JOC The Journal of Organic Chemistry

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A Synthetic Route to Chiral 1,4-Disubstituted Tetrahydro-β-Carbolines via Domino Ring-Opening Cyclization of Activated Aziridines with 2-Vinylindoles

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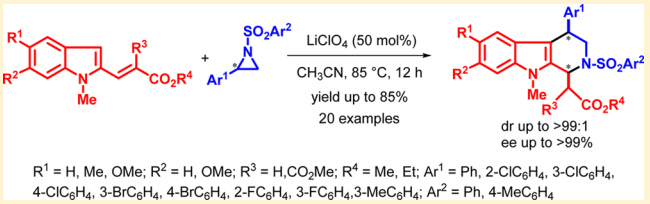
Supporting Information

ABSTRACT: A simple and efficient strategy for the synthesis of various 1,4-disubstituted tetrahydro-β-carbolines with excellent stereoselectivity (de, ee up to >99%) via domino ring opening cyclization (DROC) of activated aziridines with 2-vinylindoles is described. The reaction proceeds through $LiClO_4$-catalyzed Friedel–Crafts-type alkylation of 2-vinylindoles with activated aziridines followed by an intramolecular aza-Michael reaction in a domino fashion.



INTRODUCTION

1,2,3,4-Tetrahydro-β-carbolines (THβCs) are an important class of indole-based molecular frameworks which are integral parts of several biologically active natural alkaloids[1] and other pharmaceutically relevant synthetic compounds.[2] Some of the natural alkaloids containing tetrahydro-β-carboline core structures are shown in Figure 1.

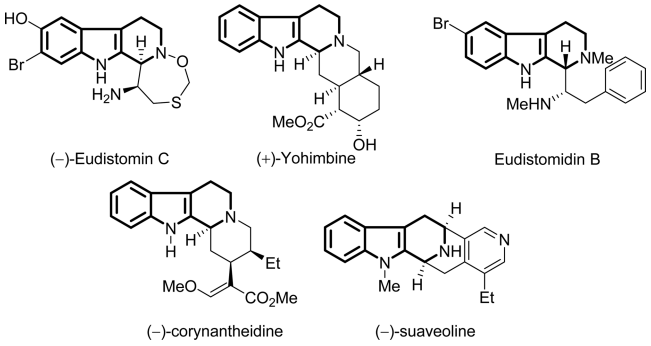


Figure 1. Natural occurring alkaloids containing tetrahydro-β-carboline scaffold.

The classical route for the synthesis of tetrahydro-β-carbolines is the Pictet–Spengler reaction involving the condensation of tryptamine with carbonyls under acidic conditions,[3] while another route is the Bischler–Napieralski reaction from *N*-acyltryptamines followed by reduction.[4] Subsequently, a number of enantioselective methods have been developed for the synthesis of THβCs.[4] Some of the important strategies for the synthesis of chiral THβCs include asymmetric Pictet–Spengler reaction,[5] asymmetric hydrogenation of dihydro-β-carbolines,[6] enantioselective nucleophilic addition to dihydro-β-carbolines,[7] etc. However, all these methods are reported with tryptophan as the starting material. Fujii and Ohno developed a copper-catalyzed three-component route to indole followed by successive cyclization at the 3-position of indole to 1,2,3,4-tetrahydro-β-carboline derivatives.[8a] Pfeffer et al. introduced another route for the synthesis of THβCs via a Pd-catalyzed domino Heck-aza-Michael reaction of 2-bromo-tryptamines where the substrate scope is limited with no chiral example.[8b] Synthesis of THβCs from aziridines are less explored in the literature.[9] Shipman et al. have developed a new strategy for the synthesis of 1,1-substituted THβCs from methyleneaziridines.[9c] Recently Wang and coworkers reported a novel [3 + 3] annulation strategy for the synthesis of THβCs from aziridines and benzyl alcohols.[9a] To the best of our knowledge, there is no report for the synthesis of chiral 1,4-disubstituted THβCs especially from chiral aziridines and 2-vinylindoles. Therefore, the development of a simple, general, and enantioselective synthetic route to substituted THβCs via ring opening of activated aziridines with 2-vinylindoles is highly desirable.

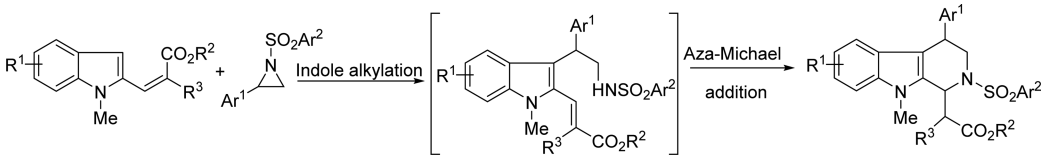
Aziridines are versatile intermediates/building blocks in synthetic organic chemistry[10] and have been utilized for the synthesis of important organic compounds including bioactive natural products and drugs.[11] Over the years, we have been exploring ring-opening/domino ring-opening cyclization (ROC/DROC) of aziridines/azetidines[12] and donor–acceptor cyclopropanes.[13] In continuation of our research activity in this area, we anticipated that ring opening of activated aziridines with 2-vinylindoles would generate the corresponding ring-opening product which would further undergo an intramolecular aza-Michael reaction with the tethered olefin moiety in a domino fashion leading to the formation of tetrahydro β-carboline scaffolds (Scheme 1).

Herein, we describe a new protocol for the synthesis of 1,4-disubstituted chiral THβCs via DROC of *N*-activated aziridines

Received: November 10, 2016
Published: February 10, 2017

DOI: 10.1021/acs.joc.6b02719
J. Org. Chem. 2017, 82, 2364–2374

Scheme 1. Synthesis of Tetrahydro β-Carbolines via DROC of 2-Activated Olefin-Tethered Indoles with Activated Aziridines

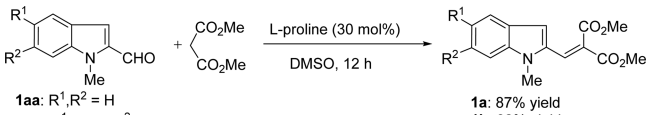


with substituted 2-vinylindoles and we report our results in detail.

RESULTS AND DISCUSSION

Our study commenced with the reaction of 2-phenyl-*N*-tosylaziridine **2a** and 2-vinylindole **1a** in the presence of $LiClO_4$ as the Lewis acid. 2-Vinylindole **1a** was synthesized from 1-methyl-1*H*-indole-2-carbaldehydes (**1aa**−**cc**) as shown in Scheme 2. Next the aziridine **2a** was treated with the indole

Scheme 2. Preparation of 2-Vinylindoles 1[20]



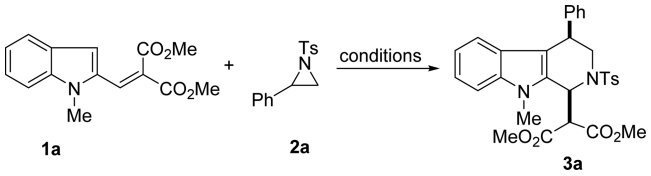
1aa: R^1,R^2 = H
1bb: R^1 = Me, R^2 = H
1cc: R^1,R^2 = OMe

1a: 87% yield
1b: 82% yield
1c: 78% yield

1a in the presence of 10 mol % of $LiClO_4$[12d] in acetonitrile at 85 °C for 20 h, and the reaction proceeds smoothly to afford the desired product **3a** in moderate yield (Table 1, entry 1).

When the amount of $LiClO_4$ was increased to 20 mol %, the product **3a** was obtained with a slightly increased yield (52%). When the amount of LA was increased to 50 mol %, the yield of the product **3a** was increased to 85% along with reduced reaction time (12 h). By enhancing the amount of LA further, **3a** was obtained in reduced yield (77%). The reaction did not proceed at all in DCE solvent. The reaction was not successful using strong Lewis acids such as $Cu(OTf)_2$, $Sc(OTf)_3$, $Zn(OTf)_2$, and $Yb(OTf)_3$ in DCM and DCE solvents. The product **3a** did not form at all; only the starting aziridine was found to decompose in the reaction mixture. However, using $BF_3{\cdot}OEt_2$ as the LA in DCE, **3a** was obtained in poor yield (25%). By changing the solvent to THF (with same LA), a complex mixture was obtained. A similar result was obtained employing $TiCl_4$ as the LA. The best result was obtained with 1.2 equiv of **1a** and 1.0 equiv of **2b** in acetonitrile in the presence of 50 mol % of $LiClO_4$, affording the corresponding tetrahydro-β-carboline **3a** in 85% yield with high diastereoselectivity (*cis*/*trans* 11:1) (Table 1, entry 3).

Table 1. Selective Optimization Study



1a **2a** **3a**

entry	reaction conditions[a]	yield (%)	dr[b]
1	$LiClO_4$ (10 mol %), CH_3CN, 85 °C, 20 h	45	11:1
2	$LiClO_4$ (20 mol %), CH_3CN, 85 °C, 20 h	52	11:1
3	**$LiClO_4$ (50 mol %), CH_3CN, 85 °C, 12 h**	**85**	**11:1**
4	$LiClO_4$ (100 mol %), CH_3CN, 85 °C, 12 h	77	11:1
5	$LiClO_4$ (100 mol %), DCE, 65 °C, 12 h	0	–
6	$Cu(OTf)_2$ (20 mol %), DCE, 85 °C, 20 h	0	–
7	$Sc(OTf)_3$ (20 mol %), DCE, 85 °C, 20 h	0	–
8	$Zn(OTf)_2$ (20 mol %), DCE, 85 °C, 20 h	0	–
9	$Yb(OTf)_3$ (20 mol %), DCE, 85 °C, 20 h	0	–
10	$BF_3{\cdot}OEt_2$ (20 mol %), DCE, 85 °C, 20 h	25	–
11[c]	$BF_3{\cdot}OEt_2$ (20 mol %), THF, 85 °C, 20 h	nd	–
12[c]	$BF_3{\cdot}OEt_2$ (20 mol %), DMF, 85 °C, 1 h	nd	–
13[c]	$TiCl_4$ (20 mol %), DCE, 85 °C, 1 h	nd	–
14[c]	$TiCl_4$ (20 mol %), THF, 85 °C, 1 h	nd	–

[a]In all the cases, 1.0 equiv of **2a** and 1.2 equiv of **1a** in CH_3CN (0.2 mL) were used. [b]Diastereomeric ratio (dr) was determined by ^1H NMR of the crude reaction mixture. [c]Complex mixture. nd: not determined.

To generalize this protocol, reactions of a number of *N*-activated aziridines **2b**−**j** possessing different aryl substituents with substituted vinyl indoles **1b**−**c** were studied under optimized DROC conditions, and the results are shown in Table 2. In the cases of 2-(4-bromophenyl)-1-tosylaziridine **2g**, the corresponding product **3g** was obtained as a single diastereomer in good yield. Aziridine with electron-donating substituents such as 2-(3-methylphenyl)-1-tosylaziridine **2e** behaved similarly to **1a** and generated the corresponding THβC **3e** in good yield and diastereoselectivity (10:1). A series of fluorinated THβCs (**3f**, **3i**, **3k**) were also synthesized in high yields with good diastereoselectivities. A methyl substituent at the 5-position of 2-vinylindole **1b** afforded the corresponding DROC product **3j** in 72% yield. Furthermore, 2-vinylindole **1c** with an electron-donating group such as methoxy at the 5,6-position afforded the desired product **3p** as a single diastereomer in 75% yield. The reaction was found to be efficient with simple benzenesulfonyl aziridine **2j**, and the corresponding product **3n** was obtained in 72% yield. All the results are shown Table 2.

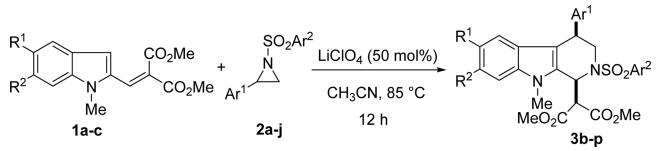
Next, we intended to study our DROC protocol with a less electrophilic indole substituted acrylate substrate. For this purpose, indole substituted acrylate **1d** was synthesized from 1-methyl-1*H*-indole-2-carbaldehyde as shown in Scheme 3. When aziridine **2a** was subjected to DROC with **1d**, the corresponding THβC product **3q** was obtained in lower yield along with uncyclized product **4a** (Table 3). Generalization of this strategy was made by studying other aziridines **2b**,**g** with **1d**. In these two cases also the expected THβCs **3r**,**s** were formed in reduced yields along with uncyclized products **4b**,**c**. The reduced yields of THβCs **3q**−**s** are probably due to the less electrophilic nature of acrylate **1d** compared to alkylidene malonate **1a**.

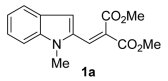
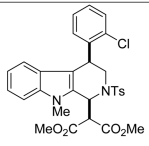
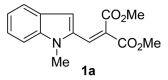
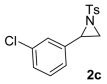
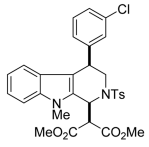
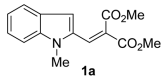
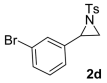
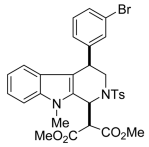
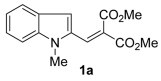
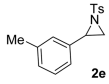
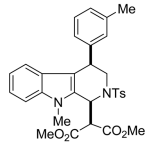
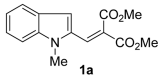
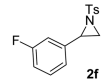
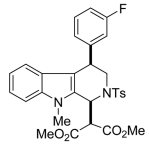
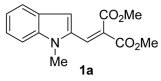
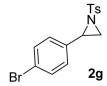
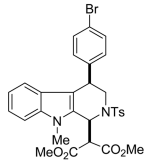
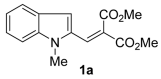
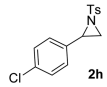
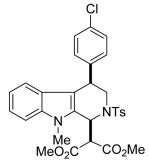
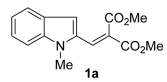
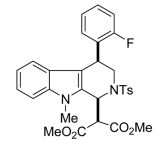
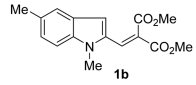
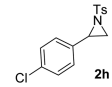
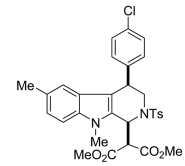
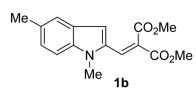
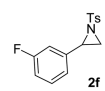
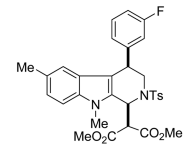
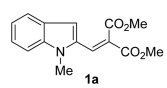
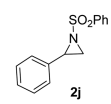
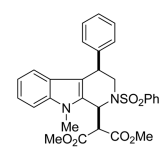
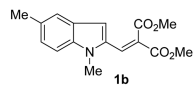
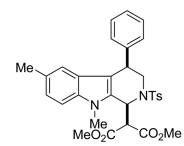
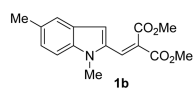
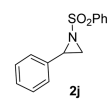
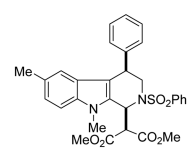
The structure and relative stereochemistry of **3k** and **3q** were unambiguously determined by single-crystal X-ray analysis.[14]

Based on our recent report when the uncyclized ring opening product **4a** was subjected to intramolecular aza-Michael addition in the presence of a catalytic amount of Pd(0)[15] in toluene, the expected THβC product **3q** was obtained in excellent yield (90%). Interestingly the reaction was successful

DOI: 10.1021/acs.joc.6b02719
J. Org. Chem. 2017, 82, 2364−2374

Table 2. Substrate Scope of Reaction[a]



entry	2-Vinylindole **1**	Aziridine **2**	Product **3**
1	 **1a**	 **2b**	 **3b**, 65%, 6/1 dr[b]
2	 **1a**	 **2c**	 **3c**, 85%, 7/1 dr[b]
3	 **1a**	 **2d**	 **3d**, 75%, 10/1 dr[b]
4	 **1a**	 **2e**	 **3e**, 69%, 10/1 dr[b]
5	 **1a**	 **2f**	 **3f**, 70%, 10/1 dr[b]
6	 **1a**	 **2g**	 **3g**, 76%, >99/1 dr[b]
7	 **1a**	 **2h**	 **3h**, 75%, 19/1 dr[b]
8	 **1a**	 **2i**	 **3i**, 78%, 7/1 dr[b]
9	 **1b**	 **2h**	 **3j**, 72%, 6/1 dr[b]
10	 **1b**	 **2f**	 **3k**, 72%, 11/1 dr[b]
11	 **1a**	 **2j**	 **3l**, 75%, 11/1 dr[b]
12	 **1b**	 **2a**	 **3m**, 75%, 11/1 dr[b]
13	 **1b**	 **2j**	 **3n**, 72%, 11/1 dr[b]
14	**1b**	**2b**	**3o**, 72%, 13/1 dr[b]
15	**1c**	**2j**	**3p**, 75%, 99/1 dr[b]

[a]Reaction conditions: **1** (0.12 mmol), **2** (0.10 mmol), $LiClO_4$ (50 mol %), acetonitrile (0.2 mL), 85 °C for 12 h. [b]The dr was determined by ^1H NMR spectroscopy of the crude reaction mixture.

DOI: 10.1021/acs.joc.6b02719
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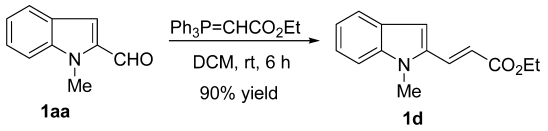
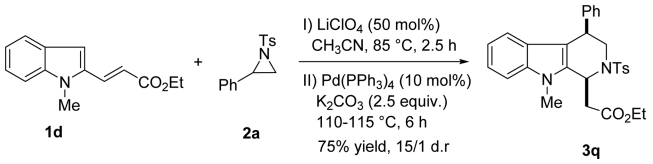
Scheme 3. Synthesis of Ethyl (*E*)-3-(1-Methyl-1*H*-indol-2-yl)acrylate 1d[21]



Scheme 4. One-Pot Synthesis for Tetrahydro-*β*-carboline 3q



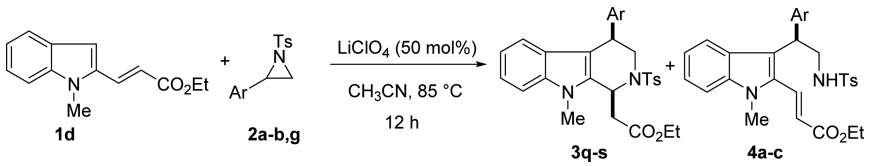
under one-pot conditions as well to furnish **3q** in high overall yield (75%) (Scheme 4).

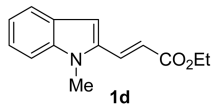
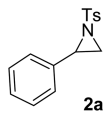
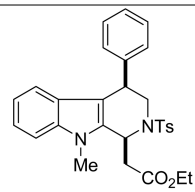
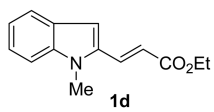
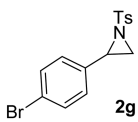
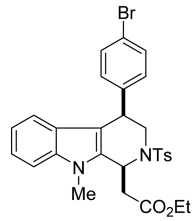
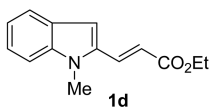
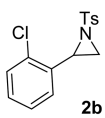
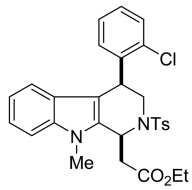
The synthetic significance of the protocol was demonstrated by the synthesis of nonracemic tetrahydro-*β*-carbolines. For this purpose, the enantiomerically pure *N*-tosylaziridines (*R*)-**2a,j** and (*S*)-**2b** were employed as the substrates. When (*R*)-**2a,j** and (*S*)-**2b** were treated with 2-vinylindoles **1a−d** under our optimized conditions the corresponding TH*β*Cs (1*S*, 4*R*)-**3l,n,p,q** and (1*R*, 4*S*)-**3o**, respectively, were obtained in good yields with good to excellent stereoselectivity (ee up to >99%, dr up to >99:1) as shown in Table 4.

To generalize our protocol in terms of substrate scope and further synthetic manipulation, 2-vinylaziridine **2k** was studied. When the indole **1a** was treated with the aziridine **2k** under optimized reaction conditions, the corresponding product **3t** was obtained in moderate yield (Scheme 5).

The mechanism of the reaction is illustrated in Figure 2. The S_N2-type ring opening of Lewis acid activated aziridine **2** with indole nucleophile **1** generates the ring opening product **A** as the intermediate which further undergoes intramolecular aza-Michael addition to the tethered activated olefin moiety to produce **3**. The self-addition of indole acrylate to another indole acrylate was not observed in our reaction conditions. This is probably due to the higher reactivity of aziridine to react faster with the indole acrylate compared to the self-addition of indole substrate. The intermediate **A** can adopt two different cyclohexene-like half chair conformations **B** and **C**. In conformer **B**, the Michael acceptor adopts a pseudo-axial

Table 3. Synthesis of Tetrahydro-*β*-carbolines from Indole Acrylate 1d[a]



entry	2-Vinylindole **1d**	Aziridine **2**	Product **3**	Product **4**
1			 **3q**, 42%, 11/1 dr[b]	**4a** (42%) Ar = Ph
2			 **3r**, 40%, 15/1 dr[b]	**4b** (38%) Ar = 4-BrC$_6$H$_4$
3			 **3s**, 35%, 13/1 dr[b]	**4c** (35%) Ar = 2-ClC$_6$H$_4$

[a]Reaction conditions: **1d** (0.12 mmol), **2** (0.10 mmol), $LiClO_4$ (50 mol %), acetonitrile (0.2 mL), 85 °C for 12 h. [b]The dr was determined by ^{1}H NMR spectroscopy of the crude reaction mixture.

DOI: 10.1021/acs.joc.6b02719
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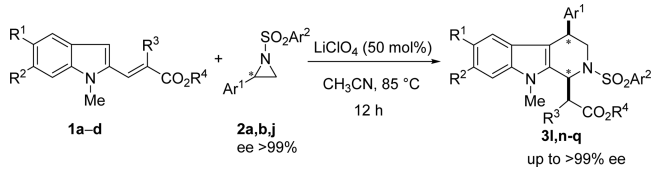
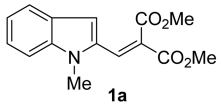
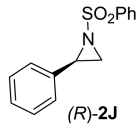
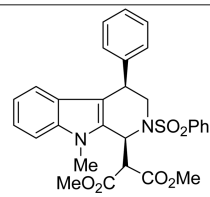
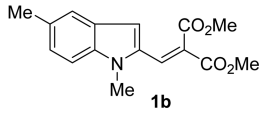
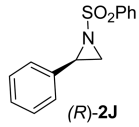
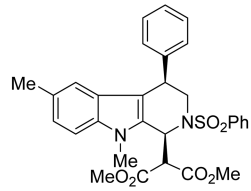
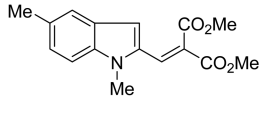
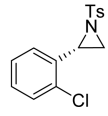
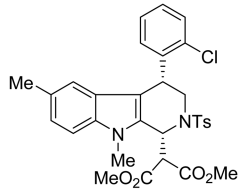
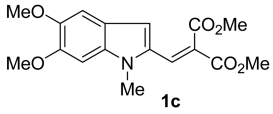
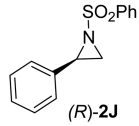
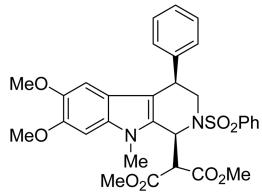
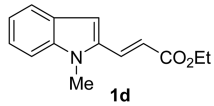
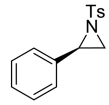
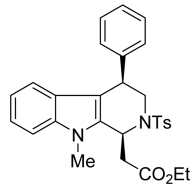
Table 4. Synthesis of Nonracemic Tetrahydro-β-carbolines from (*R*)-Aziridines[a]



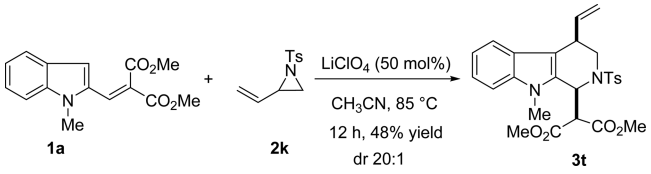
entry	2-Vinylindole **1**	Aziridine **2**	Product **3**
1	 **1a**	 (*R*)-**2J**	 (1*S*, 4*R*)-**3l**, 75%, 11/1 dr[b], ee 99%
2	 **1b**	 (*R*)-**2J**	 (1*S*, 4*R*)-**3n**, 72%, 11/1 dr[b], ee >99%
3	 **1b**	 (*S*)-**2b**	 (1*R*, 4*S*)-**3o**, 65% 6/1 dr[b], ee 94%
4	 **1c**	 (*R*)-**2J**	 (1*S*, 4*R*)-**3p**, 75%, ee 99% single diastereomer
5	 **1d**	 (*R*)-**2a**	 (1*S*, 4*R*)-**3q**, 42% 11/1 dr[b], ee >99%

[a]Reaction conditions: **1** (0.12 mmol), **2** (0.10 mmol), $LiClO_4$ (50 mol %), acetonitrile (0.2 mL), 85 °C for 12 h. [b]The dr was determined by ^1H NMR spectroscopy of the crude reaction mixture, and the ee was determined by chiral-phase HPLC.

position and faces a gauche interaction between the tosyl group and hydrogen, whereas the Michael acceptor adopts a pseudo-equatorial position in conformer **C** and faces severe gauche interaction between the tosyl and ester moiety. The more stable conformer **B** is more preferred over **C** providing tetrahydro-β-carboline with 1,4 *cis* appendages on the cyclohexyl ring.

DOI: 10.1021/acs.joc.6b02719
J. Org. Chem. 2017, 82, 2364−2374

Scheme 5. Synthesis of Tetrahydro-β-carboline 3t from 2-Vinylaziridine 2k



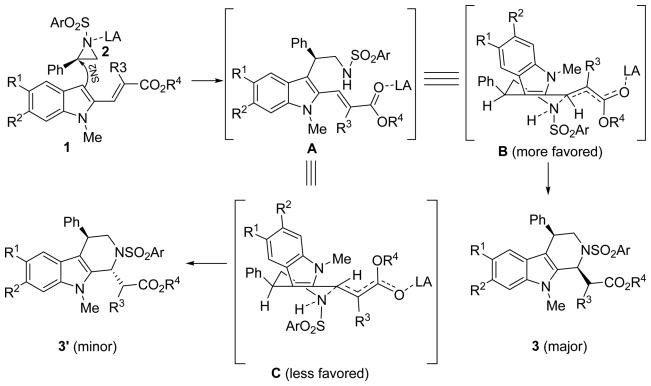


Figure 2. Proposed reaction mechanism and origin of diastereoselectivity.

CONCLUSION

In conclusion, we have developed an efficient protocol for the synthesis of racemic as well as nonracemic tetrahydro-β-carbolines via Lewis acid catalyzed domino ring opening (DROC) of activated aziridines with 2-vinylindoles. Further studies on synthetic application of the developed strategy and biological testing of the target products are in progress.

EXPERIMENTAL SECTION

General Experimental Procedure. Analytical thin layer chromatography (TLC) was carried out using silica gel 60 F_{254} precoated plates. Visualization was accomplished with UV lamp or I_2 stain. Silica gel 100−200 and 230−400 mesh sizes were used for column chromatography using the combination of ethyl acetate and petroleum ether as an eluent. Unless otherwise mentioned, all of the reactions were carried out in oven-dried glassware under an atmosphere of nitrogen using anhydrous solvents. Where appropriate, solvents and all reagents were purified prior to use following the guidelines of Perrin and Armarego[16] and Vogel.[17] 2-Aryl-1-tosylaziridines were prepared from different styrene derivatives following a reported procedure.[18] Chiral 2-phenyl-1-tosylaziridine[19] and chiral 2-(2-chlorophenyl)-1-tosylaziridine[19] were prepared from the corresponding amino alcohol following a reported procedure. All 2-vinylindoles were prepared from following a reported method.[20,21] All commercial reagents were used as received without prior purification unless mentioned. Proton nuclear magnetic resonance (^{1}H NMR) spectra was recorded at 400 and 500 MHz. The chemical shifts were recorded in parts per million (ppm, δ) relative to tetramethylsilane (δ 0.00). Splitting patterns of the ^{1}H NMR are mentioned as singlet (s), doublet (d), double doublet (dd), triplet (t), quartet (q), multiplet (m), etc. Carbon nuclear magnetic resonance (^{13}C {1H} NMR) spectra were recorded at 100 or 125 MHz. HRMS data were obtained using an (ESI) mass spectrometer (TOF). KBr plates were used for IR spectra of solid compounds, whereas liquid compounds were recorded neat. The melting points were measured using a hot-stage apparatus and are reported as uncorrected. The enantiomeric excess (ee) was determined by HPLC using Chiralpak IA, Chiralcel OD-H, and Chiralpak AS-H analytical columns (detection at 254 nm). Optical rotations were measured using a 6.0 mL cell with a 1.0 dm path length and are reported as $[\alpha]^{25}_D$ (*c* in g per 100 mL of solvent) at 25 °C.

*Procedure for the Synthesis of 2-Vinylindoles (**1a−c**).*[20] To a suspension of L-proline (0.6 mmol) in dry DMSO (4.0 mL) under a N_2 atmosphere 1-methylindole-2-carbaldehyde (2.0 mmol) was added at room temperature, and the reaction mixture was stirred at the same temperature for 10 min. Then dimethyl malonate (2.0 mmol) was added dropwise, and the reaction mixture was stirred at room temperature for 12 h. Then the reaction was quenched by adding water (4.0 mL) at room temperature. After separation of the organic layer, the aqueous layer was extracted with ethyl acetate (3 × 20.0 mL). The combined organic extract was washed with brine and dried over anhydrous sodium sulfate, and the solvent was removed under reduced pressure. The crude reaction mixture was purified by flash column chromatography on silica gel (100−200 mesh) using ethyl acetate in petroleum ether (10%) as the eluent to afford the pure product (**1a**) as a yellow solid.

*Procedure for the Synthesis of Dimethyl 2-((1-Methyl-1H-indol-2-yl)methylene)malonate **1d** from 1-Methyl-1H-indole-2-carbaldehyde **1aa**.*[21] To a solution of the 1-methyl-1*H*-indole-2-carbaldehyde **1aa** (1.0 mmol) in anhydrous CH_2Cl_2 (10 mL) was added dry Ph_3P=CHCO$_2$Et (2.0 mmol), and the mixture was stirred magnetically for 6 h at room temperature. Evaporation of the solvent and purification of the residue on silica gel column using EtOAc/hexane (1/9) as eluent gave the ester **1d** as a yellow crystalline solid.

*General Experimental Procedure for the Synthesis of Tetrahydro-β-carboline **3**.* A mixture of aziridine **2** (0.1 mmol, 1.0 equiv), 2-vinylindole **1** (0.12 mmol, 1.2 equiv), and anhydrous $LiClO_4$ (50 mol %) in dry CH_3CN (0.2 mL) was added in a two-neck round-bottom flask. The mixture was stirred under a N_2 atmosphere at 85 °C for 12 h. After that, water was added to the reaction mixture and extracted with ethyl acetate twice. The combined organic phase was dried over Na_2SO_4 and concentrated. The residue was purified by flash column chromatography on silica gel (230−400 mesh) using 15−25% ethyl acetate in petroleum ether to provide the pure products.

Spectral Data. *Dimethyl 2-((1-Methyl-1H-indol-2-yl)methylene)-malonate (**1a**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.81 (s, 3H), 3.86 (s, 3H), 3.92 (s, 3H), 6.89 (, 1H), 7.11 (t, *J* = 8.0 Hz, 1H), 7.25−7.32 (m, 2H), 7.59 (d, *J* = 8.0 Hz, 1H), 7.85 (s, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 30.0, 52.8, 53.0, 106.5, 109.8, 120.7, 122.0, 124.0, 124.6, 127.8, 130.2, 131.9, 138.9, 164.6, 167.3.

*Dimethyl 2-((1,5-Dimethyl-1H-indol-2-yl)methylene)malonate (**1b**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 2.41 (s, 3H), 3.79 (s, 3H), 3.85 (s, 3H), 3.91 (s, 3H), 6.79 (s, 1H), 7.11 (d, *J* = 8.0 Hz, 1H), 7.19 (d, *J* = 8.6 Hz, 1H), 7.36 (s, 1H), 7.83 (s, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 21.4, 30.0, 52.7, 53.0, 106.0, 109.5, 121.3, 123.5, 126.6, 127.9, 130.1, 130.3, 131.8, 137.5, 164.6, 167.5.

*Dimethyl 2-((5,6-Dimethoxy-1-methyl-1H-indol-2-yl)methylene)-malonate (**1c**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 3.77 (s, 3H), 3.83 (s, 3H), 3.90 (s, 3H), 3.92 (s, 3H), 3.96 (s, 3H), 6.69 (s, 1H), 6.80 (s, 1H), 6.96 (s, 1H), 7.80 (s, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 30.1, 52.6, 53.0, 56.2, 56.3, 92.0, 102.1, 106.7, 120.8, 120.9, 130.0, 130.3, 134.5, 146.3, 150.0, 165.0, 167.8.

*Ethyl (E)-3-(1-Methyl-1H-indol-2-yl)acrylate (**1d**).* ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, *J* = 7.5 Hz, 3H), 3.82 (s, 3H), 4.28 (q, *J* = 7.5 Hz, 2H), 6.48 (d, *J* = 16.0 Hz, 1H), 6.95 (s, 1H), 7.11 (t, *J* = 7.5 Hz, 1H), 7.26 (dd, *J* = 6.9, 1.2 Hz, 1H), 7.31 (d, *J* = 8.6 Hz, 1H), 7.60 (d, *J* = 8.0 Hz, 1H), 7.79 (d, *J* = 16.0 Hz, 1H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) δ 9.1, 24.8, 55.3, 98.5, 104.4, 113.0, 115.2, 116.1, 118.3, 122.2, 127.4, 129.7, 133.8, 162.0.

*Dimethyl 2-(9-Methyl-4-phenyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3a**).* The compound was synthesized by reacting 2-phenyl-1-tosylaziridine **2a** (27.3 mg, 0.100 mmol) with dimethyl 2-((1-methyl-1*H*-indol-2-yl)methylene)malonate **1a** (32.8 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3a** (46.5 mg, 0.085 mmol) as a white solid (11:1 diastereomeric mixture, combined yield 85%): mp 128−130 °C; R_f 0.18 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3029, 2953, 2925, 1737, 1597, 1492, 1469, 1453, 1435, 1347, 1238, 1200, 1162, 1096, 992, 941, 861,

DOI: 10.1021/acs.joc.6b02719
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744, 718, 704, 666, 618, 572; ^{1}H NMR (400 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 2.18 (s, 3H), 3.36 (dd, J = 14.5, 10.9 Hz, 1H), 3.48 (s, 3H), 3.67 (s, 3H), 3.76 (s, 3H), 3.97 (d, J = 6.3 Hz, 1H), 4.11 (dd, J = 10.9, 6.8 Hz, 1H), 4.28 (dd, J = 14.0, 6.3 Hz, 1H), 6.03 (d, J = 6.3 Hz, 1H), 6.61 (d, J = 7.7 Hz, 1H), 6.81 (dd, J = 7.7, 0.9 Hz, 1H), 7.03 (d, J = 8.2 Hz, 2H), 7.11 (dd, J = 8.2, 0.9 Hz, 1H), 7.18−7.20 (m, 3H), 7.25−7.31 (m, 3H), 7.59 (d, J = 8.2 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 21.4, 30.7, 39.4, 47.8, 51.1, 53.0, 53.2, 58.7, 109.2, 111.1, 119.4, 119.9, 122.2, 125.9, 127.1, 127.2, 128.3, 128.8, 129.4, 132.3, 136.8, 137.9, 141.5, 143.8, 166.9, 167.3; HRMS (ESI) calcd for $C_{30}H_{30}N_2NaO_6S$ $(M + Na)^+$ 569.1722, found 569.1722.

*Dimethyl 2-(4-(2-Chlorophenyl)-9-methyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3b**).* The compound was synthesized by reacting 2-(2-chlorophenyl)-1-tosylaziridine **2b** (30.7 mg, 0.100 mmol) reacted with dimethyl 2-((1-methyl-1*H*-indol-2-yl)methylene)malonate **1a** (32.8 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3b** (37.8 mg, 0.065 mmol) as a white solid (6:1 diastereomeric mixture, combined yield 65%): mp 142−144 °C; R_f 0.13 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2953, 2923, 2851, 1737, 1596, 1469, 1436, 1349, 1291, 1267, 1200, 1162, 1093, 1033, 1016, 990, 869, 812, 744, 711, 664, 558; ^{1}H NMR (500 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 2.11 (s, 3H), 3.25 (m, 1H), 3.53 (s, 3H), 3.72 (s, 3H), 3.81 (s, 3H), 4.02 (d, J = 6.9 Hz, 1H), 4.49 (m, 2H), 6.07 (d, J = 6.9 Hz, 1H), 6.54 (d, J = 8.0 Hz, 1H), 6.83 (t, J = 8.9 Hz, 1H), 6.94 (d, J = 8.0 Hz, 2H), 6.98 (d, J = 8.0 Hz, 1H), 7.08 (t, J = 7.5 Hz, 1H), 7.13 (t, J = 7.5 Hz, 1H), 7.18 (td, J = 8.0, 2.3 Hz, 1H), 7.23 (s, 1H), 7.41 (d, J = 8.0 Hz, 1H), 7.57 (d, J = 8.6 Hz, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 21.3, 30.7, 35.4, 45.4, 51.1, 53.0, 53.3, 58.8, 109.3, 110.0, 119.5, 119.7, 122.4, 125.6, 127.0, 127.4, 128.4, 129.3, 129.4, 129.6, 133.0, 134.2, 136.5, 137.9, 138.9, 143.8, 166.7, 167.0; HRMS (ESI) calcd for $C_{30}H_{33}ClN_3O_6S$ $(M + NH_4)^+$ 598.1779, found 598.1770.

*Dimethyl 2-(4-(3-Chlorophenyl)-9-methyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3c**).* The compound was synthesized by reacting 2-(3-chlorophenyl)-1-tosylaziridine **2c** (30.7 mg, 0.100 mmol) reacted with dimethyl 2-((1-methyl-1*H*-indol-2-yl)methylene)malonate **1a** (32.8 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3c** (49.4 mg, 0.085 mmol) as a white solid (7:1 diastereomeric mixture, combined yield 85%): mp 180−182 °C; R_f 0.17 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2954, 2924, 2853, 1737, 1595, 1470, 1434, 1348, 1291, 1266, 1200, 1091, 1017, 993, 790, 745, 664, 573, 556; ^{1}H NMR (500 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 2.19 (s, 3H), 3.33 (dd, J = 14.5, 10.9 Hz, 1H), 3.47 (s, 3H), 3.68 (s, 3H), 3.77 (s, 3H), 3.95 (d, J = 5.4 Hz, 1H), 4.10 (dd, J = 10.9, 6.8 Hz, 1H), 4.27 (dd, J = 14.5, 7.6 Hz, 1H), 6.04 (d, J = 5.9 Hz, 1H), 6.62 (d, J = 7.7 Hz, 1H), 6.84 (t, J = 7.7 Hz, 1H), 7.04 (d, J = 8.2 Hz, 2H), 7.12 (m, 3H), 7.23 (m, 3H), 7.58 (d, J = 8.2 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 21.4, 30.8, 39.3, 47.5, 50.9, 53.1, 53.3, 58.6, 109.4, 110.3, 119.6, 119.7, 122.4, 125.6, 127.0, 127.5, 128.3, 129.5, 130.1, 132.4, 134.6, 136.7, 137.9, 143.8, 144.0, 166.9, 167.4; HRMS (ESI) calcd for $C_{30}H_{29}ClN_2NaO_6S$ $(M + Na)^+$ 603.1333, found 603.1322.

*Dimethyl 2-(4-(3-Bromophenyl)-9-methyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3d**).* The compound was synthesized by reacting 2-(3-bromophenyl)-1-tosylaziridine **2d** (35.2 mg, 0.100 mmol) with dimethyl 2-((1-methyl-1*H*-indol-2-yl)-methylene)malonate **1a** (32.8 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3d** (46.9 mg, 0.075 mmol) as a white solid (10:1 diastereomeric mixture, combined yield 75%): mp 168−170 °C; R_f 0.20 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2954, 2923, 2852, 1595, 1567, 1468, 1435, 1339, 1316, 1266, 1196, 1100, 1017, 996, 940, 814, 787, 749, 693, 612, 556; ^{1}H NMR (400 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 2.19 (s, 3H), 3.32 (dd, J = 14.5, 10.9 Hz, 1H), 3.47 (s, 3H), 3.67 (s, 3H), 3.77 (s, 3H), 3.95 (d, J = 5.9 Hz, 1H), 4.10 (dd, J = 10.9, 6.8 Hz, 1H), 4.27 (dd, J = 15.0, 6.8 Hz, 1H), 6.04 (d, J = 5.9 Hz, 1H), 6.63 (d, J = 7.7 Hz, 1H), 6.84 (t, J = 7.3 Hz, 1H), 7.04 (d, J = 7.7 Hz, 2H), 7.11−7.12 (m, 4H), 7.32 (s, 1H), 7.39 (d, J = 9.0 Hz, 1H), 7.58 (d, J = 8.2 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 21.4, 30.7, 39.3, 47.6, 50.9, 53.1, 53.3, 58.5, 109.4, 110.3, 119.6, 119.7, 122.4, 122.9, 125.6, 127.0, 129.5, 130.4, 131.2, 132.4, 136.7, 137.9, 143.9, 144.1, 166.9, 167.4; HRMS (ESI) calcd for $C_{30}H_{33}BrN_3O_6S$ $(M + NH_4)^+$ 642.1273, found 642.1302.

*Dimethyl 2-(9-Methyl-4-(m-tolyl)-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3e**).* The compound was synthesized by reacting 2-(*m*-tolyl)-1-tosylaziridine **2e** (28.7 mg, 0.100 mmol) with dimethyl 2-((1-methyl-1*H*-indol-2-yl)methylene)-malonate **1a** (32.8 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3e** (38.7 mg, 0.069 mmol) as a white solid (10:1 diastereomeric mixture, combined yield 69%): mp 144−146 °C; R_f 0.17 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2952, 2921, 2850, 1737, 1597, 1488, 1468, 1435, 1347, 1291, 1269, 1238, 1191, 1093, 1016, 990, 942, 833, 814, 789, 744, 707, 594; ^{1}H NMR (400 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 2.17 (s, 3H), 2.29 (s, 3H), 3.34 (dd, J = 14.7, 11.0 Hz, 1H), 3.47 (s, 3H), 3.67 (s, 3H), 3.76 9s, 3H), 3.97 (d, J = 6.4 Hz, 1H), 4.07 (dd, J = 11.5, 6.9 Hz, 1H), 4.26 (ddd, J = 14.7, 6.09, 0.9 Hz, 1H), 6.02 (d, J = 6.0 Hz, 1H), 6.64 (d, J = 8.2 Hz, 1H), 6.81 (td, J = 8.2, 0.9 Hz, 1H), 6.95 (d, J = 7.8 Hz, 1H), 7.02 (d, J = 7.8 Hz, 3H), 7.06 (d, J = 7.8 Hz, 1H), 7.11 (dt, J = 8.2, 1.4 Hz, 1H), 7.15 (d, J = 7.8 Hz, 1H), 7.21 (d, J = 8.2 Hz, 1H), 7.58 (d, J = 8.2 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 21.4, 21.6, 30.7, 39.4, 47.8, 51.0, 52.9, 53.2, 58.7, 109.2, 111.2, 119.3, 120.0, 122.2, 125.2, 126.0, 127.0, 128.0, 128.7, 129.0, 129.4, 132.3, 136.9, 137.9, 138.3, 141.5, 143.7; HRMS (ESI) calcd for $C_{31}H_{36}N_3O_6S$ $(M + H)^+$ 578.2325, found 578.2327.

*Dimethyl 2-(4-(3-Fluorophenyl)-9-methyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3f**).* The compound was synthesized by reacting 2-(3-fluorophenyl)-1-tosylaziridine **2f** (29.1 mg, 0.100 mmol) with dimethyl 2-((1-methyl-1*H*-indol-2-yl)-methylene)malonate **1a** (32.8 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3f** (39.5 mg, 0.070 mmol) as a white solid (10:1 diastereomeric mixture, combined yield 70%): mp 158−160 °C; R_f 0.18 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2953, 2923, 1736, 1613, 1590, 1486, 1469, 1436, 1348, 1290, 1267, 1189, 1094, 1017, 992, 936, 833, 789, 744, 706, 690, 593, 572; ^{1}H NMR (400 MHz, $CDCl_3$) (Major cis diastereomer) δ 2.19 (s, 3H), 3.34 (dd, J = 14.7, 11.0 Hz, 1H), 3.47 (s, 3H), 3.68 (s, 3H), 3.76 (s, 3H), 3.95 (d, J = 6.0 Hz, 1H), 4.13 (dd, J = 11.0, 7.3 Hz, 1h), 4.28 (dd, J = 13.8, 6.0 Hz, 1H), 6.04 (d, J = 6.0 Hz, 1H), 6.63 (d, J = 7.8 Hz, 1H), 6.82−6.87 (m, 2H), 6.94 (td, J = 8.7, 1.8 Hz, 1H), 7.01−7.05 (m, 3H), 7.12 (td, J = 7.8, 0.9 Hz, 1H), 7.24 (d, J = 4.1 Hz, 1H), 7.28 (td, J = 7.8, 5.5 Hz, 1H), 7.59 (d, J = 8.2 Hz, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 21.4, 30.7, 39.3, 47.5, 50.9, 53.0, 53.2, 58.6, 109.3, 110.5, 114.2, 115.0, 119.7, 122.3, 124.0, 125.7, 127.0, 129.5, 130.2, 132.4, 136.8, 137.9, 143.9, 144.3, 163.2 (d, $^1J_{C-F}$ = 254.9 Hz), 166.8, 167.1; HRMS (ESI) calcd for $C_{30}H_{33}FN_3O_6S$ $(M + NH_4)^+$ 582.2074, found 582.2075.

*Dimethyl 2-(4-(4-Bromophenyl)-9-methyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3g**).* The compound was synthesized by reacting 2-(4-bromophenyl)-1-tosylaziridine **2g** (35.2 mg, 0.100 mmol) reacted with dimethyl 2-((1-methyl-1*H*-indol-2-yl)methylene)malonate **1a** (32.8 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3g** (47.5 mg, 0.076 mmol) as a white solid (single diastereomer, yield 76%): mp 138−140 °C; R_f 0.19 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3048, 2952, 1737, 1596, 1487, 1469, 1435, 1407, 1348, 1296, 1267, 1239, 1199, 1184, 1162, 1094, 1072, 993, 939, 861, 819, 744, 710, 673, 654, 595, 558; ^{1}H NMR (400 MHz, $CDCl_3$) δ 2.19 (s, 3H), 3.31 (dd, J = 14.5, 10.9 Hz, 1H), 3.46 (s, 3H), 3.67 (s, 3H), 3.76 (s, 3H), 3.93 (d, J = 5.9 Hz, 1H), 4.10 (dd, J = 10.9, 6.8 Hz, 1H), 4.25 (dd, J = 14.5, 6.8 Hz, 1H), 6.03 (d, J = 5.4 Hz, 1H), 6.61 (d, J = 7.7 Hz, 1H), 6.84 (t, J = 7.3 Hz, 1H), 7.04 (d, J = 7.7 Hz, 2H), 7.08 (d, J = 8.2 Hz, 2H), 7.13 (t, J = 7.3 Hz, 1H), 7.22 (d, J = 8.2 Hz, 1H), 7.41 (d, J = 8.6 Hz, 2H), 7.59 (d, J = 8.2 Hz, 2H);

DOI: 10.1021/acs.joc.6b02719
J. Org. Chem. 2017, 82, 2364−2374

^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) δ 21.4, 30.7, 39.0, 47.5, 50.9, 53.0, 53.3, 58.7, 109.4, 110.5, 119.6, 119.7, 121.1, 122.4, 125.7, 127.0, 129.5, 130.0, 132.0, 132.4, 136.7, 137.9, 1470.6, 143.9; HRMS (ESI) calcd for $C_{30}H_{33}BrN_3O_6S$ $(M + NH_4)^+$ 642.1273, found 642.1276.

*Dimethyl 2-(4-(4-Chlorophenyl)-9-methyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3h**).* The compound was synthesized by reacting 2-(4-chlorophenyl)-1-tosylaziridine **2h** (30.7 mg, 0.100 mmol) with dimethyl 2-((1-methyl-1*H*-indol-2-yl)-methylene)malonate **1a** (32.8 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3h** (43.6 mg, 0.075 mmol) as a white solid (19:1 diastereomeric mixture, combined yield 75%): mp 163−165 °C; R_f 0.17 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2955, 2925, 2855, 1737, 1597, 1491, 1469, 1436, 1335, 1297, 1268, 1199, 1185, 1092, 994, 952, 939, 863, 817, 743, 729, 695, 559; ^{1}H NMR (500 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 2.19 (s, 3H), 3.31 (dd, J = 14.9, 10.9 Hz, 1H), 3.46 (s, 3H), 3.67 (s, 3H), 3.76 (s, 3H), 3.94 (d, J = 6.3 Hz, 1H), 4.11 (dd, J = 11.3, 5.7 Hz, 1H), 4.25 (dd, J = 14.5, 6.8 Hz, 1H), 6.03 (d, J = 5.9 Hz, 1H), 6.61 (d, J = 8.2 Hz, 1H), 6.83 (t, J = 7.3 Hz, 1H), 7.04 (d, J = 8.2 Hz, 2H), 7.12 (m, 3H), 7.24 (d, J = 4.5 Hz, 1H), 7.26 (d, J = 8.2 Hz, 2H), 7.59 (d, J = 8.2 Hz, 2H); ^{13}C {^{1}H} NMR (100 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 21.4, 30.7, 38.9, 47.6, 50.9, 53.1, 53.3, 58.7, 109.4, 110.6, 119.6, 119.8, 122.4, 125.7, 127.1, 129.0, 129.5, 129.6, 132.4, 133.0, 136.8, 137.9, 140.1, 143.9, 166.8, 167.3; HRMS (ESI) calcd for $C_{30}H_{29}ClN_2NaO_6S$ $(M + Na)^+$ 603.1333, found 603.1335.

*Dimethyl 2-(4-(2-Fluorophenyl)-9-methyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3i**).* The compound was synthesized by reacting 2-(2-fluorophenyl)-1-tosylaziridine **2i** (29.1 mg, 0.100 mmol) with dimethyl 2-((1-methyl-1*H*-indol-2-yl)-methylene)malonate **1a** (32.8 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3i** (44.1 mg, 0.078 mmol) as a white solid (7:1 diastereomeric mixture, combined yield 78%): mp 142−144 °C; R_f 0.19 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2918, 2849, 1737, 1613, 1597, 1489, 1468, 1435, 1349, 1292, 1270, 1224, 1101, 1016, 991, 871, 813, 745, 715, 665, 558; ^{1}H NMR (500 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 2.13 (s, 3H), 3.36 (m, 1H), 3.51 (s, 3H), 3.71 (s, 3H), 3.79 (s, 3H), 4.02 (d, J = 6.9 Hz, 1H), 4.39 (m, 2H), 6.03 (d, J = 6.9 Hz, 1H), 6.62 (d, J = 7.5 Hz, 1H), 6.84 (t, J = 8.0 Hz, 1H), 6.98 (m, 4H), 7.12 (m, 2H), 7.23 (m, 2H), 7.58 (d, J = 8.2 Hz, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 21.3, 30.7, 31.9, 45.7, 51.1, 53.0, 53.1, 58.6, 109.3, 109.6, 115.5, 119.5, 122.3, 124.6, 125.7, 127.0, 128.2, 128.7, 128.8, 129.3, 129.7, 132.8, 136.6, 137.9, 143.8, 161.3 (d, 1*J*CF = 248.3 Hz, 1H), 166.8, 167.1; HRMS (ESI) calcd for $C_{30}H_{33}FN_3O_6S$ $(M + NH_4)^+$ 582.2074, found 582.2079.

*Dimethyl 2-(4-(4-Chlorophenyl)-6,9-dimethyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3j**).* The compound was synthesized by reacting 2-(4-chlorophenyl)-1-tosylaziridine **2h** (30.7 mg, 0.100 mmol) with dimethyl 2-((1,5-dimethyl-1*H*-indol-2-yl)methylene)malonate **1b** (34.5 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3j** (42.8 mg, 0.072 mmol) as a white solid (6:1 diastereomeric mixture, combined yield 72%): mp 190−192 °C; R_f 0.21 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2954, 2924, 2853, 1740, 1488, 1459, 1376, 1345, 1259, 1160, 1091, 1014, 970, 793, 722, 660, 560; ^{1}H NMR (500 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 2.20 (s, 3H), 2.21 (s, 3H), 3.29 (dd, J = 14.9, 10.9 Hz, 1H), 3.47 (s, 3H), 3.65 (s, 3H), 3.76 (s, 3H), 3.93 (d, J = 6.3 Hz, 1H), 4.08 (dd, J = 10.9, 6.9 Hz, 1H), 4.24 (dd, J = 14.3, 7.2 Hz, 1H), 6.01 (d, J = 6.3 Hz, 1H), 6.39 (s, 1H), 6.95 (d, J = 8.0 Hz, 1H), 7.03 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.0 Hz, 1H), 7.14 (d, J = 8.6 Hz, 2H), 7.27 (d, J = 8.6 Hz, 2H), 7.58 (d, J = 8.0 Hz, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 21.4, 30.7, 38.9, 47.6, 51.0, 53.0, 53.2, 58.6, 109.1, 110.0, 119.3, 124.0, 126.0, 127.0, 128.9, 129.0, 129.4, 129.6, 132.5, 132.9, 136.4, 136.8, 140.2, 143.8, 166.8, 167.3; HRMS (ESI) calcd for $C_{31}H_{30}ClN_2O_6S$ $(M - H)^-$ 593.1513, found 593.1512.

*Dimethyl 2-(4-(3-Fluorophenyl)-6,9-dimethyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3k**).* The compound was synthesized by reacting 2-(3-fluorophenyl)-1-tosylaziridine **2f** (29.1 mg, 0.100 mmol) with dimethyl 2-((1,5-dimethyl-1*H*-indol-2-yl)methylene)malonate **1b** (34.5 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3k** (41.7 mg, 0.072 mmol) as a white solid (11:1 diastereomeric mixture, combined yield 72%): mp 166−168 °C; R_f 0.26 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2954, 2923, 2853, 1741, 1713, 1590, 1613, 1486, 1463, 1377, 1290, 1267, 1162, 1097, 1019, 971, 909, 790, 722, 663, 589; ^{1}H NMR (500 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 2.20 (s, 3H), 2.21 (s, 3H), 3.32 (dd, J = 14.9, 11.5 Hz, 1H), 3.48 (s, 3H), 3.65 (s, 3H), 3.77 (s, 3H), 3.95 (d, J = 6.3 Hz, 1H), 4.10 (dd, J = 10.9, 6.3 Hz, 1H), 4.27 (dd, J = 15.5, 7.7 Hz, 1H), 6.02 (d, J = 6.3 Hz, 1H), 6.41 (s, 1H), 6.87 (dt, J = 10.3, 1.7 Hz, 1H), 6.94−6.98 (m, 2H), 7.02−7.04 (m, 3H), 7.12 (d, J = 8.6 Hz, 1H), 7.26−7.30 (m, 1H), 7.58 (d, J = 8.6 Hz, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 21.4, 30.7, 39.2, 47.5, 51.0, 53.0, 53.2, 58.6, 109.0, 109.8, 114.2, 114.9, 115.1, 119.3 126.0, 127.0, 128.8, 129.4, 130.2, 130.3, 132.4, 136.4, 136.8, 143.8, 144.4, 162.3 (d, $^{1}J_{C-F}$ = 245.9 Hz) 166.8, 167.4; HRMS (ESI) calcd for $C_{31}H_{32}FN_2O_6S$ $(M + H)^+$ 579.1965, found 579.1971.

*Dimethyl 2-((1S,4R)-9-Methyl-4-phenyl-2-(phenylsulfonyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3l**).* The compound was synthesized by reacting 2-phenyl-1-(phenylsulfonyl)-aziridine (*R*)-**2j** (25.9 mg, 0.100 mmol) with dimethyl 2-((1-methyl-1*H*-indol-2-yl)methylene)malonate **1a** (32.8 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3l** (40.0 mg, 0.075 mmol) as a white solid (11:1 diastereomeric mixture, combined yield 75%): mp 158−160 °C; R_f 0.18 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3058, 2952, 2918, 2849, 1736, 1601, 1490, 1468, 1446, 1435, 1349, 1293, 1268, 1238, 1199, 1163, 1024, 942, 861, 807, 746, 728, 690, 642; ^{1}H NMR (500 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 3.39 (dd, J = 14.3, 10.9 Hz, 1H), 3.48 (s, 3H), 3.68 (s, 3H), 3.75 (s, 3H), 3.98 (d, J = 6.3 Hz, 1H), 4.15 (dd, J = 11.5, 5.7 Hz, 1H), 4.29 (dd, J = 14.9, 6.9 Hz, 1H), 6.08 (d, J = 6.3 Hz, 1H), 6.62 (d, J = 7.6 Hz, 1H), 6.81 (t, J = 6.9 Hz, 1H), 7.12 (t, J = 7.5 Hz, 1H), 7.19−7.23 (m, 3H), 7.25−7.32 (m, 5H), 7.36 (t, J = 7.5 Hz, 1H), 7.75 (d, J = 7.5 Hz, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 30.8, 39.6, 47.8, 51.1, 53.0, 53.2, 58.8, 109.3, 111.2, 119.4, 120.0, 122.3, 125.9, 127.1, 127.3, 128.3, 128.8, 128.9, 132.3, 132.8, 138.0, 140.0, 141.4, 166.8, 167.3; HRMS (ESI) calcd for $C_{29}H_{32}N_3O_6S$ $(M + NH_4)^+$ 550.2012, found 550.2011. $[\alpha]^{25}_D$ = +60.0 (*c* 0.63, CH_2Cl_2) for a 99% ee sample; the enantiomeric excess was determined by chiral HPLC analysis (OD−H column); *n*-hexane/*i*-propanol = 95:5, flow rate = 1.0 mL/min, t_R (1) = 25.41 min (minor), t_R (2) = 26.58 min (major).

*Dimethyl 2-(6,9-Dimethyl-4-phenyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3m**).* The compound was synthesized by reacting 2-phenyl-1-tosylaziridine **2a** (25.9 mg, 0.100 mmol) with 2-((1,5-dimethyl-1*H*-indol-2-yl)methylene)malonate **1b** (40.0 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3m** (42.1 mg, 0.075 mmol) as a white solid (11:1 diastereomeric mixture, combined yield 75%): mp 133−135 °C; R_f 0.25 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3027, 2923, 2853, 1743, 1598, 1494, 1462, 1454, 1377, 1344, 1303, 1260, 1159, 1059, 1018, 907, 850, 813, 744, 712, 700, 667, 569; ^{1}H NMR (500 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 2.19 (s, 6H), 3.34 (dd, J = 14.9, 11.5 Hz, 1H), 3.49 (s, 3H), 3.66 (s, 3H), 3.77 (s, 3H), 3.98 (d, J = 6.3 Hz, 1H), 4.07−4.11 (m, 1H), 4.28 (dd, J = 14.3, 6.9 Hz, 1H), 6.02 (d, J = 6.3 Hz, 1H), 6.40 (s, 1H), 6.94 (d, J = 7.5 Hz, 1H), 7.03 (d, J = 8.0 Hz, 2H), 7.11 (d, J = 8.6 Hz, 1H), 7.20 (d, J = 6.3 Hz, 2H), 7.27 (d, J = 6.9 Hz, 1H), 7.30 (d, J = 7.5 Hz, 2H), 7.59 (d, J = 8.6 Hz, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 22.8, 30.8, 32.0, 39.4, 47.8, 51.1, 52.9, 53.1, 58.7, 109.0, 110.5, 119.5, 123.8, 126.2, 127.0, 127.2, 128.2, 128.6, 128.8, 129.4, 132.4, 136.5, 136.9, 141.7, 143.7, 166.9, 167.7; HRMS (ESI) calcd for $C_{31}H_{36}N_3O_6S$ $(M + NH_4)^+$ 578.2325, found 578.2320.

DOI: 10.1021/acs.joc.6b02719
J. Org. Chem. 2017, 82, 2364−2374

*Dimethyl 2-((1S,4R)-6,9-Dimethyl-4-phenyl-2-(phenylsulfonyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate(**3n**).* The compound was synthesized by reacting 2-phenyl-1-(phenylsulfonyl)-aziridine (*R*)-**2j** (29.5 mg, 0.100 mmol) with 2-((1,5-dimethyl-1*H*-indol-2-yl)methylene)malonate **1b** (34.5 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3n** (39.4 mg, 0.072 mmol) as a white solid (11:1 diastereomeric mixture, combined yield 72%): mp 153−155 °C; R_f 0.17 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2954, 2923, 2853, 1738, 1601, 1462, 1376, 1349, 1309, 1264, 1207, 1164, 1024, 909, 871, 755, 732, 690; ^1H NMR (500 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 2.18 (s, 3H), 3.35 (dd, J = 11.5, 3.4 Hz, 1H), 3.48 (s, 3H), 3.64 (s, 3H), 3.74 (s, 3H), 3.96 (d, J = 6.3 Hz, 1H), 4.08 (dd, J = 10.9, 4.0 Hz, 1H), 4.27 (dd, J = 14.9, 8.0 Hz, 1H), 6.04 (d, J = 5.7 Hz, 1H), 6.39 (s, 1H), 6.94 (d, J = 8.6 Hz, 1H), 7.10 (d, J = 8.0 Hz, 1H), 7.19 (d, J = 8.0 Hz, 2H), 7.25−7.32 (m, 6H), 7.35−7.38 (m, 1H), 7.74 (d, J = 8.6 Hz, 2H); ^{13}C {^1H} NMR (125 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 21.4, 30.7, 39.6, 47.9, 51.1, 53.0, 53.2, 58.7, 109.0, 110.6, 119.6, 123.9, 126.1, 127.0, 127.2, 128.2, 128.7, 128.8, 128.9, 132.4, 132.8, 136.5, 140.0, 141.5, 166.8, 167.3; HRMS (ESI) calcd for $C_{30}H_{30}N_2NaO_6S$ $(M + Na)^+$ 569.1722, found 569.1722. $[\alpha]^{25}_D$ = +35.9 (*c* 0.19, CH_2Cl_2) for a >99% ee sample; the enantiomeric excess was determined by chiral HPLC analysis (OD−H column); *n*-hexane/*i*-propanol = 95:5, flow rate = 1.0 mL/min, t_R (1) = 152.16 min (major), t_R (2) = 182.52 min (minor).

*Dimethyl 2-((1R,4R)-4-(2-Chlorophenyl)-6,9-dimethyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3o**).* The compound was synthesized by reacting 2-(2-chlorophenyl)-1-tosylaziridine **2b** (30.7 mg, 0.100 mmol) with 2-((1,5-dimethyl-1*H*-indol-2-yl)methylene)malonate **1b** (34.5 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3o** (42.8 mg, 0.072 mmol) as a white solid (13:1 diastereomeric mixture, combined yield 72%): mp 192−194 °C; R_f 0.17 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2917, 2849, 2321, 1736, 1596, 1435, 1348, 1290, 1267, 1212, 1162, 1093, 1033, 989, 870, 795, 757, 734, 584, 559; ^1H NMR (500 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 2.11 (s, 3H), 2.20 (s, 3H), 3.22 (td, J = 13.2, 8.6 Hz, 1H), 3.53 (s, 3H), 3.69 (s, 3H), 3.80 (s, 3H), 4.00 (d, J = 6.9 Hz, 1H), 4.44−4.50 (m, 2H), 6.04 (d, J = 6.9 Hz, 1H), 6.30 (s, 1H), 6.93−6.96 (m, 3H), 6.98 (dd, J = 8.0, 1.7 Hz, 1H), 7.08 (td, J = 8.0, 1.2 Hz, 1H), 7.13 (d, J = 8.0 Hz, 1H), 7.18 (td, J = 7.5, 1.7 Hz, 1H), 7.42 (dd, J = 8.0, 1.2 Hz, 1H), 7.55 (d, J = 8.0 Hz, 2H); ^{13}C {^1H} NMR (125 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 21.2, 30.7, 45.3, 51.2, 52.9, 53.3, 58.7, 109.0, 109.4, 119.2, 124.0, 125.9, 127.0, 127.5, 128.4, 128.8, 129.3, 129.4, 129.6, 133.0, 134.1, 136.4, 136.6, 139.0, 143.8; HRMS (ESI) calcd for $C_{31}H_{31}ClN_2NaO_6S$ $(M + Na)^+$ 617.1489, found 617.1488. $[\alpha]^{25}_D$ = −20.0 (*c* 0.20, CH_2Cl_2) for a 94% ee sample; the enantiomeric excess was determined by chiral HPLC analysis (AS-H column); *n*-hexane/*i*-propanol = 95:5, flow rate = 1.0 mL/min, t_R (1) = 63.79 min (major), t_R (2) = 102.94 min (minor).

*Dimethyl 2-((1S,4R)-6,7-Dimethoxy-9-methyl-4-phenyl-2-(phenylsulfonyl)-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)-malonate (**3p**).* The compound was synthesized by reacting 2-phenyl-1-(phenylsulfonyl)aziridine (*R*)-**2j** (25.9 mg, 0.100 mmol) with dimethyl 2-((5,6-dimethoxy-1-methyl-1*H*-indol-2-yl)methylene)-malonate **1c** (40.0 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3p** (44.5 mg, 0.075 mmol) as a white solid (single diastereomer, yield 75%): mp 185−187 °C; R_f 0.15 (30% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2954, 2925, 2853, 1737, 1624, 1564, 1487, 1447, 1333, 1248, 1205, 1095, 1049, 1025, 981, 908, 840, 805, 755, 730, 701, 690, 588; ^1H NMR (500 MHz, $CDCl_3$) δ 3.37 (dd, J = 14.5, 10.5 Hz, 1H), 3.47 (s, 3H), 3.49 (s, 3H), 3.62 (s, 3H), 3.74 (s, 3H), 3.89 (s, 3H), 3.95 (d, J = 5.9 Hz, 1H), 4.05 (dd, J = 10.9, 5.4 Hz, 1H), 4.27 (dd, J = 14.5, 6.3 Hz, 1H), 5.98 (s, 1H), 6.04 (d, J = 5.9 Hz, 1H), 6.67 (s, 1H), 7.18−7.21 (m, 2H), 7.26−7.32 (m, 5H), 7.38 (tt, J = 7.3, 0.9 Hz, 1H), 7.74 (d, J = 7.3 Hz, 2H); ^{13}C {^1H} NMR (125 MHz, $CDCl_3$) δ 30.9, 39.6, 47.7, 51.2, 52.8, 53.1, 56.0, 56.1, 58.8, 92.7, 101.8, 110.9, 118.5, 127.0, 127.1, 128.3, 128.7, 128.9, 130.3, 132.4, 132.7, 140.0, 141.2, 144.5, 147.2, 166.8, 167.4; HRMS (ESI) calcd for $C_{31}H_{33}N_2O_8S$ $(M + H)^+$ 593.1958, found 593.1955. $[\alpha]^{25}_D$ = +60 (*c* 0.63, CH_2Cl_2) for a 99% ee sample; the enantiomeric excess was determined by chiral HPLC analysis (AS−H column); *n*-hexane/*i*-propanol = 80:20, flow rate = 1.0 mL/min, t_R (1) = 48.55 min (major), t_R (2) = 87.55 min (minor).

*Ethyl 2-((1S,4R)-9-Methyl-4-phenyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetate (**3q**).* The compound was synthesized by reacting 2-phenyl-1-tosylaziridine (*R*)-**2a** (27.3 mg, 0.100 mmol) with ethyl (*E*)-3-(1-methyl-1*H*-indol-2-yl)acrylate **1d** (27.5 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3q** (21.1 mg, 0.042 mmol) as a white solid (11:1 diastereomeric mixture, combined yield 42%): mp 140−142 °C; R_f 0.24 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3027, 2924, 1733, 1598, 1491, 1469, 1454, 1421, 1371, 1339, 1303, 1270, 1248, 1160, 1095, 1018, 982, 904, 851, 745, 711, 664, 586, 558; ^1H NMR (500 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 1.26 (t, J = 7.5 Hz, 3H), 2.26 (s, 3H), 2.81 (dd, J = 14.3, 2.9 Hz, 1H), 2.91 (dd, J = 14.9, 9.2 Hz, 1H), 3.24 (dd, J = 14.3, 11.5 Hz, 1H), 3.75 (s, 3H), 4.06 (dd, J = 10.9, 6.3 Hz, 1H), 4.12−4.16 (m, 3H), 5.77 (dd, J = 9.7, 2.3 Hz, 1H), 6.57 (d, J = 8.0 Hz, 1H), 6.81 (td, J = 6.9, 1.2 Hz, 1H), 7.11−7.15 (m, 5H), 7.25−7.29 (m, 4H), 7.67 (d, J = 8.0 Hz, 2H); ^{13}C {^1H} NMR (125 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 14.2, 21.5, 30.0, 39.3, 41.0, 47.6, 49.2, 61.4, 108.9, 110.1, 119.3, 120.2, 121.9, 125.8, 127.1, 127.2, 128.3, 128.8, 129.5, 134.5, 137.4, 137.5, 141.3, 143.6, 169.8; HRMS (ESI) calcd for $C_{29}H_{31}N_2O_4S$ $(M + Na)^+$ 503.2005, found 503.2008. $[\alpha]^{25}_D$ = +29.4 (*c* 0.17, CH_2Cl_2) for a >99% ee sample; the enantiomeric excess was determined by chiral HPLC analysis (IA column); *n*-hexane/*i*-propanol = 95:5, flow rate = 1.0 mL/min, t_R (1) = 26.71 min (minor), t_R (2) = 41.44 min (major).

*Ethyl (E)-3-(1-Methyl-3-(2-((4-methylphenyl)sulfonamido)-1-phenylethyl)-1H-indol-2-yl)acrylate (**4a**).* Mp 167−169 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 3275, 3055, 3027, 3013, 2924, 1733, 1598, 1491, 1469, 1454, 1421, 1371, 1339, 1303, 1270, 1248, 1160, 1095, 1018, 982, 904, 851, 745, 711, 664, 586, 558; ^1H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, J = 7.5 Hz, 3H), 2.42 (s, 3H), 3.65−3.70 (m, 1H), 3.81 (s, 3H), 3.82−3.85 (m, 1H), 4.25−4.29 (m, 3H), 4.75 (dd, J = 10.3, 5.7 Hz, 1H), 6.11 (d, J = 16.0 Hz, 1H), 6.94 (t, J = 6.9 Hz, 1H), 7.16−7.28 (m, 9H), 7.33 (d, J = 8.0 Hz, 1H), 7.55 (d, J = 8.6 Hz, 2H), 7.73 (d, J = 16.0 Hz, 1H); ^{13}C NMR (100 MHz, $CDCl_3$) δ 14.3, 21.7, 31.8, 42.6, 47.0, 60.3, 110.1, 116.2, 120.5, 121.3, 124.2, 125.9, 126.9, 127.2, 127.7, 128.8, 129.9, 132.0, 133.7, 136.4, 139.1, 141.1, 143.2, 166.5; HRMS (ESI) calcd for $C_{29}H_{31}N_2O_4S$ $(M + H)^+$ 503.2005, found 503.2008.

*Ethyl 2-(4-(4-Bromophenyl)-9-methyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetate (**3r**).* The compound was synthesized by reacting 2-(4-bromophenyl)-1-tosylaziridine **2g** (35.2 mg, 0.100 mmol) with ethyl (*E*)-3-(1-methyl-1*H*-indol-2-yl)acrylate **1d** (27.5 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3r** (23.3 mg, 0.040 mmol) as a white solid (15:1 diastereomeric mixture, combined yield 40%): mp 150−152 °C; R_f 0.19 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2925, 1733, 1597, 1487, 1469, 1406, 1343, 1300, 1270, 1248, 1160, 1094, 1072, 1010, 983, 905, 818, 746, 722, 707, 673, 651, 620, 558; ^1H NMR (500 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 1.26 (t, J = 6.7 Hz, 3H), 2.27 (s, 3H), 2.80 (dd, J = 14.7, 3.1 Hz, 1H), 2.88 (dd, J = 15.3, 9.2 Hz, 1H), 3.16 (dd, J = 14.0, 10.4 Hz, 1H), 3.75 (s, 3H), 40.4−4.15 (m, 4H), 5.75 (dd, J = 9.7, 3.0 Hz, 1H), 6.58 (d, J = 8.6 Hz, 1H), 6.84 (t, J = 7.9 Hz, 1H), 7.02 (d, J = 8.6 Hz, 2H), 7.12 (d, J = 8.6 Hz, 2H) 7.15 (d, J = 7.3 Hz, 1H), 7.25 (d, J = 2.4 Hz, 1H), 7.39 (d, J = 7.9 Hz, 2H) 7.66 (d, J = 7.9 Hz, 2H); ^{13}C {^1H} NMR (125 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 14.2, 21.5, 30.0, 38.9, 40.9, 47.4, 49.1, 61.4, 109.0, 109.4, 119.5, 120.0, 121.0, 122.1, 125.5, 127.1, 129.5, 130.1, 131.9, 134.6, 137.4, 137.5, 140.4, 143.7, 169.7; HRMS (ESI) calcd for $C_{29}H_{30}BrN_2O_4S$ $(M + H)^+$ 581.1110, found 581.1119.

*Ethyl (E)-3-(3-(1-(4-Bromophenyl)-2-((4-methylphenyl)-sulfonamido)ethyl)-1-methyl-1H-indol-2-yl)acrylate (**4b**).* Mp 213−215 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}); 3271, 3061, 3026, 2956, 2925, 2854, 1711, 1625, 1489, 1466, 1406, 1367, 1329, 1286, 1160, 1093, 1073,

DOI: 10.1021/acs.joc.6b02719
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1031, 1010, 976, 907, 814, 759, 744, 699, 664; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.34 (t, J = 7.5 Hz, 3H), 2.41 (s, 3H), 3.63 (td, J = 13.2, 3.9 Hz, 1H), 3.76−3.79 (m, 1H), 3.81 (s, 3H), 4.27 (q, J = 7.5 Hz, 2H), 4.30 (dd, J = 10.9, 2.9 Hz, 1H), 4.53 (dd, J = 10.3, 6.3 Hz, 1H), 6.09 (d, J = 16.0 Hz, 1H), 6.95 (t, J = 6.9 Hz, 1H), 7.06 (d, J = 8.6 Hz, 2H), 7.19−7.22 (m, 3H), 7.25−7.28 (m, 1H), 7.34 (d, J = 8.6 Hz, 2H), 7.54 (d, J = 8.6 Hz, 2H), 7.71 (d, J = 16.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 21.6, 31.5, 42.2, 46.6, 61.0, 110.3, 115.5, 120.3, 120.7, 120.9, 121.5, 124.2, 125.7, 127.0, 127.1, 129.5, 129.8, 131.8, 131.9, 133.7, 136.4, 139.0, 140.0, 143.6, 166.4; HRMS (ESI) calcd for $C_{29}H_{30}BrN_2O_4S$ $(M + H)^+$ 581.1110, found 581.1108.

*Ethyl 2-(4-(2-Chlorophenyl)-9-methyl-2-tosyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)acetate (**3s**).* The compound was synthesized by reacting 2-(2-chlorophenyl)-1-tosylaziridine **2b** (30.7 mg, 0.100 mmol) with ethyl (*E*)-3-(1-methyl-1*H*-indol-2-yl)acrylate **1d** (27.5 mg, 0.120 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3s** (18.8 mg, 0.035 mmol) as a white solid (13:1 diastereomeric mixture, combined yield 35%): mp 190−192 °C; R_f 0.18 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2925, 1735, 1596, 1469, 1345, 1271, 1160, 1093, 1033, 978, 900, 816, 746, 711, 663, 559; ^{1}H NMR (500 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 1.29 (t, J = 6.9 Hz, 3H), 2.20 (s, 3H), 2.82 (dd, J = 13.8, 3.4 Hz, 1H), 2.91 (dd, J = 14.9, 7.5 Hz, 1H), 3.14 (t, J = 12.0 Hz, 1H), 3.77 (s, 3H), 4.19−4.21 (m, 2H), 4.32 (dd, J = 14.9, 7.5 Hz, 1H), 4.47 (dd, J = 12.0, 6.0 Hz, 1H), 5.78 (dd, J = 9.2, 3.4 Hz, 1H), 6.51 (d, J = 8.0 Hz, 1H), 6.83 (t, J = 8.0 Hz, 1H), 6.92 (d, J = 7.5 Hz, 1H), 7.05 (d, J = 8.0 Hz, 2H), 7.12−7.18 (m, 2H), 7.25 (d, J = 4.0 Hz, 2H), 7.40 (d, J = 8.0 Hz, 1H), 7.65 (d, J = 8.0 Hz, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 14.3, 21.4, 30.0, 35.3, 41.0, 45.2, 49.3, 61.5, 109.0, 119.4, 120.0, 122.0, 125.4, 127.1, 127.3, 128.4, 129.4, 129.5, 129.7, 134.2, 134.9, 137.2, 137.4, 138.4, 143.7, 169.6; HRMS (ESI) calcd for $C_{29}H_{30}ClN_2O_4S$ $(M + H)^+$ 537.1615, found 537.1616.

*Ethyl (E)-3-(3-(1-(2-Chlorophenyl)-2-((4-methylphenyl)-sulfonamido)ethyl)-1-methyl-1H-indol-2-yl)acrylate (**4c**).* Mp 192−194 °C; IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}); 3266, 3026, 2956, 2924, 2853, 1708, 1624, 1493, 1466, 1408, 1329, 1285, 1179, 1159, 1159, 1092, 1034, 975, 909, 813, 744, 699, 661, 551; ^{1}H NMR (500 MHz, $CDCl_3$) δ 1.35 (t, J = 7.5 Hz, 3H), 2.42 (s, 3H), 3.67 (td, J = 13.2, 3.4 Hz, 1H), 3.8 (s, 3H), 3.81−3.85 (m, 1H), 4.26 (q, J = 7.5 Hz, 2H), 4.42 (dd, J = 8.6, 2.3 Hz, 1H), 4.86 (dd, J = 10.3, 6.3 Hz, 1H), 5.95 (d, J = 16.0 Hz, 1H), 7.03 (t, J = 7.5 Hz, 1H), 7.08 (t, J = 6.3 Hz, 1H), 7.14 (t, J = 5.7 Hz, 1H), 7.22 (d, J = 8.0 Hz, 2H), 7.30 (t, J = 5.7 Hz, 2H), 7.34−7.35 (m, 2H), 7.46 (d, J = 8.0 Hz, 1H), 7.58 (d, J = 8.6 Hz, 2H), 7.68 (d, J = 16.0 Hz, 1H); ^{13}C NMR (125 MHz, $CDCl_3$) δ 14.4, 21.6, 31.4, 40.7, 45.4, 60.8, 110.4, 114.8, 120.2, 121.0, 121.7, 124.1, 126.4, 127.2, 128.5, 129.4, 129.7, 130.2, 131.7, 133.8, 133.9, 136.8, 138.4, 138.9, 143.5, 166.5; HRMS (ESI) calcd for $C_{29}H_{30}ClN_2O_4S$ $(M + H)^+$ 537.1615, found 537.1619.

*Dimethyl 2-(9-Methyl-2-tosyl-4-vinyl-2,3,4,9-tetrahydro-1H-pyrido[3,4-b]indol-1-yl)malonate (**3t**).* The compound was synthesized by reacting 1-tosyl-2-vinylaziridine **2k** (15.0 mg, 0.067 mmol) with dimethyl 2-((1-methyl-1*H*-indol-2-yl)methylene)malonate **1a** (22.0 mg, 0.081 mmol) in the presence of $LiClO_4$ (5.3 mg, 0.050 mmol) in dry CH_3CN (0.2 mL) at 85 °C for 12 h to afford **3s** (15.9 mg, 0.032 mmol) as a thick liquid (20:1 diastereomeric mixture, combined yield 48%): R_f 0.20 (20% ethyl acetate in petroleum ether); IR $\tilde{\nu}_{max}$ (KBr, cm^{-1}) 2955, 2924, 2853, 1738, 1597, 1493, 1467, 1435, 1348, 1292, 1260, 1162, 1082, 1018, 966, 813, 744, 728, 665, 599, 559; ^{1}H NMR (500 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 2.13 (s, 3H), 3.32 (dd, J = 14.9, 10.9 Hz, 1H), 3.56 (dd, J = 18.3, 9.1 Hz, 1H), 3.64 (s, 3H), 3.79 (s, 3H), 3.94 (dd, J = 5.7, 0.6 Hz, 1H), 4.15 (dd, J = 14.9, 7.5 Hz, 1H), 5.21 (d, J = 10.3 Hz, 1H), 5.28 (d, J = 17.2 Hz, 1H), 5.69−5.76 (m, 1H), 5.93 (d, J = 6.3 Hz, 1H), 6.95 (d, J = 8.0 Hz, 2H), 6.99 (d, J = 6.9 Hz, 1H), 7.16 (d, J = 6.9 Hz, 1H), 7.20 (d, J = 8.6 Hz, 1H), 7.33 (d, J = 8.6 Hz, 1H), 7.50 (d, J = 9.2 Hz, 2H); ^{13}C {^{1}H} NMR (125 MHz, $CDCl_3$) (Major *cis* diastereomer) δ 22.7, 30.5, 37.0, 44.6, 50.8, 52.7, 53.1, 58.6, 109.1, 109.6, 117.3, 119.2, 119.5, 122.1, 124.0, 126.8, 129.1, 131.2, 136.5, 137.6, 138.4, 143.6, 166.7, 167.2; HRMS (ESI) calcd for $C_{26}H_{28}N_2NaO_6S$ $(M + Na)^+$ 519.1566, found 519.1561.

■ ASSOCIATED CONTENT

Supporting Information

The Supporting Information is available free of charge on the ACS Publications website at DOI: 10.1021/acs.joc.6b02719.

X-ray crystallographic analysis of **3k** (CIF)
X-ray crystallographic analysis of **3q** (CIF)
NMR spectra of substrates and products; HPLC chromatograms (PDF)

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Notes

The authors declare no competing financial interest.

■ ACKNOWLEDGMENTS

M.K.G. thanks IIT-Kanpur and CSIR, India, for financial support. M.S. thanks CSIR, India and I.A.W. thanks UGC, India, for research fellowships.

■ REFERENCES

(1) (a) Martin, S. F.; Chen, K. X.; Eary, C. T. *Org. Lett.* **1999**, *1*, 79. (b) English, B. J.; Williams, R. M. *J. Org. Chem.* **2010**, *75*, 7869. (c) Herle, B.; Wanner, M. J.; van Maarseveen, J. H.; Hiemstra, H. *J. Org. Chem.* **2011**, *76*, 8907. (d) Chen, C.-H.; Chang, C.-M.; Chen, H.-Y.; Lai, J.-J.; Sun, C.-M. *J. Comb. Chem.* **2007**, *9*, 618. (e) Lebold, T. P.; Wood, J. L.; Deitch, J.; Lodewyk, M. W.; Tantillo, D. J.; Sarpong, R. *Nat. Chem.* **2012**, *5*, 126. (f) Ishikura, M.; Yamada, K.; Abe, T. *Nat. Prod. Rep.* **2010**, *27*, 1630. (g) O'Connor, S. E.; Maresh, J. *Nat. Prod. Rep.* **2006**, *23*, 532.

(2) (a) Rinehart, K. L.; Kobayashi, J.; Harbour, G. C.; Hughes, R. G.; Mizsak, S. A.; Scahill, T. A. *J. Am. Chem. Soc.* **1984**, *106*, 1524. (b) Rabindran, S. K.; He, H.; Singh, M.; Collins, E.; Annable, K. I.; Greeberger, L. M. *Cancer Res.* **1998**, *58*, 5850. (c) *Introduction to Alkaloids: A Biosynthetic Approach*; Cordell, G. A., Ed.; Wiley: New York, 1981. (d) Ulven, T.; Kostenis, E. *J. Med. Chem.* **2005**, *48*, 897. (e) Herraiz, T.; Galisteo, J. *J. Agric. Food Chem.* **2003**, *51*, 7156. (f) Laine, A. E.; Lood, C.; Koskinen, A. M. P. *Molecules* **2014**, *19*, 1544.

(3) (a) Pictet, A.; Spengler, T. *Ber. Dtsch. Chem. Ges.* **1911**, *44*, 2030. (b) Cox, E. D.; Cook, J. M. *Chem. Rev.* **1995**, *95*, 1797. (c) Stockigt, J.; Antonchick, A. P.; Wu, F.; Waldmann, H. *Angew. Chem., Int. Ed.* **2011**, *50*, 8538. (d) Hansen, C. L.; Clausen, J. W.; Ohm, R. G.; Ascic, E.; Le Quement, S. T.; Tanner, D.; Nielsen, T. E. *J. Org. Chem.* **2013**, *78*, 12545.

(4) (a) Bischler, A.; Napieralski, B. *Ber. Dtsch. Chem. Ges.* **1893**, *26*, 1903. (b) Awuah, E.; Capretta, A. *J. Org. Chem.* **2010**, *75*, 5627. (c) da Silva, W. A.; Rodrigues, M. T., Jr.; Shankaraiah, N.; Ferreira, R. B.; Andrade, C. K. Z.; Pilli, R. A.; Santos, L. S. *Org. Lett.* **2009**, *11*, 3238. (d) Gremmen, C.; Willemse, B.; Wanner, M. J.; Koomen, G.-J. *Org. Lett.* **2000**, *2*, 1955. (e) Amat, M.; Subrizi, F.; Elias, V.; Llor, N.; Molins, E.; Bosch, J. *Eur. J. Org. Chem.* **2012**, *2012*, 1835. (f) Movassaghi, M.; Hill, M. D. *Org. Lett.* **2008**, *10*, 3485. (g) Lorenz, M.; Linn, M. L. V.; Cook, J. M. *Curr. Org. Synth.* **2010**, *7*, 189.

(5) (a) Wanner, M. J.; van der Haas, R. N. S.; deCuba, K. R.; van Maarseveen, J. H.; Hiemstra, H. *Angew. Chem., Int. Ed.* **2007**, *46*, 7485. (b) Weng, J.-Q.; Deng, Q.-M.; Wu, L.; Xu, K.; Wu, H.; Liu, R.-R.; Gao, J.-R.; Jia, Y.-X. *Org. Lett.* **2014**, *16*, 776.

(6) (a) Hajipour, A. R.; Hantehzadeh, M. *J. Org. Chem.* **1999**, *64*, 8475. (b) Wu, J.; Wang, F.; Ma, Y.; Cui, X.; Cun, L.; Zhu, J.; Deng, J.;

DOI: 10.1021/acs.joc.6b02719
J. Org. Chem. 2017, 82, 2364−2374

Yu, B. *Chem. Commun.* **2006**, 1766. (c) Li, C.; Xiao, J. *J. Am. Chem. Soc.* **2008**, *130*, 13208. (d) Evanno, L.; Ormala, J.; Pihko, P. M. *Chem. - Eur. J.* **2009**, *15*, 12963. (e) Yin, Q.; Wang, S.-G.; You, S.-L. *Org. Lett.* **2013**, *15*, 2688.

(7) (a) Martin, S. F.; Chen, K. X.; Eary, C. T. *Org. Lett.* **1999**, *1*, 79. (b) Qais, N.; Nakao, N.; Hashigaki, K.; Takeuchi, Y.; Yamato, M. *Chem. Pharm. Bull.* **1991**, *39*, 3338. (c) Itoh, T.; Yokoya, M.; Miyauchi, K.; Nagata, K.; Ohsawa, A. *Org. Lett.* **2003**, *5*, 4301.

(8) (a) Ohta, Y.; Oishi, S.; Fujii, N.; Ohno, H. *Org. Lett.* **2009**, *11*, 1979. (b) Priebbenow, D. L.; Henderson, L. C.; Pfeffer, F. M.; Stewart, S. G. *J. Org. Chem.* **2010**, *75*, 1787.

(9) (a) Wang, S.; Chai, Z.; Zhou, S.; Wang, S.; Zhu, X.; Wei, Y. *Org. Lett.* **2013**, *15*, 2628. (b) Hudlicky, T.; Rinner, U.; Finn, K. J.; Ghiviriga, I. *J. Org. Chem.* **2005**, *70*, 3490. (c) Mumford, P. M.; Shiers, J. J.; Tarver, G. J.; Hayes, J. F.; Shipman, M. *Tetrahedron Lett.* **2008**, *49*, 3489. (d) Ezquerra, J.; Pedregal, C.; Lamas, C.; Pastor, A.; Alvarez, P.; Vaquero, J. J. *Tetrahedron* **1997**, *53*, 8237.

(10) For reviews on aziridines, see: (a) Singh, G. S.; D'hooghe, M.; De Kimpe, N. *Chem. Rev.* **2007**, *107*, 2080. (b) Schneider, C. *Angew. Chem., Int. Ed.* **2009**, *48*, 2082. (c) Stankovic, S.; D'hooghe, M.; Catak, S.; Eum, H.; Waroquier, M.; Van Speybroeck, V.; De Kimpe, N.; Ha, H.-J. *Chem. Soc. Rev.* **2012**, *41*, 643 and references therein. (d) Callebaut, G.; Meiresonne, T.; De Kimpe, N.; Mangelinckx, S. *Chem. Rev.* **2014**, *114*, 7954.

(11) For selected examples, see: (a) Wu, B.; Gallucci, J. C.; Parquette, J. R.; RajanBabu, T. V. *Angew. Chem., Int. Ed.* **2009**, *48*, 1126. (b) Craig, R. A., II; O'Connor, N. R.; Goldberg, A. F. G.; Stoltz, B. M. *Chem. - Eur. J.* **2014**, *20*, 4806. (c) Pathipati, S. R.; Singh, V.; Eriksson, L.; Selander, N. *Org. Lett.* **2015**, *17*, 4506. (d) Yang, H.-T.; Xing, M.-L.; Lu, X.-W.; Li, J.-X.; Cheng, J.; Sun, X.-Q.; Miao, C.-B. *J. Org. Chem.* **2014**, *79*, 11744. (e) Bailey, S. J.; Wales, S. M.; Willis, A. C.; Keller, P. A. *Org. Lett.* **2014**, *16*, 4344. (f) Takeda, Y.; Ikeda, Y.; Kuroda, A.; Tanaka, S.; Minakata, S. *J. Am. Chem. Soc.* **2014**, *136*, 8544. (g) Moens, M.; De Kimpe, N.; D'hooghe, M. *J. Org. Chem.* **2014**, *79*, 5558.

(12) (a) Ghorai, M. K.; Sayyad, M.; Nanaji, Y.; Jana, S. *Chem. - Asian J.* **2015**, *10*, 1480. (b) Sayyad, M.; Nanaji, Y.; Ghorai, M. K. *J. Org. Chem.* **2015**, *80*, 12659. (c) Sayyad, M.; Mal, A.; Wani, I. A.; Ghorai, M. K. *J. Org. Chem.* **2016**, *81*, 6424. (d) Mal, A.; Sayyad, M.; Wani, I. A.; Ghorai, M. K. *J. Org. Chem.* **2017**, *82*, 4. (e) Ghorai, M.; Bhattacharyya, A.; Das, S.; Chauhan, N. *Top. Heterocycl. Chem.* **2015**, *41*, 49 and references cited therein.

(13) (a) Talukdar, R.; Tiwari, D. P.; Saha, A.; Ghorai, M. K. *Org. Lett.* **2014**, *16*, 3954. (b) Talukdar, R.; Saha, A.; Ghorai, M. K. *Isr. J. Chem.* **2016**, *56*, 445 and references cited therein. (c) Garve, L. K. B.; Petzold, M.; Jones, P. G.; Werz, D. B. *Org. Lett.* **2016**, *18*, 564. (d) Tejeda, J. E. C.; Irwin, L. C.; Kerr, M. A. *Org. Lett.* **2016**, *18*, 4738. (e) de Nanteuil, F.; De Simone, F.; Frei, R.; Benfatti, F.; Serrano, E.; Waser, J. *Chem. Commun.* **2014**, *50*, 10912. (f) Reissig, H.-U.; Zimmer, R. *Chem. Rev.* **2003**, *103*, 1151. (e) Carson, C. A.; Kerr, M. A. *Chem. Soc. Rev.* **2009**, *38*, 3051. (h) Cavitt, M.; Phun, L. H.; France, S. *Chem. Soc. Rev.* **2014**, *43*, 804.

(14) See Supporting Information for details.

(15) Shahi, C. K.; Bhattacharyya, A.; Nanaji, Y.; Ghorai, M. K. *J. Org. Chem.* **2017**, *82*, 37.

(16) Perrin, D. D.; Armarego, W. L. F. *Purification of Laboratory Chemicals*, 3rd ed.; Pergamon Press: Oxford, 1988.

(17) Furniss, B. S.; Hannaford, A. J.; Smith, P. W. G.; Tatchell, A. R. *Vogel's Textbook of Practical Organic Chemistry*, 5th ed.; Longman Group, U.K. Ltd.: 1989.

(18) Jeong, J. U.; Tao, B.; Sagasser, I.; Henniges, H.; Sharpless, K. B. *J. Am. Chem. Soc.* **1998**, *120*, 6844.

(19) (a) Cernerud, M.; Adolfsson, H.; Moberg, C. *Tetrahedron: Asymmetry* **1997**, *8*, 2655. (b) Ghorai, M. K.; Kumar, A.; Tiwari, D. P. *J. Org. Chem.* **2010**, *75*, 137.

(20) Talukdar, R.; Tiwari, D. P.; Saha, A.; Ghorai, M. K. *Org. Lett.* **2014**, *16*, 3954.

(21) Dethe, D. H.; Erande, R. D.; Ranjan, A. *J. Org. Chem.* **2013**, *78*, 10106.

DOI: 10.1021/acs.joc.6b02719
J. Org. Chem. 2017, 82, 2364−2374