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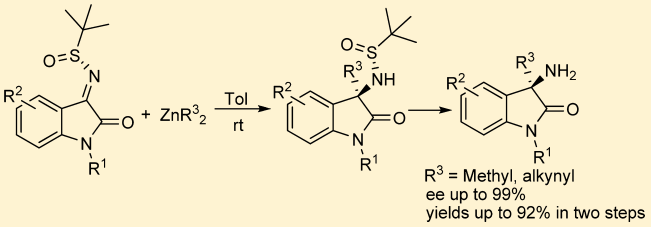
Zinc-Mediated Diastereoselective Synthesis of 3-Amino Oxindoles by Addition of Methyl and Terminal Alkynes to *N-tert*-Butanesulfinyl Ketimines

Wenjin Yan, Dong Wang, Jingchao Feng, Peng Li, and Rui Wang*

Key Lab of Preclinical Study for New Drugs of Gansu Province, School of Basic Medical Sciences, State Key Laboratory of Applied Organic Chemistry and Institute of Biochemistry and Molecular Biology, Lanzhou University, Lanzhou 730000, China

Supporting Information

ABSTRACT: A zinc-mediated addition of methyl and terminal alkynes to chiral *N-tert*-butanesulfinyl ketimines for the preparation of optical quaternary 3-amino oxindoles was reported. In general, the operationally simple reaction affords the desired products in high yields and good to excellent diastereoselectivities. Subsequent convenient cleavage of sulfinyl protecting group under mild conditions was presented without racemization.



INTRODUCTION

Optically active 3,3′-disubstituted oxindoles constitute an important structural motif in many natural products and biologically active compounds.[1] Among them, oxindoles bearing an amino group at the 3-position have been recognized as the core structure in a variety of bioactive molecules, such as the potent gastrin/CCK-B receptor antagonist AG-041R,[2] the vasopressin VIb receptor antagonist SSR-149415[3] and the antimalarial drug candidate NITD609 (Figure 1).[4]

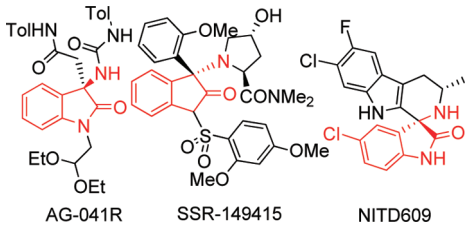


Figure 1. Selected bioactive quaternary aminooxindoles.

Owing to the usefulness of this structural motif, the development of asymmetric synthetic methods for oxindoles bearing a nitrogen atom at the C3 quaternary carbon center is highly valuable. In this field, significant advances have been achieved in the organocatalytic[5] or metal-catalyzed[6,7] asymmetric α-amination of 2-oxindole compounds with azodicarboxylates. Recently, another asymmetric synthetic method was reported by Feng and co-workers through the enantioselective hydroxyamination of *N*-unprotected 3-substituted 2-oxindoles.[8] Meanwhile, several diastereoselective approaches have also been developed for the synthesis of chiral 3-amino oxindoles using chiral auxiliaries.[9] However, in contrast to the large numbers of reports on the enantioselective formation of chiral 3-hydroxyoxindoles,[10] the asymmetric synthesis of 3-amino oxindoles still remains elusive and challenging. Herein, we describe a highly diastereoselective synthetic method of 3-amino oxindoles via the zinc-mediated addition of methyl and terminal alkynes to chiral *N-tert*-butanesulfinyl ketimines. Moreover, we present the subsequent convenient cleavage of sulfinyl protecting group to further demonstrate the synthetic potential of this protocol.

RESULTS AND DISCUSSION

The synthesis of chiral ketimines derived from isatins were easily achieved according to the library methods.[9b,c,11] With dichloromethane as a solvent, the effects of *N*-terminal substituted groups at ketimine 1-position were investigated at room temperature. As shown in Table 1, the results revealed that the substituted groups had a significant effect both on the diastereoselectivity and the reactivity of ketimines. The reactions carried out with H, $-CH_3$, $-CH_2C_6H_5$, and $-CH_2COOC_2H_5$ as the substituted group respectively, and the best result was obtained in 80% yield and 96:4 dr with *N*-benzyl-substituted substrate (entry 3, Table 1), while a lost reactivity was observed for 2,4,6-trimethylbenzyl as the bulk-substituted group (entry 5, Table 1).

With the addition of $ZnMe_2$ to the *N*-benzyl ketimine as the model reaction, the ensuing studies were focused on the effects of solvents, equivalents of $ZnMe_2$, and reaction temperature. In order to obtain more accurate stereoselectivity data, the enantiomeric excess was determined by HPLC analysis on a Chiralcel AD column after the selective deprotection of the sulfinyl group. As presented in Table 2, toluene provided the best result in contrast to other solvents (entries 1−5, Table 2). The effect of mole ratio was probed next. The results indicated

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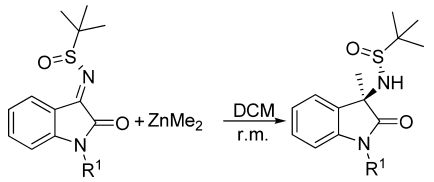
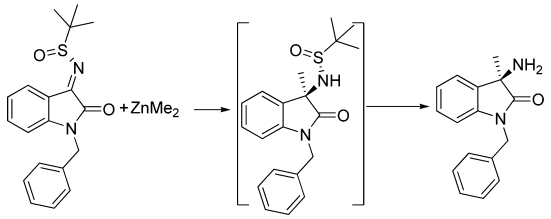
Table 1. Effects of N-Substituted Group at Ketimine 1-Position[a]



entry	R^1	product	yield (%)	dr[b] (%)
1	−H	**2a**	56	55:45
2	$-CH_3$	**2b**	78	95:5
3	$-CH_2C_6H_5$	**2c**	80	96:4
4	$-CH_2COOC_2H_5$	**2d**	62	94:6
5[c]	$-CH_2((2,4,6\text{-}(Me)_3C_6H_2)$			

[a]Reactions were carried out under argon on a 0.2 mmol scale and mole ratio of ketimine/Me_2Zn = 1:3. [b]Determined by ^1H NMR integration of crude reaction products. [c]No adduct was found.

Table 2. Selected Screening Results for the Methylation of *N*-Benzylketimine[a]



entry	solvent	$ZnMe_2$ (equiv)	time (h)	yield[c] (%)	ee[d] (%)
1	CH_2Cl_2	3	10	80	94
2	Et_2O	3	10	64	92
3	THF	3	48	42	0
4	Hex	3	10	67	96
5	Tol	3	10	82	96
6	EtOAc	3	NR	NR	NR
7	Tol	1	10	43	92
8	Tol	1.5	10	57	92
9	Tol	2	10	63	93
10	Tol	2.5	10	75	94
11	Tol	3.5	10	83	96
12[b]	Tol	3	26	80	96

[a]Reactions were carried out under argon on a 0.2 mmol scale at room temperature. [b]At 0 °C. [c]Yields in two steps. [d]The enantiomeric excess was determined by HPLC analysis on a Chiralcel AD column.

that the mole ratio had a significant effect on the yields (entries 6−11, Table 2). When the ratio of $ZnMe_2$/ketimine reached 3:1, a good result was achieved in 83% yield and 96% ee. Further increasing the amount of dimethylzinc was no help for the improvement of the yield and the diastereoselectivity. The following examinations showed that a satisfactory result could be obtained at room temperature.

Having established the optimal reaction protocol, we then evaluated different ketimines derived from various substituted *N*-benzyl isatins to define the scope of the reaction as summarized in Scheme 1. In general, the methylation tolerated a variety of substituted ketimines and provided the corresponding products in good yields and excellent stereoselectivities. These results indicated that the substrate bearing electron-drawing groups at their aromatic rings provided higher reactivity than those bearing electron-donating groups.[12] Additionally, there was no obvious effect of electronic characteristics of substituents on the diastereoselectivity. The relative and absolute configuration of the product was determined by X-ray crystal structure analysis of **3c** bearing a sulfinyl group (see the Supporting Information).

The success of the methylation of versatile ketimines prompted us to explore this highly diastereoselective zinc-mediated nucleophilic addition. On the basis of our previous studies,[13] the addition of terminal alkynes to these synthetic useful ketimines was also investigated. It is important to note that the alkynylation to these *N*-*tert*-butanesulfinyl ketimines also proceeds well after a simple modification on optimized conditions.[14]

As shown in Scheme 2, the addition of phenylacetylene to the (*S*s)- or (R_S)-*N*-*tert*-butanesulfinyl ketimine derived from the *N*-methyl isatin was efficient as well. After removal of the sulfinyl group, both enantiomers were afforded in 92% yield and 93% ee (see **4a** and **4a**′, Scheme 2), respectively. To our delight, the alkynylation of the ketimine derived from the *N*-benzyl isatin gave the product with higher diastereoselectivity in the same reaction conditions. The exploration of different substituted ketamines displayed that these alkynylation were influenced by both steric and electronic effects. In the presence

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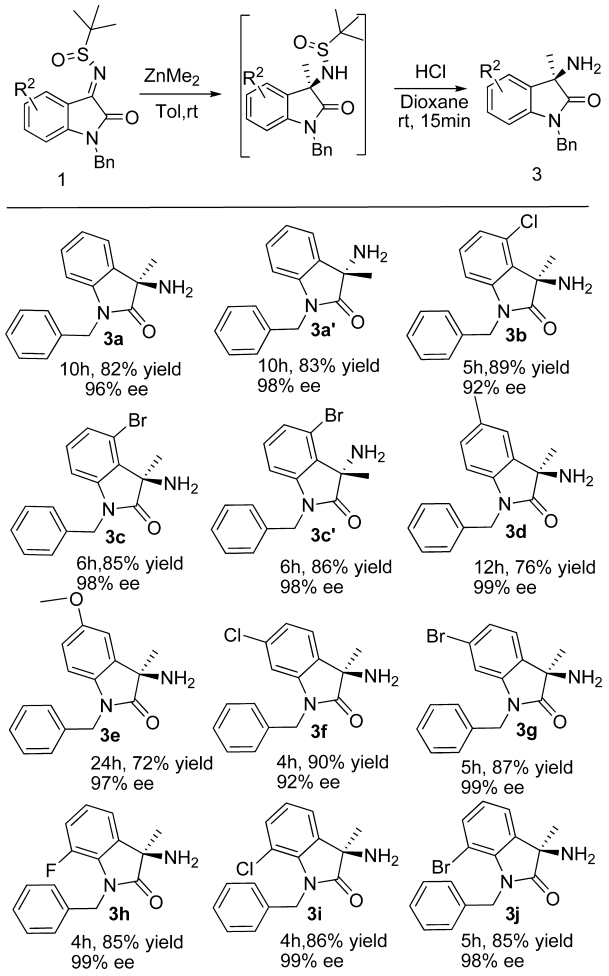
Scheme 1. Methylation of Various Ketimines[a]



[a]The reaction time required for each substrate is given. The reported yields are of the products in two steps. The ee were determined by HPLC analysis.

of methyl and methoxyl at the 5-position, relatively lower yields and diastereoselectivities were observed (**4e** and **4f**, Scheme 2).

Futhermore, it turned out that this asymmetric 1,2 addition of aliphatic alkyne also follow the same reaction pattern, which afforded the addition product in 57% yield and 83% ee (**4g**, Scheme 2).

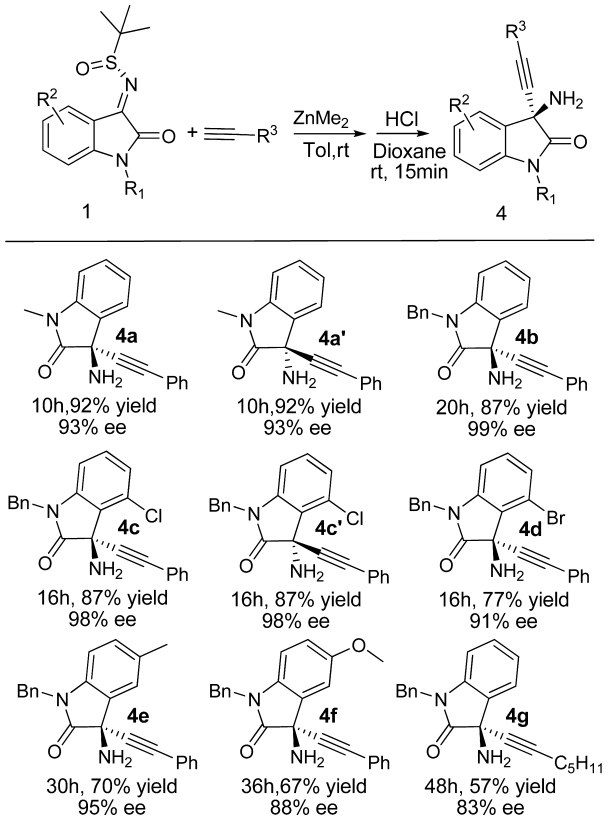
CONCLUSION

In conclusion, we have developed a highly practical method for the preparation of optical 3-amino oxindoles via the zinc-mediated 1,2-addition to chiral *N*-*tert*-butanesulfinyl ketimines. A variety of ketimines bearing electron-withdrawing or electron-donating substituents on the aromatic ring were investigated in both the methylation and alkynylation processes, which gave rise to 1,2 addition products in high yields and excellent diastereoselectivities. The current protocol provides an alternative asymmetric access to optical active 3-amino oxindoles for potential pharmaceutical utility.

EXPERIMENTAL SECTION

General Methods. All reactions were carried out under an argon atmosphere unless otherwise noted, and solvents were dried according to established procedures. Reactions were monitored by thin-layer chromatography (TLC), and column chromatography purifications

Scheme 2. Alkynylation of Various Ketimines[a]



[a]The reaction time required for each substrate is given. The reported yields are of the products in two steps. The ee were determined by HPLC analysis.

were carried out using silica gel. Proton nuclear magnetic resonance (^{1}H NMR) spectra were recorded on 300 MHz spectrometer in $CDCl_3$, and carbon nuclear magnetic resonance (^{13}C NMR) spectra were recorded on a 75 MHz spectrometer in $CDCl_3$ using tetramethylsilane (TMS) as internal standard unless otherwise noted. Data are presented as follows: chemical shift, integration, multiplicity (br = broad, s = singlet, d = doublet, t = triplet, q = quartet, m = multiplet) and coupling constant in hertz (Hz). IR absorptions are given in wavenumbers (cm^{-1}). Mass peaks are identified by the corresponding m/z values. The ee values determination was carried out using chiral high-performance liquid chromatography (HPLC) with Chiracel AD-H column.

General Procedure for the Preparation of *N*-*tert*-Butanesulfinyl Ketimines.[9b,c] To a mixture of isatins (5 mmol) and (*R*)- or (*S*)-*tert*-butanesulfinamide (726 mg, 6 mmol) in CH_2Cl_2 (15.0 mL) was added $Ti(OEt)_4$ (2.4 mL, 11.4 mmol). After that, the solution was refluxed until complete disappearance of the starting materials. The reaction was then quenched with 10 mL of saturated aqueous solution of $NaHCO_3$. The resulting mixture was vigorously stirred for 30 min and filtered through a pad of Celite. The biphasic mixture was transferred to a separatory funnel, and the organic layer was washed with brine. The organic layer was then dried over $MgSO_4$, filtered, and concentrated under reduced pressure. The crude product was purified immediately via flash chromatography on silica gel afford the corresponding ketimine.

General Procedure for the Asymmetric Methylation of *N*-*tert*-Butanesulfinyl Ketimines. In an oven-dried Schlenk flask under argon atmosphere was placed compound (R_S)- or (*Ss*)-*N*-*tert*-butanesulfinyl ketimine (0.2 mmol). After an injection of anhydrous toluene (2 mL), the mixture was cooled to 0 °C and stirred for 10 min. After a solution of dimethylzinc (0.5 mL, 1.2 M in toluene, 3 equiv) was injected, the mixture was allowed to rise slowly to room temperature. The reaction mixture was monitored by TLC. After the

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disappearance of the substrate, the reaction mixture was cooled to 0 °C again. The reaction mixture was quenched with saturated aqueous NH_4Cl (1 mL) and extracted with CH_2Cl_2 (3 × 5 mL). The combined organic layers were dried over anhydrous Na_2SO_4. After filtration and evaporation of the solvent, the crude residue was resolved in 0.3 mL of dioxane again. After addition of 0.2 mL of saturated HCl, the mixture was stirred at room temperature for 15 min, saturated aqueous $NaHCO_3$ was added dropwise until gas was no longer evolved upon addition, and the resulting mixture was extracted with CH_2Cl_2 (3 × 10 mL). The combined organic layers were dried over Na_2SO_4. After filtration and evaporation of the solvent, the crude residue was purified by flash chromatography (silica gel, hexane/ethyl acetate).

(R_S)-2-Methyl-N-(3-methyl-2-oxoindolin-3-yl)propane-2-sulfinamide (**2a**). ((R_S)-*N-tert*-Butanesulfinyl ketimine was employed initially.) White amorphous solid, 30 mg (56% yield). $[\alpha]_D^{rt}$ = −59 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 9.34 (s, 0.45H), 9.13 (s, 0.55H), 7.43 (d, J = 7.2, 0.6H), 7.27−7.20 (m, 1.4H), 7.1−7.01 (m, 1H), 6.89 (d, J = 15.6 Hz, 1H), 4.98 (d, J = 8.4 Hz, 1H), 4.57 (s, 0.45H), 4.25 (s, 0.55H), 1.66 (s, 1.6H), 1.56 (s, 1.4H), 1.23 (s, 4H), 1.19 (s, 5H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 180.0, 179.0, 141.2, 140.4, 131.0, 129.7, 129.5, 129.3, 124.9, 124.8, 122.8, 122.5, 111.1, 110.6, 61.5, 61.0, 56.4, 56.1, 24.94, 24.86, 22.7, 22.4. IR (KBr): ν = 3181, 2979, 2919, 1721, 1621, 1473, 1367, 1329, 1204, 752, 663 cm^{-1}. HRMS: calcd for $C_{13}H_{18}N_2O_2S$ + Na^+ 289.0981, found 289.0984.

(R_S)-N-((R)-1,3-Dimethyl-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**2b**). ((R_S)-*N-tert*-Butanesulfinyl ketimine was employed initially.) Pale yellow amorphous solid, 44 mg (78% yield). $[\alpha]_D^{rt}$ = −55 (c = 1.0, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$): δ 7.52 (d, J = 7.2, 1H), 7.36 (t, J = 7.5, 1H), 7.13 (t, J = 7.5, 1H), 6.88 (d, J = 7.8, 1H), 3.81 (s, 1H), 3.23 (s, 3H), 1.67 (s, 3H), 1.16 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.7, 142.7, 130.4, 129.5, 124.9, 123.1, 108.5, 61.1, 56.3, 26.4, 25.4, 22.3. IR (KBr): ν = 3216, 2959, 2924, 1720, 1613, 1472, 1370, 1058, 752, cm^{-1}. HRMS calcd for $C_{14}H_{20}N_2O_2S$ + Na^+: 303.1138, found 303.1149.

(R_S)-N-((R)-1-Benzyl-3-methyl-2-oxoindolin-3-yl)-2-methylpropane-2-sulfinamide (**2c**). ((R_S)-*N-tert*-Butanesulfinyl ketimine was employed initially.) Pale yellow solid, mp = 77−78 °C, 57 mg (80% yield). $[\alpha]_D^{rt}$ = −17 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.54 (d, J = 6.6, 1H), 7.33 − 7.20 (m, 6H), 7.10 (m, 1H), 6.74 (d, J = 7.8, 1H), 4.96 (d, J = 15.9, 1H), 4.87 (d, J = 15.9, 1H), 3.88 (s, 1H), 1.73 (s, 3H), 1.17 (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.9, 141.9, 135.4, 130.2, 129.5, 128.8, 127.7, 127.1, 125.2, 123.1, 109.6, 61.3, 56.4, 43.7, 25.6, 22.4. IR (KBr): ν = 3243, 2959, 2925, 1718, 1611, 1488, 1469, 1365, 1184, 1058, 752, cm^{-1}. HRMS calcd for $C_{20}H_{24}N_2O_2S$ + H^+ 357.1631, found 357.1636.

Ethyl 2-((R)-3-((R_S)-1,1-Dimethylethylsulfinamido)-3-methyl-2-oxoindolin-1-yl)acetate (**2d**). ((R_S)-*N-tert*-Butanesulfinyl ketimine was employed initially.) Yellow amorphous solid, 44 mg (62% yield). $[\alpha]_D^{rt}$ = −28 (c = 1.0, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$): δ 7.55 (d, J = 7.2, 1H), 7.35 − 7.28 (m, 1H), 7.15 (t, J = 7.2, 1H), 6.75 (d, J = 7.8, 1H), 4.52 (d, J = 17.4, 1H), 4.39 (d, J = 17.7, 1H), 4.21 (q, J = 7.2, 2H), 3.85 (s, 1H), 1.71 (s, 3H), 1.25 (t, J = 7.2, 3H), 1. Seventeen (s, 9H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.8, 167.2, 141.4, 130.0, 129.6, 125.2, 123.5, 123.2, 108.5, 61.9, 61.2, 56.4, 41.4, 25.7, 22.6, 22.3, 14.1. IR (KBr): ν = 3260, 2981, 2953, 1749, 1713, 1610, 1468, 1374, 1207, 1183, 1063, 1015, 760, cm^{-1}. HRMS calcd for $C_{17}H_{24}N_2O_4S$ + Na^+ 375.1349, found 375.1359.

(R)-3-Amino-1-benzyl-3-methylindolin-2-one (**3a**). ((R_S)-*N-tert*-Butanesulfinyl ketimine was employed initially.) White amorphous solid, 41 mg (82% yield). 96% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 90:10, 1.0 mL/min). Retention time: t_{major} = 14.0 and t_{minor} = 16.6 min. $[\alpha]_D^{rt}$ = +48 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (dd, J = 7.3, 0.8 Hz, 1H), 7.35 − 7.25 (m, 5H), 7.19 (td, J = 7.7, 1.3 Hz, 1H), 7.06 (td, J = 7.6, 0.8 Hz, 1H), 6.74 (d, J = 7.7 Hz, 1H), 4.98 (d, J = 15.6 Hz, 1H), 4.82 (d, J = 15.6 Hz, 1H), 1.82 (s, 2H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.2, 141.7, 135.8, 133.2, 128.9, 127.7, 127.2, 123.4, 123.0, 109.3, 57.9, 43.7, 25.7. IR (KBr): ν = 3356, 2957, 2925, 1715, 1611, 1489, 1465, 1377, 1179, 741, 706 cm^{-1}. HRMS: calcd for $C_{16}H_{16}N_2O$ + H^+ 253.1341, found 253.1336.

(S)-3-Amino-1-benzyl-3-methylindolin-2-one (**3a′**). ((S_S)-*N-tert*-butanesulfinyl ketimine was employed initially.) White amorphous solid, 42 mg (83% yield). 98% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 90:10, 1.0 mL/min). Retention time: t_{major} = 16.5 and t_{minor} = 14.2 min. $[\alpha]_D^{rt}$ = −50 (c = 1.0, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$): δ 7.41 (dd, J = 7.3, 0.8 Hz, 1H), 7.35 − 7.26(m, 5H), 7.19 (td, J = 7.7, 1.2 Hz, 1H), 7.10 − 7.02 (m, 1H), 6.74 (d, J = 7.7 Hz, 1H), 4.98 (d, J = 15.9 Hz, 1H), 4.82 (d, J = 15.6 Hz, 1H), 1.82 (s, 2H), 1.52 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$): δ 181.2, 141.7, 135.8, 133.2, 128.9, 127.7, 127.2, 123.4, 123.0, 109.3, 57.9, 43.7, 25.7. IR (KBr): ν = 3358, 2970, 2922, 1713, 1614, 1489, 1467, 1354, 1181, 1001, 753, 699 cm^{-1}. HRMS: calcd for $C_{16}H_{16}N_2O$ + H^+ 253.1341, found 253.1345.

(R)-3-Amino-1-benzyl-4-chloro-3-methylindolin-2-one (**3b**). ((R_S)-*N-tert*-butanesulfinyl ketimine was employed initially.) White amorphous solid, 51 mg (89% yield). 92% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 90:10, 1.0 mL/min). Retention time: t_{major} = 30.0 and t_{minor} = 33.1 min. $[\alpha]_D^{rt}$ = +46 (c = 1.0, $CHCl_3$).^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 − 7.21 (m, 5H), 7.10 (t, J = 8.0 Hz, 1H), 6.97 (dd, J = 8.2, 0.7 Hz, 1H), 6.63 (dd, J = 7.8, 0.6 Hz, 1H), 4.98 (d, J = 15.9 Hz, 1H), 4.81 (d, J = 15.6 Hz, 1H), 1.92 (s, 2H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 143.4, 135.3, 130.9, 129.8, 129.6, 128.9, 127.8, 127.1, 123.9, 108.0, 59.1, 43.8, 23.8. IR (KBr): ν = 3365, 2963, 2925, 2023, 1722, 1607, 1457, 1371, 1343, 1171, 779, 734, 699 cm^{-1}. HRMS: calcd for $C_{16}H_{15}ClN_2O$ + H^+ 287.0946, found 287.0952.

(R)-3-Amino-1-benzyl-4-bromo-3-methylindolin-2-one (**3c**). ((R_S)-*N-tert*-butanesulfinyl ketimine was employed initially.) White amorphous solid, 53 mg (85% yield). 98% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 90:10, 1.0 mL/min). Retention time: t_{major} = 23.6 and t_{minor} = 25.5 min. $[\alpha]_D^{rt}$ = +32 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.36 − 7.21 (m, 5H), 7.15 (dd, J = 8.2, 0.8 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 6.67 (dd, J = 7.7, 0.7 Hz, 1H), 4.99 (d, J = 15.9 Hz, 1H), 4.81 (d, J = 15.6 Hz, 1H), 1.95 (s, 2H), 1.71 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 179.3, 143.6, 135.3, 123.0, 128.9, 127.8, 127.1, 127.0, 118.9, 108.5, 59.8, 43.8, 23.7. IR (KBr): ν = 3363, 2964, 2924, 2023, 1719, 1608, 1489, 1371, 1178, 804, 700 cm^{-1}. HRMS: calcd for $C_{16}H_{15}BrN_2O$ + H^+ 331.0446, found 331.0441.

(S)-3-Amino-1-benzyl-4-bromo-3-methylindolin-2-one (**3c′**). ((S_S)-*N-tert*-Butanesulfinyl ketimine was employed initially.) White amorphous solid, 54 mg (86% yield). 98% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 90:10, 1.0 mL/min). Retention time: t_{major} = 25.5 and t_{minor} = 23.6 min. $[\alpha]_D^{rt}$ = −34 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$) δ 7.37 − 7.21 (m, 5H), 7.15 (dd, J = 8.2, 0.7 Hz, 1H), 7.03 (t, J = 8.0 Hz, 1H), 6.67 (dd, J = 7.7, 0.6 Hz, 1H), 4.99 (d, J = 15.6 Hz, 1H), 4.81 (d, J = 15.6 Hz, 1H), 1.93 (s, 2H), 1.71 (s, 3H).^{13}C NMR (75 MHz, $CDCl_3$) δ 179.3, 143.6, 135.3, 131.3, 130.0, 128.9, 127.8, 127.1, 127.0, 118.9, 108.5, 59.8, 43.8, 23.7. IR (KBr): ν = 3363, 2957, 2923, 2024, 1722, 1610, 1457, 1370, 1173, 798, 698 cm^{-1}. HRMS: calcd for $C_{16}H_{15}BrN_2O$ + H^+ 331.0446, found 331.0444.

(R)-3-Amino-1-benzyl-3,5-dimethylindolin-2-one (**3d**). ((R_S)- *N-tert*-Butanesulfinyl ketimine was employed initially.) White amorphous solid, 40 mg (76% yield). 99% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 90:10, 1.0 mL/min). Retention time: t_{major} = 12.2 and t_{minor} = 15.9 min. $[\alpha]_D^{rt}$ = +50 (c = 1.0, $CHCl_3$). ^{1}H NMR (300 MHz, $CDCl_3$): δ 7.35−7.21 (m, 6H), 6.98 (d, J = 7.9 Hz, 1H), 6.61 (d, J = 7.9 Hz, 1H), 4.96 (d, J = 15.6 Hz, 1H), 4.80 (d, J = 15.6 Hz, 1H), 2.31 (s, 3H), 1.77 (s, 2H), 1.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.2, 139.3, 135.9, 133.3, 132.6, 129.0, 128.8, 127.6, 127.2, 124.2, 109.1, 57.9, 43.7, 25.7, 21.0. IR (KBr): ν = 3284, 2964, 2923, 2022, 1713, 1602, 1496, 1373, 1262, 1178, 1099, 1026, 804, 697 cm^{-1}. HRMS: calcd for $C_{17}H_{18}N_2O$ + H^+ 267.1497, found 267.1494.

(R)-3-Amino-1-benzyl-5-methoxy-3-methylindolin-2-one (**3e**). ((R_S)-*N-tert*-butanesulfinyl ketimine was employed initially.) White amorphous solid, 41 mg (72% yield). 97% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 70:30, 1.0 mL/min). Retention time: t_{major} = 7.6 and t_{minor} = 12.2 min. $[\alpha]_D^{rt}$ =

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+99 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.32−7.26 (m, 5H), 7.04 (d, J = 2.4 Hz, 1H), 6.71 (dd, J = 8.5, 2.5 Hz, 1H), 6.62 (d, J = 8.5 Hz, 1H), 4.95 (d, J = 15.6 Hz, 1H), 4.79 (d, J = 15.9 Hz, 1H), 3.77 (s, 3H), 1.77 (s, 2H), 1.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.0, 156.3, 135.9, 135.0, 134.5, 128.8, 127.6, 127.2, 113.5, 110.3, 109.8, 58.3, 55.8, 43.8, 25.8. IR (KBr): ν = 3284, 2963, 2924, 2021, 1710, 1603, 1495, 1434, 1373, 1263, 1179, 1096, 1032, 803, 697 cm^{-1}. HRMS: calcd for $C_{17}H_{18}N_2O_2$ + H^+ 283.1447, found 283.1439.

(R)-3-Amino-1-benzyl-6-chloro-3-methylindolin-2-one (**3f**). ((R_S)-*N-tert*-Butanesulfinyl ketimine was employed initially.) White amorphous solid, 51 mg (90% yield). 92% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 90:10, 1.0 mL/min). Retention time: t_{major} = 13.0 and t_{minor} = 13.7 min. $[\alpha]_D^{rt}$ = +64 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.36−7.25 (m, 6H), 7.03 (dd, J = 7.9, 1.3 Hz, 1H), 6.73 (s, 1H), 4.95 (d, J = 15.9 Hz, 1H), 4.77 (d, J = 15.6 Hz, 1H),2.03 (s, 2H), 1.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 181.0, 143.0, 135.2, 134.6, 131.5, 129.0, 127.9, 127.2, 124.4, 122.9, 109.9, 57.6, 43.8, 25.6. IR (KBr): ν = 3357, 2967, 2924, 2024, 1720, 1611, 1490, 1436, 1373, 1180, 1072, 815, 698 cm^{-1}. HRMS calcd for $C_{16}H_{15}ClN_2O$ + Na^+ 309.0765, found 309.0762.

(R)-3-Amino-1-benzyl-6-bromo-3-methylindolin-2-one (**3g**). ((R_S)-*N-tert*-butanesulfinyl ketimine was employed initially.) White solid, mp = 106−108 °C, 57 mg (87% yield). 99% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 97:3, 1.0 mL/min). Retention time: t_{major} = 35.2 and t_{minor} = 37.1 min. $[\alpha]_D^{rt}$ = +68 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.38 − 7.25 (m, 6H), 7.21−7.16 (m, 1H), 6.87 (d, J = 1.5 Hz, 1H), 4.95 (d, J = 15.9 Hz, 1H), 4.77 (d, J = 15.6 Hz, 1H), 1.69 (s, 2H), 1.42 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.0, 143.1, 135.3, 132.2, 129.0, 127.9, 127.2, 125.9, 124.8, 122.4, 112.6, 57.6, 43.8, 25.6. IR (KBr): ν = 3353, 2964, 2921, 2022, 1713, 1608, 1488, 1372, 1181, 1077, 805, 699 cm^{-1}. HRMS: calcd for $C_{16}H_{15}BrN_2O$ + H^+ 331.0441, found 331.0443.

(R)-3-Amino-1-benzyl-7-fluoro-3-methylindolin-2-one (**3h**). ((R_S)-*N-tert*-Butanesulfinyl ketimine was employed initially.) White amorphous solid, 46 mg (85% yield). 99% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 90:10, 1.0 mL/min). Retention time: t_{major} = 11.0 and t_{minor} = 13.6 min. $[\alpha]_D^{rt}$ = +30 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.33−7.26 (m, 5H), 7.19 (dd, J = 6.8, 1.5 Hz, 1H), 7.04−6.93 (m, 2H), 5.07 (d, J = 15.3 Hz, 1H), 5.00 (d, J = 5.3 Hz, 1H), 1.74 (s, 2H), 1.49 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 180.9, 137.1, 136.2, 128.6, 127.6, 127.44, 127.42, 123.8, 123.7, 119.3, 119.2, 117.1, 116.8, 58.1, 45.3, 45.2, 25.9. IR (KBr): ν = 3276, 2921, 2851, 1957, 1721, 1596, 1463, 1380, 1070, 700 cm^{-1}. HRMS calcd for $C_{16}H_{15}FN_2O$ + Na^+ 293.1061, found 293.1067.

(R)-3-Amino-1-benzyl-7-chloro-3-methylindolin-2-one (**3i**). ((R_S)-*N-tert*-butanesulfinyl ketimine was employed initially.) White solid, mp = 139−140 °C, 49 mg (86% yield). 99% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 90:10, 1.0 mL/min). Retention time: t_{major} = 12.8 and t_{minor} = 15.6 min. $[\alpha]_D^{rt}$ = +31 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.35−7.16 (m, 7H), 7.04−6.98 (m, 1H), 5.37 (d, J = 16.5 Hz, 1H), 5.31 (d, J = 16.2 Hz, 1H), 1.70 (s, 2H), 1.51 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 181.8, 149.4, 137.9, 137.5, 136.2, 131.4, 128.6, 127.2, 126.4, 124.0, 122.0, 115.6, 57.4, 44.7, 26.1. IR (KBr): ν = 3286, 2920, 2851, 1957, 1593, 1459, 1380, 1071, 1025, 736 cm^{-1}. HRMS calcd for $C_{16}H_{15}ClN_2O$ + H^+: 287.0946, found 287.0953.

(R)-3-Amino-1-benzyl-7-bromo-3-methylindolin-2-one (**3j**). ((R_S)-*N-tert*-Butanesulfinyl ketimine was employed initially.) White solid, mp = 136−138 °C, 54 mg (85% yield). 98% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 90:10, 1.0 mL/min). Retention time: t_{major} = 13.4 and t_{minor} = 15.4 min. $[\alpha]_D^{rt}$ = +32 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.39−7.24 (m, 5H), 7.21−7.18 (m, 2H), 6.95 (dd, J = 8.2, 7.3 Hz, 1H), 5.39 (s, 2H), 1.77 (s, 2H), 1.52 (s, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 182.0, 139.3, 137.4, 136.6, 134.8, 128.6, 127.2, 126.3, 124.4, 122.6, 102.7, 57.3, 44.3, 26.2. IR (KBr): ν = 3360, 2968, 2925, 2023, 1712, 1631, 1494, 1451, 1349, 1171, 1077, 803, 698 cm^{-1}. HRMS calcd for $C_{16}H_{15}BrN_2O$ + Na^+: 353.0260, found 353.0269.

General Procedure for the Asymmetric Alkynylation of *N-tert*-Butanesulfinyl Ketimines. The alkynylation procedure was similar to the methylation procedure except for the simple replacement of dimethylzinc by preprepared alkynylzinc.[13]

(R)-3-Amino-1-methyl-3-(phenylethynyl)indolin-2-one (**4a**). ((R_S)-*N-tert*-Butanesulfinyl ketimine was employed initially.) Colorless oil, 48 mg (92% yield). 93% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 90:10, 1.0 mL/min). Retention time: t_{major} = 25.3 and t_{minor} = 23.3 min. $[\alpha]_D^{rt}$ = −7 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.56 (dd, J = 7.4, 0.8 Hz, 1H), 7.45 − 7.40 (m, 2H), 7.37 (td, J = 7.8, 1.2 Hz, 1H), 7.31 − 7.22 (m, 3H), 7.15 (td, J = 7.6, 0.9 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 3.26 (s, 3H), 2.20 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.3, 142.7, 132.0, 130.7, 129.8, 128.6, 128.2, 124.0, 123.6, 122.1, 108.8, 87.2, 83.8, 55.6, 26.7. IR (KBr): ν = 3358, 2928, 2224, 1723, 1611, 1492, 1369, 1258, 1109, 1078, 1019, 871, 755, 693 cm^{-1}. HRMS: calcd for $C_{17}H_{14}N_2O$ + Na^+ 285.0998, found 285.1005.

(S)-3-Amino-1-methyl-3-(phenylethynyl)indolin-2-one (**4a′**). ((S_S)-*N-tert*-Butanesulfinyl ketimine was employed initially.) Colorless oil, 48 mg (92% yield). 93% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 90:10, 1.0 mL/min). Retention time: t_{major} = 23.6 and t_{minor} = 25.7 min. $[\alpha]_D^{rt}$ = +6 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.56 (dd, J = 7.4, 0.8 Hz, 1H), 7.45−7.40 (m, 2H), 7.37 (td, J = 7.8, 1.3 Hz, 1H), 7.31−7.22 (m, 3H), 7.15 (td, J = 7.6, 0.9 Hz, 1H), 6.88 (d, J = 7.8 Hz, 1H), 3.26 (s, 3H), 2.09 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.3, 142.7, 132.0, 130.7, 129.8, 128.6, 128.2, 124.0, 123.6, 122.1, 108.8, 87.2, 83.8, 55.6, 26.7. IR (KBr): ν = 3279, 2962, 2222, 2020, 1722, 1612, 1492, 1370, 1259, 1078, 1018, 754, 691 cm^{-1}. HRMS calcd for $C_{17}H_{14}N_2O$ + Na^+ 285.0998, found 285.1008.

(R)-3-Amino-1-benzyl-3-(phenylethynyl)indolin-2-one (**4b**). ((R_S)-*N-tert*-Butanesulfinyl ketimine was employed initially.) Colorless oil, 59 mg (87% yield). 99% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/20propanol 70:30, 1.0 mL/min). Retention time: t_{major} =12.0 and t_{minor} = 15.8 min. $[\alpha]_D^{rt}$ = −5 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.57 (dd, J = 7.4, 0.9 Hz, 1H), 7.44 (dt, J = 6.4, 2.7 Hz, 2H), 7.36−7.19 (m, 9H), 7.11 (td, J = 7.6, 1.0 Hz, 1H), 6.74 (d, J = 7.8 Hz, 1H), 4.97 (d, J = 15.6 Hz, 1H), 4.41 (d, J = 15.9 Hz, 1H), 2.30 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 175.5, 141.8, 135.3, 132.0, 130.7, 129.7, 128.9, 128.7, 128.2, 127.8, 127.2, 124.1, 123.6, 122.1, 109.8, 87.2, 83.9, 55.7, 44.1. IR (KBr): ν = 3299, 2923, 2230, 1729, 1610, 1490, 1354, 1176, 1075, 754, 695 cm^{-1}. HRMS: calcd for $C_{23}H_{18}N_2O$ + Na^+ 361.1311, found 361.1315.

(R)-3-Amino-1-benzyl-4-chloro-3-(phenylethynyl)indolin-2-one (**4c**). ((R_S)-*N-tert*-butanesulfinyl ketimine was employed initially.) Colorless oil, 65 mg (87% yield). 98% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 75:25, 1.0 mL/min). Retention time: t_{major} = 19.9 and t_{minor} = 14.5 min. $[\alpha]_D^{rt}$ = −24 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.52−7.41 (m, 2H), 7.32−7.26 (m, 8H), 7.15 (t, J = 8.0 Hz, 1H), 7.05 (d, J = 8.3 Hz, 1H), 6.63 (d, J = 7.8 Hz, 1H), 4.94 (s, 2H), 2.61 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 143.4, 134.8, 132.1, 131.0, 130.5, 129.0, 128.7, 128.2, 127.9, 127.4, 127.1, 124.1, 122.1, 108.4, 85.8, 84.2, 55.7, 44.3. IR (KBr): ν = 3369, 2923, 2227, 1730, 1605, 1457, 1341, 1163, 758, 693 cm^{-1}. HRMS calcd for $C_{23}H_{17}ClN_2O$ + Na^+ 395.0922, found 395.0927.

(S)-3-Amino-1-benzyl-4-chloro-3-(phenylethynyl)indolin-2-one (**4c′**). ((S_S)-*N-tert*-Butanesulfinyl ketimine was employed initially.) Colorless oil, 65 mg (87% yield). 98% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 75:25, 1.0 mL/min). Retention time: t_{major} = 14.7 and t_{minor} = 20.3 min. $[\alpha]_D^{rt}$ = +23 (c = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.48 − 7.45 (m, 2H), 7.36 − 7.26 (m, 8H), 7.15 (t, J = 8.0 Hz, 1H), 7.07 − 7.00 (m, 1H), 6.62 (d, J = 7.8 Hz, 1H), 4.97 (d, J = 15.9 Hz, 1H), 4.91 (d, J = 15.9 Hz, 1H), 2.47 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 173.6, 143.4, 134.8, 132.1, 131.0, 130.5, 129.0, 128.7, 128.2, 127.9, 127.4, 127.1, 124.1, 122.1, 108.4, 85.8, 84.2, 55.7, 44.3. IR (KBr): ν = 3368, 2922, 2226, 1730, 1603, 1455, 1340, 1163, 755, 692 cm^{-1}. HRMS: calcd for $C_{23}H_{17}ClN_2O$ + H^+ 373.1102, found 373.1106.

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*(R)-3-Amino-1-benzyl-4-bromo-3-(phenylethynyl)indolin-2-one (**4d**).* ((*R*$_S$)-*N*-*tert*-Butanesulfinyl ketimine was employed initially.) Colorless oil, 64 mg (77% yield). 91% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 80:20, 1.0 mL/min). Retention time: t_{major} = 22.4 and t_{minor} = 16.3 min. $[\alpha]_D^{rt}$ = −93 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$) δ 7.50−7.48 (m, 2H), 7.47−7.26 (m, 8H), 7.22−7.19 (m, 1H), 7.11−7.05 (m, 1H), 6.69−6.66 (m, 1H), 4.94 (s, 2H), 2.63 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$) δ 173.6, 156.2, 143.5, 134.8, 132.1, 130.7, 129.0, 128.7, 128.2, 127.9, 127.1, 122.2, 119.2, 108.9, 85.8, 84.4, 56.6, 44.2. IR (KBr): ν = 2925, 2023, 1728, 1604, 1454, 1342, 1166, 862, 758, 692 cm^{-1}. HRMS calcd for $C_{23}H_{17}BrN_2O + Na^+$: 439.0422, found 439.0419.

*(R)-3-Amino-1-benzyl-5-methyl-3-(phenylethynyl)indolin-2-one (**4e**).* ((*R*$_S$)-*N*-*tert*-Butanesulfinyl ketimine was employed initially.) White solid, mp = 160−162 °C, 49 mg (70% yield). 95% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 60:40, 1.0 mL/min). Retention time: t_{major} = 7.6 and t_{minor} = 11.4 min. $[\alpha]_D^{rt}$ = −82 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.47−7.43 (m, 2H), 7.36 (s, 1H), 7.33−7.26 (m, 8H), 7.02 (dd, *J* = 8.0, 0.8 Hz, 1H), 6.62 (d, *J* = 8.0 Hz, 1H), 4.96 (d, *J* = 15.9 Hz, 1H), 4.89 (d, *J* = 15.6 Hz, 1H), 2.33 (s, 3H), 2.28 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.5, 139.3, 135.4, 133.3, 132.0, 130.7, 129.9, 128.9, 128.6, 128.2, 127.7, 127.2, 124.8, 122.2, 109.6, 87.3, 83.8, 55.8, 44.1, 21.1. IR (KBr): ν = 3380, 2921, 2228, 1714, 1602, 1496, 1366, 1191, 761, 694 cm^{-1}. HRMS calcd for $C_{24}H_{20}N_2O + Na^+$: 375.1468, found 375.1471.

*(R)-3-Amino-1-benzyl-5-methoxy-3-(phenylethynyl)indolin-2-one (**4f**).* ((*R*$_S$)-*N*-*tert*-Butanesulfinyl ketimine was employed initially.) White solid, mp = 46−47 °C, 49 mg (67% yield). 88% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 60:40, 1.0 mL/min). Retention time: t_{major} = 10.2 and t_{minor} = 18.7 min. $[\alpha]_D^{rt}$ = −62 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.47−7.43 (m, 2H), 7.33−7.26 (m, 8H), 7.19 (d, *J* = 2.5 Hz, 1H), 6.75 (dd, *J* = 8.6, 2.6 Hz, 1H), 6.63 (d, *J* = 8.6 Hz, 1H), 4.95 (d, *J* = 15.9 Hz, 1H), 4.89 (d, *J* = 15.9 Hz, 1H), 3.79 (s, 3H), 2.31 (s, 2H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 175.4, 156.6, 135.4, 135.0, 132.0, 131.8, 128.9, 128.7, 128.2, 127.8, 127.2, 122.1, 114.6, 110.9, 110.4, 87.1, 84.0, 55.9, 44.2, 29.7. IR (KBr): ν = 3283, 2920, 2024, 1717, 1603, 1494, 1347, 1272, 1178, 760, 693 cm^{-1}. HRMS: calcd for $C_{24}H_{20}N_2O_2 + Na^+$ 391.1417, found 391.1420.

*(R)-3-Amino-1-benzyl-3-(hept-1-ynyl)indolin-2-one (**4g**).* ((*R*$_S$)-*N*-*tert*-Butanesulfinyl ketimine was employed initially.) Colorless oil, 38 mg (57% yield). 83% ee determined by HPLC analysis (Daicel Chiralcel AD column, hexane/2-propanol 70:30, 1.0 mL/min). Retention time: t_{major} = 6.0 and t_{minor} = 6.8 min. $[\alpha]_D^{rt}$ = −17 (*c* = 1.0, $CHCl_3$). ^1H NMR (300 MHz, $CDCl_3$): δ 7.49 (d, *J* = 7.2 Hz, 1H), 7.32 − 7.23 (m, 5H), 7.20−7.17 (m, 1H), 7.08 (t, *J* = 7.4 Hz, 1H), 6.71 (d, *J* = 7.7 Hz, 1H), 4.96 (d, *J* = 15.9 Hz, 1H), 4.86(d, *J* = 15.6 Hz, 1H), 2.20 (t, *J* = 7.2 Hz, 2H), 2.09 (s, 2H), 1.55 − 1.23 (m, 2H), 1.29 (m, 4H), 0.87 (t, *J* = 7.0 Hz, 3H). ^{13}C NMR (75 MHz, $CDCl_3$): δ 176.0, 141.7, 135.4, 131.1, 129.5, 128.8, 127.7, 127.2, 123.9, 123.4, 109.7, 85.3, 78.0, 55.3, 44.0, 31.0, 28.1, 22.1, 18.8, 14.0. IR (KBr): ν = 3254, 2921, 2852, 1956, 1723, 1608, 1463, 1360, 1176, 1072, 752, 697 cm^{-1}. HRMS: calcd for $C_{22}H_{24}N_2O + Na^+$ 355.1786, found 355.1785.

■ ASSOCIATED CONTENT

Ⓢ Supporting Information

Crystallographic data for compound of the precursor of **2c** (CIF) and copies of ^1H ^{13}C NMR spectra for all new compounds. This material is available free of charge via the Internet at http://pubs.acs.org.

■ AUTHOR INFORMATION

Corresponding Author

*E-mail: wangrui@lzu.edu.cn.

Notes

The authors declare no competing financial interest.

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