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Diastereoselective Synthesis of Chiral 2,3-Disubstituted Indolines via Formal [3+2]-Cycloaddition of Arynes with γ-Amino-α,β-unsaturated Esters

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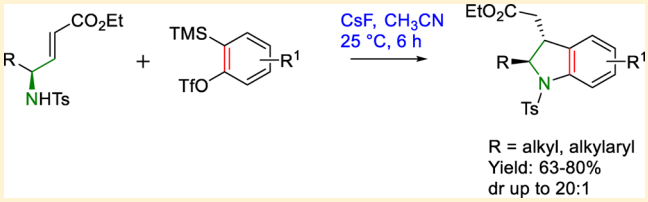
Supporting Information

ABSTRACT: A one step formal [3+2]-annulation protocol for the synthesis of 2,3-disubstituted indolines is described. The *in situ* generated aryne acts as a two-atom component, and γ-amino-α,β-unsaturated esters acting as a three-atom component to construct indoline units in a highly regio- and diastereoselective manner with yields ranging from 63 to 80%.



Chiral indoline framework is found as substructures in many naturally occurring alkaloids[1] and biologically active molecules.[2] They exhibit widespread applications not only as chiral auxiliary and building blocks in total synthesis of bioactive natural products,[3] but also as a common motif in the design of new biologically significant compounds.[4] For instance, enantioenriched 2,3-substituted indolines, such as vindoline (**1**),[5] (−)-strychnine (**2**),[6] (−)-physostigmine (**3**),[7] and antipsychotic drug WAY-163909 (**4**),[8] are considered as the privileged structures due to their diverse pharmacological activities (Figure 1).

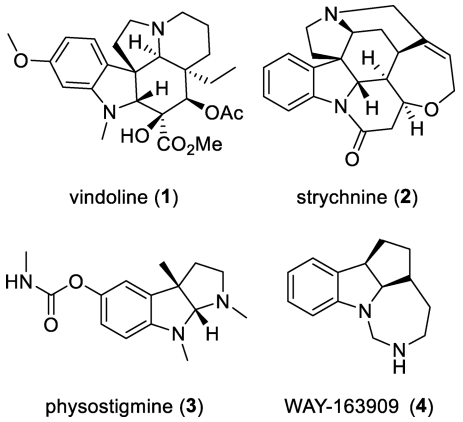


Figure 1. Bioactive chiral 2,3-disubstituted indolines (**1**−**4**).

Consequently, the development of an efficient diastereoselective method for the construction of the desired stereoisomers of chiral indolines is attracting considerable attention. Literature survey on this revealed that the indoline-containing architectures can be rapidly accessed through catalytic hydrogenation,[9] nonenzymatic kinetic resolution of indolines,[10] and a broad range of convergent methodologies, such as free radical promoted aryl aminations,[11] intramolecular shifting of sulfonyl groups,[12] diastereoselective electrophilic cyclization processes,[13] or palladium catalyzed coupling reactions.[14] Additional methods include diastereoselective protonation of chiral lactam enolates,[15] alkyne iminium ion cyclization,[16] *N*-alkyation/Michael addition[17] reductive carboborylation on indoles,[18] aryne insertion reaction of amino ketone,[19] and Cu−H catalyzed reductive cyclization of *O*-imino styrenes.[20] However, multistep processes, use of complex starting materials, expensive reagents, and catalysts limit their synthetic applications. To the best of our knowledge, one-step diastereoselective protocol for the synthesis of chiral indolines with a derivatizable functional group has not been reported in the literature.

Kobayashi's discovery of generating highly reactive aryne intermediates using very mild fluoride-induced 1,2-elimination reaction of *o*-(trimethylsilyl)aryl triflates,[21] has seen plenty of new synthetic applications in the past few years. The typical donar-acceptor property of aryne intermediates provides for an important synthetic tool for the construction of novel cyclic and heterocyclic compounds.[22−24] In recent years, our group is engaged in development of novel methodologies for the construction of pharmaceutically important chiral heterocyclic compounds using organocatalysis as well as metal catalysis.[25]

In this regard, we wish to report a novel method for the synthesis of chiral indolines via formal [3+2]-cycloaddition of arynes with chiral γ-amino-α,β-unsaturated esters, which are readily accessible from α-amino acids[26] (Table 1). As a model substrate, when valine derived γ-aminoester **4a** was treated with benzyne precursor **5a**, using TBAF as the fluoride source and THF as solvent at 25 °C, 2,3-disubstituted indoline **6a** was isolated in 32% yield (Table 1, entry 1). Further, improvement in the yield was realized when CsF was used under similar

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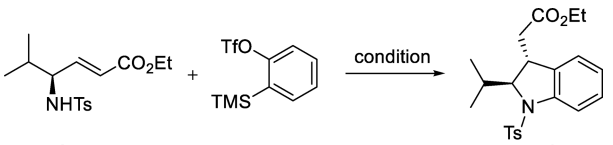
Table 1. Optimization of Reaction Conditions for [3+2]-Cycloaddition of Arynes with γ- Tosylamido 4a[a]



4a **5a** **6a**

no.	F^- source	solvent	additives	T (°C)	time (h)	yield[b] (%)	dr[c]
1	TBAF	THF		25	12	32	
2	CsF	THF		25	12	40	>20:1
3	CsF	MeCN		25	06	71	>20:1
4	CsF	MeCN		25	12	72	>20:1
5	CsF	dioxane		25	06	51	>20:1
6	CsF	MeCN		50	06	73	>20:1
7	CsF	MeCN	$NaHCO_3$	25	06	72	>20:1
8[d]	CsF	MeCN		25	12	60	>20:1
9	CsF	EtOAc		25	12	12	
10	CsF	Et_2O		25	12	trace	
11	CsF	acetone		25	12	NR	
12	CsF	toluene		25	12	22	
13	CsF	DCE		25	12	trace	
14	CsF	MeOH		25	12	0	
15	CsF	acetone		25	12	0	

[a]Reaction condition: ester **4a** (0.1 mmol), aryne precursor **5a** (0.1 mmol), F^- source (3 equiv), solvent (2 mL), temperature, time. [b]Isolated yield of product after column chromatographic purification. [c]Diastereomeric ratio was determined by ^1H NMR analysis. [d]2 equiv CsF was used.

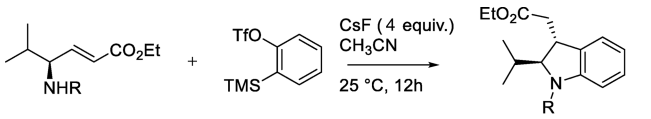
reaction condition (40%, entry 2). Switching over to MeCN as solvent provided a significant increase in yield of the product (71%, entry 3) with excellent diastereoselectivity (>20:1) in shorter reaction time. However, study of various reaction parameters, such as variation in stoichiometry between the two coupling partners, fluoride source, solvents, additives, reaction time, or temperature, all failed to offer any further improvement in yield (Table 1; entry 4−15).

With optimized reaction conditions in hand, the scope of the reaction was subsequently examined, and the results are summarized in Table 2. A range of differently substituted γ-amino-α,β-unsaturated esters underwent the tandem reaction with various aryne precursors smoothly to afford the corresponding chiral indolines with excellent diastereoselectivity. The electronic properties and varied positions of the substituted groups on the aromatic ring had no apparent effects on the reaction yields and selectivities (**6a−n**). Complete regioselectivity was indeed observed in case of unsymmetrical aryne products (Table 2, **6e−l**) which were attributed to the stability of the corresponding carbanion intermediate **7**.[25]

The relative stereochemistry of substituted indoline derivatives **6a−n** is proven unambiguously from COSY, NOESY studies. To trap the intermediate **7** in order to confirm the regioselectivity, an experiment was carried out under wet reaction condition which gave the single regioisomer of *N*-arylated product **7** (Scheme 1); its structure was confirmed from ^1H and ^{13}C NMR spectral studies.

Amino substrates having other protecting groups on nitrogen, such as Boc **8a** and Ac **8b** did not show any reactivity with aryne under the optimized reaction condition. However, using free NH_2 group **8c** with 2 equiv of **5a** provided the corresponding N-aryl indoline **9c** (Scheme 2). We were unable to prepare other donor−acceptor γ-amino-α,β-unsaturated nitrile and nitro derivatives because starting aldehydes are unstable under strong basic conditions.

Scheme 2. Reaction of Arynes with −NHBoc, −NHAc, and $-NH_2$



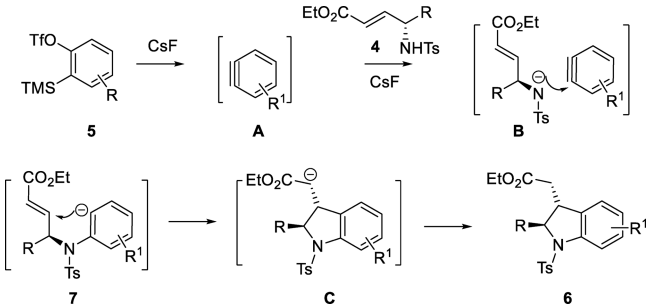
8a, R = Boc
8b, R = Ac
8c, R = H

5a

9a, R = Boc, Yield = 0%
9b, R = Ac, Yield = 0%
9c, R = Ph, Yield = 80%

On the basis of literature precedence and observed regio- and stereoselectivity, we have shown a probable reaction mechanism (Scheme 3). Initially, nucleophilic attack of tosylamido

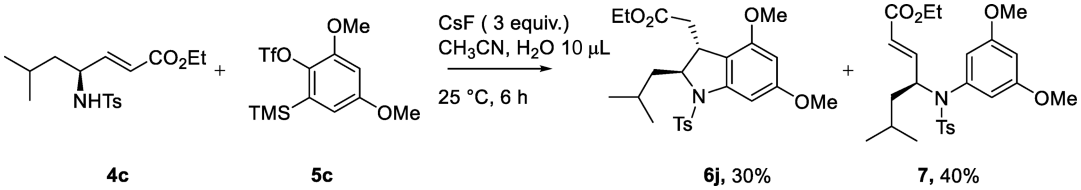
Scheme 3. Plausible Reaction Mechanism



anion **B** on aryne **A** takes place, pushing electrons onto an adjacent aromatic carbon. Then, the newly formed Zwitterion intermediate **7** undergoes intramolecular Michael addition with conjugated ester to form intermediate **C**, which on protonation releases the final product **6**.

In conclusion, we have demonstrated, for the first time, a diastereoselective formal [3+2]-cycloaddition of *in situ* generated arynes **A** with γ-amino-α,β-unsaturated esters **4** and **8c** to obtain chiral 2,3-disubstituted indolines **6a−n** and **9c** with good yields. This protocol will find wide synthetic applications in natural product synthesis and SAR (structure−activity

Scheme 1. Control Experiment



4c **5c** **6j**, 30% **7**, 40%

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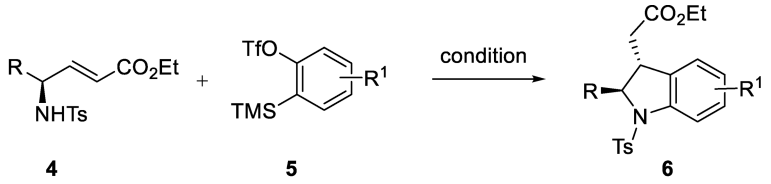
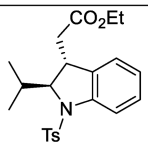
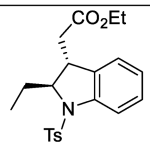
Table 2. Substrate Scope for [3+2]-Cycloaddition[a]



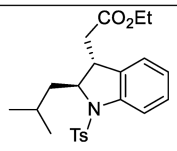
4 5 6



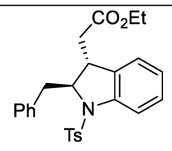
6a, 71%



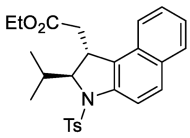
6b, 70%



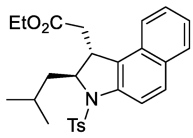
6c, 73%



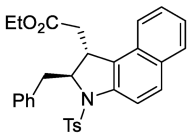
6d, 69%



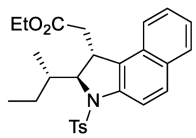
6e, 75%



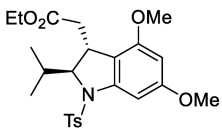
6f, 64%



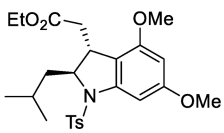
6g, 63%



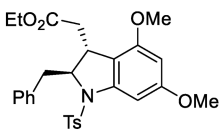
6h, 66%



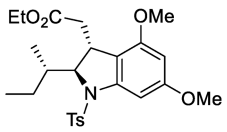
6i, 71%



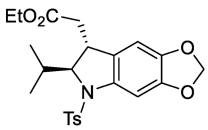
6j, 67%



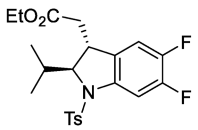
6k, 72%



6l, 68%



6m, 80%



6n, 65%

[a]Reaction conditions: γ-aminoester **4** (0.1 mmol), benzyne precursor **5** (0.1 mmol), CsF (0.3 mmol), dry CH_3CN (2 mL), 25 °C, 6 h.

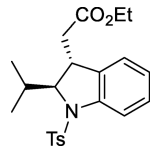
relationship) studies. Easily accessible starting materials, milder reaction conditions, good yields, and excellent diastereoselectivity are the salient features of the methodology.

EXPERIMENTAL SECTION

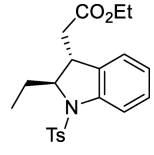
General Information. Solvents were purified and dried by standard procedures before use; petroleum ether in the boiling range of 60−80 °C was used. Melting points are uncorrected. Optical rotations were measured using sodium D line on a polarimeter. ^{1}H NMR and ^{13}C NMR spectra were recorded on 400 and 500 MHz NMR spectrometers. HRMS data for new compounds were recorded using an Orbitrap mass analyzer. Column chromatography was carried out by using silica gel with the selected particle size of 100−200 mesh or 230−400 mesh. All the amino-acids were purchased from Sigma-Aldrich. Aryne precursor[21,22] **5** and γ-amino-α,β-unsaturated esters[26] **4** and **8** were prepared following reported methods.

General Experimental Procedure. *Preparation of Chiral Indolines (**6a−n**).* To a cooled solution of γ-aminoester **4** (0.1 mmol) and benzyne precursor **5** (0.1 mmol), in dry CH_3CN (2 mL) at 0 °C was added CsF (45.6 mg, 0.3 mmol) and the mixture was stirred at 25 °C for 6 h. Removal of solvent under reduced pressure followed by flash chromatographic purification using petroleum ether and ethyl acetate as eluents (8:2) gave indolines **6a−n**.

*Ethyl 2-((2S, 3R)-2-Isopropyl-1-tosylindolin-3-yl)acetate (**6a**).* Yield: 28 mg, 71%; gum; $[\alpha]_D^{27}$ −98.6 (c 0.6, $CHCl_3$); IR (NaCl, cm^{-1}): υ_{max} 1160, 1208, 1350, 1519, 1740; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.82 (d, J = 6.9 Hz, 3H); 0.92 (d, J = 6.9 Hz, 3H), 1.15 (dd, J = 9.9, 15.3 Hz, 1H), 1.27 (d, J = 7.2 Hz, 3H), 1.72 (dd, J = 5.7, 15.3 Hz, 1H), 2.08−2.13 (m, 1H), 2.36 (s, 3H), 3.18 (dd, J = 6.1, 9.2 Hz, 1H), 3.78 (dd, J = 1.1, 4.6 Hz, 1H), 4.09 (qq, J = 7.2, 10.8 Hz, 2H), 6.99−7.03 (m, 2H), 7.17 (d, J = 8.0 Hz, 2H), 7.23−7.25 (m, 1H), 7.56 (d, J = 8.39 Hz, 2H), 7.70 (d, J = 8.0 Hz, 1H), ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.3, 17.0, 18.1, 21.5, 33.8, 39.6, 41.3, 60.5, 72.3, 117.2, 124.3, 124.7, 127.3, 128.5, 129.5, 135.2, 135.4, 141.8, 143.8, 170.8; HRMS (ESI): calcd for $C_{22}H_{27}NO_4S$ $[M+Na]^+$ 424.1553; found: 424.1543.



*Ethyl 2-((2S, 3R)-2-Ethyl-1-tosylindolin-3-yl)acetate (**6b**).* Yield: 27 mg, 70%; gum; $[\alpha]_D^{27}$ −64.1 (c 0.5, $CHCl_3$); IR (NaCl, cm^{-1}): υ_{max}



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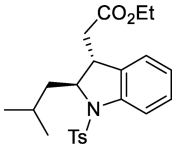
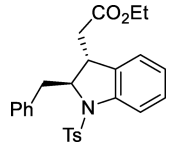
1161, 1201, 1351, 1519, 1742; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.94 (t, J = 7.3 Hz, 3H), 1.17 (dd, J = 10.3, 16.1 Hz, 1H), 1.26 (t, J = 7.0 Hz, 3H), 1.71−1.78 (m, 2H), 1.86 (dd, J = 5.1, 15.8 Hz, 1H), 2.35 (s, 3H), 3.12 (dd, J = 4.5, 9.1 Hz, 1H), 3.88 (dt, J = 1.2, 6.7 Hz 1H), 4.07−4.15 (m, 2H), 7.01−7.05 (m, 2H), 7.18 (d, J = 8.2 Hz, 2H), 7.23−7.26 (m, 1H), 7.56 (d, J = 8.2 Hz, 2H), 7.70 (d, J = 8.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 9.0, 14.2, 21.4, 29.3, 40.8, 42.4, 60.5, 68.8, 117.1, 124.6, 124.7, 127.0, 128.5, 129.5, 134.5, 135.0, 141.0, 143.9, 171.0; HRMS (ESI): calcd for $C_{21}H_{25}NO_4S$ $[M+Na]^+$ 410.1397; found: 410.1388.

*Ethyl 2-((2S, 3R)-2-Isobutyl-1-tosylindolin-3-yl)acetate (**6c**).* Yield: 30 mg, 73%; gum; $[\alpha]_D^{27}$ −76.0 (c 0.4, $CHCl_3$); IR (NaCl, cm^{-1}): υ_{max}



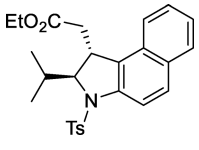
1163, 1212, 1355, 1528, 1739; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.88 (t, J = 6.5 Hz, 1 H), 0.95 (d, J = 6.5 Hz, 3H), 0.98 (d, J = 6.5 Hz, 3H), 1.12 (dd, J = 10.3, 16.0 Hz, 1H), 1.25−1.28 (m, 3H), 1.63 (td, J = 6.9, 13.7 Hz, 1H), 1.73 (dd, J = 5.3, 16.0 Hz, 1H), 1.89 (td, J = 6.7, 13.4 Hz, 1H), 2.37 (s, 3H), 3.04 (dd, J = 5.5, 10.1 Hz, 1H), 3.97 (t, J = 7.1 Hz, 1H), 4.09 (t, J = 7.4 Hz, 2H), 7.01−7.03 (m, 2H), 7.17 (d, J = 7.6 Hz, 2H), 7.25 (br s, 1H), 7.55 (d, J = 8.0 Hz, 2H), 7.69 (d, J = 8.0 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.3, 21.5, 22.6, 23.1, 23.9, 29.7, 40.7, 43.7, 45.9, 60.5, 66.1, 117.8, 124.7, 125.0, 127.2, 128.6, 129.5, 134.7, 135.6, 140.8, 143.7, 170.8; HRMS (ESI): calcd for $C_{23}H_{29}NO_4S$ $[M+Na]^+$ 438.1710; found: 438.1699.

*Ethyl 2-((2S, 3R)-2-Benzyl-1-tosylindolin-3-yl)acetate (**6d**).* Yield: 31 mg, 69%; gum; $[\alpha]_D^{27}$ + 16.2 (c 0.4, $CHCl_3$); IR (NaCl, cm^{-1}):

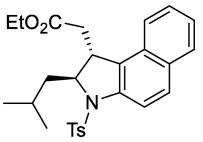


υ_{max} 1158, 1215, 1345, 1517, 1741; ^{1}H NMR (500 MHz, $CDCl_3$): δ 1.08 (dd, J = 4.8, 10.0 Hz, 1H), 1.12 (t, J = 7.0 Hz, 3H), 1.71 (dd, J = 5.4, 9.4 Hz, 1H), 2.35 (s, 3H), 2.85 (dd, J = 9.4, 13.4 Hz, 1H), 3.20 (dd, J = 5.4, 9.4 Hz, 1H), 3.24 (dd, J = 3.9, 13.1 Hz, 1H), 3.70−3.76 (m, 1H), 3.82−3.88 (m, 1H), 4.20 (dd, J = 3.3, 8.8 Hz, 1H), 6.96−7.0 (m, 2H), 7.16−7.21 (m, 3H), 7.23−7.27 (m, 5H), 7.63 (d, J = 7.9 Hz, 2H), 7.67 (d, J = 8.2 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.1, 21.5, 41.1, 41.8, 42.3, 60.3, 68.3, 116.7, 124.5, 125.0, 126.6, 127.1, 128.3, 129.6, 129.9, 133.9, 135.2, 136.4, 140.7, 143.8, 170.2; HRMS (ESI): calcd for $C_{26}H_{27}NO_4S$ $[M+H]^+$ 450.1734; found: 450.1740.

*Ethyl 2-((1R, 2S)-2-Isopropyl-3-tosyl-2,3-dihydro-1H-benzo[e]-indol-1-yl)acetate (**6e**).* Yield: 34 mg, 75%; gum; $[\alpha]_D^{27}$ −24.1 (c

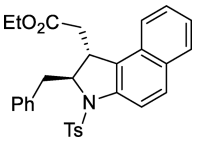


0.5, $CHCl_3$); IR (NaCl, cm^{-1}): υ_{max} 1151, 1222, 1358, 1526, 1742; ^{1}H NMR (400 MHz, $CDCl_3$): δ 0.79 (d, J = 3.6 Hz, 1H), 0.82 (d, J = 6.6 Hz, 3H), 0.94 (d, J = 7.1 Hz, 3H), 1.32 (t, J = 7.1 Hz, 3H), 2.14 (dquint, J = 1.7, 5.1 Hz, 1H), 2.31 (s, 3H), 2.39 (dd, J = 2.7, 15.4 Hz, 1H), 3.60 (dd, J = 1.4, 11.2 Hz, 1H), 4.01 (d, J = 4.2 Hz, 1H), 4.13−4.20 (m, 2H), 7.14 (d, J = 8.1 Hz, 2H), 7.39 (t, J = 7.8 Hz,, 1H), 7.46 (t, J = 7.8 Hz, 1H), 7.60 (d, J = 8.0 Hz, 2H), 7.64 (d, J = 7.3 Hz, 1H), 7.79 (d, J = 8.8 Hz, 1H), 7.84 (d, J = 7.3 Hz, 1H), 7.99 (d, J = 8.8 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.2, 17.1, 18.0, 21.4, 33.6, 39.1, 39.3, 60.6, 73.1, 117.2, 122.5, 124.7, 127.0, 127.1, 128.6, 129.0, 129.1, 129.5, 129.6, 131.6, 134.9, 139.3, 143.9, 171.2; HRMS (ESI): calcd for $C_{26}H_{29}NO_4S$ $[M+H]^+$ 452.1890; found: 452.1883.



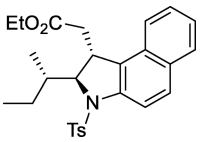
*Ethyl 2-((1R, 2S)-2-Isobutyl-3-tosyl-2,3-dihydro-1H-benzo[e]-indol-1-yl)acetate (**6f**).* Yield: 30 mg, 64%; gum; $[\alpha]_D^{27}$ −44.8 (c 0.5, $CHCl_3$); IR (NaCl, cm^{-1}): υ_{max} 1151, 1217, 1348, 1528, 1740; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.79 (dd, J = 11.8, 16.0 Hz, 1H), 0.96 (d, J = 6.4 Hz, 3H), 0.99 (t, J = 6.4 Hz, 3H), 1.31 (t, J = 7.2 Hz, 3H), 1.52 (quint, J = 6.8 Hz, 1H), 1.68 (q, J = 6.8 Hz, 1H), 1.98 (quint, J = 6.4 Hz, 1H), 2.32 (s, 3H), 2.36 (dd, J = 2.6, 16.0 Hz, 1H), 3.49 (dd, J = 1.5, 11.4 Hz, 1H), 4.10−4.15 (m, 1H), 4.16−4.21 (m, 2H), 7.15 (d, J = 8.0 Hz, 2H), 7.39 (t, J = 7.2 Hz, 1H), 7.46 (t, J = 7.6 Hz, 1H), 7.56−7.61 (m, 3H), 7.82 (d, J = 8.7 Hz, 1H), 7.85 (d, J = 8.0 Hz, 1H), 8.0 (d, J = 9.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.3, 21.4, 22.5, 22.9, 23.7, 38.8, 43.0, 45.6, 60.7, 66.9, 117.7, 122.6, 124.7, 127.0, 127.9, 129.0, 129.6, 129.7, 131.6, 135.2, 138.3, 144.0, 171.4; HRMS (ESI): calcd for $C_{27}H_{31}NO_4S$ $[M+Na]^+$ 488.1866; found: 488.1858.

*Ethyl 2-((1R,2S)-2-Benzyl-3-tosyl-2,3-dihydro-1H-benzo[e]indol-1-yl)acetate (**6g**).* Yield: 31 mg, 63%; gum; $[\alpha]_D^{27}$ −62.1 (c 0.5,



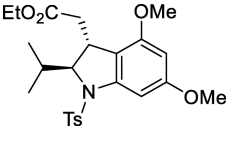
$CHCl_3$); IR (NaCl, cm^{-1}): υ_{max} 1148, 1211, 1351, 1538, 1742; ^{1}H NMR (400 MHz, $CDCl_3$): δ 1.14 (t, J = 7.3 Hz, 3H), 2.30 (s, 3H), 2.30−2.40 (m, 2H), 2.88 (dd, J = 9.2, 13.2 Hz, 1H), 3.27 (dd, J = 4.4, 13.2 Hz, 1H), 3.59 (d, J = 11.2 Hz, 1H), 3.66−3.72 (m, 1H), 3.80−3.87 (m, 1H), 4.42−4.46 (m, 1H), 7.15−7.17 (m, 5H), 7.32−7.59 (m, 5H), 7.66 (d, J = 8.3 Hz, 2H), 7.78 (d, J = 9.2 Hz, 1H), 7.83 (d, J = 8.3 Hz, 1H), 7.97 (d, J = 8.2 Hz, 1H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.0, 21.4, 39.3, 41.3, 42.0, 60.5, 68.9, 116.9, 122.5, 124.6, 126.6, 127.0, 127.1, 128.2, 128.9, 129.6, 129.7, 129.8, 131.4, 135.1, 136.4, 138.2, 144.0, 170.5; HRMS (ESI): calcd for $C_{30}H_{29}NO_4S$ $[M+Na]^+$ 522.1710; found: 522.1718.

*Ethyl 2-((1R, 2S)-2-((S)-sec-Butyl)-3-tosyl-2,3-dihydro-1H-benzo-[e]indol-1-yl)acetate (**6h**).* Yield: 30 mg, 66%; gum; $[\alpha]_D^{27}$ −50.2 (c



0.5, $CHCl_3$); IR (NaCl, cm^{-1}): υ_{max} 1172, 1220, 1344, 1528, 1738; ^{1}H NMR (500 MHz, $CDCl_3$): δ 0.74 (d, J = 6.7 Hz, 3H), 0.93 (t, J = 7.3 Hz, 3H), 1.19−1.27 (m, 2H), 1.32 (t, J = 7.0 Hz, 3H), 1.47−1.53 (m, 1H), 1.91−1.96 (m, 1H), 2.31 (s, 3H), 2.39 (dd, J = 2.7, 15.2 Hz, 1H), 3.63 (d, J = 11.6 Hz, 1H), 4.08 (d, J = 3.9 Hz, 1H), 4.10−4.19 (m, 2H), 7.15 (d, J = 8.2 Hz, 2H), 7.38 (t, J = 7.0 Hz, 1H), 7.46 (t, J = 7.3 Hz, 1H), 7.64 (d, J = 8.2 Hz, 3H), 7.80 (d, J = 7.9 Hz, 1H), 7.86 (d, J = 7.9 Hz, 1H), 8.01 (d, J = 9.1 Hz, 1H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 11.9, 13.4, 14.2, 21.4, 24.8, 38.7, 39.6, 40.7, 60.6, 72.3, 117.0, 122.5, 124.6, 127.0, 127.1, 128.6, 129.0, 129.5, 129.6, 131.5, 134.9, 139.3, 143.9, 171.2; HRMS (ESI): calcd for $C_{27}H_{31}NO_4S$ $[M+Na]^+$ 488.1866; found: 488.1859.

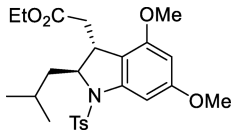
*Ethyl 2-((2S, 3R)-2-Isopropyl-4,6-dimethoxy-1-tosylindolin-3-yl)-acetate (**6i**).* Yield: 33 mg, 71%; gum; $[\alpha]_D^{27}$ −31.1 (c 0.5, $CHCl_3$); IR



DOI: 10.1021/acs.joc.7b00439
J. Org. Chem. 2017, 82, 5940−5946

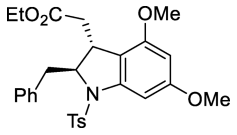
(NaCl, cm^{-1}): υ_{max} 1160, 1211, 1356, 1511, 1738; ^1H NMR (400 MHz, $CDCl_3$): δ 0.68 (dd, J = 15.2, 11.5 Hz, 1H), 0.83 (d, J = 6.8 Hz, 3H), 0.91 (d, J = 6.8 Hz, 3H), 1.28 (t, J = 7.0 Hz, 3H), 2.04−2.12 (m, 1H), 2.27 (dd, J = 15.0, 3.5 Hz, 1H), 2.37 (s, 3H), 3.17 (dt, J = 11.5, 1.7 Hz, 1H), 3.71 (s, 3H), 3.86 (s, 3H), 3.87 (dd, J = 4.8, 1.3 Hz, 1H), 4.04−4.15 (m, 2H), 6.14 (d, J = 2.0 Hz, 1H), 6.95 (d, J = 2.0 Hz, 1H), 7.21 (d, J = 8.1 Hz, 2H), 7.62 (d, J = 8.3 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.2, 17.0, 18.0, 21.5, 33.8, 37.2, 38.4, 55.1, 55.7, 60.3, 72.9, 94.3, 95.2, 114.8, 127.3, 129.5, 135.0, 143.4, 143.8, 155.8, 161.6, 171.4; HRMS (ESI): calcd. For $C_{24}H_{31}NO_6S$ $[M+H]^+$ 462.1945; found: 462.1943.

*Ethyl 2-((2S, 3R)-2-Isobutyl-4,6-dimethoxy-1-tosylindolin-3-yl)-acetate (**6j**).* Yield: 32 mg, 67%; gum; $[\alpha]_D^{27}$ −61.8 (c 0.5, $CHCl_3$);



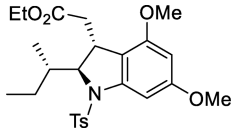
IR (NaCl, cm^{-1}): υ_{max} 1163, 1213, 1353, 1514, 1745; ^1H NMR (500 MHz, $CDCl_3$): δ 0.90 (d, J = 6.8 Hz, 3H), 1.01 (d, J = 6.4 Hz, 3H), 1.28 (t, J = 7.2 Hz, 3H), 1.33−1.40 (m, 1H), 2.07−2.13 (m, 1H), 2.32 (dd, J = 11.6, 17.5 Hz, 1H), 2.36 (s, 3H), 3.08−3.13 (m, 1H), 3.22 (dd, J = 5.3, 17.9 Hz, 1H), 3.66 (s, 3H), 3.85 (s, 3H), 4.09−4.17 (m, 2H), 4.50−4.54 (m, 1H), 6.18 (d, J = 1.9 Hz, 1H), 6.89 (d, J = 1.9 Hz, 1H), 7.15 (d, J = 8.3 Hz, 2H), 7.49 (d, J = 8.3 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.2, 21.2, 21.5, 23.7, 24.1, 32.1, 38.3, 39.5, 55.1, 55.7, 60.4, 64.6, 96.4, 97.3, 114.8, 127.0, 129.5, 135.7, 143.2, 143.7, 157.0, 160.8, 172.4; HRMS (ESI): calcd for $C_{25}H_{33}NO_6S$ $[M+H]^+$ 476.2101; found: 476.2097.

*Ethyl 2-((2S, 3R)-2-Benzyl-4,6-dimethoxy-1-tosylindolin-3-yl)-acetate (**6k**).* Yield: 37 mg, 72%; gum; $[\alpha]_D^{27}$ −58.7 (c 0.5,



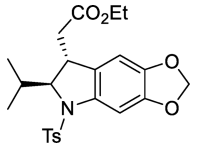
$CHCl_3$); IR (NaCl, cm^{-1}): υ_{max} 1182, 1217, 1353, 1519, 1739; ^1H NMR (400 MHz, $CDCl_3$): δ 1.12 (t, J = 7.3 Hz, 3H), 1.30−1.33 (m, 1H), 12.20 (dd, J = 3.2, 14.6 Hz, 1H), 2.35 (s, 3H), 2.86 (dd, J = 18.7, 13.2 Hz, 1H), 3.18 (dd, J = 4.1, 13.7 Hz, 2H), 3.64−3.67 (m, 1H), 3.69 (s, 3H), 3.76−3.82 (m, 1H), 3.85 (s, 3H), 4.27 (dd, J = 4.5, 8.7 Hz, 1H), 6.11 (d, J = 1.8 Hz, 1H), 6.92 (d, J = 1.8 Hz, 1H), 7.19 (d, J = 7.7 Hz, 3H), 7.27 (s, 4H), 7.65 (d, J = 8.2 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1, 21.5, 38.3, 39.6, 42.3, 55.1, 55.8, 60.2, 68.9, 94.0, 95.0, 113.1, 126.4, 127.1, 128.1, 129.6, 129.9, 135.1, 136.6, 142.6, 143.9, 156.5, 161.8, 170.9; HRMS (ESI): calcd for $C_{28}H_{31}NO_6S$ $[M+Na]^+$ 532.1764; found: 532.1758.

*Ethyl 2-((2S, 3R)-2-((S)-sec-Butyl)-5,7-dimethoxy-1-tosylindolin-3-yl)acetate (**6l**).* Yield: 30 mg, 63%; gum; $[\alpha]_D^{27}$ −38.7 (c 0.5, $CHCl_3$);



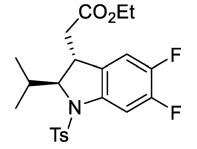
IR (NaCl, cm^{-1}): υ_{max} 1172, 1214, 1358, 1517, 1741; ^1H NMR (500 MHz, $CDCl_3$): δ 0.75 (d, J = 6.7 Hz, 3H), 0.92 (t, J = 7.3 Hz, 3H), 0.96−1.00 (m, 1H), 1.14−1.20 (m, 1H), 1.85−1.90 (m, 1H), 2.24 (dd, J = 3.6, 14.9 Hz, 1H), 2.37 (s, 3H), 3.18−3.22 (m, 1H), 3.71 (s, 3H), 3.85 (s, 3H), 3.93 (dd, J = 1.4, 4.4 Hz, 1H), 4.05−4.12 (m, 2H), 6.14 (d, J = 1.8 Hz, 1H), 6.95 (d, J = 2.1 Hz, 1H), 7.20 (d, J = 7.9 Hz, 2H), 7.62 (d, J = 8.2 Hz, 2H), ^{13}C NMR (126 MHz, $CDCl_3$): δ 11.9, 13.2, 14.2, 21.5, 24.7, 36.8, 38.6, 40.9, 55.1, 55.7, 60.3, 72.2, 94.1, 95.0, 114.7, 127.2, 129.5, 134.9, 143.5, 143.8, 155.7, 161.6, 171.4; HRMS (ESI): calcd for $C_{25}H_{33}NO_6S$ $[M+Na]^+$ 498.1921; found: 498.1911.

*Ethyl 2-((6S,7R)-6-Isopropyl-5-tosyl-6,7-dihydro-5H-[1,3]dioxolo-[4,5-f]indol-7-yl)acetate (**6m**).* Yield: 36 mg, 80%; gum; $[\alpha]_D^{27}$ −48.2



(c 0.7, $CHCl_3$); IR (NaCl, cm^{-1}): υ_{max} 1162, 1211, 1351, 1517, 1741; ^1H NMR (400 MHz, $CDCl_3$): δ 0.83 (d, J = 6.8 Hz, 3H); 0.89 (d, J = 7.0 Hz, 3H), 1.09 (dd, J = 9.2, 15.4 Hz, 1H), 1.26 (d, J = 7.0 Hz, 3H), 1.57 (dd, J = 6.1, 15.4 Hz, 1H), 2.04 (dquint, J = 2.2, 7.0 Hz, 1H), 2.37 (s, 3H), 3.04 (td, J = 1.2, 8.3 Hz, 1H), 3.73 (dd, J = 1.7, 4.8 Hz, 1H), 4.08 (q, J = 7.3 Hz, 2H), 5.94 (dd, J = 1.4, 13.4 Hz, 2H), 6.48 (s, 1H), 7.21 (d, J = 8.0 Hz, 2H), 7.28 (s, 1H), 7.56 (d, J = 8.0 Hz, 2H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.2, 17.0, 17.9, 21.5, 33.7, 39.6, 41.1, 60.5, 72.9, 99.9, 101.5, 104.3, 127.3, 129.5, 135.5, 135.6, 144.0, 145.0, 147.8, 170.9; HRMS (ESI): calcd for $C_{23}H_{27}NO_6S$ $[M+Na]^+$ 468.1451; found: 468.1455.

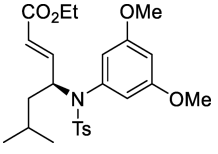
*Ethyl 2-((2S,3R)-5,6-Difluoro-2-isopropyl-1-tosylindolin-3-yl)-acetate (**6n**).* Yield: 28 mg, 65%; gum; $[\alpha]_D^{27}$ −88.3 (c 0.5,



$CHCl_3$); IR (NaCl, cm^{-1}): υ_{max} 1162, 1201, 1348, 1525, 1739; ^1H NMR (400 MHz, $CDCl_3$): δ 0.82 (d, J = 6.8 Hz, 3H); 0.90 (d, J = 6.8 Hz, 3H), 1.23 (dd, J = 8.8, 15.6 Hz, 1H), 1.25 (d, J = 7.0 Hz, 3H), 1.58 (dd, J = 6.6, 15.6 Hz, 1H), 2.08 (dquint, J = 1.9, 6.8 Hz, 1H), 2.38 (s, 3H), 3.14 (t, J = 7.7 Hz, 1H), 3.77 (dd, J = 1.7, 4.8 Hz, 1H), 4.08 (q, J = 7.0 Hz, 2H), 6.86 (dd, J = 1.2, 7.8 Hz, 1H), 7.23 (d, J = 7.8 Hz, 2H), 7.55−7.59 (m, 3H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.1, 16.8, 17.8, 21.5, 33.7, 39.0, 40.9, 60.7, 73.1, 106.7 (d, $J_{C,F}$ = 22.7 Hz), 112.9 (d, $J_{C,F}$ = 20.5 Hz), 127.2, 129.7, 131.1, 134.4, 137.7 (d, $J_{C,F}$ = 9.5 Hz), 144.5, 146.5 (d, $J_{C,F}$ = 245.7 Hz), 149.0 (d, $J_{C,F}$ = 245.7 Hz), 170.5; HRMS (ESI): calcd for $C_{22}H_{25}F_2NO_4S$ $[M+H]^+$ 438.1545; found: 438.1549.

*Preparation of N-Aryl-γ-aminoester (**7**).* To a solution of γ-aminoester **4c** (34 mg, 0.1 mmol) and benzyne precursor **5c** (36 mg, 0.1 mmol), H_2O (10 μL), in CH_3CN (2 mL) at 25 °C was added CsF (45.6 mg, 0.3 mmol) and the mixture was stirred at 25 °C for 6 h. Removal of solvent under reduced pressure followed by flash chromatographic purification using petroleum ether and ethyl acetate as eluent (8:2) gave products **7** (40%) and **6j** (25%).

*Ethyl 2-((2S, 3R)-2-Isobutyl-4,6-dimethoxy-1-tosylindolin-3-yl)-acetate (**7**).* Yield: 19 mg, 40%; gum; $[\alpha]_D^{27}$ −22.4 (c 0.5, $CHCl_3$);



IR (NaCl, cm^{-1}): υ_{max} 1175, 1221, 1346, 1535, 1722; ^1H NMR (500 MHz, $CDCl_3$): δ 0.89 (d, J = 6.7 Hz, 3H), 0.92 (d, J = 6.4 Hz, 3H), 1.20−1.28 (m, 5H), 1.65 (hept, J = 6.4 Hz, 1H), 2.41 (s, 3H), 3.69 (s, 6H), 4.16 (q, J = 7.0 Hz, 2H), 4.91 (q, J = 7.7 Hz, 1H), 5.85 (d, J = 15.9 Hz, 1H), 6.14 (d, J = 1.2 Hz, 2H), 6.45 (s, 1H), 6.69 (dd, J = 15.9, 8.2 Hz, 1H), 7.23 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 8.2 Hz, 2H); ^{13}C NMR (126 MHz, $CDCl_3$): δ 14.2, 21.5, 22.3, 22.4, 24.3, 41.5, 55.3, 58.2, 60.4, 101.3, 110.2, 123.2, 127.7, 129.3, 136.9, 137.6, 143.4, 145.5, 160.4, 165.8; HRMS (ESI): calcd for $C_{25}H_{33}NO_6S$ $[M+H]^+$ 476.2101; found: 476.2096.

*Preparation of N-Phenylindoline (**9c**).* To a solution of γ-aminoester **8c** (17.0 mg, 0.1 mmol) and benzyne precursor **5a** (60 mg, 0.2 mmol) in CH_3CN (2 mL) at 25 °C was added CsF (60.4 mg, 0.4 mmol) and the mixture was stirred at 25 °C for 6 h. Removal of solvent under reduced pressure followed by flash chromatographic

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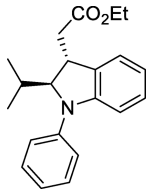
J. Org. Chem. 2017, 82, 5940−5946

purification using petroleum ether and ethyl acetate as eluents (7:3) gave product **9c**.

*Ethyl 2-((2S)-2-Isopropyl-1-phenylindolin-3-yl)acetate (**9c**).* Yield: 26 mg, 80%; gum; $[\alpha]_D^{27}$ −52.1 (c 0.5, $CHCl_3$); IR (NaCl, cm^{-1}): υ_{max}



1030, 1162, 1247, 1375, 1493, 1590, 1729; ^1H NMR (400 MHz, $CDCl_3$): δ 0.73 (d, *J* = 6.8 Hz, 3H), 0.94 (d, *J* = 6.8 Hz, 3H), 1.25 (t, *J* = 6.8 Hz, 3H), 1.27−1.31 (m, 1H), 2.12 (dhept, *J* = 4.1, 6.8 Hz, 1H), 2.56 (dq, *J* = 6.8 Hz, 3H), 3.52 (dt, *J* = 3.6, 6.8 Hz, 1H), 4.0 (t, *J* = 3.6 Hz, 1H), 4.16 (dq, *J* = 1.3, 7.3 Hz, 2H), 6.72 (dt, *J* = 1.3, 7.3 Hz, 1H), 6.93 (d, *J* = 7.8 Hz, 1H), 6.99−7.09 (m, 2H), 7.13 (d, *J* = 6.8 Hz, 1H), 7.29−7.36 (m, 4H); ^{13}C NMR (101 MHz, $CDCl_3$): δ 14.2, 16.0, 18.1, 30.7, 38.2, 42.1, 60.5, 74.2, 108.9, 118.7, 120.3, 121.1, 124.4, 127.7, 129.2, 133.1, 144.0, 147.3, 171.8; HRMS (ESI): calcd for $C_{21}H_{26}NO_2$ $[M+H]^+$ 324.1963; found: 324.1971.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.7b00439.

^1H and ^{13}C NMR spectra of compounds **6a−n**, **7**, and **9c** (PDF)

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Notes

The authors declare no competing financial interest.

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