125.1, 126.1, 126.3, 127.0, 127.2, 127.4, 127.7, 128.0, 128.1, 128.3, 130.9, 132.0, 134.1, 136.5, 137.0, 138.8, 143.1; IR (film) 3428, 3035, 2266, 1593, 1489, 1455, 1419, 1269, 1350, 1340, 1294, 1165, 1085, 972, 806, 767, 738, 694, 683, 657, 623, 551, 540, 488 cm^{-1}; HRMS (EI) exact mass calcd for ($C_{30}H_{24}N_2O_2S$) requires *m*/*z* 476.1559, found *m*/*z* 476.1555. The enantiomeric excess was determined by Daicel Chiralpak IC (25 cm), hexanes/IPA=70/30, 0.8 mL/min, λ=254 nm, t_R (major)=12.45 min, t_R (minor)=19.68 min.

*4.1.2. (R)-1-(1H-Indol-3-yl)-6-methyl-3-phenyl-2-tosyl-1,2-dihydroisoquinoline (**4b**).* White solid (67% yield, 63% ee), following silica gel column chromatography (ethyl acetate/petroleum ether=1/10, v/v). Analytical data for **4b**: mp=206–207 °C; $[\alpha]_D^{20}$ +1.8 (*c* 0.5 acetone, 63% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s,

3H), 2.25 (s, 3H), 6.11 (s, 1H), 6.54 (s, 1H), 6.66 (s, 1H), 6.84–6.91 (m, 5H), 7.16 (m, 3H), 7.23–7.37 (m, 7H), 7.80 (br, 1H), 8.40 (d, J=7.5 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.0, 21.3, 55.8, 111.0, 114.4, 120.1, 120.2, 120.5, 122.4, 124.6, 125.5, 126.1, 126.2, 127.0, 127.4, 127.9, 128.0, 128.1, 128.3, 129.2, 130.8, 134.0, 136.4, 136.8, 136.9, 138.8, 143.0; IR (film) 3420, 3373, 3053, 2923, 2853, 1595, 1545, 1492, 1458, 1343, 1325, 1305, 1293, 1166, 1156, 1086, 985, 959, 848, 826, 813, 773, 757, 743, 695, 675, 661, 637, 609, 550, 540, 449, 426 cm^{-1}; HRMS (EI) exact mass calcd for ($C_{31}H_{26}N_2O_2S$) requires m/z 490.1715, found m/z 490.1709. The enantiomeric excess was determined by Daicel Chiralpak IC (25 cm), hexanes/IPA=70/30, 0.8 mL/min, λ=254 nm, t_R (major)=14.25 min, t_R (minor)=21.08 min.

*4.1.3. (R)-1-(1H-Indol-3-yl)-6,7-dimethoxy-3-phenyl-2-tosyl-1,2-dihydroisoquinoline (**4c**).* White solid (57% yield, 32% ee), following silica gel column chromatography (ethyl acetate/petroleum ether=1/5, v/v). Analytical data for **4c**: mp=191–192 °C; $[\alpha]_D^{20}$ +14.8 (c 0.5 acetone, 32% ee). ^{1}H NMR (300 MHz, acetone-d_6) δ 2.24 (s, 3H), 3.75 (s, 3H), 3.82 (s, 3H), 6.27 (d, J=1.5 Hz, 1H), 6.58 (s, 1H), 6.74 (s, 1H), 6.77 (s, 1H), 6.84 (s, 1H), 7.04 (d, J=7.8 Hz, 2H), 7.11–7.13 (m, 3H), 7.17–7.28 (m, 2H), 7.37–7.40 (m, 3H), 7.46 (d, J=8.1 Hz, 2H), 8.36 (d, J=7.8 Hz, 1H), 10.00 (br, 1H); ^{13}C NMR (100 MHz, acetone-d_6) δ 20.8, 55.8, 55.9, 56.1, 109.6, 110.9, 112.0, 114.2, 119.7, 120.0, 121.1, 122.2, 124.5, 125.5, 125.6, 126.9, 127.2, 127.7, 127.9, 128.0, 128.8, 135.1, 135.2, 137.6, 140.1, 143.4, 149.1, 150.2; IR (film) 3370, 3320, 2920, 1598, 1512, 1463, 1454, 1341, 1300, 1253, 1229, 1165, 1126, 1088, 985, 853, 816, 768, 747, 666, 594, 564, 548, 541 cm^{-1}; HRMS (ESI) exact mass calcd for ($C_{32}H_{28}N_2NaO_4S$) requires m/z 559.1662, found m/z 559.1679. The enantiomeric excess was determined by Daicel Chiralpak IC-H (25 cm), hexanes/IPA=70/30, 0.8 mL/min, λ=254 nm, t_R (major)=18.71 min, t_R (minor)=28.61 min.

*4.1.4. (R)-7-Fluoro-1-(1H-indol-3-yl)-3-phenyl-2-tosyl-1,2-dihydroisoquinoline (**4d**).* White solid (65% yield, 89% ee), following silica gel column chromatography (ethyl acetate/petroleum ether=1/10, v/v). Analytical data for **4d**: mp=201–202 °C; $[\alpha]_D^{20}$ +28.2 (c 0.5 acetone, 89% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.24 (s, 3H), 6.11 (s, 1H), 6.56 (s, 1H), 6.74–6.84 (m, 4H), 6.94 (d, J=8.1 Hz, 2H), 7.16–7.18 (m, 3H), 7.25–7.33 (m, 5H), 7.40 (d, J=8.1 Hz, 2H), 7.86 (br, 1H), 8.39 (d, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 55.7 (d, J=1.6 Hz), 111.1, 113.4, 113.5 (d, J=22.1 Hz), 114.2 (d, J=21.4 Hz), 119.0, 119.1, 120.1, 120.4, 122.6, 124.4, 126.0, 126.6 (d, J=8.3 Hz), 127.0, 127.3 (d, J=3.1 Hz), 127.5, 128.0, 128.2, 128.4, 134.2, 134.3, 136.5, 136.7, 136.8, 138.6, 143.4, 162.2 (d, J=246.9 Hz); ^{19}F NMR (282 MHz, $CDCl_3$) δ −113.6 (m); IR (film) 3415, 3373, 3053, 2925, 1597, 1492, 1457, 1447, 1420, 1343, 1167, 1087, 985, 812, 774, 748, 695, 674, 660, 638, 610, 551, 540 cm^{-1}; HRMS (ESI) exact mass calcd for ($C_{30}H_{23}FN_2NaO_2S$) requires m/z 517.1357, found m/z 517.1373. The enantiomeric excess was determined by Daicel Chiralpak IC (25 cm), hexanes/IPA=70/30, 0.8 mL/min, λ=254 nm, t_R (major)=9.73 min, t_R (minor)=13.93 min.

*4.1.5. (R)-3-Cyclopropyl-1-(1H-indol-3-yl)-2-tosyl-1,2-dihydroisoquinoline (**4e**).* White solid (95% yield, 54% ee), following silica gel column chromatography (ethyl acetate/petroleum ether=1/5, v/v). Analytical data for **4e**: mp=183–184 °C; $[\alpha]_D^{20}$ +115.6 (c 0.5 acetone, 54% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ −0.34–0.30 (m, 1H), 0.25–0.27 (m, 2H), 0.59–0.64 (m, 1H), 1.77–1.83 (m, 1H), 2.12 (s, 3H), 5.90 (s, 1H), 6.01 (s, 1H), 6.61–6.64 (m, 2H), 6.79 (d, J=7.8 Hz, 2H), 6.90–6.95 (m, 3H), 7.10–7.12 (m, 2H), 7.17–7.18 (m, 1H), 7.36 (d, J=7.8 Hz, 2H), 7.84 (br, 1H), 8.15–8.17 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 7.2, 8.4, 16.1, 21.3, 56.1, 110.9, 114.5, 116.1, 119.9, 120.4, 122.2, 124.3, 124.4, 126.0, 126.1, 126.9, 127.1, 127.2, 128.3, 130.6, 131.5, 135.0, 136.4, 140.2, 142.9; IR (film) 3420, 3059, 1545, 1457, 1420, 1338, 1300, 1157, 1087, 1007, 869, 813, 751, 709, 673, 658, 624, 547, 427 cm^{-1}; HRMS (EI) exact mass calcd for ($C_{27}H_{24}N_2O_2S$) requires m/z 440.1559, found m/z 440.1560. The enantiomeric excess was determined by Daicel Chiralpak IC (25 cm), hexanes/IPA=90/10, 0.8 mL/min, λ=254 nm, t_R (minor)=40.54 min, t_R (major)=44.18 min.

*4.1.6. (R)-3-Butyl-1-(1H-indol-3-yl)-2-tosyl-1,2-dihydroisoquinoline (**4f**).* White solid (80% yield, 10% ee), following silica gel column chromatography (ethyl acetate/petroleum ether=1/5, v/v). Analytical data for **4f**: mp=176–177 °C; $[\alpha]_D^{20}$ +10.8 (c 0.5 acetone, 10% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 0.24 (t, J=7.5 Hz, 3H), 0.41–0.44 (m, 1H), 0.65–0.70 (m, 1H), 0.79–0.89 (m, 1H), 0.97–1.05 (m, 1H), 2.04–2.14 (m, 1H), 2.20 (s, 3H), 2.79–2.86 (m, 1H), 6.08 (s, 1H), 6.12 (s, 1H), 6.71–6.75 (m, 2H), 6.86 (d, J=7.5 Hz, 2H), 6.97–7.04 (m, 3H), 7.19–7.30 (m, 3H), 7.40 (d, J=7.5 Hz, 2H), 7.86 (br, 1H), 8.23–8.26 (m, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 13.3, 21.3, 21.4, 29.1, 35.8, 56.0, 110.8, 114.5, 119.8, 120.0, 120.4, 122.3, 124.2, 124.6, 126.1, 126.3, 127.0, 127.1, 127.2, 128.3, 130.7, 131.4, 134.7, 136.5, 138.4, 142.9; IR (film) 3397, 2956, 2930, 2854, 1595, 1539, 1492, 1458, 1429, 1346, 1327, 1168, 1155, 1086, 985, 887, 812, 746, 681, 658, 620, 609, 550, 532, 519 cm^{-1}; HRMS (EI) exact mass calcd for ($C_{28}H_{28}N_2O_2S$) requires m/z 456.1872, found m/z 456.1868. The enantiomeric excess was determined by Daicel Chiralpak AD-H (25 cm), hexanes/IPA=80/20, 1.0 mL/min, λ=254 nm, t_R (major)=14.29 min, t_R (minor)=28.78 min.

*4.1.7. (R)-3-Phenyl-1-(7-methyl-1H-indol-3-yl)-2-tosyl-1,2-dihydroisoquinoline (**4g**).* White solid (55% yield, 43% ee), following silica gel column chromatography (ethyl acetate/petroleum ether=1/10, v/v). Analytical data for **4g**: mp=188–189 °C; $[\alpha]_D^{20}$ +28.3 (c 0.5 acetone, 43% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.20 (s, 3H), 2.35 (s, 3H), 6.05 (s, 1H), 6.57 (s, 1H), 6.85–6.86 (m, 4H), 7.00–7.10 (m, 4H), 7.16–7.20 (m, 3H), 7.22–7.24 (m, 1H), 7.35–7.37 (m, 4H), 7.67 (br, 1H), 8.26 (d, J=7.8 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 16.5, 21.3, 56.0, 114.7, 117.9, 120.1, 120.2, 120.5, 123.0, 124.3, 125.0, 125.7, 126.3, 127.1, 127.2, 127.4, 127.6, 127.9, 128.1, 128.2, 130.8, 132.1, 134.1, 136.0, 137.1, 138.7, 143.0; IR (film) 3373, 3053, 2922, 2853, 1704, 1596, 1493, 1449, 1433, 1342, 1165, 1085, 978, 796, 783, 762, 685, 675, 657, 563, 549, 543, 459 cm^{-1}; HRMS (ESI) exact mass calcd for ($C_{31}H_{26}N_2NaO_2S$) requires m/z 513.1607, found m/z 513.1621. The enantiomeric excess was determined by Daicel Chiralpak IC-H (25 cm), hexanes/IPA=70/30, 0.8 mL/min, λ=254 nm, t_R (major)=12.92 min, t_R (minor)=18.99 min.

*4.1.8. (R)-3-Phenyl-1-(5-methoxy-1H-indol-3-yl)-2-tosyl-1,2-dihydroisoquinoline (**4h**).* White solid (26% yield, 48% ee), following silica gel column chromatography (ethyl acetate/petroleum ether=1/5, v/v). Analytical data for **4h**: mp=171–172 °C; $[\alpha]_D^{20}$ −19.6 (c 0.4 acetone, 48% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 4.03 (s, 3H), 6.09 (s, 1H), 6.59 (s, 1H), 6.82 (s, 1H), 6.88–6.93 (m, 4H), 7.01–7.02 (m, 1H), 7.07–7.10 (m, 2H), 7.16–7.26 (m, 4H), 7.35–7.42 (m, 4H), 7.74 (br, 1H), 7.93 (s, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 21.3, 56.0, 56.1, 101.2, 112.0, 113.2, 114.0, 120.1, 125.0, 125.2, 126.3, 126.6, 127.1, 127.2, 127.4, 127.6, 128.0, 128.1, 128.4, 130.9, 131.5, 132.0, 134.6, 137.2, 138.9, 143.1, 154.5; IR (film) 3362, 2924, 2853, 1624, 1586, 1488, 1457, 1442, 1340, 1208, 1162, 1086, 1055, 1002, 916, 801, 788, 765, 734, 680, 659, 625, 649 cm^{-1}; HRMS (MALDI) exact mass calcd for ($C_{31}H_{26}N_2O_3SNa$) requires m/z 529.1556, found m/z 529.1551. The enantiomeric excess was determined by Daicel Chiralpak AS-H (25 cm), hexanes/IPA=70/30, 0.8 mL/min, λ=254 nm, t_R (major)=18.00 min, t_R (minor)=32.41 min.

*4.1.9. (R)-3-Phenyl-1-(6-chloro-1H-indol-3-yl)-2-tosyl-1,2-dihydroisoquinoline (**4i**).* White solid (50% yield, 33% ee), following silica gel column chromatography (ethyl acetate/petroleum

ether=1/10, v/v). Analytical data for **4i**: mp=226–227 °C; $[\alpha]_D^{20}$ +11.7 (*c* 0.5 acetone, 33% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.22 (s, 3H), 6.10 (s, 1H), 6.59 (s, 1H), 6.84 (s, 1H), 6.87–6.90 (m, 3H), 7.04–7.12 (m, 3H), 7.20–7.22 (m, 3H), 7.28–7.39 (m, 6H), 7.79 (br, 1H), 8.35 (d, *J*=9.0 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 55.8, 111.1, 114.7, 120.2, 121.1, 121.2, 124.8, 125.1, 125.3, 126.3, 127.0, 127.4, 127.5, 127.7, 128.0, 128.2, 128.3, 128.4, 130.9, 131.6, 134.1, 136.9, 137.0, 138.6, 143.2; IR (film) 3402, 3059, 2956, 2923, 2853, 1590, 1539, 1493, 1455, 1401, 1336, 1164, 1082, 991, 948, 816, 801, 771, 762, 702, 674, 655, 632, 565, 550 cm^{-1}; HRMS (ESI) exact mass calcd for ($C_{30}H_{23}ClN_2NaO_2S$) requires *m*/*z* 533.1061, found *m*/*z* 533.1076. The enantiomeric excess was determined by Daicel Chiralpak IC (25 cm), hexanes/IPA=70/30, 0.8 mL/min, λ=254 nm, t_R (major)= 7.15 min, t_R (minor)=9.20 min.

*4.1.10. (R)-3-Phenyl-1-(1-methyl-1H-indol-3-yl)-2-tosyl-1,2-dihydroisoquinoline (**4j**).* White solid (41% yield, 59% ee), following silica gel column chromatography (ethyl acetate/petroleum ether=1/10, v/v). Analytical data for **4j**: mp=211–212 °C; $[\alpha]_D^{20}$ +23.5 (*c* 0.5 acetone, 59% ee). ^{1}H NMR (300 MHz, $CDCl_3$) δ 2.21 (s, 3H), 3.49 (s, 3H), 5.93 (s, 1H), 6.60 (s, 1H), 6.86–6.89 (m, 4H), 7.04–7.11 (m, 3H), 7.18–7.20 (m, 3H), 7.23–7.25 (m, 1H), 7.28–7.32 (m, 2H), 7.34–7.39 (m, 4H), 8.42 (d, *J*=6.9 Hz, 1H); ^{13}C NMR (75 MHz, $CDCl_3$) δ 21.3, 32.6, 56.0, 109.2, 112.6, 119.8, 120.2, 120.3, 122.0, 125.0, 126.3, 126.7, 127.2, 127.4, 127.6, 127.9, 128.1, 128.3, 129.1, 130.9, 132.2, 134.3, 137.1, 137.4, 138.9, 143.0; IR (film) 3053, 2920, 1595, 1548, 1495, 1484, 1474, 1456, 1348, 1331, 1304, 1184, 1159, 1085, 974, 950, 870, 813, 798, 780, 761, 747, 730, 694, 683, 653, 639, 627, 616, 552, 540, 519, 419 cm^{-1}; HRMS (EI) exact mass calcd for ($C_{31}H_{26}N_2O_2S$) requires *m*/*z* 490.1715, found *m*/*z* 490.1718. The enantiomeric excess was determined by Daicel Chiralpak IC (25 cm), hexanes/IPA=70/30, 0.8 mL/min^{-1}, λ=254 nm, t_R (major)= 26.10 min, t_R (minor)=40.93 min.

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Supplementary data

Supplementary data related to this article can be found online at doi:10.1016/j.tet.2012.02.058.

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